

Rational and fast  
receptor-flexible  
docking

Industry-validated *de  
novo* ligand design  
and optimization

CHARMm-based  
docking and scoring  
of small molecules

Choose from  
methods optimized  
for performance  
or accuracy, as you  
proceed from lead  
discovery to lead  
optimization

# Structure Based Design in Discovery Studio

## *The Power of Structure Based Design*

Structure Based Design is a powerful method for rapidly identifying new lead compounds when a receptor structure is available. In the early stages of drug discovery, virtual high throughput screening (vHTS) can lead to increased efficiency by helping to prioritize compounds in a library and by reducing library size. During the lead optimization stage, accurate docking methods, efficient *de novo* design methods, and accurate physics-based scoring can yield high-confidence compounds that are more likely to be active *in vivo*.

Discovery Studio® can streamline the entire drug discovery process with its many validated tools to dock and score small molecules, and to perform *de novo* design of lead compounds. These tools are further integrated with industry-standard protein modeling and pharmacophore tools within a single, integrated environment.

## *Accelrys Science*

### **A Rational Approach to Flexible Docking (New in Discovery Studio 2.0)**

- Leverage the proven strength of CHARMm and efficient feature-based docking in the new **DS Flexible Docking** method that shows stellar performance across a variety of receptor targets<sup>1</sup>.
- Employ a realistic approach to flexible docking in which the docking of small molecules is influenced by existing low-energy conformations of side chains in the active site.

### **Fast and Accurate Protein Ionization and pK Estimation (New in Discovery Studio 2.0)**

- Improve docking accuracy and protein-ligand binding energy estimation by using a fast GBORN-based pK estimation algorithm in **DS CHARMm**.

### **Docking Tools Optimized for vHTS Applications**

- Maximize the probability of identifying actives by using two docking methods during a vHTS experiment. Studies show that a single vHTS docking program does not give accurate results across different protein families<sup>2</sup>. Accelrys provides two well-validated vHTS applications within the Discovery Studio environment: the shape-based docking program **DS LigandFit** and the

feature-based **DS LibDock**. The two methods have been shown to complement each other and thus ensure maximum coverage of protein families.<sup>3</sup>

- Further optimize docking results with CDOCKER, a **CHARMm**-based docking method that has been shown to give highly accurate docked poses<sup>4</sup>.

### **Industry-Validated *De Novo* Ligand Generation and Optimization**

- Rapidly identify drug-like scaffolds with **DS Ludi**, a *de novo* drug discovery application that uses interaction sites in the receptor binding pocket to place and score fragments from fragment libraries.
- Reduce lead discovery time by generating complete, drug-like molecules with **DS *De Novo* Evolution** by linking and growing fragments onto a scaffold using linear, evolutionary or combinatorial methods<sup>5</sup>.

### **A Comprehensive Suite of Scoring Tools**

- Prioritize docking hits by performing rapid, high-throughput scoring of thousands of docked poses with the well-validated set of scores available in **DS LigandScore**.
- Refine the accuracy of docked poses further with physics-based scoring functions available with **CHARMm** (MM-PBSA, MM-GBSA and LIE).

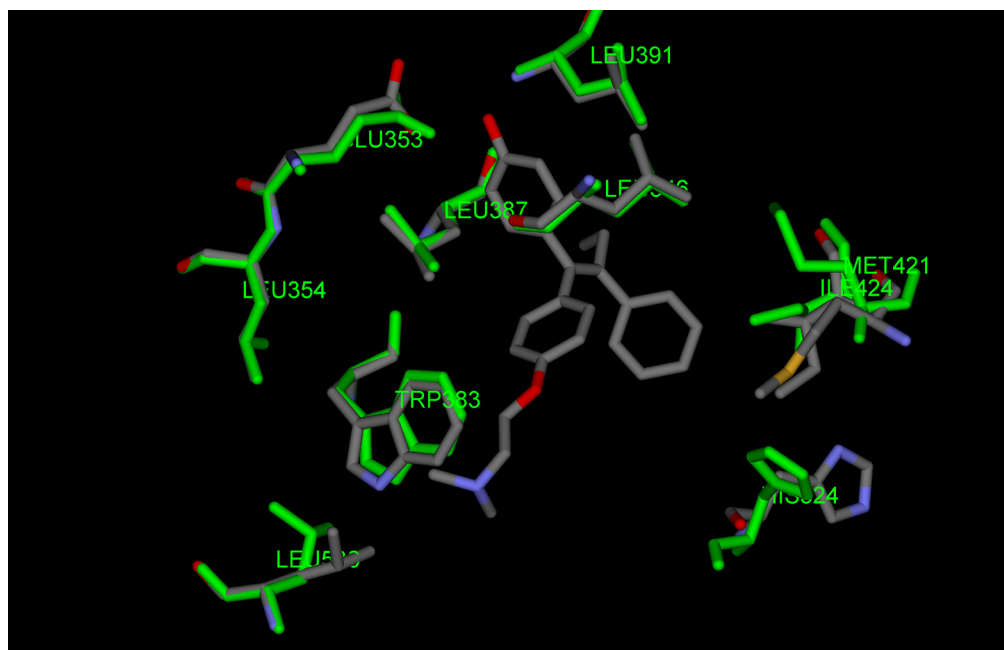


Figure 1 Top-scoring pose from a cross-docking experiment (ligand from PDB ID 3ert docked into the 1err receptor) using the rational DS Flexible Docking method. The ligand induces the 3ert conformation of side chains in the 1err binding pocket.

### The Gold Standard in Technology

**Comprehensive** – From a realistic and fast flexible docking method to industry-validated *de novo* ligand design and optimization, Discovery Studio provides a complete suite of tools for structure based design.

**Longest standing** – Accelrys has been providing cutting-edge solutions in simulation, docking and scoring that have seen continued innovation, improvement and dependable performance in the pharmaceutical industry for over 25 years.

**Easy to use interface** – DS 2.0 provides a powerful and intuitive user interface. DS 2.0 can be deployed either as a 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, based on the Pipeline Pilot™ operating platform, integrates protein modeling, pharmacophore analysis, and virtual screening as well as third-party applications for an infinitely extensible virtual discovery platform. Industry-validated applications including CHARMM, MODELER, Catalyst, and others are accessible in the graphical DS environment, the Pipeline Pilot scripting and protocol development environment, as well as from the command prompt.

**Parallel computing** – All available docking and scoring experiments in Discovery Studio have been optimized to take advantage of cluster computing as well as multi-core processors to rapidly process large tasks. Fine-grain parallelization is available for CHARMM-based experiments using new HP-MPI libraries.

### Accelrys is Your Partner in Research

**User community** – With over a thousand registered users, the academic CHARMM community continues to seed development and usage of the CHARMM engine that is at the core of Accelrys Structure Based Design solutions.

**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

### Validation

**2007** – Cross-docking experiments with the new receptor-flexible docking method DS Flexible Docking on 21 receptors spanning diverse protein families shows consistently accurate results with all ligands docked within a 2Å RMSD to X-ray poses.<sup>1</sup>

**2007** – Docking validation against the new AstexDiverse dataset shows that CDOCKER docks 94% of ligands to within 2 Å of X-ray pose, while LibDock docks 91% to within 2 Å.<sup>6</sup>

**2006** – Large-scale docking validation from GSK showed that LigandFit gave better enrichment of actives than all other docking programs (including Glide, FlexX, GOLD, and others) for some receptor targets.<sup>7</sup>

**2007** – In this study, a combined Catalyst Shape and hypothesis query was built from a KDR kinase structure and inhibitors. A database search based on Catalyst pharmacophore model identified 39 compounds that were docked into the receptor using LigandFit. The final hit from the docking experiment inhibited KDR kinase phosphorylation in an *in vitro* cellular assay.<sup>8</sup>

**2007** – Docking validation of CDK2 inhibitors using LigandFit, GOLD and FlexX shows that, “...When predicting activities by scoring programs, the combination of docking with LigandFit/plp and scoring with LIGSCORE1\_CFF gave the best correlation coefficient ( $r=0.60$ ) between experimental  $pIC_{50}$  values and top-ranked rescoring of 30 poses of each compound”.<sup>9</sup>

### References:

1. Koska, J. et al. “A Fully Automated Molecular Mechanics Based Induced Fit Protein-Ligand Docking Method,” (submitted)
2. Warren G.L., et al. “A critical assessment of docking programs and scoring functions”, *J. Med. Chem.*, **2006**, *49*, 5912.
3. Rao et al, “Validation studies of the Site-directed docking program LibDock,” *J. Chem. Inf. Model* (accepted)
4. Erickson et al., Lessons in Molecular Recognition: The Effects of Ligand and Protein Flexibility on Molecular Docking Accuracy,” *J Med Chem.* **2004**, *47(1)*, 45–55.
5. For an Application Note covering De Novo Design and CHARMM-based MM-GBSA scoring, visit [http://www.accelrys.com/reference/cases/studies/de\\_novo\\_workflow\\_app\\_note.pdf](http://www.accelrys.com/reference/cases/studies/de_novo_workflow_app_note.pdf)
6. Risal, D. et al. “Docking validation against the AstexDiverse Dataset: CDOCKER and LibDock are optimized for virtual High Throughput Screening applications”. (in preparation)
7. Warren, GL et al. “A critical assessment of docking programs and scoring functions”, *J. Med. Chem.* **2006**, *49(20)*, 5912–31.
8. Yu, H. et al. “The discovery of novel vascular endothelial growth factor receptor tyrosine kinases inhibitors: pharmacophore modeling, virtual screening and docking studies” *Chem Biol Drug Des.*, **2007**, *69(3)*, 204–11
9. Sato, H. Et al. “Prediction of multiple binding modes of the CDK2 inhibitors, anilino-pyrazoles, using the automated docking programs GOLD, FlexX, and LigandFit: an evaluation of performance”, *J Chem Inf Model.*, **2006**, *46(6)*, 2552–62.