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Radiation Damage Quantification and Comparison in the Protein Data Bank

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Perspective

Radiation damage is still a major impediment to accurate structure solution in protein crystallography. It can cause structural and chemical changes in protein crystals, making it a crucial factor to consider when evaluating the quality and biological realism of crystal structures in archives such as the Protein Data Bank (PDB). However, detecting radiation damage artefacts has typically been difficult. To remedy this, we present the Bnet metric here. By comparing the B-factor values of damage-prone and non-damage-prone atoms in a similar local environment, Bnet summarises the level of damage incurred by a crystal structure in a single value. We generate Bnet values for 93,978 PDB crystal structures after confirming that Bnet reliably detects damage in 23 distinct crystal structures that had previously been classified as damaged. Our metric identifies a variety of damage features that would otherwise go unnoticed by the other summary statistics normally generated for PDB structures. Radiation damage to crystals during X-ray diffraction investigations has long hampered precise structure determination in protein crystallography.

Despite the development of various damage mitigation strategies, such as cryo-cooling1 and data collection strategy optimization using software such as BEST or RADDOSE-3D, data collection methodologies utilising the increasing flux densities of synchrotron light sources have resulted in radiation damage remaining one of the major challenges in protein crystallography. This situation will only worsen as the freshly built fourth-generation synchrotron sources come online. Radiation damage can impact both individual asymmetric unit copies and the overall structure of the crystal lattice. Changes in diffraction pattern reflection intensities, primarily as fading and eventual loss of high-resolution reflections, indicate damage to the crystal lattice (global radiation damage). Crystallographers might thus trim their datasets to exclude diffraction patterns that have been significantly influenced by global radiation damage (within the limitation of retaining sufficient data completeness for structure solution). Damage to individual asymmetric unit copies (specific radiation damage) has, on the other hand, traditionally been difficult to detect within individual protein crystal (PX) structures. As a result, specific radiation damage is typically studied by identifying variations between subsequent datasets obtained from the same crystal(s) (for example, the radiation damage datasets gathered from six distinct proteins and deposited Differences are induced by structural rearrangements (most notably side-chain disordering) and chemical alterations triggered by electrons expelled by the sample upon absorption of incoming X-rays.

At cryotemperatures (around 100 K), these induced chemical changes have been observed to occur in a reproducible order with increasing dose: for example, in PX structures, metal ions are the first to be reduced6, followed by disulfide bond breakage; aspartate and glutamate residues are then decarboxylated; and finally, the methylthio group is cleaved from methionine residues. As a result, unlike with global radiation damage, crystallographers are frequently unable to detect and rectify specific radiation damage artefacts within their structures. For example, one might believe that an active site glutamate residue is disordered and that this disordering is potentially involved in the catalytic mechanism of its parent enzyme, while in fact the residue has been decarboxylated by the incident X-rays. Such inaccuracies can jeopardise the conclusions made from a structure, necessitating research to distinguish biologically relevant traits from those generated by radiation damage (e.g. during the bacteriorhodopsin photocycle, and the recent study of the bending of flavin in the mechanism of fatty acid photodecarboxylase).

Furthermore, and unfortunately, specific damage usually occurs before global damage: at 100 K, the experimental dose limit (corresponding to a 30% loss in summed reflection intensities from apo- and holo-ferritin crystals) was reported as 30 MGy, whereas aspartate/glutamate decarboxylation has been detected at doses as low as 4 MGy. The number of Protein Data Bank (PDB) structures containing specific radiation damage artefacts is unknown due to the difficulties in detecting them; however, given that a protein crystal held at 100 K absorbs a dose on the order of 1–10 MGy per complete dataset during a typical X-ray diffraction experiment, it is likely to be a significant fraction [1-5].

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