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The ultimate limit in resolution of protein crystal structures is determined by beam damage. Since electrons are about three orders of magnitude less damaging to biological materials than X-rays, we intend developing electron crystallography as an alternative to X-ray crystallography. Here, we discuss our progress in this endeavour:
Electron diffraction up to 0.2 nm resolution could be observed from 3D protein nano-crystals (up to 200 nm in size) and up to 0.1 nm for pharmaceutical nano-crystals;
By precessing the electron beam, a substantial fraction of spots could be made to fully pass the Ewald sphere, increasing the number of fully recorded reflections, whilst simultaneously reducing the effect of dynamical scattering;
By computer analysis of the spacings of randomly oriented diffraction patterns, we could determine the unit cells;
In favourable crystal settings, we could index the diffraction patterns; we are making progress in indexing all random diffraction patterns.
We anticipate that these steps will ultimately allow us to integrate the observed, indexed reflections, opening the way to full structure determination by cryo-electron diffraction.

Keywords: electron diffraction, structural biology, nanocrystallography

MS.41.3

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Symmetry determinations from electron precession: Comparison and advantages with CBED

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The electron precession technique displays some interesting features connected with the crystal symmetry:
The integrated intensities of the diffracted beams present on electron precession patterns can be used to identify the "ideal" symmetry of the pattern, i.e. the symmetry which takes into account both the position and the intensity. It is shown that this "ideal" symmetry is connected with the Laue class;
The precession patterns exhibit a two-beam behaviour especially at large precession angle meaning that multiple diffractions are strongly reduced. This property can be used to identify the kinematical forbidden reflections due to screw axes and glides planes. It can also be used to detect reflections which exhibit weak differences of intensity. These reflections are very useful when dealing with the study of crystal displaying small symmetry departures;
The patterns display a large number of reflections in the Zero-Order Laue Zone (ZOLZ) but also in the High-order Laue Zone (HOLZ) whose observation allows an easy and sure identification of the shifts and periodicity differences of the reflections located in the HOLZ with respect to the ones located in the ZOLZ. These features are connected with the Bravais lattice and with the glide planes, respectively. A few possible space groups can be identified from all these observations. CBED and LACBED are also valuable techniques to deduce the point and space groups but the experiments are more difficult to perform since they require a perfect alignment of the zone axis and an adapted crystal thickness.

Keywords: electron diffraction, forbidden reflections, crystal symmetry

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Quantitative 3D electron diffraction data by precession and electron rotation methods

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We present a quantitative investigation of data quality using electron precession, compared to standard selected area electron diffraction (SAED), and present the new Electron Rotation Method for collecting 3D electron diffraction data. The SAED pattern of $K_2ONb_{14}O_{35}$ (projection symmetry 4*mm*, *a* = 27.5Å) (left) in the Figure goes to 1.10 Å resolution (h = 25), while the hk0 precession pattern (right) goes to 0.76 Å resolution (h = 36). The total number of unique reflections is doubled for precession compared to SAED. Precession patterns were obtained with SpinningStar from NanoMEGAS on a JEOL 2000CX TEM with a 16-bit CCD-camera and quantified by ELD from Calidris. Rmerge = 5%. The structure was solved by Sir97, both from SAED and from precession data, and refined with SHELX. Metal atom positions were refined; R-value 19% for precession and 28% for SAED. Niobium atoms were on average within 0.04 A from those obtained by X-ray diffraction for the isomorphous $Tl_2ONb_{14}O_{35}$. We are trying to localize the oxygen atoms. Reference: Oleynikov,P. Hovmoeller,S. and Zou,X.D. Precession electron diffraction: observed and calculated intensities. Ultramicroscopy 107 (2007), 523-533

Keywords: electron diffraction, precession, quantification

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Models for simplified treatment of precession electron diffraction

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Precession electron diffraction (PED) is an experimental approach to reducing the severity of dynamical effects in electron diffraction [1]. In PED, the incident beam is tilted along a cone about the zone axis; intensities from all orientations in the cone are integrated. This reduces the number of simultaneously excited beams as well as averaging over many orientations. It will be shown that PED reduces the complexity of the intensities vs. thickness {I(g,t)}, in a statistical sense using principal component analysis. Specifically, the number of parameters necessary to describe all variation within the set {I(g,t)} for a given zone axis is reduced with respect to a direct zone axis orientation. However, this reduction of complexity does not extend to an ability to accurately describe PED I(g,t)'s using accessible parameters such as spatial frequency |g| and structure factor amplitude (as in e.g. kinematical or 2-beam models)[2]. Thus, it is necessary to include at least some details of the interactions among simultaneously excited beams in order to develop anything beyond a fairly crude approximation of PED. This explains the limitations of 2-beam and Blackman models [2,3]. The development of more sophisticated models will be discussed. It will be shown that PED intensities are relatively insensitive to structure factor phases. The phase-insensitivity may provide a basis for close approximation

of PED patterns without full knowledge of the structure, a major step in realizing the goal of inverting PED data to obtain the underlying structure factor amplitudes.

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Keywords: precession electron diffraction, dynamical electron diffraction, electron crystallography

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High-throughput crystallization-to-structure pipeline at RIKEN SPring-8 Center

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A high-throughput crystallization-to-structure pipeline for structural genomics has been developed at Advanced Protein Crystallography Research Group (APCR-group) of RIKEN SPring-8 Center, Japan. The structure determination pipeline includes three elemental technologies for automation developed in RIKEN SPring-8 Center: the automated crystallization and observation robot system TERA; X-ray diffraction data collection using the SPring-8 Precise Automatic Cryosample Exchanger SPACE; automatic X-ray data analysis from phasing to model checking/revision using the Package of Expert Researcher's Operation Network PERON. During five years from 2002, 234 of cryoloop-mountable crystals, 175 of diffraction data sets and 149 of refined structures have been produced from 437 of purified proteins in APCR-group, by seven researchers with assistance of the developed pipeline. Used protocols in this pipeline will be introduced.

Keywords: protein crystallography, structural genomics, automation

MS.42.2

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There and back again: Using simulated diffraction images to optimize data processing by Elves

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Modern data processing automation packages such as Elves work very well with high-quality diffraction data, but it is not surprising that Elves will fail to solve data sets that are of such poor quality that they cannot be solved manually. In between these extremes is a threshold of "solvability" that is critical to understand if we are to formulate optimal data collection strategies and robust data processing algorithms. To this end, a realistic simulation of the entire diffraction experiment (called MLFSOM) was constructed and includes most every source of error, including photon-counting noise, detector read-out noise, shutter jitter and radiation damage. The image files from this simulation were then fed into Elves and the transition between a successful structure determination and a hopeless data set was studied. These tests evaluated the impact of "scanning" individual parameters such as exposure time, crystal size, heavy atom occupancy, mosaic spread, and other experimental parameters. A central result was that the average error in the anomalous difference measurement must be less than the average anomalous signal for structure solution to succeed, but further improvement of the anomalous signal/noise ratio does not improve the structure quality significantly. It was also found that detector read-out noise has negligible impact on anomalous differences, suggesting that dividing MAD/SAD data sets over many more images is advisable to deal with radiation damage. This strategy was tried in practice and found to be superior to conventional MAD/SAD data collection.

Keywords: simulation X-ray diffraction, automatic structure solution, threshold of solvability

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Signal-based data collection: A novel approach to on-site auto-structure determination at SER-CAT

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At SER-CAT, beamline setup, sample handling, sample alignment, data collection strategy, data collection, data reduction, structure solution and data archive are on the verge of full automation. Building on these technologies a new data collection paradigm we term Signal-Based Data Collection (SBDC) is being developed aimed at increasing the success rate of structure determination and overall beamline efficiency. The SBDC approach differs from beamline automation being developed elsewhere in that it is driven by the goal of automatically collecting enough data from one (or more crystals) to ensure that the anomalous scattering signal in the final scaled data is sufficient to solve the structure. Key to our approach, and what differentiates from other developments, is that there is direct feedback from the data reduction process to the data collection process. To achieve our goal we are developing and refining an intelligent software system that allows fully automated data collection and data processing that is integrated with SER-CAT's beamline control and sample mounting systems. This database-driven expert system will monitor data collection and automatically make decisions about the data collection process based on predefined trigger values. The proposed system will also be linked to the SGXPro automated structure determination engine at SER-CAT so that users can leave the beamline with a structure in hand. Details of the implementation of various aspects of the SBDC approach will be presented. Work is supported in part with funds from SER-CAT, the Georgia Research Alliance, the National Institutes of Health (GM62407) and the University of Georgia Research Foundation.

Keywords: automated data collection, monitoring and feedback in data collection, automated on-site structure determination