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Navigating the 3D biological space – The bioGPS approach

Lydia Siragusa

Molecular Discovery Limited, UK

The structural characterization of protein binding sites is increasingly important in drug design; navigating through the 3D-proteome space can be useful for techniques such as drug repurposing, ligand activity profile, toxicology, and also for rationalizing the two-sided nature of poly-pharmacology, its benefit in certain therapeutic drug classes and its contribution to side effects. In order to facilitate the exploration of protein binding sites properties we built a cavity database extracted from all the Protein Data Bank (PDB) protein structures, called 'BioPockDB'. The total amount of protein cavities is about 676.347, related to 103.779 structures. Each cavity was characterized by using the GRID Molecular Interaction Fields (MIFs) in order to evaluate the type and the energy of interaction that a cavity is able of having with a putative target. A semi-automated approach, called BioGPS, which combines MIFs and pharmacophoric fingerprints has been used to navigate the 'pocketome' database BioPockDB. BioGPS comprises the automatic preparation of protein structure data, identification of binding sites, and subsequent protein-protein and ligand-protein comparison by aligning their 3D structures and directly comparing the MIFs. Chemometric approaches are included to reduce the complexity of the resulting data on large datasets, enabling focus on the most relevant information. This approach enables fast and large virtual screening by considering the entire biological information derived from the protein 3D structures, available to the scientific community. Drug repurposing, polypharmacology, off-target effects, chemical and food safety examples demonstrated significant validation of the methodology and illustrated the effectiveness of the approach.

Biography

Lydia Siragusa obtained her PhD degree in Organic Chemistry on November 2013 from University of Perugia. During her PhD, she spent 10 months at the Institute for Research for Biomedicine (IRB) in Barcelona, in the Structural Bioinformatics and Network Biology laboratory. Currently, she is Post-doc at Molecular Discovery Ltd. London, UK. She has ongoing projects with University of Modena and Reggio Emilia, University of Trieste, University of Roma "La sapienza", Technologie Servier (France), Institute for Research for Biomedicine – Barcelona (Spain), Nestlé – Chemical Food Safety – Lausanne (Switzerland).

lidia@chemiome.chm.unipg.it

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