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Crystal pathologies in macromolecular crystallography, their detection and handling

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Crystals formed by macromolecules, such as proteins or nucleic acids, contain a huge volume fraction (20-90%) of water, which envelopes the macromolecules in an ordered hydration shell, to become totally disordered as bulk solvent farther away. The macromolecules form, therefore, only sporadic, weak direct contacts and the degree of crystalline order is often less than perfect. Apart from typical physical defects and rather trivial poor quality/habit/growth or mosaicity problems, macromolecular crystals can also suffer from several kinds of pathologies, in which everything seems to be perfect, except that from the structural point of view the interpretation may be very difficult or even impossible. For some time it was believed that certain types of pathologies are not found in macromolecular crystals and, when encountered, such cases were discarded as rare curiosities. Today we have to admit that such pathologies are actually quite common. The simplest case is pseudosymmetry, or non-crystallographic symmetry (NCS), when two or more molecules are related locally by some kind of symmetry

transformation, which is not propagated further. Translational NCS (tNCS) is particularly nasty as it leads to a strong bias of reflection intensity distribution and makes molecular replacement very difficult. Lattice-translocation defects, also called order-disorder twinning (OD-twinning), occur when molecules are packed regularly in layers but the layers are stacked (without rotation) in two or more discrete modes, with a unique translocation vector. When solved, such a structure will consist of two (or more) shifted, possibly overlapping, identical models. Crystal twinning arises when small crystallites, called twin domains, have different orientation dictated by a symmetry operation that is not part of the space group symmetry of the crystal structure. When the extra symmetry belongs to the same crystal system, the alignment of the twin domains, and of the overlapping reflections, is perfect and this case is termed merohedry. Pseudomerohedral twins arise when a low-symmetry unit cell has parameters with higher metric symmetry (e.g. the monoclinic angle $\beta=90^\circ$). When the twin domains adopt two orientations the twinning is hemihedral, when four - tetartohedral, eight - ogdohedral. The separate twin domains scatter X-rays independently (incoherently) and therefore twin detection is based on intensity data statistics. The tests are complicated by the fact that some other pathologies (e.g. tNCS) have the opposite effect on intensity statistics. There are also crystals in which the periodic (lattice) order is broken or absent. When strict short-range translational order from one unit cell to the next is lost but the long-range order is restored by a periodic Atomic Modulation Function (AMF), we have a modulated crystal structure. If the period of AMF runs over an integral number of unit cells, the modulation is commensurate and can be interpreted as a case of tNCS. Otherwise the modulation is incommensurate and such a structure is very difficult to solve, refine and interpret. In quasicrystals, the periodic order in 3D space is lost completely and the diffraction pattern, which is still discrete, cannot be even indexed using three *hkl* indices. Among the presented cases only the fully aperiodic quasicrystals have not been reported yet for macromolecules. But this may be only a matter of time.