Commission on Crystal Growth and Characterization of Materials

CURRENT TRENDS AND FUTURE IN CRYSTAL GROWTH: A REPORT FROM THE COMMISSION ON CRYSTAL GROWTH AND CHARACTERIZATION OF MATERIALS OF THE INTERNATIONAL UNION OF CRYSTALLOGRAPHY

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Abstract

Despite the recent techniques that seem to enable the "crystallography without crystals" [1], progress in crystallography is inherently linked to progress in crystal growth.
Current trends in crystal growth are focused on fundamental research in crystal growth processes for complex structures at atomic scale. Fundamental research is also dealing with interface phenomena at interfaces between liquid and solid, as well as gas and solid, including in-situ observation. Therefore, specific techniques to observe these phenomena at the interfaces are required.

Novel, cross-disciplinary research reinforces that understanding crystal growth has immediate applications in such critical areas as energy, food security and the environment. Crystallization is also an extremely important topic for the production of pharmaceuticals.

Crystal growth is also important for life-sciences: the crystallization of proteins is of paramount importance to determine their internal structure and biomineralization is the basic process that organisms use to produce minerals and thus skeletons.

In the following paragraphs, the current trends of crystal growth are discussed for each of these topics.

Fundamentals and Nucleation

The true fundamentals of crystal growth have been known for a long time and the famous BCF paper from 1951 [2] remains a cornerstone in our understanding of the mechanisms of crystal growth and the structure of growing surfaces. Nevertheless, advances in both experimental and computational techniques have greatly increased our understanding of the atomic-scale processes. For solution growth, the details of the solid-liquid interface structure, including the partial ordering of the liquid, is becoming clear and the near future should see an increase in studies where the results of various techniques are combined in order to obtain a complete and reliable picture. This includes results from atomic-force microscopy (AFM) [3], X-ray diffraction [4, 5] and Monte Carlo simulations [6]. Growth takes place at steps and kinks, but also here an improved understanding is emerging, zooming in on the role of (limited) kink density [7] or the desolvation of ions at kink sites [8].

Another development in recent years that is expected to continue in the future is pushing the limits of self-assembly in the growth hierarchical structures made of (nano)crystals. Also this was studied in the past, but advances in producing tailor-made structures like DNA strands or peptides makes it possible to control self-assembly in novel ways [9, 10]. But also simple nanocrystals can be assembled into coherent superstructures using a process called oriented-attachement [11]. The growth through nanoclusters was similarly found to play a crucial role in a deracemization process called Viedma-ripening [12].

The actual genesis of crystals, i.e. crystal nucleation, is likely to remain a challenging research topic for years to come, since it involves very small clusters whose location in place and time are hard to predict. The last decades have seen a huge increase in our understanding and it is clear that classical nucleation theory is often not a correct description of the process. Rather than a direct transition from the fluid to the crystalline phase, an intermediate liquid or amorphous phase may provide a more favourable path to crystal formation [13, 14]. Moreover, like in the case of crystal growth mentioned above, also during nucleation the growth of clusters may not proceed through the addition of individual atoms or molecules, but involve larger particles

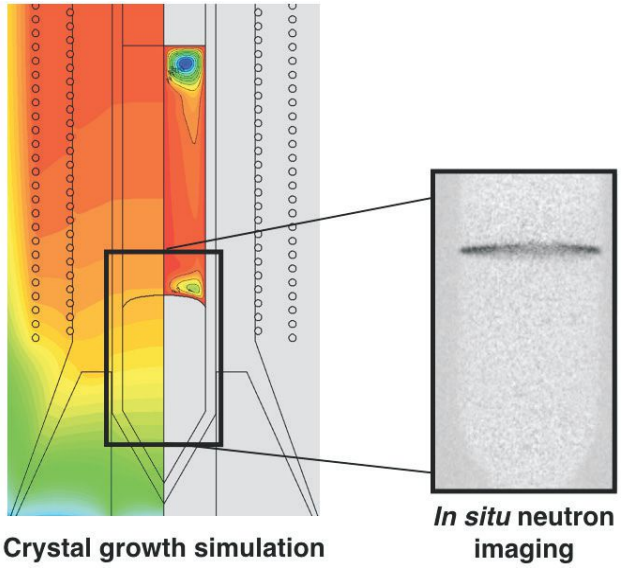

Figure 1. Continuum models of heat and mass flow during Bridgman growth (left) can be monitored in situ using neutron imaging, which shows the melt interface. In the future, feedback control of growth is envisioned. Image courtesy of J. Derby, University of Minnesota.

like oligomers, droplets, amorphous and crystalline nanoparticles [15]. Cryo electron-microscopy has shown to be able to catch the fleeting clusters that form during nucleation [16, 17], and this technique, together with computer simulations and the full control offered by micro-droplet experiments [18], is expected to complement our current understanding of 3D and 2D nucleation.

Modelling

The 9th international Workshop on Modelling in Crystal Growth, October 21-24, 2018 in Big Island, HI-USA, has been the opportunity to evaluate the current status and prospective of this research field.

Modeling of *bulk crystal growth processes from the melt* is now mature in the sense that it is able to solve complex industrial problems [19]. Several groups all around the world have the capability to answer such demands and commercial software are available. Developments concern global growth process control and a better modelling of turbulence in large melts [20].

Growth from the vapor phase is also well advanced concerning the global simulation of the process chamber. However modeling the details of layer growth at the atomistic scale remains a challenge [21].

Prediction of the shape of crystals *grown from solution* is more and more feasible. The difficulty in this field concerns a correct description of the kinetics of the growth due to solvation and impurity/solute effects [22].

Modeling of *new crystals* from various chemical or molecule mixtures is now possible thanks to molecular dynamics and atomic scale simulation [23]. However design of complex structures should be further developed.

In parallel to these rather classical fields, the use of new computing technics such as neural networks [24] or machine learning is emerging, especially in the field of process control. Physical or analytical models are occasionally used.

Important further development will be coupling modelling with the emerging field of in situ growth characterization.

Bulk semiconductors

Semiconductor materials like silicon, gallium arsenide and silicon carbide constitute the heart of modern technology. Without them, achievements such as iPods, LED screens, digital cameras, solar energy, or electronic parking assistants would not be possible. However, it would not be sufficient to have the semiconductor materials to hand in just any form: they are needed as high-purity single crystals, a form that is hardly to be found in nature and has to be manufactured. In industrial production the most important growth technique is the Czochralski type. Gallium arsenide with its major share of demand in mobile industry and as substrate for high efficiency solar cells in space industry has another major demand as bulk semiconductor.

New materials are being grown using Floating Zone technique with the advantage of high power density and the absolute freedom from crucibles.

One of the big demand is on gallium oxide and also on related materials.

Field Effect Transistor (FET) based on the compound Gallium Nitride, is set to displace the venerable silicon MOSFET. The advantages of GaN over silicon stem from its basic crystal structure — not only do electrons flow faster in GaN, the material can also withstand greater voltages before breaking down into a conductive state. These properties enable greater energy efficiency, higher power density and smaller device size. Gallium nitride, as a semiconductor material, has been around for a while. LEDs have used it.

Six-inch diameter standard silicon wafers are topped with a thin “epitaxial” gallium nitride crystal layer?—?on which FETs and other devices can be built. Gallium nitride devices for power converters are produced by the thousands each week while silicon devices are made in billions.

It’s difficult for any single company to advance the state of manufacturing art sufficiently to compete with silicon, which has benefitted from decades of research on how to purify, dope, and grow it.

Silicon carbide and gallium nitride will dominate the bulk semiconductor industry for a wide range of products and systems. History shows that it can take as much as 20 years to bring a new technology from theoretical proposal to commercial production.

SiC, Silicon, Germanium, Mercury Cadmium Telluride, Cadmium Zinc Telluride, Gallium Arsenide, Indium Phosphide, Zinc Telluride and few more are among the 12000 tons of crystalline materials produced around the world for technological applications.

Oxides

Highlighting recent advances in crystal growth and the study of physics of oxide materials is essential for the relationship between the development of basic knowledge and key areas of oxide applications.

High quality single crystal oxides are desirable for many high-tech applications, from high-power lasers to the rare-event detectors essential for the discovery of new particles [25]. Single crystals of high quality provide the opportunity to study anisotropy of physical properties, they are less contaminated and possess less structural defects. During last years the ceramic and single crystals oxides for practical applications were obtained, e.g.: ferroelectric memories (e.g. $Pb(Zr,Ti)O_3$, $SrBi_2Ta_2O_9$), actuators ($PbMg_{1/3}Nb_{2/3}O_3$, $PbTiO_3$), inductors, permanent magnets, microwave devices ($(Ni,Zn)Fe_2O_4$, $BaFe_{12}O_{19}$, $Y_3Fe_5O_{12}$), microwave resonators, filters and antennas for mobile communications and GPS devices ($BaTi_4O_9$, $Zr(Ti,Sn)O_4$, $BaMg_{1/3}Ta_{2/3}O_3$, $(Ba,Sr)TiO_3$), piro- (IR radiation detection and imaging) and piezoelectrics (transducers, actuators and resonators) ($Pb(Zr,Ti)O_3$), superconductors ($YBa_2Cu_3O_{7-x}$, MgB_2), optoelectronic materials (e.g. $LiNbO_3$) for waveguides, frequency doublers, voltage-controlled optical switches, modulators etc.

Today, one of the most important topics which attracted attention all over the world is lithium-ion batteries as a next-generation energy storage device. A key material for the all solid-state lithium batteries is inorganic solid electrolyte, including oxide or sulfide materials. Among the oxide electrolytes, garnet-type oxide exhibits the highest lithium-ion conductivity and a wide electrochemical potential window. However, they have major problems for practical realization. One of the major problems is an internal short-circuit in charging and discharging. In the polycrystalline garnet-type oxide electrolyte, dendrites of lithium metal easily grow through the void or impurity in grain boundaries of the sintered body, which causes serious internal short-circuits in the battery system. To solve these problems, a single-crystal oxide electrolyte $Li_{7-x}La_3Zr_{2-x}Nb_xO_{12}$ were grown. The first successfully grown centimeter-sized single crystals of garnet type by the floating zone method were obtained [26]. The single-crystal solid electrolyte exhibits an extremely high lithium-ion conductivity of 10^{-3} Scm^{-1} at 298 K. The garnet-type single-crystal electrolyte is a prospective technology for achieving highly safe advanced battery systems.

Terbium-scandium-aluminum garnet $Tb_3Sc_2Al_3O_{12}$ single crystals were grown for application as Faraday isolators. Faraday isolators are a key component of many contemporary laser systems (Fig. 2). They are used to prevent optical feedback leading to parasitic oscillations in multiamplifier systems and frequency instabilities in laser diodes.

The most important optical element of a Faraday isolator is the Faraday rotator providing a 45° rotation of the polarization plane of traversing light. The characteristics that one looks for in a Faraday rotator material are a high Verdet constant, a low absorption coefficient, a low nonlinear refractive index and a high damage threshold [28].

Important group of oxides are oxide semiconductors and their applications. Growth of n-type doped β-Ga_2O_3 features additional stability challenges that are also of high interest for growing other oxide compounds. Current research focuses on incorporation of the dopants (Mg, Al, Ce, Cr) and the preparation of gallates with spinel structure ($MgGa_2O_4$, $CoGa_2O_4$, $ZnGa_2O_4$, $InGaZnO_4$) for improved

Figure 2. Terbium-scandium- aluminum garnet $Tb_3Sc_2Al_3O_{12}$ (TSAG) single crystals [27].

properties as well as for novel applications, e.g. as neutron detector, scintillator, electroluminescent materials or as substrate for ferromagnetic thin films [29].

An important challenge is nowadays the preparation of crystalline complex oxide films at temperatures compatible with their direct integration in flexible devices. The variety of wet chemical methods allows the easy exploration of novel crystallization pathways for metal oxides thin films and makes them fundamental in the search of low temperature methods [30].

2D and low dimensional structures

The past decade has seen a rapid interest in the synthesis, characterization and use of low dimensional materials. These are materials where the characteristic dimension is typically nanometer in length scale in 0, 1, or 2 dimensions. These constrained or narrow dimensions lead to new and often surprising properties not seen in the fully macroscopic material. These new properties are due to quantum confinement in multiple dimensions. Quantum confinement has been used for decades to realize new properties that are often tunable over a range, such as the change in emission wavelength with thickness of a quantum well in lasers and light emitting diodes. While traditionally the formation of low dimensional structures has been carried out through the process of epitaxial growth, new classes of materials that are in themselves low dimensional have gained prominence [31]. The field of two-dimensional materials (2D) have been dominated by the interest in graphene [32] and transition metal dichalcognides (TMD) [33] where interest in thin flexible electronics, optical materials, structural composites and other forms of functional materials and structures have driven the research. The unusual electronic structure of many of these materials and their tunability by way of composition has also given rise to development of new areas of solid-state physics. These materials by virtue of their thin nature can also possess large strains when under mechanical stress without suffering from defect formation or fracture. Strain is therefore an additional means to alter or tune the electronic and optical properties of these materials.

There are many challenges in the synthesis of these materials over large areas with a low structural electronic defect density. Many promising approaches have been put forth to address this barrier to technological development.

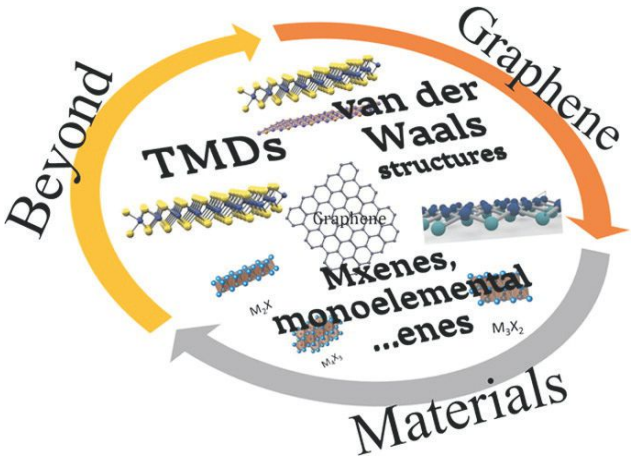

Figure 3. There are many new forms of low dimensional materials which all exhibit unique and sometimes tunable properties (reprinted with permission from [44]. Copyright 2015 American Chemical Society).

Gas phase synthesis, epitaxy, and a wide variety of solution growth methods for graphene have been investigated. The formation of wafer-scale 2D materials remains elusive but an active area of research. TMDs are a broad class of materials with new wide range of compositions and properties. TMD-based alloys provide an added measure of flexibility and further enlarge the possible application scope of these materials [34, 35]. As with graphene, most traditional approaches to material synthesis, from gas phase (CVD) to aqueous-based processing have been used. Again, wafer scale formation of TMD-based materials is an active area of research and technology development. Given the broad range of composition, TMD materials have also been investigated for their use in heterojunction structures. Due to the 2D nature of these materials, both vertical, i.e. stacked, heterostructures and lateral, i.e. edge-to-edge, heterostructures are possible and have been extensively investigated. Over the range of materials properties, TMDs will have applications in optical and electronic devices, particularly in sensing and flexible electronics.

The range of low dimensional materials extends far beyond graphene and TMDS as researchers find new ways to create these materials. MXenes, which are typically nitrides and carbides derived from MAX phases [D5], through treatment with HF. The structure of MAX phases is $M_{n+1}AX_n$ (M: early transition metal; A: group A element; X: C and/or N; n = 1–3). The treatment using HF selectively removes the group A element leaving a 2D M_nX structure [36]. The broad compositional range of possible MAX phases leads to an enormous class of MXene-based materials. The MXene materials have shown promise, as with other 2D materials, in the realm of energy storage, such as in batteries [37] and supercapacitors [38], as well as displaying intriguing properties such as superconductivity and properties useful in thermoelectric applications. This class of materials is under active investigation. Issues to be include alternative synthetic techniques to the use of HF, defect formation and compositional control.

While many of these materials are inherently stable in a 2D form, there are also classes of materials which could be stabilized in 2D planar form when attached to as substrates or when the surfaces are passivated by a chemical moiety. Silicene [39] and germanene [40] have both been synthesized in monolayer form stabilized by the deposition onto a substrate. The growth of these 2D materials typically is on a metal substrate that possesses a coincidence lattice, as in the use of Ag for silicene. As with graphene, the substrate can often play a role in modifying the materials properties from the non-attached form. There are also initial research reports of the solution-based formation of silicene from suitable precursors [41].

An allotrope of phosphorus, black phosphorus (BP), can also be produced in 2D form as is referred to as phosphorene. The structure of phosphorene is a 'puckered' sheet which is morphologically different from many of the planar 2D materials [42]. Unlike graphene, 2D BP has a room temperature bandgap of ~2 eV and a high hole carrier mobility. As with other 2D materials, the synthesis of BP can be carried out by mechanical cleavage, liquid exfoliation, and chemical synthesis. BP is considered air-sensitive which restricts the nature of the processing used to fabricate device structures. Other similar compounds have been prepared such as 2D h-BN [43]. h-BN has been used in many application areas as a 2D insulator in layered heterojunctions, substrates for graphene-based devices, passivation layers and in other integrated structures.

In all cases, the search for new 2D materials is continuing with new and interesting properties being found as the range of structural motifs and compositions are explored. The challenge remains in the formation of large area materials with known and controlled defect density, processing methodologies to handle and manipulate these 2D nanosheets, and in the interface and surface chemistry which can also influence or control their properties. These materials with their diverse properties, flexibility and low volume will be playing an increasing role in our technology.

Biomineralization and self-assembly

Biomineralization is the study of the principles used by living organisms to produce directly or indirectly minerals. The importance of this subject is enormous in different fields because the impact of life on the chemistry of our planet is ubiquitous. In addition, life has been improving their mineralogical efficiency by trial and error since almost 600 millions years ago. Therefore, the nanocrystalline texture of their mineral achievements are in some way optimized for their function. This is the reason why biominerals are the targets for advanced functional materials, opening an extremely active field known as biomimetic.

Nowadays, biomineralization studies are following different research lines. There is still a need for detailed crystallographic studies of the mineral phases and their textures. These characterization studies will be more valuable if they are correlated with the functional properties of the biomineral structures. However, the hottest point of the field Is and will be the study of the nucleation and crystal growth processes. The importance of the organic matrix in controlling the nucleation and growth of biomineralization processes is out of doubt. Today, it is well-known that many biological compounds, including aminoacids, proteins, carbohydrates, etc… have both specific and non-spe-

cific effect on the nucleation and growth of minerals by living organisms. However the detailed mechanisms by which they occurs is still under discussion. It should be solved in the future if the relevant species in the nucleation of biominerals are either ions and molecular species or prenucleation clusters. The structure of the prenucleation clusters that seems to be present in biological crystallizing fluid is still unknown. They can be simple amalgam of nanocrystalline precipitates and biomolecules or amorphous phases or high density fluids that might encode distinct structures before precipitation takes place. In any case, revealing the earliest events of homo/heterogeneous nucleation in biological fluids are pivotal to understand the phenomenon of biological crystallization. Ex-situ experimental studies and laboratory analogous using model biomolecules are today the most used tools but certainly in-situ studies are the challenge for the future. Another subject that is still open fir further investigation in the future will be the growth mechanism of biominerals. There are few cases supporting that growth rates are controlled by classical growth mechanisms, i.e. the accretion of ionic species to steps generated by two-dimensional nucleation or screw dislocations. Most recent studies suggest that growth occurs by oriented aggregation of crystalline nanoclusters or by accretion of amorphous or liquid dense nanodots, but the field is open for future findings.

Another field open for future development is the understanding of the processes by which life is able to control the crystal phase of polymorphic minerals, the nucleation site and crystal orientation, in other words, the mechanism controlling their mineral textures and their hierarchical organization. This subject is very important because is critical to develop biomimetic strategies useful in materials science, biomaterials development and nanotechnology. Nowadays, most laboratories are exploring the hybrid approach used by life and their same components, namely mineral such as calcium carbonate, calcium phosphate and others, and biological polymers of their models. So far several routes to the production of single textures have been discovered but there is a clear need for novel approaches. To give an example, we still don't know how to produce an eggshell, nor by assisted methods, much less by self-organization. Furthermore, the production of multitextural structures as those exhibited by many shells is another challenge for the future and a structural dream for materials scientists and engineers.

It should be remembered that the laboratory of life for the production of biominerals uses a trial and error strategy. Therefore, the molecular machinery and its products life has found are not necessarily models of excellence, and in principle they can be improved. The finding that the coupling precipitation of carbonate and silica produce self-organized structures that mimic the morphology and texture of biominerals has opened a hopeful non-hybrid route to the formation of complex multitextural architectures. It can be predicted that this will be a line of research for the future.

Beyond the formation of mineral skeletons, living organisms are also able to induce the formation of mineral structures without having a direct role in precipitation. They do by different mechanisms that still need to be understood. For instance, a) changing the physicochemical conditions of the local environment by their metabolism or degradation, b) as passive substrate for heterogeneous nucleation, and c) as binders of nano and microparticles of minerals through their extracellular polymeric substances. Minerals precipitated by biological induction do not usually have a function. However, their study is very interesting because it will shed light to the contribution of bacteria to precipitation, and their relation to ore mineral formation, primitive life detection and biomedical applications.

So far, most of the research has been devoted to biomineralization, i.e. to the formation of minerals in or induced by biological organisms, but it can be foreseen that the future will bring a larger number of contributions to the field of biocrystallization, i.e. the nucleation and growth of non-mineral crystals such as proteins, lipids, carbohydrates, and other polymers. Fascinating structures such mammalian stratum cornea, reptilian molts, fish scales, or butterfly wings are devoid of structural and morphogenetical studies. There is here a wide and almost unexplored niche for experts in nucleation and crystal growth.

Crystallization of proteins

The state of the art in the field of protein crystallisation is still an initial search through a large chemical space, with subsequent rounds of optimisation, if one is lucky enough to find an initial condition in the initial screening [45, 46]. Arguably, it was back in 1991 that the last significant change in the general approach to crystallization was made, which was the wide adoption of 'sparse matrix' screening [47]. However, what has changed is the technology used to set up, record and interpret crystallisation trials. Bespoke automation for crystallisation was popularised during the Structural Genomics Initiatives in the early 2000s, along with a general shift in focus from studying just one protein to studying comparative structural information on large classes of proteins.

Automation allows smaller volume crystallisation trials to be set up, enabling a greater coverage of the vast initial chemical space. Here, the most recently recruited technology is acoustic dispensing, which permits the use of very small (5-20 nL) droplets [48]. This same technology has also been used for post-growth manipulations of crystals, for example to dope crystals in their growth droplet with DMSO solutions containing small molecules [49]. This has been adopted in particular for Fragment Screening campaigns. Even before the advent of acoustic dispensing, other low volume dispensing was used, and these technologies (piezo dispensing or low volume positive displacement dispensing) are still widely used for setting up standard 'low volume' (100-500 nL) sitting drop experiments [50].

More importantly, automation has eased the process of interrogating the collection of trials for positive results. The advances here are primarily in hardware for storage of high-density crystallisation plates which allow for the hands-free collection of images, allowing time-courses of drop sets to be routinely collected [51, 52]. Although visible light inspections are most commonly used, other wavelengths (most often 280 nm) are widely used to help both find crystals and also to discriminate between protein and

salt crystals. Non-linear optical effects such as second-harmonic generation (SHG) are touted as a way to locate sub-micron crystals [53, 54]; the usefulness of this approach is limited mainly by the expense and fragility of the hardware required.

Software developments have included datamining of public resources, in particular the Protein Data Bank (PDB, [55]) to aid the development of second generation sparse matrix screens. Machine learning (ML) is just starting to gain traction within the field. Although there are vast quantities of data pertaining to protein crystallisation, in particular, images of crystallisation experiments, obtaining high-quality labelled data for machine learning studies remains the limiting factor. However, the results of an international collaboration which assembled a large, high quality labelled data set of crystallisation outcome images has shown that current ML tools such as convolutional neural nets (CNNs) have much to contribute to the field [56].

Other recent developments are in the methods used to present crystals to X-rays. The use of liquid or gel jets, initially developed for providing samples to Free Electron Lasers (FELs), requires the growth of large amounts of uniformly tiny crystals [57]. The FELs have blown open the field of time-resolved crystallography. The increased popularity of serial crystallography at synchrotron beamlines has led to the development of novel solid supports, for both mounting crystals or for *in-situ* growth of crystals [58]. In particular, microfluidic devices have been developed for this purpose, covering many different methods of crystallization: free interface diffusion [59, 60], counter diffusion [61, 62], vapor diffusion [63, 64] and batch [65, 66].

Crystals of sizes used for X-ray diffraction experiments 50 years ago are now suitable for almost real time data collection at modern neutron sources [67]. And finally, recent developments in detectors and stages are encouraging a blossoming of micro electron diffraction (ED) studies [68].

Taken together, the future looks both promising and exciting, with novel technologies enabling data collection from different sources and different sizes of crystals to allow unprecedented insight into the world of proteins.

Pharmaceutical crystals

Pharmaceutical Crystallization involves two separate processes, nucleation and growth, meaning that problematics are common to “classical” crystallization topics: experimental and modeling approaches. For instance, nucleation remains a challenge [69].

At the moment, most of the *pharmaceutical crystallization* are *from solution*. Melting crystallization and supercritical fluid crystallization are used at the laboratory scale, mainly for discovery purpose.

The increasing complexity of molecules and the chemical composition of the crystal, from mono-component to multi-component [70] (multi-component crystal composition is a way to improve solid state properties such as water solubility for a pharmaceutical ingredient; another challenging possibility is the production of nanocrystals) requires developing procedures for discovery of new crystal structures as well as innovative manufacturing processes:

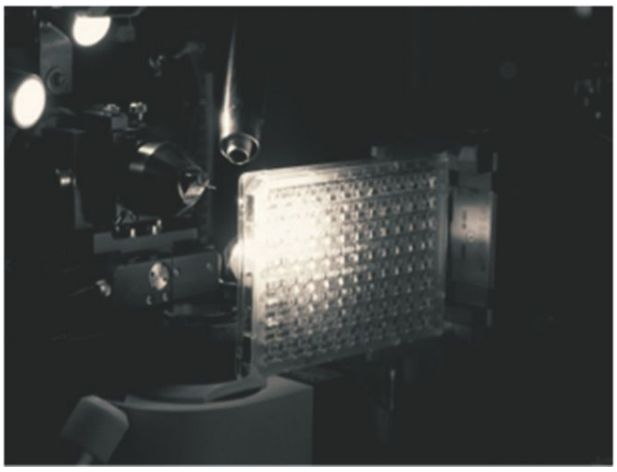

Figure 4. *In situ* X-ray diffraction experiment (photo courtesy of Dr. May Marsh, PSI).

- Screening tools for crystallization and phase discovery,
- Tools to address product separation,
- Technological challenges for the production of these new pharmaceutical solids.

Modelling, in this specific crystal growth sector, is still developing, as recently stated in section Modelling by T. Duffar. Prediction of the shape of crystals *grown from solution* is more and more feasible. The difficulty in this field concerns a correct description of the kinetics of the growth due to solvation and impurity/solute effects. Modelling of *new crystal* from various chemical or molecule mixtures is now possible thanks to molecular dynamics and atomic scale simulation, although very challenging in the case of multi-component system. However, design of complex structures should be further developed.

In situ observation and characterization

Crystal growth process from solution involves mass transfer of molecules from an environmental phase to the crystal surfaces, followed by the integration of these molecules to the crystal surfaces. Since the surface state depends on the growth mechanisms, observation of the surfaces at molecular levels has been a key method to study not only the growth mechanism but also defect characterizations.

This observation has been performed by phase-sensitive optics [71] for a long time but in last decade very fast and atom-resolving FM-AFM [72, 73] has rapidly been developing, so that atomic behaviour of growth and dissolution phenomena of the surface can be visualized in-situ. Surprising enough, this method was applied also to visualize the hydration structure over the crystals in solution. The same hydration structures have been studied in more details also by surface sensitive XRD method using synchrotron [74].

Transmission electron microscopy (TEM) has been used in-situ to study the nucleation phenomena of calcite, proteins and other crystals in real liquids. This is called in-situ liquid TEM that has advantages to get real lattice image and diffraction of the newly formed phases even before nucleation. In many cases, metastable phases and amorphous appear prior to nucleation, proving the existence of multi-step nucleation. Nucleation was the phe-

nomenon in mysterious zone but, thanks to the development of elegant liquid cells for TEM [75], various nucleation phenomena are becoming clearer.

High resolution neutron imaging, rapid in-situ structure analysis of clusters using free-electron lasers will be employed in more wide fields of in-situ observation of crystal growth and characterization. The resolution of observation is getting much better not only in space but also in time. We already gained the ability to see individual atoms on a growing/dissolving crystal surface even in solution and will get the time resolution of attosecond (10^{-18} s.) that would be powerful to understand nucleation and the pre-nucleation phenomena.

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