# New Structures from Old: Developments in Molecular Replacement

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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 Phaser[1], 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 experiments[2].

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

knowledge accumulated in the PDB) was sufficiently accurate to solve a novel structure by molecular replacement[2].

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.

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