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Automated Validation of Ligand Fitness Using "Difference of Difference" Analysis. Brian Kelley, James Nettles, OpenEye Scientific, 3600 Cerrillos Rd., Suite 1107, Santa Fe, NM 87507 USA.

Current techniques that are used to fit ligands within unoccupied electron density of protein complexes range from manually fitting rigid conformers by eye to automated fitting with conformational flexibility. The techniques for validating these poses primarily rely upon choosing a low energy conformer, and/or selection of a biologically feasible binding mode. Subsequent refinement of the complex is biased by the initial pose selection.

We propose an automated validation technique to be used prior or post refinement. Given multiple poses, it ranks them by Fourier difference analysis in the proposed active site. The efficacy of our "difference of difference" method is illustrated with examples of difficult ligands or low resolution data. Our method provides a quantitative measure of ligand fitness based upon the diffraction data as well as the protein interaction scoring of the model.