PDZ DOMAIN SIMILARITY AND LIGAND SPECIFICITY

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The large number of PDZ domains, along with the variety of their interactions and the fast growing amount of often conflicting experimental data regarding binding specificity make their classification a disputed subject across the scientific community.

We propose to study the similarity of PDZ domain proteins using reduced dimensionality representations of proteins. Two-dimensional maps were generated for 139 PDZ domains using a Monte Carlo - like technique. Similarity between proteins was computed based on the similarity of their respective two-dimensional maps. The proteins were compared on amino acid hydrophobicity, residue-replacement ability and side chain conformation. Based on the similarity scores we proposed a new objective classification of PDZ domains that accounts for both three and uni-dimensional features. The advantages of the described method are speed, ease in choosing the comparison criteria and ability to combine structural and physico-chemical properties.

PDZ domain ligand specificity was studied using molecular dynamics simulations. A representative set of 20 proteins bound to 3 different ligands each, was modelled using AMBER 10.0. The binding free energy was computed and further decomposed on a per residue basis. The results show the contribution of each residue to the binding energy. It can be observed that there are no long-range electrostatic interactions and that the hydrogen bond network is formed entirely in the PDZ domain-binding groove. The dynamics of the modelled complexes was assessed by the residue's b-factor value. Comparison of the b-factor pattern in various complexes of the same protein indicates a strong correlation between the complex dynamic and the binding free energy. It also pin points the exact residues that contribute simultaneously with significant entropic and enthalpic terms to protein ligand interaction and determine the specificity of PDZ domains.

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