• Concept of Parallel Screening or Compound Profiling
• Introduction to Ligand Profiler and HypoDB Database in Discovery Studio
• Applications to Compound Profiling
• Summary of new features and enhancements for Pharmacophore Modeling in DS 2.1
• Software demo
• Q/A
Challenge: Need a Full Understanding of Drug Characteristics and Environment

- Gain early insight into possible side-effects, toxicities, and metabolic pathways
- Refine HTS results by identifying non-selective inhibitors
- Find therapeutic targets for natural products
- Repurpose existing drugs

“At an average cost of $8.4 million, drug repurposing has become an attractive option for pharmaceutical companies ...” -- Cutting Edge Information, April 13, 2007
Solution: Reverse of Classical Modeling

• Classical modeling

  Biology (high cost, low yield) Chemistry

Select target
• Limited information about specific target
• Time-consuming, low return, guess work

Generate Pharmacophore Hypothesis

Screen compounds
• Costly HTS, synthesis
• Low success rate

• Compound profiling

Chemistry (low cost, high yield) Biology

Select compounds
• Known activity
• Known IP status
• Low cost

Match Pharmacophore Profiles

Map biological targets
• Avoid toxicity and side-effects
• Identify alternate targets
• High value outcome
Compound Profiling Can Be Used For Many Reasons

• Inverse parallel screening and selectivity profiling offer several benefits to the drug discovery lead finding and optimization workflow:

• Prioritize hits from HTS screens

• Select appropriate compounds for refinement

• Reassess pharmacology of lead compounds or failed compounds

• Performing early in-silico toxicity screening:
  – Using ADME targets (“toxicophores”)
  – Using Selectivity Profiling
  – Modeling Ion Channels like hERG

• Search for potential mode of action of acquired compounds

• Design privileged structure against desired targets

• Predict metabolic pathways

• Predict potential side effects

• Gain deeper insight into directions for scaffold hopping based on pharmacologic interaction and selectivity

• Mine project data based on high content pharmacologic interaction fingerprints to discover new lead directions from multiple project data
• Address **selectivity issue** in drug design

• Identify potential **side-effects, toxicity, or metabolic pathways** early on in your research process

• Screen against databases of known multiple therapeutic targets to discover **new applications for a known compound or marketed drug**

• Search for a potential modes of action of acquired compounds (**parallel screening**)

• Design privileged structure against desired targets, while minimizing probability of binding to any others: **library profiling**
In silico / In vitro Compound Profiling

How molecular profiling could revolutionize drug discovery

Roland B. Soughton and Stephen H. Friend

Abstract | Information from genomic, proteomic and metabolomic measurements has already benefited target discovery and validation, assessment of efficacy and toxicity of compounds, identification of disease subgroups and the prediction of responses of individual patients. Greater benefits can be expected from this application of genomics on a significantly increased scale. The experience from the same subcultures, by exploiting the quantitative accuracy of the data and by interpreting the context and the implications of increasing knowledge about large sets of molecular interactions and cell/tissue, and the genetic potential, suggests that the environment of the cell/tissue can be explored for other targets that may be matched by compounds.

In silico pharmacology for drug discovery: methods for virtual ligand screening and profiling

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Pharmacology over the past 100 years has had a rich tradition of scientists with a role in the formative qualitative or semi-quantitative relationship of molecular structure, and activity in vitro. To test these hypotheses, they have consistently used traditional pharmacology tools such as in vivo and in vitro models. Increasingly over the last decade however, we have seen that computational (in silico) methods have been developed and applied to pharmacology hypothesis development and testing. These in silico methods include databases, quantitative structure-activity relationships, pharmacophores, homology models and other molecular modeling approaches, machine learning, data mining, network analysis tools and data analysis tools that use a computer. In silico methods are primarily used alongside the generation of in vitro data both to create the model and to test it. Such models have seen frequent use in the discovery and optimization of novel molecules with affinity to a target, the clarification of absorption, distribution, metabolism, excretion and toxicity properties as well as physicochemical characterization. The aim of this review is to illustrate some of the in silico methods for pharmacology that are used in drug discovery. Further applications of these methods to specific targets and their limitations will be discussed in the second accompanying part of this review.

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- Understanding which other targets may be matched by compounds
- Risk assessment: potential side effects, toxicity, ADME
How Do We Perform Compound Profiling?

10<sup>x</sup> molecules against 10<sup>x</sup> targets

Ligand Profiler tests all geometries of each ligand against each pharmacophore in a database that represents the protein binding site.

Rapidly screen large number of ligands against thousands of targets to identify additional drug targets or side-effects.

- Need a large number of pharmacophore models
Methods to Build Pharmacophores

**Manual**
- Use custom features
- Manually control: Location Constraints, Weights
- Add Shape constraints
- Modify Projections points
- Cluster features
- Edit Features
- etc

**Structure-Based**
- Automated or Manual
- Create multiple queries for Screening libraries
- Optionally add:
  - Shape constraints
  - Excluded Vols
- Cluster features
- Edit Features
- etc

**Common Features**
- Automated
- Use custom features
- Feature-based alignment of cmpds
- Use Fit value for ranking cmpds
- Add Shape constraints
- Use model for DB searching
- Heuristic addition of excl vols based on inactivity data

**3D QSAR**
- Use activity data for a predictive model;
  - Heuristic addition of Exc Vols!
  - Custom features;
  - Calc E, ROC, DB search
Typical Pharmacophore Analysis

$10^x$ molecules against a single target

Analyze the results in a hits data table
Discovery Studio Provides out-of-the-box Solutions!
Ligand Profiler Solution in Discovery Studio

- **Ligand Profiler: Data analysis and database creation**
  - Powerful, easy to use data analysis tools
  - Build custom pharmacophore profile databases using in-house data

- **Pharmacophore Database (HypoDB) from Inte:Ligand**
  - Approximately 1,850 structure-based pharmacophores (50% with shape descriptors) covering ~190 targets
  - Highly relevant therapeutic areas
  - Compounds selected from the PDB and literature

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Selecting Targets toProfile Against

Pharmacophore Collection

3D Ligands

Target 1
Target 2
Target 3
Target 4
Target 5
Target n

Pharmacophore Collection

Selecting Targets to Profile Against

Intelligand DB Pharmacophores

- **Enzymes**
  - EC1: (oxidoreductases)
  - EC2: (transferases)
  - EC3: (hydrolases)
  - EC4: (ligases)
  - EC5: (isomerases)
  - EC6: (ligases)

- **Other proteins**
  - Bacterial proteins
  - binding proteins

- **Receptors**
  - Transduction Factor receptors
    - nuclear hormone receptors
      - ER-alpha
      - ER-beta
      - P5R
      - LXR-alpha
      - LXR-beta
      - NR1R2
      - PPAR-alpha
      - PPAR-beta
      - PPAR-gamma
      - PPAR-alpha
      - RAR-alpha
      - RAR-gamma
      - RXR-alpha
      - RXR-beta
      - Tr-alpha
      - Tr-beta
      - VDR

- **Signaling proteins**
  - Intracellular transduction
  - Surface signals
  - Transmitters

- **Structuring proteins**
  - Cellular level
    - Viral coat proteins

- **Toxins and defense proteins**
  - Antibody
  - Toxins

- **Transport proteins**
  - Extracellular proteins
    - peripharmonic binding proteins
    - NRP
    - OpiA
    - serum proteins
    - HSA
    - RBP
    - transferrin
HypoDB Content

1846 Models / 187 Unique targets

HypoDB Content - By Protein Type

- Enzymes: 38%
- Receptors: 24%
- Other: 15%

- EC1 -Oxydo reductases: 7%
- EC2 -Transferases: 2%
- EC3 -Hydrolases: 3%
- EC4 -Oxydo Lyases: 2%
- EC5 -Isomerases: 3%
- EC6 -Ligases: 1%
- Bacterial proteins: 1%
- Transduction factor receptors: 1%
- Intracellular transduction: 1%
- Surface signals: 1%
- Transmitters: 3%
- Celllar level: 0%
- Antibody: 0%
- Toxins: 0%
- Extracellular proteins: 2%

HypoDB Content: Nature of the models

- Models without Shape: 43%
- Models with Shape: 57%
Add Proprietary Pharmacophore Models

- Create your own pharmacophore model;
- add to the HypoDB database;
- Run Ligand Profiler;
- Analyze results

Example: ADMET Profiling hERG model shown here was build using literature data and 3D QSAR Pharmacophore Generation in DS!
Run Ligand Profiler Protocol
View and Analyze Ligand Profiler Results
Customization of Ligand Profiler – Web Client Interface

Pharmacophore Profiling with HypoScreen

HypoScreen is a Pipeline Pilot WebPort application that will allow compounds, either from a molecular file, (e.g., mol2, mordz, smil), internal catalysis database, or directly sketched, to be screened against HypoDB.

1. Pharmacophore selection:
- glycosidases
- glycosylases
- peptidases
- phosphatases
- phosphodiesterase
- proteases (aspartic)
- Sap7 (C. albicans)
- beta-secretase
- cathepsin D
- pepsin/pepsinopeptidase
- protease (HIV-1)

Screen:
- only models with shape
- only models without shape
- all selected models

2. Data source:
- Molecule File
- Catalyst Database
- Stretched Molecule

Select an input file:
- Browse...

Choose Your data source:
- SD File
- Catalyst Database

Select an input file:
- Browse...

Export To Excel
Cluster Molecules in Heatmap

Submit
Example 1: Viral Target Screenings

Parallel Screening: A Novel Concept in Pharmacophore Modeling and Virtual Screening†

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Parallel screening comprises a novel in silico method to predict the potential biological activities of a compound by screening it with a multitude of pharmacophore models. Our aim is to provide a fast, large-scale system that allows for virtual activity profiling. In this proof of principle study, carried out with the software tools LigandScout and Catalyst, we present a model work for the application of parallel pharmacophore-based virtual screening on a set of 50 structure-based pharmacophore models built for various viral targets and 100 antiviral compounds. The latter were screened against all pharmacophore models in order to determine if their biological targets could be correctly predicted via an enrichment of corresponding pharmacophores matching these ligands. The results demonstrate that the desired enrichment, that is, successful virtual activity profiling, was achieved for approximately 90% of all input molecules. We discuss descriptors for output validation, as well as various aspects influencing the analysis of the obtained activity profiles, and the effect of the utilized search modus for screening.

Dataset

5 viral targets
- Highly relevant viral diseases
- HIV infection, Influenza, Common cold, Hepatitis C
- Sufficient number of PDB entries
- Diverse inhibitory mechanisms

50 pharmacophore models
- Structure-based pharmacophore models generated
- Manual model check and processing
- Models include shapes, excluded volume spheres, and hydrogen bond acceptors with fluorine atoms
- Pharmacophore model validation

100 antiviral compounds
- Inhibitors both from PDB complexes and from literature
- Conformational model generation within Catalyst-BEST conformer generation algorithm
  - max. 250 conformers
  - 20kcal above the calculated lowest energy conformation

Questions Will they be attributed with the correct activity profiles?
Parallel Screening Results

Example 2: Breaking the Barriers Between Cheminformatics and Computational chemistry

• Suggested Workflow:
  – Generate list of newly registered compounds
  – Tag compounds with relevant information
  – Screen these compounds against pharmacophore databases
  – Generate an activity profile report for each compound registered
  – Email the report to Chemist registering that compound

RUN THIS REPORT DAILY!
Customized Output in Discovery Studio – make results easy to interpret and share

Please visit our Community website to download customized workflows and DS scripts!!
http://accelrys.org/
New Notable Enhancements for Pharmacophore Analysis in Discovery Studio

- Convert SMARTS rules to DS Catalyst Pharmacophore features
- Customize conformation generation by defining rigid fragments (CAESAR)
- Customize CAESAR conformation generation by constraining atoms and bonds
- Analyze results of cluster pharmacophore
- Visualize ligands aligned to pharmacophore (Ligand Profiler)
- Append to databases created with earlier versions of Catalyst using catDB
- Several enhancements to customized features

Summary

- Compound profiling is a valuable and beneficial step to small molecule discovery.
- Discovery Studio science and technology provides all the necessary computational steps as well as tools to communicate results with chemist.
- New features & enhancements enable wider applicability of Pharmacophore modeling and Analyses.

- More information can be found at:


Thank You !!

• Thank You for attending today’s webinar.

• If you have any further questions please e-mail me at raghavan@accelrys.com

• You can also contact us using the form on our website: http://accelrys.com/company/contact/

• We will be exhibiting at the following upcoming events:
  – Drug Discovery Technology and Development (August 4 – 7, Boston, Booth #512)
  – ACS Fall 2008 (August 17 – 21, Philadelphia, Booth #211)

• Reminder: upcoming webinars in this series will be...
  – July 24, 2008
    Workflow Customization with DS Developer Client
  – July 31, 2008
    Tips and Tricks in using Discovery Studio