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Abstract

Proteins belong to the most complex colloidal system in terms of their physicochemical properties, size and conformational-flexibility. This complexity contributes to their great sensitivity to any external change and dictate the uncertainty of crystallization. The need of 3D models to understand their functionality and interaction mechanisms with other neighbouring (macro)molecules has driven the tremendous effort put into the field of crystallography that has also permeated other fields trying to shed some light into reluctant-to-crystallize proteins. This review is aimed at revising protein crystallization from a regular-laboratory point of view. It is also devoted to highlight the latest developments and achievements to produce, identify and deliver high-quality protein crystals for XFEL, Micro-ED or neutron diffraction. The low likelihood of protein crystallization is rationalized by considering the intrinsic polypeptide nature (folded state, surface charge, etc) followed by a description of the standard crystallization methods (batch, vapour diffusion and counter-diffusion), including high throughput advances. Other methodologies aimed at determining protein features in solution (NMR, SAS, DLS) or to gather structural information from single particles such as Cryo-EM are also discussed. Finally, current approaches showing the convergence of different structural biology techniques and the cross-methodologies adaptation to tackle the most difficult problems, are presented.

Synopsis. Current advances in biomacromolecules crystallization, from nano crystals for XFEL and Micro-ED to large crystals for neutron diffraction, are covered with special emphasis in methodologies applicable at laboratory scale.