## MS.21.5

*Acta Cryst*. (2008). A**64**, C46

### New developments on CrysFML: Global and local optimization methods

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The library CrysFML is a set of Fortran 95 modules to be used in crystallographic and diffraction computing programs [1]. The purpose of the library is identical to that of CCSL [2], the main difference is in their structure and in the underlying language dialect. In CrysFML modern array syntax and new features of Fortran 95 are used throughout the modules. All object oriented programming techniques already available in Fortran (user-defined types, encapsulation, overload of procedures and functions) are extensively used. Mathematical methods, string utilities, parsing of commands, diffraction data structures, diffraction geometries, all aspects of symmetry and handling of reflections and structure factor calculations are treated in dedicated modules. We shall present an overview of the present status of the library and an example, useful for crystal structure determination using direct space methods, in which the combination of multi-configurational simulated annealing with local optimization will be described.

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[2] Mathewman J.C., Thompson, Brown P.J., J. Appl. Cryst. 1982, 15, 167

Keywords: computational crystallography, algorithms, modelling

## MS.22.1

*Acta Cryst*. (2008). A**64**, C46

### Protein backbone tracing and macromolecular motion by cryo-EM and single particle analysis

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In single particle analysis, electron cryomicrographs provide images of individual macromolecules in snapshots of their solution state. This means any native structural motion exhibited by the system will be represented in the 2-D image data. While such dynamics may not impact measures of resolution, depending on the amount of motion, it can impact the visibility of secondary structure and higher resolution features. Thus to achieve fully resolved high resolution structures, either the molecule must be sufficiently rigid, or the dynamics must be characterized as part of the reconstruction. A number of structures have been published over the last year demonstrating single particle reconstruction's ability to achieve resolutions of ~4 Å, and we have developed techniques for tracing the protein backbone accurately at such resolutions. The next step is developing techniques for simultaneously determining high resolution structure and measuring solution dynamics. Better characterization of dynamics simultaneously permits better resolved structures to be determined. This gives single particle reconstruction the unique ability to study large scale motions in macromolecular assemblies along with structure determination. The same method also permits study of heterogeneous populations of large assemblies which may exist in various states of association. The cost associated with such techniques is that the amount of data and computation required to achieve such results may be one to two orders of magnitude greater than the requirements for a high resolution structure of a rigid molecule. Increasing computational capacity and the development of semi-automated data collection is now permitting these concepts to be realized.

Keywords: electron microscopy analysis, protein motions, single particle analysis

## MS.22.2

*Acta Cryst*. (2008). A**64**, C46

### Backbone structure of the infectious Epsilon15 virus capsid revealed by electron cryomicroscopy

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A half-century after the determination of the first three-dimensional crystal structure of a protein, more than 40,000 structures ranging from single polypeptides to large assemblies have been reported. The challenge for crystallographers, however, remains the growing of a diffracting crystal. Here we report the 4.5Å resolution structure of a 22Mda macromolecular assembly, the capsid of the infectious epsilon15 particle, by single-particle electron cryomicroscopy. From this density map we constructed a complete backbone trace of its major capsid protein, gene product 7 (gp7). The structure reveals a similar protein architecture to that of other tailed double-stranded DNA viruses, even in the absence of detectable sequence similarity. However, the connectivity of the secondary structure elements (topology) in gp7 is unique. Protruding densities are observed around the two-fold axes that cannot be accounted for by gp7. A subsequent proteomic analysis of the whole virus identifies these densities as gp10, a 12kDa protein. Its structure, location and high binding affinity to the capsid indicate that the gp10 dimer functions as a molecular staple between neighbouring capsomeres to ensure the particle's stability. Beyond Epsilon15, this method potentially offers a new approach for modelling the backbone conformations of the protein subunits in other macromolecular assemblies at near-native solution states.

Keywords: cryo-EM, 3-D reconstruction, bacteriophage structure

## MS.22.3

*Acta Cryst*. (2008). A**64**, C46−47

### A new approach to understanding the structure and dynamics of helical polymers

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Helical protein polymers are ubiquitous in biology, yet most have been refractory to high resolution structural studies. Unless a helical polymer has exactly 2, 3, 4 or 6 subunits per turn, it cannot be