MS12-P07 | New covariance-based methods for unconventional MR of transmembrane proteins.

Sanchez Rodriguez, Filomeno (University of Liverpool, Liverpool, GBR); Rigden, Daniel (University of Liverpool, Liverpool, GBR); Keegan, Ronan (CCP4, STFC, Didcot, GBR); Evans, Gwyndaf (CCP4, STFC, Didcot, GBR); Vollmar, Melanie (CCP4, STFC, Didcot, GBR)

The most prevalent technique for the solution of the phase problem in macromolecular crystallography is molecular replacement (MR). In most cases, selection of a suitable search model, typically a solved structure homologous to the target of interest, is the key limitation of conventional MR. In those cases where no such structure is available, other more challenging and time consuming unconventional MR approaches are used. Nevertheless, recent results suggest that even in those cases where no homologous structures are found for a given target, it may still possible to find suitable search models among these unrelated structures, in the form of regions that share high, albeit local, structural similarity with the target. The challenge then becomes the accurate determination of such search models among all the solved structures.

Here we propose a novel pipeline for the solution of structures of transmembrane proteins, which exploits the latest advances in residue contact predictions for the detection of fragments later to be used as search models. Preliminary data already show that contact predictions play a pivotal role in the process of search model selection: those fragments that better match the contact information predicted for the target tend to constitute a better match. The ultimate aim is to develop a pipeline which would provide valid search models originating from already solved structures, even in those cases where no related structures have been already solved. This would enable solution of these structures without the use of experimental phasing techniques.