

PHARMACOPHORE MODELING IN DISCOVERY STUDIO

The Power of Pharmacophore Modeling. Pharmacophore modeling is a powerful method to rapidly identify new potential drugs. For the numerous therapeutically relevant drug targets with undetermined active site geometries, pharmacophore modeling provides an effective mechanism for virtual screening. Using proven pharmacophore methods, researchers can achieve astounding results from limited data. Catalyst, the most cited and successful collection of pharmacophore modeling tools, has been re-engineered for improved usability in Discovery Studio®. In addition to classical tools, Discovery Studio integrates powerful new pharmacophore tools for fragment-based design, activity profiling and structure-based design.

ACCELRYS SCIENCE

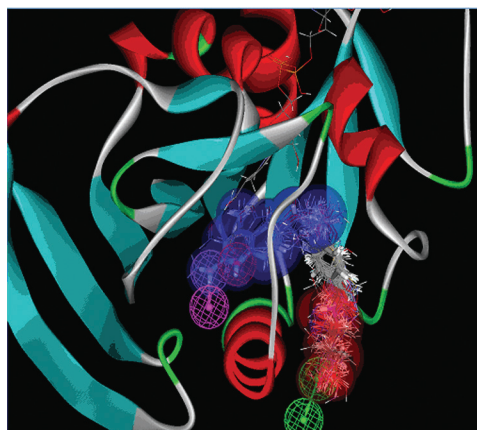
Experimentally Accurate Pharmacophore Models

- Create optimal ligand-based pharmacophore models using two methods in **DS Catalyst Hypothesis:**
- Common feature alignment can be especially useful when the mode-of-action for a series of compounds is unknown.
- Activity-based pharmacophore models correlate binding activity with specific features to optimize the model based on the known data.
- Automatically generate structure-based pharmacophore models using **DS Catalyst SBP** that can easily be combined with ligand-based hypotheses.

Features:

- Intuitive graphical interface for creating and editing customized pharmacophore features.

- Easily add excluded volumes observed from protein structures or derived from ligand data to better correlate the model with the steric constraints imposed by the target.
 - Cluster features automatically with an interactive dendrogram for easy feature selection.
- Pharmacophore Modeling in Discovery Studio



Structure based pharmacophore allows you to elucidate essential features representing binding interactions from known or putative protein active site. Easily merge shape and pharmacophore features into a more selective query.

Fast and Reliable Database Building and Searching

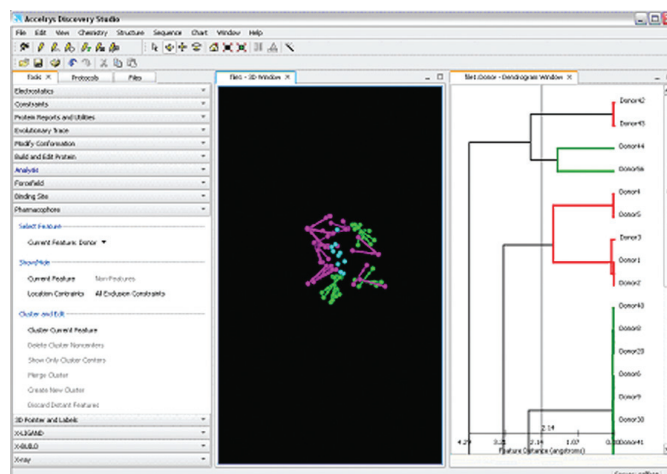
- Select from three top-ranked conformational generation algorithms each optimized for different types of uses to provide the best sampling of biologically relevant small molecule conformations in **DS Catalyst Conformation**. This module includes the new CEASAR algorithm for rapid, highly accurate, conformation generation.
- Calculate predicted fit or activity value for each compound to allow for rapid prioritization of leads and explore multiple ligand mappings to pharmacophore models with user-defined tether points for critical features with **DS Catalyst Score**.
- Integrate information-rich geometric descriptors to accelerate and add chemical diversity to pharmacophore queries using
- DS Catalyst Shape.
- Quickly and easily create 3D databases of energetically accessible conformations of extensive compound collections with DS Catalyst DB Build.
- Rapidly screen hundreds of thousands of potential drug leads with DS Catalyst DB Search using pre-designed or highly customized queries.

Cutting-Edge Pharmacophore Applications

- Generate novel lead structures by fragment-based design, a new and highly actionable method for ligand design. The De Novo Ligand Builder combines the multidimensional property matching capabilities of pharmacophores with user-specified reagent lists to identify new chemical entities.
- Compare ligands to structure-based pharmacophores from different sources to gain early insight into potential toxicities or drug targets for co-development using the Ligand Profiler in DS SBP. Leverage previously generated pharmacophores from internal sources or search high quality pharmacophore models in HypoDB from publicly available data.

THE GOLD STANDARD IN TECHNOLOGY

Comprehensive – The Catalyst set of tools allow ligand- and structure-based pharmacophore methods to be combined to generate hypotheses. Within the same integrated environment,



Interactive dendrogram for easy clustering and selection of pharmacophore points

these hypotheses can then be extensively customized using a single set of tools, and used to search multiple databases.

Proven history – The core technology has undergone over a dozen years of continuous innovation and customer driven improvement, and has demonstrated dependable performance in the pharmaceutical industry with over 100 publications.

Cutting edge – Accelrys is incorporating new scientific tools to meet current pharmaceutical needs and we are continuously working with our customers to plan for future innovation.

Easy to use interface – DS 2.0 provides a powerful and intuitive user interface. DS 2.0 can be deployed either in a complete standalone solution for individual modelers or as part of an enterprise-level client server installation for easier protocol sharing and administration in larger modeling groups.

Integrated solution – The DS 2.0 environment, built on the SciTeGic Pipeline Pilot™ open operating platform, integrates protein modeling, pharmacophore analysis, and virtual screening as well as third-party applications for an infinitely extensible virtual discovery platform. Well-tested applications including CHARMM, MODELER, Catalyst, and others are accessible in the graphical DS environment, the Pipeline Pilot scripting and protocol development environment, and from command-line prompts.

Parallel computing – The DS 2.0 platform is optimized to take advantage of grid and cluster computing as well as multi-core processors to rapidly process large tasks.

ACCELRY'S IS YOUR PARTNER IN RESEARCH

User community – Annual user group meetings world-wide attract hundreds of participants sharing new research and current results.

Scientific consulting – Accelrys has dozens of experienced Ph.D.s with expertise in implementing scientific solutions for drug design that are available for short or long-term engagements to create tailored solutions or perform modeling experiments.

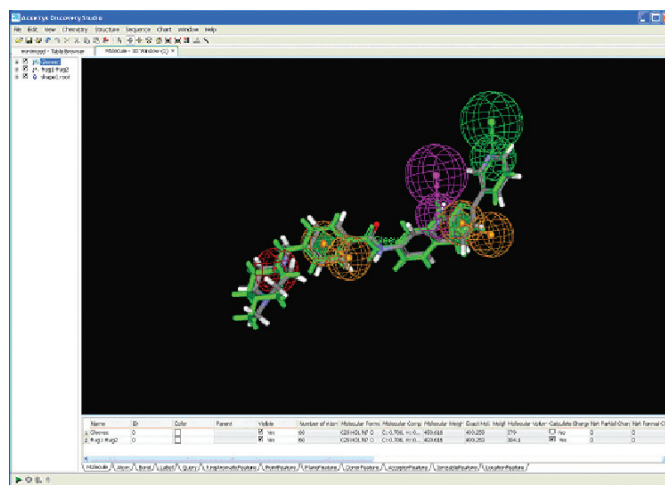
Customer support – Accelrys customers report a 98% satisfaction rate with our support team.

Committed to innovation – With over 100 Ph.D.s in the field working daily with researchers in industry and academia, Accelrys is committed to delivering cutting-edge technology to our customers.

World leading scientific advisors – Through our licensing agreements, partnerships, and scientific advisors, many of the world's foremost experts in computational drug design are involved in setting our direction.

BIOLOGICAL VALIDATION AND COMPARISON

2007 – After screening over a quarter million compounds, 17 were selected for assay. Six of these compounds were “experimentally confirmed,” and “exhibited significant human prostate cancer LNCaP proliferation inhibitory activities.”¹



Mapping of a tyrosine kinase inhibitor, Imatinib mesylate, derived from pharmacophore based de-novo fragment screening against known crystal structure ligand orientation.

2007 – Screening the NCI database, 5 compounds were selected for assay. All 5 compounds were “found to possess nanomolar to low micromolar inhibitory IC₅₀ values against h-PTP 1B.”²

2007 – J&J tests internal and commercially available conformation generation algorithms. Catalyst methods outperform all other commercial methods on every metric.³

To learn more about Discovery Studio, go to accelrys.com/discovery-studio

REFERENCES:

1. Purushottamachar P, et al, “First pharmacophore-based identification of androgen receptor down-regulating agents: discovery of potent anti-prostate cancer agents,” *Bioorg Med Chem.*, **2007**, 15, 3413-21.
2. Taha MO, et al, “Discovery of new potent human protein tyrosine phosphatase inhibitors via pharmacophore and QSAR analysis followed by in silico screening,” *J Mol Graph Model.*, **2007**, 25, 870-84.
3. Agrafiotis, DK, et al, “Conformational Sampling of Bioactive Molecules: A Comparative Study,” *J. Chem. Inf. Model.*, **2007**, 47(3), 1067-86