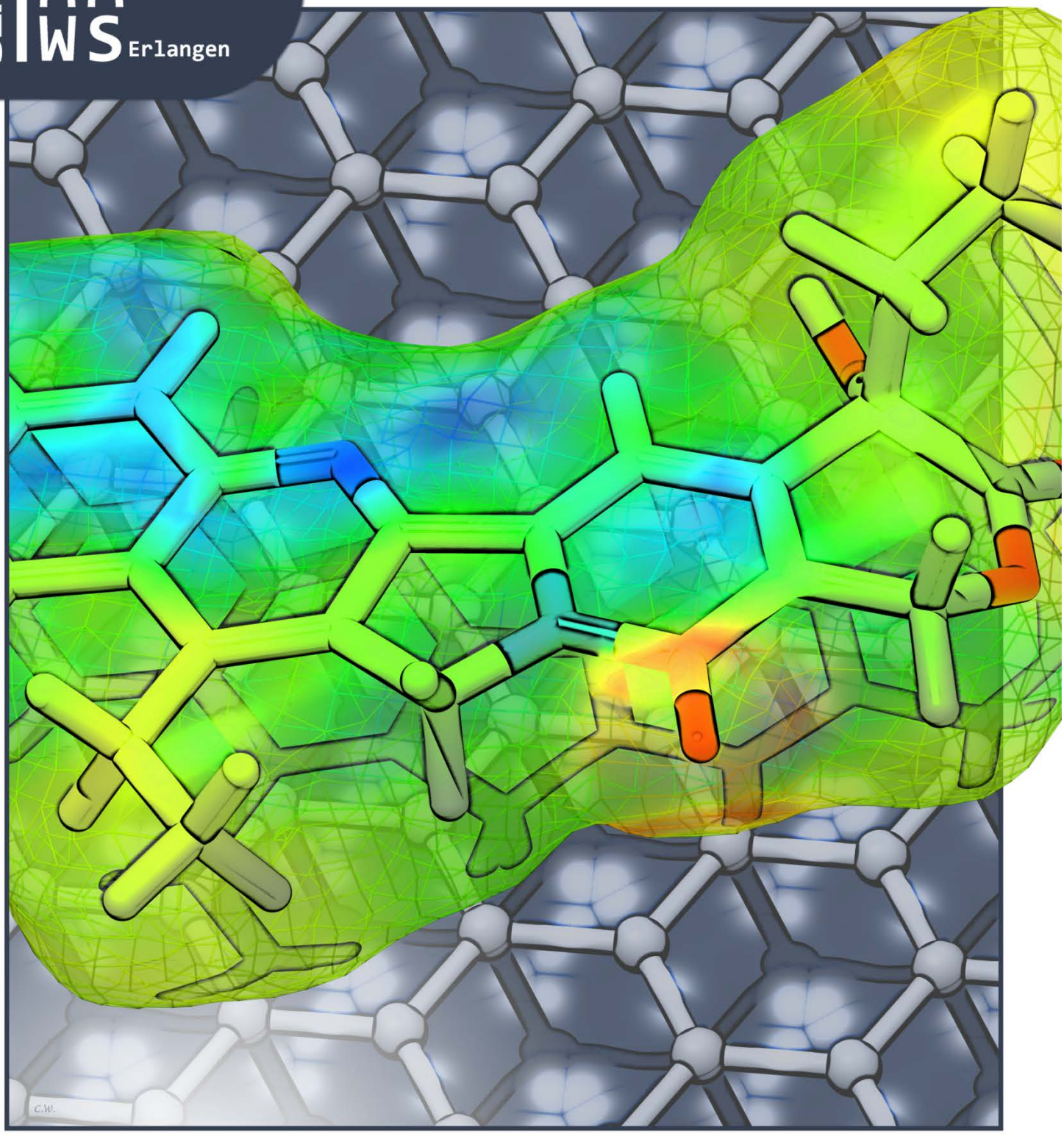
32nd MMWS Erlangen



MOLECULARMODELLING WORKSHOPERLANGEN

12/03-14/03/18 MMWS2018.MGMS-DS.DE

FAU FRIEDRICH-ALEXANDER UNIVERSITÄT ERLANGEN-NÜRNBERG

C3 Computer Chemie Centrum

ZISC Zentralinstitut SCIENTIFIC COMPUTING

MGMS molecular graphics modelling society

MOLECULAR MODELLING WORKSHOP 2018

Monday, March, 12th - Wednesday, March, 14th 2018

Welcome to the 32nd Molecular Modelling Workshop (MMWS).

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

This years's MMWS represents an intermission in the conference venue's continuity: Since Organic, Medicinal and Pharmaceutical Chemistry in Erlangen moved into the new Chemikum, the venue of the workshop temporarily moved into the Institute of Biochemistry, which belongs to the Medical Faculty of the Friedrich-Alexander-Universität Erlangen-Nürnberg. Be reassured, however, that the workshop's location will change back to the lecture hall at the Henkestraße in 2019. Again, the technical conference management of the Computer-Chemie-Centrum, CCC, is supported by the Bioinformatics group headed by Heinrich Sticht. This year's scientific MMWS program has been thoroughly compiled by Achim Zielesny from the Westphalian University of Applied Sciences.

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

This time, we have four plenary speakers for our MMWS. We are happy to welcome Bernd Engels from the University of Würzburg (Germany), Marc Hamm from the Henkel AG (Düsseldorf, Germany), Pavel Hobza from the Czech Academy of Sciences (Prague, Czech Republic), and Gerhard Wolber from the Freie Universität Berlin (Germany) 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 industrial environment, respectively. By combining these four excellent plenary speakers, we ensure to enable MMWS to keep pace with the rapidly changing face of modelling in Europe and the USA and to provide inspiration for young modelers.

Now please enjoy the 32nd Molecular Modelling Workshop.

Scientific program

Prof. Dr. Achim Zielesny

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DEAR COLLEGUES,

The 32nd Molecular Modelling Workshop (March, 12th – 14th 2018) 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. BERND ENGELS

Julius-Maximilians-Universität, Würzburg, Germay

DR. MARC HAMM

Henkel AG & Co. KGaA, Düsseldorf, Germay

PROF. PAVEL HOBZA

Czech Academy of Sciences, Prague

PROF. GERHARD WOLBER

Freie Universität Berlin, Germany

AWARDS

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

1st Winner

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

2nd Winner

up to 200 Euro travel expenses reimbursement

3rd Winner

up to 100 Euro travel expenses reimbursement

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

MGMS-DS E.V. ANNUAL MEETING

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

FEES

The conference fee amounts to 100 Euro (students: 50 Euro). This fee includes the annual membership fee for the MGMS-DS e.V.

WI-FI ACCESS

During the workshop, Wi-Fi access is possible via **eduroam** (SSID). Please have your Wi-Fi configured in advance or ask your local administrator for detailed information about your eduroam access. Links to general information about eduroam can be found on the workshop website mmws2018.mgms-ds.de

LOCATION

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

Conference location: All talks, coffee breaks, the poster sessions and the buffet dinner on Monday, March 12th will take place at the Institute for Biochemistry, Fahrstraße 17, 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. Dr. Bernd Engels

Bernd Engels studied general chemistry and theoretical chemistry in Bonn, Germany, where he also obtained his doctorate and habilitation. During his postdoc time, he stayed at Prof. F. Grein's group (University of New Brunswick). In 1999, he became full professor for theoretical chemistry at the university of Würzburg. Since then, he initiated two research training groups and organized a collaborative research center.

His research focuses mainly on structure, properties, and reactivity of molecular biradicals, the control of electronic properties of aggregated pi-conjugated molecules, and the electron density as molecular property in theory and experiment. Furthermore, he has a strong interest in drug design in the area of infectious diseases.

Selected publications:

C. Brückner et al. Structure-Property Relationships from Atomistic Multiscale Simulations of the Relevant Processes in Organic Solar Cells. I. Thermodynamic Aspects, *J. Chem. Phys. C* **2017**, *121*, 4.

T. Schirmeister et al. Quantum Chemical-Based Protocol for the Rational design of Covalent Inhibitors, *J. Am. Chem. Soc.* **2016**, *138*, 8332.

V. Settels et al. Identification of Ultrafast Relaxation Processes As a Major Reason for Inefficient Exciton Diffusion in Perylene-Based Organic Semiconductors, *J. Am. Chem. Soc.* **2014**, *136*, 9327.

Dr. Marc Hamm

Marc Hamm holds a PhD from the Department of Materials Science and Metallurgy in Cambridge, UK. Initially, he studied physics and mathematics in Kiel, Cambridge, Berlin, and Tel Aviv. After a postdoc stay in Cambridge on simulations on carbon nanotube growth and cell attachment to bones, he changed to Henkel as computational materials scientist. There, he works with a range of simulation and modelling techniques on Henkel's products.

Prof. Dr. Pavel Hobza

Born in the Czech Republic, Pavel Hobza studied physics in Prague, where he also obtained his doctorate. As visiting scientist he stayed at Montreal, Erlangen, and Munich. In 2002, he became full professor at the Charles University in Prague for physical chemistry, and since 2005 he is also full professor at the Palacký University in Olomouc. Also since then, he heads the Research Centre for Biomolecules and Complex Molecular Systems as well as the Departments of Moleclar Modelling within the Institute of Organic Chemistry and Biochemistry of the Academy of Sciences of the Czech Republic. He received numerous awards, e.g. the Schrödinger medal in 2017, and published more than 500 papers in peer-reviewed journals. Furthermore, he is an active member in the editorial boards of *Chem. Eur. J.*, *Chem. Phys. Chem.*, and *Chem. Phys.*.

His research interests are in the areae of quantum chemistry and computational chemistry, noncovalent interactions, structure and dynamics of molecular and biomolecular clusters and biomolecules, hydrogen-bonding and improper, blue-shifting hydrogen-bonding, halogen and σ-hole bonding, *in silico*- drug design, and nanosciences.

Prof. Dr. Gerhard Wolber

Gerhard Wolber is professor for Pharmaceutical and Medicinal Chemistry at the Institute of Pharmacy at the Freie Universitaet Berlin. After his studies of Pharmacy at the University of Innsbruck and Computer Science at the Technical University of Vienna, he received his PhD in medicinal chemistry at the University of Innsbruck. In 2003 he founded the company Inte:Ligand, which successfully develops and markets drug development software and services. In 2010, he changed back to academia by accepting an appointment as professor at the Freie Universität Berlin. His research focuses on rational drug design and the development of new screening tools and algorithms.

Lectures Program

PROGRAM

Monday, March 12th 2018

11:00-13:00	**Pre-conference workshop**
11:00-14:00	**Registration**
14:00-14:10	**Welcome remarks / Agenda review**
14:10-15:10	**PLENARY LECTURE I: Gerhard Wolber** Exploring Protein-Ligand Binding Using 3D Pharmacophore Patterns
15:10-15:30	**L01: Lena Hefke (Frankfurt, Germany)** Using Protein Ligand Interaction Fingerprints and Machine Learning Tools for the Prediction of Novel Dual Active Compounds
15:30-15:50	**L02: Xuejin Zhang (Zürich, Switzerland)** Novel Chemical Space Driven By Reaction Network
15:50-16:10	**L03: Arkadii Lin (Strasbourg, France)** Generative Topographic Mapping Approach as a Ligand-based Virtual Screening Tool
16:10-16:30	**Coffee Break**
16:30-16:50	**L04: Becit Bahanur (Erlangen, Germany)** Molecular Mechanisms of Mesoporous Silica Formation from Colloid Solution
16:50-17:10	**L05: Dominik Munz (Erlangen, Germany)** How to Tame Palladium Terminal Oxos and Imidos
17:10-17:30	**L06: Birgit J. Waldner (Innsbruck, Austria)** Multiscale Simulation and Experimental Characterization of Epoxy/Polyaniline Nanocomposite Coatings – Towards the Rational Design of Nanocomposite Coatings Used in Corrosion Protection
17:30-18:30	**Annual Meeting of the MGMS-DS e.V.**
19:00	**Buffet - Dinner**

PROGRAM

Tuesday, March 13th 2018

08:30-08:50	**L07: Christian A. Söldner (Erlangen, Germany)** Interaction of Glycolipids with the Macrophage Surface Receptor Mincle
08:50-09:10	**L08: Floriane Martins (Nottingham, United Kingdom)** Classical Molecular Docking Procedures in the Context of Enzyme Engineering
09:10-09:30	**L09: Denis Schmidt (Düsseldorf, Germany)** Cryptic Site Identification and Evaluation of Their Role for Allostery
09:30-09:50	**L10: David Wifling (Regensburg, Germany)** Constitutive Activity of the Human Histamine H_4 Receptor: Conmputational Studies on Wild-Type and Mutant H_4R Orthologs
09:50-10:20	**Conference Photo & Coffee Break**
10:20-10:40	**L11: Tatjana Braun (Schrödinger)** Molecular Modelling for Macrocycle Design
10:40-11:00	**L12: Gunter Stahl (Openeye)** Orion: CADD on the Cloud
11:00-12:00	**PLENARY LECTURE II: Pavel Hobza** Semiempirical Quantum Mechanis (SQM)-based Scoring Functions for Native Protein-Ligand Pose Recognition and Virtual Screening
12:00-13:30	**Lunch**
13:30-14:30	**POSTER SESSION I**
14:30-14:50	**L13: Krysztof K. Bojarski (Gdańsk, Poland)** Impact of Chondroitin Sulfate-4 on Human and Rat Cathepsin K Collagenolytic Activity
14:50-15:10	**L14: Nils-Ole Friedrich (Hamburg, Germany)** Assessment of the Diversity of Protein-bound Ligand Conformations and their Representation with Conformer Ensembles
15:10-15:30	**L15: Marko Hanževački (Zagreb, Croatia)** The Entry of CoA into Enzymes: A Case Study with Pyrovate Formate-Lyase
15:30-15:50	**L16: Ghulam Mustafaa (Heidelberg, Germany)** Influence of Mutation of the Transmembrane-Helix of Cyp17A1 on Catalytic Domain-Membrane Interactions and Function

PROGRAM

Tuesday, March 13th 2018

15:50-16:10	**Coffee Break**
16:10-16:30	**L17: Magdalena M. Scharf (Marburg, Germany)** Computer-aided Design of Ligands with Tailored Efficacies for the β_2-Adrenergic Receptor
16:30-16:50	**L18: Christian R. Wick (Erlangen, Germany)** Modelling the Reactions Catalyzed by Coenzyme B_{12} Dependent Enzymes: Accuracy and Cost-Quality Balance
16:50-17:10	**L19: Hilmi Yavuzer (Bielefeld, Germany)** Rationalizing the Enantioselectivity of Aldoxime Dehydratases
17:10-18:10	**PLENARY LECTURE III: Marc Hamm** Facets of Materials Modelling at Henkel
18:30	**Social Event: Bierkeller *(Steinbach Bräu*)**

PROGRAM

Wednesday, March 14th 2018

08:30-08:50	**L20: Dominik Budday (Erlangen, Germany)** Bridging Rigidity Theory and Normal Modes
08:50-09:10	**L21: Oliver Lemke (Berlin, Germany)** Kinetic Models of the Cyclosporines A and E
09:10-09:30	**L22: Sehee Na (Freiburg, Germany)** Thermodynamic Integration Network Study of Electron Transfer: From Proteins to Aggregates
09:30-09:50	**L23: Nicolas Tielker (Dortmund, Germany)** Prediction of Acidity Constants and pH-Dependent Microstate Populations for Drug-like Compounds
09:50-10:10	**Coffee Break**
10:10-11:10	**POSTER SESSION II**
11:10-11:30	**L24: Akinjide Oluwajobi (Ile-Ife, Nigeria)** Atomistic Modelling of Materials in Nanomachining
11:30-11:50	**L25: Zahrabatoul M. Kotena (Kuala Lumpur, Malaysia)** Investigate the Effect of OH Group's Orientation in Natural and Rare Sugars: DFT-AIM-NBO Study
11:50-12:10	**L26: Enric Herrero (Barcelona, Spain)** Hydrophobic Similarity: Application to Three-Dimensional Molecular Overlays with PharmScreen
12:10-13:30	**Lunch**
13:30-13:50	**L27: Conrad Stork (Hamburg, Germany)** Hit Dexter: A Machine-learning Model for the Prediction of Frequent Hitter
13:50-14:10	**L28: Melanie Schneider (Montpellier, France)** Improving Ligand Screening by Exploiting Structure Ensembles and Machine Learning
14:10-15:10	**PLENARY LECTURE IV: Bernd Engels** Towards the Rational Design of Covalent Inhibitors
15:10-15:30	**Poster & Lecture awards, Closing**

Poster Sessions

Poster Session I

Tuesday, March 13th 2018 13:30-14:30

P01 **Yannic Alber (Dortmund, Germany)**
Optimization of Protein-Ligand Binding Affinities Based on Integral Equation Theory

P02 **Meriem Almi (Alger, Algeria)**
Prediction of First-Order Nonlinear Optical Properties of Anderson Polyoxometalate Derivatives

P03 **Hamid A. Lordejani (Isfahan, Iran)**
New and Mild Method for the Synthesis of Alprazolam and Diazepam and Computational Study of Binding Mode of Them to $GABA_A$ Receptor

P04 **Frank Beierlein (Erlangen, Germany)**
Spin-Labelled DNA Oligomers: Simulations and Experiment

P05 **Lauritz T. Bußfeld (Hannover, Germany)**
Towards the Coarse-grained Modelling of Dimethacrylate-based Biomaterials

P06 **Ya Chen (Hamburg, Germany)**
Comparative Analysis of the Chemical Space of Known and Purchasable Natural Products

P07 **Christina de Bruyn Kops (Hamburg, Germany)**
Generating Structures of Likely Metabolites Based on Predicted Cytochrome P450 Regioselectivity

P08 **Benedikt Diewald (Erlangen, Germany)**
Study of the Hapten-Binding Properties of Antibody B1-8 Using Steered Molecular Dynamics

P09 **Jonas Dittrich (Düsseldorf, Germany)**
Converging a Knowledge-based Scoring Function: $DrugScore^{2017}$

P10 **Malti Dumbani (Berlin, Germany)**
Design of Novel Ligands for Thymic Stromal Lymphoetin

P11 **Lukas Eberlein (Dortmund, Germany)**
pH- and Pressure-Dependent Tautomeric and Conformational Equilibria

P12 **Holger Elsen (Erlangen, Germany)**
Hydrogen Activation by Complex Aluminates

Poster Session I

Tuesday, March 13th 2018 13:30-14:30

P13 **Ningning Fan (Hamburg, Germany)**
Machine Learning Models for Guiding Protein Structure Selection Lead to a Boost in the Performance of Ensemble Docking

P14 **Lena Hefke (Frankfurt, Germany)**
Using Protein Ligand Interaction Fingerprints and Machine Learning Tools for the Prediction of Novel Dual Active Compounds

P15 **Eric Herrero (Barcelona, Germany)**
From Continuum Solvation Models to Hydrophobic Descriptors: Application to Virtual Screening of Chemical Databases with PharmScreen

P16 **Peter W. Hildebrand (Berlin, Germany)**
Role of Structural Flexibility for Signal Transduction of G-Protein Coupled Receptors

P17 **Michael C. Hutter (Saarbrücken, Germany)**
Conservation and Relevance of Pharmacophore Point Types

P18 **Suresh Kumar (Guwahati, India)**
Storage Capacity of Clathrate Hydrates for Storing Small Molecules

P19 **Amir H. Hakimioun (Erlangen, Germany)**
Enzyme-Independent Chemical Reactions for Chemistry in Living Cells

Please remember to remove your posters on tuesday evening!

POSTER SESSION II

Wednesday, March 14th 2018 10:10-11:10

P01 **Julia B. Jasper (Dortmund, Germany)**
Mapping Binding Site Thermodynamics by 3D RISM Theory for Drug Design

P02 **Jan Joswig (Berlin, Germany)**
Allosteric Control of pH-Sensitive Ca(II)-Binding in Langerin

P03 **Michael Krug (Merck, Germany)**
SimDoC - Simulate Dose and Clearance

P04 **Natallia Kulik (Nové Hrady, Czech Republic)**
Computational Modelling of Effective Inhibitors of Topoisomerase IA

P05 **Oliver Lemke (Berlin, Germany)**
Kinetic Models of the Cyclosporines A and E

P06 **Ghulam Mustafa (Heidelberg, Germany)**
Simulation of Human Cytochrome P450-membrane Interactions

P07 **Sehee Na (Freiburg, Germany)**
Thermodynamic Intgegration Network Study of Electron Transfer: From Proteins to Aggregates

P08 **Jasmina Petrova (Sofia, Bulgaria))**
Study of a Mulilipid Receptor-Embedded Cell Membrane in Different Ensembles

P09 **Tim Pongratz (Dortmund, Gemany)**
Strategies for Developing Pressure-dependent Force Fields

P10 **Nicola Porta (Düsseldorf, Germany)**
Impact of Allosteric Inhibitors on MRSA Pyruvate Kinase Conformational Dynamics

P11 **Malte Schäfer (Hannover, Germany)**
Implementing Highly Selective Sorption Sites in Metal-Organic Frameworks - A Force Field Study

P12 **Melanie Schneider (Montpellier, France)**
Improving Ligand Screening by Exploiting Structure Ensembles and Machine Learning

P13 **Martin Urban (Dortmund, Germany)**
Computational Structure Analysis for Membrane-bound Potassium Channels

POSTER SESSION II

Wednesday, March 14th 2018 10:10-11:10

P14 **Vishal Nemaysh (Delhi, India)**
Plausible Involvement of K634 and T681 Mutations in Modulation of Tertiary Structure of Human PDGFR-β Protein Kinase Domain by Computational Molecular Dynamics Analysis

P15 **Birgit J. Waldner (Innsbruck, Austria)**
Multiscale Simulation and Experimental Characterization of Epoxy/Polyaniline Nanocomposite Coatings – Towards the Rational Design of Nanocomposite Coatings Used in Corrosion Protection

P16 **David Wifling (Regensburg, Germany)**
Constitutive Activity of the Human Histamine H_4 Receptor: Computational Studies on Wild-Type and Mutant H_4R Orthologs

P17 **Hilmi Yavuzer (Bielefeld, Germany)**
Rationalizing the Enantioselectivity of Aldoxime Dehydratases

P18 **Yuejin Zhang (Boehringer Ingelheim, Germany)**
Novel Chemical Space Driven By Reaction Network

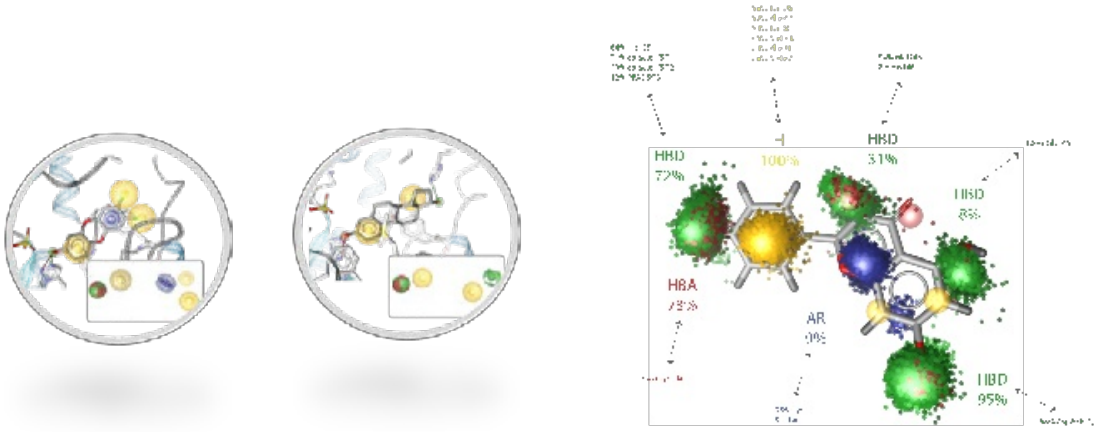
P19 **Ibrahim Maqboul (Erlangen, Germany)**
Modelling Charge-Transport Pathways in Covalent Organic Frameworks

All abstracts are available on the conference web site:
www.mmws2018.mgms-ds.de

Exploring Protein-Ligand Binding Using 3D Pharmacophore Patterns

Gerhard Wolber

Molecular Design Lab, Institute of Pharmacy, Freie Universität Berlin, Königin-Luisestr. 2+4, 14195 Berlin



Virtual screening using 3D interaction models has become an established method for in-silico drug discovery – mainly due to the ability of reflecting the way of thinking of medicinal chemists in terms of hit identification, hit expansion and lead optimization [1]. The simplicity and descriptive character of such a 3D interaction model thus enables clear communication and rapid feedback cycles between modeling and synthesis teams. Despite the established usage of the methodology, there are still several pitfalls and challenges for successful modeling – mainly related to the algorithmic challenge of flexibly fitting a molecule to a 3D interaction model in a computationally efficient way. While our static virtual screening algorithm is broadly used, our new *dynophore* concept [2,3] exploits conformational information from molecular dynamics simulations to represent interaction patterns using probability density maps and allows for a considerably more detailed analysis of binding modes and interaction patterns. While static models represent only single conformations (left figure), dynamic models can capture conformational changes in probability density functions (right figure). Both models are efficient virtual screening filters.

In this lecture, several structure- and ligand-based application studies will be presented including the challenges of difficult targets, such as metabolic enzymes [4] and receptors [2,5]. Both application examples and methods will be critically discussed in the context of screening algorithms and overlay algorithms.

[1] T. Seidel, G. Ibis, F. Bendix, and G. Wolber. *Drug Discovery Today*, **2010**, *7*, e221-e228.
[2] A. Bock, M. Bermudez, F. Krebs, C. Matera, B. Chirinda, D. Sydow, C. Dallanoce, U. Holzgrabe, M. De Amici, M. J. Lohse, G. Wolber, and K. Mohr, *J Biol Chem*, **2016**, *291*, 16375-16389.
[3] J. Mortier, J. R. C. Prévost, D. Sydow, S. Teuchert, C. Omieczynski, M. Bermudez, R. Frédérick, and G. Wolber. *Sci. Rep.*, **2017**, *7*, 13616.
[4] C. Rakers, F. Schumacher, W. Meinl, H. Glatt, B. Kleuser, and G. Wolber., *J Biol Chem*, **2016**, *291*, 58-71.
[5] M. S. Murgueitio, S. Ebner, P. Hörtnagl, C. Rakers, R. Bruckner, P. Henneke, G. Wolber, and S. Santos-Sierra., *Biochim. Biophys. Acta*, **2017**, *1861*, 2680-2689.

Using Protein Ligand Interaction Fingerprints and Machine Learning tools for the prediction of novel dual active compounds

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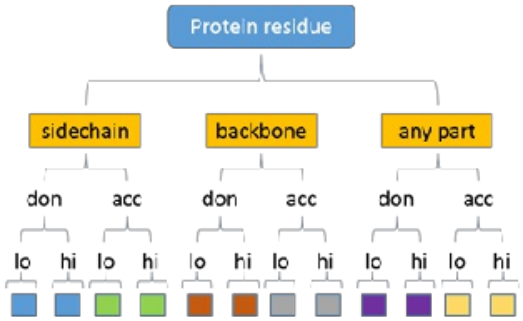
Structure-based drug design relies on accurate affinity prediction through analysis of protein-ligand interactions, which remains an only partially solved problem up to date. Furthermore, if affinities towards dual active compounds have to be approximated, the uncertainty of the prediction rises.

Here we introduce a combination of Protein Ligand Interaction Fingerprints (PLIF) and Machine Learning tools for the target-specific prediction of novel dual active compounds. The PLIF tool (Chemical Computing Group) uses a fingerprint representation of the interactions between ligands and proteins. Currently 10 types of interactions (hydrogen bonds, ionic, surface-, metal binding- and π interactions) are used to describe these interactions.[1]-[3] Using this fingerprints as a descriptor for specific protein-ligand interactions, different machine learning methods including support vector machines, self-organizing maps, neuronal networks, and random forest, were applied to classify active and inactive compounds.



Using the described workflow, we created a data set containing active co-crystallized ligands of the leukotriene A-4 hydrolase (LTA4H) and soluble epoxide hydrolase (sEH). After generating the PLIF, a random forest was trained to classify the compounds. Potential hits are manually inspected, selected compounds will be synthesized and characterized afterwards in an biochemical assay.

[1] P. Labute, *Journal of the Chemical Computing Group*, **2001**.
[2] A.M. Clark, P. Labute, M. Santavy, *J. Chem. Inf. Model.*, **2006**, *46*, 1107–1123.
[3] A.M. Clark, P. Labute, *J. Chem. Inf. Model.*, **2007**, *47*, 1933–1944.

Novel Chemical Space Driven By Reaction Network

Xuejin Zhang [♣♠], Alexander Weber [♣], Gisbert Schneider [♠], Jan Kriegl[♣]

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[♠] Institute of Pharmaceutical Sciences, ETH Zürich

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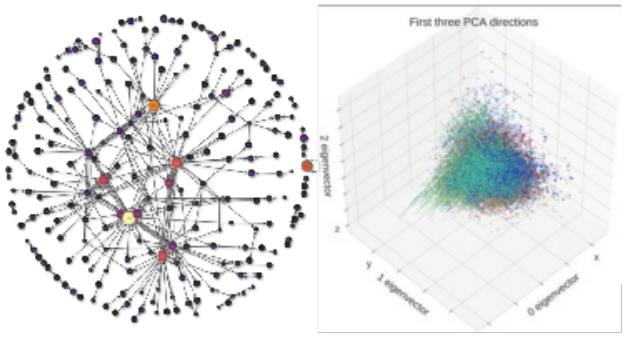

Figure left. The network of chemical reactions.

Figure right. A reaction driven chemical space presented with its first three eigenvectors.

Abstract:

21th century is undoubtedly the "BigData" era[1], especially for chemoinformatics. From reaction record's aspect, there are millions of chemical reactions stored in commercial databases[2]. Figure left exhibits the complexity of chemical reactions via directed network. This number is increasing with text-mining pipelines developed to extract chemical reactions from patents and literatures[3]. From chemical space's view, the cardinality of a typical screening compound collection from a large pharmaceutical company often exceeds one million substances[4], virtual compound pools are even larger. Given these data, one would presume that it should be easy to deliver a real chemical entity with purposed synthetic routes, *i.e.* synthetic route design[5-7]. However, despite the fact that multiple retrosynthetic computational algorithms are available, they are not broadly used by synthetic chemists. Here, we present our naïve synthetic enumeration software guided by easily accessible building blocks and commonly used, *per se*, preferred by chemists, chemical reactions with confined synthetic steps. Through our software, one could deliver a chemical space composed only by theoretically synthesizable compounds. Figure right shows a small novel product pool from ten chosen chemical reactions generated by our software. Automatic property calculation of reactants and products is performed to navigate and analyze enumerated new customized chemical space. We hope that this software could help to establish a rapport between computational and medicinal chemists.

[1] A. Klenner, V. Hähnke, G. Schneider et.al. *Mol. Inf.*, **2012**, 31, 21–26.
[2] S. Roughley, A. Jordan. *J. Med. Chem*, **2011**, 54, 3451–3479.
[3] D. Lowe, *Extraction of chemical structures and reactions from the literature (doctoral thesis)* **2012**.
[4] P. Schneider, G. Schneider, *J. Med. Chem,* **2016**, *59*, 4077-4086.
[5] E. Corey, X. Cheng. *The Logic of Chemical Synthesis, Wiley,* **1989**.
[6] Hartenfeller M, G. Schneider, et al. *PLoS Comput Biol,* **2012**, 8, e1002380.
[7] Wellenzohn, B.; Lessel, U. et.al. *J. Med. Chem.* **2012**, 55, 11031−11041.

Generative Topographic Mapping approach as a Ligand-based Virtual Screening tool

Arkadii Lin[a,b], Dragos Horvath[a], Gilles Marcou[a], Alexandre Varnek[a], and Bernd Beck[b]

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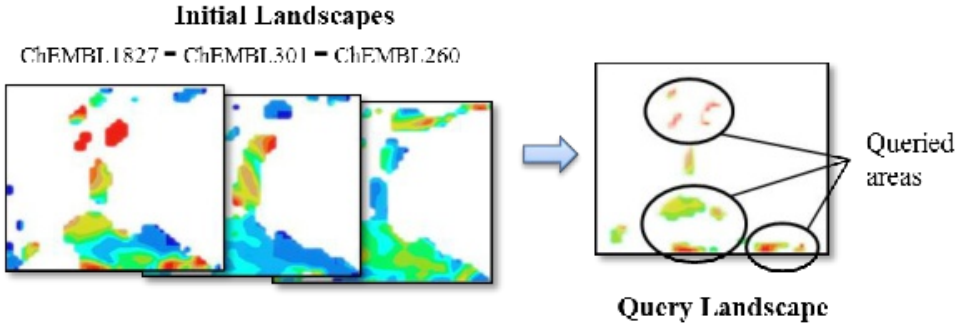
Generative Topographic Mapping (GTM) is a dimensionality reduction method that can be used for large chemical data visualization and analysis. [1] Recently it was tested as a tool for large chemical databases comparison (PubChem-17, ChEMBL-17, and FDB-17). [2] It was also tested as a machine learning method for Quantitative Structure-Activity Relation (QSAR) tasks. [3, 4] However, it was not fully tested as a tool for Ligand-based Virtual Screening (LBVS) procedure, where large chemical databases are used.

In this project, GTM is compared with the most popular methods for LBVS such as Random Forest, Neural Networks, and Similarity search with data fusion. Within the usual GTM approach, where each model is built for the particular target, a "universal" map approach is also tested as a method where only one map is used to represent activity landscapes of any number of targets or properties. This enables the querying by activity profile (focusing on zones with jointly favorable predictions for all targeted properties, see Figure below).



Benchmarking results show that GTM is competitive in terms of performance. For example, "universal" maps built and having activity landscapes calibrated on > 1.5M ChEMBL compounds are excellent discriminators for the Directory of Useful Decoys (DUD) compounds (excluding the ones present in ChEMBL, to ensure strict "external" validation). For 9 biological targets ROC AUC values ranged within 0.7÷0.8.

Furthermore, GTM has some important advantages in terms of usage, notably the ability to intuitively visualize the chemical space, and its support of multiple predictive landscapes on a single map. Calculation times are independent of reference set sizes (unlike in pairwise similarity searching).

[1] Bishop CM, Svensén M, Williams CK. GTM: *Neural computation*. **1998**, 10(1), 215-34.
[2] Lin, A., Horvath, D., Afonina, V., Marcou, G., Reymond J.L. and Varnek, A. *ChemMedChem*. doi:10.1002/cmdc.201700561.
[3] Gaspar HA, Baskin II, Marcou G, Horvath D, Varnek A. *Journal of Chemical Information and Modeling*. **2015**, 55(1), 84-94.
[4] Sidorov P, Gaspar H, Marcou G, Varnek A, Horvath D. *Journal of Computer-Aided Molecular Design*. **2015**, 29(12), 1087-108.

Molecular mechanisms of mesoporous silica formation from colloid solution

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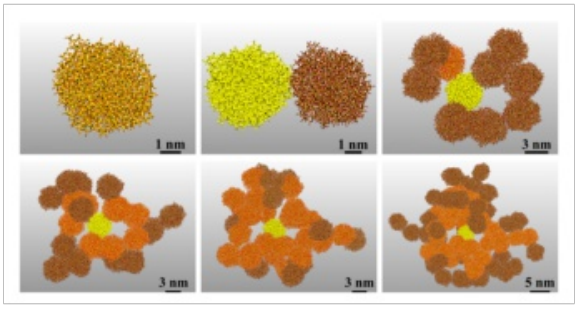
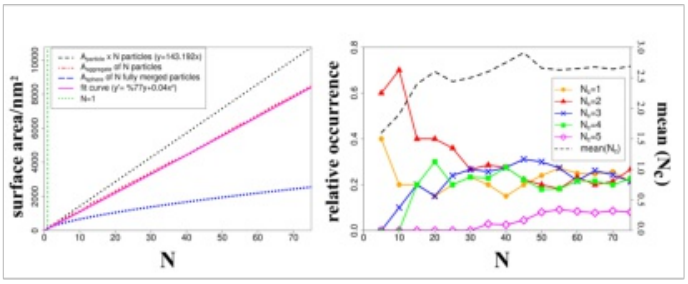
Silica particles and nanocomposites are being used in many applications ranging from catalysts to coatings, reinforced plastics and recent studies suggested silica nanomaterials to be used as biocatalyst,drug/gene delivery vehicles, and also for biomimetic processes like bone tissue engineering. For bionanotechnological applications, colloidal amorphous silica is taken as a base material to form mesoporous silica. Considering huge demand of silica nanomaterials, understanding and controlling interfacial interactions, association and aggregation is vital to the goal-oriented use of colloidal silica particles.



In this work, we investigated the agglomeration of silica nanoparticles in aqueous solution from molecular simulations through colloidal silica association of $SiO_2/Si(OH)_4$ core/shell particles, local silanole → silica ripening reactions within a limited contact zone and finally the formation of mesoporous precipitates. This calls for profound characterization of molecular interactions and the assessment of extended relaxation processes at the same time. To cope with the inherent time-length scale challenge to molecular simulation, we employ the Kawska-Zahn approach [1,2]. Implementing sufficiently fast supply from colloidal solution, our simulations show the development of silica networks comprised of covalently bound, yet not fully merged nanoparticles in which coordination numbers range from 2 to 5 and with 77% theoretical limit of porosity – which is far from the closest packing.



[1] A. Kawska, J. Brickmann, R. Kniep, O. Hochrein, D. Zahn, *J Chem Phys*, **2006**, 124, 24513

[2] A. Kawska, J. Brickmann, R. Kniep, O. Hochrein, D. Zahn, *ChemPhysChem*, **2010**, 11, 847-852.

How to Tame Palladium Terminal Oxos and Imidos

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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] Herein, I would like to report DFT (B2PLYP-D3(COSMO)/def2-TZVPP//B3LYP-D3/def2-TZVP) and CASSCF calculations, which predict which ligands are suitable for the thermodynamic stabilization of oxo and imido intermediates of palladium. [5,6] 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.

[1] K. Morokuma, K. Cao, C. L. Hill et al. *Science* **2012**, 337, 290.
[2] a) D. Milstein, J. M. L. Martin et al. *Nature* **2008**, *455*, 1093-1096.
[3] P. R. Sharp *J. Chem. Soc. Dalton Trans.* **2000**, *16*, 2647-2657.
[4] M. Soleilhavoup, G. Bertrand *Acc. Chem. Res.* **2015**, *48*, 256-276.
[5] D. Munz *Chem. Sci.* **2018**, *9*, 1155-1167.
[6] A. Grünwald, D. Munz *J. Organomet. Chem.* **2017**, **DOI:**10.1016/j.jorganchem.2017.12.034.

Multiscale Simulation and Experimental Characterization of Epoxy/Polyaniline Nanocomposite Coatings – Towards the Rational Design of Nanocomposite Coatings Used in Corrosion Protection

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Corrosion of mild steel causes massive costs due to inspection, maintenance and repair each year. Currently, for corrosion protection conductive polymers are of great interest. The most studied polymer is Polyaniline (PANI) since it is easy to synthesize and can be prepared either chemically or electrochemically [1]. The conductivity of PANI is controlled through protonation leading to an increase in conductivity (doping) and de-protonation (de-doping) causing a decrease in conductivity [2]. The electrochemical properties and performance as corrosion inhibitor are significantly influenced by the choice of doping agent [3]. Blends of PANI and epoxy resin have shown promising corrosion inhibition properties [4], [5], [6].
Despite the large number of studies on PANI and PANI containing coatings for the corrosion protection of mild steel, the mechanisms of action, influence of the doping agent and failure of the anticorrosive properties have not yet been fully understood. Therefore, we employ a combination of theoretical and experimental methods for the investigation of epoxy/PANI nanocomposites doped with different doping agents. Simulations ranging from atomistic scale to macroscale should allow to investigate the charge-transfer reactions taking place at the steel-coating interface, the role of doping agents and ferric oxide type at the interface in electron transfer reactions and interfacial adhesion (atomistic scale – first principle quantum mechanical (QM) and molecular dynamics (MD) simulations) as well as the role of surface morphology and cracks (macroscale – Finite Element (FE) modeling) in corrosion protection and failure of the coating. The results of simulations are benchmarked against experimentally determined electrochemical properties, surface morphology, interfacial energy and adhesion.
The results will point-out the factors crucial for the success or failure of employing an epoxy/PANI nanocomposite coating for the corrosion protection of mild steel. The knowledge on the electrochemical processes occurring at the metal-coating interface will not only be important for corrosion science, but also for the application of PANI in electrochemical sensors, capacitors, solar energy conversion or rechargeable batteries.

1. Boeva, Z.A. and V.G. Sergeyev, *Polyaniline: Synthesis, properties, and application*. Polymer Science Series C, 2014. **56**(1): p. 144-153.
2. Zarras, P., et al., *Progress in using conductive polymers as corrosion-inhibiting coatings*. Radiation Physics and Chemistry, 2003. **68**(3-4): p. 387-394.
3. da Silva, J.E.P., S.I.C. de Torresi, and R.M. Torresi, *Polyaniline acrylic coatings for corrosion inhibition: the role played by counter-ions*. Corrosion Science, 2005. **47**(3): p. 811-822.
4. Lu, W.-K., R.L. Elsenbaumer, and B. Wessling, *Corrosion protection of mild steel by coatings containing polyaniline*. Synthetic Metals, 1995. **71**(1-3): p. 2163-2166.
5. Talo, A., O. Forsen, and S. Ylasaari, *Corrosion protective polyaniline epoxy blend coatings on mild steel*. Synthetic Metals, 1999. **102**(1-3): p. 1394-1395.
6. Tallman, D., Y. Pae, and G. Bierwagen, *Conducting polymers and corrosion: polyaniline on steel*. Corrosion, 1999. **55**(8): p. 779-786.

Interaction of Glycolipids with the Macrophage Surface Receptor Mincle

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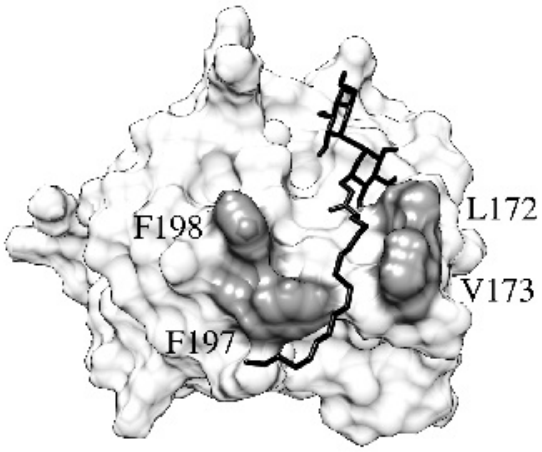
Synthetic analogues of mycobacterial trehalose-dimycolate such as trehalose acyl esters have been proposed as novel adjuvants for vaccination. They induce an immune response by binding to the macrophage C-type lectin receptor Mincle [1]. The binding site of trehalose is known [2], but there is yet only very limited structural information about the binding mode of the acyl esters.



Trehaloseoctadecanoate (black sticks) bound to Mincle (white surface representation). Key interacting residues, which form a hydrophobic groove on the surface, are colored in gray.

Here, we performed a systematic molecular dynamics study of trehalose mono- and diesters with different chain lengths. All acyl chains investigated exhibited a high flexibility and interacted almost exclusively with a hydrophobic groove on Mincle. Despite the limited length of this hydrophobic groove, the distal parts of the longer monoesters can still form additional interactions with this surface region due to their conformational flexibility. In diesters, a certain length of the second acyl chain is required to contact the hydrophobic groove. However, a stable concomitant accommodation of both acyl chains in the groove is hampered by the conformational rigidity of Mincle. Instead multiple dynamic interaction modes are observed, in which the second acyl chain contributes to binding. This detailed structural information is considered helpful for the future design of more affine ligands that may foster the development of novel adjuvants.

References

[1] A. Huber, R. S. Kallerup, K. S. Korsholm, H. Franzyk, B. Lepenies, D. Christensen, C. Foged, and R. Lang. "Trehalose diester glycolipids are superior to the monoesters in binding to Mincle, activation of macrophages in vitro and adjuvant activity in vivo". *Innate Immunity*, **2016**, *22*, 405–418.

[2] H. Feinberg, N. D. S. Rambaruth, S. A. F. Jégouzo, K. M. Jacobsen, R. Djurhuus, T. B. Poulsen, W. I. Weis, M. E. Taylor, and K. Drickamer. "Binding Sites for Acylated Trehalose Analogs of Glycolipid Ligands on an Extended Carbohydrate Recognition Domain of the Macrophage Receptor Mincle". *J. Biol. Chem.*, **2016**, *291*, 21222–21233.

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Classical Molecular Docking Procedures in the Context of Enzyme Engineering

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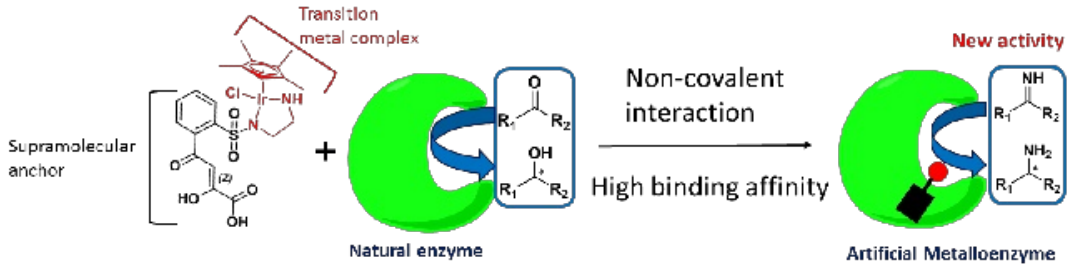
Molecular docking procedures are widely used in computer aided molecular design approaches as a central part of the computational chemist's toolbox. Particularly in the pharmaceutical industries it fills a prominent role in drug design and virtual screening for the optimisation of lead structures within drug discovery, often combined with methods of higher accuracy to predict ligand-target complexes and to estimate the binding affinities. These rational design techniques appear as a time and experimental resource saver in the drug discovery process.[1]
In those examples, the focus often lies more on binding affinity prediction over the accurate determination of orientation and direction of ligand structures positioning inside enzyme active sites. However, the correct representation of docking poses is more important when these methods are applied to engineering of new functional enzymes.

We will present examples where we have used docking procedures to support projects aiming to design and engineer enzymes with improved or altered functionality. The focus will be on an approach to design artificial metalloenzymes (Figure). In these hybrid catalysts, a synthetic metal complex is incorporated within a host enzyme, allowing non-natural synthesis of building blocks in a natural environment.[2]



In this approach, we aim to incorporate the catalyst by supramolecular anchoring. At first, docking calculations have been used in the design of metal anchors where strong binding affinities with the enzyme scaffold are explored by mimicking natural cofactors. A ranking score have thus been created to choose the best metal complexes based on their affinity for the enzyme and their optimal position/orientation for an efficient catalytic activity. From the selected structures, a short synthesis path has been designed to allow the quick construction of a metal complexes library.

[1] I. A. Guedes, C. S. de Magalhaes, L. E. Dardenne, *Biophys. Rev.* **2014**, *6*, 75–87.
[2] J. F. H. P.Dydio, H.M. Key, A. Nazarenko, J.Y.-E. Tha, V. Seyedkazemi, D.S. Clark, *Science* **2016**, *354*, 104–106.

Cryptic Site Identification and Evaluation of Their Role for Allostery

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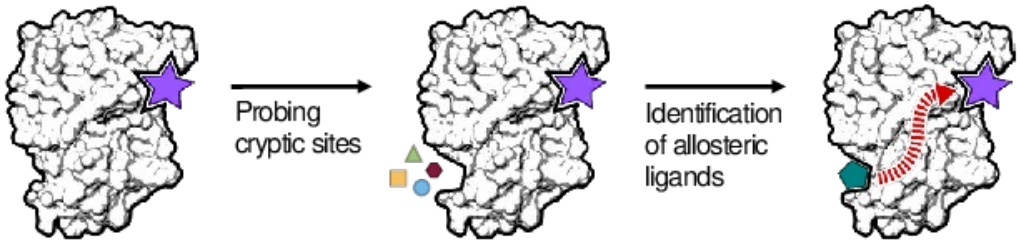
It is widely accepted that allosteric modulators have a huge potential to overcome typical hurdles in drug design. Our group recently showed that the "Constraint Network Analysis" (CNA) approach is capable of identifying allosteric pathways by means of rigidity analysis [1]. CNA hence has the potential to predict the allosteric effect of new ligands.

Even in the absence of a defined binding site, allosteric regulation might be possible via so-called "cryptic sites" ("transient pockets"). Such cryptic sites are closed in the *apo* state due to their lipophilicity. Consequently, they are hard to identify, although they are predicted to exist in many proteins [2]. Molecular dynamics simulations have been proposed as promising approach to sample cryptic sites in their open states [3,4,5,6].

Here, we systematically investigated the influence of different organic solvents on the opening of cryptic sites during molecular dynamics simulations, starting from the *apo* state. The addition of 10% phenol to the solvent significantly increased the number of frames where the cryptic site was open compared to water alone. By averaging pockets formed during these simulations, we identified and ranked spatial regions where pockets are more probable to form in the presence of organic solvent ("pocket cores"). For most test cases, i) the cryptic site opened, ii) the high-ranked pocket cores matched the known cryptic sites, and iii) the crystal ligand could be re-docked into MD-generated structures. Notably, the docking setup was based exclusively on the identified cores, thus excluding ligand bias. Unlike perturbation-based approaches [5,6], equilibrium simulations do not require *a priori* knowledge of the location of the binding site. Rather, pocket cores have the potential to locate yet unknown cryptic sites.



After their identification, we employ molecule surrogates ("fuzzy ligands") [7] to fill the cryptic sites. This way, CNA is able to quantify the allosteric potential of a ligand in this binding site. The generated fuzzy ligands subsequently serve as seeds for virtual screening.

The cryptic site identification in combination with the "fuzzy ligand" approach and CNA yields a powerful workflow to prospectively identify new sites, evaluate their allosteric potential, and ultimately predict new allosteric compounds.

[1] C. Pfleger, A. Minges, M. Boehm, C.L. McClendon, R. Torella & H. Gohlke, *J. Chem. Theory Comput.*, **2017**, *13*, 6343–6357
[2] P. Cimermancic, *et al.*, *J. Mol. Biol.*, **2016**, *428*, 709–719.
[3] S. Eyrisch & V. Helms, *J. Med. Chem.*, **2007**, *50*, 3457–3464.
[4] S.R. Kimura, *et al.*, *J. Chem. Inf. Model.*, **2017**, *57*, 1388–1401.
[5] D.B. Kokh, *et al.*, *J. Chem. Theory Comput.*, **2016**, *12*, 4100–4113.
[6] V. Oleinikovas, *et al.*, *J. Am. Chem. Soc.*, **2016**, *138*, 14257–14263.
[7] S.M.A. Hermans, *Master thesis*, Heinrich Heine University Düsseldorf, **2015**.

Constitutive activity of the human histamine H_4 receptor: Computational studies on wild-type and mutant H_4R orthologs

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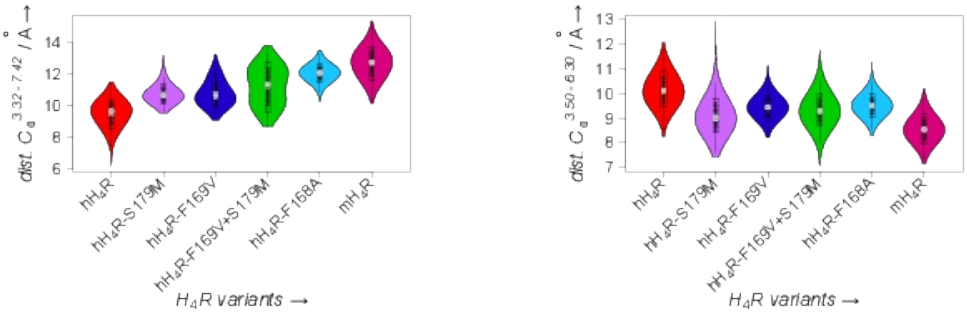
Histamine H_4 receptor (H_4R) orthologs are G-protein coupled receptors (GPCRs) that exhibit species-dependent constitutive (basal) activity. In contrast to mouse H_4R (mH_4R), human H_4R (hH_4R) shows a high degree of constitutive activity.

In a previous molecular-pharmacological study, we characterized the constitutive activity of hH_4R, mH_4R as well as a series of hH_4R mutants, comprising hH_4R-S179M, hH_4R-F169V, hH_4R-F169V+S179M [1] and hH_4R-F168A [2]. An exchange of $F169^{ECL2}$ to V significantly decreased the constitutive activity compared to wild-type hH_4R, while that of the hH_4R-S179M mutant is similar to that of hH_4R. [1] Remarkably, the basal activity of the hH_4R-F169V+S179M [1] and hH_4R-F168A [2] mutants is even comparable to that of mH_4R.

Hence, though we identified residues that account for the high constitutive activity of the hH_4R, the underlying molecular mechanism by which the basal equilibrium between inactive and active receptor states is shifted towards the inactive state is still unknown. To shed light on this matter, we have performed long-time-scale (2 µs) molecular-dynamics simulations on wild-type hH_4R, the hH_4R mutants S179M, F169V, F169V+S179M, F168A, and on mH_4R.

During the MD simulations, $F169^{ECL2}$ is dipping into the binding pocket merely in case of hH_4R and is thereby interacting with the surrounding aromatic and hydrophobic residues. Interestingly, F169 seems to take the role of an agonist, thus contributing to the stabilization of the active state. As a measure of binding pocket contraction, the distance (C_α) between $D94^{3.32}$ and $Q347^{7.42}$, starting at approximately 11 Å, increased by a maximum of ~3 Å for the hH_4R mutants and mH_4R, while, by contrast, it decreased by up to 3 Å for the basally active hH_4R. At the intracellular side, initial C_α-C_α distances of around 8.0 Å between $R112^{3.50}$ and $A298^{6.30}$ increased more for hH_4R than for the hH_4R mutants and mH_4R, thus showing an enhanced outward movement of TM6 for hH_4R compared to the other H_4R variants. This is in accordance with the fact that GPCR activation is reflected by a subtle contraction of the orthosteric binding pocket and a notable outward motion of TM6 at the intracellular side.



Hence, H_4R variant-dependent differences between essential motifs of GPCR activation correlate with experimentally determined constitutive activities and provide a molecular explanation for the differences in constitutive activation. Furthermore, the results shed new light on the molecular mechanism of basal H_4R activation that are of importance for other GPCRs.

[1] D. Wifling, et al., *Br. J. Pharmacol.*, **2015**, 172, 785-798.
[2] D. Wifling, et al., *PLoS One*, **2015**, 10, e0117185.

Molecular Modelling for Macrocycle Design

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Macrocycles are an important and growing class of clinical drug candidates due to their structural diversity, wide range of physicochemical properties, and promising biological activities. However, macrocycles are often more difficult to work with than typical drug-like small molecules, both synthetically and computationally.

Here, we present a toolkit for computational macrocycle design introduced by Schrödinger over the last few years. Key component is a new macrocycle sampling approach based on established protein structure prediction algorithms that has shown excellent accuracy, robustness, and speed on a diverse benchmarking data set of 208 macrocycles. [1]

The new sampling technology is at the core of a variety of macrocyclic workflows: macrocycle bioactive conformer stability calculation, membrane permeability predictions [2], and binding mode determination using ligand-receptor docking with Glide.

Furthermore, the results of an adapted FEP+ [3] protocol for calculating binding free energies of macrocycles are presented. [4] The approach allows studying both ring size changes and cyclization of acyclic precursors. Applied to seven pharmaceutically relevant data sets including 33 macrocyclic ligands covering a diverse chemical space, the predicted binding free energies are in excellent agreement with experimental data, with an overall root mean square error below 1 kcal/mol.

[1] Sindhikara, D.; Spronk, S. A.; Day, T.; Borelli, K.; Cheney, D. L.; Posy, S. L. Improving Accuracy, Diversity, and Speed with Prime Macrocycle Conformational Sampling. *J. Chem. Inf. Model.* **2017**, *57*, 1881-1894.

[2] Leung, S. S. F., Sindhikara, D. J., and Jacobson, M. P., "Simple Predictive Models of Passive Membrane Permeability Incorporating Size-Dependent Membrane-Water Partition," J. Chem. Inf. Model., **2016**, 56(5), 924–929

[3] Wang, L.; Wu, Y.; Deng, Y.; Kim, B.; Pierce, L.; Krilov, G.; Lupyan, D.; Robinson, S.; Dahlgren, M.K.; Greenwood, J.; et al., "Accurate and Reliable Prediction of Relative Ligand Binding Potency in Prospective Drug Discovery by Way of a Modern Free-Energy Calculation Protocol and Force Field," *J. Am. Chem. Soc.*, **2015**, 137 (7), 2695–270

[4] Yu, H. S.; Deng, Y.; Wu, Y.; Sindhikara, D.; Rask, A. R.; Kimura, T; Abel, R.; Wang, L. Accurate and Reliable Prediction of the Binding Affinities of Macrocycles to Their Protein Targets. *J. Chem. Theory Comput.* **2017**, *13*, 6290-6300.

Orion: CADD on the Cloud

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The cloud will increasingly become the destination for a wide variety of tasks, in computational chemistry and elsewhere. In this workshop we will introduce Orion, OpenEye's new cloud-native CADD platform. By seamlessly integrating almost limitless computing capacity with well validated workflows and powerful analysis tools Orion substantially increases the scale of problems that can be addressed and makes finding solutions to those problems easy for anyone.

In this presentation we will show examples how frequently occurring problems in medicinal chemistry can be addressed in ORION

The ability to set up and monitor a large-scale calculation on the cloud, analyse its results, share that analysis and make decisions based on it, all through the same interface, a standard web browser, is extremely powerful.

Semiempirical Quantum Mechanics (SQM)-based Scoring Functions for Native Protein-Ligand Pose Recognition and Virtual Screening

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General and reliable description of structures and energetics in protein-ligand binding using the docking/scoring methodology has up to now been elusive. We address this urgent deficiency of scoring functions by systematic development of corrected semiempirical quantum mechanical (SQM) methods which correctly describe all types of non-covalent interactions and are fast enough to treat systems of thousands of atoms. Two most accurate SQM methods, PM6-D3H4X and SCC-DFTB3-D3H4X, are coupled with the COSMO implicit solvation model in so called "SQM/COSMO" scoring functions and have shown unique recognition of native ligand pose in cognate docking and high enrichment in virtual screening in dozens of diverse protein-ligand systems, including challenging metalloproteins. This performance was superior to those of classical scoring functions (Glide XP, GOLD, UCSF DOCK, AutoDock 4 and AutoDock Vina). The SQM/COSMO method, due to its generality, comparability across the chemical space and no need for any system-specific parameters, gives promise to become in near future a useful computational tool in structure-based drug design and serve as a reference method for the development of other scoring functions.

Impact of chondroitin sulfate-4 on human and rat cathepsin K collagenolytic activity

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Cathepsins are a family of a protein-degrading enzymes that can be found in many living organisms. Most of them are cysteine proteases (Enzyme Commision number - EC 3.4.22) but are also cathepsins A and G which are serine proteases (EC 3.4.21) or cathepsins D and E which are aspartyl proteases (EC 3.4.23). To date there are 15 members of the cathepsin family with most of their structures experimentally available. Regardless differences in their aminoacid sequences cathepsins share the same secondary structure pattern which is reflected in the same 3D fold. It was demonstrated that enzymatic activity of cathepsins can be modulated by glycosaminoglycans (GAGs) - a group of linear negatively charged polysaccharides made of repetitive disaccharide units. Each unit consist of one aminosugar and one uronic acid. GAGs are located in the extracellular matrix. They are involved in many cellular processes including cell proliferation, angiogenesis, anticoagulation, adhesion and signalling cascades.

Cathepsin K is an enzyme consisting of 215 aminoacid residues in its mature form. Human cathepsin K is able to degrade efficently type I and type II collagens and its irregular functioning leads to osteoporosis and rheumatoid arthritis. The collagenolytic activity of human cathepsin K in bone osteoclasts is mediated specifically by complex formation with chondroitin 4-sulfate (C4-S), a sulfated glycosaminoglycan [1]. Negatively charged C4-S forms multiple contacts with basic amino acid residues on the backside of the cathepsin K molecule. However, little is known whether these electrostatic interactions between C4-S and human cathepsin K exist also in other species. Rat (*Rattus norvegicus*) is one of the most frequently used model for the study of human pathological processes including osteoporosis and rheumatoid arthritis. We chose rat cathepsin K that shares high amino acid sequence identity (88.4%) with human cathepsin K to perform molecular docking and molecular dynamic simulations with C4-S of variable length.

Calculations were performed with use of such computational methods as PBSA electrostatic potential analysis, molecular docking, molecular dynamics and free energy calculations. Our studies predict similar interactions between C4-S hexasaccharides and rat cathepsin K with those found in human cathepsin K as well as similar binding affinity to the fluorogenic substrates of cathepsin K. Nevertheless, differences were observed with longer C4-S chains which could potentially explain diverse collagenolytic activity of aforementioned enzymes measured *in vitro*.

[1] A. H. Aguda, P. Panwar, X. Du, N. T. Nguyen, G. D. Brayer, D. Brömme, *PNAS*, **2014**, *111(49)*, 17474-17479

Assessment of the diversity of protein-bound ligand conformations and their representation with conformer ensembles

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Three-dimensional computational methods for guiding the discovery and optimization of bioactive small molecules rely on the accurate representation of the protein-bound conformations of ligands.[1] We have developed a cheminformatics pipeline for the fully automated identification and extraction of high-quality structures of protein-bound ligands from the PDB.[2,3] Importantly, among many other aspects, the support of the individual atom positions of ligands by the measured electron density is evaluated as part of this workflow. Using this software infrastructure, which we will present as part of this contribution, we have compiled a complete dataset of high-quality structures of protein-bound ligand conformations from the PDB, consisting of a total of 10,936 high-quality structures ("Sperrylite Dataset") of 4,548 unique ligands. This allowed us, for the first time, to conduct a comprehensive analysis of the diversity of protein-bound ligand conformations.

In total, we have studied the conformational variability of 91 drug-like molecules represented by a minimum of ten high-quality structures. We will show that a clear trend for the formation of few clusters of highly similar conformers is observed but that several interesting examples of small molecules that can adopt two or more distinct conformations when bound to different proteins exist, such as imatinib.

A diversified subset of this dataset was also used to assess how well leading free and commercial algorithms for conformer ensemble generation are able to represent bioactive conformations. We demonstrate that the differences in accuracy, computational cost and ensemble size are much smaller between commercial algorithms than those observed for free algorithms. RDKit generally achieved a favorable balance of accuracy, ensemble size and runtime among the seven tested free algorithms and its performance was comparable to that of mid-ranked commercial algorithms (median RMSD of 0.52 Å, measured between the bioactive conformation and the closest conformer in the ensemble). OMEGA obtained the best accuracy and speed among the eight tested commercial algorithms (median RMSD of 0.43 Å).

[1] Ebejer, J.-P.; Morris, G. M.; Deane, C. M. Freely Available Conformer Generation Methods: How Good Are They? *J. Chem. Inf. Model.*, **2012**, *52*, 1146–1158.

[2] Friedrich, N.-O., Meyder, A., de Bruyn Kops, C., Sommer, K., Flachsenberg, F., Rarey, M., et al. High-Quality Dataset of Protein-Bound Ligand Conformations and Its Application to Benchmarking Conformer Ensemble Generators. *J. Chem. Inf. Model.*, **2017**, *57*, 529–539.

[3] Friedrich, N.-O., de Bruyn Kops, C., Flachsenberg, F., Sommer, K., Rarey, M., and Kirchmair, J. Benchmarking Commercial Conformer Ensemble Generators. *J. Chem. Inf. Model.*, **2017**, *57*, 2719–2728.

The Entry of CoA into Enzymes: A Case Study with Pyruvate Formate-Lyase

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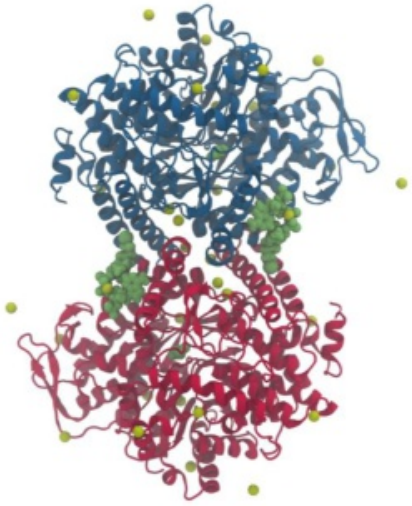
Coenzyme A (CoA) is an important coenzyme required, for example, in fatty acid synthesis and the citric acid cycle in aerobic organisms, where it is crucial for the oxidation of pyruvate. CoA also participates in pyruvate metabolism in anaerobic organisms, whereby pyruvate and CoA are transformed to formate and acetyl-CoA (AcCoA) in the presence of Pyruvate formate-lyase (PFL).[1]

PFL is a glycyl radical enzyme requiring activation by a member of the radical SAM enzyme superfamily.[2] Such radical enzymes are receiving increased interest because of their possible applications in biotechnology.[3] The mechanism of PFL is thought to be initiated by the formation of a radical at Gly734, which is subsequently shuttled to Cys 418 via Cys 419. 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 AcCoA, the final product, closes the catalytic cycle of PFL.[4]



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.[5] In search for possible solutions to this problem the models representing the PFL system before and after the first half-reaction with pyruvate were subjected to long unrestrained molecular dynamics (MD) simulations, to examine the possible effect that acetylation of the enzyme has on the necessary conformational changes. The PFL systems were also subjected to the free energy calculations used to estimate potential of mean force (PMF) for the process of CoA approaching the active site before and after the pyruvate cleavage.

[1] M. Müller, M. Mentel, J. J. van Hellemond, K. Henze, C. Woehle, S. B. Gould, R-Y. Yu, M. van der Giezen, A. G. M. Tielens, W. F. Martin, *Microbiol. Mol. Biol. Rev.*, **2012**, *76* (2), 444-495.

[2] J. M. Buis, J. B. Broderick, *Archives of Biochemistry and Biophysics*, **2005**, *433*, 288-296.

[3] L. Zelcbuch, S. N. Lindner, Y. Zegman, I. V. Slutskin, N. Antonovsky, S. Gleizer, R. Milo, A. Bar-Evan, *Biochemistry*, **2016**, *55* (17), 2423-2426.

[4] J.-D. Guo, F. Himo, *J. Phys. Chem. B*, **2004**, *108* (39), 15347-15354.

[5] A. Becker, W. Kabsch, *J. Biol. Chem.*, **2002**, *277* (42), 40036-40042.

INFLUENCE OF MUTATION OF THE TRANSMEMBRANE-HELIX OF CYP17A1 ON CATALYTIC DOMAIN-MEMBRANE INTERACTIONS AND FUNCTION

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Human cytochrome P450 (CYP) enzymes play an important role in the metabolism of drugs, steroids, fatty acids and xenobiotics. A subset of CYPs is responsible for steroidogenesis; of these CYP17 is a major drug target for prostate cancer therapy. Human CYPs are anchored to the endoplasmic reticulum membrane by their N-terminal transmembrane (TM) helix. However, the structural and functional importance of the TM-helix is unclear since, on truncation of the TM-helix or modification of the N-terminal amino acid sequence, CYPs can still associate with the membrane and maintain enzymatic activity [1-3]

In the current study, we investigated the effect of mutations in the first 8 N-terminal TM-helix residues of CYP17, originally modified by Imai et al. (1993) to increase the expression of human CYP17 in *E.Coli*, on the orientation and interactions of the globular domain of CYP17 with the membrane. Coarse-grained and all-atom simulations of CYP17 in a phospholipid bilayer were performed. The mutations in the TM-helix, especially W2A and E3L, resulted in amphipathic helix characteristics which led to an unstable TM-helix and gradual drifting of the TM-helix out of the hydrophobic core of the membrane. This instability of the TM-helix also influenced the membrane interactions and orientation of the globular domain, which was compared with experimental measurements for CYP17 in a nanodisc. In some simulations, the mutations led to the TM-helix obstructing the substrate access tunnel from the membrane to the active site, which could affect enzymatic activity.

[1] Barnes, H. J., Arlotto, M. P. & Waterman, M. R, *Proc. Natl. Acad. Sci.* **1991,** *88,* 5597–5601
[2] Imai, T., Globerman, H., Gertner, J. M., Kagawa, N. & Waterman, M. R, *J. Biol. Chem.* **1993** *268,* 19681–9
[3] Shukla, A., Huang, W., Depaz, I. M. & Gillam, E. M. J, *Xenobiotica.,* ***2009***, 39**,** 495–507

Computer-aided design of ligands with tailored efficacies for the β_2-adrenergic receptor

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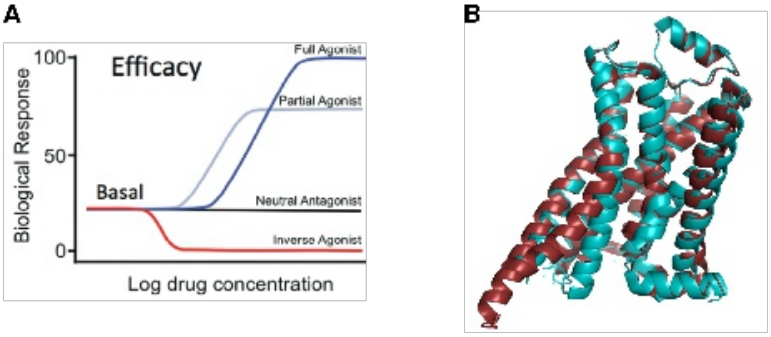
G protein-coupled receptors (GPCRs) are one of the pharmacologically most important classes of proteins with more than 800 genes in humans encoding them. Due to their function as universal signal transduction entities, they are involved in a large number of physiological processes. Therefore, GPCRs are a target for 1/3rd of present-day marketed drugs and, consequentially, highly interesting targets for the design of future drugs. [1],[2]
Ligands binding to a GPCR might have different effects on the signal transmitted into the cell (see Fig. A, [3]), acting as agonist, antagonist or inverse agonist. Hence, ligands with different efficacies have different impact on the body when used as a drug.



We aim to find new ligands with predicted efficacies for the β_2-adrenergic receptor by docking molecule libraries to this receptor. It is involved in smooth muscle relaxation processes and, therefore, useful for e.g. treating asthma. Furthermore, the β_2-adrenergic receptor offers great perspectives for *in silico* studies due to the high number of available crystal structures (e.g. Fig. B: In blue pdb 3NY9, in red pdb 3SN6).
I will show preliminary results from docking calculations against inactive and active conformations of the β_2-adrenergic receptor. In total, 3.7 million molecules were docked in each docking campaign. From these, a total of 49 molecules were selected. The chosen molecules have been or will be tested in biological assays to determine their efficacies.
The insights gained from these studies not only help to understand the effect different ligands have upon binding to the β_2-adrenergic receptor, but can potentially be applied to other GPCRs as well. Thereby, our findings can contribute to our knowledge of function and mechanism of these fascinating proteins.

[1] C. N. Cavasotto, D. Palomba, *Chem. Commun.*, **2015**, *51*, 13576-13594.
[2] J. A. Salon, D. T. Lodowski, K. Palczewski, *Pharmacol. Rev.*, **2011**, *63*, 901-937.
[3] B. Kobilka, *Nobel Lecture*, **2012**, 195-213.

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

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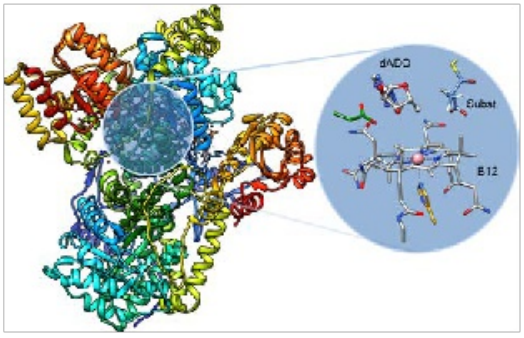
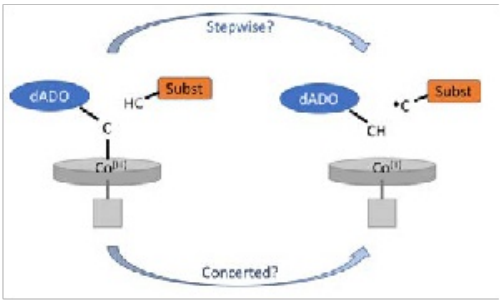
Coenzyme B12 (5'-deoxyadenosylcob(III)alamin, dAdoCbl) is one of the most prominent organometallic cofactors due to the presence of a carbon-cobalt (Co-C) bond, which is the key to enzymatic reactions utilizing coenzyme B_{12} as a cofactor: The homolytic cleavage of the Co-C bond, which leads to the formation of a 5'-dAdo radical, is highly encouraged in the enzymatic environment compared to the nonenzymatic reaction. In a (subsequent or concerted) second step, the 5'-dAdo radical is involved in an H-atom transfer reaction, generating a substrate radical and 5'-dAdo. However, the accurate theoretical description of both elementary reactions is challenging. More recently, the Co-C cleavage was investigated with dispersion-corrected DFT and LPNO-CCSD calculations utilizing the full coenzyme.[1] This and another study[2] have elucidated the importance of the model system design and, especially, the inclusion of dispersion and solvent corrections. 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 model chemistry 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, for both types of reactions. All these efforts help us to tackle the decades-long controversy about the actual mechanism among the different classes of coenzyme B_{12} dependent enzymes.





[1] Z. Qu, A. Hansen, S. Grimme, *J. Chem. Theory Comput.* **2015**, *11*, 1037-1045.
[2] K. P. Kepp, *J. Phys. Chem. A* **2014**, *118*, 7104-7117.
[3] D. J. Henry, C. J. Parkinson, P. M. Mayer, L. Radom, *J. Phys. Chem. A* **2001**, *105*, 6750-6756.
[4] M. L. Coote, *J. Phys. Chem. A* **2014**, *108*, 3865-3872.
[5] B. Durbeej, G. M. Sandala, D. Bucher, D. M. Smith, L. Radom, *Chem. – Eur. J.* **2009**, *15*, 8578-8585.

Rationalizing the enantioselectivity of aldoxime dehydratases

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The advantages of enzyme-catalysis such as high enantioselectivity and mild reaction conditions are well known. In order to increase the potential of biocatalysis further, gaining a deep insight into the mechanism and catalytic properties of enzymes appears to be of high importance. Toward this end, *in silico* assays can be a powerful tool for protein engineering approaches. Latest experiments from *Betke et al.* [1] showed an unexpected phenomenon for the enantioselective dehydration of aldoximes under formation of nitriles: in dependency of the *E*- or *Z*- conformation of a racemic aldoxime, a switch of the enantiopreference was observed. Thus, starting from the same racemic aldehyde and albeit using the same aldoxime dehydratase as an enzyme, both enantiomers are accessible. Based on a general postulated mechanism for an aldoxime dehydratase by *Nomura et al.* [2], we focused on rationalizing this unusual switch in enzyme selectivity by means of docking experiments. As a software MOE (*Molecular Operating Environment*) was used to find suitable ligand-protein conformations. First, we defined *cut off*-values, which were determined by using the co-crystal from *Sawai et al.* [3] and considering *van-der-Waals*-radii of the interacting atoms being included in the postulated mechanism. All 28

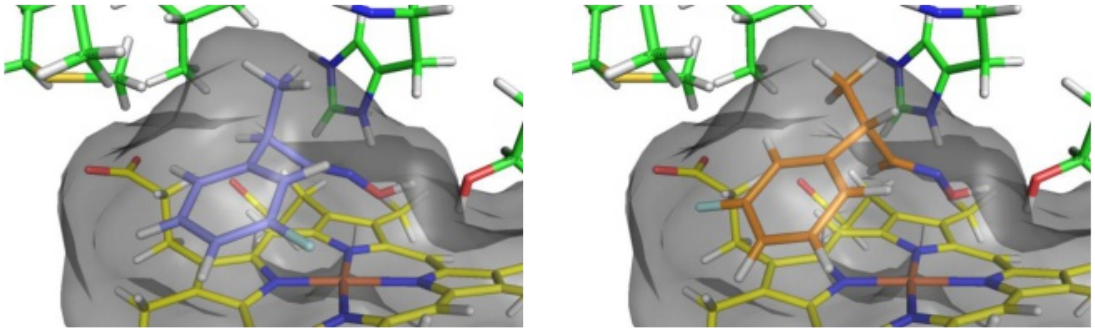

Figure 1: Comparison of docked structure with OxdRE and 3-(*E*)-fluoro-phenylpropanal oxime (FPPOX) in *R* - and *S*- conformation.

phenylpropanal-oxime (PPOX) derivatives, which were used for the docking studies showed a privileged conformation in the active site. The methyl-group of these structures were nearly always localized inside a small cavity in the active site pocket. Furthermore, the ΔΔG values of the transition states when starting from the (*E*)- or (*Z*)- isomers were determined, thus enabling a prediction of the formed enantiomers. The experimental data are consistent with the docking result for example, 3-(*E*)-*rac*-FPPOX could be converted to 3-*S*-FPPN with 49 % conv. and 81 %ee. A hypothesis for the enzyme selectivity is that the methyl-group in the cavity causes (mainly) this energy difference.

[1] T. Betke, P. Rommelmann, K. Oike, Y. Asano and H. Gröger, *Angew.. Chem. (In. Ed.)* **2017**, 56, 12361-12366

[2] J. Nomura, H. Hashimotob, T. Ohtac, Y. Hashimotoa, K. Wadaa, Y. Naruta, K. Oinuma, and M. Kobayashi, *PNAS* **2013**, *110*, 2810-2815.

[3] H. Sawai, H. Sugimoto, Y. Kato, Y. Asano, Y. Shiro, and S. Aono, *J. Biol. Chem.* **2009**, *284*, 32089.

Facets of Materials Modelling at Henkel

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Henkel AG & Co. KGaA, Düsseldorf

Simulations and modelling are an evolving discipline in the development of products and materials, which Henkel brings to market. These include adhesives as well as laundry and beauty-care products. The customer demands do structure the type of models which are applied. Here the main factor determining the modelling approach is the time scale of customer expectation. The scope of these approaches will be presented ranging from statistical models, over finite elements, dissipative particle dynamics, molecular mechanics, to density functional theory. The presentation of these models will be completed by a discussion of what makes business sense.

Bridging Rigidity Theory and Normal Modes

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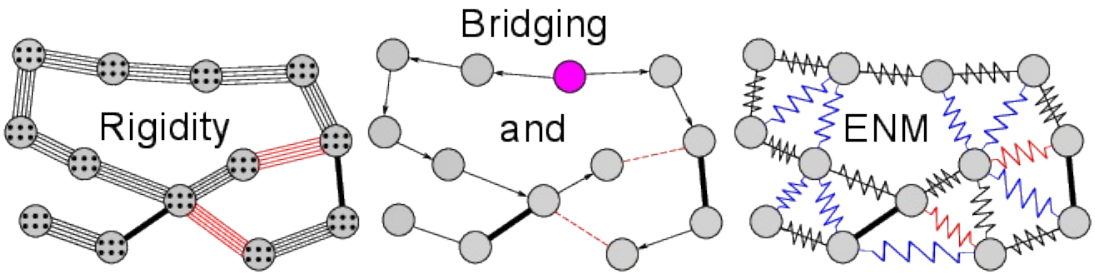

Elastic network models (ENM [1], Figure right) and constraint-based, topological rigidity analysis ([2], Figure left) are two distinct, coarse-grained approaches to study conformational flexibility of macromolecules. Over the last two decades, they have contributed significantly to insights into molecular mechanisms and function. However, despite their shared purpose, the topological nature of rigidity analysis, and the concomitant absence of motion modes, have hindered a direct comparison between them. Here, we present an alternative, kinematic approach to rigidity and flexibility analysis, which eliminates these drawbacks (Figure center). Our analysis of the Jacobian matrix **J**, obtained from treating hydrogen bonds as constraints, bridges results from topological rigidity and ENM: it provides an orthonormal basis for the full spectrum of collective motions, analogous to the eigenspectrum of normal modes, and decomposes proteins into rigid clusters identical to those from topological rigidity [3]. Our hydrogen bond network spectral decomposition allows a detailed comparison of motion modes obtained from both traditional methods. The analysis reveals that collectivity of motions, reported by the Shannon entropy, is significantly lower for rigidity theory versus normal mode approaches. Strikingly, our kinematic approach suggests that the hydrogen bonding network encodes a protein-fold specific, spatial hierarchy of motions, which goes nearly undetected in ENM. The hierarchy uncovers different motion regimes, related to the stiffness of the molecule, that qualitatively agree well with experimental observations and more detailed molecular simulations. For a set of designed, hyper-stable peptides [4], we find a clear shift towards stiffer modes, in agreement with their designed characteristics. Overall, these results suggest that hydrogen bond networks could have evolved to tailor structural dynamics and thus, fold-related function, with broad implications for protein engineering and drug design.

[1] Tirion, M. M. Large amplitude elastic motions in proteins from a single-parameter, atomic analysis. *Phys Rev Lett* **1996**, *77*, 1905.
[2] Jacobs, D. J.; Thorpe, M. F. Generic rigidity percolation: the pebble game. *Phys Rev Lett* **1995**, *75*, 4051.
[3] Budday D, Leyendecker S, van den Bedem H. Geometric analysis characterizes molecular rigidity in generic and non-generic protein configurations. *J Mech Phys Solids* **2015**, *83*, 36-47.
[4] Bhardwaj, G. et al. Accurate de novo design of hyperstable constrained peptides. *Nature* **2016**, *538*, 329–335.

Kinetic models of the Cyclosporines A and E

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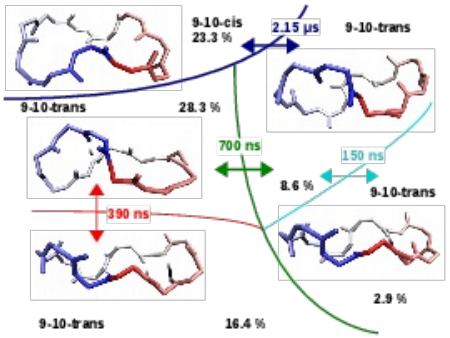

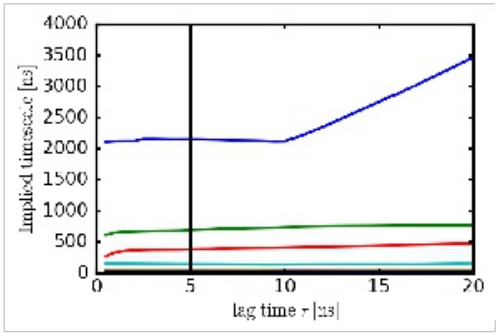

Cyclic peptides have gained high interest as potential drug candidates. However, they often suffer from a low bioavailability due to their size and complexity. One exception is the undecamer Cyclosporine A (CsA), which can passively diffuse through the membrane. The reason for this is most likely found in its dynamic behavior as it can change between an „open" and a „closed" conformation. Cyclosporine E (CsE) is a synthetic derivative of CsA, missing a backbone methylation in Val-11. Its membrane permeability, however, is one order of magnitude smaller [1,2].

To get a better understanding of the dynamics of both molecules and their kinetic differences MD-simulations in water (polar solvent) and chloroform (apolar solvent) have been performed [1,2], which are analyzed using core-set Markov-State-Models (cs-MSMs). In cs-MSMs one focuses on the metastable states of the system, called core sets. This has the advantage that only a small number of states is needed to describe the dynamics accurately [3,4]. We showed that using this kind of analysis recrossing can be reduced and disconnection of metastable states within the data set can be pointed out. In addition, we analyzed the influence of the cis-trans isomerization of the 9-10 peptide bond, which seems to be an important factor for the conformational changes of CsA and CsE, and compared both molecules using a combined discretization.

[1] J. Witek, B.G. Keller, M. Blatter, A. Meissner, T. Wagner, S. Riniker, *J. Chem. Inf. Model.*, **2016**, *56*, 1547-1562
[2] J. Witek, M. Mühlbauer, B.G.Keller, M. Blatter, A. Meissner, T. Wagner, S. Riniker, *ChemPhysChem*, **2017**, *18*, 3309-3314
[3] M. Sarich, R. Banisch, C. Hartmann, C. Schütte, *Entropy*, **2013**, *16*, 258-286
[4] O. Lemke, B.G. Keller, *J. Chem. Phys.*, **2016**, *145*, 163104

Thermodynamic Integration Network Study of Electron Transfer: from Proteins to Aggregates [1]

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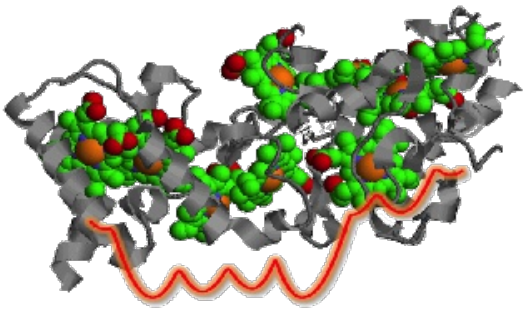

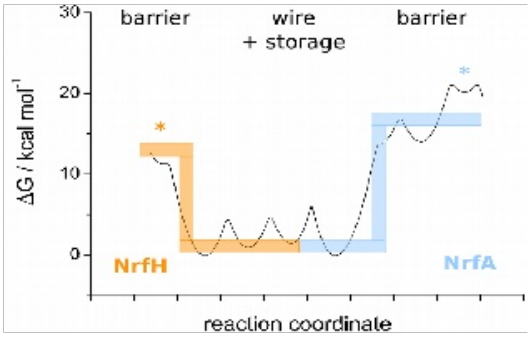

We describe electron transfer through the NrfHA nitrite reductase heterodimer [2] using a thermodynamic integration scheme based upon molecular dynamics simulations. From the simulation data, we estimate two of the characteristic energies of electron transfer, the thermodynamic driving forces, ΔG, and the reorganization energies, λ. Using a thermodynamic network analysis, the statistical accuracy of the ΔG values can be enhanced significantly. Although the reaction free energies and activation barriers are hardly affected by protein aggregation, the complete reaction mechanism only emerges from the simulations of the dimer rather than focussing on the individual protein chains: it involves an isoenergetic transprotein element of electron storage and conductivity [1].

[1] S. Na, A. Bauß, M. Langenmaier, T. Koslowski, *Phys. Chem. Chem. Phys.*, **2017**, *19*, 18938–18947.
[2] M. Rodrigues, K. Scott, M. Sansom, I. Pereira, M. Archer, *J. Mol. Biol.*, **2008**, 381, 341–350.

Prediction of acidity constants and pH-dependent microstate populations for drug-like compounds

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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 of both neutral and ionic molecules in a wide range of solvents. To accurately model the solvation of small molecules in water 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. [3]

The macroscopic acidity constants of drug-like molecules are difficult to predict since these species often contain functional groups and scaffolds that imply a multitude of tautomeric or ionic states ("microstates") at physiological pH. Moreover, the microstate relevant for a drug's mechanism of action might differ from the highest populated state in bulk solution, which is essential information for predicting binding constants accurately. In this context, the SAMPL6 challenge (Statistical Assessment of the Modeling of Proteins and Ligands [4]) was designed to specifically address such difficulties by requiring the participants to blindly predict the macroscopic pK_a values of kinase inhibitor fragments as well as their local microstate pK_a estimates and the fractional populations as a function of pH.

A workflow is described to accurately calculate the macroscopic pK_a of a given compound by determining the free energy of all tautomers of the deprotonated and the protonated form by EC-RISM calculations. Applied to small organic molecules covering a wide range of functional groups, it is shown that in total at most 5 empirically adjusted parameters (2 or 3 for free energy predictions and 2 for the final pK_a model) are required, ultimately allowing us to predict acidity constants to a root mean square error of about 1.6 pK_a units within the SAMPL6 blind prediction challenge. [4] Unlike other first-principles models there is in our case no need for distinguishing acids and bases or different compound classes. These pK_a values in combination with predicted free energy data of all tautomers within a given protonation state enable us to also predict the fractional microstate populations over the entire pH-range.

[1] E. L. Ratkova, D. S. Palmer, M. V. Fedorov, *Chem. Rev.* **2015**, *115*, 6312-6356.
[2] T. Kloss, J. Heil, S. M. Kast, *J. Phys. Chem. B* **2008**, *112*, 4337-4343.
[3] N. Tielker, D. Tomazic, J. Heil, T. Kloss, S. Erhart, S. Güssregen, K. F. Schmidt, S. M. Kast, J. Comput.-Aided Mol. Des. **2016**, *30*, 1035-1044.
[4] https://drugdesigndata.org/about/sampl6 (last accessed 2018/02/13).

Atomistic Modelling of Materials in Nanomachining

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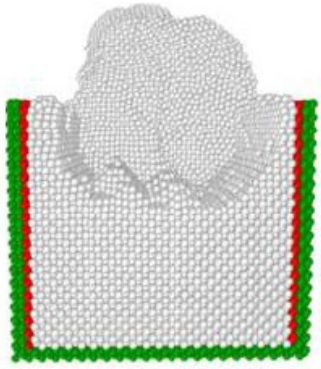

Figure 1: Nano Surface Created through MD Multipass Simulations

Many materials are employed in nanomachining; such as copper and aluminium, used as workpiece materials; and diamond and cubic boron nitride, used as the cutting tools materials. The interatomic potentials used in the atomistic modelling of these materials during nanomachining are reviewed and the associated material removal mechanisms are highlighted.
Futhermore, multi-pass nanometric atomistic simulations were carried out, with a diamond tool on a copper workpiece to create nano surfaces and the results provide the platforms from which the atomic surface roughness were evaluated. The estimated surface roughness (Sa) was in the order of 0.3 nm, but the value varies with the depth of cut and cutting velocity. It is essential that MD simulation results should be validated, and the evaluation of the surface roughness in this work, allows for comparisons with theory and experiments [1].

[1] A.O Oluwajobi, X.Chen, *Key Engineering Materials*, **2016**, *686*, 200-203.

Keywords: Interatomic Potentials, Molecular Dynamics, Nanomachining, Materials Removal Mechanisms

Investigate the effect of OH group's orientation in Natural and Rare Sugars: DFT-AIM-NBO Study

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Monosaccharide carbohydrates play in many biological processes. β-D (glucose, galactose, mannose) are sugars that occur large amounts in nature. Rare sugars such as β-D (allose, altrose, gulose, idose and talose) which are numerous but only present naturally in small amounts. These sugars are stereoisomer and differ by only the orientation of the hydroxyl group at the C2-C4 positions. Ab initio calculations based on density functional theory using B3LYP/6-31G* have been performed to investigate the effect of hydroxyl group's orientation to the nature of hydrogen bonds and its strength in these sugars. The atoms in molecules (AIM) analysis confirm the existence of regular intra-molecular hydrogen bond paths, so that gulose and glucose display single bond critical points, and allose, galactose, and mannose display two bond critical points, talose,and altrose display three bond critical points,except idose displays bifurcated acceptor intra -molecular hydrogen bond at critical points. According to the Laplacian signs and total energy electron density in the appropriate critical point (3,-1) intra-molecular hydrogen bonds: (i) atrose and mannose should be assigned to a weak; (ii) gulose and glucose should be assigned medium; (iii) talose, galactose, allose and idose with different bonds are categorized on weak and medium intra-molecular hydrogen bond closed shells of interaction. Maximum energy regular intra-molecular hydrogen bonding is measured approximately 11.73kcal/mol, while it is for bifurcated hydrogen bonds in idose is between 58% and 45% of regular hydrogen bonds. From NBO analysis, the formation of intra-molecular hydrogen bonds in monosaccharide sugars implies that certain electronic charges are transferred from the lone pair to the anti-bonding orbital. These types of sugars have different applications in the Pharmaceutical field (Chemotherapeutic), foods industry, cosmetic, treatment for skin cancer, etc. Therefore, theoretical point of view of nature hydrogen bond in these carbohydrates would provide further insight into the monosaccharaides structural maintenance and properties.

Keywords: Natural and Rare sugars, Hydrogen bonding, AIM, NBO.

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Hydrophobic Similarity: Application to Three-Dimensional Molecular Overlays with PharmScreen

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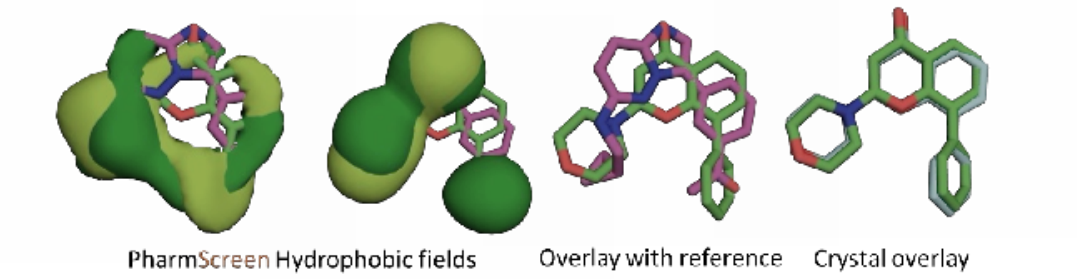
Molecular alignment is a key procedure for measurements of 3D similarity between compounds and pharmacophore elucidation. This process is influenced by several factors, including the quality of the physico-chemical descriptors utilized to account for the molecular determinants of biological activity.

Relying on the hypothesis that the variation in maximal achievable binding affinity for an optimized drug-like molecule is largely due to desolvation[1], we explore here a novel strategy for 3D alignment of small molecules that exploits the partitioning of molecular hydrophobicity into atomic contributions in conjunction with information about the distribution of hydrogen-bond donor /acceptor groups in a given compound.



A brief description of the method, as implemented in the software package PharmScreen, including discussion on the calculation of the fractional hydrophobic contributions within the quantum mechanical version of the MST continuum method[2], and the procedure utilized for searching the optimal superposition between molecules, is presented. The computational procedure is calibrated by using a dataset of 402 molecules pertaining to 14 distinct targets taken from the literature and validated against the AstraZeneca dataset that comprises 121 experimentally derived sets of molecular overlays[3]. The results point out the suitability of the MST based-hydrophobic parameters for generating molecular overlays.

[1] Lemmen, C. Langauer, T. Computational Methods for the Structural Alignment of Molecules. *J. Comput.-Aided Mol. Des*. **2000**, *14*, 215–232.
[2] Curutchet, C. Orozco, M. Luque, F. J. Solvation in Octanol: Parametrization of the Continuum MST Model. *J. Comput. Chem.* **2001**, *22*, 1180–1193
[3] Giangreco, I.; Cosgrove, D. A.; Packer, M. J. An Extensive and Diverse Set of Molecular Overlays for the Validation of Pharmacophore Programs. *J. Chem. Inf. Model.* **2013**, *53*, 852–866.

Hit Dexter: A Machine-learning Model for the Prediction of Frequent Hitters

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High-throughput screening is a key technology in early drug design that enables the screening of tens of thousands of compounds per day. [1,2] However, false-positive signals triggered by badly behaving compounds (frequent hitters, pan-assay interference compounds, aggregators and others) continue to pose a major challenge in early drug discovery and still lead to a substantial number of false hits reported in the scientific literature. [3] Few computational approaches that allow the identification of badly behaving compounds exist, and the applicability of these existing methods is limited. We present Hit Dexter, a web service that allows the identification of frequent hitters with high accuracy. [4] Hit Dexter is based on two extremely randomized tree classifiers trained on a well-prepared subset of the PubChem Bioassay database containing 311k compounds tested on at least 50 proteins each. We show that Hit Dexter is able to discriminate non-promiscuous from promiscuous and highly-promiscuous compounds of large external test sets with MCC and AUC values of up to 0.67 and 0.96, respectively. Hit Dexter is available as a free web service at http://hitdexter.zbh.uni-hamburg.de.

[1] P. Szymański, M. Markowicz, E. Mikiciuk-Olasik, *Int. J. Mol. Sci.* **2012**, *13*, 427–452.
[2] R. Macarron, M. N. Banks, D. Bojanic, D. J. Burns, D. A. Cirovic, T. Garyantes, D. V. S. Green, R. P. Hertzberg, W. P. Janzen, J. W. Paslay, et al., *Nat. Rev. Drug Discov.* **2011**, *10*, 188–195.
[3] J. Baell, M. A. Walters, *Nature* **2014**, *513*, 481–483.
[4] C. Stork, J. Wagner, N.-O. Friedrich, C. de Bruyn Kops, M. Šícho, J. Kirchmair, *ChemMedChem* **2017**, DOI 10.1002/cmdc.201700673.

Improving ligand screening by exploiting structure ensembles and machine learning

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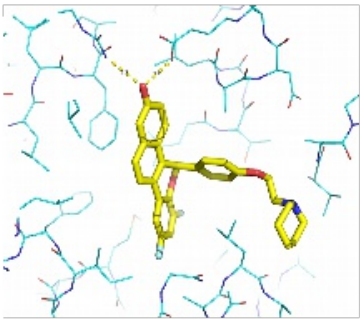

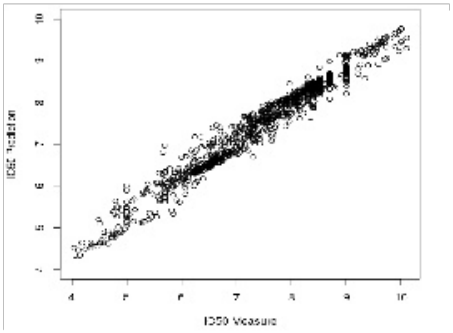

Nuclear receptors (NRs) are DNA-binding transcription factors and one of the most important cellular mediators for sensing (hormones, drugs, xenobiotics) and signal transduction. Therefore, their dysfunction and the subsequent aberrant signaling is associated with many diseases concerning cancer or reproduction and metabolism disorders. Due to their ligand binding ability they are of interest for a broad scientific field, in particular for the pharmaceutical industry as potential pharmaceutical targets and for drug development and in toxicology and environmental science for risk assessment.

Predicting the interactions between small molecules and receptors plays a critical role in drug discovery and development. In particular the Estrogen Receptor alpha (ERα) is an important target for medical treatment and among the most studied NRs.

During our study, exhaustive docking for all known ERα ligands present in BindingDB was achieved using parallel docking on conformational ensembles, which also result in more precise pose predictions. This result enables us to employ a random forest (RF) machine learning algorithm on a large high quality data set in order to predict precise binding affinities. Here, the "sampling problem" is tackled by using structure ensembles, while taking advantage of numerous scoring schemes for virtual screening to better evaluate ligand conformation and protein-ligand interactions.

These results pave the way for a web server dedicated to rapid and high-accuracy docking into the estrogen receptors.

Towards the rational design of covalent inhibitors

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Covalent ligands currently experience an intensive renaissance in academic and industrial drug development[1] (Figure 1) because they display several key advantages over their non-covalent counterparts.[2] So far, however, most covalent ligands have been identified serendipitously, since the tools for their rational optimization or *de novo* design are not well established and available methods often fail to decipher the various contributions of the multi-step inhibition processes to the overall potency of a given inhibitor. The latter renders the introduction of new compound classes for covalent inhibitors very tedious or almost impossible as it relies on trial and error strategies. To solve these challenges new approaches are necessary which unravel the various steps of the inhibition processes and which reliably predict the inhibition potency of uncharacterized or even novel compounds.
Such approaches must be able to describe the formation of a covalent bond as well as non-covalent interactions. In the talk, we discuss QM/MM approaches, which are able to elucidate the inhibition mechanisms of covalent ligands[3] and sufficiently accurate to make predictions how the inhibition potencies of a given inhibitor can be influenced.[4]

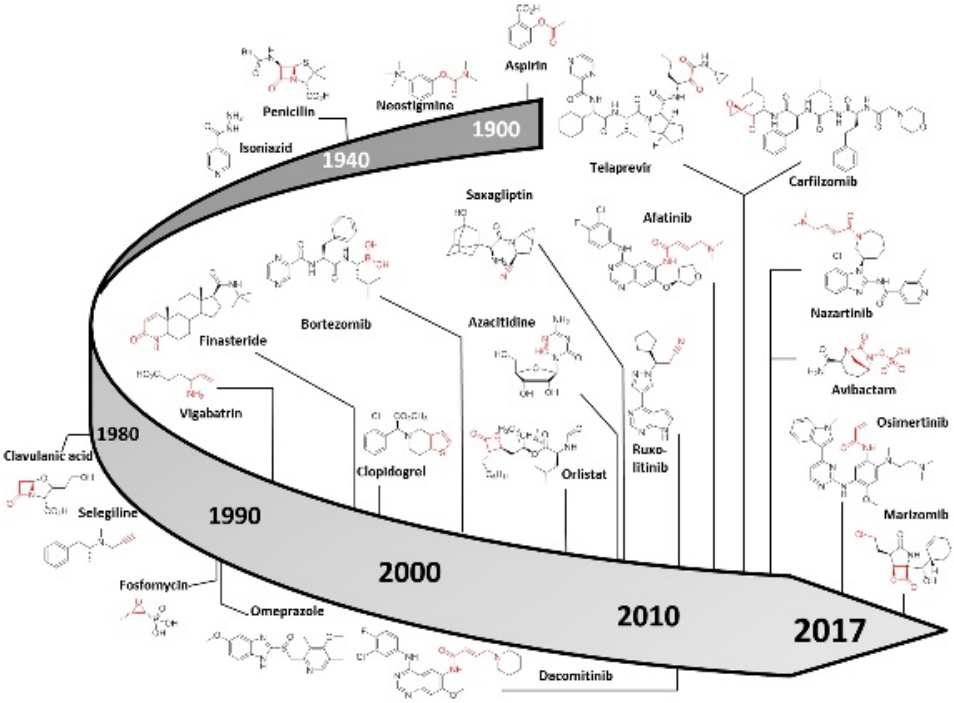

Figure 1: Timeline of selected covalent drugs with approximate dates of discovery.

[1] J. Singh, R. C. Petter, T. A. Baillie, A. Whitty, *Nature reviews Drug discovery* **2011**, *10*, 307-317.
[2] R. A. Copeland, D. L. Pompliano, T. D. Meek, *Nature reviews Drug discovery* **2006**, *5*, 730-739.
[3] a) A. Paasche, A. Zipper, S. Schäfer, J. Ziebuhr, T. Schirmeister, B. Engels, *Biochemistry* **2014**, *53*, 5930-5946; b) W. Lee, B. Engels, *Biochemistry* **2014**, *53*, 919-931.
[4] a) T. Schirmeister, J. Kesselring, S. Jung, T. H. Schneider, A. Weickert, J. Becker, W. Lee, D. Bamberger, P. R. Wich, U. Distler, S. Tenzer, P. Johe, U. A. Hellmich, B. Engels, *Journal of the American Chemical Society* **2016**, *138*, 8332-8335; b) T. C. Schmidt, A. Welker, M. Rieger, P. K. Sahu, C. A. Sotriffer, T. Schirmeister, B. Engels, *Chemphyschem* **2014**, *15*, 3226-3235; c) A. Paasche, T. Schirmeister, B. Engels, *Journal of Chemical Theory and Computation* **2013**, *9*, 1765-1777.

Optimization of protein-ligand binding affinities based on integral equation theory

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The accurate and fast prediction of protein-ligand binding affinities is one of the remaining grand challenges of computational chemistry. [1] The need for reasonably accurate and fast methods to predict and optimize the binding affinity which can drive the design process of drug-like molecules is therefore very high. Furthermore, in order to optimize current drugs or promising candidates, it is helpful to determine the most sensitive sites along with a direction in chemical space defining how a specific ligand atom should be changed in order to gain a higher binding affinity (for instance, by replacing it with a larger or more negatively charged atom). Ideas for replacing or introducing atoms and functional groups in the ligand can be distilled from those insights and rationally steer the design of new drugs.

The three-dimensional (3D) reference interaction site model (RISM) integral equation theory can be formulated and applied in a way to address the problem of complex formation thermodynamics. [2-4] More specifically, by applying the so-called solute-solute (*uu*) form it is possible to calculate rapidly the potential of mean force (PMF) between a protein a ligand sites on grid points in a binding site. The PMF is the key quantity for characterizing chemical and biological processes since it represents the free energy change along a given reaction coordinate from which the binding free energy can be computed. Furthermore, it can be differentiated with respect to, for instance, Lennard-Jones parameters and partial charges, yielding the so-called free energy derivatives (FED) [3] which encode optimal design directions defined above.

We here present novel methodology for computing these quantities efficiently based on *uu*-RISM theory. The resulting algorithms are applied to model systems comprising matched molecular pairs, where exchange of single atoms leads to substantial modulations of the binding free energy. Results are compared to reference explicit-solvent molecular dynamics simulations and experimental data in order to evaluate scope and limitations of the methodology.

[1] J. Yin, N. M. Henriksen, D. R. Slochower, M. R. Shirts, M. W. Chiu, D. L. Mobley, M. K. Gilson, *J. Comput.-Aided Mol. Des.* **2017**, 31, 1-19.
[2] T. Kloss, S. M. Kast, *J. Chem. Phys.* **2008**, 128, 134505.
[3] F. Mrugalla, S. M. Kast, *J. Phys.: Cond. Matter*, **2016**, 28, 344004.
[4] D. Plenker, M. Riedel, J. Brägelmann, M. A. Dammert, R. Chauhan, P. P. Knowles, C. Lorenz, M. Keul, M. Bührmann, O. Pagel, V. Tischler, A. H. Scheel, D. Schütte, Y. Song, J. Stark, F. Mrugalla, Y. Alber, A. Richters, J. Engel, F. Leenders, J. M. Heuckmann, J. Wolf, J. Diebold, G. Pall, M. Peifer, M. Aerts, K. Gevaert, R. Zahedi, R. Buettner, K. M. Shokat, N. Q. McDonald, S. M. Kast, O. Gautschi, R. K. Thomas, M. L. Sos, *Sci. Transl. Med.* **2017**, 9(394).

Prediction of first-order nonlinear optical properties of Anderson polyoxometalate derivatives

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Polyoxometalates (POMs) are metal-oxygen oxo-clusters with a large variety of sizes and shapes. The most known POMs types are: Wells-Dawson, Keggin, Anderson, and Lindkvist types. They are largely studied for their application in different fields such as: catalysis, materials science, and medicine.

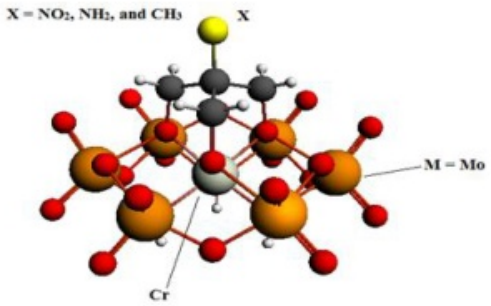

Figure. Ball and sticks representation of Anderson structure and its derivatives

POMs have been largely investigated for their chemical and physical properties: redox, photovoltaic applications, chemical reactivity, nonlinear optical properties ... etc. In order to establish the structure-property relationship, we proposed in this work to study a set of Anderson cluster's derivatives $[X\text{-}C(CH_2O)_3CrMo_6(OH)_3O_{18}]^{3-}$ (X = NO_2, NH_2, and CH_3) and substituted Polyoxometalates $[CrMo_6O_{24}]^{3-}$. The first-order hyperpolarizabilities, the partial density of states PDOS, and the electronic spectrum of those clusters have been evaluated using the density functional theory (DFT) and the time-dependent DFT (TD-DFT) methods.

New and mild method for the synthesis of alprazolam and diazepam and computational study of binding mode of them to $GABA_A$ receptor

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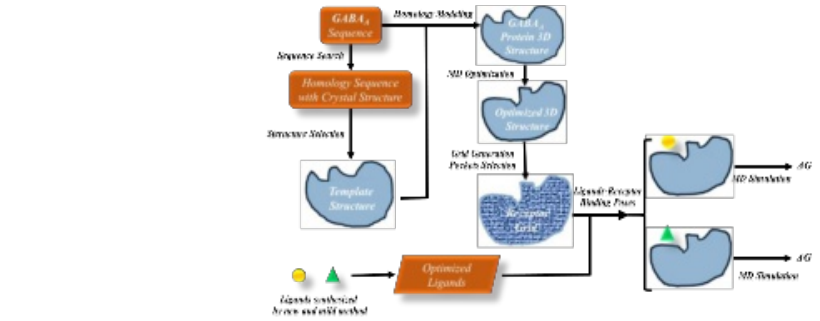

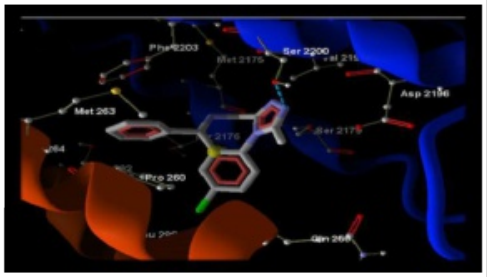

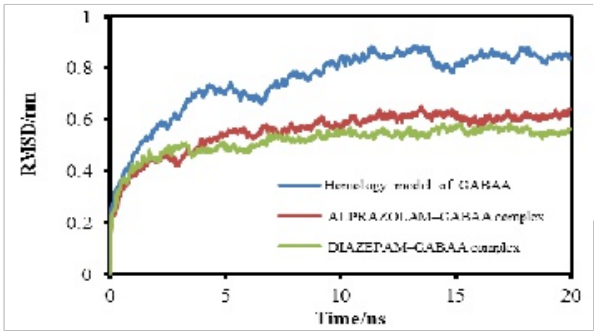

In the current study, alprazolam and diazepam were synthesized in a new and mild condition in the framework of green chemistry. Also, in order to find the 3D structure of $GABA_A$ and investigate possible interactions alprazolam and diazepam with active site of $GABA_A$, a template sequence was selected for homology modeling. The initial 3D structure obtained from homology modeling was optimized using MD simulation. Then, alprazolam and diazepam were docked into the receptor. Finally, the ligand binding free energy for the complex was calculated based on the MD simulations.

Spin-Labelled DNA Oligomers: Simulations and Experiment

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

[1] M. M. Haugland, A. H. El-Sagheer, R. J. Porter, J. Pena, T. Brown, E. A. Anderson, J. E. Lovett, *2'-Alkynylnucleotides: A Sequence- and Spin Label-Flexible Strategy for EPR Spectroscopy in DNA, J. Am. Chem. Soc.* **2016**, *138*, 9069-9072.

Towards the coarse-grained modelling of dimethacrylate-based biomaterials

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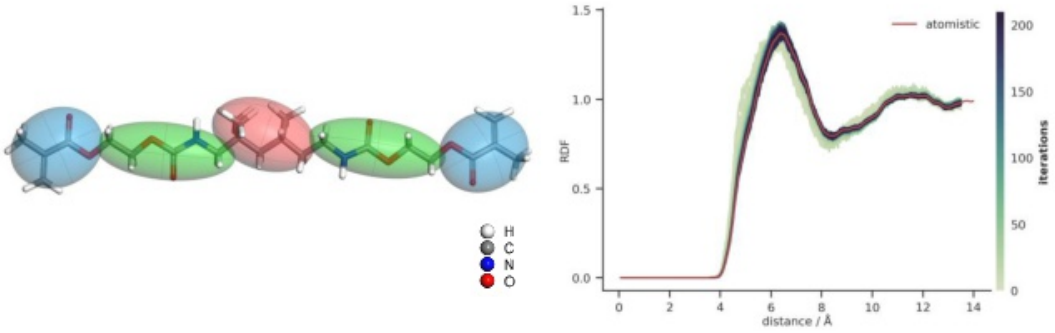
In restorative dentistry dimethacrylate-based composites are a prominent class of biomaterials due to their clinical processability and aesthetic properties. For this purpose, the monomer resins can be cured via photo-induced radical polymerisation. However, a typical decrease in volume with increasing conversion of double bonds during polymerisation is a major drawback affecting longevity of implants. The so-called polymerisation shrinkage can be compensated by both, tuning of steric hindrance of the polymer chains as well as incorporation of filler materials. [1]



For polymers, computer based simulation methods offer powerful tools for the investigation of structural and mechanical properties. In the case of polymers, the simulation requires sufficiently large ensembles of atoms leading to long calculation times on the atomistic scale. A possible solution to this challenge is the application of so-called coarse-grained (CG) models, which provide acceleration by reducing the degrees of freedom in the system. This is realised by the replacement of whole molecules or fragments by single interaction sites, often called beads or superatoms.

The parameters for coarse-grained models can be derived from atomistic reference models or experimental data. As a model system, urethane dimethacrylate (UDMA) was chosen, which is already used in dental applications nowadays. The model consists of three different types of beads for the monomer, in the left figure indicated by ellipsoids. The terminal methacrylate groups are the reactive species regarding polymerisation and are therefore defined as an individual bead type. The remaining types are chosen in a way to offer a nearly similar masses. For oligo- and polymers an additional type for the backbone is introduced. The approach followed in our work is the iterative Boltzmann inversion, where the parameters are optimised against local structures from atomistic molecular dynamics simulations e.g. radial distribution functions (RDF). [2] The sequential convergence of an example RDF is shown in the figure (right).

Employing the generated parameters, we aim for investigation of the polymer structure on the mesoscale with focus on cavity formation during polymerisation, which contribute to the reduction of shrinkage. In the future, we intent to study dimethacrylate-polymers with various composition, utilizing the combining rules to derive parameters from neat systems. [3]

[1] R. Sakaguchi, J. Powers, *Craig's restorative dental materials*, Elsevier/Mosby, 2012.
[2] V. Rühle, C. Junghans, A. Lukyanov, K. Kremer, D. Andrienko, *J. Chem. Theory Comput.*, **2009**, *5*, 3211-3223.
[3] H.J. Qian, P. Carbone, X. Chen, H. A. Karimi-Varzaneh, C. C. Liew, F. Müller-Plathe, *Macromol.*, **2008**, *41*, 9919-9929.

Comparative Analysis of the Chemical Space of Known and Purchasable Natural Products

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Natural products cover a large chemical space and exhibit a wide range of bioactivities, making them an important resource for drug discovery [1-3]. We have recently analyzed the value of 25 virtual and 31 physical natural product libraries for computer-guided drug discovery [4]. These libraries cover a total of 250,000 natural products, at least 10% of which are readily purchasable from commercial sources.

In this contribution, we present a detailed analysis of the physicochemical property space of natural products that extends beyond the reach of earlier reports. We implemented a new algorithm ("SugarBuster") that identifies and removes sugars and sugar-like moieties, which are generally undesired in the context of drug discovery, from natural products. Use of this algorithm gives a more realistic view of the physicochemical properties of aglycons that may serve as templates for drug design. We also compare the physicochemical properties and scaffold diversity of purchasable natural products to those of all known natural products. This analysis provides valuable insights into the relevance of purchasable natural products for drug discovery and points out areas in the chemical space that are only covered by a subset of natural products requiring more demanding and expensive sourcing. Furthermore, we implemented a rule-based approach for the automated recognition of several structural classes of natural products (e.g. alkaloids or flavonoids), which allowed us to quantify their abundance among various data sources.

[1] D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2016**, 79, 629–661.
[2] A. L. Harvey, R. Edrada-Ebel, R. J. Quinn, *Nat. Rev. Drug Discov.* **2015**, 14, 111–129.
[3] T. Rodrigues, D. Reker, P. Schneider, G. Schneider, *Nat. Chem.* **2016**, 8, 531–541.
[4] Y. Chen, C. de Bruyn Kops, J. Kirchmair, *J. Chem. Inf. Model.* **2017**, 57, 2099–2111.

Generating Structures of Likely Metabolites Based on Predicted Cytochrome P450 Regioselectivity

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The metabolic fate of xenobiotics such as drugs and agrochemicals impacts their safety and efficacy, because biotransformation of small organic molecules can generate metabolites with substantially different biological and physicochemical properties compared to the parent compound. [1] Prediction of regioselectivity of metabolizing enzymes, specifically the prediction of the atom positions in a molecule where metabolic reactions are initiated (sites of metabolism), is a popular computational approach to studying metabolism and can be used as a stepping stone for the prediction of the chemical structures of metabolites.

We have developed a strategy for metabolite structure prediction that is based on FAME 2, [2] our recently-developed and highly effective machine learning method for human cytochrome P450 (CYP) regioselectivity prediction. By applying known CYP-mediated reactions to the sites of metabolism predicted by FAME 2, we are able to correctly predict the vast majority of known metabolites while keeping false-positive prediction rates low. Applying the site of metabolism predictions as a preceding filter results in an approximately ten-fold reduction in the number of false positive metabolite predictions on average as compared to CYP-mediated reactions applied to all atom positions in a parent compound.

[1] J. Kirchmair, A. H. Göller, D. Lang, J. Kunze, B. Testa, I. D. Wilson, R. C. Glen, G. Schneider, *Nature Rev Drug Discov* **2015**, 14, 387-404.

[2] M. Šícho, C. de Bruyn Kops, C. Stork, D. Svozil, J. Kirchmair, *J Chem Inf Model* **2017**, 57, 1832-1846.

Study of the Hapten-Binding Properties of Antibody B1-8 Using Steered Molecular Dynamics

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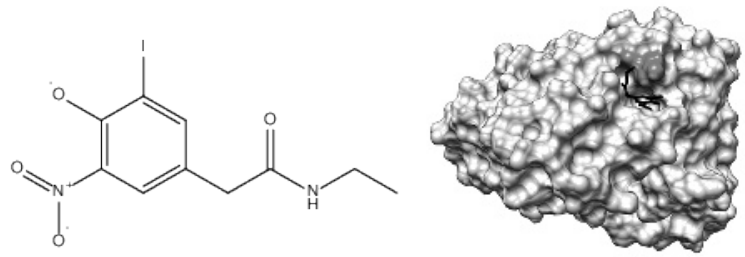

4-(2-(ethylamino)-2-oxoethyl)-2-iodo-6-nitrophenolate

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. In addition steered MD-simulations are used to pull NIP out of the binding pocket and determine the effect of the mutation on the exit path and the off-rate.

Converging a knowledge-based scoring function: DrugScore^{2017}

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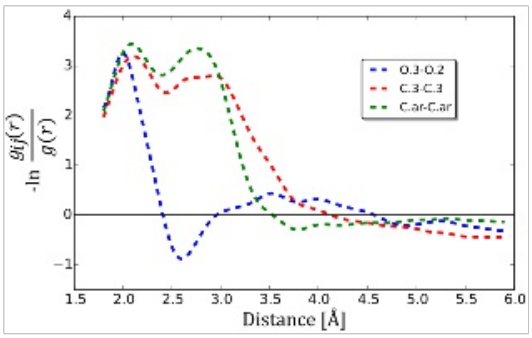
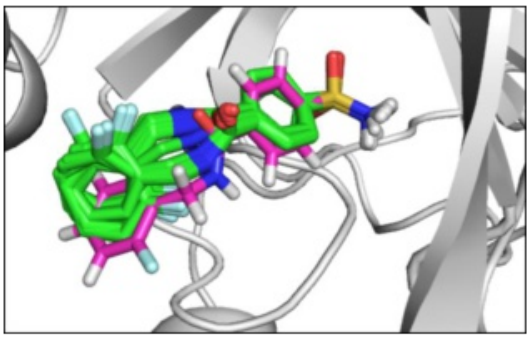
Scoring functions play a vital role in molecular modeling. They are used in docking, virtual screening, *de novo* design, lead optimization, and other applications to evaluate protein-ligand interactions.

In 2000, DrugScore, a knowledge-based scoring function for protein-ligand complexes, was presented by Gohlke *et al.* [1]. DrugScore was successfully applied to score protein-ligand interactions [2] and as an objective function for docking [3]. At that time, about 1300 protein-ligand complexes from the PDB were used to derive distance-dependent pair-preferences for 18 atom types. Since then, structural information in the PDB increased by a factor of 10. This fact provided the incentive for us to re-derive the distance-dependent pair-preferences asking how much structural information it takes to reach a converged knowledge-based scoring function and whether the additional information further improves the predictive power of DrugScore.

DrugScore^{2017} was derived from about 40,000 complexes following the protocol from the previous work [1]. The newly derived pair-preferences cover a broader range of atom types and now include also less common interactions, e.g., involving halogens or metals. For evaluating the predictive performance, we chose two data sets: the CASF-2013 test set [3], providing complexes and associated affinities and the PDBbind "Refined set" [4], comprising more than 4000 crystal structures.





DrugScore^{2017} shows a substantial and significant increase in scoring, ranking, and docking power compared to DrugScore. I) In re-docking experiments, ~ 80 % of the generated poses showed RMSD < 2 Å compared to the crystal structure. II) The Pearson correlation of predicted and experimentally determined binding energies is 0.601 ($p < 0.001$) on the CASF test set and 0.526 ($p < 0.001$) on the PDBbind "Refined set", without any further modifications or training. This makes DrugScore^{2017} the best non-trained scoring function tested on the CASF set.

Finally, re-deriving DrugScore^{2017} on several bootstrapped subsets of the currently available data yielded pair-preferences that were indistinguishable from those derived on the full complex dataset, suggesting that the available amount of data may be sufficient to obtain converged pair-preferences.

[1] H. Gohlke, M. Hendlich, G. Klebe, *J Mol. Biol.*, **2000**, *295*, 337-356.
[2] P. Ferrara *et al.*, *J. Med. Chem.*, **2004**, *47*, 3032-3047.
[3] C. A. Sotriffer, H. Gohlke, G. Klebe, *J. Med. Chem.*, **2002**, *45*, 1967-1970.
[4] Y. Li *et al.*, *J. Chem. Inf. Model.*, **2014**, *54*, 1717−1736.
[5] R. Wang *et al.*, *J. Med. Chem.*, **2004**; *47*, 2977-2980.

Design of Novel Ligands for Thymic Stromal Lymphoetin

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Thymic stromal lymphopoietin (TSLP) is a member of IL-2 cytokine family. Structurally similar to IL-7-like, TSLP plays an important role in pathophysiology of several allergic conditons such as the triad atopic diseases (asthma, atopic dermatitis and atopic rhinitis) [1]. Intracellular signalling proceeds through binding of TSLP to its cognate TSLP receptor (TSLPR) and IL-7♋ to regulate T-cell development and homoeostasis [2,3].

The importance of targeting TSLP has been revealed by Phase II trial conducted using TSLP blocking antibody, Tezepelumab for reducing allergen sensitivity and inflammation. However, due to lack of oral bioavailability and high production cost, development of small molecule inhibitors that could disrupt this protein-protein complex could be a parallel approach [3].

The objective of this study is to analyze the TSLP-TSLPR-IL-7 complex and identify compounds that disrupt the protein-protein interface. As there are no known small-molecule inhibitor till date, we identify important interactions in the binding site using molecular interaction fields (MIFs) [4]. The feature-based MIFs helps us to determine energetically favorable interaction (hotspots) using different probes such as hydrophobic moieties ("DRY"), for H-bond donors with and without charges (N1+, N1 , N2) and for acceptors (O-, O). This analysis results in a structure-based 3D pharmacophore in LigandScout [5] suitable for virtual screening. Probability density maps (dynophores) are developed for recently published ligands [6] to further characterize ligand binding for this promising and novel target.

References

[1] *Verstraete K, van Schie L. Structural basis of the proinflammatory signaling complex mediated by TSLP. Nat Struct Mol Biol. 2014 Apr;21(4):375-82.*
[2] *Ito T, Liu YJ. Cellular and molecular mechanisms of TSLP function in human allergic disorders--TSLP programs the "Th2 code" in dendritic cells. Allergol Int. 2012 Mar;61(1):35-43.*
[3] *Verstraete K, Peelman F. Structure and antagonism of the receptor complex mediated by human TSLP in allergy and asthma. Nat Commun. 2017 Apr 3;8:14937.*
[4] *Molecular Operating Environment (MOE), 2015.10; Chemical Computing Group Inc.*
[5] *Wolber G, and Langer T. LigandScout: 3-D Pharmacophores Derived from Protein-Bound Ligands and Their Use as Virtual Screening Filters. J. Chem. Inf. Model., 2005, 45 (1), pp 160–169.*
[6] *Van Rompaey D, Verstraete K. Virtual screening for inhibitors of the human TSLP:TSLPR*

pH- and pressure dependent tautomeric and conformational equilibria

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Knowledge of conformational and tautomer preferences of a molecule is essential to understand its behavior in solution and its mechanism of action in the body. The accurate pH-dependent characterization of the conformational and tautomer equilibria of ionizable species in aqueous solution is a challenging task even for well-known compounds such as the neurotransmitter histamine that is involved in the regulation of multiple physiological functions like gastric acid release and in immune system responses. The prediction of physiologically relevant protonation states and preferred conformations in solution under various conditions including pH and pressure/temperature variations is therefore important not only for drug discovery but also for understanding biochemical processes of a vast number of lifeforms that are accommodated to extreme conditions such as near deep oceanic black smokers. High pressure and/or temperature may affect the protonation patterns of biomolecules like nucleobases, leading to fundamental questions regarding the robustness and universality of the genetic code.

Because of the rapid conformational changes and the fast proton transfer between multiple tautomeric forms, it is difficult to elucidate such problems experimentally, especially under extreme conditions. We here present a computational approach, supported by experimental data, to overcome this problem with the goal to characterize the complete spectrum of tautomeric and underlying conformational states. Conceptually footed in the methodology employed within the SAMPL2 and SAMPL5 prediction challenges for tautomer equilibria [1] and partition constants, [2] we here combine exhaustive tautomer and conformational sampling followed by GIAO-NMR and vibrational frequency calculations in aqueous solution for model systems such as histamine and nucleobases. Solvent effects on energies and spectroscopic parameters in quantum-chemical calculations are considered using the polarizable continuum model (PCM) and the embedded cluster reference interaction site model (EC-RISM) integral equation theory. This methodology has been demonstrated to provide accurate estimates of thermodynamic quantities and spectroscopic features in solution even for high pressure solvents. [2,3] As a key result, we obtain the contributions of all accessible states to the molecular ensemble as a function of pH and pressure as well as their respective relevance for understanding experimental FTIR and NMR spectra.

[1] S. M. Kast, J. Heil, S. Güssregen, K. F. Schmidt, *J. Comput.-Aided Mol. Des.* **2010**, *24*, 343-353.

[2] N. Tielker, D. Tomazic, J. Heil, T. Kloss, S. Erhart, S. Güssregen, K. F. Schmidt, S. M. Kast, *J. Comput.-Aided Mol. Des.* **2016**, *30*, 1035-1044.

[3] R. Frach, P. Kibies, S. Böttcher, T. Pongratz, S. Strohfeld, S. Kurrmann, J. Koehler, M. Hofmann, W. Krener, H. R. Kalbitzer, O. Reiser, D. Horinek, S. M. Kast, *Angew. Chemie Int. Ed.* **2016**, *55*, 8757-8760.

Hydrogen Activation by complex aluminates

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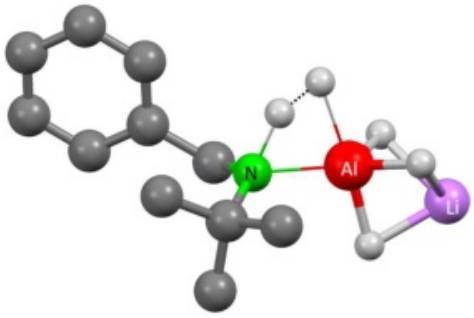
Chair of Inorganic and Organometallic Chemistry

Traditionally lithium aluminum hydride ($LiAlH_4$) is used as a stoichiometric reducing agent for among other organic multiple bonds followed by aqueous work up. This process leads to a considerable amount of waste, since $LiAlH_4$ is employed in an excess. Early main group metal complexes are known to react catalytically with C-C multiple bonds and imines in the presence of molecular hydrogen to yield the reduced substrate. [1,2] Presently we were able to observe that aluminate complexes were able to cleave hydrogen heterolytically, resulting in the formation of an aluminum hydride.

This work focuses on the reaction of $LiAlH_4$ with imines leading to the formation of an aluminum amide complex and its subsequent reaction with molecular hydrogen. Various model systems were modeled by DFT methods (B3PW91/6-311++G**) to gain an insight into the molecular processes. Understanding the reaction steps might lead to the development of a highly atom economic catalytic process.



Calculated transition state of the hydrogen cleavage

[1] J. Spielmann, F. Buch, S. Harder, *Angew. Chem. Int. Ed.* **2008**, 47, 9434-9438

[2] H. Bauer, M. Alonso, C. Färber, H. Elsen, J. Pahl, A. Causero, G. Ballmann, F. De Proft, S. Harder, *Nature Catalysis*, **2018**, 1, 40-47

Machine learning models for guiding protein structure selection lead to a boost in the performance of ensemble docking

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The use of multiple structures of target proteins for ligand docking ("ensemble docking") is an established concept in structure-based virtual screening and advantageous in particular when addressing malleable target proteins.[1] In most ensemble docking approaches, a ligand is docked against multiple receptor conformations and the highest-ranked docking pose obtained with any of these protein structures is reported as the result.[2] However, the performance of ensemble docking can often be further improved by manually selecting the most relevant protein structures for screening.[3]

In this contribution, using VEGFR-2 as an example, we introduce a new integrated approach that employs machine learning models for identifying the most suitable protein structure for docking each individual compound. We started by collecting 38 relevant protein structures of VEGFR-2 from the PDB and docking 2320 actives and 24,950 decoys from the DUD-E[4] to each of these structures with Glide.[5] The docking performance on the individual protein structures was moderate, with the maximum ROC AUC (Receiver Operating Characteristic Area Under the Curve) value of 0.78.

Based on the docking results for each of the 38 VEGFR-2 PDB structures, we labeled actives and decoys as "correctly scored" or "incorrectly scored" according to the docking score (GlideScore).[5] The labeled compounds, represented by Morgan2 fingerprints, served as input for training individual random forest classifiers for each of the protein structures. The integrated virtual screening approach runs query molecules against all of these classifiers to identify the most suitable protein structure for docking. In contrast to common ensemble docking approaches, compounds of interest are only docked to the protein structure that obtained the highest score out of all of the classifiers. Benchmarking with an independent test set showed that the integrated ensemble docking approach obtained significantly better ROC AUCs and, in particular, higher early enrichment than the stand-alone ensemble docking approach.

[1] R. E. Amaro, W. W. Li, *Curr. Top. Med. Chem.*, **2010**, *10*, 3–13.
[2] S. Rao, P. C. Sanschagrin, J. R. Greenwood, M. P. Repasky, W. Sherman, R. Farid, *J. Comput. Aided Mol. Des.*, **2008**, *22*, 621–627.
[3] M. Rueda, G. Bottegoni, R. Abagyan, *J. Chem. Inf. Model.*, **2010**, *50*, 186–193.
[4] M. M. Mysinger, M. Carchia, J. J. Irwin, B. K. Shoichet, *J. Med. Chem.*, **2012**, *55*, 6582–6594.
[5] T. A. Halgren, R. B. Murphy, R. A. Friesner, H. S. Beard, L. L. Frye, W. T. Pollard, J. L. Banks, *J. Med. Chem.*, **2004**, *47*, 1750–1759.

Using Protein Ligand Interaction Fingerprints and Machine Learning tools for the prediction of novel dual active compounds

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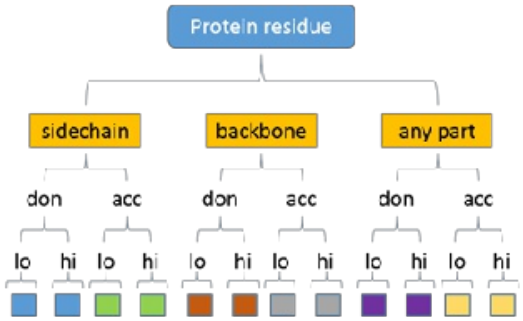
Structure-based drug design relies on accurate affinity prediction through analysis of protein-ligand interactions, which remains an only partially solved problem up to date. Furthermore, if affinities towards dual active compounds have to be approximated, the uncertainty of the prediction rises.

Here we introduce a combination of Protein Ligand Interaction Fingerprints (PLIF) and Machine Learning tools for the target-specific prediction of novel dual active compounds. The PLIF tool (Chemical Computing Group) uses a fingerprint representation of the interactions between ligands and proteins. Currently 10 types of interactions (hydrogen bonds, ionic, surface-, metal binding- and π interactions) are used to describe these interactions.[1]-[3] Using this fingerprints as a descriptor for specific protein-ligand interactions, different machine learning methods including support vector machines, self-organizing maps, neuronal networks, and random forest, were applied to classify active and inactive compounds.



Using the described workflow, we created a data set containing active co-crystallized ligands of the leukotriene A-4 hydrolase (LTA4H) and soluble epoxide hydrolase (sEH). After generating the PLIF, a random forest was trained to classify the compounds. Potential hits are manually inspected, selected compounds will be synthesized and characterized afterwards in an biochemical assay.

[1] P. Labute, *Journal of the Chemical Computing Group*, **2001**.
[2] A.M. Clark, P. Labute, M. Santavy, *J. Chem. Inf. Model.*, **2006**, *46*, 1107–1123.
[3] A.M. Clark, P. Labute, *J. Chem. Inf. Model.*, **2007**, *47*, 1933–1944.

From continuum solvation models to hydrophobic descriptors: Application to virtual screening of chemical databases with PharmScreen

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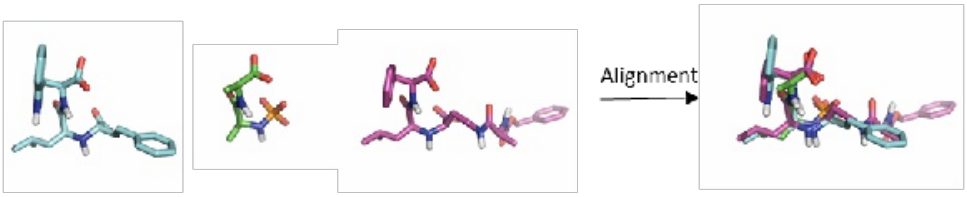
Determining the degree of similarity between two small molecules is a key step in ligand-based virtual screening of chemical libraries, which is valuable for the cost -effective identification of novel chemical scaffolds. The success of this approach is influenced by several factors, including the quality of the physico-chemical descriptors utilized to account for the molecular determinants of biological activity.

In this communication, we present PharmScreen, which is a novel 3D ligand-based virtual screening algorithm that exploits the partitioning of molecular hydrophobicity into atomic and fragmental contributions within the framework of continuum solvation models. Specifically, we have exploited the quantum mechanical version of the MST continuum method, which was parametrized to describe the solvation of small organic compounds to water and n-octanol[1],[2]. A perturbative approach permits to decompose the solvation free energy into fractional contributions, which can then be combined to obtain 3D distribution of the molecular hydrophobicity/hydrophilicity, leading to concepts such as hydrophobic dipole and hydrophobic similarity[3],[4]. The suitability of these fractional for 3D-QSAR studies has been recently examined[5].

Following this work, we describe here the calibration of these descriptors for molecular alignment and similarity studies, and its implementation within the framework of PharmScreen. Preliminary tests support the suitability of this strategy to find compounds with higher chemical diversity compared to traditional shape/structure-based solutions.



[1] Curutchet, C.; Orozco, M.; Luque, F. J., *J. Comput. Chem.*, **2001**, *11*, 1180.
[2] Soteras, I.; Curutchet, C.; Bidon-Chanal, A.; Orozco, M.; Luque, F. J., *J. Mol. Struct. THEOCHEM*, **2005**, *727*, 29.
[3] Muñoz, J.; Barril, X.; Hernández, B.; Orozco, M.; Luque, F. J., *J. Comput. Chem.*, **2002**, *23*, 554.
[4] Muñoz-Muriedas, J.; Perspicace, S.; Bech, N.; Guccione, S.; Orozco, M.; Luque, F. J., *J. Comput.-Aided Mol. Design*, **2005**, *19*, 401.
[5] Ginex, T.; Muñoz-Muriedas, J.; Herrero, E.; Gibert, E.; Cozzini, P.; Luque, F. J., *J. Comput. Chem.*, **2016**, *37*, 1147.

Role of structural flexibility for signal transduction by G protein coupled receptors

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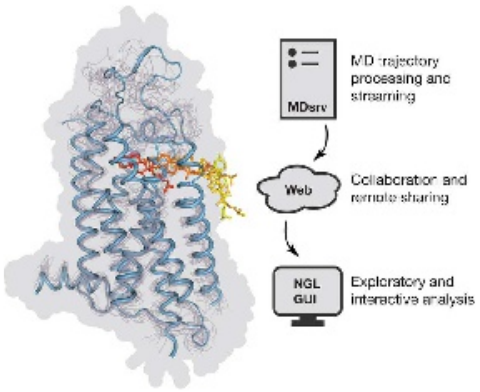

Flexibility is an essential structural feature of proteins transferring substances or information through membranes. G protein coupled receptors (GPCRs) are specialized 7-transmembrane helix bundle proteins which conduct a high variety of different extracellular signals into the cell through binding and activation of downstream signaling proteins such as heterotrimeric G proteins: Gi, Gs, Gq, G11/12 or arrestin 1-4. More than 800 different human GPCRs can couple to one or several downstream signaling partners, which raises the issue of coupling specificity, especially with regards to pharmacological intervention strategies targeting GPCRs which are major drug targets. Combination of existing structural biophysical data with data obtained from molecular dynamics simulations [1-3] suggest that structural flexibility of GPCRs does not only play a role for receptor activation but is also a key determinant for fast and specific signal transfer to G proteins. In light of increasingly interdisciplinary research and remote collaborations, it is desirable to make the atom trajectories of MD simulations widely available to facilitate interactive exploration and collaborative visual analysis as well as to promote discussions. For that purpose we developed MDsrv, a tool to stream MD trajectories and show them interactively within web browsers without requiring advanced knowledge in specialized MD software [4].

[1] Elgeti, M. *et al*. Precision vs flexibility in GPCR signaling. ***J. Am. Chem. Soc***., 2013**, 135,** 12305–12.

[2] Rose, A. S. *et al*. Position of Transmembrane Helix 6 Determines Receptor G Protein Coupling Specificity**. *J. Am. Chem. Soc.***, 2014**, 136,** 11244–11247.

[3] Rose, A. S. *et al*. Role of Structural Dynamics at the Receptor G Protein Interface for Signal Transduction**. *PLoS One***, 2015, **10,** e0143399.

[4] Tiemann, JKS et al. MDsrv: viewing and sharing molecular dynamics simulations on the web. ***Nat. Methods***, 2017, 14, 1123-1124.

Conservation and Relevance of Pharmacophore Point Types

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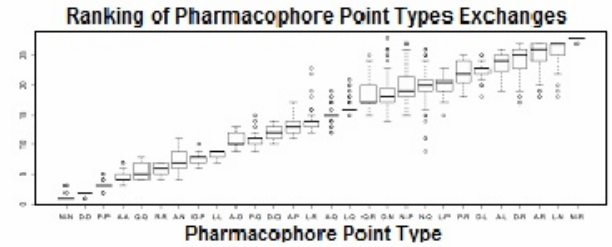
Pharmacophore models apply a variety of features to express chemical characteristics, for example hydrogen-bond donors, hydrogen-bond acceptors, positively charged, negatively charged, as well as aromatic and hydrophobic moieties. [1-3] It is generally assumed that features have to match to identical types. [4,5] To clarify if this stringent one-to-one assignment is justified, we investigated a set of 581 unique ligands from the BindingDB with know orientation inside the respective binding pockets and conducted a statistical analysis of the likelihood of observed exchanges in between the pharmacophore features, respectively their degree of conservation. To find out if certain features are obsolete, we furthermore derived a ranking to determine the most relevant ones. We found that the degree of conservation decreases in the following order: negative ionizable (N) > hydrogen-bond donor (D) > positive ionizable (P) > hydrogen-bond acceptor (A) > aromatic (R) > non-aromatic pi-systems (Q) and other hydrophobic moieties (L) The most likely exchanges were found between carboxylate groups and hydrogen-bond acceptors (A-N), and likewise between basic nitrogens and hydrogen-bond donors (D-P), which reflects the characteristics of Lewis acids and bases. Whereas the kind of target (soluble proteins, metal-containing ones, and GPCRs) did not show substantial influence on the degree of conservation, the relevance of the respective pharmacophore feature was found to be strongly dependent on the applied ranking scheme. Overall, lipophilic and aromatic features turned out to be highly important, whereas the positive ionizable feature is less relevant.



Boxplot showing the degree of conservation, respectively the likelihood of exchanges between pharmacophoric point types. Leftmost combinations are highly conserved, respectively most likely. Those in the middle are randomly occurring, whereas those on the right hand side are disfavored.

[1] A. Leach, V. Gillet, R. Lewis, R. Taylor, *J. Med. Chem.*, **2010**, *53*, 539-558.
[2] O. Güner, J. Bowen, *J. Chem. Inf. Model.*, **2014**, *54*, 1269-1283.
[3] M. Löwer, E. Proschak, *Mol. Inf.*, **2011**, *30*, 398-404.
[4] G. Wobler, T. Langer, *J. Chem. Inf. Model.*, **2006**, *45*, 160-169.
[5] V. Hänke, B. Hofmann, T. Grgat, E. Proschak, D. Steinhilber, G. Schneider, *J. Comput. Chem.*, **2009**, *30*, 761-771.

Storage capacity of clathrate hydrates for storing small molecules

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Density functional theory (DFT) based studies are carried out to understand the structure, stability and reactivity of clathrate hydrates with or without hydrogen encapsulation. All geometries of clathrate hydrates were fully optimized using B3LYP/6-31G(d), M06-2X/6-31G(d) and B97D/6-31G(d) level of theories. The storage capability of five standard clathrate hydrates (5^{12}, $4^3 5^6 6^3$, $5^{12}6^2$, 5^{12} 6^4 and $5^{12}6^8$) is systematically explored to store small molecules like Ar, CH_4, CO_2, H_2, H_2S, Kr, N_2, O_2 and Xe. The capability is depicted in the given Figure. The efficacy of trapping of small molecules inside the cages of clathrate hydrates generally depends upon the cavity sizes and shapes. The interaction energy values indicate the formation of stable gust-host system.

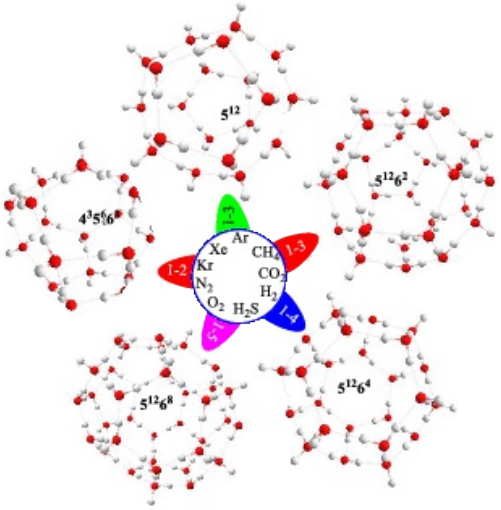

Figure: Capacity of five standard water cavities in the clathrate hydrates with various molecules

References:

1. X. Cao, Y. Su, Y. Liu, J. Zhao, C. Liu. Storage capacity and vibration Frequencies of guest molecules in CH_4 and CO_2 hydrates by first-principles calculations *J. Phys. Chem. A*, 118 2014, pp. 215-222.
2. Chattaraj, P. K., Bandaru, S., Mondal, S. Hydrogen Storage in Clathrate Hydrates *J. Phys. Chem. A* 115, 2011, 187-193.
3. Srivastava, H. K., Sastry, G. N. Viability of Clathrate Hydrates as CO_2 Capturing Agents: A Theoretical Study *J. Phys. Chem. A* 115, 2011, 7633-7637.
4. X. Cao, Y. Su, J. Zhao. Stability and vibrations of guest molecules in the type II clathrate hydrate: a firstprinciples study of solid phase *J. Phys. Chem. A*, 119 2015, 7063-7069.
5. Ramya, K. R.; Venkatnathan, A. Vibrational Raman Spectra of Hydrogen Clathrate Hydrates from Density Functional Theory *J. Chem. Phys.* 138, 2013, 124305.

Enzyme-Independent Chemical Reactions for Chemistry in Living Cells

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Enzyme-independent chemical reactions, which are orthogonal to intracellular processes, may be used for design of novel disease-specific prodrugs and for monitoring biomolecules (e.g. proteins, nucleic acids) and biochemical states (e.g. inflammation). Therefore, they can be applied for both the treatment of diseases and their diagnostics. [1]

Bond-forming reactions compatible with live cells, which can be templated by nucleic acids, are investigated in this project.

The purpose of these theoretical investigations is to provide support to synthetic groups in the selection of appropriate substrates.

In order to find the proper systems to react, we initially investigated the reaction pathways of different simple nucleophiles and electrophiles such as aliphatic and aromatic organo-selenolates, thiolates, thiols, with different types of organochlorides. The same investigations were performed for bigger nucleophiles as glutathione (GSH and GS-) and thioredoxin reductase (TrxR).

Our results show that reactions of the aliphatic organoselenolate and TrxR with organochloride have the lowest reaction energy barrier compared to the other systems calculated. We will now extend our reaction systems towards more complex systems and compare these to the available experimental data.

[1] M. Yang at al, *Chem. Soc. Rev.*, **2014**, *43*, 6511.

Mapping Binding Site Thermodynamics by 3D RISM Theory for Drug Design

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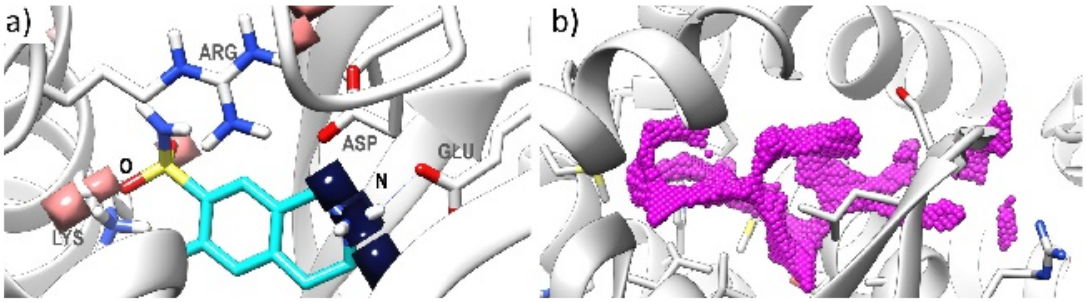
The early stages of the drug discovery process require reasonably accurate and fast methods for optimising the binding affinity of protein-ligand complexes, taking into account direct and solvent-mediated interactions. Inspired by Goodford's GRID method [1] we here present a novel physics-based approach that incorporates (de-)solvation contributions to the binding thermodynamics of probe particles mimicking functional ligand groups in a protein binding site. To this end, we calculate the potential of mean force (PMF) and the distribution functions of different probes (uncharged C, charged N and O) inside the apo protein by 3D RISM (reference interaction site model) theory. [2,3]

The method allows for an intuitive and easy visualization of probe density maps inside the binding site (Fig. 1a, N and O density maps of apo protein in overlay with ligand for 1hnn@pdb) and can be exploited for various tasks in the drug development process. Applications range from pharmacophore and docking-based virtual screening up to defining design directions for medicinal chemists. In a first proof of concept study, the PMF results were embedded into the GOLD [4] docking process on a subset of the PDBbind dataset [5]. An uncharged C probe is used to calculate hydrophobic fitting points that are used for ligand placement throughout the docking process. These 3D RISM based points (Fig. 1b, for 1nav@pdb) display a more detailed representation of hydrophobicity yielding improved docking success.



[1] P. J. Goodford, *J. Med. Chem.* **1985**, 28, 849–857.
[2] F. Mrugalla, S. M. Kast, *J. Phys. Condens. Matter* **2016**, 28, 344004.
[3] S. Güssregen, H. Matter, G. Hessler, E. Lionta, J. Heil, S. M. Kast, *J. Chem. Inf. Model.* **2017**, 57, 1652-1666.
[4] G. Jones, P. Willett, R. C. Glen, A. R. Leach, R. Taylor, *J. Mol. Biol.* **1997**, 267, 727–748.
[5] Y. Li, Z. Liu, J. Li, L. Han, J. Liu, Z. Zhao, R. Wang, *J. Chem. Inf. Model.* **2014**, 54 (6), 1700–1716.

Allosteric control of pH-sensitive Ca(II)-binding in langerin

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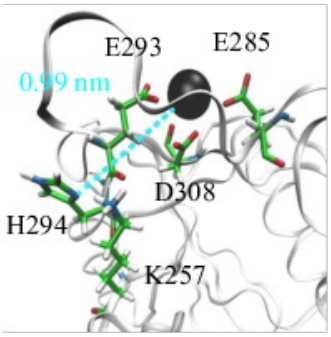

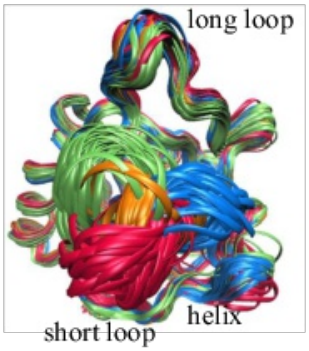

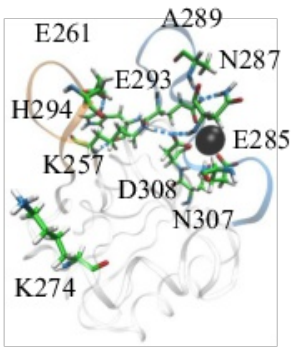

The dendritic C-type lectin receptor langerin plays an important part in the inert immune response of humans and other mammals by trapping invading pathogens like HIV. This is due to a high binding specificity for mannose that relies on the presence of a calcium cofactor. The calcium and therefore the sugar binding affinity itself is sensitive to a change in pH from neutral to weakly acidic. This pH-dependency was attributed to a H294 side chain protonation which is interesting, because this histidine residue has no direct contact to the calcium/sugar binding site (left figure). Hence the effect of the additional proton has to be transported to the binding site via some kind of allosteric mechanism that is currently under investigation.[1]

Several microseconds of MD simulation data of the holo- and apo-protein in different protonation states are analysed, compared and used for the construction of Markov state models. In particular principle component analysis and time-lagged independent component analysis are applied. Force distribution analysis proofed useful for the evaluation of long-lived conformations (centric figure) with respect to their calcium binding ability. Amongst others, a weakly binding conformation was discovered (right figure). However, no large domain involving conformational change can be observed upon protonation that would explain allosteric signal transportation. In contrast, so far a set of local structural variations have been identified that are distributed over the protein network, suggesting a rather *violin*-like model of dynamic allostery as proposed by Kornev and Taylor.[2] These structural elements cover a flexible, so called short loop, parts of the opposed long loop including the calcium binding site and a helix connecting both loops. Especially the short loop-long loop coupling over hydrogen bonded interactions is of interest.

[1]. J. Hanske, S. Aleksić, M. Ballaschk, M. Jurk, E. Shanina, M. Beerbaum, P. Schmieder, B. G. Keller, C. Rademacher, *J. Am. Chem. Soc.*, **2016**, *138*, 12176-12186.
[2]. A. P. Kornev, S. S. Taylor, *Trends Biochem. Sci.*, **2015**, *40*, 628-647.

SimDoC – Simulate Dose and Clearance

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For the development of drugs not only potency (pharmacodynamics) but also ADME (Absorption, Elimination, Meabolism, Excretion) profile (pharmacokinetics, PK) is of critical importance. To avoid drawbacks in later project stages it is essential to select the best candidate as early as possible. As a drug substance must be cleared from body but also needs be present in systemic circulation in suitable concentration, clearance (amount of elimination over time) is a key parameter. Together with other properties (from *in vitro* and *in vivo* experiment) dose can be estimated.

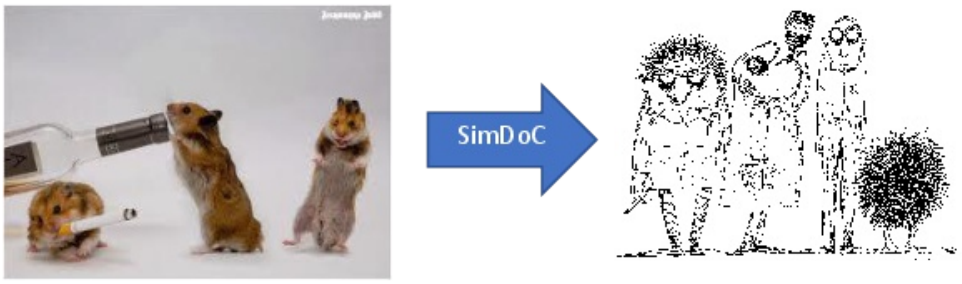
SimDoC was developed at Merck to support this process focusing on three major aspects:

1. Collect all relevant data needed for estimation of dose in human from in-house database
2. Standardize model calculation (use of same model, same physiological paramters, …)
3. Allow "what-if" simulation to gain insight in important PK processes

Elements of SimDoC are ivivc (*in vitro in vivo* correlation) and ivive (*in vitro in vivo* extrapolation) for the estimation of human clearance from experimental species data, simulation of concentration-time curves in different species and human, and sensitivity plot for dosage.

Prior to the availability of SimDoC data collection was mostly done by manual data transfer to Excel sheets followed by property calculation with Excel macros. This was cumbersome and error-prone. In addition, comparison of compounds and inter species differences was difficult or impossible.

In current version of SimDoC up to 10 compounds with 4 species plus human data are accessible and comparable. Various data visualization can guide or inspire experimental design and checks.



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♣ Current affiliation, Stefan Hecht and Carl Deutsch are at DDTech ADC

Computational modeling of effective inhibitors of topoisomerase IA

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Eukaryotic topoisomerases I (TOPO 1) are the targets of an increasing number of anti-cancer and anti-tumor drugs that act by inhibition these enzymes. Computational docking of potential active compounds would be appreciated for prediction of potential antimicrobial drugs, potentially lowering the experimental costs and time [1].

In our work we focused on the search of possible binding places for binding of different drugs, select prominent inhibitors and predict possible effects on enzyme action. Several approaches were used for search and analysis inhibitors, including characterization geometry of binding partners (Yasara [2], VMD), calculation of energy parameters such as binding affinity and charge distribution (Schrodinger [3]).

The potential inhibitors of TOPO 1 [1] where downloaded from PubChem database and used for building of pharmacophore. We also made screening of more than 325 mln entries from PubChem Database employing new approach based on filtering under MeSH classification with combination of different docking methods for inhibitor selection (rigid and flexible docking with, induced fit docking, MD simulation).
Based on our study we also proposed optimal work-flow which can be used for further search and selection other biologically active compounds.
Finally we had choose top-10 compounds based on this pharmacophore hypotheses and then we use it for rational manual construction of new compounds, that were not found in PubChem database.

[1] Y.C. Dinh, *Future,* **2015,** *7(4)*, 459-471.
[2] E. Krieger, G. Koraimann, G.Vriend, *Proteins,* **2002,** *47,* 393-402.
[3] W. Sherman, T. Day, M.P. Jacobson, R.A. Friesner, R. Farid, *J. Med. Chem.*, **2006**, *49*, 534-553.

Kinetic models of the Cyclosporines A and E

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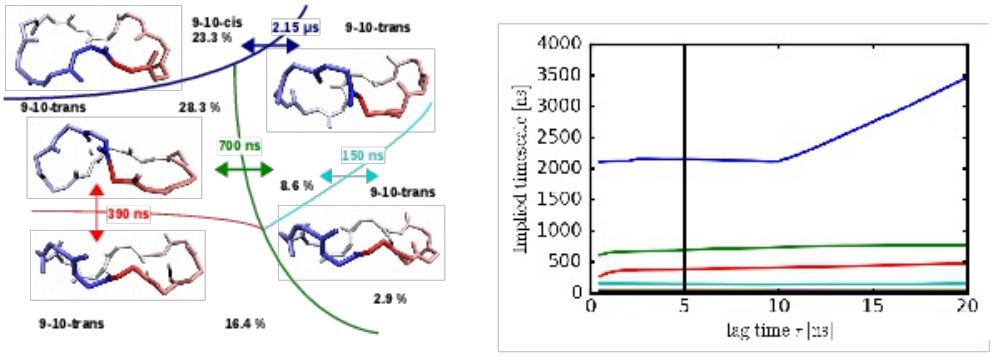

Cyclic peptides have gained high interest as potential drug candidates. However, they often suffer from a low bioavailability due to their size and complexity. One exception is the undecamer Cyclosporine A (CsA), which can passively diffuse through the membrane. The reason for this is most likely found in its dynamic behavior as it can change between an „open" and a „closed" conformation. Cyclosporine E (CsE) is a synthetic derivative of CsA, missing a backbone methylation in Val-11. Its membrane permeability, however, is one order of magnitude smaller [1,2].

To get a better understanding of the dynamics of both molecules and their kinetic differences MD-simulations in water (polar solvent) and chloroform (apolar solvent) have been performed [1,2], which are analyzed using core-set Markov-State-Models (cs-MSMs). In cs-MSMs one focuses on the metastable states of the system, called core sets. This has the advantage that only a small number of states is needed to describe the dynamics accurately [3,4]. We showed that using this kind of analysis recrossing can be reduced and disconnection of metastable states within the data set can be pointed out. In addition, we analyzed the influence of the cis-trans isomerization of the 9-10 peptide bond, which seems to be an important factor for the conformational changes of CsA and CsE, and compared both molecules using a combined discretization.

[1] J. Witek, B.G. Keller, M. Blatter, A. Meissner, T. Wagner, S. Riniker, *J. Chem. Inf. Model.*, **2016**, *56*, 1547-1562
[2] J. Witek, M. Mühlbauer, B.G.Keller, M. Blatter, A. Meissner, T. Wagner, S. Riniker, *ChemPhysChem*, **2017**, *18*, 3309-3314
[3] M. Sarich, R. Banisch, C. Hartmann, C. Schütte, *Entropy*, **2013**, *16*, 258-286
[4] O. Lemke, B.G. Keller, *J. Chem. Phys.*, **2016**, *145*, 163104

Simulation of Human Cytochrome P450-membrane Interactions

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Human cytochrome P450 (CYP) enzymes play an important role in drug metabolism, steroid biosynthesis and xenobiotic degradation. They form a large superfamily of heme-containing enzymes that catalyze substrate monooxygenation. Human CYPs are membrane-anchored proteins and the active site is buried inside the globular domain. We have developed a systematic protocol to build and simulate a CYP-membrane complex using coarse-grained (CG) and all-atom (AA) MD simulations and applied this to several drug-metabolizing CYPs.[1], [2] We observed that different CYPs can display different interactions with the membrane, caused by primary sequence and three-dimensional structure differences.

Furthermore, we employed our multiscale simulations protocol to study the steroidogenic CYPs, CYP17 and CYP19, to assess the effects of mutations in the N-terminal transmembrane (TM) region used in *in-vitro* studies on the interactions between the protein and the membrane. For CYP19, a slight difference in orientation of the globular domain in the membrane was observed due to the truncation of the N-terminal TM-helix residues. For CYP17, our observations suggest that the mutations, particularly W2A and E3L, increase the likelihood of the TM-helix being pulled out of the membrane core and lying parallel to the membrane, behaving as an amphipathic helix. The mutations thereby disrupt CYP-membrane interactions, affect the degree of insertion of the globular domain in the membrane and the position of linker in mutant CYP17, obstructing the substrate access tunnel from the membrane to the active site, could affect the catalytic activity.

References:

[1] V. Cojocaru, K. Balali-Mood, M. S. P. Sansom, and R. C. Wade, *PLoS Comput. Biol.* **2011,** 7, e1002152

[2] G. Mustafa, P. P. Nandekar, X. Yu, and R. C. Wade, *J. Chem. Phys.*, **2015**, 143, 243139.

Thermodynamic Integration Network Study of Electron Transfer: from Proteins to Aggregates [1]

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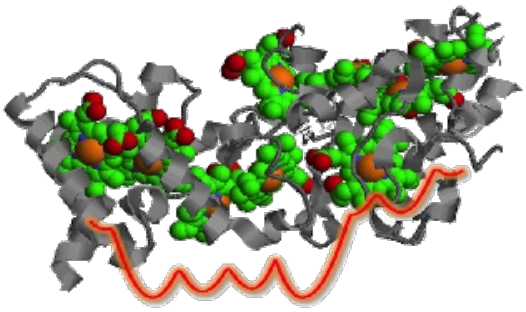

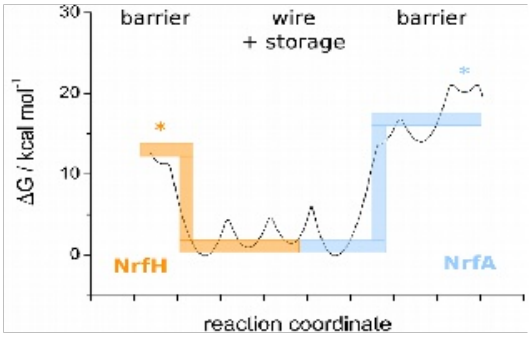

We describe electron transfer through the NrfHA nitrite reductase heterodimer [2] using a thermodynamic integration scheme based upon molecular dynamics simulations. From the simulation data, we estimate two of the characteristic energies of electron transfer, the thermodynamic driving forces, ΔG, and the reorganization energies, λ. Using a thermodynamic network analysis, the statistical accuracy of the ΔG values can be enhanced significantly. Although the reaction free energies and activation barriers are hardly affected by protein aggregation, the complete reaction mechanism only emerges from the simulations of the dimer rather than focussing on the individual protein chains: it involves an isoenergetic transprotein element of electron storage and conductivity [1].

[1] S. Na, A. Bauß, M. Langenmaier, T. Koslowski, *Phys. Chem. Chem. Phys.*, **2017**, *19*, 18938–18947.
[2] M. Rodrigues, K. Scott, M. Sansom, I. Pereira, M. Archer, *J. Mol. Biol.*, **2008**, 381, 341–350.

Study of a multilipid receptor-embedded cell membrane in different ensembles

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Nowadays, a widely adopted approach for construction of a targeted drug delivery system (DDS) is the *active targeting*. It is based on including in the DDS a ligand, which is specifically recognized by cell surface receptors overexpressed in neoplastic membranes. Such a protein is the α-folate receptor (α-FR) with folic acid as its natural ligand. One of the initial steps of the study aimed at understanding the ligand-receptor interactions is to obtain a credible model of a receptor-embedded cell membrane. This includes selection of an appropriate thermodynamic ensemble for adequate description of the receptor and membrane properties. The model neoplastic membrane is constructed in accordance with available experimental data [1, 2] and 35 different lipids are used. The X-ray structure of the receptor is taken and embedded into the membrane by a GPI anchor [3]. Classical atomistic molecular dynamics simulations of the system immersed in saline are carried out at physiological conditions. The calculations are done in three ensembles – NPT with isotropic or with semi-isotropic pressure scaling and NPγT.

The properties in the three ensembles are compared in terms of RMSD evolution and mass density profiles of the components. Order parameter of the lipid tails and average area per lipid are also calculated. The secondary structure of the protein is evaluated, too.

Similarity in the profiles of all characteristics computed in semi-iso NPT and NPγT is found. The largest difference between the three ensembles is in the RMSD and mass density profiles of the membrane. Overall, the membrane is in liquid disordered state in iso NPT, while in the other two ensembles the lipid tails adopt partial order corresponding to liquid ordered state. The latter is in correspondence with the experimentally expected behaviour. The average areas per lipid in NPγT match very well available experimental data.

The NPγT ensemble is selected for further simulations of ligand-receptor-membrane interactions.

Acknowledgement: the research is funded by the Bulgarian Scientific Fund, contract № DN09/14 from 16.12.2016.

[1] Y. Yu, M. Skočaj, M. E. Kreft, N. Resnik, P. Veranič, P. Frenceschi, K. Sepčić, G. Guella, *Mol. Bio Syst.*, **2016**, *12*, 3266-3279.
[2] T. E. Merchant, J. N. Kasimos, T. Vroom, E. Bree, J. L. Iwata, P. W. Graaf, T. Glonek, *Cancer Lett.*, **2002**, *176*, 159-167.
[3] D. Brown, G. L. Waneck, *J. Am. Soc. Nephrol.*, **1992**, *3*, 895-906.

Strategies for developing pressure-dependent force fields

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Biochemical processes of a vast number of lifeforms are accommodated to extreme conditions such as deep oceanic water where high pressure has substantial impact on the molecular basis of biological function. This poses a challenge to computational modeling approaches since the applicability of conventional empirical molecular force fields is questionable. We here report the outline and preliminary results of our strategy towards developing pressure-dependent force fields for a number of important systems.

For instance, the peptide bond links two amino acids by rotatable bonds and is therefore the key element controlling protein conformations. Its amide group is moreover an important spectroscopic beacon for detecting environmental effects on protein folding. Hence, a detailed understanding of its electronic structure at high pressure is critically important not only to predict spectroscopic features but also to develop accurate pressure-sensitive force fields used for molecular dynamics simulations. We present results from high-level quantum-chemical calculations in the gas phase, with continuum dielectric solvation models, and in conjunction with the embedded cluster reference interaction site model (EC-RISM) [1-3] for simple model systems mimicking the protein backbone, N-methylacetamide (NMA) and Ac-Gly/Ala-NHMe. The results for both, the electronic energy surface and the solvent-mediated free energy surface challenge the applicability of established protein force fields for representing extreme environmental conditions. Unlike our experience with small osmolytes such as TMAO [1] or urea in water, a simple charge scaling procedure does not adequately represent the energetic pressure response such that a reparametrization of intramolecular dihedral force field terms will be necessary.

Similarly important is the accurate determination of the solvation free energy as a function of pressure. Since experimental reference data in this context are scarce we attempt to model the pressure dependent autoprotolysis of water for which measurements are available. [4] To this end, the EC-RISM formalism requires reasonable Lennard-Jones force field parameters for hydronium and hydroxide. We report progress by applying a differential evolutionary algorithm to optimize the radial distribution functions obtained from force field-based molecular dynamics simulations with respect to ab initio simulation data.

[1] C. Hölzl, P. Kibies, S. Imoto, R. Frach, S. Suladze, R. Winter, D. Marx, D. Horinek, S. M. Kast, *J. Chem. Phys.* **2016**, *144*, 144104.
[2] S. Imoto, P. Kibies, C. Rosin, R. Winter, S. M. Kast, D. Marx, *Angew. Chemie Int. Ed.* **2016**, *55*, 9534-9538.
[3] R. Frach, P. Kibies, S. Böttcher, T. Pongratz, S. Strohfeldt, S. Kurrmann, J. Koehler, M. Hofmann, W. Kremer, H. R. Kalbitzer, O. Reiser, D. Horinek, S. M. Kast, *Angew. Chemie Int. Ed.* **2016**, *55*, 8757-8760.
[4] A. V. Bandura, *J. Phys. Chem. Ref. Data* **2006**, *35*, 15.

Impact of allosteric inhibitors on MRSA pyruvate kinase conformational dynamics

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A comparative molecular dynamics study of the methicillin-resistant *Staphylococcus aureus* (MRSA) pyruvate kinase (PK) is presented, with and without allosteric inhibitors bound. PK is an attractive target to develop novel antibiotics since it has been identified as a crucial 'hub protein' in MRSA interactome [1], implying high sensitivity to mutations and thus low probability to develop further resistance. Moreover, it has been shown to be critical for bacterial survival. Some potent and selective compounds, able to inhibit both MRSA PK enzymatic activity and bacterial growth in vitro, are already available [2, 3, 4]. However, the allosteric mechanisms governing PK inhibition in bacterial pathogens are poorly understood. Comparing all-atom MD simulations of 3 μs length of the 250 kDa *apo* and *holo* tetramers of MRSA PK, we show that binding of inhibitors at the level of the so-called small interface (between C domains) makes the lid covering the active site (B-domain) at a distance about 45 Å away from the small interface less mobile. We considered as a positive control an anti-PK natural compound (cis-3,4-dihyrohyrohamacanthin B) for which crystallographic data are available (PDB ID 3T07) and as putative inhibitors some similar new compounds with a pyrazine core. The reduced dynamic movement of the lid domain (in terms of extent or frequency) could be a mechanistic explanation for the activity of these inhibitors because this region needs both to open, to allow reagents and products to diffuse in and out, and to close, to hold back the catalytically active potassium and magnesium ions.

[1] A Cherkasov et al., J. Proteome Res., 2011, 10(3):1139-1150.

[2] R Zoraghi et al., J. Biol. Chem., 2011, 286(52):44716-25.

[3] CG Veale et al., J. Nat. Prod., 2015, 78(3):355-62.

[4] C Labrière et al., Eur. J. Med. Chem., 2017, 125:1-13.

Implementing highly selective sorption sites in metal-organic frameworks – a force field study

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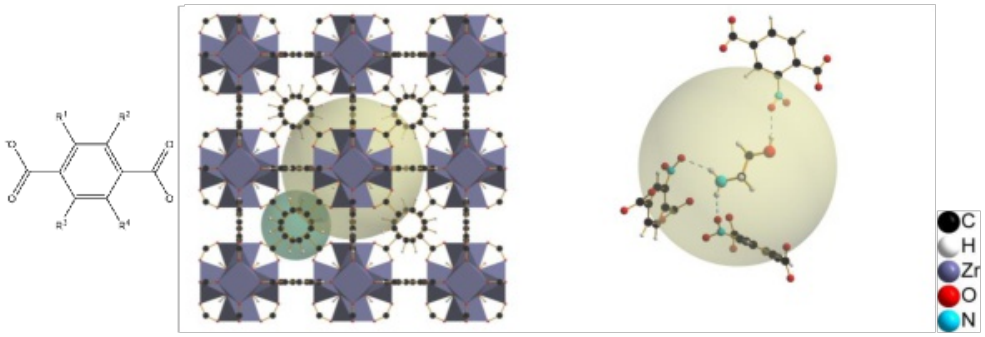
Enzymes play an essential role in biology. Due to active pockets, which are formed by certain functionalities at defined positions, these macromolecules can perform specific reactions with high selectivity. Many attempts have been made to transfer such capability to applicable devices. E.g., aptamers can be deposited on a substrate, potentially retaining their high selectivity, to create a highly selective sensing device. [1] Another example is the design of a metal-organic framework containing such active pockets, by using different substituted linker molecules. [2]

Metal-organic frameworks (MOFs) are one class of microporous coordination polymers. In general, these material exhibit large pore volumes and a high surface area. Amongst others, these properties lead to a high application potential in gas storage and separation. Especially the latter depends not only on volume and surface but on the so-called host-guest interactions between the framework and the sorbate. Due to the fact, that MOFs can be constructed using various linker molecules, these interactions can be tuned. For example, UiO-66 analogue MOFs can be synthesized by using derivatives of the linker molecule. Applying this approach, substituents can be introduced within the porous system of the MOF, which show a big impact on the adsorption of CO_2. [3] Using the structure of UiO-66 as a starting point, different substituents can be introduced at the linker molecules and a specific arrangement of the functionalities within the pores can be achieved (construction principle and linker with positions indicated carrying substituents are shown in the figure (left)). [4] This design targets the generation of an enzyme-like pocket and a sensing device employing such a MOF may enzyme-like selectivity as well. Here, we present a force field study as basis for the experiments.

For this investigation, a suitable force field needs to be identified first. Once this force field meets the requirements, different derivatives of the UiO-66 can be modelled. The interaction between the MOFs and the target analyte ethanolamine is investigated by means of molecular mechanics and dynamics. Monte Carlo simulated annealing is supported by energy minimisation procedures to find the most preferred sorption sites within the MOF structures. The resulting structures are evaluated in detail by the calculation of the interaction energy, the individual energy contributions, and the examination of the analytes' conformation as well as the inter- and intramolecular hydrogen bonds formed. An example of an ethanolamine molecule at the preferred sorption site is shown in the figure, dashed lines indicate hydrogen bonds.



[1] A. Heilkenbrinker, C. Reinemann, R. Stoltenburg, J.-G. Walter, A. Jochums, F. Stahl, S. Zimmermann, B. Strehlitz, T. Scheper, *Anal. Chem.*, **2015**, 87, 677-685.
[2] L. Liu, T.-Y. Thou, S. G. Telfer, *J. Am. Chem. Soc.*, **2017**, 139, 13936-13943.
[3] G. E. Cmarik, M. Kim, S. M. Cohen, K. S. Walton, *Langmuir*, **2012**, 28, 15606-15613.
[4] L. Valenzano, B. Civalleri, S. Chavan, S. Bordiga, M. H. Nilsen, S. Jakobsen, K. P. Lillerud, C. Lamberti, *Chem. Mater.*, **2011**, 23, 1700-1718.

Improving ligand screening by exploiting structure ensembles and machine learning

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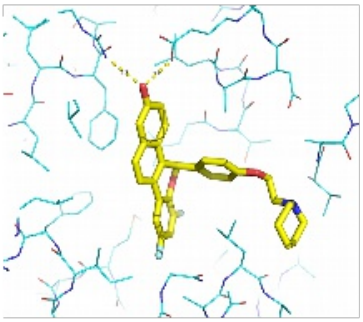

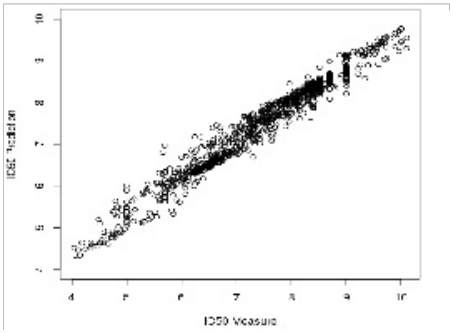

Nuclear receptors (NRs) are DNA-binding transcription factors and one of the most important cellular mediators for sensing (hormones, drugs, xenobiotics) and signal transduction. Therefore, their dysfunction and the subsequent aberrant signaling is associated with many diseases concerning cancer or reproduction and metabolism disorders. Due to their ligand binding ability they are of interest for a broad scientific field, in particular for the pharmaceutical industry as potential pharmaceutical targets and for drug development and in toxicology and environmental science for risk assessment.

Predicting the interactions between small molecules and receptors plays a critical role in drug discovery and development. In particular the Estrogen Receptor alpha (ERα) is an important target for medical treatment and among the most studied NRs.

During our study, exhaustive docking for all known ERα ligands present in BindingDB was achieved using parallel docking on conformational ensembles, which also result in more precise pose predictions. This result enables us to employ a random forest (RF) machine learning algorithm on a large high quality data set in order to predict precise binding affinities. Here, the "sampling problem" is tackled by using structure ensembles, while taking advantage of numerous scoring schemes for virtual screening to better evaluate ligand conformation and protein-ligand interactions.

These results pave the way for a web server dedicated to rapid and high-accuracy docking into the estrogen receptors.

Computational structure analysis for membrane-bound potassium channels

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Ion channels fluctuate stochastically between "open" and "closed" states, which determine the ion flux through biological membranes, also known as "gating". This crucial feature of ion channels is necessary in cellular, biological systems to regulate the ion concentration level, which is essential for the processes of homeostasis or second messaging. Yet the origin of gating is not fully understood. The structure of a channel in its various gating states, which is controlled by its amino acid sequence, plays a vital role for ion selectivity. We here focus on tetrameric potassium channels, for which very short, miniature systems exist. These ideal model systems, Kcv_{PBCV-1} and Kcv_{ATCV-1} that are found in *chlorella* viruses comprise of only 94 and 82 amino acids per monomer [1-3] and play an important role for determining elementary structure-function relations. Although these channels are comparably small, they show all essential features like gating and selectivity.

Many experimental and computational studies have shown that small changes in the sequences of these ion channels can change their functionality drastically, ultimately leading to an inversion of the open/closed probability. [4] Commonly used molecular dynamics (MD) simulations allow for a dynamic characterization of these channels in their gating states but typically cannot be used to directly observe spontaneous gating transitions due to time scale limitations. Other approaches, like integral equation theory are able to predict ion distributions within channels and therefore allow for calculations of thermodynamic properties like free energy surfaces governing ion translocation, but require reasonable average structures as a basis. In the absence of experimentally available structures, MD simulations can fill the gap based on homology models derived from suitable template structures.

A useful method to generate reasonable structures from simulations of homology models is given by the workflow developed by Tayefeh *et al.* [5,6] which utilizes a mean-field simulated annealing approach to satisfy distance distributions. Currently available computer and GPU power nowadays allows for much longer simulation time scales than were possible at the time of first application of this workflow. We apply this protocol to our Kcv model systems and mutants embedded in solvated lipid bilayers in order to generate structures based on MD simulations reaching μs time scales. Structural and thermodynamic analyses of these more refined data are compared to properties and structural features obtained from limited MD data in order to characterize the effort required for reliable results.

[1] L. A. Fitzgerald, M. V. Graves, X. Li, J. Hartigan, A. J. P. Pfitzner, E. Hoffart, J. L. Van Etten, *Virology* **2007**, *362*, 350–361.
[2] S. Gazzarrini, M. Kang, A. Abenavoli, G. Romani, C. Olivari, D. Gaslini, G. Ferrara, J. L. van Etten, M. Kreim, S. M. Kast, G. Thiel, A. Moroni, *Biochem. J.* **2009**, *420*, 295-303.
[3] C. J. Braun, C. Lachnit, P. Becker, L. M. Henkes, C. Arrigoni, S. M. Kast, A. Moroni, G. Thiel, I. Schroeder, *BBA Biomembranes* **2014**, *1838*, 1096-1103.
[4] O. Rauh, M. Urban, L. M. Henkes, T. Winterstein, T. Greiner, J. L. Van Etten, A. Morini, S. M. Kast, G. Thiel, *J. Am. Chem. Soc.* **2017**, *139*, 7494-7503.
[5] S. Tayefeh, T. Kloss, M. Kreim, M. Gebhardt, D. Baumeister, B. Hertel, H. Schwalbe, A. Morini, G. Thiel, S. M. Kast, *Biophys. J.* **2009**, *96*, 485-498.
[6] S. Tayefeh, T. Kloss, G. Thiel, B. Hertel, A. Morini, S. M. Kast, *Biochemistry* **2007**, *46*, 4826-4839.

Plausible Involvement of K634 and T681 mutations in modulation of tertiary structure of human PDGFR-β protein kinase domain by computational molecular dynamics analysis

Vishal Nemaysh, Pratibha Mehta Luthra*

Abstract:

Platelet derived growth factor receptor beta (PDGFR-β) is expressed by endothelial cells (ECs) of tumor-associated blood vessels and regulates primarily in early hematopoiesis. Human PDGFR-β is a novel therapeutic target for glioblastoma (GBM). However, a major challenge of GBM therapy is to overcome drug resistance, mostly initiated by the missense mutations in the protein kinase catalytic domain. These mutations in PDGFR-β tyrosine kinase gene are associated with the development of various diseases such as cancers, infantile myofibromatosis, atherosclerosis and nephritis. The present work is aimed to carry the in silico structural studies on PDGFR-β wild-type (WT) and mutant type (MT) to reveal the probable mechanism of resistance related to anti-angiogenic and anticancer drug sunitinib. Due to lack of crystal structure the 3D structure of PDGFR-β kinase domain (WT) and (MT) was predicted and the docking analysis with sunitinib was carried. The molecular dynamic simulations of PDGFR-β (WT) and (MT) were commenced to disclose the differential structural alterations in the PDGFR-β kinase structure, dynamics, and stability. Our result shows that the overall affect of mutations in the residues K634A, T681M, T681F, T681I, and T681A led to destabilize the 3D structure of PDGFR-β and altered the binding energy of sunitinib. Specifically, the mutation at residue lysine 634 (K634A) and gatekeeper residue threonine 681 (T681M), present in the ATP binding pocket, affected the protein stability most, thus conferring the resistance to the drug sunitinib. Present findings markedly displayed the molecular interactions of sunitinib with 3D structure of PDGFR-β kinase structure (WT and MT) demonstrating differential binding of the sunitinib in (MT) PDGFR-β leading to developed resistance to chemotherapy. This is the first time that we have reported the comparison of drug resistance in PDGFR-β (MT) and (WT) structure using in silico methodology.

Multiscale Simulation and Experimental Characterization of Epoxy/Polyaniline Nanocomposite Coatings – Towards the Rational Design of Nanocomposite Coatings Used in Corrosion Protection

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Corrosion of mild steel causes massive costs due to inspection, maintenance and repair each year. Currently, for corrosion protection conductive polymers are of great interest. The most studied polymer is Polyaniline (PANI) since it is easy to synthesize and can be prepared either chemically or electrochemically [1]. The conductivity of PANI is controlled through protonation leading to an increase in conductivity (doping) and de-protonation (de-doping) causing a decrease in conductivity [2]. The electrochemical properties and performance as corrosion inhibitor are significantly influenced by the choice of doping agent [3]. Blends of PANI and epoxy resin have shown promising corrosion inhibition properties [4], [5], [6].
Despite the large number of studies on PANI and PANI containing coatings for the corrosion protection of mild steel, the mechanisms of action, influence of the doping agent and failure of the anticorrosive properties have not yet been fully understood. Therefore, we employ a combination of theoretical and experimental methods for the investigation of epoxy/PANI nanocomposites doped with different doping agents. Simulations ranging from atomistic scale to macroscale should allow to investigate the charge-transfer reactions taking place at the steel-coating interface, the role of doping agents and ferric oxide type at the interface in electron transfer reactions and interfacial adhesion (atomistic scale – first principle quantum mechanical (QM) and molecular dynamics (MD) simulations) as well as the role of surface morphology and cracks (macroscale – Finite Element (FE) modeling) in corrosion protection and failure of the coating. The results of simulations are benchmarked against experimentally determined electrochemical properties, surface morphology, interfacial energy and adhesion.
The results will point-out the factors crucial for the success or failure of employing an epoxy/PANI nanocomposite coating for the corrosion protection of mild steel. The knowledge on the electrochemical processes occurring at the metal-coating interface will not only be important for corrosion science, but also for the application of PANI in electrochemical sensors, capacitors, solar energy conversion or rechargeable batteries.

1. Boeva, Z.A. and V.G. Sergeyev, *Polyaniline: Synthesis, properties, and application.* Polymer Science Series C, 2014. **56**(1): p. 144-153.
2. Zarras, P., et al., *Progress in using conductive polymers as corrosion-inhibiting coatings.* Radiation Physics and Chemistry, 2003. **68**(3-4): p. 387-394.
3. da Silva, J.E.P., S.I.C. de Torresi, and R.M. Torresi, *Polyaniline acrylic coatings for corrosion inhibition: the role played by counter-ions.* Corrosion Science, 2005. **47**(3): p. 811-822.
4. Lu, W.-K., R.L. Elsenbaumer, and B. Wessling, *Corrosion protection of mild steel by coatings containing polyaniline.* Synthetic Metals, 1995. **71**(1-3): p. 2163-2166.
5. Talo, A., O. Forsen, and S. Ylasaari, *Corrosion protective polyaniline epoxy blend coatings on mild steel.* Synthetic Metals, 1999. **102**(1-3): p. 1394-1395.
6. Tallman, D., Y. Pae, and G. Bierwagen, *Conducting polymers and corrosion: polyaniline on steel.* Corrosion, 1999. **55**(8): p. 779-786.

Constitutive activity of the human histamine H_4 receptor: Computational studies on wild-type and mutant H_4R orthologs

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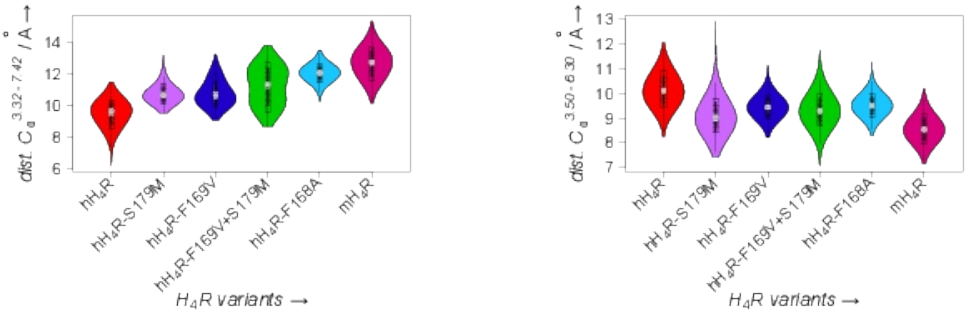
Histamine H_4 receptor (H_4R) orthologs are G-protein coupled receptors (GPCRs) that exhibit species-dependent constitutive (basal) activity. In contrast to mouse H_4R (mH_4R), human H_4R (hH_4R) shows a high degree of constitutive activity.

In a previous molecular-pharmacological study, we characterized the constitutive activity of hH_4R, mH_4R as well as a series of hH_4R mutants, comprising hH_4R-S179M, hH_4R-F169V, hH_4R-F169V+S179M [1] and hH_4R-F168A [2]. An exchange of $F169^{ECL2}$ to V significantly decreased the constitutive activity compared to wild-type hH_4R, while that of the hH_4R-S179M mutant is similar to that of hH_4R. [1] Remarkably, the basal activity of the hH_4R-F169V+S179M [1] and hH_4R-F168A [2] mutants is even comparable to that of mH_4R.

Hence, though we identified residues that account for the high constitutive activity of the hH_4R, the underlying molecular mechanism by which the basal equilibrium between inactive and active receptor states is shifted towards the inactive state is still unknown. To shed light on this matter, we have performed long-time-scale (2 µs) molecular-dynamics simulations on wild-type hH_4R, the hH_4R mutants S179M, F169V, F169V+S179M, F168A, and on mH_4R.

During the MD simulations, $F169^{ECL2}$ is dipping into the binding pocket merely in case of hH_4R and is thereby interacting with the surrounding aromatic and hydrophobic residues. Interestingly, F169 seems to take the role of an agonist, thus contributing to the stabilization of the active state. As a measure of binding pocket contraction, the distance (C_α) between $D94^{3.32}$ and $Q347^{7.42}$, starting at approximately 11 Å, increased by a maximum of ~3 Å for the hH_4R mutants and mH_4R, while, by contrast, it decreased by up to 3 Å for the basally active hH_4R. At the intracellular side, initial C_α-C_α distances of around 8.0 Å between $R112^{3.50}$ and $A298^{6.30}$ increased more for hH_4R than for the hH_4R mutants and mH_4R, thus showing an enhanced outward movement of TM6 for hH_4R compared to the other H_4R variants. This is in accordance with the fact that GPCR activation is reflected by a subtle contraction of the orthosteric binding pocket and a notable outward motion of TM6 at the intracellular side.



Hence, H_4R variant-dependent differences between essential motifs of GPCR activation correlate with experimentally determined constitutive activities and provide a molecular explanation for the differences in constitutive activation. Furthermore, the results shed new light on the molecular mechanism of basal H_4R activation that are of importance for other GPCRs.

[1] D. Wifling, et al., *Br. J. Pharmacol.*, **2015**, 172, 785-798.
[2] D. Wifling, et al., *PLoS One*, **2015**, 10, e0117185.

Rationalizing the enantioselectivity of aldoxime dehydratases

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The advantages of enzyme-catalysis such as high enantioselectivity and mild reaction conditions are well known. In order to increase the potential of biocatalysis further, gaining a deep insight into the mechanism and catalytic properties of enzymes appears to be of high importance. Toward this end, *in silico* assays can be a powerful tool for protein engineering approaches. Latest experiments from *Betke et al.* [1] showed an unexpected phenomenon for the enantioselective dehydration of aldoximes under formation of nitriles: in dependency of the *E*- or *Z*- conformation of a racemic aldoxime, a switch of the enantiopreference was observed. Thus, starting from the same racemic aldehyde and albeit using the same aldoxime dehydratase as an enzyme, both enantiomers are accessible. Based on a general postulated mechanism for an aldoxime dehydratase by *Nomura et al.* [2], we focused on rationalizing this unusual switch in enzyme selectivity by means of docking experiments. As a software MOE (*Molecular Operating Environment*) was used to find suitable ligand-protein conformations. First, we defined *cut off*-values, which were determined by using the co-crystal from *Sawai et al.* [3] and considering *van-der-Waals*-radii of the interacting atoms being included in the postulated mechanism. All 28

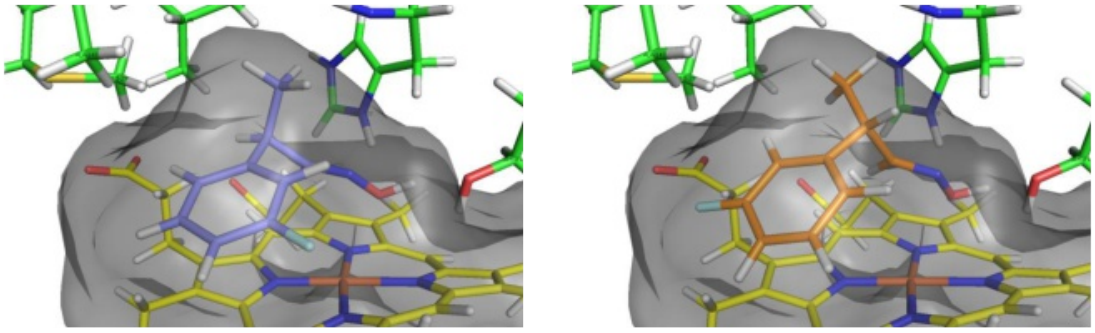

Figure 1: Comparison of docked structure with OxdRE and 3-(*E*)-fluoro-phenylpropanal oxime (FPPOX) in *R* - and *S*- conformation.

phenylpropanal-oxime (PPOX) derivatives, which were used for the docking studies showed a privileged conformation in the active site. The methyl-group of these structures were nearly always localized inside a small cavity in the active site pocket. Furthermore, the ΔΔG values of the transition states when starting from the (*E*)- or (*Z*)- isomers were determined, thus enabling a prediction of the formed enantiomers. The experimental data are consistent with the docking result for example, 3-(*E*)-*rac*-FPPOX could be converted to 3-*S*-FPPN with 49 % conv. and 81 %ee. A hypothesis for the enzyme selectivity is that the methyl-group in the cavity causes (mainly) this energy difference.

[1] T. Betke, P. Rommelmann, K. Oike, Y. Asano and H. Gröger, *Angew.. Chem. (In. Ed.)* **2017**, 56, 12361-12366

[2] J. Nomura, H. Hashimotob, T. Ohtac, Y. Hashimotoa, K. Wadaa, Y. Naruta, K. Oinuma, and M. Kobayashi, *PNAS* **2013**, *110*, 2810-2815.

[3] H. Sawai, H. Sugimoto, Y. Kato, Y. Asano, Y. Shiro, and S. Aono, *J. Biol. Chem.* **2009**, *284*, 32089.

Novel Chemical Space Driven By Reaction Network

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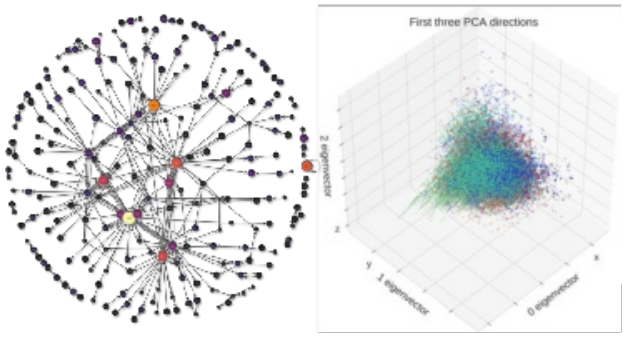

Figure left. The network of chemical reactions.

Figure right. A reaction driven chemical space presented with its first three eigenvectors.

Abstract:

21th century is undoubtedly the "BigData" era[1], especially for chemoinformatics. From reaction record's aspect, there are millions of chemical reactions stored in commercial databases[2]. Figure left exhibits the complexity of chemical reactions via directed network. This number is increasing with text-mining pipelines developed to extract chemical reactions from patents and literatures[3]. From chemical space's view, the cardinality of a typical screening compound collection from a large pharmaceutical company often exceeds one million substances[4], virtual compound pools are even larger. Given these data, one would presume that it should be easy to deliver a real chemical entity with purposed synthetic routes, *i.e.* synthetic route design[5-7]. However, despite the fact that multiple retrosynthetic computational algorithms are available, they are not broadly used by synthetic chemists. Here, we present our naïve synthetic enumeration software guided by easily accessible building blocks and commonly used, *per se*, preferred by chemists, chemical reactions with confined synthetic steps. Through our software, one could deliver a chemical space composed only by theoretically synthesizable compounds. Figure right shows a small novel product pool from ten chosen chemical reactions generated by our software. Automatic property calculation of reactants and products is performed to navigate and analyze enumerated new customized chemical space. We hope that this software could help to establish a rapport between computational and medicinal chemists.

[1] A. Klenner, V. Hähnke, G. Schneider et.al. *Mol. Inf.*, **2012**, 31, 21–26.
[2] S. Roughley, A. Jordan. *J. Med. Chem*, **2011**, 54, 3451–3479.
[3] D. Lowe, *Extraction of chemical structures and reactions from the literature (doctoral thesis)* **2012**.
[4] P. Schneider, G. Schneider, *J. Med. Chem,* **2016**, *59*, 4077-4086.
[5] E. Corey, X. Cheng. *The Logic of Chemical Synthesis, Wiley,* **1989**.
[6] Hartenfeller M, G. Schneider, et al. *PLoS Comput Biol,* **2012**, 8, e1002380.
[7] Wellenzohn, B.; Lessel, U. et.al. *J. Med. Chem.* **2012**, 55, 11031−11041.

Modeling Charge-Transport Pathways in Covalent Organic Frameworks

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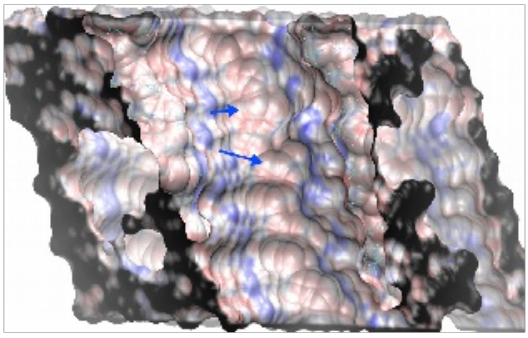
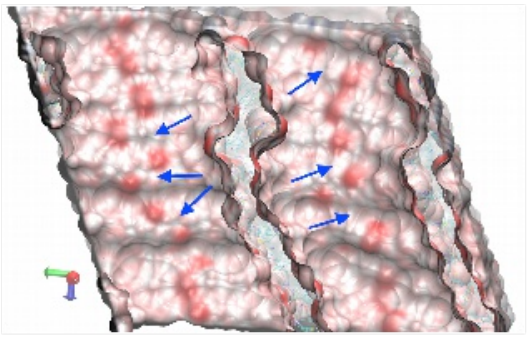
Background Covalent Organic Frameworks (COF) are highly crystalline porous materials. When central metals are inserted in the framework, it produces semiconductor COFs capable of conveying both electrons and holes for use in optoelectronics. Simulating charge transport through the molecular scaffold of the COFs is a challenging Multiscale Problem, because the time scale for the charge transfer is in a range of 10^{-15} sec, while that for the conformational movement is in 10^{-12} sec.

Results We used the co-condensation product of (5,10,15,20-tetra(4-aminophenyl)porphyrin) (TAPP) and thieno[3,2-b]thiophene-2,5-dicarboxaldehyde (TT) for our work. The crystal structure was optimized and MD simulation was done at NPT for 10 nanoseconds. The calculated powder XRD pattern confirmed structure preservation and showed identical high-intensity peaks to those in the experimental one. The electronic structure of the selected ensembles was calculated semiempirically using the AM1* Hamiltonian with *EMPIRE* software. The local electronic properties are then extracted from the wavefunction as Local Electron Affinity (A_L) and Local Ionization Energy (I_L). We then applied Metropolis Monte Carlo algorithm to track the charge carrier pathways.





Conclusions The PES of A_L and I_L (in the figures below) are color-coded with Red-White-Blue (RWB) gradation; low energy values in **red**, middle values in **white** and high values in **blue**. The arrows point to the energy barriers of the electrons and holes transport pathways. The qualitative results of the search algorithm showed that electrons prefer a pathway through the porphyrin rings and the holes prefer that pathway through the TT linker of the TAPP-TT COF.

[1] Clark T: **Simulating charge transport in flexible systems**. *Perspectives in Science* 2015, **6**:58-65.
[2] Dogru M, Bein T: **On the road towards electroactive covalent organic frameworks**. Chem Commun (Camb) 2014, 50(42):5531-5546.

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18.1% RETURN ON NET SALES

AMERICAS: EUR 6,542 million

EUROPE: EUR 5,082 million

ASIA, AUSTRALIA, AFRICA (AAA): EUR 4,226 million

RESEARCH & DEVELOPMENT

3 PILLARS

Focus on research therapeutic areas | Scientific platforms | Research Beyond Borders

EUR 2,870 million Prescription Medicines expenditure in research & development in 2016

≙ around 23.8% of Prescription Medicines net sales 2016

SOCIAL RESPONSIBILITY

MAKING MORE HEALTH

ASHOKA

Making More Health is a global initiative by Boehringer Ingelheim in cooperation with Ashoka, a non-governmental organisation. Its aim is to improve healthcare for people worldwide.

MORE THAN 80 social entrepreneurs in over 30 countries received support since 2010

APPROX. 3,700 Boehringer Ingelheim employees worldwide are involved in the initiative

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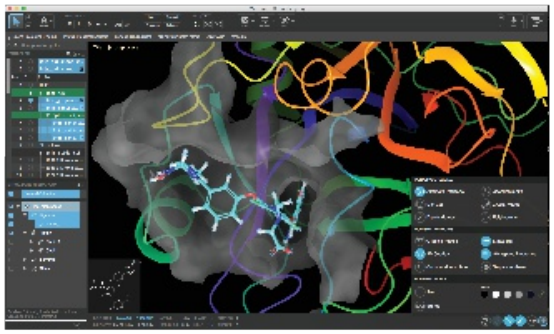

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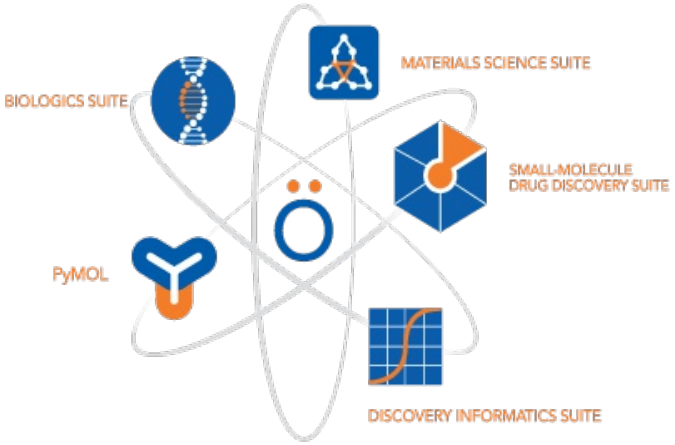

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CHALLENGE YOUR MATH SKILLS

Challenge 1
How many double-digit natural integers with three digits *abc* exist for which $(a+b)^c$ is a natural number with three digits that can be written as a power of 2?

Challenge 2
In a rectangular triangle, the sum of the three sides is 18, and the sum of the squares of the three sides is 128. What is the area of the triangle?

Challenge 3
A sequence of numbers is recursively defined as $a_{n+1} = (a_n-1)/n$, with $a_1 = -1/2017$. Calculate a_{2018}!

IMPRINT

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