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Crystal Growth

Uncovering Molecular Processes in Crystal Nucleation and Growth by Using Molecular Simulation

Jamshed Anwar and Dirk Zahn**

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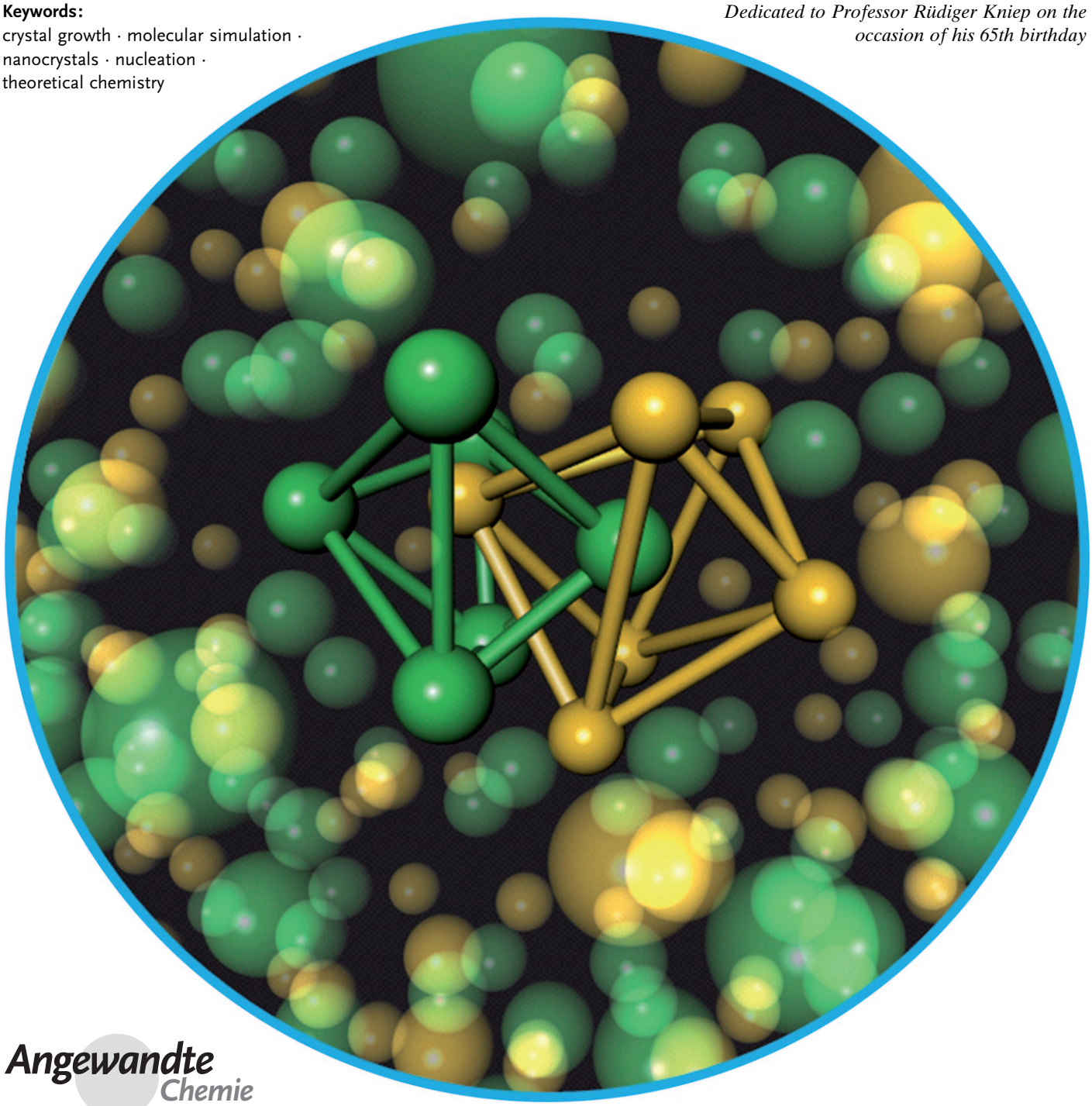
Dedicated to Professor Rüdiger Kniep on the occasion of his 65th birthday



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Exploring nucleation processes by molecular simulation provides a mechanistic understanding at the atomic level and also enables kinetic and thermodynamic quantities to be estimated. However, whilst the potential for modeling crystal nucleation and growth processes is immense, there are specific technical challenges to modeling. In general, rare events, such as nucleation cannot be simulated using a direct "brute force" molecular dynamics approach. The limited time and length scales that are accessible by conventional molecular dynamics simulations have inspired a number of advances to tackle problems that were considered outside the scope of molecular simulation. While general insights and features could be explored from efficient generic models, new methods paved the way to realistic crystal nucleation scenarios. The association of single ions in solvent environments, the mechanisms of motif formation, ripening reactions, and the self-organization of nanocrystals can now be investigated at the molecular level. The analysis of interactions with growth-controlling additives gives a new understanding of functionalized nanocrystals and the precipitation of composite materials.

From the Contents

1. Introduction

Crystal nucleation and growth is at the heart of most things solid, from the inanimate physical world to the structural components and frameworks of living forms. Not surprisingly there is an immense interest across disciplines to gain a fundamental understanding of these processes with a view to controlling and optimizing them and their consequences, and to possibly predicting their outcomes. A key focus is the earliest stages of crystallization, which is a major determinant of the structure and hence the properties of the resulting product. Despite all the interest, the mechanics of the earliest stages of the crystallization still remain an important fundamental problem.[1] The essential difficulty is that the processes taking place at the atomic scale are barely, or not at all, accessible to current experimental methods. The situation, however, is anything but bleak, as computer simulation based on atomic interactions can now provide the required molecular resolution with the potential to yield structural insights, dynamics, and estimates of thermodynamic quantities, such as nucleation free energy barriers.

We review herein the role of molecular simulation in underpinning the atomic processes characterizing the earliest stages of crystallization in both simple and complex systems. The processes of crystal nucleation and growth, by their very nature (the former being a rare event while the latter is characterized by a timescale longer than microseconds), challenge the mainstay techniques of molecular simulation. We begin with a brief outline of the main molecular-simulation techniques indentifying their potential and equally importantly their limitations for exploring nucleation processes. We then focus on the recent exciting advances in methodology and ingenuity that now enable problems in this domain to be tackled which were hitherto considered outside the scope of molecular simulation. The fundamental problems of formation and stability of emerging nuclei is an issue which is also common to nanocrystals. Consequently we include a section on applications of simulation to the phase stability of nanocrystals, and their interaction with surfactant molecules that serve as stabilizers. Throughout the Review we highlight the notable mechanistic insights gained from simulations.

2. Molecular Simulation

2.1. Molecular-Dynamics and Monte-Carlo Simulation

The basis for molecular simulations is the molecular forces between atoms and molecules which are now sufficiently well characterized. This knowledge of the forces enables us to simulate the collective behavior of a specified system as a function of time ("trajectory"), a system being comprised of, for example, a collection of solute molecules in a solvent. This method, known as molecular-dynamics (MD) simulation, employs Newtonian mechanics to calculate the evolution of the molecular system, which is dictated by the interaction forces between the molecules.[2,3] Simulations can be carried out at constant temperature and pressure (the NPT ensemble), hence enabling direct comparison of the results with those obtained from experiments. Periodic boundaries can be employed to remove unwanted surface effects. The trajectories resulting from MD simulations reveal the dynamic behavior of the molecules in the system and thus

[*] Prof. J. Anwar
Computational Biophysics Laboratory, Institute of Pharmaceutical Innovation,
University of Bradford, Bradford, BD7 1DP, U.K
E-mail: j.anwar@bradford.ac.uk
Prof. Dr. D. Zahn
Lehrstuhl für Theoretische Chemie/Computer Chemie Centrum
Friedrich-Alexander Universität Erlangen-Nürnberg,
Nägelsbachstrasse 25, 91052 Erlangen (Germany)

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provide direct mechanistic insights. Thermodynamic averages are estimated on the basis of the ergodic hypothesis in statistical mechanics, namely that the time average of thermodynamic quantities (after the system has equilibrated) can be related to the configurational average. An implicit assumption in this case is that the system is able to evolve to the equilibrium structure from the chosen initial configuration, unhindered. It is pertinent to note that whilst a system in the NPT ensemble tends towards low (Gibbs) free energy, the actual value of the free energy cannot be readily obtained from a standard MD simulation.

If the interest is primarily in equilibrated states or thermodynamic averages (rather than a trajectory or a pathway) the alternative approach to molecular dynamics is Monte-Carlo (MC) simulation. In the MC approach, the required molecular configurations are generated by means of random atomic displacement moves, which are then accepted or rejected using a potential-energy criteria based on Boltzmann statistics, such as that of Metropolis et al.[4] MC simulations can be carried out in all the standard ensembles including NPT.

2.2. Molecular Models

The accuracy of the simulations depends on the accuracy of the input parameters for the simulation, namely the chosen description and, if appropriate, the parameterization of the intermolecular interactions that define the model. The interaction potential or forces may be calculated using first principles (ab initio calculations), that is, a quantum-mechanical description (which would be appropriate if, for example, covalent bond making or breaking were involved), or if the integrity of the molecule is maintained, using a more approximate description, such as molecular mechanics. In molecular mechanics the electrons are not treated explicitly and the molecules are essentially characterized by a "ball and spring" description. The form of the model interaction potential (commonly referred to as the force field) for a molecular system comprises two components: 1) an intermolecular component, modeled by a van der Waals (typically Lennard Jones) and a Coulombic term assuming pair-wise interaction between particles, and 2) an intramolecular component that includes bond stretching, angle bending, and torsional rotation about bonds.[2] The atom-specific parameters therefore include effective radii, well depth for the van der Waals term, partial charges, and various force constants for the intramolecular terms.

The force-field parameters are determined or derived from a variety of sources (experimental and/or ab initio calculations) and then often optimized empirically on the basis of how well the simulations reproduced the experimental data. These force-field parameters directly determine the accuracy of the simulations. The general philosophy, however, is not to identify a set of parameters that accurately describe the true interaction potential for a particular molecule or molecules of interest, but rather to define a limited set of parameters that are transferable between differing molecules. This approach, of course, compromises accuracy for transferability. From the extensive crystal-structure-prediction studies,[5] where the goal is to ascertain the crystal structure given the molecular structure, it appears the accuracy in "off-the-shelf" force fields, such a AMBER,[6] GROMOS,[7] and CHARMM[8] and UFF[9] can be variable. At the very least a set of force-field parameters should be identified that reproduce the known liquid/solution and solid-state properties of the material of interest to an accuracy of about 5%. A failure in this respect would require that the force-field parameters be optimized for the particular material of interest.[10–12]

More specific force fields perform significantly better in terms of accuracy, but are limited to dedicated classes of materials, such as pure metals,[13] or metal halides[14] and metal oxides.[15] Further up (in terms of scale) from the atom-based force-field models are the coarse-grained models, where a group of atoms (typically three to five atoms) are represented by a single particle. These compromise chemical detail in favor of more computationally efficient models that provide a more generic understanding.

The choice of the model depends on the nature of the problem, but there are technical issues that may effectively determine this choice. The major limitations of the molecular-dynamics simulation technique are the system size that can be simulated and the timescales that can be accessed. Given a modest computing resource, for a system for which the electrons need to be considered explicitly, for example, first principles MD, the current limit is approximately 1000 par-

Jamshed Anwar has a degree in pharmacy, and a PhD in chemical physics/crystallography from Birkbeck College, University of London. He worked at King's College London from 1989, being appointed a Reader in 2000. In 2005 he took up a Chair in Computational Pharmaceutical Sciences at the Institute of Pharmaceutical Innovation (IPI), University of Bradford, and is currently a Director of Research for the Bradford School of Pharmacy and the IPI. His research field is molecular simulation and statistical thermodynamics of organic solids and soft matter with emphasis on pharmaceuticals and drug delivery. He is a recipient of the R. P. Scherer Award (1986) and the Pfizer Award (1999).

Dirk Zahn (born in 1972) has a degree in physics, and a PhD in chemistry from the University of Darmstadt. He worked at the Max-Planck Institut (MPI) für Festkörperforschung in Stuttgart, the ETH Zürich, and the MPI für Chemische Physik fester Stoffe, in Dresden where after his Habilitation in 2006 he stayed as a Heisenberg fellow. In 2010 he became Professor of Theoretical Chemistry at the University of Erlangen-Nürnberg. His research is molecular modeling and simulation focusing on nucleation and self-organization processes. He has developed specific MD simulation methods to tackle the time-length scale problems in crystal nucleation.

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ticles simulated for 10–100 ps. For a force-field model the current typical size is approximately 10000–50000 particles and simulation times reaching 10–100 ns. The system size and simulation time are, of course, coupled that is, fewer particles can be simulated for a longer time given a fixed computing resource. So, if the desire is to access long time scales given a fixed computing resource, then we must either reduce the number of particles in the systems or reduce the complexity of the interaction potential so that it is numerically efficient to evaluate, or both. Coarse graining reduces the number of particles in the system whilst keeping the number of molecules fixed.

2.3. The Time- and Length-Scale Problem

Both crystal nucleation and growth challenge standard brute-force MD simulations, but for different reasons. Crystal growth is a relatively slow process, but is just accessible to MD simulations for simple systems. Nucleation on the other hand is an activated process belonging to a class of rare event phenomena, and has a spatial dimension. For an aqueous solution that is 10–20% supersaturated, the nucleation rate is of the order of one nucleus per cubic centimeter per second. In contrast, the system size in simulations is of the order of 100000 particles that occupy a simulation box with dimensions of about $12\times12\times12\ nm^3$ (estimated for an aqueous solution), that is, we only sample a volume of about $10^{-24}\ cm^3$. This equates to a nucleation rate of $10^{-24}\ s^{-1}$, that is, in our simulation we should observe on average one nucleation event every 10^{24} s, which equals 10^{16} years![16] MD simulations currently barely access the μs scale. Clearly, a brute-force approach involving standard MD simulations, where we wait for the nucleation event to occur, will not work. The issue is well illustrated by the study of Matsumoto et al.,[17] on the spontaneous nucleation of ice, where they employed standard MD to simulate a number of trajectories, each taking several months on a supercomputing facility, of which only one was observed to yield ice nucleation.

Given these challenges, can the processes of crystal nucleation be simulated? More generally, can simulations still add value to fundamental research on crystal nucleation and growth? The way forward is to employ more directed simulation methods and/or to focus on those aspects of the problem which are amenable to simulation. The objective then is not to simulate nucleation and/or crystal growth in a holistic way but rather to employ simulation in a judicious manner to explore particular amenable aspects of the problem and then pool the learning.

Directed simulation approaches to nucleation generally require the use of an order parameter that can distinguish between a solid and a melt (or a solution). To drive the simulation model to nucleate, the order parameter is gradually altered towards that characterizing the solid state using a specified scheme. These methods can also yield the free energy of the system as a function of the size of the nucleus, thus giving access to the activation free energy for nucleation, the critical radius, as well as structural insights. There are many variants of directed simulation methods, the most prominent being umbrella sampling, constrained dynamics, and metadynamics.

Do we gain something for nothing with these directed simulations? Apparently not as there is a trade off. In directing simulations we make certain choices; we choose the final state as well as the pathway. In reality a system may nucleate by following an alternative pathway. Clearly, every effort must be made to utilize order parameters that minimize the bias in both the final state as well as the chosen pathway. For example, a good order parameter for nucleation should enable nucleation of any solid state irrespective of its final structure, and hence enable the simulations to capture any phase transformations along the way (a feature of Ostwald's rule of stages[18]).

There is an alternative unbiased approach, trajectory path sampling (TPS), but for this we are required to simulate an ensemble of trajectories. This method focuses on the nucleation event itself, which occurs in a relatively short time, and largely ignores the waiting time required for the spontaneous formation of a nucleus. As a starting point, a single trajectory that successfully (but see qualifier below) captures the process of interest, in this case nucleation, from either brute-force or directed MD, suffices. Further pathways are explored by perturbing the preceding trajectories and following them through both in the forward and backward direction, giving rise to a MC type of sampling of trajectory space (not phase space) with some of these trajectories being successful in leading to a nucleation event. Hence, a manifold of pathways each covering the nucleation event is obtained by un-directed iteration. The TPS procedure is rather powerful as it has been shown that even if the initial pathway is not realistic (possibly owing to strong directing of the crystallization process), the procedure nevertheless evolves to successful pathways with lower free-energy transition states. Upon convergence of trajectory sampling, or at least adequate relaxation from the initial route, TPS will hence provide realistic routes for the process of interest that in principle may be free from any bias.[19,20]

If the crystallization kinetics are not determined by the formation of a critical nucleus, but are rather hindered by solute diffusion towards forming an aggregate, focused MD approaches may help to reduce the computational effort. By accounting for solute diffusion in an implicit way, MD simulations may be dedicated just to the important association events and the structural relaxation of the aggregate.

The choice of an appropriate simulation approach to investigate crystallization processes depends strongly on the system of interest and the type of insights that are desired. In the following, simulation studies of nucleation and phase stability of nanocrystals are detailed with a focus on the simulation methodology.

3. Nucleation

3.1. Classical Nucleation Theory and Its Limitations

At the microscopic level, liquids and solutions are characterized by continual density fluctuations with respect

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to their components. In a supersaturated solution, these fluctuations are thought to give rise to transient solute clusters that may either re-dissolve or become stable and grow, depending on whether they are smaller or larger than a certain critical size. This situation implies a free-energy barrier to the nucleation process, which is indeed reflected experimentally in that liquids can be supercooled well beyond their freezing points and saturated solutions exhibit a metastable region in which nucleation does not occur, provided the solution is free from impurities and is not perturbed.

At a first glance the thermodynamics of crystallization appear rather simple, being encompassed by the phase diagram. Phase diagrams denote whether a compound should crystallize or remain as a liquid or in solution as a function of concentration, temperature, and/or pressure. However, apart from phase stability, kinetic aspects are also of significant relevance to many crystal-growth scenarios, particularly when controlling (or possibly engineering) the internal structure, crystallite size, and/or habitus. A fundamental approach to the kinetics of crystallization is given by the classical nucleation theory (CNT) which is a simple, and for many systems, an effective way to rationalize crystal growth on a quantitative basis. More complex crystal-formation processes which cannot be adequately described by CNT are denoted as nonclassical nucleation and will be addressed later. We focus herein on homogeneous nucleation; for heterogeneous nucleation we refer the reader to a very accessible account by Sear.[21]

Within CNT the energetic balance of crystal nucleation is modeled by two competing terms as a function of solute aggregate size. What favors the formation of a crystalline phase is the gain in free energy (enthalpy if investigated at constant pressure) that results when the material is organized so as to yield the lowest energy structure. This process requires the formation of an interface—between either the nucleus and the melt or the nucleus and the solvent. The overall energy is hence associated with an unfavorable surface-energy term and a favorable bulk term that accounts for the difference in chemical potential between the bulk crystal and the melt or the solution.

In most applications of CNT, the nuclei are taken to be spherical and the two energy terms are written as a function of the radius. Since nuclei need not be spherical and could exhibit a variety of morphologies, we outline a shape-independent formulation of CNT. For this purpose, the surface- and the bulk-energy terms are considered as a function of the number of particles N in the aggregate. For all regular shapes (e.g. cubes, polyhedra, spheres, cylinders, prisms), N scales linearly with the volume whilst the surface area scales with $N^{2/3}$. This approach allows a shape independent description of the free energy per particle [Eq. (1)] where μ is the bulk energy per particle.

$$G(N) = c_{\text{surface}} N^{2/3} - \mu N \tag{1}$$

Depending on the shape of the crystallite, this expression may be transformed to the conventional notation based on the radius of the nucleus. Hence, the conventional form of CNT for a spherical aggregate shape is expressed by

$$N = \rho \frac{4}{3} \pi r^3 \text{ and } 4\pi r^2 \gamma = c_{\text{surface}} N^{2/3}$$

enabling Equation (1) to be rewritten as Equation (2)

$$G(N) = \left(\sqrt[3]{36\pi} \cdot \rho^{-2/3}\right) \cdot \gamma \cdot N^{2/3} - \mu \cdot N \tag{2}$$

where ρ is the particle density and γ is the surface energy density. Taking the derivative of this expression with respect to the aggregate size defines the number of particles that comprise a critical nucleus and the corresponding free-energy barrier to nucleation [Eq. (3)].

$$0 = \left.\frac{dG(N)}{dN}\right|_{N_{\text{crit}}} \Rightarrow N_{\text{crit}}, \quad \Delta G^* = G(N_{crit}) \tag{3}$$

The probability for the formation of a nucleus (hence the rate) is then given by Equation (4)

$$I_{\text{nucleation}} = I_0 \exp\left(-\frac{\Delta G^*}{k_B T}\right) \tag{4}$$

where I_0 denotes the kinetic prefactor. The kinetic prefactor may be assessed from investigating the average relaxation time needed for the critical nucleus configuration to reach a stable state (inverse of the decay rate). The direct assessment of such relaxation times may prove very demanding in terms of computational resources. We consider the alternative approach developed by Auer and Frenkel to be more effective.[22–24]

The central merit of CNT is that it links the kinetics of nucleation to the interfacial and bulk free energies, and hence provides a simple rationalization of what is in fact a very complex process.[25] Whilst the theory has served well in rationalizing experimental observations involving homogeneous and heterogeneous nucleation and yielding insights into fundamental mechanisms, it often fails when it comes to detail and quantitative comparisons. A core issue with CNT is that it utilizes bulk thermodynamic quantities, the volume and surface/interface free energies, and yet applies them to clusters comprising tens to hundreds of atoms. We are learning, in particular from simulations, that we cannot treat emerging nuclei as tiny crystallites with bulk properties. At the atomic scale, the picture of an idealized periodic structure is not only a drastic simplification, but perhaps completely wrong. For such small structures we are probably dealing with a manifold of transition states, which might be poorly represented by just a single critical-nucleus configuration. Furthermore, simulations show that the nucleus–melt or nucleus–solvent interface tends to be diffuse adopting a structure that minimizes the interfacial free energy.[26] There is increasing evidence that solvents pre-select particular molecular motifs (growth units or synthons) that go on to appear in the crystalline form, rather than the solvent just affecting the interfacial free energy of the emerging nuclei in a general way.[27] Also, it remains difficult to rationalize how trace impurities promote or inhibit nucleation within a framework based on CNT.

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Perhaps the biggest challenge to face CNT is the idea that nucleation can be a multi-stage process. There is a large body of experimental data which indicates that under certain circumstances, nucleation of crystallites appears to occur by at least two distinct stages, the formation of a stable disordered cluster or a mesocrystal and subsequent nucleation of the crystalline phase within the cluster (by a structural transformation).[28–31] This nonclassical nucleation behavior may be considered as a special case of Ostwald's step rule[18] (with Stranski's and Totamov's qualification[32]), which proposes that the phase that first nucleates is that with the lowest energy barrier, and the system then evolves stepwise to the most stable phase. The subsequent evolution of different crystalline structures involving solid–solid phase transitions must involve a nucleation step at each stage, albeit in a solid matrix. How this occurs and the associated energetics largely remain a mystery, though recent studies have started to shed some light on this issue. Indeed, for directed MD approaches relying on a liquid–solid order parameter, many aspects of such processes are elusive and might simply remain unnoticed because free-energy differences can only be calculated along the model reaction coordinate. Solid–solid transformations may not give rise to changes in the order parameter even though the free energy is not constant. Hence, in such cases, the free-energy profile obtained may be severely wrong. Clearly, to deal with the various limitations of CNT and nonclassical aspects of crystal nucleation we need to focus on the microscopic nature of molecular clustering and even on individual molecular interactions.

3.2. Brute-Force Molecular Dynamics Simulations of Pre-Nucleation Processes and of Nucleation

3.2.1. Realistic Models

Despite the acknowledged difficulty of observing nucleation in MD simulations, researchers continue to explore the possibility, often making some judicious decisions regarding the choice of system and variables (e.g. supersaturation, under-cooling) in a bid to make the process accessible to simulation. Perhaps the most celebrated study is that of spontaneous nucleation of ice,[17] which required years (sum total) of supercomputing resource. Homogenous nucleation of ice at the subsurface for a system with a water–vapor interface has also been simulated,[33] as has nucleation of NaCl from the melt in nanodroplets.[34] Other notable studies include simplified models of acetic acid in carbon tetrachloride (no ordered structures were observed)[35] and NaCl in water (simulations yielded crystallites of rocksalt structure),[36] for both of which solute aggregation was promoted by enabling the solvent to evaporate.

More promising is to employ MD simulations to understand the molecular interactions and clustering that may precede nucleation. A number of studies on a variety of small molecules including saccharin, sulphathiazole, and dihydroxybenzoic acid, suggest that particular molecular-packing motifs that appear in the resulting crystals may in fact be present in solution prior to nucleation.[27] In protein crystallization, there are examples of the crystallizing units being oligomers rather than monomers; insulin is known to exist as either dimers or hexamers in supersaturated solutions.[37] Further, it appears that a particular solvent may in fact pre-select a motif, for example, dimers, and hence determine the resulting crystalline form. A better understanding of the molecular pre-assembly may enable us to manipulate nucleation by way of solvent choice. Other than a few simulation studies, the notable ones being concerned with solution chemistry and crystal formation of tetrolic acid[38,39] and 5-fluorouracil,[40] this area of research remains largely unexplored by simulations.

Furthermore, studies related to pre-nucleation processes are of considerable value for the rationalization of nucleation hindering by additives in the solution. A prominent example of such investigations employing realistic models is given by the work of Parrinello and co-workers on the precipitation of $CaCO_3$ from aqueous solution and the effect of polyacrylate ions. In this work, the detailed exploration of the association of just a few ions proved sufficient to provide conclusive mechanistic insights.[41,42]

3.2.2 Simple Generic Models

The simplest model employed in molecular simulations of crystallization is the hard sphere. This model is often considered as academic, but it has an experimental analogue, the hard-sphere colloid, the crystallization of which has been extensively studied experimentally.[43] The next level of sophistication is a soft particle with a continuous short-ranged interaction potential, a specific version being the Lennard-Jones (LJ) particle with a 12-6 potential (the repulsion scales by r^{-12} and while attraction scales r^{-6}). The choice of the exponents in the interaction potential determines the degree of softness of the particle; higher values of the exponents yield a harder particle. The LJ potential (12-6) itself corresponds to the noble gases. These models offer computational efficiency but may also provide correspondence with a particular class of materials (rather than a specific material).

The earliest MD simulations of nucleation utilized both hard spheres as well as Lennard-Jones particles and focused on nucleation from the melt.[44] To investigate crystal nucleation from solution, the identification of an appropriate model is somewhat more challenging.[45,46] At least two species of particles are required to mimic the solute and the solvent. Moreover, at a defined temperature and pressure only the solute must crystallize whilst the solvent remains in the liquid state. This situation was successfully implemented by characterizing the solute and solvent species as LJ particles but with differing parameters.[45] The key to selecting the appropriate parameters was the LJ phase diagram which had been calculated earlier[47] (a simulation tour de force in its own right). Thus the parameters and thermodynamic conditions could be chosen such that the solute species yielded the solid phase, whilst the solvent remained in the liquid phase.

Starting from a configuration in which the solute particles were interdispersed in the solvent, Anwar and Boateng observed the rapid clustering of the solute species to form an

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amorphous structure.[45] The amorphous structure then underwent self-organization in favor of crystalline motifs. These formed in a sequential manner, hinting at an Oswald step rule type of process. The observation of an amorphous liquid-like structure in these and other simulations is significant, being now linked with similar observations in real systems, such as "oiling out" in crystallization of small organic solutes,[28] dense liquid-like phases observed during protein crystallization,[30] and the direct observation of a dense liquid-like precursor in a 2D colloidal model system.[29]

The combined insights from simulation coupled with experimental data have now led to a new perspective on the mechanics of nucleation. The idea implied in CNT, that the fluctuations in density that cause nucleation are simultaneously coupled with ordering of the solute molecules has been relegated to being only applicable to a specific case. The insights suggest de-coupling of the density fluctuations from the ordering of the solute molecules. Thus, a density fluctuation may give rise to a metastable high-density liquid-like phase (stabilized by a low interfacial free energy) rather than directly to an ordered structure. The segregated solute then proceeds to order in a subsequent process.[30] Hence two barrier crossing events are encountered 1) the barrier to solute segregation and 2) the nucleation barrier.

More recently, the Lennard-Jones nucleation study has been complemented by including designer additives into this solute–solvent system, which has enabled the elucidation of the general mode of action and design rules for additives that promote or hinder crystal nucleation.[45] This result is quite a breakthrough given that this area of research was essentially devoid of testable ideas, except for the predominant (but inappropriate) view that nucleation modulators acted in much the same way as crystal-growth modulators that is, molecular recognition being the important feature. The key determinants of an additive that can modulate crystal nucleation appear to be 1) its strength of interaction with the solute, 2) its disruptive (which may be steric, entropic, or energetic-based) or templating ability, and 3) its interfacial properties. For example, an effective nucleation inhibitor should have a strong interaction with the solute and have a structure that is able to disrupt the periodicity which characterizes the emerging nucleus. A strong affinity for the solute (relative to solvent and itself) not only ensures that the additive molecules end up within the emerging solute aggregates, but also serves to disrupt the crystal packing by forcing the solute particles to align themselves around the additive at the expense of the solute–solute interactions and packing. These pre-requisites of having a strong affinity for the solute and a disruption capability are quite different from those required for crystal-growth inhibition. Figure 1 a illustrates the effect of a large single-particle additive in disrupting the emerging lattice and inhibiting nucleation, whilst Figure 1 b shows an amphillic dimer molecule that promotes nucleation.

A somewhat similar study was performed by Cacciuto and Frenkel focusing on colloid nucleation on a variety of template surfaces.[48] This work also describes an extension of CNT to nucleation on surfaces, aspects of which we consider to be applicable to heterogeneous nucleation scenarios in general.

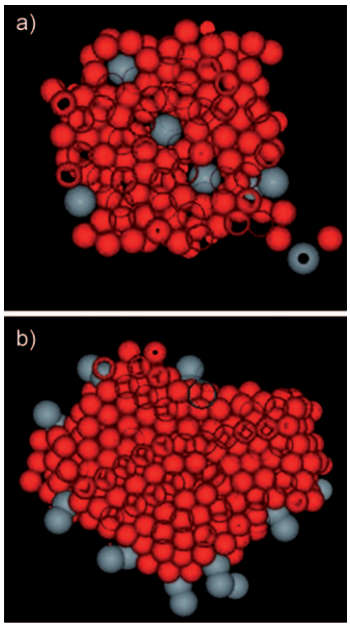

Figure 1. Case studies of aggregation from solution in the presence of additives. a) solute-philic additives (gray spheres) of a misfitting (large) radius disturb the ordering within the emerging solute nucleus (red spheres) by forcing the solute particles to align themselves around the additive at the expense of the solute–solute interactions and packing. b) additive dimers (gray) of amphiphilic character lower the solvent–aggregate interface energy and hence promote crystal nucleation. For clarity, the solvent is not shown in both pictures.[45]

While these studies demonstrate the potential of simplified models, the time- and length-scale problem persists even for these computationally efficient particle systems. Indeed, the standard MD simulations described above were performed at strong supersaturations to accelerate the crystallization. The occurrence of rare events such as nucleation, can indeed be enhanced by subjecting the system to a high chemical potential (by way of supercooling, application of pressure, or supersaturation) but care has to be taken in interpreting the results. Insights from simulations at a high chemical-potential difference may, for example, be applicable to typical production conditions, such as batch crystallizers or crystallization by spray drying, but are unlikely to characterize protein crystallization where the thermodynamic driving force may be lower and crystallization occurs over days to months. Excessive driving of a process may easily lead to important intermediates being skipped or even cause the system to follow completely different mechanistic routes from those important at a low chemical-potential difference.

3.3. Directed Simulations of Nucleation

About ten years ago, Frenkel and co-workers pioneered the study of nucleation from the melt by means of directed simulation methods. The initial studies utilized hard spheres and LJ particles,[22–24,49] but later studies have included NaCl.[50] Other researchers have used the methodology to study nucleation in ice,[51–53] diamond,[54] and aluminum.[55]

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Directed simulations employ an order parameter Φ, which is a function of the coordinates of the crystallizing species. A particular value of the order parameter $\Phi = \nu_0$ would characterize the disordered structure, that is, liquid or solute randomly dispersed in a solvent, whilst another value $\Phi = \nu_1$ would characterize a crystalline structure. Directed simulations systematically coerce the system to follow a structural evolution from the disordered to the ordered state, as the value of the order parameter is ramped up from ν_0 to ν_1. It is critical that the chosen order parameter clearly discriminates the disordered liquid or solution state from the end-state crystalline structure. While the optimal choice of the order parameter Φ would be the real reaction coordinate for nucleation, lacking such detailed information, the order parameter, and hence the model reaction coordinate, must be predefined as a reasonable guess. As mentioned earlier, this is a crucial issue as the desired free-energy profile can only be assessed as a function of the model reaction coordinate, and poor reaction-coordinate models will lead to energy profiles that are not representative of the nucleation process. Examples of Φ are the radius of the nucleus or the number of solute molecules that are separated from solution; these in turn are, of course, a function of the criteria for identifying whether a specific particle is in the solid state or otherwise, which also is not a trivial task. Frenkel and coworkers employed more versatile order parameters based on spherical harmonics to describe nearest-neighbor interactions using a local bond-order concept that takes into account both distance and the angular distribution of the interactions[49,56] For simulating the nucleation of NaCl from the melt[50] the number of solid-like particles in an emerging cluster was assessed using the Steinhardt local bond-order parameter Q4.[56]

In a directed simulation, the standard method (be it MD or Monte Carlo) is complemented with a bias potential, typically a harmonic term of the form $U = (\Phi - \Phi_0)^2$, to drive the simulation to a desired value of the order parameter, Φ_0. A particular value of Φ_0 identifies a desired state somewhere between the liquid (or solution) and the formed crystal. A series of such simulations (or a single set of parallel simulations exploiting efficiency-enhancing techniques, such as parallel tempering) are carried out to sample the entire nucleation process. The generic application of a bias potential is termed "umbrella sampling" and hence the above methodology goes under the same name. A recent variation on this technique is metadynamics,[57] which explores the configurational manifold of a system with a small set of descriptive coordinates. The metadynamics approach continuously disfavors regions in phase space such that otherwise stable states are abandoned. However an important limiting factor is that the free-energy profiles are obtained as a function of the previously chosen set of descriptive coordinates. A series of applications have been reported mainly for crystal-structure prediction,[58–60] but there is also a recent application to ice nucleation.[61]

The directed simulation studies, particularly of Frenkel and colleagues, have provided extensive insights into the nucleation process. These simulations have highlighted and confirmed some of the limitations of CNT, namely, that the interface between nucleus and melt need not be sharp but is more likely to be diffuse, that the structure of the interfacial atoms may be consistent with one phase (to reduce interfacial free energy) whilst the inner core of the nucleus could be another phase,[24] and that the nucleus is often not spherical and in some cases is strongly faceted.[55] Some of these features are borne out in experiments on colloidal particle systems for which nucleation can be observed directly.[29]

A particularly notable contribution employing directed simulations concerns the origin of the "crystallization window" in protein crystallization.[62] At low supersaturations, crystallization is rarely observed while at higher supersaturations, above a certain limit, amorphous precipitation occurs. It appears that the crystallization window is linked to a particular region in the protein phase diagram.[63] The behavior of colloids in solution can be mapped onto a molecular phase diagram with the dilute colloidal phase corresponding to the vapor, the dense phase to the liquid, and the colloidal crystal to the solid phase (Figure 2). The phase diagram of globular proteins does not show a vapor–liquid, that is, a fluid (low density)–fluid (high density), coexistence line or a triple point. This feature does not rule out a metastable fluid–fluid coexistence line below the stable fluid–solid curve. The simulations employed a modified LJ potential to model a globular protein and calculated the free-energy barrier to nucleation at four distinct points on the protein phase diagram as indicated in Figure 2. The results were significant in that the nucleation barrier decreases and hence the kinetics of nucleation are considerably enhanced close to the metastable fluid–fluid critical point because of the presence of large density fluctuations, confirming the crystallization window and suggesting a strategy for identifying optimum conditions for protein crystallization. The increase

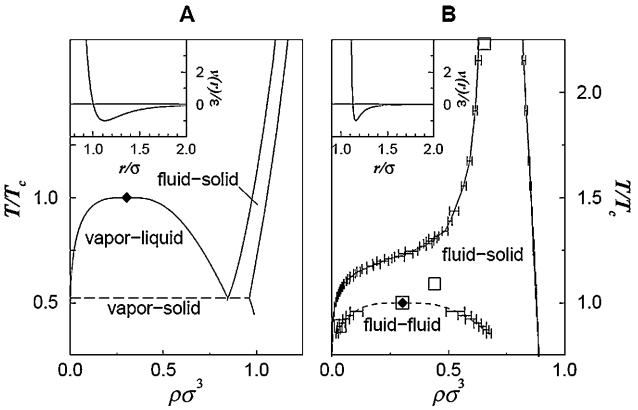

Figure 2. A) Typical phase diagram of a molecular substance characterized by a Lennard-Jones potential (inset); dashed line: triple point; ◆ vapor–liquid critical point. B) Phase diagram of a protein colloid with short-ranged attraction (inset), which does not show a stable fluid–fluid coexistence (corresponding to the vapor–liquid coexistence in a standard phase diagram) or a triple point. The dashed curve in (B) indicates the metastable fluid–fluid coexistence. Crystal-nucleation barriers were computed for the selected points (□). The nucleation barrier was found to be significantly lower (indicating an enhanced nucleation rate) in the vicinity of the metastable critical point. Figure reproduced from Ref. [62] with kind permission of *Science*.

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in protein nucleation rate in the vicinity of the metastable fluid–fluid critical point has been confirmed in experiments on lysozyme.[64]

Another success story of directed simulations is the simulation of ice nucleation. Radhakrishnan and Trout employed a combination of the Steinhardt two-body (Q_6) and a three-body tetrahedral bond-orientation order parameters to nucleate ice and to calculate the associated free-energy barrier for the TIP4P model of water using umbrella sampling.[51,52] The hexagonal form of ice Ih was observed in all cases. The nucleation barrier was calculated to be to be 54, 58, and 63 $k_B T$ at temperatures of 140, 160, and 180 K, which as expected is significantly higher than the corresponding value for Lennard-Jones fluids which is approximately 20 $k_B T$. The freezing point of the TIP4P water model is 232 K at 1 bar.[65] The process of ice nucleation was also tackled using the alternative method of metadynamics with a similar set of order parameters but also including potential energy, again using the TIP4P water model.[61] These simulations yielded a higher nucleation barrier, 79 $k_B T$ at 180 K and the cubic ice phase Ic, rather than the hexagonal phase Ih observed by Radhakrishnan and Trout. The differences have been largely attributed to the small system sizes simulated relative to the size of the nucleus, and the consequent effect of the periodic boundaries of the simulation cell.

Despite these successful applications, a consistent understanding of the nucleation of ice clearly still eludes us. There remain issues of what might be an appropriate order parameter for enabling competitive growth of the two ice phases Ih and Ic.[53] Also, simulation systems need to be larger to minimize periodic boundary effects. The physical picture being proposed is that of a two-stage process.[53] Initially, short tetrahedrally arranged threads and rings of water molecules emerge and become correlated to form a diffuse ice-genic network. Later, hydrogen-bond arrangements within the amorphous ice-like structure gradually settle down and 'tune-in' neighboring water molecules, resulting in an ice core that spreads throughout the system.

While the application of directed approaches to nucleation is elegant they remain technically challenging, we note that there are no applications to molecular crystals of any significant size, other than ice nucleation. The essential challenge lies in identifying an appropriate order parameter that can discriminate between the liquid/solution state and the solid, without specifying a particular crystalline structure. The point is that it is essential not to predefine a model reaction coordinate that yields a particular crystalline form. In the real world the system may not nucleate directly to this structure and the choice of the model reaction coordinate could be inappropriate. Therefore, although the system is being directed to nucleate, the choice as to which solid-form, crystalline or otherwise, nucleates, whatever precedes nucleation, and subsequent transitions post nucleation should be left unbiased. To make matters worse order parameters tend to be system specific. While Frenkel et al. have been successful in identifying "unbiased" forms of order parameters for the close-packed structures of colloids that have been investigated, identification of an appropriate order parameter for water, for instance, still remains a challenge.[51–53,61]

Despite the progress, for many systems, comparisons with experiment (particularly kinetics based on CNT) reveal severe shortcomings, and it is not entirely apparent whether the problem lies with simulation methods or the applicability of CNT. Even a simple generic model of polar soft spheres has a complex nucleation mechanism involving different types of ordered structures.[49] Whilst, in principle, the underlying competition between different crystalline motifs is accessible to directed MD simulations, the choice of the order parameter however remains an unresolved problem. Hence, to investigate the evolution of different structures in the spirit of Ostwald's step rule, or the formation of an amorphous or a mesostructure and its subsequent reorganization, unprejudiced approaches are desired.

3.4. Unbiased MD Simulation Approaches to Nucleation Processes

The direct investigation of structural changes of an aggregate whose evolution follows Ostwald's step rule would imply long-term MD simulations. As these are unfeasible for most systems, an intuitive way to promote the crossing of the energy barrier(s) to induce reorganization is given by imposing strain or by simulated elevated temperature. Such strategies may also be used to obtain realistic final configurations from artificially prepared states. A demonstrative example of this strategy was recently given by Thi et al.[67] for the formation of a nanocrystal from an amorphous structure. By inducing tension and high temperature to a cubic block of MnO_2 the model was first amorphized and then allowed to recrystallize whilst lowering temperature and switching off the tension. On this basis, nanocrystals may be promoted to an amorphous (or even molten) state of high atomic mobility. The subsequent recrystallization is not biased by constraints along a predefined order parameter, but it is clearly heavily influenced by the rapid nucleation from a state that is strongly disfavored thermodynamically.

Many of the limitations of brute force methods and directed approaches mentioned above may be overcome by the method of transition-path sampling (TPS), introduced by Chandler and co-workers[68,69] or its variations, such as transition interface or forward flux sampling. These techniques have been developed specifically for so-called rare events such as nucleation, where there can be a long wait for the process to initiate, but once initiated the process goes to completion relatively quickly. TPS focuses the MD simulations on the rare event itself, that is, the relatively short time-interval in which the process of interest takes place and largely ignores the lengthy waiting period required for the process to initiate, which is typically inaccessible by unconstrained simulation.

As a prerequisite to TPS iterations, a starting trajectory (a set of configurations each comprising atomic coordinates and velocities as a function of time) of the rare event is needed. The initial trajectory or pathway need not be a favorable one and is typically prepared artificially. During a path-sampling iteration, a configuration of the system at a particular time is taken from the preceding transition pathway and perturbed

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either by slightly modifying the atomic coordinates or the velocities whilst keeping the total momentum, torque, and free energy of the system unchanged. The modified configuration is then propagated in both directions in time by MD simulations and the resulting trajectory is checked to see whether it does span the process or event of interest. In the case that the desired event is covered by the new trajectory, this trajectory is then chosen for generating further trajectories. Harvesting successful trajectories in an iterative manner leads to a manifold of dynamic pathways, each reflecting a possible transition route.[68,69]

To study nucleation an individual configuration from an earlier nucleation simulation would be taken. This configuration may be from a directed simulation utilizing a biased potential or an order parameter to induce nucleation. The configuration is then slightly perturbed and propagated using MD in the forward and backward directions in time. A successful trajectory would be one which bridges the initial disordered state (liquid or solution) and the nucleated state. Unsuccessful trajectories would be those that converge to a disordered state in both the backward and forward directions, nucleate in the forward direction but do not converge to a disordered state in the backwards direction, or vice versa. The successful trajectory would then be perturbed for the next iteration. The collection of successful trajectories represents the possible pathways by which nucleation could proceed.

This sampling of transition pathways reflects a Monte-Carlo simulation in trajectory space and—after convergence—the likelihood of a specific mechanism may directly be related to its probability of occurrence in the manifold of successful transition pathways. Less-preferred pathways or mechanisms are associated with larger barriers and would appear only rarely during conventional transition-path sampling. Unlike the first nucleation pathway which needs to be prepared artificially, the mechanistic analysis is performed after convergence of the transition-path sampling procedure and is therefore not biased from predefinitions. This feature makes transition-path sampling a very powerful tool using MD simulations for investigating reaction mechanisms of rare events or processes.

TPS is particularly suitable for crystallization processes which are not limited by diffusion, but triggered by a single energy barrier. Such characteristics may be encountered for nucleation from the melt, but typically not for aggregation from solution. For example, Moroni et al. investigated crystal nucleation from the melt using TPS yielding an insightful analysis of the corresponding transition-state regime.[70] The analysis revealed considerable differences in both size and shape of the critical nuclei for the various different crystal-formation pathways. Hence, the often used picture of a single critical nucleus (that forms the basis of CNT) appears to be a rather gross simplification, which needs to be replaced by a manifold of transient states resulting from a collection of different crystallization pathways.

TPS simulations have also been extended to investigate the interaction of impurities with nucleation processes. A recent TPS study explored the interplay of crystal nucleation and impurity segregation[71] in molten NaCl, incorporating F^- and Br^- ions as impurities. Comparing the eutectic system (NaCl/NaF) to nucleation of pure sodium chloride or solid solutions (bromide incorporation) the underlying atomistic mechanisms were identified. In particular, crystal nucleation was found to occur in regions of the melt that are sparse of unfavorable impurities, with subsequent crystal growth and impurity diffusion being strongly correlated so that incorporation of the impurity in the crystal is avoided.

Although there is one study on transition-path sampling of ion aggregation from solution,[72] there are strong limitations imposed by diffusion-controlled processes. This problem is absent for crystallization from pure melts, and of minor importance for melts comprising only a few impurities, but becomes a critical issue when exploring nucleation from solution, particularly of materials with low solubility. Indeed, Zahn's work on NaCl aggregation from an aqueous solution could only offer insights into the very early stages of ion association and motif formation.[72] After the formation of even a small nucleus, the uptake of further ions requires the transport of solutes to the aggregate. For this the diffusion of solutes must be considered which cannot be accomplished by direct MD simulations without provoking unreasonable computational effort.

Crystal formation from dilute solution is mainly diffusion controlled, that is, it is slowed down by random walks over small (but many) energy barriers. While transition-path sampling performs excellently for single barrier crossing, the tackling of diffusion-controlled crystal formation requires a different approach.

3.5. Simulation Approaches to Diffusion-Controlled Aggregation

Compounds with low solubility constants impose a rather different precipitation scenario than that envisaged by CNT. The crystallization of these compounds is restricted to very dilute solutions even at relatively high supersaturations. We will illustrate this issue for CaF_2 crystallization from aqueous solution. To dissolve just one formulae unit of fluorite, about a million water molecules are required. In this case, the ion–ion interactions are markedly stronger than the ion–water interactions and, in terms of potential energy, aggregate growth is exothermic from the very beginning, that is, for the formation of an ion pair. Thermodynamically, precipitation can only be avoided by a considerable gain in entropy through ion dispersion in a large volume (solution). Such demands imply enormous amounts of solvent molecules. Direct simulation approaches, therefore, do not only need to cope with large model systems, but—much worse—they need to provide extremely long trajectories to ensure proper statistics. This scenario may easily exceed the scope of available supercomputing resources by 5–10 orders of magnitude.

This challenge has been addressed recently by Zahn and co-workers who developed a specific method in which diffusion processes are mimicked in an approximate manner, which avoids the need for large systems and long simulations.[73] The uptake of a solute molecule by a forming aggregate is modeled using an inexpensive docking-type approach, whilst the incorporation of the associated solute into the aggregate is explored by a detailed atomistic

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simulation. Hence, the simulation protocol is divided into several steps each focusing on (and in some instances reducing) the different aspects of system complexity. The aggregate growth is explored particle-by-particle within an iterative procedure, starting typically from the very beginning, that is, the association of a pair of atoms or ions.

While there might not be a barrier to ion association, there may well be barriers to aggregate reorganization. Hence kinetic hindering may prevent full relaxation of the aggregate structure to the global energy minimum and realistic approaches to aggregate growth must also consider transient structures which reflect local energy minima. As an important feature of the Kawska–Zahn approach, the applied relaxation procedure does not necessarily involve global energy minimization after each growth event, but instead describes crystal growth as a series of structurally related configurations which may also represent local energy minima. In the spirit of Ostwald's step rule, a continuous evolution of the aggregate structure during crystal growth is observed.[73,74]

Such studies of ion association and aggregate growth from solution can yield details of the interplay of the solvent molecules with the forming aggregate. Moreover, a combined quantum/classical MD scheme was developed to explore ripening reactions during crystal growth. A prominent example for such processes is given by the nucleation of ZnO from ethanolic Zn^{2+}/OH^- solutions. In the embryonic stage of aggregate formation a metastable agglomerate of Zn^{2+} and OH^- ions is formed. However, instead of forming a $Zn(OH)_2$ crystal, proton-transfer reactions lead to the formation of O^{2-} ions (Figure 3, left) and the nucleation of a ZnO domain in the aggregate core (Figure 3, right).[75]

3.6. Nucleation of Nanocomposites

The importance of nanocrystal–polymer composite materials has inspired considerable theoretical effort towards revealing both structural insights as well as understanding the mechanisms of self-assembly in these systems.[76] The self-assembly issue is typically explored from investigating nanocrystals embedded in a polymer melt or (anticipating solidification from the melt) directly within a solid polymer matrix.[77–83] To reduce system complexity, implicit models were developed for the polymer matrices. Using such focusing on the nanocrystal arrangement only, the phase behavior at the nano- to mesoscale became accessible. Along this line, Sides et al. identified the arrangement of nanocrystals in polymer and co-block polymer matrices in convincing agreement with experiment.[77]

For nanocomposite precipitation from solution, the gap between experimental advance and the development of suitable simulation protocols for exploring synthesis mechanisms is particularly large. Indeed, most simulation studies are dedicated to the interaction of single surfactant molecules with specific surfaces of a given nanocrystal as described in Section 4.2. While this approach may form at least a starting point for understanding the precipitation of nanocrystals that are stabilized by surfactant molecules, additive molecules that directly act as nucleation seeds require different simulation approaches. The explicit consideration of such additives in investigations of the nucleation process using generic models was outlined by Anwar et al. (Ref. [45] see also Figure 1), a study that has been discussed in Section 3.2. For an explicit model dedicated to apatite–collagen composite formation, Zahn and co-workers demonstrated the interplay of ion association to collagen and the formation of hierarchical composites.[84–86]

The importance of apatite–collagen composites as the predominant component of bone and teeth has motivated a large number of (biomimetic) experimental and theoretical studies.[87–90] To cope with the enormous complexity of metabolic processes, setups of biomimetic synthesis were developed to focus on only the key aspects of composite nucleation.[87] In a somewhat similar fashion, atomistic

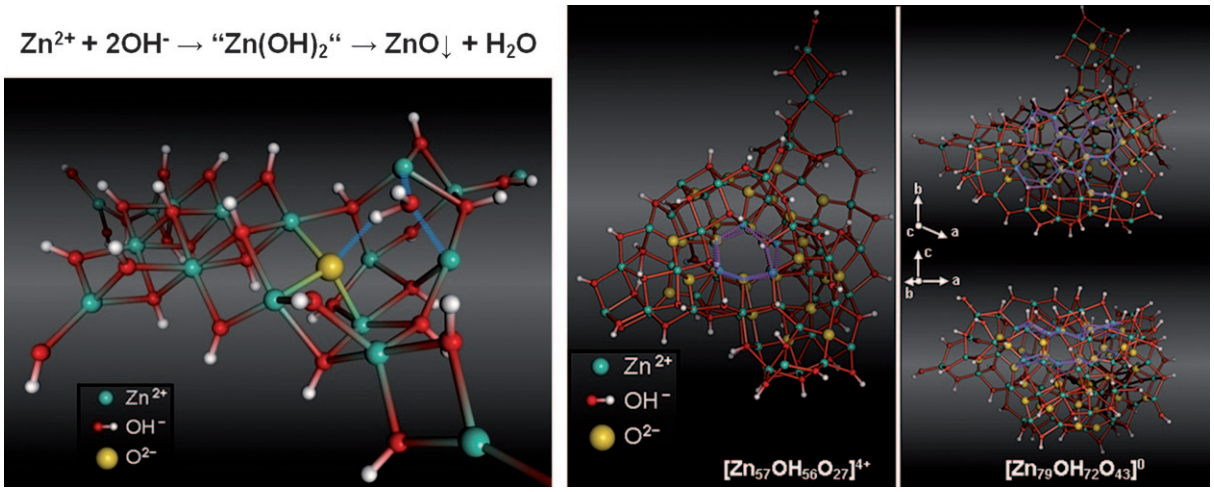

Figure 3. Nucleation of ZnO from ethanolic solution (solvent not shown). Left: Aggregation of Zn^{2+} and OH^- ions and pre-ordering of octahedral motifs until ripening sets in. The ripening reaction formally reflects an $OH^- + OH^- \rightarrow O^{2-} + H_2O$ proton transfer which is however, strongly promoted by the Coulombic interaction that is due to Zn^{2+} ions nearby. The resulting water molecule migrates into the ethanolic solution. Right: nucleation of ZnO motifs and growth of $ZnO/Zn(OH)_2$ core–shell nanoparticles.[75]

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simulations too have focused on model systems that account for individual aspects of the complex interplay of inorganic matter with biomolecules. For example, model studies mimicking the association of single ions to collagen fibers in aqueous solution provided an atomistic understanding of collagen stiffening or bending by calcium or phosphate pre-impregnation, respectively, which accounts for changes in the growth mechanisms governing the composite's form development at the mesoscale.[84]

In a subsequent study, the mechanisms of aggregate formation and of growth-control by collagen fibers at the atomistic scale were investigated.[86] This study was dedicated to the embryonic stage of the nucleation process—both in water and in aqueous solutions containing collagen molecules. In this way the (self)organization in different environments and the elaborate atomistic interplay governing the formation of apatite–collagen composites were explored. The studies addressed ion aggregation promoted by "capture" of ions in the tails of a collagen fiber and calcium phosphate nucleation at the triple-helical backbone of collagen. Both aspects were explored in separate simulation setups and contrasted to a third model system corresponding to calcium, phosphate, and fluoride ion aggregation from aqueous solution in the absence of collagen molecules. From this comparative approach, the preferred Ca_3F motifs (highlighted in Figure 4) induced by incorporation into the triple-helix during the embryonic stage of ion association could be identified. These peculiar motifs represent nucleation seeds for the formation of the apatite crystal structure oriented in accordance to the alignment of the collagen fibers—a microscopic phenomenon giving rise to hierarchical composite growth on the mesoscale.[85] Accordingly, ion association to collagen followed by motif design and orientation is suggested as an atomistic mechanism of growth control governing the nucleation of apatite–collagen composites.[86]

4. Nanocrystals

4.1. Simulations of Nanocrystal Stability and Phase Transformations

Nanocrystals and their composites can exhibit markedly different properties with respect to bulk phases and hence offer new opportunities for materials design. For example, for pharmaceuticals, nanocrystals promise to resolve the issue of poor bioavailability of poorly soluble drugs.[91] Their immense surface area enables these crystals to dissolve much quicker, resulting in higher bioavailability. Other examples of important nanocrystal applications include nanoelectronics, optoelectronics, photonics, and heterogeneous catalysis. These applications result from new electronic and optical properties at this length scale, as well as enhanced mechanical properties in the case of nanocomposites. The difficulty in exploiting these new perspectives is the technical challenge of generating and stabilizing nanocrystals. Empirical development of methods to generate nanocrystals and nanocomposites is severely limited by the lack of a theoretical framework, which in principle could be developed using molecular simulation. Technological needs include the ability to rationally select

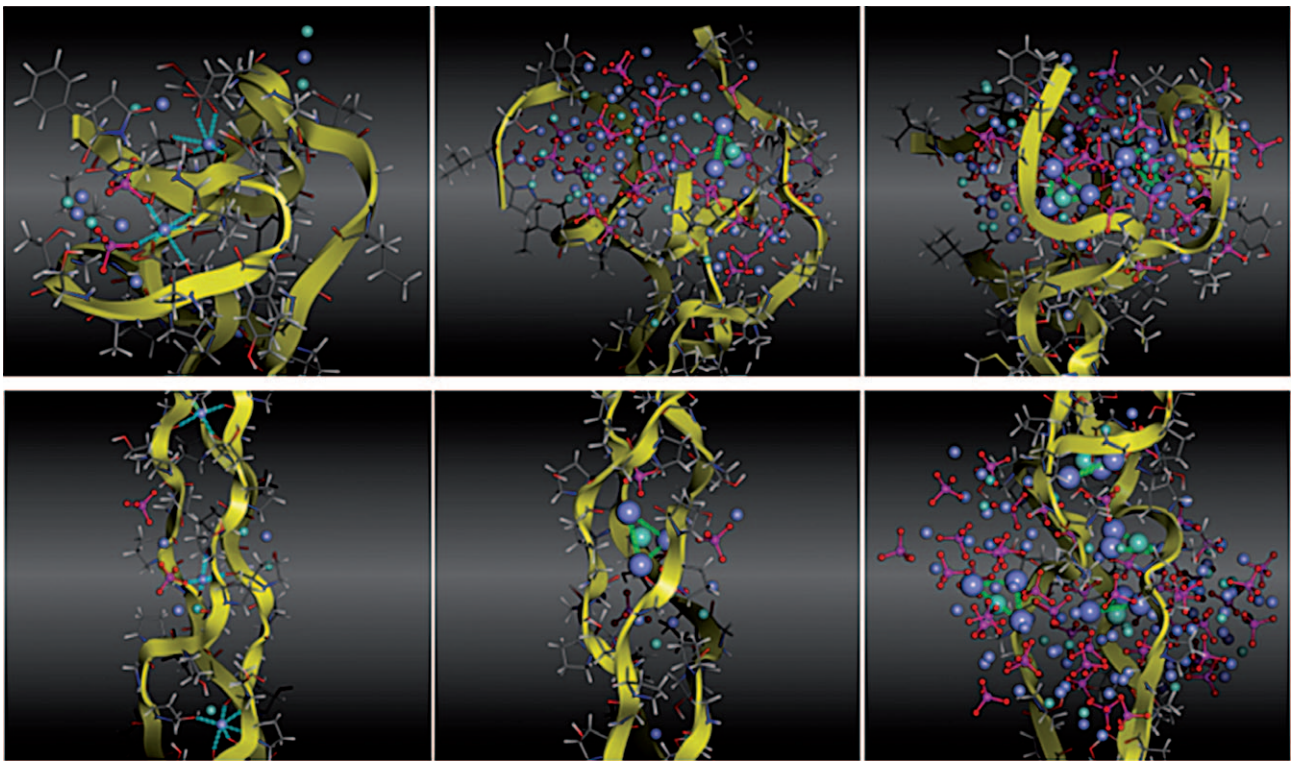

Figure 4. Nucleation of a biocomposite from aqueous solution with collagen proteins acting as seeds. Left: Aggregation of calcium (blue), phosphate (red), and fluoride (green) ions. Middle and Right: nucleation and growth of apatite-type motifs induced by a collagen triple-helix.[86]

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appropriate surfactants, polymers, or a matrix to stabilize nanoparticles of a particular size in a required phase for a given substance.

Going down the length scales gives rise to some new physics with respect to phase stability. As a crystal decreases in size, its surface or interfacial free energy (the choice depends on whether the crystal is stand alone or surrounded by some medium) becomes significant relative to its bulk free energy and the thermodynamics of the crystal are now determined by the interplay of these two energies. Depending on the crystal size, the surface (interfacial) energy can favor a particular phase that otherwise may be unstable in the bulk, or even an entirely new phase, hence enabling phase stability to be modulated. The phase stability issue prompts a number of fundamental questions: How does the phase diagram for a system exhibiting multiples phases vary as we go down the length scale? At what length scale do the macroscopic ideas of bulk free energy (periodic structure) and surface (interfacial) free energy break down? How are the kinetic barriers to phase transformation influenced by length scale?

From the molecular simulation perspective, the emergence of nanotechnology has in a way, referring to the adage "can't see the wood for the trees", returned the focus from the wood (the bulk system, which was always a challenge to molecular simulation) back to the tree (the nanosystem, which has been accessible to simulation). Thus nanosystems, and in the current context, nanocrystals, particularly at the lower size scale, can be investigated by molecular simulation. Whilst the formation of nanocrystals using a bottom up approach (in contrast to top down processing, such as milling) is a nucleation issue and hence presents specific challenges to molecular simulation, the other key nanocrystal issues including phase stability, tendency to aggregate, and morphology can all be studied to some extent using standard simulation methods.

We alert the reader to a distinction between nanocrystals and molecular clusters that sometimes go under the term nanoparticles in the literature. Molecular clusters may exhibit symmetry but do not show periodicity, and each lowest-energy configuration for a given number of molecules can be unique. Phase stability of molecular clusters can provide invaluable insights into pre-nucleation clustering. An algorithmic challenge in this case is to find the lowest free-energy configuration (a global optimization problem), which very quickly becomes intractable as the number of molecules and/or their complexity increases. The general area and technical details of the methods employed are reviewed in a recent text by Wales.[92] Whilst each global energy minimum reflects the most stable structure of a cluster of a given size, a growing aggregate is nevertheless unlikely to follow a pathway where it adopts only its global energy minimum configurations. A continuous evolution by structurally related local energy minima appears much more reasonable (cf. Ostwald's step rule). Using the example of copper clusters Milek and Zahn recently outlined the study of continuous structural evolution between particularly stable high-symmetry cluster configurations.[74] This involved a series of structural transitions from icosahedra/dodecahedra with fivefold symmetry to face-centered cubic (fcc)-type motifs and vice versa (the transformations between high-symmetry clusters and fcc-crystallites reflect the competition between bulk (favoring fcc-structure) and surface (favoring polyhedra) energy and can be observed only for small nanocrystals with less than around 10000 atoms).[74]

While bulk crystals generally transform through multiple nucleation events leading to multiple domains and a polycrystalline product, nanocrystals appear to transform coherently in a single nucleation event. This makes nanocrystals excellent models for investigating transformation mechanisms that might otherwise be obscured. Indeed, simulations of phase transitions in nanocrystals as a function of environment, temperature, and pressure is an area of considerable interest. Notable studies include the molecular mechanism of the pressure-induce transformation of wurtzite (B1) to rock salt (B4),[93–95] and the temperature-induced phase transformation behavior of tetrolic acid as a function of crystallite size.[96] Note that when exploring effects of high pressure on nanocrystals, it is necessary to include a pressure-transmitting fluid akin to high-pressure experiments. Typically the fluid is a binary Lennard-Jones mixture that does not crystallize under high pressure.[93–95]

The idea that the phase diagram can show particle size dependency, particularly as we go down the length scale to nanocrystals, has attracted considerable attention. Experimental observations reveal that phase stability can indeed be modulated for a number of materials in the nanoparticle domain including the metal oxides TiO_2, ZrO_2, and Al_2O_3[97–99] as well as carbon.[100] As yet there are no examples for small organic molecules, though the possibility has been suggested from potential-energy calculations.[101] A key issue with the above observations is whether the observed nanocrystal phase is truly thermodynamically stable or just highly metastable. Nanocrystals, having few if any potential nucleation sites, tend to require a greater driving force (supercooling/superheating or excess pressure) to induce a transformation, indicative of a high barrier. To address the issue of metastability it is necessary to either experimentally determine or to calculate the surface and bulk free energies. These thermodynamic quantities are accessible by both experiment and simulation, but not without technical difficulty. Researchers often resort to potential energies but while these can serve as a reasonable approximation, they neglect entropy and hence would be inappropriate for surfaces that show extensive disorder.

Whilst molecular simulations (MD or MC) in the constant temperature constant volume (NVT) or constant temperature constant pressure (NPT) ensembles tend towards low free energy, the actual value of the free energy of the system is not readily available and explains the widespread use of potential energy as an alternative to free energy. The free energies (Gibbs G, Helmoltz F) belong to the thermal class of quantities (rather than mechanical) and depend on the accessible volume of phase space; they are not just explicit functions of phase-space coordinates. The implication is that free energy cannot generally be obtained as an ensemble average. Consequently its determination is both conceptually and technically challenging, and demanding with respect to computational resource.

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Whilst there is an array of methods for estimating the free energy, which include direct evaluation of the partition function, the so-called perturbation method, thermodynamics integration, and probability or histogram methods,[3,102] many of the general methods are not applicable to solids. At the same time, in some respect, solids do represent a conceptually easier case, as for such systems the configurational space is severely limited because the atoms are restrained to their lattice sites and diffusional motion is assumed to be absent. The two general methods for estimating free energies of solids include lattice dynamics using the quasi-harmonic approximation;[103] and thermodynamic integration involving the Einstein crystal approach.[3,104,105]

In the lattice-dynamics approach the partition function is directly calculated from an estimate of the phonon density of states. The density of states is obtained by transforming the coupled motion of the atoms about their lattice positions into normal coordinates (modes). The method is limited by the harmonic approximation, restricting applications to low temperatures but good results have been obtained up to about two thirds of the melting point of the investigated solid. The Einstein crystal approach involves the setting up of an Einstein crystal where the individual atoms or molecules are tethered to their lattice sites using a harmonic potential and do not interact with each other. For such a system the partition function and hence the free energy can be calculated analytically. To get the free energy of the real system, the free energy of the Einstein crystal is added to the free-energy difference obtained from thermodynamic integration from the Einstein crystal to the real system. Example studies using the lattice-dynamics approach include the calculation of free energies for MgO, MgF_2, and polyethylene.[103] Notable studies of the Einstein-crystal approach include NaCl[105] and ice.[65] More significant and broader applications of free-energy calculation of the solid phase include the determination of the phase diagrams of iron at the high temperatures and pressures of the Earth's mantle,[106] and ice as a function of temperature and pressure.[65]

The discussion above refers largely to the calculation of bulk free energies. Calculation of the surface free energy follows the conceptual route of estimating the work done for creating a surface of a unit area. The procedure is to calculate the bulk free energy of the crystalline solid using either lattice dynamics or the Einstein approach and then to remove the simulation periodic boundaries along the axis perpendicular to the surfaces of interest to create a slab, and repeat the calculation. The surface free energy is then given by the difference between that of the crystal slab and the periodic system (note that both systems contain the same number of molecules, hence there is no need to normalize) divided by the created surface area, that is, the two created faces. Whilst such calculations have been carried out for key surfaces of various materials,[107,108] there have been no applications to characterizing the overall surface energy of a nanocrystalline system that rigorously take into account the free energies and the surface areas of all the dominant faces.

Surface, or more precisely, the interfacial free energy is also the key quantity for characterizing nanocrystals that are stabilized by embedding within a sugar or a polymer matrix, and for nucleation in confined spaces. Clearly, the ability to calculate these quantities from molecular simulation will be central to understanding the role of the surface and interfaces in stabilizing emerging nuclei and resultant nanocrystals (both stand alone and in confinement). Thus, molecular simulations may help to identify appropriate surfaces or materials for enhancing (heterogeneous) nucleation of materials that are difficult to crystallize, selective nucleation of particular polymorphs, and for nanocrystal stabilization.

4.2. Nanocrystal–Surfactant Interactions

In general terms, simulations of the interaction of nanocrystals with stabilizing molecules, such as surfactants or specific capping molecules, can be tackled by standard simulation methods, but can still be challenging in terms of the size of system required. There is another important issue that arises as a result of the choice of materials being studied. Whilst we have good force fields for various classes of materials including organic and inorganic species and metals, modeling the interactions of organic molecules with metals is far from straight-forward as the application of conventional mixing rules leads to poor accuracy. Hence, the investigation of metal nanocrystals with surfactant molecules (an area of much research interest) by simulation has been problematic.

The interaction of a single surfactant molecule with a specific surface of a metal nanocrystal, being a relatively small system can in fact be modeled by means of accurate quantum calculations. Such calculations, however, are simply too demanding to investigate large systems in which the relaxation of metal nanoparticles as a result of surfactant interaction occurs.

Within the last few years, Schapotchnikow and Vlugt presented a series of studies which we feel reflects a particularly successful story of investigating metal nanocrystal–surfactant systems by molecular simulations. A key contribution was the creation of a force field for gold–gold and gold–surfactant interactions to enable the modeling of gold nanocrystals with a surface coverage of alkylthiol molecules.[109] Based on this force field, MC simulations were then used to explore the structure of a self-assembled monolayer (SAM) of alkylthiol molecules on gold icosahedra.[110] Within a grand-canonical approach this included attempts to insert/remove surfactants in parallel with structural relaxation. As a consequence, unbiased simulation models of nanocrystal–SAM colloids were obtained in good agreement with experiment. This approach paved the way to detailed investigations of colloid–colloid interactions offering unique insights into the interplay between the surfactant SAMs of approaching nanocrystals.[111] Using explicit solvent models, the association of pairs and triples of nanocrystals were investigated.[112]

Clearly, even such small agglomerates of nanocrystals imply considerable computational demands and we are still far from the precipitation of a composite material. However, through coarse graining of the models (which to some extent has already been done[109]) and the application of suitable algorithms for tackling nucleation processes as described in

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Section 2, the understanding of gold nanocrystal–alkylthiol SAM composite formation from molecular simulations appears in reach.

5. Future Perspectives

It is clear from the above discussion that there has been considerable progress in recent years in our understanding of crystal nucleation, coming both from elegant experiments (many of them on colloids) and new molecular simulation techniques. Yet, it must be acknowledged that at best we are still essentially scratching at the surface. Whilst we have a handle on the mechanics and thermodynamics aspects of nucleation in simple spherical model systems, more complex systems, such as ice nucleation, still challenge us. The gap between the more fundamental systems and molecules or materials of technological interest is of course vast, making the prospect of engineering crystals to design, from a given a chemical or molecular structure, outside our reach for some years to come. The enhanced understanding of fundamental systems obtained to date is however not just of academic interest, but is and will continue to influence the design of experiments in crystal engineering, thus limiting the factorial space to fewer and more dedicated experiments.

To date much of the molecular-simulation work dedicated to nucleation has focused on method development and the investigation of case studies. Clearly, alongside the research of the fundamental kind we must move from proof-of-principle studies to realistic models describing actual syntheses of crystalline materials of immediate interest. Additional priority must be to link and bridge our current fundamental knowledge to real problems, a domain where a range of open questions remains to be answered. How can simulations aid the design of optimal crystallization setups? Could we predict suitable seeds and contact surfaces for heterogeneous nucleation processes? In addition, apart from controlling shape and size of crystallites, a mechanistic understanding from atomistic simulations could be a key to controlling polymorphism. As the fate of a forming solid material is often determined at the early stage of structure development, insights into nucleation mechanisms remain of crucial importance. The technological implications are immense—being able to selectively promote desired polymorphs or enantiomorphs of a given chemical, or maybe the deliberate inhibition of an unwanted polymorph could deliver great benefits to pharmaceutical production processes, for example.

We expect the continued, almost exponential, increase in computing power and greater parallel processing to drive brute-force approaches. It is possible to envisage a rather large number (of the order of 100s) of parallel simulations of a critical system using commodity computing (a grid based on PCs) with view to identifying nucleation pathways in an unbiased manner. Coupled to computing power we expect to see implementation of algorithmic efficiencies into simulation codes, and a better representation of models, that is, more accurate force fields and associated parameters to specify the chemistry of our systems. An area of much current activity is that of order parameters as structural descriptors: important issues being addressed include how to assess order parameters for a particular system, how to deal with the multidimensional aspects, minimizing bias and yet being able to drive a system to a particular endpoint. We expect a greater, more unified understanding of nucleation to result from such generic order parameters, coupled with an increased use of them in associated approaches.

A key concept in computer modeling and simulation is that of scaling. The length and time scales of processes such as nucleation and crystal growth span many orders of magnitude making it difficult for a given modeling technique to capture all aspects, suggesting a need for multi-scale modeling. Thus some critical interactions between molecules may be modeled using quantum mechanics, which are then mapped into a molecular mechanics force field. The force-field method is in turn employed to simulate the process of interest to ascertain the critical properties, which are then characterized by parameters that become the input for the next higher level modeling. This approach is well illustrated by the study of Gale and colleagues to characterize the kinetics of crystal growth for urea from various solvents at the micron scale.[113] They estimated rates of transitions for molecule attachment by direct counting during crystal growth in an MD simulation and then linked these to probabilities in a higher-level kinetic Monte-Carlo simulation to model the kinetics of crystal growth in the micron-size range, and in so doing were able to reproduce and rationalize the experimentally observed crystal morphologies. Apart from kinetic Monte-Carlo approaches, phase-field modeling[114] is a prominent approach for exploring crystal growth on the mesoscale and may similarly benefit from multi-scale modeling starting from the atomistic level of detail.

We expect a greater interplay between higher and lower level modeling approaches, both bottom up and top down. In the bottom-up manner (as discussed earlier) the approach would be hierarchical, going from, for example, atomistic to coarse-grained resolution. A good illustration of the usefulness of such de-focusing is the elucidation of the potential of mean force (the free-energy change along a reaction coordinate) for two aggregates or nanocrystals to come together. This situation can be modeled at an atomistic level,[112,115] which then serves as the nanocrystal–nanocrystal interaction potential in higher level modeling to enable the investigation of nanocrystal aggregation. The converse, top-down approach, could be equally productive, it may be possible to identify a critical event/issue from coarse-grained modeling and then focus on it using a fully atomistic model.

With respect to complex materials, while the age of man-made nanomaterials is still in its infancy, hierarchical biocomposites, such as teeth, bones and exoskeletons, already demonstrate the new and enhanced materials properties that are within reach. We feel that if the rational design of such and other complex (nano)materials is to become accessible, the way forward must be paved by a capability of characterizing interfacial free energies and a more profound understanding of the mechanisms of nucleation and growth.

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6. Summary

Molecular simulation is a powerful tool that complements experiment by way of providing mechanistic understanding at atomic resolution and enabling the estimation of kinetic and thermodynamic quantities. Whilst the potential for modeling crystal nucleation and growth processes is immense, there are technical challenges specific to modeling these processes, the key issue being the limited time and length scales that can be accessed by conventional molecular-dynamics simulations. Indeed, in general rare events, such as nucleation, cannot be simulated using a brute-force approach. Despite this conceptual difficulty, there have been a number of exciting advances in methodology and ingenuity in tackling problems that were considered outside the scope of molecular simulation.

In terms of general insights and features the approach of representing molecules in a coarse grained way has been extremely successful, now enabling relatively complex processes, such as the role of additives in inhibiting or promoting nucleation or crystal growth, to be studied. Coupled to this advance has been the development of various methods that are specific but highly efficient and effective for particular problems. These newer methods and approaches, which include umbrella sampling using complex order parameters to characterize nucleation, transition-path sampling and its variants, and kinetic Monte-Carlo or combined Monte-Carlo/molecular-dynamics simulation methods, are able to investigate many aspects of the entire domain of crystal engineering, albeit still only for judiciously chosen problems. Thus realistic crystal nucleation scenarios with direct relation to solid-state chemistry have become accessible. Starting from the association of single ions in solvent environments, insights range from the mechanisms of motif formation, ripening reactions, and the self-organization of nanocrystals, to interactions with growth-controlling additives. The latter issue yields a new perspective toward understanding the structure of functionalized nanocrystals and the precipitation of hybrid materials. In addition to explicitly modeling nucleation, smart algorithms, pioneered by Jansen and co-workers allow the efficient prediction of crystal structures from simulation.[117] Thus, molecular simulation is now a mature technique and ready to play a significant role in the rational design and engineering of crystalline products.

Finally it is important to convey that the ultimate test of any insights gained from molecular simulation is the confrontation with experimental data. Whilst accessing the earliest stages of crystal growth is still a challenge for experimental methodology, there have been significant advances in this respect too,[115] often driven by hypotheses or theoretical ideas emerging from a molecular perspective. This interplay of experiment and theory coupled with respective in-tandem developments is absolutely vital in addressing many of the outstanding problems in crystal nucleation and growth.

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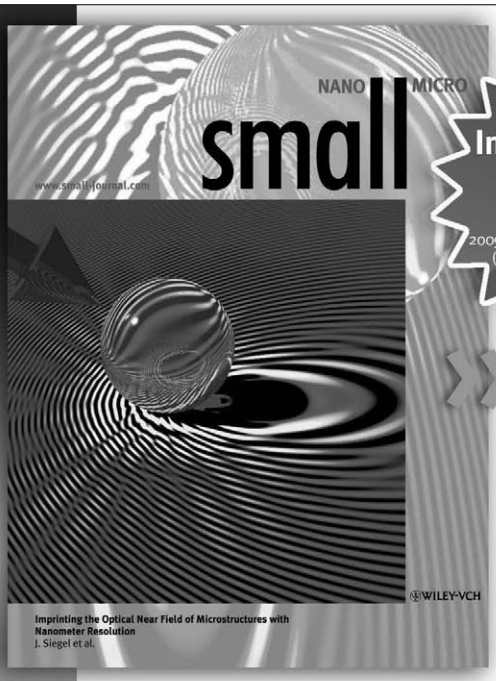

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