

# SIMULATION IN DISCOVERY STUDIO

**The Power of Simulation.** Interactions between macromolecules and ligands, cofactors, membrane surfaces, metal ions, etc. are fundamental to biomolecular processes. Computational simulation of biomolecular systems helps in the understanding of these processes by providing a visual representation of the molecular geometries, spatial alignments, and energetics that contribute to molecular interactions.

The powerful set of CHARMM-based molecular mechanics and molecular dynamics methods available in Discovery Studio® (DS) enable simulation of all types of biomolecular systems. Well-validated forcefields ensure reliable results. The output trajectory files can be efficiently analyzed in a high-throughput and graphical manner using a set of user-friendly analysis tools. The simulation methods are integrated with industry-standard protein modeling, docking, scoring and pharmacophore tools within the single, unified environment of Discovery Studio.

## ACCELRYS SCIENCE

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

- Improve docking accuracy, protein-ligand binding energy estimation, and the stability and accuracy of protein simulations significantly by using a GBORN-based pK estimation algorithm in DS CHARMM. The method is faster and more accurate than existing methods, taking only a few minutes per protein structure<sup>1</sup>.
- Use this method to explore the pH-stability of your protein, and to detect active site residues during early stages of drug discovery.

### Entropy Estimation for Accurate MM-PBSA/ MM-GBSA Scoring (New in Discovery Studio 2.0)

- Increase the accuracy of physics-based scoring such as MM-PBSA and MM-GBSA using several

DS CHARMM-based methods for estimating the translational, rotational and vibrational entropy of protein-ligand systems.

### CHARMM-based Methods for Computational Drug Discovery

- The well-established computational engine CHARMM has been fully integrated into Accelrys drug discovery applications within Discovery Studio.
- Leverage the power of CHARMM to perform small molecule docking using CDOCKER.
- Minimize pre-docked poses and adjacent receptor atoms/residues using DS CHARMM or DS CHARMM Lite.
- Sample receptor flexibility during docking using CHARMM-based methods for side-chain and loop-sampling/refinement. The method is available either within the highly accurate receptor-flexible docking program, DS Flexible Docking, or as individual components.

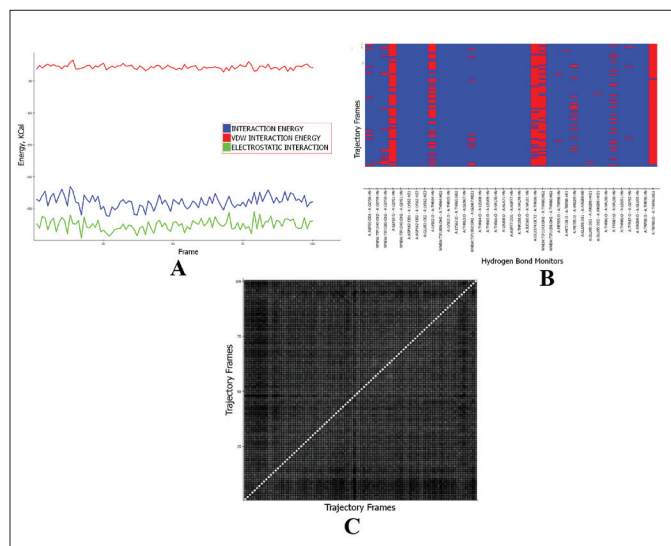
- Further refine the accuracy of docked poses with physics-based scoring functions available with DS CHARMM (MM-PBSA, and MM-GBSA).

### A Complete Simulation Package for Macromolecules

- Perform molecular mechanics and dynamics calculations using DS CHARMM, the gold standard for computational simulation.
- Access the most validated implicit solvent models, minimization methods and production schemes ever assembled in one integrated, visual environment.

### Industry-Standard Force Fields in a Unified, Graphical Interface

- Access the most comprehensive collection of protein and small-molecule force fields explicitly developed for drug discovery research. Discovery Studio now provides easy, graphical access to the following industry-standard force fields: CHARMM, charmm(19,22,27), MMFF, and CFF.



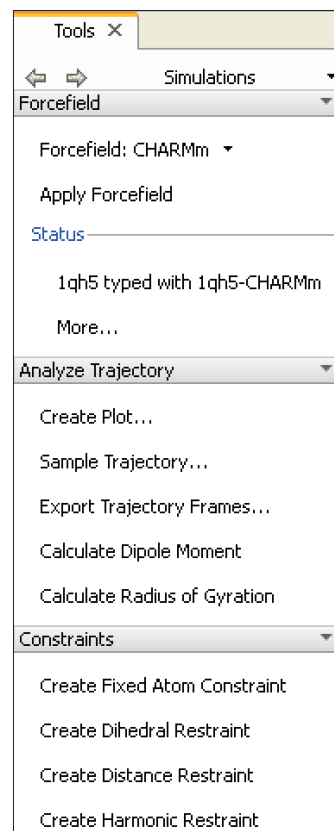
**Figure 1:** A powerful set of analysis tools allows you to calculate interaction energies between arbitrary subsets of atoms (A); monitor the formation and breakage of specific hydrogen bonds during simulation (B); and calculate pairwise Ca RMS deviations between frames in the trajectory (C).

## THE GOLD STANDARD IN TECHNOLOGY

**Comprehensive** – From molecular mechanics and molecular dynamics to a complete set of analysis tools including trajectory clustering, normal modes, radius of gyration and Principle Component Analysis, Discovery Studio provides a complete suite of tools that are optimized for computational drug discovery research.

**Longest standing** – Accelrys has been providing cutting-edge solutions in simulation and force fields 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 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.



**Figure 2:** Quickly prepare your molecular system for simulation and analyze the results using a rich set of interactive tools

**Integrated solution** – The DS 2.0 environment, based on the Pipeline Pilot™ operating platform, integrates simulation with 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 CHARMM-based 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 molecular dynamics using new HP-MPI libraries.

## ACCELRY'S IS YOUR PARTNER IN RESEARCH

**User community** – With over a thousand registered users, the academic CHARMM community continues to seed development and usages of the CHARMM engine that is the core of Accelrys' Life Science 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

**2005** – CHARMM-based MM-PBSA scoring of docked poses correctly identified the proper binding mode of Chk1 inhibitors that were previously missed by docking studies. This study shows that early scoring of docked poses using CHARMM can result in significant savings in time and resources.<sup>2</sup>

**2007** – A CHARMM-based simulation study of the mechanism by which a biofuel-synthesizing enzyme breaks down cellulose. This study shows how CHARMM-based research can be brought to bear in the increasingly critical field of bio-fuel synthesis.<sup>3</sup>

**2007** – A publication that describes the method and validation results on a CHARMM-based protein side chain sampling and refinement algorithm called ChiRotor. ChiRotor and its variants are at the heart of the new Flexible Docking method<sup>4</sup> in Discovery Studio.<sup>5</sup>

**2007** – A paper that describes the accurate and fast CHARMM-based loop sampling algorithm, Looper. Looper has been shown to perform better than existing loop-sampling methods, and can be easily integrated into the Discovery Studio Flexible Docking method.<sup>6</sup>

To learn more about Discovery Studio, go to [accelrys.com/discovery-studio](http://accelrys.com/discovery-studio)

## REFERENCES:

1. Spassov, V. et al. A fast and accurate CHARMM-based protein-ionization and pK prediction method, in preparation.
2. Foloppe, N. et al. "Structure-based design of novel Chk1 inhibitors: insights into hydrogen bonding and protein-ligand affinity" *J. Med. Chem.*, 2005, 48(13), 4332-45.
3. Nimlos, MR et al. "Molecular modeling suggests induced fit of Family I carbohydrate-binding modules with a broken-chain cellulose surface", *Protein Eng. Des. Sel.*, 2007, 20(4), 179-87.
4. [http://accelrys.com/products/datasheets/ds\\_structure\\_based\\_design\\_1107.pdf](http://accelrys.com/products/datasheets/ds_structure_based_design_1107.pdf)
5. Spassov, VZ, et al. "The dominant role of side-chain backbone interactions in structural realization of amino acid code. ChiRotor: a side-chain prediction algorithm based on side-chain backbone interactions", *Protein Sci.*, 2007, 16(3), 494-506.
6. Spassov, VZ, et al. "LOOPER: A Molecular Mechanics Based Algorithm for Protein Loop Prediction", Accepted, *Protein Engineering, Design and Selection*