MOLECULAR MODELLING WORKSHOP 2012

Computer-Chemie-Centrum
Nägelsbachstr. 25
91052 Erlangen
Germany

Monday, March, 12th -Wednesday, March 14th 2012

Once again, we in CCC are happy to welcome you to the Molecular Modelling Workshop 2012. This year, it is the 26th Molecular Modelling Workshop and the tenth time it was hosted by the University of Erlangen-Nuremberg. The research group of Professor Tim Clark at the CCC will be responsible for the technical organization. Prof. Dr. Dirk Zahn, Theoretical Chemistry, University of Erlangen-Nuremberg, 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

Prof. Dr. Dirk Zahn

Theoretische Chemie
Computer-Chemie-Centrum
Friedrich-Alexander-Universität
Erlangen-Nürnberg

Nägelsbachstraße 25
91052 Erlangen

Tel: + 49 (0)9131 85 26938
Fax: + 49 (0)9131 85 26565

dirk.zahn@chemie.uni-erlangen.de

Technical coordination

Dr. Harald Lanig

Computer-Chemie-Centrum
Friedrich-Alexander-Universität
Erlangen-Nürnberg

Nägelsbachstraße 25
91052 Erlangen

Tel: +49 (0)9131 85 26525
Fax: +49 (0)9131 85 26565

harald.lanig@chemie.uni-erlangen.de

DEAR COLLEGUES,

The 26th Molecular Modelling Workshop (March, 12th - 14th) 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):

TIM CLARK

Computer-Chemie-Centrum
Friedrich-Alexander-Universität
Erlangen-Nürnberg

PETER COMBA

Institut für anorganische Chemie
Universität Heidelberg

FRANCESCO LUIGI GERVASIO

Computational Biophysics Group
Spanish National Cancer Research Centre
Madrid

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

200 Euro travel expenses reimbursement

3rd Winner

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 deligates to participate in the annual meeting of the society.

FEES

The conference fee amounts to 50 Euro (Students: 25 Euro). This fee includes the annual membership fee for the MGMS-DS e.V.

Program

PROGRAM

Monday, March 12th 2012

11:30-14:00 **Registration**

14:00-14:15 **Welcome remarks / Agenda review**

14:15-15:15 **Plenary Lecture I: Peter Comba (Heidelberg)**
Structure and function
Fundamental principles and case studies with transition metal compouds

15:15-15:40 **Prakash C. Rathi (Düsseldorf)**
Understanding the thermostabilization of citrate synthase using Constraint Network Analysis

15:40-16:05 **Susann Vorberg (Frankfurt)**
Sodium Dependent Glucose Transporter (SGLT) 1 / 2 - Elucidating Inhibitor SAR and Selectivity using Homology Modelling and 3D QSAR Studies

16:05-16:30 **Ashwani Sharma (Erlangen)**
Assessment of Protein-Ligand binding affinity with Molecular docking approach and Application

16:30-16:50 **Coffee Break**

16:50-17:15 **Elke Sponsel (Erlangen)**
Micelle/water partition coefficients using COSMO-RS: Conformational Study

17:15-17:40 **Ahmed El Kerdawy (Erlangen)**
Predicting the sites and energies of non-covalent intermolecular interactions using local properties

17:45-18:45 **Annual Meeting of the MGMS-DS e.V.**

19:30 **Buffet - Dinner**

PROGRAM

Tuesday, March 13th 2012

08:30-08:55 **Maxim Tafipolsky (Würzburg)**
Intermolecular Force Field Parameterization from First Principles

08:55-09:20 **Roland G. Huber (Innsbruck)**
Calculating Hydration Entropy of Ionic Systems from MD Trajetories

09:20-09:45 **Sabine Schweizer (Freising)**
Structural Basis of Drug Resistance in Hepatitis C Viral NS3/4A Serine Protease

09:45-10:10 **Felix Rausch (Halle)**
Protein Modeling and Molecular Dynamic Studies of two new Surfactant Proteins

10:10-10:35 **Patrick Duchstein (Erlangen)**
Disaccharides mediate the interplay between collagen and carbonate ions in biomineralization processes

10:35-11:00 **Coffee Break & Conference Photo**

11:00-12:00 **Plenary Lecture II: Francesco Luigi Gervasio (Madrid)**
Drug binding kinetics and free energy profiles from all-atom simulations

12:10-13:30 **Lunch**

PROGRAM

Tuesday, March 13th 2012

13:30-14:30 **Poster Session I**

Company Presentations

14:30-14:55 **Ute Seidel, Cepos InSilico GmbH, Erlangen**
Cepos InSilico SAR System - CeSAR

14:55-15:20 **Johann Carlsson, Accelrys Ltd., Cambridge**
Modeling of defective graphene to investigate the effects of grain boundaries and oxidation

15:20-15:45 **Guido Kirsten, Chemical Computing Group, Köln**
MOE: New Features that Enhance the Drug Design Process

15:45-16:10 **Alexander Kos, AKos GmbH, Steinen**
Workflow Applications

16:10-16:30 **Coffee Break**

16:30-16:55 **Jarmila Husby (London)**
MD studies of the STAT3:DNA complex: STAT3 mutations and protein-DNA recognition

16:55-17:20 **Karolina Mikulska (Turoń)**
Steered MD (and AFM) study of neuronal protein neurexin

17:20-17:45 **Anna Gogolinska (Turoń)**
Interactions of antibodies with selected antigens – computational modeling

18:30 **Bierkeller**

PROGRAM

Wednesday, March 14th 2012

08:30-08:55 **Andrea Frank (Konstanz)**
Towards Quantum Chemical NMR Chemical Shifts of Proteins 2: Level of Theory, Basis Set, and Solvents Model Dependence

08:55-09:20 **Oliver Krahe (Mülheim a. d. Ruhr)**
Interplay of theory and spectroscopy: Study of an FeV-nitride complex and its photolytic formation

09:20-09:45 **Albert Poater (Girona)**
(De)Activation of olefin metathesis catalysts

09:45-10:15 **Coffee Break**

10:15-11:15 **Poster Session II**

11:15-11:40 **Pavlo O. Dral (Erlangen)**
Application of Semiempirical UNO–CI and CI Methods in Nanoelectronics

11:40-12:05 **Thomas Steinbrecher (Karlsruhe)**
Non-adiabatic QM/MM Simulations of Fast Charge Transfer in E. Coli DNA Photolyase

12:05-12:30 **Jochen Heil (Dortmund)**
The EC-RISM quantum solvation model for predicting tautomer ratios

12:30-14:00 **Lunch**

14:15-15:15 **Plenary Lecture III: Tim Clark (Erlangen)**
If you don't try, you'll never know

15:15 **Poster & Lecture awards, Closing**

POSTER SESSION I

Tuesday, March 13th 2012 13:30-14:30

P01 **Nursel Acar (Bornova)**
Cu Ion Binding of MXCCX Peptide: A DFT Study

P02 **Akin Azizoğlu (Balikesir)**
Computational Study on the Isomerization of Silacyclopropylidenoid Structures to Silaallenes

P03 **Frank Beierlein (Erlangen)**
Predicting the Effects of Base-Pair Mutations in DNA-Protein Complexes by Thermodynamic Integration

P04 **Sebastian Breuer (Köln)**
Predicting Molecular Self Organisation in Sugar Based Liquid Crystals Using Grid Computing Facilities

P05 **Zlatko Brkljača (Erlangen)**
Calculation of the CD spectrum of a peptide from its conformational phase space

P06 **Johan M. Carlsson (Cambridge)**
Theory and hierachical calculations of the structure and energetics of [0001] tilt grain boundaries in graphene

P07 **Emanuele Ciglia (Düsseldorf)**
Inhibiting protein-protein interactions in HSP90 dimerization as a novel approach for targeting cancer

P08 **Patrick Duchstein (Erlangen)**
Disaccharides mediate the interplay between collagen and carbonate ions in biomineralization processes

P09 **Evgenia V. Dueva (Moscow)**
Molecular design of fusion inhibitors for flaviviruses

P10 **Christina Ebensperger (Erlangen)**
Modification of NiO(111) surfaces by hydroxylation and carbonate formation

P11 **Philipp Ectors (Erlangen)**
Nucleation of molecular crystals

P12 **Ahmed El Kerdawy (Erlangen)**
Predicting the Sites and Energies of Non-Covalent Intermolecular Interactions Using Local Properties

POSTER SESSION I

Tuesday, March 13th 2012 13:30-14:30

P13 **Julian E. Fuchs (Innsbruck)**
Local Dynamics in Protease Recognition

P14 **Jakub Goclon (Erlangen)**
Interaction of Hydrogen with the ZnO(10-10) Surface

P15 **Susanne von Grafenstein (Innsbruck)**
Impact of Tetramerization on Neuraminidase Dynamics and Binding Site Conformations

P16 **Elke Haensele (Portsmouth)**
The necessity of long-term molecular dynamics simulations: Deamino-oxytocin - novel conformational insights

P17 **Jochen Heil (Dortmund)**
Computationally efficient and accurate 3D-RISM calculations

P18 **Stefan Henrich (Heidelberg)**
Comparative computational analysis of enzyme allosteric sites and the bindig of allosteric effectors

P19 **Roland G. Huber (Innsbruck)**
Molecular Dynamics Investigation of Cooperative Binding Within the KIX Domain

P20 **Christof Jäger (Erlangen)**
Very large scale Semi-empirical MO-Calculations on SAM-OFETs

P21 **Christophe Jardin (Erlangen)**
Protein-Protein Docking:
The Scoring Problem Addressed by Concepts of Information Theory

P22 **Anna Kahler (Erlangen)**
How Quartenary Strucure Influences the Conformation of Fibrillar Aβ-Oligomers

P23 **Kristin Kassler (Erlangen)**
One Interface - Two Perspectives
Exploration of the HIV-1 gp120 - CD4 Interaction

Please remember to remove your posters on tuesday evening

POSTER SESSION II

Wednesday, March 14th 2012 10:15-11:15

P01 **Nursel Acar (Bornova)**
Investigation of Complex Formation between Pyrene and Selected Drug Molecules by Spectroscopic and Semiempirical Methods

P02 **Katharina Kopp (München)**
Molecular Docking of Peptides and Small Molecules into TRAF Proteins

P03 **Sara Kramar (London)**
Conformational flexibility of small molecules in different solvent environments

P04 **Andreas Krause (Erlangen)**
Simulating Selfassembly

P05 **Natallia Kulik (Nove Hrady)**
Structural analysis of different substrate affinity in fungal hexosaminidases

P06 **Rashmi Kumari (New Delhi)**
High througput re-scoring of docking hit-list using MD Simulation and MM/PBSA method through open source packages

P07 **Theodor Milek (Erlangen)**
Molecular Modeling of ZnO Nanoparticle Nucleation:
from pre-nucleation clusters to functionalized particles

P08 **Zoran Miličevic (Erlangen)**
Hydration of small hydrophobic objects: The effects of an electric field

P09 **Florian Mrugalla (Dortmund)**
Computational analysis of ion distribution in K^+ channels

P10 **Rasoul Nasiri (Tehran)**
Computational Studies on Cross-Linking Process: Evidence for Multiple-Novel Reaction Pathways in Pentosidine, MODIC and GODIC Formation

P11 **Ionut Onila (Konstanz)**
Guiding Protein-Ligand Docking with Different Experimental NMR-Data

P12 **Sebastian Schenker (Erlangen)**
Assessing QM methods for calculating small energy barriers in enantioselective organocatalysis

P13 **Dmitriy Sharapa (Erlangen)**
Charge transfer in Fe-intercalated SWCNT

POSTER SESSION II

Wednesday, March 14th 2012 10:15-11:15

P14 **Tatyana Shubina (Erlangen)**
Binding of small molecules to Metalloporphyrins

P15 **Dhiraj Sinha (Nove Hrady)**
In silico characterization of the motorsubunit of *e.coli.* restriction-modification system EcoR1241

P16 **Eileen Socher (Erlangen)**
Tetramer of Chimeric Aβ-IgNARs as a Model for Amyloid-β Oligomer Fromation in Alzheimer´s Disease

P17 **Kai Stueckenschneider (Dortmund)**
Adsorption of Alanine and Phenylalanine on MFI-type Zeolite: DFT Calculations and Experimental Results

P18 **Joachim D. Stump (Erlangen)**
Investigating the Effect of Q27 Mutation on Receptor-binding Properties of Glycoprotein D in Herpes Simplex Virus-1

P19 **Veronika Temml (Prague)**
Pharmacophore Modeling of Cyclooxygenase-2 in LigandScout and Discovery Studio - A comparison

P20 **Matthias Trautwein (Konstanz)**
Fragment-based Optimization of Large System Using Quantum Mechanics

P21 **Anna Vourinen (Innsbruck)**
Refinement of pharmacophore models for inhibitoin of 11β-hydroxysteroid dehydrogenases, regulators of intracellular glucocorticoid concentrations

P22 **Christian R. Wick (Erlangen)**
Prolyl-hydroxylase domain containing protein 2:
Structural insight from MD Simulations

P23 **Avik Sanyal (Heidelberg)**
Development of a Fluctuating Charge Model for Transition Metal Complexes

Poster abstracts can be found on the internet:
www.chemie.uni-erlangen.de/ccc/conference/mmws12

Structure and function.
Fundamental principles and case studies with transition metal compounds

Peter Comba, Anorganisch-Chemisches Institut, Universität Heidelberg, Germany

The computation of electronic structures of transition metal complexes has been developed in recent years to an extent where a large variety of spectroscopic properties and reactivities of mono- and oligonuclear transition metal compounds can be efficiently and reliably computed and interpreted with ab-initio quantum-chemical and DFT-based methods. These are often based on known structural data, and the interpretation of the electronic structures usually involves the comparison of computed with experimentally observed spectra, stabilities and/or reactivities. The prediction of molecular properties, which eventually may lead to a rational design of novel complexes with given properties, requires as an important additional step a reliable structure prediction. The identification of factors which influence molecular structures of transition metal complexes and the ensuing approaches for a reliable structure optimization are an important basis for electronic structure calculations. In many cases these can and must be based on efficient and accurate molecular-mechanics-based methods, and electronic structure calculations are in some important examples best done with ligand-field-based approaches. Apart from the fundamental principles and possible pitfalls, various case studies from our lab will be discussed, and these may include (i) the Cu^{II} chemistry of natural cyclic peptides and their possible biological function; (ii) the oxidation catalysis of high-valent nonheme iron model systems; (iii) the design, synthesis and characterization of single molecule magnets; (iv) the design, synthesis and characterization of enzyme model systems such as catecholase, catechol oxygenase, carboanhydrase, and purple acid phosphatase.

Understanding the thermostabilization of citrate synthase using Constraint Network Analysis

Prakash C. Rathi, Sebastian Radestock, and Holger Gohlke

Department of Mathematics and Natural Sciences,
Heinrich Heine University, Düsseldorf, Germany

Citrate synthase (CS) is a homodimeric enzyme which catalyzes the first step of the TCA cycle – the conversion of oxaloacetate to citrate employing acetyl-CoA. Being a central enzyme in carbohydrate metabolism, CS is found in nearly all life forms. CS is one of the rare proteins for which crystal structures are available in the PDB from organisms living at temperatures from as extreme as 0°C to 100°C. To understand structural implications that lead to such a range of thermostability of CS, we apply Constraint Network Analysis (CNA) on five citrate synthase (CS) structures over a temperature range from 37°C to 100°C. CNA is a front-and-backend for the FIRST software [1] for characterizing mechanical rigidity (and flexibility) of proteins modeled as networks of atoms (sites) connected by covalent and non-covalent interactions (edges). [2-4] In the present study, for the first time, we introduce an ensemble-based variant of CNA in order to circumvent the sensitivity of the method on the input structure. Furthermore, we model the temperature dependence of hydrophobic interactions in the constraint network as hydrophobic interactions strengthen at higher temperatures.

From a macroscopic point of view, a very good correlation between the predicted thermostabilities of CS and optimal growth temperatures of their source organisms ($R^2 = 0.88$, $p = 0.017$) is obtained, which validates that CNA is able to quantitatively discriminate between less and more thermostable proteins even within a series of orthologs. From a microscopic point of view, the top 5% structural weak spots predicted by CNA on a less thermostable CS show a higher mutation ratio in the corresponding more thermostable CS than other sequence positions. Furthermore, highly ranked weak spots that are otherwise highly conserved in a multiple sequence alignment of CSs are nevertheless found to be mutated in the next more stable CS in the series of structures analyzed. Finally, while deducing the mechanisms at an atomic level that lead to reinforcement of weak spots, we observe that the thermophilic CSs incorporate a better hydrogen bonding in order to achieve a higher thermostability whereas hyperthermophilic CSs employ more hydrophobic contacts for the same. All in all, these findings suggest that CNA can be applied as a pre-filter in data-driven protein engineering for suggesting residues that, when mutated will more likely improve thermostability. [5]

[1] D. J. Jacobs, et al., *Proteins*, **2001**, *44*, 150-165
[2] P. C. Rathi, et al., Statics of biomacromolecules. In: Comba, P. (Ed.), *Molecular Modeling*, Wiley-VCH, Weinheim, **2011**, 281-299.
[3] S. Radestock, H. Gohlke, *Eng. Life Sci.*, **2008**, *8*, 507-522.
[4] S. Radestock, H. Gohlke, *Proteins*, **2011**, 79, 1089-1108.
[5] P. C. Rathi, et al., *J. Biotechnol.*, **2012**, doi:10.1016/j.jbiotec.2012.01.027

Sodium Dependent Glucose Transporter (SGLT) 1 / 2 - Elucidating Inhibitor SAR and Selectivity using Homology Modelling and 3D QSAR Studies

Susann Vorberg[1,2*], Christian Buning[1]

[1] *Sanofi-Aventis Deutschland GmbH, Industriepark Höchst, Building G838, 65926 Frankfurt a.M., Germany*
[2] *University Frankfurt, Institute for Computer Science, Department for Molecular Bioinformatics, 60325 Frankfurt a.M., Germany*
*Susann.Vorberg@gmx.de

Inhibiting sodium-dependent glucose transporters (SGLTs) has been proposed as a new therapy for the treatment of diabetes [1]. SGLT2 as the most prominent member of this family is mainly expressed in the kidney and responsible for the reabsorption of the vast majority of the filtered glucose. This key role in the blood glucose homeostasis makes SGLT2 a promising target which has been clearly underlined by the results of preclinical and clinical studies. Therapeutic goals of SGLT2 inhibition are reduced plasma glucose levels and weight loss. In conjunction with the therapeutic benefits fewer side effects are expected than observed with other known diabetes drugs. Potential side effects in case of SGLT2 inhibition are expected to be mediated by a lack of selectivity towards SGLT1 that is mainly expressed in the intestine and responsible for glucose- and galactose absorption from food sources. Therefore, inhibition of SGLT1 leads to glucose- and galactose malabsorption, dehydration, and diarrhoea.
Consequently, any drug discovery project aiming for promising SGLT2 inhibitors has to take into account significant selectivity towards SGLT1. In order to describe the selectivity on a structural basis we extensively used molecular modelling techniques since no x-ray structural data is available for neither SGLT1 nor SGLT2. For both transporters homology models were generated using the published x-ray structure from vSGLT (PDB-code 3DH4) [2]. Structure based alignments of published SGLT2 inhibitors including selectivity data for SGLT1 were followed by 3D-QSAR studies utilizing CoMFA fields. Given a detailed analysis of the inhibitor SAR for both transporters the two structural models of SGLT1 and SGLT2 were compared leading to the identification of relevant differences and selectivity hot spots. In the future, the presented models could serve as a basis for the identification of new potent SGLT2 inhibitors that are selective towards SGLT1, too.

[1] E. Chao, R.R. Henry, *Nat.Rev.Drug.Disc.*, **2010**, 9, 551 - 559
[2] S. Faham et al., *Science*, **2008**, 321, 810 - 814

Assessment of Protein-Ligand binding affinity with Molecular docking approach and Application.

[1]Ashwani Sharma, [2]Dirk Zahn

[1,2]Computer-Chemie-Center, University of Erlangen-Nuremberg, Erlangen, 91052, Germany.

Abstract

Molecular docking determines the affinity of the ligand molecule towards a target whose 3D structure is known. The most important goals of molecular docking are: **1.** Characterization of the binding sites **2.** Positioning of the ligand into the binding site and **3.** Evaluating the strength of interaction for a specific ligand receptor complex [1]. During the docking process, the ligand generates multiple binding geometries (binding modes) in relation to the receptor. Only the stable conformation of the ligand binds with the receptor [2]. However, the main drawback in the docking process is to account for the flexibility of both, protein and receptor molecule. Therefore, in our work, we study performance of the docking process for deriving protein-ligand affinity.

Firstly, we used molecular docking approach to find alternative inhibitor for Thymidine kinase enzyme of HSV-1. A total of 62 antiviral plant metabolites and 13 drug molecules were docked against both the chains of Thymidine kinase enzyme using Patchdock tool. The plant metabolite Geraniin has produced higher score (5680 (chain A), 6562 (chain B)) than the commercially known anti-herpes compound Acyclovir (3504 (chain A), 3264 (chain B)). In addition, Gemdockv2.0 also produced the lower best fitness values for Geraniin (-130.123226 (chain A), -132.309075 (chain B)) as compared to Acyclovir (-102.182402 (chain A), -84.599474 (chain B)). Furthermore, docking through Autodock4 also produced lowest docking energy of -13.40 kcal/mol (chain A), -15.17kcal/mol (chain B) for Geraniin compound in comparison to Acyclovir -7.48kcal/mol (chain A), -7.96kcal/mol (chain B).

Further, the docking study is extended to analyze binding affinity of 7-azaindole-scaffolds inhibitors against Renin enzyme. One of the 7-azaindole-scaffold with 6-methoxy and methyl substituent is proven to be a potent inhibitor of Renin enzyme with IC50 of 3nM [3]. This affinity is also predicted by computational docking approach with docking energy of -15.85 kcal/mol. However, the other substituents are failed to reproduce binding affinity by computational means. Therefore, we implemented a novel molecular dynamics approach to derive binding affinity for 7-azaindole-scaffolds inhibitors against Renin enzyme. This approach accounts for fully flexible docking favorable protein-ligand arrangements.

Reference:

[1] W.P. Walters, M. Namchuk, *Nature Reviews Drug Discovery*, **2003**, *2(4),* 259-266.

[2] L.J. Gershell, J.H. Atkins, *Nature Reviews Drug Discovery*, **2003,** *2(4),* 321-327.

[3] H. Matter *et al*., *Bioorganic & Medicinal chemistry letters*, **2011**, *21*, 5487-5492.

Micelle/water partition coefficients using COSMO-RS: Conformational Study

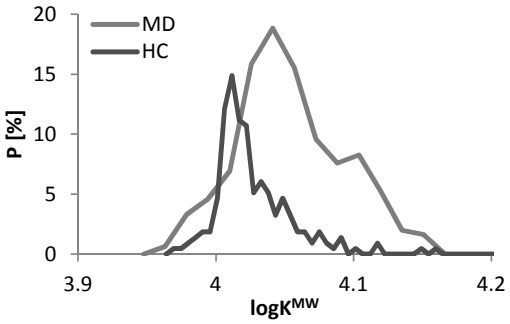
E. Sponsel, L. Mokrushina, W. Arlt, Chair of Separation Science and Technology,

Friedrich-Alexander-University of Erlangen-Nuremberg, Erlangen, Germany

In the field of chemical engineering and life sciences, the prediction of phase equilibria in complex multicomponent systems is of growing interest. One of the most popular and effective methods here is the COSMO-RS model, which allows for the predictions based only on the chemical structure of the system components. As shown by our group, the results depend strongly on the choice of conformations. For small molecules, sets of minimum energy conformations from the common conformational analysis made in vacuum give adequate results. Large flexible molecules however may have a huge number of conformations and the prediction results vary significantly for different conformations. Therefore, the reliable conformations of large flexible molecules, which afford reproducible results and lead to stable *a-priori* predictions on phase equilibria, should be identified.

In this work, the partitioning of small solutes (alkanes, alcohols, etc.) in the micellar solution of the non-ionic surfactant Triton X-100 (TX100) in water is studied as an example. Micelles hereby are treated as a macroscopic phase being in equilibrium with the aqueous surrounding (pseudo-phase approach), so that the partitioning of a solute between these coexisting pseudo-phases is determined by the thermodynamic equilibrium and thus the micelle/water partition coefficient (K^{MW}) can be calculated based on the solute limiting activity coefficients in the two pseudo-phases. For any small solute molecule with the limited number of conformations, the same set of the minimum energy conformations was used in all calculations. However, both pseudo-phases also contain large flexible amphiphilic molecules, for which adequate conformations have to be found. The conformations of TX100 were generated using two methods: the force-field-based energy-minimization method (hyperchem HC) and the condensed phase molecular dynamics (MD, Gromacs). The HC conformational search was carried out in vacuum, while the MD simulations were made in water and in octanol (the model solvent for micellar pseudo-phase) to account for the solvent effects. The conformations obtained by both methods were then used to calculate K^{MW} of the solutes using COSMO-RS and their influence on the latter was studied.

The figure shows the probability distribution of the logarithmic K^{MW} of octanol calculated by COSMO-RS for different single conformations. The maxima observed in the distributions indicate that some of the conformations occur more often than the others and thus will lead to the more reproducible values of K^{MW}, i.e., are reliable for K^{MW}. However, using this method to identify reliable conformations, great calculation efforts have to be made. Thus, it would be advantageous to be able to select such conformations directly from the conformational space obtained from MD or HC, even before performing the time-consuming DFT/COSMO geometry optimization calculations. Such a selection should be based on physical parameters. In this study, we consider two of them, the radius of gyration and conformation specific energy as well as their combination. It has been shown that if the selection is made from the 20% most probable conformations of any of criteria, the outliers in the probability distributions of K^{MW} are avoided. If both criteria are considered simultaneously, a single surfactant conformation can be identified that leads to the most probable result for K^{MW}. Thus, the probability-based methodology leads to reliable and stable *a-priori* predictions of solute partitioning in micellar systems as well as of phase equilibria in general.



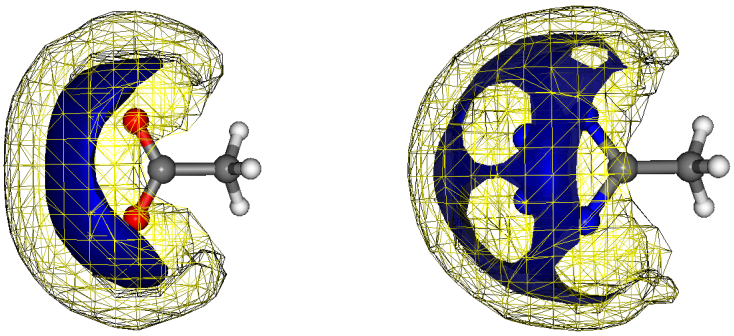
We thank DFG (MO 2199/1-1) for the financial support.

Predicting the Sites and Energies of Non-Covalent Intermolecular Interactions Using Local Properties

Ahmed El Kerdawy, [a] *Christian R. Wick*,[a] *Matthias Hennemann* [a,b] *and Timothy Clark* [a,b,c]

[a] Computer-Chemie-Centrum, Friedrich-Alexander-Universität Erlangen-Nürnberg, Nägelsbachstraβe 25, 91052 Erlangen, Germany.
[b] Interdisciplinary Center for Molecular Materials, Friedrich-Alexander-Universität Erlangen-Nürnberg, Nägelsbachstraβe 49, 91052 Erlangen, Germany.
[c] Centre for Molecular Design, University of Portsmouth, King Henry Building, Portsmouth PO1 2DY, United Kingdom.

Despite the essential importance of the non-covalent interactions and their key role in many natural processes, they are not treated well by currently available *in silico* techniques. Non-covalent interactions are important on the micro and macro scales and include protein-ligand, protein-protein and protein-DNA binding. [1] Being able to predict such interactions, especially unusual (non-classical) ones, would be of immense value for the molecular modeling field and especially for drug design. We have therefore set out to define a systematic protocol for detecting interaction sites of different types in the vicinity of ligands or receptors and to estimate the strength of the interactions in order to provide a more consistent and complete picture of the intermolecular binding properties of small molecules and biopolymers. Since the points of interaction of molecules lie at or near the molecular surface, surface-based molecular descriptors were used to construct feed-forward artificial neural nets to recognize H-bond donors and acceptor sites on drug-like molecules based on local properties (electron density, molecular electrostatic potential and local ionization energy, electron affinity and polarizability) calculated at grid points around the molecule. Interaction energies for training were obtained from B97-D and ωB97X-D/aug-cc-pVDZ density-functional theory calculations on a series of model central molecules and H-bond acceptor and donor probes constrained to the grid points used for training. The resulting models provide maps of both classical and unusual H- and halogen-bonding sites. Some examples demonstrate the ability of the models to take the electronic and steric nature of the central molecule into consideration and to provide semi-quantitative estimates of interaction energies at low computational cost.



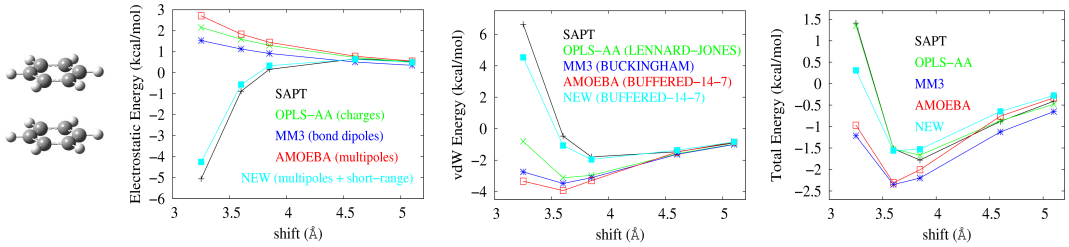
[1] P. Hobza, R. Zahradnik, K. Muller-Dethlefs, *Collect. Czech. Chem. Commun.* **2006,** 71, (4), 443-531.

Intermolecular Force Field Parameterization from First Principles

Maxim Tafipolsky and Bernd Engels

Institut für Physikalische und Theoretische Chemie, Universität Würzburg, Campus Hubland Nord, Emil-Fischer-Str. 42, D-97074 Würzburg, Germany

Accurate intermolecular forces are needed for simulations of aggregates of large organic chromophores, such as perylene bisimide [1], where a highly anisotropic charge distribution due to the extensive π-conjugation calls for a reliable force field since high quality fully ab initio calculations are computationally very demanding [2]. Recent developments in the symmetry adapted perturbation theory (SAPT) [3] allow partitioning of the total intermolecular energy into different physically well-defined contributions (electrostatic, exchange-repulsion, dispersion and induction) against which the corresponding terms in the force field can be separately parametrized. An approach is described to include the missing charge penetration energy term directly into a force field using a sum over pairwise electrostatic energies between spherical atoms as originally suggested by Spackman [4]. This important contribution to the intermolecular potential can be further refined to reproduce the accurate electrostatic energy between monomers in a dimer by allowing for the radial contraction-expansion of atomic charge densities. This new short-range term is supplemented by a long-range electrostatic contribution described with atomic multipoles (up to quadrupoles) based on distributed multipole analysis [5, 6]. The other components of a force field (exchange-repulsion and dispersion) are parametrized to reproduce the accurate data calculated by SAPT(DFT) [7]. As a proof-of-concept, we have derived the force field parameters suitable for modeling intermolecular interactions between polycyclic aromatic hydrocarbons (PAH) [8]. It is shown that it is possible to have a balanced force field suitable for molecular simulations of large molecules avoiding error cancellation to a large extent.



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Calculating Hydration Entropy for Ionic Systems from Molecular Dynamics Trajectories

Roland G. Huber[1], Julian E. Fuchs[1], Susanne von Grafenstein[1], Hannes G. Wallnoefer[1], Monika Laner[1], Romano T. Kroemer[2], Klaus R. Liedl[1]

[1] Leopold Franzens University Innsbruck
Faculty of Chemistry and Pharmacy, CCB
Innrain 80/82, A-6020 Innsbruck, Austria

[2] Sanofi-Aventis, CRVA
13 Quai Jules Guedes, F-94000 Vitry sur Seine, France

Entropy calculation is a crucial topic in computational chemistry.[1] The Gibbs free energy governing the reactivity in chemical processes comprises of enthalpy and entropy. An accurate estimation method for entropy facilitates the computational investigation of chemical processes significantly. Hydration entropy is of special interest in drug design applications.[2] The association of a hydrated biomolecule and a hydrated small molecule leads to displacement of surface-bound waters into the bulk.[3] Therefore, calculating the affinity contributions from this displacement process is predicated on understanding the individual hydration entropy contributions in the non-associated state.

In our study we investigate monovalent cations as test systems to illustrate a novel approach to calculate hydration entropy from molecular dynamics simulation trajectories. Ions were chosen as a test set, as their spherical symmetry enables us to choose a convenient order parameter for the surrounding solvent molecules. We calculated the distribution of relative angular orientations of the dipole moment and the gradient of the electrostatic potential of the central ion within concentric shells around the ion. This allows us to represent the ordering influence of the ion within a scalar parameter. For validation we included Mg^{2+} into the test set due to the availability of consistent parameters. Results for the bivalent Mg^{2+} demonstrate that the approach extends to systems of a significantly different surface charge density. Other bivalent cations where omitted, as no parameters where available within the set of Aqvist et al.[4] included in the AMBER simulation package.

With the presented methodology we provide an approach to entropy calculation which does not require an assumption of harmonic potential energy surfaces. Furthermore, the density estimation procedure allows to generate a nonparametric estimate of state space probability density functions with limited sampling times. It should be noted, that the proposed procedure in it's presented form is only applicable to systems, wherein the ordering can be expressed within a one-dimensional parameter, which is the case for the spherically symmetric potential of the ions within this study. This limitation originates from the density estimation procedure used in this study. Using multidimensional density estimation, one can extend the approach to more complex systems.

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Structural Basis of Drug Resistance in Hepatitis C Viral NS3/4A Serine Protease

Sabine Schweizer[1], Christoph Welsch[2], and Iris Antes[1]

[1]Protein Modelling, Center for Integrated Protein Science Munich at the Department of Life Science, Technical University Munich, Emil-Erlenmeyer-Forum 8, D-85354 Freising

[2]Department of Internal Medicine, J. W. Goethe University, Theodor-Stern-Kai 7, D-60590 Frankfurt/Main

Hepatitis C virus (HCV) infections affect 3% of the world's population and are a serious global health problem [1]. The virus is spread as a mixture of genetic variants so-called quasispecies. This genetic heterogeneity is a major problem in HCV vaccine and drug development as it allows the virus to easily escape under selective pressure and to become resistant against direct-acting antiviral agents (DAA) [2-5]. The HCV NS3/4A serine protease is considered a most promising drug target in DAA development [6,7].

We present molecular dynamics studies of the wild type NS3/4A serine protease and two types of protease inhibitor-resistance related viral variants. The analysis of the structural influence of low- to medium-level resistance mutations V55A/I and R155K/Q/T on the protease ligand-binding properties suggests two structure-based escape mechanisms: First, conformational changes in the hydrophobic core region of the enzyme lead to constriction of the binding cavity sterically hampering inhibitor binding. This effect is especially important for ketoamide inhibitors, a class of drugs, from which Victrelis™ (boceprevir) and Incivek™ (telaprevir) have been approved by the U.S. Food and Drug Administration (FDA) only recently. Second, mutations that affect the salt bridge network within the binding pocket can entail a weakening of electrostatic interactions with the inhibitor and lead to conformational changes that influence the shape of the binding site and thus the binding behavior. Overall, our studies provide an explanation of the experimental resistance data on a molecular basis and reveal a deeper insight into general molecular mechanisms conferring resistance, which will help to improve the efficacy of next-generation DAAs.

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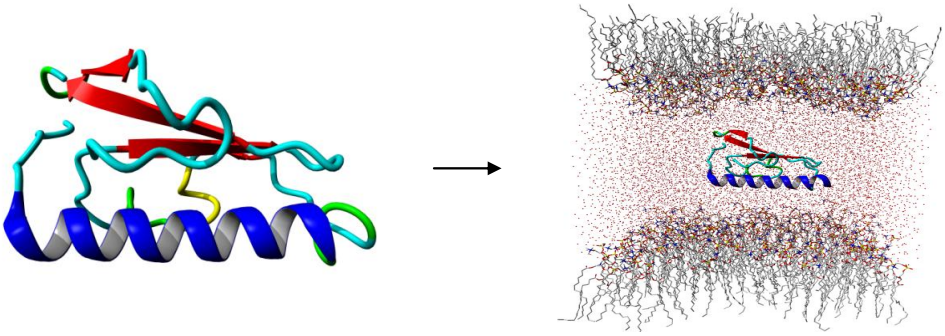
Protein Modeling and Molecular Dynamic Studies of two new Surfactant Proteins

Felix Rausch[1], Wolfgang Brandt[1], Martin Schicht[2], Lars Bräuer[2], Friedrich Paulsen[2]

[1] *Department of Bioorganic Chemistry, Leibniz Institute of Plant Biochemistry, Weinberg 3, 06120 Halle, Germany*

[2] *Department of Anatomy II, University of Erlangen-Nuremberg, Universitätsstr. 19, 91054 Erlangen, Germany*

Surfactant proteins are of major importance for the stability and flexibility of lipid layers on air-liquid surfaces like the lung surface or the tear film. They can aid the adsorption of new phospholipids into an existing layer or specifically alter the surface tension of a lipid surface [1]. Furthermore, immunological functions were described for some of the already known surfactant proteins SP-A, SP-B, SP-C and SP-D [2]. For that reason, they are of great interest in the investigation of diseases like the "acute respiratory distress syndrome" (ARDS) or the "dry eye syndrome" (DES). Recently sequences of two new surfactant proteins, called SP-G and SP-H, were identified.



To get insights into the function of SP-G and SP-H, protein structure models were generated for both proteins. These models successfully guided the design of antibodies for the detection and localization of SP-G and SP-H in different human tissues. To verify the stability of the obtained models for further *in silico* experiments, MD simulations in a water box were performed. These were carried out with the GROMACS program package for 50 ns. Since both models showed to be stable they were transferred to a simple lung surface model system, consisting of two dipalmitoylphosphatidylcholine monolayers separated by a water phase. Again, 50 ns MD calculations were performed with GROMACS starting from different orientations of the protein models. During these simulations, it was possible to track the accumulation of the proteins to the lipid layer. Furthermore, the interactions between protein surfaces and lipid head groups could be observed on an atomic scale. The obtained results can give hints for further experimental studies and help to determine the functions of SP-G and SP-H *in vivo*. In addition, future simulations may support the development of new therapies for ARDS and DES.

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Disaccharides mediate the interplay between collagen and carbonate ions in biomineralization processes

Patrick Duchstein[1], Rüdiger Kniep[2], Dirk Zahn[1]

[1]*Computer Chemie Centrum, Friedrich Alexander Universität Erlangen-Nürnberg*

[2]*Max-Planck-Institut für Chemische Physik fester Stoffe, Dresden*

Biominerals, such as bone, teeth, otoconia, and mollusc shells are composite materials, composed of an inorganic mineral, closely interacting with organic tissue, in many cases collagen. Otoconia in particular consist of calcite and collagenous proteins, enamel comprises a calcium hydrogen phosphate matrix with embedded collagen fibers[1]

We investigated crystal nucleation of calcium carbonate and of carbonated calcium hydrogen phosphate along various types of collagen. Our method of choice consisted in the Kawska-Zahn approach [2,3] which allows for the simulation of crystal growth ion by ion along a triple helical collagenous strand. By analyzing various collagen types with different degrees of glycosylated lysine residues we found out that a very high degree of glycosylated amino acids is necessary to ensure calcification along a collagenous triple helix, and thus embedding of the collagen fiber.

Simulations with biological, i.e. carbonated, calcium hydrogen phosphate yielded similar results. We therefore conclude that glycosated lysine residues are crucial to allow carbonate ion association to collagen fibers without compromising the protein structure.

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Predicting binding kinetics and free energy profiles of drug receptor complexes from all-atom simulations

Francesco Luigi Gervasio

Computational Biophysics Group, Spanish National Cancer Research Centre, Madrid

The manipulation of binding kinetics is emerging as a critical parameter to optimize the efficacy and minimize the toxicity of lead compounds in vivo. A computational method able to link the structure of the ligand to the observed binding kinetics would be very valuable. Unfortunately, computing accurate free energy profiles along physical association pathways, let alone the binding kinetics is extremely complex. Long sampling times, significant conformational changes of the target protein and shortcomings with current ligand force-fields concur in frustrating the long ongoing efforts.

Here I report on our efforts in combining approaches based on metadynamics [1,2] together with multiple-replicas [3] and path-sampling [4] can be used to converge the free energy profile along a physical association pathway, to quantify the effect of large-scale conformational changes [5] and to compute binding kinetics with (force-field permitting) reasonable accuracy.

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Company Presentations

Cepos InSilico SAR System - CeSAR

Ute Seidel

Cepos InSilico GmbH, Computer-Chemie-Centrum, Nägelsbachstr. 25, 91052 Erlangen; http://www.ceposinsilico.com

Cepos InSilico SAR is a web-based system designed to find linear and non-linear relationships between data. It can predict the physical, chemical and biological behaviors of compounds based on measured or calculated information in order to develop predictive models. The software is especially designed as an easy-to-use tool for both beginners and experts. In addition, the Cepos InSilico SAR system includes an integrated database for data storage. In order to guarantee the optimum accuracy of the predictive models, partial least squares (PLS), [1,2] Bagged Stepwise Multiple Linear Regression using the descriptor-pool-size corrected F-value, [3] Random Forests and Artificial Neural Networks (ANNs) [4] are all available.

An important feature of the SAR-system is its ability to predict likely model errors and to describe the applicability domain exactly.

The system is designed primarily to use the surface-based descriptors and surface-integral models available in ParaSurf™. [5] These proved powerful and robust models, as will be shown using several examples.

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Modeling of defective graphene to investigate the effects of grain boundaries and oxidation

Johan M. Carlsson[1], Luca Ghiringhelli[2], and Annalisa Fasolino[3]

[1]*Accelrys Ltd, 334 Science Park, CB4 OWN Cambridge, UK*

[2]*Fritz-Haber-Institut der Max-Planck-Gesellschaft, Faradayweg 4-6, D-14195 Berlin, Germany*

[3]*Institute for Molecules and Materials, Radboud University Nijmegen, Heyendaalseweg 135, 6525 AJ Nijmegen, The Netherlands*

Graphene has extraordinary properties, but utilizing these properties in electronic applications requires the ability to grow large scale, defect-free graphene sheets. Several routes are currently pursued to synthesize graphene, but the samples are often found to be polycrystalline. The defects in the as-grown polycrystalline graphene samples can, on the one hand, be detrimental for the properties of graphene, but on the other hand, offer a method to control its mechanical and electronic properties. However, grain boundary engineering at the atomic level is still very challenging because no general theory is available, which is able to describe the various structures that have been observed in experiments. Scanning tunneling microscopy (STM) investigations of a variety of [0001] tilt grain boundaries in graphene have shown that small angle grain boundaries have the shape of periodic arrays of asymmetric hillocks with large separation [1], while a grain boundary with a misorientation angle $\theta = 21°$ could be characterized as a flat array of 5-7 ring complexes [2]. The shape and properties of the defects may be further tailored by controlled oxidation [3]. However, oxidation of graphene is a very complex process, where the individual steps are not yet completely understood. In order to improve the understanding of imperfect graphene, we have investigated the shape and effects of point defects and grain boundaries in graphene and how oxidation influence as-grown graphene.

Our density-functional (DFT) calculations[4] showed that point defects in graphene form a complex of non-hexagonal rings in the hexagonal graphene lattice [5]. Further analysis revealed that these defects form semi-localized defect states, indicating that defects in graphene would have an increased chemical activity. This was later confirmed by our investigation of oxidation of graphene, which revealed a two-step process for the low temperature oxidation of graphene[6]. Bare vacancies are very reactive towards O_2, such that the vacancies quickly get saturated by ether groups. These O-groups are stable with respect to CO-desorption at low temperatures, but they are more reactive towards additional O_2-molecules. The dissociation of the oxygen molecules at the ether groups forming more volatile O-groups, which as a second step leads to desorption of CO_2.

In addition, we have developed a general theory for the structure of [0001] tilt grain boundaries in graphene based on the coincidence site lattice (CSL)-theory [7]. The combination of force field, bond order potential and DFT calculations[4] showed that low energy grain boundaries in graphene can be identified as dislocation arrays. Grain boundaries with small misorientation angles tend to form hillocks in agreement with STM observations of grain boundaries in epitaxial grown graphene [1]. Our calculations have also shown that contrary to the usual bulk behaviour, there is an attractive interaction between dislocation cores in graphene. This interaction decreases the strain energy, so dislocation arrays flatten out with increasing misorientation angles. The attractive interaction decreases the formation energy for grain boundaries with large misorientation angles so that a minimum occurs for $\theta = 32.2°$.

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Guido Kirsten

MOE: New Features that Enhance the Drug Design Process

Chemical Computing Group, Cologne

MOE (Molecular Operating Environment) is the leading software system for drug design and protein modeling in the pharmaceutical industry.

Fragment Based Design has recently assumed great prominence as a strategy for lead optimization. Methods like Scaffold Replacement, Breed, MedChemTransformations and Combinatorial Builder produce huge libraries of potential leads. Unfortunately many of them will fail later in the process because of incompatibilities with the binding pocket. Chemical Computing Group has brought these methods in context with the binding pocket. Using the 3D information of the active site helps the researcher to focus on structures with high potential. A common interface gives the user flexible control over all tools.

For the analysis of non-bonded interactions Extended Hückel Model calculations have been implemented in MOE. Researchers can investigate interactions like hydrogen, halogen, proton-π or CH-X bonds in 2D and 3D diagrams. Desolvation binding free energy maps can be calculated in minutes using the 3D-Reference Interaction Site Model (RISM). Water, salt and hydrophobe solvation densities can be visualized for the complex or the apo structure.

For protein modeling, Kinase and GPCR family databases and analysis tools have been developed. The Kinase Explorer allows browsing aligned kinases based on core, pocket or canonical structural views. The GPCR tools identify and annotate transmembrane regions automatically. Alignment constraints can be added by a few mouse clicks to improve the sequence alignment of GPCR's. Kinase and GPCR databases can be augmented with in-house data by an automated protocol.

All these tools can now be used together with well-known MOE applications for QSAR-, homology-, Pharmacophore modeling.

Workflow Applications

Dr. Alexander Kos

AKos Consulting & Solutions Deutschland GmbH (AKos GmbH), Austr. 26, 79585 Steinen, Germany, www.akosgmbh.eu, email: akos@akosgmbh.eu

We chemists have a mind-boggling amount of software available to help us in our research tasks. For all this software we hardly can do our work in the lab anymore. Instead of learning many programs, we can let a few gurus select programs and develop workflows. Then we chemists can push one button to get the results. Even if it is more than one button that we have to push many tasks can be automated. In general most things that we do are part of workflows.

A project starts with a literature search. Today, we cannot exclude Internet anymore and for this we have developed CWM Global Search, the Internet search engine for chemists. This would be the perfect place to start collecting ligand-protein complexes to define our target.

Sometimes we have specific problems, like finding the perfect binding site (pose) for a ligand. Molegro's Virtual Docker could predict in a study 87% of 77 compound perfectly. The results of other docking programs are shown below.

Docking Product	Accuracy (RMDS < 2Å)
MVD	87.0%
Glide	81.8%
Surflex	75.8%
FlexX (76)	57.9%
GOLD (55)	78.2%

Very often we want to find lead compounds and want to decide which compounds have the highest chance of success. Why start with 1000, or 100'000 compound? Download the whole PubChem database and start whittling down the huge number to a manageable number of compounds for testing. A workflow program like KNIME can help you to filter by fragments (no NO_2 groups, no metals, etc.), a PASS node can reduce the millions to thousand using a knowledge base, at the same time you already can set flags for toxicity. Using a MVD node supporting graphical processing units (GPU) you can dock accurately ligands in less than a second. Knowing the target you can reduce the final list to hundreds, and with automatic substructure matches against a database like Toxicity and Metabolite you can weed out unfavorable leads. All of this, and much more can be combined into one workflow.

We will shortly present CWM Global Search, KNIME client, PASS, Molegro's Virtual Docker, and Data Modeller.

LECTURES

TUESDAY

Contributed Talks

Molecular dynamics studies of the STAT3 homodimer:DNA complex: relationships between STAT3 mutations and protein-DNA recognition

Jarmila Husby[1], Alan K. Todd[1], Shozeb M. Haider[1,2], Giovanna Zinzalla[1], David E.Thurston[1,3] and Stephen Neidle[1]

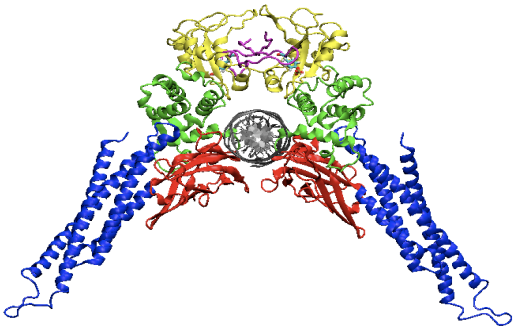
[1]CRUK Biomolecular Structure Group, UCL School of Pharmacy, London, UK

[2]School of Biomedical Sciences, Queen's University, Belfast, UK

[3]Institute of Pharmaceutical Sciences, King's College London, UK

Signal Transducers and Activators of Transcription (STAT) proteins are a group of latent cytoplasmic transcription factors involved in cytokine signalling. STAT3 is a member of the STAT family and is expressed at elevated levels in a large number of diverse human cancers; and is now a validated target for anticancer drug design. Understanding the dynamics of the STAT3 dimer interface, accounting for both protein-DNA and protein-protein interactions, with respect to the dynamics of the latent, unphosphorylated STAT3 monomer, is important for designing potential small-molecule inhibitors of the activated dimer.

Molecular dynamics (MD) simulations have been used to study the activated STAT3 homodimer:DNA complex, the unphosphorylated STAT3 homodimer:DNA complex, and the latent unphosphorylated STAT3 monomer in an explicit water environment. Analysis of the data obtained from MD simulations over a 50 ns time-frame has suggested how the transcription factor interacts with DNA, the nature of the conformational changes, and ways in which function may be affected. Examination of the dimer interface, focusing on the protein-DNA interactions, including involvement of water molecules, has revealed the key residues contributing to the recognition events involved in STAT3 protein-DNA interactions. This has shown that the majority of mutations in the DNA-binding domain are found at the protein-DNA interface. These mutations have been mapped in detail and related to specific protein-DNA contacts. Their structural stability is described, together with an analysis of the model as a starting-point for the discovery of novel small-molecule STAT3 inhibitors.



Steered MD (and AFM) study of neuronal protein neurexin

Karolina Mikulska, Janusz Strzelecki, Wieslaw Nowak

Theoretical Molecular Biophysics Group,
Institute of Physics, Nicolaus Copernicus University, Grudziadzka 5, Torun, Poland

Neurexins (NRXNs) are large family of synaptic cell-adhesion molecules that connect presynaptic and postsynaptic neurons at synapses. They may form complexes with presynaptic protein neuroligin, mediate signalling across the synapse and shape the properties of neural networks [1]. There is increasing evidence that NRXNs are associated with schizophrenia and autism spectrum disorders [2].

We apply, for the first time, steered molecular dynamics (SMD) simulations using NAMD program (version 2.8) and CHARMM force field, in order to better understand nanomechanics of NRXNs. Fourteen SMD explicit solvent simulations (total length about 0.5 μs) with three different direction of pulling of NRXN1α (1296 amino acids, over 64 000 atoms) have been preformed. In our SMD study we want to recognize the mechanical properties of NRXN1α and characteristic hinge occurrence presented in our Atomic Force Microscopy (AFM) experiment [3].

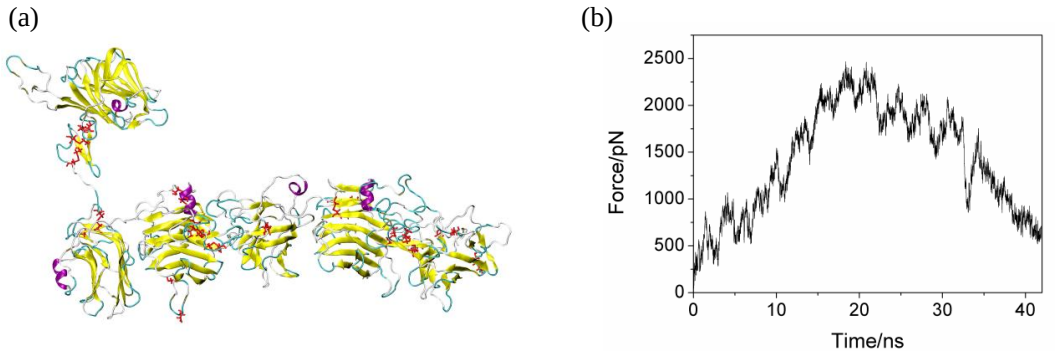


Fig. 1. (a) 3D structure of NRXN1α (1296 aa), (b) Force vs. time curve from SMD simulation.

We combine different types of research methods (theoretical SMD and experimental AFM) to discern the mechanical stability and the characteristic behaviour of NRXN in synaptic junctions.

Acknowledgements: The calculations were performed at TASK computer center and supported by Polish Funds for Science (grant No. N202 262038) and grant NCU 408-F. KM acknowledges grant ”Krok w przyszlosc” from Kujawsko-Pomorskie Voivodeship and Young Scientists Scholarship funded by Institute of Physics NCU.

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Interactions of antibodies with selected antigens – computational modeling

Anna Gogolinska[1,2], Wieslaw Nowak[1]

1) Faculty of Physics, Astronomy and Informatics, Nicolaus Copernicus University, Toruń, Poland

2) Faculty of Mathematics and Computer Science, Nicolaus Copernicus University, Toruń, Poland

The immune (IS) system is a part of defense against bacteria, viruses and other pathogens. Millions of cells are involved in that activity. Important part of the immune response is the humoral response. Basic elements of that response to antigens invading an organism are antibodies (immunoglobulins, Ig). Igs are Y-shaped proteins and have a common structure, they differ only in an antigen-binding site. The antibodies are extremely specific and interact very strongly with appropriate antigens. In our work we used computer modeling tools to study two antigens: a major grass pollen allergen Phl p 2 and a chemokine MCP-1, both in complexes with their specific human antibodies.

The Phl p 2 and the specific human immunoglobulin E (IgE) had been isolated from a pollen allergic patient [1]. Interactions of that antigen and the antibody induce the IS response and allergic symptoms. Studies of the complex of Phl p 2 and IgE may help in better understanding the allergy. MCP-1 belongs to chemokines - a family of cytokines, that are produced by immune cells. Their main function is chemoattraction. Chemokines recruit immune cells to the place of infection and cause the IS response in that region. MCP-1 is present in central nervous system and its elevated level can be related with autism (ref). Thus our studies of the complex of MCP-1 and antibody could help in diagnosis of autism.

In order to understand molecular recognition processes in atomic detail we performed classical MD [2] simulations of both complexes and then more than 20 of 2 ns SMD simulations [3] of enforced dissociations of the complexes. Different directions rupture forces were tested. We divided their directions into two groups: "vertical" (parallel to the main axis of the antibody) and "lateral". Our results show that in both complexes the separation the antigen from the antibody in the "vertical" direction requires about 30 % higher values of the force than in the "lateral" direction . We have identified amino acids crucial for interactions between the antigens and the antibodies. Appropriate hydrogen bonds and salt bridges, contribute to the strong specific interactions. The methodology established in this study may help to understand better Lateral Atomic Force experiments, especially related to complexes of fibronectin and its antibody [M. Lekka, A. Kulik, W. Nowak – unpublished results].

Acknowledgement: This study was supported by Polish Funds for Science Grant N N202 262038.

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Towards Quantum Chemical NMR Chemical Shifts of Proteins 2: Level of Theory, Basis Set, and Solvents Model Dependence

Andrea Frank, Heiko M. Möller, and Thomas E. Exner

Department of Chemistry and Zukunftskolleg, University of Konstanz,78457 Konstanz, Germany, Thomas.Exner@uni-konstanz.de

Calculations of accurate NMR chemical shifts of proteins, protein-protein and protein-ligand complexes are highly valuable in many applications like NMR structure evaluation and complex-structure predictions. We will present calculations using our fragment-based quantum chemical method: the adjustable density matrix assembler (ADMA) [1, 2]. In such calculations the target system is subdivided into small fragments, for which separate quantum chemical calculations are performed and which are then combined to get an approximation of the macromolecule.

A systematic investigation was performed in which the influence of the theory, the basis set size, the inclusion or exclusion of an implicit solvent model, and partial charges were used for the description of additional parts of the macromolecule [3]. The results of ^{13}C chemical shifts are in good agreement with the experiment. An even better agreement with the experiment is observed in the calculation of the 1H chemical shifts, when polar protons are not taken into account. The polar protons and ^{15}N chemical shifts deviate more strongly from experiment due to the insufficient treatment of solvent effects and conformational averaging. Approaches to overcome these limitations will be outlined.

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Interplay of theory and spectroscopy: Study of an Fe^{V}-nitride complex and its photolytic formation

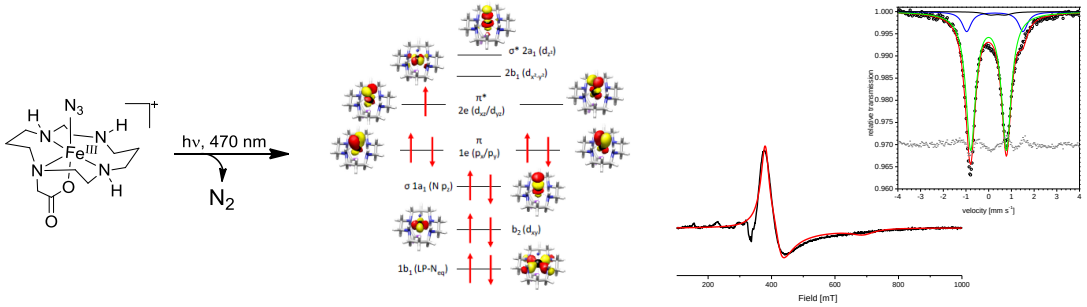
Oliver Krahe, Eckhard Bill, Taras Petrenko, Frank Neese

Max-Planck Institut für Bioanorganische Chemie, Mülheim a.d. Ruhr

In bioinorganic chemistry a wide range of highly developed spectroscopic methods have been used in the study of bio-relevant complexes and over the last two decades, computational chemistry has gained prominence as a powerful tool to provide insight into e.g. bio-relevant reactions from an additional perspective. DFT is of course the most frequently used method, but with contemporary computers and software it is possible to handle bio-relevant systems with higher level theory, such as correlated single- and multi reference methods.

Both fields, spectroscopy and theory, are individually very powerful, but a combination of both can facilitate the interpretation of data and permits an even more detailed understanding of the studied systems. The ORCA software package developed in our group features all common standard functionality, but is particularly well suited for the calculation of spectroscopic parameters.[1] Therefore we can experimentally verify our calculated electronic structures and confirm or rule out proposed intermediates by comparing calculated and experimental parameters.

We are interested in iron nitrides, which are believed to be key intermediates in the industrial and biological fixation of N_2.[2] Given the difficulties in isolating and characterizing transient intermediates, model complexes of low molecular weight are synthesized and studied and the results have a high impact on the understanding of real biological systems.



The nitridoiron model system we have chosen to focus upon is a six coordinated Fe^{V}-nitride supported by a cyclam derived ligand which is formed by photolysis of its Fe^{III}-azide counterpart in frozen solution with 470nm light[3]. Combining spectroscopy and theory we have been investigating the formation process of Fe^{V} by N_2 elimination and the electronic structure of the resulting high-valent iron complex. Using DFT we are able to accurately model the measured Mößbauer parameters, but a more sophisticated insight in the electronic structure was obtained by multi-reference calculations (CASSCF/NEVPT2), which also made it possible to reproduce the measured g-values accurately. To map the processes that accompany photo excitation, resonance Raman spectroscopy is a very applicable method, with DFT once again very useful in band assignment.

The presentation will demonstrate how theory and spectroscopy was combined in the study of an Fe^{V}-nitride complex.

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(De)Activation of olefin metathesis catalysts

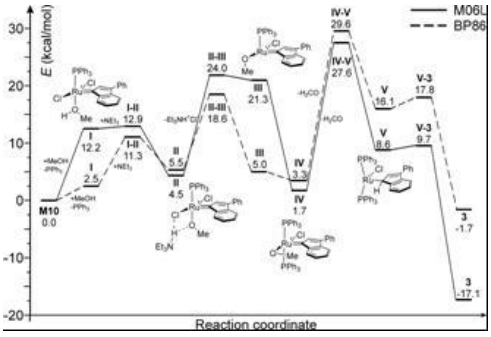
Albert Poater[1,2] and Luigi Cavallo[2]

1 Catalan Institute for Water Research (ICRA), H2O Building, Scientific and Technological Park of the University of Girona, Emili Grahit 101, E-17003 Girona, Spain; apoater@icra.cat (A.P.); mpoch@icra.cat (M.P.)

2 Dipartimento di Chimica e Biologia, Università di Salerno, Via ponte don Melillo, I-84084 Fisciano (SA), Italy

In recent years olefin metathesis catalyzed by N-heterocyclic carbene ruthenium complexes has attracted remarkable attention as a versatile tool to form new C=C bonds. [1] The last developed (pre)catalysts show excellent performances, and this achievement has been possible because of continuous experimental and computational efforts to understand the laws controlling the behavior of these systems. This perspective talk rapidly traces the ideas and discoveries that computational chemistry contributed to the development of these catalysts, with particular emphasis on catalysts presenting a N-heterocyclic carbene ligand. Specifically, one of the most important challenges in ruthenium-catalyzed olefin metathesis is to increase the stability of the catalysts under reaction conditions and this hopefully without loss of activity. Although, in the solid state, most ruthenium-based olefin metathesis catalysts are stable to oxygen and moisture, in solution decomposition usually occurs readily. Understanding the decomposition routes of catalysts is extremely important as any insight gained in this area can guide catalyst design efforts.

The well-defined and easily accessed $[RuCl_2(PPh_3)_2(3\text{-phenylindenylidene})]$, although not efficient in olefin metathesis itself, is an important synthon used in the preparation of a number of classes of ruthenium-based olefin metathesis catalysts. Although slightly stable in solution under anaerobic and anhydrous conditions, it exhibits rapid decomposition in the presence of alcohols. The instability of ruthenium olefin metathesis complexes to alcohols is often encountered. Indeed, in methanol, these complexes are prone to methanolysis and lead to the formation of hydrido-carbonyl complexes.



An unusual indenylidene to indenyl rearrangement has been uncovered,[2] leading to the rather facile formation of a new ruthenium indenyl complex. This complex, formally a decomposition product from an olefin metathesis catalyst, displays exceptional activity in the racemisation of chiral alcohols. DFT calculations permitted assembling all the experimental information into an energy profile. To facilitate the computational effort, MeOH was used as the model alcohol.[2] The discussed energies have been calculated with the M06L and BP86 functionals.

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Financial support: Ramón y Cajal (RYC-2009-05226), Career Integration Grant (CIG09-GA-2011-293900)

Application of Semiempirical UNO–CI and CI Methods in Nanoelectronics

Pavlo O. Dral, Timothy Clark

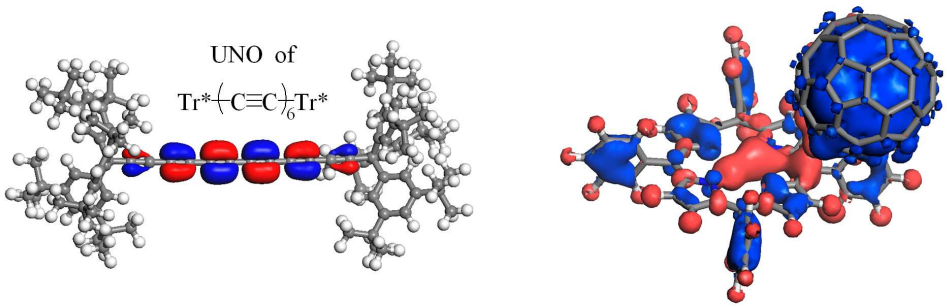
Computer-Chemie-Centrum and Interdisciplinary Center for Molecular Materials, Friedrich-Alexander-Universität Erlangen-Nürnberg, Nägelsbachstr. 25, 91054 Erlangen

MNDO-like semiempirical configuration interaction (CI) methods have been applied successfully for calculating excited states (ES) of large systems. The inclusion of dynamic and static electron correlations in these methods provides the accuracy of the determination of ES energies comparable with that of time-dependent density functional theory (TDDFT) methods. [1]

We recently introduced semiempirical UNO–CI methods that perform CI calculations using unrestricted natural orbitals (UNOs). [2] UNOs and their occupation numbers (**σ**) are the eigenvectors and the eigenvalues of the total unrestricted Hartree–Fock (UHF) density matrix $\mathbf{P}^{T}$, respectively. [2, 3] One of the advantages of UNO–CI methods is that orbitals (active space) for CI calculations are determined automatically by choosing orbitals with physically meaningful significant fractional occupation numbers (SFONs). Using SFONs between 0.02 and 1.98 to choose UNOs is sufficient in most cases, though sometimes using a broader range of SFONs may improve results. Moreover, occupations of frontier semiempirical UNOs predict diradical characters of singlet ground state PAHs better than those of *ab initio* and DFT UNOs. [2]

We have demonstrated that optical band gaps (E_g) of polyynes and polycyclic aromatic hydrocarbons (PAHs) calculated using semiempirical UNO–configuration interaction singles (UNO–CIS) are in good agreement with experimental values. Generally E_g values calculated using UNO–CIS are better than those calculated using conventional semiempirical CIS and comparable or better than those calculated by TDDFT. Noteworthy, UNO–CIS calculations are faster by one or several orders of magnitude than TDDFT calculations. The accuracy of UNO–CIS calculations can be improved further by performing full CI in the active space. Nevertheless, the latter approach, called UNO–CAS (UNO–complete active space), is much more computationally expensive than UNO–CIS. [2]

More recently semiempirical CI and UNO–CI methods have been used successfully to calculate absorption UV/vis spectra of cumulenes. Furthermore, experimental band gaps of polymers consisting of metal centers and heterocycles were reproduced well by the title methods. Another application of semiempirical CI methods is revealing the nature of charge separated (CS) states of porphyrin-fullerene dyads. In summary, semiempirical CI and UNO–CI methods are very reliable and fast approaches for predicting and explaining electronic properties of nanomaterials.



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Non-adiabatic QM/MM Simulations of Fast Charge Transfer in *E. coli* DNA Photolyase

Paul Benjamin Woiczikowski, Thomas Steinbrecher, Tomáš Kubar,

and Marcus Elstner

Department for Theoretical Chemical Biology,

Institute for Physical Chemistry,

Kaiserstr. 12, Karlsruhe Institute of Technology, D-76131 Karlsruhe, Germany

In this work, we study the photo-activation process in *E. coli* DNA photolyase, involving long-range electron transport along a conserved chain of Trp residues between the protein surface and the FAD cofactor. Fully coupled non-adiabatic (Ehrenfest) QM/MM simulations allow us to follow the time evolution of charge distributions over the natural time scale of multiple charge transfer events and conduct rigorous statistical analysis. Charge transfer rates in excellent agreement with experimental data are obtained without the need for any system-specific parameterization. The simulations are shown to provide a more detailed picture of electron transfer than a classical analysis of Marcus parameters. The protein and solvent both strongly influence the localization and transport properties of a positive charge, but the directionality of the process is mainly caused by solvent polarization. The time scales of charge movement, delocalization, protein relaxation and solvent reorganization overlap and lead to nonequilibrium reaction conditions. All these contributions are explicitly considered and fully resolved in the model used and provide an intricate picture of multi-step biochemical electron transfer in a flexible, heterogeneous environment.

The EC-RISM quantum solvation model for predicting tautomer ratios

Jochen Heil, Stefan M. Kast

Physikalische Chemie III, Technische Universität Dortmund

The "embedded cluster reference interaction site model" (EC-RISM) approach couples statistical-mechanical integral equation theory for predicting 3D solvent site distribution functions and quantum-chemical calculations [1]. The electronic structure of a solute is determined self-consistently with the solvent structure by mapping the continuous distribution onto a set of discrete background charges ("embedded cluster") as an additional contribution to the molecular Hamiltonian. Free energy data in solution including cavity and dispersion contributions is obtained directly from the integral equation results [2] without empirical adjustment of parameters. A particular advantage of the method is that the atomic, granular structure of the solvent is preserved which is important for the adequate treatment of directional effects such as H-bonding. Moreover, the approach is not restricted to dipolar solvent models as in continuum methods, making it suitable for modeling nonaqueous solvents such as benzene.

We outline the general framework and show that the EC-RISM method can be applied successfully to the problem of predicting tautomer free energy differences in aqueous solution that determine the species ratios. On the example of the compound set collected for the SAMPL2 prediction challenge [4] we analyze the influence of various factors on the accuracy such as the choice of the geometry (vacuum vs. solution phase), basis sets and quantum-chemical level of theory, and the parametrization of dispersive solute-solvent interactions. Without adjustments, a total r.m.s. error of ca 2 kcal mol^{-1} is achievable, while reparametrization of certain Lennard-Jones interaction terms can reduce the error to "chemical accuracy" of 1 kcal mol^{-1}.

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If you don't try, you'll never know

Timothy Clark

Computer-Chemie-Centrum der Friedrich-Alexander-Universität Erlangen-Nürnberg, Nägelsbachstr. 25, 91052 Erlangen
and
Centre for Molecular Design, University of Portsmouth, King Henry Building, Portsmouth PO1 2DY, UK.

Molecular modeling and its application in both drug design and materials modeling is increasingly limited by its own modesty (or lack of imagination) and a failure to appreciate the capabilities of modern hard- and software. We tend to perform calculations that are not truly predictive for ever more molecules, rather than trying to get something right by investing in the physical model.

The ***hpCADD***[1] project is an attempt to rectify this trend and to initiate a step change in the way that computer-aided drug design interacts with the experimental research and development process.

At the same time, the domain of molecular modeling can now be extended into new areas that have thus far been the subject of only limited attention. Modeling organic electronic devices is one such area.

The lecture will describe new techniques and software designed to take advantage of the features of modern hardware and to make a start towards truly predictive modeling.

1. www.hpcadd.com

Posters

Cu Ion Binding of MXCXXC Peptide: A DFT Study

Ergi Terzioglu[1], Z. Petek Cakar[2], Cemal Kopruluoglu[3], Saltuk M. Eyrilmez[3], Nursel Acar[4], Cenk Selcuki[3]

[1]Molecular Biology, Genetics and Biotechnology Programme, Istanbul Technical University, 34469 Maslak/Istanbul/TURKEY

[2]Department of Molecular Biology and Genetics, Istanbul Technical University, 34469 Maslak/Istanbul/TURKEY

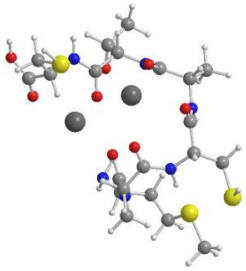
[3]Ege University, Department of Biochemistry, 35100 Bornova/Izmir/TURKEY

[4]Ege University, Department of Chemistry, 35100 Bornova/Izmir/TURKEY

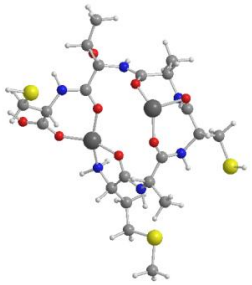
This study aims to investigate the copper binding mechanism of MXCXXC peptide by computational tools. Alanine (A), Glycine (G), Threonine (T), Valine (V), Serine (S) and Cysteine (C) are used in all possible combinations in MXCXXC for X. Most stable structures of the peptides are chosen for modeling the interactions with Cu^{+} and Cu^{2+} ions.

Conformational analysis has been carried out with molecular mechanics using the CHARMM22 force-field in HyperChem [1]. The calculations are repeated with Density Functional Theory (DFT) methods in Gaussian09 [2] at B3LYP/6-31G* level. Additionally, solvent effects will be investigated by the help of PCM models at the same level of theory.

The presence of Cu ions significantly changes the properties of the studied peptide and the stability of the formed complexes highly depends on the amino acids in the positions shown with X. Since the calculations are still in progress, we are yet unable to claim strongly that this effect is also very effective in the main protein. On the other hand, it can be concluded that the effect of the amino acids at positions X is not negligible as it is mostly believed in the literature.



MACATC-2Cu^{+}



MACATC-2Cu^{2+}

Our preliminary results indicate that the X residues are important in selective binding. Further studies and the detailed information gained in this study on the mechanism of peptide-metal interactions will provide useful data in many fields of health, biotechnology and bionanotechnology.

This work is supported by TUBITAK Grant No: 109T616 as part of the COST Action CM0902 “Molecular machineries for ion translocation across biomembranes”.

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Computational Study on the Isomerization of Silacyclopropylidenoid Structures to Silaallenes

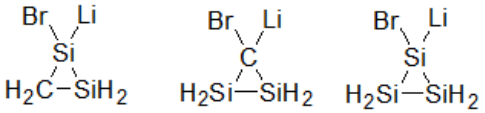
Akın Azizoğlu*, Cem Burak Yıldız

Department of Chemistry, University of Balikesir, TR-10145 Balikesir, Turkey

The theoretical and experimental investigations of silaallenes have been attracting more and more interest in the past few decades because of their unique structures and the broad differences in their properties compared to the corresponding carbon compounds. [1-2]

More recently, theoretical calculations elucidated the ring-opening reactions of 1-bromo-1-lithiosilirane and 2-bromo-2-lithiosilirane to 2-silallene and and 1-silaallene, respectively. The ring-opening of 1-bromo-1-lithiosilirane to 2-silallene can proceed in a stepwise fashion with the intermediacy of a free silacyclopropylidene. In contrast, the ring-opening of 2-bromo-2-lithiosilirane to 2-silallene can occur in a concerted fashion. [3]

Herein, we wish to report the results of DFT calculations on the isomerization of 1-bromo-1-lithiodisilirane, 3-bromo-3-lithiodisilirane, and 1-bromo-1-lithiotrisilirane, shown below to silaallenes. All theoretical calculations are carried out using the Gaussian03 suite of programs. [4]



On the basis of theoretical calculations we predict that the ring-opening reaction of 1-bromo-1-lithiodisilirane to 1,2-disilaallene can occur either in a concerted fashion or through a stepwise process with the intermediacy of a free silacyclopropylidene. In contrast, the ring-opening reactions of 3-bromo-3-lithiodisilirane and 1-bromo-1-lithiotrisilirane can occur in a concerted fashion. The activation energy barrier for the isomerization of 3-bromo-3-lithiodisilirane to the complex of 1,3-disilaallene with LiBr was determined to be only 2.6 kcal/mol at B3LYP/6-31+G(d,p) level, and the reaction is highly exothermic, which makes this reaction for a promising strategy for the synthesis of 1,3-disilaallenes. However, the energy barrier for the conversion of 1-bromo-1-lithiotrisilirane to trisilaallene is calculated to be quite high, 27.2 kcal/mol, and in this case the reaction is endothermic.

This work was supported by grants from the Scientific and Technical Research Council of Turkey (TUBITAK) (Grant No. TUBITAK TBAG-210T113).

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Predicting the Effects of Base-Pair Mutations in DNA-Protein Complexes by Thermodynamic Integration

Frank R. Beierlein,[†,‡] *G. Geoff Kneale*[§] *and Timothy Clark*[†,‡,¶]

[†]Computer-Chemie-Centrum, Friedrich-Alexander-Universität Erlangen-Nürnberg, Nägelsbachstraße 25, 91052 Erlangen, Germany, [‡]Excellence Cluster "Engineering of Advanced Materials", Friedrich-Alexander-Universität Erlangen-Nürnberg, Nägelsbachstraße 49b, 91052 Erlangen, Germany, [§]Institute of Biomedical and Biomolecular Sciences, School of Biological Sciences, University of Portsmouth, King Henry Building, Portsmouth PO1 2DY, United Kingdom, [¶]Centre for Molecular Design, University of Portsmouth, Mercantile House, Portsmouth PO1 2EG, United Kingdom.

Thermodynamically rigorous free-energy methods in principle allow the exact computation of binding free energies in biological systems. Here, we use thermodynamic integration together with molecular dynamics simulations of a DNA-protein complex to compute relative binding free energies of a series of mutants of a protein-binding DNA operator sequence. A guanine-cytosine base-pair that interacts strongly with the DNA-binding protein is mutated into adenine-thymine, cytosine-guanine and thymine-adenine. It is shown that base-pair mutations can be performed using a conservative protocol that gives error estimates of about 10% of the change in free energy of binding. Despite the high CPU-time requirements, this work opens the exciting opportunity of being able to perform base-pair scans to investigate protein-DNA binding specificity in great detail computationally. [1]

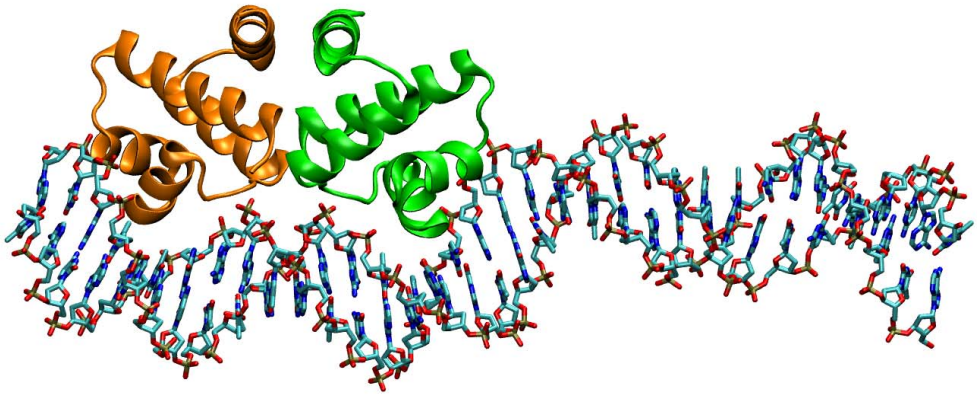

Figure 1. DNA-protein complex used in this study. Only the higher-affinity operator sequence (O_L) is bonded to a C-protein dimer (orange, green). The perturbation base-pair formed by DNA residues 3 and 68 is located on the left hand side of the 35 bp operator sequence. Hydrogen atoms, water molecules and counter-ions were omitted for clarity.

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Predicting Molecular Self Organisation in Sugar Based Liquid Crystals Using Grid Computing Facilities

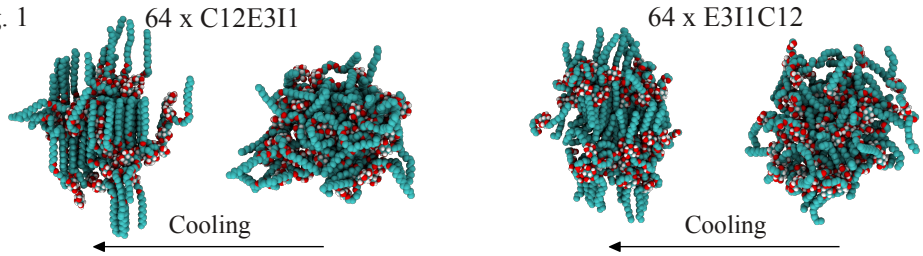
Sebastian Breuers, Dirk Blunk*

Department of Chemistry, University of Cologne, d.blunk@uni-koeln.de

The prediction of transition temperatures of liquid crystalline compounds is a currently highly investigated topic in the field of materials sciences.[1] However, the simulation of bulk materials is a demanding research topic both scientifically and computationally.

Here, the self-organization of two sugar based model systems is discussed. Although both systems consist of an inositol moiety (I1), a dodecyl function (C12), and a triethoxy moiety (E3) only the combination C12E3I1 exhibits a liquid crystalline (SmA) phase in experimental findings while E3I1C12 transits directly from the isotropic to the crystalline phase.[2] Both systems have been MD-simulated with 64 molecules each, respectively, in a stepwise cooling approach (sampling time/temperature: 72 ns), cf. Fig. 1. The obtained trajectories are characterized by means of their nematic order parameter $<P_2>$.

Fig. 1



The quite flexible alkyl and triethoxy chains lead to a high degree of freedom, which becomes more prominent in bigger simulation systems. Furthermore, the hydrogen bond interactions slow down the motility of the system in comparison to pure alkyl or aryl systems. In a simulation run with 64 molecules a self organization process became visible. Although a raise in order can be observed in both systems (C12E3I1 and E3I1C12) only the C12E3I1 system remains stable in its order while the E3I1C12 system destabilizes again (cf. Fig. 2).

These results were not reproduced with a system of 216 molecules and 72 ns sampling time (cf. Fig. 3). A possible explanation would be that the sampling time of the bigger system has to be significantly increased.

Fig. 2

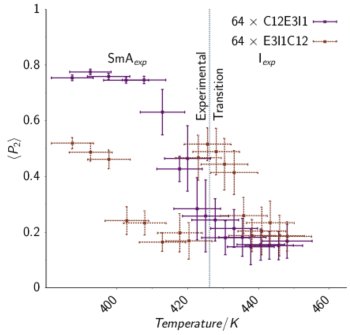
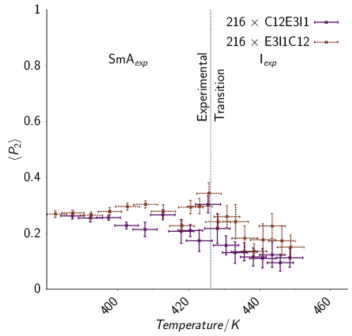


Fig. 3



The calculations were achieved within the MoSGrid (Molecular Simulation Grid) project which aims to facilitate the access to high performance computational resources for chemical simulation purposes.[3]

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Calculation of the CD spectrum of a peptide from its conformational phase space

Zlatko Brkljača[1,2], Karmen Čondić-Jurkić[1,3], David M. Smith[3,4], Ana-Sunčana Smith[1,2]

[1]*Cluster of Excellence: Engineering of Advanced Materials, University Erlangen-Nürnberg, Erlangen, Germany*

[2]*Institute for Theoretical Physics, University Erlangen-Nürnberg, Erlangen, Germany*

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

[4]*Computer Chemie Centrum, University Erlangen-Nürnberg, Erlangen, Germany*

Met-enkephalin (Tyr-Gly-Gly-Phe-Met) and its unnatural analogue Ada-enkephalin are opioid peptides which act as inhibitors of tumor cells in a receptor-mediated fashion. We have investigated the structural preferences of these peptides in 2,2,2-trifluoroethanol in an attempt to calculate their respective CD spectra. To this end, we have characterized the conformational preferences of the zwitterionic and neutral forms of Met-enkephalin and of both the *R*- and the *S*-epimers of Ada-enkephalin, as obtained by replica exchange molecular dynamics. The CD spectrum for each peptide was subsequently obtained with a procedure of successive averaging, which accounts for the sidechains and the backbone variations of the peptides and the effect of the solvent on the CD spectra. To make a proper comparison with the experiment, we have produced composite spectra that account for the appropriate contributions of the zwitterionic and neutral forms of the peptides as well as the expected epimeric ratio. Such a procedure results in theoretically obtained CD spectra that successfully reproduce the most important features of the experimentally measured spectra. Consequently, the link between the CD spectra and the conformational phase space of flexible peptides can be established.

Theory and hierarchical calculations of the structure and energetics of [0001] tilt grain boundaries in graphene

Johan M. Carlsson[1], Luca Ghiringhelli[2], and Annalisa Fasolino[3]

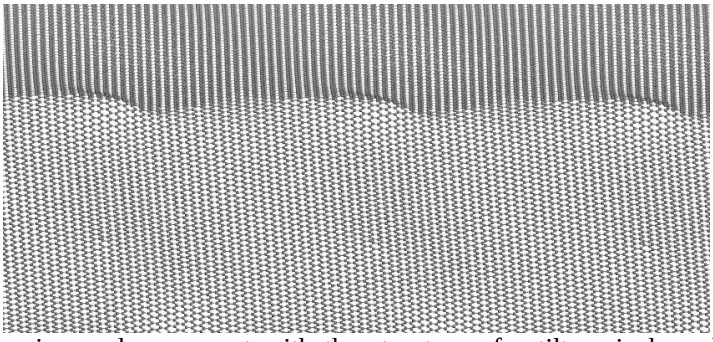
[1]*Accelrys Ltd, 334 Science Park, CB4 OWN Cambridge, UK*

[2]*Fritz-Haber-Institut der Max-Planck-Gesellschaft, Faradayweg 4-6, D-14195 Berlin, Germany*

[3]*Institute for Molecules and Materials, Radboud University Nijmegen, Heyendaalseweg 135, 6525 AJ Nijmegen, The Netherlands*

Defect-free graphene has extraordinary properties, but several experiments have revealed the presence of grain boundaries in graphene that may change its electronic and elastic properties[1-3]. Here we present a general theory for the structure of [0001] tilt grain boundaries in graphene based on the Coincidence Site Lattice (CSL) theory. We show that the CSL-theory uniquely classifies the grain boundaries in terms of the misorientation angle θ and periodicity d using two grain boundary indices (m,n), similar to the nanotube indices. The CSL-theory is convenient to derive supercell models for grain boundaries and we have implemented the method into a script in Materials Studio [4]. The script is able to generate grain boundary models for a particular misorientation angle θ with two grain boundaries per supercell.

The structure and formation energy of a large set of grain boundaries generated by the CSL theory for $0° < \theta < 60°$ (up to 15608 atoms) were optimized by force field[4] and bond order potential calculations[5] and validated by density-functional (DFT) calculations[4]. Our calculations show that low energy [0001] tilt grain boundaries in graphene can be identified as dislocation arrays[6]. For small θ do the dislocations form hillocks as can be seen in the Figure below.



These hillocks are in good agreement with the structure of a tilt grain boundary in graphene grown on Ir(111) that has θ=2°, which was observed by Scanning Tunneling Microscopy(STM) [1]. Grain boundaries with larger misorientation angle have an array of dislocation cores with short periodicity in agreement with STM observation of grain boundaries in HOPG[2].

We find that, in contrast to three-dimensional materials, the strain created by the grain boundary can be released via out of plane distortions that lead to an effective attractive interaction between dislocation cores. Therefore, the dependence on θ of the formation energy parallels that of the out-of-plane distortions, with a secondary minimum at θ=32.2° where the grain boundary is made of a flat zigzag array of only 5 and 7 rings. For θ>32.2°, also other non-hexagonal rings are possible in agreement with STM observations of a large angle grain boundary[3].

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Inhibiting protein-protein interactions in HSP90 dimerization as a novel approach for targeting cancer

Emanuele Ciglia, Holger Gohlke

Institute for Pharmaceutical and Medicinal Chemistry, Department of Mathematics and Natural Sciences, Heinrich-Heine University, Düsseldorf, Germany

HSP90 (heat shock protein of 90 kDa) is a molecular chaperone intervening in protein folding and in refolding processes taking place after stress stimuli. In eukaryotes, HSP90 is essential for cell viability and growth, tuning the function of several regulatory and signaling client proteins [1]. Several studies demonstrated an involvement of HSP90 in cancer, stabilizing oncogenic proteins and allowing malignant transformation [2]. Clinical studies on small molecules acting as HSP90 inhibitors established HSP90 as an attractive and validated target for cancer therapy [3, 4]. On a structural side, HSP90 is a homodimer, each monomer consisting of three domains: an N-terminal ATP binding domain, a middle domain, and a C-terminal dimerization domain, responsible for the permanent association of the two monomers [1]. Most of the known HSP90 inhibitors act by binding at the N-terminus, impeding ATP binding and hydrolysis, therefore blocking the chaperone activity. None of the inhibitors so far reported target the dimerization of the HSP90, however. Thus, the aim of this project is to characterize determinants of the dimerization of human HSP90 and to use this information to develop α-helix mimetics and non-peptidic small-molecules disrupting HSP90 dimerization. For this, we first generated a homology model of the human HSP90. The homology model obtained was subjected to molecular dynamics simulations, and the conformational ensemble generated was used for the identification of residues mostly involved in the dimer formation, (hot spots). For this purpose, *in silico* alanine scanning using DrugScore^{PPI} and binding energy decomposition on a per-residue level using MM-GBSA were performed. Remarkably, results from the two approaches were convergent, suggesting that eight amino-acids located at the dimer interface account for the highest contribution to the binding free energy. Utilizing this information, short peptides derived from the interface are currently being designed that should inhibit dimerization. Furthermore, the hot spot information is used to guide the design of α-helix mimetics and the screening of non-peptidic small molecules directed to the dimerization interface of the protein.

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Disaccharides mediate the interplay between collagen and carbonate ions in biomineralization processes

Patrick Duchstein[1], Rüdiger Kniep[2], Dirk Zahn[1]

[1]*Computer Chemie Centrum, Friedrich Alexander Universität Erlangen-Nürnberg*

[2]*Max-Planck-Institut für Chemische Physik fester Stoffe, Dresden*

Biominerals, such as bone, teeth, otoconia, and mollusc shells are composite materials, composed of an inorganic mineral, closely interacting with organic tissue, in many cases collagen. Otoconia in particular consist of calcite and collagenous proteins, enamel comprises a calcium hydrogen phosphate matrix with embedded collagen fibers[1]

We investigated crystal nucleation of calcium carbonate and of carbonated calcium hydrogen phosphate along various types of collagen. Our method of choice consisted in the Kawska-Zahn approach [2,3] which allows for the simulation of crystal growth ion by ion along a triple helical collagenous strand. By analyzing various collagen types with different degrees of glycosylated lysine residues we found out that a very high degree of glycosylated amino acids is necessary to ensure calcification along a collagenous triple helix, and thus embedding of the collagen fiber.

Simulations with biological, i.e. carbonated, calcium hydrogen phosphate yielded similar results. We therefore conclude that glycosated lysine residues are crucial to allow carbonate ion association to collagen fibers without compromising the protein structure.

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Molecular design of fusion inhibitors for flaviviruses

Evgenia V. Dueva[a], Dmitry I. Osolodkin[a,b], Liubov I. Kozlovskaya[b], Vladimir A. Palyulin[a], Galina G. Karganova[b], Nikolay S. Zefirov[a]

[a] *Moscow State University, Department of Chemistry, Moscow 119991, Russia*

[b] *Chumakov Institute of Poliomyelitis and Viral Encephalitides Russian Academy of Medical Sciences, Moscow 142782, Russia*

Flaviviruses comprise a large group of related viruses, significantly threating human health over the world. However, effective specific anti-flaviviral therapies do not exist yet. The entry of flavivirus into a host cell by pH-dependent endocytosis is mediated by its major envelope (E) protein that possesses a hydrophobic pocket occupied by a detergent molecule (n-octyl-β-D-glucoside) in one of the dengue E protein crystal structures [1]. Potential inhibitors of low-pH-induced membrane fusion can interact with this pocket. This opens an avenue for identifying anti-flaviviral agents active in early steps of viral infection [2]. In this work homology model of 'closed' conformation (corresponding to the resting state) of Powassan virus (POWV) E protein have been constructed using crystal structures of dengue serotype 2 and tick-borne encephalitis virus (TBEV) E proteins as templates (PDB IDs 1OAN and 1SVB, respectively). To obtain 'open' POWV and TBEV E protein models required for docking (corresponding to fusion-inactive state), the structure of dengue E protein in a complex with n-octyl-β-D-glucoside (PDB ID 1OKE) was utilized along with closed forms. The docking-based virtual screening of chemical databases revealed several putative hit compounds against both, POWV and TBEV. Preliminary *in vitro* assays results were obtained for identified substances.

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Modification of NiO(111) surfaces by hydroxylation and carbonate formation

Christina Ebensperger, Bernd Meyer

CCC, University Erlangen-Nürnberg

NiO is used as main or co-catalyst in heterogeneous catalysis. H_2O, CO and CO_2 are commonly present at catalytic reactions and strongly interact with NiO surfaces. It is observed that they block surface sites or alter the surface structure by hydroxylation and carbonate formation and thereby poison the catalyst.

In our study of the response of NiO to these gas phases we focused on the polar NiO(111) surface. The bulk-truncated structures are intrinsically unstable and especially susceptible to reactions with adsorbates. We performed spin-polarized GGA+U calculations for possible reconstructions of NiO(111) in contact with water, hydroxyl groups and protons or CO and CO_2. A thermodynamic formalism was applied to deduce phase diagrams of the energetically most stable surface structures depending on temperature and pressure conditions.

The O-H phase diagram is dominated by a fully hydroxylated (1x1)-OH surface at ambient and low temperature UHV conditions and an adsorbate free (2x2)-O-octopolar structure after high temperature annealing [1]. A transformation between these two stable phases includes not only the adsorption or desorption of water molecules but also the diffusion of Ni and O surface atoms. NEB calculations for reaction barriers of subprocesses of this phase transformation explain the experimentally observed high thermal stability of surface hydroxylation.

The interaction of CO and CO_2 with NiO(111) leads to the formation of tridentate carbonate complexes including O surface atoms which are interconnected by Ni surface atoms. Again, the molecules strongly alter the surface configuration. A transition path between adorbate covered and adsorbate free surface structures has to involve a mass transport of Ni and O surface atoms. As expected from our theoretical results, a high thermal stability of carbonates is observed in experiment.

We showed that the adsorption of small molecules on NiO(111) alters the surface considerably. These modifications have to be considered when modeling catalytic reactions.

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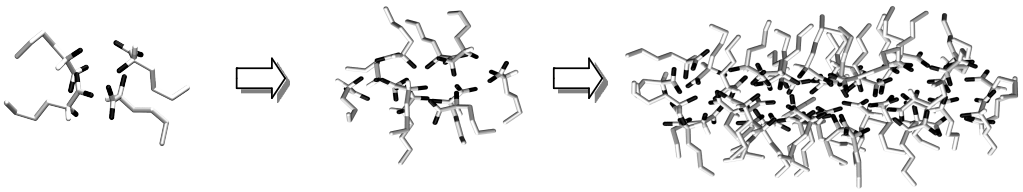
Nucleation of molecular crystals

Philipp Ectors[1], Jamshed Anwar[2], Dirk Zahn[1]

Chair of Theoretical Chemistry / Computer Chemistry Center

University of Erlangen-Nürnberg[1],

Institute of Pharmaceutical Innovation, University of Bradford[2]



4 molecules *10 molecules* *50 molecules*

We investigate the early stages of molecular crystal nucleation by means of the Kawska-Zahn approach [1]. Along this line, molecular association, the formation of pre-nucleation clusters, nucleation and aggregate growth is explored.

Currently, our focus is set to two systems, i.e. D/L - norleucine using the excellent force field of Anwar et al [2] and benzamide for which we are developing a force field of similar accuracy.

The pictures illustrate the early stages of D/L - norleucine molecule association (left) and the transition (middle) to later stages of aggregate growth with reflect the formation of layered structures (right).

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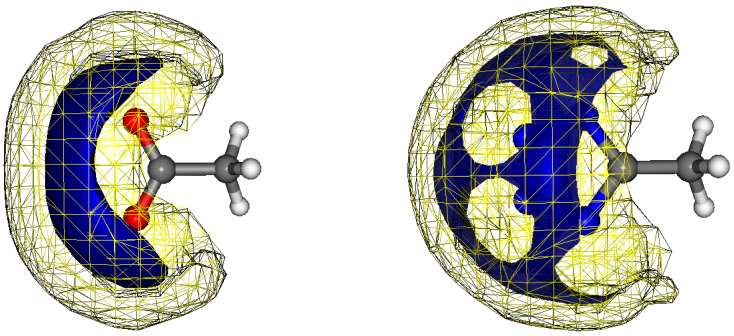
Predicting the Sites and Energies of Non-Covalent Intermolecular Interactions Using Local Properties

Ahmed El Kerdawy, [a] *Christian R. Wick*,[a] *Matthias Hennemann* [a,b] *and Timothy Clark* [a,b,c]

[a] Computer-Chemie-Centrum, Friedrich-Alexander-Universität Erlangen-Nürnberg, Nägelsbachstraβe 25, 91052 Erlangen, Germany.
[b] Interdisciplinary Center for Molecular Materials, Friedrich-Alexander-Universität Erlangen-Nürnberg, Nägelsbachstraβe 49, 91052 Erlangen, Germany.
[c] Centre for Molecular Design, University of Portsmouth, King Henry Building, Portsmouth PO1 2DY, United Kingdom.

Despite the essential importance of the non-covalent interactions and their key role in many natural processes, they are not treated well by currently available *in silico* techniques. Non-covalent interactions are important on the micro and macro scales and include protein-ligand, protein-protein and protein-DNA binding. [1] Being able to predict such interactions, especially unusual (non-classical) ones, would be of immense value for the molecular modeling field and especially for drug design. We have therefore set out to define a systematic protocol for detecting interaction sites of different types in the vicinity of ligands or receptors and to estimate the strength of the interactions in order to provide a more consistent and complete picture of the intermolecular binding properties of small molecules and biopolymers. Since the points of interaction of molecules lie at or near the molecular surface, surface-based molecular descriptors were used to construct feed-forward artificial neural nets to recognize H-bond donors and acceptor sites on drug-like molecules based on local properties (electron density, molecular electrostatic potential and local ionization energy, electron affinity and polarizability) calculated at grid points around the molecule. Interaction energies for training were obtained from B97-D and ωB97X-D/aug-cc-pVDZ density-functional theory calculations on a series of model central molecules and H-bond acceptor and donor probes constrained to the grid points used for training. The resulting models provide maps of both classical and unusual H- and halogen-bonding sites. Some examples demonstrate the ability of the models to take the electronic and steric nature of the central molecule into consideration and to provide semi-quantitative estimates of interaction energies at low computational cost.



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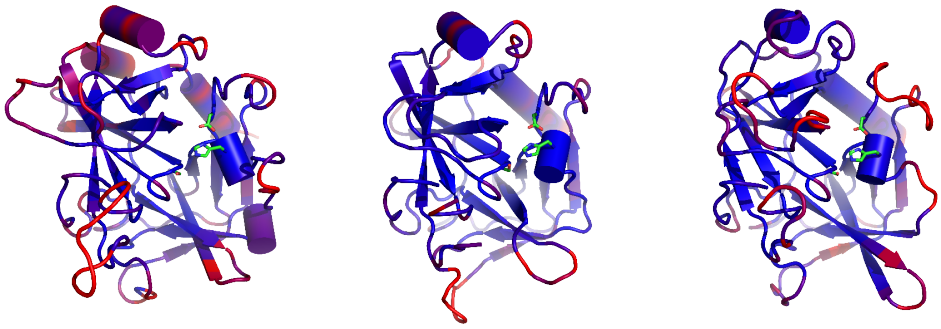
Local Dynamics in Protease Recognition

Julian E. Fuchs, Hannes G. Wallnoefer, Susanne von Grafenstein, Roland G. Huber, Gudrun M. Spitzer, Klaus R. Liedl

Theoretical Chemistry, Faculty of Chemistry and Pharmacy, University of Innsbruck
Innrain 80/82, A-6020 Innsbruck, Austria
julian.fuchs@uibk.ac.at

Proteases catalyze cleavage of peptide bonds and are vitally important in a wide range of fundamental cellular processes. Far more than 500 proteases have been identified in the human genome individually tied to a unique cleavage pattern [1]. These patterns reach from specificity for a single peptide in case of proteases involved in signaling cascades to broad spectra of cleaved peptides for digestive enzymes.

To analyze the impact of local dynamics on protease specificity, a series of homologous chymotrypsin-like serine proteases including highly specific as well as unspecific proteases was selected. Inspired by information theory, subpocket-wise substrate cleavage entropies are presented based on cleavage data from the MEROPS database [2]. Calculated entropy scores, ranging from 0 for a conserved substrate to 1 for a random distribution of substrates, appear to be qualitatively linked to local flexibility of the binding site region. Consequently, temperature factors from X-ray structures as well as all-atom 100ns molecular dynamics trajectories using the AMBER package [3] are compared in respect to subpocket specificity.



Analysis of specificity and flexibility patterns reveal a consistent correlation of binding site rigidity and specificity. As conformational plasticity is paralleled by a broader conformational space, a mechanism of conformational selection [4] in the binding process of proteases is proposed. According to this model, the whole conformational ensemble contributes to the substrate specificity of proteases rather than single interactions derived from a static point of view. This finding implies the need for refined rules for substrate cleavage considering binding site flexibility in accordance to earlier findings for snake venom metalloproteases [5].

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Interaction of Hydrogen with the ZnO(10-10) Surface.

Jakub Goclon and Bernd Meyer

Interdisziplinäres Zentrum für Molekulare Materialien (ICMM) and Computer-Chemie-Centrum (CCC), Universität Erlangen-Nürnberg, 91052 Erlangen, Germany

The chemisorption of gases on ZnO surfaces has been studied extensively for more than 40 years. This interest is based on the application of zinc oxide in heterogeneous catalysis for hydrogenation and dehydrogenation reactions. Hydrogen adsorption on ZnO is one of the steps in methanol production from syngas. Therefore the understanding of the interaction of hydrogen with ZnO is of major importance.

In the current study we have focused on the mixed terminated nonpolar (10-10) surface of ZnO, which is the natural cleavage plane of ZnO crystals. Experimentally it was observed that upon hydrogen exposure at low temperatures an ordered adsorbate structure with a (1x1) periodicity is formed where both, zinc and oxygen dangling bonds are saturated by H atoms [1]. With increasing temperature, however, the Zn sites loose their H atom and the surface transforms into a reduced state which shows a metallic behavior [1,2]. No significant desorption of H_2 molecules was observed during this transformation process, which led to the speculation that the H atoms diffuse into the bulk. Furthermore, water may play a key role in the stability of different surface structures. Water adsorbs as a partially dissociated monolayer [3, 4], but can also lead to a full hydroxylation of the surface.

The aim of our calculations is to study the hydrogen adsorption and migration at different coverages of the ZnO(10-10) surface. The calculations are based on density functional theory (DFT) with a Hubbard-U correction using the PBE exchange-correlation functional and a pseudopotential/plane wave approach as implemented in the PWSCF code. The coverage dependence of the hydrogen adsorption was investigated by using different supercell sizes representing (1x1), (1x2), (2x1), (2x2) and (4x2) unit cells of the ZnO(10-10) surface. Hydrogen adsorption on the O as well as the Zn sites was taken into account. From the adsorption energies a phase diagram of the lowest-energy adsorbate structures for a ZnO(10-10) surface in thermodynamic equilibrium with a hydrogen gas phase at finite temperatures and pressures is constructed. In addition, zinc hydroxide formation via dissociative water adsorption was taken into account. The stability of these structures is analyzed in terms of a 2-dimensional phase diagram representing the admissible range of hydrogen and water chemical potential. For two limiting cases of a high and a low hydrogen coverage (using a (4×2) supercell) we determined the most stable configurations of H atoms in deeper surface layers, and energy barriers for the H atom migration along different diffusion paths were calculated with the help of the nudge elastic band (NEB) method.

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Impact of Tetramerization on Neuraminidase Dynamics and Binding Site Conformations

Susanne von Grafenstein[1], Hannes G. Wallnoefer[1], Julian E. Fuchs[1], Roland G. Huber[1], Judith M. Rollinger[2], Johannes Kirchmair[3], Klaus R. Liedl[1]

[1]Institute of General, Inorganic and Theoretical Chemistry and Center for Molecular Biosciences, University of Innsbruck
Innrain 52a, Innsbruck, Austria
[2]Institut of Pharmacy and Center for Molecular Biosciences, University of Innsbruck
Innrain 52c, Innsbruck, Austria
[3]Unilever Centre for Molecular Informatics, University of Cambridge
Lensfield Road, Cambridge, United Kingdom

Influenza neuraminidase is a tetrameric surface protein of the influenza virus and the target for antiviral drugs e.g., oseltamivir and zanamivir [1]. The conformational diversity of the 150-loop was revealed by crystal structures of the group 1 neuraminidases [2] and investigated by molecular dynamics (MD) simulations [3], [4]. The open state conformation shows an additional sub-pocket (150-cavity) exploitable for drug design [1], [5], [6].

We compared tetrameric influenza neuraminidase with monomeric neuraminidases of other organisms and identified a unique insertion typical for the influenza variant. These residues are part of the protein-protein-interface as well as the flexible 150-loop. We assume this insertion to mediate the tetramerization effects via dynamics.

Therefore, we present a systematic analysis of three neuraminidases (avian 2005, pandemic 1918, pandemic 2009) with all-atom, explicit solvent MD simulations applying the Amber forcefield ff99SB. Comparative simulations of monomeric, dimeric and tetrameric systems show, that the sampled conformational phase space for tetramer is distinct from monomer simulations. We demonstrate, that interactions with adjacent neuraminidase subunits alter the dynamics of the 150-loop.

These results underline the importance of protein-protein-interactions in the influenza neuraminidase tetramer for the examination of molecular flexibility, especially for the loop forming the 150-cavity. In consequence, considering these interactions is crucial for drug development.

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The necessity of long-term molecular dynamics simulations: Deamino-oxytocin - novel conformational insights

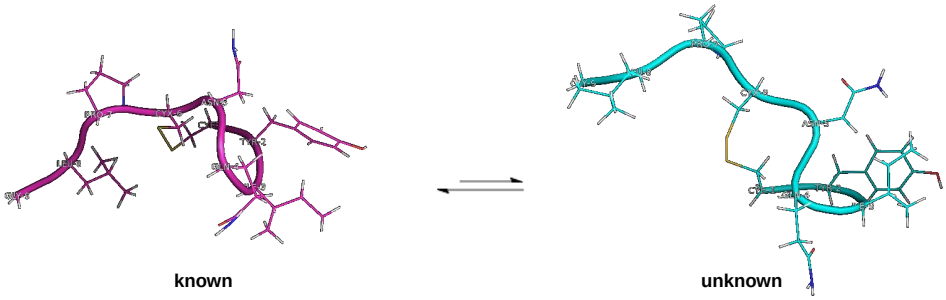
Elke Haensele[1,✉], Lee Banting[2], and Timothy Clark[1,3]

[1]*Faculty of Science, Pharmacy and Biomedical Sciences, Centre for Molecular Design, University of Portsmouth, King Henry Building, King Henry I Street, Portsmouth PO1 2DY, UK*

[2]*Faculty of Science, Pharmacy and Biomedical Sciences, University of Portsmouth, St Michael´s Building, White Swan Road, Portsmouth PO1 2DT, UK*

[3]*Computer-Chemie-Centrum and Interdisciplinary Center for Molecular Materials, Friedrich-Alexander-Universität Erlangen-Nürnberg, Nägelsbachstraße 22, 91052 Erlangen, Germany*

✉*E-Mail: Elke.Haensele@port.ac.uk*



Extended molecular dynamics (MD) simulations (> 1 μs) show great promise in delivering significant, practically relevant, insight into conformational processes that occur within molecular systems. If long enough, MD simulations can reveal conformational interconversions particularly in peptides and proteins. Conformational equilibria may be unfavourable and dominated by the highly populated more stable conformation. However, the less favoured conformer is often the physiologically relevant one and may present significant difficulties for quantification by experimental techniques. Close coordination of MD analysis and experiment helps shed light on pharmacologically relevant molecular phenomena.

This work is part of a series of long-term MD simulations [1] (≥ 3 μs) applied to the cyclic nonapeptides oxytocin, 8-Arg-vasopressin, and deamino-oxytocin (dOT). Their moderate size and multitude of structural features presents an ideal test case to emphasize the necessity of extended simulations and to apply diverse conformational-analysis methods [2, 3].

The MD on dOT shows that (i) the results achieved with a runtime of 3 μs are in very good agreement with experimental data [4, 5] and (ii) employing DASH [2] in the analysis of these systems proves powerful and reliable in characterising conformational clusters. Furthermore, a previously undetected ring conformation of dOT was significantly populated in the simulation trajectory (390 ns/ 3000 ns, 8 transitions). This conformation indicates greater conformational flexibility of dOT vs. OT/ VP and thus helps explain its super-agonist properties [6].

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Computationally efficient and accurate 3D-RISM calculations

Jochen Heil, Roland Frach, Daniel Tomazic, Franziska Hoffgaard, Stefan M. Kast

Physikalische Chemie III, Technische Universität Dortmund

The three-dimensional "reference interaction site model" (3D-RISM) integral equation theory is a statistical-mechanical approach to predict liquid state structural and thermodynamic features [1]. It is based on approximate solute-solvent correlation functions to be computed on a 3D grid as a function of the interaction potential between the solute and the solvent sites, circumventing the need of costly sampling of explicit solvent degrees of freedom. In combination with quantum-chemical calculations within the embedded cluster (EC-) RISM framework [2], the theory also allows for studying chemical reactions in solution, outperforming traditional continuum solvation methods, for instance pK_a shift calculations and conformational equilibria [2], and the prediction of tautomer ratios [3].

Extending the scope of 3D-RISM applications to very large systems such as those involving biological macromolecules as well as to non-aqueous environments poses particular challenges on both the conceptual and the software implementation side. At the same time, it is necessary to systematically improve the inherent 3D-RISM approximations and to add typical capabilities used in computational chemistry in order to make the theory routinely usable. Here we show that we can make progress by developing novel methodical and software features:

- The expensive treatment of long-range Coulomb interactions is circumvented by implementing a "particle-mesh Ewald" (PME) approach [4] that exploits the computational efficiency of the fast Fourier transformation (FFT). Furthermore, a multipole renormalization scheme eliminates the need to compute the costly real-space potential at any stage of the calculations.
- The performance of key routines is improved by implementing MPI parallelization in order to facilitate porting of the 3D-RISM software to massively parallel hardware architectures.
- Semi-empirical free-energy functionals for improved accuracy are currently parametrized with respect to quantitative agreement between simulated and 3D-RISM free energies of solvation [5,6].
- Gradient formulations [7] for geometry optimization in solution are developed in order to allow for characterizing reaction thermodynamics and mechanisms.

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Comparative computational analysis of enzyme allosteric sites and the binding of allosteric effectors

Nadine Veith*, Anna Feldman-Salit*, Lisa Kaschel, Stefan Henrich, Rebecca C. Wade

Heidelberg Institute for Theoretical Studies (HITS), Schloss-Wolfsbrunnenweg 35, D-69118 Heidelberg
** Present address: University of Heidelberg, Bioquant, Im Neuenheimer Feld 267, D-69120 Heidelberg*

Kinetic modeling of biochemical networks requires the correct modeling of allosteric effects. One of the challenges in modeling allosteric effects is that these can differ considerably between related organisms. In the European SysMO-LAB project, the central metabolism of four Lactic Acid Bacteria (LAB), *Lactococcus lactis, Enterococcus faecalis, Streptococcus pyogenes*, and *Lactobacillus plantarum*, is compared using experimental and computational systems biology approaches, including modelling of the metabolic pathways and the reaction kinetics.

With a focus on the central metabolic pathway, we have studied the allosteric regulation of the enzymes L-lactate dehydrogenase (LDH, EC number 1.1.1.27) and pyruvate kinase (PYK, EC number 2.7.1.40), two particularly important enzymes of the primary anaerobic energy metabolism. The activity of LDHs is known to be strongly activator-dependent, with the allosteric activation mostly being due to fructose-1,6-bisphosphate (FBP). Furthermore, the enzymatic activity is influenced by inorganic phosphate (P_i). Both compounds, FBP and P_i, are also involved in the regulation of PYK and other enzymes. Therefore, to understand the cross-talk between pathways, it is important to investigate the role of these compounds.

We used comparative modelling, molecular interaction fields, Protein Interaction Property Similarity Analysis (PIPSA), data mining and molecular docking techniques, to study the binding of effectors at the allosteric binding sites of these enzymes in LABs. Despite the similarity in the allosteric activators, the allosteric binding sites in LDH and PYK differ strongly. Moreover, the results show significant differences in the binding of allosteric effectors to these enzymes in the four LABs studied. Whereas LDHs from *L. lactis* and *S. pyogenes* are expected to behave similarly in the presence of FBP and P_i, the LDH from *L. plantarum* does not appear to be FBP-regulated. For PYKs, there is also a high similarity between *L. lactis* and *S. pyogenes*, whereas differences are observed for the activator binding site in the *E. faecalis* and *L. plantarum* enzymes.

In extension to the comparisons of particular enzymes of different organisms, we are working on data mining and modelling techniques for comparing interactions between compounds and enzymes in a broader and more systematic way. It is planned to make this accessible as a workflow via the modelling platform http://sycamore.h-its.org.

Molecular Dynamics Investigation of Cooperative Binding Within the KIX Domain

Roland G. Huber[1], Julian E. Fuchs[1], Susanne von Grafenstein[1], Hannes G. Wallnoefer[1], Martin Tollinger[1], Romano T. Kroemer[2], Klaus R. Liedl[1]

[1] Leopold Franzens University Innsbruck
Faculty of Chemistry and Pharmacy, CCB
Innrain 80/82, A-6020 Innsbruck, Austria

[2] Sanofi-Aventis, CRVA
13 Quai Jules Guedes, F-94000 Vitry sur Seine, France

It has been established, that flexibility plays a crucial role for a variety of biochemical processes.[1] Molecular Dynamics (MD) computer simulations are a suitable technique to study biomolecular dynamics at atomic resolution.[2] We present a method to derive backbone torsional entropies for various complexes of the KIX domain[3] with the transcription factors MLL and cMyb. From states sampled by MD simulations, we obtain a continuous probability density function of state space by Kernel Density Estimation.[4] Subsequent numerical integration over $S = p(t) \ln p(t)$ directly yields entropy in where p denotes the probability density function of the state vector t.[5] We predict changes in the backbone conformational ensemble upon transcription factor binding and conclude that the stabilization induced by formation of a binary KIX-ligand complex is on the same order of magnitude than required to form a ternary complex.
Based on the PDB structure 2AGH 100 ns MD Simulations for various KIX complexes where obtained using the AMBER force field ff99SB. From these simulations, backbone torsional entropies were calculated. The holo structure shows a significantly higher flexibility, whereas each binary complex, either with MLL or cMyb induces stabilization. This stabilization is on the order of magnitude of the ternary complex.
Therefore we conclude that the cooperative binding effect observed for the KIX domain is caused by a global stabilization of the KIX secondary structure induced by the formation of any binary complex.

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Very Large Scale Semiempirical MO Calculations on SAM-OFETs

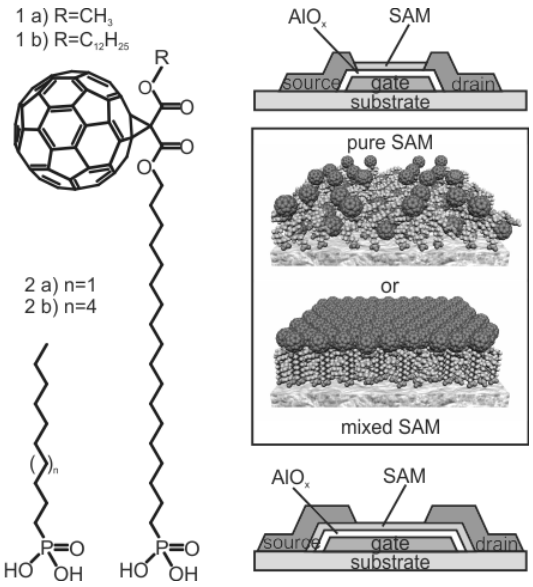
Christof Jäger[†], Matthias Hennemann[†], Marcus Halik[‡] and Timothy Clark[†]

[†]Computer-Chemie-Centrum, Universität Erlangen-Nürnberg, Nägelsbachstraße 25, 91052 Erlangen

[‡]Institut für Werkstoffwissenschaften, Universität Erlangen-Nürnberg, Martensstraße 7, 91058 Erlangen

Self-assembled monolayers (SAMs) consisting of mixtures of phosphonic acids **1** and **2** can potentially act as semiconductors in organic field-effect transistors (OFETs).[1] Atomistic molecular-dynamics simulations have been used to study the structural and dynamic properties of these systems.

With our new program EMPIRE, we are now able to look beyond the structural properties and investigate electronic properties by semiempirical molecular orbital (MO) calculations for tens of thousands of atoms.



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Protein-Protein Docking:

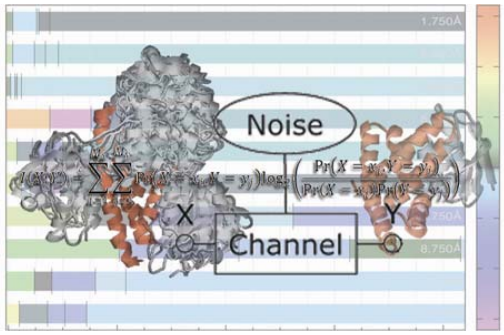
The Scoring Problem Addressed by Concepts of Information Theory

Christophe Jardin[1], Arno Stefani[2], Olaf Othersen[1], Johannes Huber[2], Heinrich Sticht[1]

[1]Institute for Biochemistry and [2]Institute for Information Transmission, Friedrich-Alexander University Erlangen-Nuremberg, Germany

Molecular docking represents a versatile and important computational method for determining the structure of protein-protein complexes. Despite considerable efforts, a general solution to this problem is not yet within reach. One major challenge is the definition of suitable criteria for a scoring function that allows the identification of a good docking solution among many false arrangements.

Our previous work has demonstrated that concepts from information theory can actually be adapted to treat the biological problem of protein-protein docking: the concept of mutual information (MI) can be used to investigate structural features for their information content in protein docking, and the MI-values can be converted into a scoring function [1].



However, these first "proof-of-concepts" also emphasized aspects that have to be improved to result in a robust and widely applicable approach. We present here an extended MI-based approach that relies on a larger dataset and allows a more flexible treatment of structural features in the scoring function.

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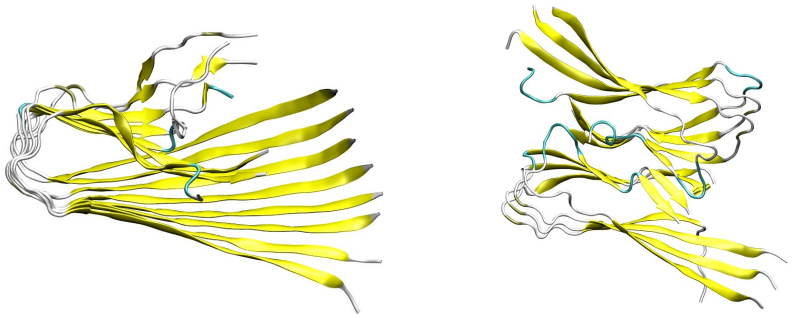
How Quartenary Structure Influences the Conformation of Fibrillar Aβ-Oligomers

Anna Kahler, Anselm H.C. Horn, Heinrich Sticht

Bioinformatik, Institut für Biochemie,
Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany

For quite some time it is known that amyloid-β oligomers play a crucial role in Alzheimer's disease due to their neurotoxic properties but they can also act as seeds for fibril formation[1]. Due to the plasticity of Aβ it is difficult to experimentally characterize oligomeric structures so there exists a dynamically equilibrium of structurally different oligomers and even macroscopic fibrils. It is decisive to know how fibrillar conformation is affected by oligomeric size and formation of single- and double-layered structures.

Thus, all-atom molecular dynamics (MD) simulations in explicit solvent were performed on single- and double-layered oligomers of different size ranging from the tetramer up to the 48-mer; the following figure shows the final MD structure of an Aβ octamer in single-layered (left) and double-layered (right) conformation.



Our simulations indicate that the initial U-shaped topology of each oligomer with its two β-sheets and the connecting turn per monomer is maintained over time in accord with our previous study[2]. However, analyses show that deviations from the starting structure increase significantly with size caused by the twisting of the in-register parallel β-sheets which leads to an overall torsion of the oligomers along the longitudinal growth axis. The twist angle per Aβ monomer is similar for single- and double-layered oligomers (tetramer to hexamer), leading to a better shape compatibility for smaller oligomers suggesting that they can form double-layered fibril structures. In contrast to the double-layered oligomers which generally remain rather stable, large single-layered oligomers show a large twist and global instabilities.

The shape complementarity of the hydrophobic interface in double-layered systems is increasing from octamer to decamer but is not further changed for higher oligomers.

Additionally, we performed binding free energy calculations with MM/GBSA as available with the Amber program suite. The MM/GBSA results are in agreement with the structural findings and show that large single-layered oligomers are rather unstable while the association of a double layer stabilizes large oligomers.

Our results suggest, that fibrillar Aβ oligomers are stable in both single- and double-layered conformation for small oligomers while large single-layered oligomers exhibit structural instabilities. This suggests that the formation of these species is unfavoured as supported by experiment[3]. Double-layered oligomers on the other hand are expected to represent potent seeds for fibril formation because they possess the necessary structural characteristics of fibrils.

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One Interface – Two Perspectives
Exploration of the HIV-1 gp120 – CD4 Interaction

Kristin Kassler[1], Julia Meier[2], Jutta Eichler[2], and Heinrich Sticht[1]

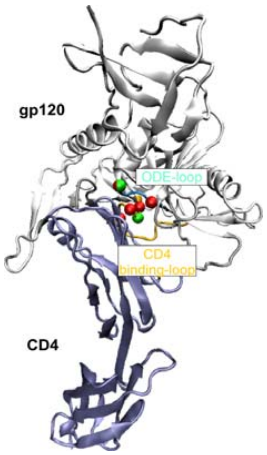
[1]Bioinformatics, Institute of Biochemistry, Friedrich-Alexander-Universität Erlangen-Nürnberg, Fahrstraße 17, 91054 Erlangen, Germany. [2]Department of Medicinal Chemistry, Friedrich-Alexander-Universität Erlangen-Nürnberg, Schuhstrasse 19, 91052 Erlangen, Germany

The initial step of HIV-1 infection is the recognition and the binding of the cellular receptor CD4 by the viral surface protein gp120. A detailed understanding of this interaction from perspective of gp120 or CD4 can help in the rational design of HIV-1 drugs.

In order to explore the CD4 interface mediating the gp120-CD4 interaction, the differences between human and murine CD4 (hCD4 and mCD4) were investigated. Murine CD4 is not bound by HIV-1 gp120 despite a high sequence homology between hCD4 and mCD4. Strikingly, peptides derived from both human and murine CD4 bind with similar affinity and specificity. Molecular modeling indicates that mCD4 protein cannot bind gp120 due to steric clashes, while the larger conformational flexibility of mCD4 peptides allows an interaction. Molecular dynamics simulations reveal that the mCD4-peptide stably interacts with gp120 via an intermolecular β-sheet, while an important salt-bridge formed by a C-terminal lysine is lost. Fixation of the C-terminus by introducing a disulfide bridge between the N- and C-termini of the peptide significantly enhanced the affinity to gp120. [1]

The gp120-part of the interface was inspected by exploring two natural gp120 mutants (termed ALM and EM) with decreased CD4-binding affinity. In molecular dynamics simulations of wild type and mutant gp120-CD4 complexes, essential intermolecular β-sheet contacts are disrupted in the mutant gp120-CD4 complexes while stably maintained by wild type gp120. Particularly, the crucial loop anchor is totally or at least partially lost in ALM and EM, respectively. Mutant glutamates offer an explanation for disruption of those key contacts. Interestingly, though located at different sites in ALM and EM they exert a similar effect.

The authors thank the BioMedTec International Graduate School of Science (BIGSS) and the SFB796 for financial support.



The gp120-CD4 interface. Interacting loops of the CD4-binding side are colored in yellow and cyan. Residues mutated in ALM and EM are visualized as red or green balls, respectively.

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Investigation of Complex Formation between Pyrene and Selected Drug Molecules by Spectroscopic and Semiempirical Methods

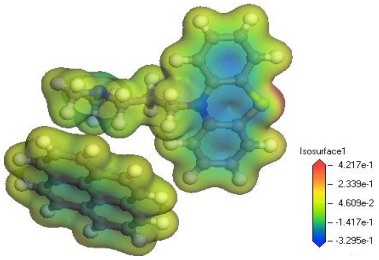
Nilgun Yener[1], Nursel Acar[2]

[1]*Dokuz Eylul University, Department of Biochemistry, Inciralti/Izmir/TURKEY*
[2]*Ege University, Department of Chemistry, 35100 Bornova/Izmir/TURKEY*

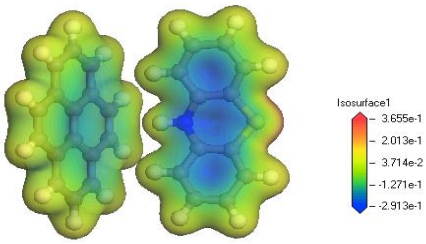
Pyrene and its derivatives are natural or synthetic aromatic hydrocarbons that are found in the environment in large quantities. Because of their amounts in the environment, they could easily enter the metabolism of living organisms. Their π-electronic system allows them to interact with several molecules in metabolism.

Phenothiazine and its derivative promazine are drug molecules especially used as antidepressants. Due to the presence of heteroatoms (especially nitrogen) in their structure, they may interact in many reactions in biological systems.

In this study, possible interactions between pyrene and the drugs phenothiazine and promazine have been investigated in ground and excited states. In addition to experimental methods like UV and fluorescence spectroscopy, semiempirical calculations have also been performed by using the VAMP module [1] as implemented in Materials Studio package [2].



Py-Prom



Py-Pheno

The results indicate that there is no complex formation in the ground state, thus there are no interactions. On the other hand, fluorescence quenching has been observed in the excited state and it has been concluded that these interactions show weak charge/electron transfer processes. Experimental and semiempirical methods used in the study are in qualitative agreement.

This work is supported by TUBITAK Grant No: 108T084 and EBILTEM Grant No: 2009/BIL/007.

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Molecular Docking of Peptides and Small Molecules into TRAF Proteins

Katharina Kopp[1], Iris Antes[1]

[1] *Department of Life Sciences and Center for Integrated Protein Science Munich, Technical University Munich, Emil-Erlenmeyer-Forum 8, D-85354 Freising*

We present molecular docking studies of small and peptidic ligands binding to the TRAF6 and TRAF2 proteins. When a member of the tumor necrosis factor receptor (TNFR) family associates with a tumor necrosis factor (TNF) ligand, TNFR-associated factors (TRAFs) are the first molecules to bind to the activated TNFR. TRAF6 is the only TRAF family member that is known to participate in signal transduction of both the TNFR family and the interleukin-1/Toll-like receptor family. It is important for lymph node organogenesis and for the development and maturation of dendritic cells, mammary glands, skin, and the central nervous system. As TRAF6 plays a major role in the immune response to severe bacterial infection, it was proposed as a suitable target in septic shock with multiple organ failure. We performed molecular docking experiments of TNFR family peptides into TRAF6 protein using DynaDock [1]. Re- and cross-docking experiments of TRAF6 protein-peptide crystal complexes showed that this algorithm is capable of predicting docked conformations of high accuracy. Thus, DynaDock [1] was applied for TRAF6 protein-peptide docking of different TNFR peptide fragments which were experimentally identified as TRAF6 binding sequences. The peptides were modeled by means of the side chain prediction tool IRECS (Side-Chain Prediction by Iterative REduction of Conformational Space) [2].

TRAF2 protein is involved in B and T-cell signalling, inflammatory responses, organogenesis and cell survival. This protein interacts with a wide range of TNFRs like TNFR1, TNFR2, LMP1, CD40, and RANK. It is important for classical and alternative NF-κB activation pathways as well as for MAPK and JNK activation. TRAF2 plays a role as tumor suppressor in B-lymphocytes and therefore in the pathogenesis of chronic lymphatic leukemia. We investigated the binding modes of two peptide fragments of the LMP1 and CD40 proteins known to bind to TRAF2 by DynaDock [2] and studied the potential inhibition of the TRAF2 peptide binding site by small compounds using the docking tool AutoDock [3]. In accordance with ELISA-based assays, we could predict energetically favorable bound conformations for three compounds which specifically interfere with LMP1 binding to the TRAF2 protein.

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Conformational flexibility of small molecules in different solvent environments

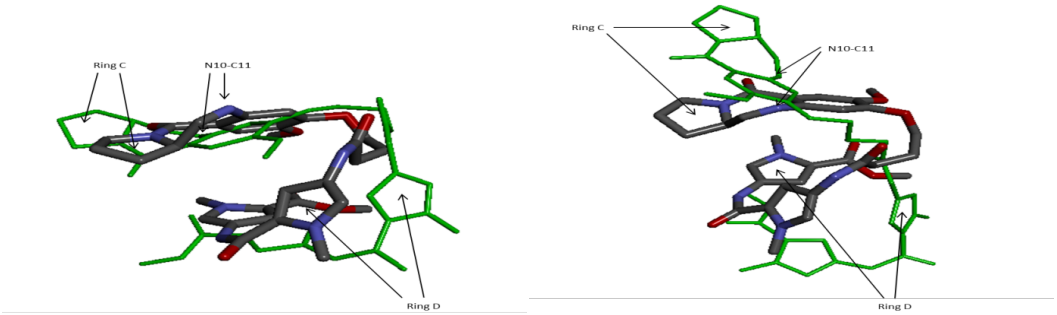
Sara Kramar[1], David E. Thurston[2], Khondaker M. Rahman[2], Mire Zloh[1]

[1]*UCL School of Pharmacy, 29-39 Brunswick Square, London WC1N 1AX*

[2]*Department of Pharmacy, King's College London, 150 Stamford Street, London SE1 9NH*

The pyrrolobenzodiazepines (PBDs) are a family of DNA sequence-selective antitumour agents, the best known member of which is anthramycin [1]. They bind in the minor groove of DNA, forming a covalent bond between the electrophilic N10-C11 imine moiety of the PBD and the N2 amino group of a guanine.

GWL-78 and SJG-136 are examples of PBD monomers and dimers, respectively, and the latter agent is presently in Phase II clinical trials in ovarian cancer and leukaemia. This study involves the use of molecular dynamics simulations to study the effect of different solvent environments on the conformation of GWL-78, SJG-136 and anthramycin. Calculations have been carried out using the Desmond 2.2 software [2] and OPLS_2005 force fields [3] with Maestro 9.2 as the Graphics User Interface [4]. 2000 conformations were obtained during 10 ns of simulations, and these were separated into five clusters. The most frequently observed conformations for each cluster were then compared by calculating RMSD values.



Superposition of the most frequent conformations extracted from molecular dynamics simulations of GWL-78 in two different solvent systems. Thick sticks in CPK colours represent the GWL-78 conformation in explicit water with 100 mM NaCl. The thin green sticks show the conformation of GWL-78 simulated in explicit water with 100 mM NaCl, and with an additional H_3O^+ (left)/OH^- ion (right).

Significant conformational changes of these flexible molecules were observed for different pH and salt concentrations, potentially providing information relating to how these molecules interact with DNA prior to the formation of covalent bonds. Our results suggest the importance of the explicit solvent composition for molecular dynamics studies. Further work is required to evaluate whether similar conformational behaviour is observed using different molecular dynamics software and force fields.

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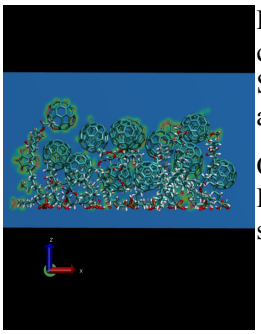
Simulating Selfassembly

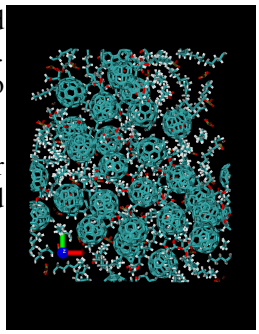
†Andreas Krause, †Christof Jäger, ‡Marcus Halik, †Tim Clark

†Computer-Chemie-Centrum, Universität Erlangen-Nürnberg, Nägelsbachstr. 25 ,91052 Erlangen, Germany.
‡Werkstoffwissenschaften, Universität Erlangen-Nürnberg, Martensstr. 7 ,91058 Erlangen, Germany.



Printable devices would offer a simple and cheap way for synthesis of nanoelectronics. Selfassembly seems to be a comfortable way to achieve this goal.

On this poster we will present Molecular Dynamics simulations of the selfassemled system of phosphonic acids on aluminumoxid.



Structural analysis of different substrate affinity in fungal hexosaminidases

Natallia Kulik[a], Rudiger Ettrich[a], Kristyna Slamova[b], Pavla Bojarova[b], Petr Simon[b], Vladimir Kren[b], Karel Bezouska[c]

[a] *Institute of Nanobiology and Structural Biology of GCRC, Academy of Sciences of the Czech Republic ,Zamek 136, 373 33 Nove Hrady, Czech Republic*

[b] *Institute of Microbiology, Laboratory of Molecular Structure Characterization, Academy of Sciences of the Czech Republic, Videnska 1083, 142 20 Prague 4, Czech Republic*

[c] *Department of Biochemistry, Faculty of Science, Charles University, Albertov 2030, CZ-128 40 Prague 2, Czech Republic*

Beta-N-acetylhexosamnidases (HEX) are glycoside hydrolases from the family 20 (EC 3.2.1.52). They cleave terminal glucose/galactose residue from di-/oligosaccharides by a retaining mechanism. Apart of the ability to cleave hexoses specifically, fungal HEX tolerate a variety of substrate modifications [1-3]. This feature together with the ability to hydrolase the transglycosylation reaction makes these enzymes useful in biotransformation to produce modified carbohydrates with defined structures [2-3].

Despite the high primary structure identity (more than 50 %), enzymes from *A. oryzae*, *P.oxalicum* and *T. flavus* have different affinity to modified substrates [4]. To analyze the underpinning structural differences we built homology models of these enzymes, that share the TIM-barrel catalytic domain with identical active site amino acid residues, involved in substrate binding. However long loops close to the active site of the fungal enzymes differ from human and bacterial structures.

Docking of substrates into the active site of HEXs followed by MD revealed some differences in the dynamical behavior of the loops in the vicinity of the active site. Changes in the enzyme structure bound in the substrate-enzyme complexes let us propose a critical role of some loop residues responsible for different affinity of HEXs to modified substrates. This study demonstrated that substrate affinity of fungal HEX is determined not only by amino acids in direct contact with the substrate, but also regulated by some weaker but still important interactions.

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High throughput re-scoring of docking hit-list using MD Simulation and MM/PBSA method through open source packages

Rashmi Kumari and Andrew M Lynn
School of Computational and Integrative Sciences
Jawaharlal Nehru University

Virtual screening through docking is one of the important computational tools for the identification of the lead molecules. Major drawback of docking methods concerns the application of scoring functions that largely fail to estimate ligand binding energies in reasonable agreement with experiments and docking techniques still lack reliable simulation of the flexibility of both ligands and receptor. Also the presences of water molecules which may play an important role in the complex formation are ignored during docking process. In the recent years, MM/PBSA combined with the molecular dynamics (MD) simulations has emerged as a fast and approximate method for the calculation of binding free energy [1-2]. This approach is employed in the re-scoring of the docked complex to remove false positives obtained from the docking methods [3]. GROMACS is one of the most widely open source MD simulation package but it does not include the implementation of the MM/PBSA method. Also, protein – ligand simulations could be performed through this package using AMBER force field, one of the most widely used force field for proteins. In this work, we implemented MM/PBSA methods through GROMACS and APBS where former was used for the MD simulations and later was used for Poisson-Boltzmann calculation. Variants of PB solvation and SA parameters have been used to compare the results for achieving high correlation between predicted and experimental results. Large data-sets are needed to be validated to show high throughput capability of this implementation and also, there are lot of scope for the optimization of the entire protocol and the method. Therefore, the whole method is implemented using a perl script written in-house and validated on the HIV Protease I with inhibitors that have a broad K_i range. After optimization, good correlation was obtained between calculated relative binding energy and the experimental $logK_i$ values. This optimized method is used to re-score the docked complexes of DHDP (DiHydroDiPicolinate) reductase, a key enzyme of Diaminopimelate pathway of *M. tuberculosis*. Docked complexes of some other known *M. tuberculosis* target are also re-scored which clearly discriminate between active and in-active compounds from docking hit-list. Re-scoring of top ranking inhibitors from docking experiments by MM/PBSA can be used as a filter to more accurately select molecules for experimental validation.

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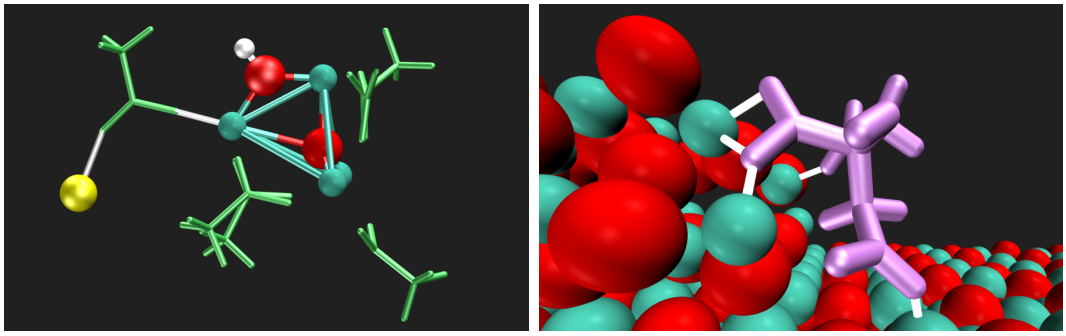
Molecular Modeling of ZnO Nanoparticle Nucleation: from pre-nucleation clusters to functionalized particles

Theodor Milek, Patrick Duchstein, Dirk Zahn

Computer Chemistry Center, Friedrich-Alexander University Erlangen-Nürnberg



We demonstrate the molecular modeling of ion cluster formation, ripening reactions, nucleation and growth of zinc oxide nanomaterials. Furthermore molecular mechanisms of growth control, stabilization and functionalization by surfactants are elaborated. This is aiming at a fundamental understanding needed for the guided formation of nanostructures with tailor-made properties. Our simulation scheme (Kawska-Zahn method [1,2]) allows to explore the evolution of a forming aggregate ion-by-ion. In doing so, the method combines Molecular Dynamics, Monte-Carlo and quantum/classical modeling to tackle the time/length-scale problem inherent to crystallization from solution [3]. Mechanistic insights are presented for the very initial steps of pre-nucleation cluster formation of Zn^{2+},OH^- and $Zn_4O(Ac)_6$ precursors (figure 1). Moreover, cluster ripening and nucleation of $ZnO/Zn(OH)_2$ core/shell nanoparticles are shown [4]. Subsequent stages of particle growth are explored for various crystal surfaces, along with the association of surfactants (figure 2). Based on such detailed information, scale-up models are formulated and applied for the investigation of nanoparticle solvation and stabilization in colloidal solutions.

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Hydration of small hydrophobic objects: The effects of an electric field

Zoran Miličević[1,2], David M. Smith[3,4], Ana-Sunčana Smith[1,2]

[1]*Institute for Theoretical Physics, University Erlangen-Nürnberg, Staudtstraße 7, 91058 Erlangen, GERMANY*

[2]*Excellence Cluster: Engineering of Advanced Materials, University of Erlangen-Nürnberg, Nägelsbachstraße 49b, 91052 Erlangen, GERMANY*

[3]*Ruđer Bošković Institute, Bijenička 54, 10000 Zagreb, CROATIA*

[4]*Computer-Chemie-Centrum, University Erlangen-Nürnberg, Nägelsbachstraße 25, 91052 Erlangen, GERMANY*

It is well established that the hydrophobicity of an interface, droplet or a particle can be modulated by an external electric field. However, the electric field effects on water structure around a hydrophobic object are not understood to a satisfactorily level. We study the organization of water around a Lennard-Jones particle and an oil droplet in the presence and absence of a static electric field. We perform extensive MD simulations using the GROMACS software package and the SPC/E model of water. The structure of water is analyzed by means of the total solute-solvent correlation function, which includes the orientational degrees of freedom of the solvent. We find that a structure of water arises from the competition between optimal orientation of water with respect to the field and with respect to the solute, yielding an asymmetric distribution of solvent charges around the particle. The particle thus appears a small dipole. Another consequence of the field are very long range solvent-solute effective interactions. We furthermore evaluate the force correlations as a function of time and find them sensitive to the treatment of van der Waals interactions in simulations, which may explain some discrepancies in the observed mobilities of small droplets in simulations reported previously in the literature.

Computational analysis of ion distributions in K^+ channels

Florian Mrugalla, Leonhard M. Henkes, Stefan M. Kast

Physikalische Chemie III, TU Dortmund, D-44227, Germany

Classical molecular dynamics (MD) simulations are a computational tool for modeling structure, dynamics, and thermodynamics of nanometer-sized biomolecular systems on time scales of nanoseconds up to microseconds. Due to its atomic resolution, MD simulations are used to reveal principles of biochemical mechanisms and interactions which are difficult to be obtained by experimental techniques [1-3]. Ion translocation in membrane-bound potassium channels is, however, a comparatively slow process which requires alternative theoretical approaches in order to understand structure-function correlates.

Here we present a modeling workflow which facilitates the rapid screening of point mutation effects on ion concentration profiles along channel protein pores. We use the viral potassium channel Kcv as a suitable model system since it represents an extremely short, yet fully functional structural K^+ channel motif [4]. The basis structure for virtual mutation scanning is taken from a homology model of the wild-type channel that has been extensively refined by fully atomistic MD simulations of the protein in a solvated, explicit lipid bilayer system. Starting with structures obtained from these simulations, the workflow consists of a sequence of homology modeling steps for introducing the point mutations and subsequent 3D-RISM ("reference interaction site model") integral equation calculations [5]. The latter provide data about equilibrium ion distributions within the channel pore that yield concentration profiles upon radial integration [6]. Analysis of the integrated concentration profiles as a function of the mutation state yields important information to correlate apparent experimental conductance data with the amino acid sequence. These correlations can be used to design functional mutant channels with desired properties.

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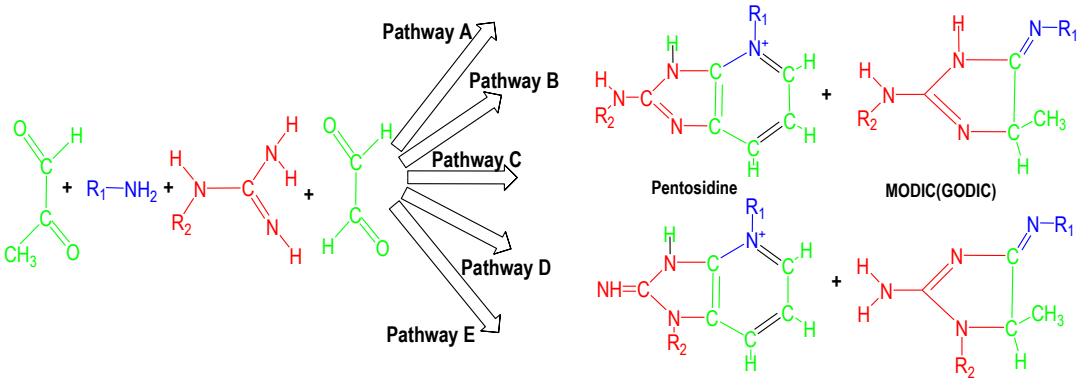
Computational Studies on Cross-Linking Process: Evidence for Multiple-Novel Reaction Pathways in Pentosidine, MODIC and GODIC Formation

Rasoul Nasiri[1,2]

[1]*Department of Chemistry, Faculty of Sciences, Shahid Beheshti University, Evin, 19839-63113, Tehran, Iran*
[2]*Institution: Département de Chimie Moléculaire, Chimie Théorique, UMR-5250, Université Joseph Fourier, BP53, 38041, Grenoble Codex9, France*

Cross-linking in proteins by α, β-dicarbonyl compounds is one of the most damaging consequences of reactive carbonyl species *in vivo* and in foodstuffs. In this study, cross-linking of glyoxal and methyl glyoxal with lysine and arginine residues were investigated computationally using density functional theory and the wB97XD dispersion-corrected functional. Five pathways, **A**-**E**, for pentosidine [1], methyl glyoxal-derived imidazolium cross-linking (MODIC) [2] and glyoxal-derived imidazolium cross-linking (GODIC) [2] have been characterized. In pathways A and B, the reaction proceeds via formation of the Schiff base, aldimine, followed by addition of arginine for MODIC(GODIC) formation and also glyoxal (GO) in third stage of process for pentosidine. By contrast, in pathways C-E, direct addition of arginine to the dicarbonyl compounds occurs first, leading to a dihydroxyimidazolidine intermediate, which then reacts with lysine after dehydration and proton transfer reactions, resulting in the formation of MODIC (GODIC) and then reacts with GO to give pentosidine. The finding reveal that pathways **A**, **C** and **E** are competitive whereas reactions via pathways **B** and **D** are much less favorable. Inclusion of up to five explicit water molecules in the proton transfer and dehydration steps is found to lower the free energy barriers in the feasible pathways by about 5–20 kcal/mol.



Our calculations show that the reaction process for pentosidine is highly exergonic, and comparison of the mechanisms of MODIC and GODIC shows that the activation barriers are lower for GODIC than MODIC in agreement with experimental observations. These results served to underline the potentially important role that α-oxoaldehydes play as precursors upon the aforementioned cross-links formation and provided new insights on how formation of cross-links by reactive carbonyl species occurs and should be useful in better understanding cross-linking processes in the complex field of glycation.

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Guiding Protein-Ligand Docking with Different Experimental NMR-Data

Ionut Onila[1*], Tim ten Brink[1], Adam Mazur[2], Oliver Korb[1], Heiko M. Möller[1], Christian Griesinger[2], Teresa Carlomagno[3], Thomas E. Exner[1, 4]

1 Department of Chemistry, University Konstanz, 78457 Konstanz, Germany

** ionut.onila@uni-konstanz.de*

2 Department of NMR-Based Structural Biology, MPIbpc, 37077 Göttingen, Germany

3 Structural and Computational Biology Unit, EMBL, 69117 Heidelberg, Germany

4 Zukunftskolleg, University Konstanz, 78457 Konstanz, Germany

Today's scoring functions are one of the main reasons that state-of-the-art protein-ligand dockings fail in about 20 % to 40 % of the targets due to the sometimes severe approximations they make. However, these approximations are necessary for performance reasons. One possibility to overcome these problems is the inclusion of additional, preferably experimental information in the docking process. Especially ligand-based NMR experiments that are far less demanding than the solution of the whole complex structure are helpful.

Here we present the inclusion of three different types of NMR-data into the ChemPLP [1] scoring function of our docking tool PLANTS [2]. First, STD and intra-ligand trNOE spectra were used to obtain distant constraints between ligand and protein atoms. This approach proved beneficial for the docking of larger peptide ligands i. e. the epitope of MUC-1 glycoprotein to the SM3 antibody [3].

In the second part the usefulness of INPHARMA data [4, 5] is shown by combining a score, evaluating the agreement between simulated and measured INPHARMA spectra, with the PLANTS ChemPLP scoring function. First results from rescoring after local optimization of the poses and full docking experiments are shown.

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Assessing QM methods for calculating small energy barriers in enantioselective organocatalysis

Sebastian Schenker[a], Timothy Clark[a,b]

(a) Computer-Chemie-Centrum der Friedrich-Alexander-Universität Erlangen-Nürnberg, Nägelsbachstrasse 25, 91052 Erlangen, Germany

(b) Centre for Molecular Design, University of Portsmouth, Mercantile House, Portsmouth PO1 2EG, United Kingdom

In the field of enantioselective catalysis, DFT and post-HF quantum-mechanical methods were shown to perform well for the calculation of properties of particular interest. A key feature, which can be described by calculations, better than by any other mean is the energy and geometry of transition states. Accurate data on transition states allows the prediction of (enantio-)selectivity of reactions, and thus can play an important role in the development of improved catalysts.

A particular challenge in the case of enantioselective organocatalytic reactions is the low energy difference of the transition states, leading to the different product enantio- and diastereomers. In typical kinetically controlled reactions, energy barrier differences of 1 kcal/mol or lower can rule over the selectivity of a reaction. For the DFT methods typically used to optimize the reaction systems of interest, it is not known what accuracy they achieve, especially for large molecules.

In this study we present a systematic assessment of commonly employed DFT and post-HF methods, in order to come up with a recipe on how to calculate to predict enantiomer distributions.

We are able to show that modern dispersion corrected DFT method allow to calculate small energy differences with the necessary accuracy.

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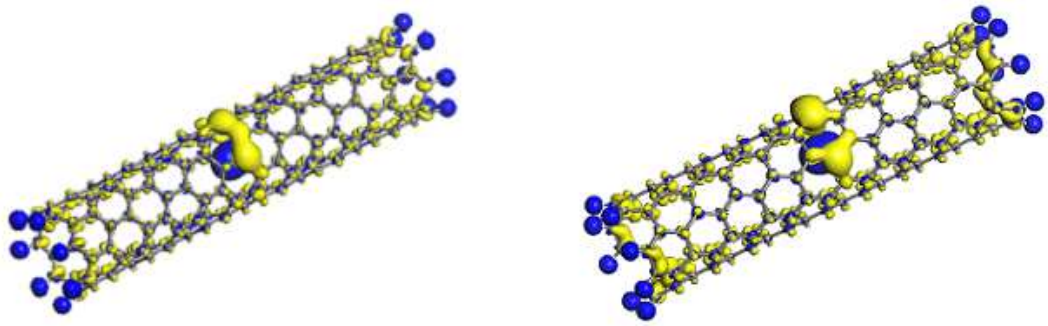
Charge transfer in Fe-intercalated SWCNT

Sharapa D.I., Dral P.O., Shubina T.E., Clark T.

Computer-Chemistry-Center, University Erlangen-Nuremberg



Metal-intercalated nanotubes are perspective materials for nanoelectronics. Up to now, only calculations for nanotubes with alkali metal inclusions were performed. [1, 2, 3] We executed computational simulations of single-wall carbon nanotubes (SWCNT) intercalated by an iron atom. Results of our calculation show, that there is a charge transfer between the iron atom and the nanotube. The nanotube can donate or accept electrons from the iron atom depending on the charge of the whole system. Irrespective to the one of the whole system (taking into account the possible oxidation states of the iron atom, the charges 0, +1, +2, +3 were considered) the charge of the iron atom was in the range of +0.88…+1.08.

No sensitive charge delocalization was found. The negative charge was mainly localized on the two carbon atoms, which are closed to the metal ion. The simulations performed for H-terminated nanotubes showed that the carbon part of the nanotubes was negatively charged even when the charge of the whole system reached +3 (charge of whole NT ≈ +2). So, there seem to be a charge transfer from the hydrogen atoms to the carbon part of the nanotubes.

Similiar results of charge transfer were found for metallic (4.4) and semiconducting (7.0) nanotubes.

Investigations with other metals, nanotubes of other diameters and other terminated atoms are in process.

All calculations were performed by using VAMP, UHF, AM1*.

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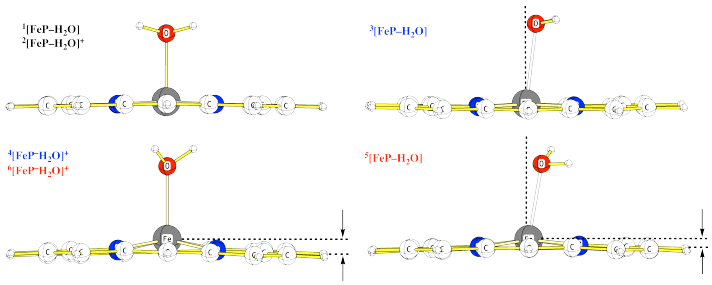
Binding of small molecules to Metalloporphyrins

Tatyana E. Shubina

Computer-Chemie-Centrum and Interdisciplinary Center for Molecular Materials, Friedrich-Alexander-Universität Erlangen-Nürnberg

The investigation of the binding of small ligands has provided valuable insights into the relations among structure, dynamics, and function of proteins. The interaction of small molecules such as O_2, NO and CO with hemoglobin (Hb) and myoglobin (Mb) play a central role in living cells and is important for the respiration and regulation processes. For example, heme proteins (which contain iron porphyrins) serve many roles, such as O_2 storage and transport (myoglobin and hemoglobin), electron transport (cytochromes b and c), and O_2 activation and utilization (cytochrome P450 and cytochrome oxidase). Chlorophylls (which have a central magnesium ion) and pheophytins (which are metal free) are found in the photosynthetic apparatus of plants and bacteria, whereas vitamin B12 (which contains cobalt) is present in bacteria and animals.

It is thus very important and challenging to understand and predict/reproduce binding energies of these ligands reliably by quantum-chemical calculations. Additionally, the accuracy of such calculations serves as a good benchmark for the modeling of similar bioinorganic processes. Despite the increasing number of theoretical studies on this topic, the results still remain inconsistent and somewhat puzzling.



We present our computational studies involving some of the metalloporphyrins (Fe(II)P, Co(II), and others). The present investigation also explores the accuracy of several DFT methods. The geometries of MP–XO complexes and XO binding energy were found to depend very strongly on the functional and basis set used. In many cases, model systems should be described at least with a triple-ξ quality basis set.

Although relatively expensive and difficult to use, CASSCF/ CASPT2 methods often provide meaningful chemical descriptions. This, coupled with the continuing increase in computational power, suggests that the study of properties and reactions involving metalloporphyrins should be pursued with these accurate methods.

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In silico characterization of the motorsubunit of the *e.coli.* restriction-modification system EcoR1241

Dhiraj Sinha, Morteza Khabiri, David Reha and Rudiger Ettrich
Institute of Nanobiology and Structural Biology of GCRC, Academy of Sciences of the Czech Republic, and Faculty of Sciences, University of South Bohemia, Nove Hrady, Cz-37333, Czech Republic

Type1 restriction modification system are intriguing multifunctional multisubunit molecular motors that can catalyze both restriction and modification activity .The type 1 RM enzymes binds to its target sequence and its activity as an endonuclease or methyltransferase is determined by the methylation state of the target sequence. If the target sequence is unmodified, the enzyme while bound to its target site is believed to translocate or pull the DNA towards itself simultaneously in both directions in an ATP dependent manner.

The crystal structure of the motor subunit R has been determined by our group but the molecular mechanism by which these enzymes translocate and cleave the DNA is not fully understood.
Our current research effort focuses on full-length three-dimensional structures of the R-subunit, utilizing computational and bioinformatics methods. Optimization of intersubunit contacts is performed by energy minimization followed by molecular dynamics simulations in solution at 300K. The dynamic behavior of WT and mutant holo and apo systems is explored by molecular dynamics simulation in GROMACS using the AMBER99SB force field. Conformational changes connected to coupling of translocation and endonuclease activity are observed and QM/MM methods are applied to calculate binding energies.

Acknowledgements: ***We gratefully acknowledge support from the Czech Science Foundation (project number GACR P207/12/2323), and the Grant Agency of the University of South Bohemia (grant no. 170/2010/P). Some computations were performed in MetaCentrum SuperComputer facility.***

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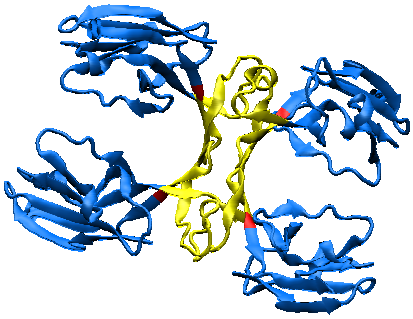
Tetramer of Chimeric Aβ-IgNARs as a Model for Amyloid-β Oligomer Formation in Alzheimer's Disease

Eileen Socher, Anselm H. C. Horn, Heinrich Sticht

Bioinformatik, Institut für Biochemie,
Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany

Alzheimer's disease (AD) is the most common neurodegenerative disorder: an estimated 30 million people worldwide are affected with AD.[1] AD can be diagnosed post mortem for instance by the increased presence of amyloid plaques in the brain. Due to the fact that amyloid plaques are extracellular deposits, which are primarily composed of insoluble Aβ fibrils, it is widely believed that amyloid-β peptides (Aβ) have a causal role in AD.

In recent studies, the small Aβ oligomers were in the centre of interest because they showed a higher cytotoxicity than insoluble Aβ fibrils.[2] However, structural information on these Aβ species is restricted, because of their noncrystalline and unstable nature. Recently, Streltsov et al. described a crystal structure of the amyloidogenic residues 18-41 of the Aβ peptide genetically engineered into the CDR3 loop region of a shark Ig new antigen receptor (IgNAR) single variable domain antibody.[3] The chimeric proteins build a homo-tetramer as a quaternary structure through interactions mediated by the inserted Aβ peptide component and the authors suggested this tetrameric structure as a potential model system for nonfibrillar oligomer formation in AD.[3]



The objective of our study is to investigate the stability and dynamics in solution of the crystallised chimeric structure (PDB ID code 3MOQ) and the inserted amyloid-β p3 fragment by means of molecular dynamics simulations.

For our investigations, we not only examined the tetrameric structure itself, we also split the structure into different dimers and all possible monomers. Our first results show a stable dynamical behaviour of the structures in explicit solvent and no changes of the protein fold. Furthermore, we observed that every single subunit of the tetrameric structure is conformationally more stable than the whole dimer or tetramer, because the individual subunits exhibit large hinge motions with respect to each other. Additionally, we noticed the highest structural flexibility in the region of the Aβ peptide component and found some crystal packing effects of the published structure.

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Adsorption of Alanine and Phenylalanine on MFI-type Zeolite: DFT Calculations and Experimental Results

Kai Stueckenschneider[1]*, Achim Zielesny[2], Gerhard Schembecker[1]

[1]*Department of Biochemical and Chemical Engineering, TU Dortmund, Dortmund, 44227, Germany*

[2]*Institute for Bioinformatics and Chemoinformatics, University of Applied Sciences Gelsenkirchen, Recklinghausen, 45665, Germany*

**Kai.Stueckenschneider@bci.tu-dortmund.de*

Adsorption is a common unit operation in separation and purification of biotechnological products where chromatography steps can make up more than half the amount of the total purification costs. Quantum mechanics (QM) calculations may help to facilitate process design in a more cost efficient manner by predicting binding patterns to select adequate adsorbents. As a first step to investigate adsorption characteristics of biotechnological products such as proteins and peptides we want to explore the interaction of amino acids with zeolite surfaces, as potential of amino acid separation using zeolites was shown.

In this work the interaction of MFI-type zeolite MFI-27 (Al/Si=13) with Alanine and Phenylalanine is investigated by experimental adsorption isotherms accompanied by Isothermal Titration Calorimetry (ITC) at different pH values. The results are compared to corresponding QM data. For the QM calculations a T3-cluster is used as MFI-27 surface model. In order to model different pH values Alanine and Phenylalanine are applied in their protonated, zwitterionic and deprotonated state. Geometry optimisations and frequency analysis of all molecular structures are performed with Density Functional Theory (DFT) using the B3LYP functional. Calculated complex energies are corrected for BSSE and ZPE.

Obtained adsorption isotherms follow simple electrostatic considerations: high adsorption of Alanine and Phenylalanine on MFI-27 takes place at low pH values (near the pKa of the amino acids). Less adsorption occurs with an increased pH equalling the amino acids' isoelectric points. At the pH of the amico acids' pKb values adsorption is no longer observed.

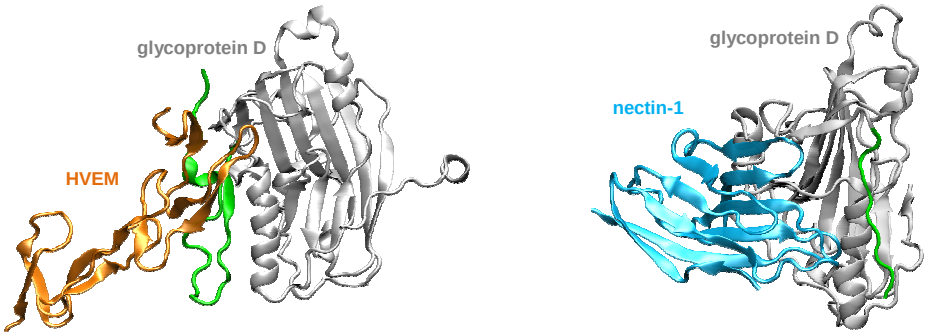
These trends can be qualitatively correlated with the corresponding QM calculations. High binding energies are calculated for the protonated amino acids. Zwitterionic states lead to lower binding energies. The deprotonated amino acids do not show any binding affinity to MFI-27. Results from accompanying ITC measurements provide enthalpies of adsorption, which further help drawing assumptions on the binding characteristics of amino acids on MFI-27.

Investigating the Effect of Q27 Mutation on Receptor-binding Properties of Glycoprotein D in Herpes Simplex Virus-1

Joachim D. Stump, Pia Rücker, Heinrich Sticht

Bioinformatik, Institut für Biochemie,
Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany

Many studies have identified herpes simplex virus-1 (HSV-1) as a possible candidate for anti-cancer therapy. The goal is to reprogram the virus in such a way that it specifically infects cancer cells and lyzes them. However, to accomplish this task, it is necessary to fully understand the fusion of the virus with its target cell, which is fundamental for infection. To infect the cell, HSV-1 makes use of an entry-fusion system consisting of four glycoproteins: gD, gB, gH and gL. gD plays a pivotal role initiating the fusion mechanism by binding to membrane proteins of the target cell (HVEM and nectin-1). Experiments have shown that Q27A mutation in gD leads to an inability to bind HVEM, therefore abolishing HVEM mediated cell entry. On the other hand, the mutation increases binding affinity of gD to nectin-1, facilitating the viral cell entry [1]. Our goal was to investigate the important role of Q27 in different steps of the binding mechanism and understand the ambivalent effect of mutation.



In our study all molecular dynamics simulations were performed with AMBER/parm99SB force field in explicit solvent. For energetic analyses and in silico alanine scan MM_GBSA (IGB Model 2) implemented in AMBER 11 was used. We simulated gD in four different states: bound to HVEM [3] and nectin-1 [4], unbound with the resolved C-terminal region [2], and unbound with the N-terminal hairpin-like loop. Both unbound states were simulated as wild-type (WT) and Q27A mutant.

Our results show that Q27A mutation affects each investigated step of the binding mechanism differently. Therefore, we provide a first comprehensive insight into the ambivalent effect of Q27A mutation and point out the important role of this amino acid for multiple steps of the binding mechanism.

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Pharmacophore Modeling of Cyclooxygenase-2 in LigandScout and Discovery Studio – A comparison

Veronika Temml[1], Zsofia Kutil[2], Premysl Landa[2], Daniela Schuster[1]

[1]Computer-Aided Molecular Design Group, Institute of Pharmacy / Pharmaceutical Chemistry and Center for Molecular Biosciences Innsbruck (CMBI), Innrain 80/82, 6020 Innsbruck, Austria, [2]Laboratory of Plant Biotechnologies, Institute of Experimental Botany AS CR, v.v.i., 165 02 Prague 6 - Lysolaje, Czech Republic.

In structure-based pharmacophore modeling, interaction patterns between a small active molecule and a target protein are translated into a three dimensional array of chemical features (e. g. hydrogen bond (HB) donor, HB acceptor, lipophilic, ionic, aromatic). This pharmacophore can then be used to select other molecules from virtual compound libraries that could show similar activity (virtual screening). Several software packages for this kind of modeling are available. DiscoveryStudio (DS), formerly Catalyst, is one of the longest established software packages for pharmacophore-based virtual screening, while LigandScout (LS), where a screening function became newly available in the 3.0 version, is one of the more recently developed programs. Both programs use different screening algorithms, so it is interesting to compare their performance in terms of predictive power. In this case study the two software packages are evaluated on the target cyclooxygenase (COX) 2, including the biological testing of predicted virtual hits from both programs.

COX 1 and 2 are important and very well examined targets in inflammation. A wide variety of active compounds and crystal structures are available. In this study pharmacophore modeling for COX 2 from a previous study [1] with the software DS [2] was compared to newly generated pharmacophore models generated with the software package LigandScout 3.0 [3].

Two models (one from each program) based on the protein databank entry 6COX were employed to screen commercially available substance libraries in the respective programs. The 10 top ranked hits (by geometrical fit value) for each model, respectively, were biologically tested in a cell-free enzymatic assay [4]. Both models retrieved five biologically active hits, respectively, of which two found by LS were highly active, one in the nanomolar range.

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Fragment-based Optimization of Large System Using Quantum Mechanics

Matthias Trautwein, Thomas E. Exner

Universität Konstanz, Theoretische chemische Dynamik

The calculation of properties of proteins is essential for the understanding of biochemical processes. Quantum mechanics allow calculations with very high accuracy, but they scale in the third or higher power with the size of the system. Thus, today it is not possible to calculate large molecules like proteins using standard methods. A solution to this problem are fragment-based approaches. One of these, on which this work is based, is the adjustable density matrix assembler (ADMA) [1-4]. ADMA divides a macromolecule into fragments of only 5-10 atoms surrounded by additional regions (surroundings) to include short-ranged interactions up to 3 Å to 12 Å depending on the desired accuracy. By combining the results from each separately performed fragment calculation, the electron density matrix, the forces acting on each atom and the total energy can be obtained. This information can now be used for the energy optimization of large molecules by interfacing ADMA with DL-FIND [5], a library of optimization procedures especially developed for quantum-mechanical calculations.

An interesting application of this new method is to study influences of structural changes on calculated NMR chemical shifts. The Trp-cage miniprotein is used here as an examples. In earlier work [6] it has been shown, that calculated NMR chemical shifts for a tyrosine side chain show larger deviations from the experiment than nuclei from any other amino acid. To analyze if these deviations result from an incorrect orientation of this side chain, it was energetically optimized keeping the remaining protein fixed and the NMR chemical shift calculations were rerun on these optimized structures.

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Refinement of pharmacophore models for inhibition of 11β-hydroxysteroid dehydrogenases, regulators of intracellular glucocorticoid concentrations

Vuorinen A[1], Fürstenberger C[2], Odermatt A[2], Schuster D[1]

[1]Computer-Aided Molecular Design Group and Center for Molecular Biosciences Innsbruck, Institute of Pharmacy / Pharmaceutical Chemistry, University of Innsbruck, Innrain 80/82, 6020 Innsbruck, Austria

[2]Division of Molecular and Systems Toxicology, Department of Pharmaceutical Sciences, University of Basel, Klingelbergstr. 50, 4056 Basel, Switzerland

11β-Hydroxysteroid dehydrogenases (11β-HSDs) regulate the local concentrations of cortisone and cortisol in human tissues: 11β-HSD1 converts the inactive cortisone to active cortisol and 11β-HSD2 catalyzes the opposite reaction. [1] Selective 11β-HSD1 inhibitors could be used in the treatment of metabolic syndrome and type 2 diabetes, while inhibition of 11β-HSD2 causes hypokalemia and hypertension. [2-3]. We have previously reported pharmacophore models for 11β-HSD inhibition, which are used for virtual screening, drug discovery and toxicological studies. [4-5] Since new 11β-HSD inhibitors are constantly reported, it is important to regularly re-evaluate the performance of the models to confirm good model quality. For the model refinement purposes, all our 11β-HSD models were employed for virtual screening of following databases: Innhouse (own development), Specs (www.specs.net), Maybridge (www.maybridge.com), DrugBank (www.drugbank.ca), Endocrine disrupting chemical library [6] and DIOS [7]. From these screenings, 43 compounds, including endocrine disruptors, natural products and currently used drugs were tested *in vitro* for their 11β-HSD activity. The results of the enzyme activity tests were used for refining the models: all the compounds were fitted to the models and several model refinement steps were taken to increase the model performance. During this study we have discovered new 11β-HSD inhibitors and optimized our 11β-HSD pharmacophore models.

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Prolyl-hydroxylase domain containing protein 2: Structural insight from MD Simulations

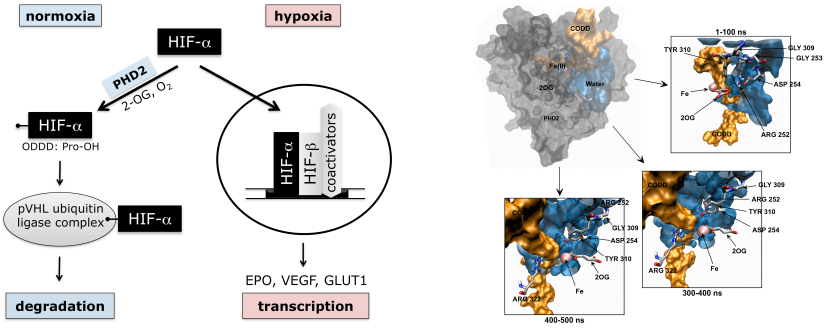
Christian R. Wick,[a] Harald Lanig,[a] Christof Jäger,[a] Nicolai Burzlaff,[b] and Timothy Clark[a,c]

[a] Department of Chemistry and Pharmacy, Computer-Chemie-Centrum, FAU Erlangen-Nürnberg, Nägelsbachstraße 25, 91052 Erlangen

[b] Department of Chemistry and Pharmacy, Institute of Inorganic Chemistry, FAU Erlangen-Nürnberg, Egerlandstraße 1, 91058 Erlangen

Prolyl-hydroxylase domain containing protein 2 (PHD2) is an iron(II), oxygen and 2-oxoglutarate (2OG) dependent dioxygenase that catalyses the hydroxylation of two proline residues (oxygen dependent degradation domains, ODDD) of the α-subunit of hypoxia-inducible factor (HIF-1α), one part of an α,β heterodimeric transcription factor.[1] Hydroxylation at one ODDD triggers recognition by the Von Hippel-Lindau tumor suppressor (pVHL) protein and leads to degradation of HIF-1α via the proteasome. In situations with low oxygen availability (hypoxia), HIF-1α levels increase in the cytoplasm and the transcription factor can translocate into the nucleus, where it up-regulates the transcription of genes that enable mammalian cells to adapt to hypoxia (e.g. EPO, VEGF, GLUT1).[2]

We describe computational studies of the mode of action of PHD2. Long-term Molecular Dynamics (MD) Simulations were performed to investigate the rigidity of the crystallographically observed conformations of PHD2 in solution. Furthermore we describe the influence of the C-terminal ODDD on the overall behavior of the protein, including the effect of the natural ligand 2-oxoglutarate and an isoquinoline inhibitor.



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Development of a Fluctuating Charge Model for Transition Metal Complexes

Peter Comba, Bodo Martin and Avik Sanyal

Anorganisch-Chemisches Institüt, Universität Heidelberg, Germany

The concept of partial atomic charges is fundamental for the accurate description of molecules with Molecular Mechanics. This is because, a significant part of non-bonded interactions between polar species (atoms or atom groups) is electrostatic. Traditionally, force fields assign fixed partial charges to specific sites within a molecule and allow them to interact via a Coulomb-type interaction. This method fails for systems where polarization effects are important. One method of treating polarization that has found widespread applications in various chemical and biological systems is the geometry-dependent fluctuating charge model[1,2]. While variable charge schemes are available for organic and biological force fields, our aim is to develop a method that can be used with comparable accuracy for transition metals as well. Such a scheme for calculation of geometry-dependent charges is presented here. In this method the total electrostatic energy of a molecule is expressed as a function of partial charges as:

$$E(Q_1..Q_N) = \sum_{i=1}^{N}\left(E_i(0) + \left(\frac{\delta E}{\delta Q}\right)_{Q_i} Q_i + \frac{1}{2}\left(\frac{\delta^2 E}{\delta Q^2}\right)_{Q_i} Q_i^2 \right) + \sum_{i=1}^{N}\sum_{j<i} Q_i Q_j D_{ij}$$

Our model contains two parameters per atom type. To test the validity of the scheme we have developed a small reference set of organic molecules containing common elements and optimized the model parameters by fitting to DFT-based charges. This new fluctuating charge force field is then used to calculate observables, like dipole moments, of various organic molecules. Comparison with experimental and Quantum Chemical dipole moments show close correlation and similar trends. We are currently in the process of incorporating effects arising due to variable spin states of transition metal ions in this model. This fast yet accurate charge scheme will be part of the new version of our Molecular Mechanics program Momec3[3].

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