



COMPUTER-CHEMIE-CENTRUM

Universität Erlangen-Nürnberg



19. Darmstädter Molecular Modelling Workshop

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

Dienstag 3. Mai und Mittwoch 4. Mai 2005

Der Darmstädter Molecular Modelling Workshop in Erlangen dient vor allem dem Erfahrungsaustausch der aktiv auf dem Gebiet des "Molecular Modelling" Arbeitenden sowie der Vorstellung und Diskussion neuer Konzepte und Ergebnisse, auch aus nicht abgeschlossenen Projekten.

Die Veranstaltung gibt einen aktuellen Überblick über Arbeitsfelder und Berufsbilder im Molecular Modelling und angrenzenden Gebieten. Dies soll vor allem jungen Kolleginnen und Kollegen helfen, Berufsziele zu definieren sowie eigene Arbeiten einzuordnen, vorzustellen und zu diskutieren.

Inhaltliche Koordination

Dr. Harald Mauser

F.Hoffmann-La Roche Ltd
Pharmaceuticals Division

CH-4070 Basel, Switzerland

Tel.: +41 61 68 88604
Fax: +41 61 68 86459
EMail: harald.mauser@roche.com

Technische Koordination

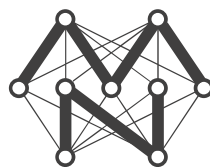
Dr. Harald Lanig
Dipl.-Chem. Jörg Marusczyk

Computer-Chemie-Centrum
Universität Erlangen-Nürnberg

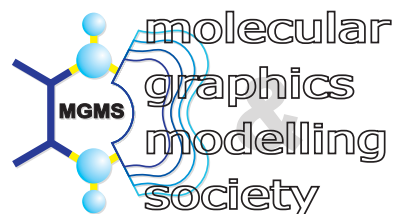
Nögelsbachstrasse 25
91052 Erlangen

Tel.: +49 (0) 9131-8522948
Fax: +49 (0) 9131-8526565
EMail: da.workshop@chemie.uni-erlangen.de

Wir danken unseren Sponsoren!



Molecular Networks



Liebe Kolleginnen und Kollegen,

der Darmstädter Molecular-Modelling-Workshop findet auch im Jahr 2005 traditionell an den beiden Tagen vor Himmelfahrt vom 3. bis zum 4. Mai statt. Der Workshop wird nun zum dritten Mal in Erlangen abgehalten. Die Arbeitskreise von Prof. Gasteiger und Prof. Clark am Computer-Chemie-Centrum der Universität Erlangen-Nürnberg übernahmen die technische Organisation vom Arbeitskreis Prof. Brickmann. Für die inhaltliche Organisation ist dieses Jahr Dr. H. Mauser, F. Hoffmann-La Roche, Basel verantwortlich.

Ziel des Workshops ist es, jungen Kolleginnen und Kollegen, insbesondere Diplomanden und Doktoranden, ein Forum zur Präsentation und Diskussion ihrer Forschungsarbeiten zu geben. Für Kolleginnen und Kollegen aus der Industrie ergibt sich so die Gelegenheit, einen Überblick über die aktuelle Forschung an den Hochschulen zu gewinnen.

Beiträge aus allen Gebieten des Molecular Modelling von "Life Sciences" bis "Materials" sind willkommen!

Wir freuen uns folgende renommierte Wissenschaftler für Plenarvorträge gewonnen zu haben:

Prof. Hugo Kubinyi

Universität Heidelberg

Prof. Josef Michl

Universität Colorado, Boulder, USA

Dr. Gerhard Müller

GPC-Biotech München

Die offizielle Tagungssprache ist Deutsch, englischsprachige Vorträge sind ebenfalls möglich. Folien und Poster sind in Englisch abzufassen. Tagungsbeiträge können in Form von Kurzvorträgen (20 Minuten einschließlich Diskussion) oder Postern (Hochformat; 90x140 cm) eingereicht werden.

Vortrags- und Posterwettbewerb

Zusätzlich zu zwei Posterpreisen von je € 100, werden in diesem Jahr auch erstmals Preise für die besten Vorträge vergeben:

1. Preis: **Reise zum Young-Modellers-Forum in London** (Unterstützung max. € 500)
2. Preis: **€ 200** (allgemeiner Reisekostenzuschuß zu einer wissenschaftlichen Veranstaltung)
3. Preis: **€ 100** (allgemeiner Reisekostenzuschuß zu einer wissenschaftlichen Veranstaltung)

Teilnahme berechtigt für Poster und Vortragspreise sind Studenten und Doktoranden.

Wie im letzten Jahr, werden rein kommerzielle Vorträge, in denen offensichtlich lediglich ein Produkt beworben wird, nicht mehr angenommen. Plattform für detaillierte Produktinformationen bietet die Software-/Hardwareausstellung an beiden Tagen.

Web Award

Wie im letzten Jahr wird auch dieses Jahr wieder ein Web Award von € 500 für eine herausragende netzbasierte, wissenschaftliche Anwendung im Bereich Molecular Modelling vergeben. Bewerbungen sind bis zum 31. März 2005 über die Webseiten der MGMS-DE (www.mgms-ds.de/web_award.html) abzugeben. Hier stehen auch weitere Informationen über die Bewerbungskriterien.

Reisekostenzuschuss

Die MGMS-DS vergibt erstmalig bis zu 20 Reisekostenzuschüsse (max € 100) zum Besuch des Modelling-Workshops. Die Unterstützung ist speziell für Studenten, Diplomanden oder Doktoranden und kann beantragt werden bei:

- **Willi von der Lieth** (w.vonderlieth@dkfz.de)
- **Tim Clark** (clark@chemie.uni-erlangen.de)
- **Michael Krug** (Michael.Krug@merck.de)

Lageplan Computer-Chemie-Centrum

Postersession und Büfett

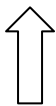
2. Stockwerk

Nägelsbachstr. 25

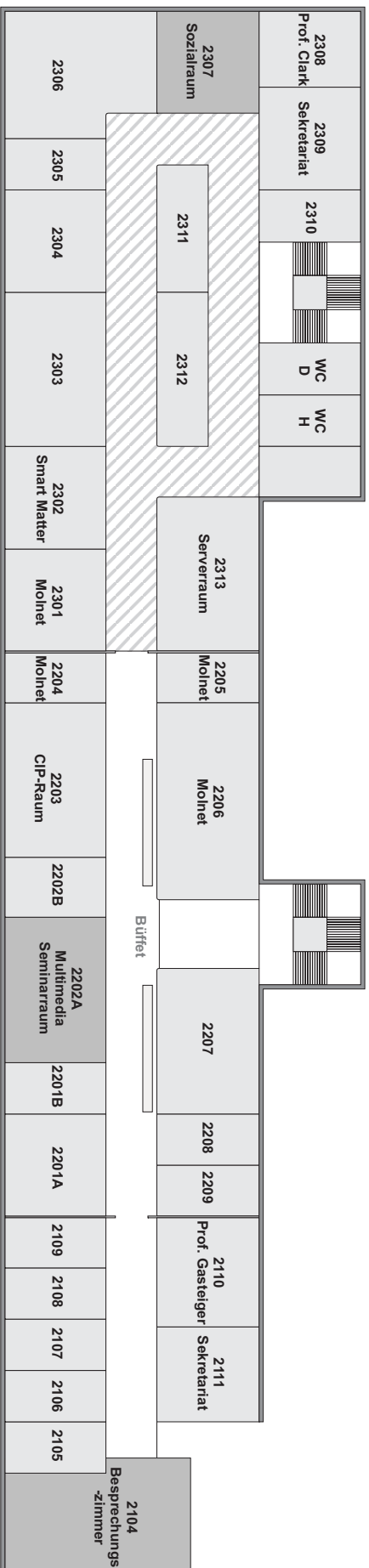
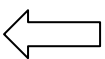
91052 Erlangen



Nägelsbachstrasse



Haupteingang



Programm: Dienstag, 3. Mai 2005

08:00	Anmeldung	
09:00-09:15	Begrüßung	
09:15-10:15	Hugo Kubinyi Virtuelles Screening - Der Weg zum Erfolg	<i>Universität Heidelberg</i>
10:15-10:35	Kaffee	
10:35-10:55	Alexander Böcker Hierarchical Clustering of Huge Compound Libraries	<i>Boehringer Ingelheim Pharma GmbH und Co. KG</i>
10:55-11:15	Juri Pärn 2D Visualizing and Navigation in Fragment-Based Chemistry Spaces	<i>Universität Hamburg</i>
11:15-11:35	Alrun Koller Molecular recognition properties of 'universal' fluorobases investigated by potential of mean force calculations	<i>Universität Frankfurt</i>
11:35-11:55	Aqeel Ahmed Multi-scale modelling of macromolecular conformational changes (combining concepts from rigidity and elastic network theory)	<i>Universität Frankfurt</i>
11:55-13:00	Mittagessen	
13:00-13:20	Hubert Kuhn Molecular Fragment Dynamics (MFD). A new mesoscopic Molecular Modelling Simulation Method	<i>CAM-D Technologies GmbH</i>
13:20-13:40	Josef Scheiber Conformational flexibility in QSAR analyses - Extensive validation of the novel alignment-independent 4D-QSAR technique xMaP	<i>Universität Würzburg</i>
13:40-14:00	Markus Lill Exploring QSAR beyond 3D: From optimization of binding affinities to prediction of adverse drug reactions	<i>Universität Basel, Schweiz</i>
14:00-14:20	Daniela Schuster Pharmacophore-based Database Mining for the Discovery of Novel Cytochrome P450 17 and Cytochrome P450 19 Inhibitors	<i>Universität Innsbruck, Österreich</i>
14:20-14:40	Andrea Straßer A Module for approximate Calculation of a Ligands Pathway into the Binding-Pocket of a Receptor - Application on the H1-Receptor	<i>Universität Regensburg</i>
14:40-15:00	Kaffee	
15:00-15:20	Gordon Thie Development of New Nanostructured Pollutant Adsorbers with Advanced Molecular Modelling Techniques	<i>CAM-D Technologies GmbH</i>
15:20-15:40	Sarah Schulz Mesoscopic Simulations of the Embedding of Nanoparticles in Phospholipid Multilayers	<i>CAM-D Technologies GmbH</i>

Programm: Dienstag, 3. Mai 2005

15:40-16:00	Axel Schunk Der GDCh-Forschungsführer - Online	<i>GDCh, Frankfurt</i>
16:00-17:00	Josef Michl New Vistas in Polyalkylated Icosahedral Anions, "Ylides", and Radicals	<i>University of Colorado, Boulder, USA</i>
17:00-17:30	Hard & Software Ausstellung	
17:00-18:00	Jahresversammlung der MGMS-DS, Institut für Organische Chemie, kleiner Hörsaal	
18:00-19:30	Postersession I, Computer-Chemie-Centrum	
19:30-22:00	Büffet, Computer-Chemie-Centrum	

Programm: Mittwoch, 4. Mai 2005

10:00-10:20	Thomas Herz In silico - in vitro - in vivo - in progression: The long road for a small molecule compound	<i>4SC AG</i>
10:20-10:40	Finn Bauer Experimental and computational characterization of the influence of conformational flexibility on protein affinity and stability	<i>Universität Erlangen-Nürnberg</i>
10:40-11:00	Thomas Steinbrecher A Multistep Approach to Structure Based Drug Design: Studying Ligand Binding at the Human Neutrophil Elastase	<i>Universität Freiburg</i>
11:00-11:20	Sebastian Radestock Improving binding mode predictions by docking into protein-specifically adapted potential fields	<i>Universität Frankfurt</i>
11:20-11:40	Paul Czodrowski To charge or not to charge? Protonation states in proteins and its complexes	<i>Universität Marburg</i>
11:40-12:00	Olaf Othersen Structure Quest: Chameleonic Tetracycline Magnesium Ion Complexes	<i>Computer-Chemie-Centrum, Universität Erlangen-Nürnberg</i>
12:00-13:00	Mittagessen	
13:00-14:30	Postersession II, Computer-Chemie-Centrum	
14:40-15:00	Kaffee, Hard & Software Ausstellung	
15:00-16:00	Gerhard Müller Design of selective kinase inhibitors: Facts or Fantasy?	<i>GPC-Biotech</i>
16:00-16:30	Preise	

Poster

P1	José Castro Arce	DPD Simulation amphiphiler Moleküle
P2	Finn Bauer	Affinity of SH3-ligand interaction influenced by conformational flexibility of the receptor
P3	Frank Beierlein	Simulating FRET: A Combined Molecular Dynamics-QM/MM Approach
P4	Carsten Beyer	Process Optimization of Grid Computing for High Throughput Docking Experiments
P5	Andrea Böcker	Hierarchical Clustering of Huge Compound Libraries: Interactive SAR Analyses
P6	Frank Böckler	Combining Ligand- and Structure-Based Methods Leads to the Development of Advanced Binding Mode Hypotheses for Dopamine D3 Receptor Agonists
P7	Benjamin Breu	Predicting binding affinities from homology models by AFMoC: A case study on serine proteases
P8	Helen F. Chappell	DFT Calculations of the Properties of Si-Substituted Hydroxyapatite
P9	Fernando. B. Da Costa	Classification of natural terpenoids from the family Asteraceae
P10	Ulf Frieske	Molecular Fragment Dynamics (MFD). A new mesoscopic Molecular Modelling Simulation Method
P11	Christof Gerlach	Temptation of High-Throughput Docking: Possible Strategies and the Development of Required Tools
P12	Jens Gimmler	Continuous global optimization: Finding the right algorithm for a problem
P13	Holger Gohlke	Incorporating quantitative experimental chemical shifts information into protein-ligand docking algorithms
P14	Stephanie Gulde	Step-wise approaches to the in silico screening of large 3D-databases to identify ligands for a receptor protein
P15	Gudrun Hackspiel	Pharmacophore Modelling of Minor Groove DNA-binding Ligands
P16	Dimitar Hristozov	Comparison between Natural Compounds and Known Ligands
P17	Teresa Jimenez	Comparing binding pockets based on knowledge-based potential fields
P18	Anette Klinger	Assessment of Covalent Docking for Virtual Screening
P19	Oliver Koch	Secbase Secondary structure elements and ligand binding
P20	Oliver Korb	When Ants Dock Molecules
P21	Andreas Krasky	Flavin-disulfide oxidoreductases as targets for the development of new antiparasitic drugs
P22	Ananda Rama Krishnan S.	DFT and MD studies on banana-shaped mesogens

- P23 **Markus A. Lill** Protein-based multidimensional QSAR: From cytochrome P450 mediated drug-drug interactions to endocrine disruption
- P24 **Harald Mauser** Putting the Pieces Together: Application of Fragment-based Methods in Lead Generation
- P25 **Rene Meier** Impact of Scoring Functions on the Results of Molecular Docking Studies
- P26 **Wolfgang Müller** Identification of protein-protein interactions by structure based scoring functions
- P27 **Ralph Puchta** DFT and mechanistic studies on the reactivity of Pt(II) complexes in imidazolium-based ionic liquids
- P28 **Monika Rella** Virtual Screening for novel ACE2 Inhibitors using Structure-based Pharmacophore Hypotheses
- P29 **Jörg Saßmannshausen** A DFT Studie of CpCp(XH₂Ph)ZrCl Cations (X = C, Si)
- P30 **Josef Scheiber** Conformational flexibility in QSAR analyses - Extensive validation of the novel alignment-independent 4D-QSAR technique xMaP
- P31 **A. Schulenburg** π Electron Distribution in Push-Pull-Alkenes
- P32 **Stephan Tatzel** The molecular basis of 21-Hydroxylase deficiency in mice
- P33 **Sascha Tayefeh** Modeling and molecular dynamics of a miniature viral potassium channel
- P34 **Philipp Wacker** NMR and quantum chemical investigations of conformation, ring current effects and NH-tautomerism of porphyrins
- P35 **Björn Windshügel** Modelling versus crystallisation - The basal activity of constitutive androstane receptor (CAR)
- P36 **James Smith** A Procedure for Investigating Halide Anion Complexation to Radical Clocks
- P37 **Matthias Hennemann** Semiempirical MO Molecular Dynamics and DFT Calculations on a Fluxional Molybdenum Complex with 1,3-Diphosphete Ligands
- P38 **Olaf Othersen** Structure Quest: Chameleonic Tetracycline Magnesium Ion Complexes
- P39 **Urszula Uciechowska** A Comparison of Two Geometric Superposition Approaches for exploring the Conformations of an Unstructured Polypeptide Tail
- P40 **Horst Bögel** Molecular Modelling with WebMO
- P41 **Jr-Hung Lin** An analytical, variable resolution, complete description of static molecules and their intermolecular binding properties
- P42 **Rong Xu** Analytical Computation of the Post-SCF for the Acetylene Dimerization at Cobalt Center
- P43 **Sergio Sánchez Ríos** A Web Interface for the Parameterization Database
- P44 **Ken Byler** Surface-Integral QSPR Models: Local Energy Properties
- P45 **Stefan Henrich** The Application of COMBINE Analysis to Generate Target-Specific Scoring Functions

- P46 **Heike Meiselbach** Computational Approaches to identify the Determinants of SH3-Binding Specificity
- P47 **Christian Weyera** Designing Specificity of SH3 Domain Binding Ligands
- P48 **Anselm H. C. Horn** Dynamical behaviour of the Prion Protein: Influence of pH Change and F198S Mutation
- P49 **Nadine Homeyer** Molecular Dynamics Simulations of HPr and the Structural Implications of Phosphorylation

Vorträge

Dienstag, 3. Mai 2005

VIRTUELLES SCREENING - DER WEG ZUM ERFOLG

Hugo Kubinyi

*Universität Heidelberg,
c/o Donnersbergstrasse 9, D-67256 Weisenheim am Sand.
E-mail kubinyi@t-online.de,
URL www.kubinyi.de*

In den letzten beiden Dekaden änderten sich die Paradigmen der Pharmaforschung auf signifikante Weise. In vitro-Modelle zur Untersuchung der biologischen Aktivität und neue Technologien für die Leitstruktursuche und -optimierung werden immer wichtiger. Die Gentechnologie liefert nicht nur therapeutisch wertvolle Proteine, sie trägt auch auf besondere Weise zur rationalen Wirkstoffsuche bei. Sequenz und Funktion eines Proteins lassen sich aus der Gensequenz ableiten; die Eignung als therapeutisches Target wird in transgenen Tieren untersucht; Expression des Proteins in Bakterien oder in Zellkultur liefert das Material für Hochdurchsatz-Testsysteme und für eine 3D-Strukturbestimmung mittels Proteinkristallographie, NMR-Techniken oder Elektronenkryomikroskopie. Die Kombinatorische Chemie wandelte sich nach schwierigem Start mehr und mehr zu einer automatisierten Parallelsynthese von Bibliotheken, die unter medizinisch-chemischen Aspekten geplant werden. Molecular Modelling spielt eine zunehmend wichtige Rolle. Struktur-basierte und computergestützte Methoden der Ligandensuche werden eingesetzt, um die Wirkstoffsuche und -optimierung rational und mit möglichst geringem Aufwand durchzuführen. Hohe Affinität zur Bindestelle eines krankheits-relevanten Targets ist aber nur eine wichtige Eigenschaft; zusätzlich muss der Wirkstoff oral verfügbar sein und er darf keine gravierenden Nebenwirkungen aufweisen.

Die Wirkstoffsuche wird oft mit der sprichwörtlichen "Suche nach der Nadel im Heuhaufen" verglichen. Virtuelles Screening reduziert die Größe des Heuhaufens durch Selektion von Verbindungen mit Leitstruktur-Eigenschaften, Wirkstoffcharakter, potentieller Bioverfügbarkeit oder Ähnlichkeit zu einer Leitstruktur, mit Regeln (z.B. die Lipinski-Regeln), neuronalen Netzen (z.B. zur Unterscheidung von Wirkstoffen und Chemikalien), Pharmakophoranalysen, Ähnlichkeitsanalysen, "Scaffold hopping" oder Docking und Scoring. Ausgewählte Beispiele werden die Anwendungsbreite, mögliche Fehlerquellen und die Grenzen der einzelnen Methoden erläutern.

J. Sadowski und H. Kubinyi, A Scoring Scheme for Discriminating Between Drugs and Non-Drugs, *J. Med. Chem.* 41, 3325-3329 (1998).

G. Klebe, Hrsg., Virtual screening: an alternative or complement to high throughput screening, *Persp. Drug Discov. Design* 20, 1-287 (2000).

H.-J. Böhm und G. Schneider, Eds., Virtual Screening for Bioactive Molecules, (Band 10 der Reihe *Methods and Principles in Medicinal Chemistry*, R. Mannhold, H. Kubinyi und H. Timmerman, Hrsg.), Wiley-VCH, Weinheim, 2000.

H. Kubinyi, Random vs. rational drug discovery, *Curr. Drug Discov.* 2001 (Oktober), 9-11.

H. Kubinyi, Drug research: myths, hype and reality, *Nature Rev. Drug Discov.* 2, 665-668 (2003).

J. Alvarez und B. Shoichet, Hrsg., *Virtual Screening in Drug Discovery*, CRC Press, Taylor & Francis Group, Boca Raton, FL, USA, 2005

Hierarchical Clustering of Huge Compound Libraries: Theory and Application

A. Böcker^{1,2}, G. Schneider², A. Teckentrup¹

¹ *Boehringer Ingelheim Pharma GmbH und Co. KG, Department of Lead Discovery, Birkendorfer Straße 65, D-88397 Biberach an der Riss, Germany.*

² *Johann Wolfgang Goethe-University, Institute of Organic Chemistry und Chemical Biology, Marie-Curie-Str. 11, D-60439 Frankfurt, Germany*

High throughput screening (HTS) of compound collections with up to one million small organic molecules provides a rich primary source of compound activity data. Consequently software requirements for data mining and model building have changed towards methods, being able to handle large data sets.[1] Exploiting the knowledge of both the “actives” and “non-actives” to extract structure-activity relationships (SAR) from HTS data is pivotal, since it helps formulating crude SAR hypotheses at early stages of a drug discovery project. Unsupervised data clustering provides one possibility to get a quick first overview of potential groups of active and non-active compounds. Visualising and analysing structures in these clusters helps finding decisive molecular features. In this context a hierarchical relationship between the clusters is of utmost importance since it additionally allows to navigate in the data, focussing in or out of data clusters.

Two clustering techniques - NIPALSTREE [2] and hierarchical k-means [3, 4] - have been implemented, capable to hierarchically cluster compound collections with more than one million data points in high dimensional space. The NIPALSTREE algorithm projects a data set via principle component analysis onto one dimension. The data set is sorted according to this one dimension and split at the median position. To avoid distortion of clusters lying around the median position, the algorithm searches additionally for a better split point left and right of the median. The hierarchical k-means algorithm separates the data set in two parts, using the standard k-means algorithm. Both procedures are applied recursively on the data set, until the maximum distance between two data points in a cluster falls below a predefined threshold. Our software was designed in such a way that the clusters can be graphically represented by a dendrogram, and activity data (e.g. IC50 values, class labels) can be assigned to the individual data points. The results are displayed in an interactive window, enabling the user to quickly navigate through the tree and interpret the results.

Retrospective analyses were performed using MDDR [5], COBRA [6] and the Specs catalogue [7], showing the validity of both clustering approaches and the usability of the algorithms in context of virtual screening for new inhibitors.

- [1] Böcker, A.; Schneider, G.; and Teckentrup, A. Status of HTS Data Mining Approaches. *QSAR Comb. Sci.* 2004, 23, 207-213.
- [2] Böcker, A.; Teckentrup, A. and Schneider G., NIPALSTREE: A New Approach for Clustering Large Data Sets. 18. Darmstädter Molecular Modelling Workshop 2004.
- [3] Böcker, A.; Derksen, S.; Schmidt, E.; Teckentrup, A.; and Schneider, G. A Hierarchical Clustering Approach for Large Compound Libraries. *J. Chem. Inf. Model.* 2005, in press.
- [4] Barnard, J.M.; Downs, G.M.; Wild, D.J. and Wright, P.M. Better Clusters Faster. Third Joint Sheffield Conference on Chemoinformatics 2004.
- [5] MDL Drug Data Report. www.mdl.com .
- [6] Schneider, P. and Schneider, G. Collection of Bioactive Reference Compounds for Focused Library Design. *QSAR Comb.Sci.* 22, 713-718. 2003.
- [7] SPECS <http://www.specs.net/>

2D Visualizing and Navigation in Fragment-Based Chemistry Spaces

Juri Pärn, Matthias Rarey

*Zentrum für Bioinformatik, Universität Hamburg, Bundesstraße 43
20146 Hamburg, Germany, {paern|rarey}@zbh.uni-hamburg.de*

Fragment-based chemistry spaces consist of a set of fragments and a set of rules which specifies how the fragments can be connected. These spaces can be the underlying search space for typical tasks in pharmaceutical research like library design, de novo design or lead optimization. Since the fragment spaces may become very large it would be useful to have a tool to visualize and navigate in fragment-based chemistry spaces.

We present the tool FragView developed for these tasks. FragView allows the user to visualize fragments as 2D structure diagrams. To overcome the problem of visualizing large fragment spaces the tool allows to reduce the set of shown fragments to those with desirable features. For example, the user can specify allowed ranges for physicochemical properties like number of atoms or link types. To have a better overview of fragments with compatible link types, it is possible to orientate the fragments according to their links employing an algorithm for constrained structure diagram generation¹. Further on, the fragments can be inspected in a spreadsheet which allows the user to see all fragment attributes like number of atoms or number of links.

Beside visualization and orientation of fragments, FragView can also be used to build up new fragments according to the rules of the chemistry space². This can be done by explicitly selecting two or more fragments which will then be connected in all possible combinations. For a more automated build up, two subsets of fragments with desirable properties can be selected by means of a query. Each fragment of the first set would then be connected with every compatible fragment of the second set. Since the new generated fragments are also part of the fragment space, all operations of the program can be used in an iterative fashion, e.g. the new fragments can be used to build up further fragments.

The functionality of FragView will be shown on sample chemistry spaces resulting from combinatorial chemistry programs and compound shredding (RECAP-Procedure).

¹ P. C. Fricker, M. Gastreich, M. Rarey, *J. Chem. Inf. Comput. Sci.*, **44**, 1065 (2004)

² M. Rarey, M. Stahl, *J. Comput.-Aided Mol. Design*, **15**, 497 (2001)

Molecular recognition properties of “universal” fluorobases investigated by potential of mean force calculations

Alrun Koller, Holger Gohlke

*Molekulare Bioinformatik,
Fachbereich Biologie und Informatik,
J. W. Goethe-Universität,
Marie-Curie-Str. 9, 60439 Frankfurt*

Fluorobases (such as difluorobenzene (1) or difluorobenzimidazole (2), which are nonpolar base isosters (NBI) of the natural pyrimidine and purin bases) provide a means to investigate the forces (hydrogen bonding and stacking) that determine the structure and stability of nucleic acids [1]. Interestingly, when incorporated into a 12mer duplex RNA, 1 and 2 lead to rather low destabilization and discriminate only little between natural paired bases. Hence, 1 and 2 can be considered “universal” bases [2].

To gain insight into the molecular recognition properties of NBIs in atomic detail, in this study, we used umbrella-sampling techniques to generate free-energy profiles of association of NBIs with natural bases. In particular, we were interested in the role of organic fluorine in non-covalent interactions, which may have implications on the field of medicinal chemistry. To this end, potentials of mean force (PMF) were calculated for planar configurations of paired bases or stacked base configurations in explicit water applying the AMBER suite of programs, using the distance between bases as a reaction coordinate.

The following results stand out: I) No differences in base pairing interactions between difluorobases (1, 2) and different natural bases (A, C) are found, in agreement with experiment. II) Base pairing involving 1 and 2 is disfavored compared to Watson-Crick base pairing, but more favorable than if benzene (3) is used as NBI. This is the result of similar desolvation costs of 1-3, but decreased attractive base-base interactions of 3 compared to 1, 2. The latter indicates the occurrence of C-F dipolar interactions and C-H...N interactions in the case of fluorinated bases, albeit no hydrogen bonds involving fluorine are found. III) A decomposition of PMFs into enthalpic and entropic contributions shows that base pairing is entropy driven. IV) The above results, together with contributions by stacking interactions, can be used in an additive approach to estimate changes in the RNA stability due to incorporation of NBIs. V) We propose a 7-N-linked purine to be able to act as a “universal” base. Experiments are currently underway to test this.

[1] E. T. Kool, J. C. Morales, K. M. Guckian, *Angew. Chem. Int. Ed.* 2000, 39, 990-1009.

[2] J. Parsch, J. W. Engels, *J. Am. Chem. Soc.* 2002, 124, 5664-5672.

Multi-scale modelling of macromolecular conformational changes combining concepts from rigidity and elastic network theory

Aqeel Ahmed, Holger Gohlke

*Molekulare Bioinformatik,
Fachbereich Biologie und Informatik,
J. W. Goethe-Universität,
Marie-Curie-Str. 9, 60439 Frankfurt*

Modelling protein flexibility and plasticity is computationally challenging but important for understanding the function of biological systems. Furthermore, it has great implications for the prediction of (macro)molecular complex formation. Normal mode analysis based on an atomic-level force field representation of the macromolecules has been successfully applied to the problem, but is limited by requirements of memory and computational time. Recent developments to overcome this limitation use coarse-grained models. Here, the proteins are either modelled as elastic networks or as collections of rigid blocks connected by flexible links. The decomposition into rigid blocks was done so far on ad hoc basis, assuming the rigidity of small units (like residues or secondary structures). This procedure breaks down, however, if high levels of coarse-graining are aspired.

In this work, we combined concepts from rigidity theory and elastic network theory to model protein conformational changes using a two-step multi-scale approach. In the first step, the protein flexibility is analysed using the well established FIRST approach (based on rigidity theory) and the protein is decomposed into rigid clusters utilizing information at an atomic level. Subsequently, a protein representation consisting of rigid clusters connected by flexible links is used to determine directions and amplitudes of motions using a block normal mode approach.

Our method was tested on a dataset of ten proteins, and the results were compared to experimentally observed conformational changes in terms of both the directions and the amplitudes. Very good agreement was found for both cases, even if block sizes comprising more than 60% of the whole protein were considered. This shows that a computationally efficient high coarse-graining level can be attained without affecting the predicted motion. Our approach will also be interesting for the field of flexible docking where the method can be iteratively applied.

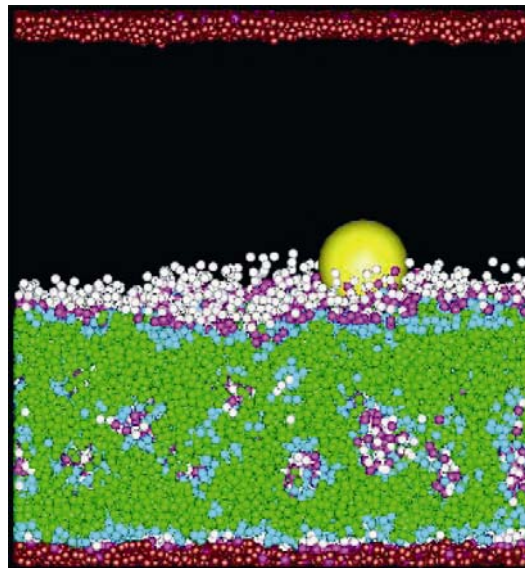
Molecular Fragment Dynamics (MFD). A new mesoscopic Molecular Modelling Simulation Method

Hubert Kuhn, Sarah G. Schulz, Ulf Frieske

*CAM-D Technologies GmbH, Essen, Gerlingstrasse 65, D-45139 Essen
(T.: 0201 3657 400, Mail: kuhn@molecular-dynamics.de)*

We have developed a new mesoscopic Molecular Modelling simulation method useful for simulations of specific dynamical processes at the microsecond and micrometer scale. This method can be generally applied in Materials and Life Science simulation studies.

The MFD algorithm is based on the recently introduced Dissipative-Particle- Dynamics method (DPD). In DPD the system is divided into different regions of fluid materials. However, the MFD scheme overcome these limitations and MFD is generally applicable to molecules. In MFD the interactions between molecular fragments are calculated. Consequently, with MFD, computer simulations of biopolymers, nanoparticles, surfactants and complex structured materials are possible.



MFD-Simulation of the interaction between Fe-Pt-nanoparticles and DPPE-phospholipid-bilayers

In order to obtain reliable simulation results the precise calculation of the interaction parameters between molecular fragments is crucial.

In this lecture an introduction to the MFD theory and the procedure is given. The calculation method of the molecular fragment interaction parameters will be explained in detail. Some Modelling results are shown to reveal the potential of this new method.

Conformational flexibility in QSAR analyses - The alignment-independent 4D-QSAR technique xMaP

Josef Scheiber, Nikolaus Stiefl and Knut Baumann

*Department of Pharmacy and Food Chemistry,
Am Hubland, D 97074 Wuerzburg, Germany*

A novel molecular descriptor called xMaP (extended MaP descriptor) is presented. The descriptor is the 4D extension of the previously published alignment-independent MaP descriptor (Mapping Property distributions onto the molecular surface) [1]. In addition to MaP, xMaP is independent of the chosen starting conformation of the encoded molecules. This is achieved by using ensembles of conformers which are generated by employing conformational searches or molecular dynamics simulations. This step of the procedure is similar to Hopfingers 4D-QSAR [2].

A five step procedure is used to compute the xMaP descriptor. First, the conformers for all the molecules are determined. Next, for each of the conformers an approximation to the molecular surface with equally distributed surface points is computed. Third, molecular properties are projected onto this surface. The properties are afterwards assigned at most two out of five property categories (H-bond acceptor/donor, hydrophilic, weakly/strongly lipophilic). Third, areas of identical properties are identified and are subsequently merged to so-called patches. Finally, the distribution of the patches representing surface area size and surface properties are converted into an alignment-independent descriptor which is based on the entire conformer ensemble. The resulting descriptor can be interpreted by superimposing the most important descriptor variables and the molecules of the data set. The most important descriptor variables are identified with chemometric regression tools.

The novel descriptor was applied to several benchmark data sets. It was compared to the original MaP procedure [1] and to 4D-QSAR [2]. In all cases the results of xMaP were comparable to MaP or 4D-QSAR with respect to model quality and model interpretability. However, as opposed the former descriptor xMaP is based on conformer ensembles which renders the novel descriptor more robust. As compared to 4D-QSAR, xMaP is alignment independent which avoids the necessity of an alignment rule.

[1] Stiefl N, Baumann K. Mapping Property Distributions of Molecular Surfaces (MaP): Algorithm and Evaluation of a Novel 3D-QSAR Technique. *J. Med. Chem.* 2003;46:1390-1407.

[2] Hopfinger AJ, Wang S, Tokarski JS, Jin B, Albuquerque M, Madhav PJ, Duraiswami C. Construction of 3D-QSAR Models Using the 4D-QSAR Analysis Formalism. *J. Am. Chem. Soc.* 1997;119:10509-24.

Exploring QSAR beyond 3D: From optimization of binding affinities to prediction of adverse reactions

Markus A. Lill and Angelo Vedani

*Institute for Molecular Pharmacy, University of Basel,
Klingelbergstrasse 50, CH-4056 Basel,
Switzerland and Biographics Laboratory 3R,
Friedensgasse 35, CH-4056 Basel, Switzerland*

Quantitative structure-activity relationships (QSAR) are often employed to establish a correlation between structural features of potential drug candidates and their binding affinity towards a macromolecular target. In 3D-QSAR, the structures of the involved molecules are represented by three-dimensional entities, allowing to quantify electrostatic forces, hydrogen bonds and hydrophobic interactions at the atomic level. Models based on 3D-QSAR typically represent a binding site surrogate with physico-chemical properties mapped onto its surface or a grid surrounding the ligand molecules, superimposed in 3D space. Unfortunately such a single construct interacts with all ligands simultaneously, thus disabling the simulation of induced fit (receptor-to-ligand adaptation) — a fundamental shortcoming of the technology. As this entity represents all but a receptor surrogate, the bioactive conformation, orientation and protonation state of the ligand molecules might be guessed at best. Multidimensional QSAR represents a subtle extension of 3D-QSAR attempting to overcome both shortcomings.

In this lecture, we present two novel concepts (Quasar and Raptor) and demonstrate their use to predict binding affinities of chemically diverse sets of ligand molecules binding to G-protein coupled receptors.

Furthermore, it is our objective to establish a virtual laboratory allowing for a reliable in silico estimation of harmful effects triggered by drugs, chemicals and their metabolites. In the recent past, we have developed the underlying computational technology — automated flexible docking (Yeti) combined with multidimensional QSAR (Quasar and Raptor). Using this concept, we then validated protein-based models to predict the inhibitory or toxic potential of diverse molecules binding to cytochrome P450 3A4 (CYP3A4) and receptors mediating endocrine disruption (Ah, estrogen and androgen receptor), respectively. The results suggest that our approach may be used for the reliable prediction of binding affinities and adverse effects of drugs and chemicals prior to their synthesis.

Pharmacophore-based Database Mining for the Discovery of Novel Cytochrome P450 17 and Cytochrome P450 19 Inhibitors

Daniela Schuster, Anja Paluszczak[§], Rolf W. Hartmann[§], and Thierry Langer*

**Institute of Pharmacy, Department of Pharmaceutical Chemistry,
University of Innsbruck, Innrain 52c, A-6020 Innsbruck, Austria
§FR 8.5 Pharmazeutische und Medizinische Chemie
Postfach 151150, D-66041 Saarbrücken, Germany*

Sex hormones play a crucial role in living organisms: They regulate growth, maturing, and reproduction of most life forms on earth. Apart from their physiological role, sex hormones can be involved in pathophysiological processes such as tumorigenesis and -growth. About 80% of all prostate cancers and 66% of all breast cancers are sex hormone dependent [1-2]. In this context, a promising approach to lower blood sex hormone levels is to block their biosynthesis. The enzyme cytochrome P450 17 (CYP17; 17 α -hydroxylase, 17,20-lyase) catalyzes the last steps of androgen biosynthesis while cytochrome P450 19 (CYP19; aromatase) is essential for estrogen biosynthesis.

It was shown that aromatase inhibitors frequently inhibit CYP17 and other enzymes involved in sex hormone biosynthesis [3]. Non-selective inhibition of two or more target proteins by a new drug candidate often leads to potentially severe side effects. Such compounds are very unlikely to become drugs. Accordingly, the design and discovery of highly selective enzyme inhibitors is essential for the development of new drugs.

We created ligand-based pharmacophore models for selective, non-steroidal CYP17 and aromatase inhibition by using the software package CATALYST [4]. Subsequently, the models were employed for database mining to identify new potential leads for these targets. By performing additional in silico filtering for lead likeness, predicted toxicity, and potential side effects such as hERG potassium channel block, further enrichment of compounds likely to enter clinic was aimed. Promising database search hits that passed this extensive filtering process were submitted to biological testing.

[1] Hartmann RW et al. Inhibition of CYP17, a New Strategy for the Treatment of Prostate Cancer. Arch. Pharm. Pharm. Med. Chem. 2002; 335: 119-28

[2] Sainsbury R. Aromatase inhibition in the treatment of advanced breast cancer: is there a relationship between potency and clinical efficacy? Br. J. Cancer 2004; 90: 1733-9

[3] Recanatini M et al. A New Class of Nonsteroidal Aromatase Inhibitors: Design and Synthesis of Chromone and Xanthone Derivatives and Inhibition of the P450 Enzymes Aromatase and 17 α -Hydroxylase/C17,20-Lyase. J. Med. Chem. 2001; 44: 672-80.

[4] CATALYST Version 4.9, MSI, San Diego, CA, USA

A Module for approximate Calculation of a Ligands Pathway into the Binding-Pocket of a Receptor - Application on the H1-Receptor

Straßer, A., Regensburg/D; Wittmann, H.-J., Regensburg/D

*Dr. Andrea Straßer, Institute of Pharmacy, University of Regensburg,
D-93040 Regensburg; E-Mail: andrea.strasser@chemie.uni-regensburg.de*

In general a ligand has to penetrate deep into the binding pocket of a receptor to show an agonistic or antagonistic effect. In order to construct new drugs with high potency it is not only essential for the drug to show an appropriate interaction with the amino acids in the binding pocket, but the ligand has to be able to reach this pocket. So in molecular modelling studies especially regarding the binding pocket, the modelling of a ligands pathway with the amino acids, involved in the process of transportation, has to be included.

Molecular Dynamics Simulations are insufficient for calculating this pathway due to the large computing time needed. Because of that we developed a new algorithm (in combination with the software package SYBYL [1] and GROMACS [2,3] respectively) for an approximate calculation of this pathway. Our intention is not to calculate the exact pathway, instead we want to calculate one or more possible pathways only on basis if the potential energy surface without kinetics, especially to get knowledge which amino acids are involved in the transportation process. The main problem, solving this question is the immense CPU time needed. To get results after a few days of calculation without using large computer clusters one has to put presumed information into the calculation. Logically it would be appropriate to give a source structure as one and a destination structure as an additional information. Due to the fact, that a systematic search of the potential energy surface is not possible, our algorithm is based on a sequence of iterations including limited Monte-Carlo search, minimization and directional guiding of the ligand.

So far we calculated the pathway of the natural ligand histamine into the proposed binding pocket of the guinea-pig H1-receptor.

[1] SYBYL 7.0, Tripos

[2] GROMACS 3.2.1

[3] Lindahl, E.; Hess, B.; v. d. Spoel, D.; GROMACS 3.0 : A package for molecular simulation and trajectory analysis; J. Mol. Mod., 7, 306-317 (2001)

Development of New Nanostructured Pollutant Adsorbers with Advanced Molecular Modelling Techniques

Gordon Thie¹, Hubert Kuhn¹, Sarah G. Schulz¹, Jörg Peggau², Felix Müller²

¹ *CAM-D Technologies GmbH,
Essen, Germany*

² *Degussa AG, Goldschmidt GmbH - Care Specialties -,
Essen, Germany*

The adsorption of active molecules or surfactants on nanostructured surfaces opens a wide range of applications. This activated surfaces bind pollutants and odor molecules effectively. Possible applications are NO_x filters for vehicles or pollutant and odor filters in air-conditioning systems.

Molecular Modelling studies on active substances revealed the binding mechanism of pollutants to specific surfactant. As a result of combined theoretical studies with Molecular Mechanics and Quantum Mechanics methods it was possible to develop a nanostructured metal oxide surface coated with a pollutant adsorbing surfactant. This active surfactant is being adsorbed on the surface in the nanostructure which is essential for the function of the system.

With Molecular Modelling Simulations this surfactant was designed as a highly efficient absorber of nitrogen and sulfur containing pollutants. The Computer Simulations showed that the presence of water is crucial for the activation of the system. Consequently, this odor absorbing component was so far unsuitable in solid applications. However, with the new developed nanostructured metal oxide surface it is now possible to use it in solid filters to bind pollutants and odors in the air.

In this lecture we present results of the experimental and theoretical investigations of the system which give interesting insides into this highly innovative odor absorbing filter. We present Computer Simulations as well as experimental studies to understand the mechanisms which helped to optimize this innovative system with a wide range of novel applications.

Mesoscopic Simulations of the Embedding of Nanoparticles in Phospholipid Multilayers.

Sarah G. Schulz¹, Ulf Frieske¹, Hubert Kuhn¹, Christian Mayer²

¹ *CAM-D Technologies GmbH, Essen*

² *Institut für Physikalische Chemie, Universität Duisburg-Essen, Duisburg*

The simulation of the aggregation of complex systems represent a challenge for conventional methods of simulation. The length and time scales of the dynamics of such phenomena overcome the limits of most simulation methods. In this lecture we present a new developed mesoscopic simulation method (MFD = Molecular Fragment Dynamics). The introduction of nanoparticles in the mesoscopic simulation technique opens new insights into the behavior of nanoparticles in complex systems.

Experimental investigations shows the embedding of nanoparticles in phospholipid multilayers on a silicon substrate. The self-aggregation of the particles in regular two-dimensional arrangement has been observed. These results could be reproduced with our new simulation method, moreover new insight into the mechanism and dynamics of the aggregation of the nanoparticles in the lipid layers were obtained. Thereby structural data e.g. the nanoparticle distances and arrangement of the phospholipids was determined.

The presented simulation results of nanoparticle systems show a novel application of mesoscopic computer simulations and yield an important contribution to the understanding of such systems. Experimental data could be reproduced as well as experimentally unavailable information obtained.

Schulz, S. G., Frieske, U., Kuhn, H., Schmid, G., Müller, F., Mund, C. and Venzmer, J.: *Tenside Surfactants Detergents* 41 (2004) 230.

Schulz, S. G., Kuhn, H., Schmid, G., Mund, C. and Venzmer, J.: *J Colloid Polym Sci* 283, (2004), 284.

Annegret Terheiden, Christian Mayer, Karsten Moh, Burkhard Stahlmecke, Sonja Stappert, Mehmet Acet, Bernd Rellinghaus, *Applied Physics Letters* 84 (2004), 3891.

Chemiker-Netzwerke: Der GDCh-Forschungs- und Technologieführer

Axel Schunk, Florian Moritz, Swantje Rietfort, Leonhard Kießling

Gesellschaft Deutscher Chemiker, Frankfurt am Main

In einer immer mobileren und stärker vernetzten Welt müssen auch die wissenschaftlichen Fachgesellschaften neue Aufgaben übernehmen. Von besonderer Bedeutung ist der Aufbau neuer und Ausbau bestehender Netzwerke und Forschungsverbünde.

Die Gesellschaft Deutscher Chemiker ist seit ihrer Gründung bestrebt, Kooperationen zwischen Wissenschaftlern zu fördern. Sie tut dies durch die Einrichtung von Fachgruppen und die Organisation von Tagungen und Kongressen. In den 1980er Jahren wurde der Forschungs- und Technologieführer „Chemie und Biochemie in Deutschland“ begründet. In diesem Werk sind Chemikerinnen und Chemiker verzeichnet und über verschiedene Register erschlossen, die selbständig Forschung betreiben. Das Buch dient als wichtige Informationsquelle für alle, die Spezialisten oder Kooperationspartner im Bereich Chemie suchen. Es erschien 1994 letztmalig in gedruckter Form.

Die GDCh hat 2004 begonnen, den Forschungs- und Technologieführer neu als online-Datenbank aufzulegen. Alle Wissenschaftler/innen, die im Bereich Chemie, Biochemie und angrenzenden Gebieten selbständig forschen, sind nun eingeladen, sich in die Datenbank einzutragen.

Das neue System ermöglicht es, den Forschungsführer nach Bedarf zu aktualisieren und zu ergänzen. Es können erweiterte Informationen abgelegt werden, er enthält neben den Kontaktdaten und Angaben zu den Forschungsgebieten auch Hinweise zum wissenschaftlichen Werdegang und zu Mitarbeitern. Publikationsverzeichnisse können in der Datenbank angelegt werden, externe Quellen lassen sich über Links anbinden. Der Nutzer hat erweiterte Suchmöglichkeiten: Zu den Institutionen und Fachbereichen, sowie zu den Arbeitsgebieten wurden Kataloge angelegt. Schlagwort- und Stichwortsuchen sind auch im Volltext möglich. Die Suche in der Datenbank ist ohne Login möglich.

Der Forschungs- und Technologieführer wird um Angaben zu den Fachbereichen ergänzt. Die Hochschulen werden gebeten, Adressen und Informationen zu den Studienangeboten einzugeben. Die neue Datenbank übernimmt damit auch Funktionen des Studienführers und bietet damit umfassende Suchmöglichkeiten für Wissenschaftler, Studierende und Interessenten außerhalb des Hochschulbereichs.

Das Projekt wird vom BMBF gefördert. Der Aufbau der Datenbank erfolgt in Kooperation mit dem Fachinformationszentrum (FIZ) Chemie Berlin und der Technischen Informationsbibliothek (TIB) Hannover. Sie ist wesentlicher Bestandteil der neuen „Informations- und Wissensplattform Chemie“.

Weitere Informationen: <http://www.gdch.de/fofue/>

New Vistas in Polyalkylated Icosahedral Anions, "Ylides", and Radicals

Prof. Josef Michl

*University of Colorado,
Boulder,
Colorado, USA*

Advances in the preparation of regiospecifically alkylated anions of the type $\text{CB}_{11}\text{Me}_{12}(-)$ and related polymers will be described. Their Li^+ salts have particularly intriguing properties, including catalytic activity. The interaction of $\text{R-CB}_{11}\text{Me}_{11}(-)$ with a variety of Lewis acids ranges from weak ion pairing contact to methide anion abstraction. The latter produces highly electrophilic "boronium ylides" carrying a naked boron vertex. An analogous "carbonium ylide" with a naked carbon vertex also reacts with nucleophiles eagerly and reveals remarkable substituent effects in reactions with aromatics. Oxidation of simple and twinned anions produces stable radicals and biradicals.

Vorträge

Mittwoch, 4. Mai 2005

in silico - in vitro - in vivo - in progression
The long road for a small molecule compound

¹Rolf Krauss, ¹Martin Lang, ¹Thomas Herz, ¹Wael Saeb, ¹Stefan Tasler,
²Frank Totzke, ²Jan Ehlert, ²Ute Zirrgiebel,
²Michael Kubbutat, ²Daniel Vitt, ²Christoph Schächtele

¹ 4SC AG, Am Klopferspitz 19a, D-82152 München, Germany
² ProQinase GmbH, Breisacher Str. 117, D-79106 Freiburg, Germany

Protein kinases play a pivotal role in the regulation of cellular functions. These include processes like cell growth and division, cell differentiation and cell death, but also many other cellular activities.

The intention of the project is the identification so-called multi-target protein kinase inhibitors, which inhibit at least two different protein kinases playing a role in two or more different molecular mechanisms of tumor progression. Although this approach is much more challenging than the development of a monospecific inhibitor, recent results in clinical trials displayed the lack of efficacy problem of the latter ones.

ProQinase provides disease relevant protein kinase targets using its integrated technology platform, including cell based assays and in vivo models.

4SC provides its proprietary virtual High-Throughput Screening technology, 4SCan, to identify new hit structures. Out of a library of 5 Mio compounds, ligands docking into the ATP-binding site of the desired protein kinases were selected, resulting in a hit rate of 16 % in the enzyme assay. Modification of selected hit compounds by Medicinal Chemistry led to the identification of new classes of selective inhibitors of cancer relevant protein kinases with low nanomolar activity, e.g. on Aurora and VEGF-R2 kinases. Compounds showing this selectivity profile are expected to inhibit cell proliferation and tumor angiogenesis at the same time.

Experimental and computational characterization of the influence of conformational flexibility on protein affinity and stability

F. Bauer^{1,2}, K. Schweimer², P. Rösch², H. Sticht¹

¹*Abteilung Bioinformatik, Institut für Biochemie, Emil-Fischer-Zentrum, Friedrich-Alexander-Universität Erlangen-Nürnberg, Fahrstr. 17, 91054 Erlangen, Germany*
²*Lehrstuhl Biopolymere, Universität Bayreuth, Universitätsstr. 30, 95440 Bayreuth, Germany*

The Src homology (SH3) domain is one of the most commonly found molecular protein domains in eukaryotic genomes attesting to its adaptability to a huge variety of specific interactions. Previous studies have implicated that not only the exact structure but also the flexibility of the binding site of the SH3 domain comprising the RT loop, the n-Src loop and the 310-helix to play a decisive role in determining the binding affinity.[1]

Therefore, we investigated a proline to glycine mutation at position 17 within the RT loop of SH3 domain of the tyrosine kinase Lck. NMR-spectroscopic characterization revealed that the overall structure of Lck SH3_P17G remains unaffected by the point mutation, whereas the thermodynamic stability observed by CD spectroscopy decreases. Thermal unfolding molecular dynamics simulations in explicit water showed not only a qualitatively faster denaturation of Lck SH3_P17G compared to the wildtype, but also differences in the unfolding pathway (Figure 1), which can be attributed to changes in the interaction network around the site of mutation.

Fluorescence titration and stopped flow experiments show an increase in affinity of the mutant SH3 domain for a herpesviral ligand by almost one order of magnitude and a distinct contribution of an increased association rate to it. Equilibrium molecular dynamics simulations of the wt and mutant Lck SH3 reveal an increased flexibility which is not restricted to the site of the mutation but can be observed throughout all regions of the binding interface. Based on a model of the Lck SH3-ligand complex the molecular dynamics simulation revealed that the increased association rate is achieved by increasing the population of binding-competent conformations resulting from a faster conformational sampling.

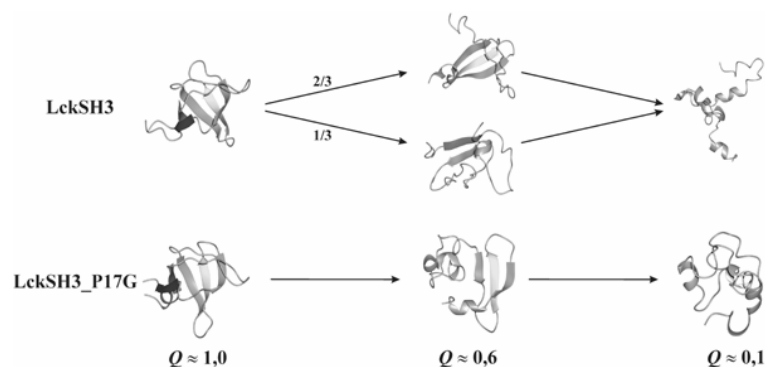


Figure 1: different unfolding pathways of wt and mutant Lck SH3 derived from molecular dynamics calculations at 498 K

[1] Arold et al. (1998) Biochemistry 37(42): 14683-91.

A Multistep Approach to Structure Based Drug Design: Studying Ligand Binding at the Human Neutrophil Elastase

Thomas Steinbrecher^{a, b}, David A. Case^b, Andreas Labahn^a

^{a)} *Institut für Physikalische Chemie, Universität Freiburg,
Albertstr 23a, 79104 Freiburg, Germany*

^{b)} *Department of Molecular Biology, Scripps Research Institute,
10550 North Torrey Pines Road, San Diego, CA 92037, U.S.A.*

In this study we show that a combination of different theoretical methods is a viable approach to calculate the binding affinities of new ligands for the human neutrophil elastase (HNE). This protease degrades elastin and likely aids neutrophils in fulfilling their immunological functions. Abnormally high HNE levels are involved in several diseases, therefore inhibitors of HNE are of interest as targets for drug design.

A recent study has revealed that cinnamic acid and bornyl ester derivatives bind to HNE, but ΔG values from ligand docking results exhibited no correlation with those calculated from the IC₅₀ values [1]. To accurately compute binding affinities, we generated possible protein-ligand complex structures by ligand docking calculations similar as described in Ref. [1], using an X-ray structure of HNE [2]. For each of the ligands, the 30 most likely placements were used as starting point of nanosecond lengths molecular dynamics simulations. The binding free energies for these complex structures were estimated using a continuum solvent (MM-PBSA) approach [3]. These results along with structural data from the molecular dynamics runs, allowed the identification of a group of similar placements that serve as a model for the natural protein ligand complex structure. This structural model was used to perform thermodynamic integration (TI) calculations to obtain the relative binding free energies of similar ligands to HNE. The TI results were in quantitative agreement with the measured binding affinities. Thus the presented approach can be used to generate a probable complex structure for known ligands to HNE and to use such a structure for lead compound optimization, possible leading to new inhibitors with improved binding affinities.

[1] Siedle B., Murillo R., Hücke O., Labahn A., Merfort I. (2003) *Pharmazie* 58, 337

[2] Navia M.A., McKeever B.M., Springer J.P., Lin T.Y., Williams H.R., Fluder E.M., Dorn C.P., Hoogsteen K. (1989) *Proc. Natl. Acad. Sci. USA* 86, 7

[3] Srinivasan J., Cheatham T.E., Cieplak, P., Kollman P.A., Case D.A. (1998) *J. Am. Chem. Soc.* 120, 9401

Improving binding mode predictions by docking into protein-specifically adapted potential fields

S. Radestock, M. Böhm, H. Gohlke

Molekulare Bioinformatik, Fachbereich Biologie und Informatik, J. W. Goethe-Universität, Marie-Curie-Str. 9, 60439 Frankfurt

Accurately predicting ligand binding modes by docking techniques is an essential step for the success of structure-based drug design and virtual screening. Only recently, however, general docking approaches have been improved by exploiting structural information about known ligands binding to the target protein (“similarity-driven docking”) [1]. An even more convincing approach would be to include also energetic information.

Hence, in this study, structural and energetic information about known protein-ligand complexes is exploited to tailor knowledge-based potentials using a “reverse”, protein-based CoMFA-type (= AFMoC) approach [2]. That way, effects due to protein flexibility and information about multiple solvation schemes can be implicitly incorporated. Interaction fields specifically adapted to one protein are developed starting from knowledge-based DrugScore potentials [3] by considering additional ligand-based information in a CoMFA-type approach. Then, the interaction fields serve as objective function in docking optimizations with AutoDock. Compared to the application of AFMoC for binding affinity predictions, a Shannon-entropy based column filtering of the descriptor matrix and the capping of adapted repulsive potentials within the binding site have turned out to be crucial for the success of this method.

The new developed approach was validated on a data set of 66 HIV-1 protease inhibitors, for which structural information was available. Convincingly, for ligands with up to 20 rotatable bonds, in more than 75 % of all cases a binding mode below 2 Å rmsd has been identified on the first scoring rank when AFMoC-based potentials were used as objective function in AutoDock. With respect to non-adapted DrugScore or AutoDock fields, the binding mode prediction accuracy was significantly improved by 14 %. Noteworthy, very similar results were obtained for training and test set compounds, demonstrating the strength and robustness of this method. We are convinced that our approach represents an important step in improving the accuracy of binding mode predictions.

[1] X. Fradera, M. A. Knegetel, J. Mestres, *Proteins* 2000, 40, 623.

[2] H. Gohlke, G. Klebe, *J. Med. Chem.* 2002, 45, 4153.

[3] H. Gohlke, M. Hendlich, G. Klebe, *J. Mol. Biol.* 2000, 295, 337.

To charge or not to charge? Protonation states in proteins and its complexes

Paul Czodrowski#, Ingo Dramburg*, Christoph A. Sotriffer#, Gerhard Klebe#

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

* *BioSolve IT GmbH, An der Ziegelei 75, 53757 Sankt Augustin, Germany*

Protonation states in proteins can be significantly affected by ligand binding. The experimental determination of protonation states in protein-ligand complexes, however, is not easily possible in most of the cases, such that reliable computational methods would be required for estimating these effects. The major contribution to changes in protonation states comes from electrostatic interactions which can be modeled by continuum methods based on the Poisson Boltzmann (PB) equation. A crucial initial step for PB calculations is the assignment of partial atomic charges. Several charge sets, e.g. from common force fields, exist, but they often lack the general applicability for protein-ligand complexes.

The development of new partial charges is described and its application on protein pKa calculations is shown. The fundamental idea is the adaptation of the PEOE (partial equalisation of orbital electronegativity) procedure which is commonly used for small organic molecules [1]. A limitation of this well-established charge scheme is the fact that it was parameterised on gas phase data. In contrast, our method assigns partial charges for which the influence of the solvent has been taken into account by parameterisation on experimental solvation free energies. Since solvation free energies are computed in PB calculations as a major component to estimate pKa values, the newly derived partial charges should also be suitable for pKa estimations in proteins and protein-ligand complexes.

The agreement of the calculated pKa values with experimental data is in a convincing agreement and compares well with other studies using established charge sets. Furthermore, initial results from applications on protein-ligand complex structures with known changes in protonation states show the suitability of the PB method in conjunction with the newly derived partial charge set for the prediction of protonation changes upon ligand binding.

[1] Gasteiger, J., Marsili, M., *Tetrahedron*, 1980, 36, 3219 .

Structure Quest: Chameleonic Tetracycline Magnesium Ion Complexes

Olaf Othersen, Harald Lanig, Tim Clark

*Computer Chemistry Center
Friedrich-Alexander University Erlangen-Nuremberg
Nägelsbachstr. 25, 91052 Erlangen, Germany*

Modeling the interaction of tetracycline with cell compounds represents a threefold challenge because very different targets exist in antibiotic-resistant bacteria. These targets are not only the membrane-embedded tetracycline antiporter protein, which is responsible for the efflux of tetracycline magnesium ion complexes, but also the 30s ribosome subunit, which provides the antibiotic effect, and the tetracycline repressor protein, which switches transcription on and off. None of these processes is clearly understood as the tetracycline magnesium ion complex exhibits very strong structural diversity.

In order to model some of these interactions, we need a clear picture of this structural diversity. Therefore, we have developed a systematic scan technique that takes different tautomers, conformations, magnesium ion positions, and numbers of explicit water molecules into account [1]. As computational time became cheaper, we upgraded this technique with an additional step of DFT geometry optimizations. Previously obtained conformations were grouped and representatives were optimized using B3LYP/6-31G*, followed by frequency, PCM, and MP2 single-point calculations.

This study provides an energetic ranking at the DFT level for the different tautomers and conformations of the tetracycline magnesium ion complex, and therefore represents a further step towards the final task of modeling tetracycline interactions.

[1] Othersen O.G., Lanig H., Clark T. J. Med. Chem. 2003, 46(26), 5571.

Design of selective kinase inhibitors: Facts or Fantasy?

Gerhard Müller

*GPC-Biotech, Max-Lebsche-Platz 32, 81377 München, Germany
e-mail: gerhard.mueller@gpc-biotech.com*

Biological signal transduction pathways control the essential functions in all cells and tissues. Extracellular signals are transduced by complex signalling cascades within each cell, ultimately eliciting specific cellular responses. Aberrant signals transduction processes have been identified for a broad range of diseases. Consequently, numerous novel molecular targets have been suggested for therapeutic intervention, most prominent representatives being protein kinases. Selective inhibition of distinct members of that target family offers novel opportunities for drug discovery and development for numerous diseases, including various cancer types, inflammatory, cardiovascular, metabolic, neurodegenerative, and even viral and bacterial diseases. Today, a total of approximately 530 human protein kinases have been identified that, together with around 150 protein phosphatases, exert a precise and reversible control of protein phosphorylation events in the cell, thus establishing the main constituents of intracellular signal transduction networks. Consequently, almost any research unit within the pharmaceutical industry currently pursues at least one, if not multiple projects aimed at finding and optimising selective low-molecular weight inhibitors for distinct protein kinases.

Currently pursued kinase inhibitor design strategies will be briefly reviewed, highlighting design principles derived from crystallographically determined high-resolution structures of kinase-inhibitor complexes. Numerous substructures have been described by various research groups specifically targeting a highly conserved structural determinant of the ATP-binding site within the kinase family, notably an alternating hydrogen bonding pattern displayed by the so-called hinge peptide portion connecting the N- and C-terminal domain of kinases (see Fig. 1 for inhibitor-hinge peptide interaction modes).

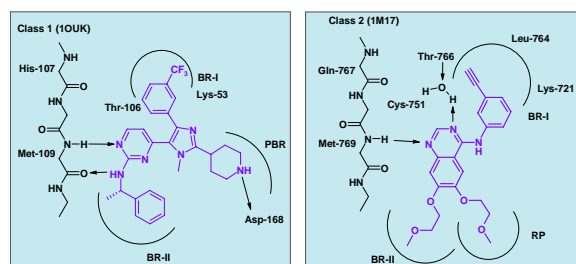


Figure 1: Schematic presentations of kinase-inhibitor binding modes taken from crystallographically refined complex structures. The polypeptide portion of the hinge part of the respective protein kinase is depicted on the left. Inhibitors utilize protein backbone functionalities for forming hydrogen bonds, while peripheral groups are oriented towards (i) the backpocket (BR-1, binding region-1), (ii) the phosphate binding region (PBR), and (iii) towards the front pocket (BR-II). Protein structure database entries are given explicitly.

In most cases, saturation of one, two, or even three hydrogen bonding functionalities displayed by the hinge peptide backbone allows to position a heterocyclic core structure within the adenine-binding region, while specificity seems to be achieved mainly by addressing cavities adjacent to the ATP-binding pocket.

After introducing the commonly applied design paradigm for ATP-competitive kinase inhibitors, the emphasis of the talk will focus on the “exceptions of those rules”. It will be demonstrated that chemical similarity among kinase inhibitors fails to correlate with biological similarity, i.e. target specificity. On one hand, chemically diverse sets of compounds are described to more or less selectively inhibit a distinct target kinase, while on the other hand, closely related analogues of the same chemotype are shown to bind to totally different kinases, even utilising different binding modes, thus rendering a rational approach within Medicinal Chemistry as challenging (see figure 2).

The main focus of the talk will then be laid on those structural determinants that govern target selectivity. It will be shown that the small-molecule binding partner in a kinase-inhibitor complex is capable of inducing conformational rearrangements of critical sidechains, thus altering shape and physicochemistry of the binding pocket. Further, subtle structural modifications in inhibitors also lead to conformational flexibility in the kinase backbone, even in the most conserved portion, i.e. the hinge peptide part. Finally, the binding mode of allosteric inhibitors that dramatically change the conformational state of the activation loop in kinases will be highlighted.

One of the main objectives of this presentation is to introduce kinases as structurally flexible entities in which binding site shape and size is to a large extent determined by the ligand, convincingly corroborated by allosteric inhibitors as shown in figure 3.

In the final part of the presentation, an experimental technology developed at Axxima Pharmaceuticals AG that specifically addresses the selectivity issue of kinase inhibitors is introduced. Within all Medicinal Chemistry projects at Axxima, a powerful tool is employed to identify kinase targets for a given compound class following a chemoproteomics technology, branded as KinaTor™. This affinity chromatography-based technology allows to experimentally identify target kinases from tissue-derived cell lysates and thus qualifies as the navigational tool through the protein kinase space. Following this approach, kinases are identified that are not included in the in-house selectivity panel or in any other commercially accessible battery of kinase assays. The KinaTor™ technology itself relies on classical affinity chromatography using immobilized kinase inhibitors. Axxima has optimised this process over the last years to such an extent that kinase enrichment factors in the order of 10.000 are routinely achieved, which is a precondition for successful target fishing, since the intracellular signalling proteins account for less than 2% of the entire cellular proteome (Figure 4).

In order to demonstrate the inherent potential of that technology, a baseline study was carried out for a known selective p38 MAP kinase inhibitor, notably SB 203580. The

compound was coupled and a variety of kinases were identified from cell lysates originating from different tissues (figure 5).

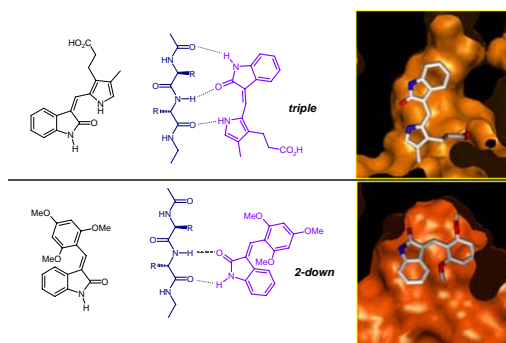


Figure 2: Indolinone-based inhibitors bind to the ATP-binding site of protein kinases in different topologies, depending on the configuration of the extracyclic double bond.

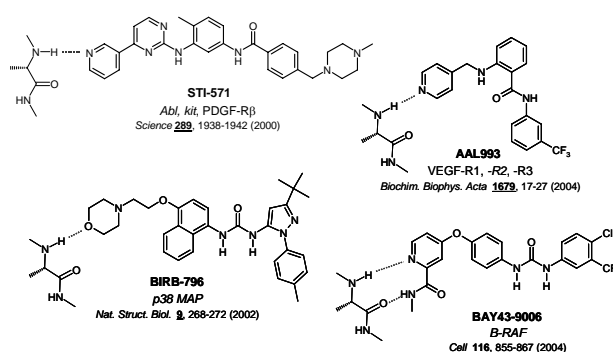


Figure 3: Low-molecular weight kinase inhibitors that have been proven to inhibit target kinases by a distinct and comparable allosteric mechanism.

Affinity chromatography using immobilised protein kinase inhibitors

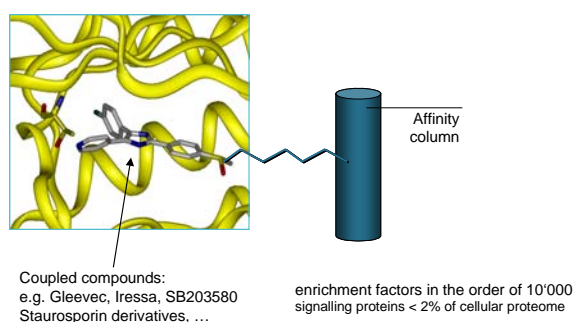


Figure 4: Low-molecular weight kinase inhibitors are immobilized via a chemical ligation strategy to an affinity column. Chromatography is carried out with cell lysates from numerous different tissue sources.

Interestingly, we were able to uncover numerous kinase targets for that p38 MAP kinase inhibitor, even with lower (!) IC₅₀ values when compared to the primary target (e.g. RICK). In addition to kinases, other enzymes were identified as binding partners for SB 203580, e.g. different cytochrome P450 enzymes, a dehydrogenase, and a hydratase. This result not only demonstrates the intrinsic potential of the KinaTor™ technology for navigating the kinome, but also shows the power of the technique in terms of selectivity profiling of any given kinase inhibitor. To further highlight the KinaTor™-intrinsic

potential, we have carried out comparable experiments for more than 20 different compound classes, a few of them shown in Figure 6.

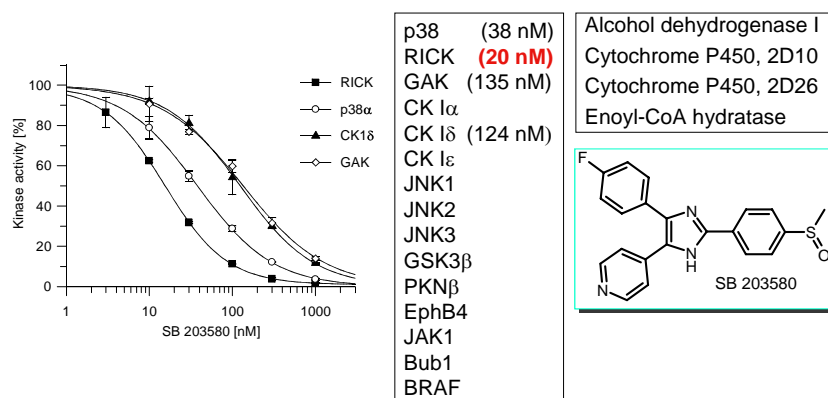


Figure 5: Axxima's chemical proteomics approach revealed numerous protein binding partners for the immobilized p38 MAP kinase inhibitor SB 203580..

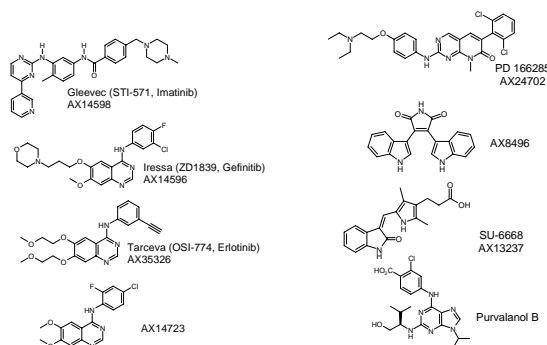


Figure 6: Numerous structurally different kinase inhibitors have been profiled for their corresponding binding partners originating from different cell lysates.

At Axxima, the technology is routinely used in in-house projects to experimentally assess the selectivity profile of compounds in the course of lead optimisation. We estimate the KinaTor™ technology as the ultimate approach to derive the selectivity profile of a given kinase inhibitor. Any panel of biochemical kinase assays remains arbitrary in its composition, since it is not feasible to test a compound against all 534 protein kinases encoded in the human genome. In addition to the above outlined application of the KinaTor, the technology further qualifies to experimentally determine the selectivity profile of e.g. putative development candidates, thus identifying potential off-targets that might relate to unwanted side-effects prior to any pre-clinical or clinical studies.

Summarising, low-molecular weight kinase inhibitors not only constitute a promising route towards novel therapies for currently unmet medical needs, but also serve as valuable tools to identify and subsequently validate cellular target kinases. Rigorous application of Axxima's KinaTor™ technology further reveals kinase inhibitors as a rich source for a chemogenomics approach, finally yielding in both, highly validated target kinases in combination with selective inhibitors that qualify to be transferred into viable pre-clinical development candidates.

Poster

DPD Simulation amphiphiler Moleküle

José Castro Arce , Hans-Jörg Bart

*TU Kaiserslautern, Fachbereich Maschinenbau und Verfahrenstechnik
Lehrstuhl für Thermische Verfahrenstechnik
<http://www.uni-kl.de/LS-Bart>*

Komplexe hydrodynamische Prozesse können mit Molekulardynamik (MD), „Dissipative Particle Dynamics“ (DPD) oder Lattice-Boltzmann Methoden simuliert werden. Aufgrund der komplexen Struktur, Anzahl und Größe der Moleküle ist der MD Simulation insbesondere bei Polymerlösungen oder Lipidmembranen enge Grenzen gesetzt. Deshalb müssen mesoskopische Simulationsverfahren, wie DPD, eingesetzt werden. Bei DPD werden Atome zu größeren Einheiten in sogenannte „Beads“ zusammengefasst um eine vertretbare Rechenzeit zu erhalten. Zusätzlich werden die Interaktionskräfte zwischen den Beads als Softpotentiale beschrieben. Dies erlaubt die Verwendung von größeren Zeitschritten in den Berechnungen, was auch zu kleineren Rechenzeiten führt.

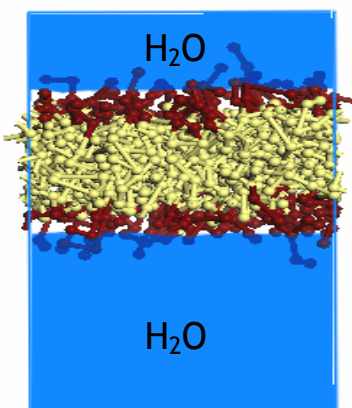


Fig.1: DPD Simulation einer Lipidmembran

Wie die Atome in den Beads zusammengefasst werden, spielt eine entscheidende Rolle in den Simulationsergebnissen. Z. B. muss ein DPD-Modell eines amphiphilen Moleküls wenigstens zwei Beads enthalten, die den polaren Teil und den unpolaren Teil des Moleküls beschreiben. Systembedingt werden die Volumen der verschiedenen Beads einer Simulation bei DPD als gleich genommen. Aus diesem Grund sollen die Beads Atomgruppen mit ungefähr dem gleichen Volumen repräsentieren.

Groot und Warren³ beschreiben in ihren Arbeit, wie die DPD-Interaktionskräfte mit der Flory-Huggins Theorie für Polymere gekoppelt werden können. Die Flory-Huggins χ -Parameter selbst können für ein bestimmtes Stoffsystem experimentell oder theoretisch bestimmt werden. Beispielsweise kann die Kohäsionsenergie durch MD Simulationen ermittelt werden und anschließend der Flory-Huggins χ -Parameter berechnet werden.

Allerdings ist die Flory-Huggins Theorie nur schlecht geeignet für die Beschreibung Stoffsystems mit polaren Substanzen, wie z.B. bei Lipidmembranen (Fig. 1). In Rahmen dieser Arbeit wird das Verhalten amphiphiler Moleküle (Tenside, Lipide) in wässrigen Lösungen mit DPD simuliert. Um eine genaue Beschreibung der DPD Interaktionskräfte zu erreichen, werden andere Gibbs'sche Exzessansätze (UNQUAC, COSMO-RS) als Alternative zum Flory-Huggins Modell eingesetzt. Analog zum Verfahren von Groot und Warren wird eine Zusammenhang zwischen die DPD Interaktionsparameter und diesen gE-Ansätzen gesucht. Eine detaillierte Beschreibung der DPD Simulationstechnik wird dazu vorgestellt.

³ Groot, R. D. und Warren P. B. (1997). *Journal of Chemical Physics* **107** (11) 4423-4435

Affinity of SH3-ligand interaction influenced by conformational flexibility of the receptor

F. Bauer^{1,2}, K. Schweimer², P. Rösch², H. Sticht¹

¹*Abteilung Bioinformatik, Institut für Biochemie, Emil-Fischer-Zentrum,
Friedrich-Alexander-Universität Erlangen-Nürnberg,
Fahrstr. 17, 91054 Erlangen, Germany*

²*Lehrstuhl Biopolymere, Universität Bayreuth,
Universitätsstr. 30, 95440 Bayreuth, Germany*

The affinity (KD) of a protein complex is a function of the rates of association (kon) and dissociation (koff), with the simple relation $KD = koff/kon$ holding for all 2-step reactions. A clear distinction between the interactions contributing to kon and koff has been observed. Dissociation is a first order reaction whose rate is dictated by the strength of short range interactions between the proteins (van der Waals interactions, hydrophobic interactions and salt bridges). Conversely, the rate of association is dictated by diffusion and can be increased by favorable electrostatic interactions (encounter complex).[1]

In this study we investigated receptor flexibility as an additional mechanism to increase the rate of association. Therefore we modulated the conformational flexibility of the Lck SH3 domain binding interface without changing its electrostatic composition. Previous studies have implicated that not only the exact structure but also the flexibility of the binding site of the SH3 domain comprising the RT and n-Src loop and the 310-helix to play a decisive role in determining the binding affinity.[2] Therefore, we investigated a proline to glycine mutation at position 17 within the RT loop of Lck SH3. Lck SH3_P17G exhibits not only a local increase in flexibility of the RT loop, but an increased global flexibility throughout the whole domain - especially the flexible regions of the binding interface. Fluorescence titration and stopped flow experiments show an increase in affinity to a herpesviral ligand Tip by almost one order of magnitude and a distinct contribution of an increased association rate to it. MD simulations of the wt and mutant Lck SH3 and a NMR-based model of the Lck SH3-Tip complex revealed the tighter binding is achieved by increasing the population of "binding-competent" conformations resulting from a faster conformational sampling.

[1] Selzer et al. (2000) Nat Struct Biol 7(7): 537-41.

[2] Arold et al. (1998) Biochemistry 37(42): 14683-91

Simulating FRET: A Combined Molecular Dynamics-QM/MM Approach

Frank Beierlein,¹ Olaf G. Othersen,¹ Harald Lanig,¹ Siegfried Schneider² and Timothy Clark¹

¹ *Computer-Chemie-Centrum, Friedrich-Alexander-Universität Erlangen-Nürnberg, Nägelsbachstr. 25, 91052 Erlangen, Germany*

² *Institut für Physikalische und Theoretische Chemie, Friedrich-Alexander-Universität Erlangen-Nürnberg, Egerlandstr. 3, 91058 Erlangen, Germany*

Abstract. We present a computational model study designed to simulate the results of time-resolved fluorescence spectra of tryptophan in proteins. In such measurements, the occurrence of more than one fluorescence lifetime is generally attributed to the existence of several tryptophan rotamers and/or structural conformations of the protein structure. The protein system we chose for this initial study is the tetracycline repressor/tet operator (TetR/tetO) system, an interesting model system for the investigation of the mechanisms of transcriptional regulation. Fluorescence resonance energy transfer (FRET) from tryptophan to tetracycline is frequently observed in complexes of the Tet-repressor with the antibiotic tetracycline. We use a combined classical/quantum mechanical approach to model the structure and the spectroscopic properties of the TetR-tetracycline complex. A classical molecular dynamics simulation provides input geometries for semiempirical QM/MM CI calculations, which are used to calculate tryptophan absorption and fluorescence spectra as well as fluorescence resonance energy transfer (FRET) rate constants. We show how a biexponential tryptophan fluorescence decay can be obtained from a molecular dynamics (MD) trajectory containing two tryptophan rotamers by calculating the exact FRET rate constant for every MD snapshot. Our results indicate that the classical “rotamer model”, used to explain the multiexponentiality of time-resolved tryptophan emission spectra, can be extended to systems with FRET acceptors present in the protein matrix.

Process Optimization of Grid Computing for High Throughput Docking Experiments

Beyer C., Cramer J., Selzer P.M.

Intervet Innovation GmbH, Zur Propstei, 55270 Schwabenheim, Germany

In structure based drug design several methods have been recently established for the in silico screening of large chemical databases against a target protein of interest. One of these methods is high throughput docking. For this approach many tools have been developed which allow the accurate reproduction of binding modes and the ranking of active ligands against a number of inactives. One of these docking tools is the software AutoDock 3.0, which has implemented a genetic algorithm as a search method for the prediction of experimentally observed ligand poses. Although AutoDock is capable of reproducing the correct binding modes of experimentally determined protein-ligand complexes, the official version has not been used for high throughput docking of large datasets. Most likely this is because ligand preparation and the analysis of the results have not been automatised so far.

High throughput docking is a computational intense approach, which became more interesting in the last few years, since it can be done on compute clusters. A promising approach to obtain the needed resources is the networked deployment of common personal computers resembling a virtual supercomputer controlled by grid-computing software.

Here we describe our implementation of AutoDock as a high throughput docking tool. We designed a framework for improved ligand preparation using the "Cactvs" toolkit. Applying the scripting language Tcl, as it is implemented in Cactvs, we combined the process of automated ligand preparation with the storage in an Oracle database. Furthermore the framework also manages the grid-computing software EnFuzion 8.2. With this framework we are able to perform high throughput docking on a large number of PC nodes. The automatisation of the process from ligand preparation to the assembly of docked ligands in an SD file allows the routinely use of AutoDock as a virtual screening tool.

Hierarchical Clustering of Huge Compound Libraries: Interactive SAR Analyses

A. Böcker^{1,2}, G. Schneider², A. Teckentrup¹

¹ *Boehringer Ingelheim Pharma GmbH und Co. KG, Department of Lead Discovery, Birkendorfer Straße 65, D-88397 Biberach an der Riss, Germany.*

² *Johann Wolfgang Goethe-University, Institute of Organic Chemistry und Chemical Biology, Marie-Curie-Str. 11, D-60439 Frankfurt, Germany*

Two hierarchical clustering techniques have been implemented, NIPALSTREE [1] and hierarchical k-means [2, 3], both being able to hierarchically cluster more than one million data points in high dimensional space. The first algorithm projects a N-dimensional data set onto one dimension using principle component analysis, sorts the data according to this dimension and sets the split point onto the median position. The second algorithm separates the data set in two parts, using the standard k-means algorithm. Both procedures are applied recursively on the resulting data subsets, until the maximum distance in these collections falls below a predefined threshold.

The program was designed in such a way that the clusters can be graphically represented by a dendrogram, and activity data (e.g. percent control values) can be assigned to the individual data points. Various program functions are presented helping the user to interactively derive crude structure activity relationships present in the data: To get a quick first overview about the separation of “actives” and “non actives” in the dendrogram, average enrichment factors are calculated for each dendrogram level. Highlighting functions allow a differential coloring of the dendrogram according to certain properties. Navigation functions enable the user to zoom into or out of data clusters. Search options help finding data points, nearest neighbours or clusters of interest. Expert systems analyse end clusters to determine singletons, putative false positives and differentially enriched clusters. Structures can be displayed for each cluster and are sorted by activity.

Results are shown for a combined data set consisting of MDDR [3], CORBA [4] and the Specs catalogue [5]. An online demo of the program will be given.

References

- [1] Böcker, A.; Teckentrup, A. and Schneider G., NIPALSTREE: A New Approach for Clustering Large Data Sets. 18. Darmstädter Molecular Modelling Workshop 2004.
- [2] Böcker, A.; Derksen, S.; Schmidt, E.; Teckentrup, A.; and Schneider, G. A Hierarchical Clustering Approach for Large Compound Libraries. *J. Chem. Inf. Model.* 2005, in press.
- [3] Barnard, J.M.; Downs, G.M.; Wild, D.J. and Wright, P.M. Better Clusters Faster. Third Joint Sheffield Conference on Chemoinformatics 2004.
- [4] MDL Drug Data Report. www.mdl.com .
- [5] Schneider, P. and Schneider, G. Collection of Bioactive Reference Compounds for Focused Library Design. *QSAR Comb.Sci.* 22, 713-718. 2003.
- [6] SPECS <http://www.specs.net/> .

Combining Ligand- and Structure-Based Methods Leads to the Development of Advanced Binding Mode Hypotheses for Dopamine D3 Receptor Agonists

F. Böckler, P. Gmeiner

Lehrstuhl für Pharmazeutische Chemie, Emil Fischer Centrum, Friedrich-Alexander Universität Erlangen-Nürnberg, Schuhstrasse 19, D-91052 Erlangen

The family of dopamine receptors, as members of the class A rhodopsin-like G protein-coupled receptors, are divided into two groups, mainly based on molecular structural features and the type of G protein-coupling: a D1-like group comprising D1 and D5 receptors and a D2-like group including the subtypes D2, D3 and D4. In 1990, Sokoloff and co-workers have succeeded in cloning the D3 receptor from a rat cDNA library discovering that the D3 receptor mRNA has a high abundance in limbic brain areas associated with cognitive and emotional functions.[1] In the following years, the D3 receptor has been regarded as an interesting therapeutic target for the treatment of Parkinson's disease, drug-induced dyskinesia, cocaine addiction and schizophrenia.

Based on an ex-chiral pool synthesis approach, a series of 7-aminotetrahydroindolizines, including FAUC 54, have been developed as dopamine D3 receptor agonists. Considering the structural features of both series of enantiomers, we established a novel alignment hypothesis for D3 agonists, allowing for the placement of the aromatic moieties on two alternative, adjacent positions. CoMFA and CoMSIA analyses yielded significant crossvalidated q^2 values of 0.726 and 0.590, respectively, when a newly invented program application (IRAS) controlling the alignment selection proved to be useful. Employing the CoMFA/CoMSIA contribution maps, we were able to transform a previously constructed homology model of the D3 receptor[2] from an inactive into a presumably active state. Thus, we demonstrated a good consistence between our ligand- and structure-based approaches, which allowed us to interpret the 3D-QSAR fields in terms of molecular interactions and, thus, it exemplifies the putative value of such a combination of methods. Besides the established ionic interaction with ASP3.32, we propose π -stacking with PHE6.51 and a hydrogen bond between HIS6.55 and the acyl moiety to be primarily involved in the D3 receptor binding of FAUC 54 and its analogues.

Taking advantage of this recently developed pharmacophore hypothesis,[3] we were able to suggest that the most reasonable explanation for the good D3 affinity of FAUC 510, as a representative of a novel series of 5-aminotetrahydropyrazolo[1,5-a]pyridines, implies that the ligand-receptor interactions are effectively mediated through a water molecule. Further, we found evidence that this hypothesis may be extended to pramipexole and similar dopaminergics.

[1] Sokoloff P, Giros B, Martres MP, Bouthenet ML, Schwartz JC, Nature 1990, 347, 146.

[2] Böckler F, Lanig H, Gmeiner P, J. Med. Chem. 2005, 48, 694.

[3] Böckler F, Ohnmacht U, Lehmann T, Utz W, Hübner H, Gmeiner P, J. Med. Chem. 2005, 48, 2493

Predicting binding affinities from homology models by AFMoC: A case study on serine proteases

B. Breu, H. Gohlke

*Molekulare Bioinformatik, Fachbereich Biologie und Informatik, J. W. Goethe-Universität,
Marie-Curie-Str. 9, 60439 Frankfurt/Main*

The post-genomic era is expected to provide us with a large number of experimentally determined protein structures. Thus, generating realistic protein models for any given sequence by comparative modeling techniques will become increasingly possible, which may then be used for computational structure-based drug design approaches. So far, however, little attention has been paid to binding affinity prediction methods that take into account the approximate character of these models. Hence, in this study, we investigate and extend the applicability of the structure-based 3D-QSAR approach AFMoC [1] to predict ligand binding affinities using homology models.

Using a data set of 79 diverse thrombin and trypsin inhibitors [2], good AFMoC models ($q^2 > 0.6$; $r^2 > 0.8$) were derived initially for ligand superimpositions modeled into crystallographically determined protein structures. Encouragingly, these models show significantly superior predictive power compared to CoMSIA models [2], which are solely based on ligand information. This finding emphasizes that valuable additional information is provided by taking into account the protein environment in the AFMoC approach.

Subsequently, several homology models of thrombin were built (using MODELLER [3] and template structures with less than 40 % sequence identity) with varying structural deviations of residues in the binding pocket. This series of models is currently being used to investigate the influence of the model quality on the outcome of the AFMoC analysis. Furthermore, AFMoC is being extended in order to include the information of multiple homology models during the analysis step in a consensus-like manner.

[1] H. Gohlke, G. Klebe, *J. Med. Chem.* 2002, 45, 4153-4170.

[2] M. Böhm, PhD thesis, University of Marburg, 2002.

[3] M. A. Marti-Renom, A. C. Stuart, A. Fiser, R. Sanchez, F. Melo, A. Sali, *Annu. Rev. Biophys. Biomol. Struct.* 2000, 29, 291-325.

DFT Calculations of the Properties of Si-Substituted Hydroxyapatite

Helen F. Chappell & Paul D. Bristowe

Hydroxyapatite has a hexagonal crystal structure and is the main mineral component of all mammalian hard tissue. *Ab initio* density functional plane-wave calculations were performed on silicon-substituted hydroxyapatite (SiHA) using the CASTEP program. Each phosphorus atom was substituted in turn by a silicon atom and the resulting formation energies were calculated. It was found that the co-removal of a hydroxyl group, to maintain charge neutrality, is energetically favourable and the calculated cell volumes for the single silicon substitutions agree extremely well with experimental observations.

Classification of natural terpenoids from the family Asteraceae

F. B. Da Costa^{1,2}, D. Hristozov¹, J. Gasteiger¹

¹*Computer-Chemie-Centrum und Institut für Organische Chemie, Universität Erlangen-Nürnberg, Nägelsbachstr. 25, 91052 Erlangen, Germany*

²*Faculdade de Ciências Farmacêuticas de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, SP, Brazil*

In a recent publication [1] we described the classification of three tribes of the plant family Asteraceae based on a small data set composed of 144 structures of sesquiterpene lactones (STLs). The methodology employed was based on unsupervised learning using Self-Organising Maps (SOM). This approach allowed the evaluation of structural similarities among different sets of 3D structures of STLs represented by their Radial Distribution Functions (RDF) codes as well as the correlation of STLs with the current taxonomic classification of Asteraceae.

In continuation of our investigations, in this work we describe a study based on supervised classification methods using two different types of structure representation. The supervised methods employed were Counterpropagation (CP) Neural Networks and k-Nearest Neighbours (KNN) while the structures were represented by their RDF codes and atom counts. The STLs data set was expanded and now is composed of 921 structures from seven tribes of Asteraceae. The validation on external data set was successful, thus proving the usability of the proposed methods for chemotaxonomic studies of Asteraceae based on STLs.

[1] F.B. Da Costa, L. Terfloth, G. Gasteiger (2005). *Phytochemistry* 66, 345-353.

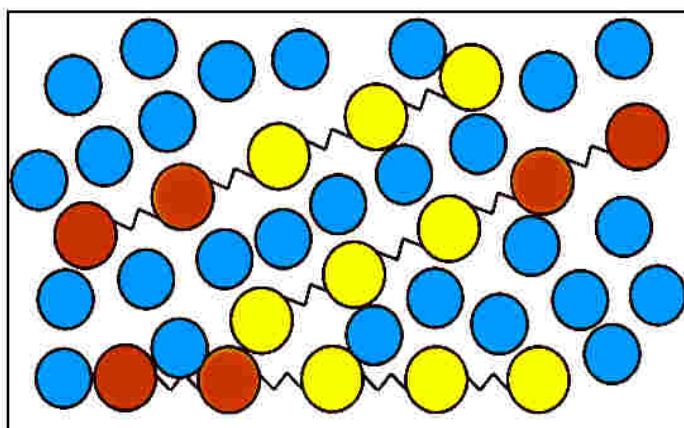
Molecular Fragment Dynamics (MFD). A new mesoscopic Molecular Modelling Simulation Method

Ulf Frieske, Sarah G. Schulz, Hubert Kuhn

*CAM-D Technologies GmbH, Essen, Gerlingstrasse 65, D-45139 Essen
(T.: 0201 3657 402, Mail: frieske@molecular-dynamics.de)*

In this poster the theoretical background of a new developed mesoscopic Molecular Modelling simulation method is presented. Additionally, the application of the method is demonstrated on some specific examples like the formation of phospholipid bilayers or the structural properties of polysaccharides.

In this poster the high demanding and crucial procedure for the interaction parameter calculation is explained in detail. The MFD-method is based on the assumption that molecules can be divided into specific groups which represent the chemical properties of the molecule. A molecular fragment is defined as a group.



MFD-model of a complex system of an amphiphilic polymer in aqueous solution

The interactions between the groups are determined from an interaction potential in the form like

$$E_{ij} = a_1 + a_2 \cdot \hat{r}_{ij}^2 + a_3 \cdot \hat{r}_{ij}^3 + \dots + \hat{r}_{ij}^n a_n$$

where E_{ij} is the potential energy, \hat{r}_{ij} is the distance and a_{ij} is the interaction parameter between two fragments.

Temptation of High-Throughput Docking: Possible Strategies and the Development of Required Tools

Ch. Gerlach, P. Block, G. Klebe

*Institut für Pharmazeutische Chemie, Philipps-Universität Marburg,
35032 Marburg, Germany*

Recent improvements in both software and hardware principally allows to use docking in high-throughput mode as tool for virtual screening without prior application of sophisticated pharmacophore filters. Due to computational demand, ligand docking is usually applied as final step in virtual screening. As it is no longer the methodological bottleneck, it now can be used to generate ensembles of binding conformers which have to be post-processed with respect to sophisticated pharmacophore models and robust scoring schemes. This puts increasing demand on the reliability of the latter tools and affords efficient protocols for analyzing protein-ligand interaction geometries to filter vast amounts of docking solutions for various molecules to retrieve reliably the most promising candidates in automated fashion.

As a test example, we used the binding of Fusicocin, a fungal phytotoxin stabilizing the interaction between the C-terminus of the plant plasma membrane H⁺-ATPase and 14-3-3 proteins. This stabilization leads to permanent activation of the proton pump resulting in wilting of the plant. Recently, the crystal structure of the ternary complex between a plant 14-3-3 protein, Fusicocin, and a pentapeptide representing the C-terminus of the H⁺-ATPase has been solved[1]. We selected the Fusicocin binding site as target for our high-throughput docking attempt to screen for potential new ligands stabilizing the protein-protein interaction.

We used FlexX 2.0[2] as docking tool, tested on i386 and amd64 architectures. The results were analyzed with the Oracle-based Docking Database DDB[3]. Scoring functions newly developed in our group have been applied to rank the obtained data.

1. Wurtele, M., Jelich-Ottmann, C., Wittinghofer, A., Oecking, C. (2003). EMBO J 987-994
2. Rarey, M., Kramer, B., Lengauer, T. and Klebe, G. (1996). J Mol Biol (3): 470-89
3. Claussen, H., Gastreich, M., Apelt, V., Greene, J., Hindle, S., Lemmen, C. (2004) CDDT 49-60.

Continuous global optimization: Finding the right algorithm for a problem

Jens Gimmler¹, Thomas Stützle¹, Thomas Exner²

¹*Intellektik, Technische Universität Darmstadt*

²*Theoretische Chemische Dynamik, Universität Konstanz*

Chemical problems are often approximated by high-dimensional mathematical optimization models, which must be efficiently solved, that is, ideally a globally optimal solution for the model needs to be found. For this task, optimization algorithms are used that try to find values of the variables of the n-dimensional functions such that the results function value is optimal.

There have been many different attempts for finding efficient specialized optimization algorithms, but these have the disadvantage of a very limited range of applicability. Another stream tries to find high-performing general purpose optimization tools. Given the complexity of the resulting optimization problems, there does not exist a provably high-performing universal optimizer. Hence, the best optimizer must be found by experimental research.

Here, we introduce a framework that simplifies the combination and comparison of different local and global optimizers and give an extensive experimental comparison of their performance. In particular, we have implemented a wide range of optimization algorithms in our framework including the Nelder-Mead Downhill Simplex, Powell Direction Set, Improving Hit-and-Run, Real Coded Genetic Algorithm, Random-Restart Local Search, Hide-and-Seek Algorithm and Iterated Local Search. Exemplary results are presented for established test functions as well as for the important problem of Protein-Ligand docking using the PLP scoring function.[1]

[1] Gehlhaar, D. K.; Verkhivker, G. M.; Rejto, P. A.; Sherman, C. J.; Fogel, D. B.; Fogel, L. J.; Freer, S. T. *Chem.Biol.* 1995, 2, 317.

Incorporating quantitative experimental chemical shifts information into protein-ligand docking algorithms

D. González-Ruiz, H. Gohlke

Molekulare Bioinformatik, Fachbereich Biologie und Informatik, J. W. Goethe-Universität, Marie-Curie-Str. 9, 60439 Frankfurt

Current docking approaches fail when targeting protein-protein interfaces. The lack of large steric constraints and an inappropriate treatment of solvent effects and entropy changes may be responsible for this [1]. In this regard, incorporating experimental information to guide the docking algorithm is seen as the most direct way to improve both accuracy and efficiency [2]. The use of quantitative chemical shifts (CS) in structure elucidation has largely been unexploited due to the impossibility of deriving pairwise restraints from them [3]. Nonetheless this fact, a qualitative use is applied in the well established “SAR by NMR” technique [4]. Here, changes of CS at the receptor part due to the perturbation of the chemical environment by ligand binding are monitored to characterize binding sites and approximate orientations of the ligand.

We are currently developing a new docking scheme for protein-ligand docking in which knowledge-based potentials from DrugScore [5] and experimentally measured chemical shift changes upon complexation are combined as guiding restraints. In our empirical function not only ring currents but also electrostatic contributions and anisotropy effects from unsaturated bonds are taken into account. One of the most challenging obstacles to be dealt with is protein flexibility, as this may influence CS in the same extent than ligand binding. Weighting contributions from different protons according to their “quality”, i.e., their expected influence from these conformational changes, might help to overcome this situation. The new scoring function has been implemented into AutoDock [6]. Preliminary results on idealized test cases show a good performance and indicate a smooth objective function suitable for global optimization.

1. Gadek, T.R. and Nicholas, J.B., *Biochem. Pharmacol.* 2003, 65, 1-8.
2. Fradera, X. and Mestres, J., *Curr Topics in Med. Chem.* 2004, 4, 687-700.
3. Redfield, C. and Dobson, C.M., *Biochemistry* 1990, 29, 7201-7214.
4. Shuker, S.B., Hajduk, P.J., Meadows, R.P. and Fesik, S.W. *Science* 1996, 274, 1531-1534.
5. Gohlke, H., Hendlich, M. and Klebe, G., *J. Mol. Biol.* 2003, 295, 337-356.
6. Morris, G., Goodsell, D., Halliday, R., Huey, R., Hart, W., Belew, R. and Olson, A., *J. Comp. Chem.* 1999, 19, 1639-1662.

Step-wise approaches to the in silico screening of large 3D-databases to identify ligands for a receptor protein

Stephanie Gulde, Claudia Bobach, Wolfgang Brandt, Ludger A. Wessjohann

*Leibniz Institute of Plant Biochemistry, Department of Bioorganic Chemistry,
06120 Halle, Germany*

Based on a X-ray structure of a native Ligand in a receptor protein, we wished to identify ligands with high affinity.

For this purpose, two databases with optimized 3D-structures (conformations) were used. The first one is an in house database containing more than 100.000 compounds with about 9 million conformations. The second database used was provided by MOE (1) and contains 930.000 commercially available compounds with altogether 57 million conformations. In a first step, a pharmacophore model of the active site was developed. The active site was scanned by probes like methane (hydrophobic), benzene (aromatic), ammonium (kation, H-bond donor), and methanolate (anion, H-bond acceptor) using simulated annealing molecular dynamics with flexible side chains of the proteins active site to identify preferred interaction sites with corresponding properties. The resulting low energy areas of the interactions of the probes with the proteins were translated to pharmacophores using the corresponding tools of MOE. The volume defined by the active site was additionally used as criterium for screening the databases. With this approach, some 13.000 and 48.000 compounds could be identified from the two databases as potential hits. To reduce the large data set, the compounds were docked together with some ligands of which the experimental affinity was available, using GOLD (2). The fitness-values and predicted pK-values based on several scoring functions were compared with the experimental one, but gave no satisfying results. Therefore, in a next step a QSAR model was developed based on the binary VSA descriptors of MOE. With this model, the experimental values could be predicted with a correlation coefficient of $r^2 = 0.97$ and a cross-validated correlation coefficient of $r^2 = 0.85$. The model was then applied to the data set to predict the putative affinities of all remaining compounds. All compounds with a pK-value smaller than 4 were removed from the data set to further reduce the number of potential hits. Finally, properties according to Lipinski's rule of five, blood-brain distributions, and solubility's in water were calculated. As a final result, some 100 compounds which fulfill all criteria could be selected and proposed for experimental tests. The first compound test showed the predicted affinity to the protein.

References

1. Molecular operating environment Chemical Computing Group Inc., Montral, Canada
2. M. L. Verdonk, J. C. Cole, M. J. Hartshorn, C. W. Murray, R. D. Taylor, *Proteins*, 52, 609, 2003

Pharmacophore Modelling of Minor Groove DNA-binding Ligands

Gudrun Hackspiel¹, Bernd Wellenzohn², Christian Laggner¹,
Thierry Langer¹, Klaus Liedl¹

¹ *Center of Molecular Biosciences Innsbruck (CMBI),
University of Innsbruck, A-6020 Innsbruck, Austria*

² *Boehringer Ingelheim Pharma GmbH & Co. KG,
Birkendorfer Strasse 65, D-88397 Biberach/Riss, Germany*

DNA information is important, whenever DNA has to be replicated or transcribed. Replication is relevant during cell division whereas transcription is performed to get RNA templates for protein formation. Both processes, as well as cleavage or repair are catalysed by enzymes which therefore have to interact with the DNA. These interactions can be modified by small molecules, in particular pyrrole-imidazole-polyamides, bound to the minor groove. Dimeric ligands have been shown to specifically recognize 6 bp DNA sequences.

The aim of this study was to create a model - using methods of the software package Catalyst - which is able to predict the binding specificity of minor groove binders. A first test with one half of a hairpin ligand and one strand of a 80 bp DNA was promising. Some refinements will be necessary to obtain a more general model. If the strategy succeeds, the model can be used in virtual screening in order to find ligands of different structure but with similar binding properties.

Comparison between Natural Compounds and Known Ligands

Dimitar Hristozov, Johann Gasteiger

Computer-Chemie-Centrum und Institut für Organische Chemie, Universität Erlangen-Nürnberg, Nägelsbachstr. 25, 91052 Erlangen, Germany

The properties of a chemical substance are closely related to its structure; therefore a significant amount of information can be derived from the structure including physical-chemical properties, biological activities, etc. In the present work, a dataset of natural products (NatPool, 8'378 compounds) [1] is compared with a large database of known ligands (WOMBAT, 76'165 compounds) [2]. As the activity of the natural compounds is unknown, a general representation of the 2D or 3D structures has been chosen, which takes into account various fast and easily calculable physical-chemical properties. The 2D structures were encoded as 27 dimensional autocorrelation vectors [3] ranging from 2 to 10 topological distances and weighted by partial atomic π -charge ($q\pi$), partial atomic charge (q_{tot}), and effective atom polarizability (α_d). All properties were calculated by PETRA [4]. A single low-energy 3D conformation for each structure was obtained with CORINA [5, 6]. They were described as 96 dimensional RDF code [3], weighted by the same atomic properties. This set up allows us to a) study the diversity of NatPool in the chemical space spanned by WOMBAT; b) examine the extent of overlap between natural compounds and different types of active compounds in WOMBAT. Clusters with high degree of overlap can be considered as an indicator for the "ligand-likeness" of the natural compounds.

References:

- [1] Naturstoff-Pool Project, Leibniz-Institut für Naturstoff-Forschung und Infektionsbiologie e.V. - Hans-Knöll-Institut, Jena, Deutschland
- [2] Olah, M., Mracec, M., Ostopovici, L., Rad, R., Bora, A., Hadaruga, N., Olah, I., Banda, M., Simon, Z., Mracec, M., Oprea, T., in *Chemoinformatics in Drug Discovery*, Oprea, T. (ed.), 2004, 223-239
- [2] WOMBAT - World of Molecular Bioactivity, Sunset Molecular Discovery LLC, <http://www.sunsetmolecular.com>
- [3] Gasteiger, J., in *Handbook of Chemoinformatics - From Data to Knowledge*, Gasteiger, J. (ed.), 2003, 1034-1061
- [4] PETRA - Parameter Estimation for the Treatment of Reactivity Applications. Version 3.2, MolNet GmbH, <http://www.mol-net.de>, <http://www2.chemie.uni-erlangen.de/services/petra/index.html>, Erlangen
- [5] Sadowski, J., Gasteiger, J., *Chem. Rev.*, 1993, 93, 2567-2581
- [6] CORINA, version 3.0, MolNet GmbH, <http://www.mol-net.de>, http://www2.chemie.uni-erlangen.de/services/corina/free_struct.html, Erlangen

Comparing binding pockets based on knowledge-based potential fields

T. Jimenez, S. Derksen, E. Schmidt, H. Gohlke

*Molekulare Bioinformatik, Fachbereich Biologie und Informatik,
J.W. Goethe-Universität, Marie-Curie-Str. 9, 60439 Frankfurt am Main*

It can be expected that the number of 3D protein structures will considerably increase over the next years due to structural genomics initiatives and large-scale comparative modeling efforts. In many cases, however, the functions of these proteins will not be known and predictions based on sequence- or fold-similarities may not be applicable. However information about protein function may be inferred from structural information of binding sites regions. Hence, the goal of this project is to predict protein function by comparing binding site regions characterized by potential fields. This idea originates from the fact that protein function is often intimately connected with the recognition of ligands in well-defined binding sites.

An efficient data handling capability will be crucial to do large scale comparisons of binding pockets. For that we set up a MySQL-based relational database BIF (= "Binding Interfaces") that contains information about protein binding pockets of all PDB entries. This information was augmented with additional relations based on a hierarchical molecule model and a mol2 atom type classification. Finally, information from the SCOP and CATH databases was added such that structural relationships between different protein structures can be investigated.

Binding site regions were then described by molecular interaction fields calculated with the DrugScore approach. Subsequently, fields were transformed to a discrete representation by only considering peaks of favorable potential values. These peaks are used for superimposing binding sites applying pose clustering techniques, which originate from the field of pattern recognition.

Assessment of Covalent Docking for Virtual Screening

Klinger A., Schröder J., Selzer P. M.

*Intervet Innovation GmbH, BioChemInformatics, Zur Propstei,
55270 Schwabenheim, Germany*

The covalent docking of ligands into a protein binding site was examined for the application in a structure-based virtual screening process using the covalent docking facility of GOLD2.1. The aim was to evaluate, whether the scoring functions GOLDScore and ChemScore, in their implemented modifications for covalent docking, are able to enrich docking solutions of ligands with known activity compared to docking solutions of virtual ligands with unknown activity. For our case study we selected the two cysteine proteases Cathepsin K (human) and Cruzipain (*Trypanosoma cruzi*) as model enzymes, for which K_i/IC_{50} values about covalently binding ligands and X-ray structures are available from literature and public databases. Additionally, compounds with a substructure similar to the substructures undergoing the covalent binding in the known ligands were selected from a virtual database, with a focus on ketones, nitriles, vinylsulfones and thiosemicarbazones. The known ligands and the virtual compounds were transformed to their bound structural form, regarding both stereoisomers where necessary, and docked using the standard default set up of the covalent docking option of GOLD2.1. For Cathepsin K an enrichment of the ligands with an activity $< 1.0 \mu\text{M}$ (K_i/IC_{50}) of up to 83 % in the top 50 % of the ranking lists was achieved, and for Cruzain an enrichment of up to 70 %. However, the scores of the different structural inhibitor classes cluster obviously in different scoring ranges. Thus for some classes the enrichment were significantly better, if their scores were analyzed only among themselves (e. g. up to 93 % for nitriles docked in Cathepsin K and up to 86 % for ketones in Cruzain). Based on the scoring results several compounds with unknown activity will be selected for experimental validation of the scoring by in vitro activity tests.

Secbase Secondary structure elements and ligand binding

Koch, O., Klebe, G.

*Philipps-Universität Marburg, Institut für Pharmazeutische Chemie,
Marbacher Weg 6, 35032 Marburg, Deutschland
Oliver.Koch@Staff.Uni-Marburg.de*

Relibase is an object-orientated data management system[1] and stores the three dimensional structural information of protein-ligand complexes deposited in the PDB. Secbase is a modular extension of Relibase and integrates the information about secondary structural elements assigned to each individual protein structure with additionally derived data stored in Relibase. Furthermore, algorithms are integrated to detect kinks and bends in α -helices and β -strands so that geometric descriptions expressed in terms of vectors are available.

Recent analyses of cooperative effects of hydrogen bonds in helices and β -sheets show statistically significant differences between both secondary structural elements. The comparison of the average hydrogen-bond length in α -helices and parallel β -sheets and 310-helices and antiparallel β -sheets shows an opposing trend. Considering the peptide bond dipoles and the hydrogen bond geometries leads to some interesting similarities between these secondary structure elements as a possible explanation for the different behaviour.[2]

The further development of Secbase is aimed at the comparison of complex secondary structural patterns up to motifs or domains. Together with the functionalities of Relibase analysis of the interactions between ligands and reoccurring patterns of secondary structural elements of the protein is then possible. Additionally, cross reactivities between related protein families with similar folding but diminishing sequence homology could be detected by this approach.

Literature:

[1] Hendlich, M., Bergner, A., Günther, J., Klebe, G., J. Mol. Biol., 2003, 326, p. 607-620.

[2] Koch, O., Bocola, M., Klebe, G., Proteins, in press

When Ants Dock Molecules

Oliver Korb¹, Thomas Stützle², Stefan M. Kast³ and Thomas E. Exner¹

¹*Universität Konstanz, Theoretische Chemische Dynamik*

²*Technische Universität Darmstadt, Intellektik*

³*Technische Universität Darmstadt, Physikalische Chemie I*

In the past years, many different strategies for performing protein-ligand docking have been proposed. Especially the class of stochastic optimization methods turned out to be very suitable for this task. Methods like simulated annealing, genetic algorithms and evolutionary programming are well established in the chemistry community and have been investigated intensively for the docking problem. In this work, we introduce a docking algorithm based on a relatively new class of stochastic optimization algorithms called ant colony optimization (ACO) [1, 2]. ACO is inspired by the behavior of real ants finding a shortest path between their nest and a food source. The ants use indirect communication in the form of pheromone trails which mark paths between the nest and a food source. In the case of protein-ligand docking, an artificial ant colony is employed to find a minimum energy conformation of the ligand. These ants are used to mimic the behavior of real ants and mark low energy ligand conformations with pheromone trails. The artificial pheromone trail information is modified in subsequent iterations to generate low energy conformations with a higher probability. We present the theory behind the method as well as some preliminary results for the task of docking rigid and also flexible ligands into rigid binding sites.

[1] M. Dorigo and T. Stützle. *Ant Colony Optimization*. MIT Press, Cambridge, MA, USA, 2004.

[2] Thomas Stützle and Holger H. Hoos. MAX-MIN Ant System. *Future Generation Computer Systems*, 16(8):889-914, 2000.

Flavin-disulfide oxidoreductases as targets for the development of new antiparasitic drugs

Andreas Krasky¹, R. Luise Krauth-Siegel², R. Heiner Schirmer² and Paul Selzer¹

¹*Akzo Nobel Intervet Innovation GmbH,
Zur Propstei, 55270 Schwabenheim,*

²*Biochemie-Zentrum der Universität Heidelberg,
Im Neuenheimer Feld 504, 69120 Heidelberg*

FAD-disulfide oxidoreductases are a family of structurally homologous enzymes that catalyze the pyridine nucleotide-dependent reduction of their respective disulfide substrates. Glutathione reductase and thioredoxin reductase occur in nearly all organisms including mammals and *Plasmodium falciparum*, the causative agent of tropical malaria. In trypanosomes and leishmania, both enzymes are missing. Trypanosomatids have a unique thiol metabolism which is based on the glutathionylspermidine conjugate trypanothione and trypanothione reductase.

Trypanosomatids and Plasmodia lack catalase and the selenoenzyme glutathione peroxidase and are known for their sensitivity towards oxidative stress. These findings render the parasite disulfide reductases promising targets for the rational design of new antiparasitic drugs. The plasmodial as well as the human erythrocyte glutathione reductase are both considered as attractive targets for antimalarial drug development. Trypanothione reductase is one of the most attractive target molecules for the development of antitrypanosomal drugs. The structurally closely related lipoamide dehydrogenase readily catalyses the single electron reduction of nitrofurans and naphthoquinones and is involved in the mode of action of drugs such as Nifurtimox. The crystal structures of *P. falciparum* glutathione reductase and of *T. cruzi* lipoamide dehydrogenase have been solved recently.

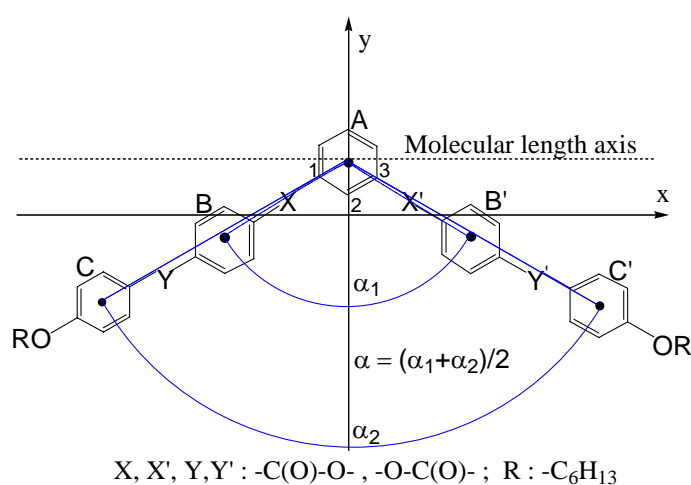
Virtual high throughput screening approaches aim at the elucidation of lead compounds interacting with the different flavoenzymes individually or in combination. The simultaneous interference with two enzymes, for instance with *T. cruzi* trypanothione reductase and lipoamide dehydrogenase, should have synergistic effects on the redox metabolism of the parasites and may prevent or at least slow down drug resistance development

DFT and MD studies on banana-shaped mesogens

Ananda Rama Krishnan S., Wolfgang Weissflog and Rudolf Friedemann

*Department of Chemistry, Martin-Luther-University Halle-Wittenberg,
Kurt-Mothes-Str. 2, D-06120 Halle(Saale), Germany*

The influence of the direction of polar ester connecting groups on structural and electronic properties of banana-shaped molecules with a central 1,3-phenylene unit has been investigated including 10 isomers (Figure). DFT studies on the B3LP/6-31G(d) level were performed on the conformational behavior of the isomers in a systematic way. The one- and two-fold potential energy scans show that the flexibility of the wings significantly depends on the orientation of the ester connecting groups.



Moreover, the different directions of the ester groups between the aromatic ring cause remarkable changes on the dipole moment of the molecules within a range of 8 Debye.

The amount of the μ_y component can be related in some way to the different liquid crystal phase behavior of the compounds. These findings are supported by investigations on the global charge pattern of the molecules calculated from ESP group charges. The molecular length and the bending angle α obtained from simple models for the five-ring bent-core molecules can be correlated with phase properties of the mesogens.

Calculations of the molecules in an external electric field in x and y directions show remarkable effects with respect to the flexibility and polarity of the isomers.

First molecular dynamics simulations on the banana-shaped molecules are performed within the AMBER7 package. The trajectories of relevant structural parameters support the findings of the DFT studies.

**Protein-based multidimensional QSAR:
From cytochrome P450 mediated drug-drug interactions
to endocrine disruption**

Markus A. Lill and Angelo Vedani

*Institute for Molecular Pharmacy, University of Basel, Klingelbergstrasse 50, CH-4056
Basel, Switzerland and Biographics Laboratory 3R, Friedensgasse 35, CH-4056 Basel,
Switzerland*

It is our objective to establish a virtual laboratory allowing for a reliable in silico estimation of harmful effects triggered by drugs, chemicals and their metabolites. In the recent past, we have developed the underlying computational technology — automated flexible docking (Yeti) combined with multidimensional QSAR (Quasar and Raptor). Using this concept, we then validated protein-based models to predict the inhibitory or toxic potential of diverse molecules binding to cytochrome P450 3A4 (CYP3A4) and receptors mediating endocrine disruption (Ah, estrogen and androgen receptor), respectively. The results suggest that our approach may be used for the reliable prediction of binding affinities and adverse effects of drugs and chemicals prior to their synthesis. More information may be found under:

<http://www.biograf.ch/projects.html>

Putting the Pieces Together: Application of Fragment-based Methods in Lead Generation

Harald Mauser and Martin Stahl

*F. Hoffmann-La Roche Ltd, Pharmaceuticals Division
CH-4070 Basel, Switzerland
e-mail: harald.mauser@roche.com*

The challenge in drug discovery is often, to convert information contained in large datasets into knowledge so that it can be used for building computational tools. One way of extracting knowledge, is to reduce the information present in a set of molecules to key fragments and to use these for assembling novel molecules with desired properties. Another approach is to use fragments or substructures for building knowledge-based prediction models. As an example for the first approach, we will illustrate the generation of fragments from known drugs and the strategies of identifying a representative subset of fragments for de novo design. In particular, we are seeking for novel starting points that are synthetically accessible. Thus, we benchmarked different approaches of filtering and selecting subsets of fragments against a random selection. To evaluate the quality of selection, we compared firstly, how close the de novo designs came to the original molecules, and secondly, how Chemists assessed the synthetic feasibility. We obtained as best result a combination of two complementary approaches, a diversity-oriented selection and a selection favouring the frequently occurring fragments in the dataset. The second example shows an application of a substructure-based prediction tool. The quality assessment of screening compounds is typically done by Liquid Chromatography combined with Mass Spectroscopy (LC/MS) and UV purity control. To facilitate the analysis of the analytical data, we have built different models to predict UV signal intensities. Hereby, we compared a substructure-based approach based on recognition of motifs that are characteristic for UV-activity to a linear PLS model. The knowledge-based model was found to be as reliable as the PLS model. Ultimately, we found that an ensemble of both models gave best results with over 95% correct predictions.

Impact of Scoring Functions on the Results of Molecular Docking Studies

Rene Meier and Wolfgang Sippl

*Institut für Pharmazeutische Chemie,
Martin-Luther-Universität Halle-Wittenberg,
Halle/Saale, Germany*

The in silico testing of large number of compounds, known as virtual screening, is well-established in pharmaceutical research. When used prior to experimental testing, virtual screening can be considered as powerful filters to reduce labor and cost. A widely spread concept is that the major weakness of today's docking programs lie not in sampling techniques but in scoring methods. As a matter of fact, considerable effort has undertaken to the development of computational methods for describing protein ligand interaction in a quantitative way. These methods have been validated on various sets of protein-ligand complexes and are implemented in the various docking programs. However, it is important to know which scoring functions generally perform better than others.

In the present study we have compared two docking programs, AUTODOCK and GOLD, and different scoring functions. The test set for our study was compiled from the PDBBIND[1] database, which contains about 800 protein-ligand complex structures as well as experimental determined binding affinities. In the first step, we have analysed the programs ability to reproduce the known X-ray structures of protein-ligand complexes. Furthermore the built-in scoring functions as well as post docking scoring methods were tested for their ability to find the experimentally determined structure among all generated docking poses. To improve the quality of the docking results we have applied a force field based refinement and calculated the protein-ligand interaction energy. The obtained interaction energies were tested for their ability to improve the quality of the scoring. In addition, the analyzed procedures were applied for predicting the binding affinities of several ligand data sets.

[1] Wang, R.; Fang, X.; Lu, Y.; Wang, S. "The PDBbind Database: Collection of Binding Affinities for Protein-Ligand Complexes with Known Three-Dimensional Structures", J. Med. Chem., 2004, 47(12), 2977-2980.

Identification of protein-protein interactions by structure based scoring functions

Wolfgang Müller^a, Nicol^a Horstmann^b, Wolfgang Hillen^b, Heinrich Sticht^a

^a*Abteilung für Bioinformatik, Institut für Biochemie, Friedrich-Alexander-Universität Erlangen-Nürnberg, Fahrstr. 17, 91054 Erlangen, Germany*

^b*Lehrstuhl für Mikrobiologie, Friedrich-Alexander-Universität Erlangen-Nürnberg, Staudtstr. 5, 91058 Erlangen, Germany*

Protein-protein interactions play central roles in various aspects of the structural and functional organization of the cell, and their complete description is indispensable to a thorough understanding of the cell. In order to improve the prediction of protein-protein interactions we developed a structure-based computational method which aims at the identification of novel interaction partners. For this purpose an empirical pair potential is derived from a group of orthologous complexes and subsequently used to identify paralogues which may interact in the same fashion. This approach was tested for the identification of novel transcriptional regulators that interact with the bacterial HPr protein. One novel protein identified by this search was the ribose operon repressor RbsR which was subsequently verified by experimental methods to bind HPr. In principle our method can be applied to various types of interactions for which at least one three-dimensional complex structure exists.

DFT and mechanistic studies on the reactivity of Pt(II) complexes in imidazolium-based ionic liquids

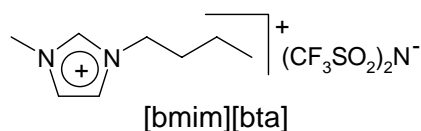
P. Illner^a, C. F. Weber^a, R. Puchta^b, N. van Eikema Hommes^b, R. van Eldik^a.

^a*Institute for Inorganic Chemistry, University of Erlangen-Nürnberg, Egerlandstr. 1, 91058 Erlangen, Germany.*

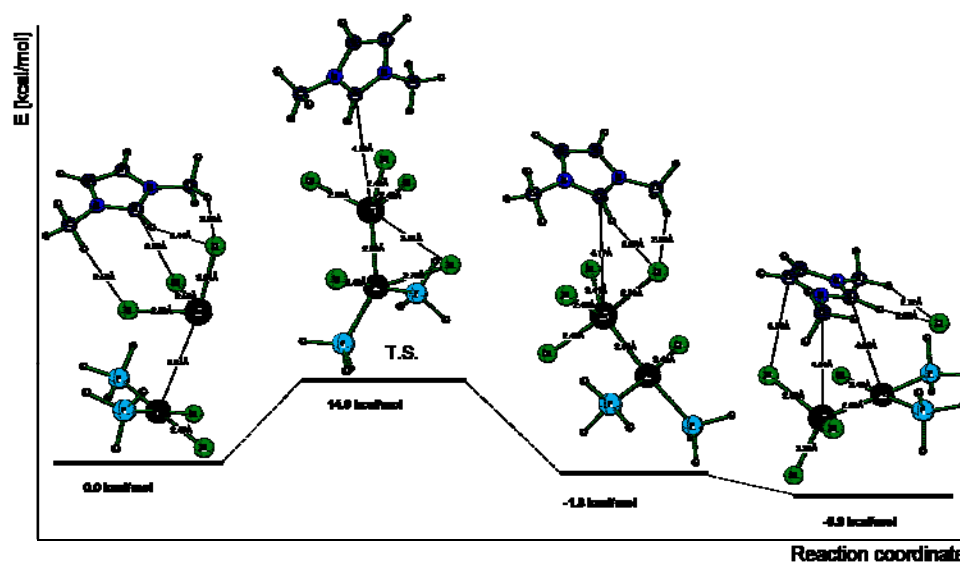
Peter.Illner@chemie.uni-erlangen.de

^b*Computer Chemistry Center, University of Erlangen-Nürnberg, Nägelsbachstr. 25, 91052 Erlangen, Germany*

We present DFT investigations on the substitution of chloro ligands in $[\text{Pt}(2,6\text{-bisaminomethylpyridine})\text{Cl}]^+$ by thiourea and iodide in comparison with experimental studies in $[\text{bmim}][\text{bta}]^{[1]}$



Furthermore the formation of the active species $\text{cis-}[\text{Pt}_{\text{II}}(\text{PPh}_3)_2\text{Cl}(\text{SnCl}_3)]$ and $\text{cis-}[\text{Pt}_{\text{II}}(\text{PPh}_3)_2(\text{SnCl}_3)_2]$ from the hydroformylation catalyst $\text{cis-}[\text{Pt}_{\text{II}}(\text{PPh}_3)_2\text{Cl}_2]$ that occurs on addition of SnCl_2 , was studied using DFT calculations and kinetic techniques in two imidazolium-based ionic liquids^[2]. Plausible mechanisms will be presented on the basis of DFT calculations and kinetic data.



[1] C.F. Weber, R. Puchta, N. van Eikema Hommes, P. Wasserscheid, R. van Eldik, *Angewandte Chemie*, submitted.

[2] P. Illner, A. Zahl, R. Puchta, N. van Eikema Hommes, P. Wasserscheid, R. van Eldik, *J. Organomet. Chem.* in press.

Virtual Screening for novel ACE2 Inhibitors using Structure-based Pharmacophore Hypotheses

M. Rella ^a, R. M. Jackson ^a, T. Langer ^b

^a School of Biochemistry and Microbiology, University of Leeds, UK

^b Dept. of Pharmaceutical Chemistry, University of Innsbruck, Austria

Angiotensin-Converting Enzyme (ACE) is an important drug target for hypertension and heart disease. Recently, a close and unique human ACE homologue termed ACE2 has been identified involved in hypertension, heart and kidney disease [1]. In addition, ACE2 was found to be a functional receptor of the SARS-Coronavirus. This surprising role and its assumed counter-regulatory function to ACE make ACE2 an interesting new cardio-renal disease target.

With the recently resolved ACE2 structure in complex with a potent inhibitor available [2], a structure-based drug design project has been undertaken to identify novel potent and selective inhibitors. The strategy comprises computational structure-based drug design approaches as well as chemical synthesis of promising candidates or purchase of existing compounds and bioassay-based potency evaluation. Computational approaches involve combinatorial library design and docking as well as pharmacophore-based virtual screening of large compound databases.

A structure-based pharmacophore model was created integrating several chemical features such as hydrogen bonding and hydrophobicity aligned in 3D resembling specific drug-receptor interactions [3, 4]. Selectivity of the model was ensured by screening for ACE inhibitors and improved through repeated optimisation cycles. The final model was used for virtual screening of ~2.5 million unique compounds originating from 28 commercial 3D databases for matching compounds exhibiting the required pharmacophore features. Top scoring hits were evaluated for “ACE2 drug likeness” and the most promising candidates proposed for purchase and biological testing.

[1] Turner AJ, Tipnis SR, Guy JL, Rice G, Hooper NM. *Can J Physiol Pharmacol.* 2002, 80(4):346-53.

[2] Towler P, Staker B, Prasad SG, Menon S, Tang J, Parsons T, Ryan D, Fisher M, Williams D, Dales NA, Patane MA, Pantoliano MW. *J Biol Chem.* 2004, 279(17):17996-8007.

[3] Wolber G, Langer T. *J Chem Inf Model.* 2005, 45(1):160-9

[4] CATALYST Version 4.9, MSI, San Diego, CA, USA

A DFT Study of CpCp(XH₂Ph)ZrCl Cations (X = C, Si)

Jörg Saßmannshausen

*ICTOS, TU-Graz, Stremayrgasse 16/1 8010 Graz, Austria
email: sassy@ictos.tugraz.at*

Cationic group 4 compounds are meanwhile recognized to be the active catalyst in Kaminsky-Type polymerisation chemistry.

However, the cation is not 'naked' in solution, and recent investigations by us¹ and others² showed interactions between the cation [Cp₂ZrR]⁺ and weakly coordinating ligands L (anion, monomer, solvent).

In particular, aryl-groups tethered to the cyclopentadienyl-ligand serve as models for solvent-adducts in cationic group 4 chemistry. Here we show the latest results of a rather comprehensive DFT study of the cationic compound CpCp(XH₂Ph)ZrCl (X = C, Si).

Referenzen:

- 1) M. Bühl, J. Saßmannshausen, J. Chem. Soc., Dalton Trans. 2001, 79-84
- 2) M. Bochmann, J. Organomet. Chem. 2004, 689, 3982-3998

Conformational flexibility in QSAR analyses - Extensive validation of the novel alignment-independent 4D-QSAR technique xMaP

Josef Scheiber, Nikolaus Stiefl and Knut Baumann

Department of Pharmacy and Food Chemistry, Am Hubland, D 97074 Wuerzburg, Germany

The novel molecular descriptor xMaP (extended MaP descriptor) is introduced and validated. It is the 4D extension of the previously published alignment-independent MaP descriptor (Mapping Property distributions onto the molecular surface) [1]. In addition to MaP, xMaP is independent of the chosen starting conformation of the encoded molecules. This is achieved by using ensembles of conformers which are generated with conformational searches or molecular dynamics simulations. This step of the procedure is similar to Hopfingers 4D-QSAR [2].

A five step procedure is used to compute the xMaP descriptor. First, the conformers for all the molecules are determined. Next, for each of the conformers an approximation to the molecular surface with equally distributed surface points is computed. Third, molecular properties are projected onto this surface. The properties are afterwards assigned at most two out of five property categories (H-bond acceptor/donor, hydrophilic, weakly/strongly lipophilic). Third, areas of identical properties are identified and are subsequently merged to so-called patches. Finally, the distribution of the patches representing surface area size and surface properties are converted into an alignment-independent descriptor which is based on the entire conformer ensemble. The resulting descriptor can be interpreted by superimposing the most important descriptor variables and the molecules of the data set. The most important descriptor variables are identified with chemometric regression tools.

The novel descriptor was applied to various benchmark data sets. It was compared to the original MaP procedure [1] and to 4D-QSAR [2]. In all cases the results of xMaP were comparable to MaP or 4D-QSAR with respect to model quality and model interpretability. Especially the options of backprojecting the results to original molecular space are shown.

However, as opposed the former descriptor xMap is based on conformer ensembles which renders the novel descriptor more robust. As compared to 4D-QSAR, xMaP is alignment independent which avoids the necessity of an alignment rule.

- [1] Stiefl N, Baumann K. Mapping Property Distributions of Molecular Surfaces (MaP): Algorithm and Evaluation of a Novel 3D-QSAR Technique. *J. Med. Chem.* 2003;46:1390-1407.
- [2] Hopfinger AJ, Wang S, Tokarski JS, Jin B, Albuquerque M, Madhav PJ, Duraiswami C. Construction of 3D-QSAR Models Using the 4D-QSAR Analysis Formalism. *J. Am. Chem. Soc.* 1997;119:10509-24.

We searched for a method to qualify the push-pull-character of push-pull-alkenes with different substitution and central double bond. Good results were found due to a correlation of the bond length of the central partial double bond with the ratio of the occupation numbers π^*/π of the central partial double bond for a series of push-pull-alkene and 3 groups of model compounds. So this correlation can give a hint to the push-pull-character.

The molecular basis of 21-Hydroxylase deficiency in mice

Stephan Tatzel¹, Felix G. Riepe², Rolf D. Schmid¹, Jürgen Pleiss¹

*¹Institute of Technical Biochemistry
University of Stuttgart*

Allmandring 31, 70569 Stuttgart

*²Division of Paediatric Endocrinology, Department of Paediatrics,
Universitätsklinikum Schleswig-Holstein,
Christian-Albrechts-Universität Kiel, Germany.*

Steroid 21-hydroxylase (CYP21), a microsomal NADPH-dependent cytochrome P450 enzyme, plays a key role in adrenal steroid synthesis. Insufficient activity of this enzyme, caused by various gene alterations, is responsible for one of the most frequent fatal inborn errors of metabolism in humans, congenital adrenal hyperplasia (CAH). The only available animal model, a special mouse strain was used to study CAH in man. Several point mutations are present in the investigated murine Cyp21. To understand the role of each mutation and the impact on the molecular level enzyme activity has been determined in vitro and the structure-function relationship has been studied by sequence conservation analysis and a three-dimensional Cyp21 structure model.[1]

The mutations are classified in three classes: (I) no or minor decrease in enzyme activity: R238Q, P465L, R361K, A362V, P458L; (II) loss of enzyme activity caused by inefficient electron flux: R346H, R400C; (III) loss of activity due to deficient substrate binding: I462F, L464F. The combination of in vitro protein expression and three-dimensional structure modelling provides a valuable tool to understand the role of the different mutations and polymorphisms on the resulting enzyme activity. Our homology model of the murine Cyp21 provides a good basis for further studies of the effect of polymorphisms on the activity of the enzyme.

[1] F.G.Riepe, S.Tatzel, W.G. Sippell, J. Pleiss, N. Krone "Congenital adrenal hyperplasia: the molecular basis of 21-hydroxylase deficiency in H-2 aw18 mice." Endocrinology (2005)

Modeling and molecular dynamics of a miniature viral potassium channel

Sascha Tayefeh,^{1,2} Gerhard Thiel,² and Stefan M. Kast¹

¹ *Physikalische Chemie I, TU Darmstadt, Petersenstr. 20, 64287 Darmstadt*

² *Institut für Botanik, TU Darmstadt, Schnittspahnstr. 3, 64287 Darmstadt*

The virus-encoded potassium channel Kcv plays an essential role in replication of the virus PBCV-1 [1] and represents the smallest protein known (probably the minimal structural motif [2]) to form a functional potassium ion channel. The Kcv system therefore appears to be an ideal system for establishing essential structure-function relationships of potassium channels and for gaining deeper insight into viral metabolism, respectively. A number of specific experimental facts about Kcv have been elaborated in the past raising important questions as to their explanation: For instance, deletion of 14 N-terminal amino acids result in loss of measurable current in HEK 293 cells [2], and long-distance interactions within the channel pore have been unveiled [3].

The answer to these questions requires direct insight into the microscopic structure and dynamics of the channel constituents involved in transport processes. This can be gained from an atomistic model of the channel protein embedded into a model membrane and a solvent phase, small enough to be accessible to molecular dynamics (MD) computer simulations on the nanosecond time scale, yet large enough for capturing the presumed essential features.

The present talk discusses the necessary steps for creating an initial structural model to be used in MD simulations. Since no experimental data about the three-dimensional Kcv structure is known we must rely on empirical template-guided modeling strategies. Starting from available sequence information, multiple-alignment and energy minimization techniques were applied on the basis of spatial restraints derived from the related KirBac1.1 channel protein. The results are discussed and evaluated as to their plausibility and reliability. The next steps comprise (1) embedding the protein into a hydrated membrane environment (according to a protocol yielding conformational states close to thermodynamic equilibrium as described in [4]), (2) treatment of protonation states, and (3) initial simulations in order to establish the equilibrium structure and Kcv-specific structural features.

[1] Mehmel M, Rothermel M, Meckel T, Van Etten JL, Moroni A, Thiel G, FEBS Lett. 552, 7 (2003).

[2] Moroni A, Viscomi C, Sangiorgio V, Pagliuca C, Meckel T, Horvath F, Gazzarrini S, Valbuzzi P, Van Etten JL, DiFrancesco D, Thiel G, FEBS Lett. 530, 65 (2002).

[3] Gazzarrini S, Kang M, Van Etten JL, Tayefeh S, Kast SM, DiFrancesco D, Thiel G, Moroni A, J. Biol. Chem. 279, 28443 (2004).

[4] Woolf TB, Roux B, Proc. Natl. Acad. Sci. U.S.A. 91, 11631 (1994)

NMR and quantum chemical investigations of conformation, ring current effects and NH-tautomerism of porphyrins

Philipp Wacker*, Claudia Ryppa**, Katja Dahms**, Julia Richter**,
Mathias O. Senge**, Erich Kleinpeter*

** Department of Chemistry, University of Potsdam
Karl-Liebknecht-Strasse 24-25, D-14476, Golm*

*** Department of Chemistry, Trinity College Dublin
Dublin 2, Ireland*

Porphyrins exhibit a wide range of interesting biological and physicochemical properties[1]. They play an important role in a wide range of applications in the nature and in science. Many of their properties are dominated by the conformation and NH- tautomerism of the respective porphyrin derivatives.

The variable temperature ¹H NMR spectra of 1,3-Dithianylporphyrins[2] indicate a complex conformational behaviour. It seems that a superimposition of different dynamic effects is responsibly for the splitting of ¹H NMR signals at low temperature. To solve this problem we through a glance on the calculation of rotational barriers, NH- tautomerism and alternative conformations.

Also the calculation of ring current effects[3] of phenyl or anthracene substituents helps to assign the ¹H NMR spectra of porphyrins in general and to describe the high field shift of adjacent protons.

But not only the ring current effects of attached substituents are of interest, also the dimension of the ring current dependent on the distortion of the aromatic macrocyclic porphyrin moiety by bulky substituents can be explored by quantitative calculation of the overall ring current.

[1] K. M. Kadish, K. M. Smith, R. Guilard, Eds; The porphyrin handbook; Academic Press: New York, 2002.

[2] M. O. Senge, S. S. Hatscher, A. Wiehe, K. Dahms, A. Kelling, J. Am. Chem. Soc., 2004, 126, 13624.

[3] S. Klod, E. Kleinpeter, J. Chem. Soc., Perkin Trans. 2, 2001, 1893.

Modelling versus crystallisation - The basal activity of constitutive androstane receptor (CAR)

Björn Windshügel¹, Johanna Jyrkkärinne, Antti Poso,
Paavo Honkakoski & Wolfgang Sippl¹

¹*Institute for Pharmaceutical Chemistry,
Martin-Luther-University Halle-Wittenberg
Wolfgang-Langenbeck-Strasse 4, 06120 Halle (Saale), Germany
bjoern.windshuegel@pharmazie.uni-halle.de*

The constitutive androstane receptor (CAR) belongs to the superfamily of nuclear hormone receptors that function as ligand-activated transcription factors. CAR plays an essential role in the metabolism of xenobiotics and is also involved in drug-drug interactions which makes it an interesting pharmacological target. In contrast to other nuclear receptors CAR shows constitutive activity for which a structural basis was unknown.

Since a x-ray structure was not available when starting the work a homology model of the CAR ligand binding domain (LBD) was established based on the related pregnane X receptor (PXR) and vitamin D receptor (VDR). Molecular dynamics (MD) simulations were used to verify the models and to examine the molecular basis of constitutive activity.

Our studies revealed a tyrosine residue to be essential for basal activity of CAR [1]. Docking procedures of known agonists and site-directed mutagenesis (in vitro and in silico) supported the idea of a “molecular mimicry” in which the tyrosine side-chain mimics a bound agonist. Additionally a new hydrogen bond was predicted to be contributing to constitutive activity which could be verified by experimental studies [2].

Recently x-ray structures of human and mouse CAR complexed with various ligands have been published [3].

This allowed to compare the quality of homology modelling with x-ray crystallisation. The x-ray crystal structures and the homology model show a nearly identical structural organisation. This is also reflected by the low root mean square (RMS) deviation of 1.7 Å for all atoms lining the ligand binding pocket (LBP). Other stereochemical parameters are almost identical.

In contrast to the homology model the x-ray structures of CAR contain an additional helix that has been proposed as main feature of constitutive activity. Also a specific salt bridge was proposed to be essential for CAR function. The actual role of „helix X“ for basal activity is unclear. The constitutively active retinoid acid receptor-related orphan receptor B (RORB) also shows a „helix X“. The same holds true for the VDR which is definitely not active in absence of any ligand. Therefore a ligand induced formation of “helix X” cannot be excluded.

[1] B. Windshügel, J. Jyrkkärinne, A. Poso, P. Honkakoski, W. Sippl, *J. Mol. Mod.*, 11, 69-79 (2005)

[2] J. Jyrkkärinne, B. Windshügel, J. Mäkinen, M Ylisirniö, M. Peräkylä, A. Poso, W. Sippl, P. Honkakoski, *J. Biol. Chem.*, 280, 5960-5971 (2005)

[3] R.X. Xu, M.H. Lambert, B.B. Wisely, E.N. Warren, Weinert E.E., G.M. Waitt, J.D. Williams, J.L. Collins, L.B. Moore, T.M. Willson, J.T. Moore, *J. Mol. Biol.*, 16, 919-928 (2004)

A Procedure for Investigating Halide Anion Complexation to Radical Clocks

James Smith, Anselm H.C. Horn, & Timothy Clark

*Computer-Chemie-Centrum der Universität Erlangen-Nürnberg,
Nägelsbachstrasse 25, 91052 Erlangen, Germany*

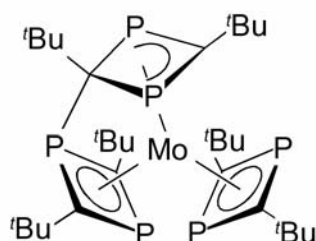
Radical clocks are frequently used as a diagnostic tool for detecting radical intermediates in chemical reactions. The intermediate radical is well characterized and undergoes a rearrangement at a specific rate regardless of reaction conditions. *Ab initio* molecular orbital and density functional calculations at the CBS-RAD (QCISD,B3-LYP) level are being used to investigate halide anion complexation to 1-hexenyl-6-yl radical (“ $\Delta(5)$ -hexenyl”) and more specifically to assess whether the interaction with the double bond alters the energy barrier to ring-closure. It is hoped that these calculations will support a previous study with metal cations. Both studies will hopefully act as controls for a wider investigation into the use of radical clocks as probes to further explore reaction intermediates in the mechanisms of P450 active sites.

Semiempirical MO Molecular Dynamics and DFT Calculations on a Fluxional Molybdenum Complex with 1,3-Diphosphete Ligands

Matthias Hennemann, Ulrich Zenneck, Timothy Clark

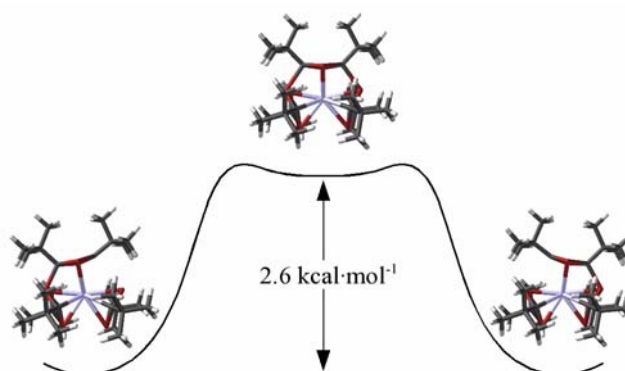
*Computer-Chemie-Centrum der Universität Erlangen-Nürnberg,
Nägelsbachstrasse 25, 91052 Erlangen, Germany,
E-mail: Matthias.Hennemann@chemie.uni-erlangen.de*

Semiempirical AM1*[1] molecular orbital theory has been used to investigate the dynamics of the molybdenum complex 1. The results indicated a third, symmetrical minimum not revealed by our earlier model studies[2] on the methyl substituted prototype complex.



Structure 1

These results were used as the basis for a detailed density functional theory (DFT) study of the t-butyl substituted compound investigated experimentally. The DFT calculations confirmed the existence of a symmetrical minimum in addition to the two unsymmetrical isomers. The calculated energy profile for interconversion of these structures is shown below.



Schematic diagram showing the energy profile of the interconversion

[1] P. Winget, A. H. C. Horn, C. Selçuki, B. Martin, T. Clark, *J. Mol. Model.* 2003, 9, 408-414.

[2] C. Topf, T. Clark, F. W. Heinemann, M. Hennemann, S. Kummer, H. Pritzkow, U. Zenneck, *Angew. Chemie* 2002, 114, 4221-4226; *Angew. Chem, Int. Ed. Engl.* 2002, 41, 4047-4052.

Structure Quest: Chameleonic Tetracycline Magnesium Ion Complexes

Olaf Othersen, Harald Lanig, Tim Clark

*Computer-Chemie-Centrum der Universität Erlangen-Nürnberg,
Nägelsbachstrasse 25, 91052 Erlangen, Germany*

Modeling the interaction of tetracycline with cell compounds represents a threefold challenge because very different targets exist in antibiotic-resistant bacteria. These targets are not only the membrane-embedded tetracycline antiporter protein, which is responsible for the efflux of tetracycline magnesium ion complexes, but also the 30s ribosome subunit, which provides the antibiotic effect, and the tetracycline repressor protein, which switches transcription on and off. None of these processes is clearly understood as the tetracycline magnesium ion complex exhibits very strong structural diversity.

In order to model some of these interactions, we need a clear picture of this structural diversity. Therefore, we have developed a systematic scan technique that takes different tautomers, conformations, magnesium ion positions, and numbers of explicit water molecules into account [1]. As computational time became cheaper, we upgraded this technique with an additional step of DFT geometry optimizations. Previously obtained conformations were grouped and representatives were optimized using B3LYP/6-31G*, followed by frequency, PCM, and MP2 single-point calculations.

This study provides an energetic ranking at the DFT level for the different tautomers and conformations of the tetracycline magnesium ion complex, and therefore represents a further step towards the final task of modeling tetracycline interactions.

[1] Othersen O.G., Lanig H., Clark T. J. Med. Chem. 2003, 46(26), 5571.

A Comparison of Two Geometric Superposition Approaches for exploring the Conformations of an Unstructured Polypeptide Tail.

Urszula Uciechowska, James Smith, Harald Lanig and Tim Clark

*Computer-Chemie-Centrum der Universität Erlangen-Nürnberg,
Nägelsbachstrasse 25, 91052 Erlangen, Germany,*

The N-terminal tail of a thioredoxin dodeca peptide fusion contains seventeen amino-acids (including a linker region) and is known to be unstructured. This peptide is a suitable system for exploring a wide range of molecular conformations. Molecular dynamics gas phase simulations were performed using AMBER7 using the Cornell forcefield for 1ns at 1000K. A hundred conformations were sampled and the resulting PDB files were simultaneously superposed according an optimization procedure by Gerber & Müller that minimizes the weighted sum of their mutual least-squared deviation. The two superposition approaches used (i) only the alpha carbons for each residue and (ii) the corresponding coordinate positions of the plane of the four backbone atoms for each peptide bond: the alpha carbon, carbonyl carbon, backbone nitrogen and the neighbouring alpha carbon. We demonstrate that the former approach is only appropriate for studies that focus on conformational similarity and the latter is appropriate for conformational studies that focus on conformational diversity.

This is part of an on-going study that examined the conformational behaviour of both the C- and N-terminal tails of thioredoxin at a range of temperatures starting at 300K.

Molecular Modelling with WebMO

H. Bögel

*Martin-Luther-Universität
Institut für Organische Chemie
Kurt-Mothes-Str. 2
06120 Halle
boegel@chemie.uni-halle.de*

Within the last two years we are using WebMO [1] for training our students in computer applications. Because WebMO is installed on our server it can be reached every time to the learners needs. All members of the team have identical logins, so they can have a look to all jobs have been executed. This enables for stimulating research and teamwork. Everybody can share the available results and can add their own new job for solving their problems.

WebMO is out tools for doing computer experiments using different methods and approximations (molecular mechanics, semi empirical MO and ab initio methods) are available in a user-friendly environment (client server architecture) for computational chemistry.

Some of the key features are:

- Users draw structures in a java editor to generate 3D structures, run calculations, and view results, all from their web browser
- Simple enough for undergraduate computational chemistry curriculum
- Flexible enough for computational chemistry research
- Support for Gaussian 94/98/03, GAMESS, MolPro 2002, and MOPAC 7/93/200x, NWChem 4.6+, QChem 2.1+, and Tinker 4.2+
- Import existing XYZ, MOL or PDB structures directly into the editor
- Visualisation of 3D-structures, atomic charges, IR-spectra and normal modes

A three dimensional structure can be created from a sketch and is submitted for computation using a true 3-D editor, via Java technology. A computational engine is chosen and the job is submitted for computation. After the job is completed, the results of computation can be viewed without ever leaving the comfort of the web browser.

[1] <http://www.webmo.net>

An analytical, variable resolution, complete description of static molecules and their intermolecular binding properties

Jr-Hung Lin and Timothy Clark

*Computer-Chemie-Centrum der Universität Erlangen-Nürnberg,
Nägelbachstrasse 25, 91052 Erlangen, Germany*

A fully analytical description of molecular shape, as defined by the shrink-wrap isodensity or solvent-excluded surfaces and local properties related to Coulomb, donor/acceptor and polarizability (dispersion) interactions is described. The molecular surface and four local properties adequate for describing intermolecular interactions (the molecular electrostatic potential and the local ionization energy, electron affinity and polarizability) are fitted to spherical-harmonic expansions, which provide a compact and information-rich description of the properties of the static molecule. The spherical harmonics are a generalization of Fourier series and form a complete orthonormal basis on the unit circle. Hence the resolution of the description can be varied from isotropic to near atomistic detail by adjusting the order of the individual spherical-harmonic expansions.

Analytical Computation of the Post-SCF for the Acetylene Dimerization at Cobalt Center

Rong Xu, Paul Winget, Timothy Clark

*Computer-Chemie-Centrum der Universität Erlangen-Nürnberg,
Nägelsbachstrasse 25, 91052 Erlangen, Germany*

Cobalt-catalyzed Oligimerization of acetylene $\text{CpCo}(\text{C}_2\text{H}_2)_2$ provides a prototypical example of the activation of small molecules by complexation to transition metal centers via electron transfer catalysis. In this work we limit our attention to one of the reaction paths of $\text{CpCo}(\text{C}_2\text{H}_2)_2$. A Quadratic CI methods and the Complete Active Space Multiconfiguration SCF method have been used to get insight into the energetical characters for this reaction path. The results obtained show that the Post-SCF methods can must better describe the energetic characteristics of $\text{CpCo}(\text{C}_2\text{H}_2)_2$.

A Web Interface for the Parameterization Database

S. Sánchez Ríos, Tim Clark

*Computer-Chemie-Centrum der Universität Erlangen-Nürnberg,
Nägelsbachstrasse 25, 91052 Erlangen. Germany
E-mail: clark@chemie.uni-erlangen.de*

In the effort of finding optimal sets of parameters to be used in semi-empirical methods, our group designed a database to store the result of the many and time consuming calculations involved in this process. The Parameterization Database holds information on thousands of compounds, reactions and calculations made by the group.

In order to make this results accessible to those who need them, we have implemented a Web Interface, which lets our users browse and search the information they need using a standard browser (like Internet Explorer or Firefox). Users of the database can also export basic compound information to SDF format, for use with other programs. Furthermore, the Web interface also supports levels of access, giving privileged users the right to add, delete or update information stored in our Parameterization Database.

Surface-Integral QSPR Models: Local Energy Properties

Ken Byler[1], Bernd Ehresmann[1], Marcel J. de Groot[2], and Timothy Clark*[1]

[1] *Computer-Chemie-Centrum, Universität Erlangen-Nürnberg, Nögelsbachstraße 25, 91052 Erlangen, Germany.*

[2] *MISD, Pfizer Ltd., Global Research and Development, Sandwich Laboratories, Sandwich, Kent CT13 9NJ, UK.*

Surface-integral models based on AM1 semiempirical molecular orbital calculations are presented for the free energies of solvation in water, n-octanol and chloroform and for the enthalpy of solvation in water. A parameterized function of four local properties calculated at the isodensity surface (the molecular electrostatic potential, local ionization energy, electron affinity and polarizability) is integrated over the triangulated surface area to obtain the target quantity. The resulting models give results only slightly less accurate than those reported for parameterized generalized Born/polar surface area models despite relying only on gas-phase calculations. The water and octanol free-energy models were validated by calculating the water-octanol partition coefficient for a test set of organic compounds with moderate success. The models lead to a local solvation energy, which can be projected onto the molecular isodensity surface and provides insight into "hot" areas for solvation in water or the other solvents.

The Application of COMBINE Analysis to Generate Target-Specific Scoring Functions

Stefan Henrich¹, Ting Wang¹, Niklas Blomberg², Rebecca C. Wade¹

¹ EML Research gGmbH, Schloss-Wolfsbrunnenweg 33, 69118 Heidelberg, Germany

² DECS Chem Comp Dep, SC 2, AstraZeneca R&D Mölndal, S-43183 Mölndal, Sweden

Quantitative structure-activity relationship (QSAR) analysis is an essential method to correlate the properties of a series of molecules with their biological activities and to predict the activities of new compounds. Tailor-made scoring functions can be constructed by using structure-based COMparative BINDing Energy (COMBINE) analysis (ref. 1-3). This method provides the possibility to derive 3D QSARs for a set of receptor-ligand complexes whose 3D structures can be modeled. The resultant QSARs can guide modifications of either receptor, e. g. in protein engineering, or ligand, e. g. in drug design.

COMBINE analysis starts with an energy minimized model of a receptor-ligand complex, which is divided for energy calculations into parts according to their spatial location, normally its amino acid residues. These parts are used together with the ligand (and some important water molecules) for calculating electrostatic and van de Waals interaction energies between the ligand and all parts of the receptor. The resultant energy terms of many receptor-ligand complexes are correlated to bioactivity values by Partial Least Squares (PLS) coupled with suitable variable selection and data pretreatment.

We have already applied COMBINE analysis successfully to many different types of receptor-ligand complexes. For example, in the case of influenza neuraminidase (ref. 4), where several subtypes and mutants were used as a target, the binding affinity of inhibitors could be predicted. We will describe in the present work the application of the COMBINE analysis approach to the problem of predicting the selectivity against different trypsin-like serine proteases.

1. Wade, R.C., Henrich, S., Wang, T. (2004) Using 3D protein structures to derive 3D-QSARs. *Drug Discovery Today: Technologies* 1:241-246.

2. Ortiz, A.R., Pisabarro M.T., Gago F., Wade R.C. (1995) Prediction of drug binding affinities by comparative binding energy analysis. *J. Med. Chem.* 38:2681-2691.

3. Wade, R.C., Ortiz, A.R., Gago F. (1998) Comparative Binding Energy Analysis. *Persp. Drug Disc. and Des.* 9:19-34.

4. Wang, T., Wade, R.C. (2001) Comparative Binding Energy (COMBINE) Analysis of Influenza Neuraminidase-Inhibitor Complexes. *J. Med. Chem.* 44:961-971.

Computational Approaches to identify the Determinants of SH3-Binding Specificity

Heike Meiselbach, Finn Bauer, Heinrich Sticht

*Institut für Biochemie - Abteilung für Bioinformatik
Emil-Fischer-Zentrum,
Friedrich-Alexander-Universität Erlangen-Nürnberg,
Fahrstraße 17, 91054 Erlangen, Germany*

The Src Homology 3 (SH3) domains are found in a wide variety of unrelated proteins, many of which are involved in signal transduction, indicating their important role in protein-protein interactions. The herpesviral tyrosine kinase interacting protein (Tip) binds with different affinities to the Src-family kinases Lyn and Lck. In this peptide, the consensus binding sequence XPPLPXR forms a left-handed type II polyproline helix that lies along the binding site of SH3 domain, with its prolines interacting with the aromatic residues on the hydrophobic groove of the SH3 domain [1].

The residues 186-187 of Tip were shown to increase binding affinity of Lyn by of magnitude while the affinity for Lck remains almost unaffected [1]. Structure determination of the Lyn-Tip complex suggests that a nonconserved histidine (H41) of Lyn might play a role in mediating increased affinity by interacting with L186 of Tip. We studied the role of H41 and of L186/187 for binding affinity by molecular dynamics and free energy calculation. Binding free energies calculated using the molecular mechanics Poisson-Boltzmann surface area (MM-PBSA) method [2] confirm the importance of these residues for Lyn binding specificity.

[1] F. Bauer, K. Schweimer, S. Hoffmann, P. Rösch, and H. Sticht submitted.

[2] J. Srinivasan, T.E. Cheatham, P. Cieplak, P.A. Kollman, and D.A. Case *Journal of the American Chemical Society*, 1998, Vol. 120, pp. 9401-9409.

Designing Specificity of SH3 Domain Binding Ligands

Christian Weyera, Anselm H. C. Horna, Martin Stiebritzb, Yves Mullerb, Heinrich Stichta

*aAbteilung für Bioinformatik und bLehrstuhl für Biotechnik
Friedrich-Alexander-Universität Erlangen-Nürnberg, Fahrstr. 17, D-91054 Erlangen*

Many protein-protein interactions are mediated by peptide binding domains, such as SH2, SH3, WW and PDZ. These domains can bind short peptide sequences and play a critical role in a wide array of biological processes. Complete genome sequences have revealed thousands of these domains, requiring improved methods for identifying their physiological relevant binding sequences.

The Src Homology 3 (SH3) domain is the most abundant adapter module in eukaryotic genomes and one of the most actively studied interaction domains to date. While the general proline-rich binding motif of the ligand is well characterized, the specificity of a peptide sequence for a special SH3 domain remains still less clear.

A SH3 domain has three different regions which form contacts to the ligand (Figure 1) and within which there are diverse amino acids which may mediate specificity of ligand recognition.

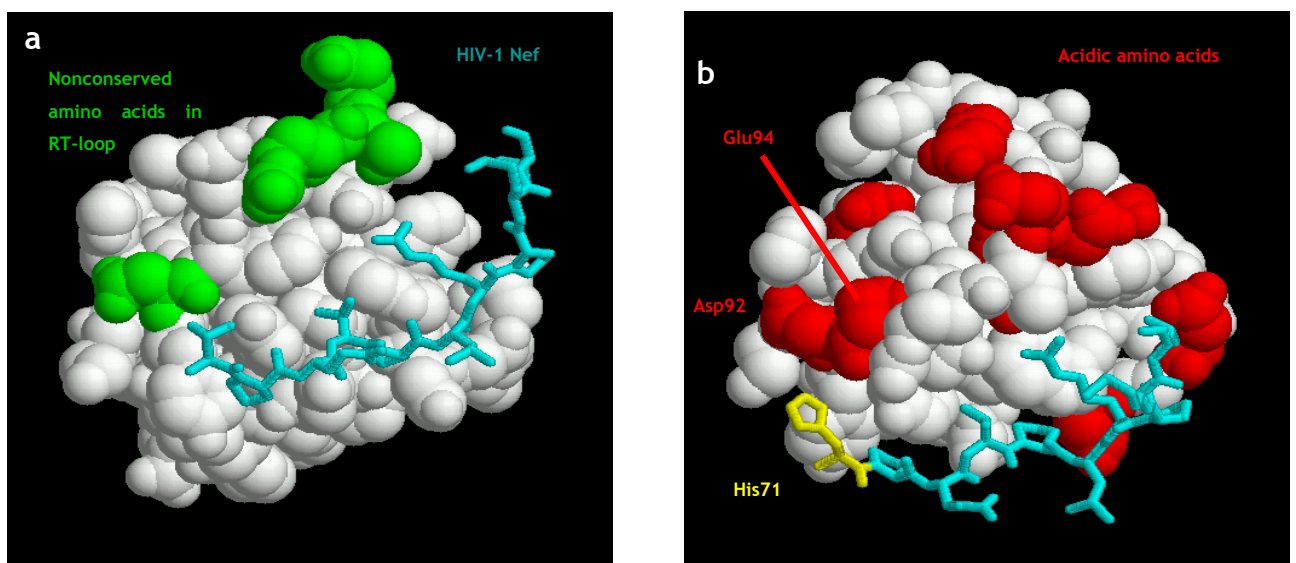


Figure 1: Fyn SH3 domain in complex with HIV-1 NEF (truncated). a, green amino acids within the RT loop can be used for specificity design. b, acidic amino acids are coloured red. For position 71 basic amino acids (e.g. Histidine, yellow) generally represent candidates with potential enhanced specificity for Fyn binding.

In order to tune ligand specificity we chose two sample SH3 domains (Fyn and Lyn) starting from an X-ray complex structure[1] and mutated ligand position 71 subsequently to all 20 amino acids applying lowest energy sidechain rotamer determination using MUMBO[2].

Protein-ligand interaction energies were calculated using the Charmm force field and indicated some candidate residues for enhanced affinity.

- [1] S. Arold, P. Franken, M.P. Strub, F. Hoh, S. Benichou, R. Benarous, C. Dumas
Structure 1997, 5, 1361-72.
- [2] M. Striebritz, Y. Muller, Mumbo, Erlangen 2004-2005.

Dynamical behaviour of the Prion Protein: Influence of pH Change and F198S Mutation

Anselm H. C. Horn, Heinrich Sticht

*Abteilung für Bioinformatik, Institut für Biochemie, Emil-Fischer-Zentrum
Friedrich-Alexander-Universität Erlangen-Nürnberg
Fahrstraße 17, D-91054 Erlangen, Germany*

Prions are infectious pathogens that cause a group of fatal, neurodegenerative diseases known as transmissible spongiform encephalopathies (TSE), which can be sporadic, inherited, or acquired by infection. According to the protein-only hypothesis the cellular form of the prion protein PrPC is converted into a misfolded oligomeric form PrPSC, of which still no experimental structure is available, yet. The dynamics of this conversion is influenced by several factors (mutations, environment pH, temperature). Because of its threat on public health many disease-associated mutations have been subjected to experimental and theoretical investigations in the past.

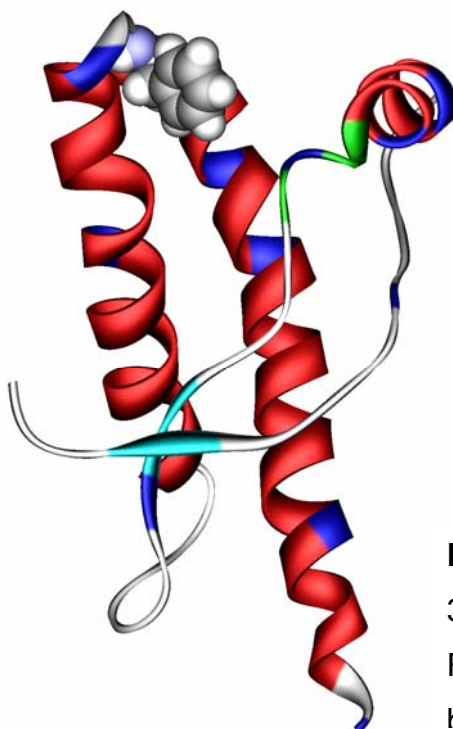


Figure 1

3D-structure of PrP with the F198 mutation site in CPK and basic residues marked blue

Here we try to elucidate the impact of the F198S mutation (causing the Gerstmann-Sträußler-Scheinker syndrome in human [1]) at normal and low pH on the dynamics of the prion protein fragment huPrP125-228 [2] using molecular dynamics techniques.

- [1] D.V. Vanik, W.K. Surewicz J. Biol. Chem. 2002, 277, 49065-49070.
- [2] R. Zahn, Al. Liu, R. Lührs, R. Riek, C. von Schroetter, R.L. Garcia, M. Billeter,
L. Calzolari, G. Wider, K. Wüthrich PNAS 1999, 97, 145-150.

Molecular Dynamics Simulations of HPr and the Structural Implications of Phosphorylation

Nadine Homeyer, Anselm H. C. Horn, Heinrich Sticht

*Abteilung für Bioinformatik, Institut für Biochemie, Emil-Fischer-Zentrum,
Friedrich-Alexander-Universität Erlangen-Nürnberg, Fahrstraße 17, 91054 Erlangen*

Phosphorylation and dephosphorylation processes are important mechanisms in many regulatory pathways controlling fundamental cellular functions. The properties of many proteins are regulated post-translationally by phosphorylation at particular sites. This leads to structural modifications of the proteins enabling them to fulfill specific tasks in regulatory networks. The dephosphorylation and phosphorylation of proteins thus serves as a means to govern metabolic processes in cells and tissues.

HPr (Histidine-containing Protein) belongs to a group of proteins, whose functions are highly influenced by their phosphorylation state. It plays a major role in regulating uptake and metabolism of carbohydrates as well as transcriptional control in bacteria. Its phosphorylation on His15 is an essential reaction of the phosphotransferase system (PTS) responsible for the detection and uptake of carbohydrates into the bacterial cell. In Gram-positive bacteria HPr can also be phosphorylated at Ser46. (Ser46-P)-HPr, which is formed in the presence of high intracellular carbohydrate concentrations, builds a complex with the catabolite control protein A (CcpA) mediating then carbon catabolite repression. Since (Ser46-P)-HPr cannot be used by PTS and His15-phosphorylated HPr does not bind CcpA, the ratio of (Ser46-P)-HPr/(His15-P)-HPr determines the current state of the carbohydrate metabolism.

To reveal the dynamic behavior of HPr / HPr-P as well as the structural changes occurring upon phosphorylation molecular dynamics (MD) simulations using the Amber program suite were performed. Three types of initial coordinate sets for HPr were extracted from experimental structures, resembling the unphosphorylated [1] as well as the two phosphorylated [1,2] species. Simulations were performed with each structure phosphorylated at either His15 or Ser46.

Analysis of the MD trajectories showed distinct hydrogen bonds between the phosphate group and the neighbouring amino acid residues in both phosphorylation cases. Further MD simulations of HPr from the HPr/CcpA complex [3] complement the experimental findings of inter- and intramolecular hydrogen bond interactions.

[1] S. Fieulaine, S. Morera, S. Poncet, I. Mijakovic, A. Galinier, J. Janin, J. Deutscher, S. Nessler Proc.Nat.Acad.Sci. 2002, 99, 13437.

[2] B. E. Jones, P. Rajagopal, R. E. Klevit Protein Sci. 1997, 6, 2107.

[3] M.A. Schumacher, G.S. Allen, M. Diel, G. Seidel, W. Hillen, R.G. Brennan, Cell 2004, 118, 731.

Teilnehmer

Aqeel Ahmed

J. W. Goethe-Universität,
 Fachbereich Biologie und Informatik
 Institut für Mikrobiologie
 Marie-Curie-Str. 9
 60439 Frankfurt
 Germany
 Tel: 069-79829410
 aqeel@bioinformatik.uni-frankfurt.de

Susanne Aust

probiodrug
 Weinbergweg 22
 06120 Halle
 Deutschland
 Tel: 0345/5559930
 susanne.aust@probiodrug.de

Anastasia Bakulina

State Research Center of Virology and Biotechnology
 "Vector"
 Koltsovo
 630559 Koltsovo
 Russia
 Tel: +7-913-987-4748
 Fax: +7-3833-366479
 nastya@ns.uic.nsu.ru

Finn Bauer

Abteilung Bioinformatik, Institut für Biochemie
 Emil-Fischer-Zentrum, Friedrich-Alexander-
 Universität Erlangen-Nürnberg
 91054 Erlangen
 Germany
 Tel: 0921 553862
 Fax: 0921 553544
 finn.bauer@biochem.uni-erlangen.de

Bernd Beck

Boehringer Ingelheim Pharma GmbH & Co.KG
 88397 Biberach an der Riss
 Germany
 Tel: 07351-548151
 Fax: 07351-838151
 Bernd.Beck@bc-boehringer-ingelheim.com

Frank Beierlein

Computer-Chemie-Centrum,
 Universität Erlangen-Nürnberg
 Nägelsbachstr. 25
 91052 Erlangen
 Germany
 Tel: +49 9131 85-26581
 Fax: +49 9131 85-26565
 frank.beierlein@chemie.uni-erlangen.de

Nicolas Bernhard

FAU - Molecular-Science
 Erwin-Rommel-Straße 59
 91058 Erlangen
 Bayern/Deutschland
 Tel: 09131/401749
 nicolas.bernhard@gmx.de

Carsten Beyer

Intervet Innovation GmbH (Uni Tübingen)
 Zur Propstei
 55270 Schwabenheim
 Deutschland
 Tel: 06130 948 162
 Fax: 06130 948 517
 carsten.beyer@intervet.com

Peter Block

Philipps Universität Marburg
 Institut für Pharmazeutische Chemie
 Marbacher Weg 6
 35037 Marburg/Lahn
 Germany
 Tel: +49 6421 2825930
 Fax: +49 6421 2825994
 blockp@staff.uni-marburg.de

Alexander Böcker

Boehringer Ingelheim Pharma GmbH & Co. KG
 Birkendorfer Strasse 65
 88397 Biberach an der Riss
 Germany
 Tel: 0049 7351 5492199
 Alexander.Boecker@bc.boehringer-ingelheim.com

Fabian Bös

Institut für Technische Biochemie
 Allmandring 31
 70569 Stuttgart
 Deutschland
 Tel: 0711 685 7481
 fabian.boes@itb.uni-stuttgart.de

Wolfgang Brandt

Leibniz-Institut für Pflanzenbiochemie Halle
 Weinberg 3
 06120 Halle
 Tel: 0345-55821360
 Fax: 0345-55821309
 wbrandt@ipb-halle.de

Benjamin Breu

J. W. Goethe-Universität, Fachbereich Biologie und
 Informatik
 Marie-Curie-Str. 9
 60439 Frankfurt
 Germany
 Tel: 069-79829410
 Fax: 069-79829826
 breu@bioinformatik.uni-frankfurt.de

Jürgen Brickmann

MOLCAD GmbH i.Gr.
 Petersenstr. 20
 64807 Darmstadt
 Germany
 Tel: 06151-162198
 brick@pc.chemie.tu-darmstadt.de

Isabelle Bundesmann

Computer-Chemie-Centrum
Nägelsbachstr. 25
91052 Erlangen
Germany
Tel: 09131-8526582
Fax: 09131-8526565
isabelle.bundesmann@chemie.uni-erlangen.de

Jos? Castro Arce

TU Kaiserslautern
POB 3049
D-67663 Kaiserslautern
Germany
Tel: 0049 631 2053773
Fax: 0049 631 2052119
castro@mv.uni-kl.de

Helen Chappell

Computer-Chemie-Centrum
Nägelsbachstr. 25
91052 Erlangen
Germany
Helen.Chappell@chemie.uni-erlangen.de

Holger Claußen

BioSolveIT GmbH
An der Ziegelei 75
53757 Sankt Augustin
Deutschland
Tel: 02241 / 25 25 0
Fax: 02241 / 25 25 525
Holger.Claussen@biosolveit.de

Paul Czodrowski

Philipps University Marburg - Department of
Pharmaceutical Chemistry
Marbacher Weg 6
35037 Marburg
Germany
Tel: ++49-6421-2825908
Fax: ++49-6421-2828994
Paul.Czodrowski@staff.uni-marburg.de

Fernando B. Da Costa

Computer-Chemie-Centrum
Nägelsbachstr. 25
91052 Erlangen
Germany
Tel: 9131/85-26579
Fax: 9131/85-26566
Fernando.DaCosta@chemie.uni-erlangen.de

Holger Dinkel

Universität Erlangen
Abteilung f. Bioinformatik
Institut f. Biochemie
Fahrstrasse 17
91054 Erlangen
Deutschland
Tel: 09131-852-4675
holger.dinkel@biochem.uni-erlangen.de

Krisztina Feher

Bayer Healthcare AG
Aprather Weg
42113 Wuppertal
Deutschland
Tel: 0202 368107
krisztina.feher@bayerhealthcare.com

Rudolf Friedemann

FB Chemie, Martin-Luther-Universität Halle-
Wittenberg
Kurt-Mothes-Str. 2
06120 Halle(Saale)
Deutschland
Tel: 0345-5525668
Fax: 0345-5527608
rudolf.friedemann@chemie.uni-halle.de

Ulf Frieske

University of Duisburg-Essen, CAM-D TEchnologies
GmbH
Gerlingstrasse 65
45139 Essen
Germany
Tel: 0201 3657 402
Fax: 0201 3657 403
frieske@molecular-dynamics.de

Michael Galle

Computer-Chemie-Centrum
Nägelsbachstr. 25
91052 Erlangen
Tel: 09131/8526534
Fax: 09131/8526565
endc01@rzmail.uni-erlangen.de

Johann Gasteiger

Computer-Chemie-Centrum
Universität Erlangen-Nürnberg
Nägelsbachstr. 25
91052 Erlangen
Germany
Tel.: +49 9131 85 26570
Fax.: +49 9131 85 26566
Gasteiger@chemie.uni-erlangen.de

Christof Gerlach

Philipps Univeristät Marburg
Institut für Pharmazeutische Chemie
Marbacher Weg 6
35037 Marburg/Lahn
Germany
Tel: +49 6421 2825908
Fax: +49 6421 2825994
gerlachc@staff.uni-marburg.de

Jens Gimmler

TU-Darmstadt Informatik: Fachgebiet Intellektik
Hochschulstr. 10
64289 Darmstadt
Deutschland
Tel: 06151 917273
gimmler@rbg.informatik.tu-darmstadt.de

Holger Gohlke

J. W. Goethe-Universität, Fachbereich Biologie und Informatik
Marie-Curie-Str. 9
60439 Frankfurt
Germany
Tel: 069-79829411
Fax: 069-79829826
gohlke@bioinformatik.uni-frankfurt.de

Andreas Göller

Bayer Healthcare AG
Aprather Weg 18a
42096 Wuppertal
Deutschland
Tel: 0202-365442
Fax: 0202-365461
andreas.goeller@bayerhealthcare.com

Domingo Gonzalez-Ruiz

J. W. Goethe - Universität
Marie-Curie-Str. 9
60439 Frankfurt
Germany
Tel: +49.69.798.29410
dgruiz@bioinformatik.uni-frankfurt.de

Christian Grunwald

elbion AG
Meissner Strasse 191
01445 Radebeul
Tel: 0351 - 40 43 15 52
Fax: 0351 - 40 43 55 52
christian.grunwald@elbion.de

Stephanie Gulde

IPB Halle
Malderitzstr. 4a
06132 Halle/S.
Deutschland
Tel: 0345-7757563
Stephanie.Gulde@ipb-halle.de

Stefan Güssregen

Sanofi-Aventis
Industriepark Höchst, Building G878
65926 Frankfurt am Main
Germany
Tel: ++49 69 305 26616
Fax: ++49 69 33 13 99
stefan.guessregen@sanofi-aventis.com

Gudrun Hackspiel

Universität Innsbruck
Institut für Allgem. Anorg. und Theoret. Chemie
Innrain 52a
6020 Innsbruck
Österreich
Tel: +43/0699/10840831
Fax: +43/512/507/5269
csac5270@uibk.ac.at

Yongquan Han

Computer-Chemie-Centrum und Institut fuer Organische Chemie, Uni-Erlangen
Naegelsbachstr. 25
91052 Erlangen
Germany
yongquan.han@chemie.uni-erlangen.de

Manfred Hendlich

Sanofi-Aventis
Industriepark Höchst H831
65926 Frankfurt
Deutschland
Tel: 069 305 81349
Fax: 069 305 15829
manfred.hendlich@aventis.com

Matthias Hennemann

Computer Chemie Centrum, Universität Erlangen
Nägelsbachstr. 25
91052 Erlangen
Deutschland
Tel: +49 9131/85-26534
Matthias.Hennemann@chemie.uni-erlangen.de

Stefan Henrich

EML Research gGmbH
Schloss-Wolfsbrunnenweg 33
69118 Heidelberg
Deutschland
Tel: 06221 533 223
Fax: 06221 533 298
stefan.henrich@eml-r.villa-bosch.de

Achim Herwig

Molecular Networks GmbH Computerchemie
Nägelsbachstr. 25
91052 Erlangen
Germany
Tel: +49 9131 9790623
Fax: +49 9131 815669
achim.herwig@mol-net.com

Thomas Herz

4SC AG
Am Klopferspitz 19a
82152 Martinsried
Germany
Tel: +49 (0)89-700763-0
Fax: +49 (0)89-700763-29
thomas.herz@4sc.com

Kerstin Hoehfeld

Boehringer Ingelheim Pharma KG
Waldseer Str. 63
88400 Biberach
Germany
Tel: 07351-373079
kerstin.hoehfeld@web.de

Angelika Hofmann

Computer-Chemie-Centrum
Nägelsbachstr. 25
91052 Erlangen
angelika.hofmann@chemie.uni-erlangen.de

Hakan Kayi

Computer-Chemie-Centrum, Uni-Erlangen
Nägelsbachstr. 25
91052 Erlangen
Deutschland
Tel: +49-9131-8526583
Fax: +49-9131-8526565
kayi@chemie.uni-erlangen.de

Nadine Homeyer

Abt. f. Bioinformatik, Inst. f. Biochemie, Universität
Erlangen-Nürnberg
Fahrstrasse 17
91054 Erlangen
Germany
Tel: +49 9131 85 24675
nadine.homeyer@biochem.uni-erlangen.de

Paul Keller

University of Wollongong
Department of Chemistry
2522 Wollongong
Australia
Tel: +61 2 4221 4692
Fax: +61 2 4221 4287
keller@uow.edu.au

Anselm Horn

Bioinformatik / Institut f. Biochemie
Fahrstraße 17
91054 Erlangen
Germany
Anselm.Horn@biochem.uni-erlangen.de

Anette Klinger

Intervet Innovation GmbH
Zur Propstei
55270 Schwabenheim
Germany
Tel: +49 (0)6130-948-165
Fax: +49 (0)6130-948-517
Anette.Klinger@intervet.com

Dimitar Hristozov

Computer Chemistry Center
Nägelsbachstrasse 25
91052 Erlangen
Germany
Tel: 091318526579
Dimitar.Hristozov@chemie.uni-erlangen.de

Oliver Koch

Institut für Pharmazeutische Chemie, Philipps-
Universität Marburg
Marbacher Weg 6
35032 Marburg
Tel: 06421/2825071
Fax: 06421/2828994
Oliver.Koch@Staff.Uni-Marburg.de

Qian-Nan Hu

Computer-Chemie-Centrum und Institut fuer
Organische Chemie, Universitaet Erlangen-Nuernberg
Naegelsbachstr. 25
D-91052 Erlangen
Tel: +49-9131-85 26578
Fax: +49-9131-85 26566
qian.hu@chemie.uni-erlangen.de

Jean-Pierre Kocher

Molecular Networks
Naeglesbachstr. 25
91052 Erlangen
Germany
Tel: +49 9131 979 06 24
jpkocher@mol-net.com

Teresa Jimenez Vaquero

Fachbereich Biologie und Informatik, J. W. Goethe-
Universität
Marie-Curie-Str. 9
60439 Frankfurt am Main
Germany
Tel: +49.69.798.29410
t.jimenez@bioinformatik.uni-frankfurt.de

Alrun Koller

Molekulare Bioinformatik, Fachbereich Biologie und
Informatik, J. W. Goethe-Universität
Marie-Curie-Str. 9
60439 Frankfurt am Main
Deutschland
Tel: 069-77015930
akoller@stud.uni-frankfurt.de

Bernd Kallies

Konrad-Zuse-Zentrum für Informationstechnik Berlin
Takustraße 7
14195 Berlin
Germany
Tel: 030 84185 270
Fax: 030 84185 311

Oliver Korb

Universität Konstanz, Fachbereich Chemie
78457 Konstanz
Germany
Tel: 07531 / 885191
oliver.korb@uni-konstanz.de

Thomas Kostka

Sirenade AG
Am Klopferspitz 19a
82152 Martinsried
Deutschland
Tel: +49 89 700760110
Fax: +49 89 700760222
kostka@sirenade.biz

Daniela Ladstätter

University of Innsbruck; Dept. Pharm. Chem., CAMD
Group
Innrain 52c
6020 Innsbruck
Austria
Tel: +43/676/7531742
dani.ladstaetter@gmx.at

Andreas Krasky

Intervet Innovation GmbH BioChemInformatics
Zur Propstei
55270 Schwabenheim
Germany
Tel: 06130 948326
Fax: 06130 948517
andreas.krasky@intervet.com

Harald Lanig

Computer-Chemie-Centrum, Universitaet Erlangen
Nuernberg
Naegelsbachstr. 25
91052 Erlangen
Germany
Tel: 09131/8526525
Fax: 09131/8526565
lanig@chemie.uni-erlangen.de

Selvaraj Ananda Rama Krishnan

Department of Chemistry, Martin Luther University
Halle-Wittenberg
Kurt-Mothes-Str. 2
06120 Halle (Saale)
Germany
Tel: 0345-5525683
ananda@chemie.uni-halle.de

Silvia Lehenberger

Computer-Chemie-Centrum
Universität Erlangen-Nürnberg
Nägelsbachstr. 25
91052 Erlangen
Germany
Tel.: +49 177 7462894
tubbie@vr-web.de

Michael Krug

Merck KGaA
Pha R&D GT BCI
Frankfurter Str. 250
62471 Darmstadt
Germany
Tel: 06151-72-6255
Fax: 06151-72-7635
Michael.Krug@merck.de

Markus Lill

Biographics Laboratory 3R and Institute for Molecular
Pharmacy, University of Basel
Friedensgasse 35
4056 Basel
Switzerland
Tel: ++41 61 2614259
Fax: ++41 61 2614258
markus.lill@unibas.ch

Hugo Kubinyi

Universität Heidelberg
c/o Donnersbergstrasse 9
67256 Weisenheim am Sand
Deutschland
Fax: 06353-508233
kubinyi@t-online.de

Jr-Hung Lin

Computer-Chemie-Centrum
Nägelsbachstrasse 25
91052 Erlangen
Germany
Tel: +49 9131 85-26583
Fax: +49 9131 85-26565
Jr-Hung.Lin@chemie.uni-erlangen.de

Hubert Kuhn

CAM-D Technologies GmbH
Gerlingstrasse 65
45139 Essen
Germany
Tel: 0201 3657 400
Fax: 0201 3657 403
kuhn@molecular-dynamics.de

Andreas Löffler

Tripos GmbH
Martin-Kollar-Str. 17
81829 München
Germany
Tel: 089 4510300
Fax: 089 45103030
aloeffler@tripos.com

Michael Kühnel

Institut für betriebswirtschaftliches Management im
Fachbereich Chemie und Pharmazie
Westfälische Wilhelms-Universität Münster
Leonardo-Campus 1
48149 Münster, Germany
Tel: 0251/8331823
Fax: 0251/8331818
mkuehnel@uni-muenster.de

Jörg Marusczyk

Computer-Chemie-Centrum
Universität Erlangen-Nürnberg
Nägelsbachstr. 25
91052 Erlangen
Germany
Tel.: +49 9131 85 26580
Fax.: +49 9131 85 26566
joerg.marusczyk@chemie.uni-erlangen.de

Harald Mauser

F. Hoffmann - La Roche
Molecular Design and Cheminformatics
4070 Basel
Switzerland
harald.mauser@roche.com

Olaf Othersen

Computer Chemie Centrum
Nägelsbachstr. 25
91052 Erlangen
Deutschland
Tel: 09131 / 85-26581
olaf.othersen@chemie.uni-erlangen.de

Rene Meier

Universität Halle
Wolfgang-Langenbeck-Str.4
06120 Halle (Saale)
Germany
Tel: 0345/5525043
Fax: 0345/5527355
rene.meier@pharmazie.uni-halle.de

Juri Pärn

Zentrum für Bioinformatik, Universität Hamburg
Bundesstrasse 43
20146 Hamburg
Deutschland
Tel: 040 42838 - 7362
Fax: 040 42838 - 7352
paern@zbh.uni-hamburg.de

Heike Meiselbach

Abt. f. Bioinformatik, Inst. f. Biochemie, Universität
Erlangen-Nürnberg
Fahrstrasse 17
91054 Erlangen
Germany
Tel: +49 9131 85 24675
heike.meiselbach@biochem.uni-erlangen.de

Berta Perez

Computer-Chemie-Centrum
Nägelsbachstrasse 25
91052 Erlangen
Germany
Tel: +49 9131 85-26581
Fax: +49 9131 85-26565
berta.perez@chemie.uni-erlangen.de

Thomas Mietzner

BASF Aktiengesellschaft
Abt. GVW/C
Bau A30
67056 Ludwigshafen
Germany
Tel: 0621/60-41469
Fax: 0621/60-20440
thomas.mietzner@basf-ag.de

Arnold Perez-Goicochea

IMPRS/Dortmund University
Otto-Hahn Str. 6
44221 Dortmund
Germany
Tel: 0231-755-3938
Fax: 0231-755-3937
arnold@heineken.chemie.uni-dortmund.de

Peter Monecke

Sanofi-Aventis, Gebaeude G838
Industriepark Hoechst
65926 Frankfurt
Deutschland
Tel: 069/305-20537
Fax: 069/331399
Peter.Monecke@sanofi-aventis.com

Matthias Pfortner

Molecular Networks GmbH
Nägelsbachstr. 25
91052 Erlangen
Deutschland
Tel: 09131-815668
Fax: 09131-815669
pfoertner@mol-net.com

Wolfgang Müller

Abteilung für Bioinformatik, Institut für Biochemie
Friedrich-Alexander-Universität Erlangen-Nürnberg
Fahrstr. 17
91052 Erlangen
Germany
Tel: 09131/854619
Fax:
wolfgang.mueller@biochem.uni-erlangen.de

Hendrik Preuss

University of Regensburg
Institute of Pharmacy
Universitätsstr. 31
93040 Regensburg
Deutschland
Tel: 0941 943 3329
Fax: 0941 943 4820
hendrik.preuss@chemie.uni-regensburg.de

Michael Nowak

CCC, FAU Erlangen-Nürnberg
Hartmannstr. 125
91052 Erlangen
Germany
thesaint_mn@hotmail.com

Joanna Procelewska

Max Planck Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1
45470 Mülheim an der Ruhr
Germany
Tel: 0208-3062360
Fax: 0208-306 2995
jprocelewska@mpi-muelheim.mpg.de

Ralph Puchta

Computer-Chemie-Centrum
Nägelsbachstr. 25
91052 Erlangen
Germany
Tel: 09131/8526567
Fax: 09131/8526565
ralph.puchta@chemie.uni-erlangen.de

Sarah Schulz

CAM-D Technologies GmbH
Gerlingstr.65
45139 Essen
Deutschland
Tel: 0201 3657 401
Fax: 0201 3657 403
sarah.schulz@molecular-dynamics.de

Sebastian Radestock

Universität Frankfurt
Institut für Mikrobiologie, Molekulare Bioinformatik
Marie-Curie-Strasse 9
60437 Frankfurt
Deutschland
Tel: 069 798 29410
radestock@bioinformatik.uni-frankfurt.de

Axel Schunk

GDCh
Varrentrappstr. 40-42
60486 Frankfurt/Main
Germany
Tel: 069/7917-325
Fax: 069/7917-475
a.schunk@gdch.de

Martin Reitz

Computer-Chemie-Centrum, Uni Erlangen
Nägelsbachstr. 25
91052 Erlangen
Germany
Tel: 091318526580
martin.reitz@chemie.uni-erlangen.de

Gudrun Schürer

LFG
Cauerstr. 4
91058 Erlangen
Germany
gudrun.schuerer@chemie.uni-erlangen.de

Monika Rella

University of Innsbruck
Dept. of Pharmaceutical Chemistry
Innrain 52
A6020 Innsbruck
Austria
Tel: 0043 512 291394
Monika.Rella@uibk.ac.at

Daniela Schuster

University of Innsbruck, Dept. Pharm. Chem., CAMD
Group
Innrain 52c
6020 Innsbruck
Austria
Tel: +43/512/507-5253
Fax: +43/512/507-2940
Daniela.Schuster@uibk.ac.at

Sergio Sanchez

CCC - FAU Erlangen - Nürnberg
Nägelsbachstr. 25
91052 Erlangen
Germany
Tel: 499131624731
sanchez@chemie.uni-erlangen.de

Christof H. Schwab

Molecular Networks GmbH
Nägelsbachstr. 25
91052 Erlangen
Germany
Tel: +49 (0)9131 815670
Fax: +49 (0)9131 815669
schwab@mol-net.com

Jörg Saßmannshausen

Institut für Chemische Technologie Organischer
Stoffe, TU-Graz
Stremayrgasse 16/1
8010 Graz
Austria
Tel: +43 (0)316 873 8954
Fax: +43 (0)316 873 4959
sassy@ictos.tugraz.at

Thomas Seidel

Computer Chemie Centrum
Naegelsbachstrasse 25
91052 Erlangen
Germany
thomas.seidel@chemie.uni-erlangen.de

Josef Scheiber

Institut für Pharmazie und Lebensmittelchemie,
Universität Würzburg
Am Hubland
97072 Würzburg
Deutschland
Tel: 0931-888-5473
Fax: 0931-888-5494
josef.scheiber@mail.uni-wuerzburg.de

James Smith

Computer-Chemie-Centrum
University of Erlangen-Nuernberg
Nägelsbachstr. 25
91052 Erlangen
Germany
james.smith@chemie.uni-erlangen.de

Christoph Steinbeck

Cologne University Bioinformatics Center (CUBIC)
Zuelpicher Str. 47
50674 Koeln
Germany
Tel: 0221-470 7426
Fax: 0221-470 7786
c.steinbeck@uni-koeln.de

Thomas Steinbrecher

Universitaet Freiburg
Institut fuer physikalische Chemie
Albertstr. 23a
79108 Freiburg
Deutschland
Tel: ++49 761 203 6231
Fax: ++49 761 203 6189
thomas.steinbrecher@physchem.uni-freiburg.de

Alexander Steudle

Institut für Technische Biochemie, Uni Stuttgart
Allmandring 31
70569 Stuttgart
Deutschland
Tel: 0711/685-7481
Fax: 0711/685-3196
Alexander.Steudle@itb.uni-stuttgart.de

Heinrich Sticht

Bioinformatik / FAU Erlangen-Nürnberg
Fahrstrasse 17
91054 Erlangen
Germany
Tel: 09131-8524614
Fax: 09131-8522485
H.Sticht@biochem.uni-erlangen.de

Andrea Straßer

Institut für Pharmazie, Universität Regensburg
Universitätstraße 31
93040 Regensburg
Deutschland
Tel: 0941/943-4530
andrea.strasser@chemie.uni-regensburg.de

Stephan Tatzel

Institut für Technische Biochemie, Universität
Stuttgart
Allmandring 31
70569 Stuttgart
Germany
Tel: +49-711-6855749
Fax: +49-711-6853196
Stephan.Tatzel@itb.uni-stuttgart.de

Sascha Tayefeh

Technische Universität Darmstadt
Physikalische Chemie I
Petersenstr. 20
64287 Darmstadt
Deutschland
Tel: 06151-165297
Fax: 06151-164298
sascha@pc.chemie.tu-darmstadt.de

Peter Tentscher

Computer Chemie Centrum
Nägelsbachstrasse 25
91052 Erlangen
Deutschland
Tel: 09131 / 531985
peter.tentscher@chemie.stud.uni-erlangen.de

Lothar Terfloth

Computer-Chemistry-Center and Institute for Organic
Chemistry
Universität Erlangen-Nürnberg
Nägelsbachstrasse 25
91052 Erlangen, Germany
Tel: +49 9131 8526569
Fax: +49 9131 8526566
lothar.terfloth@chemie.uni-erlangen.de

Gordon Thie

CAM-D Technologies GmbH
Gerlingstrasse 65
45139 Essen
Deutschland
Tel: 0201 173 1710
gordon.thie@degussa.com

Clark Timothy

Computer-Chemie-Centrum, Universität Erlangen
Nägelsbachstr. 25
91052 Erlangen
Germany
Tel:
Fax:
clark@chemie.uni-erlangen.de

Ulrike Uhrig

Tripos GmbH
Martin-Kollar-Str. 17
81829 München
Germany
Tel: 089 4510300
Fax: 089 45103030
ulrike@tripos.com

Nico van Eikema Hommes

Computer-Chemie-Centrum, Universitaet Erlangen-
Nuernberg
Naegelsbachstrasse 25
91052 Erlangen
Germany
Tel: 09131 8526532
Fax: 09131 8526565
hommes@chemie.uni-erlangen.de

Claus-Wilhelm von der Lieth

Deutsches Krebsforschungszentrum - Zentrale
Spektroskopie
Im Neuenheimer Feld 280
69120 Heidelberg
Germany
Tel: 06221-424541
Fax: 06221-424554
w.vonderlieth@dkfz.de

Alexander von Homeyer

Computer-Chemie-Centrum and Institute for Organic
Chemistry
Nägelsbachstrasse 25
91052 Erlangen
Germany
Tel: 09131 8526569
Fax: 09131 8526566
Alexander.von.Homeyer@chemie.uni-erlangen.de

Horst Bögel

Martin-Luther-Universität
Institut für Organische Chemie
Kurt-Mothes-Str. 2
06120 Halle
Germany
Tel: 0345 5525628
boegel@chemie.uni-halle.de

Philipp Wacker

Universität Potsdam
Institut für Chemie
Karl-Liebknecht-Str. 24/25
14476 Golm
Deutschland
Tel: 0331 977 54 21
Fax: 0331 977 50 57
wacker@chem.uni-potsdam.de

Guido Wagner

Johann Wolfgang Goethe-Universität Frankfurt am
Main
Marie-Curie-Straße 11
60439 Frankfurt am Main
Deutschland
Tel: +49 (0)69/798 -29232
Fax: +49 (0)69/798 -29239
wagner@chemie.uni-frankfurt.de

Christian Weyer

Institut für Biochemie
Fahrstr.17
91054 Erlangen
Deutschland
Tel: 09131 / 85 24682
christianweyer@web.de

Björn Windshügel

Institut für Pharmazeutische Chemie, Martin-Luther-
Universität Halle-Wittenberg
Wolfgang-Langenbeck-Str. 4
06120 Halle (Saale)
Deutschland
Tel: 0345-55-25043
Fax: 0345-55-27355
bjoern.windshuegel@pharmazie.uni-halle.de

Rong Xu

Computer-Chemie-Centrum
Nägelsbachstrasse 25
91052 Erlangen
Germany
Tel: +49(0) 9131 85 26581
Fax: +49(0) 9131 85 26565
rong.xu@chemie.uni-erlangen.de

Jinhua Zhang

Computer-Chemie-Centrum
Universität Erlangen
Nägelsbachstr. 25
91052 Erlangen
Germany
jinhua.zhang@chemie.uni-erlangen.de

