Making the most of crystal polymorphism in fragment-based lead discovery

Alessandro T. Caputo[1], Roberta Ibba[2,3], James D. Cornu[2,4], Benoit Darlot[2], Mario Hensen[2], Colette B. Lipp[2], Gabriele Marcianò[2], Snežana Vasiljević[2], Nicole Zitzmann[2], Pietro Roversi[5,6]

1 Commonwealth Scientific and Industrial Research Organisation, Clayton, VIC, Australia,

2 Biochemistry Department, University of Oxford, Oxford, United Kingdom,

3 Department of Medicine, Surgery and Pharmacy, University of Sassari, Sassari, Italy,

4 Wellcome Trust Centre for Cell Biology, University of Edinburgh, Scotland, United Kingdom,

5 IBBA-CNR Unit of Milano, Institute of Agricultural Biology and Biotechnology, Milano, Italy,

6 Department of Molecular and Cell Biology, Leicester Institute of Structural and Chemical Biology, University of Leicester, Leicester, United Kingdom

Email of alex.caputo@csiro.au

Keywords: UGGT, crystal polymorphism, fragment-based lead discovery

Polymorphism in protein crystals is a regular occurrence and can lead to ambiguities in assignment of point-group symmetry and cell parameters. In fragment screening using X-ray crystallography, many datasets are collected and processed through automated pipelines that involve minimal user intervention. In presence of crystals belonging to different polymorphs, crystal lattice parameters and symmetry can be incorrectly assigned and hamper the subsequent analysis. We describe here a semi-automated procedure for assigning each fragment screen dataset to one of a set of known polymorphs. The protocol is implemented in a series of scripts called CoALLA (crystal polymorph and ligand likelihood-based assignment) [1]. Each dataset is processed and the structure refined in each of the known polymorphs; the polymorph with the lowest refinement R_{free} is then chosen as the most likely one (Fig. 1). Using examples from fragment screens and subsequent hit-to-lead elaboration across a variety of target classes, we illustrate the use of CoALLA to automatically assign polymorphs to large set of fragment screening X-ray diffraction data. The CoALLA protocol can be used for routine assessment of polymorphism in fragment-based lead discovery by X-ray diffraction.
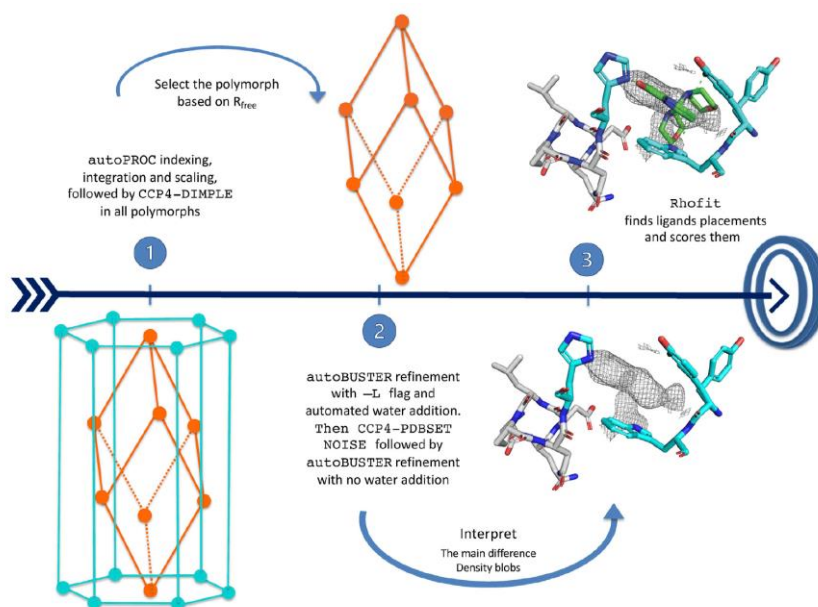
Figure 1. Overview of the CoALLA decision flow

[1] Caputo, A. T., Ibba, R., Cornu, J. D. L., Darlot, B., Hensen, M., Lipp, C. B., Marcianò, G., Vasiljević, S., Zitzmann, N. & Roversi, P. (2022). Frontiers Mol Biosci 9, 960248.