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PocketFEATURE: Using Multiple Microenvironments to Find Similar Ligand-Binding Sites

Small molecule drugs may interact with many proteins. Some of these interactions may cause unexpected effects, including side effects or potentially useful therapeutic effects. One way to predict these effects is to analyze the three-dimensional structure of target proteins, and identify new binding sites for small molecule drugs. Several methods have been proposed for predicting new binding sites, relying on geometric and functional complementarity of the sites and the small molecules.

Stanford researchers have come up with an algorithm that seeks similar microenvironments within two binding sites, and assesses overall binding site similarity by the presence of multiple shared micro environments. PocketFEATURE is a new method for identifying novel protein-drug interactions. It seeks similar microenvironments within two binding sites, and assesses overall binding site similarity by the presence of multiple shared microenvironments. The method has relatively weak geometric requirements (to allow for conformational change or dynamics in both the ligand and the pocket) and uses multiple biophysical and biochemical measures to characterize the microenvironments (to allow for diverse modes of ligand binding). It has proved that geometric flexibility is useful for effectively comparing sites.

Applications

- The method can be applied to compare drug-binding sites. The recognition of cryptic drug-binding sites in protein structures is important for understanding off-target side effects and for recognizing potential new indications for existing drugs.

Advantages

- PocketFEATURE can better discriminate sites that bind similar ligands from those that do not. It can recognize FAD-binding sites on a proteome scale with Area Under the Curve (AUC) of 92%.
- PocketFEATURE can also recognizes evolutionarily distant relationships, and predicts unexpected shared ligand binding.

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