echeminfo

Community of Practice for
Drug Discovery & Development

DRUG DISCOVERY
DESIGN METHODS & APPLICATIONS

July 21– 25, 2014,
St. Hugh's College, Oxford, UK

Structure-based drug design, cheminformatics, bioinformatics and molecular modelling supporting drug design & discovery

A hands-on 5 Day eCheminfo workshop week with a case study focus in anti-malarial drug design.

FACILITATED BY BARRY HARDY

Work through in detail and discuss case studies, practical examples, methods and emerging techniques with leading modelling experts!

DRUG DISCOVERY 2014 PROGRAM

MONDAY

08.30	Registration Open
09.00	Overview of Workshop Activities, presented by Barry Hardy (Douglas Connect)
09.15	Functional kinomics of Plasmodium-infected erythrocytes Presented by Christian Doerig (Monash University)
09:45	Genome wide functional analysis of Plasmodium kinases and phosphatases, Presented by Rita Tewari (University of Nottingham)
10:15	Discussion
10.45	Homology Modelling and Loop Re nement using Phosphoglycerate Kinase, Led by Jas Bhachoo (Schrödinger)
12.30	Lunch
13.15	A Real World Drug Discovery Study: Homology Modelling and Loop Re nement for the Design of Novel Anti-bacterial agents for Histidine Kinase, Led by Jas Bhachoo (Schrödinger)
15.00	Group Work and Discussion on Workshop Case Study Problems
17.00	Poster Session with Refreshments and Food

TUESDAY

08.45	Structure Preparation and Docking Experiments with SPORES/PLANTS, led by Thomas Exner (Universität Konstanz)
11.30	Group Work on Workshop Case Study Problems
13.00	Lunch
14.00	Docking Strategies, led by Garrett Morris (Crysalin)
16.30	Group Work on Workshop Case Study Problems
18.00	Punting Trip

WEDNESDAY

08.45	Virtual Screening with Shape: How well will we do? Led by Paul Hawkins (OpenEye)
11.45	Group Work on Workshop Case Study Problems
13.15	Lunch
14.00	MM-PBSA/GBSA Free Energy of Binding Calculations on Protein Kinase Ligands – part 1, led by Alessandro Contini (University of Milan)
16.15	Group Work on Workshop Case Study Problems
18.00	End of Workday

THURSDAY

08.45	ADME & Toxicology Profiling, led by Barry Hardy (Douglas Connect)
09.45	Group Work on Workshop Case Study Problems (with coffee break)
13.00	Lunch
14.00	MM-PBSA/GBSA Free Energy of Binding Calculations on Protein Kinase Ligands – part 2, led by Alessandro Contini (University of Milan)
15.00	Group Work on Workshop Case Study Problems
18.00	End of Workday

FRIDAY

09.00	Group Work on Workshop Case Study Problems (with coffee break)
12.00	Lunch
13.00	Group Presentation of Workshop Case Study Results
16.00	Review, Further Work, Experimental Testing of Predictions
17.00	End of Workshop

ABSTRACTS

BARRY HARDY
Douglas Connect

ADME & TOXICOLOGY PROFILING

This half day workshop will provide practical guidance on the use of predictive toxicology applications with an emphasis on Open Source-based software tools and Internet resources. Users will learn about concepts and methods, and apply them in practice with a hands-on approach to exercises, and the drug discovery libraries studied during the week.

Software and databases will be used by the instructor and participants to work through predictive toxicology problems.

Participants will also have ample opportunity to work in small groups on problems and case studies and to discuss their perspectives and criticisms of the cases and methods studied.

The topics covered will include:

- The OpenTox Framework
- Using Internet-based Toxicology Resources
- Searching and integrating existing toxicology data
- Mechanism-based use of in vitro assay data
- Integrated Analysis using Weight of Evidence Methodology
- Evaluating the impact of Chemical Modifications on Toxicities
- Predicting Metabolites
- Application to anti-Malarial Drug Discovery Libraries

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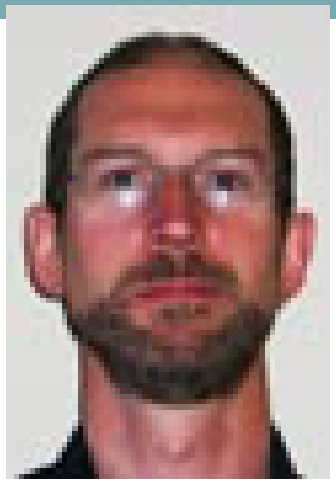
PAUL HAWKINS
OpenEye

VIRTUAL SCREENING WITH SHAPE



When confronted with a problem in computational drug design there often exist a large number of tools that the computational chemist could apply to the problem. The difficulty lies in predicting which tool will be the most useful for that problem. There are a number of simple yet robust statistical tests that can easily be applied to help in deciding which tool is likely to perform better in prospective work, based on retrospective data.

The application part of the session will focus on using shape-based methods for virtual screening and lead-hopping using the OpenEye tool ROCS.

In the workshop participant will learn:

- About searching in shape space
- Using shape in virtual screening and the visual query editor vROCS
- How to merge multiple molecules into a single query
- Edit molecules (separate molecule structure from the idea of a query)
- Validate those queries in retrospective virtual screens
- About robust statistical methods that can be applied to virtual screening experiments and will use these methods to compare queries that they generate, enabling them to choose the best query
- Class members working in small groups will be able to apply shape-based virtual screening to their case studies.

>> MORE <<

THOMAS EXNER

University of Tübingen

STRUCTURE PREPARATION AND DOCKING EXPERIMENTS WITH SPORES/PLANTS

Protein-ligand docking is a useful tool to find new lead compounds and to get ideas of important interactions between the ligands and the target especially in the early drug design phases.

Using virtual screening, a very large (virtual) database can be docked with almost negligible time and financial demand and the most prominent hits can then be tested experimentally.

Besides a reasonable description of the interactions in the complex using state-of-the-art scoring functions, it has become evident that the preparation of the structures used in docking is of almost equivalent importance.

In this workshop, we will discuss criteria for generating an optimal screening library and how to perform the structure preparation using SPORES including the generation of different protonation states, tautomers, and stereoisomers. These will then be docked using the PLANTS software and the results will analyzed to find leads for experimental testing and further optimization by derivatization.

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ALESSANDRO CONTINI

University of Milan

MM-PBSA/GBSA BINDING ENERGY CALCULATIONS

Molecular Mechanics Poisson-Boltzmann Surface Area (MM-PBSA) and Molecular Mechanics Generalized Born Surface Area (MM-GBSA) are interesting techniques for drug design/discovery applications.

Sometimes the correlation between predicted and experimental binding energies might lead to unsatisfactory results.

The inclusion of explicit water molecules in MM-PBSA/GBSA binding energy predictions is controversial, and special care needs to be taken when selecting those waters to be included in the calculation.

In this workshop, we are going to see how to run MM-GBSA calculations including explicit waters, to estimate the relative free energies of binding for a selection of protein kinases inhibitors. We will also:

- Develop docking protocols for protein-protein interaction inhibitors
- Develop method using protein-protein complex structure
- Develop method using crystal structure with co-crystallized inhibitor
- Analyze complexes, finding and fixing all possible sources of error
- Test protocols through docking of compounds with known activity
- Develop consensus protocols across multiple procedures
- Compare hits obtained from different protocols

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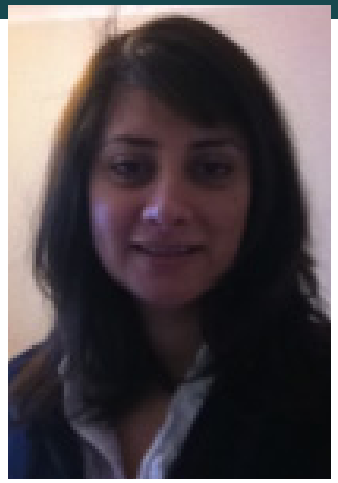
ABSTRACTS

JAS BHACHOO

Schrödinger



HOMOLOGY MODELLING AND LOOP REFINEMENT

•Includes: Homology Modelling, Loop Refinement of predicted model, Model analysis for quality assessment
•Tools: Prime Homology Modelling, Prime Refinement, Ramachandran plot, Protein Report, Maestro
•Useful techniques to predict a structure for our starting target protein, using a single template 1VPE and predict the structure of a Phosphoglycerate Kinase.

A REAL WORLD DRUG DISCOVERY STUDY

•Includes: Homology Modelling, Loop Refinement of the predicted model, Model analysis for quality assessment
•The principals of building a simple homology model for human staph-aureus' YYCG-histidine kinase and model in a loop which is missing in the bacterial thermatoga template structure.

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CHRISTIAN DOERIG

Monash and Nottingham Univ.

FUNCTIONAL KINOMICS OF PLASMODIUM-INFECTED ERYTHROCYTES

P. falciparum possesses 65 sequences conforming to the "eukaryotic protein kinase" (ePK) signature (to be compared to ~500 in the human kinome), many of which do not have orthologues in the mammalian kinome (Ward, P., et al., BMC Genomics, 2004. 5:79).

Systematic reverse genetics has determined that about half the P. falciparum ePKs are required for asexual proliferation in erythrocytes (Solyakov, L., et al., Nature Communications, 2011, 2:565).

To elucidate the function of these enzymes in parasite development, we are implementing imaging, interactomics and comparative phosphoproteomic approaches. This allowed us to assign functions of selected kinases in processes such as chromatin assembly (Dastidar, E.G., et al., BMC Biol, 2012. 10:5), mRNA splicing, proliferation rate (Dorin-Semblat, D., et al.. Kinome, 2013. 1:4-16) and nuclear division (Reininger, L., et al., Mol. Microbiol., 2011. 79: 205-21), and to establish that the parasite uses kinase cascades, based on phosphorylation of the kinase activation loop, including on tyrosine residues (Solyakov, L., et al., Nature Communications, 2011, 2:565).

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RITA TEWARI

University of Nottingham, UK

GENOME WIDE FUNCTIONALANALYSIS OF PLASMODIUM KINASES ANDPHOSPHATASES

Signal transduction pathways controlled by reversible protein phosphorylation (catalyzed by protein kinases(PKs)and protein phosphatases (PPs) in the malaria parasite Plasmodium are of great interest, for both better understanding of parasite developmental biology and identification of novel drug targets.

We have systematically performed genome wide functional analysis of both the kinase and phosphatase gene family in Plasmodium to unravel their role in parasite developmental pathway.

These studies have revealed the functional clusters of kinases/phosphatases required for sexual development and sporogony.

Overall, our two major studies identifies how kinase and phosphatases regulate parasite development and differentiation, provides a systematic functional analysis for all PKs/PPs in Plasmodium, and can inform identification of novel drug targets in malaria.

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A VARIETY OF SOFTWARE PACKAGES WILL BE AT YOUR DISPOSAL TO WORK THROUGH THE PROBLEMS POSED BY THE INSTRUCTORS.

INTERACTIVE PRAGMATIC WORKSHOPS WITH LEADING EXPERTS AND INDUSTRY PRACTITIONERS...

- Protein Target & Ligand Modelling
- Virtual Screening & Docking
- Pharmacophore Models
- Consensus Strategies
- Focused Library Design
- Molecular Simulation & Binding Energy
- Predicting ADME & Toxicities
- Fragment-based Drug Design

YOU WILL HAVE AMPLE OPPORTUNITY TO DISCUSS YOUR PERSPECTIVES AND CRITICISMS OF THE METHODS STUDIED AND YOU'LL TAKE-AWAY KEY NUGGETS OF UNDERSTANDING FROM THESE INTENSIVE SESSIONS.

GROUP WORK & DISCUSSION ON WORKSHOP CASE STUDY PROBLEMS

At the beginning of the week, participants will form themselves into small groups depending on their interests and team diversity. These groups will be given case studies and the associated data and, having agreed on which problem they wish to focus, they will decide on their strategy using the methods and software studied during the workshop. Finally, they will present their results to the rest of the participants for discussion.

JOIN THIS INTERNATIONAL COMMUNITY OF LEADING SCIENTISTS...

Founded in 2003, eCheminfo is an ongoing Community of Practice (CoP) committed to the core value of outreach with diverse groups in the commercial, government and academic sectors for the sharing of best practices and the development of strategies, resources and methodologies that address specific issues in improved drug discovery and productivity.

The network involves a diversity of subject matter expertise comprised of experienced professionals from the life science and pharmaceutical industry, vendors, research institutes, universities and government.

A strong emphasis on science and innovation in addition to networking and personal contacts and discussion is followed at eCheminfo events. Collaborative research projects furthering drug discovery and safety innovation goals are currently being pursued to advance the creation of a community of research approach to challenging problems and issues.

>> echeminfo.com <<

USE LEADING-EDGE METHODS AND SOFTWARE APPLIED TO DRUG DISCOVERY PROBLEMS. DISCUSS PRACTICAL EXAMPLES, METHODS AND EMERGING TECHNIQUES.

- Class facilitation, discussions and support led by Community Manager Dr. Barry Hardy and an international faculty team of expert drug discovery application practitioners
- Use leading drug discovery software packages including OpenEye, PLANTS, Schrodinger, CCG, OpenTox
- Integrating a case study approach and group work throughout the week on methods, datasets, challenging problems and discussion of results obtained
- One year's membership of eCheminfo included

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REGISTER NOW FOR ECHEMINFO'S WORKSHOP WEEK ON

DRUG DISCOVERY DESIGN METHODS & APPLICATIONS

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Douglas Connect
Working communities

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