21. Darmstädter Molecular Modelling Workshop

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

Tuesday, May 15th - Wednesday, May 16th 2007

Once again, we in CCC are happy to welcome you to the *21st Darmstädter Molecular Modelling Workshop*. The goals of the Workshop are to give graduate students and young postdocs an opportunity to present their work, to provide a forum for molecular modeling and to give young researchers the opportunity to meet established researchers, both industrial and academic. The *Molecular Graphics and Modelling Society – Deutschsprachige Sektion* (MGMS-DS) is, as always the organizer of the Workshop and provides financial support to students so that they can attend the workshop.

We especially thank our sponsors, who have not only this year enabled us to provide an excellent program at a very low price, but many of whom have supported the *Darmstädter Molecular Modelling Workshop* consistently and generously over its entire history.

Coordination of scientific program

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Dear colleagues,

The *Darmstädter Molecular Modelling Workshop* takes place every year on its traditional dates of the Tuesday and Wednesday before *Christi Himmelfahrt (Ascension Day)*; this year May 15th and 16th. This is the fifth time that the Workshop has taken place in Erlangen after 16 years in Darmstadt. The Workshop is organized by Prof. Tim Clark's group from the *Computer-Chemie-Centrum* (CCC) *der Friedrich-Alexander-Universität Erlangen-Nürnberg*. The organization of the scientific program traditionally alternates between scientists from industry or academia. In this year, Dr. Stefan Güßregen from Sanofi-Aventis, Frankfurt is responsible for the scientific program.

The goal of the Workshop is to allow young scientists, especially graduate students, to present their work to an audience that consists of modeling specialists from industry and universities.

Contributions from all branches of modeling, from life-sciences to materials modeling, are welcome.

Our Plenary Speakers this year are

Wilfred F. van Gunsteren
ETH Zürich

Thierry Langer
University of Innsbruck and Inte:Ligand GmbH

The official language of the Workshop is English.

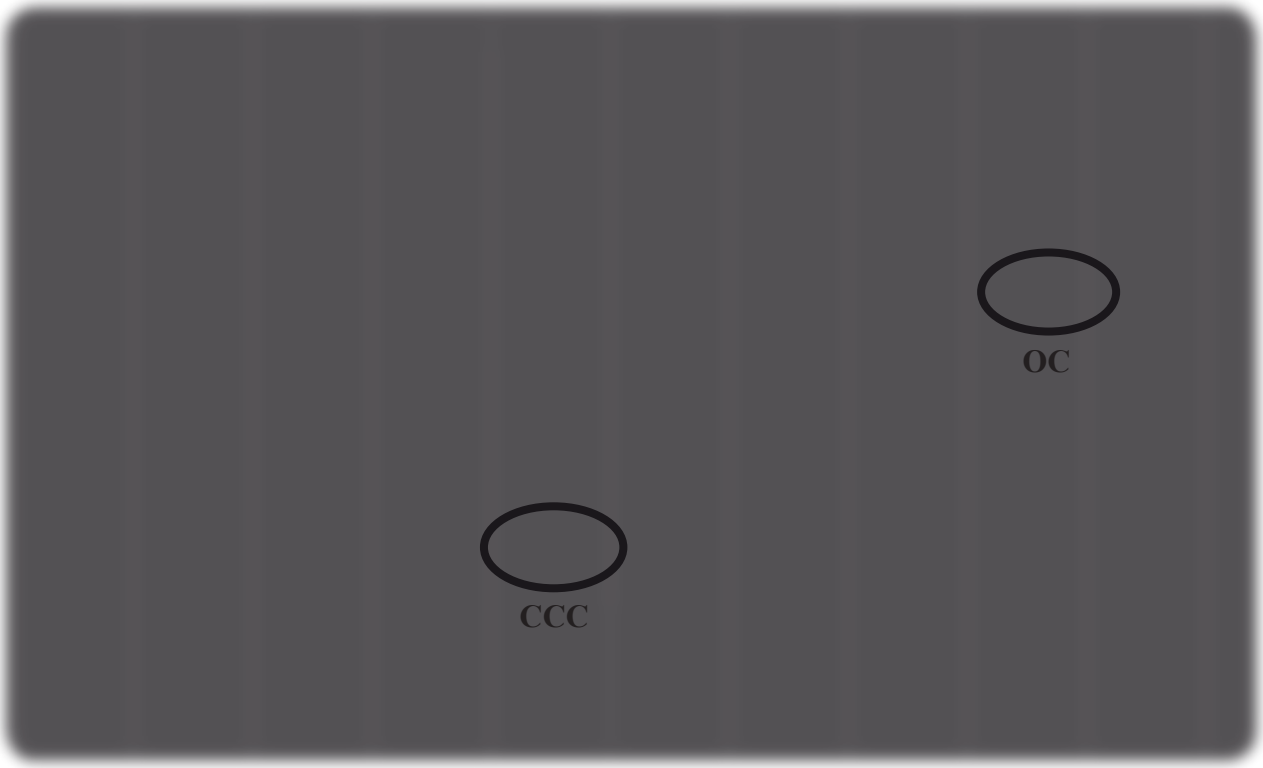
Awards

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 EUR 500)
2nd Winner: EUR 200 travel expenses reimbursement
3rd Winner: EUR 100 travel expenses reimbursement

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

Locations



This years workshop will take part in **two different locations**.
The regestration and all lectures will proceed in the Institute of Organic Chemistry (OC), wheras the poster session and the dinner on tuesday evening will take place in the Computer-Chemie-Centrum (CCC).

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Universität Erlangen-Nürnberg

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Universität Erlangen-Nürnberg

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Program: Tuesday, May 15th 2007

8:00-9:15	Registration
9:15-9:20	Welcome remarks / Agenda review
9:20-10:35	**Plenary Lecture: Wilfred van Gunsteren** Computer simulation of biomolecular systems: Where do we stand?
10:35-11:05	Coffee break
11:05-11:30	**Abinav Verma** All-atom protein folding and structure prediction in a transferable universal free-energy force-field
11:30-11:55	**Christoph Hartmann** IRECS: Accounting for side-chain flexibility by prediction of conformation ensembles
11:55-12:20	**Andreas May** Global receptor flexibility in kinase cross-docking calculations utilizing elastic network normal modes
12:20-12:45	**Simone Fulle** Analyzing the flexibility of RNA structures: the ribosomal exit tunnel as a case study
12:45-13:45	Lunch break
13:45-14:10	**Florian Sieker** Correlation between structural flexibility and tapasin dependence of MHC class I molecules analyzed by molecular dynamics studies
14:10-14:35	**Vlad Cojocaru** Gating motions limit the access to the burried active site of cytochrome P450 2C9
14:35-15:00	**Florian Haberl** New Insights into the Induction of Tetracycline Repressor Proteins
15:00-15:35	Coffee break
15:35-16:00	**Kristin Engels** Cyclin-Dependent Kinases of Apicomplexan Parasites as Target Proteins for the Rational Design of Antiparasitic Drugs
16:00-16:25	**Martin Sippel** Targeting HIV Integrase - Discovering peptidomimetics as a novel class of inhibitors

Program: Tuesday, May 15th 2007

16:25-16:50	**Barbara Gioffreda** 5-Benzyl-2-hydroxy-5H-benzo[b]carbazole-6,11-dione derivatives as potential inhibitors of the molecular chaperone HSP90
16:50-17:15	**Sebastian Radestock** Homology model based virtual screening for GPCR ligands using docking and target-biased scoring
17:15-18:15	Annual Meeting of the MGMS-DS
18:00-22:00	Poster Presentation / Buffet

Program: Wednesday, May 16th 2007

The morning lectures all take place in the 'kleiner Hörsaal'

9:00-9:25	**Jr-Hung Lin** Spherical harmonic functions based non-atomistic molecular dynamics simulation
9:25-9:50	**JGO Ojwang** Modelling of complex metal hydrides - a force field approach
9:50-10:15	**Arvydas Tamulis** Quantum Processes of Self-Assembly, Photosynthesis and Molecular Computing in Artificial Minimal Living Cells
10:15-10:45	Coffee break

The morning lectures all take place in the 'kleiner Hörsaal'

10:45-11:10	**Robert Fischer** SwiFT: An index structure for reduced graph descriptors in virtual screening and clustering
11:10-11:35	**Hannes Wallnoefer** Generation of a Special Iron-binding Feature – Pharmacophore Modeling of CYP17
11:35-12:45	Lunch break
12:45-13:45	**Plenary Lecture: Thierry Langer** In silico polypharmacology: Techniques for bio-activity profiling of potential drug candidates
13:45-14:10	**Patrick Markt** Pharmacophore Modeling and Parallel Screening for PPAR Ligands
14:10-14:40	Coffee break
14:40-15:05	**Gudrun Spitzer** Evaluation of Pharmacophore Modeling Based Virtual Screening: Comparative Assessment of Catalyst, Phase and MOE at the Example of HRV Coat Protein
15:05-15:30	**Thi Hoang Thuan Huynh Buu** A scoring function to rank pharmacophoric alignments and its application to H1 antagonists
15:30-15:55	**Johannes Kirchmair** Towards maximum computational performance: Does a lower number of conformations increase screening efficiency?
15:55-16:10	Poster & Lecture awards

Poster

P1	**N. Schneider**	Separating Drugs from Nondrugs
P2	**Mohamed Abdel Rahman Shaaban**	Molecular modeling of new synthesized pyrazolo[3,4-d]pyrimidine-4-ones as phosphodiesterase-5 inhibitors
P3	**Daniel Cappel**	Effects of Water Molecules on Protein-Ligand Interactions in a Charged Model Binding Site
P4	**Klaus Roman Liedl**	DNA Minor Groove Pharmacophores Describing Sequence Specific Properties
P5	**Kerstin Höhfeld**	Workflow-based Alternative Scaffold Identification
P6	**Urszula Uciechowska**	Docking Studies and Molecular Dynamics Simulations of Novel Sirtuin2 Inhibitors
P7	**Haijun Jiao**	Diasteroselectivity of Chiral N-Dienyl Lactams in Diels-Alder Reaction
P8	**Kanin Wichapong**	Molecular docking studies of Dengue NS2B/NS3 protease with its inhibitors
P9	**Kanin Wichapong**	3D-QSAR studies on tetra-peptide inhibitors of West Nile Virus NS2B/NS3 protease using CoMFA and CoMSIA
P10	**Silke Pienkny**	Characterization and homology modelling of a new plant O-methyltransferase from Papaver somniferum
P11	**Jeremy Curuksu**	Design of Advanced Biased Sampling for Molecular Dynamics Simulations of Nucleic Acids
P12	**S. Bayat**	The Interaction of Metal Ions with Thymine Tautomers: A Computational Study
P13	**Carsten Wittekindt**	COSMOtherm: A Universal Tool for the Prediction of ADME Parameters
P14	**Jens Gimmler**	Protein structure calculation with a Max-Min Ant System
P15	**Guido Wagner**	The Molecular Modelling Program MOMO: Experiments on the Automatic Parameterization of Empirical Point Charge Models
P16	**Alexander Metz**	Hybrid solvation model for MM – PB/SA free energy calculations
P17	**Amsaveni Muruganantham**	Mechanism of alkene aziridination with Cu-bispidines: A DFT exploration
P18	**Bernd Schilling**	Theoretical adsorption model of guest molecules in nanoporous alumina
P19	**S. Distinto**	Computational and experimental study of non covalent monoamine oxidase inhibitors
P20	**Marta Zajaczkowski**	Copper-catalyzed aziridination: tailor-made ligands for higher reactivity

Poster

P21	**Christopher Pfleger**	Investigating the plasticity of protein-protein interfaces by MD and constrained geometric simulations
P22	**Tatyana E. Shubina**	Electron-Transfer Catalysis on the Surface of Anhydrous Copper Sulfate
P23	**Tatyana E. Shubina**	Experimental and QSPR Study of the Thermodynamics of Complexation of Methyl Substituted Benzenes and the Silver Cation
P24	**Geun-Yung Ko**	Using molecular modelling tools to define the putative binding site of a human $P2Y_2$-receptor model
P25	**Christian Laggner**	Refining pharmacophores for PPAR with information from the binding site shape
P26	**Tim ten Brink**	The influence of ligand protonation in protein-ligand-docking
P27	**Sascha Tayefeh**	Computational study of the Kcv potassium channel: functional impact of mutations and the protonation state
P28	**Hakan Kayi**	Parameterization of Zinc for AM1*
P29	**R. Paparcone**	On the Generation of intrinsic electric dipole fields as the basis for the understanding of the morphogenesis of fluoroapatite-gelatine nano-composites
P30	**Srinivasaraghavan Kannan**	Enhanced Sampling of Peptides and small Protein Conformations using Biasing Potential Replica Exchange Molecular Dynamics Simulations
P31	**O. Korb**	When Ants Design Scoring Functions
P32	**J. Selent**	Binding Properties of Butyrophenone Derivatives with a Multi-Receptor Profile Similar to Clozapine
P33	**Nico Riemann**	A Theoretical Investigation on the Geometries of Glucagon-like Peptide-1 and some Analogues, and their interactions with Dipeptidyl Peptidase DPP-IV
P34	**A. Cho**	Importance of accurate charges in molecular docking: QM Polarized Ligand Docking approach
P35	**Valeria Antonazzo**	Development of a GBPM-based pharmacophore for virtual screening of PKB/Akt inhibitors
P36	**Rene Meier**	A new approach for flexible protein-ligand docking based on Particle Swarm Optimisation
P37	**Dennis M. Krüger**	Extensive comparison of structure - and ligand-based virtual screening protocols considering enrichment factors and hitlist complementarity
P38	**Christian Kramer**	In-Silico Prediction of hERG blockade
P39	**Mohamed Zerara**	New insights in the penetration of local anesthetics into membranes using the molecular free energy surface density model (MolFESD)
P40	**Mohamed Zerara**	Parametrization of the molecular free energy surface density (MolFESD) for various systems

P41	**Arjen-Joachim Jakobi**	ParaFrag: A Novel Tool for Surface-Based Fragment Comparison
P42	**W. Sherman**	Flexible Receptor Docking to Account for “Induced Fit” Effects
P43	**Ute Seidel**	Molecular Dynamics Characterization of the Induction Mechanism of a Reverse Phenotype of the Tetracycline-Repressor
P44	**R. Heinke**	Virtual and Biological Screening of Novel Histone Arginine Methyltransferase PRMT1 Inhibitors
P45	**Christophe Jardin**	A QM/MM investigation of the phosphoryl transfer between protein IIA^{Glc} and the cytoplasmic domain IIB^{Glc} of the glucose transporter $IICB^{Glc}$ of the Escherichia coli glucose phosphotransferase system
P46	**Stefan Henrich**	Comparative Binding Energy Analysis for Binding Affinity and Target Selectivity Prediction in Virtual Screening
P47	**Sergio Sanchez**	An Optimal Coordinate System for Geometry Optimization in VAMP
P48	**Barbara Zdrazil**	Molecular Dynamics Simulations of new putative human DNA pol α inhibitors for treatment of excessive keratinocyte proliferation
P49	**Anselm H. C. Horn**	Improving Semiempirical MO Methods: Sample Parametrization of an OM3-like Hamiltonian
P50	**Christoph Hartmann**	IRECS: Prediction of side-chain conformation ensembles for flexible docking
P51	**O.G. Othersen**	Automated Generation of Fragment-Based Rules for Mutagenicity Prediction
P52	**Ralph Puchta**	Why does $[IrH_2(R_2PCH_2CH_2NH_2)_2)]^+$ favour Transfer Hydrogenation over direct H_2-Hydrogenation? − A Computational Approach
P53	**B. Fischer**	Receptor specific Scoring-Function: Improving classical forcefields with quantum mechanical calculations
P54	**Andreas Koch**	Through space NMR shielding of aromatic compounds
P55	**Christof Jäger**	Molecular-Dynamics Simulations of a Structurally Defined Micelle
P56	**W. Wenzel**	De novo protein structure prediction and folding with free energy models
P57	**M. Wielopolski**	Electron-Transfer Systems Based on C_{60} – Relationship Between Chemical Nature and Long-Range Electron Transfer
P58	**Maximilian Werk, André Heber**	Selective Inhibition of CDKs

Lectures

Tuesday, May 15th 2007

Computer simulation of biomolecular systems: where do we stand ?

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Computation based on molecular models is playing an increasingly important role in biology, biological chemistry, and biophysics. Since only a very limited number of properties of biomolecular systems is actually accessible to measurement by experimental means, computer simulation can complement experiment by providing not only averages, but also distributions and time series of any definable – observable or non-observable – quantity, for example conformational distributions or interactions between parts of molecular systems. Present day biomolecular modelling is limited in its application by four main problems: 1) the force-field problem, 2) the search (sampling) problem, 3) the ensemble (sampling) problem, and 4) the experimental problem. These four problems will be discussed and illustrated by practical examples. Perspectives will be outlined for pushing forward the limitations of molecular modelling.

All-atom protein folding and structure prediction in a transferable universal free-energy force-field.

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Exploiting Anfinsen's thermodynamic hypothesis, all-atom free-energy force-fields offer a promising alternative to kinetic molecular mechanics simulations of protein folding and association. Here we report an accurate, transferable all-atom biophysical force-field (PFF02[1]) that stabilizes the native conformation of a wide range of proteins as the global optimum of the free-energy landscape. For 32 proteins of the ROSETTA decoy set and 6 proteins that we have previously folded with PFF01 we find near native conformations with an average backbone RMSD of 2.14Å to the native conformation and an average z-score of -3.46 to the corresponding decoy set[2]. Generating continuous folding trajectories starting from completely extended conformations we predicatively and reproducibly fold three non-homologous hairpin-peptides, a three-stranded beta sheet, the all-helical 40 amino-acid HIV accessory protein and a zinc-finger ββα motif to near-native conformations. In addition, we demonstrate all-atom folding of the 54 amino-acid engrailed homeodomain in about 24 hours using a massively parallel evolutionary algorithm[3] on a distributed computational architecture. These data demonstrate the viability and efficiency of the free-energy approach for de-novo protein folding and offer perspectives for rational force-field evolution and protein structure prediction.

[1] A Verma & W Wenzel; Towards a universal free-energy approach for all-atom protein folding and structure prediction; **2007**; submitted.
[2] A Verma &WWenzel; Protein structure prediction by all-atom free-energy refinement; *BMC Structural Biology*; 7:12 (**2007**)
[3] A Verma, SM Gopal, KH Lee, JS Oh & W Wenzel; De novo all atom folding of a 40 amino acid three helical protein in a scalable evolutionary algorithm; *J. Comp. Chem* (**2007**); in press

IRECS: Accounting for side-chain flexibility by prediction of conformation ensembles

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Many side chains of proteins are so flexible that their structural description by a single conformation is inadequate. However, their conformational space is constrained by their molecular environment, especially in the core of the protein, and thus can be limited to quite small ensembles of conformations. Our side chain prediction tool IRECS[1] (Iterative REduction of Conformational Space) is able to identify ensembles of most probable conformations for all side chain in a protein. The probability of each conformation is computed using a knowledge-based statistical potential called ROTA, which was constructed for IRECS. The potential was optimized to discriminate between side-chain conformations of native and rotameric decoys of protein structures. On the basis of a given rotamer library IRECS ranks side chain rotamers of a protein according to the probability with which the side chain adopts the respective rotamer conformation. IRECS allows for the selection of rotamer ensembles of arbitrary size and various levels of flexibility. These ensembles are useful for all structure-based studies of proteins where the flexibility of side chains plays a major role, which is the case in many docking scenarios.
By restricting the number of rotamers per side chain to one, IRECS can optimize side chains for a single conformation model. The average accuracy of IRECS for the χ_1 and χ_{1+2} dihedral angles amounts to 84.7% and 71.6%, respectively, using a 40° cutoff. We compared IRECS with SCWRL[2] and SCAP[3], the performance of IRECS is comparable to both methods for single conformation models. IRECS is available for download from the URL *http://irecs.bioinf.mpi-inf.mpg.de*.

[1] C. Hartmann, I. Antes, T. Lengauer, *Protein Sci*, **2007**, *15*, accepted.
[2] A. A. Canutescu, A.A Shelenkov, R. L. Dunbrack, *Protein Sci* **2001,** *12*, 2001-2014.
[3] Z. Xiang, B. Honig, *J Mol Biol, **2001**, 311*, 421-430.

Global receptor flexibility in kinase cross-docking calculations utilizing elastic network normal modes

Andreas May, *Martin Zacharias*
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Protein-ligand association can frequently involve significant side chain and backbone conformational changes of the protein partners. In most current protein-ligand docking approaches conformational flexibility is only included on a local level. A computationally rapid method has been developed that allows to approximately account for global conformational changes during protein-protein as well as protein-ligand docking[1]. The approach employs pre-calculated collective degrees of freedom as additional variables during docking minimization. The global collective degrees of freedom are obtained from normal mode analysis using a Gaussian network model for the protein. The approach was applied to several protein-protein test systems, as well as in a cross-docking study using several kinase structures, which have been co-crystallized with different inhibitors. The results indicate that docking including global flexibility can significantly improve the agreement of near-native docking solutions with the corresponding experimental structures at a very modest increase of computational demands compared to rigid receptor docking. Efforts to couple the approach with an efficient treatment of side chain flexibility will also be reported.

[1] A. May, M. Zacharias, *Biochim. Biophys. Acta* **2005**;*1754*:225-231.

Analyzing the flexibility of RNA structures: the ribosomal exit tunnel as a case study

Simone Fulle, *Holger Gohlke*
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Understanding the flexibility characteristics of biomacromolecules is crucial to understanding their biological function. This holds true particularly for RNA molecules which require large conformational changes to undergo their diverse functional roles. Here a new topological network representation of RNA structures is presented that allows analyzing RNA flexibility/rigidity in just a few seconds based on constraint counting. The method extends the FIRST [1] approach, which identifies flexible and rigid regions in atomic detail in a single, static three-dimensional molecular framework. So far, the algorithm has been primarily applied to identify the flexible and rigid regions in proteins but nucleic acids such as RNA structures remain unexplored so far.[2]

Initially, the network rigidity of a canonical A-form RNA is analyzed by counting on constraints of network elements of increasing size. These considerations demonstrate that it is the inclusion of hydrophobic contacts into the RNA topological network that is crucial for an accurate flexibility prediction. The counting also explains why a protein-based parameterization results in overly rigid RNA structures. The new network representation is validated on a $tRNA^{ASP}$ structure and NMR-derived ensembles of RNA structures. Thereby, the flexibility predictions demonstrate good agreement with the experimental mobility data, and the results are superior compared to predictions based on two previously used network representations.

Remarkably, the approach can be applied to very large systems on the order of several hundreds of thousands of atoms, such as the ribosome. As a case study, we finally focus on an analysis of the flexibility properties of the protein exit tunnel region. The following results stand out: I) In agreement with experiment that no large-scale conformational changes can be observed in the vicinity of the tunnel, we also identified large parts of the tunnel neighboring regions to be rigid. II) Even more interesting, FIRST detects regions inside the tunnel to be flexible that are known to participate in the dynamic regulation of the ribosomal function. In particular, the tunnel lining protein L22 plays an important role in sequence specific gating of nascent chains by adopting one of two known conformations. With the new parameterization developed here, hinges responsible for the conformational change of L22 are identified and new insights into the intrinsic mobility of the protein are obtained.

[1] D. J. Jacobs, A. J. Rader, L. A. Kuhn, M. F. Thorpe, *Proteins*, **2001**, *44*, 150-165.
[2] H. Gohlke, L. A. Kuhn, D. A. Case, *Proteins*, **2004**, *56*, 322-337.

Correlation between structural flexibility and tapasin dependence of MHC class I molecules analyzed by molecular dynamics studies

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MHC class I molecules load antigenic peptides in the endoplasmatic reticulum and present them at the cell surface. Efficiency of peptide loading depends on the class I allele and can involve interaction with tapasin and other proteins of the loading complex. Previous molecular dynamics simulations performed in our lab[1] showed that the flexibility of a-helices flanking the binding groove is increased if no peptide is bound to the MHC molecule. Here we present results of two class I alleles in presence and absence of peptide cargo in correlation with their dependence on tapasin. Allele HLA-B*4402 (Asp at position 116) depends on tapasin for efficient peptide loading whereas HLA-B*4405 (identical to B*4402 except for Tyr116) can efficiently load peptides in the absence of tapasin. Both alleles adopt very similar structures in the presence of the same peptide. Comparative unrestrained molecular dynamics simulations on the a1/a2 peptide binding domains have been performed and resulted in structures close to experiment in the presence of bound peptides for both alleles. In the absence of peptides allele-specific conformational changes occurred in the first segment of the a2-helix that flanks the peptide C-terminus binding region (F-pocket) and contacts residue 116. This segment is also close to the proposed tapasin contact region. For B*4402, a shift towards an altered F-pocket structure deviating significantly from the bound form was observed. Subsequent free energy simulations on induced F-pocket opening confirmed a conformation that deviated significantly from the bound structure in case of B*4402. For B*4405 a free energy minimum close to the bound structure was found. The simulations suggest that B*4405 has a greater tendency to adopt a peptide-receptive conformation already in the absence of peptide allowing tapasin-independent peptide loading. A possible role of tapasin could be the stabilization of a peptide receptive class I conformation in case of HLA-B*4402 and other tapasin-dependent alleles[2]. Recently, experimental results on the mode of action of tapasin[3] largely confirmed our theoretically derived model. Based on these findings we proposed a rapid approach to predict tapasin dependent and independent behavior, respectively for HLA-B*44 alleles with different substitutions at position 116. This model makes use of the MM-PBSA method[4] to calculate the total free energy of a system which can be correlated to tapasin dependence of the respective allele.

[1] M. Zacharias, S. Springer, *Biophys J.*, **2004**; 87(4), 2203-2214.
[2] F. Sieker, S. Springer, M. Zacharias, *Protein Sci*., **2007**, 16(2), 299-308.
[3] M. Chen, M. Bouvier, *EMBO J*., **2007,** 26(6), 1681-90.
[4] J. Srinivasan, T. E. Cheatham, III, P. Kollman, D. A. Case, *J. Am. Chem. Soc*., **1998**, 120, 9401-9409.

Gating motions limit the access to the burried active site of cytochrome P450 2C9

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The human cytochrome P450 2C9 (CYP2C9) is a member of the hepatic endoplasmic reticulum membrane-bound monooxygenases and contributes to the metabolism of about 20 of all xenobiotics. Dangerous metabolic interactions between medicines, different rates of detoxification among human races, the biosynthesis of essential compounds, or the production of carcinogens, are among the most important consequences of the cytochrome P450 function. Substrate ingress and product egress require dynamic opening of channels from the deeply buried catalytic center to the protein surface. From 360 distinct simulations of two conformations of CYP2C9 we found that ligands use four main routes to egress from the active site, three short hydrophilic (2c, 2ac, 2e) and one long hydrophobic (2a) pathways, all opening towards the protein surface surrounding the B-C loop. Ligand egress also occurred via four secondary pathways opening towards the opposite side of the protein surface. The distribution of egress routes depends on the enzyme conformation, and on the ligand protonation state. Egress via the longest hydrophobic pathway, 2a requires the opening of an internal phenylalanine gate formed by PHE 100, PHE 114, and PHE 476. Two types of interactions contribute to the selection of alternative egress routes: (i) transient stacking interactions between aromatic rings of ligands and aminoacids, and (ii) hydrogen bonds between the ligand's acidic group and the positively charged residues located at the pathway entraces. Based on these findings, and on experimental data available, we propose that the initial selection of small acidic substrates by CYP2C9 is determined by the positively charged residues located at the pathway entrances. Lipo-soluble substrates ingressing via the 2a route are delivered to the site of catalysis by a network of transient pi-pi stacking interactions between ligands and aromatic side-chains. The closing of the phenylalanine gate may play a role in locking the substrate into the optimal position for catalysis, as well as in prohibiting egress of products via pathway 2a. Water soluble substrates might use pathways 2c, 2ac, and/or 2e both for ingress to and egress from the CYP2C9 active site. These findings also suggest that substrate channeling between different P450s or between one P450 and other metabolizing enzymes could occur via the 2c, 2ac, 2e routes. Additionally, we cannot rule out the possibility that the enzyme undergoes conformational changes that might lead to ingress and/or egress via the secondary pathways.

New Insights into the Induction of Tetracycline Repressor Proteins

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The tetracycline-repressor protein (TetR) has achieved immense importance as the archetypical signal-transduction system. It is important both clinically (because it controls expression of the tetracycline-antiporter protein (TetA), which actively pumps tetracyclines out of the bacterial cell) and as a versatile gene-switch in microbiological research[1] Normally, TetR is induced by a tetracycline complexed with Mg^{2+}. We[2] recently determined the mechanism of induction by this route using long time-scale molecular dynamics simulations. However, Hillen et al.[3] recently discovered that TetR can be induced by small peptides in the absence of Mg^{2+} and Muller et al[4] have been able to determine the X-ray structure of TetR complexed to an inducer peptide. We now report molecular-dynamics simulations designed to determine the mechanism of induction of tetR in this case without Mg^{2+}.

This work was supported by the Deutsche Forschungsgemeinschaft as part of Sonderforschungsbereich 473 “Mechanisms of Transcriptional Regulation” (http://www.biologie.uni-erlangen.de/mibi/sfb473.html).

[1] Saenger, W.; Orth, P.; Kisker, C.; Hillen, W.; Hinrichs, W. The Tetracycline Repressor - A Paradigm for a Biological Switch. *Angew. Chem., Int. Ed.* **2000**, *39*, 2042-2052.
[2] Lanig, H.; Othersen, O.; Seidel, U.; Clark, T. Structural changes and bonding characteristics of the Tetracycline-Repressor binding site on induction; *J.Med. Chem.*, **2006**,. *49*, 3444-3447.
[3] Klotzsche, M.; Berens, C.; Hillen ,W. A peptide triggers allostery in tet repressor by binding to a unique site. *J Biol Chem.* **2005,** *26*, 24591-9.
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Cyclin-Dependent Kinases of *Apicomplexan* Parasites as Target Proteins for the Rational Design of Antiparasitic Drugs

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Apicomplexan parasites enclose several human-pathogenic as well as animal-pathogenic protozoans, like *Eimeria tenella*, *Toxoplasma gondii* and *Plasmodium falciparum.* The animal-pathogenic representative *E. tenella* provokes coccidiosis a poultry disease, which cause tremendous economic losses to the world poultry industry. Considerable increase of drug resistance makes it necessary to develop and pursue new therapeutic strategies. Cyclin-dependent kinases (CDKs) are key molecules in the regulation of the cell cycle and are therefore prominent target proteins in parasitic diseases. To date several proteins from *apicomplexan* parasites, which are homologous to *mamalian* CDKs have been characterized using classical molecular biology techniques. Our extensive bioinformatics analysis revealed additional candidate proteins and especially two new CDK-like proteins were identified for *E. tenella*. Using an x-ray crystal structure of human CDK2 as template, protein models were built by comparative homology modelling. A structural comparison of the resulting protein models, especially within the active site, revealed structural differences and could be used for the optimization of specific CDK inhibiting compounds for *apicomplexan* parasites. A virtual screening campaign on EtCRK2, a CDK of *E. tenella* resulted in hits, which have been verified *in vitro*. These verified hit compounds were used for a substructure search in an in house compound database leading to a set of potential inhibitors. In order to select inhibitors of higher potency and selectivity, docking studies were performed and the ligand-receptor binding interactions were analyzed in detail. LIE and MM-GBSA calculations provide the opportunity to accurately predict the relative potencies of the selected substructures.

Targeting HIV-1 Integrase – Discovering peptidomimetics as a novel class of inhibitors

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HIV Integrase is one of the three enzymes of the HI virus. In contrast to reverse transcriptase and protease, it is not yet exploited by a marketed drug for antiretroviral therapy. Accordingly, the search for new integrase inhibitors is a very active area of anti-HIV research[1].
HIV-1 integrase acts as a multimer (at least dimer) in its active state; thus, it is reasonable to conceive multimerization disruption as an alternative approach to enzyme inhibition. A small number of peptides has been reported as disruptors of multimerization[2][3]. These peptides were derived from integrase dimer interface helices which are crucial for multimerization through protein-protein interactions. Due to the poor bioavailability of natural peptides, efforts have been directed to the search for compounds capable of mimicking the inhibitory properties of peptides, but with higher bioavailability. Several such peptidomimetics of a-helices have been described, and successful inhibition by these non-peptidic molecules has been reported[4][5]. In this study, peptidomimetics against HIV-1 integrase multimerization are designed and a series of compounds based on an imidazole scaffold is analysed in a comparative docking study. The most promising candidates will finally be subjected to synthesis and experimental testing via *in-vitro* assays.

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5-Benzyl-2-hydroxy-5H-benzo[b]carbazole-6,11-dione derivatives as potential inhibitors of the molecular chaperone HSP90

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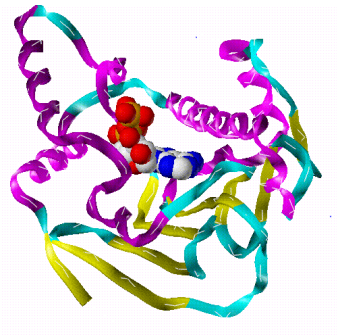
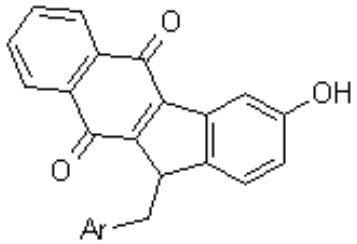
In the 90th of the last century it could be shown, that heat-shock proteins or chaperones can protect proteins from unfolding and aggregation caused by cell stress. HSP90 is an ATP-dependent chaperone protein (see figure 1) essential for the maturation and activity of a diverse group of proteins involved in signal transduction, cell cycle regulation and apoptosis. It was observed, that blocking of HSP90 can interrupt regulatory mechanism of the cell. Tumour cells suffer from cell stress, caused by immune system or anti tumor therapy, so heat-shock proteins like HSP90 show an increased activity. Therefore antagonists of HSP90 seem to be good anticancer candidates.
The ATPase activity can be inhibited with some selectivity by various antibiotics such as geldanamycin[1].



►*Structure of the ADP/ATP-binding site of HSP90 with ADP inside (PDB:1BGQ).*

As naturally derived structures the geldanamycin analogues are difficult to synthesize. Therefore it seems to be useful to develop small, easy to synthesise molecules as HSP90 binders.
It could be shown, that 5-Benzyl-2-hydroxy-5H-benzo[b]fluorene-6,11-dione derivatives show a cytostatic activity up to a micromolar range[2].
For that reason, we used molecular modelling methods to proof the capability of these compounds as novel HSP90 binders.



► *Structures of potential new HSP90 binders*

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Homology model based virtual screening for GPCR ligands using docking and target-biased scoring

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G-protein coupled receptors (GPCRs) are one of the most important drug targets for the pharmaceutical industry.[1] For instance, metabotropic glutamate receptors (mGluRs) have attracted interest due to their role as modulators of major neurotransmitter systems in the central nervous system. Detailed structural information about GPCRs is lacking. As a consequence, computational design of modulators for GPCRs can only be accomplished by using structure-based approaches grounded on homology models, or by using ligand-based virtual screening methods.

In the present study, we investigated the combination of two recently reported techniques for the improvement of homology model based virtual screening. First, we applied ligand supported homology modeling.[2] Clues to infer the binding modes of the ligands were provided by data from mutagenesis studies. Second, to rank order docking solutions, we developed a scoring scheme that exploits the patterns of interactions between ligands already known to bind to the target, and the binding site. As reference ligands, the compounds that have already been employed to support homology modeling were used. Patterns of interactions were modeled using binary ligand receptor fingerprints,[3] as pioneered by Singh *et al*.[4] The similarity of two fingerprints was evaluated using the Tanimoto coefficient.

Our methodology, subsequently referred to as interaction fingerprint based similarity (IFS), has been tested in retrospective virtual screening experiments against mGluR subtype 5. It is expected that the identification of negative allosteric modulators of mGluR5 will open up new therapeutic possibilities to treat pain, anxiety, or Parkinson's disease.[5] To put the results into proper perspective, docking solutions were also rank ordered using conventional scoring functions (D-Score, PMF-Score, G-Score, Chemscore, and FlexX-Score). Using IFS, the enrichment rates could significantly be improved. We also show that the power of IFS to discriminate between active and inactive compounds is superior to the discriminatory power of the conventional scoring functions. Our results indicate that the presented approach might serve as a general setup for successful GPCR virtual screening.

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Lectures

Wednesday, May 16th 2007

Spherical harmonic function-based non-atomistic molecular-dynamics simulation

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The necessary computational (CPU) time of an atomistic molecular dynamics (MD) simulation at the atomic level is roughly proportional to the square of the number of atoms in the simulation system. For large systems, the calculation of explicit atomic interactions is especially computationally expensive. Despite the incredible progress in computer in recent decades, most simulations are still limited to the nanosecond range because larger and larger systems are being simulated. Moreover, much of the computational effort expended on such simulations is needed to reproduce high-frequency motions that have little chemical or biological relevance. It is therefore necessary to improve the performance of traditional MD-simulations in order to increase simulation efficiency even faster than the increase in computer performance.

We have developed a non-atomistic method for MD-simulations based on spherical-harmonic functions in order to extend the time and size ranges accessible to MD-simulations. The idea is that if the atomic details of the structures and motions of essentially rigid subunits of molecules are irrelevant for the macroscopic properties of interest, the subunits can be regarded as structural units whose internal interactions are neglected. Only the interactions between the structural units need to be computed. Then, the number of the non-atomistic interactions is proportional to the square of the number of the structural units and fewer than the normal atomistic interactions. Hence the computational time can be saved.

The force fields associated with the structural units are reproduced explicitly using spherical-harmonic functions. The simulation is based on rigid-body physics, and the dynamics of the structural units are described by the Euler‘s motion equations. These can be solved efficiently using Buchberger‘s algorithm.

Modelling of complex metal hydrides – a force field approach.

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Bogdanovic[1] pioneered the interest in the complex metal alanates by establishing that $NaAlH_4$ could be rehdrogenated by doping with metal catalysts of which, titanium is the most thoroughly investigated. However, there are still unresolved problems in understanding of H_2 dissociation process in the structure. Among this include the role of titanium (is it a dopant or a catalyst?) and long range transport mechanism of Al during the dissociation process.

In this work we are developing a reactive force field($ReaXFF_{NaAlH4}$)[2] to study the structural and dynamical details of hydrogen absorption/desorption processes in $NaAlH_4$ system. Towards this end we are parameterizing a force field, ReaxFF, to simulate large clusters containing NaH, Na_3AlH_6, $NaAlH_4$ and Al phases plus catalysts atoms with a view to understanding the dynamics governing hydrogen absorption/desorption.

We have already sufficiently parameterized $ReaXFF_{NaH}$ to adequately describe H_2 desorption process in NaH. It will be shown that a clear signature for H_2 dissociation is the fall in potential energy during heating process in a molecular dynamics simulation run.

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Quantum Processes of Self-Assembly, Photosynthesis and Molecular Computing in Artificial Minimal Living Cells

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Quantum mechanical (QM) electron correlation interactions density functional theory methods were used for the investigations of self-assembly of photoactive bioorganic systems of artificial minimal living cells[1]. The cell systems studied are based on peptide nucleic acid (PNA) and are 3.0 – 4.2 nm in diameter. QM experiments of above described artificial minimal living cells show that these cells are complex systems because only entire ensemble of PNA, sensitizer, precursor of fatty acid, fatty acid and water molecules is stable and perform quantum photosynthetic processes[2]. The electron tunneling and associated light absorption of most intense transitions as calculated by the time dependent density functional theory method differs from spectroscopic experiments by only 0.2 - 0.3 nm, which are within the value of experiment error [3]. This agreement implies that the quantum mechanically self-assembled structure of artificial minimal living cells very closely approximate the realistic ones. The corresponding of experimental absorption spectra peaks and our QM calculated confirm that our chosen method of designing single electron nano photocells might be useful not only for artificial living organisms but also for wide implementation in the nano photodevices, and molecular computers. We are creating molecular electronics and spintronics logical gates regulating the photosynthesis, growing and dividing of artificial living cells and nanobiorobots[4, 5]. Designed of variety of the molecular spintronics devices will regulate photosynthesis and growth of artificial minimal living cells in the conditions of external magnetic fields, while also providing a perspective of the requirements for success in the synthesis of new forms of artificial living organisms: http://www.daviddarling.info/encyclopedia/M/molecular_quantum_computing_cloud.html

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SwiFT: An Index Structure for Reduced Graph Descriptors in Virtual Screening and Clustering

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A reduced graph descriptor represents molecules by small node-labeled graphs. They allow fast similarity calculation, while retaining the overall arrangement of functional groups. The feature tree[1] as an example of this descriptor type abstracts a molecule by a node-labeled, unrooted tree. One available algorithm for pairwise feature tree comparison is the match-search algorithm[1] which matches the subtrees of two feature trees on each other and therefore creates an alignment. In this work, we document the extension to re-use partial results on the global level of the whole feature tree dataset where a high number of identical subtrees exists. The method is based on indexing all occurring subtrees in a dataset. Based on this index, the similarity value between every subtree combination has to be computed only once. While calculating identical similarities, this approach leads to a substantial reduction in run time by up to 80% and can be used in a parallel cluster computation. The search tree built for indexing can also be used to identify duplicated feature trees.

The SwiFT approach was integrated in the free-accessible FTrees web interface[2].

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Generation of a Special Iron-binding Feature – Pharmacophore Modeling of CYP17

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Pharmacophore modeling has proven to be a valuable tool for drug discovery in recent years. However, there are problems describing the interactions of ligands with metal-containing proteins, as is the case for other methods in molecular modeling. In the program Catalyst[1] usually a hydrogen bond acceptor feature is used for that type of binding. Obviously this is not a very accurate description. Therefore, we implemented a special metal binding feature for the use within Catalyst.

For this purpose 17α-Hydroxylase, 17, 20-Lyase (CYP17) was chosen as model target. It plays a crucial role in the biosynthesis of steroids and is related with diseases like prostate cancer and benign prostatic hyperplasia[2]. The new feature should describe the iron ion in the binding pocket of CYP17. Applying the Relibase+[3], the Brookhaven Protein Databank (PDB) was searched for iron-containing proteins. The resulting 1359 PDB-entries were screened for iron-coordinating substructures. Combining them with information gained from known active CYP17 ligands several iron-binding features were designed and evaluated by generating pharmacophore hypotheses and using them in virtual screening. Models with the standard hydrogen bond acceptor feature were used for comparison.

This procedure resulted in three different models for CYP17 ligands. One for steroidal inhibitors and two for non-steroidal inhibitors. All three models performed better than the comparable models with standard hydrogen bond acceptor features when screening the World Drug Index (WDI) and several other commercial databases resulting in the isolation of promising compounds. A biological testing of these compounds is intended in near future.

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In silico polypharmacology: Techniques for bio-activity profiling of potential drug candidates

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In silico or virtual screening has gained a high impact for the efficient discovery of novel potential bio-active compounds in the modern pharmaceutical research. The concept of chemical feature-based pharmacophore models has been established as state-of-the-art technique for characterizing the interaction between a macromolecule and a potential ligand. While in ligand-based drug design, feature-based pharmacophore creation from a set of bio-active molecules is a frequently chosen approach, structure-based pharmacophores are still lacking the reputation to be an alternative or at least a supplement to docking techniques. Nevertheless, 3D pharmacophore screening bears the advantage of being faster than docking and to transparently provide the user with the relevant information that is used by the screening algorithms to characterize the ligand-macromolecule interaction. As an extension of such an approach, we have successfully introduced parallel pharmacophore-based screening as an in silico method to predict the potential biological activities of compounds by screening them with a multitude of pharmacophore models. We present an overview of our technology together with the results of an application example employing a set of antiviral compounds that were submitted to in silico activity profiling using our pharmacophore building platform LigandScout. The results of the screening experiments show a clear trend towards correct prediction of activity profiles.

Pharmacophore Modeling and Parallel Screening for PPAR Ligands

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The first part of the lecture is about the structure-based and ligand-based generation of 50 pharmacophore models for peroxisome proliferator-activated receptors (PPARs) using Catalyst and LigandScout as software. To determine the best models for PPAR agonists, partial agonists and antagonists, the concept of parallel screening was utilized. For these purposes, 416 PPAR ligands were screened against our 50 pharmacophore models using our screening platform.

In the second part, a validation of the activity profiling ability of parallel screening is represented. Therefore, our structure-based PPAR models were integrated into our in-house database which includes 1537 structure-based pharmacophore models created for 181 targets. This database was screened using the 416 PPAR ligands as query to see if compounds with known PPAR activity were able to enrich within the structure-based PPAR models. As measure of activity prediction quality, a score was created that ranks - according to the fraction of retrieved models - the targets for each PPAR compound.

The conclusion of the study is that the majority of PPAR ligands was predicted correctly which underscores the significance of parallel screening for activity profiling of compounds.

Evaluation of Pharmacophore Modelling Based Virtual Screening: Comparative Assessment of Catalyst, Phase and MOE at the Example of HRV coat protein

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[4]Inte:Ligand GmbH

The three pharmacophore modeling programs Catalyst (Accelrys), Phase (Schrödinger), and MOE (Chemical Computing Group) are evaluated with respect to their virtual screening algorithms with either a given structure based pharmacophore model generated by LigandScout (Inte: ligand) or a ligand based model created within the respective program. Several models are generated at the example of Human Rhinovirus (HRV) coat protein. The most restrictive ones are introduced in more detail, including information about the tools available to increase the selectivity of the models. The hits found by at least two search algorithms within the Derwent World Drug Index 2006 are mostly virucides, proving the selectivity of the models in each program.

A scoring function to rank pharmacophoric alignments and its application to H1 antagonists

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Virtual screening using 3D pharmacophores has evolved into an important and successful method for drug discovery over the last few decades. Flexible, ligand - based pharmacophore elucidation starting from multiple conformations of bio- active molecules is a method to develop hypotheses for interaction patterns of a small organic molecule with a macromolecule, and can be used even if the macromolecular structure of the target has not been experimentally determined.

In this work, a validation set of selected, active H1 antagonists has been elaborated and used to collect criteria for evaluating elucidated pharmacophores. Therefore, assessing the performance of commercially available indust ry software (Catalyst, Phase, MOE[1]) capable of generating flexible, ligand - based 3D pharmacophore models was essential. Also a pseudo - structure - based approach, where selected active Histamin H1 receptor ligands were docked to a homology model using GOLD, was performed. All th is data has been used to further develop and implement an enhanced scoring function for the selection and ranking of three - dimensionally aligned pharmacophore models within the program LigandScout[2],[3].

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Towards maximum computational performance: Does a lower number of conformations increase screening efficiency?

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3D in silico screening methods[1] have been established in pharmaceutical industry as part and parcel of lead structure fishing and are currently gaining importance in ADME prediction. The predictive quality of all these methods rises and falls with the accurate representation of the protein-bound ligand conformation. In continuation of our efforts to optimize conformational model generator parameters for both virtual high throughput screening (vHTS) and exhaustive sampling of conformational space[2,3] we provide novel insights on the impact of conformational ensemble characteristics on virtual 3D screening methods. Our experiments show that the choice of the size and type of the conformational ensemble that is used to represent a molecule significantly influences screening results, and that oversampling conformational space can result in a dramatic decrease of the signal/noise ratio. Moreover, we provide evidence that the RMSD between the bioactive conformation and the generated model is not sufficient to characterize the performance of conformational model generators during screening; the correct representation of key interactions is more important.

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Posters

Separating Drugs from Nondrugs

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To determine the most significant descriptors that allow the separation of pharmaceutical drugs from ordinary chemical, a decision tree strategy was applied. The aim of the presented approach is to enable fast *in silico* screening of large substance libraries for potential drugs. Therefore, descriptors are wanted that can be determined rapidly from the two-dimensional chemical structure to perform a pre-filtering. In later stages where the number of compounds has been reduced, also computational more expensive descriptors can be used. Decision trees are ideally suited to derive an according successive filtering scheme. In contrast to other machine learning algorithms they allow an unequivocal interpretation of the underlying classification scheme, whereby the most significant descriptors appear at early branching points in the tree topology.
Among the variables for this purpose were simple descriptors such as the count of elements, functional groups, and rings as well as molecular properties calculated from atomic contributions, i.e. logP and the molar refractivity. Computationally more expensive descriptors comprised SMARTS strings of fragments and chemical groups. Some of these render substances as being either reactive, toxic, or difficult to synthesize.[1, 2] Also included were drug-like indices e.g. Lipinski's rule of five, the criteria for drugs by Ghose, Viswanadhan and Wendoloski, and by Oprea.[3],[4] Present was furthermore a newly introduced index that quantifies the drug-*likeliness* based on the statistical distribution of atom types and their pair-wise combinations in molecules.[5] The underlying data set of drugs and nondrugs will be available as part of the upcoming round of the Comparative Evaluation of Predictive Algorithms (CoEPrA) contest.[6] The results show that the majority of chemical compounds can be correctly assigned solely by the use of computationally inexpensive descriptors. Hutter's index[5] was found at earlier branching points than other drug-like indices.

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Molecular modeling of new synthesized pyrazolo[3,4-d]pyrimidine-4-ones as phosphodiesterase-5 inhibitors

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The SAR of Zabrinast, sildenafil revealed that the oxygen group of alkoxy group is essential for hydrogen bonding with amidic NH proton of pyrmindine ring to keep the ring systems in co-planarity. The alkylpiprazinosulphonyl group was non essential for activity as there are many phosphodiesterases are devoid of this moiety. Also, the side of fusion of pyrazole ring with pyrimidinone ring is different between different classes of pde-5 inhibitors. In view of these findings we prepared phosphodiesterase-5 inhibitors, pyrazolo[3, 4-d] pyrimidine-4-one derivatives in analogous with sildenafil and vardenafil[1]. Biological investigation and docking studies were done for the newly synthesized compounds (complexed with vardenafil) using DOCK6[2] program.

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Effects of Water Molecules on Protein-Ligand Interactions in a Charged Model Binding Site

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Liquid water is the universal solvent in biological systems. The solvent environment around biomolecules controls their structure and biological function and plays important roles in protein-ligand interactions. It is difficult to predict, however, whether a water molecule is displaced by a ligand binding to a protein or remains in the binding pocket bridging the interaction between enzyme and inhibitor.

Here we present an attempt to examine the contributions of water molecules to protein-ligand interactions in a model binding site with the help of computer simulations. This negatively charged and buried cavity was created by the mutation of Trp191 to Gly in cytochrome *c* peroxidase and is located directly next to the hem cofactor.[1] Due to the high degree of burial, it is possible to study the effects of structural waters without taking into account the influences from the bulk phase.

A series of MD simulations has been performed for complexes between cytochrome *c* peroxidase W191G and eleven known small molecule binders.[2-4] The systems contain different numbers of water molecules in the binding pocket depending on the structural features of the ligand. In addition a simulation of the holo structure has been carried out for comparative purpose. To better understand interactions with and among the water molecules and the dynamic nature of these interactions, first analyses of the simulations have been carried out in order to elucidate the mobility of the solvent molecules and their hydrogen bonding network.

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DNA Minor Groove Pharmacophores Describing Sequence Specific Properties

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The more is known about human and other genome sequences and the correlation between gene expression and the course of a disease, the more evident it seems to choose DNA as drug target instead of proteins which are built with the information encoded by DNA. According to this approach, small minor groove binding molecules have been designed to bind the DNA sequence specifically and thereby downregulate genes. Because of their lack of drug-likeness, we plan to use them as templates for forthcoming virtual screening experiments to discover molecules with the same bioactivity and a different scaffold. In this proof of principle study, carried out with the software tool Catalyst, we present a model work for description of a ligand-DNA complex with the aid of pharmacophore modeling methods. The successful reproduction of sequence specifity of a polyamide minor groove binding ligand is the precondition for later model application to virtual screening.

Workflow-based Alternative Scaffold Identification

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Scaffold hopping is an important task in drug design to improve e.g. the activity, bioavailability or selectivity of lead structures[1]. The general aim of changing the compound class can be extended by simultaneously retaining the orientation of a set of substituents. Mostly these substituents are relevant for binding or show other import properties. Methods considering these constraints already exist. A pure geometrical approach is implemented by CAVEAT[2]. Recore[3] combines the CAVEAT method with pharmacophore features and SHOP[4],[5] performs a geometrical search combined with GRID Molecular Interaction Fields.

A workflow is presented, which identifies proposals for alternative scaffolds by combining a geometric search with semiempirically calculated electronic properties. This workflow consists of a database-preparation module, a search and several filtering modules. The application of some of the filter modules is optional.

First a conformational analysis is performed for all 3D-structures in the database. A query structure must be determined that consists of a set of exit vectors, built by the bonds connecting the query substituents to the core of the molecule. When query and database are prepared, the workflow performs a pure geometrical search for new scaffold structures in the database molecules. In further steps, the resulting scaffold proposals are filtered to eliminate similar or identical hits.

New molecules are constructed by connecting the scaffolds identified with the query substituents. To check that these structures are valid, their geometries are optimized, using the program VAMP. If the steric and energetic deviation of the minimized structure relative to the one generated is lower than a defined threshold, the structure passes this filtering step.

In a subsequent module, the influence of the new scaffold on the electronic properties of the substituents is investigated. For this, electron-isodensity surfaces with local electronic properties, like the electrostatic potential, are calculated for the molecules constructed. The calculations are performed by the program ParaSurf[6].

On this poster, example structures are presented, showing new scaffolds before and after optimization as well as differences in local electronic properties on electron isodensity surfaces of substituents.

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Docking Studies and Molecular Dynamics Simulations of Novel Sirtuin2 Inhibitors

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Sirtuins belong to class III histone deacetylases (HDAC) which are known as nicotinamide adenine dinucleotide (NAD^+) dependent proteins. Seven human sirtuin type (Sirt) homologues are known so far. Sirt2 is required for several cellular functions, for example, chromatin silencing, cell cycle, metabolism, and life span. The NAD^+-dependent deacetylase activity is inhibited by the cleaved nicotinamide. Besides nicotinamide, there are only a few inhibitors reported so far. To better understand the biology of Sirt2 and to generate potential therapeutics, we started to develop novel potent and selective inhibitors of this enzyme.

In this study available crystal structures of human Sirt2 and homologues from bacteria were used as a starting point for molecular docking and molecular dynamics simulations. The derivatives of splitomicines which were synthesized in our group showed good inhibitory activity for Sirt2. Based on docking studies it was suggested that only one stereoisomer of the chiral splitomicines is highly active. Docking of the splitomicines was carried out using program GOLD. We targeted our interest to the polar residues of the binding pocket, which are the potential binding partner for the polar lactone ring of the splitomicines, as well as for the amide group of other known inhibitors. During the docking studies we found that the crystal water molecules in a deep cavity of Sirt2 are necessary to mediate hydrogen bonds to the splitomicines. Molecular dynamics simulations for the R- (active) and S-stereoisomer (inactive) were performed using AMBER 9 in order to explain the different experimental data.

P7

Diasteroselectivity of Chiral N-Dienyl Lactams in Diels-Alder Reaction

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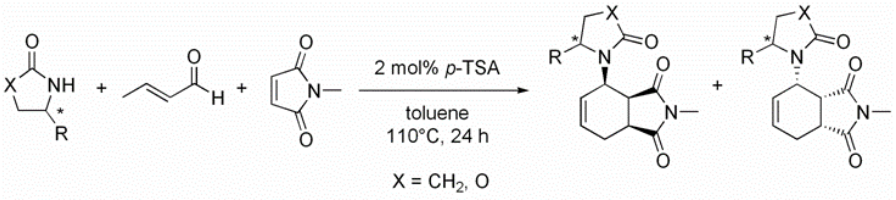
The Diasteroselectivity of Diels-Alder reaction of chiral N-dienyl lactams, generated from a three-component-reaction, has been computed at the level of B3LYP density functional theory. It shows clearly that steric influence of R (phenyl, benzyl, t-butyl and iso-propyl) is the main factor for the high diasteroselectivity. Nice agreement between theory and experiment has been found.



Molecular docking studies of Dengue NS2B/NS3 protease with its inhibitors

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Dengue virus is a member of the Flaviviridae family which causes dengue fever and dengue hemorrhagic fever in millions of people each year in tropical and subtropical regions of the world. Currently, there is no vaccine or effective antiviral therapy for the four known serologically related virus types. The dengue virus genome contains a trypsin-like protease with a classical serine protease catalytic triad which constitutes part of the nonstructural protein 3 (NS3). The enzymatic activity of NS3 protease is enhanced by interactions with the NS2B protein, which acts as an essential cofactor. Therefore, dengue NS3 protease is an attractive therapeutic target for dengue virus infections. Homology models of Dengue NS2B/NS3 protease with its covalent bound peptidic inhibitor (Bz-Nle-Lys-Arg-Arg-H) were generated using the related West Nile NSB2B/NS3 Protease X-ray structure (2FP7) as template. The derived homology models were analyzed by means of molecular dynamics (MD) simulation. Known peptidic inhibitors[2-3] were docked to representative frames obtained from the MD simulations. The docking solutions of most compounds showed similar interactions at the different binding pockets P1-P3. The most potent inhibitors show in addition a hydrogen bond interaction to Tyr161 (NS3). These results together with the experimental K_i values indicated that Tyr161 at NS3 plays a significant role for inhibitor binding. The docking results of small non-peptidic inhibitors[4], which contain a basic guanidinyl group, showed that most compounds mainly interact with the P1-pocket, whereas interactions at the S2 and S3 pockets were not observed. The reduced interaction possibilities is possibly the reason for their high K_i values. The obtained results provide better understanding about the enzyme-ligand interactions and a guideline to assist the development of new potent inhibitors.

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3D-QSAR studies on tetra-peptide inhibitors of West Nile Virus NS2B/NS3 protease using CoMFA and CoMSIA

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West Nile Virus is becoming a widespread pathogen, infecting people on at least four continents with no effective treatment for these infections or many of their associated pathologies. A key enzyme that is essential for viral replication is the viral protease NS2B/NS3, which is highly conserved among all flaviviruses. 3D-QSAR techniques, namely in the present study CoMFA (Comparative Molecular Field Analysis) and CoMSIA (Comparative Similarity Indicies Analysis), were applied to a set of 28 tetra-peptide inhibitors[1] of West Nile virus NS2B/NS3 protease. Several models, which are based on ligand-based alignment, automated alignment derived from molecular docking, as well as an alignment obtained by energy minimization of the ligands in the binding pocket, were employed for comparison purpose. The ligand-based alignment which was derived by using the Multifit method in SYBLY7.2 and the co-crystallized peptide inhibitor structure (PDB code 2FP7)[2], yielded the highest statistical values in the CoMFA and CoMSIA analysis. The CoMFA model gave a leave-one-out-cross-validated q^2 of 0.720 and a non-cross-validated r^2 of 0.964. The statistical values of the CoMSIA model were found to be comparable (q^2 = 0.576 and r^2 = 0.961). The graphical interpretation of the CoMFA and CoMSIA models together with the X-ray structure of the West Nile virus protease NS2B/NS3 suggested that steric substituents should be located at the P1-pocket whereas the P4-pocket is unfavourable for bulky groups. Electrostatic contour plots derived from both models are very similar and indicated the favor of positively charged groups at the P2-pocket and negatively charged gropus at the P3-pocket. Moreover, the hydrogen bond donor contour plot derived from the CoMSIA model revealed that Asp129 and Tyr130 in the NS3 domain are important residues for hydrogen bonding interactions, whereas Phe85 and Gln86 in the NS2B domain are predicted to play a less significant role in enzyme-ligand interaction. Information derived from the CoMFA and CoMSIA models are helpful for the design and development of new potent, more drug-like inhibitors.

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Characterization and homology modelling of a new plant *O*-methyltransferase from *Papaver somniferum*

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The investigation of the differential expression of ESTs in *Papaver somniferum* and other *Papaver* species led to the identification of a new *O*-methyltransferase (OMT) from *P. somniferum*. Identification of the full length sequence showed that this gene shares 69% homology to the norcoclaurine-6-*O*-methyltransferase.[1] To elucidate the substrate specificity of the enzyme a homology model was built based on the x-ray structure of isoflavone-O-methyltransferase of *Medicago sativa*.[2] Thereafter, docking experiments with several putative substrate structures favoured the benzylisoquinoline *S*-norreticuline. Even though this compound is not yet regarded as an intermediate of known alkaloid biosynthesis pathways, it was previously identified as a minor intermediate among the benzylisoquinolines of *P. somniferum* in FT-ICR-MS analysis of plant extracts.[3] *In vitro* activity tests of the heterologously expressed protein showed very selective substrate specificity towards *S*-norreticuline. In further analysis the kinetic parameters for *S*-norreticuline and the cofactor *S*-adenosyl-L-methionine were determined, which correlate with published data of other OMTs.[1,4]

This adds an OMT with a new substrate specificity to the already known benzylisoquinoline OMTs. Phylogenetic analysis of *P. somniferum*, *Thalictrum flavum*, *Coptis japonica* and *Eschscholzia californica* benzylisoquinoline OMTs suggests that the substrate specificity of these OMTs is conserved over speciation. To see the structural basis for recognition of the different substrates the binding sites of the four OMTs of *P. somniferum* should be identified by homology modelling and subsequent docking. The outcome will be used for site-directed mutagenesis experiments in the new OMT, that may alter its substrate specificity.

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Design of Advanced Biased Sampling for Molecular Dynamics Simulations of Nucleic Acids

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Conventional all atom Molecular Dynamics (MD) of nucleic acids is restricted, as for proteins, by the problem known as kinetic trapping (system trapped in local energy minima). A possible solution to enhance sampling efficiency with MD is to introduce an appropriate biasing term along a predefined reaction coordinate in the potential energy function and to carry out a number of parallel simulations. Such Umbrella Sampling simulation scans in a systematic way those conformational regions that should contain the desired solutions. Because kinetic trapping can also occur in each of the non-interacting biased sampling windows, a procedure identical in theory to the Hamiltonian Replica Exchange protocol can be applied by exchanging the biased simulation conditions at regular intervals with a specific transition probability between replica pairs. Such a coupled Umbrella Sampling/Replica Exchange method has been applied to study the free energy change associated with bending and kinking of DNA and with elbow-like dynamics of kink-turn RNA motifs. In addition, we developed a similar replica exchange methodology to enhance the sampling of meta-stable conformational states of the nucleic acid backbone. This approach could be useful to study the fine structure of isolated DNA but also in complex with proteins and other ligands.

The Interaction of Metal Ions with Thymine Tautomers: A Computational Study

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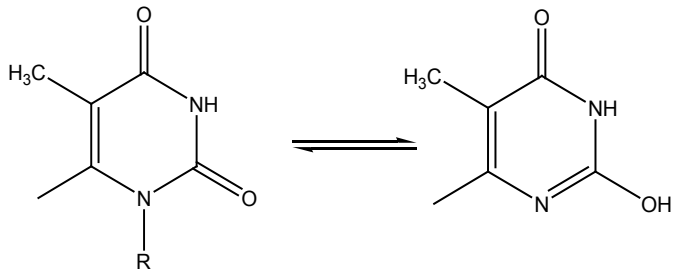
The interaction of metal ions with nucleic acids is one of the main studies in biochemistry. Cations play an important role in stabilizing bases, base pairs and the deoxyribonucleic acids (DNA) double helix[1]. Although the nucleotide bases are in the form of keto tautomer, there are other forms of tautomers involved in various biochemical processes including point mutation[2]. It is known that the interaction energies of cations with organic bases are very large which affects the tautomeric equilibria. The aim of this study is to investigate the interactions of monovalent and divalent metal ions (Li^+, Na^+, K^+, Be^{2+}, Mg^{2+}, Ca^{2+}, Cu^+, Cu^{2+} and Fe^{2+}) with all possible tautomers of thymine and its methylated derivatives (Figure 1). For this purpose, density functional theory (DFT) has been used at B3LYP/6-31++G** level.

It is found that cations bind very similarly to different tautomers. Due to the methyl substitution on tautomers, slight changes on geometry (distances, planarity etc.), charge distribution and change in energy are observed. In addition, it is also observed that metals have an effect on the structural and electronic properties. Compared to the most stable form of thymine, rare tautomers are stabilized by metalation. Methyl substitution causes increase in relative energies on different conformers of the thymine derivatives.



►*Keto and enol form of thymine where R represents H or* CH_3

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COSMO*therm*: A Universal Tool for the Prediction of ADME Parameters

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The COSMO-RS method[1,2], an efficient combination of dielectric continuum quantum chemistry and statistical thermodynamics, and its program implementation COSMO*therm* meanwhile are widely accepted as a most fundamental and most predictive access to the chemical potential and derived properties of almost any molecular species in pure solvent, solvent mixture and pseudo liquids. While COSMO-RS initially was mainly used for chemical engineering thermodynamics, it has been extended to drug design and agrochemical applications in the last years. A straight forward application in the area of drug development are the prediction of pharmocokinetic properties of drug candidates.

Within drug discovery, a large amount of potential candidates fail because of their poor absorption, distribution, metabolism or excretion (ADME) behavior. ADME prediction is therefore becoming an increasingly important tool in the early stage of the drug discovery process. Several models has been developed applying the COSMO*therm* method like the prediction of: aqueous solubility, octanol - water partition , pKa and pKb values, blood brain partitioning, human serum albumin binding and intestinal absorption[3-7]. Since the COSMO*therm* method is based on pure quantum mechanics and statistical thermodynamics, the models are robust for extension to novel chemical situations and new models can easily be created.

A new program COSMO*frag*[8], a combination of COSMO*therm* with a huge database of about 50000 pre-calculated drug-like compounds, meanwhile allows for very fast, but slightly more approximate calculation of these ADME parameters and makes the COSMO-RS approach applicable to high-throughput projects.

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Protein structure calculation with a Max-Min Ant System

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The 3D structure of a protein is the key to predicting and characterizing the protein function. NMR spectroscopy is a frequently used experimental method for the determination of this structure. In this context especially NOESY experiments are of major interest because of the possibility to extract distance constraints. Usually the analysis and interpretation of the experimental data is very time consuming. Hence, in the past years many different programs have been developed for the interpretation of the experimental data and for the calculation of 3D protein structure based on this data.

We introduce the first steps towards a new expandable approach to calculate the 3D structure of proteins from distance constraints. Here a special kind of Ant Colony Optimization algorithm, namely a Max-Min Ant System[1] (MMAS) is used to optimize the protein conformation only considering torsional degrees of freedom. The optimization is done with respect to a target function that scores the different conformations concerning the distance constraint violations. To improve the search performance we combined MMAS with a Quasi-Newton method as well as with a Nelder-Mead-Simplex algorithm.

In this work we present the employed algorithms as well as some preliminary results.

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The Molecular Modelling Program MOMO: Experiments on the Automatic Parameterization of Empirical Point Charge Models

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The force-field program MOMO[1] has been developed in our group during the last decade. Its main purpose is to serve as a basis for research on methods in molecular modelling. MOMO is available as a LINUX version for Intel CPUs from the authors upon request. A version of the MOMO force field for use with MMTK[2] is under development and was used for this work.

The electrostatic potential plays an important role in the description of intra- and intermolecular interactions. MM and MD programs commonly calculate the electrostatic energy based upon atomic point charges. However, these are neither available from experiment nor extractable from quantum-mechanical calculations. So a number of methods for determining monopoles have been developed. The basic ideas of these algorithms differ and it seems not even possible to match the behavior of each quantum-mechanical method for all classes of "reference compounds" to each empirical scheme due to this fact.

In order to permit the choice of an appropriate empirical method together with a parameter set, the Pareto-optimal parameters for a given training set have to be known. To speed up the optimization knowledge about the parameterized algorithm was used to enhance well-established optimization procedures. We present the application of these techniques to a training set of 41 compounds and two algorithms for determining atomic partial charges: the PEOE model of Gasteiger and Marsilli[3] and a new algorithm based on that of Abraham[4].

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Hybrid solvation model for MM – PB/SA free energy calculations

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Biological molecules are embedded in an aqueous environment and, thus, water has a crucial effect on their behavior. Atomistic consideration of water in molecular modeling causes a considerable increase in complexity of the examined systems and is computationally demanding. Continuum solvation models greatly reduce this complexity at the cost of neglecting the influence of individual water molecules. Combination of a detailed atomistic representation of water molecules in the examined area of interest with a continuum representation of the surrounding solvent volume results in a hybrid solvation model. This provides a detailed view of important molecular interactions at reduced computational cost.

Here we introduce such a hybrid approach in the realm of MM–PB/SA[1] (Molecular Mechanics – Poisson-Boltzmann / Surface Area) calculations. The MM–PB/SA approach is an endpoint free energy calculation technique. In the conventional model solvation effects are incorporated by a continuum representation. That means electrostatic and non-polar solvation contributions are treated on the Poisson-Boltzmann level and in a surface area-dependent manner, respectively. Most often the ensemble averaged free energies of the endpoint states are calculated based on the representative snapshots of a MD trajectory. Although such a simulation is carried out in explicit solvent, information about the solvent is normally discarded. In this study, we do make use of the explicit solvent information in the vicinity of the solute based on a linear response approximation. We complement this term by a reaction field contribution in the outer region.

Ligand binding to the periplasmic oligopeptide binding protein (OppA) strongly depends on structural water molecules located in the binding site. Thus, this system seems ideally suited to validate our hybrid approach. In fact, when applying the hybrid solvation model in the context of MM–PB/SA, an improved correlation between calculated and experimental binding affinities is found compared to using only the continuum representation.

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Mechanism of alkene aziridination with Cu-bispidines: A DFT exploration

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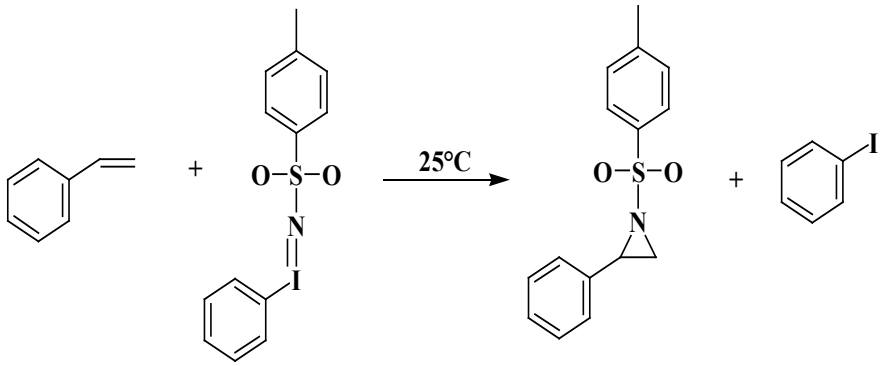
Aziridines (Figure 1) are nitrogen analogues of epoxides and are attractive intermediates for many organic reactions. [1, 2] Despite the significance of the aziridines the mechanism of formation of these compounds are rarely explored. We report here an ongoing investigation into the mechanism of aziridination with $Cu^{I/II}$-bispidine catalysts using DFT. The current study provides more insight into issues such as reactive intermediates, oxidation state of the Cu centre, denticity of the nitrene source, spin state dependency etc. Different pathways are also explored for the formation of aziridine, where the two N-C bonds are formed either in a concerted or consecutive manner. Along the mechanistic pathway, interesting features such as spin-crossovers and two-state reactivity scenarios are also addressed. The difference in the catalytical activity among different Cu bispidines [3] is also considered.

► *General aziridination reaction*



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[2] D.A. Evans, M. M. Faul, M. T. J. Bilodeau, *J. Org. Chem.*, **1991**, *56*, 6744.
[3] P. Comba, M. Merz, H. Pritzkow, *Eur. J. Inorg. Chem*., **2003**, 1711.

Theoretical adsorption model of guest molecules in nanoporous alumina

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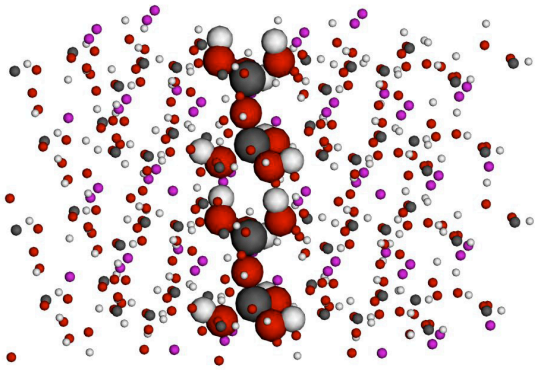
Nano- and mesoporous alumina membranes with highly ordered parallel pores of adjustable diameter can serve as chemical nanoreactors for the fabrication of devices on a nanometer scale. In cooperation with J. J. Schneider (Darmstadt) and G. Grampp (Graz) we are investigating basic properties of these host/guest systems by combining synthetic, spectroscopic, and theoretical efforts. We use the TEMPO (2,2,6,6-tetramethylpiperidine-N-oxyl) radical as an ESR-active probe for measuring and understanding basic adsorption properties.



►*Crystal structure of $K_2[Al_2O(OH)_6]$, H positions from NVT simulation, and minimization based on CLAYFF highlighted $Al_2O(OH)_6$ substructures.*

From a theoretical and computational perspective this host/guest system requires a hierarchy of approaches, starting from the electronic structure of the adsorbate and ultimately leading to a model for condensed phase properties under specific confinement conditions. We present our recent results on modeling the realistic substrate surface based on the experimentally known $K_2[Al_2O(OH)_6]$ crystal structure. A mixed QM/MM strategy is applied to the adsorption of TEMPO molecules on the model surface in order to parameterize an adequate effective force field. We will consequently be able to study medium-sized reactor systems by means of classical molecular dynamics simulation and ultimately large reactor geometries by integral equation theories.

Computational and experimental study of non covalent monoamine oxidase inhibitors

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Monoamine oxidases (MAO) are key role enzymes in the metabolism of monoamine neurotransmitters. Therefore, MAO inhibitors (MAOI) are studied for the treatment of several psychiatric and neurological diseases. MAO-B inhibitors are co-adjuvants in the treatment of Parkinson's and Alzheimer's diseases; MAO-A inhibitors are used as antidepressant and antianxiety drugs. In a previous work[1] we have investigated the inhibition properties of a series of 2-thiazolylhydrazone derivatives with respect to the A and B isoforms of monoamine oxidase (MAO). All the compounds showed high activity in the nM range against both the MAO-A and the MAO-B isoforms. As the most interesting compound was 2-(2-methylcyclohexyliden)hydrazo-4-phenylthiazole we decided to synthesise and test different cyclohexylidenhydrazo-4-arylthiazole derivatives. Several compounds exhibit a remarkable activity and selectivity in particular towards human MAO-B.
With the aim of understanding the reason of this behaviour we carried out a computational study. Due to a tautomeric equilibrium, different isomers can be proposed for the new compounds. Monte Carlo conformational search has been applied to all different isomers and *ab initio* energy evaluation has been used in order to identify the most stable forms. Each global minimum energy structure has been submitted to the Glide docking procedure taking into account both the R and S enantiomers, where applicable. The most stable configurations will be used as receptor-based alignment for further CoMFA studies. This approach gave best results in a previous study performed by some of us[2]. The final purpose is to rationalize the structure-activity relationships of these compounds to derive a suitable selectivity model.

[1] F. Chimenti, E. Maccioni, D. Secci, A. Bolasco, P. Chimenti, A. Granese, O. Befani, P. Turini, S. Alcaro, F. Ortuso, M.C. Cardia, S. Distinto, *J. Med. Chem.,* **2007,** *50*, 707-712.
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Copper-catalyzed aziridination: tailor-made ligands for higher reactivity

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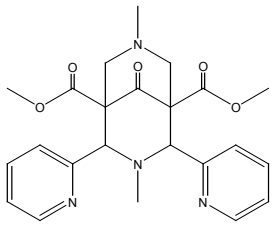
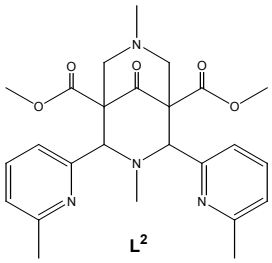
Aziridines are very interesting molecules and play different roles in chemical research. On one hand, they can act as versatile electrophilic reagents in organic synthesis.[1] On the other hand, many aziridinine-containing molecules have attracting biological properties.[2] One of the most promising synthetic routes to aziridines is the copper-catalyzed addition of nitrenes to olefins.[3]
In this work, bispidines (3,7-diazabicyclo[3.3.1]nonane derivatives, see figure) are used as ligands for copper-catalyzed aziridination. Simple synthesis at high yields and the possibility to tune physical and chemical properties of the copper(II) complexes by varying the donor set favors this class of ligands for exploration of structure-reactivity relationships.[4]



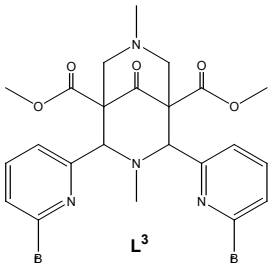
L¹

E^0 (vs. $AgNO_3$, MeCN) = - 413 mV
TON = 7 (max. = 20)
t = 7 h



L²

E^0 (vs. $AgNO_3$, MeCN) = - 94 mV
TON = 7 (max. = 20)
t = 2 h



L³

E^0 (vs. $AgNO_3$, MeCN) = + 53 mV
TON = 13 (max. = 20)
t = 15 min

As a high redox potential of the used copper(II) complex seems to be essential for reactivity in aziridination,[5] a correlation of this property with different calculated parameters, like HOMO-LUMO-gap and atomic charges would be a useful help for tailoring new ligands.

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[3] D.A. Evans, M. M. Faul, M. T. Bilodeau, *J. Org. Chem.*, **1991**, *56*, 6744-6746.
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Investigating the plasticity of protein-protein interfaces by MD and constrained geometric simulations

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The ability of proteins to interact with each other plays an important role for the function of living organisms. Protein-protein interactions (PPI) are involved in almost all cellular processes and are modulated by a complex network of interactions. Due to their universal occurrence, protein-protein interactions provide an important class of drug targets. A promising approach is to modulate PPI by small organic molecules. Approaches to rationally design such small molecule-modulators are hampered, however, by the planarity of protein-protein interfaces: In contrast to enzymes, protein-protein interfaces are lacking an explicit binding pocket in general. Yet, it is well known that distinct pockets are required for the binding of small molecules with high affinity and specificity.

Encouragingly, experimental evidence is accumulating that proteins can populate conformational states that show open pockets in interface regions, as demonstrated in the case of interleukin-2[1]. The theoretical foundation for this is given by the "conformation-selection model"[2], according to which a protein state consists of a multitude of rapidly interchanging conformations.

Consequently, this study aims at identifying potential binding pockets in interface regions by molecular dynamics and constrained geometrical simulations, starting from an unbound protein conformation. For the latter, the FRODA algorithm was used, which is based on a reduced ("coarse-grained") protein representation. Here, new conformations are generated by fulfilling geometrical constraints. The approach was tested on the unbound structure of interleukin-2 and the monomer structures of a dataset of 20 protein-protein complexes. The simulation data was analyzed in terms of the conformational space spanned and the stereochemical quality of the structures.

For several interface residues conformations as in the bound state could be observed, but in no case the full bound conformation was sampled. In addition to the FRODA simulation, a MD simulation of interleukin-2 was performed. Although the MD simulation results in structures of higher stereochemical quality, the FRODA algorithm is an attractive alternative for studying the dynamics of proteins due to a significant decrease of computational requirements.

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Electron-Transfer Catalysis on the Surface of Anhydrous Copper Sulfate

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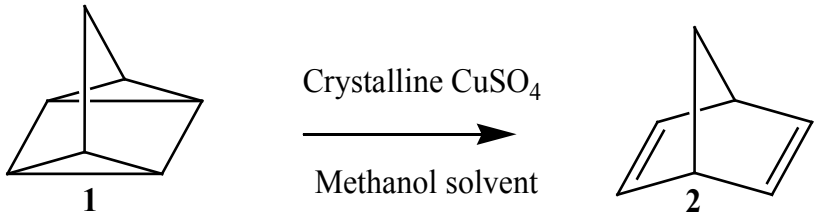
The principle of electron-transfer catalysis is that the catalyst, which may be a metal center in a complex or the surface of a redox-active solid, transfers an electron to or from the reactive substrate temporarily during the reaction. The starting materials and products are not generally affected, only intermediates or transition states along the reaction path. We have investigated this novel catalysis mechanism extensively using non-periodic DFT and *ab initio* techniques on molecular complexes, gas-phase metal atoms and molecular models for redox-active salts as well as with the state-of-the-art periodic DFT calculations.

As the first example of such a reaction that we have investigated is the catalysis of the quadricyclane, **1** to norbornadiene, **2** rearrangement on the surface of $Cu(I)SO_4$ crystals:



This reaction is well know as a so-called "hole-catalyzed" rearrangement that has been investigated very thoroughly for the radical-cation system that is the basis of the redox-catalyzed reaction. The reaction can be catalyzed by soluble redox-active reagents such as $SnCl_2$ but also heterogeneously by copper sulfate crystals. Calculations for a model system with one "molecule" of copper sulfate showed the redox catalysis very clearly. The calculated activation energy is calculated to be only 2.9 kcal/mol (CCSD(T)/6-31G*).

The reaction on the copper sulfate surface (VASP, GGA-PW91) proceeds via a highly unsymmetrical pathway starting from the adsorption of quadricyclane on a $CuSO_4$ surface, formation of the intermediate structure and the final formation of norbornadiene. The geometry of the intermediate is very similar to the one observed for the one-electron oxidation of **1** to **2**.

Experimental and QSPR Study of the Thermodynamics of Complexation of Methyl Substituted Benzenes and the Silver Cation

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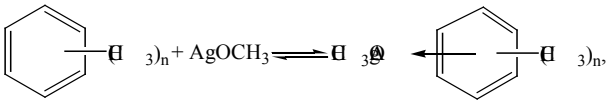
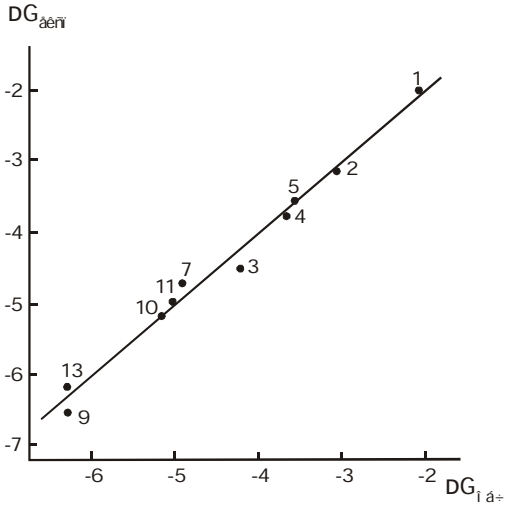
The interaction of methyl substituted benzenes with silver (I) cation was investigated by the HPLC. DFT calculations were performed for the different models of silver ion-containing species: free, explicitly solvated Ag(I) and silver methylate. Based on the computed chemical descriptors as well as the experimentally defined ones, the correlation analysis for all models have been performed.

The step-by-step regression analysis allowed to choose the best correlation model, which was able to predict the equilibrium constants from the computational data on the silver (I) complexes. These correlations contain, besides the complexation energetics, the indicatory variables that reflect the influence of the position of the substituents on the properties of the aromatic substrate (*ortho*- and *pery*-effects), as well as the experimental values for the degree of desolvation.



►ΔG_{exp} vs ΔG_{calc} according to the equation



$$\Delta G_{comp} = a_0 + a_1 R_{12} + a_2 \Delta H + a_3 N_{desolv} + a_4 \left(-\frac{T\Delta S_{rot}}{1000} \right)$$

Using molecular modelling tools to define the putative binding site of a human $P2Y_2$-receptor model

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The $P2Y_2$-receptor belongs to the superfamily of G protein-coupled receptors (GPCR) and is activated almost equipotently by the physiological nucleotides ATP and UTP. So far, potent and selective agonists, and especially antagonists for this receptor, are hardly known, but they are urgently needed as pharmacological tools to study the (patho)physiological role and the pharmacological potential of $P2Y_2$-receptors. The first moderately potent and selective $P2Y_2$-receptor agonists are currently in clinical development for the treatment of dry eye syndrome and cystic fibrosis[1].

In order to discover highly potent and selective ligands and to establish the putative binding mode for these already known agonists (e.g. derivates of ATP and UTP) and antagonists (e.g. derivates of Suramin and the anthraquinone dye Reactive Blue 2) a three-dimensional model of the human $P2Y_2$-receptor was generated by homology modelling using the most actual crystal structure (2.2 Å) of bovine rhodopsin (PDB 1U19) as template[2]. To gain deeper insight into the putative binding site of the receptor model automatic docking with SURFLEX-DOCK[3], molecular dynamics simulations (MDS) using the GROMACS package[4], calculation of interaction-fields with GRID[5] and determination free volumes with SURFNET[6] were performed to further characterize the protein as well as the protein-ligand complexes. Moreover, functional data was included which support the localization of the putative binding site. In order to allow a clearer statement concerning the binding mode of agonists and antagonists both groups were considered separately. Thus, for agonists movements of the helices especially the flexibility of helix six are observed during the MDS and for antagonists Coulomb and Lennard-Jones interaction potentials are analyzed and compared to the experimental IC_{50} values.

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[4] GROMACS, version 3.3, BIOSON Research, Institute and Laboratory of Biophysical Chemistry, University of Groningen, The Netherlands

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Refining pharmacophores for PPAR with information from the binding site shape

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Experimental X-ray crystal structures of drug target proteins in complex with small ligand molecules are frequently used to create structure-based pharmacophore models, in order to find new promising drug candidates by virtual screening. A few authors have also described the inclusion of the shape of the binding site to reduce the number of those false-positive hits which are simply too big to fit the binding pocket.[1,2]
In order to study the effect of such exclusion shape models and to establish guidelines for binding site assisted structure-based pharmacophore modeling, we created models for various drug targets in LigandScout[3] and used them for database screening in Catalyst. Our models' ability of retrieving known actives from a collection of drug-like molecules was visualized with the help of ROC curves.[4] The effects that different parameters such as number, size, and flexibility of the features creating the shape restriction have on the sensitivity and specificity was studied, as well as their effect on the computational time. We use models based on X-ray crystal structures of PPAR to exemplify the workflow.

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The influence of ligand protonation in protein-ligand-docking

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With the use in Virtual Screening (*VS*) in experiments Protein-Ligand-Docking has gained more and more importance in pharmaceutical research over the past years. To model the interactions between the protein and a ligand empirical scoring functions are used in many programs. These scoring functions consist of different terms, which describe physical and chemical properties important for an attractive interaction between the protein and the ligand. Most scoring functions use hydrogen bonds and salt bridges as descriptors. For both the knowledge of the protein's and the ligand's protonation state is important but experimental methods like x-ray crystallography do not resolve the hydrogen atom positions in protein structures.
To estimate the influence of the ligand's protonation on the docking results with PLANTS[1] and Gold[2] different protonation states of each ligand of the ASTEX clean test set[3] where automatically generated using a combinatorial method. First, all hydrogen atoms are removed from the ligand structures. Afterwards, the most likely standard protonation is generated. Starting from this, all possible protonation states are generated by adding additional protons to likely positions or removing acid protons from the ligand structure. The number of different protonation states ranged from 1 to 64 depending on the ligand's structure. First a test docking was performed with Gold using standard settings, which showed that the standard protonation reached the best scoring value in nearly half of the test cases. To improve the significance of the docking study and to reduce statistical influences longer docking runs in which all structure where docked 25 times, were conducted with Gold and with PLANTS.

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P27

Computational study of the Kcv potassium channel: functional impact of mutations and the protonation state

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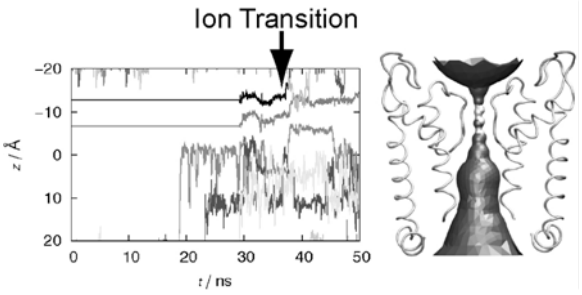
The Kcv K^+ channel represents the shortest sequence of a functional channel known to date. As a minimal working model Kcv can be considered as close to prototypical, enabling basic insight into channel design principles and into fundamental transport mechanisms.
We present the results from our computational studies of Kcv wild-type and some experimental knock-out and hyperactive mutants[1,2]. Based on initial structures constructed by homology modeling which takes into account experimental data wherever possible, fully atomistic molecular dynamics simulations of the proteins in a DMPC bilayer and electrolyte solution where performed with and without an external field. Various protonation states for titratable key residues where also studied in order to establish a sound computational model in accord with electrophysiological findings. With the final model, spontaneous ion transitions through the entire pore were observed for the first time in a simulation system.



►*Ion transition event observed for the Kcv wild-type model.*

Besides analysis of the dynamics of ion passage we also applied a novel symmetrizing simulated annealing protocol for the extraction of average structures from very long trajectories.[3] This enabled us to interpret results from the perspective of structural biology and allowed the application of advanced theoretical tools like the three-dimensional reference interaction site model (3D-RISM) integral equation theory. The latter directly yields the ionic distribution around and within the channel pore, revealing the influence of mutations on ion permeability. We found close correspondence between alterations of salt bridge patterns near the intracellular mouth with changes of conductivity. These results are compared with those found earlier for a Kcv-analog KirBac1.1 mutant model.[3]

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Parameterization of Zinc for AM1*

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An extension of AM1 [1] semiempirical molecular orbital theory, named AM1* [2], uses the original AM1 parameters and theory unchanged for the elements H,C, N, O and F and *d*-orbitals for the elements starting from second long row on the periodic table [2,3]. In this work, zinc has been parameterized using a filled *d*-shell and with two-center core-core parameters. The typical errors of AM1* for zinc are discussed. Now AM1* parameters are available for H, C, N, O and F (which use the original AM1 parameters), Al, Si, P, S, Cl, Ti, Cu, Zr, Mo (slightly modified Voityuk and Rösch's AM1(d) [4] parameters for Mo) and Zn.

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On the Generation of intrinsic electric dipole fields as the basis for the understanding of the morphogenesis of fluoroapatite-gelatine nano-composites†

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Systems of ordered fractal aggregates of fluoroapatite-gelatine composites were chosen to mimic the growth of the biosystem apatite-collagen, which plays an important role in the human body as functional material of teeth and bones. The morphogenesis of these particles starts with elongated hexagonal prismatic seeds, followed by fractal branching and the development of growing dump-bell states. In order to gain insight into structure formation a lot of experimental investigations were performed[1]. High resolution TEM micrograph of the [001] zone of a composite seed showed also the presence of triple-helical macromolecules oriented along the *c*-axis[2]. The general principles of the dramatic self organization process are not yet understood. It is proposed that they should be manifested already in the structure of the seed. Molecular dynamics simulations on the basis of atomistic resolution models offer some ideas for the organisation principle. However, the effort is typically immense and unacceptable for systems with increasing size. The simulation scenario has to be drastically simplified. Our approach starts from the assumption of the formation of an intrinsic electric field - built by the permanent dipoles contained in each individual composite crystal[3] - which takes over control of the aggregate-growth. This assumption is consistent with the observation of the biological significance of electric fields (pyro-piezo electricity) during bones formation. The simulation strategy can be described as follows. Adopting a coarse grained model, the first main task is the calculation of the electric field[4] (on the basis of given dipole arrangements). Each collagen molecule, is represented by two beads with opposite charges, in the hypothesis that all the C-termini and N-termini are completely deprotonated and protonated, respectively. All the beads are arranged in the seed according to the experimental geometrical parameters. A Monte Carlo simulation is performed in

order to optimise the still missing geometrical parameters. According to the resulting force field lines, the orientation of the seeds belonging to the following generations can be predicted.

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Enhanced Sampling of Peptides and small Protein Conformations using Biasing Potential Replica Exchange Molecular Dynamics Simulations

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The application of classical molecular dynamics (MD) simulations for studying biomolecules is limited by the accuracy of current force fields and the simulation time scale. Peptides and proteins can adopt several locally stable conformations separated by high energy barriers. Conformational transitions between these stable states can be rare events even on the time scale of hundreds of nanoseconds simulation time. Among the various methods proposed to tackle the sampling problem, replica exchange molecular dynamics (RexMD) simulation is a successful method to enhance conformational sampling[1]. However, it is limited to small systems since the number of required replicas increases rapidly with increasing system size. Recently we have proposed[2] an alternative "Hamiltonian" replica-exchange method by employing a biasing potential that focuses on backbone flexibility of a biomolecule of interest and tested it successfully on dipeptides and small peptides. The aim of this biasing potential is to reduce the energy barriers associated with peptide backbone dihedral transitions. The level of biasing is gradually changed along the replicas such that frequent transitions are possible at high levels of biasing and thus the system can escape from getting trapped in local energy minima. Since exchanges between replicas are independent of the number of solvent molecules our method requires much fewer replicas for efficient sampling compared to standard temperature RexMD. In the current work we have applied this Biasing Potential Replica Exchange MD (BP-RexMD) on folding of the trp-cage mini protein, both in implicit and explicit solvent simulations. We have also applied the BP-RexMD method to the villin head piece protein and HIV-1 accessory protein in implicit solvent. Starting from an extended conformation the BP-RexMD method allows for sampling near native conformations with a small number of 5-7 required replicas.

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When Ants Design Scoring Functions

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The performance of today's docking programs depends, besides the *sampling algorithm*, mainly on the employed *scoring function*. Their main tasks are, on the one hand, to identify experimentally observed ligand conformations in the conformational ensemble generated by the sampling algorithm and, on the other hand, to rank different ligands correctly aiming at reproducing experimentally observed binding affinities. Designing new scoring functions fulfilling these requirements across large test sets is still a major challenge in the drug-design field. The best of the proposed scoring functions in the literature show a reasonable to good average performance across these test sets but sometimes fail completely on specific protein target classes. Therefore, so called *tailored scoring functions* for specific targets have been introduced.

In this work, we present a new approach based on *Ant Colony Optimization* (ACO)[1], which treats the parameterization of a given set of partial scoring functions as a continuous optimization problem by minimizing an objective function that takes into account pose prediction results produced by our docking algorithm PLANTS[2] and optionally affinity information. This fully automated approach takes as input a set of known protein-ligand complex structures along with experimentally determined affinity data, if available, and outputs a scoring function parameterization, which is in first instance aimed at identifying the correct ligand pose as the top-ranked solution and second at reproducing experimentally observed binding affinities.

Besides the theory of this approach, we show results for different protein targets with respect to the tasks *pose prediction* as well as *virtual screening*.

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Binding Properties of Butyrophenone Derivatives with a Multi-Receptor Profile Similar to Clozapine

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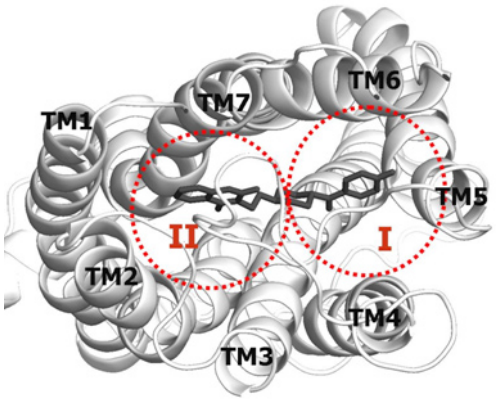
Schizophrenia is the most frequent and debilitating of the psychotic disorders that affects up to 1% of the general population. The atypical antipsychotic drug clozapine is still considered to be the gold standard in the treatment of schizophrenia, possessing a multi-receptor profile with affinities to serotonin, dopamine, alpha-adrenergic, muscarinic and histamine receptors. The serotonin 5-HT_{2A} and dopamine D_2 receptor have been of particular interest as a screening criterion for atypical antipsychotics[1].



►*Model of the ketanserin/5-HT_{2A} receptor complex.*

The present study focuses on the 5-HT_{2A}/D_2 affinity profile of conformationally constrained butyrophenones (ketanserin, QF2004B[2]). In order to elucidate essential receptor-ligand interactions of butyrophenones derivatives, 3D models of the 5-HT_{2A} and the D_2 receptor have been generated by homology modelling, using the bovine rhodopsin crystal structure as template. The putative binding site deduced from receptor models revealed conserved microdomains in TM3 (D3.32), TM5 (S5.43 and S.5.46) and TM6 (W6.48, F6.51, F6.52) (region I, Figure). These microdomains are also known for being involved in the binding of the natural agonist serotonin and dopamine. A distinct receptor affinity of butyrophenones derivatives at 5-HT_{2A}/D_2 has to be ascribed to nonconserved microdomains located in the TM2/TM3 interface (residues 2.61, 3.28, and 3.29) as well as in the TM1/TM7 interface (residues 1.35, 1.39, 7.35, 7.36, 7.39) (region II, Figure). Docking studies of butyrophenone derivatives into 5-HT_{2A} and D_2 receptor will provide further insight into critical ligand interactions at the D_2 receptor resulting in a decreased affinity in comparison to 5-HT_{2A}.

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A Theoretical Investigation on the Geometries of Glucagon-like Peptide-1 and some Analogues, and their interactions with Dipeptidyl Peptidase DPP-IV

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Glucagon-like peptide-1 (GLP-1) is an interesting candidate for pharmaceutical use in cases of diabetes mellitus type 1 and 2 since it controls the early insulin response to nutrient ingestion of glucose. Unfortunately, GLP-1 imposes a very short half life of only a few minutes in vivo due to degradation by dipeptidyl peptidase DPP-IV. Several studies have been carried out to modify the sequence of GLP-1 in order to prevent degradation while conserving its valuable function. In contrast, CellMed AG investigated in vivo degradation of different GLP-1 analogues that are C-terminally elongated by different amino acid sequences. Some of them showed significantly reduced degradation while conserving the GLP-1 function, but dependence on peptide length and sequence remained unsolved.

In order to unravel the conformational features leading to the experimental observations, GLP-1 and three of its artificially extended analogues have been investigated using molecular dynamics (MD) simulations, molecular modeling, and docking. A realistic structure of the active GLP-1 – DPP-IV complex was modeled using the docking program PLANTS[1] to approach the geometries at the binding interface. To date it is the first modeled structure of this complex. Here, the large side opening was identified as the dynamical path used by GLP-1 to approach the binding site. Subsequently, the atom positions at the interface were refined using the software packages MOLCAD, MolArch, and SYBYL.

The MD simulations revealed that distant charged residues can form temporary salt-bridges leading to a strong bending of the peptide. For the elongated GLP-1 analogues it has been shown that existence of charged residues increased the possibility to form temporary coils that may prevent the GLP-1 analogues from entering the DPP-IV opening. Thereby, the residues mediating the peptide's function remained unburied.

The results of the theoretical studies by MOLCAD could be confirmed in further in vitro studies and may lead to a new class of C-terminally elongated GLP-1 analogues.

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Importance of accurate charges in molecular docking: QM Polarized Ligand Docking approach

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Accurate treatment of electrostatic charges is crucial to the success of any docking algorithm. The greater the role charge polarization plays in determining a ligand's bound conformation, the more difficult it will be for docking algorithms to perceive the correct binding mode. Schrödinger has developed QM-Polarized Ligand Docking (QPLD) protocol[1], which uses ab inito charge calculations within the protein environment to overcome this limitation. QPLD combines docking steps with Glide with the accurate QM/MM charge calculation using QSite.
QPLD has been shown to provide substantial improvements in docking accuracy over pure MM methods. Across a test set of 271 protein-ligand complexes taken from the PDB, QPLD succeeded in docking the ligand with an average RMSD of less than one angstrom. This protocol is especially useful for applications that demand the highest level of binding mode prediction accuracy.

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Development of a GBPM-based pharmacophore for virtual screening of PKB/Akt inhibitors

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Protein kinase B (PKB/Akt) is implicated in the cellular response to insulin, radiation, the regulation of immune response, and cell cycle.[1,2] However, the enzyme substrates that are responsible for many of its actions remain unidentified. Furthermore, there is only little information of low molecular affectors available. We present the development of structure-based pharmacophore filters for virtual screening in order to retrieve novel PKB inhibitors. The GRID-based pharmacophore model (GBPM) approach[3] was used to elucidate important protein-ligand interactions. Thereby, GRID molecular interaction fields were converted to Catalyst hypotheses[4] for virtual screening with several commercial and public compound libraries. Our screening results show that the GBPM approach is a potent technique for the elucidation of selective pharmacophore models that are able to retrieve novel lead structure candidates.

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A new approach for flexible protein-ligand docking based on Particle Swarm Optimisation

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Particle Swarm Optimiser (PSO) use a general-purpose, iterative, heuristic search algorithm. It considers a population of individuals to probe promising regions of the search space in an effective manner. In this context, the population of solutions is called a swarm, and the individuals are called particles. Each particle moves within the search space and retains in its memory the best position and the overall best position that has been encountered. The velocity of each particle is adjusted during each iteration toward the personal best position as well as the overall best position, thus mimicking swarm intelligence. In our recent work we have implemented PSO in a ligand-docking program. The fitness landscape of the docking program is modeled by a modified version of the scoring function X-Score[1]. X-Score is an empirical scoring function which shows a significant correlation between calculated docking scores and experimentally derived ligand geometries. Preliminary investigations show promising results in terms of speed and accuracy. Special attention during the development will be paid to a modular design of the program in order to easily implement different scoring functions as well as to perform parallel computing.

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Extensive comparison of structure - and ligand-based virtual screening protocols considering enrichment factors and hitlist complementarity

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Five structure- and ligand-based virtual screening methods (docking, pharmacophore searching, 2D-similarity and 3D-similarity searching) were analysed for their effectiveness in virtual screening against four different targets. The relative performance of the tools was compared by examining the ability to recognize known active compounds from a set of actives and non-actives. We furthermore investigated whether the application of different virtual screening methods in parallel provides complementary or redundant hit lists. Docking was performed with GOLD, GLIDE, FlexX, SURFLEX and FLEXSCREEN. The obtained docking poses were rescored using nine different scoring functions. Ligand-based virtual screening was done with Catalyst (pharmacophore searching), Feature Trees, ROCS (3D-similarity searching) and Scitegic Functional Fingerprints (2D-similarity searching). The results show that structure- and ligand-based virtual screening methods provide comparable enrichments in detecting active compounds. Interestingly, the hit lists which are obtained from different virtual screening methods are generally highly complementary. These results suggest that a parallel application of different structure- and ligand-based methods increases the chance of identifying more (and more diverse) active compounds from a virtual screening campaign.

In-Silico Prediction of hERG blockade

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hERG Blockade is one of the major toxicological problems in lead-structure optimization. Reliable in silico models for predicting hERG blockade therefore have considerable potential for saving time and money, as patch-clamp measurements are very expensive and no crystal structures of the hERG-encoded channel are available.
Drug induced blockade results in prolongation of the QT interval of the heartbeat which can be seen on the electrocardiograph[1]. Patients with prolongated QT interval show a significant predisposition for cardiac arrhythmia of the *torsades des pointes* type. These may result in potentially fatal ventricular fibrillation. Some of the most prominent drugs having been withdrawn from the market due to hERG activity are astemizole, sertindole and terfenadine[2].
We have built QSAR models based on semiempirically derived descriptors of local properties on the surface of molecules.[3] For model generation we have used a variety of methods, such as partial least squares, support vector regression and Bayesian regularized neural networks. The best results have been achieved using support vector regression models, giving R^2y values for test and validation sets > 0.72. Significant descriptors have been identified using stepwise MLR on subsets with a specially adjusted F-value.
In a second approach, we have built pharmacophores and split the dataset according to pharmacophore hits. For the subgroups PLS models have been generated. The prediction accuracy of these exceeds previous models and offers novel insights into molecular features leading to hERG blockade.[4]

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New insights in the penetration of local anesthetics into membranes using the molecular free energy surface density model (MolFESD)

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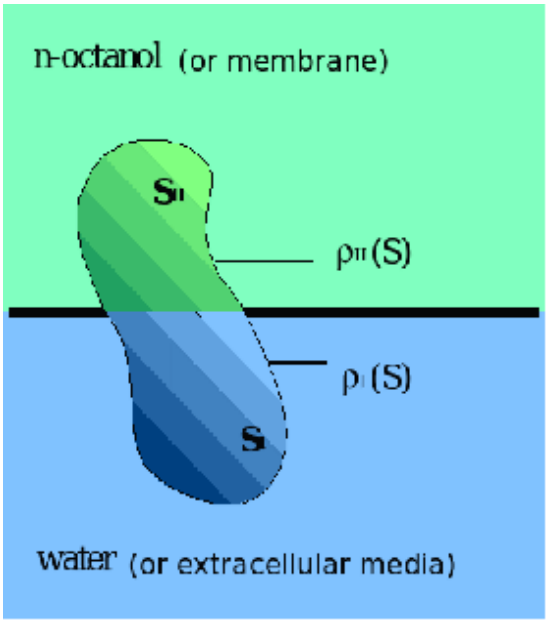
The molecular basis of the pharmacological action of local anesthetics (LA) is still unclear. Following the work of Skou[1,2], anesthetics of the procaine type are thought to interact with phospholipid membranes rather than with specific receptors.[3] Since then, several[4,5] experimental studies have been performed on the penetration of LA into lipid mono-bi-layers showing a clear correlation between penetration and potency. In the present study, molecular free energy surface density model (MolFESD) has been applied to theoretically predict the optimal position and orientation of LA (procaine analogues) at the interface of membrane and water phases. This approach showed a correlation between the volumes and surfaces of immersed regions of various LA and their anesthetic activity.



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Parametrization of the molecular free energy surface density (MolFESD) for various systems

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Quantitative information of solvation and transfer free energies is often needed for the understanding of many physicochemical processes, e.g the molecular recognition phenomena, the transport and diffusion processes through biological membranes and the tertiary structure of proteins. Recently, the molecular free energy surface density concept (MolFESD) has been introduced.[1,2] This model is based on the assumptions that the overall hydrophobicity can be obtained as a superposition of fragment contributions and that the corresponding free energy can be calculated as an integral of the MolFESD over the molecular solvent accessible surface. The scalar quantity 3D-FED, the three-dimensional free energy density offers a physical basis to the establishment of a new predictive model with limited empirical character. Although this volume density is accessible from more accurate methods e.g. Monte-Carlo methods, the *Grid* program[3] has proved to be suitable for a rapid evaluation of the 3D-FED. It uses empirical force field to determine the interaction energy of a particular probe molecule (e.g water) for all points of a regular three dimensional grid in which the target molecule is enclosed. In the present study, parametrization of the MolFESD is done in two steps using the same strategy described in the previous work of Jäger et al. [1,2]; some model parameters were fitted to computed data (provided by *Grid* program) while other parameters were fitted to experimental logP values. Unlike most fragment based predictive models for logP, the MolFESD concept calculates logP values which depend on the area and shape of molecular surfaces and in turn, on the corresponding molecular conformations. A detailed description of the parametrization of the MolFESD is presented followed by its application to different solvent systems.

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ParaFrag: A Novel Tool for Surface-Based Fragment Comparison

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We present a novel method for fragment similarity comparison based on surface properties. Isodensity surfaces are calculated for the electrostatic potential (MEP), and the local properties[1] ionization energy (IEL), electron affinity (EAL) and atomic polarizability (POL) by the program ParaSurf[2]. A molecular fragment can then be represented by the extremes of each property surface. This atom-independent representation of a fragment allows similarity searching in a procedure analogous to pharmacophore comparison. In the first evaluation study we focused on comparing rigid fragments for scaffold hopping. Suitable fragments are identified by exit vector matching onto a query fragment. Then the fragments' similarity is calculated by evaluating the feature distances between the local property pharmacophores. A retrospective analysis of known examples for scaffold hopping shows that our method performs well also in cases where other similarity metrics fail.

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Flexible Receptor Docking to Account for "Induced Fit" Effects

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Glide's flexible ligand docking into rigid receptor has been proven to be an effective means to predict ligand-receptor complexes – docking accuracy for native co-crystallized complexes are well documented. However, cross-docking of active ligands into different receptor conformations have generally been less successful, due to the error introduced by not accounting for conformational changes induced in the receptor structure by the docking ligand.

In order to account for induced fit effects in docking, we have developed the Induced Fit Docking (IFD) protocol. Induced Fit Docking is a novel methodology [1] for computing induced fit effects in protein-ligand complexes by combining rigid receptor docking and protein structure prediction techniques in an iterative fashion. Validation studies have demonstrated the robustness of the sampling and scoring algorithm, and have generated a wide range of pharmaceutically relevant examples.

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Molecular Dynamics Characterization of the Induction Mechanism of a Reverse Phenotype of the Tetracycline-Repressor

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Molecular-dynamics simulations have been used to investigate the mechanism of induction of a reverse phenotype (revTetR) of the Tetracycline Repressor protein. In contrast to the wild-type protein (TetR), revTetR is induced in the absence of tetracyclines and not in their presence. Based on the criteria established for class D TetR ($TetR^D$), a low-frequency normal mode analysis revealed a vibration similar to the "induction mode" for revTetR. Inter-binding-head distances plots demonstrate that in the "induced" reverse phenotype (revTetR) the DNA-binding heads are closer than the ideal distance needed for DNA-binding. This distance increases on binding an inducer. The same mechanism is found for the wild-type TetR, but whereas this distance increase makes the inter-head distance too large in the wild type, it increases to the ideal value in revTetR. Thus, the induction movement is generally the same for the two proteins but the consequences are opposite because of the smaller inter-head distance in revTetR without inducer.

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Virtual and Biological Screening of Novel Histone Arginine Methyltransferase PRMT1 Inhibitors

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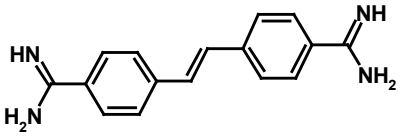
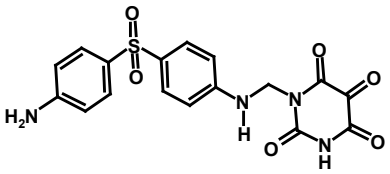
Lysine and arginine methyltransferases participate in the posttranslational modification of histones and regulate key cellular functions. So far only one arginine methyltransferase inhibitor discovered by random screening was available. We present the first target based approach to protein arginine methyltransferase (PRMT) inhibitors. Homology models of human PRMT1 were generated from available X-ray structures of rat PRMTs. The NCI Diversity Set, chosen as an initial database for lead compound identification, includes 1990 compounds derived from around 140 000 compounds submitted to the NCI from a range of sources worldwide. In using this diverse subset of molecules as a compound source, we were able to screen a wide range of chemical structures for binding to PRMT1 using less extensive computational resources than would be needed to screen a more typically sized database. A combination of docking and pharmacophore-based filtering resulted in 36 potential hit molecules. Employing a fungal PRMT for screening and a human enzyme for validation seven inhibitors of PRMTs *in-vitro* were identified. Hit validation was achieved for two new inhibitors (Fig. 1) by antibody mediated detection of histone hypomethylation as well as Western blotting in cancer cells. Functional activity was proven by an observed block of estrogen receptor activation. Thus, valuable chemical tools and potential drug candidates could be identified.

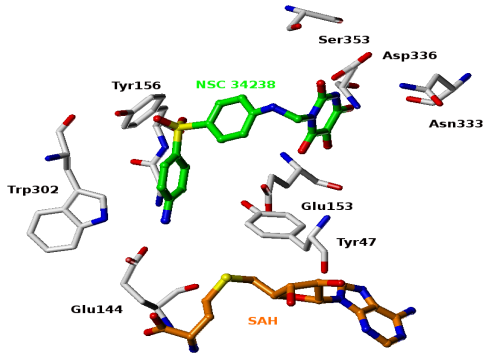
►*Stilbamidin*



►*Allantodapson*



►*Docking solution for Allantodapson*



A QM/MM investigation of the phosphoryl transfer between protein IIA^{Glc} and the cytoplasmic domain IIB^{Glc} of the glucose transporter $IICB^{Glc}$ of the *Escherichia coli* glucose phosphotransferase system

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Transfer of phosphoryl is one of the fundamental biological processes. An enormous number of enzymes are involved in cell signaling, such as phosphatases, which catalyze nucleophilic substitution at phosphorus. Theoretical studies of complex transphospho-rylation mechanisms in real biomolecular environment require fast and precise quantum mechanical methods. However, high-level ab initio or DFT calculations, as well as semiempirical calculations are far too expensive for systems with many thousands of atoms. In this sense, quantum mechanical/molecular mechanical (QM/MM) techniques have been widely used to investigate enzyme reaction mechanisms during the last decades. They allow a quantum mechanical description of the active site, which is essential for investigating chemical reactions, and a simultaneous consideration of important long-range effects of the enzyme environment.

The phosphoenolpyruvate:sugar phosphotransferase system (PTS) is a classical example of a metabolic pathway involving phosphoryl transfer. In this system, a phosphoryl group originating from phosphoenolpyruvate is transferred to the translocated carbohydrate via a series of three bimolecular protein-protein complexes. The first two steps are common to all sugars: enzyme I is autophosphorylated by phosphoenolpyruvate and consequently donates the phosphoryl group to the histidine phosphocarrier protein HPr. The protein downstream from HPr is sugar specific. In the case of glucose, the phosphoryl group is transferred from HPr to IIA^{Glc} and then from IIA^{Glc} to the cytoplasmic domain IIB^{Glc} of the glucose transporter $IICB^{Glc}$.

In our group we have investigated the mechanism of the phosphoryl transfer in the glucose branch of the PTS. In particular, the results for the phosphoryl transfer in the complex between protein IIA^{Glc} and the cytoplasmic domain IIB^{Glc} of the glucose transporter $IICB^{Glc}$ of the *Escherichia coli* glucose phosphotransferase system using mixed quantum mechanical (semiempirical MO, AM1 and MNDO) and molecular mechanical (Tripos force field) geometry optimizations will be presented here.

The transfer reaction pathway consists of two steps, the first one being the transfer of the phosphoryl group itself, from residue His-90 of enzyme IIA^{Glc} to residue Cys-35 of enzyme IIB^{Glc}. The transfer is followed by a rearrangement in the orientation of the imidazol ring of His-90 to provide a second intermediate that prevents the reverse transfer reaction.

Comparative Binding Energy Analysis for Binding Affinity and Target Selectivity Prediction in Virtual Screening

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Thrombin, trypsin and urokinase are structurally related serine proteases with similar substrate specificities but distinct functions. The design of highly specific inhibitors towards these medically relevant targets is important for potent drugs with minimal side effects. To assist drug design and virtual screening, we applied COMparative BINding Energy (COMBINE) analysis[1-3], a 3D quantitative structure activity relationship (QSAR) method, to a training set of 24, 37 and 26 receptor-ligand complexes of crystal structures of thrombin, trypsin and urokinase, respectively. Structurally derived van der Waals, electrostatic and desolvation energy terms were correlated to experimentally determined inhibition constants, and specific scoring functions for each of the targets were generated.
The COMBINE models attained good R2, Q2 and standard error of prediction (SDEP) values greater than 0.8, 0.6 and less than 1.0 kcal/mol, respectively. Important residues for ligand binding could be highlighted and the target-specific scoring functions were used to predict the binding free energy of docked ligands. After re-ranking of the docking solutions with the COMBINE models, the selectivity of ligands towards thrombin and the other two targets, trypsin and urokinase, could be predicted.

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An Optimal Coordinate System for Geometry Optimization in VAMP

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Geometry optimization on VAMP and other programs is done generally using Internal coordinates or Cartesian coordinates. The objective of this work is to develop a mixed coordinate system, which we refer to as Optimal Coordinate System (OCS). The general idea behind such a coordinate system is that an optimization algorithm is more efficient in some cases when using Cartesian coordinates (rings), while on other cases when using internal coordinates (chains).
Hence we propose an OCS representation of the molecule. The molecule is analyzed and broken into segments of two types: rings segments, and chain segments. Algorithms used range from ring perception, efficient conversion from internal to cartesian coordinates[1], and breadth first search graph algorithms[2],[3]. Ring segments are represented in Cartesian coordinates, plus six additional transformation parameters (translation and rotation). Chain segments are represented in internal coordinates, plus the rotation and translation parameters. A connection matrix stores information regarding which segment is connected to which other in order to restore the original molecule after the optimization process.
So far, we have tested the conversion from Cartesian coordinates to OCS coordinates with around 6000 compounds from the Maybridge database. Once the OCS is integrated fully into VAMP we intend to run optimizations and benchmarks using the Maybridge database.

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Molecular Dynamics Simulations of new putative human DNA pol α inhibitors for treatment of excessive keratinocyte proliferation

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The DNA-dependent DNA polymerases α (pol α) or B family are essential for DNA replication and cell division. Representativ members of this family are the prokaryotic pol II, several eukaryotic and archaeal polymerases, as well as the viral adenovirus, herpes simpex virus, bacteriophage RB69, T4 and T6 polymerases. Inhibitors of pol α are interfering with DNA synthesis. To date they are used for the treatment of viral diseases, like herpes and HIV-infections.
We aim at a similar effect in the topical treatment of skin pre-cancerous and cancerous lesions. Currently, actinic keratosis is treated with topically applied 5-fluorouracil, photodynamic therapy, diclofenac/ hyaluronic acid or with imiquimod. Typical problems in the therapy are severe local irritations, pain and secondary infections[1]. Pol α inhibitors should offer an alternative for the treatment of skin carcinomas and minimal micro-lesions. They are supposed to increase cure rates and allow topical application to larger UV exposed ski areas.

Previously, we built a homology model of the active site of human DNA pol α based on the crystal structure of bacteriophage RB69 DNA pol[2]. This 3D model was now used for Molecular Dynamics Simulations (MDS) of new putative ligands of human DNA pol α. In total we tested ten different putative ligands that all possess one common scaffold. As we observed a hydrophobic cavity within the active site, we wanted to test whether the exchange of a sidechain for a more or less lipophilic carbohydrate-chain would alter the affinity to the binding site.
MDS was performed with GROMACS[3]. Coulomb- and Lennard-Jones-interaction energies between the respective ligands and the protein in the course of the simulation served to evaluate binding affinities.
The results suggest that indeed a higher lipophilicity of the sidechain would increase the interaction with the target protein.

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Improving Semiempirical MO Methods: Sample Parameterization of an OM3-like Hamiltonian

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Semiempirical quantum chemistry methods bridge the world of molecular and quantum mechanics: They are cheap enough to handle even a large database of intermediate-sized compounds or deal with some structures with the size of huge biomolecules.

In our opinion the OMx[1-3] (x=1,2,3) methods developed in Thiel's group are a step in the right direction, towards a next-generation semiempirical method:[4] Two- and three-center pseudopotential terms are added to the MNDO[5] one-electron operator H^{core}. They treat the inner-shell electrons' influence upon valence electrons via effective core potentials (ECP), include electron penetration effects via analytical electron-core integrals, and overcome shortages of missing orbital orthogonalisation by adding suitable corrections. With those e.g. the description of rotational barriers improves significantly.

Our OM3-like method resembles most of the original OM3 method; we, however, use Slater-type orbitals instead of Gaussian-functions, because they describe the electron density much better than their Gaussian counterparts and have been used in all established semiempirical methods.

The mathematical formulation of our OM3-like method in terms of one-center ($\mu\mu$, $\mu\nu$) and two-center ($\mu\lambda$) elements of H^{core} is thus

$$H_{\mu\mu} = U_{\mu} d_{\mu} + V_{\mu}^{ana} + V_{\mu}^{ECP} + V_{\mu}^{ORTH}$$
$$H_{\mu\lambda} = b_{\mu\lambda} + V_{\mu\lambda}^{ORTH}$$

where the terms V represent the different pseudopotentials, and $\beta_{\mu\lambda}$ is the resonance integral (see Poster for details). We here present some sample parameterisation results for our OM3-like method following a similar strategy as with the AM1*-method.[6]

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IRECS: Prediction of side-chain conformation ensembles for flexible docking

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Our side chain prediction tool IRECS[1] (Iterative REduction of Conformational Space) is able to identify ensembles of most probable conformations for all side chain of a protein structure. This is quite useful for protein-ligand docking, as the ligand binding process can induce conformational changes of the protein, and often this involves a flipping of side chains. We predict flexible protein models with IRECS and device the docking software FlexE[2] to dock ligands into the active sites of these protein models to account for these induced-fit effects. Our implementation of FlexE uses a SCMF[3] minimization algorithm to pick the most suitable side-chain conformation from the conformational ensembles generated with IRECS during the construction of the ligand conformation into the binding pocket. This allows the simulation of the conformational adoption of the protein to the ligand during the whole docking process. We evaluate our approach on the targets of the Database of Useful Decoys (DUD)[4], using a redocking and screening setup. Additional docking experiments were performed with FlexX[5] and rigid protein models predicted with IRECS. The results show that the IRECS-FlexE tandem produces much more accurate solutions than the standard approach using the rigid protein assumption by the cost of extended runtime.
IRECS is available for download from the URL *http://irecs.bioinf.mpi-inf.mpg.de*.

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Automated Generation of Fragment-Based Rules for Mutagenicity Prediction

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Mutagenicity is a killing property for compounds in drug development and therefore *in silico* prediction of mutagenicity is of great interest to pharmaceutical R&D. The accuracy of currently available prediction methods is, however, not satisfactory for druglike compounds, [1,2] and therefore this remains an area of active research.

The steady growth of in-house as well as publicly available data on the mutagenicity of different compounds asks for automated methods to analyze this data and derive predictive toxicophores for mutagenicity. We have developed a fully automated procedure to derive fragment-based rules from large databases of mutagenicity data. It builds upon a previously reported manual work-flow that resulted in a set of rules with good performance.[3] Special attention is paid to the relationships and interdependencies between fragments and their visualization in order to select a non-redundant set of rules.

The approach consists of four consecutive steps:

1. Exhaustive generation of fragments from a training set
2. Selection of fragments statistically significant for mutagenicity as *mutagenicity alerts*
3. Analysis of relationships and dependencies between significant alerts to identify and exclude redundant alerts
4. Identification of *detoxifying subfragments* for the remaining *mutagenicity alerts*

This approach results in *mutagenicity alerts* and corresponding *detoxifying fragments* represented as SMARTS strings which can be used easily to predict whether a compound is potentially mutagenic or not. Additionally, a hierarchical, interactive HTML-document is created, in which the dependency of the mutagenicity alerts and the data for the rule generation can be examined. This can be utilized to compare the rules generated from different training datasets, e.g. the mutagenicity of metabolic activated and non-activated compounds.

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Why does $[IrH_2(R_2PCH_2CH_2NH_2)_2)]^+$ favour Transfer Hydrogenation over direct H_2-Hydrogenation? – A Computational Approach

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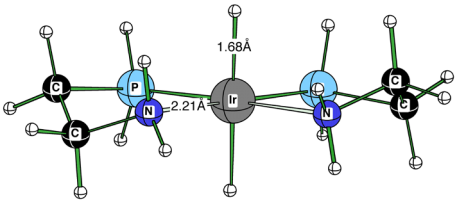
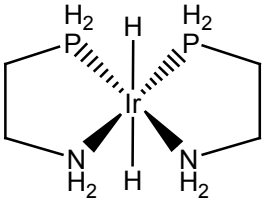
Among the most efficient known catalysts for the transformation of ketones to secondary alcohols with dihydrogen as a reductant are bis(phosphane)/diamine-coordinated ruthenium(II) complexes $[Ru(X)(Y)(PR_3)_2(H_2N\cap NH_2)]$ (X, Y, = Cl, H), where $H_2N\cap NH_2$ stands for a chiral or achiral chelating 1,2-diamine and $(PR_3)_2$ represents two monodentate or one chiral bidentate phosphane, especially the BINAP ligand. H_2-hydrogenations supported by such systems are exceptional with because of their consistently high enantioselectivity, their chemoselectivity for carbonyl over olefin reduction and the very large substrate-to-catalyst ratios (up to 10^6) that can be attained.[1] In contrast, the isoelectronic Ir(III) hydrido complexes do not catalyze the direct hydrogenation by molecular H_2, but rather the transfer hydrogenation of the C=O bond.[2]





►*Structure (RB3LYP/LACV3P+**) of the catalyst's model*

Based on DFT (RB3LYP/LACV3P+** and RPW91PW91/LACV3P+**) and *ab initio* (MP2) calculations for a model of the Ir-based catalyst, we have explored the reaction mechanism in order to explain why direct hydrogenation cannot be observed.

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Receptor specific Scoring-Function: Improving classical forcefields with quantum mechanical calculations

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We demonstrate how the inclusion of QM-calculations for a protein-ligand complex with the Fragment Molecular Orbital Method is used to construct a protein-specific scoring-function for the complex .
In comparing the new specific scoring function for protein and ligand with a standard scoring-function, using parameters calculated by standard forcefields (ESFF), we realize a performance gain (an increased correlation to an experimentally measured or QM calculated binding energy).
Even in the mixed case (using the QM-scoring-function for the protein and the standard scoring function for the ligands) the docking correlation improves compared to the pure ESFF docking case; which is important, since for the high-throughput screenings quantum mechanical calculations for all ligands are not feasible.
Additional we want to report docking accuracy results of our docking tool FlexScreen using a subset of the Astex/CCDC data set.

Through space NMR shielding of aromatic compounds

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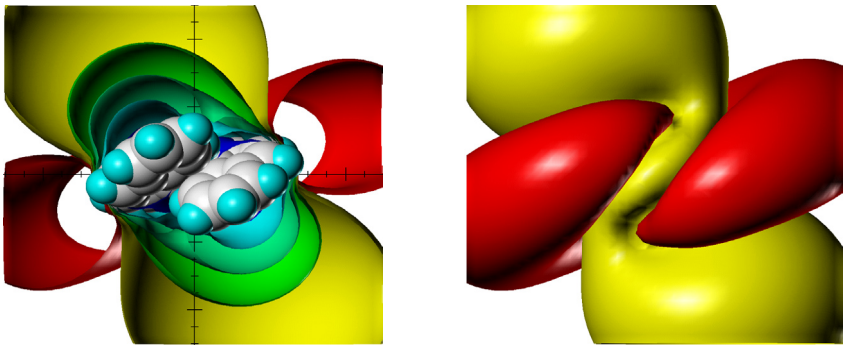
Through space NMR shielding of aromatic (benzene, ferrocene, [14]-annulene, phenylenes and tetra- to heptahelicenes) and anti-aromatic molecules (cyclobutadiene and tetraflurocyclobutadiene) were assessed by *ab initio* MO calculations. Employing the nucleus-independent chemical shifts (NICS) concept, these through space NMR shielding were visualized as *Iso*-Chemical-Shielding Surfaces (ICSSs) and can be applied quantitatively to determine the stereochemistry of proximal nuclei.



►*ICSSs of hexahelicene*

The distances in Å of the ICSS at values of ±0.1 ppm *in-plane* and *perpendicular-to-center* of the studied systems were employed as a simple means to compare and estimate qualitatively aromaticity / antiaromaticity of these systems.

Molecular-Dynamics Simulations of a Structurally Defined Micelle

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Specifically designed T-shaped amphiphilic calix[4]aren derivatives[1] form structurally persistent heptameric micelles in water. Experimental investigations by NMR and cryo-TEM techniques confirmed that these spherical aggregates consist of exactly seven monomers.[1] Moreover, 3D-reconstruction at a resolution of 12 Å showed a highly developed topological arrangement of the micelles[2,3]. We have used molecular-dynamics (MD) simulations to investigate the behavior and structure of the micelles in aqueous solution.

Simulations that used different starting conditions and geometries gave stable heptameric micelles with a relatively rigid topology. More precisely, the stable structures consist of two pairs of intercalating calix[4]arenes with three additional molecules clipped around them. This suggests that the discrete monomers in the micelle are not chemically equivalent. This effect will be investigated further by MMPSA calculations and the results will be compared to other possible calicarene aggregates as trimers or pentamers.

However, in contrast to the experimental findings, which suggest C_2-symmetry, no discrete static symmetry was found in the simulations as the polar head groups move slowly throughout the simulations. Furthermore, velocity calculations show that the aliphatic core of the micelle is highly disordered, whereas the movement of the hydrophobic head groups is restricted through interactions with the solvent.

Future investigations will target the stability of the micelle in its heptameric form and the specific role of water in the grooves of the micelle. In order to be able to compare the results of the simulations with cryo-TEM, we will simulate the TEM pictures directly using standard scattering factors applied to a series of snapshots taken from the trajectories.

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De novo protein structure prediction and folding with free energy models

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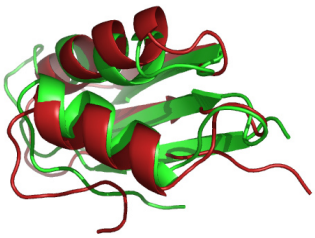
De novo prediction of protein tertiary structure on the basis of amino acid sequence remains one of the outstanding problems in biophysical chemistry. According to the thermodynamic hypothesis, the native conformation of a protein can be predicted as the global optimum of its free energy surface with stochastic optimization methods orders of magnitude faster than by direct simulation of the folding process.



►*Overlay of the experimental and the predicted conformations of a 72 amino acid protein (1AFI)*

We have developed an all-atom free energy forcefield PFF01/02[1] which stabilizes a wide array of proteins. With efficient stochastic optimization methods we are able to predictively and reproducibly fold a variety of proteins containing both alpha-helices and beta-sheets from random starting conformations: the trp-cage protein[2], the villin headpiece[3], the HIV accessory protein[4] , protein A, the 60 amino acid, 4-helix bacterial ribosomal protein L20[5] and several beta-sheet peptides (14-28 amino acids)[6] and zinc-finger motifs[7].

We used several stochastic optimization methods: the stochastic tunnelling method, an adapted version of parallel tempering, basin hopping techniques and distributed evolutionary optimization strategies. We will discuss advantages and limitations with respect to further improvements of this approach to in-silico all-atom protein structure prediction.

We have also extended our approach to larger proteins by combining our free energy model with heuristic techniques that generate large libraries of protein conformations on the basis of the amino acid sequence. When we ranked ROSETTA decoy sets for 30 different proteins according to their energy in our model, we find that near-native conformations are selected for all high-quality decoy-sets (see figure for an example). For low-quality decoy sets, the approach generates usable low-resolution models in over 80% of the cases, but still has difficulty treating disulfide-bridged proteins, protein-protein complexes and proteins which are stabilized only in complex with other molecules.

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Electron-Transfer Systems Based on C_{60} – Relationship Between Chemical Nature and Long-Range Electron Transfer

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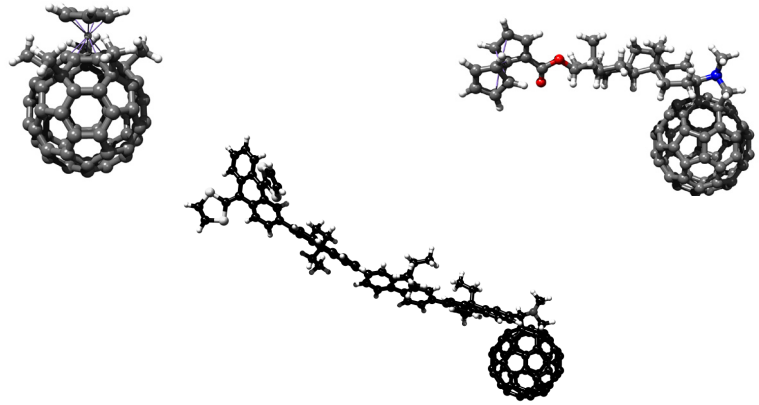
Understanding and testing novel electron-transfer systems is at the forefront of science, since they provide promising tools for solar-energy conversion. Among these systems, the electron-accepting properties of C_{60}-fullerenes are well established. Together with various electron-donating species and π-conjugated oligomers, i.e. molecular wires, they provide an extensive toolkit for the synthesis of supramolecular donor-acceptor architectures capable of photoinduced electron transfer[1][2][3].
By means of photophysical and quantum chemical methods **C_{60}-WIRE-DONOR** triads and **C_{60}-DONOR** dyads were investigated as part of supramolecular electron-transfer ensembles, in which **exTTF** and **Fc** act as electron donors and **C_{60}** as electron acceptor. In the triads electron transfer is mediated by **oPPV**, **oPPE** or **oFL** bridges, whereas in the dyads the **DONOR** is directly linked to **C_{60}**. In respect to photoinduced charge separation between **DONOR** and **C_{60}** the influence of the π-conjugated bridges has been examined.



►*Schematic representation of the donor-acceptor architectures.*

Spectroscopy measurements provided insights into the charge-separation processes and proved the existence of the **DONOR $^{\cdot+}$ / $C_{60}^{\cdot-}$** radical ion pairs.
Charge-separation and charge-recombination dynamics were determined in all systems and analyzed as a function of distance. In the triads, small attenuation factors (β), which are 0.01 $Å^{-1}$ for **oPPVs**, 0.21 $Å^{-1}$ for **oPPEs** and 0.09 $Å^{-1}$ for **oFLs,** facilitate long-range electron transfer processes.

The quantum chemical characterization using semi-empirical C.I. methods and DFT calculations provided insights into the electron-transfer properties of the different molecules. Ground-state and excited-state electronic structure calculations were performed using Gaussian 03, VAMP 10, Parasurf and Tramp 1.1d for representations.[4][5].

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[2] For a recent review on molecular electronics, see: Carroll, R.L ; Gorman, C.B. *Angew. Chem., Int. Ed.* **2002**, *41*, 4378
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Selective Inhibition of CDKs

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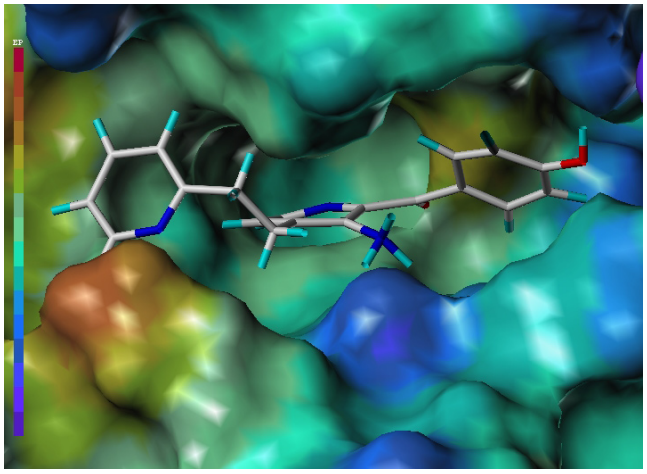
Cyclin-dependent kinases (CDKs) are important regulators in the cell cycle.
Different CDKs have a high homology but different functions. CDK2 has a high relevance concerning cancer. In contrast CDK5 has regulatory functions of neurons.

We searched for ligands binds only at CDK2 but not at CDK5 with the help of modelling software Sybyl7.1[1)]. For this reason we firstly studied the performance of different known ligands in the binding site of both kinases and characterized the binding sites.

With the gained knowledge we designed 2-(4-hydroxybenzoyl)-4-[2-(6-hydroxypyridin-2-yl)ethyl]pyridin-3-aminium as a selective inhibitor. MD simulations of 150000 fs show this ligand has a high affinity for CDK2 and leaves the active site of CDK5 in a quite short time.



►*SYBYL7.1 Tripos Inc. 1699 South Hanley Road, St. Louis MO 63144 (2005)*