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Joint Neutron/X-ray crystallogrpahic study on the mechanism of pectate lyase

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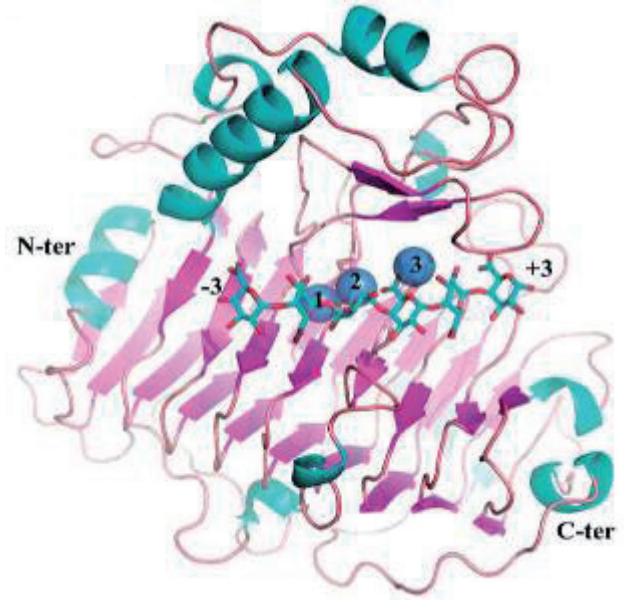
Bacterial soft-rot disease is a major problem for plants in the field and in storage. It is caused by the invasion of pathogens after cell wall damage by pectate lyases secreted by bacteria such as *Bacillus subtilis* (BsPel).

BsPel belongs to a family of lyases that cleave α-1,4-linked galacturonic acid units of the pectate component of plant cell walls via an *anti*-β-elimination reaction. A proposed catalytic mechanism [1] features a conserved arginine acting as a base as low as pH4.5. Where calcium ions are required for activity; a primary Ca^{+2} ion binds substrate and an additional 2 stabilise the intermediate.

At present the major mechanistic question is the protonation state of this active site arginine, which at physiological pH (7.0) is expected to be protonated. Therefore, proton abstraction initiating the reaction is likely to result from a local shift of pKa that has yet to be proven.

A joint Neutron and X-ray study has been carried out to study the structure of BsPel and the active site residues in particular. We have produced perdeuterated BsPel, crystallised it, and collected both Neutron and X-ray data on the same crystal sample.



Above: Cartoon representation of the parallel β-helix architecture (arrows) and 3 calcium ions (spheres).

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Transthyretin amyloidosis – insights from neutron crystallography

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Human Transthyretin (TTR) is a homotetramer protein that transports thyroxine in the blood and cerebrospinal fluid. TTR is intrinsically amyloidogenic and associated with three major amyloid diseases. Familial amyloydotic polyneuropathy (FAP) manifests itself by deposition of fibrils and amorphous aggregates in the liver, whereas familial amyloidotic cardiomyopathy (FAC) afflicts the heart. Both diseases are hereditary and due to point mutations in the genome, rendering the protein more labile and thus prone to dissociation and aggregation. The third, senile systemic amyloidosis (SSA) is linked to native TRR and is the most widespread; it affects about 25% of the population over 80 years old. Early diagnosis and new therapies, including small molecule compounds stabilizing the native fold, offer the possibility of a prolonged remission of this otherwise inexorable disease. The analysis of the protonation states of the subunit interface and changes occurring upon ligand binding is therefore of great interest for an understanding of the factors that stabilise the homotetramer, prevent dissociation and ultimately amyloidosis. Perdeuterated human TTR has been overexpressed in *E. coli* in fermenters of the ILL Deuteration Laboratory and large crystals have been grown. Neutron quasi-Laue data to 2.1 Å resolution and room temperature X-ray data to 1.9 Å resolution were collected on perdeuterated TTR crystals and used for a joint X-ray/neutron structural refinement with phenix.refine. The results are being used to study protonation and hydration in native TTR with a view to follow-up studies of TTR in complex with a number of promising ligands.

Keywords: ttr, amyloidosis, neutron crystallography

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The first neutron structure analysis of protein with ibix in j-parc

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Since 2004, Ibaraki prefecture has constructed the TOF neutron