

## **Biomacromolecular crystallization: theoretical and practical aspects**

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Unlike the crystallization of small inorganic molecules, the problem of protein crystallization was first approached by trial and error methods without any reference to theory. Later, a physico-chemical approach was chosen because crystallographers and biochemists needed criteria to rationally select crystallization conditions, as well as to optimize the crystallization conditions in order to obtain single crystals for structural purposes. In fact, the problem of producing homogeneous and structurally perfect protein crystals is the same in the production of crystals for pharmaceuticals as in optoelectronics or nanomaterials, because in all these cases crystal growth mechanisms are the same. In other words, biological macromolecules and small organic or mineral molecules follow the same rules concerning crystallization even though each material exhibits specific characteristics.

In practice, the usual approach to solution crystallization is to study the respective influence of temperature, supersaturation, chemical composition and hydrodynamics. However for protein crystallization, due to the chemical complexity of solutions, most studies look at solution composition: pH, salt type and concentration, and additives such as polymers or polyols. This approach is usually named protein crystallization screening.

The aim of this lecture is to provide the scientists who intend to tackle protein-crystallization with theory and practical examples. Crystallization involves two separate processes, nucleation and growth, which are rarely completely unconnected. The lecture introduces the fundamental physical concepts in protein crystallization: solubility, supersaturation, nucleation, growth, phase transformation and ripening of crystals. I will give an overview of the physics of crystal growth, presenting practical examples of protein nucleation, growth and phase transition. My goal is to convince the audience that a thorough knowledge of the phase diagram is vital to the selection of starting position and kinetic pathway for any crystallization experiment.