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KN13

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Bacterial pathogenesis and peptidoglycan degradation machines

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The bacterial cell wall is comprised of cross-linked strands of peptidoglycan (PG), which encase the entire cytoplasm. A healthy cell wall is critical for survival of bacteria and serves as a docking station for bacterial surface proteins, some of them representing key players in adhesion, colonisation and virulence. Therefore cell wall remodeling is critical in host-pathogen interactions, cell division, virulence, PG recycling and antibiotics resistance. Choline-binding proteins (Cbp) are pneumococcal surface proteins that have received considerable attention because of their versatility, and their sophisticated role in the interaction with host proteins. The three-dimensional structure of Pce (70 KDa), in complex with the reaction product and choline analogs has been solved [1]. We have showed that Pce hydrolyses PAF, a potent lipidic first messenger of inflammatory processes. Besides, the structural analysis indicated that Pce selectively remodels the bacterial surface impairing the ability of host proteins to efficiently bind the bacteria, and would provide a mechanism for pneumococci escaping attack by the host defense system [1].

CbpF (38 KDa) has been solved [2] demonstrating that CbpF inhibit the activity of autolysin LytC and providing the first example of a regulatory system to tune the activity of an autolysin. LytC is involved in the virulence mechanism of fratricide. Pneumococci that are competent for natural genetic transformation kill and lyse non-competent sister cells or members of related species that are present in the same environment. This phenomenon has been termed fratricide. We have reported the functional characterization of the key effector of pneumococcal fratricide CbpD [3] and the crystal structure of LytC in a ternary complex with choline and a PG fragment [4] that explain the activation of LytC by CbpD in fratricide and provide the first structural insights into the critical and central function that LytC plays in pneumococcal virulence.

During homeostasis, including growth, cell wall is simultaneously biosynthesized and degraded. Lytic transglycosylases (LTs) initiate the degradative events on cell wall. The products of LTs are internalized to the cytoplasm, and hydrolised by glucosaminidase NagZ and amidase AmpD. The reaction products of AmpD play roles in both PG recycling events and in an induction event that leads to the expresion of β-lactamase, a key β-lactam antibiotic resistance enzyme. Despite the 3D structure for AmpD enzyme was known by NMR techniques, we have performed crystal structure determination of some LTs and AmpD. Unexpectedly we have observed that AmpD undergoes an activation mechanism from an inactive form (that determined by NMR) to an active form we solved. Changes produced in the activation process are among the largest structural rearrangements ever reported for a single domain protein.

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Keywords: Biocrystallography, Disease, Pathogenesis

KN14

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Coherence in crystallography for imaging materials and biology

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In crystallography, we consider nanometre-sized crystals to be a new frontier of opportunity to tailor physical properties using 'size' as a control variable. This general view of crystallography "beyond the unit cell" opens a wide field of opportunity for methods development. However, when we think about nanostructures, we must reconsider the standard bulk concepts of lattices and crystal defects. Changes here provide nanomaterials with new and exciting properties. This lecture is about coherence-based methods for the determination of crystal structures using coherence. One example is micron-sized ZnO crystals, attached by bonding to a SiO_2 substrate, which showed internal strain arising from accidental damage during manipulation. Use of more than one Bragg peak from the same crystal allows components of the full strain tensor to be mapped inside the crystal.

These new crystallographic methods have a fundamental need for beam coherence, so benefit directly from 3rd generation synchrotron sources. The coherence leads to interference fringes in the diffraction patterns of sufficiently small crystals. When the fringes are measured using a fine-pixel detector the data can be oversampled beyond their Nyquist/Shannon frequency. To invert the diffraction, we then solve the crystallographic 'phase problem' using a support-constrained HIO algorithm. This leads to quantitative three-dimensional maps of the density of the crystal with a real-space phase, which is interpreted as the deformation of a crystal from its equilibrium lattice spacing.

We have also used the methods to examine twin domain structures within crystals as well as real-space phase domains due to ordering. In biology, we have investigated collagenous tissue, which shows an analogous phase domain structure. For extended objects such as these, we are applying the principles of 'ptychography', in which the crystallographic phase information emerges from overlaps between coherent diffraction patterns.

Keywords: phasing, nanomaterials, ptychography

KN15

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Structure-Property Relationships of Inclusion Compounds

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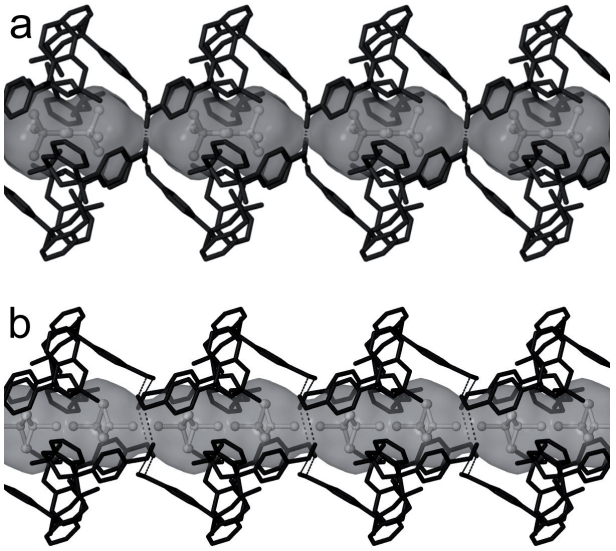
Multicomponent crystals based on the encapsulation of guest molecules by suitable hosts may exhibit a number of interesting properties and structural phenomena. For example, guest-templated

host frameworks may become porous if the guest molecules can be extracted without significant collapse of the host packing arrangement. When these processes occur as single-crystal to single-crystal transformations, it is possible to use crystallographic methods to establish structure-property relationships.

When multicomponent systems are able to include a range of different guest molecules within a predictable host framework, it is possible to tune properties by means of judicious choice of the guest. Examples involving polar ordering of guest molecules within well-defined host channels will be presented.



Keywords: inclusion compounds, porous materials, polar ordering

KN16

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Validation and errors in protein structures

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To err is human, and all macromolecular crystallographers are human - therefore, they are not immune to making errors during 3D model building and refinement [1]. Fortunately, many errors can be detected and fixed prior to publication and deposition by using common sense [1], appropriate protocols [2] and validation procedures [3].

In my lecture, I will discuss why errors are made and why some of them persist in published and deposited models, and hence why validation of 3D structure models is so important. I will describe what validation entails (both in general and for protein crystallography specifically) and explain why some validation criteria are more informative than others [4].

The Worldwide Protein Data Bank (wwPDB) recognises that validation is critically important for an archive of experimental structures and has therefore convened several Validation Task Forces or VTFs (for X-ray, NMR and EM). These VTFs are composed of community experts and have been asked to recommend procedures and criteria for the validation of models and data upon deposition in the PDB. The X-ray VTF has recently completed its report, and its recommendations are currently being implemented in a wwPDB validation pipeline. Its recommendations for model-only validation (e.g., geometry, torsion angles, clashes) will be adopted by the NMR and EM VTFs as well. The NMR VTF is expected to report its findings within the next year. Validation of EM maps and assessment of the fit between EM maps and models is still in its infancy and therefore the validation requirements for EM are anticipated to evolve slowly over the next 5 or so years. One important result of the work of all three VTFs is the identification of areas in which further research is required before consensus validation recommendations can be made. The use of comprehensive validation procedures will hopefully lead to fewer errors going undetected. Moreover, information about the quality of PDB and EMDB entries will be invaluable for structure users, many of whom are not experts in experimental structural biology [5]. However, challenges for the validation-research community remain, in particular in validating low-resolution models (X-ray, EM, SAXS) and hybrid models based on multiple heterogeneous sources of both experimental data and fitted models.

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Keywords: protein structure, validation, Protein Data Bank

KN17

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Prenucleation clusters and crystallization control by additives

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Prenucleation clusters are a stable species which was recently discovered for calciumcarbonate, -oxalate or –phosphate.[1] They already exist even in undersaturated solution, can have different solubilities / structures and were found to form amorphous nanoparticles by aggregation, which are the precursor structures for the final crystals. These clusters will be introduced and the driving force for their formation is discussed. If additives are added to a crystallization reaction, many parameters which characterize a nucleation reaction are influenced. Among them are supersaturation, nucleation inhibition / enhancement, change of the prenucleation cluster equilibrium, ion complexation and more. For several examples, it will be shown how the early stages of additive controlled crystallization can be quantitatively characterized and that additives usually play multiple roles in a crystallization reaction. The consequences of the different additive interactions for the final crystals will also be discussed.

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Keywords: nucleation, prenucleation clusters, crystallization additives