Resolution and Dose Dependence of Radiation Damage in Biomolecular Systems

Robert E. Thorne, Hakan Atakisi, Lauren Conger, and David Moreau
Physics Department, Cornell University, Ithaca, NY, 14853, USA

The fundamental relation of interest in understanding radiation damage in diffraction and imaging is the local Fourier-space relation between diffracted intensity *I*, diffraction wavevector *q*, and dose *D*, $\tilde{I}(q,D)$. Models used in protein crystallography for the last 50 years provide good fits to experimental $I(q)$ vs nominal dose data but have unclear physical significance. A fit to diffraction and imaging experiments suggested that the maximum tolerable dose varies as q^{-1} or linearly with resolution. However, the connection between experimental $I(q,D)$ relations, measured under often complex conditions of sample illumination and diffraction data collection, and the underlying local $\tilde{I}(q,D)$ relation had not been examined or established.

Initial insight came from measurements [1] of the time-, dose- and temperature-dependent evolution of crystal diffraction under conditions of microbeam illumination at peak dose rates up to ~50 MGy s^{-1}. At all temperatures and dose rates the integrated diffraction intensity for a fixed crystal orientation shows nonexponential decays with dose. A substantial fraction of measured intensity vs dose curves show an apparent delayed onset of radiation damage with dose. Both non-exponential decays and the apparent delayed onset are a consequence of non-uniform illumination and the resulting spatial evolution of diffracted intensity within the illuminated crystal volume. For Gaussian beams the diffraction weighted dose, which reflects the average damage state of the crystal regions contributing to diffraction at a given dose, becomes nearly independent of actual dose at large doses, as a result of “hole burning” by the intense beam centre.

Previous data for $I(q)$ versus dose was then reanalyzed to account for the effects spatially nonuniform crystal irradiation and diffraction during data collection. The reanalyzed data are consistent with a purely exponential local dose dependence, $\tilde{I}(q,D) = I_0(q)\exp\left(-D/D_e(q)\right)$, where $D_e(q) \propto q^{\alpha}$ with $\alpha \approx 1.7$. A physics-based model for radiation damage, in which damage events occurring at random locations within a sample each cause energy deposition and blurring of the electron density within a small volume, predicts this exponential variation with dose for all *q* values, and a decay exponent $\alpha \approx 2$ in 2D and 3D, roughly consistent with both diffraction and imaging experiments over more than two orders of magnitude in resolution [2]. This strong q/resolution dependence implies that the "dose limit" when collecting complete data sets cannot be meaningfully represented by a single number, but in fact varies rapidly with desired maximum resolution. For a typical resolution of 1.5-1.8 Å, the dose limit is ~10 MGy, consistent with results obtained by Teng and Moffat in 2000 and 2002 but a factor of three smaller than the currently accepted dose limit.

References

[1] Warkentin, M., et al., IUCrJ 4, 785-794 (2017).
[2] Atakisi, H., Conger, L, Moreau, D., and Thorne, R. E. IUCrJ 6, 1040-1053 (2019).