

New Structures from Old: Developments in Molecular Replacement

R. J. Read

*Cambridge Institute for Medical Research, University of Cambridge,
Cambridge, United Kingdom*

To solve the three-dimensional crystal structure of a novel protein (or other macromolecule), the crystallographer generally resorts to experimental phasing methods. However, with the exponential increase in the size of the Protein Data Bank, there are fewer novel structures, and there is often a reasonably close homologue of known structure. In this case, the method of molecular replacement can be used to solve the structure; currently about two-thirds of protein structures are solved this way.

The recent growth in the use of molecular replacement is also fueled by increases in the power of the method. By using maximum likelihood-based algorithms implemented in our program Phaser¹, structures can routinely be solved when the best available template has a sequence identity of only about 30%, and in favourable cases structures can be solved with templates sharing less than 20% sequence identity.

It has long been hoped that homology modeling could expand the applicability of molecular replacement even further by improving the quality of templates from distant relatives, but until very recently homology modeling algorithms were not up to the challenge. However, we have shown, in collaboration with David Baker, that homology modeling with the program Rosetta can significantly improve the quality of template structures, whether they are obtained from distant relatives or NMR experiments².

The most striking result shows that it may even be possible to dispense with templates from known structures, at least in favourable cases. An ab initio model obtained by Rosetta without a template (but drawing heavily on the structural

**Proceedings of The Joint 2nd Pacific Rim International
Conference on Protein Science and 4th Asian-Oceania
Human Proteome Organization, Cairns- Australia, 22-26
June 2008**

knowledge accumulated in the PDB) was sufficiently accurate to solve a novel structure by molecular replacement².

1. A.J. McCoy, R.W. Grosse-Kunstleve, P.D. Adams, M.D. Winn, L.C. Storoni & R.J. Read (2007), "Phaser crystallographic software", J. Appl. Cryst. 40, 658-674.
2. B. Qian, S. Raman, R. Das, P. Bradley, A.J. McCoy, R.J. Read & D. Baker (2007), "High-resolution structure prediction and the crystallographic phase problem", Nature 450, 259-264.

**Proceedings of The Joint 2nd Pacific Rim International
Conference on Protein Science and 4th Asian-Oceania
Human Proteome Organization, Cairns- Australia, 22-26
June 2008**
