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Specific radiation damage is a lesser concern at room temperature

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There are two types of radiation damage in protein X-ray crystallography [1]. The first one, global damage, has been known since the beginning of X-ray crystallography. Global damage accounts for the decrease in the diffraction properties of a crystal during data collection due to the interaction of X-rays with the atoms of the crystal, which, in particular, generates free electrons and radicals in the bulk solvent, progressively destroying the crystalline order. Global damage is slowed down by roughly two orders of magnitude on the dose scale when the diffraction experiment is performed at cryogenic rather than at room temperature. Cryo-crystallography has led to the explosion in the number of crystallographic protein structures in the 1990's as it allows determining a structure from a single crystal. However, it was then realized that a second type of radiation damage was at play in cryogenic experiments: specific damage. This damage affects certain specific chemical groups that are sensitive to electrons, for instance disulphide bonds, carboxylate groups or metal cations, which can be found in protein active sites. This can be explained by the fact that X-ray induced free electrons can still diffuse at cryogenic temperature. Therefore, specific damage may lead to artefacts in structural analysis of reaction intermediate states and thus in mechanistic interpretation. The discernibility of specific damage at cryogenic temperature means that there is a significant difference between the rates of the two types of damage, i.e. a 'decoupling'between the two phenomena. As room temperature protein crystallography is quickly developing thanks to the development of faster, noiseless detectors, of improved sample environment at room temperature and of the concept of serial crystallography, the question of the comparison of the respective rates of specific and global damage build-up at room temperature has become a hot topic. We have compared the rates of both damage build-up at cryogenic and room temperature for various proteins, including the reaction intermediate state of a fragment of a photoreceptor [2]. While the two types of damage are largely decoupled at cryogenic temperature (decoupling factor between 12 and 1600), they occur on a similar dose scale at room temperature (decoupling factor between 1 and 8). This indicates that depending on the studied protein, specific damage may not be a primary concern in crystallographic structure determination at room temperature, provided diffraction data can be collected from a single crystal. This should stimulate the development of time-resolved crystallography experiments at synchrotrons.

[1] Holton (2009) 'A beginner's guide to radiation damage'J. Synchrotron Rad. 16, 133–142.
[2] Gotthard et al. (2019). 'Specific radiation damage is a lesser concern at room temperature'IUCrJ, 6, 665-680.

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