X-RAY CRYSTALLOGRAPHY IN BIOVIA DISCOVERY STUDIO

DATASHEET

X-ray crystallography is a technique commonly used in the structure determination process of molecules, such as proteins, nucleic acids, etc. This experimental method is often used to improve our understanding of complex molecular relationships such as a ligand bound to a receptor. Modeling tools in BIOVIA Discovery Studio are designed to assist in the interpretation of complex data that result from X-ray experiments. In addition to building and refining structural models of protein-ligand complexes, BIOVIA Discovery Studio can generate and visualize electron density maps, as well as perform X-ray structure refinement tasks, and automatically fit ligands into available density. BIOVIA Discovery Studio uses the XPROLIG typing engine to quickly assign topology and parameters fully automatically and with high accuracy for parameter estimation.

SOLUTIONS

X-ray crystallography data is routinely gathered to help validate the binding of candidate drugs that have been designed to selectively interact with a biological target with high affinity. By solving the structure of a protein-ligand complex, scientists can use virtual screening techniques to search large libraries of ligands and find potential binders in hopes of finding better drugs for their selected receptor. Structure based approaches have proven time and time again to have a higher degree of efficiency than traditional high throughput screening efforts. X-ray crystallography experiments are now a critical part of the structure based drug design process, and will continue to play a key part for various stages of new drug development.

BIOVIA Discovery Studio offers a suite of components and protocols used in the X-ray refinement process. Through the integration of CNX (Crystallography and NMR Explorer) as the main X-ray engine and BIOVIA Pipeline Pilot as the platform, BIOVIA Discovery Studio is focused on workflow development and proper data management. With these capabilities the X-ray functionality is a true "plug and play" environment, and represents the next generation technology for X-ray workflow development.

Generate Electron Density Maps

Generate one or more electron density maps from a molecular structure and its corresponding X-ray reflection data.

- Model Maps
- Annealed Omit Maps
- Composite Omit Maps
- Customize the map generation parameters.
- Adjust the definition of the reflection data limits.
- Optimize the reflection data test set.
- Automatically execute multiple methods of molecular typing using CHARMm based XPROLIG.
- Use client side interactive tools to fit ligand coordinates to your newly generated electron density maps

Pick Waters

- Automatically search through unoccupied density and detect water molecules based on customizable distance and geometry criteria.
- Refine newly placed waters using coordinate minimization and B-factor strategies.
- Generate an electron density map of the final solvated system.

Place Ligands

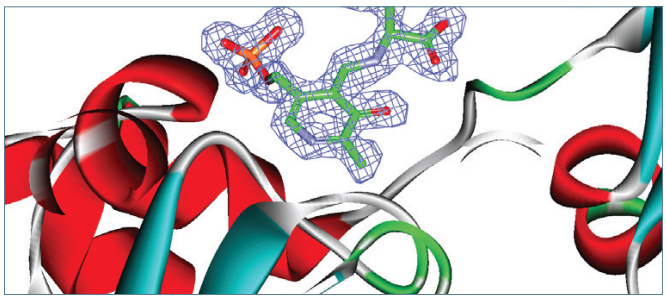
Automatically place ligands into unoccupied electron density.

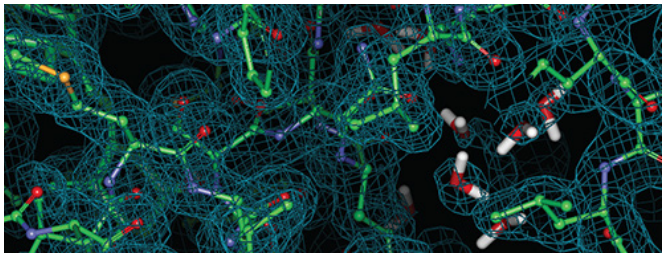
- Site Search: Search for plausible ligand locations by detecting and ranking unoccupied electron density.
- Conformational Search: Generate ligand conformations and rank them according to their fit to the electron density.
- Real-Space Refinement: Automatically optimize the position of the ligand using real-space fitting techniques to improve the overall fit to the density.
- Accurately place multiple ligands to a single receptor suspected of having multiple ligands bound.

EXECUTE REFINEMENT CASCADES

Perform a series of thorough refinement steps on a molecular structure such as:

- Rigid Body Minimization
- Simulated Annealing
- Coordinate Minimization
- Group B-factor Minimization
- Individual B-factor Minimization
- Residue B-factor Minimization
- Generate Electron Density Maps
- Create customized refinement strategies tailored towards your experiment.





Validate Model Molecules

- Perform a diverse series of structural checks in order to ensure the integrity of the protein structure.
- Monitor deviations from known values gathered from high-resolution crystal structures.
- Choose from partially refined, fully refined, or high resolution protein models.

CAPABILITIES

- Use interactive and semi-automated tools to speed up the model-building stage of crystallographic structure determination.
- Manually set the side-chain conformation of a selected residue based on rotamer library.
- Refine an X-ray structure by manually adding atoms, water molecules, or residues. Other abilities include:
  - Grid searching about torsions.
  - Torsion-angle real-space gradient refinement.
  - Monte Carlo fitting
- Manipulate conformations, mutate amino acids, and fit to the electron density.
- Search and evaluate the suitability of different side-chain rotamers in a 3D protein structure.

EXAMPLE PROTOCOLS

- Molecular replacement and X-ray refinement cascade.
- Building new BIOVIA Pipeline Pilot components from CNX scripts.
- Crystal Neighbor generation.
- Full structure solution process of protein-ligand complexes.
  - Molecular replacement and refinement
  - CHARMm based ligand minimization
  - Ligand placement and refinement
  - Water picking and refinement

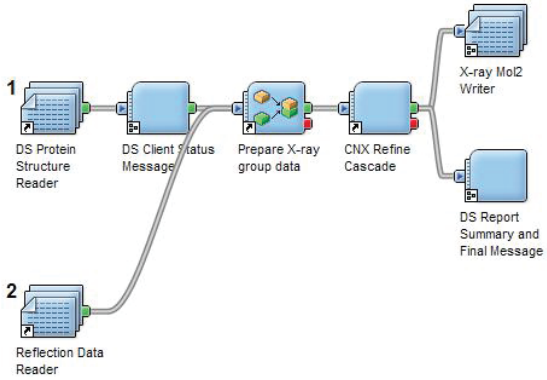
INTEGRATION

CNX

- Integrates X-ray diffraction and NMR spectroscopic data with molecular mechanics, dynamics, and energy minimization.
- Provides a flexible multilevel hierarchical approach for the most commonly used algorithms in macromolecular structure determination.
- Extends the capabilities of the widely used programs X-PLOR and CNS.

BIOVIA Pipeline Pilot

- The industry standard for data pipelining methods.
- Development of X-ray refinement jobs without the need to edit scripts.
- Flexibility to create new workflows by "plug and play" enablement.
- Automation of complex processes.
- Client/Server architecture coupled with close integration to the DS Client.



OTHER CAPABILITIES

Protein Databank

- A standard means of information exchange in macromolecular structure determination.
- Mine the PDB databank via protocol with a specific query.
- Search using protocols specifically for X-ray applications, fragment based design, structure based design, etc.

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

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