MS11-O4 Protein-ligand interaction energy for crystallographic model building and validation

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As the number of crystallographic studies undertaken by non-experts is increasing, the availability of powerful validation techniques to verify the correctness of built models before their deposition in the PDB is essential. While for protein models existing approaches allow detection of many classes of errors, for ligand-protein structures the validation protocols are less well developed and the electron density is often difficult to interpret.

We propose a new addition to the crystallographic ligand building in electron density maps that is based on the estimation of the inter-molecular energy of the ligand-protein complex. We will demonstrate that taking into account three major energetic terms - van der Waals, hydrogen-bonding and electrostatic interactions - helps enhance the interpretation of electron density maps. During ligand fitting the method allows to identify the ligand conformation with the most plausible ligand-protein contacts and the lowest energy. The method can also be applied for validation of fitted ligands or deposited protein-ligand complexes and can be used as additional scoring criterion for guessing the ligand identity in difference electron density maps.

Keywords: inter-molecular energy, crystallographic model building, validation

MS11-O5 DipSpace and DipCheck: A Distance Geometry-Based Description of Protein Main-Chain Conformation

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The knowledge of the structures of biological macromolecules is imperative for the understanding of their function in cellular processes and their role in human diseases. Deciphering and validating these structures is therefore essential for biological research.

By searching for a convenient notation of polypeptide conformation, Ramachandran *et al.* suggested the use of two main-chain torsion angles, φ and ψ, which provide elegant description of protein local conformational space. However, a 2D description of the polypeptide conformational space is a simplification and does not account for the natural variation of the interatomic and angle-bonded distances of the protein backbone. It also lacks the information about the stretched geometry around the Cα atom: the stretching angle τ. Therefore, validation methods such as WHAT_CHECK or MolProbity check for the Ramachandran angles as well as for the stretching angles, bond angles, bond lengths and the possibility for clashes.

Here, we propose a new distance-based 3D space for the description of protein polypeptide conformation, at a given $C\alpha_i$ position using a 5-atom representation of a dipeptide unit ($C\alpha_{i-1}$-O_{i-1}-$C\alpha_i$-O_i-$C\alpha_{i+1}$). We consider the apparent planarity of the trans-peptide unit, which arises from the fact that the almost double-bonded nature of the peptide bond forces the ω torsion angle to be around 180°. The polypeptide chain can thus be seen as a set of connected peptide planes defined by the positions of its $C\alpha_i$, O_i and $C\alpha_{i+1}$ atoms. T

he method is based on the premise that molecular conformation can be defined by the relative position of atoms in the 3D space and on the chirality of asymmetric atomic groups, and accounts for all conformations that a dipeptide unit can adopt as well as for the natural variations of bond lengths and bond angles. The resulting Euclidian orthogonal 3D space, DipSpace, in combination with a chirality measure, allows description of protein stereochemistry and points to residues in an unusual conformation which may not be detectable with other approaches. The method was implemented within a tool, DipCheck, whose application to the validation of protein models will be demonstrated.

Keywords: validatio, backbone description, distance geometry