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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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Keywords: experimental phasing, molecular replacement, MR-SAD

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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

search with the program PHASER [2] coupled to density modification with the program SHELXE [3] and runs on a grid of computers using CONDOR [4]. This method has been successfully used for ab Initio solution at 2 Å of several previously unknown proteins.

Currently available software, is not suited for the analysis of small fragments, made up of less than 30 residues. Underlying methods are focused on generality, or fold optimization, which is misleading given that in our case the environment is unknown.

ARCIMBOLDO can exploit extremely small fragments as long as they are very precise. BORGES has been conceived so as to identify the most similar fragments to the one requested by the user, but its main aim is to collect the most variable and clustered fragment libraries around the given model, rather than an exact replica. In fact the user may well choose to give as input a predicted model that should be close to a part of the structure but fails to solve it. It is obvious that variation from this point is essential to make solution possible at all.

We are running such a project in cooperation with the firm CATON S.L. and the supercomputer FCSCL in Leon. The increase in computational power provided by the supercomputer environment will allow to fully exploit the implementation of alternative pdb-based search fragments.

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Keywords: computation, macromolecular phasing, databases

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New features in ARCIMBOLDO: a tutorial

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ARCIMBOLDO[1] is a program originally designed to phase macromolecules *Ab Initio* at resolutions as low as 2 Å. It can be downloaded free to academics from (http://chango.ibmb.csic.es/ARCIMBOLDO). This method has successfully phased several previously unknown proteins, in different spacegroups, with up to 2x300 residues in the asymmetric unit. It is based on the combination of localizing small model fragments with PHASER[2], and density modification with SHELXE[3]. Such models consist, for example, in polyalanine alfa-helices, expected to be present in the structures by secondary structure prediction. The method operates on a multisolution basis, as many different structural hypotheses have to be ensembled at early stages, when figures of merit cannot effectively discriminate between correct substructures, eventually leading to a solution, and false ones that will remain unsuccessful. Therefore, the computations are distributed over a grid using CONDOR[4].

The new features implemented ARCIMBOLDO and their use to exploit prior information within different phasing scenarios (*Ab Initio*, low homology models or fold prediction, NMR models, combination with anomalous phasing information, etc) will be illustrated in the format of a tutorial illustrated through various test cases. ARCIMBOLDO is now also adapted to run on the supercomputer Calendula at the FCSCL (http://www.fcsc.es/).

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CCP4 6.2 – New and enhanced software for Protein Crystallography

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CCP4 [1] has been serving the software needs of the protein crystallography community for more than 30 years. In this time the CCP4 Suite of software has been refined through contributions from some of the leading developers in the field of protein crystallographic software and the feedback of both expert and novice users. Today it is a highly comprehensive suite, providing tools and packages covering all aspects from data collection through to structure deposition.

Here we present details of the latest release series of the Suite, version 6.2. This release brings updates to many of the key programs. The latest version of the data processing program Mosflm and its graphical interface, iMosflm are included. The new interface puts emphasis on making the program much more easy to use and guiding the user through each of the steps involved in processing X-ray image data. This release also sees the return of the xia2 automated data processing program, which takes as input a set of raw images and produces a merged MTZ file. Other updates include the Pointless program for Laue group and spacegroup determination, Phaser for experimental phasing, molecular replacement and combining both in its MRSAD function, and Buccaneer for automated model building which now facilitates building using phases derived from molecular replacement. The refinement program Refmac has also been updated with new features including Jelly-body refinement for refinement at low resolution and the use of map sharpening to help refinement.

In addition, some new programs have been incorporated. Most notably Multicomb for multivariate density modification, and Sloop which performs loop building by finding gaps in a chain and using fragments from the Richardson's Top500 library of structures to fill the gaps. CCP4 also aims to enhance its functionality related to the maintenance and use of data on small molecules (ligands). Firstly, a considerably larger library of chemical compounds will be provided with the Suite. Extended search functions will be provided to allow for efficient retrieval of known compounds or their close analogs. Secondly, existing functions for generating restraint data for new ligands will be enhanced by the inclusion of relevant software, such as ProDRG, as well as a new graphics program, jLigand, for the creation and manipulation of ligands.

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