[P13] PPIome – 3D mapping of protein-protein interfaces: Druggable cavity detection and ligand design

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Modulating protein-protein interactions by low molecular-weight ligands is a novel and promising approach in drug discovery, opening novel therapeutic avenues and extending the scope of applicability of currently known macromolecular targets. Detection and characterization of protein-protein interfaces (PPi) is a key but at the moment there are few tools to study protein-protein interfaces. Nowadays we can only detect a PPi but not characterize their properties for drug design.

Thus our work is to develop a tool which can analyze and characterize PPis. The development of this software contains three main parts. We have to detect first the biological interface. In protein structures we can observe two types of interface, biological and crystallographic. It is essential to separate them to work only with the biologically relevant ones. This separation is determined by a machine-learning model generated trained on known data.

Next we characterize interactions between proteins chains with an in-house tool [1]. It describes all non-covalent interactions between two chains by type (hydrogen bond, aromatic interactions, etc …). The final part is the detection of allosteric cavities. We developed a method to detect cavities up to 8 Å around PPis and to calculate a druggability index using Volsite [2]. Detecting a cavity means to determine all possible interactions between a protein and a ligand (not determined). We use a regularly-spaced grid in a buried part of the surface of the protein, each cell of it having a specific property, that we call ligand site. The druggability value is calculated by a Support Vector Machine model. It shows if a cavity can host a drug or not. All these information characterize a protein-protein interaction.

Our project aims at charting, for the first time, the ensemble of all druggable protein-protein interfaces of known 3D structures as well as their allosteric binding sites. With all these data we wish to screen commercial compound libraries to find novel compounds that can interact, stabilize or inhibit protein-protein interactions.

Bibliography:

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2. Desaphy, J., Azdimousa, K., and Rognan, D. J. Chem. Inf. Model., 52 (2012), 2287-2299.