uF2D Database Optimization for Fragment Hit Identification using Protein Interaction Patterns

Khelfet, L.[1*], Mao, X.[1], Ansar, S. [1], Bourg, S.[1], Aci-Sèche, S. [1], Bonnet, P.[1]
* lina.khelfet@univ-orleans.fr
[1] *Institute of Organic and Analytical Chemistry (ICOA), Université d'Orléans, CNRS, UMR 7311, F-45067, Pôle Chimie, Orléans, France*

Over the past two decades, Fragment-Based Drug Design (FBDD) has gained significant interest in the discovery of new chemical compounds[1]. By using smaller molecules (usually < 300 Da) as starting points, FBDD enables the design of tailor-optimized drug candidates that cover a broader chemical space[2]. Herein, we introduced universal Frag2Drugs (uF2D), a structure-based *in silico* tool for fragment hit identification based on the repositioning of fragments sharing similar protein interaction patterns. To this end, uF2D relies on a library of three-dimensional fragment local environments derived from co-crystallized protein-ligand complexes. For each fragmented molecular moiety, its local environment is defined by the combination of the 3, 4 and 5 nearest residues within a 4 Å distance cutoff.

On a limited dataset consisting of 314 representative protein-ligand complexes, the tool has successfully repositioned ligand fragments in approximately 90% of cases. However, the current version remains limited by an incomplete database containing multiple fragment-residue interaction files that introduces redundancy, while some inconsistencies also persist across residue-level environments. The present work focuses on improving uF2D through two main developments: (1) updating the database using the Legacy Protein Data Bank (PDB)[3], and (2) rebuilding fragment local environments to ensure greater consistency and structural reliability. In parallel, the database architecture has been redesigned into a single-file format to improve data management and computational efficiency. Altogether, these improvements represent the starting point for enhancing the robustness, scalability, and applicability of the tool for fragment-based drug discovery.

Bibliography :

[1] Xu, W.; Kang, C. J. Med. Chem. 2025, 68, 5000-5004.
[2] Hall, R.J.; Mortenson, P.N.; Murray, C.W. Prog. Biophys. Mol. Biol. 2014, 116, 82-91.
[3] Berman, H. M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T. N., Weissig, H., Shindyalov, I. N., & Bourne, P. E. Nucleic Acids Res., 2000, 28(1), 235-242.