Universitat Pompeu Fabra Barcelona | Master in Bioinformatics for Health Sciences

Master project 2020-2021

Personal Information

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Project

Structural bioinformatics

Project Title:

Ligand optimisation for drug discovery: Use of MDmix for activity cliff prediction

Keywords:

Computer-aided drug design, structure-activity relationships, drug discovery, lead optimisation, binding free energy, molecular dynamics

Summary:

The goal of the Barril's lab is to discover bioactive molecules that bind to unexplored sites of action, exploiting novel mechanisms to achieve a therapeutic effect. To do so, we apply state of the art structure-based drug discovery methods, many of which have been developed in-house. We introduced the use of molecular dynamics with mixed solvents (MDmix) for druggability prediction,[1] as a computational counterpart of binding site detection by solvent screening.[2,3] This strategy turned out to be extremely successful and the method became widely adopted, with different adaptations (see reference [4] for a recent review). Since then, we have explored and extended the applicability of the method, describing its relationship with protein flexibility,[5] demonstrating its performance in mapping binding hot spots on protein surfaces and predicting water displaceability,[6] or as a guide in docking.[7] An open-source software was produced to help other users adopting the technique: http://mdmix.sourceforge.net Some preliminary work indicates that MDmix can also be used in predicting binding free energies of protein-ligand complexes.[7] In this project we will investigate its efficacy in predicting activity cliffs (i.e. pairs of structurally similar compounds presenting large potency difference). In medicinal chemistry, activity cliffs are crucial in systematic structure− activity relationship (SAR) analysis to identify structural modifications that determine SAR characteristics [8]. An analysis of a large set of matched molecular pairs compiled from the literature[4,5] and already available in our lab will be performed, comparing the performance of MDmix with other computational tools. This project is synergistic with other projects in our lab, and will benefit from substantial previous work and of close collaboration with other group members.

References:

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for Structure-Based Drug Design. J. Chem. Theory Comput. 10, 2608–14 (2014). 6. D. Alvarez-Garcia, X. Barril, Molecular simulations with solvent competition quantify water displaceability and provide accurate interaction maps of protein binding sites. J. Med. Chem. 57, 8530–9 (2014). 7. J. P. Arcon et al., Molecular Dynamics in Mixed Solvents Reveals Protein-Ligand Interactions, Improves Docking, and Allows Accurate Binding Free Energy Predictions. J. Chem. Inf. Model. 57, 846–863 (2017). 8. A. M. Wassermann, M. Wawer, J. Bajorath, Activity Landscape Representations for Structure−Activity Relationship Analysis. J. Med. Chem. 53, 8209–8223 (2010). 9. Y. Hu, N. Furtmann, M. Gütschow, J. Bajorath, Systematic identification and classification of three-dimensional activity cliffs. J. Chem. Inf. Model. 52, 1490–8 (2012). 10. X. Hu, Y. Hu, M. Vogt, D. Stumpfe, J. Bajorath, MMP-Cliffs: systematic identification of activity cliffs on the basis of matched molecular pairs. J. Chem. Inf. Model. 52, 1138–45 (2012).

Expected skills::

molecular dynamics, protein-ligand docking, structure-based drug discovery

Possibility of funding::

To be discussed

Possible continuity with PhD: :

To be discussed

Comments:

The group will offer a fellowship (“Beca de col·laboració”) through the Fundació Bosch i Gimpera, for a period of 6 to 12 months. The fellowship is legally capped at 617€ per month. (Subject to funds availability).