Universitat Pompeu Fabra Barcelona

Master in Bioinformatics for Health Sciences

Master project 2021-2022

Personal Information

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Project

Structural bioinformatics

Project Title:

Enhanced Sampling Molecular Dynamics for Virtual Screening Applications

Keywords:

Computer-aided drug discovery, virtual screening, binding kinetics, binding free energy, molecular dynamics

Summary:

The goal of the Barril's lab is to discover first-in-class bioactive molecules, with special emphasis on non-standard mechanisms of action (e.g. allosterism, protein-protein glue). 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 Dynamic Undocking (DUck), a very efficient form of steered molecular dynamics.[1] The method can provide a fast approximation to protein-ligand dissociation rates (k-1),[2] reveal the structural stability of the complex,[3] or be used to predict binding modes.[4] Most importantly, it is sufficiently fast that it can be used as a post-docking tool in virtual screening (VS) applications, removing up to 80% of docking false positives.[1] To further improve the VS success rate, we are developing a complementary tool (LigBinder), that will be applied in cascade, after docking and DUck. LigBinder is a particular implementation of biased molecular dynamics to provide a fast estimate of the protein-ligand association rates (k1). In this project you will validate LigBinder, first for on-rate prediction, comparing with experimental data.[5] Then, in prospective VS applications. This project is synergistic with other projects in our lab and will benefit from substantial previous work and close collaboration with other group members.

References:

1. Ruiz-Carmona, S., Schmidtke, P., Luque, F. J., Baker, L., Matassova, N., Davis, B., Roughley, S., Murray, J., Hubbard, R., & Barril, X. (2017). Dynamic undocking and the quasi-bound state as tools for drug discovery. Nature Chemistry, 9(3), 201–206. https://doi.org/10.1038/nchem.2660 2. Schmidtke, P., Luque, F. J., Murray, J. B., & Barril, X. (2011). Shielded hydrogen bonds as structural determinants of binding kinetics: application in drug design. Journal of the American Chemical Society, 133(46), 18903–18910. https://doi.org/10.1021/ja207494u 3. Majewski, M., Ruiz-Carmona, S., & Barril, X. (2019). An investigation of structural stability in protein-ligand complexes reveals the balance between order and disorder. Communications Chemistry, 2(1). https://doi.org/10.1038/s42004-019-0205-5 4. Majewski, M., & Barril, X. (2020). Structural Stability Predicts the Binding Mode of Protein-Ligand Complexes. Journal of Chemical Information and Modeling, 60(3), 1644–1651. https://doi.org/10.1021/acs.jcim.9b01062 5. Kokh, D. B., Amaral, M., Bomke, J., Grädler, U., Musil, D., Buchstaller, H.-P., Dreyer, M. K., Frech, M., Lowinski, M., Vallee, F., Bianciotto, M., Rak, A., & Wade, R. C. (2018). Estimation of Drug-Target Residence Times by τ-Random Acceleration Molecular Dynamics Simulations. Journal of Chemical Theory and Computation, 14(7), 3859–3869. https://doi.org/10.1021/acs.jctc.8b00230

Expected skills::

molecular dynamics, structure-based drug discovery

Possibility of funding::

Yes

Possible continuity with PhD: :

To be discussed

Comments:

We are willing to consider other projects in the field of structure-based drug discovery that match your interests and skills. Do not hesitate to get in contact.