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Is protein crystallization a challenge to God ?

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Now it is well known that protein crystals grow or dissolve following the same manner as an inorganic material. But this was not accepted as common knowledge some ten years ago. It was believed that proteins, which are essential material for life, are different from an inorganic material and they show unique behavior in the crystallization. For instance they never grow larger than certain size which is called " terminal size ".

It was in a plenary talk in ICCG-10 (the 10th International Conference on Crystal Growth) held in San Diego that Dr. Steve Durbin showed us VTR on spiral growth of a lysozyme crystal taken by AFM. It arose the admiration of the audience and I was deeply affected by the fact that protein also crystallizes by spiral growth mechanism.

Since 1985 ICCBM (International Conference on Crystallization of Biological Macromolecules)have been held every 2 years among USA and European countries. By applying the theory of solution growth considerable efforts have been paid for understanding the growth mechanism of proteins. But decisive experimental evidence has not been presented. Durbin's observation has cleared out prejudice against protein.

However, protein is too complex to be treated by simple theories of solution growth. As an example, let's look at supersaturation, which is the driving force for crystallization. Protein needs supersaturation two orders of magnitudes higher than that of an ordinary inorganic material for growth. Why such an extraordinary supersaturation is required is not clear yet. Dislocations in a crystal have not been observed in spite of the spiral growth. After all we have experienced unusual character of protein in past 10 years.

Protein is available in extremely small amount besides the short life, compared to an ordinary material. The purity is several orders of magnitudes lower than semiconductor materials. Those natures of protein force non-biochemist to handle only limited kind of proteins. This is why physicists still deal with notorious lysozyme.

So far optical microscopy, in combination with light scattering and AFM, has been beneficially used in studying growth processes. Optical microscopy is simple and nondestructive to protein . By magnifying the object we can save not only the quantity of the sample but also the time and space for experiments, since microscopic motion of a crystal is enlarged. Furthermore high precision optical interferometry can be applied on top of it to secure quantitative measurement. A combination of optical

microscopy with

AFM is effective to observe the relation between macroscopic and microscopic phenomena.

To what extent does one need to know the factors for satisfactory crystallization ? Just list up the terms related to growth; purity of the material, phase diagrams (salt concentration, pH and temperature in the case of ternary phase diagrams) , structure of the solution(agglomeration ; clusters, oligomers, growth unit), growth layer (step energy , kinetic coefficient , bonds at a kink site , rotational diffusion of growth unit at the kink site) , desolvation energy , diffusion coefficients , hydrodynamic constants and so on.

Nucleation is more obscure than growth and no satisfactory theory for protein has been established. Epitaxy related to nucleation control has been scarcely studied. How defects are induced after nucleation ? What is the optimum growth rate ? So many unknown factors are left for study. One to one correspondence between crystal quality and the growth conditions is far beyond the present knowledge.

The extraordinary nature of protein molecules can be attributed to the anisotropy originated from the diversity of polypeptide chains of amino acids. The three dimensional characteristics of protein molecule are anisotropic not only in shape and bonding sites but also in surface charge distribution. The complexity of molecules demands more than three parameters for solubility and yields various hydration states, which lead to agglomeration at high supersaturation, in which crystals really grow. The growth units of protein molecules must diffuse through the solution to a kink site . Then the molecules must rotate to the exact position with respect to the kink .Eventually the growth unit will weakly bind to the crystal after partly dehydrated.

The above mentioned situations are never met in a silicon crystal growth. Highly symmetrical atom binds together with strong covalent bond. Giant perfect single silicon crystals can be routinely produced without exact knowledge of the melt structure . This is contrasting to protein crystals.

God is wise enough to produce life by materials which are difficult to form crystals, which is a settling into a minimum potential state.

Crystallization of protein might be an awful challenge to God.