MOLECULAR MODELLING WORKSHOP 2013

Computer-Chemie-Centrum
Nägelsbachstr. 25
91052 Erlangen
Germany

Monday, February, 25th -Wednesday, February 27th 2013

Once again, we in CCC are happy to welcome you to the Molecular Modelling Workshop 2013. This year, it is the 27th Molecular Modelling Workshop and the eleventh time it was hosted by the University of Erlangen-Nuremberg. The research group of Prof. Tim Clark at the CCC will be responsible for the technical organization. Dr. Stefan Güssregen, Sanofi-Aventis Deutschland GmbH, will be responsible for the scientific organization.

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

Scientific program

Dr. Stefan Güssregen

Sanofi-Aventis Deutschland GmbH
R&D LGCR/Struct., Design &
Informatics FF

Industriepark Hoechst
65926 Frankfurt am Main

Tel: +49 (0)69 305 26616
Fax: +49 (0)69 305 942 333

Stefan.Guessregen@sanofi.com

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 27th Molecular Modelling Workshop (February, 25th - 27th) 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):

PROF. JAMSHED ANWAR

Department of Chemistry
Lancaster University

DR. HANS MATTER

R&D LGCR/Structure, Design & Informatics
Sanofi, Frankfurt am Main

PROF. DR. CARSTEN SCHMUCK

Department of Organic Chemistry
University Duisburg-Essen

SUSAN B. SINNOT PH.D.

Department of Materials Science and Engineering
University of Florida

AWARDS

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

Winner

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

2nd Winner

up to 200 Euro travel expenses reimbursement

3rd Winner

up to 100 Euro travel expenses reimbursement

Only undergraduate and graduate research students qualify for the poster and lecture awards. A Web Award for WWW-based scientific applications in the field of molecular modelling will not be awarded this year.

MGMS-DS E.V. ANNUAL MEETING

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

FEES

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

PROF. JAMSHED ANWAR

Professor Anwar has an appointment in Computational Chemistry at the Lancaster University. He studied Pharmacy in London and wrote his PhD thesis in Chemical Physics/Crystallography. Afterwards he held a chair in Computational Pharamceutical Sciences at the University of Bradford. Before he joined academia he spent some time in the pharmaceutical industry.

Now, Professor Anwars reasearch area deals with the fundamental understanding of organic molecular assemblies by using computer modelling and simulation. He is interested in self assembly, phase transformations and interactions between assembled structures, and how assembled structures can be perturbed or dissolved. Crystal nucleation and growth, nanocrystals, phase transformations in crystals are investigated. Further, drug delivery systems such as nanoemulsions and particles and their interaction with biological membranes are a field of his interest.

DR. HANS MATTER

Hans Matter is currently working as a senior scientist in the computer-aided drug design group of Sanofi-Aventis in Frankfurt / Germany. He joined this group at former Hoechst Marion Roussel in 1996. He is involved in structure- and ligand based drug design, QSAR and ADMET modeling to support interdisciplinary project teams in several therapeutic areas. He completed his academic studies in 1992 at the Technical University of Munich, Germany, in the group of Prof. Horst Kessler, where he was working on conformational analyses of bioactive peptides and glycopeptides using NMR spectroscopy and molecular modeling. Subsequently he joined Tripos, a company focused on software development, and compound libraries for drug discovery programs, where he worked a senior scientist in Munich / Germany.

PROF. DR. CARSTEN SCHMUCK

Professor Schmuck holds a chair for Organic Chemistry at the "Universität Duisburg-Essen". He studied Chemistry at the "Ruhr-Universität Bochum" and also wrote his PhD thesis there. For his postdoctoral research he worked at the Columbia University, New York City, together with Prof. Ronald Breslow. Afterwards he habilitated in supramolecular and bioorganic chemistry at the "Universität Köln" and had an appointment for Organic Chemistry at the "Julius-Maximilian-Universität Würzburg".

His main research interests are the design of artificial receptors for biological relevant substrates such as peptides and carbohydrates using both de-novo design and combinatorial methods, the study of self-assembling zwitterions as building blocks for supramolcular polymers and soft nanomaterials in water and the thermodynamic study of non-covalent interactions in general.

SUSAN B. SINNOT PH.D.

Professor Sinnott has an appointment as Alumni Professor in Materials Science at the University of Florida. She studied Chemistry at the University of Texas in Austin, afterwards she wrote her PhD thesis at the Physical Chemistry Department at the Iowa State University in Ames, Iowa. For her postdoctoral research she worked on Surface Chemistry at the Naval Research Laboratory. Since then, Prof. Sinnott has worked in the area of Materials Sciences and Engineering at the University of Kentucky and Florida.

Her main research interest is on the investigation of properties and processing of materials using theoretical and computational tools. She works on Surface Chemistry in the area of heterogeneous interfaces. With her group she developed a model for analyzing charge transfer at heterogeneous interfaces. She uses DFT calculations coupled with thermodynamics to investigate the formation and segregation energies of point defects, defect complexes, and grain boundaries as a function of defect charge state, oxygen partial pressure, and temperature. Further, she works on solid-state lubricant materials with desirable tribological performance, and on mechanical responses of Nnnostructures such as nano-switches, nano-sensors, nano-actuators, and nano-tweezers, electronic devices, and as additives in composites and lubricancts.

Program

PROGRAM

Monday, February 25th 2012

11:30-14:00	**Registration**
14:00-14:15	**Welcome remarks / Agenda review**
14:15-14:35	**Christian Wick (Erlangen)** Structural insight into the prolyl hydroxylase PHD2
14:35-14:55	**Sarah Schäfer (Halle)** Molecular dynamics simulation of RNA-dependent RNA polymerase of Hepatitis C virus
14:55-15:15	**Ewa Chudyk (Bristol)** Extension of specificity in the new β-lactamases: A combined theoretical and experimental study
15:15-16:15	**Plenary Lecture I:** **Prof. Dr. Carsten Schmuck (Essen)** Quantifying noncovalent interactions using artificial receptors as model systems
16:15-16:35	**Coffee Break**
16:35-16:55	**Dhiraj Sinha (Nove Hrady)** Interdomain communication and interaction in the motor subunit of restriction modification system EcoR1241 from *E. coli*
16:55-17:15	**Tillmann Utesch (Berlin)** Adsorption simulations of biomolecules on modified surfaces
17:15-17:35	**Dr. Po-chia Chen (Göttingen)** Guiding MD-simulations with WAXS-spectra - preliminary report
17:45-18:45	**Annual Meeting of the MGMS-DS**
19:00	**Buffet - Dinner**

PROGRAM

Tuesday, February 26th 2013

08:30-08:50	**Dr. Jeremy Richardson (Erlangen)** The hows and whys of multidimensional instantons: Tunneling effects in gas- and condensed-phase systems
08:50-09:10	**Daniel Tomazic (Dortmund)** Towards a thermodynamically consistent, quantitatively accurate integral equation theory
09:10-09:30	**Andreas Krause (Erlangen)** Liquid-liquid interface in simulation
09:30-09:50	**Roland Frach (Dortmund)** Modeling chemical reaction mechanisms in nonaqueous solution by integral equation theory
09:50-10:10	**Coffee Break & Conference Photo**
10:10-10:30	**Dr. Fabian Burggraf (Freiburg)** Electron transfer in bacterial photosynthesis: New insights from atomistic theory and simulation
10:30-10:50	**Michael Limb (Bristol)** Application of QM/MM methods to probe HEWL reaction
10:55-11:55	**Plenary Lecture II:** **Prof. Dr. Susan Sinnot (Florida)** Next generation classical potentials for modeling many-body interactions in materials
11:55-13:00	**Lunch**

PROGRAM

Tuesday, February 26th 2013

13:00-14:00 **Poster Session I**

14:00-14:20 **Dr. Grygoriy Dolgonos (Kirovograd)**
Diatomic molecules encaged in fullerene C_{60}: A high-level exploration of their energetic, structural, and vibrational properties

14:20-14:40 **Alexander Krotaev (Moskau)**
Empirical electrostatic description of organic molecules with formally charged groups

14:40-15:00 **Matthias Wildauer (Erlangen)**
Prediction of complexation-induced shifts of ^{1}H-NMR signals of ligands based on structures generated by MD simulations

15:00-15:20 **Coffee Break**

15:20-15:40 **Dr. Guido Kirsten (Chemical Computing Group, Köln)**
MOE: protein surface patches and properties

15:40-16:00 **Dr. Guido Capitani (Zürich)**
Protein interface classification by evolutionary analysis

16:00-16:20 **Dr. Björn Sommer (Bielefeld)**
CELLmicrocosmos - Membrane modeling at the molecular and mesoscopic level

16:20-16:40 **Dr. Serdar Durdagi (Magdeburg)**
Protein-protein docking analysis and refinement of the Ubiquitin- and Tetraubiquitin-associated IkBa/NF-kB complex

16:40-17:40 **Plenary Lecture III:**
Prof. Dr. Jamshed Anwar (Lancaster)
An approach for developing simple physics-type force field models for molecular simulation

18:30 **Gasthaus - Biergarten am Röthelheim**

PROGRAM

Wednesday, February 27th 2013

08:30-08:50	**Dr. Anselm Horn (Erlangen)** Alzheimer's disease and Amyloid-beta oligomers: An endeavor in rational drug design
08:50-09:10	**Oleg Titov (Moskau)** Comparison of electrostatic approaches for halogen bonding description
09:10-09:30	**Ahmed El Kerdawy (Erlangen)** Quantum-Mechanics based Molecular Field Analysis (QMFA)
09:30-09:50	**Timo Krotzky (Marburg)** Efficient comparison of protein binding sites using distance histrograms
09:50-10:10	**Coffee Break**
10:10-11:10	**Poster Session II**
11:10-11:30	**Ralf Kling (Erlangen)** Revealing the selectivity determinants of ternary GPCR-complexes by homology modeling and molecular dynamics simulations
11:30-11:50	**Callum Dickson (London)** Molecular dynamics simulation of lipid membranes with AMBER and application to the study of radioimaging pharmaceuticals
11:50-13:20	**Lunch**
13:20-13:40	**Jagmohan Saini (Düsseldorf)** What determines oxazolidinone binding to the large ribosomal subunit?
13:40-14:00	**Julian Fuchs (Innsbruck)** Dynamics direct specificity of effector caspases
14:00-15:00	**Plenary Lecture IV:** **Dr. Hans Matter (Sanofi- Aventis GmbH, Frankfurt am Main)** Interactions of halogen atoms to protein binding sites and contributions to binding affinity
15:00	**Poster & Lecture awards, Closing**

POSTER SESSION I

Tuesday, February 26th 2013 13:00-14:00

P01 **Nursen Azizoglu (Balıkesir)**
A theoretical study on the structures of Monosila[5.7]$_n$cyclacenes

P02 **Thilo Bauer (Erlangen)**
SAMs on α-Al_2O_3(0001): Chemical bonding of linker groups and thermodynamic stability of surface structures

P03 **Frank Beierlein (Erlangen)**
β-lactoglobulin at the water-air interface:
MD simulations on different time and length scales

P04 **Zlatko Brkljača (Erlangen)**
Benchmarking TDDFT functionals in calculations of CD spectra of flexible peptides

P05 **Vladimir Chashchikhin (Moskau)**
Benchmark calculations of absorption spectra for fluorescein and related dyes in various environments

P06 **Vladimir Chashchikhin (Moskau)**
Modeling of the structure and properties of amorphous layers for organic light-emitting diodes

P07 **Grygoriy Dolgonos (Kirovograd)**
Diatomic molecules encaged in fullerene C_{60}: A high-level exploration of their energetic, structural, and vibrational properties

P08 **Pavlo O. Dral (Erlangen)**
Doped polycyclic hydrocarbons for nanoelectronics and energy conversion

P09 **Roland Frach (Dortmund)**
Structure and thermodynamics of nonqueous solvation by integral equation theory

P10 **Julian E. Fuchs (Innsbruck)**
Local dynamics in protease recognition

P11 **Stefan Güssregen (Sanofi-Aventis GmbH, Frankfurt am Main)**
3D-QSAR based on Quantum-Chemical molecular fields:
Towards an improved description of halogen interactions

POSTER SESSION I

Tuesday, February 26th 2013 13:00-14:00

P12 **Elke Hänsele (Portsmouth)**
Molecular dynamics and umbrella sampling simulations of 8-Arg-Vasopressin

P13 **Jochen Heil (Dortmund)**
pK_a prediction for small organic molecules in dimethyl sulfoxide (DMSO)

P14 **Leonhard M. Henkes (Dortmund)**
Predicting ion selectivity of biological and synthetic nanopores by MD simulations and 3D integral equation theory

P15 **Markus Huber (Innsbruck)**
In silico identification of precursors for CYP profiling breath tests

P16 **Christof Jäger (Erlangen)**
Modeling charge transport in "soft" organic electronic devices

P17 **Christophe Jardin (Erlangen)**
An information-theoretic classification of amino acids for the optimization of interfaces descriptions in protein-protein docking

P18 **Anna Kahler (Erlangen)**
Local tuning of the conformational flexibility of RfaH

P19 **Michael Margreiter (Innsbruck)**
Probing aromatic- heteroaromatic Interactions for ligand optimization

Please remember to remove your posters on tuesday evening!

POSTER SESSION II

Wednesday, February 27th 2013 10:10-11:10

P01 **Alessandra Lacetera (Innsbruck)**
In silico SAR rationalization and evaluation of pharmacokinetic properties σ_1 receptor ligands

P02 **Michael Limb (Bristol)**
Application of QM/MM m to probe reaction mechanisms

P03 **Johannes Margraf (Erlangen)**
Quantum dots for solar energy conversion

P04 **Theodor Milek (Erlangen)**
Molecular modeling of Silver nanoparticle nucleation & growth

P05 **Zoran Miličević (Erlangen)**
Determining the shear viscosity of a solvent in the presence of electric fields

P06 **Markus Mühlbacher (Erlangen)**
Recent developments in the prediction of drug-induced phospholipidosis

P07 **Anastasia Roshko (Moskau)**
Molecular modeling of small molecules thin film on the surface

P08 **Maria Schill (Freiburg)**
Sensing molecules by charge transfer through Aptamer-Target-Complexes

P09 **Volodymyr P. Sergiievskyi (Glasgow)**
Fast 3DRISM algorithms for biochemical applications

P10 **Dmitriy Sharapa (Erlangen)**
Fullerene dimers and their anions

P11 **Eileen Socher (Erlangen)**
Amyloid-β tetramer: Structural stability of a new fold

P12 **Björn Sommer (Bielefeld)**
CELLmicrocosmos 2.2 MembraneEditor - Modeling membranes for MD simulations

P13 **Alexander Steudle (München)**
On- and Off-Target prediction using 2D and 3D molecular similarity

POSTER SESSION II

Wednesday, February 27th 2012 10:10-11:10

P14 **Joachim Stump (Erlangen)**
Molecular dynamics of the viral IE1 protein that represents a novel protein fold

P15 **Daniel Tomyzic (Dortmund)**
Towards a thermodynamically consistent, quantitatively accurate integral equation theory

P16 **Yin Wang (Innsbruck)**
Parametrization of a coarse-grainedmodel for Ceramides

P17 **Cem Burak Yıldz (Aksaray)**
Susbstituent effects on the ring-opening mechanism of 1-bromo-1-litiosilirane to silaallenes: DFT study

P18 **Suzan Abdurrahmanoglu (Marmara)**
A DFT study of modelling cellulose radicals

P19 **Markus Pfau (Erlangen)**
Band gap calculation of ZnO

All poster abstracts are available here:
www.mmws2013.mgms-ds.de/

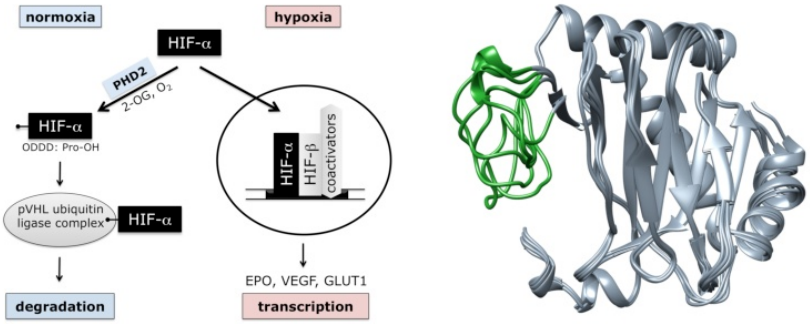
Structural Insight into the Prolyl Hydroxylase PHD2

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

[a] Department of Chemistry and Pharmacy, Friedrich-Alexander-Universität Erlangen-Nürnberg, Computer-Chemie-Centrum, Nägelsbachstr. 25, 91052 Erlangen
[b] Department of Chemistry and Pharmacy, Friedrich-Alexander-Universität Erlangen-Nürnberg, Inorganic Chemistry, Egerlandstr. 1, 91058 Erlangen
[c] Centre for Molecular Design, University of Portsmouth, King Henry Building Portsmouth PO1 2DY, United Kingdom

Hypoxia-inducible factors (HIF) play a constitutive part in the cellular response to hypoxia at the transcriptional level.[1] In states of low oxygen availability (hypoxia), the levels of the α-subunit of these α,β heterodimeric transcription factors (HIF-1α) increase in the cytoplasm. Therefore, HIF-1α can translocate into the nucleus, where it dimerizes with the β subunit and up-regulates the transcription of genes that enable mammalian cells to adapt to hypoxia (e.g. EPO, VEGF, GLUT1).[2] In situations with normal oxygen supply (normoxia), continuous degradation of HIF-1α takes place in the cytoplasm. This degradation is directly connected to oxygen availability by α-ketoglutarate (α-KG) dependent dioxygenases, e.g. the prolyl hydroxylase domain containing protein 2 (PHD2). PHD2 is an iron(II), oxygen and α-KG dependent dioxygenase that catalyzes the hydroxylation of two proline residues (oxygen dependent degradation domains, ODDD) of HIF-1α. 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.

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.



[1] J. Cassavaugh, K. M. Lounsbury, *J. Cell. Biochem.* **2011**, *112*, 735-744.
[2] R. Chowdhury, A. Hardy, C. J. Schofield, *Chem. Soc. Rev.* **2008**, *37*, 1308-1319.

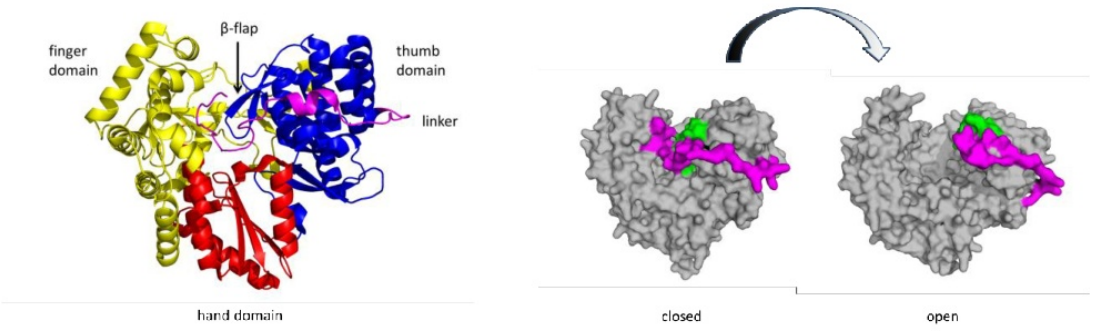
Molecular dynamics simulation of the RNA-dependent RNA polymerase of Hepatitis C Virus

Sarah Schäfer, Iris Thondorf

Institute for Biochemistry and Biotechnology, Martin Luther University Halle-Wittenberg

The Hepatitis C virus (HCV) causes severe damage to the liver and can lead to liver cirrhosis or liver cancer.[1] One common target in the pharmaceutical research against Hepatitis C is the non-structural Protein 5B (NS5B), which is the RNA-dependent RNA polymerase of the virus and therefore responsible for the replication of the viral genome. The three dimensional structure of NS5B has already been solved in more than 120 crystal structures as apoprotein or as complex with ligands. They all represent a closed conformation of the protein, which can bind NTP and RNA, but is structurally not able to perform the elongation process.[2] Mainly two regions of the protein are responsible for the closed conformation, the "linker" and the "β-flap" (Figure). They occlude the catalytic center and hinder the transition from the initiation to the processive RNA synthesis.[3]-[5]

We have investigated the conformational flexibility of the NS5B protein by means of molecular dynamics simulations in an implicit solvent environment. The starting crystal structures had been co-crystallized with GTP and the inhibitor HCV-796 (PDB-Codes 2XI3 and 3FQK). The resulting trajectories reveal the opening of the enzyme in the presence of GTP while the closed conformation was observed with bound HCV-796. The linker and β-flap segments mentioned above play indeed an important role during the alteration of conformation, in addition to the rotation of the thumb domain of the protein. Geometrical analysis of the trajectory also indicates a correlated movement of linker and β-flap.



[1] D. Lavanchy, Liver Int., **2009**, 29(S1), 74–81.
[2] S. Bressanelli, L. Tomei, A. Roussel, I. Incitti, R. L. Vitale, M. Mathieu, R. De Francesco, F. A. Rey, Proc. Natl. Acad. Sci. U.S.A., **1999**, 96, 13034-13039.
[3] H. Ago, T. Adachi, A. Yoshida, M. Yamamoto, N. Habuka, K. Yatsunami , M. Miyano, Structure, **1999**, 7, 1417-1426.
[4] C. A. Lesburg, M. B. Cable, E. Ferrari, Z. Hong, A. F. Mannarino, P. C. Weber, Nat. Struct. Biol., **1999**, 6, 937-943.
[5] B. K. Biswal, M. M. Cherney, M. Wang, L. Chan, C. B. Yannopoulos, D. Bilimoria, O. Nicolas, J. Bedard,M. N. James, J. Biol. Chem., **2005**, 280, 18202-18210.

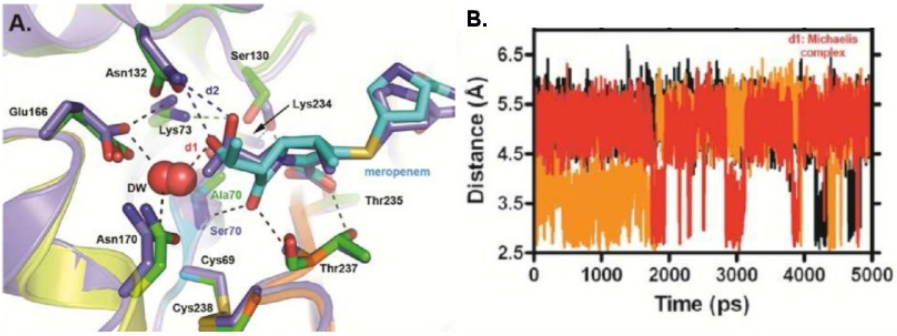
Extension of Specificity in the New β-Lactamases: A Combined Theoretical and Experimental Study

Ewa Chudyk[1], Marc van der Kamp[1], Jim Spencer[2], Adrian J. Mulholland[1]

1. Centre For Computational Chemistry, School of Chemistry, University of Bristol, UK,
2. School of Cellular and Molecular Medicine, University of Bristol, UK

Bacterial antibiotic resistance has become a real treatment problem in medicine. It is mostly due to the activity of β-lactamases – enzymes produced by Gram-negative pathogens, responsible for cleavage of β-lactam rings in penicillins, cephalosporins and carbapenems, inactivating these drugs. In clinical use there are only a few inhibitors of β-lactamases, however, antibiotic resistance is still developing due to their clinical overuse [1]. Therefore further investigation of the reaction mechanisms of β-lactamases followed by rational inhibitor design becomes a very challenging medical need.

Carbapenems are the most potent β-lactam antibiotics and key drugs for treating infections by Gram-negative bacteria. As proven experimentally, carbapenems effectively escape activity of most beta-lactamases due to slow deacylation of the acyl-enzyme intermediate. However, the SFC-1 enzyme from *Serratia fonticola* hydrolyzes antibiotics, and so there is no effective treatment against those bacteria. In this study, we present crystal structures of the class A carbapenemase SFC-1 from *Serratia fonticola* complexed with the carbapenem meropenem as its Ser70 Ala (Michaelis) and Glu166 Ala (acylenzyme) mutants [2].



Molecular dynamics simulations indicated the mode of binding that occurs in both the Michaelis and acylenzyme complexes of wild-type SFC-1 (Figure A). In carbapenem-inhibited class A β-lactamases, it is proposed that the deacylating water molecule is deactivated by interaction with the carbapenem 6α-1R-hydroxyethyl substituent. Structural comparisons with such enzymes suggest that in SFC-1 subtle repositioning of key residues (Ser70, Ser130, Asn132 and Asn170) enlarges the active site, permitting rotation of the carbapenem 6α-1R-hydroxyethyl group and abolishing this contact (Figure B). Further comparison of the deacylation reaction mechanisms by quantum mechanics/molecular mechanics approach reflected the significant difference in activation energy barriers for different β-lactamases.

[1] E.P. Abraham; E. Chain; Nature 1946, 46: 837
[2] F. Fonseca, E.I. Chudyk, M.W. van der Kamp, A. Correia, A.J. Mulholland, J. Spencer; J. Am. Chem. Soc. 2012, 134: 18275

Quantifying noncovalent interactions using artificial receptors as model systems

Prof. Dr. Carsten Schmuck, Universität Duisburg-Essen, Institut für Organische Chemie, Universitätsstr. 7, 45141 Essen, email: carsten.schmuck@ uni-due.de

We are interested in supramolecular systems that form stable aggregates even under the most challenging conditions, namely in water. As the strength of most specific non-covalent interactions such as H-bonds or ion pairs significantly decreases in polar surrounding the design of such systems is still rather difficult. We use both rational design and combinatorial methods in this context. Currently, we mainly are exploring H-bond enforced ion pairing to obtain stable aggregates in water. Our focus is a better molecular understanding of the underlying recognition event and its thermodynamics and the application of such supramolecular systems.

For example, we developed a new and highly efficient binding motif for the complexation of carboxylates in water, the guanidiniocarbonyl pyrroles. Using “knock-out” analogues the energetic contributions of individual interactions within this multiple point binding sites can be assessed both experimentally and theoretically. Based on this binding motif a host of different applications such as polymers and gels, artificial gene transfection vectors or ligands for protein surface binding could be developed.

An even more challenging task besides a quantitative understanding of noncovalent interactions is to elucidate the role the solvent plays in supramolecular complexation experimentally. Some first approaches into this direction are also discussed.

Interdomain communication and interaction in the motor subunit of restriction modification system EcoR1241 from *E. coli*

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. These 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.

The type I motor subunit has a square planar arrangement of globular domains with a prominent cleft that can accommodate DNA extending between two canonical helicase domains to the endonuclease active site. ATP binding is proposed to play a major role in coupling the both the activities as the crystal structure shows an unexpected contact of endonulease LYS220 to the translocase bound ATP. We believe this contact play a major role in signal transfer.
To explain the underpinning molecular mechanisms of coupling ATP-dependent DNA translocation and DNA cleavage and the communication pathway through the motor subunit, we carried out molecular dynamics simulations with selected mutations on the endonuclease 220 and 180 loop, that could be potentially engaged in conformational changes that occur once translocation is stalled and a signal is transmitted to the endonuclease.
Additional in silico mutants and their simulations demonstrate the importance of inter domain interactions between helical-helicase2 domain and at the helical-endonulease interface close to the proposed DNA path for DNA translocation and consequent restriction activity.

Acknowledgments: ***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.***

[1] *A.Obarska,A.Blundell,M.Bujenciki and Keith Firman:* ***Nucleic Acid Research 2006,Vol 34***
[2] *Chritopher K.Kennaway,A.Obarska,John H.White:* ***Nucleic Acid Research Dec 11,2008***
[3] *M. Lapkouski, S. Panjikar, P. Janscak, I. Kuta-Smatanova, J. Carey, R. Ettrich, E. Csefalvay:* ***NatStruct Mol Biol 16: 94–95, 2009.***

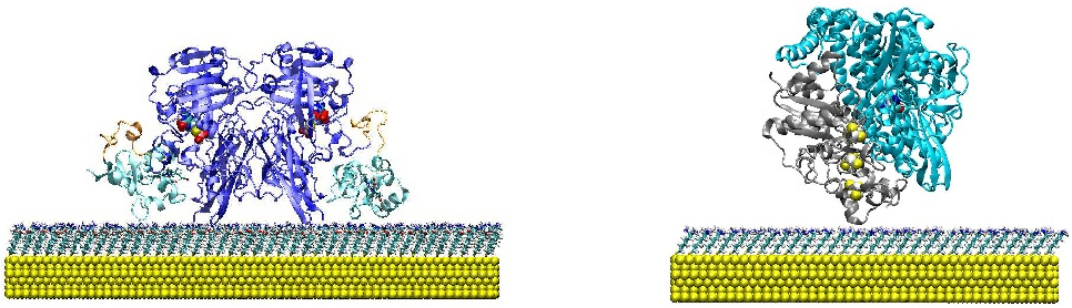
Adsorption simulations of biomolecules on SAM coated surfaces

Tillmann Utesch[a], Nina Heidary[a], Murat Sezer[a] Maria Ana Castro[b], Diego Millo[c], Peter Hildebrandt[a], Anna Fischer[a], Inez Weidiger[a], Ingo Zebger[a], Maria Andrea Mroginski[a]

[a]*Insitut für Chemie, Technische Universität Berlin*

[b]*Departamento de Quimica Inorganica, Analitica y Quimica Fisica, Universidad de Buenos Aires*

[c]*Biomolecular Spectroscopy / LaserLAB Amsterdam, Vrije Universiteit Amsterdam*



The adsorption of biomolecules onto surfaces is an important issue in many fields. Here, we apply classical molecular dynamics simulations complemented by spectroscopy to investigate the immobilization of the sulfite oxidase and [NiFe] hydrogenases, which are of interest for the development of biosensors and biofuel cells, respectively.

For the sulfite oxidase catalyzing the oxidation of sulfite to sulfate, it was demonstrated that the adsorption process is strongly ionic strength dependent. While under low ionic strength the flexibility of the enzyme is strongly restricted upon immobilization, it stays more mobile under high ionic strength conditions [1]. This observation is of special interest, because predicted domain motion events have a strong effect on the electron transfer [2].

[NiFe] hydrogenases catalyze the reversible cleavage of hydrogen into protons and electrons. They are grouped into oxygen sensitive (standard) and tolerant hydrogenases.

In a first study, the electrostatically driven adsorption of standard hydrogenases was investigated by changing the protonation level of the self-assembled monolayer (SAM) coating the gold surface [3]. We observed that higher charge densities on the SAM led to a stronger immobilization, but affected protein stability beyond a certain value.

Furthermore, the immobilization of the oxygen tolerant membrane bound [NiFe] hydrogenase (MBH) was probed. This adsorption process was more challenging, because the MBH contains an additional membrane anchor and a much weaker dipole moment. Therefore, the influence of the anchor and different surfaces was studied [4]. The work showed that both, the anchor and the surface constitution, had strong effects on the immobilization.

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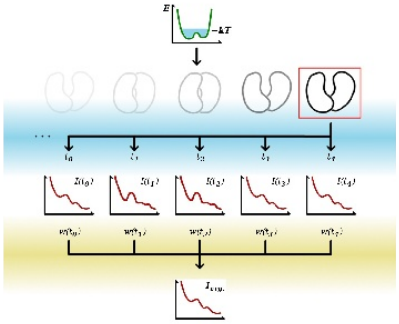
Guiding MD simulations with WAXS spectra - Preliminary Report

Chen, Po-chia and Hub, Jochen

Georg-August University, Goettingen, Geromany



Recent advances in Wide-angled X-ray Scattering techniques (WAXS) offer the ability to probe transient changes in protein conformations down to picosecond levels, [1] and at resolutions down to secondary structure levels where their fluctuations become apparent. [2] These information can be translated into constraints on conformational averages which are complementary to distance-based constraints such as NMR, and will assist in the characterisation of large-macromolecular complexes.

Improvements in computational techniques, such as explicit modelling of the solvent environment, [3] are increasing our understanding of the relationship between spectral features and underlying structural characteristics. Incorporation of WAXS-based constraints into MD-simulations will also guide the direction of simulation trajectories so as to avoid regions irrelevant to the states being studied. However, in order to convert the ensemble-average spectra into instantaneous forces, an understanding of the conformational averaging probed by WAXS is required. We show preliminary results of on-going efforts to integrate WAXS-prediction and WAXS-coupling tools into GROMACS.

This presentation shall include a brief discussion on our planned approach, its validation on trivial systems, and an analysis of how structural-features are linked to features in WAXS-spectra.

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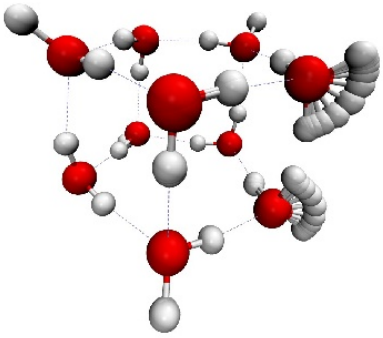
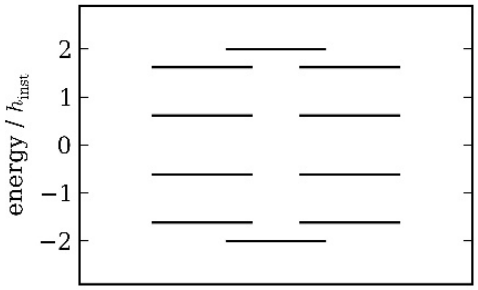
The Hows and Whys of Multidimensional Instantons: Tunnelling effects in gas- and condensed-phase systems

Jeremy O. Richardson,[1,2] Stuart C. Althorpe[1], Michael Thoss[2]

[1] *Department of Chemistry, University of Cambridge, UK*

[2] *Institut für Theoretische Physik und Interdisziplinäres Zentrum für Molekulare Materialien, Friedrich-Alexander-Universität Erlangen-Nürnberg, Staudtstraße 7/B2, D-91058 Erlangen*





We describe a simple method for locating semiclassical instantons in multidimensional systems (figure left) [1]. Using steepest-descent integration of a discretized form of Feynman's path integral, these instantons can be used to compute chemical reaction rates in the deep-tunnelling regime and the energy-level splitting pattern (figure right) resulting from tunnelling between degenerate potential wells [2]. Applications are shown for systems in full dimensionality using ab initio potential-energy surfaces including proton-transfers and water cluster rearrangements [3,4].

The discretized instantons are closely related to the method of ring- polymer molecular dynamics [5], which explains why the latter is able to obtain reaction rates so reliably in the deep-tunnelling regime [1]. An extension to simulate nonadiabatic quantum dynamics using the mapping representation [6] in ring-polymer form is discussed.

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Towards a thermodynamically consistent, quantitatively accurate integral equation theory

Daniel Tomazic, Martin Urban, Stefan M. Kast*

Physikalische Chemie III, TU Dortmund, D-44227 Dortmund, Germany
e-mail: daniel.tomazic@tu-dortmund.de

The integral equation (IE) formalism of theories of the liquid and solution state is based on a set of nonlinear equations that connect the total and the direct correlation functions by a convolution product and by a so-called closure relation which also contains the interaction potential. In contrast to explicit molecular simulations the solution to an IE theory allows for fast, noise-free calculations of structural properties such as the pair distribution functions as well as of thermodynamic quantities like the free energy or the chemical potential. The quality of an IE calculation relies on the accuracy of the so-called bridge function that is in principle, though not easily, obtained from simulations, but for which several approximations have been described.

Here we follow-up on our earlier formally exact result concerning conditions on the bridge function leading to thermodynamic consistency in the sense that the free energy is required to be a path-independent state function [1]. We demonstrate for the Lennard-Jones fluid that bridge data taken directly from a simulation can be used in an analytical expression [2] for the free energy which matches reference data from molecular dynamics simulations very accurately. Moreover, a novel exact result is presented by deriving an inequality between the renormalized direct correlation function and the bridge function which is useful for the development of bridge approximations and for controlling the numerical stability of IE solutions [3].

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Liquid-Liquid Interface in Simulation

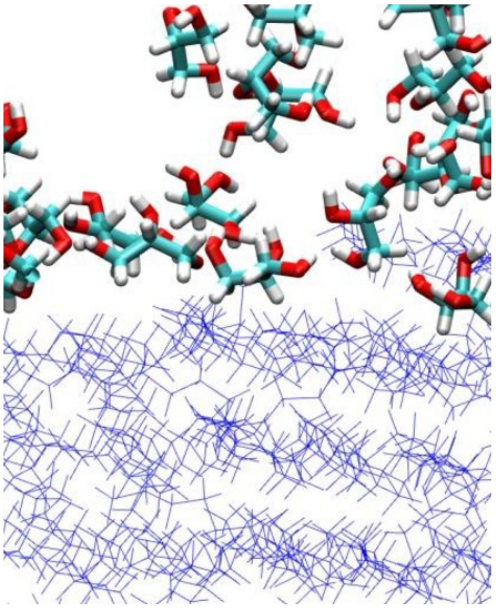
Andreas Krause,[a,b,*] Frank R. Beierlein,[a,b,*] Christof M. Jäger,[a,b] Piotr Fita,[c,d] Eric Vauthey[c] and Timothy Clark*[,a,b]

[a] Computer-Chemie-Centrum and Interdisciplinary Center for Molecular Materials, Friedrich-Alexander-Universität Erlangen-Nürnberg, Nägelsbachstr. 25, 91052 Erlangen, Germany

[b] Excellence Cluster Engineering of Advanced Materials, Friedrich-Alexander-Universität Erlangen-Nürnberg, Nägelsbachstr. 49b, 91052 Erlangen, Germany

[c] Department of Physical Chemistry, University of Geneva, 30 quai Ernest-Ansermet, CH-1211 Geneva 4, Switzerland

[d] Institute of Experimental Physics, Faculty of Physics, University of Warsaw, ul. Hoza 69, 00-681 Warsaw, Poland



Interfaces, at which different phases are in close contact, are of special interest because the properties of the molecules at the interface can differ decidedly from those in the bulk. Due to the asymmetry of the forces, molecules at interfaces are frequently observed to be more ordered than in the bulk, where more random orientations are usually observed. [1,2] As a result, even such fundamental characteristics as pH and equilibrium constants can differ dramatically.

While it is difficult to probe interfaces with linear optical spectroscopy because of the preponderance of molecules in the bulk, non-linear optical techniques such as Second Harmonic Generation (SHG), have been used increasingly to study interfaces in recent years.[3,4]

Experimental SHG-measurements were performed on a glycerol/water dodecane interface.[5,6] In order to obtain a detailed view of the interface structure, we have performed extensive molecular-dynamics simulations of a two-phase system formed by glycerol/water and dodecane, with MG and BG at the interfaces, and over a wide range of glycerol concentrations.

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Modeling chemical reaction mechanisms in nonaqueous solution by integral equation theory

Roland Frach, Stefan M. Kast*

Physikalische Chemie III, TU Dortmund, D-44227 Dortmund, Germany
e-mail: roland.frach@tu-dortmund.de

The prediction of thermodynamic and kinetic parameters of chemical reactions in solution is an important task in computational chemistry. Particularly challenging are situations where the commonly employed dielectric continuum models of solvation such as PCM (polarizable continuum model) fail due to the lack of directional solute-solvent interactions or due to the properties of nondipolar (quadrupolar or higher, or fully apolar) solvent species which cannot be adequately described. As an alternative, we have developed the embedded cluster reference interaction site model (EC-RISM) approach which combines statistical-mechanical 3D-RISM integral equation theory and quantum-chemical calculations in a self-consistent manner [1,2]. As a result of these calculations, we obtain the solvent-induced component of the free energy surface governing chemical reaction pathways along with the electronic polarization. Taken together, these data can be used to characterize reaction mechanisms quantitatively.

As an example, we here show the capabilities of the EC-RISM approach by studying an organocatalytic Michael addition in benzene and hexafluorobenzene solutions for which it has been shown experimentally that the two relatively similar solvents exhibit different stereoselectivities [3]. We show that the computed solvent distribution functions agree well with costly quantum-chemical calculations with ad hoc placement of single solvent molecules and that the resulting free energy data of the transition states correspond to observed product ratios.

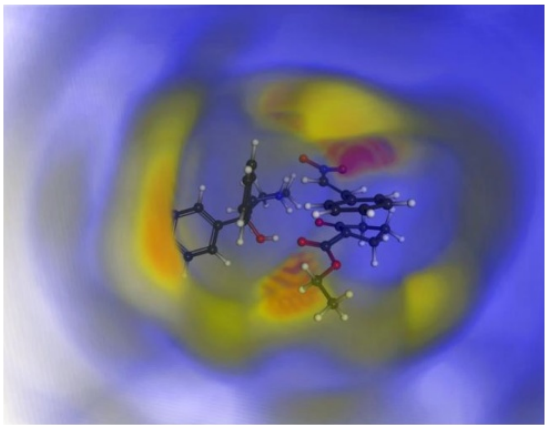

Fig. 1. Distribution of carbon atoms of hexafluorobenzene around the putative transition state of an organocatalytic Michael addition [3].

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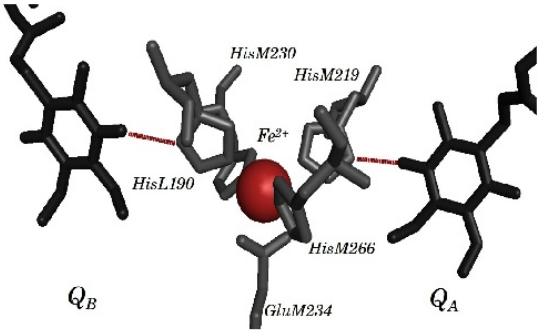
Electron transfer in bacterial photosynthesis: New insights from atomistic theory and simulation

F. Burggraf and T. Koslowski

Institut für Physikalische Chemie, Albert-Ludwigs-Universität Freiburg

Although the bacterial photoreaction center was the first membrane protein characterized structurally [1], many charge transfer steps in this paradigmatic enzyme still are under a cloud. Here, we use atomistic molecular dynamics simulations and large-scale electronic structure computations to address charge transfer between i) the Q_A and Q_B quinones, ii) four heme centers in the cytochrome subunit and iii) the cytochrome subunit and the bacteriochlorophyll special-pair.



The results show that an extraordinary, hydrogen-bound non-heme iron complex is essential for efficient interquinone charge transfer allowing a bridge-mediated superexchange mechanism [2]. Furthermore, thermodynamic integration calculations enabled the computation of free enthalpy values for the interheme charge transfer in the cytochrome subunit. Additionally, in the final rereduction step of the photooxidized special-pair by the last of the four heme moieties of the cytochrome subunit, several charge transfer pathways involving different amico acids at the protein-cytochrome interface could be identified and it was shown, that the kinetics of these pathways is not affected by photoinduced changes in the protein structure.

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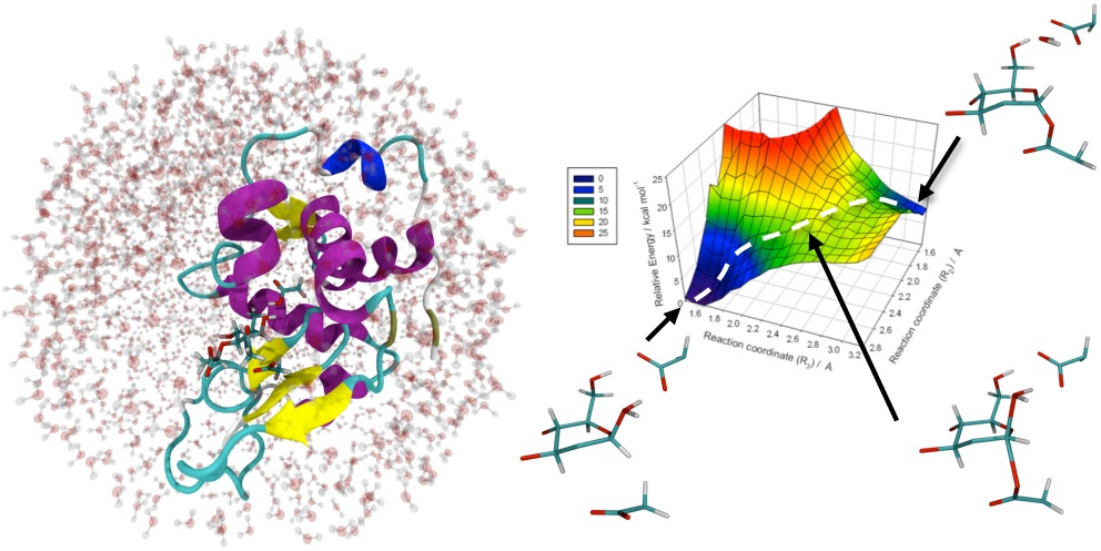
Application of QM/MM Methods to probe reaction mechanisms

Michael Limb, Adrian J. Mulholland

Centre for Computational Chemistry, School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS

QM/MM (Quantum Mechanics/ Molecular Mechanics) methods are increasingly important in analyzing and predicting enzyme activity. QM/MM methods allow a detailed atomic level investigation of reactions in enzymes by coupling quantum chemical calculations on the active site with a simpler, empirical 'molecular mechanics' treatment of the rest of the protein. This has the significant advantage of probing possible reaction mechanisms in enzymes with quantum methods of potentially high accuracy, while retaining the ability to produce results for large, solvated enzymes, on reasonable time scales and at relatively small computational expense [1].

An example of QM/MM analysis of the effects of mutations, and investigations of alternative substrates, is provided by HEWL (Hen Egg White Lysozyme). GPU (Graphics Processing Unit) aided, long timescale MD (Molecular Dynamics) simulations were performed on the enzyme system allowing suitable 'reactive frames' to be generated for the reaction. QM/MM calculations where then used to determine the nature of the catalytic intermediate formed during the enzyme-catalyzed reaction [2]. Reactions of mutant enzymes and alternative (fluorinated) substrates were then modeled, for comparisons with experimental studies: such modifications were necessary for the experimental trapping of a reaction intermediate [3]. QM/MM calculations compared the reactions with the wild-type and native substrate, and analyzed the changes caused by these modifications, testing the conclusions drawn from mutant enzymes and non-natural substrates.



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Abstract for the 27th Molecular Modeling Workshop in Erlangen, Germany

February 25-27, 2013

Next Generation Classical Potentials for Modeling Many-Body Interactions in Materials

Susan B. Sinnott, Department of Materials Science and Engineering, University of Florida, Gainesville, FL, 32611-6400, USA

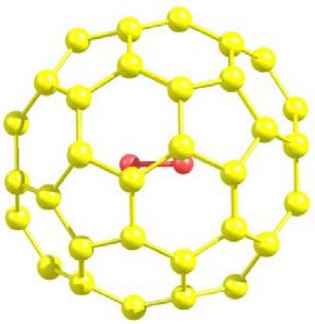
Reactive force fields, which are also called potentials, are used in atomic-scale simulations to predict interatomic forces and energies. The next generation of these force fields allow for the prediction of sophisticated chemical reactions at scales larger than can be achieved with first-principles quantum-based methods. This presentation will present several examples of charge optimized many-body (COMB) potentials being used in atomic-scale molecular dynamics and adaptive Monte Carlo simulations to model surface and heterogeneous interfacial chemistry.

Diatomic molecules encaged in fullerene C_{60}: a high-level exploration of their energetic, structural and vibrational properties

G. A Dolgonos,[1] G. H. Peslherbe[2]

[1] *Computational Centre of Chizevsky's Regional Scientific Library, 24 V. Perspektyvna str., Kirovograd, Ukraine 25006*

[2] *Centre for Research in Molecular Modeling (CERMM) and Department of Chemistry & Biochemistry, Concordia University, 7141 Sherbrooke St. West, Montreal, QC, Canada H4B1R6*



The possibility to encapsulate guest molecules into the cavity of a fullerene (such as C_{60}) is one of the most outstanding properties of this allotropic form of carbon. Many endohedral complexes involving H_2, N_2, H_2O and NH_3 guests with C_{60} have been successfully synthesized via so-called 'molecular surgery' approach (see, for instance, Table 1 of Ref. [1]). However, there is still a lack of accurate computational studies for such endohedral complexes as the large number of atoms to be considered precludes the usage of post-Hartree-Fock methods for these systems. As early as in 1991, Cioslowski predicted [2] stabilization effects of polar and nonpolar diatomic guests in C_{60} cage based on low-level Hartree-Fock calculations, some of which (i.e., harmonic frequency shifts) were not confirmed experimentally. We recently demonstrated [3] that the results of more advanced density-fitting local second-order Møller-Plesset (DF-LMP2) calculations with a triple-zeta basis set lead to an excellent agreement of equilibrium geometries, stabilization energies and harmonic frequencies of the $H_2@C_{60}$ complex with some other sophisticated theories and with experiment.

In the present study, we concentrate on the encapsulation effects associated with the formation of complexes consisting of C_{60} host and diatomic guest molecules by means of (DF-L)MP2 theory. The guest molecules studied include homonuclear (N_2, O_2) as well as heteronuclear (HF, CO, LiH, LiF) species. Stabilization energies, changes in equilibrium bond lengths and harmonic frequencies will be presented and discussed.

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Empirical electrostatic description of organic molecules with formally charged groups

A.V. Korotaev, D.A. Shulga, V.A. Palyulin, N.S. Zefirov

Lomonosov Moscow State University

Many potential objects for molecular design such as ionic liquids, proteins, oligosaccharides, nucleic acids contain formally charged groups. For description of such structures electrostatic interactions, which are usually described as point charges coulomb interaction, play an important role. However most standard methods of charge distribution prediction are well studied and tuned for neutral molecules. When structures containing formally charged groups are considered, accurate description of charge distribution is often not pursued, supposing that group formal charges play leading role. But the question arises regarding the relevance of such approach and which distortions of results in numerical experiments it may cause.

To test the hypothesis of significance of accurate accounting of charge distribution for structures with formally charged groups, molecular dynamics simulations of 1,3-dimethylimidazolium chloride ionic liquid were performed. Simulations contained 4096 ionic pairs and were carried out at 423 and 500K during 5 ns. These calculations were performed with different atomic charges: AM1-BCC, MK-ESP, RESP, Mulliken and Gasteiger. The predicted properties of ionic liquids differ substantially for different charge distributions, especially such dynamics properties as self diffusion coefficients and structural properties as radial distribution functions.

Methods for calculating charge distribution can be divided into non-empirical, semi-empirical and empirical. The latter are more convenient for wide use in molecular modeling because they are fast and have ability to adjust the accuracy of calculation depending on the task and in some cases are topologically symmetrical. In this work for describing structures with formally charged groups a scheme based on dynamical electronegativity relaxation (DENR) [1] is used, as in addition to the advantages listed above it also takes into account inductive effect.

For verifying the adequacy of scheme preliminary parameter optimization was carried out on a structure set obtained by the following way. First, the patterns for structure generation were derived, including specification of most frequently occurring in organic molecules both formally charged and neutral groups and the ways they may be connected. Second, complete generation of a set the structures based on the above patterns was conducted. Third, the set was clustered to give a compact and diverse set of 500 structures, divided into training (450) and test (50) sets. Calculated charges were examined by ability to reproduce reference molecular electrostatic potential computed quantum chemically at HF/6-31G* level. The results were compared with AM1-BCC, Gasteiger, EEM, MMFF94, Lowdin, Mulliken, MK-ESP, RESP schemes. Even in case of rough optimization DENR charges have average RMSD-values comparable to that for existing empirical schemes.

Thus, the significance of accurate accounting charge distribution for structures with formally charged groups was pointed out. Current DENR scheme may be used for such calculations as fast and precise tool to improve electrostatic description of these structures.

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Complexation-induced ^{1}H-NMR shifts of ligands calculated from MD-simulations

Matthias Wildauer[1)], Christof M. Jaeger[1)], Jürgen Schatz[2)], Timothy Clark[1)]

[1)] *Computer-Chemie-Centrum, Friedrich-Alexander-Universität Erlangen-Nuürnberg, Nägelsbachstraße 25, D-91052 Erlangen, Germany*

[2)] *Institute of Organic Chemistry, Friedrich-Alexander-Universität Erlangen-Nürnberg, Henkestraße 42, D-91054 Erlangen, Germany*

NMR-titration experiments are used to observe complexation-induced chemical shifts (CIS) of the ligand's protons in order to measure association constants of host guest complexes. Since these chemical shifts are caused by anisotropic shielding and deshielding effects due to the ligand's environment in the complex, it is also possible to determine general features of the structure, orientation and conformation of the ligand within the host.

In this study, we calculate the ^{1}H CIS of four phenyl-based ligands in two different calix[4]arene hosts that were experimentally measured and published prior to this study.[1] The aim is to gain deeper insights into how small geometrical changes of the host-guest interactions may influence the chemical shifts and how those are represented in equilibrium.

Atomistic molecular dynamics (MD) simulations of all complexes and free ligands were used to generate a large number of structures that represents conformational flexibility as a basis for DFT calculations in order to obtain the NMR shieldings and subsequently the desired CIS. The calculated and the experimental CIS values will be compared and some conformations will be discussed.

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Proteins: Properties and Surface Patches

Guido Kirsten

Chemical Computing Group

Since the introduction of the first recombinant protein therapeutic 25 years ago the number of protein therapeutics has increased dramatically. [1] Getting experimental data on solubility, hydrodynamic and electrophoretic properties is laborious as it requires a significant amount of purified protein. Thus an in-silico method for protein property prediction is desirable. In this talk we will discuss the theoretical background and results obtained by an algorithm as implemented in MOE 2012 [2].

However looking at whole molecule properties is not sufficient to explain protein aggregation behavior in all cases. Therefore we implemented a surface patch analysis and visualization tool that allows getting further insights in the solubility behavior of proteins and gives hints mutants might lead to improved protein therapeutics.

Another new tool to apply site directed mutagenesis to wild type proteins completes the toolbox of protein design applications.

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Protein interface classification by evolutionary analysis

Jose M Duarte[1], Adam Srebniak[2], Martin A. Schärer[1,2], Guido Capitani[1]

[1]*Biomolecular research, Paul Scherrer Institut, Villigen, Switzerland*
[2]*ETH Zürich, Switzerland*

Macromolecular crystallography is currently producing a wealth of information about protein-protein interactions and often tackles very complex assemblies. Such complexity, however, often makes it difficult to distinguish which of the interfaces observed in the crystal lattice are biologically relevant and which are simply crystal contacts. To computationally address this issue, we have developed a general protein interface classification method (EPPIC, Evolutionary Protein Protein Interface Classifier [1]). EPPIC uses a simple geometric measure, number of core residues (defined as in Schärer et al. [2]) and two evolutionary indicators based on the sequence entropy of homolog sequences [3]. One indicator measures the difference in selection pressure between interface core and rim, while the other compares interface core and rest of the surface, minimizing bias with a Z-score like approach. EPPIC is available both as a command-line tool and as a web server (www.eppic-web.org). It provides a classification (biological contact or crystal contact) and a detailed analysis of each interface in a given crystal structure. We are currently extending our method to further applications, like the analysis of membrane protein interfaces. The EPPIC approach and the web server will be presented.

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CELLmicrocosmos – Membrane Modeling at the Molecular and Mesoscopic Level

Björn Sommer

Bio-/Medical Informatics Department, Bielefeld University, Bielefeld, Germany

bjoern@CELLmicrocosmos.org

The modeling of biological cells is an extremely complex and eclectic topic. Various cell modeling approaches exist. For example, it is possible to compute and simulate intracellular molecular interactions and – on the other side – to generate cell models based on microscopic images.

The combination of both approaches is a complex task for different reasons. One problem is the large variance in scale. Molecular Dynamic simulations (MD) usually operate on scales of a few Ångstrom, while the modeling of microscopy-based cell components takes scales of a hundreds to thousands of Nanometers into account.

CELLmicrocosmos introduces an Integrative Bioinformatics approach bridging the gap between molecular and mesoscopic modeling and visualization.

The CELLmicrocosmos 2.2 MembraneEditor (CmME) is a freely available software tool to model complex heterogeneous membranes based on the PDB format [1]. The membranes can be exported and used in conjunction with external MD packages like GROMACS [2]. CmME is a Java Web Start Application which can be downloaded from

http://Cm2.CELLmicrocosmos.org

CmME represents the molecular level, whereas the CELLmicrocosmos 1.1 CellExplorer (CmCX) operates on the mesoscopic level. It can be used to model abstract shape-based cell models or to import microscopy-based cell component structures, which could be acquired from the Cell-Centered Database [3]. The interactive cell environment can be used for educational as well as scientific purposes [4]. Potential future objectives and current developments of this work will be discussed.

Information about the team behind the different software tools can be found at

http://team.CELLmicrocosmos.org

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Protein-Protein Docking Analysis and Refinement of the Ubiquitin- and Tetraubiquitin-associated IκBα / NF-κB Complex

Serdar Durdagi, Samira Yazdi, Matthias Stein

Max Planck Institute for Dynamics of Complex Technical Systems, 39106 Magdeburg, Germany

The discovery about 40 years ago that certain proteins are ubiquitinated before degradation was awarded the Nobel Prize in Chemistry in 2004. Ubiquitin-mediated destruction and signaling play essential roles in DNA repair, cell-cycle regulation, cell growth, and immune response function. [1]

Nuclear Factor- κB (NF-κB) is a dimeric transcription factor that contains p50 and p65 subunits and is involved in the control of a large number of physiological cellular and organismal processes (i.e., cell growth, apoptosis, immune and inflammatory responses). The inhibitor proteins (i.e., IκBα) bind directly to the NF-κB and inhibit its transcriptional activity. In resting cells, the half-life of NF-κB dimers bound to IκBα is on the order of days, thus virtually no dissociation of the complex is seen in the cell in the absence of stimulation. However, when IκBα is phosphorylated at Serine amino acids at positions 32 and 36 and then ubiquinated at positions Lys21 and/or Lys22 and degraded by the proteasome, it frees NF-κB. Thus, ubiquitin signaling in the NF-κB pathway is so crucial that misregulation may lead to serious diseases such as cancer, neurodegenerative and immunological diseases. [2, 3]

We investigated the ubiquitination of IκBα / NF-κB at positions Lys21 and Lys22 in the phosphorylated and unphosphorylated IκBα forms. ROSETTA Molecular Modeling Suite is used for rigid-body protein/protein docking and for each complex 10000 docking poses is generated. *Clustering* module is then used for filtering out the similar conformations using a certain threshold value of RMSD. Final models are then energy minimized using MM/OPLS force field and structures that have the lowest energy is selected for further analyses (MD simulations). In this talk, protein-protein interaction analysis and refinement of the ubiquitin and tetraubiquitin-associated IκBα / NF-κB complex will be detailed.

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An approach for developing simple physics-type force field models for molecular simulation

Jamshed Anwar

Faraday Building, Department of Chemistry, Lancaster University, Lancaster LA1 4YB
EMail: j.anwar@lancaster.ac.uk

Coarse grained models, wherein groups of atoms are represented by a single interaction site, are often employed for large systems and/or when there is need to access longer time-scales. This representation means fewer particles in the system and hence enables larger systems to be simulated for longer times. There are two other additional gains: on coarse graining the interaction potential becomes softer, enabling the timestep to be increased from 0.002 ps to about 0.040 ps – a 20-fold advantage in the time-stepping process; the free energy surface also becomes softened which enables the system to equilibrate rapidly. Such coarse graining can be rigorous in that the loss in chemical specificity of the model is kept to a minimum. A similar but philosophically different approach is to use simpler models for the molecular system, which is a physics-type approach where the model represents a generic molecule, say a general phospholipid, rather than a specific lipid. Simulations using simplified models can be very powerful in that the insights are generic representing the behavior of a whole class of molecules, rather than a particular chemically-specified molecule.

A number of approaches to developing coarse grained models have been proposed. Of these perhaps the most widely employed is the semi-quantitative force field Martini [1]. Martini employs a 3-to-1 or 4-to-1 mapping to represent a chemical moiety comprising 3 or 4 atoms by a single coarse-grained particle. The coarse grained particles are generally uncharged and described by a Lennard Jones (LJ) interaction potential. Whilst the choice of the LJ σ parameter is dictated by the chemical moiety being represented, the parameter ε, which characterizes the affinity between the particles, is selected empirically from a set of 10 discrete levels depending on how polar the particle is perceived to be. This decision is informed by the characterization of certain building blocks based on free energies of vapourization, hydration and partitioning. The building blocks are limited focusing on phospholipids but have recently been extended to amino acids.

I shall present a new approach for developing simple, physics-type molecular models based on phase coexistence data. As with the Martini force field, the coarse grained particles are represent by a LJ interaction potential and utilize the well characterized LJ phase diagram to identify the appropriate LJ parameters for any given chemical moiety. The approach, which we term *PhaseD*, is simple, rapid and potentially universal, not being limited to a restricted set of building blocks. Furthermore, the approach augments the Martini force field in that it enables a more informed selection of the LJ ε parameter for a given chemical moiety being represented by a coarse grained particle.

Alzheimer's Disease and Amyloid-β Oligomers: An Endeavor in Rational Drug Design

Anselm H. C. Horn, Heinrich Sticht

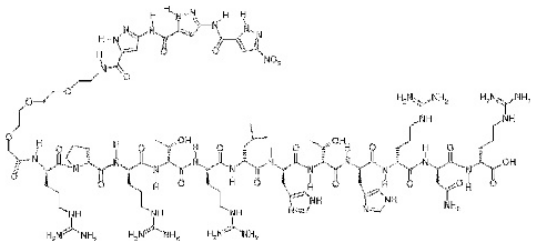
Bioinformatik, Institut für Biochemie, Friedrich-Alexander-Universität Erlangen-Nürnberg

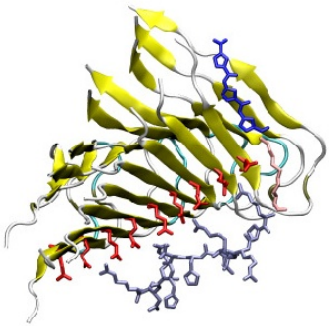
Alzheimer's disease (AD) has become a major threat to public health. Notwithstanding the impressive research efforts in many areas over the last years, a viable medication to AD is still not available to date. As converging lines of evidence suggest amyloid-β (Aβ) peptide oligomers to be the main neurotoxic species in AD,[1] investigation of the interaction of potential drug candidates with these species has gained much interest.[2]

This contribution will summarize our findings from molecular dynamics (MD) simulations about the conformational stability of small fibrillar Aβ oligomers (up to the pentamer).[3]

In the second part we present results from rational drug design of ligands targeting fibrillar Aβ oligomers. Starting point for this development was the aminopyrazole trimer ligand, which is known to possess β-sheet-breaking properties. By the design of suitable substituents which target different regions of the Aβ peptide the binding properties of the trimer ligand were significantly improved.[4]

A major activity enhancement of the trimer ligand-class was achieved, when it was covalently linked to another anti-Aβ substance, the D3-peptide.[5] This can be rationalized, as both molecules, the aminopyrazole trimer and the D3 peptide, target distinct Aβ regions in spatial proximity. The resulting hybrid ligand showed anti-Aβ properties superior to the isolated educt molecules.[6]





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Comparison of electrostatic approaches to halogen bonding description

Oleg I. Titov, Dmitry A. Shulga, Vladimir A. Palyulin, Nikolay S. Zefirov.

Department of Chemistry, M.V. Lomonosov Moscow State University, Moscow, Russia

Recently, the phenomenon of favorable interaction between heavy halogen atom (Cl, Br, I) and Lewis bases was rediscovered. It is called halogen bonding (XB) and attracts much attention [1,2] for several reasons. First, it is found in many different systems such as organic crystals, liquid crystals, polymers, biological macromolecules and their complexes. Second, the interaction energy is comparable to traditional hydrogen bonding energies. Third, it is able to form directional interactions in hydrophobic environment and complement [2] identified previously and widely used interaction patterns, such as hydrogen bonding, electrostatic interactions, dispersion interactions, hydrophobic interactions, aromatic stacking. At last, XB contradicts traditional conception of halogen in molecule being only a Lewis base.
Although the nature of XB is still under investigation, the main hypothesis states that electrostatic interaction is the main factor determining its energetics [3]. Despite several models for empirical description of XB were reported earlier, none became a scheme of common choice, due to lack of systematic investigation comparing different approaches. Moreover, development of fast empirical models capable of reliable description of XB is of crucial significance to progress in its better understanding and its successful application.

We conducted a systematic study of different approaches to description of molecular electrostatic potential (MEP) anisotropy for a set of halogen-containing organic molecules and Lewis bases (hydrides, fluorides, methyl and trifluoromethylderivatives of Cl, Br, I as XB donor and ammonia as XB acceptor). We studied extra-point charge and distributed atom-centered multipole expansion approaches. Both MEP and potential energy surface (PES) reproduction were investigated. $MP2_{cp}$/aug-cc-pVTZ level of theory was used as ab initio reference. Both models performed well in describing halogen bonding by combining enhanced electrostatics with van-der-waals potentials from widely used force fields. It is shown that multipolar approach is more prospective for further development, however it is less convenient for applied modeling.

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Quantum-Mechanics Based Molecular Field Analysis (QMFA)

Ahmed El Kerdawy, [a] Stefan Güssregen, [b] Matthias Hennemann [a,c] and Timothy Clark [a,c,d]

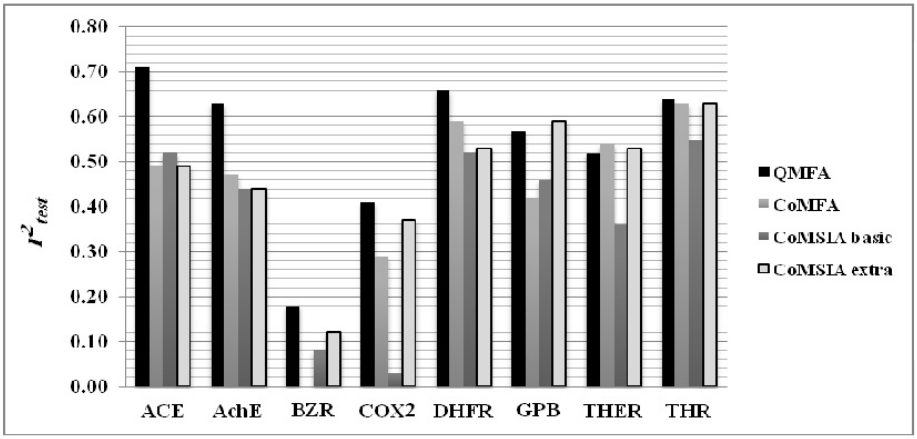
[a] *Computer-Chemie-Centrum, Friedrich-Alexander-Universität Erlangen-Nürnberg, Nägelsbachstraße 25, 91052 Erlangen, Germany.*

[b] *Sanofi-Aventis Deutschland GmbH,R&D, LGCR, Structure, Design and Informatics, Building G 878, 65926, Frankfurt am Main, Germany.*

[c] *Interdisciplinary Center for Molecular Materials, Friedrich-Alexander-Universität Erlangen-Nürnberg, Nägelsbachstraße 49, 91052 Erlangen, Germany.*

[d] *Centre for Molecular Design, University of Portsmouth, King Henry Building, Portsmouth PO1 2DY, United Kingdom.*

Despite the steady development in the techniques used for elucidating biomolecular structures, many therapeutic targets are still challenges to structural biology. [1] In such cases, ligand-based drug design (LBDD) plays a crucial role with its different approaches. Currently 3D-QSAR with its CoMFA and CoMSIA techniques is the most widely used LBDD approach for designing ligands with improved activity. [2] In these techniques, statistical analysis of the molecular interaction fields (MIFs) is carried out. The success of 3D-QSAR studies depends strongly on the quality, completeness and balance of the MIFs used. [3] Conventional MIFs have the drawbacks of being not very accurate where they are force field based and using heuristic description of intermolecular interactions. Additionally, they are unable to describe some intermolecular forces involving halogen atoms and hypervalent atoms such as sulfur. [4] In this work, we present a set of four quantum-mechanics based MIFs as descriptors for 3D-QSAR in a trial to overcome the conventional MIFs drawbacks. The new MIFs have been tested on several datasets and they showed comparable performance to the currently available 3D-QSAR techniques or surpass them for some datasets.



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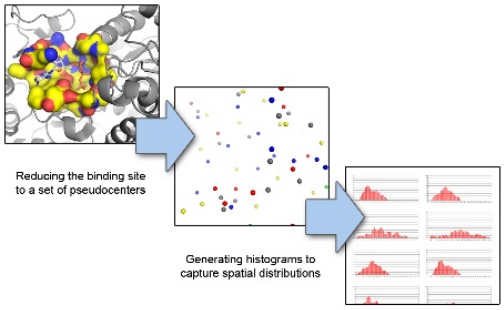
Efficient Comparison of Protein Binding Sites using Distance Histograms

Timo Krotzky, Gerhard Klebe

Institute of Pharmaceutical Chemistry, Philipps-Universität, 35032 Marburg/Lahn, Germany



Efficient determination of structural similarities between protein binding sites is one of the remaining challenges in computational chemistry and drug design as it can help to understand selectivity considerations and to predict unexpected cross-reactivity. The mutual comparison is often approached by using graphs as a way to represent and calculate metrics such as the maximum shared common subgraph to estimate a degree of similarity. Cavbase [1, 2] was developed as a tool for the automatic detection, storage and classification of putative binding sites. Cavbase assigns so-called pseudocenters to the cavity-flanking amino acids, which characterize their physicochemical properties with respect to molecular recognition. Subsequently, the pseudocenters are used as graph nodes to accomplish mutual binding site comparisons. However, the modeling of protein binding sites by means of graphs tends to be computationally very demanding, which often leads to very slow computations of the similarity measures. While this is acceptable when just a couple of structures are compared, it becomes inadequately slow for large data sets or the screening of entire databases.

In this study, we propose a Pocket Comparison using Spatial Distributions (PoCuSD), a new modeling formalism for Cavbase structures which allows for an ultrafast comparison procedure that performs similarity calculations very efficiently. Here, protein binding sites are represented by sets of distance histograms based on specific spatial reference points [3]. They characterize the distribution of pseudocenters within the cavity and can be both generated and compared with linear complexity. Attaining a speed of approximately 20,000 comparisons per second, similarity calculations across large data sets and even screenings of entire databases become easily feasible.

We demonstrate the discriminative power and the very fast runtime of this method by carrying out several classification and retrieval experiments. Among others a well studied data set of protein cavities binding either ATP or NADH is used for a classification experiment, where PoCuSD results in a considerably higher rate of correct classifications than many of the hitherto approaches while requiring only a fraction of their runtime.

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Revealing the selectivity determinants of ternary GPCR-complexes by homology modeling and molecular dynamics simulations

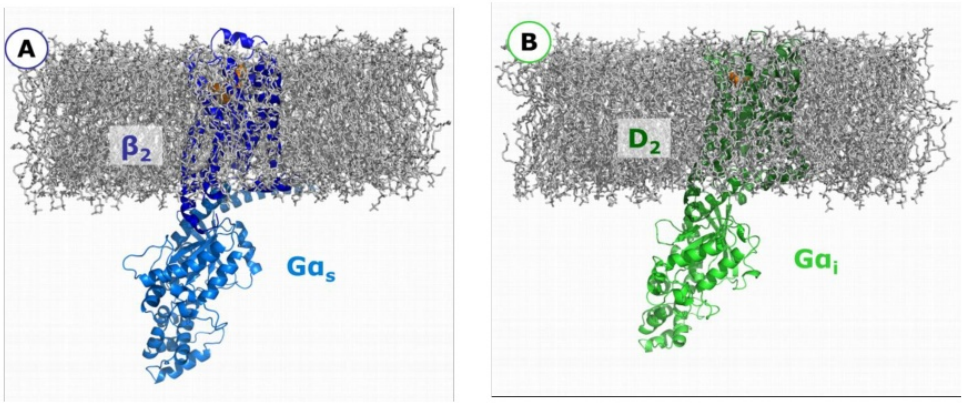
Ralf C. Kling [1, 2], Harald Lanig [2], Tim Clark [2], Peter Gmeiner [1]

[1] *Department of Chemistry and Pharmacy, Computer Chemistry Center, Friedrich Alexander University, Naegelsbachstr. 25, 91052 Erlangen*

[2] *Department of Chemistry and Pharmacy, Emil Fischer Center, Friedrich Alexander University, Schuhstr. 19, 91052 Erlangen*

G protein-coupled receptors (GPCRs) are proteins that enable signal transduction through membranes by activating G proteins. Despite many investigations, the selectivity determinants of this interaction on the amino-acid level remain to be discovered.

A recent publication on the crystal structure of the β_2-adrenergic receptor in complex with its cognate G_s protein offers important structural insights into the nucleotide-free ternary signaling complex [1]. We use the β_2-Gα_s-structure (A) as a template to generate a homology model of the D_2-Gα_i complex (B). For both systems, β_2-Gα_s and D_2-Gα_i, long term all-atom molecular dynamics simulations in a hydrated lipid bilayer identify distinct amino-acid contact sites within the receptor-G-protein interface. Investigation of these interfaces by computational alanine scanning reveals amino-acid hot spot residues that presumably contribute to receptor-G-protein selectivity.



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Molecular dynamics simulation of lipid membranes with AMBER and application to the study of radioimaging pharmaceuticals

Callum Dickson,[1] Antony Gee,[2] Ian Gould[1]

[1]*Department of Chemistry and Institute of Chemical Biology, Imperial College London, South Kensington, SW7 2AZ, United Kingdom*

[2]*Division of Imaging Sciences, King's College London, St Thomas' Hospital, London, SE1 7EH, United Kingdom*

Positron emission tomography (PET) scanning is a molecular imaging technique allowing the detection and analysis of biological processes, including metabolism and disease. PET scanning is regularly implemented in the imaging and study of diseases such as cancer, Alzheimer's and Parkinson's disease and is also becoming increasingly popular to aid the drug discovery process.

To perform a PET scan, the patient is administered a small molecule radiotracer, which emits a trace amount of radiation and binds to the site of interest, allowing an image to be constructed. In order to image new targets, novel radiotracers must be designed. However a limitation in the design of new radiotracers is non-specific binding, whereby the tracer binds to off-target species, such as cell membranes, creating an uninformative image with poor contrast. An in silico indicator, able to predict the level of non-specific binding a new radiotracer may undergo in vivo prior to synthesis and testing, would be extremely beneficial to the PET community.

In this work we investigate non-specific binding using molecular dynamics (MD) to study the interaction of PET radiotracers with lipid bilayers, a simple model for the cell membrane, using the AMBER MD package. To accurately model lipid bilayers, suitable parameters were first constructed.[1] These parameters are currently being combined with the AMBER Lipid11 modular lipid force field [2] to create an updated, unified AMBER lipid force field. The potential of mean force (PMF) method has been inserted into AMBER, in order to calculate the free energy of transfer of radiotracers through a lipid membrane. The PMF method is currently being applied to a dataset of well characterised PET radiotracers to investigate the relationship between membrane permeability and non-specific binding.

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What determines oxazolidinone binding to the large ribosomal subunit?

Jagmohan Saini, Simone Fulle, Nadine Homeyer, Holger Gohlke

Institute of Pharmaceutical and Medicinal Chemistry, Heinrich-Heine-University, 40225 Düsseldorf, Germany

The ribosome is an attractive target for antibiotics that inhibit protein synthesis by binding to the peptidyl transferase center (PTC) and exit tunnel of the large ribosomal subunit. Structural determination by X-ray crystallography only provides static views of the binding processes but does neither reveal the dynamics involved in antibiotics binding nor energetic determinants of binding. Computational approaches such as molecular dynamics (MD) simulations in combination with free energy calculations are suitable to fill this gap.

In the present study, we aim at investigating the determinants of binding of oxazolidinone antibiotics. This class is one of the only three new classes of synthetic antibiotics that have entered the market during the last 30 years especially for the treatment of Gram-positive infections. [1] In particular, we investigate linezolid, its derivative radezolid, and a structurally related oral anti-coagulant drug rivaroxaban in complex with the H. marismortui (H50S) archaeal structure. [2] The molecular mechanics adaptive Poisson Boltzmann surface area (MM-APBSA) method is used to determine the effective free energy of binding, also on a per-residue level. [3] Furthermore, we are investigating the influence of mutations that are not directly in contact with the ligand but still confer resistance to linezolid. [4]

The structural and energetic analysis identifies radezolid as better binder than linezolid, and rivaroxaban as a non-binder to the H50S subunit. As to the influence of mutations, we observe that a double mutant confers linezolid resistance, which is in concert with published data.

The information gained from this study provides insights into the binding of oxazolidinones to H50S and can be used to develop new oxazolidinone antibiotics rationally.

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Dynamics Direct Specificity of Effector Caspases

Julian E. Fuchs, Susanne von Grafenstein, Roland G. Huber, Klaus R. Liedl

Department of Theoretical Chemistry, University of Innsbruck, Centre for Chemistry and Biomedicine, Innrain 80/82, 6020 Innsbruck, Austria

The caspase family of cysteine proteases plays a key role in programmed cell death and inflammation, turning caspases into interesting drug targets [1]. Unfortunately, specific ligand binding to one particular caspase isoform is difficult to achieve, as substrate specificities of caspases are highly similar.

In an effort to rationalize subtle differences in substrate specificity of two closely related caspases [2], we investigated the substrate promiscuity of the effector caspases 3 and 7 by data mining [3] and by molecular dynamics simulations. We found a strong correlation between binding site rigidity and substrate readout for individual caspase subpockets explaining more strigent substrate readout of caspase 7 via its narrower conformational space. Caspase 3 subpockets S3 and S4 show elevated flexibility explaining the more unspecific substrate readout of this isoform in comparison to caspase 7. We show by *in silico* exchange mutations in the S3 pocket of the proteases, that a proline residue in caspase 7 contributes to the narrowed conformational space of the binding site.

These findings explain substrate specificities of caspases via a mechanism of conformational selection [4] and highlight the crucial importance of conformational dynamics in substrate recognition of proteases. The ensemble perspective of substrate specificity is proposed to be extended to general protein-protein-interfaces. Hence, we hypothesize that molecular dynamics simulations could lead the way to identify specific anchor points for targeting this challenging target class.

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Interactions of Halogen Atoms to Protein Binding Sites and Contributions to Binding Affinity

Hans Matter*, Stefan Güssregen, Marc Nazaré

* Hans.Matter@sanofi.com
Sanofi-Aventis Deutschland GmbH
R&D LGCR/Structure, Design & Informatics FF
Industriepark Hoechst
Bldg. G878, Room 408
D-65926 Frankfurt am Main

Experimental evidence suggests that organic chlorine and bromine atoms are involved in non-bonded protein-ligand interactions, thus contributing to binding affinities. These interactions include halogen-bonding and contacts to aryl rings. Introducing halogen atoms at distinct positions of factor Xa inhibitors consistently improves free energy of binding by interaction to a tyrosine ring in the active site. The nature of these interactions was studied to understand the contribution to affinity. Geometric preferences for this contact were revealed by investigations in protein and small-molecule databases. It will be discussed how these atypical interactions can be introduced into field-based molecular descriptions. As classical force-fields can not adequately account for halogen-mediated interactions due to missing treatment of the "sigma"-hole, we have extracted local properties from quantum-mechanical techniques that do not suffer from these limitations. Regression models from those fields provide a significant advantage to understand SAR features.