

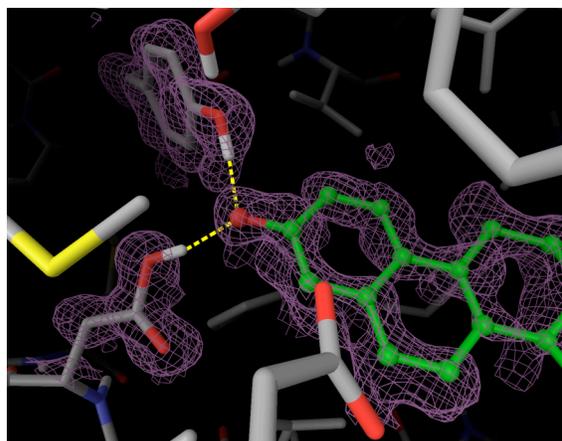
PrimeX

A comprehensive package for accurate protein crystal structure refinement

The prevailing geometric restraints employed in protein crystallography apply experimental bond length and angle terms as well as other restraint terms that have been subsequently added. However, some potential issues arise when refined structures are used in downstream computational modeling. For example, peptide planarity may be over-restrained while close contacts may be under-restrained when compared to better-balanced, all-atom force fields.

Two key characteristics of protein crystal structures that could affect the accuracy of subsequent structure-based modeling are:

- High-energy contacts interfere with computational chemistry calculations, and are often removed by the application of restrained energy minimization to the crystal structure; the danger with this procedure is the introduction of changes in the structure not supported by the X-ray data.
- Most protein crystal structures at typical resolutions do not include hydrogens in the model, which must be added after the end of refinement for many molecular mechanics calculations.



PrimeX provides a full complement of both graphics and refinement tools. Shown here, the X-ray crystal structure of ketosteroid isomerase complexed with equilenin.

Traditionally, attempts to remediate the aforementioned issues are done after refinement, which shifts the control of structural results away from the scientists who are most familiar with the interpretation of diffraction experiments. PrimeX directly addresses these concerns by restraining protein geometry to OPLS-AA (one of the most accurate and widely-deployed force fields for studying protein/ligand systems) during X-ray refinement, and by adding hydrogens during refinement and fully accounting for their existence in all energy computations. Furthermore, just as the inclusion of hydrogen atoms provides

important information for structure validation of refinement results, PrimeX also features improved accounting of non-bonded interactions during refinement, which are central to understanding ligand binding. Thus, PrimeX provides a complete environment that facilitates refinement and produces accurate structures suitable for further computational modeling.

Obtaining the best structure for drug discovery

PrimeX performs refinement of protein crystal structures from initial model to finished coordinates. Rigid-body refinement, individual coordinate and B-factor refinement, and grouped occupancy refinement can be performed in reciprocal space, with maximum likelihood and least-squares targets. Simulated annealing refinement is also available. Real space refinement tasks build and optimize loops, fit side chains, and facilitate the placement of water and small molecules. Protein structure validation tools evaluate molecular geometry and model fit to electron density.

Important features that distinguish PrimeX from other X-ray refinement packages include:

- Ability to build loops up to 40-residues in length, using technologies in the well-validated Prime protein modeling program and guided by electron density fit
- Placement of ligands and other small molecules into electron density using technologies in the Glide docking program, which has demonstrated superior accuracy in ligand-receptor docking
- Simulated annealing refinement
- Choices of minimizers, including conjugate gradient, truncated Newton, and quasi-Newton (LBFGS), to optimize performance and accuracy
- Novel application of the OPLS-AA force field as restraints during refinement
- Automatic parameter generation for ligands and other small molecules, as well as modified residues
- Automated addition and treatment of hydrogens that are consistent with the physical chemistry as prescribed by the OPLS-AA force field
- An intuitive user interface integrated into Maestro with step-by-step organization of refinement statistics in the Project Table and easy analysis of protein structure geometry through interactive tables and plots
- Added control and customizable operations through command-line input as well as scripting with Python

PrimeX provides crystallographers state-of-the-art computational technologies to refine protein structures that are immediately ready for all computational simulations.

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