



Seascape



Shape and Electrostatics Best Practices for Virtual Screening and Lead-Hopping

Session Leaders: Dr. Paul Hawkins, OpenEye Scientific
Prof. Indira Ghosh, JNU
Seascape Learning

JNU-New Delhi: 28 & 29 Jan 2010

JNU in collaboration with Seascape Learning and OpenEye Scientific, is pleased to offer an Interactive session on Shape and Electrostatics Best Practices for Virtual Screening and Lead-Hopping in Drug Discovery Research

Sponsored By : Department of Biotechnology,GOI (COE Grants)

Agenda

28 Jan 2010

A. Introduction

B. Shape Screening and Lead-Hopping – Dr. Paul Hawkins, OpenEye Scientific

Since validation/comparison metrics are a significant piece of virtual screening, we will examine metrics, statistics and validation methods in virtual screening. This is critical to compare and contrast between different methods, applications, parameter sets etc.

- An introduction to virtual screening
- Outline of the process of virtual screening
- How to validate a virtual screening tool
 - How do we know if it works
 - How do we assess future performance
 - ROC curves, AUC, p-values
- Virtual screening with shape
 - Screening the right compounds
 - Using OMEGA/ROCS
 - Conformer database generation
 - Introduction to conformer generation
 - Introduction to OMEGA
 - Some common misconceptions about conformer sampling
 - Shape and chemistry matching
 - Introduction to ROCS theory
 - Retrospective case studies
 - Prospective case studies
- Query generation and comparison using vROCS
 - Multi-molecule queries
 - Feature weighting
 - Query comparison using statistical measures
- C. Lead-Hopping with shape and electrostatics
 - Introduction to electrostatics
 - Introduction to EON
 - ROCS & EON in lead-hopping
 - Retrospective examples
 - Prospective examples

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D. Hands-on work session

- Brief tutorial on new GUIs in vROCS, BROOD 2.0 and the extensions in VIDA (overlay and alignment, conformer generation)
- vROCS – generating multi-molecule queries, editing queries to alter both shape and color properties, series of validations with different queries, generate statistics to compare the queries
- BROOD – generate a query, edit its properties, set constraints, use protein information in the search, analyze results in VIDA
- VIDA extensions – generate conformations, perform shape-based overlays

E. Hands-on workshop – Prof. Indira Ghosh & Om Prakash (JNU)

Preamble: In post-genomic era of drug discovery, enormous advances in genomics and proteomics have resulted in a large increase in the number of potential therapeutic targets that are available for investigation. This growth in potential targets has increased the demand for reliable target validation, as well as technologies that can identify rapidly several quality lead candidates. Virtual screening, and in particular structure/receptor-based virtual screening (SBS), has emerged as a reliable, inexpensive & quick method for identifying leads.

In this symposium, we will explore the current strengths and weaknesses of the SBS technology, and the work-flow of a virtual screening campaign, from preparation through to post-screening analysis will be discussed.

An introduction to Structure based virtual screening (SBS) / High Throughput Docking (HTD)

- Outline of the process of SBS / HTD
- Introduction to FRED docking tool
- SBS with FRED
 - o Protein Preparation using Fred_receptor
 - Active site identification
 - Atom Constraints
 - Scoring Function
 - Trail Docking
 - o Ligand Preparation

- Filtering of database of chemical compounds
 - Charge assignment and tautomers generation of compounds (Using QUACPAC)
 - Conformer generation using OMEGA
- o Docking with FRED
 - Protein Charge assignment (MMFF)
 - Full coordinate ligand optimization (MMFF)
 - Generate exhaustive ensemble of poses
 - Filter using negative image and atom constraints
 - Exhaustive search using ShapeGauss, ChemGauss, or PLP function
 - Score: ShapeGauss, ChemGauss, PLP, ChemScore or/and ZapBind
 - Multiple Active Site Correction (MASC)
 - Docking
 - Consensus Scoring
- o Analysis and Validation of docking results
 - RMSD with respect to reference compounds
 - Enrichment factor analysis
- o Visualization of docking results
 - FRED View using VIDA
 - Protein Surface
 - H-Bond identification
- Hands-on work session with case studies
- Reference:
 - o <http://www.eyesopen.com>
 - o Schneider, G.; Bohm, H. J. Virtual screening and fast automated docking methods. *Drug Discovery Today* **2002**, 7, 64–70.
 - o Lyne, P. D. Structure-based virtual screening: an overview. *Drug Discovery Today* **2002**, 7, 1047–1055.

- o Bleicher, K. H.; Bohm, H. J.; Muller, K.; Alanine, A. Hit and lead generation: beyond high-throughput screening. *Nat. Rev. Drug. Discovery* **2003**, 2, 369–378.
- o Shoichet, B. K. Virtual screening of chemical libraries. *Nature* **2004**, 432, 862–865.
- o Jorgensen, W. L. The many roles of computation in drug discovery. *Science* **2004**, 303, 1813–1818.
- o Lengauer, T.; Lemmen, C.; Rarey, M.; Zimmermann, M. Novel technologies for virtual screening. *Drug Discovery Today* **2004**, 9, 27–34.

Speaker Profiles

About Dr. Paul Hawkins. OpenEye Scientific. Paul got his Ph.D from University in Southampton. After a post-doc in the U.S. and Australia he settled, in New England (Boston) to work in biotech as a medicinal chemist. In this capacity he was involved in a variety of project areas, making a wide range of compounds. After a number of years at the bench he became an applications scientist for Tripos, covering the New England area. Paul has numerous publications and patents to his credit. His professional experience includes OpenEye Scientific, Tripos, Arqule, Paratek & Ariad Pharmaceuticals.

OpenEye's guiding philosophy is that it is sufficient to accurately quantify the shape and electrostatics of a molecule for the purposes of lead discovery. Following that philosophy, OpenEye provides tools that vastly increase the scale of operation of computational chemistry in drug design. Since there are an almost infinite (10^{200}) number of feasible drug-like molecules, a productive discovery process will lead to effective drug candidates.

About Seascape Learning. Seascape is an international collaborative engaged in computational science software and related projects in emerging areas of drug discovery, material sciences and smart grid. Seascape operates from Silicon Valley and India.

About Prof. Indira Ghosh, Dean, School of Information Technology, JNU. Indira is engaged in drug designing since her Ph.D research at I.I.Sc. With a brief Fulbright scholarship post-doc with Prof. J.A.McCammon at Houston she has worked in research institute in an out of country and has 13 years experience at AstraZeneca, Bangalore as leader of the CADD & Bioinformatics. Since 2003 she worked as Director, Bioinformatics center at Pune as a Professor, IBB. In JNU since 2008 she is working as project leader in the COE-DBT supported Center for Computational Biology & Bioinformatics. Her area of research encompasses gene based identification & validation of target, design of compounds for hit to lead phase. Recently her team has been working on an EU-supported FP7 project (OpenTox) on "Toxicity Prediction".

For Registration Details, please visit http://www.seascapelearning.com/oe_symp

Registration Fee

Academic: Rs. 2000

Govt. Rs. 3000

Commercial: Rs. 5,000

The registration fee includes attendance at the two day symposium and provision of all supporting materials to use and take-home from the symposium. The fee also includes a lunch each day in addition to 2 tea breaks per day.

Registration at the symposium also includes a support for open eye software license.
Group Discounts: Group discounts for more than one attendee per institution/company are available. Please contact Sunil Chawla with your registration details.

Registration Process

Please send an email to Sunil@seascapelearning.com providing us your full contact information and background (JRF/SRF/RA working in the research lab or academia or industry) by email, snail mail or online (www.seascapelearning.com).

Last date for Registration : Jan 20th. 2010

Mode of Payment

Please send us a DRAFT in the name of “Finance Officer, JNU” payable at New Delhi.

Please send the payment draft to:

- Jawaharlal Nehru University, School of Information, New Mehrauli Road, New Delhi-110067. Attn: Dr. Indira Ghosh

Accommodation

No accommodation is provided. Please make your own accommodation arrangements in/around JNU - New Delhi at the following addresses:

Jawaharlal Nehru University, School of Information Technology, New Mehrauli Road
New Delhi - 110067