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Molecular Recognition Principles in Protein-Ligand Interactions as a Prerequisite for the Design of Specific and Selective Leads
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In order to bind to a protein, a ligand has to exhibit correct shape and interaction properties complementary to the residues exposed towards the binding pocket of a target protein. Since protein-ligand binding is a process of mutual molecular recognition, rational drug design is greatly concerned with understanding the principles of molecular recognition. The statistical analysis of geometries of protein-ligand complexes provides a powerful tool to retrieve and correlate information about recognition patterns with respect to protein binding. To efficiently access such data, we have developed Relibase [1,2] as a database system particularly tailored to handle protein-ligand related problems, e.g. the induced adaptation of proteins upon ligand binding, the role of water in the binding process, the mapping of hot-spots of ligand binding or analyzing the versatile molecular recognition properties of functional groups.

The function of proteins is almost invariably linked with the specific recognition of substrates and ligands in well-defined binding pockets. In consequence, proteins of related function should share comparable recognition properties exposed to these pockets. Cavbase has been developed as new module for Relibase that stores protein cavities in terms of simple surface-exposed physicochemical properties [3]. These descriptors allow for fast retrieval of proteins with functional relationships independent of a particular sequence or fold homology. The approach also allows to detect unexpected cross-reactivity of ligands among unrelated proteins. Via the alignment of binding pockets across protein family members, the consensus pattern representative for individual protein families can be extracted and mutually compared. By decomposing binding pockets into elementary sub-pocket motifs the analysis of preferred ligand occupants can be achieved.

Mapping preferred interaction sites in binding pockets in terms of knowledge-based approaches such as SuperStar [4] or DrugScore [5,6] “hot spots” of ligand binding can be elucidated. Such information can be translated in a protein-based pharmacophore hypothesis and serves as guideline for ligand docking and virtual screening [7].

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Keywords: protein-ligand interactions, molecular recognition, drug discovery

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Structural Studies of Macromolecular Complexes: Cytochrome b_6f
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Seeing protein complexes in states relevant to their biological function is one of the challenges of macromolecular crystallography. The integral-membrane cytochrome b_6f complex carries out electron and proton transfer reactions in the photosynthetic membrane of oxygen-evolving photosynthetic organisms, and is the electronic connection between photosystems II and I. The 220-kDa dimeric b_6f complex consists of a total of 16 subunits and 14 chromophores. The 3.0-Å crystal structure [1] was solved by isomorphous replacement and anomalous scattering, with reference to previously determined structures of the extrinsic domains of two subunits. Dimer formation creates two central cavities with access to electron transfer sites for exchange of the lipid-soluble substrate. The most significant finding was an unexpected and novel heme group, bound to the protein by a single thioether bond. Motion of one extrinsic domain between electron-transfer sites within the b_6f complex is suggested by the overall organization of subunits.

Preparation of pure, monodisperse complex and its crystallization required a significant period of testing poorly diffracting crystals to optimize purification and crystallization protocols. In general, crystals of complexes are frequently quite small or imperfect. A synchrotron X-ray beam that can be tailored to the size of a small crystal or to a region of a crystal is optimal for such samples. The GM/CA Collaborative Access Team has developed dual undulator beamlines at the Advanced Photon Source to deliver small X-ray beams and the goniometry to orient and visualize small samples [2].

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Keywords: membrane protein complexes, synchrotron radiation applied to biomedical sciences, photosynthetic proteins

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Metal-Organic Frameworks: Assembly and Crystal Dynamics of Functional Materials
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Many efforts have been made for the design and synthesis of metal-organic frameworks (MOFs) having specific topologies and functions. MOFs containing pores and channels of controllable sizes and shapes can be applied to adsorption and separation processes, ion exchange, catalysis, and sensor technology. An exciting, yet little explored area is the transformation of the structures in the solid state by the input of external stimuli. Retaining single crystallinity even after chemical reaction is relevant to the development of certain devices. We have assembled porous metal-organic frameworks by various synthetic strategies such as 1D-, 2D-, and 3D- network construction from the pre-designed metal and organic molecular building blocks. Some exhibit simultaneously permanent porosity, high H_2 gas sorption capacity, thermal stability, and selective guest binding property. In particular, certain solids respond to the external stimuli, and change their colors and luminescence. In addition, some solids have flexible frameworks and undergo structural transformations, with retention of the single crystallinity, via shrinkage and swelling, sliding, or rotational motion of the molecular components.[1-4]

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Keywords: metal-organic frameworks, crystal dynamics, structure transformation

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Nano Structures Studied by Convergent Beam Electron Diffraction
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Lattice defect and interface analyses by using the large angle technique [1] of convergent-beam electron diffraction are reviewed. The large angle convergent-beam electron diffraction (LACBED) enables us to obtain real- and reciprocal-space information of lattice defects and interfaces.

The technique can determine the shift vector of a stacking fault and the Burgers vector of a dislocation much more reliably than the traditional electron-microscope-image method can. Screw and edge dislocations can be distinguished easily by the technique [2]. The angular change at a twin boundary can be determined with an accuracy of less than 0.1 degree, while a better accuracy than 1 degree is not possible in ordinary or spot electron diffraction.

The high accuracy to the angular change of a crystalline specimen was applied to the studies of strain in multilayers [3]. And then, many strain measurements at the interfaces of various multilayer materials have been successfully conducted. Recent years, strain analysis can be conducted using automatic analysis programs, which take account of dynamical diffraction effects [4].

In the present review, the large angle technique is explained, analyses of stacking faults and dislocations are demonstrated and examples of strain measurements of semiconductor layer materials are presented .

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Keywords: LACBED, lattice defect identification, interface analysis

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Ultrafast Electron Crystallography

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In this talk, we will overview recent advances in crystallography bringing in the dimension of time in what we term ultrafast electron crystallography (UEC). The new approach make it possible to record frames of diffraction at different times and with resolution reaching the picosecond-femtosecond time scale. Examples will be given to recent studies of crystals, interfaces, and macromolecular structures. We will also compare with studies of isolated molecular systems. UEC promises to be a powerful advancement for many applications and we will conclude by highlighting some of the new directions.

Keywords: ultrafast crystallography, interfaces, macromolecules

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Structural Studies of Amyloid

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Numerous soluble proteins convert to insoluble amyloid fibrils having common properties. These fibrils are associated with neurodegenerative diseases, such as Alzheimer's and Parkinson's, and can also be formed in vitro. In the case of the yeast protein Sup35, conversion to amyloid fibrils is associated with a transmissible infection akin to that caused by mammalian prions. A seven-residue peptide segment from Sup35 forms both amyloid fibrils and closely related microcrystals, which reveal the atomic structure of an amyloid spine. It is a double β-sheet, with each sheet formed from parallel segments stacked in-register. Sidechains protruding from the two sheets form a dry, tightly self-complementing steric zipper, bonding the sheets. Within each sheet, every segment is bound to its two neighbouring segments via stacks of both backbone and sidechain H-bonds. The structure illuminates the stability of amyloids as well as their self-seeding characteristic.

Amyloid structure has also presented long-standing, fundamental puzzles of protein structure. These include whether amyloid-forming proteins have two stable states, native and amyloid, and whether all or only part of the native protein refolds as it converts to the amyloid state. We find that a designed amyloid of the well-characterized enzyme ribonuclease A contains native-like molecules capable of enzymatic activity. Also these functional molecular units are formed from a core ribonuclease A domain and a swapped complementary domain. These findings are consistent with the zipper-spine model for amyloid3 in which the fibrils are formed from 3D domain-swapped functional units, retaining native-like structure.

Keywords: amyloid, protein structures, biological macromolecules

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The Surface Structure of Model Catalyst in Action Investigated by X-ray Diffraction

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There are few techniques which allow to investigate surfaces at atmospheric pressures. One of them is surface x-ray diffraction which has detection limits of adsorbed gases bellow one atomic layer. The talk will describe experimental results on the adsorption of CO , H_2 and their reaction to form methane on a Ni (111) single crystal surface in a range of pressures from Ultra High Vacuum to 1 bar. The important role of surface carbide will be discussed . Also, results on the oxidation of CO to CO_2 on Pt(110) surfaces at atmospheric pressures will be reported . The experiments show that Pt oxides are better catalysts than pure Pt and that metastable oxides are formed under reaction conditions.

Keywords: synchrotron X-ray diffraction, heterogeneous catalysis, adsorption

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Strategies and Design Principles in Biomineralization

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Organisms are able to produce mineralized skeletons with complex architectures, having unusual shapes and organization. This is the result of sophisticated strategies that control the design and construction of the materials at all hierarchical levels, from Angstroms to millimeters.

In order to understand the mechanisms used by organisms to build their skeletal materials, we study the various components of the mineralized tissues, the interfaces between them, their structures and relations of structure to function.

The minerals are deposited in a matrix composed of biological macromolecules. Common minerals used are the calcium carbonate polymorphs aragonite and calcite in the form of single crystals or polycrystalline ensembles. Organisms are able to override the crystal natural propensities, and can shape calcite and aragonite almost "at will". These features depend also on the involvement of transient amorphous precursor phases, which transform into single crystals in a slow controlled process [1]. All these properties stem from direct or indirect control of specialized macromolecules, whose sequences, structures and functions are only beginning to be undersood [2].

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