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KN-15

Phasing by SAD and Molecular Replacement in Phaser.

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Phaser is the program we are developing to apply maximum likelihood to phasing macromolecular crystal structures [1]. The current version can solve structures using molecular replacement, single-wavelength anomalous diffraction (SAD), or a combination of the two.
Molecular replacement can place one or more copies of one or more components. Each component can be specified by a single structure or by a superimposed ensemble, which is used as a statistically-weighted average structure. Searches are carried out to maximize rotation and translation likelihood targets, which can take account of the information from previously-placed molecules.
SAD phasing is carried out by maximizing a SAD likelihood target, which accounts for the effect of correlated errors in the plus and minus hands of the Friedel pair [2]. Phasing is initiated from an anomalous substructure, which need not be complete. Log-likelihood-gradient maps provide a sensitive indication of additional sites or the presence of anisotropy.
The substructure for SAD phasing can actually be a set of normal scatterers, such as a protein model obtained by molecular replacement. Even a poor molecular replacement model can be sufficient for log-likelihood-gradient maps to find the anomalous scatterers from weak anomalous differences. Alternatively, the log-likelihood-gradient maps can be used to identify anomalous scatterers at the end of refinement, even if the anomalous signal is too weak to contribute significantly to phasing.

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KN-16

Relevance of X-ray Structure Data to Kinetic Studies.

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Detailed knowledge of the different reaction steps by which many a 'small molecule' chemical process proceed, is of prime importance for understanding the complete reaction system. This knowledge allows subsequent manipulation of the process to ensure better yields, less by-products, and by implication, a smaller carbon footprint.
This presentation deals with a number of model systems in industrial process and metal based drugs chemistry and will discuss the importance of known structures, coupled with the kinetic behaviour, on the reaction mechanisms thereof. The solution behaviour of some homogeneous catalytic processes and model pharmaceuticals will be described, illustrating the importance of the detailed ground state structures as obtained primarily from X-ray diffraction, but integrated with spectroscopic and other techniques [1-7]. Moreover, different activated states, and the utilization of reaction kinetics, coupled with computational techniques, to produce overarching and more holistic perspectives on the complete reaction mechanisms, will be discussed.

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KN-17

Crystallographic studies of P-type ATPase cation pumps .

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P-type ATPase cation pumps energise the biomembranes by establishing and maintaining steep electrochemical gradients. The electrochemical gradients formed are of fundamental importance in physiology as they control ionic conditions in the cell, energise secondary transport and signalling through ion channels. The P-type pumps are essential to all eukaryotes and include for example Na^+,K^+-ATPase, H^+,K^+-ATPase, Ca^{2+}-ATPase and Cu^+-ATPase
From studies of the sarcoplasmic reticulum Ca^{2+}-ATPase we have gained a deep insight on the catalytic mechanisms in formation and breakdown of the phosphoenzyme intermediate and on conformational changes providing the basis of vectorial ion transport. We also gained a signficant insight on the structures of Na+,K+-ATPase and other pumps, and of the regulatory effects of inhibitors, cellular factors and modulatory effects of ATP as probed by biochemistry and electrophysiology.
The crystallographic studies providing our background for analysis of structure-function relationships have challenged us in all aspects of membrane protein crystallography such as in heavy-atom derived phasing from poorly diffracting crystals and model building from low-resolution electorn density maps, although in other cases higher resolution studies revealing putative proton-transport pathways have allowed us to establish new models of function.