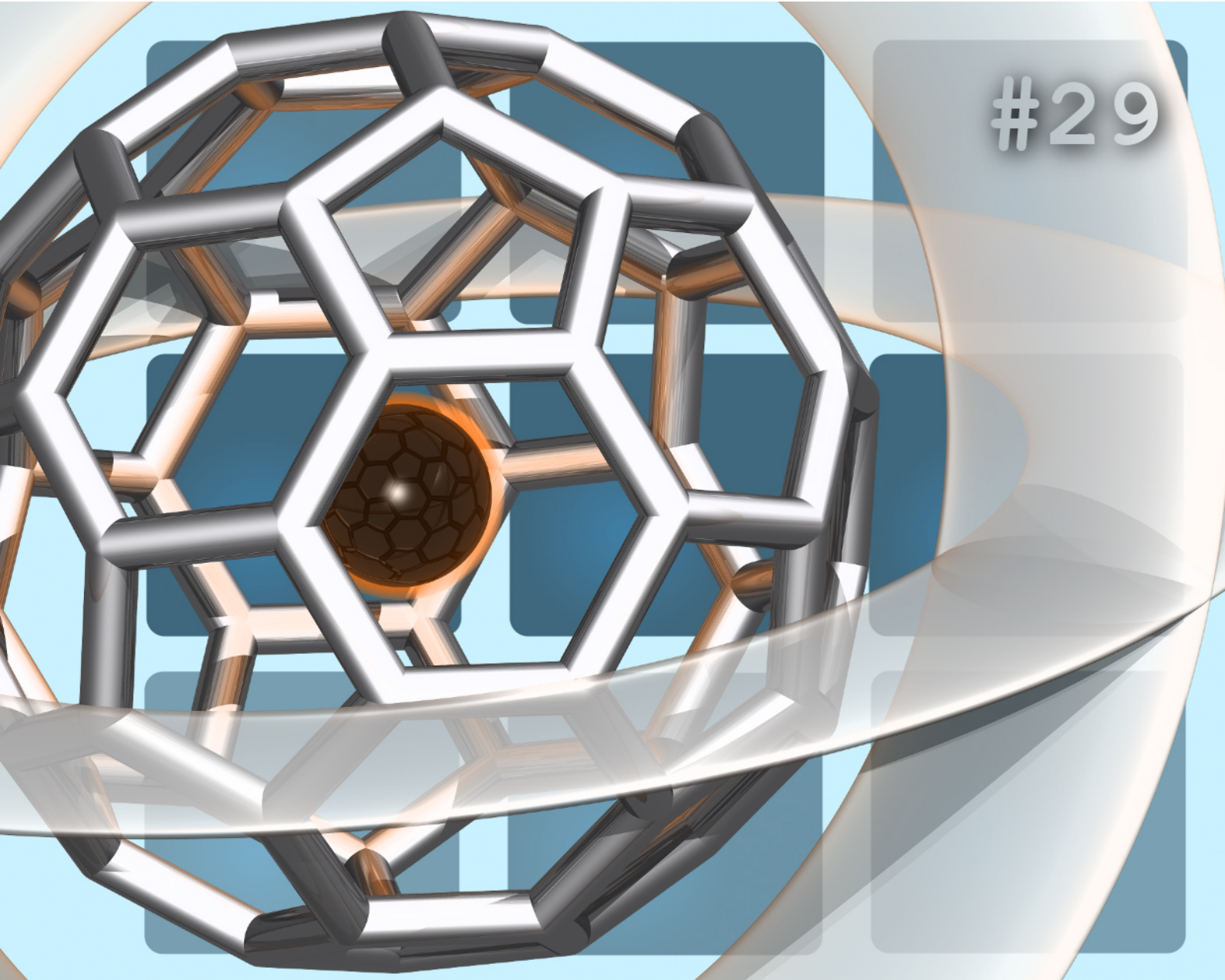

#29

[MOLECULAR]
[MODELING]
[WORKSHOP]
[2015]

ERLANGEN | MARCH | 09th-11th

FRIEDRICH-ALEXANDER
UNIVERSITÄT
ERLANGEN-NÜRNBERG

Computer Chemie
Centrum

molecular
graphics
modelling
society

MOLECULAR MODELLING WORKSHOP 2015

Computer-Chemie-Centrum
Nägelsbachstr. 25
91052 Erlangen
Germany

Monday, March, 9th - Wednesday, March 11th 2015

Once again, we in CCC are happy to welcome you to the Molecular Modelling Workshop 2015. This year, it is the 29th Molecular Modelling Workshop and the thirteenth time it is hosted by the University of Erlangen-Nuremberg. The research group of Prof. Tim Clark at the CCC will be responsible for the technical organization. Dr. Bernd Beck from Boehringer Ingelheim Pharma GmbH, will be responsible for the scientific organization.

The Molecular Graphics and Modelling Society – German Section (MGMS-DS e.V.) is, as always the organizer of the Workshop and provides financial support to enable students to attend the meeting. We especially thank our sponsors, who have not only this year enabled us to provide an excellent program at a very low price, but also have supported the Molecular Modelling Workshop consistently and generously over its entire history.

Scientific program

Dr. Bernd Beck

Boehringer Ingelheim Pharma GmbH & Co. KG
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DEAR COLLEGUES,

The 29th Molecular Modelling Workshop (March, 9th - 11th) 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. KARL-HEINZ BARINGHAUS

Sanofi-Aventis Deutschland GmbH
Frankfurt am Main

PROF. ANNA LINUSSON

Department of Medicinal Chemistry
University of Umeå

AWARDS

As in the past years, there will be two Poster Awards of 100 Euro each and three Lecture Awards for the best talks:

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. A Web Award for WWW-based scientific applications in the field of molecular modelling will not be awarded this year.

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.

DR. KARL-HEINZ BARINGHAUS

Karl-Heinz Baringhaus obtained his Ph.D. in synthetic organic chemistry from the University of Muenster, Germany. After a postdoctoral fellowship at Stanford University he joined Hoechst AG where he was working six years in Medicinal Chemistry. Then he moved into Molecular Modeling and in 2000 he became Head of Computational Chemistry at Aventis Pharma.

From 2005 to 2010 he was Director of Drug Design at Sanofi-Aventis Pharma Deutschland GmbH. In 2010 he was promoted to Head of Structure, Design & Informatics consisting of Computational Biology & Bioinformatics, Computer-aided Drug Design, Scientific Computing & Data Management as well as Structural Biology. Since October 2012 Karl-Heinz is Site Director of R&D in Frankfurt.

PROF. ANNA LINUSSON

Anna Linusson has a master degree in biology at the University of Gothenburg. She obtained her doctorate in organic chemistry in 2000 at Umeå University with a thesis on library selection in combinatorial chemistry. Directly after, Anna Linusson joined AstraZeneca R&D Mölndal for a position as computational chemist in drug discovery projects.

In 2004, she returned to Umeå University for a faculty position in computational chemistry at the Department of Chemistry. In the summer of 2013, she was appointed full Professor in Medicinal Chemistry at Umeå University. The focus of her research is directed towards fundamental aspects of interactions of small-molecular ligands with proteins, using both experimental and computational techniques. The research is performed within pharmaceutical relevant projects to contribute to the discovery of new molecules against for example rheumatoid arthritis, malaria and dengue fever.

Program

PROGRAM

Monday, March 9th 2015

11:30-14:00	**Registration**
14:00-14:15	**Welcome remarks / Agenda review**
14:15-14:40	**Giulia Pagani (Düsseldorf)** Characterization of the HPA-1 polymorphism by MD simulations and FRET measurements
14:40-15:05	**Hugo Gattuso (Nancy)** Theoretical study of DNA photosensitized by an artifical nucleobase: a model toward the 6-4 photoproduct
15:05-15:30	**Noureldin Saleh (Erlangen)** Arginine-Vasopressin and its V2 Receptor: Binding Pathways, Kinetics and Thermodynamics
15:30-15:55	**Tommaso D'Agostino (Cagliari)** Enhanced samping techniques and their application to the study of small substrate translocation
15:55-16:15	**Coffee Break**
16:15-16:40	**Guido Humpert (Essen)** Protein interfaces and assembly of heteromeric Nav1.8 ion channels
16:40-17:40	**Plenary Lecture I:** **Prof. Anna Linusson (Umeå)** Targeting Fundamental Aspects of Protein-Ligand Interactions to Improve Computer-Aided Molecular Design
17:40-18:45	**Annual Meeting of the MGMS-DS**
19:00	**Buffet - Dinner**

PROGRAM

Tuesday, March 10th 2015

08:30-08:55 **Hanno Dietrich (Erlangen)**
Modeling Self-Assembly of Phosphonic Acids on α-Aluminum Oxid

08:55-09:20 **Andreas Krause (Erlangen)**
Simulating Nanostructures: 2D-periodic organic semiconductors

09:20-09:45 **Adriana Supady (Berlin)**
First principles sampling and representation of a reduced molecular potential energy surface

09:45-10:10 **Daniel Tomazic (Dortmund)**
Integral equation-based quantum solvation model for quantitative prediction of hydration free energies

10:10-10:35 **Coffee Break & Conference Photo**

10:35-11:00 **Benjamin Meyer (Nancy)**
Exploiting the Transferability of Extremely Localized Molecular Orbitals to Study Large Biological Systems

11:00-12:00 **Plenary Lecture II:**
Dr. Karl-Heinz Baringhaus (Sanofi-Aventis)
Molecular Design in Drug Discovery: Applications and Challenges

12:00-13:30 **Lunch**

PROGRAM

Tuesday, March 10th 2015

13:30-13:55	**Patrick Kibies (Dortmund)** Conformational sampling of drug-like molecules in solution with quantum-chemical accuracy
13:55-14:20	**Eva Nittinger (Hamburg)** EDIA – A New Estimate of Electron Density of Individual Atoms for Validating Water Molecules
14:20-14:45	**Daniel Mulnaes (Düsseldorf)** TopModel: A multiple-template meta-approach to homology modeling
14:45-15:15	**Discussion Session with Prof. Anna Linusson and Dr. Karl-Heinz Baringhaus; Moderator Prof. Tim Clark**
15:15-15:35	**Coffee Break**
15:35-16:35	**Poster Session I**
16:35-17:00	**Christoph G. W. Gertzen (Düsseldorf)** An experimentally validated binding mode model of TGR5 agonists
17:00-17:25	**Tobias Brinkjost (Dortmund)** On our Way to the Automated Search for Ligand-Sensing Cores
18:30	**Gasthaus - Steinbachbräu**

PROGRAM

Wednesday, March 11th 2015

08:30-08:55	**Dr. Pavlo O. Dral (Mülheim)** The Quest for Accurate Semiempirical Methods
08:55-09:20	**Dr. Harpreet Shah (München)** Computer-aided modelling of protein conformations and ligand binding
09:20-09:45	**Dr. Jeremy Richardson (Erlangen)** Including quantum nonadiabatic effects into molecular dynamics simulations
09:45-10:10	**Dr. Akinjide Oluwajobi (Ife-Ife)** Imperfect Interatomic Potentials in the Molecular Dynamics Simulation of Copper and Diamond in Nanomachining
10:10-10:30	**Coffee Break**
10:30-11:30	**Poster Session II**
11:30-13:00	**Lunch**
13:00-13:25	**Dr. Marco Marazzi (Nancy)** Modeling the Electronic Absorption and Circular Dichroism Spectra of a Photo-switchable Bistable Peptide
13:25-13:50	**Dr. Thomas Steinbrecher (Schrödinger)** Free energy calculations to predict the effect of single point mutations on protein stability
13:50-14:15	**Dr. German Erlenkamp (Düsseldorf)** Identifying Pathways out of the Aspartate Binding Pocket of the Phosphoenolpyruvate Carboxylase in C4 Plants
14:15	**Poster & Lecture awards, Closing**

POSTER SESSION I

Tuesday, March 10th 2015 15:35-16:35

P01 **Anna Bauß (Freiburg)**
Storage, transport, release: heme versatility in nitrite reductase electron transfer studied by molecular dynamics simulations

P02 **Frank Beierlein (Erlangen)**
The Effects of Alkali Ions on the Aggregation and Interfacial Adsorption of β-Lactoglobulin

P03 **Christiane Ehrt (Dortmund)**
Repurposing of known kinase inhibitors for inhibition of trypanothione synthetase

P04 **Hugo Gattuso (Lorraine)**
Modeling the Electronic Circular Dichroism of DNA and photosensitized DNA

P05 **Christian A. Hanke (Düsseldorf)**
Ligand-mediated and tertiary interactions cooperatively stabilize the P1 region in the guanine-sensing riboswitch

P06 **Anselm H. C. Horn (Erlangen)**
A Consistent AMBER Parameter Set for Zwitterionic Amino Acid Residues

P07 **L. Humbeck (Dortmund)**
Chemogenomics analysis of small molecule bioactivity data:
Privileged scaffolds and conserved structural elements in proteins

P08 **Michael C. Hutter (Saarbrücken)**
Anthraniloyl transfer in PqsD works without a catalytic triad

P09 **Christof M. Jäger (Nottingham)**
Metal binding in the radical SAM enzyme QueE – influencing the mechanistic outcome of radical reactions

P10 **Christophe Jardin (Erlangen)**
Binding properties of SUMO-interacting motifs

P11 **Anna Kahler (Erlangen)**
Dynamics of the Autoinhibited Transcription Factor RfaH

Poster Session I

Tuesday, March 10th 2015 15:35-16:35

P12 **Patrick Kibies (Dortmund)**
Electronic structure at high hydrostatic pressure

P13 **Kerstin Klauer (Erlangen)**
MD simulations of DNA recognition by the repressor AmtR

P14 **Dennis M. Krüger (Dortmund)**
In silico affinity optimization of modified peptides using non-natural amino acids

P15 **Marco Marazzi (Lorraine)**
Modeling the Electronic Absorption and Circular Dichroism Spectra of a Photo-switchable Bistable Peptide

P16 **Johannes T. Margraf (Erlangen)**
Periodic Calculations with NDDO Hamiltonians

P17 **Daniel Mulnaes (Düsseldorf)**
TopModel: A multiple-template meta-approach to homology modeling

P18 **Andreas M. Krause (Erlangen)**
Simulating Nanostructures: 2D-periodic organic semiconductors

P19 **Markus Pfau (Erlangen)**
Periodic DFT Study on the Adsorption of Different Linker Moieties on ZnO-Surface

Please remember to remove your posters on tuesday evening!

POSTER SESSION II

Wednesday, March 11th 2015 10:30-11:30

P01 **Harpreet Shah (München)**
Computer-aided modelling of protein conformations and ligand binding

P02 **Işılay Öztürk (Izmir)**
A Computational Study on Carboxymethylation Mechanism of Gluconate

P03 **Mehmet Ali Öztürk (Heidelberg)**
Brownian Dynamics Simulations of Linker Histone - Nucleosome Binding

P04 **M. Paulikat (Göttingen)**
Hybrid QM/MM studies of the UV-Vis absorption spectra of ThDP-dependent enzymes

P05 **J. Riehm (Saarbrücken)**
Redox Potentials of Bovine Adrenodoxins: Quantifying the Effects of Mutations

P06 **Anna Rudo (Dortmund)**
New approaches towards small molecular protein-protein interaction modulators

P07 **Achim Sandmann (Erlangen)**
Investigation of the Protein-DNA Binding Mechanism of Carbon Catabolite Protein A

P08 **Eileen Socher (Erlangen)**
pH-Dependent Dissociation of HdeA and HdeB Dimers

P09 **Thomas Steinbrecher (Schrödinger Inc.)**
Free Energy Calculations in Fragment Based Drug Design: Applying FEP in Practical Ligand Optimization

P10 **Alexander Steudele (Cetara, München)**
MUSE INVENT: Automated Reaction Driven Molecular Inventions Applied on a Fragment Growing Example

P11 **Joachim D. Stump (Erlangen)**
Molecular Dynamics of Viral IE1 Protein and Its Relevance for PML Interaction

Poster Session II

Wednesday, March 11th 2015 10:30-11:30

P12 **Martin Urban (Dortmund)**
Ionic conductance and selectivity of hydrophobic nanopores

P13 **S. Weigang (Dortmund)**
Design, analysis and virtual screening of an in silico dynamic combinatorial compound library with focus on protein-protein interaction inhibitors

P14 **Thorsten Will (Saarbrücken)**
Batch tautomer generation and more with MolTPC

P15 **A. Wuttke (Göttingen)**
Dispersion through the eyes of local orbital spaces

P16 **Dmitry Sharapa (Erlangen)**
Cubic C8 – An Aromatic Carbon Cluster?

P17 **Tanushree Jaitly (Erlangen)**
Properties of Confined Water Between two Hydrophilic Surfaces

P18 **Muhammad Akram (Innsbruck)**
Pharmacophore modeling and virtual screening to discover cytochrome P450 17 inhibitors among environmental chemicals

P19 **Lara A. Zimmermann (Florianópolis)**
Synthesis of new heterocyclic compound, as analogue derivative of grandisin and veraguensin neolignans, with potential anti-trypanosomatid activity

All poster abstracts are available here:
www.mmws2015.mgms-ds.de/

Characterization of the HPA-1 polymorphism by MD simulations and FRET measurements

Giulia Pagani[1], Joana Patrícia Ventura Pereira[2], Nadine Homeyer[1], Volker R. Stoldt[2], Rüdiger E. Scharf[2], Holger Gohlke[1]

[1]Dept. of Pharmaceutical and Medicinal Chemistry, Heinrich Heine University, [2]Dept. of Experimental and Clinical Hemostasis, Hemotherapy, and Transfusion Medicine, Heinrich Heine University Medical Center

The human platelet antigen (HPA)-1 is a diallelic alloimmune system carried by the megakaryocyte/platelet-specific integrin $\alpha_{IIb}\beta_3$, which mediates platelet adhesion and aggregation; $\alpha_{IIb}\beta_3$ is essential for hemostasis but can also induce pathological thrombus formation. The HPA1 polymorphism of $\alpha_{IIb}\beta_3$ is characterized by a leucine-to-proline exchange at residue 33 of the mature β_3 subunit. Consequently, the HPA-1 pattern can be expressed as either HPA-1a (Leu33) or its variant isoform HPA-1b (Pro33) [1]. This mutation is clinically relevant, since patients with coronary artery disease, who carry the HPA-1b allele, experience their myocardial infarction 5.2 years earlier than HPA-1a/1a patients [2]. Thus, HPA-1b is a prothrombotic variant of $\alpha_{IIb}\beta_3$, as also shown by increased adhesion, increased thrombus stability, and increased outside-in signaling. However, the underlying mechanism by which the mutation contributes to the prothrombotic properties of the variant integrin has remained elusive so far.

Integrins exist in two main and mutually exclusive conformations: The bent, closed form and the unbent, open structure. Local and global structural rearrangements are required in going from the closed to the open form, thereby leading to integrin activation. In the present study, a combined strategy, integrating large-scale all-atom molecular dynamics (MD) simulations with FRET measurements, was used to characterize the consequences of the Leu33→Pro33 exchange on the structural dynamics of $\alpha_{IIb}\beta_3$ at an atomic level. For MD simulations, the ectodomains of the two $\alpha_{IIb}\beta_3$ variants in the closed conformation were used as model systems, and simulations of in total 3 μs length were carried out. For the FRET measurements, transfected HEK293 cells stably expressing either the Leu33 or Pro33 isoform of $\alpha_{IIb}\beta_3$ were generated; cyan or yellow fluorescent proteins (CFP; YFP) were cloned to the C-termini of the α_{IIb} or β_3 subunits prior to transfection, respectively. FRET measurements were applied to explore conformational changes in the cytoplasmic tails upon integrin activation.

Comparative analyses of the MD trajectories revealed that Leu33 is involved in stabilizing interactions connecting the PSI domain in the head region and the nearby EGF-I and EGF-II domains in the leg region of the β_3 subunit. The absence of this network of interactions in the Pro33 variant gives rise to an instability that gradually affects the entire structure, thus leading to the system being globally less stable. In agreement to our findings, upon integrin activation, FRET analyses indicated a more extended spatial separation (> 100 Å) of the cytoplasmic tails in Pro33 than in Leu33 cell clones ($p = 0.003$). Taken together, these results provide an explanation how the fine-tuned conformational equilibrium of the integrin can be allosterically influenced by a single-point mutation located more than 90 Å away from any ligand binding sites of the integrin.

[1] Kunicki, T.J., Newman, P.J., *Blood*, **1992**, *80*, 1386-1404.
[2] Scharf R.E. et al., *J. Thromb. Haemost.*, **2005**, *3*, 1522-1593.

Theoretical study of DNA photosensitized by an artifical nucleobase: a model toward the 6-4 photoproduct.

Hugo Gattuso[a], Emmanuelle Bignon[b], Elise Dumont[b], Xavier Assfeld[a], Antonio Monari[a].

[a] *Université de Lorraine/CNRS, Théorie-Modélisation-Simulation, SRSMC, Nancy, France.*

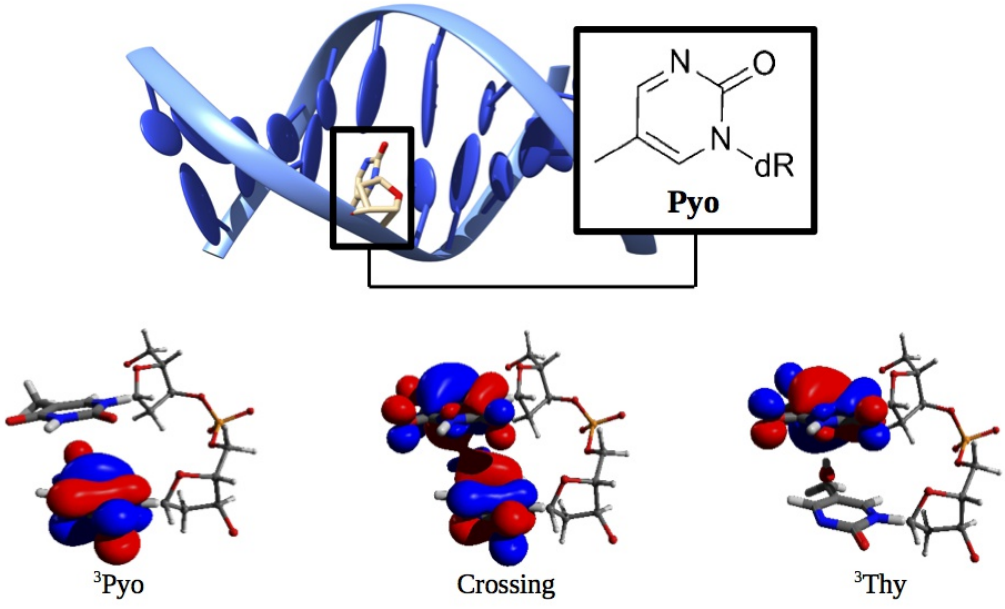
[b] *Ecole Normale Superieure de Lyon, Laboratoire de Chimie, Lyon, France.*

The photosensibility of DNA may cause structural modifications of its nucleobases structure under the irradiation of ultraviolet light (UV). This phenomenon can lead to mutations of DNA genes resulting by example in some cases to skin cancer. One famous lesion is the formation of thymidine dimers 6-4 photoproduct (6-4PP) which has been deeply studied to understand the mechanistic details of its formation. From experimental researches [1], it as been described that the main active chromophore of the 6-4PP is the 1-(β-D-2'-deoxyribosyl)-5-methyl-2-pyrimidone (Pyo).

According to this, we decided to investigate, in the DNA environment, the photoactivity of Pyo as a model toward a further study of 6-4PP [2]. This chromophore thus represents an artificial nucleobase directly integrated in the DNA helix.

The system we choose for this work is a crystallographic structure from the PDB databank of a double stranded B-DNA dodecamer (the sequence is CGCATPyoACGC). Then, several properties were obtained by using molecular modeling:

- The stability and the structural global induced distortion of the Pyo-containing double helix from **molecular dynamic simulations** (MD).
- Using a **QMMM** formalism, the **absorption**, **emission** and **circular dichroim** of the system.
- Finally the **triplet energy transfer** of Pyo to the close-by thymine (Thy) was characterized by obtaining adiabatic energy profiles for the phenomenon.



[1] V. Victoria-Criado et al., *Angew. Chem. Int. Ed.*, **2013**, 52, 6476-6479.
[2] H. Gattuso et al. In preparation.

Arginine-Vasopressin and its V2 Receptor: Binding Pathways, Kinetics and Thermodynamics

Noureldin Saleh,[a] Elke Haensele,[b] Lee Banting,[b] Jana Sopkova-de Oliveira Santos,[c] David C. Whitley,[b] Giorgio Saldino,[d] Francesco L. Gervasio,[d] Ronan Bureau[c] and Timothy Clark*[a, b]

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[c] Prof. J. Sopkova-de Oliveira Santos, Prof. R. Bureau

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UPRES EA 4258 - FR CNRS 3038 INC3M

Boulevard Becquerel, 14032 CAEN Cedex, France.

[d] Dr. G. Saladino, Prof. F. L. Gervasio

Department of Chemistry and Institute of Structural and Molecular Biology, University College London, London WC1E 6BT, United Kingdom.

G-protein coupled receptors, GPCRs, are a family of highly similar membrane proteins that plays a critical role in cell communication. However, the crystallization of GPCRs remains far more challenging than for soluble proteins. Despite the absence of crystal structures for the vasopressin receptor subtypes, mutagenesis studies aimed at characterizing the receptor-ligand binding and essential interacting domains have shed some light on interactions between the receptor and the peptide hormone. Arginine vasopressin (AVP) is a neuropeptide most well known for its antidiuretic and vasopressor effects. The vasopressin 2 receptor (V2R) is of particular interest because it is localized in the renal collecting duct and represents a selective target for the antidiuretic effect of AVP.

We used a neurotensin carrier protein complex (PDB ID: 4GRV)[1] as a template after reconstruction of a missing N-terminusm that has been described to be essential for AVP binding [2]. Long-scale molecular dynamics (MD) simulations were used to determine the structure of the V2R-AVP complex and, in conjunction with enhanced sampling techniques to simulate the docking event and estimate the binding free energy. Possible binding pathways were thus identified and potential allosteric binding site for the design of V2R antagonists detected.

[1] White, J. F.; Noinaj, N.; Shibata, Y.; Love, J.; Kloss, B.; Xu, F.; Gvozdenovic-Jeremic, J.; Shah, P.; Shiloach, J.; Tate, C. G.; Grisshammer, R. Nature 2012, 490, 508.
[2] Hawtin, S. R.; Wesley, V. J.; Parslow, R. A.; Patel, S.; Wheatley, M. Biochemistry 2000, 39, 13524.

Enhanced samping techniques and their application to the study of small substrate translocation

Tommaso D'Agostino, Matteo Ceccarelli

Department of Physics, University of Cagliari

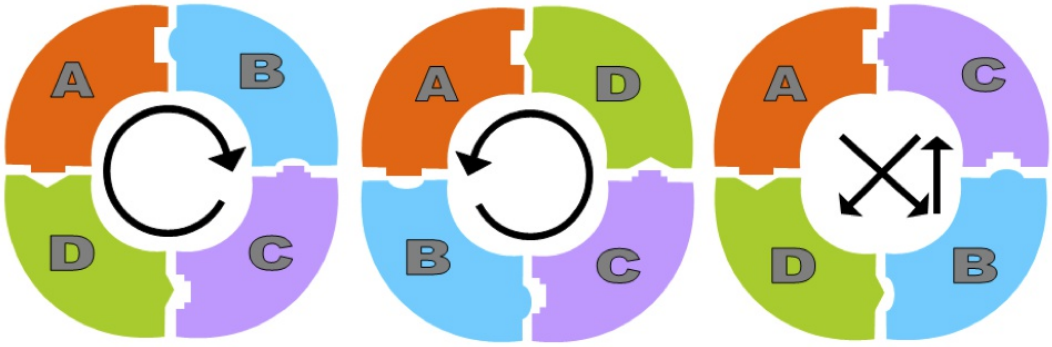
In the last years, computational methods have acquired a great importance in the study of biological processes, allowing to study the differences caused by point-charge mutations and interactions between single pairs of molecules. One the major problems of molecular dynamics simulations is that the time scales that are currently accessible through this technique are restricted to the order of microseconds. Enhanced sampling techniques allow to speed up specific processes by biasing the evolution over time of the systems of interest, either by forcing the change of variables that are thought of characterizing the processes under study, or by periodically changing the temperature of the system, thus enabling increased transition rates between processes with low probabilities. In this work, we discuss the most known enhancing sampling techniques, with particular emphasis on metadynamics, see Bonomi et al. [1]. We then apply this technique to the study of the permeability of the outer membrane of gram negative bacteria, a problem that is directly correlated to the multidrug resistance that many re-emerging pathogens are showing in the last decade. We show that metadynamics offers a novel way of studying processes that are characterized by steep free energy barriers, allowing not only to speed up the exploration of the system, but also to determine the relative probabilities of different paths in the exploration of the free energy of the process.

[1] M. Bonomi, D. Branduardi, G. Bussim C. Camilloni, D. Provasi, P. Raiteri, D. Donadio, F. Marinelli, F. Pietrucci, R.A. Broglia, M. Parrinello, Comp. Phys. Comm., **2009**, 180, 1961-1972

Protein interfaces and assembly of heteromeric Nav1.8 ion channels

Guido Humpert[1,2], Daniel Hoffmann[2] and Achim Kless[1]

[1] *Grünenthal GmbH, Drug Discovery, Aachen, Germany,* [2] *University Duisburg-Essen, Center for Medical Biology, Research Group Bioinformatics, Essen, Germany*



Clockwise (cw) **Counter-clockwise (ccw)** **Cross-linked (cross)**

In this work we analyse the formation of heteromeric voltage gated ion channels. In contrast to bacterial homomeric ion channels that have been investigated in the last decade by crystallographic methods, the assembly of heteromeric human ion channels has yet to be studied. Subsequently, we have built homology models of human Nav1.8 sodium channels with all possible associations to study their assembly by computational methods. This includes the possible orientations of clockwise, counter-clockwise and cross-linked models. The side chain conformational landscape has been explored with molecular dynamics simulations.

The focus of the presentation will include the analysis of protein interfaces between the domains as well as the formed patches of these models with various energetic measures. Herein the Rosetta program suite including implemented scores and forcefield energies at different time points play a decisive role.

As a result the key drivers for the domain associations will be summarized with respect to the applied methods.

[1] Rosetta program suite: A. Leaver-Fay, M. Tyka, S. Lewis, O. Lange, J. Thompson, et al., Methods Enzymol., 2011, 487, 545–574.
[2] R. A. Li, I. L. Ennis, R. J. French, S. C. Dudley Jr., G. F. Tomaselli, E. Marbán, J. Biol. Chem., 2001, 276, 11072-11077.
[3] S. C. Dudley Jr., N. Chang, J. Hall, G. Lipkind, H. A. Fozzard, R. J. French, J Gen Physiol., 2000, 116, 679-690.
[4] Molecular Operating Environment (MOE), 2013.08; Chemical Computing Group Inc., 1010 Sherbooke St. West, Suite #910, Montreal, QC, Canada, H3A 2R7, 2013.

Targeting Fundamental Aspects of Protein-Ligand Interactions to Improve Computer-Aided Molecular Design

Anna Linusson

University of Umeå

Molecular recognition, based on non-covalent interactions between protein and ligands, plays a key role in biological processes. Currently we lack detailed knowledge and understanding of the factors influencing protein-ligand binding, which substantially retards rational drug design. Our approach is to design and synthesize sets of organic molecules that are used as chemical probes to target fundamental aspects of protein-ligand interactions, including the electronic properties, enthalpy/entropy components, dynamics, and solvent effects. The experimental data is scrutinized and used for model building using chemometrics, quantum mechanics and molecular modelling. The presentation will, for example, include studies of aromatic interactions and non-classical hydrogen bonds between protein and ligands, using acetylcholinesterase as the model system. The research is conducted with the objective to contribute to increased mechanistic knowledge, and to the discovery of antidotes for nerve agent/pesticide intoxication and new insecticides to combat mosquito-borne vector diseases.

Modeling Self-Assembly of Phosphonic Acids on α-Aluminum Oxide

Hanno Dietrich[1,2], Dirk Zahn[1,2]

[1] *Computer-Chemie-Centrum and Interdisciplinary Center for Molecular Materials, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Nägelsbachstraße 25, 91052 Erlangen, Germany*

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

Computational modeling of diffusion-limited processes such as the formation of self-assembled monolayers (SAMs) is still a challenging task due to the large timescales. [1] Here, we present a modified Kawska-Zahn approach, [2] in which steered dynamics simulations and Monte-Carlo steps are combined to mimic chemisorption of various phosphonic acids (PAs) on the α-Al_2O_3 (0001) surface.

Our studies reveal that in vacuum the aliphatic PA molecules first form patches on the surface, analogous to the striped phase in the early stage of SAM formation of alkanethiols on gold. [3] Subsequent adsorption leads to a disordered amorphous phase with a high concentration of gauche defects from which ordered domains emerge upon further adsorption. In 2-propanol, by contrast, the unpolar chains do not cling to the polar surface as they are better stabilized by the solvent. Thus the overall order of the wet SAM is higher than in the dry state.

In agreement with experimental evidence from Peukert *et al*., the simulations show that molecules from solution are also incorporated in inverted adsorption geometry with the PA anchor remaining solvated. These loosely bound molecules increase order when the solvent is evaporated, but are dissolved again after subsequent re-immersion, whereby the ordering in the monolayer is diminished. Repeated de-wetting and re-immersion can hence improve the SAM quality as molecules bound in inverted adsorption geometry are dissolved and reincorporated into the monolayer in correct binding geometry. [6]

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Simulating Nanostructures: 2D-periodic organic semiconductors

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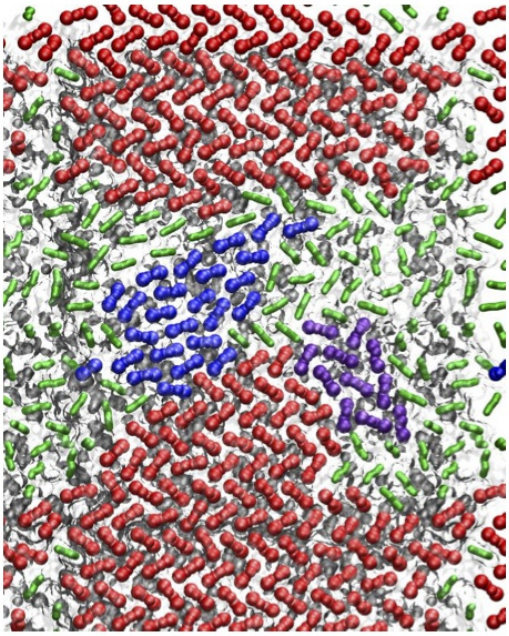
Organic semi-conductors surround us in daily life. Two years ago we have presented an n–type semiconductor system of C_{60}–C_{18}–PA.[1] Now we have simulated and analysed a p–type organic semi-conductor system of benzothieno[3,2—b][1]benzothiophene (BTBT) on an aluminum oxide surface. Special focus in this part of the work is the structure of organic molecules. Differences in structure between C_{11} and C_{12} BTBT have been worked out which agree with experimental results. In this talk we present results we have gained from molecular dynamic simulations we have performed on this 2D system.



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First principles sampling and representation of a reduced molecular potential energy surface

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Flexible organic molecules can adopt a variety of conformations that can interconvert. Here we describe our efforts to employ first principles to study the dynamics of such conformational ensemble and to investigate the potential energy surface (PES) of a well-characterized synthetic peptide γα [1].

We utilize a genetic algorithm based search for sampling the conformational space of the γα peptide. We combine the conformers found by the algorithm with reference conformers [1] and create a conformational ensemble of 73 conformers with a relative energy below 0.3 eV. A transition between two conformers can be direct, with a single barrier, or indirect, i.e. combined from multiple direct transitions. We assume that pairs of conformers connected by a direct transition are geometrically similar and interconvert via a limited number of rotations around single bonds. We construct a similarity matrix by calculating torsional RMSD for all conformer pairs. Subsequently, we remove all values exceeding a threshold of 0.3 rad and convert the matrix to a network, where the nodes represent conformers and the edges their distance in torsion angle space. We employ the shortest path Dijkstra algorithm in order to connect the 10 energetically lowest conformers to obtain a reduced network. For each of the pairs of conformers from the reduced network we suggest a transition path. The paths are optimized by the aimsChain routine that implements the string method and the corresponding transition states are identified. We present the results in form of a barrier tree and in form of a disconnectivity graph. Furthermore we use the obtained information to verify the conformational coverage of the global search. In addition we investigate the relation between the alternatives to the torsional RMSD as a similarity metric and the composition of the reduced network.

Our approach does not only provide a reduced and meaningful representation of the PES, it also provides an ideal starting point to refer to experiments and towards generation of free energy surfaces by biased molecular dynamics techniques.

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Integral equation-based quantum solvation model for quantitative prediction of hydration free energies

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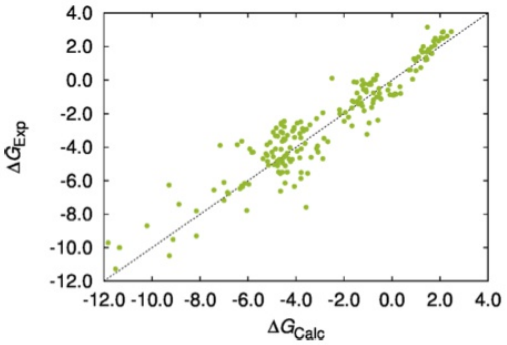
The "embedded cluster reference interaction site model" (EC-RISM) [1] combines statistical-mechanical 3D RISM integral equation (IE) theory and quantum-chemical calculations in a self-consistent manner. In the past, application of approximate closure relations allowed us to compute relative thermodynamic quantities such as pK_a shifts [1,2] and tautomer ratios [3] in aqueous and nonaqueous solution with high accuracy; the quality of the wave function in solution has been demonstrated by successful calculation of chemical shifts related to nuclear magnetic resonance (NMR) spectroscopy. [4]

However, absolute solvation free energies suffer from well-known systematic deficits with available closure approximations. One way to semiempirically compensate for these artifacts is to fit a corrective term related to the partial molar volume (PMV) of the solute [5,6] such that experimentally measured hydration free energies match IE predictions. Since such an approach has not been attempted for a self-consistent quantum solvation model, we here present a two-step correction workflow by fitting EC-RISM hydration free energies to data taken from the MNSOL database [7]. We demonstrate the promising performance in the context of the chosen levels of theory, conformational sampling, and different forms of the PMV correction.



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Exploiting the Transferability of Extremely Localized Molecular Orbitals to Study Large Biological Systems

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Nowadays, one of the goals of theoretical chemistry consists in developing new quantum mechanical strategies to study large molecular systems at a sensitively reduced computational cost. In this context several research groups have developed different linear scaling methods [1-3] that have been successfully used in important fields, such as molecular material modeling and drug design.

A very interesting option to address this challenge is based on the observation that molecules are generally constituted by recurrent functional groups that roughly maintain the same properties in different chemical environments. Therefore, following a sort of LEGO approach [4], one could imagine to define transferable localized Molecular Orbitals (MOs) describing the above mentioned functional units, which would allow to almost instantaneously obtain the wave function (or the electron density) of a very large system.

Unfortunately, the canonical Hartree-Fock MOs and the traditional localized MOs are completely or partially delocalized on the whole systems on which they are calculated and, therefore, they are not suitable for our purpose. Nevertheless, it is possible to resort to the concept of Extremely Localized Molecular Orbitals (ELMOS) [5] that are orbitals strictly localized on small molecular functional units and can be easily transferred [6, 7] from a molecule to another one.

Our main goal is to construct a database of ELMOs that cover all the possible functional groups of the twenty natural amino acids. To accomplish this task we have started investigating in detail the transferability of the Extremely Localized Molecular Orbitals to quite large biomolecular systems (e.g. Leu-enkephalin polypeptide). In particular, we have compared the resulting electron densities to charge distributions both calculated by means of more traditional and expensive methods, and obtained through the transfer of experimental pseudo-atoms [8], which are used to refine protein crystallographic structures.

The obtained results are in good agreement with the considered benchmarks and a general database of ELMOs is currently under construction.

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Molecular Design in Drug Discovery: Applications and Challenges

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Molecular Design plays an important role in modern Drug Discovery. It is applied in lead generation for identification and fine-tuning of suitable hits and leads. Furthermore, in lead optimization Molecular Design plays a pivotal role in turning lead series into preclinical candidates.

This presentation outlines Molecular Design principles in particular in small molecule lead optimization. For example, application of our SALI Explorer in structure-activity relationships (SAR) fosters the early identification of SAR hot spots within lead series. Subsequent quantitative structure-activity relationship is then applied to optimize compounds against the target of interest.

Most often lead series suffer from poor ADMET profiles and/or anti-target activities which have to be taken into account in optimization. We have implemented several predictive data mining tools in the field of ADMET- and anti-target (e.g. hERG, CYPs) modeling. A few examples outline the scope and applicability of these tools for Medicinal Chemists and Drug Designers. In addition, in silico profiling of molecules against off-targets allows fast and early identification of liabilities of putative lead series.

The ultimate challenge of multidimensional compound optimization (MDCO) requires an early definition of the candidate profile in order to derive the multidimensionality of the problem. Suitable fitness functions can then be derived and applied in MDCO.

The increasing interest in peptides and biologicals (e.g. proteins, antibodies) as drugs opens new opportunities for Molecular Modeling. For example, peptide design becomes more and more important in order to synthesize only the most important peptides while taking into account their physicochemical properties. In the field of antibodies, Molecular Design plays an important role to ensure proper physicochemical properties (e.g. solubility, aggregation) of the biologicals.

Conformational sampling of drug-like molecules in solution with quantum-chemical accuracy

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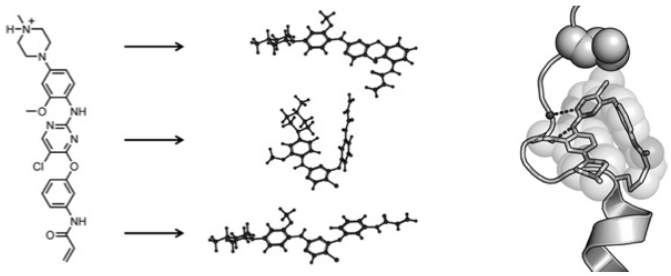
Accurate assessment of the conformational space of drug-like molecules in free solution is a frequently underestimated, yet relevant ingredient of molecular design. In particular, predicting and controlling free ligand conformations is essential for minimizing the entropic penalty to reorganize a ligand's geometry upon binding to a protein. Overcoming the deficiencies of common small molecule force fields represents a particular challenge due to the considerable computational cost of high-level quantum-chemical calculations for predicting the conformational manifold.



Here we demonstrate the performance of a hierarchical filtering scheme that allows for the identification of dominant conformations together with their proper statistical weights measured by their free energies in solution with quantum-chemical accuracy. The automated workflow implies a sequence of force field-based high-temperature molecular dynamics simulations using implicit solvent models, clustering and filtering steps, and high-level geometry optimizations in solution employing the polarizable continuum model (PCM) as well as the embedded cluster reference interaction site model (EC-RISM) [1] for scoring and calculation of theoretical NMR spectra [2] to be compared with experiments. We apply the workflow to variants of the protein kinase inhibitor WZ4002 that is highly active against a drug-resistant mutant of the epidermal growth factor receptor (EGFR-T790M). [3,4] The relative significance of conformational pre-arrangement in comparison with modulation of direct protein-ligand interactions upon chemical substitution is discussed.

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EDIA – A New Estimate of Electron Density of Individual Atoms for Validating Water Molecules

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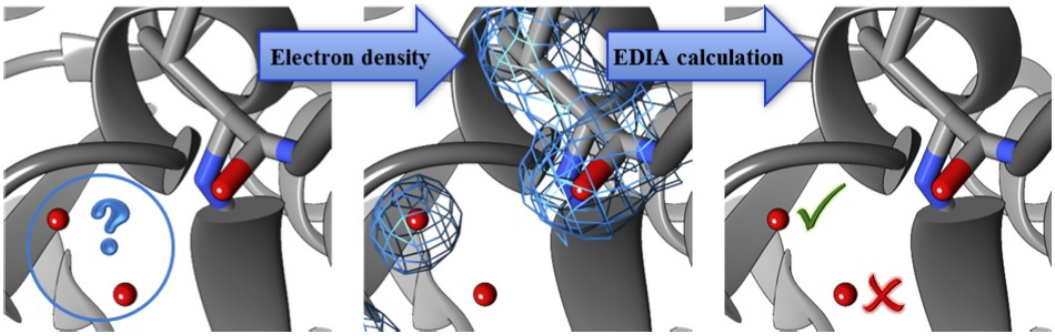

Water plays a key role in all biological systems. It forms part of the environment for biological macromolecules, mediates between protein-ligand as well as protein-protein interactions, and is indispensable for thermodynamic properties such as the hydrophobic effect.

Lately, more attention was put on water molecules being predicted and classified by a broad range of methods, such as WaterMap [1], SZMAP [2], or WaterScore [3]. Rarely those methods have been correlated in an extensive statistical analysis with water molecules from PDB structures. The only experimental evidence available for water molecules is the electron density, which has so far been completely neglected. Existing measurements concerning electron density quality like RSR and RSCC show drawbacks especially on single water molecules. [4],[5]

Therefore, we have developed a new estimate of electron density around individual atoms, called EDIA. It is an intuitive value, taking into account the experimental data from electron density within the van-der-Waals radius of an atom. A high-resolution subset from the PDB [6] with resolution better than 1.5 Å was compiled, consisting of 5,485 PDB structures containing more than 2.3 million water molecules. EDIA values were calculated for all water molecules. According to existing electron density a further characterization was performed into resolved and unresolved water molecules. In a subsequent analysis diverse structural criteria such as number of hydrogen bonds, the hydrogen bonding partners, as well as preferred environments, were evaluated.

About 9% of water molecules of the whole data set were not characterized as well resolved. This highlights the importance of taking electron density into account in order to avoid incorporating noise into any analysis concerning water molecules. Our data set will be made freely available, including EDIA values and our analysis concerning structural characteristics. This data set can help improving and validating computational methods for placing water molecules.

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TopModel: A multiple-template meta-approach to homology modeling

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Protein structure prediction is one of the most important problems in computational biology, and is key to understanding structural evolution, protein function, protein-ligand and protein-protein interactions, and for data-driven protein- or drug-design [1,2]. However, the current rate of structure determination by experimental methods is far exceeded by that of next-generation sequencing, to the point where only for 1/1000th of the known protein sequences a structure is known. For this problem, computational structure prediction is considered the best solution [3]. In the last decade, many methods have been developed in each of the computational fields necessary for automated structure prediction. The bi-annual community-wide blind experiment CASP evaluates the accuracy of work flows that integrate a subset of these methods, and has shown the value of meta- and consensus-approaches [3,4]. This work presents TopModel, a multiple-template meta-approach to homology modeling, which combines multiple state-of-the-art threading, alignment, and model quality assessment programs to provide a versatile work flow and toolbox for structure prediction. TopModel yields high-quality structures [5,6] and performs well even for low sequence identities. When benchmarked against CASP10 targets, TopModel shows an accuracy above the average state-of-the-art work flow. We anticipate that as more programs are integrated, the accuracy and sensitivity of our methods will improve. Hence, we aim to expand TopModel to achieve more accurate modeling of proteins with multiple domains and protein-protein complexes as well as to use it to evaluate alignment and threading software in a consistent manner based on the quality of models produced by the generated alignments.

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An experimentally validated binding mode model of TGR5 agonists

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The structurally unknown G-protein coupled bile acid receptor (GPCR) TGR5 is the first bile acid sensing GPCR and directly interacts with $G\alpha_s$, $G\alpha_{i3}$, and $G\alpha_q$ subunits of the G-proteins [1]. TGR5 is highly expressed in the brain, the liver, and the gastrointestinal tract. Furthermore, TGR5 is an emerging target for the treatment of metabolic diseases [2-4]. Hence, much effort has been dedicated to the synthesis of potent and selective TGR5 agonists [5]. However, the lack of an experimentally determined binding mode makes the rational design of compounds with improved activity difficult. Recently, Macchiarulo *et al.* [6] proposed a binding mode of natural and synthetic bile acids in TGR5 based on single template homology modeling, molecular docking, and mutational analysis. However, this binding mode lacks interactions with transmembrane helices (TM) 5 and 6, which are considered essential for GPCR activation [7, 8]. Furthermore, the binding mode of Macchiarulo *et al.* does not address E169 in TM 5, which is a conserved residue within the TGR5 family and important for receptor activation [6].

Here, we present an experimentally validated binding mode of 68 TGR5 agonists, including natural and synthetic bile acids and neurosteroids. We employed a combined strategy of multi-template homology modeling, molecular docking, and structure-based 3D-QSAR analysis using the AFMoC approach with subsequent mutational analysis and molecular dynamics simulations. After two cycles of this strategy, the superimpositioning of all ligands within the orthosteric site of TGR5 results in a good AFMoC model (q^2 = 0.50), thus indicating that differences in the agonist structures correlate with differences in experimentally determined pEC_{50} values in the predicted binding mode. Based on this binding mode, mutations of eight amino acids were suggested that should either influence agonist binding or TGR5 activation. Activity analysis using cAMP reporter gene assays and FACS analysis for membrane localization confirmed these predictions in all cases. This provides strong support to the validity of the binding mode. Our binding mode differs from the binding mode by Macchiarulo *et al.* in three important aspects: I) The cholane moiety is rotated by 180°; II) the sidechains of bile acids bind to R79, which is 12 Å away from the respective interaction partner postulated in [6]; III) agonists address residues in TM 5 and 6, which are essential for receptor activation. The binding mode is expected to aid in the structure-based design of new TGR5 agonists.

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On our Way to the Automated Search for Ligand-Sensing Cores

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The investigation of protein-ligand interactions is one of the prerequisites for structure-based design of small molecule modulators of protein function. These interactions can be regarded based on structural similarity of secondary structure elements with impact on rational drug design [1]. The basic idea of the presented approach is the fact that a similar spatial arrangement of secondary structure elements around the binding site ('ligand-sensing cores') can recognize similar scaffolds independent of the overall fold [2]. The discovery of Namoline as a lysine-specific demethylase [1] (LSD1) inhibitor, which impairs the growth of prostate cancer cells, by Willmann et al. demonstrated the pharmaceutical relevance of this concept [3]. However, to date there is no automated procedure available to compare 'ligand-sensing cores' of various proteins.

We will present the results of our ongoing progress to develop an automated computational method to identify 'ligand-sensing cores' in binding pockets of otherwise unrelated proteins for all known protein structures and possibilities. Our current approach is based on detecting maximum common sub-graphs (MCS) of labeled graphs determined by variants of the Bron Kerbosch [4] maximum clique detection algorithm in appropriately defined product graphs.

In the end, the complete information of all similar ligand-sensing cores within all known protein structures will provide access to previously unused data to predict polypharmacology and to identify new lead structures. Therefore, this development leads to a valuable tool for rational drug design which will be demonstrated by the presentation of interim results achieved on test data sets based on different targets. On top of that, we are very confident to be able to determine all ligand-sensing cores of all known proteins any time soon.

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The Quest for Accurate Semiempirical Methods

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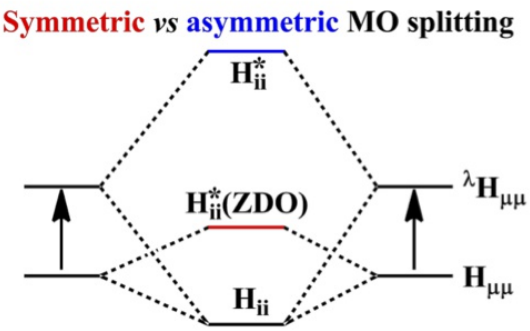
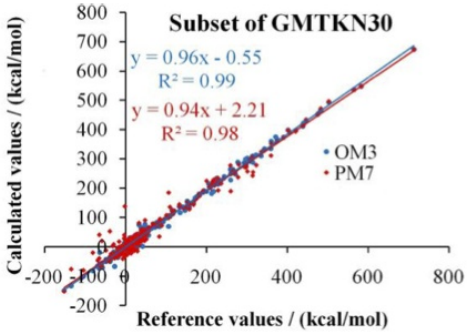
Semiempirical quantum chemical (SQC) methods are computationally efficient techniques for calculating electronic structure properties of very large systems or for a huge number of smaller systems, for which other quantum chemical methods would not be computationally feasible. Over the last decades SQC methods were systematically improved mainly using two distinct approaches, both starting from the MNDO model.

The first one concentrated on enhancements within the MNDO framework, primarily by modifying the core-core repulsion function and increasing the number of reference data used to fit the SQC parameters for more and more elements. The most widely used methods of this class are (in chronological order) AM1, PM3, MNDO/d, PDDG-MNDO and PDDG-PM3, AM1*, RM1, PM6, and PM7. [1]

The second methodology focused on introducing explicit corrections to the MNDO model to account for the non-orthogonality of the basis set. Corresponding orthogonalization-corrected methods (OM*x*) OM1, OM2 and OM3 appear to be a practical tool for many applications, especially in excited-state studies. [1] Early excited-state benchmark studies revealed the higher accuracy of OM*x* methods compared to traditional SQC techniques, which is attributed to the asymmetric MO splitting in OM*x* methods. [1] Moreover, OM*x* methods were shown to be robust techniques for calculating ground-state properties with accuracy often similar to that of DFT. [2]





Here we significantly extend previous ground-state benchmark studies [1, 2] to test more SQC methods on huge collections of high-quality reference data. Our studies confirm the high robustness of OM*x* methods in comparison with other SQC methods and provide guidelines for choosing an appropriate SQC method for the problem at hand. [3]

We also benchmarked various explicit dispersion corrections to SQC methods on high-quality benchmark sets and determined the best combinations of SQC method and dispersion correction for different types of noncovalent interactions. [3]

Finally we outline current developments for improving the accuracy of SQC methods by using both traditional techniques and novel approaches based on machine learning.

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Computer-aided modelling of protein conformations and ligand binding

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Abstract

Processes like ligand binding, chemical modifications or changes in environmental conditions may result in conformational switching in proteins, affecting their function. The loss of associated function may also result in disease causing pathological conditions. Computer-aided modelling and simulations of protein systems serve as an important tool to study protein dynamics. By employing certain proteins and peptide models we have tried to understand two aspects of protein dynamics: folding and ligand binding. For folding, we modelled systems involved in local conformational changes such as Alzheimer's causing α→β transitions and sequences involved in early events of protein folding. Characterization of these model systems, with or without the protein context, revealed the importance of primary sequence, environmental conditions, and tertiary contacts provided by the pre-existing protein environment. In ligand binding studies, blind docking simulations and structure-based screening methods were used. Investigation of structural features and specific protein-ligand interactions determined binding pose and hence distinguished binders from non-binders. These features may be used to design scoring functions for developing accelerated screening methods and drug designing.

Keywords Protein Folding, Conformational Modelling, Ligand Binding, Molecular Dynamics, Molecular Docking

Including quantum nonadiabatic effects into molecular dynamics simulations

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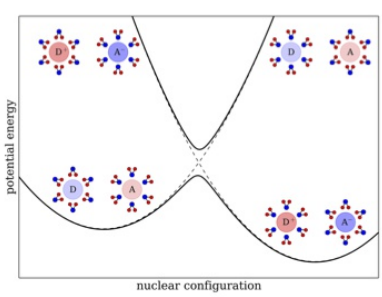

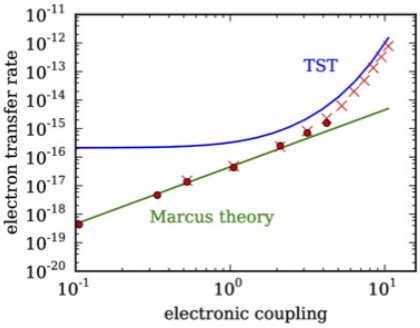

Nonadiabatic processes, such as those induced by photoabsorption or which describe electron transfer, are present in many areas of physical and biological science including chemical reactions, solar cells, vision, photosynthesis, DNA radiation damage and electronic spectroscopy. It is necessary to consider the excited electronic states in order to describe such processes correctly, and thus standard molecular dynamics techniques, which rely on the Born-Oppenheimer approximation, are not appropriate.

We have recently developed a nonadiabatic dynamics method [1], which like molecular dynamics simulations is based on trajectories and can therefore be applied to complex systems of interest. This new method employs a ring-polymer molecular dynamics (RPMD) [2] formulation of the nonadiabatic mapping approach [3] and is capable of describing the quantum effects of delocalization, zero-point energy and tunnelling as well as nonadiabaticity, without requiring the expensive propagation of nuclear wavefunctions.

We employ our nonadiabatic RPMD method to compute the rates of electron-transfer reactions and show how the important concept of the transition-state can be generalized to this type of reaction. This provides a simple extension to the commonly-used Marcus theory for systems with free-energy surfaces which cannot be described as harmonic oscillators [4].

The method also has the ability to simulate electronic spectroscopy in the condensed phase and describes the dynamics in a novel way with the ring polymer delocalized simultaneously over both the ground- and excited-states. As the method can in princple be efficiently combined with an on-the-fly calculation of the potential energy surfaces, it provides an excellent opportunity to interpret the absorption spectra of a wide variety of complex molecular systems.

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Imperfect Interatomic Potentials in the Molecular Dynamics Simulation of Copper and Diamond in Nanomachining

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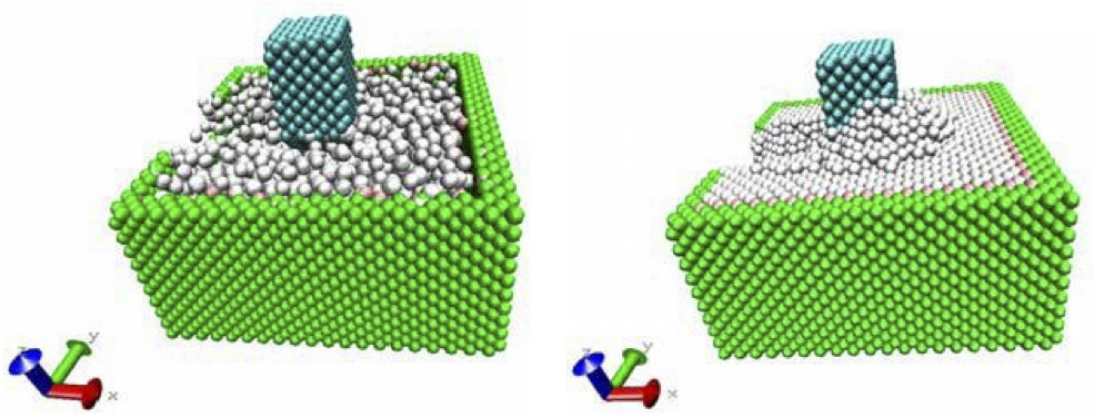

(a) (b)

Figure 1: Simulation results with (a) LJ potential (b) EAM potential

One crucial task in classical Molecular Dynamics (MD) simulation is the selection of appropriate interatomic potentials for the materials under investigation. If this is not properly done, it may lead to nonsensical results. In view of this, three popular interatomic potentials, namely the Lennard-Jones (LJ), Morse and Embedded Atomic Method, were used for the modeling of copper workpiece in nanometric machining. (The diamond cutting tool was treated as a rigid body). Figure 1 [1], [2] clearly shows the effects of the various potentials in the simulation. The EAM appears to model the copper atoms most accurately, as it best describes the metallic bonding of the atoms.

In other set of simulations, the effect of interatomic potentials on the prediction of the onset of plastic deformation in nanomachining was studied [3]. The pile-up volume and the force ratio were indicative of the onset of plasticity during the machining. The pile-up volume showed that ploughing starts from around 0.2 – 0.3nm, whereas the force ratio predicted the onset of plastic deformation from 0.1nm – 0.3nm. Also, the effects of interatomic potentials on the determination of the minimum depth of cut in nanomachining were investigated [4]. It was observed that the formation of chip initiates from the depth of cut thickness of 1.5nm. It is evident that for the MD method to be a viable predictive tool, suitable potentials are needed and the simulation results must be validated by experiments.

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Modeling the Electronic Absorption and Circular Dichroism Spectra of a Photo-switchable Bistable Peptide

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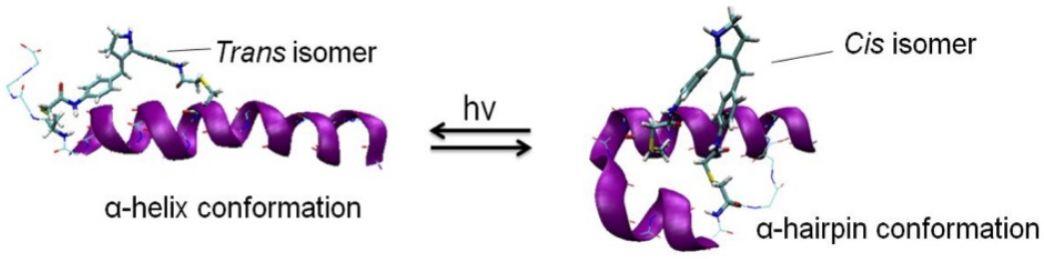
The control of biomolecular systems can be achieved through the application of photo-switches. Especially, a retinal like photo-switch based on E/Z photo-isomerization was experimentally shown to be a relevant candidate for reversible control of the alpha helix peptide conformation [1].

Here, we focus on the understanding of the mechanism leading to the final response of the overall peptide. More in detail, molecular dynamics simulations were performed for the E- and Z-isomer linked peptide, as well as for the unlinked peptide, in order to reveal the overall conformational changes induced by the attachment of the photo-switch. Our results, supported by experimental data [1], show on average how the unlinked peptide is partially unfolded in water, whether the E-isomer linked peptide tends to increase the helical content, and the Z-isomer linked peptide produces peptide bending leading to an alpha hairpin conformation (see Figure).

In order to monitor the photo-switch conformation, its electronic absorption properties were calculated along the trajectory at the CASPT2//CASSCF/AMBER level of theory, while a spectral signature of the overall peptide conformational change was recorded by modeling the circular dichroism spectra in the framework of the Frenkel exciton theory [2,3] at the M062X/AMBER level of theory, including a polarizable force field.



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Free energy calculations to predict the effect of single point mutations on protein stability

Thomas Steinbrecher

Schrödinger

Predicting the effect of amino acid point mutations on protein stability via structure based computational modelling is a difficult but potentially very valuable task for protein engineering. Over the last few years, substantial experience has been accumulated in the related field of predicting ligand binding strengths from MD-based free energy (FEP+) calculations and we have found the overall approach to be highly transferable to questions of protein energetics. The general idea of mutating protein side chains via free energy simulation tool is not new, but has never been rigorously tested in practice. We have undertaken a large scale study of applying FEP+ to over 200 protein side chain mutations and have found very encouraging results on established public test data sets. The method matches or outperforms the predictive power of several alternative computational tools and is capable of correctly categorizing mutations as stabilizing or destabilizing in >85% of cases. We now aim at applying FEP+ for protein stability on real-world protein engineering questions.

Identifying Pathways out of the Aspartate Binding Pocket of the Phosphoenolpyruvate Carboxylase in C4 Plants

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Phosphoenolpyruvate carboxylase (PEPC) is an important enzyme for the process of carbon-fixation in plants. While in C3 plants carbon is stored in 3-phosphoglyceric acid, in C4 plants carbon is fixated as oxaloacetic acid. Most severe weeds known today are C4 plants. Therefore, inhibiting PEPC of C4 plants is a promising strategy for the development of novel and selective herbicides [1]. The activity of PEPC is negatively allosterically regulated by aspartate [2]. We aim at targeting the aspartate binding site of PEPC by structure- and ligand-based inhibitor design, making use of a recent crystal structure of PEPC from the C4 plant *Flaveria trinervia* [3] and initial hits identified recently [1]. However, visual inspection of the crystal structure revealed a very tight entrance region into the aspartate binding site. We thus investigated possible pathways out of this binding site in order to identify conformational adaptations of PEPC that may facilitate ligand escape and, in turn, to estimate which inhibitor size can still be accommodated for access.

We applied RAMD (Random Acceleration Molecular Dynamics) simulations implemented in NAMD [4] starting from complex models of aspartate or the inhibitor AG1433 [1] bound to PEPC. We performed 100 RAMD simulations of 1 ns length each. We investigated PEPC in the monomeric and dimeric state in order to investigate if and how the oligomeric state influences the escape.

We identified two main pathways out of the binding site, which are differently populated for aspartate and AG1433. The one uninfluenced by a second protomer passes by a positively polarized surface region of PEPC, which suggests favorable access for aspartate that way. Currently, the energetics of ligand access/escape along this pathway is investigated by MD simulations employing umbrella sampling, aiming at computing a potential of mean force.

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Storage, transport, release: heme versatility in nitrite reductase electron transfer studied by molecular dynamics simulations

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Nitrite reductases play an important role in the bacterial assimilation of nitrogen and the global nitrogen cycle. They use a notably large number of six electrons to reduce nitrite to ammonia. Applying molecular dynamics simulations of the thermodynamic integration type [1,2], we study the energetics and kinetics of electron transfer through the nitrite reductase enzyme of *Sulfospirillum deyleianum*, *Wolinella succinogenes* and *Campylobacter jejuni*. In all of these five-heme proteins, the storage of an even number of electrons within a monomeric chain is thermodynamically favoured. Kinetically, electrons are usually transferred in pairs. Although the free energy landscape for charge transfer varies significantly from organism to organism, the heme cofactor closest to the interface of a protein dimer always exhibits a particularly low ΔG, suggesting that protein dimerization is functional.

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The Effects of Alkali Ions on the Aggregation and Interfacial Adsorption of β-Lactoglobulin

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We report a combined experimental and computational study of the whey protein β-lactoglobulin (BLG) in different electrolyte solutions. Vibrational sum-frequency generation (SFG) and ellipsometry were used to investigate the molecular structure of BLG modified air-water interfaces as a function of LiCl, NaCl and KCl concentrations. Molecular dynamics (MD) simulations and thermodynamic integration provided details of the ion pairing of protein surface residues with alkali-metal cations. Our results at pH 6.2 indicate that BLG at the air-water interface forms mono- and bilayers preferably at low and high ionic strength, respectively. Results from SFG spectroscopy and ellipsometry are consistent with intimate ion pairing of alkali-metal cations with aspartate and glutamate carboxylates, which is shown to be more effective for smaller cations (Li^+ and Na^+). Ion pairing has several consequences: macroscopically, charge neutralization and even overcharging of the protein can be observed, while microscopically the local chemical environment of a solvated carboxylate is dramatically changed by complexation with a cation. MD simulations show not only carboxylate-alkali-metal ion pairs, but also ion multiplets with the alkali-metal ion in a bridging position between two or more carboxylates. Consequently, alkali-metal cations can bridge carboxylates not only within a monomer but also between monomers, thus providing an important dimerization mechanism between hydrophilic surface patches. Using MD simulations, we have investigated three protein surface areas involved in the formation of dimers, and identified one that is rich in carboxylate groups and thus likely to be involved in the formation of alkaline-bridged dimers.

Repurposing of known kinase inhibitors for inhibition of trypanothione synthetase

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Trypanothione synthetase (TryS) catalyzes the two-step biosynthesis of trypanothione, which is a key intermediate in trypanosomatid parasites of the species Trypanosoma and Leishmania. Thus, TryS is an attractive drug target to cope with diseases like Chagas disease, leishmaniasis, or African trypanosomiasis that affect approximately 15 to 20 million people worldwide. Interestingly, paullones, a chemical class of potent kinase (GSK-3) inhibitors, were shown to inhibit TryS. [1] Based on a comparison of available X-ray structures, the binding of paullones to TryS seems to be in accordance with the principle of 'ligand-sensing cores'. [2] The spatial arrangement of secondary structure elements around the ATP binding sites of TryS and kinases is quite similar, independent of the overall fold, which indicates binding of similar ligands.

Unfortunately, the available Leishmania major TryS X-ray structure (pdb-id 2vps) was solved without substrates and an important loop region of the ATP grasp fold is missing. Preliminary modeling and molecular dynamics (MD) simulation studies revealed possible binding modes of ATP, GSH and glutathionylspermidine (GSP). However, the bound state of the loop region remained unexplained. [3] A more detailed analysis that utilizes X-ray structure information of a related GSP synthetase from E. coli (pdb-id 2io7) led to a complete model of LmTryS, containing all substrates and the closed ATP grasp fold loop. Exhaustive MD simulations have confirmed this model as reasonable and revealed that the presence of ATP leads to a partial closure of an associated β-sheet over the bound triphosphate. Furthermore, this validated model gave us the possibility to model the structures of TryS from other pathogenic species of Trypanosoma and Leishmania and to compare their ATP binding sites with respect to rational drug design.

Here we present the results of different MD simulations and show how the obtained models can be used to identify further (kinase) inhibitors that own a similar molecular scaffold. These inhibitors can then be diversified to obtain selective TryS inhibitors. The approach includes a detailed comparison of the full ATP binding pocket of TryS to known kinase X-ray structures as well as docking studies of kinase inhibitors received from different kinase databases. Biochemical testing of newly identified kinase inhibitors for inhibition of TryS will be carried out.

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Modeling the Electronic Circular Dichroism of DNA and photosensitized DNA

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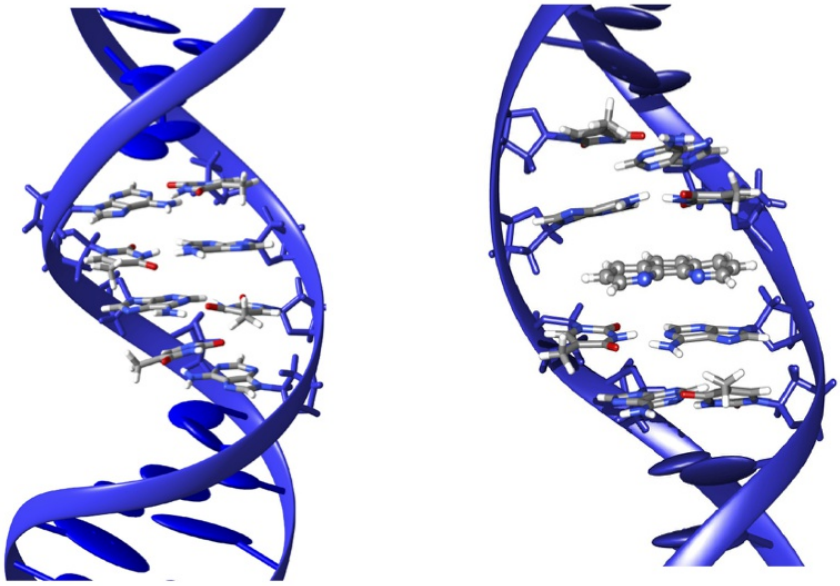
The modeling of DNA photochemistry and its interactions with photosensitizers have recently gained interest because it allows the understanding of DNA photodegradation processes. Moreover photosensitization can be exploited for cancer treatment or simply DNA probing. One of the key aspects that need to be better characterized are the specific modes with whom sensitizers interact with DNA as well as the structural modifications induced in its global structure.

To do so, we studied the electronic circular dichroism (ECD) of two types of B-DNA, the poly(d[AT]) and poly(d[CG]) double strands, with and without photosensitizers and we compared the evolution occurring in the spectra. ECDs were simulated using the Frenkel exciton theory and the conformational space was explored using classical molecular dynamics. Excited states were obtained using QM/MM methods at the TD-DFT level of theory.



Ligand-mediated and tertiary interactions cooperatively stabilize the P1 region in the guanine-sensing riboswitch

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Riboswitches, short genetic regulatory elements, are commonly found in the 5' untranslated region of bacterial mRNA. These regulatory mRNA segments usually consist of two domains: the aptamer domain, which binds small ligand molecules with high specificity, and the expression platform, which, upon binding of the ligand to the aptamer domain, undergoes a conformational change and subsequently alters the expression of the downstream genes.

Transcriptionally acting riboswitches, like the guanine-sensing riboswitch from the *xpt-pbuX* operon of *Bacillus subtilis*, typically only have a short time window for folding, binding a ligand molecule, and transferring the information about the bound ligand to the expression platform and the subsequent conformational change. If this process is not fast enough, the conformational change will happen too late to influence the transcription by the RNA polymerase. In order to understand the decision for one of the two mutually exclusive folding pathways, detailed knowledge about the unbound state of the riboswitch is required.

While crystal structures of guanine-sensing and related riboswitches are available in their ligand-bound state, atomic level information about the unbound state and its dynamics is still scarce. Furthermore, knowledge about the interplay of tertiary interactions in the loop region and ligand binding site on the stabilization of the terminal P1 region would be beneficial towards the understanding of the regulatory decision.

In order to shed light on the complex network of long-range interactions in the unbound state of the guanine-sensing riboswitch aptamer domain (Gsw), we performed molecular dynamics (MD) simulations in explicit solvent of the wildtype Gsw and a mutant, which exhibit different stability of the tertiary interactions in the loop region. We simulated six variants of the system with three replications each, yielding a total simulation time of more than 10 μs. Using the wildtype and the mutant of Gsw, we are able to observe a dynamic coupling between the tertiary interactions in the loop region and the ligand binding region, which is located ~25 Å away. Furthermore, we found this coupling to be dependent on the presence of Mg^{2+} ions. We performed rigidity analyses with a modeled ligand in the binding site in order to investigate the influence of the presence of a ligand on the rigidity of the aptamer domain. Results from these rigidity analyses indicate a cooperative effect between the tertiary interactions in the loop region and the distant ligand binding site on the terminal P1 region of the aptamer domain.

Our results indicate that information on ligand binding to the binding site, in connection with that on the stability of the tertiary interaction, is transferred across the aptamer domain via changes in the domain's dynamics, rather than by conformational changes. This would allow for a quick response of the riboswitch upon ligand binding, in accordance with the kinetic control mechanism found for this riboswitch.

A Consistent AMBER Parameter Set for Zwitterionic Amino Acid Residues

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Isolated amino acids play an important role in biochemistry e.g., as neurotransmitter transporters, transcriptional regulators, or disease-mediators. They are therefore an interesting object of study. Molecular dynamics (MD) simulations can provide detailed insights into the dynamics of these species, especially in their biological environment.

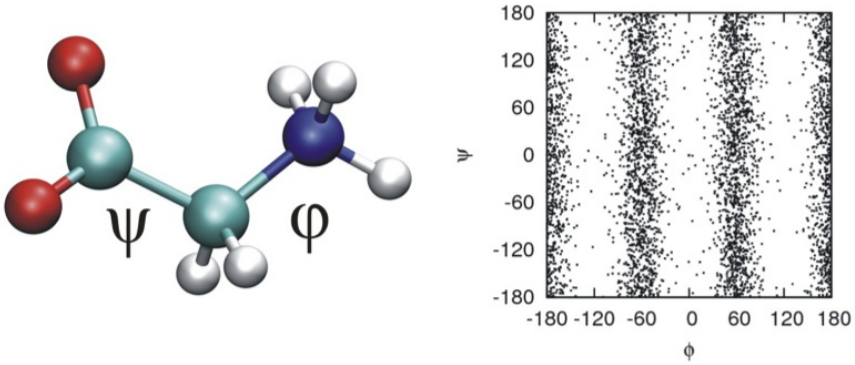
Unfortunately, most standard force field packages lack predefined parameter libraries for isolated amino acids in their zwitterionic form. Although several MD studies have used ad-hoc parameterizations for single amino acids, a consistent force-field parameter set for these molecules is still missing.

Here, we present such a parameter library derived from and compatible with the widely used parm99SB set from the AMBER program package.[1] The parameter derivation for all 20 proteinogenic amino acids transparently followed established procedures. For the sake of completeness, histidine was treated in three different protonation states.

For comparison, MD simulations of all amino acids in four different forms were performed: zwitterionic, N-teminally capped with acetyl, C-terminally capped with N-methyl, and capped at both termini. Simulation results show similarities between the different forms. A subset of five zwitterionic amino acids (E, F, G, L, R) was simulated in its respective protein environment, where proteins and ligands generally retained their initial structure.

Additionally, a set of eight isolated zwitterionic amino acids (A, C, I, K, L, M, R, T, R) was simulated in a aqueous solvent and their orientations were utilized as a pseudo-random number generator.

The new parameter set is freely available [2] and will thus facilitate future atomistic simulations of these species.



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Dedicated to Prof. Tim Clark on behalf of his 65th birthday.

Chemogenomics analysis of small molecule bioactivity data: Privileged scaffolds and conserved structural elements in proteins

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The term "privileged scaffolds" is often used for multiple molecules that show bioactivity on different targets but consist of the same scaffold. [1] Within proteins, conserved structural elements can also be found in different proteins, ranging from conserved motifs that interact with specific functional groups to similar spatial arrangements of secondary structure elements around the ligand binding site (the "ligand sensing core") in proteins with different folding patterns that can bind similar scaffolds. [2] Information about similar ligand sensing cores can be useful for rational identification of new lead structures [3] or predicting polypharmacology. [2]

Chemical compound databases like DrugBank (http://www.drugbank.ca/) or ChEMBL (https://www.ebi.ac.uk/chembl/) contain a huge amount of data about molecules and their bioactivity on different protein targets. Therefore we decided to develop a python based tool for knowledge discovery to get new insights about the relationship of privileged scaffolds and conserved structural elements in proteins. The main idea of this data mining approach is the identification of scaffolds that bind to different and unrelated protein targets for analyzing potential conserved structural elements.

In a first step, a command line version of Scaffold Hunter [4] is used to reduce all molecules in a database to their containing scaffolds. The second step analyses the sequence similarity of protein targets of all molecules sharing a common scaffold. Only protein targets with identity below 40 % are regarded as unrelated. The last step visualizes the results for an in-depth analysis of the results.

We will present the overall workflow and the result of an exhaustive chemogenomics analysis of the DrugBank. Around 1500 scaffolds were identified that are active against different protein targets. An analysis of one example already ended up in a new ligand sensing core that is shared between four different protein targets and can help to identify new lead structures for the respective targets.

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Anthraniloyl transfer in PqsD works without a catalytic triad

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PqsD mediates the conversion of anthraniloyl-coenzyme A (ACoA) to 2-heptyl-4-hydroxy-quinoline (HHQ), a precursor of the *Pseudomonas* quinolone signal (PQS) molecule. [1] Due to the role of the quinolone signaling pathway of *Pseudomonas aeruginosa* in the expression of several virulence factors and biofilm formation, PqsD is a potential target for controlling the nosocomial pathogen that exhibits a low susceptibility to standard antibiotics. [2] PqsD belongs to the β-ketoacyl-ACP synthase family and is similar in structure to homologous FabH enzymes in *E. coli* and *Mycobacterium tuberculosis*. We used molecular dynamics simulations to obtain the structural position of the substrate ACoA in the binding pocket of PqsD and semiempirical AM1 molecular orbital calculations to study the reaction mechanism of the catalytic cleavage of ACoA. [3] Our findings suggest a nucleophilic attack of the deprotonated sulfur of Cys112 at the carbonyl carbon of ACoA and a switch of the protonation pattern of His257 whereby Nδ is protonated and the proton of Nε is shifted to the sulfur of CoA during the reaction. In contrast to a catalytic triad, the doubly protonated histidine is stabilized by hydrogen-bonds with water molecules instead of aspartate. Furthermore, we found that the reaction barrier for the proton shift from Cys112 to His257 is lowered upon inclusion of the electrostatic interactions exerted by the α-helix that spans from Cys112 to Ala128. This indicates a facilitated deprotonation of Cys112 due to the helix dipole. Experimentally we found a decreased catalytic activity of the Cys112Ser mutant that goes along with a strongly increased activation barrier, whereas the Cys112Ala, His257Phe, and Asn287Ala mutants are all inactive. ESI mass spectrometric measurements of the Asn287Ala mutant show that anthraniloyl remains covalently bound to Cys112, thus further supporting our computed mechanism that Asn287 does not take part in the cleavage of ACoA. Consequently, this mutant is inactive.

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Metal binding in the radical SAM enzyme QueE – influencing the mechanistic outcome of radical reactions

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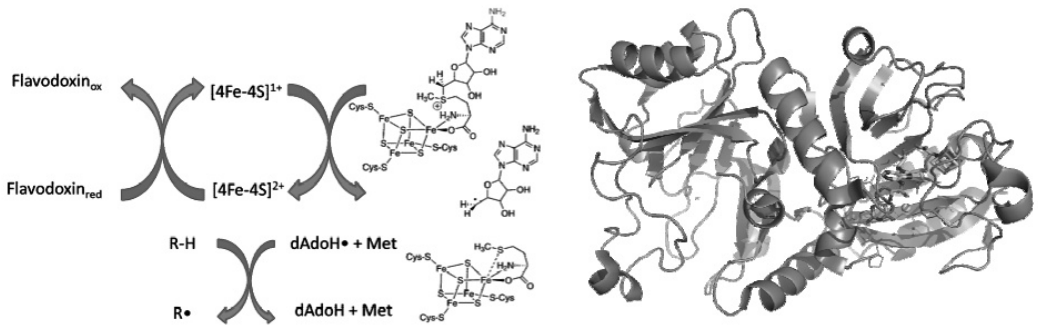
Radical enzymes have attracted recent interest because of their involvement in chemical processes leading to products of potential use for anti-viral, anti-cancer and antibiotic treatments. As such, they are excellent targets for protein engineering to access a variety of new drugs that are difficult to access via traditional synthetic methods. One of the most diverse radical enzyme families is the so-called radical SAM enzyme family,[1] the members of which all share a central S-adenosyl methionine (SAM) molecule as either a cofactor or co-substrate for catalysis. The manifold diversity of chemical reactions catalysed by these enzymes is outstanding, including methyl transfer, sulphur insertion and complex chemical rearrangements. While a general framework for the initial catalytic mechanism has been established over the past years[2] (see Figure), much less is known about the subsequent chemical rearrangements in most cases.

7 carboxy-7-deazaguanine (CDG) synthase (QueE) is one of the very recently solved enzyme structures that uses SAM as cofactor.[3] It catalysis the rearrangement of 6-carboxy-5,6,7,8-tetrahydropterin (CPH4) into CDG and also shows a clear dependence on the presence of Mg^{2+} in the active site - a complete novel feature reported for radical SAM enzymes. Still unclear is how the ion influences the catalysis of the chemical rearrangement.

We show first results from *ab initio* and DFT calculations on a model system to investigate effect of the ion on the chemical rearrangement and first molecular-dynamics simulations of the enzyme to investigate the dynamical behaviour of the entire protein-substrate complex and its influence on metal and substrate binding. Further, we will outline our systematic approach to investigate the enzyme's catalytic mechanism in detail.



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Binding properties of SUMO-interacting motifs

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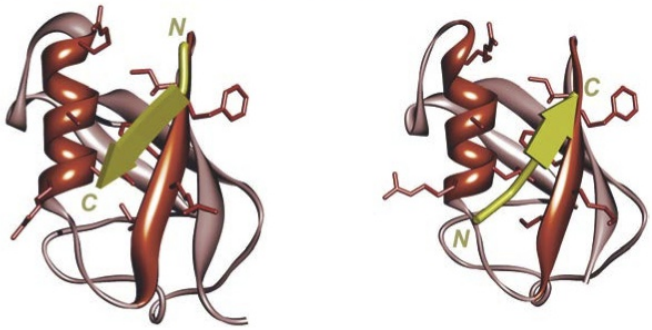
A large number of yeast proteins is known to interact non-covalently with Small Ubiquitin-like Modifiers (SUMO) via short SUMO-interacting Motifs (SIMs), but the structural details of this interaction were poorly characterized. The sequence analysis of a large dataset of 148 yeast SIMs [1] revealed the existence of a hydrophobic core binding motif and a preference for acidic residues either within or adjacent to the core motif. Thus the sequence properties of yeast SIMs are highly similar to those described for human. We performed Molecular dynamics simulations to investigate the binding preferences for four representative SIM peptides differing in the number and distribution of acidic residues and assessed the relative stability of the two observed alternative binding orientations (parallel, antiparallel).



Structure of ySUMO in complex with different ligands. Left: detailed view of the Srs-2 SIM (yellow) bound to the ySUMO (red) in a parallel orientation [2]. Right: detailed view of the Fibronectin III-derived monobody SIM (yellow) bound antiparallel to ySUMO (red) [3]. The SUMO structural elements involved in SIM binding are highlighted in darker color

For all SIMs investigated, the antiparallel binding mode remained stable in the simulations and the SIMs were tightly bound via their hydrophobic core residues supplemented by polar interactions of the acidic residues. In contrary, the stability of the parallel binding mode is more dependent on the sequence features of the SIM motif like the number and position of acidic residues or the presence of additional adjacent interaction motifs. This information should be helpful to enhance the prediction of SIMs and their binding properties in different organisms to facilitate the reconstruction of the SUMO interactome.

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Dynamics of the Autoinhibited Transcription Factor RfaH

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Transcription factors control the flow of genetic information from DNA to messenger RNA rendering understanding of their function highly important for the modulation and optimization of protein expression. Molecular and structural biology have provided a wealth of information for transcription factors, however, the dynamic processes underlying their activation are yet not fully understood.

We applied molecular dynamics (MD) simulations to supplement the structural information available for the transcription factors RfaH from Escherichia coli and NusG from Thermotoga maritima. Both proteins are autoinhibited proteins; in NusG, the β-barrel C-terminal domain (CTD) is tightly bound to the larger N-terminal domain (NTD), whereas RfaH consists of a structurally similar NTD and a bound CTD in α-helical conformation[1]. Upon activation of RfaH, the CTD is released and undergoes a large-scale $\alpha \rightarrow \beta$ structural transition[2].

Investigation of RfaH under different environmental conditions revealed that not only high temperatures, but also a decrease in ionic strength significantly enhances CTD dynamics. Despite this enhanced dynamics, none of the conditions investigated caused CTD dissociation suggesting that this process needs to be triggered by the interaction with DNA or other proteins of the transcription machinery. Further, we were able to see a transition from the α- to a β-conformation in a microsecond long MD simulation of the isolated CTD.

0 μs $\rightarrow$ 1.0 μs $\rightarrow$ 2.0 μs $\rightarrow$ 4.5 μs $\rightarrow$ 6.0 μs

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Electronic structure at high hydrostatic pressure

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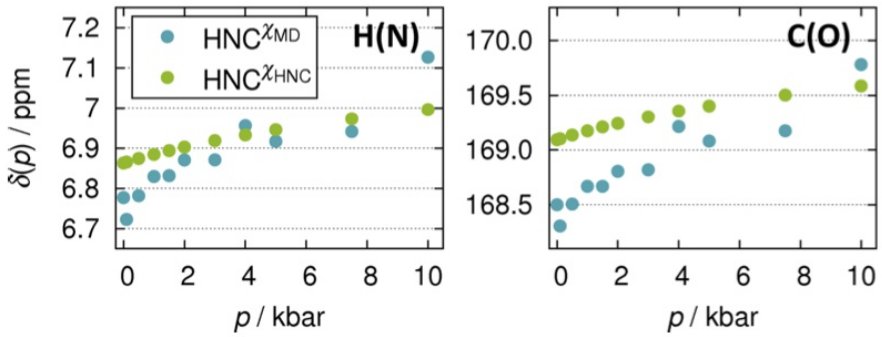
While the majority of life on earth is adapted to ambient pressure conditions, on average about 88% of the oceanic water on earth is 3800 m deep, corresponding to a hydrostatic pressure of 380 bar, which is by far not the highest value on earth. [1] Biochemical processes for the vast number of lifeforms accommodated to these extreme conditions are barely understood.

Applying high hydrostatic pressure to biomolecules has substantial impact on their free energy surfaces that govern structure, function, dynamics, and thermodynamics. This poses a challenge to computational modeling approaches since the applicability of conventional empirical molecular interaction functions (force fields) is not known. As a step toward clarifying the situation, we need to account for high pressure in quantum-chemical calculations. A suitable methodology is provided by molecular integral equation theories, in particular the "embedded cluster reference interaction site model" (EC-RISM) [2,3] that combines statistical-mechanical 3D RISM integral equation theory and quantum-chemical calculations self-consistently. In this context the impact of pressure is naturally accounted for since the solvent susceptibility function that enters the theory contains the pure solvent correlation functions at the pressure chosen, derived from either an integral equation theory or molecular simulations. Here we illustrate the methodology for several benchmark applications in a pressure range of 1 bar up to 10 kbar, including the effect of pressure on molecular structure, the relevance of electronic polarizability under extreme conditions, and the pressure dependence of nuclear magnetic resonance shieldings.



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MD simulations of DNA recognition by the repressor AmtR

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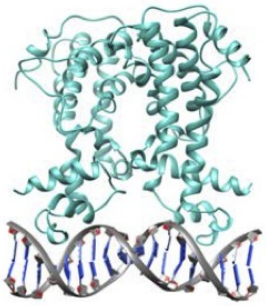
The protein AmtR occurs in the gram positive *Corynebacterium glutamicum* in which it is a master regulator and represses genes of the nitrogen metabolism and the signal transduction pathway. Each subunit of the dimeric AmtR recognizes a conserved four base motif ("CTAT"). A comparison between the known binding sites and those genomic sites that are not regulated by AmtR reveal significant differences for those bases that are adjacent to the CTAT recognition motif. Therefore, we investigated whether these adjacent bases also play a role for AmtR binding specificity.



Molecular simulations (MD) of free DNA and AmtR-DNA-complexes were used to study the dynamics of these two systems and the interactions between DNA and AmtR. There are several specific contacts to the flanking bases formed during the MD simulation. Besides direct base recognition also unspecific contacts to the phosphate backbone of the DNA were detected. These contacts correlate with a local deviation from the ideal B-DNA geometry which is not observed in the simulation of free DNA. This suggests that the specific DNA recognition by AmtR relies on a larger binding motif than previously known.

In silico affinity optimization of modified peptides using non-natural amino acids

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Bioactive peptide conformations can be stabilized by macrocyclization resulting in increased target affinity and activity. In this regard, a 12mer peptide from the C-terminal end of Pseudomonas aeruginosa virulence factor exoenzyme S binding to its human adaptor protein 14-3-3 was stabilized by introduction of a hydrophobic cross-link,[1] thus providing the basis for *in silico* optimization.

Computational protein-peptide docking is still a challenging task because exposed solvent plays an important role in protein-protein interfaces and water is usually not considered during docking. More important, long peptides imply a large number of computational degrees of freedom where current docking approaches reach their limit.[2] Beside these docking limitations, currently available computational approaches for peptide affinity optimization are only based on the 20 canonical amino acids.

In this work, we try to overcome these issues by (1) developing a molecular docking strategy suitable to handle large peptide ligands, and (2) optimizing the affinity of modified peptides by introducing side-chain mutations from a library of non-natural amino acids.

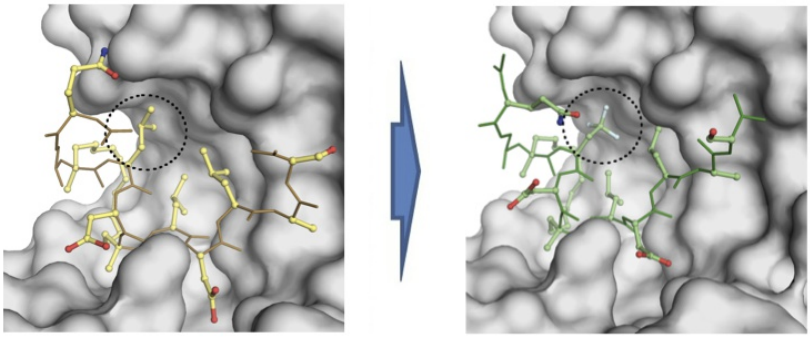

Figure: Residue-based screening of a library of non-natural amino acids by peptide-adapted molecular docking leads to optimized modified peptides with improved affinity.

Left: X-ray structure depicted in yellow. Right: docking prediction depicted in green.

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Modeling the Electronic Absorption and Circular Dichroism Spectra of a Photo-switchable Bistable Peptide

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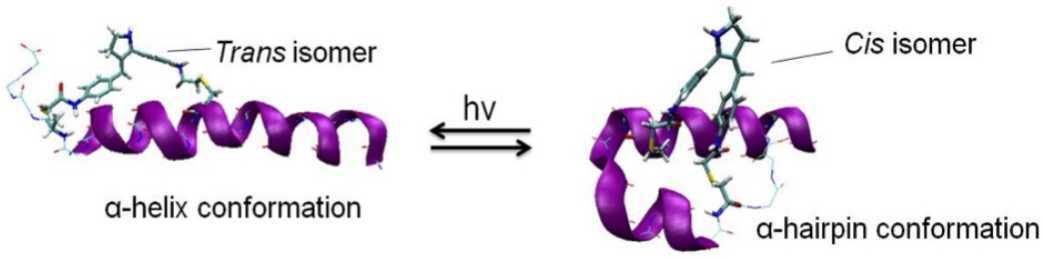
The control of biomolecular systems can be achieved through the application of photo-switches. Especially, a retinal like photo-switch based on E/Z photo-isomerization was experimentally shown to be a relevant candidate for reversible control of the alpha helix peptide conformation [1].

Here, we focus on the understanding of the mechanism leading to the final response of the overall peptide. More in detail, molecular dynamics simulations were performed for the E- and Z-isomer linked peptide, as well as for the unlinked peptide, in order to reveal the overall conformational changes induced by the attachment of the photo-switch. Our results, supported by experimental data [1], show on average how the unlinked peptide is partially unfolded in water, whether the E-isomer linked peptide tends to increase the helical content, and the Z-isomer linked peptide produces peptide bending leading to an alpha hairpin conformation (see Figure).

In order to monitor the photo-switch conformation, its electronic absorption properties were calculated along the trajectory at the CASPT2//CASSCF/AMBER level of theory, while a spectral signature of the overall peptide conformational change was recorded by modeling the circular dichroism spectra in the framework of the Frenkel exciton theory [2,3] at the M062X/AMBER level of theory, including a polarizable force field.



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Periodic Calculations with NDDO Hamiltonians

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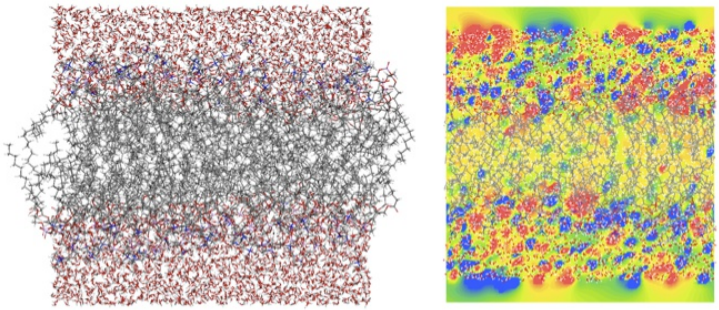
We have implemented periodic boundary conditions (PBC) in the massively parallel semiempirical MO theory code EMPIRE using the cyclic cluster approach. By using sufficiently large unit cells, the calculations are performed entirely in real space. This is easily affordable due to the low computational cost of these methods, and the efficient parallelization of EMPIRE[1].



Specific features of PBCs in EMPIRE include the treatment of very large systems in 1-, 2- or 3D, and the calculation of local properties such as the molecular electrostatic potential and the local electron affinity and ionization potentials. The figure shows the 2D periodic unit cell of a lipid bilayer membrane in water, containing more than 25,000 atoms. On the right, the molecular electrostatic potential of the system is shown on a slice cutting through the unit cell.

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TopModel: A multiple-template meta-approach to homology modeling

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Protein structure prediction is one of the most important problems in computational biology, and is key to understanding structural evolution, protein function, protein-ligand and protein-protein interactions, and for data-driven protein- or drug-design [1,2]. However, the current rate of structure determination by experimental methods is far exceeded by that of next-generation sequencing, to the point where only for 1/1000th of the known protein sequences a structure is known. For this problem, computational structure prediction is considered the best solution [3]. In the last decade, many methods have been developed in each of the computational fields necessary for automated structure prediction. The bi-annual community-wide blind experiment CASP evaluates the accuracy of work flows that integrate a subset of these methods, and has shown the value of meta- and consensus-approaches [3,4]. This work presents TopModel, a multiple-template meta-approach to homology modeling, which combines multiple state-of-the-art threading, alignment, and model quality assessment programs to provide a versatile work flow and toolbox for structure prediction. TopModel yields high-quality structures [5,6] and performs well even for low sequence identities. When benchmarked against CASP10 targets, TopModel shows an accuracy above the average state-of-the-art work flow. We anticipate that as more programs are integrated, the accuracy and sensitivity of our methods will improve. Hence, we aim to expand TopModel to achieve more accurate modeling of proteins with multiple domains and protein-protein complexes as well as to use it to evaluate alignment and threading software in a consistent manner based on the quality of models produced by the generated alignments.

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Simulating Nanostructures: 2D-periodic organic semiconductors

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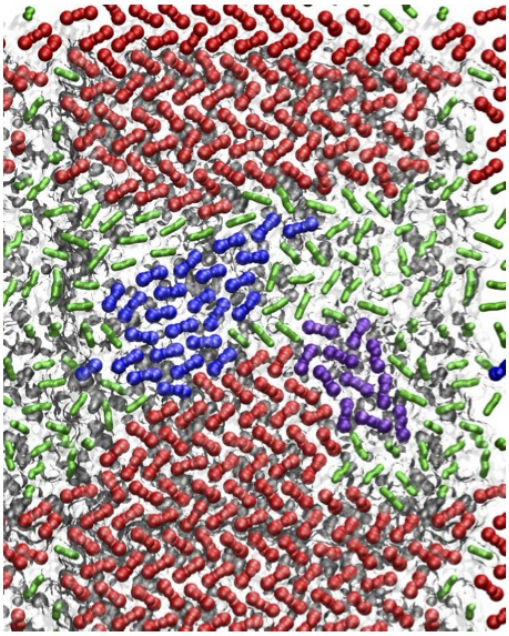
Organic semi-conductors surround us in daily life. Two years ago we have presented an n–type semiconductor system of C_{60}–C_{18}–PA.[1] Now we have simulated and analysed a p–type organic semi-conductor system of benzothieno[3,2—b][1]benzothiophene (BTBT) on an aluminum oxide surface. Special focus in this part of the work is the structure of organic molecules. Differences in structure between C_{11} and C_{12} BTBT have been worked out which agree with experimental results. In this talk we present results we have gained from molecular dynamic simulations we have performed on this 2D system.



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Computer-aided modelling of protein conformations and ligand binding

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Abstract

Processes like ligand binding, chemical modifications or changes in environmental conditions may result in conformational switching in proteins, affecting their function. The loss of associated function may also result in disease causing pathological conditions. Computer-aided modelling and simulations of protein systems serve as an important tool to study protein dynamics. By employing certain proteins and peptide models we have tried to understand two aspects of protein dynamics: folding and ligand binding. For folding, we modelled systems involved in local conformational changes such as Alzheimer's causing α→β transitions and sequences involved in early events of protein folding. Characterization of these model systems, with or without the protein context, revealed the importance of primary sequence, environmental conditions, and tertiary contacts provided by the pre-existing protein environment. In ligand binding studies, blind docking simulations and structure-based screening methods were used. Investigation of structural features and specific protein-ligand interactions determined binding pose and hence distinguished binders from non-binders. These features may be used to design scoring functions for developing accelerated screening methods and drug designing.

Keywords Protein Folding, Conformational Modelling, Ligand Binding, Molecular Dynamics, Molecular Docking

A Computational Study on Carboxymethylation Mechanism of Gluconate

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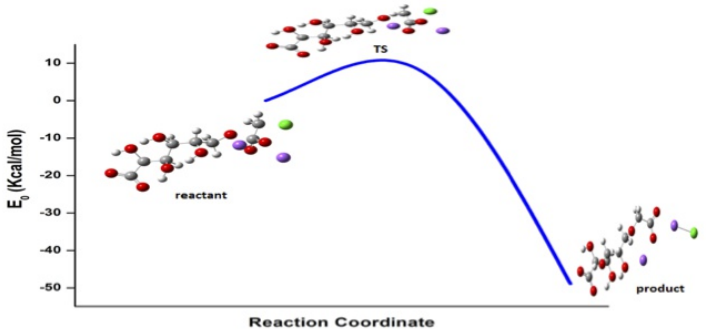
Pharmacologically active anticancer drugs reach to tumor tissue with low specificity; therefore they frequently damage healthy tissues. Nowadays, it is possible to reduce these harmful side effects by using nano particle containing drug delivery systems [1,2]. For example, when α-D-glucose coated iron oxide (magnetite) nanoparticles are loaded with doxorubicin, an anticancer drug, this drug loaded iron oxide nanoparticles can be directed to tumor tissues via an external magnetic field by mostly eliminating the side effects of classical oral treatment [3-5]. During the loading, the doxorubicin molecules must be somehow connected to gluconate molecules on the surface. The first step on this bonding passes through the carboxymethylation of gluconate.



In the present study, we have computationally investigated the carboxymethylation mechanism of gluconate bonded to the surface. The gluconate coated iron oxide nanoparticle systems are enormously large for quantum chemical calculations. Therefore, to model the system, the two oxygen atoms in carboxyl group of gluconate bonded to the surface were frozen instead of using whole gluconate coated iron oxide nanoparticle system. The semiempirical PM6 and DFT-M06-2X methods were employed in the reaction mechanism calculations. The results of the calculations are revealed that the reaction between gluconate and chloroacetate has one step mechanism passing through a low energy transition state while it is a highly exothermic reaction.

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Brownian Dynamics Simulations of Linker Histone - Nucleosome Binding

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Abstract:

The binding of linker histone (LH) proteins to nucleosomes plays an important role in chromatin compaction and regulation of transcription. Currently, the sequence determinants of the binding site, orientation and dynamics of different LHs to nucleosomes are not well understood. In this study, Brownian dynamics (BD) simulations were performed to simulate the association of the globular domains of H1 and H5 LH wild-type and mutant proteins with a 167 bp nucleosome, including two flanking 10 bp long linker-DNAs. Diffusional encounter complexes were obtained and the results were compared for the LHs and their mutants. The results give insights into important interactions that determine LH-nucleosome binding.

Hybrid QM/MM studies of the UV-Vis absorption spectra of ThDP-dependent enzymes

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The identification of reaction intermediates in enzymatic systems is a continuing challenge, both for theoretical and experimental approaches. UV-Vis and circular dichroism (CD) spectra are commonly used to follow the progression and the appearance of such intermediates. However, the unequivocal assignment of a band to a particular compound can be a difficult task. Electronic structure methods can provide invaluable informations in this context, but only when an adequate description of the environment effects and the chromophore itself are available.

The thiamin diphosphate (ThDP) coenzyme participates in a multitude of enzymatic reactions and their progression is commonly followed by absorption spectra. [1] Even in the resting state of such enzymes, ThDP can be present in three different protonation states each having its own signature in the absorption spectra. [2] Therefore, a detailed knowledge about these native forms of ThDP is warranted to identify reaction intermediates by absorption spectroscopy. In order to better understand the signature of the different states, we have carried out time-dependent density functional theory (TDDFT) calculations for model systems, as well as for the pyruvate decarboxylase system in a QM/MM approach.

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Redox Potentials of Bovine Adrenodoxins: Quantifying the Effects of Mutations

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Adrenodoxin (Adx) belongs to the family of vertebrate [2Fe2S]-cluster ferredoxins and plays an essential role in the steroid biosynthesis. Its task is to supply electrons from a NADPH-dependent Adx reductase (Adr) to Cytochrome P450 enzymes. The next step includes activation of molecular oxygen whereby one oxygen atom is introduced into the substrate and the other one is reduced to water [1]. The efficiency of the electron transfer also depends on the redox potential of the Adx. In the past years many different Adx mutations from bovine have been established and quantified [2]. To elucidate the effects of a certain mutation at the protein level we investigated the set of Adx mutants listed in [2] and computed the individual energy contributions to the redox potentials. Solvation effects were obtained via the Poisson-Boltzmann theory by applying the APBS program [3]. The electronic reorganization energy that comes along with the reduction of the Adx [2Fe2S]-cluster was derived from density functional theory calculations on $[Fe_2S_2(SC_2H_5)_4]$ model compounds at B3LYP/cc-pVTZ level of theory. Surface analysis of the homology models of the Adx mutants was performed via the VADAR webserver [4]. Our findings show that the energy gap between the reduced and the oxidized state of the [2Fe2S]-cluster is caused by the different orientations of the ligating sulfur atoms. This was clearly shown when comparing the geometrical non-constraint energy optimization of the $[Fe_2S_2(SC_2H_5)_4]$ model compounds vs. the constraint ones. Also the local protein environment plays an important role. Investigation of the T49 deletion mutant showed a substantially lower redox potential compared to the wildtype, essentially due to the rearrangement of the [2Fe2S]-cluster and the surrounding geometry, ending up in a change of 0.08 eV of the adiabatic ionization potential.

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New approaches towards small molecular protein-protein interaction modulators.

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Protein-protein interactions (PPIs) are ubiquitous in nature and essential to almost all biological processes including signal transduction, gene-expression and pathogenicity. Therefore, modulation offers attractive therapeutic opportunities. [1] One major challenge of targeting PPIs arises from the chemical space of appropriate molecules which differs from the chemical space of conventional small molecule drugs in a way that is not yet completely understood. Thus, the hit rate of commercial compound collections is typically rather low since these are designed around the traditional drug´s chemical space. [2] A reason for this observation is the intrinsic planarity of these interfaces and their lack of well-defined binding-pockets.

Our approach for the design of PPI inhibitors is to elucidate and mimic the important, limited-sized elements that actually act as protein recognition motifs. [3] Up to now, only strand and helix mimetics were successfully used as interaction inhibitors, although irregular turn structures prevail as regions of high affinity binding in weak and transient heterodimer interfaces of greater pharmacological interest. [4] The turn backbones provide valuable information for the design of new drugs since they act as scaffolds for positioning the relevant side chains in the correct specific orientation. [5]

As a first example, our analysis of a bacterial GTPase-activating PPI [6] (responsible for the correct formation of flagella) leads us to a crucial interaction turn entity of type n(4)I. This type of β-turns is already known to be well-replaced by the benzodiazepine scaffold. The synthesis of the basic scaffold has been successfully established and now our focus is on identifying the required functionalization pattern using structure-based design and docking. Subsequently, the synthesis of these rationally designed benzodiazepine-based turn mimetics will lead to a small library to be tested for its capability to modulate the bacterial GTPase-activating PPI.

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[2] O. Sperandio, C. H. Reynès, A. C. Camproux, B. O. Villoutreix, *Drug Discov. Today*, **2010**, *15*, 220-229.
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Investigation of the Protein-DNA Binding Mechanism of Carbon Catabolite Protein A

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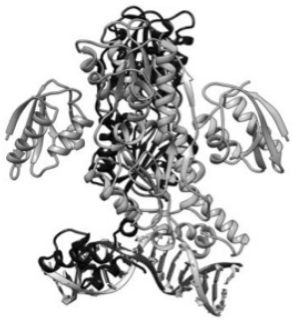
The global regulator Carbon catabolite Protein A (CcpA) controls carbon metabolism in *Bacillus subtilis*. It does so by binding to the degenerate consensus site WTGNNARCGNWWWCAW [1]. To investigate how CcpA can bind to such diverse sequence motifs, we tried to identify contributions to binding selectivity. On the one hand, direct contacts via hydrogen bonds and nonpolar interactions to the nucleotide bases ('base readout') strongly influence the preference of proteins for specific sequences. On the other hand, the base composition also influences the shape and flexibility of the DNA, thereby modulating the strength of the interactions.



The strongest conserved bases of the consensus site are the central CG bases, at which the DNA is bent in the complex structure. The direct contacts of the bases are hydrogen bonds with the CcpA backbone via a guanine amine group in the centre of the minor groove and two intercalated leucine side chains. In addition, CG represents a pyrimidine-purine base step, which is known to facilitate kinks, which might favour shape readout at this site.

To dissect the individual contributions of base and shape readout, the CcpA-DNA complex was simulated as wild type and compared to a mutant, in which the central CG base step was replaced by GC. Interestingly, the CcpA-DNA hydrogen bonds remained stable throughout the simulation of the mutant, whereas MMPBSA analyses showed a higher energy requirement to bend the mutant DNA sequence.

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pH-Dependent Dissociation of HdeA and HdeB Dimers

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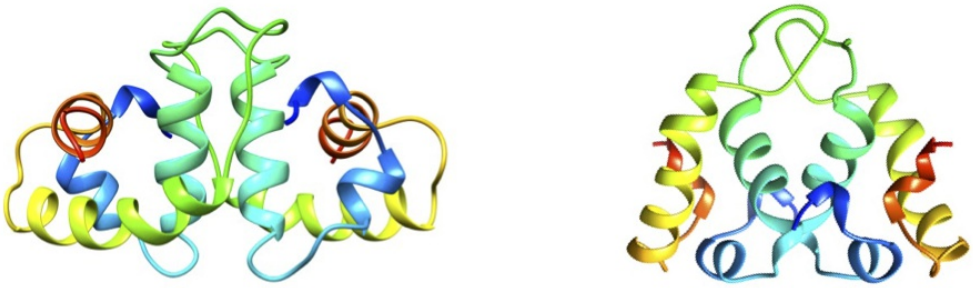
Enteric bacteria, like *Escherichia coli*, have to pass through the stomach before they can infect the intestinal mucosa. However, the lumen of the stomach is a very acidic environment with a pH usually between 1 and 3. To survive this acid trip, *E. coli* has evolved different systems to tolerate acid stress in the cytoplasm and periplasm, which is enveloped by an outer membrane permeable for protons. As consequence, the pH in the periplasm decreases rapidly to the same level as the environmental pH when *E. coli* enters the stomach and the proteins in the periplasm are vulnerable to acid-induced damage. In order to prevent denaturation and aggregation of periplasmic proteins, *E. coli* has two acid-activated chaperones, HdeA and HdeB, which support acid resistance in the periplasm. Their genes are encoded in the *hdeAB* operon in the genomic acid fitness island.

Despite their low sequence identity (< 20%), HdeA and HdeB monomers are structural homologues, which was proven by the crystal structures. However, the HdeA dimer (left picture) uses a different dimerization interface than the HdeB dimer (right picture). Both have in common that the well-folded dimers, which were mainly observed at neutral pH, are inactive. If the pH decreases, the dimers dissociate to partially disordered and chaperone-active monomers. These HdeA and HdeB monomers then bind to other proteins using a hydrophobic surface and prevent the aggregation of their substrates. After neutralization, HdeA monomers release these proteins and refold back into the inactive conformation.



In our study, we have investigated the behavior of the HdeA and HdeB dimers over a broad pH range. We developed, therefore, a new MD simulation protocol, which allows the imitation of pH titrating experiments resembling the entering of *E. coli* into the acidic stomach. For both proteins we were able to monitor their dissociation at low pH values and to characterize the titration properties of individual ionizable groups. The observed differences between HdeA and HdeB suggest a fine-tuning in the pH response of *E. coli*.

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Free Energy Calculations in Fragment Based Drug Design: Applying FEP in Practical Ligand Optimization

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Schrödinger

It has long been considered the holy grail of computational drug design to accurately predict binding free energies for novel compounds. This task is of special importance in fragment-based drug design, where multiple rounds of potency improvement starting from initial weak binders are necessary to generate highly active lead structures. Molecular Dynamics based free energy calculations (or FEP for free energy perturbation) are among the most suitable methods to reach this goal, which would significantly impact the modern drug design process. Many of the issues previously encountered with FEP have been mitigated by our introduction of the FEP+ (free energy perturbation plus REST, i.e. replica-exchange with solute tempering) methodology along with the OPLS2.1 force field, together with the computational power offered by GPU computing.

The lack of large scale validation studies on diverse series of ligands are another obstacle for the practical application of FEP, due to the lack of computational resources and the time consuming process of simulation setup and analysis. Recently, we have conducted a validation study of FEP results on more than 10 targets and more than 500 compounds, offering an order of magnitude more data than typical FEP studies and allowing statistically valid conclusion about their efficacy.

Here, we extend this validation study to several fragment hit series, among them the Mcl-1 protein, HSP90 and DNA Ligase A. Relative binding free energies can be calculated with good accuracy, typically with R2 values in the range of 0.5-0.8 and mean unsigned errors (MUE) of less than 1 kcal/mol when comparing to experimental data. This shows that FEP binding energy predictions offer unsurpassed accuracy for fragments and lead precursors as well as for drug-like molecules.

MUSE INVENT: Automated Reaction Driven Molecular Inventions Applied on a Fragment Growing Example

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Successful drug discovery often requires optimization against a set of biological and physical properties. Muse Invent is a molecular invention tool that operates on an initial population of structures for the invention of new structures with improved characteristics. It is possible to combine almost any property calculation and scoring function to guide the invention process to molecules that are in accordance with the desired attributes. Ligand- and structure-based methods may be applied as well as a combination of them.

Molecular invention experiments on PPAR-γ will be presented in order to grow a thiazolidinedione fragment back into full molecules. A "reaction driven" evolutionary algorithm approach to de novo molecular design was applied to generate new structures and propose a synthesis path at the same time intended to aid the medicinal chemist in assessing the synthetic feasibility of the ideas that are generated.

Reactions can be adjusted to make use of specific chemistry or fragments. The methodology for reaction driven molecular evolution we have developed is independent of how the design ideas are scored..

Molecular Dynamics of Viral IE1 Protein and Its Relevance for PML Interaction

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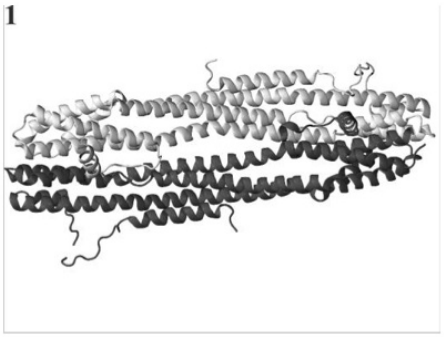
The recently solved crystal structure of the immediate-early protein 1 of rhesus cytomegalovirus (IE1) revealed a novel protein fold with an elongated, all α-helical homodimeric topology (Figure 1). [1] Interestingly, IE1 crystallized in two slightly different dimeric forms indicating a certain degree of conformational flexibility, which was further investigated by molecular dynamics (MD) simulations.



All MD simulations were performed with AMBER/parm99SB force field in an octahedral box of explicit solvent. We simulated the two dimeric structures for 50 ns and three monomers for 100 ns, which were taken from the dimer structures.

Our results show that the interface of the asymmetric dimer is more stable indicating that IE1 has the propensity to form asymmetric protein-protein complexes probably also with other proteins. MD simulations of monomeric IE1 revealed hinge-like motions that explain the occurrence of slightly different backbone conformations of IE1 in the crystal. Interestingly, we detected a local structural similarity to the evolutionary conserved coiled-coil domain (CCD) of TRIM (tripartite motif family) proteins (Figure 2), which is also present in PML (TRIM19) a target protein of IE1. Our computational study suggests that the detected dynamics of the IE1 fold might enable a better interaction with the elongated, α-helical CCD of PML.

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Ionic conductance and selectivity of hydrophobic nanopores

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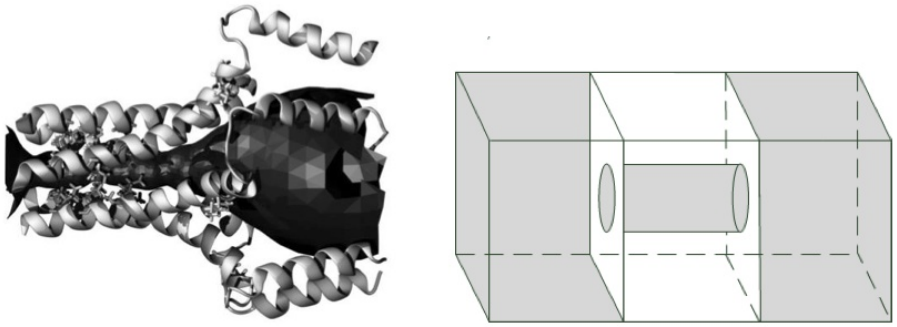
Over the last years various hydrophobic pores with selectivity features were identified, including ion channels. [1-3] Yet the origin of their intrinsic ion discrimination is still not understood, while properties such as overall pore geometry, chemical detail of the interior, or wall charges all play a role for modulating ion conductance. One controversially discussed example of a hydrophobic nanopore that exhibits ion channel properties is the pentameric membrane protein phospholamban (PLN) [4], for which available structures reveal a narrow constriction that is only slightly larger than the diameter of passing ions. [5]

Here we apply three-dimensional reference interaction site model (3D RISM) integral equation theory for deriving the relevant free energy surface governing ion translocation, the potential of mean force (PMF) at finite electrolyte concentration. Combined with an expression connecting the equilibrium PMF with ion conductance [3] we obtain selectivity orders in agreement with experimentally measured values. Together with ion-specific partition coefficients along the translocation pathway we construct a coherent picture of ionic selectivity for this particular channel, supplemented by results from a simplified nanopore model comprised of hard-wall interactions between pore lining and the solvent.



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Design, analysis and virtual screening of an *in silico* dynamic combinatorial compound library with focus on protein-protein interaction inhibitors

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Enabling the protein target to direct the synthesis of its strongest binder via dynamic combinatorial chemistry is an interesting strategy for *de-novo* design and identification of new bioactive compounds. Employing a reversible reaction in solution with different building blocks an enrichment of the strongest binder occurs, since it is removed from equilibrium during binding to the protein target. One successful example is the formation of acylhydrazones from aldehydes and hydrazides which led to the identification of new inhibitors of endothiapepsin. [1]

As commercial compound collections show low hit rates for protein-protein interaction (PPI) targets due to a non-suitable chemical space, *de-novo* design of small molecule libraries within a new chemical space is of uttermost importance for the elucidation of PPI inhibitors. [2] For this purpose chemoinformatics tools were utilized for the analysis of the acylhydrazone libraries chemical space. Usage of an *in-silico* reaction between all available aldehydes and hydrazides contained in the ZINC database (http://zinc.docking.org) created a virtual library of about 1.2 billion highly diverse acylhydrazones of appropriate physicochemical properties.

Previous high-throughput docking studies by Koch et al. identified an acylhydrazone based inhibitor of the PPI between mycobacterial thioredoxin reductase and thioredoxin. [3] Therefore it can ideally be screened for new inhibitors of the thioredoxin reductase as proof of concept study employing the dynamic combinatorial chemistry approach for a highly diverse subset of the newly obtained acylhydrazone library.
We will present the results of the exhaustive chemoinformatics based analysis of the virtual acylhydrazone library together with the docking results leading to aldehyde and hydrazide building blocks for *in-vitro* application of the dynamic combinatorial chemistry approach.

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Batch tautomer generation and more with MolTPC

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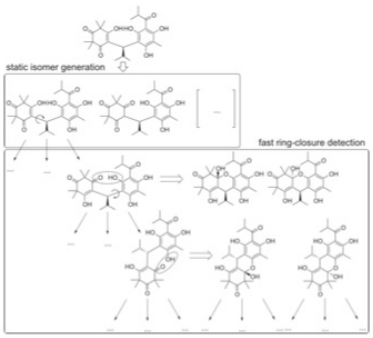
Besides all their conformational degrees of freedom, drug-like molecules and natural products often also undergo tautomeric interconversions. Compared to the huge efforts made in experimental investigation of tautomerism, open and free algorithmic solutions for prototropic tautomer generation are surprisingly rare. The few freely available software packages limit their output to a subset of the possible configurational space by sometimes unwanted prior assumptions and complete neglection of ring-chain tautomerism.

We described an adjustable fully automatic tautomer enumeration approach, which is freely available and also incorporates the detection of ring-chain variants. [1]

Furthermore, we provide functionality for the generation of reasonable protonation variants and a fast unified conformational as well as configurational search procedure.

All algorithms are implemented in the MolTPC framework and accessible on SourceForge via https://sourceforge.net/projects/moltpc/.



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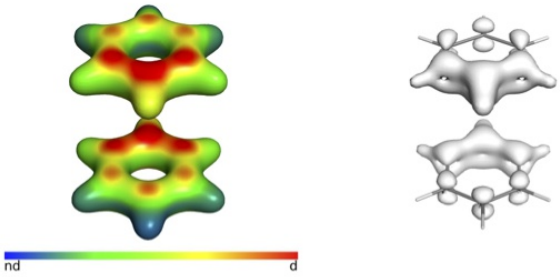
Dispersion through the eyes of local orbital spaces

A. Wuttke, R. A. Mata

IPC Göttingen

As the saying goes, „one look is worth a thousands words“. This principle can also be applied to the study of chemical phenomena. There are several visualization techniques in chemistry which are used to ease the interpretation of “raw data” (MEP, Orbitalmaps, and so on). Our work is inspired by the idea of MEP´s, which visualize electrostatic potentials of molecules by color coding a predefined electronic density. These images help to design novel compounds or to understand transition state stabilization effects.

London dispersion is a significant driving force for molecular aggregation, ubiquitous in molecular systems. Representations targeting such interactions are definitely warranted. Based on local orbital approaches we are able to restrict electron correlation to a certain region of a molecule.[1] The calculated correlation energy can then be split up in physically meaningful contributions, including dispersion effects.[2,3] These two properties of local correlation methods lead us to the proposal of a straightforward method to represent what could be described as a dispersion interaction density (DID) in molecules. This method will help us to obtain a better understanding of intra- and intermolecular interactions. Examples are given for the benzene dimer, a typical benchmark system for dispersion, as well as selected dispersion-driven aggregation phenomena.



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Cubic C8 – An Aromatic Carbon Cluster?

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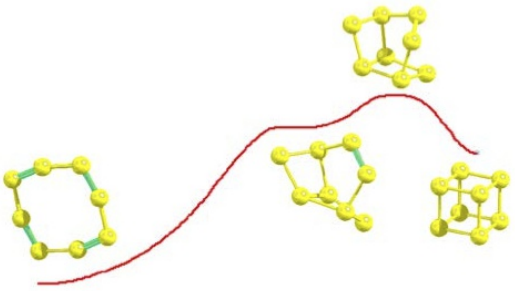
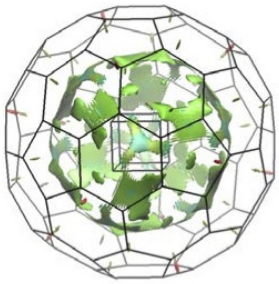
The cubic C_8 unit is represents the proposed primitive cell of the high-density carbon allotrope first described in 1978. Cubic C_8 and its isomers have been the subject of several theoretical studies.[1,2,3,] This cluster obeys Hirsch's $2(N+1)^2$ rule of spherical aromaticity. According to our high-level calculations O_h-symmetrical C_8 is a relatively stable strained cluster. The bond length is quite independent of the calculation level but unusually sensitive to the basis set used and varies between 1.47 and 1.51 Å. The lowest frequency normal vibration calculated with different levels of Møller–Plesset perturbation theory is degenerate and inconsistent with the results of coupled-cluster calculations.

The calculated electron affinity of cubic C_8 is 69 kcal/mol and ionization potential over 226 kcal/mol. The singlet-triplet gap is 17 kcal/mol, both the triplet and the cation radical are Jahn-Teller species with D_{2h} and D_{4h} symmetry, respectively. The cubic cluster is 100 kcal/mol more strained than the global minimum (C_{4h}-symmetrical ring) and can transform to it with a 62 kcal/mol barrier.



Rearrangement pathway



Non-covalent interaction in C8@C80

The exothermic reaction of C_8 with $^3O_2$ has a low barrier; 7 kcal/mol. The product is a triplet peroxide (energy gain 13 kcal/mol in comparison to separated molecules). The next step of the oxidation sequence is formation of dioxetane cycle, breaking of the propellane bond (to form a molecule familiar as to 9,10-dioxa-perdehydro-basketane) and further fragmentation. The barrier of this process is around 24 kcal/mol and is followed by spin-crossing from the triplet to the singlet state.

The cubic C_8 cluster can be encapsulated in C_{60} and C_{80} fullerenes (Russian doll structures), accompanied by strong electron transfer from C8 to fullerenes.

UV-spectra predicted by TDDFT and CASPT2 approaches are rather similar and exhibit peaks near 6.0, 7.9, 8.5, and 9.0 eV.

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Properties of Confined Water Between two Hydrophilic Surfaces

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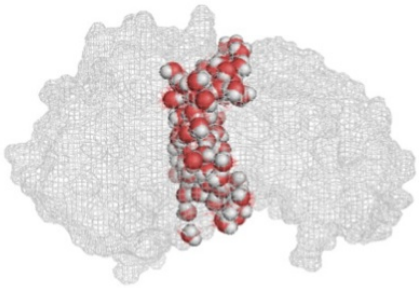

Hydrophilic protein-protein interfaces constitute a major part of protein-protein interfaces and thus are of great importance. However, the qualitative characterization of their association is still an ongoing challenge, and the driving force behind their association remains poorly characterized [1]. Here we present a study of the association of hydrophilic proteins and the role of water through the analysis of extensive molecular-dynamics simulations using three well studied protein complexes: Barnase – Barstar, Cytochrome c – Cytochrome c peroxidase, and the N-terminal domain of enzyme I - Histidine-containing Phosphocarrier protein. We investigated the properties of interfacial water confined between two protein surfaces, which is very important for protein-protein association. The analysis was performed using newly implemented Gromacs plug-ins. Our analysis shows that the confined water between the hydrophilic partners deviates from the bulk values, especially at close separation of the confined proteins.

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Pharmacophore modeling and virtual screening to discover cytochrome P450 17 inhibitors among environmental chemicals

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The modulation of endocrine receptors by environmental chemicals is intensively studied. However, the inhibition of cytochrome P450 17 (CYP17) by environmental chemicals is not very well investigated. CYP17 is a central enzyme for steroid synthesis and has a critical role in androgen production in humans. The inhibition of CYP17 has a strong impact on androgen synthesis and on sperm count [1]. It has been known recently that the inhibition of CYP17 is also an important option for the treatment of castration-resistant prostate cancer [2,3,4,5].

In this study, we have generated structure-based and ligand-based pharmacophore models for CYP17 inhibition. These pharmacophore models were used to perform a virtual screening to identify potential CYP17 inhibitors from environmental chemical databases like food contact compounds, food flavoring agents, cosmetic ingredients, industrial chemicals, endocrine disruptors, approved drugs, and pesticides. The most relevant hits will be tested for CYP17 inhibition *via* an enzymatic assay. Molecular docking studies will be performed to propose protein-ligand interactions of the experimentally tested hits.

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Synthesis of new heterocyclic compound, as analogue derivative of grandisin and veraguensin neolignans, with potential anti-trypanosomatid activity

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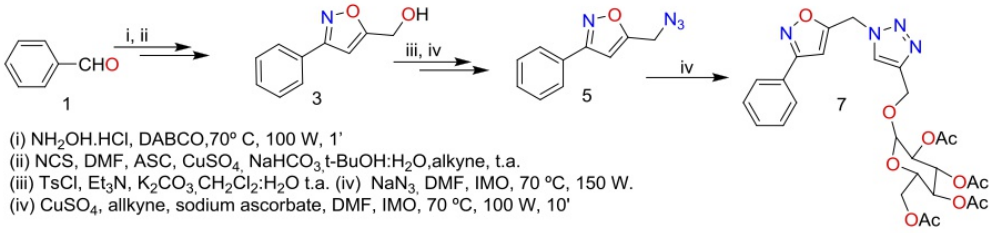
The currently available compounds for the treatment of Chagas disease (*Trypanosoma cruzi*) are not satisfactory, limited, and can have toxic side effects. There is the urgent need to develop new drugs and tools for the treatment of trypanosomatids. [1] Thus, we synthesized analogs of the anti-trypanosomatid lignans grandesin and veraguensin. The synthetic strategy involved the synthesis of the intermediate azide isoxazole, which is prepared in four steps, and it is used to make a cycloaddition reaction with an sugar alkyne, catalyze by copper (I), under heating by microwave irradiation, resulting the bisheterocyclic compound in good yield (17%). [2;3;4;5;6;7] Their antichagasic properties on trypomastigotes of *T. cruzi* and cellular toxicity activity has been evaluated. While the antichagasic effects of **7** were confirmed *in vivo*, there is currently no information on the actual drug target. Therefore, we will use publicly available virtual prediction tools to find the targets that this compound could act on in this parasite. The anti-trypanosoma targets suggested by the target fishing tools will be presented and discussed.

Figure1: Synthetic route to obtain the bisheterocyclic compound.



(i) $NH_2OH.HCl$, DABCO,70º C, 100 W, 1'
(ii) NCS, DMF, ASC, $CuSO_4$, $NaHCO_3$,t-BuOH:H_2O,alkyne, t.a.
(iii) TsCl, Et_3N, K_2CO_3,CH_2Cl_2:H_2O t.a. (iv) NaN_3, DMF, IMO, 70 ºC, 150 W.
(iv) $CuSO_4$, allkyne, sodium ascorbate, DMF, IMO, 70 ºC, 100 W, 10'

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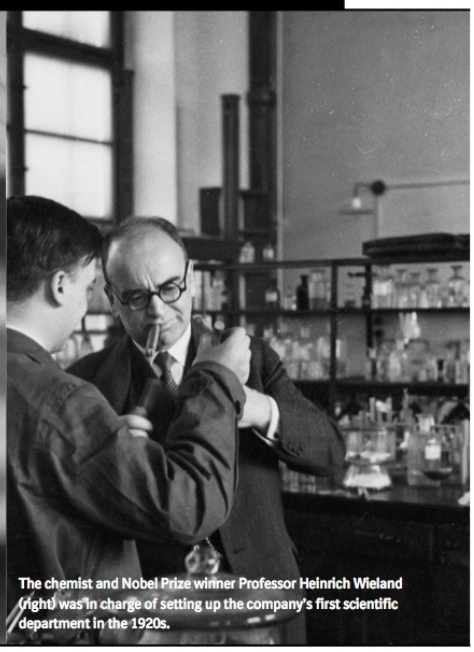

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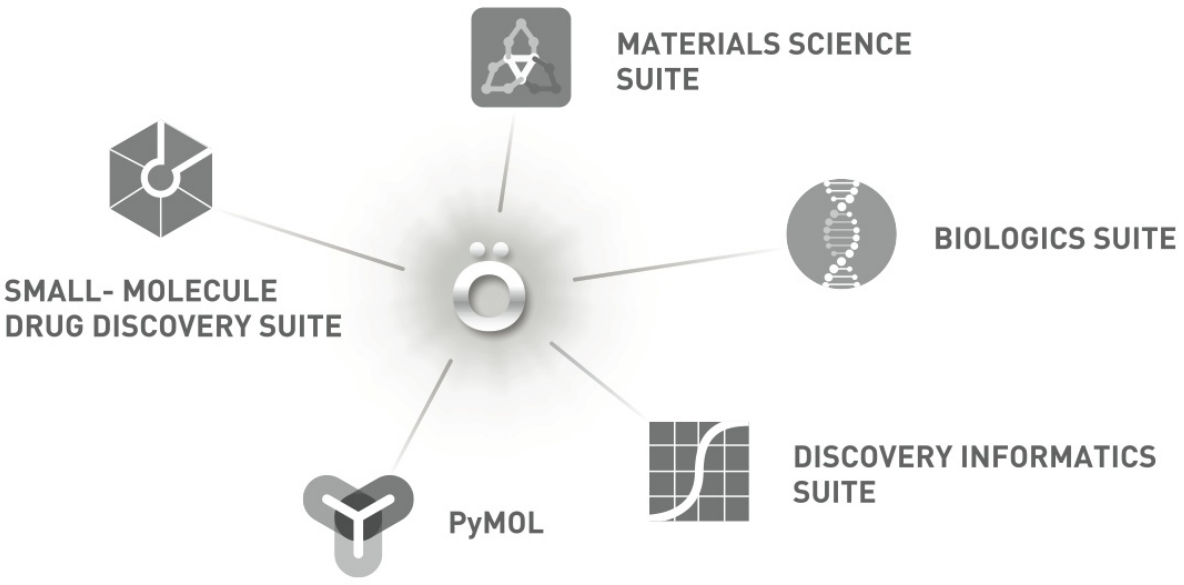

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