MOLECULAR MODELLING WORKSHOP 2016

Monday, April, 4th - Wednesday, April 6th 2016

Welcome to the 30th Molecular Modelling Workshop (MMWS).

This is the 14th 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 organic institute in Erlangen since the 17th edition in 2003. However, this will be the last MMWS in Henkestraße as Organic, Medicinal and Pharmaceutical Chemistry in Erlangen will move into the first phase of the new Chemikum and the venue of the workshop will move within Erlangen next year.

This year's MMWS is also the first for which the technical conference management of the Computer-Chemie-Centrum, CCC, is supported by the Bioinformatics group headed by Heinrich Sticht.

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

As always, we have two plenary speakers for this year's MMWS. We are happy to welcome Brian Shoichet from the University of California, San Francisco and Marcus Neumann from Avant-Garde Materials Simulation Deutschland GmbH as our plenary speakers this year. Brian Shoichet represents the traditional drug design area that has been the mainstay of the MMWS since its conception. Marcus Neumann, on the other hand, represents the materials modeling community, an increasingly important section of our discipline. By combining these two excellent plenary speakers, we hope to enable MMWS to keep pace with the rapidly changing face of modeling in Europe and the USA and to provide inspiration for young modelers.

So now, please enjoy the 30th Molecular Modelling Workshop.

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

Scientific program

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DEAR COLLEGUES,

The 30th Molecular Modelling Workshop (April, 4th - 6th) 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 or lecture contributions in English or German from all areas of molecular modelling including life sciences, physical sciences, material sciences and the nano sciences.

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

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

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

DR. MARCUS A. NEUMANN

Avant Garde Materials Simulation Deutschland GmbH, Freiburg
www.avmatsim.de

PROF. BRIAN SHOICHET

University of California, San Francisco
www.bkslab.org

AWARDS

As in the past years, 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 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 mmws2016.mgms-ds.de

DR. MARCUS A. NEUMANN

has a M.Sc. in Physics from the *Heinrich-Heine University* in Düsseldorf, Germany, and holds a Ph.D. in Physics from the *University of Grenoble*, France.

During his Ph.D. at the Institute *Laue-Langevin*, Dr. Neumann investigated proton quantum dynamics in molecular solids by neutron scattering and developed software for the numerical solution of the nuclear Schrödinger equation.

He joined *Accelrys Ltd.* in Cambridge, UK, as product specialist for crystallisation and analytical simulation in 1999 and was promoted to product manager in 2001. At Accelrys, Dr. Neumann invented the X-Cell algorithm for powder indexing.

In 2002 Dr. Neumann founded *Avant-garde Materials Simulation SARL*, a French company specializing in the development of novel methodology for Crystal Structure Prediction that opened a fully owned subsidiary, *Avant–Garde Materials Simulation Deutschland GmbH*, in Freiburg, Germany, in December 2007.

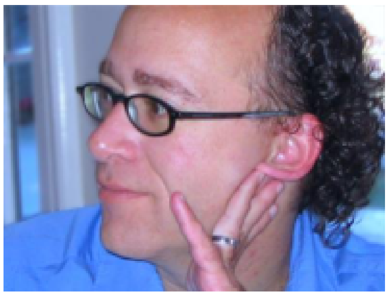
PROF. BRIAN SHOICHET

received a B.Sc. in Chemistry and a B.Sc. in History in 1985, from *MIT.* In 1991, he received his Ph.D. for work with Tack Kuntz on molecular docking from *UCSF.* Shoichet's postdoctoral research was largely experimental, focusing on protein structure and stability with Brian Matthews at the *Institute of Molecular Biology in Eugene*, Oregon, as a Damon Runyon Fellow.

Shoichet joined the faculty at *Northwestern University* in the Dept. of Molecular Pharmacology & Biological Chemistry as an Assistant Professor in 1996. Shoichet was promoted to a tenured Associate Professor in 2002. Around that time he was recruited back to *UCSF,* where he is now a Professor in the Department of Pharmaceutical Chemistry.

Research in the Shoichet Lab seeks to bring chemical reagents to biology, combining computational simulation and experiment. An unanticipated observation emerging from the theory/experiment cycle was the colloidal aggregation of organic molecules. This phenomenon has great effects in early and late drug discovery.

Markus A. Neumann / Avmatsim



Brian Shoichet / UCSF

Lectures Program

PROGRAM

Monday, April 4th 2016

11:30-14:00	**Registration**
14:00-14:10	**Tim Clark: Welcome remarks / Agenda review**
14:10-14:35	**Willem Jespers (Leiden, NL)** Binding mode prediction using Free Energy Perturbations
14:35-15:00	**Ilaria Passarini (Hatfield, UK)** Exploring the conformational space of cationic antimicrobial peptides
15:00-15:25	**Eileen Edler (Magdeburg, Germany)** Phospholipid signaling of geranylgeranyl-Rab5 peripheral membrane protein
15:25-16:00	**Coffee Break**
16:00-16:25	**Athina Meletiou (Nottingham, UK)** Parallel grid computing for modelling mycolic acids from *Mycobacterium tuberculosis*
16:25-16:50	**Robert Stepic (Erlangen, Germany)** Benchmarking the interaction of amino acids with calcite
16:50-17:15	**Markus Kossner (Cologne, Germany)** Organizing 3D Project Data for Structure-Based Drug Design
17:15-18:15	**Poster Session I**
18:15-19:00	**Annual Meeting of the MGMS-DS**
19:00	**Buffet - Dinner**

PROGRAM

Tuesday, April 5th 2016

09:00-09:25	**Stevan Aleksic (Berlin, Germany)** Dynamic regulation of Ca^{2+} binding to Langerin carbohydrate recognition domain by an allosteric network
09:25-09:50	**Birgit Waldner (Innsbruck, Austria)** From Substrate Specificity to Small Molecule Specificity
09:50-10:15	**Jonas Kaindl (Erlangen, Germany)** Design and Molecular Modeling of D_2R/NTS_1R Heterodimer-Selective Ligands
10:15-10:40	**Antonella DiPizio (Jerusalem, Israel)** Molecular recognition in bitter taste GPCRs
10:40-11:15	**Conference Photo & Coffee Break**
11:15-12:00	**PLENARY LECTURE I: Marcus Neumann** Organic crystal structure prediction – from fundamental research to industrial application
12:00-12:25	**Maximilian Kriebel (Erlangen, Germany)** Charge-carrier mobilities in acene crystals
12:25-12:50	**Tomas Asche (Hannover, Germany)** Atomistic modeling of hybrid polymers
12:50-14:00	**Lunch**
14:00-14:25	**Markus Dick (Cologne, Germany)** Trading off stability against activity in extremophilic aldolases
14:25-14:50	**Christina Roggatz (Hull, UK)** Quantum chemical methods help unravel effects of pH on marine communication
14:50-15:15	**Eileen Socher (Erlangen, Germany)** Mimicking titration experiments with MD simulations: A protocol for the investigation of pH-dependent effects on proteins
15:15-16:00	**Coffee Break**

PROGRAM

Tuesday, April 5th 2016

16:00-16:25	**Tobias Kröger (Düsseldorf, Germany)** Structural modeling of EDTA aggregates that lead to artifacts in a fluorescence-based biophysical assay
16:25-16:50	**Luca Donati (Berlin, Germany)** Markov State Model with reweighting
16:50-17:15	**Noureldin Saleh (Erlangen, Germany)** How different are nanobody-stabilized GPCR structures from their G-protein-stabilized equivalents?
17:15-18:15	**Poster Session II**
18:30	**Evening in the brewery Steinbach Bräu**

Wednesday, April 6th 2016

09:00-09:25	**Lena Kalinowsky (Frankfurt, Germany)** A Diverse Test Set for the Validation of Scoring Functions based on Matched Molecular Pairs
09:25-09:50	**Alexandra Freidzon (Moscow, Russia)** Multireference Quantum Chemistry for Organic Electronics
09:50-10:15	**Adria Gil-Mestres (Lisboa, Portugal)** Trying to understand the modulation in the activity of the DNA intercalating anticancer drugs: The importance of CH-π interactions
10:15-10:40	**Marko Hanževački (Erlangen, Germany)** Activin Receptor Type IIA Protein Kinase Inhibitors: Free Energy Calculations and Ligand Binding
10:40-11:15	**Coffee Break**
11:15-12:00	**PLENARY LECTURE II: Brian Shoichet** A metabolic code for signaling
12:00-12:25	**Thomas Steinbrecher (Schrödinger GmbH, Germany)** OPLS3 - Recent developments in the OPLS force field
12:25	**Harald Lanig: Poster & Lecture awards, Closing**

Poster Sessions

POSTER SESSION I

Monday, April 4th 2016 17:15-18:15

P01 **Christian R. Wick (Zagreb)**
Semiempirical MO-Theory for Large Systems

P02 **Birgit J. Waldner (Innsbruck)**
From Substrate Specificity to Small Molecule Specificity

P03 **Stevan Aleksić (Berlin)**
Dynamic regulation of Ca^{2+} binding to Langerin carbohydrate recognition domain by an allosteric network

P04 **Joulia Alizadeh-Rahrovi (Tehran)**
Human apo-myoglobin structural stability in the presence of ligands: a molecular dynamics study

P05 **Thomas Asche (Hannover)**
Performance of the COMPASS force field for inorganic-organic hybrid polymers

P06 **Frank Beierlein (Erlangen)**
DNA-dye-conjugates: conformations and spectra of fluorescence probes

P07 **Zlatko Brkljača (Erlangen)**
Biomineralization and biomineralization-inspired drug design: Calcite – peptide interactions

P08 **Karina van den Broekl (Essen)**
Mesoscopic simulation of the membrane disrupting activity of the cyclotide Kalata B1

P09 **Markus Dick (Jülich)**
Trading off stability against activity in extremophilic aldolases

P10 **Benedikt Diewald (Erlangen)**
Design of antibody-based peptide inhibitors to disrupt important protein-protein interactions in HIV and HCMV

P11 **Luca Donati (Berlin)**
Markov State Models with reweighting

POSTER SESSION I

Monday, April 4th 2016 17:15-18:15

P12	**Mirja Duderstaedt (Hannover)** Dynamic generation of inorganic and organic polymer structures in hybrid polymers
P13	**Christiane Ehrtl (Dortmund)** Ligand-sensing cores – Large Scale Analysis and Application
P14	**Holger Elsen (Erlangen)** Mechanistical Insight on the Hydrosilylation of Conjugated Alkenes Catalyzed by Early Main-Group Metal Catalysts
P15	**Marko Hanževački (Erlangen)** Investigation of the effect of β-Cyclodextrin on Peptide Deamidation: A Molecular Dynamics Study
P16	**Susanne M.A. Hermans (Düsseldorf)** Towards Identifying Novel Allosteric Drug Targets using a "Dummy" Ligand Approach
P17	**Anselm H. C. Horn (Erlangen)** Conformational Stability of Non-Fibrillar Amyloid-$\beta_{17\text{-}38}$ – A Molecular Dynamics Study

Please remember to remove your posters on monday evening!

POSTER SESSION II

Tuesday, April 5th 2016 17:15-18:15

P01	**Lina Humbeck (Dortmund)** Discovery of a novel relationship between two proteins by a chemogenomics analysis
P02	**Patrick Kibies (Dortmund)** Electronic polarization induced by high solvent pressure
P03	**Zoran Miličević (Erlangen)** The Role of Water in the Electrophoretic Mobility of Hydrophobic Objects
P04	**Zahrabatoul M. Kotena (Kuala Lumpur)** Bifurcated hydrogen bondin in carbohydrate sugars
P05	**Jan L. Riehm (Saarbrücken)** The many faces of Cyp106A2: How does rational protein design work
P06	**Achim Sandmann (Erlangen)** Different Types of Ca^{2+} binding sites in SiiE
P07	**Cenk Selçuki (Izmir)** Conformational analysis of neutral and ionic forms of lysine
P08	**Dmitry I. Sharapa (Erlangen)** Pitfalls in the accurate determination of non-covalent interaction energies in large systems using the example of the C_{60} dimer
P09	**Eileen Socher (Erlangen)** Investigation of pH-dependent effects on proteins by mimicking pH titration experiments with MD simulations
P10	**Anne Steimecke (Halle)** In silico screening and testing of new phytoeffectors to enhance drought stress tolerance in plants
P11	**Maxim Tafipolsky (Würzburg)** Challenging Dogmas: What is inside a Hydrogen Bond?
P12	**Nicolas Tielker (Dortmund)** Transfer free energies between aqueous and nonaqueous phases from an integral equation-based quantum solvation model
P13	**Martin Urban (Dortmund)** Molecular gating characteristics in variant of the potassium ion channel KcvATCV

POSTER SESSION II

Tuesday, April 5th 2016 17:15-18:15

P14	**Nataša Vučemilović-Alagić (Erlangen)** Organization and Wetting of [C_4Mim][Ntf_2] Ionic Liquid at the Neutral Sapphire Interface
P15	**Nursel Acar (Izmir)** Computational investigation of the exciplexes formed between pyrene and selected monoamines
P16	**Nursel Acar (Izmir)** DFT and TDDFT study some pyrene derivatives in excited state

All abstracts are available on the conference web site:
www.mmws2016.mgms-ds.de

Binding pose prediction using Free Energy Perturbations

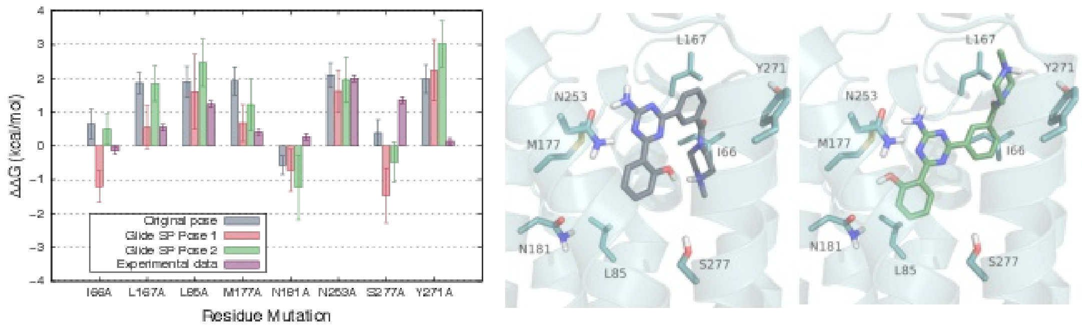
W. Jespers[1], H. Keränen[1], H. Gutiérrez–de–Terán[1], J. Åqvist[1]

1 Department of Cell and Molecular Biology, Uppsala University, Biomedical Center, Box 596, SE-751 24 Uppsala, Sweden

Background: Our group has recently published a protocol for the computation of the effect of site directed mutagenesis (SDM) on ligand-binding affinities, based on the free energy perturbation (FEP) methodology. [1–3] The protocol was thoroughly applied to characterize both agonist (NECA) and antagonist (ZM241385) binding to the Adenosine A_{2A} Receptor, with excellent results.

Objective: To characterize the binding mode and SAR of novel A_{2A} antagonist scaffolds recently published. [4-5]

Methodology: We use our FEP protocol in combination with exhaustive docking. The *in silico* exploration is integrated with all available experimental data publicly available for the compound series reported by Heptares. This includes crystal structures, pharmacological data/SAR and biophysical mapping (BPM) data on three ligand series for 8 alanine mutations.



Results: We initially characterized the effect of the 8 binding-site mutations on the binding affinity of two 1,2,4-triazines, starting from the corresponding crystal structures (PDB codes 3UZA/3UZC). [4] The calculated values are in good qualitative correlation with experimental data (not shown). We thereafter applied this protocol to predict the binding poses of compounds where no crystal structure is available.

The second scaffold explored was compound 15 from the preceding 1,3,5-triazines hit series, a highly potent and moderately selective antagonist for the A_{2A}-receptor for which BPM data is available. [5] We considered different binding modes, including one proposed in the original publication and two additional docking poses obtained with GLIDE-SP. [6] For all binding modes, we calculated the effect on ligand affinity for each of the 8 mutations. The binding mode proposed in the original publication [5] was revealed as the most promising. Unfavourable interactions with $Asn253^{6.55}$ suggested a rotation of the phenol group, in a conformation stabilized by an internal hydrogen bond. As illustrated in the figure (grey), this binding mode showed the best correlation with available experimental data. However, the effect on the $N181A^{5.42}$ mutation was still incorrectly predicted, similar to co-crystallized 1,2,4-triazines. This is most probably due to the indirect effect of this mutation, involved in inter-helical contacts between TM5 and TM6 bridged through a water molecule.

Conclusions: A binding mode for the 1,3,5-triazine series was successfully proposed based on the best explanation of the BPM data with our combined docking/FEP protocol.

Future perspectives: We are currently generating a semi-automated workflow to characterize the effect of point mutations on class A GPCRs to characterize binding modes of additional compounds.

[1] Keränen, H.; Gutiérrez-de-Terán, H.; Åqvist, J. Structural and Energetic Effects of A2A Adenosine Receptor Mutations on Agonist and Antagonist Binding. *PLoS One* **2014**, *9* (10), e108492.
[2] Keränen, H.; Åqvist, J.; Gutiérrez-de-Terán, H. Free Energy Calculations of A 2A Adenosine Receptor Mutation Effects on Agonist Binding. *Chem. Commun.* **2015**, *51* (17), 3522–3525.
[3] Boukharta, L.; Gutiérrez-de-Terán, H.; Åqvist, J. Computational Prediction of Alanine Scanning and Ligand Binding Energetics in G-Protein Coupled Receptors. *PLoS Comput. Biol.* **2014**, *10* (4), e1003585.
[4] Congreve, M.; Andrews, S. P.; Doré, A. S.; Hollenstein, K.; Hurrell, E.; Langmead, C. J.; Mason, J. S.; Ng, I. W.; Tehan, B.; Zhukov, A.; Weir, M.; Marshall, F. H. Discovery of 1,2,4-Triazine Derivatives as Adenosine A(2A) Antagonists Using Structure Based Drug Design. *J. Med. Chem.* **2012**, *55* (5), 1898–1903.
[5] Langmead, C. J.; Andrews, S. P.; Congreve, M.; Errey, J. C.; Hurrell, E.; Marshall, F. H.; Mason, J. S.; Richardson, C. M.; Robertson, N.; Zhukov, A.; Weir, M. Identification of Novel Adenosine A(2A) Receptor Antagonists by Virtual Screening. *J. Med. Chem.* **2012**, *55* (5), 1904–1909.
[6] Friesner, R. a; Banks, J. L.; Murphy, R. B.; Halgren, T. a; Klicic, J. J.; Mainz, D. T.; Repasky, M. P.; Knoll, E. H.; Shelley, M.; Perry, J. K.; Shaw, D. E.; Francis, P.; Shenkin, P. S. Glide: A New Approach for Rapid, Accurate Docking and Scoring. 1. Method and Assessment of Docking Accuracy. *J. Med. Chem.* **2004**, *47* (7), 1739–1749.

Exploring the conformational space of cationic antimicrobic peptides

Ilaria Passarini, Sharon Rossiter, John Malkinson*, Mire Zloh

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**UCL School of Pharmacy, 29/39 Brunswick Square, London, WC1N 1AX, UK*

The number of new antibiotics being released on the market in the last decades has dramatically decreased, whilst on the other hand we assist to a constant increase of multi- or even pan-drug resistant bacterial strains. There is the risk of returning to a pre-antibiotic era, with childbirth of even small surgical procedures becoming a life threat once again. [1] There is therefore an urgent need for new antibacterial drugs.

Cationic peptides with net positive charge at neutral pH have promising antimicrobial activity. However, very few entered into clinical trials due to their poor bioavailability and toxicity.[2]

The aim of our work is to investigate and compare the structures of such peptides, in order to identify the presence of common features, both in terms of recurring patterns in the amino acid sequence and 3D structure similarity. These data will then be used to design novel peptido-mimetic molecules with antibiotic activity.

A set of short sequence antimicrobial peptides with activity against Gram-negative bacteria was generated and cross-referenced against available databases. A multiple sequence alignment of such peptides was carried out and the repetition of the WKW, FRF and FKF patterns was observed with high frequency.

Initial 3D structures of peptides with sequences longer than 9 amino acids were predicted using PEP-FOLD online server, while the conformations of 7 and 8 amino acids long peptides were obtained using simulated annealing instead. Further molecular dynamics simulations of all peptides were carried out in presence of the solvent, salt and at relevant pH to mimic physiological conditions. Both the simulated annealing and the MD simulations were performed with Desmond, using Maestro (Schrödinger) as graphic user interface.

The MD trajectories are being analysed and representative conformations will be superimposed to investigate the presence of common features in terms of shape and electronic distribution. The identified recurring patterns in the amino acid sequences and their 3D molecular similarities will allow us to design peptido-mimetic molecules which will hopefully provide us with a lead to more effective and less toxic antibiotic drugs.

1. Liu, Y.-Y., et al., Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. *The Lancet Infectious Diseases*, **2016**, *16* (2): p. 161-168.
2. Hancock, R.E.W., Peptide antibiotics. *The Lancet*, **1997**, *349* (9049): p. 418-422.

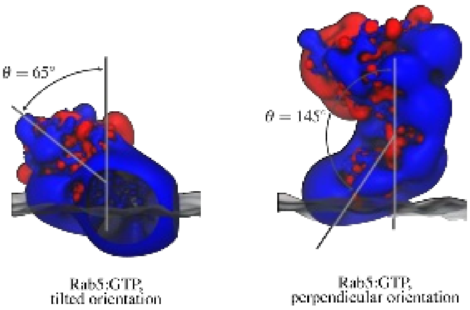
Phospholipid signaling of geranylgeranyl-Rab5 peripheral membrane protein

E. Edler, E. Schulze, M. Stein

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

Rab5 is a small GTPase that serves as a membrane-associated molecular switch in early endosome fusion. Membrane anchoring is achieved via two posttranslationally attached geranylgeranyl chains at the protein C-terminus. Rab5 shuttles between the cytosol and the membrane in its inactive (GDP-bound) state, whereby solely membrane-localized active (GTP-bound) Rab5 is able to recruit effector proteins. Protein crystallography resolved the 3D structure of the catalytic G domain; however, the hypervariable N- and C-terminal regions mediating membrane association were not experimentally accessible.

Here, we present structural and dynamic properties of membrane-bound full-sequence Rab5. Models for the active and inactive states were generated by iterative structural loop refinement followed by all-atom Molecular Dynamics simulations. Rab5 associated to membranes of increasing complexity was investigated in multiple long-time MD simulations. A pure POPC bilayer as well as a simple uncharged ternary lipid mixture were found to oversimplify the plasma membrane structure and electrostatics. In contrast, a physiological six-component membrane containing the negatively charged signaling lipid PI3P allowed a detailed description of the early endosome membrane properties. Independent of the bound nucleotide our simulations revealed a high orientational flexibility of the protein. Rab5 binding to membranes is characterized by two orientation populations. On the one hand, the protein adopts a highly solvent accessible orientation perpendicular to the membrane surface. This orientation is stabilized by Rab5 association with regulatory effector proteins and preserves switch region accessibility and functionality. Moreover, we observed a tilted orientation close and almost parallel to the membrane plane. With negatively charged lipids in the membrane the protein is forced into this tilted orientation due to electrostatically favorable lipid-protein interactions. In this position, interestingly, the two switch regions mediating effector protein binding were partially buried between the protein and membrane surface. We propose that the tilted orientation may represent a reversibly formed inactive state, which can be reactivated by approaching binding partners. Thus, this behavior may allow a fast and transient deactivation mechanism on a time scale of only a few nanoseconds.



Parallel grid computing for modelling mycolic acids from *Mycobacterium tuberculosis*

Athina Meletiou[a], Gareth Shannon[b], Wilma Groenewald[c], Christof Jäger[a], Anna Croft[a]

[a]*Department of Chemical and Environmental Engineering, University of Nottingham, University Park, Nottingham, NG7 2RD, UK*

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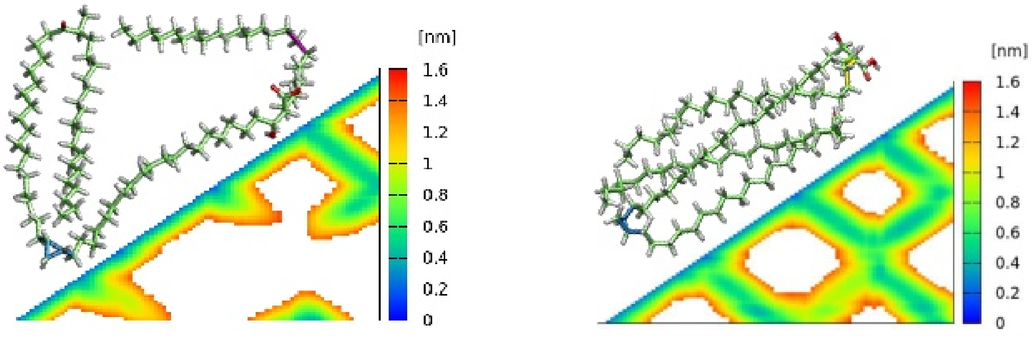
[c]*School of Chemistry, Bangor University, Bangor, Gwynedd, LL57 2UW, UK*

Mycolic acids (MAs) are significantly long fatty acids that occur as dominant constituents in the cell walls of mycobacteria. This group of bacteria includes the pathogen *Mycobacterium tuberculosis* (*M. tb*), the causative agent of the disease tuberculosis (TB). Although largely curable, TB is the world's deadliest disease with 9.6 million new cases and 1.5 million TB-related deaths reported in 2014 alone. The pathogen's defiance of medical treatment, because of its drug resistance, pathogenicity and cell wall impermeability, is largely attributed to the MA's chemical nature[1], which allows *M. tb* to establish a lethal persistent infection. MA's chemical nature primarily determines the molecules' conformational preferences and folding patterns.[2,3] MAs tend to assume different conformations, and this may impact the structure and function of the inner leaflet of the bacterium's cell wall.

Numerous studies[4-6] have focused on the structure-function relationships of MAs, however these are only beginning to be unraveled. We now want systematically to investigate differences in folding dynamics and conformations of a comprehensive set of MAs in order to retrieve insights into their complex structure-function relationships and the correlation of MA conformation and biological function. This information will further provide the basis for more complex and coarse grained simulations of the bacterial cell wall.

A grid computing approach is being used to generate a large set of long-timescale atomistic molecular dynamics (MD) simulations. These simulations provide detailed structural data, which is being collated for a representative set of 166 natural and unnatural MAs. We will present our attempts for efficient analysis of selected examples from the vast amount of simulation data we will retrieve from the grid computing approach and will focus on dihedral clustering and distance matrix analysis methods (example of a semi-folded and a fully folded MA and corresponding carbon atom distance matrix below).



[1] E. Dubnau *et al.*, *Mol Microbiol*, **2000**, *36*, 630-637.
[2] W. Groenewald *et al.*, *Chem Phys Lipids*, **2014**, *180*, 15-22.
[3] M. Villeneuve *et al.*, *Microbiology*, **2013**, *159*, 2405-2415.
[4] S. Vander Beken *et al.*, *Eur J Immunol*, **2011**, *41*, 450-460.
[5] M. Beukes, *et al.*, *Chem Phys Lipids*, **2010**, *163*, 800-808.
[6] V. Rao *et al.*, *J Clin Invest*, **2006**, *116*, 1660-1667.

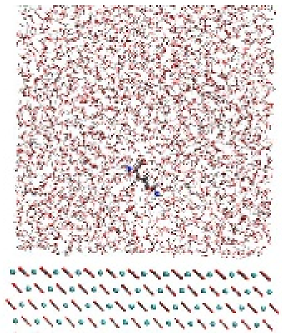
Benchmarking the interaction of amino acids with calcite

Robert Stepić[1,2], Zlatko Brkljača[1,2,3], Ana-Sunčana Smith[1,2,3], David M. Smith[2,3]

[1]*PULS Group, Institute for Theoretical Physics, FAU, Erlangen*

[2]*Cluster of Excellence, EAM, Erlangen*

[3]*Group for Computational Life Sciences, Ruđer Bošković Institute, Zagreb*



Calcium carbonate or calcite is one of the most widespread minerals found on earth. It interacts favourably with a number of biomolecules, including peptides and proteins. If this interaction takes place during calcite crystal growth, biominerals of remarkable mechanical properties may be formed [1]. These types of minerals have a wide variety of applications in drug delivery systems, oil reservoirs and CO2 storage.

In this study we benchmark the interactions of protected and zwitterionic amino acids with the stable (104) surface of calcite using two different classical force fields [2,3]. Our methodology encompasses fully atomistic molecular dynamics simulations in combination with umbrella sampling. We find that the zwitterionic forms of amino acids generally bind better to the surface. Presence of polar groups or charged groups in side chains and compactness of amino acids also leads to more significant binding.

We apply the same methodology to the unstable (001) surface of calcite exhibited during the nucleation process, description of which is less unique. In the representation of our choice we show that the presence of either negative or positive charged group in the peptide is necessary for binding to this surface.

These results provide a force field benchmark and reference data on binding energies and conformations of specific amino acids which could help interpret the experimental data on peptide and protein mediated calcite functionalization and growth.

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Organizing 3D Project Data for Structure-Based Drug Design

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It is often desirable to organize disparate crystallographic project data into a common homogeneous format, ready to use for modelling. We present a web-based application that permits users to specify numerous options controlling superposition and alignment of structures in a family or project, ligand specification, and whether electron densities or other grids are to be included. The final result is a project database containing superposed structures all in the same frame of reference. From here, structures can be dynamical regrouped, for example by scaffold class, for easy management, and can be easily browsed and used as a starting point for further research. The system is able to handle multi-subunit complexes, including structures which may be missing subunits, by using a novel algorithm to determine which subunits of each complex correspond to each other.

Specific applications of the output database files include family-based homology modeling, which benefit from a highly enriched source for templates and loop conformations; and family-specific searching and further filtering of structures.

Dynamic regulation of Ca^{2+} binding to Langerin carbohydrate recognition domain by an allosteric network

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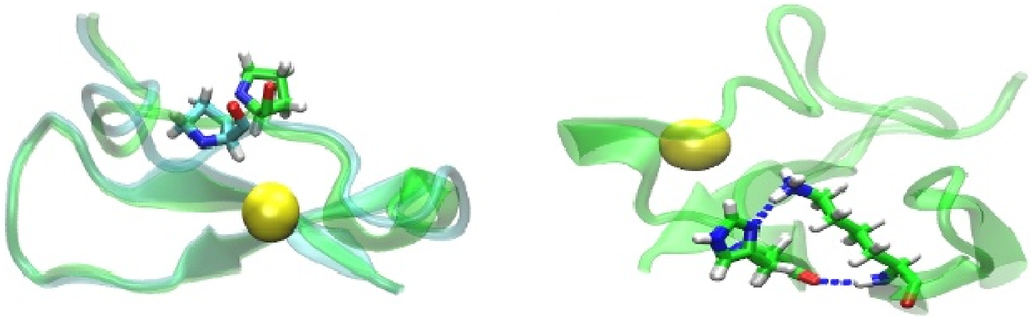

C-type lectin Langerin is a receptor of mucosal dendritic cells expressed as a trimer. Langerin facilitates endocytotic uptake of HIV viral particles through glycan recognition and in a Ca^{2+} dependent fashion. Endosomal Ca^{2+} channels open to reduce the effective concentration of Ca^{2+}, resulting in release of the cargo in endosome. The loss of Ca^{2+} ion causes a change of the conformational dynamics of Langerin. [1] We present a study on the Ca^{2+} binding to the Langerin carbohydrate recognition domain (CRD) investigated by NMR and all atom Molecular Dynamics (MD) simulations.

Residue P286 in Ca^{2+} binding loop undergoes slow cis/trans isomerization to accommodate the Ca^{2+} ion. Ca^{2+} binds only to the cis-P286 form of Langerin CRD. Chemical shift pertubation data suggested the existence of an allosteric network upon binding of the Ca^{2+} ion. We investigated the possibility of inter-residue communication in Langerin CRD by employing mutual information (MI) theory, and we confirmed, that the allosteric network existed. The hub residues of the allosteric network were mutated, and NMR data on the mutants showed the robustness of the allosteric network. H294 is an important residue, that couples the movement between the Ca^{2+} binding site, and β2-β2' loop (the region of the highest backbone flexibility). It establishes two hydrogen bonds with K257 of β2-β2' loop. H294A mutant has greater affinity towards Ca^{2+} ion compared to wild type Langerin. We also observed the decoupling in the movement of two loops in this mutant. Though, the allosteric network was still present. H294 was partially protonated in the acidic environment of the endosome, and lacked the hydrogen bond with the sidechain of K257.

In conclusion, the role of the allosteric network comprises cis/trans isomerization of P286 residue (tremendous conformational change in the binding pocket), and coupling of the movement between Ca^{2+} binding site, and β2-β2' loop.

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From Substrate Specificity to Small Molecule Specificity

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We present a way to use the rapidly growing amount of knowledge about protease peptide substrates as basis for a new virtual screening approach. We use the information on the specificity of the proteases and the physico-chemical features of the protease peptide substrates to find small molecule inhibitors. Modern database technology allows for easy access and sharing of the collected data on protease specificity and characteristics. The MEROPS database represents the biggest collection of known protease peptide substrates and is constantly improved and updated. The method represents a rapid and straightforward way of putting the MEROPS data on protease substrates to use for finding new small molecule inhibitors. We downloaded the peptide substrate sequences from the MEROPS database and used 3-4 substrate positions of each substrate to build the training set. Conversion of the 2D substrate sequences to 3D structures was carried out by mutating the residues in a template peptide for the corresponding protease taken from an X-ray structure of the protease-peptide complex. Considering the relative frequencies of substrate features, queries were created in ROCS. We show that the shape-based virtual screening gives good performance for four proteases, thrombin, factor Xa (fXa), factor VIIa (fVIIa) and caspase-3 (casp-3) with the DUD and DUD-E dataset. Thus, the method works for proteases with different specificity profiles as well as with different active site mechanisms and therefore should be applicable to any kind of protease.

1

Design and Molecular Modeling of D_2R/NTS_1R Heterodimer-Selective Ligands

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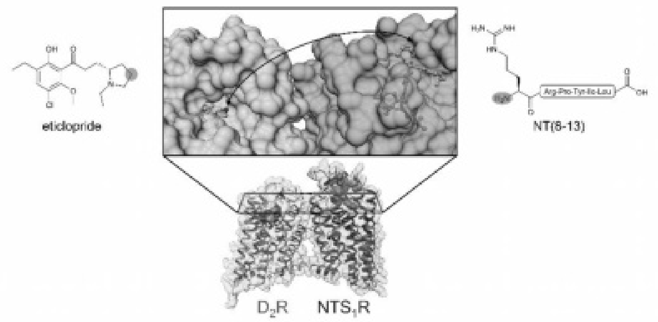
Dopamine D_2 receptors (D_2Rs) regulate a large number of physiological functions and are involved in a number of neuropsychiatric disorders including schizophrenia and Parkinson's disease. Along with numerous other GPCRs, dopamine D_2Rs have been proven to form both homodimers [1] and heterodimers [2]. Among receptors interacting with D_2Rs in the CNS, the neurotensin receptor subtype 1 (NTS_1R) has gained substantial interest. Both GPCRs are closely associated and highly co-localized in vivo [3].

A powerful tool to address GPCR dimers are bivalent ligands bridging the two neighbored orthosteric binding sites, of which the design can be quite challenging. However, high resolution crystal structures of GPCRs revealing a dimeric orientation opened new opportunities to design bivalent ligands in a rational way.



We made use of the crystal structure of the β_1-adrenergic receptor [4] and build a D_2R/NTS_1 heterodimer model, with the dimer protomers based on a D_2R homology model (based on D_3R [5]) and a crystal structures of NTS_1R [6]. The crystal structure revealed a dimer interface involving transmembrane helix 1 (TM1), TM2 and helix 8. The dimer model could be used to select linker attachment points for both D_2R and NTS_1R pharmacophores as well as to determine suitable linker lengths. Molecular dynamics simulations with 3 representative ligands, performed to validate ligand design, showed stable receptor-ligand complexes supplying a good basis for further experimental evaluation.

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Molecular recognition in bitter taste GPCRs

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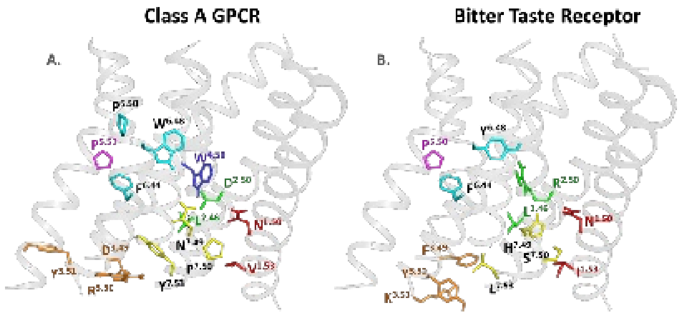

Bitter taste is one of the basic taste modalities and is typically considered as anti-ingestive signal against poison consumption. Bitter taste perception is mediated by bitter taste receptors (T2Rs), a subfamily of G-protein coupled receptors (GPCRs). [1] Recently T2Rs were shown to be expressed extraorally, emerging as potential novel drug targets, and a better understanding of molecular recognition of bitter compounds may be helpful not only for rational design of functional foods but also to discover novel drugs.

In this talk, I will present our research on exploring T2R molecular recognition and activation mechanisms using computational approaches. Integrating structure modeling and docking simulations with experimental mutagenesis studies, we found that the ligand binding pocket of T2Rs coincides with the canonical binding site of GPCRs. [1, 2] However, T2Rs similarity to Class A GPCRs is very low (13-29% for the TM domains) and this difference can be noticed not only in the binding site composition, but also in the regions of some typical Class A sequence motifs (shown above), such as the TM3 D[E]RY and the ECL2-TM3 disulfide bridge. [3] Since most of the conserved motifs are involved in GPCR activation mechanism, the differences in conserved residues suggest an alternative mode of regulating conformational states, with possibly a less stabilized inactive state for T2Rs compared to Class A GPCRs. Moreover, most of the known bitter ligands are agonists, with only a few antagonists documented thus far. The agonist-to-antagonist ratios of GPCRs are much lower than for T2Rs. We have previously found that GPCR promiscuity towards antagonists correlates with binding site exposure and hydrophobicity, [4] and similar features were also found to underlie the promiscuity of T2Rs towards their agonists. [5] Our findings show that, while promiscuity towards ligands is a general GPCR feature, T2Rs are unique in terms of their high agonist-to-antagonist ratio and overall low affinity towards ligands. [3] These characteristics may be related to the T2R sequence and structural motifs, but require further investigation.

Lady Davis Fellowship to ADP is gratefully acknowledged.

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Organic crystal structure prediction – from fundamental research to industrial application

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Crystal structure prediction is the task of deriving the observable three-dimensional crystal structures of organic molecules from their chemical structure alone. Prediction methods face the mathematical challenge of sampling a search space that grows exponentially with the number of degrees of freedom and the physical challenge of calculating lattice free energy differences with an accuracy that should be better than the order of magnitude of typical lattice energy differences between polymorphs.

The state-of-the-art was assessed by a series of blind tests in 1999, 2001, 2004, 2007, 2010 and 2015. In the last three blind tests, the highest success rate was scored with an approach implemented in the computer program GRACE. Dispersion-corrected density functional theory (DFT-D) calculations [1] are used to first generate reference data to which a tailor-made force field is fitted from scratch [2] for every chemical compound under consideration. The tailor-made force field is then used in conjunction with a Monte Carlo parallel tempering algorithm to generate crystal structures that are further optimized at DFT-D level. Statistical control mechanisms ensure that all crystal structures in a user-defined target energy window are found with a user-defined level of confidence.

The 2015 blind test [3] has demonstrated the ability of GRACE to perform crystal structure predictions using fully automated workflows, to handle two flexible molecules per asymmetric unit and to predict the crystal structure of the hydrate of a chloride salt.

Looking back on a dozen case studies published on drug-like molecules by various authors and an equal number of confidential studies with GRACE, a picture emerges how crystal structure prediction in an industrial working environment helps to rationalize crystallization behaviour, to understand solid-state forms, to solve crystal structures and to flag missing more stable forms. The emerging ability to find new crystal forms by rational crystallization experiment design based on the knowledge of the computed crystal energy landscape is illustrated by the example of Dalcetrapib [4].

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Charge transport in organic materials: Calculation of mobilities in polyacene single crystals

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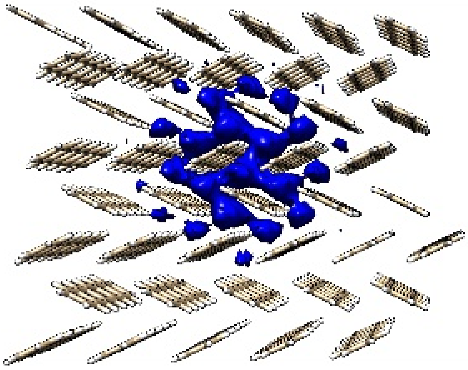
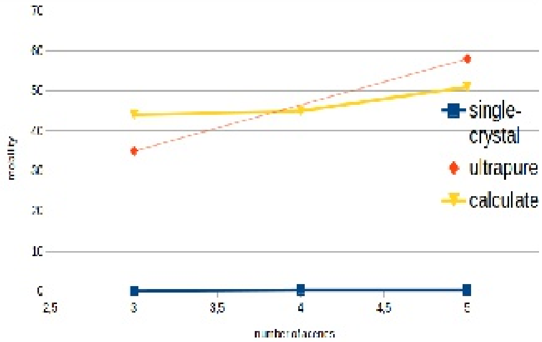
The local molecular properties, local electron affinity[1,2] and local ionization energy[3] can be understand as scalar potentials embedded in 3-dimensional space which represents the interaction of charge carriers with a complicated quantum mechanical system. It is possible to perform quantum dynamics of an electron or hole using these energy maps as external potentials in the Hamiltonian operator. The crux is that this approach drastically reduces the number of entities that need dynamic treatment drastically and reveal information about conduction characteristics.



Hole in pentacene crystal (isovalue 0.00005)



values taken from [5],[6],[7],[8],[9]

We have performed periodic molecular-orbital calculations of polyacene single crystal structures of anthracene, tetracene and pentacene with the massively parallel program "EMPIRE"[4] based on experimental geometries. The orbitals and their energies are generated with NDDO-based semiempirical MO-theory to produce local electron affinities and ionization energies. With a linear term added to the Hamiltonian to represent a homogeneous field, imaginary time propagation of an excess charge carrier is simulated by stepwise matrix multiplication. Mobility values of different structures are calculated by the shift of the location expectation value. Compared to experimental data of mobilities on anthracene, tetracene and pentacene single crystals, we calculated a mobility of tetracene an order of magnitude higher ~44 $cm^2V^{-1}s^{-1}$. We thus propose a theoretically attainable hole mobility of tetracene at least an order of magnitude higher than the current experimental value. The higher mobility is consistent with those found experimentally in the other acene crystals. The low experimental value found for tetracene is likely caused by impurities in the crystal.

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Atomistic modeling of hybrid polymers

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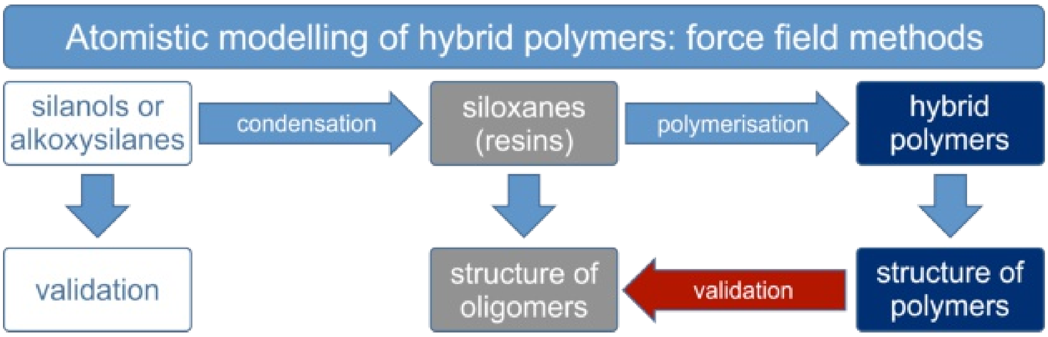
Hybrid polymers are a special class of hybrid materials, not only combining inorganic and organic compounds on a molecular scale, but joining inorganic and organic polymer structures covalently bonded to each other. They are synthesized in a two-step process from silanol and alkoxysilane precursors containing polymerizable functionalities: First, a polycondensation leads to the so-called resin, containing siloxane oligomers. These oligomers are subsequently polymerized, initiated thermally or photochemically, to form the hybrid polymer.

These materials are highly versatile, offering many possible technical or biomedical applications [1]. Except for first basic atomistic modeling studies [2,3], the atomistic structure of the resin or the final hybrid polymer remains often unknown – mainly because the materials are not well defined on a molecular scale and experimental data is very difficult to obtain. Some knowledge on the oligomer structure in the resin can be obtained by ^{29}Si-NMR spectroscopy, while the degree of conversion in the polymerization reaction can be determined by Raman spectroscopy.



The vast amount of possible oligomeric species and their large size limit the simulations on an atomistic scale to force field methods. However, Monte Carlo and Molecular Dynamics methods can be applied for model generation and investigations on material properties at ambient conditions.

Over the last years, we developed strategies and methods to perform force field modeling studies on these complex materials, a general approach is shown in the flow-chart above. The materials investigated differ in the number and type of precursors utilized, but follow the described two-step procedure. Depending on the number of different oligomeric species, we present alternative strategies to handle the process of model generation. They all have in common the large number of models to be considered. The structure of the polymer – and in particular the shrinkage behavior – allows to draw conclusions on the resin models evaluated.

We chose to design our simulations and strategies to be employable at comparably low computational cost, making the strategies presented available to many modeling scientists and even experimental scientists without access to large cluster systems.

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Trading off stability against activity in extremophilic aldolases

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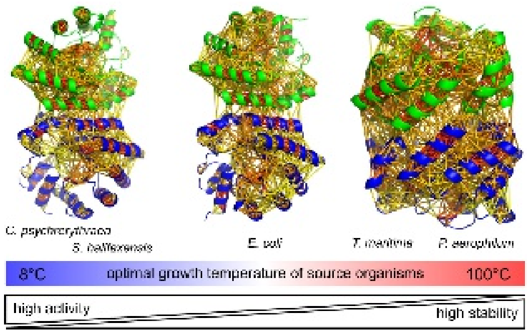
Understanding what determines thermostability and activity of enzymes has always been an important issue. To investigate factors that describe the relationship between stability and flexibility, we performed comparative studies with variants from psychrophilic (cold loving), mesophilic and hyperthermophilic organisms. As model enzymes we are investigating acetaldehyde dependent aldolases, specifically 2-deoxy-D-ribose-5-phosphate aldolases (DERAs), which have a high potential as biocatalysts: they form chiral building blocks for organic synthesis *via* a highly selective aldol reaction.[1]

Using X-ray crystallography and rational enzyme design, supported by computational methods in terms of contraint network analysis (CNA),[2] we were able to identify hot spot positions in the dimeric interface responsible for the high heat tolerance in hyperthermophilic DERAs.[3] With this knowledge at hand, we have successfully implemented these stabilisation factors into psychrophilic DERAs, resulting in increased thermostability. Furthermore, CNA revealed particularly sparse interactions between the substrate pocket and its surrounding α-helices in psychrophilic DERAs, which indicates that a more flexible active centre underlies their high turnover numbers.[3]



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Quantum chemical methods help unravel effects of pH on marine communication

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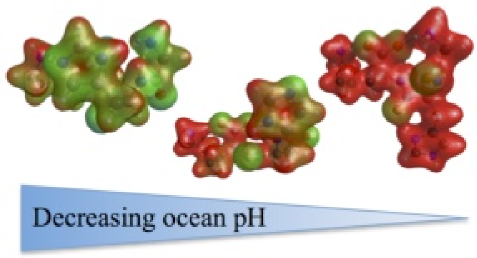
Marine organisms use a large variety of small chemical compounds to communicate. These signalling molecules are used, for example, to detect predators, find mating partners, locate the best place to settle or the next meal. Increasing amounts of atmospheric CO_2 that dissolve into the oceans cause a drop of ocean pH. This process called ocean acidification is known to affect the physiology and fitness of organisms. Lately it has also been reported to affect numerous animal behaviours that are mediated by chemical signalling cues. However, little is known about the underlying mechanisms, especially in invertebrates.

We investigate the molecular effects of decreasing ocean pH on the structure and function of peptide signalling cues as one potential mechanism to explain altered animal behaviour in high CO_2 conditions. This requires a multi-disciplinary approach including NMR spectroscopy to determine the peptide cues' susceptibility to protonation and quantum chemical calculations to explore the differences in conformation and charge distribution of the relevant protonation states. Here we present first results of our structural molecular investigation and highlight the quantum chemical methods required to successfully model molecular conformation and molecular electrostatic potential in solution.



Mimicking titration experiments with MD simulations: A protocol for the investigation of pH-dependent effects on proteins

Eileen Socher, Heinrich Sticht

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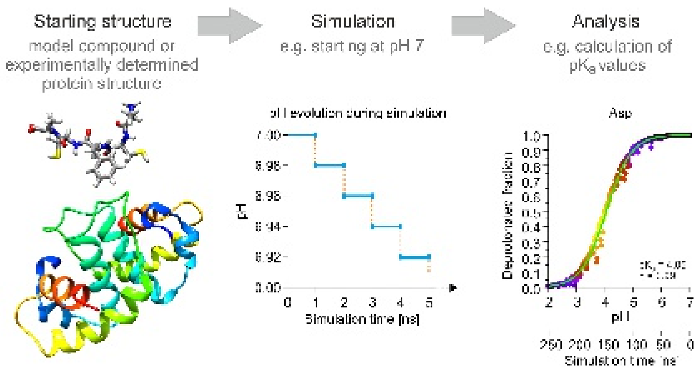
Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany

Protein structure and function are highly dependent on the environmental pH. However, the temporal or spatial resolution of experimental approaches hampers direct observation of pH-induced conformational changes at the atomic level. Molecular dynamics (MD) simulation strategies (e.g. constant pH MD) have been developed to bridge this gap. However, one frequent problem is the sampling of unrealistic conformations, which may also lead to poor pK_a predictions. To address this problem, we have developed and benchmarked the pH-titration MD (pHtMD) approach, which is inspired by wet-lab titration experiments. We give several examples how the pHtMD protocol can be applied for pK_a calculation including peptide systems, Staphylococcus nuclease (SNase), and the chaperone HdeA. For HdeA, pHtMD is also capable of monitoring pH-dependent dimer dissociation in accordance with experiments.



We conclude that pHtMD represents a versatile tool for pK_a value calculation and simulation of pH-dependent effects in proteins [1].

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Structural modeling of EDTA aggregates that lead to artifacts in a fluorescence-based biophysical assay

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Differential scanning fluorimetry (or thermofluor assay (TA)) is a fast and cost efficient approach to investigate the melting point of purified proteins or protein complexes [1]. The assay is based on a fluorescent dye, Sypro Orange, that interacts with hydrophobic residues becoming available when a protein unfolds with increasing temperature. However, we observed a fluorescence signal also in the presence of EDTA at high pH even if no protein is present, leading to an artifact in TA. Here, we used a combined experimental and computational approach to investigate the origin of this artifact.

Our experimental approach revealed an EDTA concentration-dependent effect, where the EC_{50} = 36.3 mM is within the range of concentrations practically applied. Furthermore, the artifact emerges at pH > 9, indicating that the $EDTA^{4-}$ sup-population of EDTA causes the fluorescence signal. This signal is also observed in the presence of EGTA. For both EDTA and EGTA, the fluorescence signal can be quenched by adding Ca^{2+} ions (EC_{50}= 100 mM).

In molecular dynamics simulations of free diffusion of EDTA-Na^{+} and Sypro Orange of in total 27 μs length, we observe an aggregation of the $EDTA^{4-}$ molecules that leads to the formation of an inverted bilayer. While the observed aggregation of EDTA is in agreement with previous experimental studies [2], our results for the first time provide a structural model at the atomic level. The results are independent of the applied force field parameters for ions.

In all, we provide evidence that suggests that $EDTA^{4-}$, but not $EDTA^{3-}$, at basic, yet physiologically relevant pH, forms aggregates that interact with Sypro Orange, which can lead to a fluorescence signal in TA. As EDTA is widely used in the fields of biology and pharmacy, e.g. for investigating proteins with a calcium-dependent activity and structure [2], these results are highly relevant for future applications of TA.

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Markov State Models with reweighting

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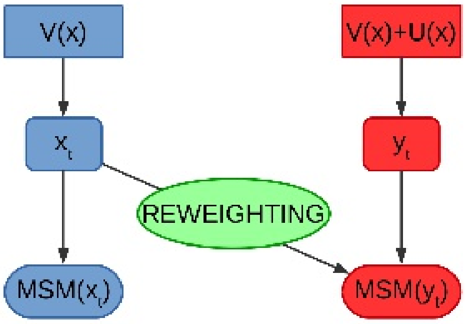

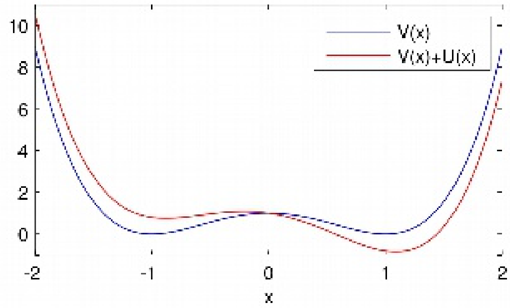

Molecular Dynamics (MD) is characterized by metastable states and transitions that occur at different timescales. Recent studies [1] have proven, through Markov State Models (MSM) analysis, that the timescales are very sensitive on the potential energy function of the molecule and that different force fields of the same molecular system show different dynamic properties. This result suggests the need to improve the current force fields analyzing the effects caused by parameters variation. To address this issue, it would be necessary to produce a MD trajectory and to construct the respective MSM, for each parameter set. This approach is computationally expensive and requires the development of a validation method that acts directly on the MSM.

Taking a force field as reference, each parameter variation can be considered as an external perturbation of the potential energy function. Because the potential energy perturbation affects the stationary distribution of the system, we can exploit the Girsanov theorem [2] to reweight the dynamics and to rewrite the transition probability matrix of the original MSM in terms of the new stationary distribution [3]. The method can be used to predict the timescales of a molecular system in a perturbed potential energy function without rerunning molecular dynamics simulation and could be relevant to force field optimization.

We performed tests of one-dimensional diffusive processes verifying the limits of applicability of the method. Then we have tested many-body systems in three-dimensional space, formulating an extension of the method when the MSM is constructed on a conformational space not directly perturbed. We present also preliminary results for alanine dipeptide and a benchmark test that shows the efficiency of the method.

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How different are nanobody-stabilized GPCR structures from their G-protein-stabilized equivalents?

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The G-protein coupled receptor (GPCR) family constitutes the majority of drug targets.[1] Despite the diversity of their biological roles, GPCRs adapt the same structural architecture of seven transmembrane (TM) helices[2] and signal mainly through coupling to hetreotrimeric G-proteins.[3,4] However, G-proteins are extremely sensitive to detergents, pH and nucleotides, which are often needed to crystallize GPCRs for X-ray crystallography.[5] Nanobodies represent a successful alternative to G-proteins in stabilizing active-state GPCRs.[5,6] Their importance in GPCR structural biology is emphasized by their role in crystallization of all but one of the stabilized active-state, Class A rhodopsin, GPCRs.[7-9] Extensive molecular-dynamics simulations including metadynamics enhanced sampling were used to compare the effect of these nanobodies on the binding modes of the co-crystalized agonists and the organization of the binding pocket of the three nanobody-stabilized GPCR's crystals structures with the G-protein complexes. Our results show ligand-specific changes that can alter the agonist binding modes.

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A Diverse Test Set for the Validation of Scoring Functions based on Matched Molecular Pairs

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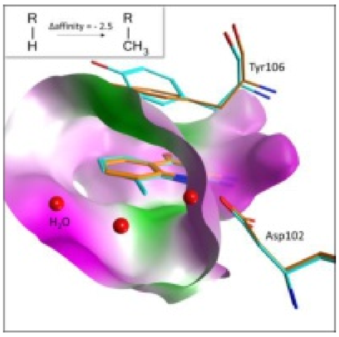

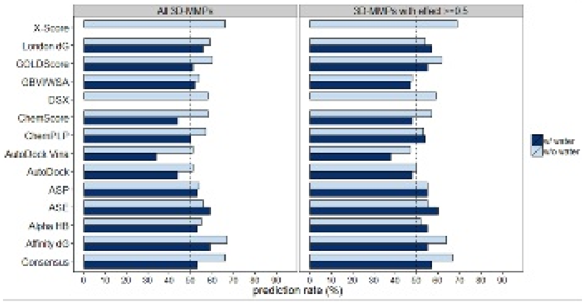

In structure-based drug design the prediction of protein-ligand interactions and their contribution to the binding free energy is a challenging task. Scoring function evaluation has shown that docking already gives valuable results. However, the "scoring" problem is still a very ambiguous. Today, scoring functions are not able to precisely predict the binding free energy of protein-ligand complexes. In this study we established a diverse data set of 99 Matched Molecular Pairs (3D-MMPs). This data set was used to study the predictive power of scoring functions and to investigate their disadvantages. The 13 most commonly used scoring functions (i.a. MOE, GOLD, AutoDock 4.2) have been used to score and evaluate the binding free energy predictive capability. None of the scoring functions reached a satisfactory result in our evaluation. Only two scoring functions reached a prediction rate of more than 60% in the prediction of the trend of a transformation effect. By analyzing the correlation between the score and the molecule size we could show that in 67% the affinity increases when the size of the molecules increases. Most of the scoring functions themselves correlate more with the changes in molecule size than with the changes in binding affinity.

Multireference Methods in Organic Electronics and Photonics

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The computational problems that typically arise in organic electronics are the problems of light absorption and emission, charge separation and recombination, and charge transport. These problems are usually addressed with the relatively cheap and fast density functional theory, which allows for large-scale calculations. However, this approach has intrinsic deficiencies that lead to qualitatively wrong results. Among these are overestimation of charge delocalization in extended molecular systems, underestimation of the energy of charge-transfer states, and different errors in the energies of singlet and triplet states, which lead to wrong transition probabilities of nonradiative processes.

Multireference methods, such as CASSCF/XMCQDPT, provide qualitatively correct and accurate description of the processes of interest. In particular, they correctly describe charge and exciton localization in extended systems through including the states with different localization with equal weights. They also provide balanced treatment of states of different multiplicity and different orbital character. Therefore, multireference methods give deeper insight into the nature of the systems under study. Understanding the mechanism of the target process will help one to find simple molecular descriptors that can be calculated by cheap methods in large scale.

We outline the problems in which multireference treatment is necessary, give some basics of the CASSCF and XMCQDPT methods, and demonstrate the application of multireference computational methods to the problems of light emission, charge and energy transfer, and chemical stability of typical OLED materials.

This work was supported by Russian Science Foundation (project № 14-43-00052).

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Trying to Understand the Modulation in the Activity of the DNA Intercalating Anticancer Drugs: The Importance of CH/π Interactions

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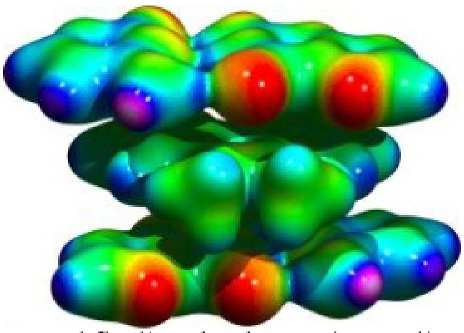

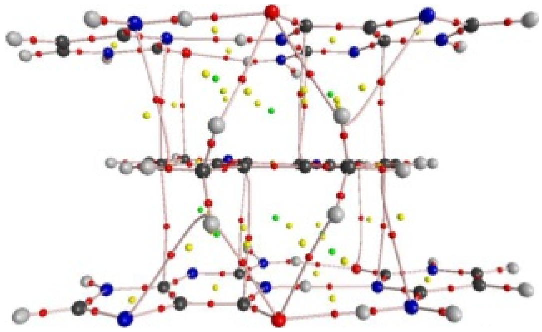

Several flat ligands, alone or in coordination complexes (CCs), are active against tumor cells and can be used in chemotherapy.[1] Such activity is related to their mode of interaction with DNA and intercalation is a binding mode associated to cytotoxicity towards tumor cells.[1,2] Phenanthroline (phen) proved to be effective against different tumor cell lines,[3] and methylated phen derivatives also exhibited cytotoxicity, which was found to be deeply connected to the number and position of $-CH_3$ groups.[2] Several works addressing the intercalation of small molecules in DNA have appeared recently in the literature [4,5] and there is still some debate about the intercalation/deintercalation process [4-7] and the mechanism that could explain the tuning of cytotoxicity. We tried to rationalize the intrinsic forces and substitution patterns ruling the intercalation to get some insight on the relation with cytotoxicity by means of DFT methods including dispersion, models consisting on the intercalator and four DNA bases, Energy Decomposition Analysis (EDA) and Atoms in Molecules (AIM) analysis. The results given by the AIM analysis confirm the existence of CH/π interactions and the Energy Decomposition Analysis shows a perfect direct correlation between the increasing number of CH/π interactions found in the studied systems and the stabilization of ΔE_{Int}. This finding is fundamental to understand the connection between substitution in number and position and cytotoxicity. Moreover, despite the important role of dispersion energy in the systems with more methyl groups, dispersion cannot yet compensate the Pauli repulsion term, ΔE_{Pauli}. The role of attractive contributions, namely the orbital contribution, ΔE_{orb}, and the electrostatic contribution, ΔE_{elstat}, become crucial for the stabilization of the structures in the intercalation process.

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Activin Receptor Type IIA Protein Kinase Inhibitors: Free Energy Calculations and Ligand Binding

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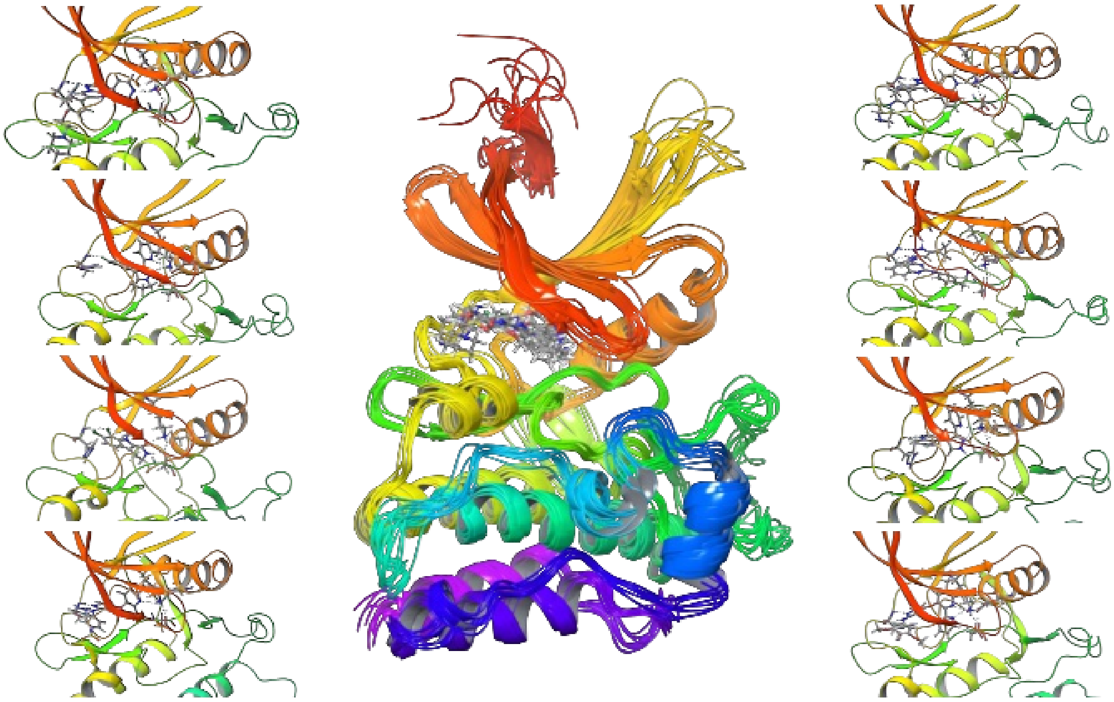

In the present research, we reviewed the use of Molecular Mechanics combined with Poisson-Boltzmann and Generalized Born Surface Area (MM-PB(GB)/SA), as well as the Linear Interaction Energy (LIE) method, for calculating ligand binding free energies. With an aim towards better understanding a variety of biological functions, including muscle growth and bone formation as well as viability and adhesion of prostatic epithelial cells, Dorsomorphin (K_D = 58 nM), LDN-193189 (K_D = 14 nM), and seven other ligands [1] were investigated as Activin Receptor Type IIA Protein Kinase (ActRIIA) [2] ATP-binding site inhibitors. Due to the lack of experimental structural information for the binding of these ligands, 10 ns Molecular Dynamics (MD) simulations in explicit water using Amber 14 software package were performed for each receptor-inhibitor complex.

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A metabolic code for signaling

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Proteins are typically classified by structural or sequence similarity, but many drugs disregard these associations and boundaries, exhibiting profound off-target activity and polypharmacology. From this activity emerges their side effects, but also often their therapeutic efficacy.

Here we ask whether we can use ligand polypharmacology to organize coherent pharmacologically related targets. Comparing ligand-based and sequence- and proteomic-organizations of proteins and signaling networks, we find drug targets that are often unrelated by biological metrics, but neighbors by ligand similarity. Because this method is articulated by specific molecules, it is readily tested, and on experiment we find several pairs of unrelated targets that can be modulated with a single small molecule ligand, with potencies ranging from nanomolar to micromolar. Ligand similarities among these targets reflect the conservation of identical signaling molecules among sequence-unrelated receptors, which often respond in different time domains to an identical chemical signal. The evolutionary origins of this polypharmacology of endogenous signaling molecules, and the drugs that imitate them, is considered, as are applications to the discovery of new signaling networks and of therapeutics with designed and specific polypharmacology.

OPLS3 - Recent developments in the OPLS force field

Thomas Steinbrecher, Rita Podzuna

Schrödinger GmbH

We report the parameterization and validation of the new small molecule and protein force field OPLS3, a significant enhancement with respect to the previous version (OPLS2.1). OPLS3 includes off-center charge sites to better represent halogen bonding and heteroatom lone pairs as well as a complete refit of peptide dihedral parameters to high-level QM data to improve protein structure modeling.

To adequately cover medicinal chemical space, OPLS3 employs over an order of magnitude more reference data and associated parameter types relative to other commonly used small molecule force fields (eg. MMFF and OPLS_2005). We show that a high level of accuracy is achieved in describing small molecule conformational and solvation properties. The newly fitted peptide dihedrals, lead to significant improvements in the representation of secondary structure elements in simulated peptides and native structure stability over a number of proteins.

In a first practical application of the new force field, we show that protein-ligand binding affinities from MD-based free energy calculations are significantly more accurate over a wide range of targets and ligands (less than 1 kcal/mol RMS error) for OPLS3 representing a 30% improvement over earlier variants of the OPLS force field.

Semiempirical MO-Theory for Large Systems

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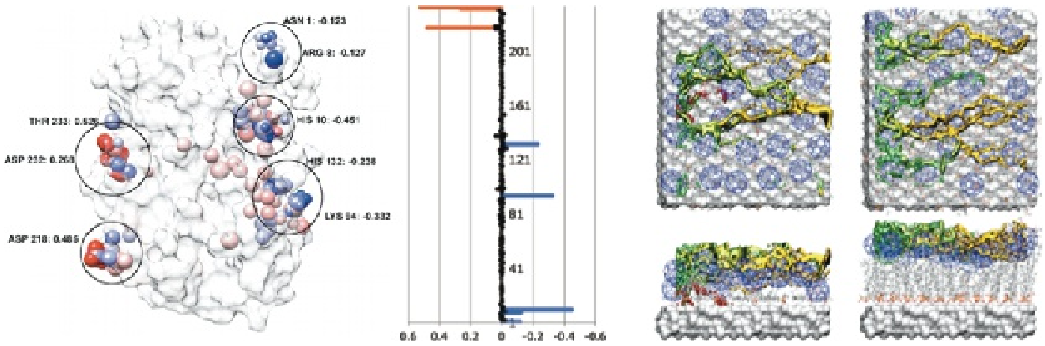

We present a comparison of conventional semiempirical wavefunction based MNDO-like methods and approximate linear-scaling methods for large molecules. Until recently, linear-scaling methods such as divide and conquer (D&C) [1] or localized-molecular-orbital (LMO) [2] techniques were essential for the treatment of large systems by means of semiempirical MO theory. However, conventional full SCF calculations based on a massively parallel code (EMPIRE [3]) now allow very large systems to be treated without local approximations. The comparison revealed a very slow SCF convergence for gas-phase calculations on zwitterionic proteins using a full SCF routine, whereas LMO SCF converges rapidly. Further comparative calculations with both techniques showed that the very slow inductive charge-transfer process that made the conventional SCF calculations so slow to converge is prevented in the LMO-SCF scheme. Therefore, the LMO procedure can lead to artificially over-polarized wavefunctions in gas-phase calculations. Example molecules have been constructed to demonstrate this behavior.[4] Further, recent applications of semiempirical MO-theory in the field of Self-Assembled Monolayer Field-Effect Transistors (SAMFETs) are presented.[5–7]

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From Substrate Specificity to Small Molecule Specificity

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We present a way to use the rapidly growing amount of knowledge about protease peptide substrates as basis for a new virtual screening approach. We use the information on the specificity of the proteases and the physico-chemical features of the protease peptide substrates to find small molecule inhibitors. Modern database technology allows for easy access and sharing of the collected data on protease specificity and characteristics. The MEROPS database represents the biggest collection of known protease peptide substrates and is constantly improved and updated. The method represents a rapid and straightforward way of putting the MEROPS data on protease substrates to use for finding new small molecule inhibitors. We downloaded the peptide substrate sequences from the MEROPS database and used 3-4 substrate positions of each substrate to build the training set. Conversion of the 2D substrate sequences to 3D structures was carried out by mutating the residues in a template peptide for the corresponding protease taken from an X-ray structure of the protease-peptide complex. Considering the relative frequencies of substrate features, queries were created in ROCS. We show that the shape-based virtual screening gives good performance for four proteases, thrombin, factor Xa (fXa), factor VIIa (fVIIa) and caspase-3 (casp-3) with the DUD and DUD-E dataset. Thus, the method works for proteases with different specificity profiles as well as with different active site mechanisms and therefore should be applicable to any kind of protease.

1

Dynamic regulation of Ca^{2+} binding to Langerin carbohydrate recognition domain by an allosteric network

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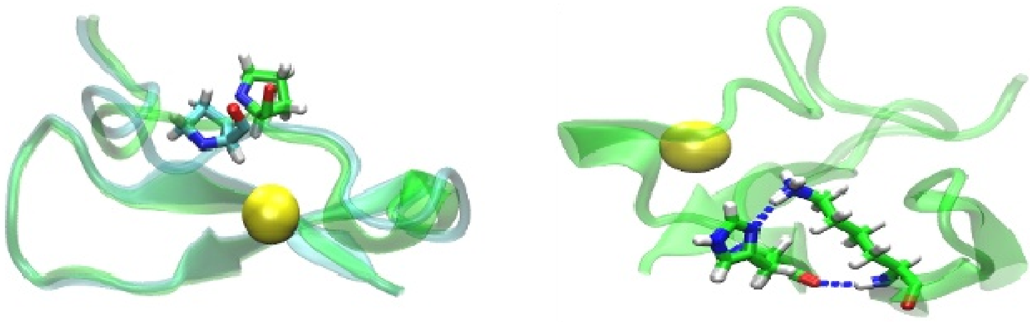

C-type lectin Langerin is a receptor of mucosal dendritic cells expressed as a trimer. Langerin facilitates endocytotic uptake of HIV viral particles through glycan recognition and in a Ca^{2+} dependent fashion. Endosomal Ca^{2+} channels open to reduce the effective concentration of Ca^{2+} , resulting in release of the cargo in endosome. The loss of Ca^{2+} ion causes a change of the conformational dynamics of Langerin. [1] We present a study on the Ca^{2+} binding to the Langerin carbohydrate recognition domain (CRD) investigated by NMR and all atom Molecular Dynamics (MD) simulations.

Residue P286 in Ca^{2+} binding loop undergoes slow cis/trans isomerization to accommodate the Ca^{2+} ion. Ca^{2+} binds only to the cis-P286 form of Langerin CRD. Chemical shift pertubation data suggested the existence of an allosteric network upon binding of the Ca^{2+} ion. We investigated the possibility of inter-residue communication in Langerin CRD by employing mutual information (MI) theory, and we confirmed, that the allosteric network existed. The hub residues of the allosteric network were mutated, and NMR data on the mutants showed the robustness of the allosteric network. H294 is an important residue, that couples the movement between the Ca^{2+} binding site, and β2-β2' loop (the region of the highest backbone flexibility). It establishes two hydrogen bonds with K257 of β2-β2' loop. H294A mutant has greater affinity towards Ca^{2+} ion compared to wild type Langerin. We also observed the decoupling in the movement of two loops in this mutant. Though, the allosteric network was still present. H294 was partially protonated in the acidic environment of the endosome, and lacked the hydrogen bond with the sidechain of K257.

In conclusion, the role of the allosteric network comprises cis/trans isomerization of P286 residue (tremendous conformational change in the binding pocket), and coupling of the movement between Ca^{2+} binding site, and β2-β2' loop.

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Human apo-myoglobin structural stability in the presence of ligands: a molecular dynamics study

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A protein's structure defines its interactions with other molecules. Indeed structure integrity is of high importance for a protein proper function. Environmental factors affecting proteins structure may lead to conformational disorders by causing functional changes. Thus, it is important to investigate factors that influence structure stability of proteins, particularly the proteins which play crucial roles in biological systems. Myoglobin (Mb), a globular metalloprotein, is noteworthy due to its role in oxygen transport in muscle cells which occurs through its heme prosthetic group. Influence of substitution of some small molecules such as Nile red instead of heme in different environmental conditions has been studied previously [1, 2].

In the present study, the 3-D x-ray crystallographic structure of human Mb with the PDB code of 3RGK has been used after applying required modifications [3]. Using docking methods, small molecules structurally similar to Nile red were replaced in the heme binding site of Mb. The systems were set in a periodic box and SPC water model was selected as the solvent. Next, molecular dynamics simulation (MDS) at 500K was performed on the structures with the use of GROMACS and the GROMOS96 53a6 force field. Analysis of the trajectories was made and RMSD, hydrophilic and hydrophobic areas, secondary structure (SS) percentages, and energies were extracted for each protein-ligand complex. Finally, ligands with high overall rank were selected according to a decision matrix incorporating these parameters. Pharmacophore features of these ligands may be used to seek for other more potent compounds.

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Performance of the COMPASS force field for inorganic-organic hybrid polymers

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Inorganic-organic hybrid polymers combine inorganic and organic polymer structures in one homogenous material. Their properties can be tuned for a wide range of specific demands. Therefore these materials are of huge commercial interest. Possible applications for hybrid polymers include coatings, filling materials for dental restoration and sophisticated optical materials [1].

These hybrid polymers are synthesized in a two-step procedure, a polycondensation of the precursors – usually alkoxysilanes and/or silanols – and a subsequent polymerization of organic functionalities which are covalently bonded to the precursors. The polymerization can be initiated by two-photon absorption processes, which allows to obtain tunable microstructures with feature sizes in the 100 nm range [2,3].

Experimental results on the atomistic structures of these materials are rare, but first molecular modeling studies give a first insight [3,4]. However, extensive validation calculations are necessary to ensure proper description of the materials with a sophisticated class II force field. Until now, no validation of the thermal influence during molecular dynamics has been published.

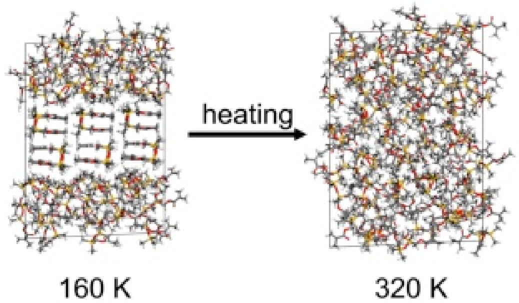

Fig. 1

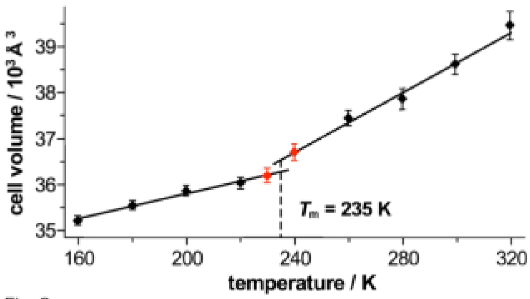

Fig. 2

The validation of the COMPASS force field [5] is performed to demonstrate the suitability of this force field for the simulation of inorganic-organic hybrid polymers. In particular, bond lengths, valence angles, and vibrational frequencies are compared for molecular structures of precursors and a small oligomer of the condensation product. The comparison with crystalline structures shows very good agreement for cell constants, symmetry, and overall structure agreement.

As the materials are usually used and evaluated under ambient conditions, their behavior during molecular dynamics is evaluated. It is shown, that densities at ambient conditions can be reproduced precisely for crystalline solids and amorphous liquids exhibiting only very small deviations. This is used for the prediction of glass transitions and melting temperatures of a small oligomer: Fig.1 shows the partially crystalline structure which is heated stepwise for the prediction of the melting temperature [6]. The resulting cell volume is depicted in Fig. 2. The melting temperature is found to be 235 K, which matches the experimental value of 238 K.

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DNA-Dye-Conjugates: Conformations and Spectra of Fluorescence Probes

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

Biomineralization and Biomineralization-Inspired Drug Design: Calcite - Peptide Interactions

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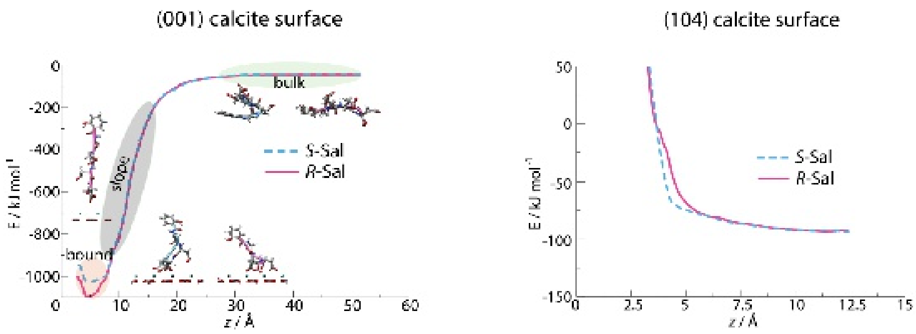
The field of interface chemistry has been heavily focused in recent years on the development of systems that could be used for the controlled introduction and release of active pharmaceutical compounds in the living organisms and tissues. Some of the most interesting systems in this respect, attracting interest from both the pharmaceutical and food industry, are the bioinorganic composites of calcite (calcium carbonate, $CaCO_3$) functionalized by small, biologically active molecules, with the aim of controlled drug delivery. [1] In this respect, we decided to investigate the interactions of calcite with two highly active biomolecules, which are experimentally found to strongly interact with the biomineral, [2] in an attempt to uncover the roles of flexibility and chirality in biomineralization and biomineralization-inspired drug design.



More precisely, using advanced simulation techniques we characterized the adsorption behavior of two epimeric peptides, namely *R*- and *S*-Sal (N-Sal-Gly-*S*-Asp-*R*-Asp-*S*-Asp and N-Sal-Gly-*S*-Asp-*S*-Asp-*S*-Asp respectively, where N-Sal denotes the N-terminal residue which is a salicylic acid derivative), on both the stabile (104) and growing (001) surfaces of calcite. This, on one hand, allowed us to analyze the conformational behavior of the adsorbed peptides in detail, while, on the other hand, permitted us to investigate the underlying thermodynamics of the process by calculating free energy profiles of adsorption. We thereby found that even small differences, such as the change in the chirality of only one constituent amino acid, can change the conformational behavior of the peptide to an extent significant enough to induce different binding patterns and interactions on mineral surfaces, leading to an overall different adsorption of active biomolecules/peptides.

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

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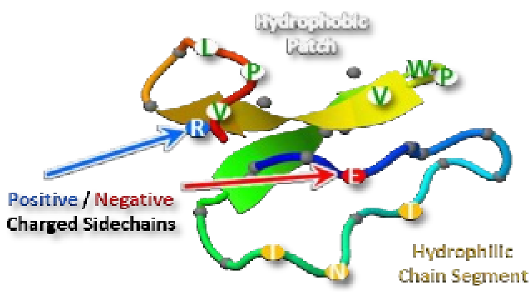
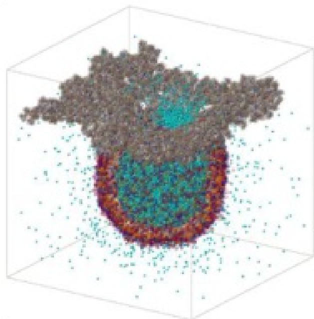
Dissipative Particle Dynamics (DPD) is an established simulation technique to study condensed matter systems on mesoscopic scales. Whereas its coarse-grained interacting units (beads) may not necessarily be identified with distinct chemical compounds at all, the DPD variant Molecular Fragment Dynamics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





Recent studies with the MFD technique demonstrate the membrane disrupting activity of the cyclotide Kalata B1 (left figure), a 29 amino acid self-defense associated peptide expressed in plants [2]. This work aims at establishing better test systems for membrane pore formation due to Kalata B1 activity like a 30 nm 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC) bilayer vesicle filled with water molecules (right figure). The effects of single and multiple amino acid replacements within Kalata B1 on membrane pore formation are compared to experimental results and may finally be utilized to predict the bioactivity profiles of specifically mutated cyclotids. These studies may support the understanding of pharmaceutical active peptides with cyclotide scaffold which are applied e.g. for anti-HIV treatment [3].

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[2] Truszkowski, A.; van den Broek, K.; Kuhn, H.; Zielesny, A.; Epple, M.: Mesoscopic Simulation of Phospholipid Membranes, Peptides and Proteins with Molecular Fragment Dynamics. *Journal of Chemical Information and Modeling* **2015**, 55: 983-997.
[3] Sangphukieo, A.; Nawae, W.; Laomettachit, T.; Supasitthimethee, U.; Ruengjitchatchawalya, M.: Computational design of hypothetical new peptides based on a cyclotide scaffold as HIV gp120 inhibitor. *PLoS One* **2015**;10: 1–15

Trading off stability against activity in extremophilic aldolases

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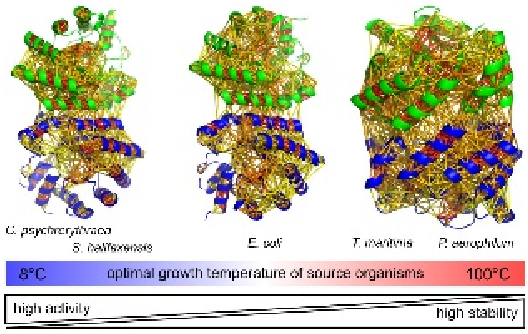
Understanding what determines thermostability and activity of enzymes has always been an important issue. To investigate factors that describe the relationship between stability and flexibility, we performed comparative studies with variants from psychrophilic (cold loving), mesophilic and hyperthermophilic organisms. As model enzymes we are investigating acetaldehyde dependent aldolases, specifically 2-deoxy-D-ribose-5-phosphate aldolases (DERAs), which have a high potential as biocatalysts: they form chiral building blocks for organic synthesis *via* a highly selective aldol reaction.[1]

Using X-ray crystallography and rational enzyme design, supported by computational methods in terms of contraint network analysis (CNA),[2] we were able to identify hot spot positions in the dimeric interface responsible for the high heat tolerance in hyperthermophilic DERAs.[3] With this knowledge at hand, we have successfully implemented these stabilisation factors into psychrophilic DERAs, resulting in increased thermostability. Furthermore, CNA revealed particularly sparse interactions between the substrate pocket and its surrounding α-helices in psychrophilic DERAs, which indicates that a more flexible active centre underlies their high turnover numbers.[3]



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[2] C. Pfleger, P. C. Rathi, D. Klein, S. Radestock, H. Gohlke, *J. Chem. Inf. Model.*, **2013**, *53*, 1007-1015.

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Design of Antibody-based Peptide Inhibitors to Disrupt Important Protein-Protein Interactions in HIV and HCMV

Benedikt Diewald, Heinrich Sticht

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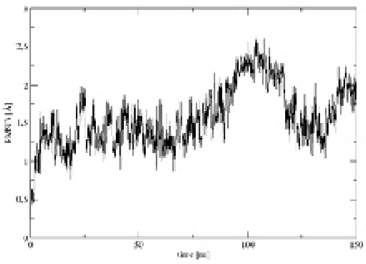

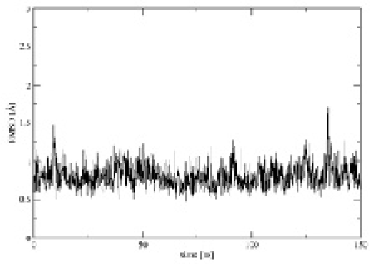

Over the last decades the versatility and quality of computational techniques, such as docking, high throughput virtual screening, and molecular dynamics (MD), as a tool in Drug Discovery and protein research have increased considerably. One promising approach on the development of new drugs is the computer supported design of peptides as protein binding site mimetics [1].

Some antibodies, such as anti-HIV antibody b12 [2] or anti-HCMV antibody SM5-1 [3] competitively bind to epitopes that are essential for the pathogens' entry into the cell, thus encumbering the infection. The complementarity determining regions (CDR) of these and several other antibodies were used as basis for the design of peptidic ligands to their respective antigens.

To ensure that these peptides retain the conformation they take up in the antibodies head-to-tail cyclization and disulfide bridges were utilized as stabilizing measures. The figure above illustrates the effectiveness of artificial disulfide bonds: The left plot shows the RMSD of CDR H3 of SM5-1 without any modifications, the right plot depicts the RMSD of a construct with disulfide bond.

By using those principals on several anti-HIV and anti-HCMV antibodies, and also introducing point mutations into the peptides, antigen binding ligands could be discovered. However, in order to create peptides rivaling the antibodies' binding affinity further refinement is necessary.

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Markov State Models with reweighting

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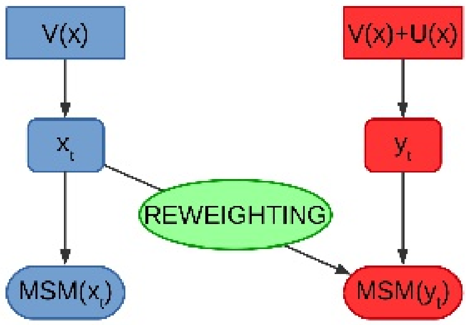

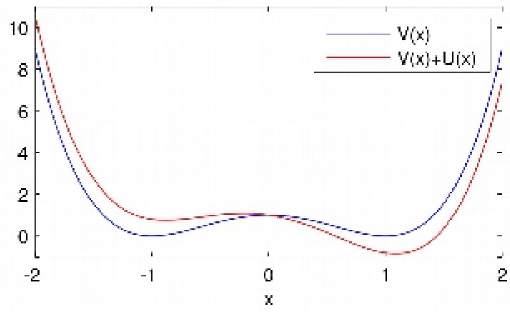

Molecular Dynamics (MD) is characterized by metastable states and transitions that occur at different timescales. Recent studies [1] have proven, through Markov State Models (MSM) analysis, that the timescales are very sensitive on the potential energy function of the molecule and that different force fields of the same molecular system show different dynamic properties. This result suggests the need to improve the current force fields analyzing the effects caused by parameters variation. To address this issue, it would be necessary to produce a MD trajectory and to construct the respective MSM, for each parameter set. This approach is computationally expensive and requires the development of a validation method that acts directly on the MSM.

Taking a force field as reference, each parameter variation can be considered as an external perturbation of the potential energy function. Because the potential energy perturbation affects the stationary distribution of the system, we can exploit the Girsanov theorem [2] to reweight the dynamics and to rewrite the transition probability matrix of the original MSM in terms of the new stationary distribution [3]. The method can be used to predict the timescales of a molecular system in a perturbed potential energy function without rerunning molecular dynamics simulation and could be relevant to force field optimization.

We performed tests of one-dimensional diffusive processes verifying the limits of applicability of the method. Then we have tested many-body systems in three-dimensional space, formulating an extension of the method when the MSM is constructed on a conformational space not directly perturbed. We present also preliminary results for alanine dipeptide and a benchmark test that shows the efficiency of the method.

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Dynamic generation of inorganic and organic polymer structures in hybrid polymers

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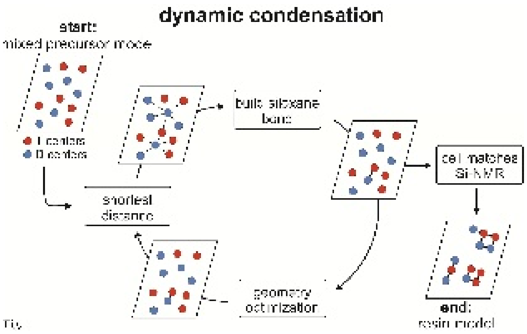
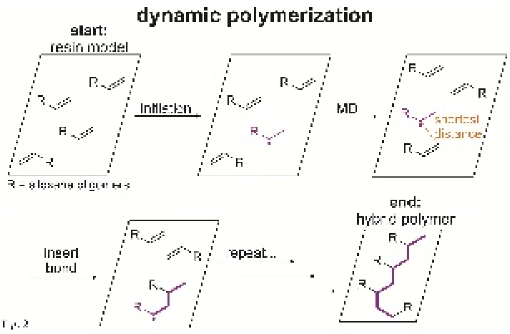
*Org*anically *mo*dified *cer*amics – Ormocer®s – belong to the Sol-Gel derived hybrid materials and combine typical properties of organic polymers like flexibility or processability with the hardness of the ceramics. They cover a wide range of applications, from coatings and dental filling materials to optical waveguides [1]. They are synthesized in a two-step process. In a polycondensation reaction silanols and alkoxysilanes act as precursors to form the so-called resin. The alkoxysilanes are bound covalently to the polymerizable organic moieties. In the following, these moieties can undergo a polymerization reaction, which is initiated thermally or photochemically, to form the hybrid polymer [2]. Force field methods are used to get a better understanding of the atomistic structures of the resin and of the hybrid polymer.

In classical force field methods, no reactions can be described. To reflect the formation of the structures in the synthesis of these materials, pseudo-reactive algorithms are used to obtain realistic structure models. For this purpose, we developed two different methods to generate models for the products of the condensation and polymerization respectively.





The dynamic condensation process, shown in Fig. 1, is useful to form resin structures for systems with more than two different precursors. From cells containing the precursors in the experimental ratio, the algorithm creates resin cells which reflect the experimental determined ^{29}Si-NMR results of the resin. In this process parameters are added to avoid certain structures like three membered rings and ringspearing structures or promote favourable arrangements like four membered rings [3]. Additionally, certain parameters are added to be able to adjust the algorithm to represent either acidic or basic conditions, leading to long siloxane chains or more branched clusters.

The dynamic polymerization method shown in Fig. 2 is used to create polymer structures of the previously created resins. The polymerization is modeled to represent a radical chain-growth polymerization by searching for the closest distance between a radical and an unreacted polymerizable group during molecular dynamics, and creating a bond between them. Two different variants of this method are presented, differing in the search time modes. Fixed and a flexible search times can be used, varying in the required calculation time and the quality of the obtained models. The suitability and the quality of the modeling approach is presented for both simulation steps, the resin and the polymer, for two different Ormocer® systems.

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[3] S. Fessel et al., *J. Sol-Gel. Sci. Technol.*, **2012**, *63*, 356–365.

Ligand-Sensing Cores - Large Scale Analysis and Application

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The structure-based design of small molecule modulators of protein function is a crucial step in medicinal chemistry. Different approaches deal with the exploitation of structural knowledge in combination with data of known ligands of the target of interest. The automated method developed in our group aims to find so-called 'ligand-sensing cores', i.e. a similar arrangement of secondary structure elements constituting the binding site that leads to the binding of similar scaffolds [1]. The presented results show two basic application domains of this approach: idea generation for drug design and the prediction of potential off-target effects.

First, the method was applied on Trypanothione Synthetase (TryS). This enzyme is crucial for the survival of different organisms of the species Trypanosoma and Leishmania - the causative agents of so-called neglected diseases like Chagas disease or african trypanosomiasis. Encouraged by the knowledge, that TryS and certain protein kinases share similar ATP-binding site ligands [2], the similarities between TryS and ATP-binding proteins were analysed using the 'ligand-sensing cores' approach. Based on the results, a virtual screening workflow was established to exploit this knowledge. MD simulation studies and molecular docking contributed to the selection of promising molecules and we now strive to provide a proof of concept using biochemical assays.

The second outcome presented here is the analysis of an all-against-all comparison of all Ligsite-defined [3] binding sites of all structures stored in the Protein Databank. Preliminary analysis showed a huge amount of similar ligand-sensing cores within proteins showing a low overall structural and sequence similarity. Using the established database of common 'ligand-sensing cores' throughout the PDB, it is now possible to analyze interesting targets within seconds. This approach is especially useful for the prediction of possible off-targets or the establishment of interesting polypharmacology.

[1] M. A. Koch, H. B. Waldmann, *Drug Discov. Today*, **2005**, *10*, 471-483.
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Mechanistical Insight on the Hydrosilylation of Conjugated Alkenes Catalyzed by Early Main-Group Metal Catalysts

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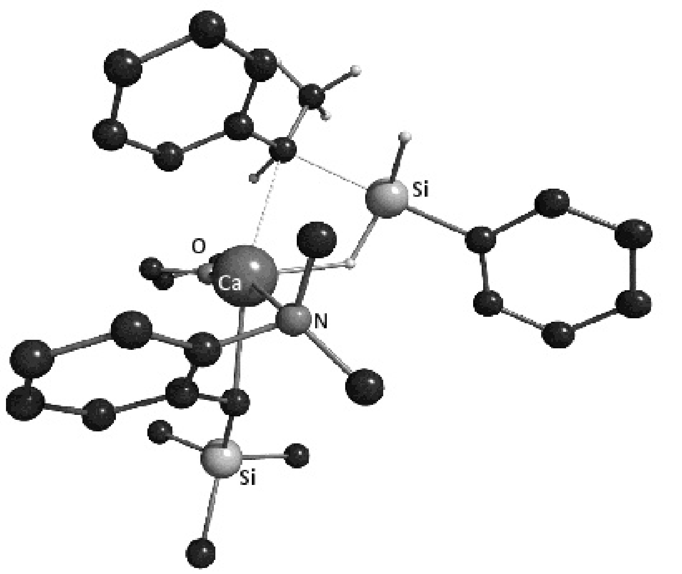
The key to developing highly efficient catalysts is to fully comprehend the reaction mechanism. Computational chemistry allows us to model the reactions and possible alternatives. We here present density functional calculations on the catalysts introduced by Harder *et al.* [1] for the hydrosilylation of conjugated alkenes. The Markovnikov or anti-Markovnikov regiochemistry strongly depends on the catalyst and on the reaction medium. We compare gas-phase and PCM/CPCM solvent model calculations for prototype models and for the full potassium and calcium-based catalysts. These provide mechanistic details and allow the identification of the catalytically active species.



Transition structure for the reaction of [Bz(Me)CaDMATxthf] with $PhSiH_3$: formation of the hydro-silylated styrene product and regeneration of the [HCaDMATxthf] catalyst (some hydrogen atoms omitted for clarity)

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Investigation of the effect of β-Cyclodextrin on Peptide Deamidation: A Molecular Dynamics Study

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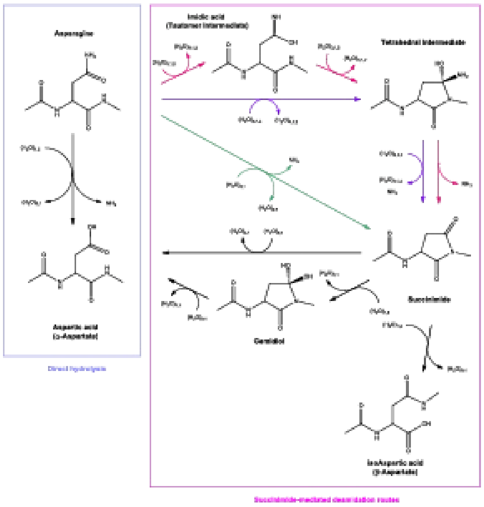
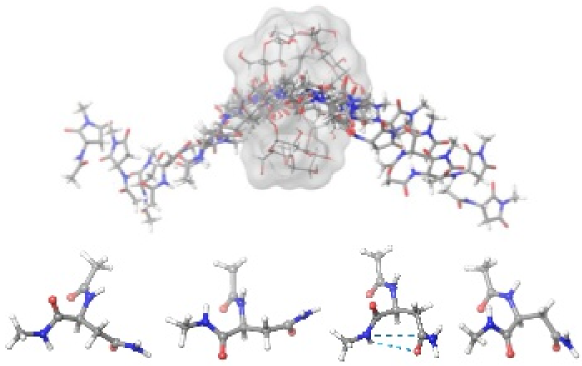
[1]*EAM Cluster of Excellence, Erlangen, Germany*

[2]*Ruđer Bošković Institute, Zagreb, Croatia*





The deamidation of asparagine-containing peptides is associated with a relatively complex mechanism including tautomerization, isomerization and hydrolysis steps [1]. The resulting product distribution is known to be sensitive to the presence of a β-Cyclodextrin (β-CD) host [2]. To investigate this sensitivity, we have applied a number of classical molecular modelling based methods to peptide containing motifs in aqueous solution, namely Asparagine (Asn) and Succinimide (Succ) guests, in the presence of β-CD. We find that unbiased/standard molecular dynamics (MD) simulations are not appropriate for obtaining a converged ensemble of structures, due to the fact that the inclusion host–guest complexes dissociate in a relatively short period of time and re-association events are rare. To circumvent this issue we employed advanced sampling techniques such as umbrella sampling and replica exchange molecular dynamics (REMD), which allowed us to derive the free energy profile (Potential of Mean Force (PMF)) along the host–guest binding coordinate. The derivation of these profiles as well as their relevance to the mechanism of the deamidation reaction in the presence of β-CD will constitute the focus of the presentation.

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Towards Identifying Novel Allosteric Drug Targets using a "Dummy" Ligand Approach

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Allosteric regulation is the coupling between separated sites in biomacromolecules such that an action at one site changes the function at a distant site. The identification of novel allosteric pockets is complicated by the large variation in allosteric regulation, ranging from rigid body motions to disorder/order transitions, with dynamically dominated allostery in between.[1] Here, we present a new and efficient approach to probe information transfer through proteins in the context of dynamically dominated allostery that exploits "dummy" ligands as surrogates for allosteric modulators.

In a preliminary study to test the general feasibility, the approach was applied to conformations extracted from a MD trajectory of the *holo* and *apo* structures of LFA1. The grid-based PocketAnalyzer program[2] is used to detect putative binding sites. "Dummy" ligands were generated for each detected pocket along the ensemble. Finally, the Constraint Network Analysis (CNA) software, which links biomacromolecular structure, (thermo-)stability, and function, is used to probe the allosteric response by monitoring altered stability characteristics of the protein due to the presence of the "dummy" ligand.[3–5] The results were compared to those of the *holo* structure with the bound allosteric ligand to validate the "dummy" ligand approach.

Remarkably, the usage of "dummy" ligands almost perfectly reproduced the results obtained from the known allosteric effector. Although it turned out that the intrinsic rigidity of the "dummy" ligands over-stabilizes the LFA1 structure, these results are already encouraging. Even for the LFA1 apo structures, where the allosteric pocket is partially closed, the results are in agreement with known allosteric effectors. Overall, the results obtained from the validation of the "dummy" ligand approach are encouraging. This suggests that our "dummy" ligand approach for the characterization of unexplored allosteric pockets is a promising step towards identifying novel drug targets.

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Conformational Stability of Non-Fibrillar Amyloid-$\beta_{17\text{-}38}$ – A Molecular Dynamics Study

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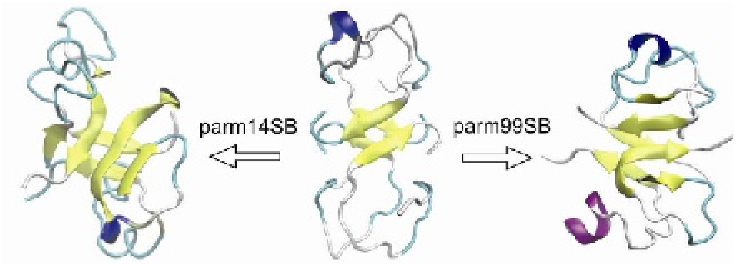
Alzheimer's Disease (AD) is the most prevalent neurodegenerative disorder in industrial nations. Patients suffering from AD develop senile plaque deposits in their brains, which mainly consist of fibrillary aggregates of amyloid β (Aβ) peptides. Recent findings, however, suggest that neurotoxicity is conferred by small soluble Aβ oligomers instead of unsoluble Aβ fibrils. Unfortunately, Aβ peptides exhibit a vast conformational variety and plethora of oligomeric states, which has been making experimental studies of their structure a major challenge.

In 2011, Streltsov et al. succeeded in capturing a non-fibrillar tetramer structure of $A\beta_{18\text{-}41}$ with its sequence fused into a loop region of a shark Ig new antigen receptor.[1] Recently, we investigated the stability of this isolated Aβ tetramer structure in dependence of the C-terminal length and found, that the longer species $A\beta_{17\text{-}42}$ and $A\beta_{17\text{-}43}$ were conformationally stable already at the level of the monomer, whereas $A\beta_{17\text{-}40}$ completely lost the initial fold.[2]

Here, we present complementing molecular dynamics simulations of the C-terminally further truncated species $A\beta_{17\text{-}38}$. The isoform $A\beta_{38}$ is found in plaque deposits as well as in cerebrospinal fluid and blood [3] and exhibits different neuronal properties in mixtures: while it shows neuroprotective effects upon the longer species $A\beta_{42/43}$, it increases the neurotoxicity of $A\beta_{40}$. This work aimed at elucidating the $A\beta_{38}$ tetramer dynamics in relation to the other Aβ species.[4]

Like in our previous work, the structure 3MOQ [1] served as template for the generation of $A\beta_{17\text{-}38}$ tetramer as well as derived dimer and monomer structures. The systems were simulated with AMBER14 in two runs using two different force fields (parm99SB, parm14SB) in explicit water.



All monomer structures of $A\beta_{17\text{-}38}$ quickly lost their initial conformation and unfolded displaying a pronounced flexibility. The two kinds of $A\beta_{17\text{-}38}$ dimers showed slight differences in their dynamics, but were not conformationally stable as well. Surprisingly, the tetramer kept the characteristics of the starting structure, independent of the force field used: the interfaces between the peptide chains were stabilized by an antiparallel β-sheet and hydrophobic contacts within the core of the tetramer. These dynamical properties of $A\beta_{38}$ are in accord with the notion that the distinct molecular plasticity of different Aβ species regulates their oligomerization and cytotoxicity.[4]

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Discovery of a novel relationship between two proteins by a chemogenomics analysis

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The term "privileged scaffolds" was coined for the collective core structure of multiple molecules exhibiting bioactivity on different targets [1]. Within proteins, conserved structural elements are similarly common. A recently discovered level of conservatism, the ligand-sensing core, is a similar spatial composition of secondary structure elements around the ligand binding site in proteins with distinct folding patterns that can bind similar scaffolds [2]. Knowledge about ligand-sensing cores facilitates rational identification of new lead structures [3] or prediction of polypharmacology [2].

Compound databases like DrugBank [4] or ChEMBL [5] contain a wealth of data about molecules and their bioactivity on diverse proteins. Hence, a python-based tool for knowledge discovery aiming at new insights into the relationship of privileged scaffolds and ligand-sensing cores was developed. Its main objective is the identification of scaffolds that bind to unrelated proteins for revealing conserved structural elements. In a first step, a command line version of Scaffold Hunter [6] assigns scaffolds to all imported molecules. Afterwards a sequence similarity analysis of proteins whose ligands share a scaffold is performed. Only protein targets with identity below 40 % are considered as unrelated. Finally, the results are visualized for an in depth analysis.

We will present the overall workflow and the result of a chemogenomics analysis of the DrugBank. Around 1500 scaffolds were identified that bind to different proteins. An analysis of one of these scaffolds already ended up in a new ligand-sensing core that is shared between five different proteins. Based on this information an enriched library of molecules that show a similarity to known inhibitors of four of these proteins was selected. Testing this library for inhibitory activity against the fifth protein led to IC_{50} values down to the nanomolar range and to an initial hit rate of ~11 % within the molecule series that was selected based on known inhibitors of one of the proteins. This clearly indicates a relationship and similar ligand binding of one pair of these proteins sharing a similar ligand-sensing core and proves the usefulness of this approach. Currently, we investigate the hits using orthogonal assays and crystallization experiments to solve complex structures with the most promising hits.

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Electronic polarization induced by high solvent pressure

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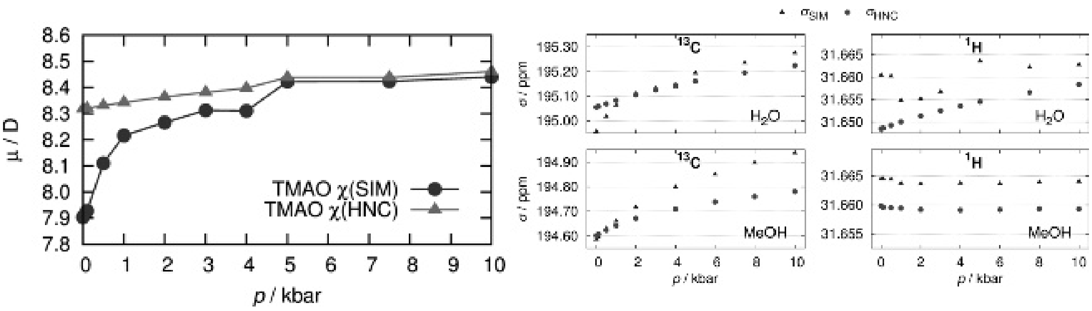
Biochemical processes of a vast number of lifeforms accommodated to extreme conditions such as deep oceanic water depend on the subtle interplay of solvent components. For instance, trimethylamine-*N*-oxide (TMAO) is known to stabilize proteins under high hydrostatic pressure conditions [1] which is barely understood. Applying high hydrostatic pressure has substantial impact on free energy surfaces underlying biological function. This poses a challenge to computational modelling approaches since the applicability of conventional empirical molecular force fields is questionable.

As a step toward clarifying the situation, we need to account for high pressure in quantum-chemical (QC) calculations. A suitable methodology is provided by the "embedded cluster reference interaction site model" (EC-RISM) [2,3] that combines statistical-mechanical 3D RISM integral equation theory and QC calculations. In this context the impact of pressure is introduced by using solvent susceptibility functions containing all pressure dependent properties.

Here we illustrate the methodology for several examples in a pressure range of 1 bar up to 10kbar to demonstrate the relevance of electronic polarization under extreme pressure conditions. In particular, it is shown that the TMAO dipole moment increases strongly with high pressure, which turns out to be decisive for constructing force field parameters suitable for high pressure simulations [4] as well as for interpreting pressure-dependent vibrational spectra. Furthermore, evidence is found that high-pressure NMR (nuclear magnetic resonance) experiments on proteins measure an intrinsic, polarization-related chemical shift baseline which has to be accounted for if conformational transitions are correlated with chemical shift variations [5].



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The Role of Water in the Electrophoretic Mobility of Hydrophobic Objects

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It is well established that hydrophobicity of an interface, droplet or a particle can be modulated by an external electric field. However, the provided explanations why these essentially uncharged objects like oil droplets exhibit a directional specific movement in the presence of electric fields remain controversial and continuously challenged. Here we study the static and the dynamic behaviour of a model hydrophobic object (Lennard-Jones particle) in water (SPC/E model), by performing extensive molecular dynamics simulations in the absence and the presence of electric fields using the GROMACS software package. We first combine simulations with the linear response theory to show that shear viscosity of water increases with the strength of the electric field. Furthermore, we identify a novel relaxation process in the water network. We then show that both the diffusion and the friction coefficient of the particle can be calculated independently, which allows us to demonstrate the validity of the Stokes-Einstein relation at the nanometer length scale, subject to clearly identified constraints on the mass and the size of the spherical particle, as well as the size of the system. After establishing a sound simulation protocol, we show that the electric field evokes on an average asymmetric distribution of the water molecules around the Lennard-Jones particle. This acts as a steady state density gradient, inducing a phoretic motion of the hydrophobic object towards the region of higher concentration of water. We interpret our data on a basis of Derjaguin theory for diffusiophoresis which predicts the steady state velocity of a colloidal particle as a function of the first moment of the concentration gradient, the effective hydrodynamic radius of the particle, and the shear viscosity of the solvent. This theoretically predicted driving velocity agrees exceptionally well with the results of the simulations.

Bifurcated hydrogen bondin in carbohydrate sugars

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Abstract

The eight aldohexoes series of carbohydrate sugars namely, β-D -allose, altrose, gulose, idose, talose, glucose, galactose and mannose, are stereoisomer, they differ by only the orientation of the hydroxyl group at the C2-C4 positions. *Ab initio* calculations based on density functional theory (DFT) using B3LYP/6-31G* have been performed to investigate intra-hydrogen bond characteristics of hydroxyl groups in aldohexose sugars. The atoms in molecules (AIM) approach and natural bond orbital analysis (NBO) are used to measure strength and energy intramoleculare hydrogen bonding in aldohexoes. It has been found that all aldohexose sugars display regular intra-hydrogen bond (two-centered), except idose sugar displays bifurcated acceptor (three-centered) intramolecular hydrogen bonds. Maximum energy regular intra-molecular hydrogen bonding are measured approximately 11.73kcal/mol, while it is for bifurcated hydrogen bonds in idose is between 58% and 45% of regular hydrogen bonds. A theoretical point of view in intra-molecular hydrogen bond in carbohydraaldohextes would pr ovide further insight into the monosaccharaides structural maintenance and properties.

Keywords: Aldohexose, Bifurcated Hydrogen bonding, Hydroxyl group, DFT, AIM, NBO

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The many faces of Cyp106A2: How does rational protein design work

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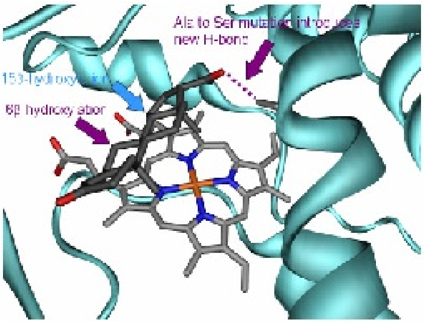
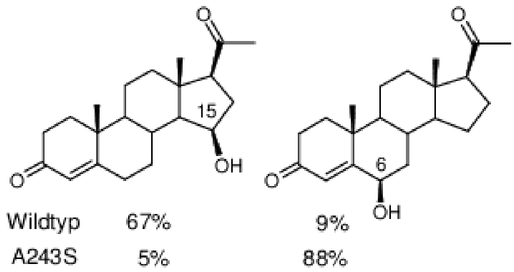
Cytochrome P450 enzymes are not only involved in the metabolism of pharmaceutical drugs, but also in biosynthesis. This can be exploited for the biotechnical production of substances that are otherwise difficult to obtain. CYP106A2 from *Bacillus megaterium* ATCC 13368 is a bacterial steroid hydroxylase that also accepts a variety of terpenoids as substrates. Surprisingly, abietic acid shows a type-II difference UV spectrum, which is typical for inhibitors, and induces a bending of the heme-cofactor. [1] We therefore carried out quantum chemical calculations of the UV/VIS spectrum for bound water and CO as model type-I, respectively type-II ligands. Our results suggest that heme distortion alone causes the unusual spectroscopic behavior.





Progesterone as substrate produces a variety of products whereby 15-OH-progesterone is the major one (67%). [2] To obtain a larger fraction of the minor side product 6β-hydroxy-progesterone we inspected the different docking conformations produced by AutoDock (Version 4.2). [3] Introducing a new hydrogen-bond suggested to stabilize the substrate orientation from which this hydroxylation product was formed. The corresponding Ala243Ser mutant that was subsequently constructed showed 6β-hydroxy-progesterone as selective main product (88%) and a lower fraction of side products (<10%) than the original wild-type form of the enzyme (33%).

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Different Types of Ca2+ binding sites in SiiE

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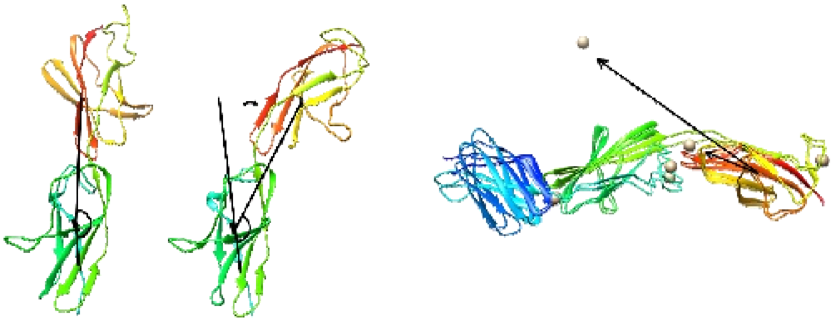
The adhesion protein SiiE mediates contact between Salmonella enterica and the host cell. It consists of 53 repetitive bacterial immunoglobulin (BIg) domains. It binds two Ca^{2+} ions per domain in two structurally different types of coordination sites. It very likely recruits the Ca^{2+} ions upon secretion from the membrane while passing through the bivalent cation filled bacterial lipopolysaccharide layer (see Griessl et al [1]).

Chelation experiments showed distortion of the straight, rod-like structure in the absence of Ca^{2+} coordination. Infection experiments showed distinct changes of SiiE mediated characteristics upon deactivation of type I versus type II coordination sites.



We used MD simulations to characterize the flexibility of SiiE wild type and mutant proteins. For this we used the X-ray structure of BIg 50-52 (PDB code 2YN5) which contains the typical conserved SiiE domain interface between BIg 51 and 52. Mutants contain either deactivated type I, type II or type I&II coordination sites. The systems show different behavior with respect to domain-domain bending as well as rotation.

We used steered molecular dynamic simulations to estimate the relative binding energies and maximal binding forces for type I versus type II Ca^{2+} binding sites. A larger work was required to remove Ca^{2+} from the type II binding site within BIg 51 compared to the type II binding site between BIg 51 and 52. The maximal required force was comparable for the two binding sites.

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Conformational Analysis of Neutral and Ionic Forms of Lysine

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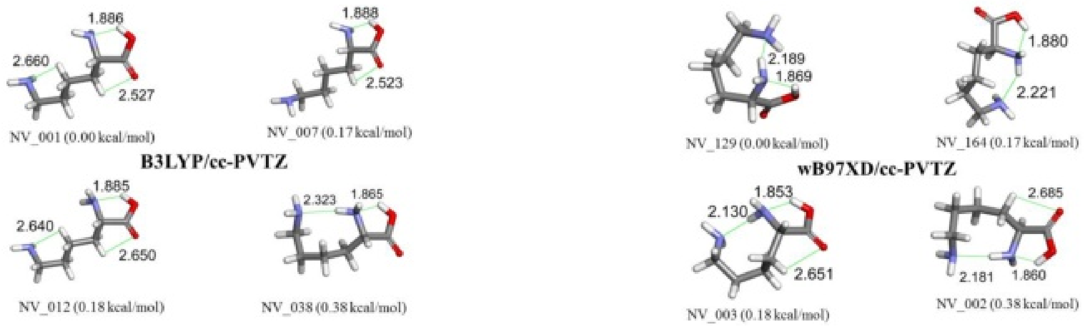
Lysine which contains a primary amine at its terminal group, is an essential amino acid. Under physiological conditions ε-amino group is positively charged. It is basic and prone to be out of hydrophobic surfaces of proteins. Because of this property, reactive group of lysine is essential for protein stability [1]. Ionization states of lysine side chain can regulate biological functions of membrane proteins like sodium channels, acetylcholine receptors, integrins, etc.[2].

In our study, conformational analysis of neutral and ionic lysine forms have been performed and isolelectronic forms were compared.



Conformational analysis has been carried out by using molecular mechanics methods for neutral and all possible charged states of lysine. All molecules have been fully optimized at B3LYP/cc-PVTZ and wB97XD/cc-PVTZ levels. Afterwards frequency analysis has been carried out at same levels for characterizing stationary points. Calculations have been carried out by using Spartan '08 [3] and Gaussian 09 program packages [4].

Lysine has 8 possible charged states. After conformational analysis; 369 structures for neutral lysine, 228 structures for anion, 26 structures for cation1, 60 structures for cation2, 39 structures for cation3, 44 structures for dication, 66 structures for zwitterion1, 35 structures for zwitterion2 have been determined. These numbers decreased after optimization and frequency analysis. Optimization of the conformers with different functionals has altered the stability order of the conformers.

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Pitfalls in the accurate determination of non-covalent interaction energies in large systems using the example of the C_{60} dimer

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Fullerene-fullerene interactions dominate the behavior of all supramolecular systems containing fullerenes. Many methods for describing the van der Waals interaction have been proposed in the last 30 years, but until recent only DFT with Grimme's corrections was possible for such large systems. Ruzsinszky [1] questioned this approach. We have now performed rigid scans of the C_{60}-C_{60} interaction (following methodology used in Hobza's S66 dataset) at different levels of theory: DFT-functionals from different rungs of Jaccob's ladder, including double hybrids, MP2 and finally DLPNO-CCSD(T) and DLPNO-CEPA/1 methods.

For DFT - influences of D3BJ and nonlocal (NL) corrections were checked and compared.

For double hybrids and MP2 methods with varied spin-same and spin opposite coefficients were examined (DSD-DH, DOD-DH and SCS-MP2, SOS-MP2). While overestimation of dispersion by MP2 is well known, usage of SCS- and especially SOS-schemes improves the results significantly, but MP2-schemes modified for molecular interaction (SCS- and SOS-MI-MP2) unexpectedly give the wrong answers.

A strong effect of basis set was found for DLPNO-CoupledCluster and CEPA methods: TZV and def2-TZVP(-f) basis sets gives results nearly twice as high as cc-pVDZ and cc-pVTZ. The results obtained with Dunning basis sets seemed to be more correct for the following reasons: 1) CBS extrapolation is possible and the extrapolated result is relatively close to cc-pVTZ 2) the results obtained with this basis sets are much closer to an estimation based on the heat of sublimation (known from experiment) 3) strong overestimation of dispersion interaction by the TZV basis set also was observed for the anthracene dimer – a system that is much better described in the literature.

The results obtained have both methodological and practical relevance: some methods that have been claimed to describe noncovalent interactions well were shown to give large errors, the effect of basis sets on DLPNO calculations was explored, and the curve obtained allows us to parametrize a semiempirical correction for the correct description of large fullerene ensembles by computationally efficient methods.

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Investigation of pH-dependent effects on proteins by mimicking pH titration experiments with MD simulations

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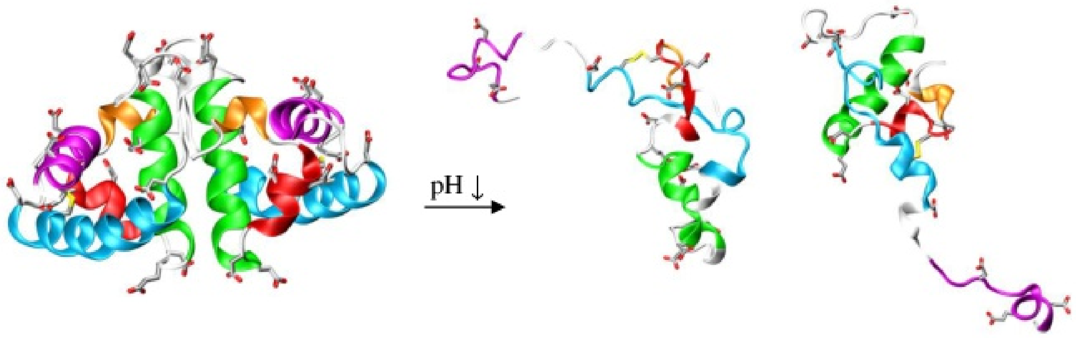
Protein structure and function are highly dependent on the pH of the surrounding environment. However, due to the temporal or spatial resolution of experimental approaches, it is extremely difficult to observe pH-induced conformational changes directly on the atomic level. Molecular dynamics (MD) simulations, which can simulate the atomic motions within biological (macro)molecules were developed to bridge the gap of the resolution. Today, it is also possible to simulate proteins in an environment with constant pH, with so called CpHMD simulations. CpHMD simulations are a huge advantage in comparison to classical MD simulations with constant protonation, because the titrating side chains can switch between different, appropriate protonation states. However, as the name of this CpHMD method suggests, the pH is constant during these simulations. Therefore, we have developed a new application protocol for the CpHMD approach in order to study pH-dependent proteins, in which the change of the pH induces conformational changes. With this pH titrating molecular dynamics (pHtMD) simulation protocol it is possible to decrease or increase the environmental pH over simulation in order to resemble real wet-lab titration experiments. We have validated our pHtMD simulation protocol successfully by investigating small model compounds, Staphylococcus nuclease (SNase) and the bacterial chaperone HdeA as test systems [1].



Here, we present the application of the pHtMD simulation protocol to several different protein systems, which show that pH-dependent processes are widely spread through nature. In each case, our results are comparable to experimental findings. So, we conclude that our protocol provides a versatile and powerful technique for the imitation of pH-dependent effects in proteins.

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In silico screening and testing of new phytoeffectors to enhance drought stress tolerance in plants

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Biotic and particularly abiotic drought stress caused enormous loss in crop yield during the last years. Being a highly relevant problem for central Germany, there is a strong interest in finding new phytoeffectors which could help plants to overcome and survive drought periods. Several proteins (enzymes) could be identified as potential targets addressable by inhibition with phytoeffectors. Among others the plant alcohol dehydrogenases (ADH's) are believed to be such potential targets [1]. These enzymes are widely spread in many plants and are in the focus of drought stress research projects.

The X-ray structure (pdb: 4RQU) of the alcohol dehydrogenase (ADH) from *Arabidopsis thaliana* was used [2]. Within MOE, a pharmacophore was created consisting of nine features, one metal, six hydrophilic and two hydrophobic features, to search in several structural databases [3]. These databases include the lead like database delivered by MOE, an *in house* database of compounds available in our institute and some others containing agrochemicals and natural products.

The screening procedure led to the identification of more than 1500 first hits. Based on subsequent docking and scoring with GOLD, 130 promising compounds remained to pass for experimental studies [4].

Fast experimental screening in the lab was performed with a *Lemna minor* assay system [5].

From these first tests of 15 compounds, five provoked a considerable enhancement of drought stress tolerance. In comparison to the untreated duckweed, one compound added to the assay led to an increase in leaf area (related to the standard growth of *Lemna minor)* of more than 30% under drought stress conditions.

The project was financially supported by the Ministry of Sciences and Economic Affairs of Saxony-Anhalt and the Agrochemical Institute Piesteritz.

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Challenging Dogmas: What is inside a Hydrogen Bond?

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Hydrogen bond directionality in the water dimer is explained based on symmetry-adapted intermolecular perturbation theory, SAPT [1], which directly separates the intermolecular interaction energy into four physically interpretable components: electrostatics, exchange-repulsion, dispersion, and induction. Analysis of these four main contributions to the binding energy allows a deeper understanding of the dominant factors ruling the mutual arrangement of the two monomers. A preference for the linear configuration is shown to be due to a subtle interplay of all the four energy components. While the first-order terms, electrostatic and exchange-repulsion, almost perfectly cancel each other near the equilibrium geometry of the dimer, the importance of the second and higher-order terms, induction and dispersion, becomes evident.

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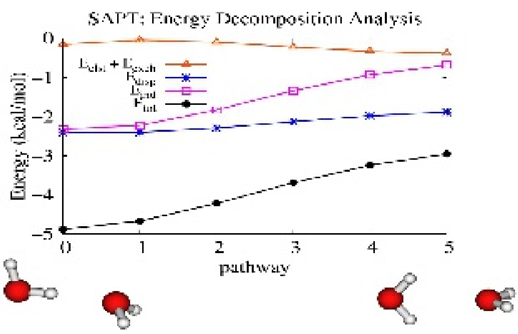

Transfer free energies between aqueous and nonaqueous phases from an integral equation-based quantum solvation model

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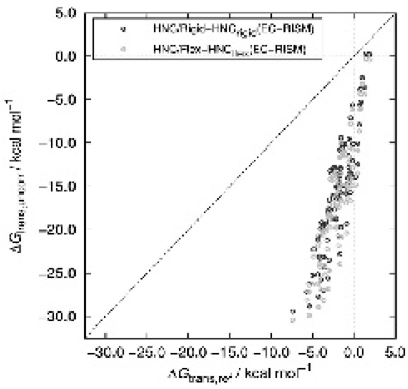
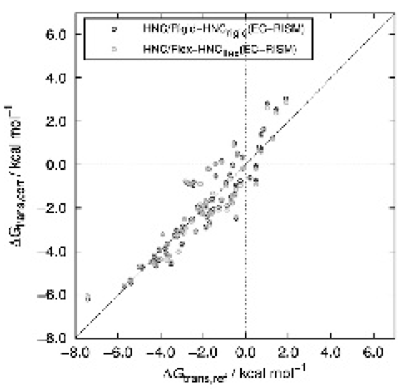
Reliable yet fast prediction of free energies of solvation or of partition coefficients of molecules between immiscible or partly miscible phases such as water and *n*-octanol requires proper theories as for instance provided by the integral equation approach to fluid phase thermodynamics [1]. To accurately model the solvation of small molecules we here combine such a statistical-mechanical description of the solvent with a quantum level description of the solute in the form of the "embedded cluster reference interaction site model" (EC-RISM). This combination takes into account both the electronic relaxation and the excess chemical potential governing the solvation process for predicting the free energy of solvation [2].

To extend the scope of EC-RISM theory to complex solvents other than water we here examine several models for *n*-octanol, taking molecular flexibility into account. This is achieved by parameterizing suitable analytical expressions for the intramolecular distribution functions with respect to reference data from explicit molecular dynamics simulations. One known drawback of the RISM formalism is an overestimation of the free energy contribution accompanying the formation of the solute cavity, leading to significant errors in the absolute free energy of solvation. This error is highly correlated with the partial molar volume (PMV) of the solute [3]. To address this issue we parametrize a PMV correction to increase the accuracy of the calculated free energies of solvation within the EC-RISM context. We discuss the application of this framework to the calculation of the octanol-water partition coefficients (log *P*) for a structurally and chemically diverse set of compounds.





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Molecular gating characteristics in variants of the potassium ion channel Kcv_{ATCV}

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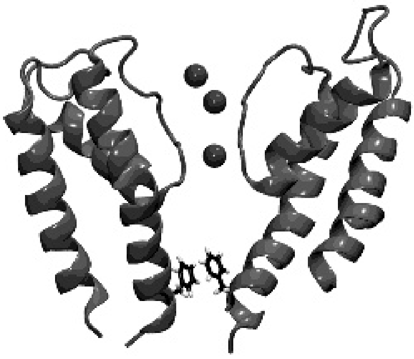
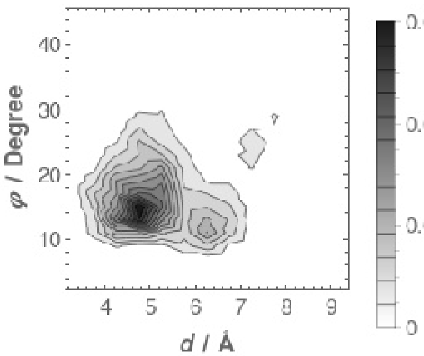
Ion channels fluctuate stochastically between "open" and "closed" states, which determine the ion flux through biological membranes, also known as "gating". This crucial feature of ion channels is necessary in cellular, biological systems to regulate the ion concentration level, which is essential for the processes of homeostasis or second messaging. Yet the origin of gating is not fully understood. A suitable ion channel model for investigations of gating is the tetrameric potassium-selective ion channel $Kcv_{ATCV\text{-}1}$. This minimalistic channel is found in chlorella viruses, and comprised of only 82 amino acids per monomer [1-3]. While electrophysiological experiments have already identified two gates in the wild-type channel, an additional 3rd gating state is found in the related channel Kcv_{ATCV}-"Smith" ($Kcv_{ATCV\text{-}S}$). This 3rd gate leads to a predominantly closed channel (over 70%) in comparison with the wild-type Kcv_{ATCV} and the related Kcv_{ATCV}-"next to Smith" ($Kcv_{ATCV\text{-}NTS}$) channel, which both lack this additional gate. Site directed mutagenesis experiments revealed a significant dependency of this gate on the presence of phenylalanine at position 78.

To investigate the characteristics of this 3rd gate with molecular dynamic (MD) simulations, initial homology models were created for the three related channels $Kcv_{ATCV\text{-}1}$, $Kcv_{ATCV\text{-}S}$ and $Kcv_{ATCV\text{-}NTS}$. For the description of the different behavior in gating, potential π-π-interactions of the Phe78 residues were analyzed in terms of angle/distance probabilities, considering also interactions between different monomers. The results allow for a microscopic interpretation of the gating states in Kcv_{ATCV} variants.





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Organization and Wetting of [C_4Mim][Ntf_2] Ionic Liquid at the Neutral Sapphire Interface

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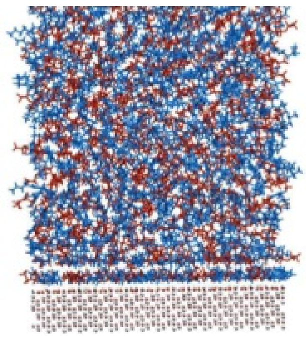

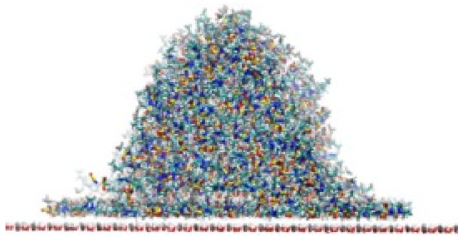

Understanding the molecular-level behavior of ionic liquids (ILs) at IL−solid interfaces is of fundamental importance with respect to their application in, for example, electrochemical systems and electronic devices. [1] In this respect, we employed atomistic molecular dynamics (MD) simulations to investigate the behavior of an archetypical imidazolium-based IL, namely [C_4Mim][NTf_2], at the neutral sapphire interface. [2] This enabled us to describe the nature of the model IL−solid interface in appreciable detail. More precisely, we observed pronounced structural ordering of the IL constituents in the vicinity of the sapphire surface, which, in turn, induces the multidimensional layering of cations and anions. Moreover, we investigated the surface-wetting capabilities of [C_4Mim][NTf_2] by employing cylindrically shaped nanodroplets [3] with three different radii, thereby measuring the contact angle between the IL and the sapphire surface.

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Computational investigation of the exciplexes formed between pyrene and selected monoamines

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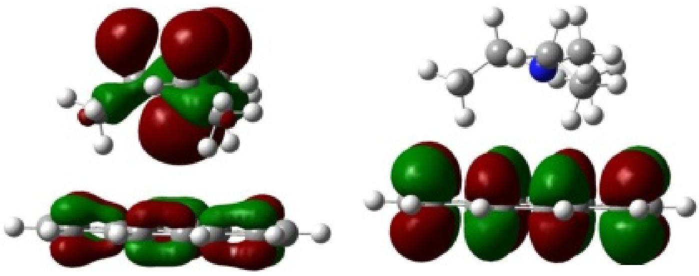
Intermolecular electron transfer processes were investigated computationally. Pyrene (Py) was used as acceptor and some aliphatic amines trimethylamine (TEA), tripropylamine (TPA), and 1-azabicyclo[2.2.2]octane (ABCO) were used as donors. Calculations were performed by density functional theory (DFT) with the ωB97XD functional, where 6-311++G(d,p) basis set employed for molecules. Time-dependent density functional theory (TDDFT) with the B3LYP functional and same basis set was used for excited state calculations. 40 lowest singlet excited states were calculated for each molecule. Molecular orbital energies and the UV-Vis spectra of the studied molecules were illustrated with the same method using the Gaussview5 program [1] using the ground state geometries. The total electron density surface of pyrene and its derivatives mapped with the electrostatic potential values in gas state and various solvents for the excited state. All calculations were performed using Gaussian09 software [2].



HOMO LUMO

Analyses of first excited singlet states have revealed that there are charge transfers between Pyrene and investigated amines. Figure shows charge transfer between Pyrene (Py) and trimethylamine (TEA) in gas phase. $S_0 \rightarrow S_1$ transition (376 nm) between H→L orbitals for Py-TEA system has a CT character from TEA to Py.

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DFT and TDDFT study some pyrene derivatives in excited state

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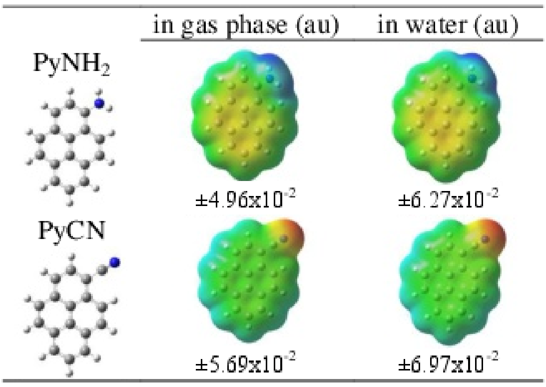
This study presents a computational investigation of Pyrene and its -OH, -NH_2, and -CN, substituted derivatives at position 1 in gas phase and in different solvents in excited S_1 state. Calculations were performed by density functional theory (DFT) with the B3LYP functional, where 6-311++G(d,p) basis set employed for 1-substituted Pyrene derivatives. Time-dependent density functional theory (TDDFT) with the same functional and basis set was used for the analysis of excited states of molecules and emission spectra. 40 lowest singlet excited states were calculated for each molecule. Molecular orbital energies and the UV-Vis spectra of the studied molecules were illustrated with the same method using the Gaussview program [1] with ground state geometries. The total electron density surfaces of pyrene and its derivatives mapped with the electrostatic potential values in gas state and various solvents for the excited state equilibrium geometry were shown below. Similar to the observation in our former study [2], there is a charge transfer from the pyrene ring to the electron withdrawing CN group (red: negative electron density). The Polarizable Continuum Method (PCM) [3, 4] have been applied for all gas phase optimized structures to evaluate the solvation effect on the transitions of the investigated molecules in nonpolar (CH, cyclohexane), medium polar (THF, tetrahydrofuran) and polar solvents (ACN, acetonitrile and H_2O, water).



The results showed that the stability of the investigated systems increased with increasing solvent polarity. E_{00} energies and fluorescence lifetimes were calculated using computed emission spectra. All calculations were performed using Gaussian09 software [5].

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List of Participants

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