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Keywords: plasticity, dynamics, accuracy

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Improving molecular replacement solutions with SHELXE

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The program SHELXE [1],[2] was originally designed for *experimental phasing* of macromolecules followed by improvement of the resulting map by *density modification* using the *sphere of influence* [2] and *free lunch* [3], [4], [5] algorithms. The latest beta-test version iterates between density modification and generation of a *poly-Ala trace* [6], enabling an interpretable map to be obtained from even weaker initial phase information.

This phase information must not necessarily originate from anomalous scattering. An MR solution representing a rather small percentage of the total scattering power can be a sufficient starting point for iterative density modification and poly-Ala tracing in SHELXE, given native data to good resolution.

In small molecule direct methods, a multi-solution approach is often attempted, using random or somewhat better-than-random phases obtained by *Patterson seeding*. By analogy, our approach starting from many potential molecular replacement solutions could be called *MR seeding*. When and if longer chains can be traced (with a correlation coefficient to the native data better than 25%), one can be sure the structure is solved. This approach is also exploited in the program ARCIMBOLDO, [7] where a large number of possible MR solutions for small fragments such as α-helices are expanded with SHELXE running on a computer cluster.

If anomalous data is available, but the anomalous signal is too weak for the immediate location of the anomalously scattering atoms by direct and Patterson methods, a molecular replacement (MR) solution can provide starting phases for the SHELXE density modification. An anomalous map is calculated in order to locate the heavy atoms as starting point for further iterative density modification and poly-Ala tracing. With this MR-SAD approach [8], phase information from anomalous scatterers, molecular replacement and density modification can be combined in SHELXE. Model bias, a major problem with MR, is also substantially reduced.

Here, we will present general guidelines, remarks and examples of these applications of SHELXE, with particular reference to MR-SAD involving native sulfur atoms as the anomalous scatterers.

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New approach to structure determination: Envelop-based Phase Extension

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A new method is proposed to solve the Crystallographic Phase Problem utilizing the protein envelope information[1] obtained from small-angle X-ray scattering (SAXS) or electron-microscopy (EM) data.

The method involves three steps.(1) Once SAXS scattering pattern has been collected, the three-dimensional molecular envelope will be recovered from this one dimensional pattern using the spherical harmonics method or Mont Carlo method. (2) FSEARCH is able to perform a real space search for orientation and translation of envelope within the crystallographic unit cell, which provides low resolution phases for a starting point of phase extension.(3) The last step is to extend low resolution phases to higher resolution ones by applying the genetic algorithm(GA) or iterative-projections method.

Three types of data has been tested as input: coordinate data, real SAXS spherical harmonics data, and calculated solution scattering data.[2] As coordinate input, atoms have been fuzzed to create a mask while spherical harmonics input can be used as envelope directly. Three known protein structures have been used as test models: SOD, Cyclase, and HMG. SOD and Cyclase are crystal structures while HMG is an NMR structure. An Input-Output Algorithm [3] is applied on phase retrieving. Phase errors against known structures are introduced to monitor iterative quality, as well as several other adjustable parameters, aiming on finding out best optimization process that leads to correct structure solution.

In our tests, FSEARCH was able to find the proper orientation and translation of envelope in the crystallographic unit cell. Furthermore, our phase extension program was used to extend low resolution phases to a higher level within an acceptable phase error.

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BORGES a tool to generate customised, secondary structure libraries for phasing

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Macromolecular crystallography is computationally intensive. In the midst of the vertiginous increase in computation speed experienced in the last years, crystallography, unlike modelling, has largely turned its back on the use of massive calculations and large scale parallelisation. In our group, we intend to exploit this aspect to tackle the phase problem with multi-solution methods, relying on the information available in the databases. BORGES is an interactive tool, whose aim is to generate pdb-based, customized, secondary structure fragment libraries, to be used as search fragments by our *ab Initio* crystallographic phasing program ARCIMBOLDO [1], which performs parallel model fragment