

Keynote Lectures

Keywords: electron density models, photocrystallography, intermolecular interactions

KN15

Acta Cryst. (2008). A64, C7

Nanostructure refinement and solution

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A diverse array of complex materials and structures are driving the nanotechnology and molecular biology revolutions. To understand and design these materials, it is essential to perform high precision structural characterization at the nanoscale. Often, even sub-Angstrom changes in inter-atomic bond lengths have profound consequences for the chemistry and functionality of these structure-sensitive materials. Crystallographic methods are the gold standard for atomic structure determination, however a broad and growing class of materials and/or nanophase morphologies do not yield to a crystallographic analysis. The scattering is diffuse and Bragg-peaks become broad and overlapped. This is “the nanostructure problem” which currently has no robust solution. I will discuss recent developments using the atomic pair distribution function (PDF) analysis of x-ray and neutron diffraction data that results in quantitative structural information on the nanoscale. I will describe the data collection and modelling methods that allow this, using a number of examples from materials science, physics and chemistry.

Keywords: nanocrystalline materials, pair distribution function, complex materials structure

KN16

Acta Cryst. (2008). A64, C7

Structural insights into immune defense by the complement system

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The complement system is a regulatory pathway in mammalian plasma and tissues that enables the host to recognize and mark invading pathogens and altered host cells for destruction, while protecting healthy host tissue. We study the large multi-domain proteins and the molecular mechanisms underlying this regulatory pathway. Structures of the large multi-domain proteins (up to 13 domains) of the central opsonization step revealed intricate domain arrangements and marked conformational changes that lead to covalent labelling of the target membrane [1-3]. Most recently, we determined the structures of protein complexes involved in the central amplification and regulatory steps. These data provide unprecedented insights into formation, specificity, activity and regulation of the short-lived (half-life time ~90 s) protease complexes that amplify the complement response. One of the effects of complement activation is lysis of the targeted cell through the formation of 100-Å wide pores in the membrane. The structure of the central domain of human C8α revealed a surprising structural homology to bacterial cholesterol-dependent cytolysins [4]. This similarity indicates a possible mechanism of membrane attack and pore formation of these immune defence proteins.

[1] Janssen, B.J.C. et al. *Nature* 437, 505-511 (2005).

[2] Janssen, B.J.C. et al. *Nature* 444, 213-216 (2006).

[3] Milder, F.J. et al. *Nature Structural and Molecular Biology* 14, 224-228 (2007).

[4] Hadders, M.A. et al., *Science* 317, 1552-1554 (2007).

Keywords: complement immune system, multi-domain plasma proteins, protein complexes

KN17

Acta Cryst. (2008). A64, C7

Some structure property relationships

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The lecture will outline methods and describe instrumentation used to study structure evolution as a function of temperature, time, pressure, light or other external stimuli. It will relate the changes, often subtle, in the molecular structures to the macroscopic properties observed, for example the magnetic, optical and electrical characteristics. One interesting class of compounds that undergo subtle structural transitions that do map closely to their interesting macroscopic properties are the Spin Cross Over compounds, containing primarily, but not exclusively, Fe (II) centres. These bi-stable compounds are of potential commercial application, but we are investigating the various structural types from a fundamental science point of view and from these results, we hope to extrapolate to the design of new materials. The majority of the high resolution experiments described in detail will relate to single-crystal-to-single-crystal transitions.

Keywords: inorganic organic compounds, iron complexes, low temperature single crystal diffraction

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Acta Cryst. (2008). A64, C7-8

Electron diffraction intensities and structure analysis

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Two basic principles for intensity measurement from crystals were known from X-ray crystallography: integrated intensities - and the high resolution “rocking curve”. In electron diffraction the latter was established by P. Goodman in the 1960’s (following earlier work by G. Möllenstedt and others). The convergent beam technique, CBED, was found particularly suited to small, perfect regions of crystals with small unit cells. Precise refinement, including charge distribution, became an option based on extensive dynamical scattering calculations. Crystal symmetries were revealed by inspection of symmetry features in the patterns. Several attempts were made to establish a practical way to collect well-defined integrated intensities from crystals by electron diffraction. In 1994 R. Vincent and P.M. Midgley introduced a precession technique based on a double conical scan in the electron microscope, that emulates the precession camera in X-ray crystallography. It has since been demonstrated that three-dimensional data can be collected by this technique. Dynamical scattering is suppressed to an extent that allows standard crystallographic procedures to be applied with confidence. Dynamical calculations can then be left to a refinement stage. Recent commercial development has made the technique generally available. Relations between these techniques, and with the parallel beam

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techniques utilizing selected area or microdiffraction modes will be discussed. Examples include dispersed metastable phases that are common in alloy systems.

Keywords: electron diffraction, precession technique, precipitate phases

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Acta Cryst. (2008). A64, C8

Combined methods: Small-angle scattering with NMR and crystallography

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Small-angle scattering from macromolecules in solution yields low-resolution structural information that complements higher resolution information from crystallography and NMR. The ever increasing desire to understand more complex and often dynamic biomolecular systems, has brought about a surge in interest in the technique, greatly facilitated by recent developments in sources, instrumentation, and the availability of 3D modelling capabilities. Modelling 3D structures from solution scattering data does not always lead to a uniquely determined solution, and there are inherent limits to the information content of a scattering profile beyond the issue of resolution. The inclusion of scattering data with contrast variation can increase the information content, especially for biomolecular complexes with components having distinct scattering densities. We have combined small-angle X-ray scattering and neutron contrast variation data with crystallographic and NMR results to study protein complexes involved in signalling and regulation; specifically looking at the regulatory mechanisms controlling bacterial responses to environmental signals (1) and the actions of heart muscle proteins (2). In parallel we have been developing methods to improve the accuracy of structural analysis of individual protein structures in solution by co-refinement of NMR and small-angle X-ray scattering data (3). This presentation will describe the strengths and limitations of these approaches in the context of understanding bio-molecular function.

1. Whitten et al (2007) *J. Mol. Biol.* 368, 407.
2. Jeffries et al (2008) *J. Mol. Biol.* 377, 1186.
3. Grishaev et al. (2008) *J. Biomol. NMR* 40, 95.

Keywords: small-angle scattering, neutron contrast variation, combined methods

KN20

Acta Cryst. (2008). A64, C8

Advances in high-pressure neutron scattering

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High pressure is a window to view matter in unusual states. In this talk I will show what neutron scattering is able to contribute to a better understanding of matter under extreme pressures. I will discuss the considerable efforts made recently by various groups to extend the capabilities of high pressure neutron scattering, i.e. to achieve higher pressures and better data quality, and to make it available to a broad scientific community. The methods involved are all based on opposed-anvil techniques which allow sample volumes of up to 100

mm³. I will give a few illustrations which will cover structural studies of molecular systems, both at high and low temperatures, disordered as well as magnetic systems. This talk will be dedicated to the memory of Igor Goncharenko, a pioneer in high pressure neutron scattering who passed away in November 2008.

Keywords: high pressure, neutron scattering, extreme conditions

KN21

Acta Cryst. (2008). A64, C8

Charge flipping

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The talk is a brief review on charge flipping, a recently developed algorithm of *ab initio* structure determination. Its iterative scheme is based on the simplest Fourier cycle, where constraints are alternately prescribed in dual spaces. While the basic Fourier scheme is extremely sensitive to stagnation, charge flipping breaks it by introducing weak perturbations. The name-giving step is the most straightforward example of a fine balance: the sign change of electron density below a small positive threshold simultaneously forces positivity and a nearly orthogonal perturbation of structure factors. The method requires high-resolution data but no other information, like atom types, chemical composition or symmetry. Such a working principle significantly differs from that of classical direct methods and offers complementary applications. The new method has been successfully applied in practice: examples are periodic and aperiodic crystals using single crystal and powder diffraction data measured with X-ray and neutron radiation. Charge flipping can be used in different ways and at different stages of the structure solution process. It can either operate in a truly *ab initio* manner, can be applied to complete a partially known structure, it can check the stability of a solution, but can also be adapted to work as an ingredient of other dual-space schemes. Development of the algorithm is still very active. The list of various improvements will be discussed, as well as future prospects and the availability of user programs where the principles can be put into action. Finally, we emphasize the role of charge flipping in crystallographic teaching, now students can easily write their own code and experience firsthand success. This research was supported by OTKA 67980K.

Keywords: *ab-initio* structure determination, direct methods, software

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Acta Cryst. (2008). A64, C8-9

Neutron protein crystallography, beyond the folding structure of biological macromolecules

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Neutron diffraction provides an experimental method of directly locating hydrogen atoms in proteins, a technique complementary to ultra-high-resolution X-ray diffraction. 1) Three different types of neutron diffractometers for biological macromolecules have been constructed in Japan, France and the U.S.A., and they have been