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Exploring binding site flexibility using a library of binding site models; tools for superposition, classification and morphing with molecular graphics

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A geometry force field[1] was used to *optimize* 3500 PDB protein-ligand complexes of moderate X-ray quality. The *optimized* models had similar energies and geometric profiles to those found in atomic resolution X-ray models. To explore the relationship between ligand structure and binding site geometry, several tools were developed. A superposition program, SupPro, automatically superimposes pairs of complexes using alpha carbons of amino acids close to the ligand. The program reports differences in amino acid sequence, backbone RMSD, amino acid rotamer, ligand 2D-structural difference. When applied to a large set of models, a table listing these differences for each pair of complexes can be generated. The table can be used to create clusters of models with defined characteristics such as similarity of backbone geometry. A second tool gives a molecular graphics display of binding site differences by morphing pairs of complexes. Preliminary findings for thrombin and HIV protease illustrate these applications. Thrombin has a fairly stable backbone but some amino acids show limited flexibility. With HIV protease short segments of the backbone are flexible and there are at least 8 "labile" amino acid side-chains which undergo torsion jumps to alternative conformers.

Biography

Colin McMartin owns a computational soft-ware company, FLO/QXP, which specializes in force field development/application. A recent publication based on atomic resolution protein crystal geometries describes a new geometry force field as well as methods for developing complete models with explicit water and hydrogen bond networks suitable for structure based design.

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