Contribution ID: **22** Type: **Poster**

# New developments in CCP4 to tackle the phase problem in Macromolecular Crystallography

The success of Deepmind in CASP14 has resulted in a new era in structural biology where highly accurate predictions for macromolecular structures can be generated computationally in just a few minutes or less. This has presented new challenges and opportunities to the experimental structural biology community. With the availability of accurate predictions, solving the phase problem in macromolecular crystallography through the molecular replacement technique (MR) has become much more tractable. Despite this, performing MR using a predicted model is not straight forward in many cases. Differences in the relative conformations of domains in a prediction and what has been crystallised, as well as low confidence in predicted residues, can hinder MR and result in difficulties determining a solution. Other problems can also stifle resolving the phases, such as the problem of crystal contamination. Here we present several new applications that have been developed and made available through the CCP4 suite to help with optimising the chances of successful MR when using a predicted model as well as tackling the problem of contamination. MrParse [1] is designed to assist users in searching for and preparing MR search models from both the PDB and the new and vast EBI Alphafold and ESMAtlas prediction databases. Slice'N'Dice [2], an automated MR pipeline, makes use of machine learning clustering algorithms to identify domains or tightly grouped clusters of atoms in a predicted model that are likely to make suitable MR search models. Developed to tackle the problem of contamination, SIMBAD [3] is a sequence-independent automated MR pipeline that can be used to quickly test a processed X-ray dataset for possible contamination during crystallisation.

[1] Simpkin, A. J., Thomas, J. M. H., Keegan, R. M. & Rigden, D. J. (2022). Acta Cryst. D78, 553–559.
[2] Simpkin, A. J., Elliott, L. G., Stevenson, K., Krissinel, E., Rigden, D. & Keegan, R. M. (2022). Slice'N'Dice: Maximising the value of predicted models for structural biologists
[3] Simpkin, A. J., Simkovic, F., Thomas, J. M. H., Savko, M., Lebedev, A., Uski, V., Ballard, C., Wojdyr, M., Wu, R., Sanishvili, R., Xu, Y., Lisa, M.-N., Buschiazzo, A., Shepard, W., Rigden, D. J. & Keegan, R. M. (2018). Acta Cryst. D74, 595–605.

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