

Validated methodology for placement and refinement of ligands

Interface to CNX for refinement of protein-ligand complexes

Fully automated and interactive tools for refinement of backbone and side chain atoms into electron density

X-BUILD

X-BUILD combines functionality previously available in X-LIGAND and X-BUILD. As such, X-BUILD is a powerful drug discovery tool that automatically fits ligand molecules to electron density maps of protein-ligand complexes. The software combines advanced algorithms for rapid conformational analysis, geometry regularization, and torsional- and all-atom real-space refinement. You can fit ligands in seconds, thereby significantly increasing your laboratory's productivity. X-BUILD can also be used to build and refine a protein model into electron density, with options for fully automated and interactive building.

Structure-based drug design relies heavily on crystallography as a practical means of further understanding a protein's structure and function. X-ray crystallography provides insights at the molecular level into protein-ligand interactions, and it suggests structure-based modifications of existing compounds. X-BUILD allows you to rapidly evaluate the detailed information available from careful fitting and refinement of crystallographic data. This contributes to your drug discovery process by quickly providing valuable information about where and how a ligand binds. X-BUILD requires only an electron density map, a set of previously solved protein coordinates, and one or more sets of ligand coordinates in any conformation. Using X-BUILD's simple and intuitive application palette, you can automatically fit your ligand in a matter of seconds.

X-BUILD also contains a rich collection of innovative tools designed specifically to assist you in building macromolecular structures into electron density maps¹. X-BUILD is closely linked with X-AUTOFIT, Accelrys' *de novo* map tracing module. X-BUILD contains all the functionality normally associated with electron density fitting programs, plus an additional collection of innovative tools. A key feature of Accelrys' X-ray crystallographic software is that it has been developed in constant collaboration with active crystallographic groups, which has thereby led to a set of organized, streamlined applications that are geared precisely to the needs of crystallographers.

About the Software

Through automation², X-BUILD eliminates the tedious task of manually fitting your ligand to an electron density map. X-BUILD carries out all the steps involved in building a ligand into electron density maps. It:

- searches the map for all regions of unsatisfied electron density and sorts the search findings in order of decreasing volume
- fits the ligand to the first site in its current conformation, which can be viewed by a single mouse-click
- searches the ligand conformational space (at thousands of conformations per second) to find the best fit to density for the ligand; X-BUILD also retains the best twenty conformations so that you can select alternate conformations from the list of solutions
- refines the ligand into the electron density map
- allows the placement of multiple ligands in one calculation

Despite being fully automated, X-LIGAND also gives you the option to manually fit the ligand by allowing you to maneuver the ligand by rotation or turning it through 180 degrees. This enables you to test possible conformations visually.

Real Space Torsion Angle Refinement of Ligands

By default, X-LIGAND refines the model using Real Space Torsion Angle Refinement to produce a final fitted ligand. The advantage of Torsion Angle Refinement is that there are fewer parameters to refine, which significantly speeds up the fitting process. Also, the density fit surface, as a function of the number of parameters, is considerably less complex than with other refinement methods. This means the radius of convergence is much higher with torsion angle refinement, and, therefore the sensitivity and accuracy is greater.

Grid Search and Monte Carlo Search Methods for Ligands

If there are a large number of internal degrees of freedom, X-AUTOFIT uses a Monte Carlo search method or an exhaustive grid search. These refinement methods can search large conformational spaces and are used as initial search methods before employing the gradient refinement method, which gives a more precise solution for fitting a ligand to an electron density map. Once you have fit the ligand, you can easily generate parameter and topology files that enable you to further refine the complex using structure refinement software.

Real Space Refinement of Protein Models

For the protein model building process, X-BUILD features real space refinement using grid, gradient, and Monte Carlo algorithms. Each algorithm is used in different model building functions, leading to maximum productivity in electron density fitting.

Grid refinement searches all possible conformations for a very limited number of torsion angles. The same solution is always found regardless of the starting conformation, hence, the radius of conversion is only limited by the size of the residue.

X-BUILD uses gradient refinement when the starting positions of the coordinates are within the radius of convergence (2\AA) of the map position algorithm. The gradient refinement method moves atoms towards electron density regions up to 2\AA away, which is four times more sensitive than reciprocal space refinement. This approach is particularly effective for fitting regions of structures where the density is reasonably well defined.

X-BUILD employs Monte Carlo refinement for loop and terminal fitting in proteins where there is some density, but it is uncertain where the chain should be built. It is common that most loop structures are indeterminate at the initial stages of refinement, making this type of algorithm a very powerful modeling tool. Hence, significant time is saved in the overall process of crystal structure determination.

Powerful Regularization of Geometry

X-BUILD includes a fast interactive regularization routine that optionally optimizes non-bond interactions, as well as the geometry of the protein. The implementation is very rapid, making it possible for the user to drag atoms in the molecular structure while the regularizer continues to maintain proper geometry.

Ramachandran Plot During Building Process

X-BUILD has a Ramachandran plot that is continuously updated. If editing affects the backbone atoms, Ramachandran angles are displayed only for the affected residues. You can therefore edit backbone torsion while simultaneously observing the effect on the 2 phi/psi angle pairs. You can pick a plot, and the display will move directly to the picked residue.

Text Editor

You can label any 3D point in the display with a text string, and return to this position later. This is a very useful tool for marking areas of interest or pointing to earlier work. It is also possible to load pre-defined text strings, such as termini, into the text editor. The text editor feature allows you to move around your structure quickly, thereby speeding up the whole model building and editing process.

Validation Tools

X-BUILD's validation process searches for areas with poor or invalid geometry, and provides a hydrogen bond check. If the application finds any errors (bad planes, chiral and prochiral centers, or improper hydrogen bonding) it flags the position of the error with a text string. X-BUILD automatically corrects nomenclature errors that are possible with molecules such as tyrosine, phenylalanine, aspartamine, and glutamine, in accordance with IUPAC standards.

Features

Ligand Fitting Features

- Automatic identification of unsatisfied electron density
- Novel methodology for placement and refinement of ligands
- Option to fit-in-stages or to fix specific atoms in the ligand
- Automatic set up of CNX topology files of protein-ligand complexes
- Automatic assignment of sequence to the C α trace

Model Building Features

- Fully automated tool steps through the structure and fits the main chain and side chain atoms into density

- Performs fast geometry regularization with optional fixed atoms
- Fits side chains and main chains quickly by real space angle refinement and interactive moving of atoms
- Uses Monte Carlo refinement for fitting loops and termini by real space angle refinement
- Full torsion angle refinement protocol
- Adds, deletes, and mutates residues and alternate conformations
- Full support for nucleic acids (RNA, DNA and hybrids)
- Rebuilds residues with undefined or missing atoms
- Manually edits atoms, zones, chi angles, peptideplanes, and termini
- Places side chains using rotamer libraries
- Automatic generation and update of symmetry atoms

Complementary Software

- X-AUTOFIT, a set of tools that let users go from *de novo* electron density maps to sequence-assigned C α trace with only a few mouse clicks; includes three fully automated C α tracing options (one for high- resolution structures and two for low-resolution structures) and a fully automated sequence assignment.
- X-SOLVATE for rapid searching and placement of water molecules into an electron density map
- CNX for x-ray and NMR structure determination
- CHARMM for simulation of biological macromolecules
- MODELER for automatic homology model generation

References

1. Oldfield, T.J., "A Number of Real-Space Torsion-Angle Refinement Techniques for Proteins, Nucleic Acids, Ligands and Solvent," *Acta Cryst.*, **2001**, D57, 82-94.
2. Oldfield, T.J., "X-LIGAND: an Application for the Automated Addition of Flexible Ligands into Electron Density" *Acta Cryst.* **2001**, D57, 696-705.

System Requirements:

QUANTA runs on Linux and SGI work stations.

Dial Box is supported for QUANTA on both the Linux and SGI IRIX platforms.

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