

SCHRÖDINGER

FIFTH SCHRÖDINGER EUROPEAN USER GROUP MEETING

11. – 13. SEPTEMBER 2005

STRASBOURG

HÔTEL RÉGENT PETITE FRANCE

Sponsored by



Agenda, continued

Monday, 12. September 2005

10:30 - 10:35	How Grid Computing Enables Innovation in Life Sciences	Dan Durkin, United Devices <i>VP Life Sciences</i>
10:35 - 10:55	Break, Coffee	
10:55 - 11:35	When SBVS met HTS	Dave Timms, AstraZeneca, Alderley Park <i>Principal Scientist, Computational Chemistry</i>
11:35 - 12:05	Docking study of phosphodiesterase inhibitors and Glide performance	Céline Anézo, Altana Pharma, Konstanz <i>Research Scientist, Molecular Modeling</i>
12:10 - 14:00	Lunch	
14:00 - 16:00	Session: Structure-Based Drug Design II	Chairman: Peter Shenkin, Schrödinger <i>VP Software Development</i>
14:00 - 14:30	Ligand Bias of Scoring Functions in Structure-Based Virtual Screening	Micael Jacobsson, Biovitrum, Stockholm <i>Scientist, Molecular Modeling</i>
14:30 - 15:00	Evaluation of Glide in a Heterogeneous Distributed Computing Environment	Daniel Kuhn, Boehringer Ingelheim, Wien <i>Postdoctoral Scientist, Structural Research</i>
15:00 - 15:20	Break, Coffee	
15:20 - 16:00	Prediction of the Structure and Binding Affinity of Protein-Ligand Complexes	Richard Friesner, Schrödinger <i>Chairman, Scientific Advisory Board</i>
16:00 - 17:45	Workshop: Structure-Based Drug Design	Gerd Räther and Woody Sherman, Schrödinger <i>Applications Scientists</i>
18:15 - 19:45	Boat Tour in Strasbourg	
20:00	Dinner	

Agenda

Tuesday, 13. September 2005

8:00 - 16:00	Registration Location: Conference room, Hôtel Régent Petite France	
8:30 - 10:50	Session: Ligand-Based Drug Design I	Chairman: Richard Lewis, Novartis, Basel <i>Global Head, Computer-Assisted Drug Design</i>
8:30 - 9:00	In and Out of Phase	David Thorner, Eli Lilly, Windlesham <i>Computational Chemist</i>
9:00 - 9:30	Pharmacophore Modeling of Phosphodiesterase Inhibitors using Phase	Tina Dahlerup Poulsen, Leo Pharma, Ballerup <i>Research Scientist, Computational Chemist</i>
9:30 - 9:50	Break, Coffee	
9:50 - 10:20	A new Phase in pharmacophore modeling?	Ulf Norinder, AstraZeneca, Södertälje <i>Principal Scientist</i>
10:20 - 10:50	Three Dimensional Pharmacophore Methods for Ligand Based Drug Design	Richard Friesner, Schrödinger <i>Chairman, Scientific Advisory Board</i>
10:50 - 11:10	Break, Coffee	
11:10 - 12:10	Panel Discussion “ <i>Integration of Computational Chemistry Methods into the Drug Discovery Process</i> ”	Alexander Hillisch, Bayer HealthCare <i>Director, Medicinal Chemistry, Head of Computational Chemistry</i> Richard Lewis, Novartis <i>Global Head, Computer-Assisted Drug Design</i> Ross McGuire, Organon <i>Section Head, In Silico Drug Discovery</i> Günther Metz, Santhera Pharmaceuticals <i>VP Computational Discovery</i>
12:15 - 14:15	Lunch	
14:15 - 16:00	Workshop: Ligand-Based Drug Design	Jas Gata-Aura, Schrödinger <i>Applications Scientist</i>

OUR WORKSHOPS

The afternoon sessions with live demos and workshops will focus on the application of workflows in structure-based drug design (SBDD) and ligand-based drug design (LBDD). Schrödinger will demonstrate the many facets of its software in a streamlined 'workflow' style, with emphasis on increasing efficiency with python scripting as well as parallelization of time-consuming tasks.

Case studies include HIV-protease (SBDD) and p38 (LBDD) and each workshop topic will be considered in terms of individual tasks, from preparation through to screening and accurate docking, as well as pharmacophore identification and QSAR. The purpose will be to stimulate open discussions with questions to a panel of Schrödinger Applications Scientists and Developers where we endeavor to answer questions with live demos. Emphasis will be on developing customized python workflows to address a wide range of requirements.

OUR PARTNERS

Schrödinger is pleased to provide a forum for users of Schrödinger software to discuss various aspects of integration and performance with our IT partners. We would like to thank our hardware partner SGI, as well as our grid technology partners Platform Computing and United Devices for sponsoring the User Group Meeting.



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DIRECTIONS TO THE HOTEL

Hôtel Régent Petite France
5, rue des Moulins
67000 Strasbourg
France
Tel : 00 33 (0)3 88 76 43 43
Fax : 00 33 (0)3 88 76 43 76

COMING FROM THE SOUTH (Colmar, or Strasbourg Airport, A35)

Take the exit "Strasbourg Centre" and at the first traffic light, follow straight on the main street. Keep the direction "Petite France", cross the bridge "Frères Matthis" and at the second traffic light follow again the direction "Petite France" (always on your left).
Now, turn left again in direction of "Petite France" and "Ponts Couverts".
At the beginning of the pedestrian area, after the restaurant "Marco Polo", turn right on the quay "Woerthel", the Régent Petite France is at the end of the quay.

COMING FROM THE NORTH (Paris)

Take the exit "Porte Blanche", follow the direction "Petite France". At the traffic light turn right, after 10 meters you will see another traffic light, then turn left and keep driving straight on in direction of the "Petite France".
Cross the bridge "Frères Matthis" and after the traffic light turn left in direction of "Ponts Couverts".
At the beginning of the pedestrian area, after the restaurant "Marco Polo", turn right on the quay "Woerthel", the Régent Petite France is at the end of the quay.

COMING FROM GERMANY (Kehl)

After the frontier, keep the direction « Strasbourg Centre » during 2 kilometers and you will come to the « Place de l'Étoile ».
Take the direction « Centre Ville - Hôpital Civil », and at the third traffic light, turn right and follow now « Petite France - Hôpital Civil ». Take the direction « Petite France - Hôtel du Département » and at the 2nd traffic light, turn left in direction of « Petite France - Ponts Couverts ». At the beginning of the pedestrian area, after the restaurant "Marco Polo", turn right on the quay "Woerthel", the Régent Petite France is at the end of the quay.

Homology Modeling of the MC4 Receptor - Insights and Limitations

Günther Metz, Santhera Pharmaceuticals, Heidelberg
VP Computational Discovery

The melanocortin receptor 4 (MCR4) belongs to the G protein-coupled receptor (GPCR) superfamily and plays an essential role in energy homeostasis and sexual behavior. Small molecule agonists and antagonists of this receptor are considered to be attractive drug candidates for obesity, cachexia and sexual dysfunction. The lack of X-Ray based structural models for GPCRs – except for bovine rhodopsin - has spurred the interest in homology modeling techniques. Recently, MC4R structural models have been published based on the 3D coordinates of rhodopsin as well as mutational studies and structure activity relationships of natural and synthetic ligands.

The Schrödinger tool Prime has been used to generate an in-house MC4R model. This approach will be discussed in light of the published homology models. In addition, first efforts to generate plausible binding modes for small molecule agonists and antagonists using the Schrödinger Induced Fit Routine will be reported.

Homology Modeling of Nuclear Receptors

Alexander Hillisch

Bayer HealthCare, Wuppertal

Director, Medicinal Chemistry, Head of Computational Chemistry

Advances in bioinformatics and protein modeling algorithms as well as the enormous increase in experimental protein structure information have aided in the generation of databases with homology models including a significant portion of known genomic protein sequences. Currently for up to 56% of all known proteins at least some 3D-structure information can be generated. There exists a great body of controversy on the real value of homology models for drug design. This talk provides an overview of the latest developments and selected examples of successful applications of the homology modeling technique to pharmaceutically relevant questions.

These include:

- design of mutagenesis experiments
- tool compound design for probing biological function
- homology model-based ligand design
- prediction of animal model suitability

Examples discussed include homology models of nuclear receptors such as estrogen receptors, the glucocorticoid and the mineralocorticoid receptor.

When SBVS met HTS

Dave Timms

AstraZeneca, Alderley Park

Principal Scientist, Computational Chemistry

The output of an HTS to identify inhibitors of ACP-enoyl reductase that was originally undertaken in 1997 forms the basis for an examination of current approaches to SBVS and in particular of GLIDE flexible ligand docking. The problems in using an HTS dataset in this context are addressed. These include the size of the screening database, the uncertainty in the experimental designation of hits and those chemical features in the ligands which are inimical both to SBVS and to development as drugs. Factors affecting the level of false negatives and false positives are investigated with particular reference to the influence of the target protein structure. The ability of PRIME to elaborate an initial X-ray structure and thereby provide a viable ensemble for SBVS is investigated in this context.

Docking study of phosphodiesterase inhibitors and Glide performance

Céline Anézo, Altana Pharma, Konstanz
Research Scientist, Molecular Modeling

19 PDE4 ligands (with available protein-ligand crystal structures) have been docked into two different PDE4 crystal structures using Glide v3.5 and RMS deviations between the docking poses and the native ligands have been systematically determined. A series of parameters have been adjusted to improve the docking results. The number of correct docking poses could be increased in some cases by saving 10 poses instead of only 1 pose, including water molecules, applying a constraint on the amino group of Gln443, and/or using the XP instead of the SP glide precision. The correlation found between Glide docking scores and experimental pIC₅₀ values was better with XP than with SP. Although a satisfying docking pose could be generated for almost all of the 19 docked ligands throughout the different docking runs, the major problem still resides in the scoring of the generated docking poses.

Ligand Bias of Scoring Functions in Structure-Based Virtual Screening

Micael Jacobsson
Biovitrum, Stockholm
Scientist, Molecular Modeling

945 known actives and 10,000 decoy compounds have been docked and scored to 8 different targets, using Glide 3.5 for docking and 10 different scoring functions for scoring. The resulting scores are used to compare enrichment between the different scoring functions, targets and three different score post-processing procedures. The three procedures are multi-active site correction (MASC) as proposed by Rizzi and Vigers (J. Med. Chem. 47:80-89, 2004), a variation of MASC where corrections terms are predicted from simple, size-related descriptors through PLS and simple size normalization. High to intermediate linear correlation between score and number of heavy atoms is found for most scoring functions. There is a relation between the size-dependence of a score and the effectiveness of size-normalization to increase enrichment.

By fitting simple size descriptors to mean score over all targets using PLS and use the resulting linear relation, meant to mirror the ligand-dependant bias of a scoring function, to predict mean scores, the enrichment is improved more often than by straightforward MASC. These results taken together mean that size-dependence of scoring-functions is a source of false positives in structure-based virtual screening. The number of false positives caused by ligand-bias might be possible to decrease using e.g. the PLS MASC procedure which will be described.

Evaluation of Glide in a Heterogeneous Distributed Computing Environment

Daniel Kuhn
Boehringer Ingelheim, Wien
Postdoctoral Scientist, Structural Research

Distributed computing uses the resources of many computers connected by a network to solve large-scale computational problems and involves the incorporation of heterogeneous computer architectures. Since several chemoinformatic applications are available also on the windows platform distributed computing is increasingly used in pharmaceutical industry. In this study we investigate the platform dependency of Glide. We report a detailed evaluation of Glide running on a Linux and on a Windows desktop cluster. We illustrate the platform dependency and show how the robustness of the Glide results can be improved. Finally, we compare virtual screening success parameters (enrichment rates, retrieval of chemotypes) on both platforms.

Prediction of the Structure and Binding Affinity of Protein-Ligand Complexes

Richard Friesner

Schrödinger

Chairman, Scientific Advisory Board

Over the past several years, we have been developing new methods for prediction of protein-ligand binding modes and binding affinities. Binding mode prediction can be improved substantially by taking into account polarization effects (which we do via a QM/MM docking protocol) and by enabling the receptor to alter its conformation in response to the ligand, using a combination of docking and protein structure prediction techniques. In practice, QM/MM docking is accomplished by combining Glide with QSite, while the induced fit methodology is constructed via a coupling of Glide and Prime. We have developed a new scoring function for the prediction of binding affinities, which is implemented in the XP Glide methodology. The underlying physical principles of this scoring function, which differ qualitatively from existing scoring functions in the literature, will be discussed, as well as an extensive evaluation of performance. Finally, a combinatorial version of Glide XP, CombiGlide, will be available in the 2005 release, and preliminary results from CombiGlide will be discussed.

In and Out of Phase

David Thorner, Eli Lilly, Windlesham
Computational Chemist

This work is split into two parts. The first part of the evaluation considers a couple of models constructed from the literature with the Phase GUI and compares them with the published results for Catalyst and CoMFA, giving comment on issues found and lessons learned.

The second part involves the evaluation of two scripts. The first script automates the testing of multiple models in a similar manner to the Phase GUI using multiQSAR. The second script is used to automate model building where only a small dataset is available. Data sets are split into training and test and sets times randomly. Many such models are constructed for each data set.

All the constructed hypotheses are tested using multiQSAR. The results from some literature sets are considered.

Pharmacophore Modeling of Phosphodiesterase Inhibitors using Phase

Tina Dahlerup Poulsen

Leo Pharma, Ballerup

Research Scientist, Computational Chemist

A virtual screening has been performed on a phosphodiesterase with recently purchased HTS compounds. Using seven known ligands, a 4-site pharmacophore model was build. Being ligand-based, the method is normally employed when no structural data of the target protein exist. However, in this particular case, a significant amount of structural information does exist. The structural information about ligand binding in phosphodiesterase was used to check the consistency of the pharmacophore model and to define an “excluded volume”, a region supposed to be occupied by the protein. As an additional selection criterion, docking calculations have been performed on a limited number of compounds in order to further reduce the number of compounds send to *in vitro* test. Based on the virtual screenings, 79 of the compounds were selected to *in vitro* test. A high hit rate was obtained, and new interesting scaffolds were recognized that could serve as starting point for a lead optimization.

A new Phase in pharmacophore modeling?

Ulf Norinder

AstraZeneca, Södertälje

Principal Scientist

Phase is a new three-dimensional pharmacophore elucidation and structure-activity modeling tool by Schrödinger. The presentation will cover some examples of public datasets where both pharmacophore elucidations as well as quantitative structure-activity relationships have been used in order to derive useful models. Both atom and pharmacophore based models will be discussed. Comparisons to corresponding models using other software will be presented.

Three Dimensional Pharmacophore Methods for Ligand Based Drug Design

Richard Friesner

Schrödinger

Chairman, Scientific Advisory Board

A brief update of Schrödinger's Phase program for 3D pharmacophore hypothesis generation and database screening, will be presented, with an emphasis on the new features and improvements that have been incorporated into the upcoming 2005 release. An important novel capability in the new release is the ability to generate multiple binding mode predictions. A case study on p38 MAP kinase, in which DFG-in and DFG-out binders are sorted by Phase into distinct clusters, will be presented.

Panel Discussion: "Integration of Computational Chemistry Methods into the Drug Discovery Process"

Alexander Hillisch, Bayer HealthCare
Director, Medicinal Chemistry, Head of Computational Chemistry

Richard Lewis, Novartis
Global Head, Computer-Assisted Drug Design

Ross McGuire, Organon
Section Head, In Silico Drug Discovery

Günther Metz, Santhera Pharmaceuticals
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