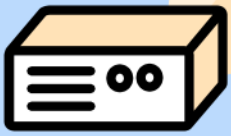
MOLECULAR MODELING WORKSHOP 2010

March, 15th - 16th



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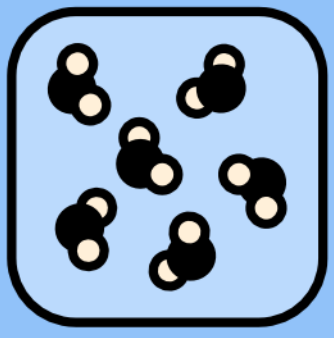

C3 Computer Chemie Centrum

Friedrich-Alexander-Universität Erlangen-Nürnberg

Molecular Modeling Workshop 2010

Computer-Chemie-Centrum
Nägelsbachstr. 25, 91052 Erlangen
Germany

Monday, March 15th - Tuesday, March 16th 2010

Once again, we in CCC are happy to welcome you to the Molecular Modeling Workshop 2010. The goals of the Workshop are to give graduate students and young postdocs an opportunity to present their work, to provide a forum for molecular modeling and to give young researchers the opportunity to meet established researchers, both industrial and academic. The Molecular Graphics and Modelling Society – German Section (MGMS-DS) is, as always the organizer of the Workshop and provides financial support to enable students to attend the workshop.

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 Modeling Workshop consistently and generously over its entire history.

Coordination of scientific program

Prof. Dr. Rainer Böckmann

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Preamble

Dear colleagues,

This year, the 24th Molecular Modeling Workshop will take place on March, 15th and 16th. For the eighth time, the workshop will be hosted by the University of Erlangen-Nürnberg. The research group of Professor Tim Clark at the Computer-Chemistry-Center will be responsible for the technical organization. Professor Dr. Rainer Böckmann, lecturer for computational biology, Erlangen, will be responsible for the scientific organization.

This workshop encourages young scientists - especially graduate students - to present and discuss their research topics. Young scientists at the beginning of their academic careers will be able to meet new colleagues from academia and gain feedback from industrial colleagues.

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

Our Plenary Speakers this year are

Holger Gohlke
Institute for Pharmaceutical and Medicinal Chemistry
Heinrich-Heine-Universität, Düsseldorf

David M. Smith
Department of Organic and Biochemistry
Rudjer Boskovic Institute, Zagreb

Dirk Zahn
Theoretische Chemie / Computer-Chemie-Centrum
Friedrich-Alexander-Universität
Erlangen-Nürnberg

The official language of the Workshop is English.

Awards

As in the past years, there will be two Poster Awards of EUR 100 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 EUR 500)
2nd Winner: EUR 200 travel expenses reimbursement
3rd Winner: EUR 100 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 modeling will not be awarded this year.

Travel Bursaries

We are very happy to be able to grant two EUR 250 travel bursaries sponsored by the **Chemical Computing Group** to:

Ignasi Buch
Municipal Institute for Medical Research, Barcelona, Spain

Pinar Güloglu
Ege University, İzmir,Turkey

We are further very happy to be able to grant EUR 100 travel bursaries sposored by the **MGMS-DS** to:

Daniel Escudero
Friedrich-Schiller Universität Jena, Germany

Andrea Frank
Universität Konstanz, Gemany

Daniela Grimme
Heinrich Heine Universität Düsseldorf, Germany

Christian Hanke
Universität des Saarlandes, Saarbrücken, Germany

Doris Klein
Heinrich Heine Universität Düsseldorf, Germany

Wenjin Li
Heidelberg Institute for Theoretical Studies, Heidelberg, Germany

Ionut Onila
Universität Konstanz, Gemany

Sophie Weggler
Universität des Saarlandes, Saarbrücken, Germany

Program: Monday, March 15th 2010

11:00-13:15 **Registration**

13:15-13:30 Welcome remarks / Agenda review

13:30-13:55 **Mazen Ahmad**
Saarland University, Saarbrücken
Multiple mechanisms of protein- protein interaction

13:55-14:20 **Angela Götz**
Friedrich-Alexander Universität, Erlangen
Molecular dynamics simulations of the ß2-adrenergic receptor in complex with a peptide derived from the Gα subunit of the heterotrimeric G_s-protein

14:20-14:45 **Carola von Deuster**
Max Planck Institute of Colloids and Interfaces Potsdam
How does the antimicrobial peptide NK-2 distinguish between procaryotic and eucaryotic membranes?

14:45-15:10 **Madeleine Kittner**
MPI KG, Golm
Amyloid-ß(25-35) oligomers in solution: structure and thermodynamics

15:10-15:40 Coffee break

15:40-16:30 **Plenary Lecture: Holger Gohlke**
Heinrich-Heine-Universität, Düsseldorf

Molecular recognition properties of “general” fluorobases – Unveiling the Janus face of organic fluorine

16:30-16:55 **Christophe Jardin**
Friedrich-Alexander Universität, Erlangen
Elucidating the specificity of STAT proteins recognition by dual-specificity phosphatases

16:55-17:20 **Iris Antes**
Technische Universität München
Receptor Flexibility in Molecular Docking

17:20-17:45 **Nadine Schaadt**
Saarland University, Saarbrücken
Substrate Prediction of Membrane Transporters in Arabidopsis thaliana

17:45-18:30 **Annual Meeting of the MGMS-DS**

18:30-22:00 **Poster Session and Buffet**

Program: Tuesday, March 16th 2010

08:30-08:55 **Julian Fuchs**
University of Innsbruck, Innsbruck
Shape Description of the Minor Groove

08:55-09:20 **Senbo Xiao**
Heidelberg Institute for Theoretical Studies Heidelberg
Molecular modeling and mechanical analysis of polyamides

09:20-10:10 **Plenary Lecture II: David Smith**
Rudjer Boskovic Institute, Zagreb

Studying Enzymatic Mechanisms with QM/MM Techniques: An Application to the Dehydration of Glycerol

10:10-10:35 Coffee break

10:35-11:00 **Wenjin Li**
Heidelberg Institute for Theoretical Studies Heidelberg
Mechanical Regulation on the Thiol/ disulfide Exchange: A QM/MM Study

11:00-11:25 **Daniel Escudero**
Friedrich-Schiller Universität, Jena
Emissive or non-emissive? Theoretical mixed methodology (TD-DFT/CASSCF) to rationalize phosphorescence rates of Ru(II) polypyridyl complexes

11:25-11:50 **Oscar Rubio-Pons**
Friedrich-Alexander Universität, Erlangen
Electron Injection Dynamics in Au(111)-Molecule Interfaces: A theoretical Study

11:50-12:00 Conference Photo

12:00-13:15 Lunch break

Program: Tuesday, March 16th 2010

13:20-14:10 **Plenary Lecture: Dirk Zahn**
Friedrich-Alexander Universität, Erlangen

"Understanding reaction mechanisms from transition path sampling molecular dynamics simulations"

14:10-14:35 **Francesco Gervasio**
CNIO, Madrid
Free Energy methods to study complex biological phenomena.

14:35-15:00 **Ignasi Buch**
Universitat Pompeu Fabra, Barcelona
High-throughput all-atom molecular dynamics simulations using distributed computing

15:00-15:25 **Sophie Weggler**
Saarland University, Saarbrücken
Numerical simulations on reentrant condensation of proteins

15:25-15:45 Coffee break

15:45-16:10 **Ilona Baldus**
HITS GmbH, Heidelberg
The influence of mechanical stress on redox potentials in proteins

16:10-16:35 **Pawel Rodziewicz**
Friedrich-Alexander Universität, Erlangen
First-principles study of superhard SiN_X /TiN nanocomposites

16:35-17:00 **Susanne von Grafenstein**
University of Innsbruck, Innsbruck
Targeting the TrxR protein- protein interface by knowledge based virtual screening

17:00-17:15 **Poster & Lecture awards / Closing remarks**

Posters

P1	**Mazen Ahmad**	Adhesive water networks facilitate binding of protein interfaces
P2	**Ilona Baldus**	The influence of mechanical stress on redox potentials in proteins
P3	**Caroline Becker**	Concoord/PBSA: Prediction of Mutational Effects on Protein-Protein Binding and Protein Stability
P4	**Horst Boegel**	QSAR for the Prediction of the Basicity of Nitrogen Heterocycles
P5	**Daniel Cashman**	An Analysis of the Difference between the Generalized Born Solvent Model and the Distance Dependent Dielectric Model for Normal Mode Analysis
P6	**Pia Dirauf**	Comparative dynamics study of HIV-1 and HTLV-I proteases reveals a conserved interaction network
P7	**Thomas Exner**	QM/MM Border Region Treatment: Recent Improvements
P8	**Andrea Frank**	Chemical Shift Calculations in Priteins with a Fragment-based Quantum Chemical Approach
P9	**Daniela Grimme**	Identification of protein-protein complexes that are potentailly suited for inhibition by alpha-helix mimetics
P10	**Pinar Güloglu**	Computational Investigation of Intermolecular Interactions of Pyrene and Aminopyrene with Phenothiazine and Promazine
P11	**Anselm Horn**	Amyloid-ß42 Oligomer Structures from Fibrils: A Systematic Molecular Dynamics Study
P12	**Michael Hutter**	Classification of metabolic CYP P450 substrates: Improved sensitivity due to balanced data sets
P13	**Christophe Jardin**	Elucidating the specificity of STAT proteins recognition by dual-specificity phosphatases
P14	**Siti Azma Jusoh**	Molecular Dynamics Simulations of Polar and Charged Amino Acids in Transmembrane Domains of Envelope Gylcoproteins
P15	**Srinivasaraghavan Kannan**	Application of BP-Rex MD for refinement and loop modeling of proteins in explicit solvent

P16	**Jens Karl**	Development of a phospholipidosis classification model
P17	**Kristin Kassler**	Computation Study of HIV-1 gp120 Antibody Recognition and Binding
P18	**Waqasuddin Khan**	Molecular and Structural Determinants of Adamantyl Susceptibility to HLA-DRs Allelic Vairants
P19	**Doris Lenore Klein**	Improving protein thermostability by identifying and reinforcing structural weak spots
P20	**Prashant Kumar**	Structure based drug design of HIV protease
P21	**Mohamed Maatallah**	theoretical study of aluminium hydrides
P22	**Jennifer Metzger**	Classifying Membrane Exposure of Transmembrane Helices
P23	**Zoran Milicevic**	The study of the hydration of hydrophobic particles by molecular dynamics simulations
P24	**Vigneshwaran Namasivayam**	Flexible Receptor Molecular Docking: Performance of molecular docking methods on physiologically important protein targets
P25	**Daniele Narzi**	Evidence for proton shuffling in a thioredoxin-like protein during catalysis
P26	**Kristyna Pluhackova**	Membrane interactions with the FIS1 peptide
P27	**Spaniol, Christian**	Mebitoo - A bioinformatics sequence analysis tool
P28	**Paul Strodel**	Guided QSAR Model Building for Experts
P29	**Reaz Uddin**	New Inhibitors of Pantothenate Synthetase from a Hierarchical Virtual Screening Campaign
P30	**Ikemefuna Uzochukwu**	Predictive hepatotoxicity of drugs:data mining and modelling mix
P31	**Peter Walter**	ABC database - a database for analysis of biomolecular contacts
P32	**Markus Walther**	Influence of nitrogen donor ligands on water exchange at solvated Be^{2+}-Ions $[Be(L)(H_2O)_3]^{2+}$

Poster abstracts can be found on the internet:
http://www.chemie.uni-erlangen.de/ccc/conference

Lectures

Multiple mechanisms of protein-protein interaction

Mazen Ahmad, Prof.Volkhard Helms
Zentrum für Bioinformatik, Universität des Saarlandes, D-66041 Saarbrücken

Protein-protein interaction is a fundamental event in the regulation of biological processes and in the development of many diseases. Previous experimental and computational studies have provided information about the diffusion phase and the nature of the intermediate complexes. However, the complete mechanism of the binding processes especially the last steps are still unclear. To get the atomistic picture of these steps, we have used real-time molecular dynamic simulation with explicit solvent representation to study the complete binding process of two main classes of protein complexes:
1. The case of hydrophobic interfaces and the role of hydrophobic dewetting.
2. The case of hydrophilic interfaces and water mediation of the interaction.

As an example for the complexes with a hydrophobic interface, we have studied the binding of an SH3 domain with its binding partner [1]. The simulations showed the three phases of binding from diffusion through the intermediate encounter complexes and recovered the known crystal structure of the complex. The analysis of the simulations showed a dual mechanism of binding where the long range electrostatic interactions play an essential role in accelerating and guiding the diffusion phase that finishes with the formation of intermediate encounter complexes of electrostatic nature stabilized by salt bridges. In the last steps of binding, the hydrophobic dewetting that results from the hydrophobic nature of the interfaces, mediates the desolvation of the interfaces to form vapor-like layers around the interfaces. This decrease in the interfacial water density plays a driving force role in the collapse of the interfaces and reaching the specific complex.

In a following study, we have studied the mechanism of protein binding in the case of completely hydrophilic interfaces. For this, we have studied the binding process between Barnase and Barstar. The MD simulations have reproduced the crystal structure of the complex on a time scale of hundreds of nanoseconds. The simulations showed that the structured water in the interfacial gap forms an adhesive hydrogen bond network between the interfaces. This network already plays an important role during the diffusive phase in reducing the dielectric shielding properties of the water and stabilizes early intermediate states before native contacts are formed. The transformation from these intermediates to the stereo-specific complex is then accompanied by maximization of the interfacial water-mediation.

[1] Ahmad, M., W. Gu, and V. Helms, *Angew. Chem. Int. Ed.,* **2008**. 47(40): p. 7626-30.

Molecular dynamics simulations of the β_2-adrenergic receptor in complex with a peptide derived from the Gα subunit of the heterotrimeric G_s-protein

Angela Götz[1], Peter Gmeiner[1], Tim Clark[2], Harald Lanig[2]

[1] Department of Chemistry and Pharmacy, Emil Fischer Center, Friedrich Alexander University, Schuhstrasse 19, 91052 Erlangen.

[2] Department of Chemistry and Pharmacy, Computer Chemistry Center, Friedrich Alexander University,Nägelsbachstrasse 25, 91052 Erlangen.

The β_2-adrenergic receptor is a member of the large family of G-protein coupled receptors (GPCRs). It belongs to the subfamily of rhodopsin-like receptors. Ligand binding to the transmembrane domain leads to conformational changes within the receptor and to activation of intracellular G-proteins.

In 2007, the β_2-adrenergic receptor was crystallized in its inactive conformation and the structure was widely-used for drug design studies. One year later, opsin was crystallized in its G-protein-interacting conformation. It was stabilized by an 11 amino acid synthetic peptide derived from the C-terminus of the Gα subunit of the G_t-protein interacting with the cytoplasmic part of the seven transmembrane (TM) helices.

The aim of our studies was to construct a receptor-peptide complex derived from the crystal structure of the β_2-adrenergic receptor and the C-terminus of the Gα subunit of the G_s-protein. Following, the impact of the C-terminal end of Gα on the structure of the ligand binding site and the interactions between receptor and the synthetic agonist Isoprenaline should be investigated.

By applying molecular dynamics simulations, the cytoplasmic half of TM6 of the β_2-adrenergic receptor was shifted outwards of the helical bundle by 6-7 Å to accommodate the C-terminal end of $G_s\alpha$ in the cytoplasmic part of the receptor as observed in the crystal structure of opsin. Following, the peptide-receptor complex as well as the original crystal structure of the β_2-adrenergic receptor were subjected to molecular dynamics simulations in a DOPC membrane. The simulations in both systems were carried out in presence and absence of Isoprenaline.

Although the peptide, interacting with the cytoplasmic part of the receptor, is not in close proximity to the ligand binding site, it significantly affects the structure of the binding pocket. Hydrogen bond patterns within the receptor and between receptor and ligand as well as root mean square deviation and fluctuation data are used to characterize the binding crevice. In addition, the binding site is divided into three different layers parallel to the membrane orientation. For each layer the helix-helix distances were calculated to monitor in detail changes in the structure of the binding pocket.

In this presentation, the results of the analyses will be discussed to elucidate the influence of the peptide on structure and dynamics of the ligand binding site.

How does the antimicrobial peptide NK-2 distinguish between procaryotic and eucaryotic membranes?

Carola von Deuster, Reinhard Lipowsky, Volker Knecht

Max Planck Institute on Colloids and Interfaces, Am Mühlenberg 1, 14476 Potsdam

Antimicrobial peptides are part of the innate immune system of many animals and plants and may kill bacteria via permeabilization of the bacterial cell membrane. A peptide showing high antimicrobial activity combined with low toxicity for eucaryotic cells is the highly cationic and alpha-helical peptide NK-2 [1]. Its selectivity for procaryotes is attributed to the difference in lipid composition of the outer leaflets of pro- and eucaryotic cell membranes [2]. In vitro studies by others have revealed significant affinity of NK-2 for phosphatidyl-ethanolamine (PE) exposed by procaryotes but not phosphatidyl-choline (PC) exposed by eucaryotes, both lipids being zwitterionic. We reproduce this behavior by means of molecular dynamics simulations using a coarse grained model and thermodynamic integration and reveal the underlying mechanism.

[1] T. Jacobs, H. Bruhn, I. Gaworski, B. Fleischer, and M. Leippe, *Antim. Agent. Chemot*h. , **2003,** 47**,** 607

[2] R. Willumeit, M. Kumpugdee, S. S. Funari, K. Lohner, B. P. Navas, K. Brandenburg, S. Linser, and J. Andrä, *Biochim. Biophys. Acta-Biomemebr.*, **2005**, 1669(2), 125

Amyloid-β(25-35) oligomers in solution: structure and thermodynamics

Madeleine Kittner, Volker Knecht

Max-Planck-Institute of Colloids and Interfaces, Dep. Theory and Bio-Systems, Am Mühlenberg 1, 14476 Golm

Amyloidoses such as Alzheimer's disease are associated with the conversion of proteins from a soluble and functional form into β-sheet rich structures that often tend to precipitate in the form of fibrils. The development of specific agents against amyloidoses requires an understanding of the early stages of fibril nucleation at the microscopic level.

We have used all atom replica exchange molecular dynamics simulations to study the fibrillogenic Alzheimer amyloid-β(25-35) peptide in dimeric and trimeric form in explicit water. As known from previous studies on monomers, this fragment forms β-hairpin structures in water [1]. The dimers predominantly form compact structures in which peptides adopt β-hairpin-like or unstructured U-shaped conformations with a broad distribution of relative orientations. In addition, we observe dimer structures in which peptides form extended, marginally stable, anti-parallel in- or out-of-register intermolecular β-sheets. We find that compact conformations are entropically favored while extended conformations are stabilized due favorable covalent and coulombic peptide-peptide interactions.

The trimer system also shows a variety of different, poorly populated conformations. Although, we find compact as well as partly extended structures a simple two state model is not appropriate for this system. Here, we focus on the formation of trimers by analyzing the equilibrium between trimer *versus* dimer and monomer. The thermodynamic forces driving the aggregation are dissected.

[1] G. Wei, J. Shea, *Biophys. J.*, **2006**, *91*, 1638-1647.

15:40 - 16:30

Molecular recognition properties of "general" fluorobases – Unveiling the Janus face of organic fluorine

Alrun N. Koller[1], Hannes Kopitz[1], Jelena Božilović[2], Aleksandra Živković[2], Joachim W. Engels[2], Holger Gohlke[1]

[1]Heinrich-Heine-University, Institute for Pharmaceutical and Medicinal Chemistry, 40225 Düsseldorf; [2]Goethe-University, Institute for Organic Chemistry and Chemical Biology, 60438 Frankfurt

Fluorine-substituted base analogues have proven invaluable as nonpolar nucleoside isosteres (NNI) to probe the physical forces that govern the stability of nucleic acids. When paired against natural bases, fluorinated analogues destabilize DNA and RNA helices and exhibit little binding sequence specificity. When paired opposite themselves, a considerable degree of stability is regained, and a selective pairing of fluorinated bases in the context of nucleic acids is observed. Apparently, the role of fluorine in molecular recognition strongly depends on the surrounding molecular environment.

Towards the goal of addressing the influence of the environment on the molecular recognition thermodynamics of organic fluorine, we, first, have undertaken a combined experimental/computational free energy study of fluorobenzene *self-pairing* in the context of duplex RNA.[1] The study reveals the determinants of the surprising stability of fluorobenzene self-pairs with increasing fluorine-substitution and demonstrates that it may generally not be sufficient to discuss molecular recognition properties of organic fluorine in terms of global molecular properties. Instead, analyses at an atomic level are required.

Second, potentials of mean force have been calculated for planar configurations of *NNIs with natural bases*.[2] No differences in base pairing interactions between difluorobases and different natural bases are found, in agreement with experiment. Base pairing involving difluorobases is disfavored compared to Watson-Crick base pairing, but more favorable than if toluene is used as NNI. This is the result of similar desolvation costs of the NNIs, but decreased attractive base-base interactions involving toluene compared to difluorobases. Based on isosteric considerations, we proposed a 7-*N*-linked purine as a new "general base", which was confirmed experimentally. A modified 7-*N*-linked 9-deaza-purine finally emerged to be the least destabilizing general base in the context of duplex RNA known to date.

[1] H. Kopitz; A. Zivkovic; J.W. Engels; H. Gohlke, *ChemBioChem* **2008**, *9*, 2619-2622.
[2] A.N. Koller; J. Bozilovic; J.W. Engels; H. Gohlke, *Nucl Acids Res* **2010**, *doi: 10.1093/nar/gkp1237*.

Elucidating the specificity of STAT proteins recognition by dual-specificity phosphatases

Christophe Jardin and Heinrich Sticht

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University of Erlangen-Nuremberg, Fahrstraße 17, 91054 Erlangen, Germany

Kinases and phosphatases play complementary roles in maintaining an equilibrated balance between phosphorylated and unphosphorylated proteins within the cell. This equilibrium is of critical importance, and aberrations generally lead to the pathogenesis of numerous diseases, including cancer, diabetes, and immune deficiencies.
Negative regulation of the classical JAK/STAT signalling pathway can be exerted, e.g. via dephosphorylation of a C-terminal phosphotyrosine residue of activated (i.e. phosphorylated) STAT proteins by protein tyrosine phosphatases (PTPs).
In the recent years, it has been shown that members of the dual-specificity phosphatases (DSPs), a subfamily of the PTPs, exhibit enzymatic activity towards specific STAT protein partners: VHR specifically dephosphorylates STAT5 [1], whereas VH1 dephosphorylates both STAT1 and STAT2 but neither STAT3 nor STAT5 [2].
Mutational and kinetic experiments have provided first information about the existence of multiple interaction sites between these atypical DSPs and STAT factors [1]. However, there is up-to-date no structural explanation for the specific recognition of STAT proteins by these phosphatases.

Therefore, a combined approach of docking and MD simulations was developed, which allows to investigate the individual relevance of the different interaction sites formed between the phosphatases VHR and VH1 and their respective substrates STAT5 and STAT1. This approach did not only allow us to characterize these interactions, but it also provided us the basis for the specific recognition of STAT proteins by the dual specificity phosphatases. Briefly, these simulations reveal that the primary interactions formed at the active site of the phosphatase are highly similar for different ligands suggesting that they play only a minor role for binding specificity. In contrary, numerous specific interactions are formed within a second interface involving the SH2-domain of the STAT factors.

[1] R. Hoyt, W. Zhu, F. Cerignoli, A. Alonso, T. Mustelin and M. David. *J. Immunolog.*, **2007**, 179, 3402–3406.
[2] B.A. Mann, J.H. Huang, P. Li, H.C. Chang, R.B. Slee, A. O'Sullivan, M. Anita, N. Yeh, M.J. Klemsz, R.R. Brutkiewicz, J.S. Blum and M.H. Kaplan. *J. Interferon Cytokine Res.*, **2008**, 28, 367–380.

Receptor flexibility in protein-ligand docking

Christoph Hartmann, Vigneshwaran Namasivayam, and Iris Antes

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During the last decade computational methods have become an indispensable part of pharmaceutical, medical, and biotechnological research. One of the most important application areas is computer-aided drug design, in which molecular docking methods play a predominant role. Although molecular docking methods are meanwhile in a very mature state, from a methodological perspective two topics are still a challenging task: the efficient treatment of protein flexibility upon ligand binding and docking of ligands with many degrees of freedom. In this context, two approaches will be presented for the inclusion of side chain [1, 2] and backbone flexibility [3] into molecular docking algorithms. In addition, the application of the methods to protein-peptide docking and docking into flexible binding sites will be discussed.

[1] C. Hartmann C., I. Antes, and T. Lengauer, *Protein Science*, **2007**, 16(7), 1294-1307.

[2] C. Hartmann C., I. Antes, and T. Lengauer**,** *Proteins,* **2009**, 74(3), 712-726.

[3] I. Antes I., *Proteins*, **2010**, 78(5), 1084-1104.

Substrate Prediction of Membrane Transporter in *Arabidopsis thaliana*

Nadine Schaadt, Volkhard Helms

Chair of Computational Biology, Saarland University, Saarbrücken

Membrane transporters catalyze active one- and bi-directional transport of small chemicals across biological barriers such as lipid bilayer membranes. Based on their genome sequences, it has been postulated that model organisms such as *Escherichia coli* or *Arabidopsis thaliana* contain between 500 and 700 membrane transporters among their 4000 (*E.coli*) and 25.000 (*Arabidopsis*) protein coding genes. Unfortunately, the experimental annotation of which transporters transport which substrates is far from complete and will likely remain so for much longer. Therefore, it is highly desirable to develop statistical methods that may aid in the substrate annotation of putative membrane transporter proteins.
Here, we have present an analysis of the dataset on the *Arabidopsis* transporters compiled in the database Aramemnon (http://aramemnon.botanik.uni-koeln.de/). Various measures for the similarity of membrane transporter sequences were tested based on their amino acid composition, higher sequence order informations, amino acid characteristics or sequence conservation. We defined several positive sets including amino acid, oligopeptide, ion and sugar transporters and trained two classification schemes either based on ranked lists or on a SVM for classifying unknown sequences into these positive sets. We found that the amino acid profile allows ranking transporter sequences with an accuracy of 75% or higher according to the substrate type. Integrating additional information further improved the prediction performance. This study shows that substrate annotations of membrane transporters are well feasible based on their bare amino acid compositions. We hope that this work may prove useful for biological applications.

Shape Description of the Minor Groove

Julian E. Fuchs[1], Gudrun M. Spitzer[1], Adam Biela[2], Christoph Kreutz[1], Ameera Javed[1], Bernd Wellenzohn[3], Gerhard Klebe[2], Klaus R. Liedl[1]

1 Faculty of Chemistry and Pharmacy, University of Innsbruck, Innrain 52a, A-6020 Innsbruck, Austria

2 Department of Pharmaceutical Chemistry, Philipps University Marburg, Marbacher Weg 6, D-35032 Marburg, Germany

3 Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer Strasse 65, D-88397 Biberach/Riss, Germany

Since sequence-dependent shape is recognized more and more important in the binding of proteins to DNA [1], large molecule databases were screened for molecules potentially binding to the minor groove of DNA using a shape-based virtual screening protocol. The traditional view of DNA binding as realization of hydrogen bonding patterns was left towards a more general description of DNA by its characteristic three-dimensional shape. Since chemical properties and shape of DNA are closely related [2], this virtual screening approach was considered promising for the discovery of new minor groove binders, a group of molecules known to influence gene expression [3] and to prevent transcription factors from binding to DNA [4]. Several previously unknown minor groove binders were discovered with this method and confirmed experimentally by means of isothermal titration calorimetry (ITC), ^{1}H-NMR experiments, UV spectroscopy and DNA melting experiments [5].

ROCS [6] was used for virtual screening of the NCI database [7] using minor groove binders in bioactive conformation from X-ray structures as queries. ROCS represents heavy atoms by Gaussians with parametrized decay constants according to the van der Waals radii of the respective atoms. This depiction allows a fast comparison of molecules due to the straightforward calculation of volume overlaps being used as a measure for similarity of the molecules. Besides shape description ROCS includes “Color Force Fields” allowing basic inclusion of chemical information as additional “Color Gaussians”. Nevertheless the shape focus of this virtual screening application provides structurally diverse hits known as scaffold or lead hopping [8]. In our case four structurally uncommon minor groove binders were discovered, one of them completely lacking the traditional hydrogen bond donor functions in the central part of the molecule suggesting that this compound would not have been detected with conventional virtual screening approaches.

[1] R. Joshi, J. M. Passner, R. Rohs, R. Jain, A. Sosinsky, M. A. Crickmore, V. Jacob, A. K. Aggarwal, B. Honig, R. S. Mann, *Cell*, **2007**, *131*, 530-543.
[2] R. Rohs, S. M. West, A. Sosinsky, P. Liu, R. S. Mann, B. Honig, *Nature*, **2009**, *461*, 1248-1254.
[3] J. M. Gottesfeld, L. Neely, J. W. Trauger, E. E. Baird, P. B. Dervan, *Nature*, **1997**, *387*, 202-205.
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Silk fiber mechanics from models at different length scales

Senbo Xiao, Murat Cetinkaya, Frauke Graeter

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Silk is one of the most resilient fibers in nature. Consisting of an amorphous matrix cross-linked by beta-sheet rich crystalline units, silk is a hierarchically organized material the molecular details of which remain largely unknown. In order to decipher the structural determinants of its mechanical properties, we model silk at different length scales by combining molecular dynamics simulations, force distribution analysis, and finite element methods. We predict the distinct mechanics of anti-parallel versus parallel silk crystals as force-bearing cross-links [1], and the impact of chain entanglement and crystallinity on fiber mechanics [2]. Our predictions can serve as a guide for the design of artificial silk protein analogues.

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9:20 - 10:10

Studying Enzymatic Mechanism with QM/MM Techniques: An Application to the Dehydration of Glycerol

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The ubiquitous difficulty facing researchers studying the mechanisms of chemical reactions in biological systems is that the computational expense of techniques that are satisfactorily accurate is too large to apply to macromolecular systems. Of the many suggestions put forward, the combination of ab initio quantum mechanics (QM) with classical molecular mechanics (MM) has enjoyed the most success. This contribution will discuss such techniques briefly and highlight the continued need for high-accuracy QM methods in the context of biological mechanistic studies. A case study, demonstrating two similar yet different strategies for the biological dehydration of glycerol will be employed to demonstrate the ability of QM/MM methods to provide useful mechanistic information, as well as testable predictions.

Evidence of Mechanical Regulation on Thiol/disulfide Exchange from TPS and QM/MM Study

Wenjin Li, Frauke Graeter

CAS-MPG Partner Institute for Computational Biology; and Heidelberg Institute for Theoretical Study.

Abstract: The ability of mechanical force to regulate chemical reactions has interested generations of researchers and theoretical efforts have been taken to understand this mechanical phenomenon. [1] As evidences that force tilted the free energy profile and thus shifted transition state (TS) accumulated, more advanced model other than Bell's model have been proposed to describe the force-dependency of rate constant. [2] Here, by the combination of TPS and QM/MM we investigated thiol/disulfide exchange under forces ranging from 200pN to 2nN. The total simulation time added up to 20ns. We demonstrated that at low force reactions went along almost the same pathway while reaction paths became diverged at high force, which rationalized the limitation of Bell's model. A new model, which is expected to be valid at any applied force , is also proposed. We suggested that TS moved towards reactant state (RS) along reaction coordinate (R_C) driven only by the component of force along R_C and broad reaction pathways became possible at high force.

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11:00 - 11:25

Emissive or non-emissive? TDDFT-CASSCF calculations to rationalize phosphorescence rates of Ru(II) polypyridyl complexes

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Light-activation processes in organometallic complexes are a promising field with strong applications in e.g. artificial photosynthesis or dye sensitized solar cells. Concerning these photocatalytic systems, light-harvesting antenna complexes are usually activated through high-absorbing low-lying metal-to-ligand charge transfer (MLCT) states that undergo efficiently intersystem crossing (ISC) to ^{3}MLCT states, which feature lifetimes up to microseconds and hence allow for electron transfer processes. Additionally, effective phosphoresce emission can also be achieved in some cases, as e.g. in Ir cyclometalated complexes, and thus making them good candidates as photoactive systems in light emitting diodes technology.

To get an insight into the photophysical properties of systems with more than one hundred atoms, state of the art calculations involve the use of DFT theory and its time-dependent (TD-DFT) version. When considering solvent effects and using a hybrid functional, DFT and TD-DFT methods provide a fairly good agreement with the experimental absorption and emission spectra.[1] After irradiation, ISC between the singlet and triplet manifolds takes place, due to large spin-orbit couplings (SOC). To determine the SOC matrix elements a multiconfigurational method (as e.g. the Complete Active Space Self Consistent Field, CASSCF) is demanded. Here we present a mixed DFT/CASSCF methodology to rationalize the phosphorescence radiative rates; which determine, together with the non-radiative decays, the quantum yields. Using such methodology, we have successfully rationalized the very different emissive behaviour of two similar Ru complexes.

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"Electron Injection Dynamics in Au(111)-Molecule Interfaces: A theoretical Study"

Oscar Rubio-Pons[1,2] *and Michael Thoss*[2]
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We present a study of electron transfer and electron transport processes in molecular systems at metal substrates. In particular, photoinduced electron transfer in molecules at metal surfaces and voltage driven electron transport in single-molecule junctions are investigated, see Figure 1. The methodology is based on a combination of first-principle electronic structure methods to characterize the systems and dynamical basis-set as well as nonequilibrium Green's function methods to study electron transfer dynamics and transport properties, respectively[1].

The results show the ultrafast character of electron transfer at molecule-metal interfaces and demonstrate the importance of electronic-vibrational coupling in single-molecule junctions. Furthermore, a mechanism for photoinduced switching of molecular junctions based on hydrogen translocation[2] is discussed.

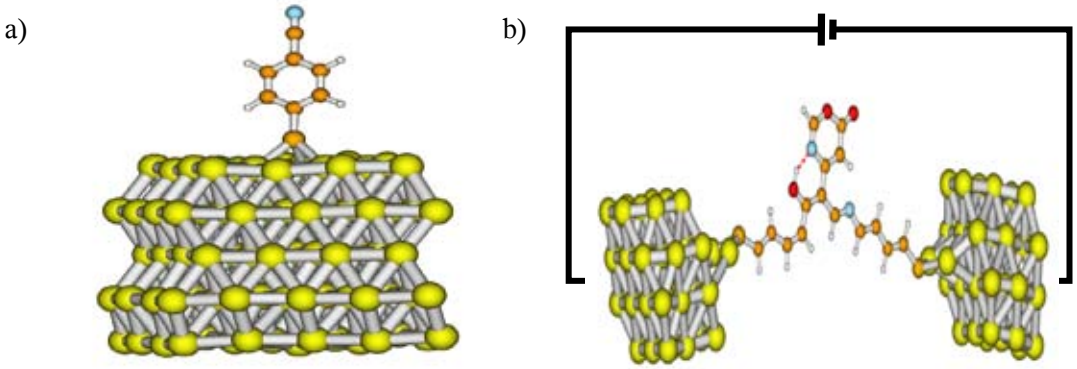

Figure 1. a) Molecule at metal surface and b) single-molecule junction

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Understanding reaction mechanisms from transition path sampling molecular dynamics simulations

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Transition path sampling (TPS) is an increasingly prominent simulation method for exploring processes that are triggered by large activation barriers. By efficiently tackling the inherent time-length scale problem, TPS molecular dynamics simulations allow very detailed insights into the mechanisms of reactions, phase transitions, structural reorganization and other kinds of barrier crossing events.

The method is particularly suited to the investigation of complex systems, in which the guessing of model reaction coordinates is likely to bias the simulation results. TPS represents a Monte-Carlo iteration in the trajectory space of reactive events and hence converges to the preferred mechanisms in an unprejudiced manner. Thus, initial pathways -which are needed as prerequisites- may be chosen essentially arbitrarily.

The method and its implementation aspects are illustrated by the example of reactions, phase transitions and phase separation processes. In each case, we deliberately use 'wrong' reaction mechanisms for preparing a starting pathway and then demonstrate the evolution of trajectories in favor of the real mechanism.

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Free Energy methods to study complex biological phenomena

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Protein plasticity represents both a challenge and an opportunity for computational drug design. Exploring the conformational space of a target with sufficient detail is computationally very demanding and often beyond the reach even for state-of-the-art atomistic molecular simulations techniques. If it were possible, however, it could open the avenue to the design of more selective drug candidates. Here we show how methods developed to accelerate rare events can be used to study both large-scale conformational transitions and ligand binding.

Using a new sampling method which is able to find the low free energy channel between an initial and final state [1] we determined the atomistic dynamics of the open-to-closed movement of the cyclin dependent kinase 5 (CDK5). We found that the inactivation movement has a two-step mechanism in which Arg149 plays a key role, allowing a concerted movement of the C-terminal and N-terminal lobes. A complementary method, Metadynamics [2] was used to study the undocking path of a congeneric series of ligands to CDK2 and of selective inhibitors from COX and COX-2 [3]. Also in these cases the large scale dynamics of the target proteins plays a fundamental role.

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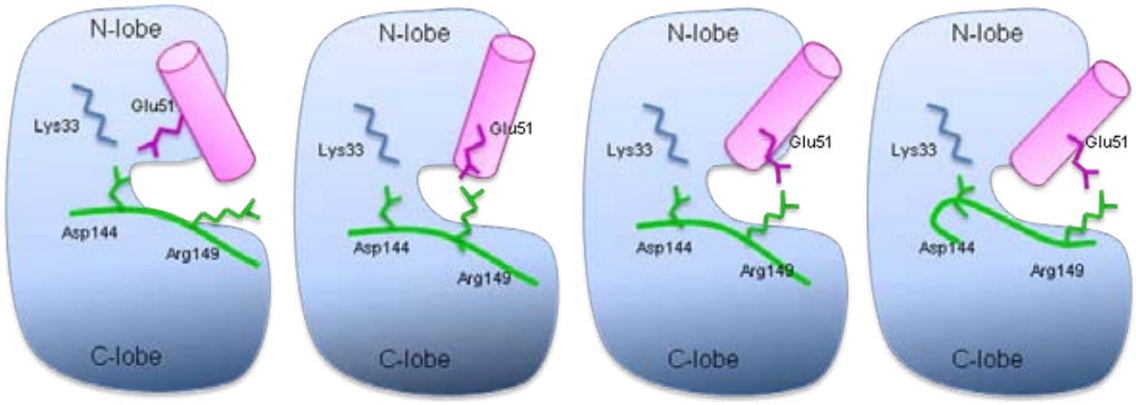


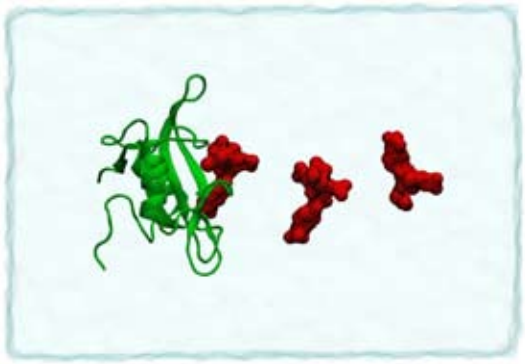
Mechanism of CDK2 deactivation obtained with path collective variables [1].

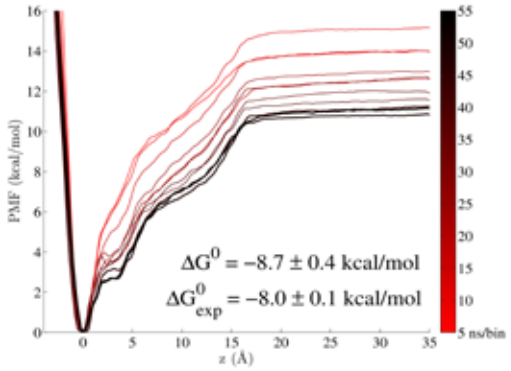
High-throughput all-atom molecular dynamics simulations using distributed computing

I. Buch (1), M.J. Harvey (2), T. Giorgino (1), D.P. Anderson (3) and G. De Fabritiis (1)*

(1) Computational Biochemistry and Biophysics Lab (GRIB), IMIM/Universitat Pompeu Fabra, PRBB, Barcelona-Spain. (2) High Performance Computing Service, Information and Communications Technologies, Imperial College London, London-UK. (3) Space Sciences Laboratory, University of California, Berkeley-USA.

** gianni.defabritiis@upf.edu*





Although molecular dynamics simulation methods are useful in the modeling of macromolecular systems, they remain computationally expensive, with production work requiring costly high-performance computing (HPC) resources. We review recent innovations in accelerating molecular dynamics on graphics processing units (GPUs), and we describe GPUGRID, a volunteer computing project that uses the GPU resources of non-dedicated desktop and workstation computers. In particular, we demonstrate the capability of simulating thousands of all-atom molecular trajectories generated at an average of 20 ns/day each (for systems of ~30,000-80,000 atoms). In conjunction with a potential of mean force (PMF) protocol for computing binding free energies [1], we recently demonstrated the use of GPUGRID in the computation of accurate binding affinities of the Src SH2 domain-pYEEI ligand complex by reconstructing the PMF over 20.5 μs of umbrella sampling data. We obtain a standard free energy of binding of −8.7 ± 0.4 kcal/mol within 0.7 kcal/mol from experimental results [2].

We are now working on an optimized version of the protocol to make the system suitable for routine high-throughput protein-ligand accurate binding affinity prediction s.

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Numerical Simulations on reentrant condensation of proteins

Sophie Weggler[1], Michael Ziller[2], Oliver Kohlbacher[2], Andreas Hildebrandt[1]
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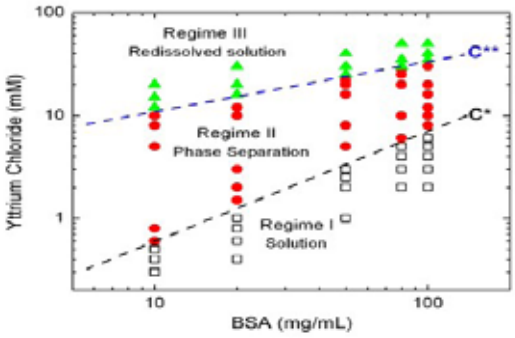
The highly interesting phenomenon of reentrant condensation of DNA and protein is imputed to correlations of multivalent ions. Reentrant condensation describes the phenomenon of the solution entering a condensed phase, which once again dissolves. This happens when adding multivalent ions to the solution, see left figure. While reentrant condensation has already been observed in systems like DNA or polyelectrolytes, it is a new and important but also to a large extent unknown field of research concerning proteins [1].



The whole phase diagram is shown on the right for the protein Bovine Serum Albumin with Y^{3+} as multivalent counter ions. The phase transitions, c* and c**, separate the different regions in the diagram. In [2] a set of proteins is studied and it turned out that the phase transition curves exhibit a linear dependence of counter ion and protein concentration. In addition, experimental measurements reveal that electrostatic interactions play a crucial role.

We developed a heuristic, general concept of metal ion-protein binding, where we assume a coordinative attachment of metal ions to the protein's surface: we combine the linear Poisson-Boltzmann theory with specific interactions between the strongly positive ions and local acidic sites to incorporate the correlation effect. This coordinative attachment is interpreted as an acid-base affinity. Thus, to elucidate the process a generalized titration model based on electrostatic interactions is developed. By introducing an affinity constant for the multivalent counter ions to bind to the acidic sites of the protein, the counter ions consecutively bind when increasing the counter ion concentration. By means of Monte Carlo Simulations we scanned the partition function to find the energetically optimal binding state of the ion-protein complex. From this we can deduce physical quantities such as the effective total charge and the effective dipole moment of the protein. Despite of the simplicity of our theoretical model the numerical results agree well with the experimental data.

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15:45 - 16:10

The influence of mechanical force on redox potentials

Ilona Baldus and Frauke Gräter

Heidelberg Institute for Theoretical Studies (HITS), PICB, Max-Planck Society and Chinese Academy of Sciences

The von Willebrand factor (vWf) is one of the major factors regulating bleeding. As bleeding enhances the shear flow experienced by the von Willebrand factor, disulfide bonds of cystine present in the vWf are reduced under mechanical stress. It is well-known that factors such as Temperature and pH values influence the thermodynamic behaviour of chemical bonds. We now aim at understanding the impact of mechanical stress. Our results show that redox potentials rise with mechanical force.

First-principles study of superhard SiN_x /TiN nanocomposites

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Nanocomposite materials based on TiN nanocrystalites embedded in an amorphous silicon nitride matrix with thickness of only a few atomic layers and composition close to Si_3N_4 show a superhardness similar to that of diamond. To elucidate the chemical origin of the material hardness and the exceptional strength of the SiN_x /TiN interfaces we have used DFT calculations in combination with Car-Parrinello molecular dynamics (CPMD) simulations to create and to investigate model SiN_x /TiN interface structures. As the first step we studied the initial stages of SiN_x layer formation on TiN(001) by adding successively silicon and nitrogen atoms to the TiN surface to form up to two monolayer thick SiN_x films with different composition. For a selected set of configurations, chosen on the basis of thermodynamic stability, we then applied a stepwise procedure based on heating, quenching and final geometry optimization to search for stable and energetically favorable amorphous structures of SiN_x films and stacks of SiN_x /TiN multilayers. The relative stability of the different model interface structures is analyzed in terms of Ti, Si and N coordination numbers, and the mechanical strength of the interfaces is assessed by the calculation of stress–strain curves to determine the ideal decohesion strength.

Targeting the TrxR protein-protein interface by knowledge based virtual screening

Susanne von Grafenstein, Riccardo Rubbiani, Ingo Ott, Gerhard Wolber

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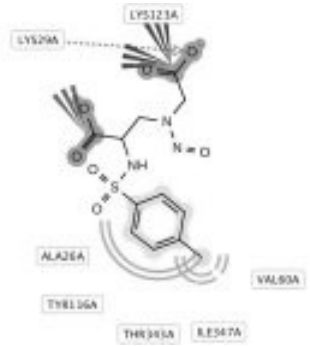
Institute of Pharmaceutical Chemistry, Technische Universität Braunschweig, Pharmaceutical Chemistry, Freie Universität Berlin

Thioredoxin reductase (TrxR) is a selenoprotein involved in various processes regulating the cell's redox state. It represents a promising target enzyme for cancer therapy and the treatment of arthritic diseases. Therapeutic organometals form a complex with selenocysteine, a C-terminal residue decisive for the catalytic activity. Further catalytic cysteine residues and the co-factor binding site are more centrally located in the 499 amino acid protein. Crystal structures reveal that two TrxR proteins dimerize in a head-to-tail arrangement. The substrate binding site is formed by the groove between the two subunits and both of them are involved in the catalytic mechanism [1]. The first crystal structure containing selenium (PDB codes 3EAN and 3EAO) and mutation experiments revealed new insights on the position of the C termination within the voluminous groove [2].

We intend to identify metal-free inhibitors of TrxR targeting the catalytic site of the homodimer. Since the binding mode of the substrate is unknown, we focused on the crucial contact between the selenocysteine with the second subunit.

We examined the protein-protein interface with a probe based method [3]. Within the potential binding site we performed de-novo design for hypothetical ligands serving as templates for virtual screening. The most relevant chemical features for the putative interactions between the protein and the virtual ligands were represented by a 3D pharmacophore model [4].

Biological testing of 18 compounds selected from the screening results identified four compounds with micromolar activity.



Binding poses suggested by docking experiments encourage our hypothesis of a binding mode, which blocks the positioning of the selenocysteine. The most active compound is placed in a small cavity next to the catalytic disulfid bridge. Especially ionic interactions with lysine residues resemble those of the selenocysteine motive in the C termination of the second subunit.

This new inhibitors of TrxR are not only relevant due to their biological activity, but might be first leads for the structure guided development of TrxR inhibitors.

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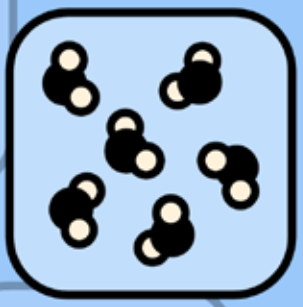

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