The Statistical Mechanics of Dynamic Pathways to Self-assembly

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Abstract We describe some of the important physical characteristics of the 'pathways', i.e. dynamical processes, by which molecular, nanoscale and micron-scale self-assembly occurs. We highlight the fact that there exist features of self-assembly pathways that are common to a wide range of physical systems, even though those systems may be different in respect of their microscopic details. We summarize some existing theoretical descriptions of self-assembly pathways, and highlight areas – notably, the description of self-assembly pathways that occur 'far' from equilibrium – that are likely to become increasingly important.

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1 Introduction

1.1 Self-assembly

The term ‘self-assembly’ describes dynamical processes in which components of a system organize themselves, without external direction, into ordered patterns or structures. The range of scales on which self-assembly happens is enormous: we might say that atoms are self-assembled from protons, neutrons and electrons, and that galaxies are self-assembled from their component stars. Here we focus on assembly undergone by components that range in size from a few angstroms (for example, atoms and molecules) to a few microns (for example, colloids). Assembly of such components is important both in the natural world and, increasingly, the laboratory (1, 2, 3, 4). Structures assembled in the laboratory include three-dimensional crystals (5, 6, 7), two-dimensional lattices (8, 9), closed polyhedral shells (10, 11), and other tailored nanoscale shapes (12, 13). In this review, we use statistical mechanics to describe some of the pathways by which these kinds of structure are formed. Figure 1 displays several examples of self-assembly, taken from computer simulations and experiments.

One motivation for studying self-assembly is its potential for making new and useful materials. Since many biological systems are formed by self-assembly, we might imagine using similar processes to build new functional materials. Although we are far from this ideal, rapid progress is being made, driven by several recent advances in the synthesis of self-assembling components. On the molecular scale, design and selection of molecular shapes has enabled the assembly of novel structures (14, 15, 16), and DNA-mediated interactions have been used to assemble a range of complex structures (17, 18, 19, 20), some of which can perform basic functions (13). On the colloidal scale, two key avenues for progress have been ‘patchy’ particles, with anisotropic interactions due to chemical patterning (21, 22), and particles with controllable geometrical shapes (23, 24). At the same time, advances in imaging now allow us to watch self-assembly almost as one would a computer-generated movie. Imaging techniques such as atomic-force microscopy (25) and in situ electron-beam methods (26, 27) permit atomic resolution of assembled structures (28, 29), and can achieve time resolution within the conditions under which self-assembly occurs (30, 31).

These experimental advances raise important questions for theory and modeling. Self-assembly illustrates the complex behavior accessible to simple components interacting by short-ranged forces, particularly as regards the emergence of order from disorder. Phase-ordering processes have been studied for more than a century (36, 37, 38, 39), and the resulting paradigm of nucleation and growth is central to our understanding of self-assembly. However, now that assembly can be analyzed quantitatively and even visualized directly in experiments, we often find
To limit the scope of our discussion, we shall restrict our focus to the extent to which these assumptions are valid in practical settings. We shall also stress the molecular details. We shall highlight some of the important ‘conserved’ features applying to a range of systems that may appear different in respect of their atomic or which self-assembly takes place. Many aspects of these pathways are generic, applying to a range of systems that may appear different in respect of their atomic or molecular details. We shall highlight some of the important ‘conserved’ features that appear in a wide range of examples of self-assembly. We shall also stress the assumptions underpinning different theoretical descriptions of self-assembly, and the extent to which these assumptions are valid in practical settings.

To limit the scope of our discussion, we shall restrict our focus to undriven systems, to which no energy is supplied by external means, and inactive components, whose motion is driven only by thermal fluctuations, such as those they receive from the solvent. Such components may fluctuate and undergo changes of con-
formation, but their motion is purely diffusive and they do not consume energy. Pattern formation in driven systems or by active components is often called ‘self-organization’ (41). Further, we shall consider only components small enough to undergo Brownian motion, which sets a size range from atoms to roughly microns. Thus, the self-assembly on which we focus is typified by an experiment in which a set of inactive components – such as molecules, proteins, or colloids – are dispersed in solvent, poured into a beaker, and then left alone. Given the laws of statistical mechanics, such systems can be expected to evolve toward configurations ever lower in free energy, but with no guarantee that they will achieve the thermodynamically stable state on experimental timescales. How do we describe the fate of such systems?

To address this question, Section 2 describes some of the key physical characteristics shared by self-assembling system. We summarize insights obtained from several studies in terms of simple diagrams and a statistical mechanical ‘toy model’ of self-assembly. Section 3 contains a brief discussion of the methods used in computational modeling of self-assembly. In Section 4 we present some of the most important dynamic pathways seen in self-assembling systems, and Section 5 outlines the theoretical ideas put forward to describe these pathways. Finally, Section 6 summarizes our outlook on the field.

2 The physical character of self-assembly

2.1 Thermodynamic and dynamic factors in self-assembly

Self-assembly is a nonequilibrium process in which a system evolves from an initial disordered state toward a stable state that is usually ordered in some way. For the systems that we consider, the driving force for this process is thermodynamic in nature – assembled structures are lower in free energy than their unassembled components – but this does not guarantee that what self-assembles will be the equilibrium structure, or indeed a structure with special thermodynamic status. It has been known for over a century that some components self-assemble first as a thermodynamically metastable structure, a ‘local minimum’ of free energy distinct from the ‘global minimum’ characteristic of the stable structure (39, 42, 43). It has been known for almost as long that sometimes the structure formed first does not correspond even to a local minimum of free energy (44, 45), although it may look ordered (46), and it need not relax to a thermodynamically-preferred structure (i.e. a minimum of free energy, local or global) an any timescale of relevance to a laboratory experiment or computer simulation.

In the following, it will be useful to distinguish two kinds of behavior: near-equilibrium assembly, in which thermodynamic factors play a dominant role, and
far-from-equilibrium assembly, for which dynamic effects are vital in determining the outcome. A typical self-assembling system can display both kinds of behavior, depending on the conditions under which it is observed. Experiments and computer simulations reveal that, in a majority of examples, successful self-assembly of a stable ordered structure occurs only when system parameters are tightly controlled, so balancing two factors: a thermodynamic impetus for components to form ordered structures, and conditions that allow components moving randomly to arrange themselves into these ordered structures (47,11,48,49,50). These factors tend to oppose each other: conditions that are optimal from a thermodynamic viewpoint are often unsuitable for dynamic reasons, and vice versa.

Figure 2: Schematic illustration of the conflict between the requirements for the thermodynamic stability and kinetic accessibility of a desired structure, intended to summarize the collective work of many authors (see main text). Interactions between components are characterized by their strength and specificity. (a) Schematic phase diagram, as dictated by thermodynamics. (b) Illustration of parameter regimes in which dynamic effects dominate assembly. (c) These competing factors result in near-equilibrium assembly occurring only for a narrow range of interaction parameters. (d) Illustration of the structures that might be formed by an example component, at the parameter sets labeled 1–4 in (a,b). 1) Interactions with the ‘right’ amount of strength and specificity lead to assembly of the stable ordered structure; 2) overly-strong interactions lead to kinetically-trapped structures; 3) insufficiently-specific interactions lead to alternative assembled structures; and 4) overly-specific interactions lead to no assembly. Figure adapted from Refs. (51,52).
As an illustration of this balance, imagine that our goal, as sketched in Fig. 2, is to design a set of components that will self-assemble in solution into a desired, thermodynamically stable structure. To ensure stability of the desired structure the interactions between components must be strong enough that an assembled structure is lower in free energy than its unassembled components. Interactions should also be ‘specific’ in some way, so that the desired structure is lower in free energy than other possible assembled structures. Such specificity can be achieved through directional binding, as in the case of anisotropic building blocks (53, 54) or ‘patchy’ nanoparticles (55, 21), or through selective binding, as in the case of protein-protein interactions (56) or chemical complementarity (20, 7, 18).

These requirements of strength and specificity tend to inhibit the microscopic dynamics required for successful assembly. If interactions between components are too specific, typical encounters will not result in binding, and assembly will not happen on accessible timescales. Interactions should therefore have some characteristics that are not completely specific (indeed, many nanoscale components, such as proteins, possess nonspecific attractive forces (57)). But non-specific interactions lead to ‘mistakes’: the random collision of components will not always result in geometries commensurate with the desired assembled structure. Therefore, inter-component bonds must be weak enough that ‘incorrect’ bonds can be disrupted by thermal fluctuations. If so, components can dissociate and bind anew, in effect sampling their local environment in order to select the most favorable modes of binding. This property of microscopic reversibility is a crucial method of error-correction in self-assembly. If inter-component binding is too strong then this mechanism is suppressed, and the result is a kinetically-trapped structure (47, 11, 48).

This general tension between thermodynamic and dynamic factors means that assembly of a thermodynamically stable structure typically happens only in a small subset of the available parameter space (see Fig. 2). This is near-equilibrium assembly in the sense defined above, in which the consequences of a microscopic dynamical process can be understood in essentially thermodynamic terms. Such behavior can be seen in e.g. one-component systems near a phase boundary between ordered and disordered phases, where inter-component bonds are only moderately strong (42, 58, 59, 60). However, one-component systems also undergo far-from-equilibrium assembly when inter-component bonds are strong, resulting in kinetically-trapped disordered structures (61).

Theoretical work on self-assembly usually aims to determine conditions under which near-equilibrium assembly can happen (62), or aims to design thermodynamically stable assemblies (63, 64, 65). Understanding far-from-equilibrium assembly, though currently under-developed by comparison, may ultimately prove to be a more generally applicable strategy for building structures with desir-
able properties (66), especially for systems with fundamentally slow dynamical features, such as components with many interaction degrees of freedom (35), or collections of multiple component types (46,67). The far-from-equilibrium regime of undriven, inactive systems will perhaps be understood using ideas similar to those used to address self-assembly driven by external fields, or of active components (68,69).

2.2 Metastable and kinetically-trapped states can persist throughout experimental observation times

We have emphasized that both thermodynamic and dynamic factors are important in self-assembly. Since the laws of thermodynamics state that an isolated system, given sufficient time, will arrive at its global free-energy minimum, it follows that the dynamic considerations of the previous section must be considered in conjunction with the time elapsed in a self-assembly experiment or computer simulation. To see this, consider Fig. 3(a), which shows a toy model (70) designed to illustrate the interplay of entropic, energetic and dynamic factors inherent to self-assembly.

We consider a large number of particles, each of which can inhabit any of three microscopic states, corresponding to distinct microscopic environments. The first state corresponds to ‘unbound’ particles, which are free in solution. The second state corresponds to a set of $M$ ‘misbound’ environments, in which particles make bonds that are not consistent with the final assembled structure. The third state corresponds to ‘optimally bound’ particles, whose local binding is consistent with the thermodynamically stable assembled structure. The energies of misbound and optimally-bound particles are $\epsilon_{\text{mis}}$ and $\epsilon_{\text{opt}}$ respectively: both are likely to depend on the ‘interaction strength’ of Fig. 2. The number of misbound states, $M$, is likely to depend on ‘interaction specificity’. Particles begin in the unbound state, and rates for subsequent binding and unbinding depend on particle concentration and activation energy barriers, respectively, as shown in Fig. 3.

The equilibrium ‘yield’ of this process, meaning the fraction of particles found in the optimally-bound environment at infinite time, is largest when the energy reward for binding is as large as possible. Equilibrium yield is shown as a black line in Fig. 3(b) (the red arrow shows how changing the bond strength within this toy model might be related to the general scenario shown in Fig. 2).

Dynamically, though, large binding energies act to frustrate equilibration. If bonds are strong ($\epsilon_{\text{opt}}, \epsilon_{\text{mis}} \gg k_B T$), then the system evolves rapidly to a configuration in which the fraction of optimally-bound particles is only $1/(1 + M)$ (because misbound states are more accessible dynamically than is the optimal state). For the system to reach its equilibrium yield requires a time of order
exp ($\epsilon_{\text{mis}}/k_B T$): the exponential dependence on $\epsilon_{\text{mis}}$ means that this time can be large. Given a fixed observation time, the observed yield is a non-monotonic function of interaction strength, because the increased thermodynamic driving force to populate the optimally-bound environment is counteracted by the slowness of escaping from misbound environments. Hence, yield also depends on observation time: see the solid and dashed lines on panel (b). This basic phenomenology is seen in many examples of self-assembly \cite{11,48,50}.

Figure 3: Toy statistical mechanical model of self-assembly, demonstrating the dependence of outcome on observation time, as well as the the basic requirements for kinetic trapping. (a) Particles transfer between the three microscopic environments with the rates shown. (b) When there exists the possibility of misbinding ($M > 0$), the dynamic yield depends on observation time, and at fixed time is a non-monotonic function of interaction strength. Figure adapted from Ref. \cite{70}.

3 Numerical methods for the study of self-assembly

Computer simulations play an important role in studies of self-assembly. Components with precisely-designed interactions can be made straightforwardly on the computer, even if the experimental synthesis of the corresponding component is difficult. Following the motion of many particles in detail is simple within a computer; obtaining similar data from experimental systems is much more challenging. Here we provide a brief survey of some computer methods for the study of self-assembly.

In accordance with the preceding discussion, we separate methods into a ‘thermodynamic’ category, which provide information about equilibrium behavior and free energies, and a ‘dynamic’ category, designed to model the assembly process. The standard tools of molecular simulation \cite{71} are widely used: in the thermodynamic category, one typically uses Monte Carlo or molecular dynamics simulations, which may be combined with thermodynamic integration to arrive at phase diagrams \cite{72}. Some Monte Carlo schemes allow different phases to be
sampled directly within a single simulation, allowing accurate calculation of their relative free energy \((73)\). If the likely stable phases of an assembling system are known, these methods work well. In systems that display many possible ordered structures, special algorithms can be useful for identifying candidate structures for phases \((74)\), or to identify component interactions able to stabilize chosen structures \((64, 65)\).

To obtain dynamical information about self-assembly, molecular simulation is again widely used. However, to reproduce accurately the Brownian motion of nanoscale particles, it is necessary to include an explicit representation of the solvent in which particles are dispersed. This is computationally expensive, and so effort has been devoted to the development of methods in which solvent is treated implicitly, either through the inclusion of random forces, as in Brownian dynamics \((71)\), or through collective-move Monte Carlo methods \((75, 76, 77)\). In some cases, explicit and implicit solvent models show similar behavior, at least qualitatively \((50, 11)\). In other cases, an accurate representation of solvent effects may be important, e.g. if hydrophobic effects drive assembly \((78)\), or if hydrodynamic effects are important \((79, 80, 81)\). Given a microscopic dynamical model, rare-event-sampling methods such as forward-flux sampling \((82)\) and transition-path sampling \((78)\) are valuable if assembly involves a rare but short-lived event, such as nucleation \((83, 84)\).

Whichever method is chosen, computational models of self-assembly represent approximate, coarse-grained representations of an experiment, typically involving approximate ‘effective interactions’ between particles and a highly-simplified model of solvent. Such effective interactions may be derived systematically, in a multi-scale approach \((85, 50)\); fit to experimental data \((86, 87)\); or simply chosen in order to reproduce qualitative features of experiments \((11, 52)\). Although fully quantitative agreement with experiment is difficult to achieve, especially when considering dynamical quantities \((88)\), simple models can provide useful qualitative insight into self-assembly \((6, 48, 11, 89)\).

4 Dynamic pathways to self-assembly

4.1 Pathways can be near equilibrium or far from it

Section 2 illustrates why, in general, thermodynamic and dynamic factors must be considered in order to understand self-assembly. The message derived from several studies is that even when the interactions between components are chosen so that a particular ordered structure is stable, assembly of this structure may not be observed in experiments or computer simulations. Thus, full understanding of self-assembly requires consideration of both the desired structure and its assembly
In this section we discuss a range of self-assembly pathways. By ‘pathway’ we mean a description of structures that self-assemble as time progresses. Several important pathways are shown in Fig. 4 whose graphics, inspired by Fig. 2 of Ref. (59), are cartoons of the objects – monomers, stable phases, kinetically-trapped structures, etc. – that appear during self-assembly. A given set of components may self-assemble via more than one pathway, depending on model parameters or environmental conditions (93, 94). Shown at right in Fig. 4 are schematic free-energy profiles, presented as a function of ‘progress’ along each pathway. In many cases it is useful to think of the progress coordinate as the size of an assembled structure. The barrier (maximum) in free energy seen in each panel is a generic feature of phase change, familiar from classical nucleation theory (95, 96): growing a cluster of a stable bulk phase results in a free energy reward that scales as the volume of the cluster, but incurs a free energy cost that scales with its surface area. Only for clusters larger than a ‘critical’ size does reward outweigh cost, and will a cluster grow spontaneously.

We divide pathways into two general categories: near-equilibrium pathways, shown in panels (a) to (c) of Fig. 4 and far-from-equilibrium pathways, shown in panels (d) to (f). Near-equilibrium pathways can be understood in terms of evolution on a thermodynamic free-energy surface, with the dynamics of the system serving only to convey it along favored paths on that surface. By contrast, far-from-equilibrium pathways can be understood only by considering dynamic effects explicitly. These effects result from the microscopic motion of assembling particles, hence the more ‘microscopic’ nature of the cartoons in panels (d) to (f). Far-from-equilibrium pathways typically involve a competition between several slow timescales, leading to motion on the underlying free-energy surface that is strongly biased by dynamic effects (67). The theoretical underpinnings of the ‘near-or-far’ distinction are discussed in Section 5.1.

4.2 A survey of some important self-assembly pathways

In the remainder of this section we shall survey the pathways of Fig. 4. Panel (a) illustrates a near-equilibrium pathway in which components self-assemble into a thermodynamically stable structure, via the nucleation and growth of clusters with the same properties as the stable structure. This is the scenario anticipated by classical nucleation theory (36, 95, 96), in which the crossing of a single free-energy barrier is the rate-limiting step to formation of the stable phase. Such ‘classical’ or ‘single-step’ pathways have been inferred in a variety of physical systems, e.g. (94), and have been seen with molecular-scale resolution in a few cases (25). In simulation, classical pathways are seen in the Ising lattice gas in
Figure 4: Examples of self-assembly pathways that are ‘near’ equilibrium ((a) to (c)), in the sense that they result in structures with special thermodynamic status, and ‘far from’ equilibrium ((d) to (f)), in the sense that they can be described only with reference to the microscopic dynamics undergone by building blocks (indicated by the “microscopic” detail in the pictures). These pathways are described in Sections 4 and 5. Figure graphics are inspired by Ref. (59).

bulk (97) and at surfaces (98), in patchy colloid models (9)(99)(100), and in atomic crystal self-assembly (83). Methods used to describe such pathways are discussed in Section 5.2.

Fig. 4(b) describes a near-equilibrium pathway in which the transformation between unassembled components and the stable assembled structure is ‘indirect’, or ‘multi-step’, occurring via clusters whose microscopic structures are representative of thermodynamically metastable bulk phases. An important example is the ‘two-step’ liquid-to-crystal pathway observed during crystallization of spheres with isotropic short-range interactions (59), and during the crystallization of pro-
teins \([101, 31]\). Multiple transformations between metastable solid polymorphs are sometimes seen \([102]\). Model systems with anisotropic (“patchy”) interactions can exhibit such behavior \([48, 103, 104]\), as can simple lattice models \([105]\). Methods used to describe such pathways are discussed in Section 5.3. In this pathway, the schematic ‘progress’ coordinate in Fig. 4 typically includes information about the microscopic structure of the assembling cluster.

Fig. 4(c) describes a near-equilibrium pathway whose intermediate structures are selected by the free-energy surface but are not directly related to bulk thermodynamic phases. Structured free-energy surfaces of this nature can result generically from faceting exhibited by finite-size clusters when component interactions are strong \([106]\), or from directional interactions that result in preferred geometries for small clusters \([11, 107, 33]\). Assembly of this nature is often hierarchical, with thermodynamically-preferred clusters serving as the building blocks for larger structures. Examples of this pathway type can be found in models and experiments of virus capsid self-assembly \([108, 109]\), and in the assembly of extended structures in computer simulations \([107, 33, 110]\). Methods used to describe such pathways are discussed in Section 5.4.

Fig. 4(d) describes a far-from-equilibrium pathway in which components form structures that have no special thermodynamic status. The most familiar examples are the malformed, kinetically-trapped structures that result when component interactions are strong, and binding errors fail to anneal on the timescale of observation. Although kinetically-trapped structures are usually regarded as undesirable, some have interesting or useful properties: consider gels \([111, 61]\), fractal diffusion-limited aggregates \([112]\), or nonperiodic networks \([89]\). Methods used to describe such pathways are discussed in Section 5.5.

Fig. 4(e) illustrates a far-from-equilibrium pathway in a system of more than one component type. Here, the physical structure may be ordered (and may be similar to the equilibrium one), but the arrangement of the particle types comprising that structure is not consistent with equilibrium. Multicomponent alloys display dynamically-dominated self-assembly pathways \([113]\); two-component colloidal crystals in experiment \([46]\) or on the computer \([84, 67]\) can be self-assembled with nonequilibrium component-type arrangements. The slow mobility of components within a solid structure prevents the equilibration of these arrangements on the timescale of observation.

Fig. 4(f) describes a far-from-equilibrium pathway in which kinetic trapping occurs because particles’ internal degrees of freedom relax too slowly. An important example in this category is DNA-linked particles \([114]\) when linkers sample their configuration space more slowly than structures grow \([35]\). Conformation change of proteins or synthetic particles can also allow particles’ internal dynamics to effect dynamic control of self-assembly pathways \([115, 116]\). We comment in Sec-
tion 5.6 on the methods used to describe this pathway type, and the type sketched in panel (e).

In addition to these well-characterized pathways, there exist several pathways seen in experiments that have yet to be classified. For instance, the thermodynamic status of clusters seen during self-assembly of mineral phases (117,118) or some proteins (119,120) is not yet clear. The fact that recently-developed experimental techniques allow molecular-scale, temporal resolution of these pathways should be seen as an exciting challenge for theory.

5 Statistical mechanical descriptions of self-assembly pathways

5.1 Near-equilibrium assumptions

As discussed in Sec. 2.1, we classify ‘near-equilibrium’ pathways as those in which thermodynamic factors govern the outcome of an assembly process. From a theoretical perspective, the idea of a near-equilibrium pathway is related to the existence of good reaction coordinates. Reaction coordinates (121) are collective variables that allow an accurate representation of a non-equilibrium process, such as a chemical reaction or an assembly pathway. A natural reaction coordinate for self-assembly is often the size \( n \) of an assembling cluster (122, 96), while other coordinates, denoted here by \( m \), might describe the composition or shape of that cluster. Let \((n_t, m_t)\) be the values of the reaction coordinates in the assembling system at time \( t \). If these reaction coordinates provide a good description of the self-assembly process, then the assembling system should have the same properties as an equilibrium system in which \((n, m)\) are constrained to be equal to \((n_t, m_t)\). That is, if two microscopic configurations of the assembling system have the same values of \( n \) and \( m \), and differ in energy by an amount \( \Delta E \), then the ratio of the probabilities with which these configurations are seen should be \( e^{-\Delta E/(k_B T)} \). This is an example of a *quasiequilibrium* condition: the only deviations of the system from equilibrium can be accounted for through the reaction co-ordinates \( n, m \), with other degrees of freedom remaining equilibrated. On time scales short enough that \((n_t, m_t)\) do not change significantly, the system then behaves as if it were at equilibrium. Quasiequilibrium conditions hold for the ‘reversible’ processes of classical thermodynamics (123).

Many theoretical descriptions of self-assembly employ a quasiequilibrium assumption, choosing a few reaction coordinates on which to focus. Such strong assumptions greatly simplify the resulting analysis. In systems with a single type of component, quasiequilibrium can be expected to hold if bond formation and bond breaking both occur rapidly on the timescale of cluster growth. The importance of reversibility and quasiequilibrium ideas in rationalizing the outcomes of
self-assembly has been noted in many studies \cite{47, 11, 48, 50}. The link between quasiequilibrium conditions and successful assembly has also been tested explicitly in simple models \cite{124}. The conjecture of Stranksi and Totomanow \cite{38}, that a system will transform most rapidly into the phase that requires crossing of the lowest free-energy barrier, can be justified by a quasiequilibrium assumption. When the quasiequilibrium assumption is not valid, explicit dynamical information is required in order to describe the assembly pathway.

5.2 Classical nucleation theory

Panel (a) of Fig. 4 represents a near-equilibrium pathway that can be described by classical nucleation theory (CNT) \cite{36, 95, 96}. This theory assumes that phase change happens via the rare nucleation of clusters, and that the structures of these clusters mimic the structure of the bulk assembled phase. As described in several review articles \cite{95, 96}, the free-energy cost for generating a cluster of size $n$, $\Delta G(n)$, is assumed in the simplest forms of CNT to be $\Delta G(n) = \gamma n^{2/3} - n\Delta \mu$, where $\Delta \mu$ is the bulk free-energy change for formation of the stable phase, and $\gamma$ is proportional to the surface tension between the starting phase and the stable phase. The resulting free-energy barrier, $\Delta G(n^*) \propto \gamma^3/((\Delta \mu)^2)$, enters the rate for nucleation per unit volume, $k_{\text{nuc}} = k_0 \exp[-\Delta G(n^*)/k_B T]$, where $k_0$ is a microscopic rate. If $\Delta G(n^*)$ is large compared to $k_B T$, this nucleation step is expected to control the rate for assembly of an ordered phase.

CNT is a valuable starting point for describing self-assembly, especially of crystals \cite{83, 99}. If intermediate states on the assembly pathway have the same kind of order as the stable state, one can expect CNT to provide at least a useful qualitative picture. Quantitative prediction of assembly rates by CNT is much rarer \cite{122, 88, 125}, partly because small uncertainties in calculated free-energy barriers translate into large uncertainties in nucleation rate, and because critical clusters are often not the spherical droplets assumed by simple versions of CNT \cite{126}. The essential features of CNT-like “assembly” can be reproduced by the Ising model \cite{127, 97, 128}, but even in this controlled setting one requires additions to the simple CNT assumptions described above in order to have quantitative agreement between theory and simulation \cite{97, 128}.

5.3 Beyond CNT: more than one reaction coordinate

Pathway (b) of Fig. 4 illustrates a scenario in which an assembly process begins with the formation of clusters whose structure is different from that of the final assembled state. The paradigmatic example of this pathway occurs in crystallization of attractive spherical particles \cite{59}, which can assemble into clusters of a metastable liquid phase during assembly; the crystal then nucleates within the
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liquid clusters. As a result, assembly of the crystal occurs much more quickly than would be anticipated for a ‘direct’ CNT pathway (59). In experiment, an important example of ‘two-step’ assembly is seen in protein crystallization (101,96).

Many authors have generalized the simple CNT free-energy argument so as to describe include the possibility of such a pathway: instead of a free energy $\Delta G(n)$ that depends only on cluster size, one considers a free-energy surface $\Delta G(n, m)$, in which $m$ is a measure of cluster properties (crystallinity, for instance). Instead of a single nucleation barrier at some critical cluster size $n^*$, one should consider the saddle points on the free-energy surface that separate the unassembled and assembled free-energy minima. This general problem falls within the framework of multidimensional reaction-rate theory (121,129).

Different assembly pathways are then expected as the shape of the free-energy surface changes. For example, in a ‘double-nucleation’ two-step process, assembly occurs via a pathway that passes through two saddle points, the first of which might correspond to nucleation of liquid clusters, and the second being crystal nucleation within the liquid. In other ‘two-step’ pathways, a single nucleation process may lead to a cluster with one kind of order, followed by the appearance of a different kind of order, as the cluster grows. For example, nuclei in systems of attractive spherical particles may be largely unstructured (59) or have a body-centred cubic (bcc) structure (42), but on long times, the system forms a face-centered cubic (fcc) crystal (without any subsequent nucleation event). Similar pathways have been found for ‘patchy’ particles and for particles with other anisotropic interactions (48,104,130).

From a theoretical perspective, classical density functional theory, which assumes that the ‘direction’ of phase change is governed by the shape of the free-energy surface, is a suitable way of describing two-step self-assembly pathways within the quasiequilibrium assumption (131,60,58). Ostwald’s rule of stages (39) is the assumption that multi-step assembly will happen if there exist bulk phases intermediate in free energy between the parent phase and the stable assembly. Although often upheld (42), the statement has no theoretical underpinning, and is not predictive. Simple systems such as Potts models (132,105) can display two-step ‘assembly’ pathways, helping to identify molecular features that dispose systems toward multi-step assembly. In general, one expects metastable phases to appear during phase change if particles possess a certain range of interaction (59), or possess different types of microscopic interactions that stabilize distinct condensed phases (103,52,104).
5.4 Assembly via specific structured clusters

Panel (c) of Fig. 4 describes near-equilibrium assembly which occurs via structured intermediates that combine into larger assemblies. A natural way of describing this pathway type is through a set of kinetic rate equations (133, 37) for the fission and fusion of clusters of specific morphologies. The dynamical quantities in these equations are the concentrations (number densities) of the various clusters; the equations also include rate parameters that are determined partially by kinetic considerations and partly by thermodynamic factors (for example, detailed balance relations). Such rate equations have been used extensively to study viral capsid assembly (134, 10, 108): in such cases one typically assumes a dominant assembly pathway, by considering a single cluster morphology for any given size. Comparison of theory and experiments has demonstrated that such pathways occur during virus capsid assembly in vitro (108), and rate equation approaches also give a good description of the assembly of amyloid fibrils (135), which are one-dimensional protein filaments known to cause a variety of degenerative diseases.

This pathway is also relevant for some examples of hierarchical self-assembly in which components first assemble into structured clusters, which then combine to form a larger assembly. Examples of structured clusters might be dimeric or tetrameric protein complexes (107), or ‘micelle-like’ clusters formed from amphiphiles (136). The essential distinction between pathways (a) and (c) in Fig. 4 is that a theoretical description of pathway (c) must account explicitly for the presence of small clusters with specific morphologies: a simple picture of monomer addition to a growing ‘droplet’ of the ordered phase is not sufficient.

5.5 Far-from-equilibrium assembly in one-component systems

We now turn to far-from-equilibrium pathways, for which a small number of reaction coordinates are no longer sufficient to describe assembly (see panel (d) of Fig. 4). In these situations, a crucial question is how one accounts for the variation in morphology (shape) among clusters of a given size. In principle, one may generalize the rate equation approach of the previous section, but instead of considering the concentrations of clusters of different sizes, one must consider separately clusters of all possible morphologies (133). Practically speaking, the enumeration of all these possibilities is an intractable task, so the rate-equation approach is of limited applicability. Instead, we have sketched schematic free-energy surfaces in panels (d)–(f) of Fig. 4, where we have indicated the role of cluster morphology by a schematic “structural” axis, as a proxy for the complex range of possible cluster morphologies. If changes in the structure of growing clusters happen quickly compared to cluster growth, one may neglect the structural...
axis and we recover the quasiequilibrium pathways of (a) to (c). The far-from-equilibrium regime corresponds to the opposite limit, where clusters grow quickly enough that their structures cannot relax to their (local) equilibrium state, leading to assembled states that do not minimize the system’s free energy.

The most common manifestation of these far-from-equilibrium effects is sketched in the third panel of Fig. 2(d-2), where strong bonds between particles prevent the formation of ordered structures. Quantitative links between the breakdown of quasiequilibrium and the degree of order in assembled states have been confirmed by computer simulations. For example, in (124) the quasiequilibrium assumption was tested directly in the assembly of model viral capsids. It was found that effective assembly was associated with weak deviations from quasiequilibrium, and that the kinetic trapping regime was associated with a breakdown of quasiequilibrium. Other measurements of reversibility and quasiequilibrium can be achieved by counting events in which clusters increase or decrease in size (50,70) or by using relations between out-of-equilibrium correlation and response functions (137,138).

In practice, successful self-assembly of an ordered structure typically involves a trade-off between cluster growth that is rapid enough for extended assemblies to form, but slow enough to achieve quasiequilibrium. Self-assembly may involve several stages (for example, nucleation and growth): it may be that particle interactions that are optimal for one stage of assembly may be less effective in other stages. In these situations, time-dependent interactions may be useful for optimizing assembly (92).

We also note that while the aim of self-assembly is often to create an equilibrium structure, typically via a near-equilibrium pathway, far-from-equilibrium assembly may also be useful. Single-component systems of strongly attractive particles may form gels – disordered networks that percolate throughout the system (111,61), leading to rigid (or viscoelastic) macroscopic behaviour. Gelation is an example of a far-from-equilibrium assembly process with important applications (139). In contrast to near-equilibrium assembly, the structure of assembled gels depends strongly on dynamic effects (140,141), and the assembled structures also undergo aging (dynamic effects that persist on long times), which can result in large-scale structural rearrangements (142). The effects of dynamic factors on far-from-equilibrium assembly and gelation are not understood in detail: this remains an area in which theory and modeling have the potential to yield new insights.

5.6 Far-from-equilibrium assembly in more complex systems

We now turn to panel (e) of Fig. 4 which connects systems of more than one kind of component. In contrast to pathway (d), where the quasiequilibrium regime
breaks down because of strong bonds ‘twixt particles, the presence of multiple
component types can lead to kinetic traps that emerge even when bonds be-
tween particles are weak. In a solid (e.g. a crystal) containing two component
types, components interchange their positions only very slowly (if at all), and
so the arrangement of component types within the assembled crystal is likely to
‘remember’ the process by which the crystal was formed. The resulting arrange-
ment will not in general correspond to a free-energy minimum (46, 143, 84, 67).
Treatments of this problem have included the development of kinetic theories
in which rate parameters depend on the underlying microscopic particle dynam-
ics (45, 144, 145, 143). CNT can in principle be modified to describe similar
examples of far-from-equilibrium self-assembly, accounting for slow internal re-
 laxation of a growing cluster through the rates of change of different co-ordinates
for the free-energy surface $\Delta G(n, m)$ [recall Section 5.3]. However, these rates are
not calculable within CNT: they must be obtained independently, for example by
computer simulation. This approach has been used to describe the dynamics of
assembly of two-component colloidal crystals (67). Moreover, structures formed
away from equilibrium may have no special thermodynamic status, and well-
defined ‘phases’ may not exist. Arguments of nonequilibrium statistical physics
can provide qualitative predictions for the nature of kinetically-trapped multi-
component structures within simple models (146), but we possess, in general,
limited understanding of this phenomenon.

Polydisperse colloidal systems can also be regarded as multicomponent systems,
whose components differ in size. With sufficient polydispersity the stable equilib-
rium state may involve coexistence of two or more crystals (147), each composed
of particles of a particular size range. However, phase separation or fractiona-
tion typically happens so slowly that crystal coexistence cannot be achieved on
the timescale of an experiment, with systems either forming a single crystal or
remaining in a disordered “glassy” state (148).

Multicomponent systems can also be made to self-assemble in quasiequilibrium (33,
20). Given that multicomponent self-assembly can happen near and far from
equilibrium, and the fact that natural functional materials are generally multi-
component ones, there appears to be an enormous parameter space within which
to design interesting self-assembled multicomponent structures, stable and kinet-
ically trapped. Such design awaits guidance from new developments.

The kinetic trapping seen in panel (f) of Fig. 4, in which nonequilibrium struc-
tures form because of slow sampling of interaction conformations, has been seen
in experiments (149, 35) and simulations (115, 116), but awaits a full micro-
scopic dynamic description. This should be seen as a challenge to the com-
unity: given the usefulness of e.g. DNA as a mediator of interactions in self-
assembly (12, 17, 20, 18, 7, 19), and the slowness with which DNA linkers can sample
their conformational space (114), it is possible that the kind of kinetic trapping seen in (35) could be further developed so as to allow assembly of functional nonequilibrium structures.

6 Outlook

We have described some of the important physical characteristics of self-assembly. We have highlighted the fact that there exist generic features of self-assembly pathways that are seen in a wide range of physical systems, even though these systems may appear different in respect of their microscopic details. We have also summarized some existing theoretical descriptions of self-assembly pathways. In general, we possess as a community an understanding of several important general principles that apply to self-assembly. Simple theories (e.g., CNT, kinetic rate equations) can capture the qualitative behavior of many examples of self-assembly, and in some cases can give us quantitative understanding of self-assembly. Simple model systems, including Ising- and Potts-like models, model colloids, and a wide range of ‘patchy particle’ models, have been used to reproduce the complex behavior seen in real systems without accounting for all of their microscopic details.

The foundations of the community’s description of self-assembly rest on well-developed near-equilibrium ideas, and there is clear need for continuing the development of theories that are fundamentally dynamic in nature (150). Far-from-equilibrium self-assembly is likely to occur in a larger regime of parameter space than is near-equilibrium assembly; it can result in functional assemblies; and it will likely connect naturally with intrinsically nonequilibrium phenomena like driven systems and active matter (59). We therefore anticipate that theoretical guidance for the far-from-equilibrium regime of self-assembly will prove increasingly important, motivated by ongoing developments in component synthesis and in-situ imaging of self-assembly pathways.

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1. Glotzer SC, Solomon MJ, 2007. Anisotropy of building blocks and their assembly into complex structures. *Nature Materials* 6:557–562
2. Barth JV, Costantini G, Kern K, 2005. Engineering atomic and molecular nanostructures at surfaces. *Nature* 437:671–679
3. Whitesides GM, Grzybowski B, 2002. Self-assembly at all scales. *Science* 295:2418–2421
4. Blake AJ, Champness NR, Hubberstey P, Li WS, Withersby MA, Schröder M, 1999. Inorganic crystal engineering using self-assembly of tailored building-blocks. *Coordination chemistry reviews* 183:117–138
5. Leunissen ME, Christova CG, Hynninen AP, Royall CP, Campbell AI, *et al.*, 2005. Ionic colloidal crystals of oppositely charged particles. *Nature* 437:235–240
6. Zhang ZL, Keys AS, Chen T, Glotzer SC, 2005. Self-assembly of patchy particles into diamond structures through molecular mimicry. *Langmuir* 21:11547–11551
7. Nykypanchuk D, Maye MM, van der Lelie D, Gang O, 2008. DNA-guided crystallization of colloidal nanoparticles. *Nature* 451:549–552
8. Blunt MO, Russell JC, del Carmen Giménez-López M, Garrahan JP, Lin X, *et al.*, 2008. Random tiling and topological defects in a two-dimensional molecular network. *Science* 322:1077–1081
9. Chen Q, Bae SC, Granick S, 2011. Directed self-assembly of a colloidal kagome lattice. *Nature* 469:381–384
10. Zlotnick A, 2005. Theoretical aspects of virus capsid assembly. *Journal of Molecular Recognition* 18:479–490
11. Hagan MF, Chandler D, 2006. Dynamic pathways for viral capsid assembly. *Biophys. J.* 91:42–54
12. Rothemund PW, 2006. Folding DNA to create nanoscale shapes and patterns. *Nature* 440:297–302
13. Andersen ES, Dong M, Nielsen MM, Jahn K, Subramani R, *et al.*, 2009. Self-assembly of a nanoscale DNA box with a controllable lid. *Nature* 459:73–76
14. Nam KT, Shelby SA, Choi PH, Marcili AB, Chen R, *et al.*, 2010. Free-floating ultrathin two-dimensional crystals from sequence-specific peptoid polymers. *Nature Materials* 9:454–460
15. Gibaud T, Barry E, Zahkary MJ, Henglin M, Ward A, *et al.*, 2012. Reconfigurable self-assembly through chiral control of interfacial tension. *Nature* 481:348–351
16. Stannard A, Russell JC, Blunt MO, Salesiotis C, Giménez-López MdC, *et al.*, 2012. Broken symmetry and the variation of critical properties in the phase behaviour of supramolecular rhombus tilings. *Nature Chem.* 4:112–117
17. Winfree E, Liu F, Wenzler LA, Seeman NC, 1998. Design and self-assembly of two-dimensional DNA crystals. *Nature* 394:539–544
18. Park SY, Lytton-Jean AK, Lee B, Weigand S, Schatz GC, Mirkin CA, 2008. DNA-programmable nanoparticle crystallization. *Nature* 451:553–556
19. Valignat MP, Theodoly O, Crocker JC, Russel WB, Chaikin PM, 2005. Reversible self-assembly and directed assembly of DNA-linked micrometer-sized colloids. *Proc. Natl. Acad. Sci. USA* 102:4225–4229
20. Ke Y, Ong LL, Shih WM, Yin P, 2012. Three-dimensional structures self-assembled from DNA bricks. *Science* 338:1177–1183
21. Pawar AB, Kretzschmar I, 2010. Fabrication, assembly, and application of patchy particles. *Macromolecular Rapid Commun.* 31:150–168
22. Kraft DJ, Groenewold J, Kegel WK, 2009. Colloidal molecules with well-controlled bond angles. *Soft Matter* 5:3823–3826
23. Rossi L, Sacanna S, Irvine WTM, Chaikin PM, Pine DJ, Philipse AP, 2011. Cubic crystals from cubic colloids. *Soft Matter* 7:4139–4142
24. Sacanna S, Korpics M, Rodriguez K, Colón-Meléndez L, Kim SH, *et al.*, 2013. Shaping colloids for self-assembly. *Nature Commun.* 4:1688
25. Yau ST, Vekilov PG, 2001. Direct observation of nucleus structure and nucleation pathways in apoferritin crystallization. *J. Am. Chem. Soc.* 123:1080–1089
26. Zheng H, Smith RK, Jun Yw, Kisielowski C, Dahmen U, Alivisatos AP, 2009. Observation of single colloidal platinum nanocrystal growth trajectories. *Science* 324:1309–1312
27. Li D, Nielsen MH, Lee JR, Frandsen C, Banfield JF, De Yoreo JJ, 2012. Direction-specific interactions control crystal growth by oriented attachment. *Science* 336:1014–1018
28. Turchanin A, Weber D, Buenfeld M, Kisielowski C, Fistul MV, *et al.*, 2011. Conversion of self-assembled monolayers into nanocrystalline graphene: Structure and electric transport. *ACS Nano* 5:3896–3904
29. Zhang X, Xie Y, 2013. Recent advances in free-standing two-dimensional crystals with atomic thickness: design, assembly and transfer strategies. *Chemical Society Reviews* 42:8187–8199
30. Nielsen MH, Li D, Zhang H, Aloni S, Han T, *et al.*, 2014. Investigating processes of nanocrystal formation and transformation via liquid cell TEM. *Microscopy and Microanalysis* 20:425–436
31. Chung S, Shin S, Bertozzi C, De Yoreo J, 2010. Self-catalyzed growth of S layers via an amorphous-to-crystalline transition limited by folding kinetics. *Proc. Natl. Acad. Sci. USA* 107:16536
32. Rapaport D, 2012. Molecular dynamics simulation of reversibly self-assembling shells in solution using trapezoidal particles. *Physical Review E* 86:051917
33. Grünwald M, Geissler PL, 2014. Patterns without patches: Hierarchical self-assembly of complex structures from simple building blocks. *ACS Nano* (in press)
34. Haji-Akbari A, Engel M, Keys AS, Zheng X, Petschek RG, *et al.*, 2009. Disordered, quasicrystalline and crystalline phases of densely packed tetrahedra. *Nature* 462:773–777
35. Vial S, Nykypanchuk D, Yager KG, Tkachenko AV, Gang O, 2013. Linear mesostructures in DNA–nanorod self-assembly. *ACS Nano* 7:5437–5445
36. Gibbs JW, 1878. On the equilibrium of heterogeneous substances. *American Journal of Science* 96:441–458
37. Becker R, Döring W, 1935. The kinetic treatment of nuclear formation in supersaturated vapors. *Ann. Phys* 24:719–752
38. Stranski IN, Totomanov D, 1933. Rate of formation of (crystal) nuclei and the Ostwald step rule. *Z. Phys. Chem* 163:399–08
39. Ostwald W, 1897. Studies on formation and transformation of solid materials. *Z. Phys. Chem.* 22:289
40. Savage JR, Dinsmore AD, 2009. Experimental evidence for two-step nucleation in colloidal crystallization. *Phys. Rev. Lett.* 102:198302
41. Nicolis G, Prigogine I, 1977. *Self-organization in nonequilibrium systems*. Wiley New York
42. ten Wolde PR, Frenkel D, 1999. Homogeneous nucleation and the Ostwald step rule. *Phys. Chem. Chem. Phys.* 1:2191–2196
43. Cardew P, Davey R, 1985. The kinetics of solvent-mediated phase transformations. *Proc. Royal Soc A: Mathematical and Physical Sciences* 398:415–428
44. Stauffer D, 1976. Kinetic theory of two-component (“hetero-molecular”) nucleation and condensation. *J. Aerosol Sci.* 7:319–333
45. Kremer K, 1978. Multi-dimensional theory of heteromolecular nucleation and condensation. *J. Aerosol Sci.* 9:243–246
46. Kim A, Scarlett R, Biancaniello P, Sinno T, Crocker J, 2008. Probing interfacial equilibration in microsphere crystals formed by DNA-directed assembly. *Nature Materials* 8:52–55
47. Whitesides GM, Boncheva M, 2002. Beyond molecules: Self-assembly of mesoscopic and macroscopic components. *Proc. Natl. Acad. Sci. USA* 99:4769
48. Wilber AW, Doye JP, Louis AA, Noya EG, Miller MA, Wong P, 2007. Reversible self-assembly of patchy particles into monodisperse icosahedral clusters. *J. Chem. Phys.* 127:085106
49. Nguyen HD, Reddy VS, Brooks CL, 2007. Deciphering the kinetic mechanism of spontaneous self-assembly of icosahedral capsids. *Nano Lett.* 7:338–344
50. Rapaport D, 2008. Role of reversibility in viral capsid growth: A paradigm for self-assembly. *Phys. Rev. Lett.* 101:186101
51. Whitelam S, Feng EH, Hagan MF, Geissler PL, 2009. The role of collective motion in examples of coarsening and self-assembly. *Soft Matter* 5:1251–1262
52. Whitelam S, 2010. Control of pathways and yields of protein crystallization through the interplay of nonspecific and specific attractions. *Phys. Rev. Lett.* 105:88102
53. Smit B, Hilbers P, Esselink K, 1993. Computer simulations of surfactant self assembly. *Int. J. Mod. Phys. C* 4:393–400
54. Damasceno PF, Engel M, Glotzer SC, 2012. Predictive self-assembly of polyhedra into complex structures. *Science* 337:453–457
55. Zhang Z, Glotzer SC, 2004. Self-assembly of patchy particles. *Nano Letters* 4:1407–1413
56. Fusco D, Headd JJ, De Simone A, Wang J, Charbonneau P, 2014. Characterizing protein crystal contacts and their role in crystallization: rubredoxin as a case study. *Soft Matter* 10:290–302
57. Prasad Bahadur R, Chakrabarti P, Rodier F, Janin J, 2004. A dissection of specific and non-specific protein–protein interfaces. *J. Mol. Biol.* 336:943–955
58. Shen YC, Oxtoby DW, 1996. BCC symmetry in the crystal-melt interface of Lennard-Jones fluids examined through density functional theory. *Phys. Rev. Lett.* 77:3585–3588
59. ten Wolde PR, Frenkel D, 1997. Enhancement of protein crystal nucleation by critical density fluctuations. *Science* 277:1975
60. Lutsko JF, Nicolis G, 2006. Theoretical evidence for a dense fluid precursor to crystallization. *Phys. Rev. Lett.* 96:046102
61. Lu PJ, Zaccarelli E, Ciulla F, Schofield AB, Sciortino F, Weitz DA, 2008. Gelation of particles with short-range attraction. *Nature* 453:499–504
62. Johnston IG, Louis AA, Doye JP, 2010. Modelling the self-assembly of virus capsids. *J. Phys.: Condens. Matt.* 22:104101
63. Sciortino F, Bianchi E, Douglas JF, Tartaglia P, 2007. Self-assembly of patchy particles into polymer chains: A parameter-free comparison between Wertheim theory and Monte Carlo simulation. *J. Chem. Phys.* 126:194903
64. Rechtsman MC, Stillinger FH, Torquato S, 2005. Optimized interactions for targeted self-assembly: Application to a honeycomb lattice. *Phys. Rev. Lett.* 95:228301
65. Rechtsman MC, Stillinger FH, Torquato S, 2006. Designed interaction potentials via inverse methods for self-assembly. *Phys. Rev. E* 73:011406
66. Rabani E, Reichman DR, Geissler PL, Brus LE, 2003. Drying-mediated self-assembly of nanoparticles. *Nature* 426:271–274
67. Peters B, 2009. Competing nucleation pathways in a mixture of oppositely charged colloids: Out-of-equilibrium nucleation revisited. *J. Chem. Phys.* 131:244103
68. Tailleur J, Cates M, 2008. Statistical mechanics of interacting run-and-tumble bacteria. *Phys. Rev. Lett.* 100:218103
69. Ramaswamy S, 2010. The mechanics and statistics of active matter. *Ann. Rev. Cond. Matt. Phys.* 1:323–345
70. Grant J, Jack RL, Whitelam S, 2011. Analyzing mechanisms and microscopic reversibility of self-assembly. *J. Chem. Phys.* 135:214505
71. Frenkel D, Smit B, 2001. *Understanding Molecular Simulation: From Algorithms to Applications*. Academic Press
72. Vega C, Sanz E, Abascal JLF, Noya EG, 2008. Determination of phase diagrams via computer simulation: methodology and applications to water, electrolytes and proteins. *Journal of Physics: Condensed Matter* 20:153101
73. Bruce AD, Wilding NB, 2003. Computational strategies for mapping equilibrium phase diagrams. *Adv. Chem. Phys.* 127:1
74. Filion L, Marechal M, van Oorschot B, Pelt D, Smallenburg F, Dijkstra M, 2009. Efficient method for predicting crystal structures at finite temperature: Variable box shape simulations. *Phys. Rev. Lett.* 103:188302
75. Babu S, Gimel JC, Nicolai T, De Michele C, 2008. The influence of bond rigidity and cluster diffusion on the self-diffusion of hard spheres with square well interaction. *J. Chem. Phys.* 128:204504
76. Bhattacharyay A, Troisi A, 2008. Self-assembly of sparsely distributed molecules: An efficient cluster algorithm. *Chem. Phys. Lett.* 458:210–213
77. Whitelam S, 2011. Approximating the dynamical evolution of systems of strongly interacting overdamped particles. *Molecular Simulation* 37:606–612
78. ten Wolde PR, Chandler D, 2002. Drying-induced hydrophobic polymer collapse. *Proc. Natl. Acad. Sci. USA* 99:6539–6543
79. Spaeth JR, Kevrekidis IG, Panagiotopoulos AZ, 2011. A comparison of implicit- and explicit-solvent simulations of self-assembly in block copolymer and solute systems. *J. Chem. Phys.* 134:164902
80. Roehm D, Kesselheim S, Arnold A, 2014. Hydrodynamic interactions slow down crystallization of soft colloids. *Soft Matter* (in press)
81. Radu M, Schilling T, 2014. Solvent hydrodynamics speed up crystal nucleation in suspensions of hard spheres. *EPL* 105:26001
82. Allen RJ, Frenkel D, ten Wolde PR, 2006. Simulating rare events in equilibrium or nonequilibrium stochastic systems. *J. Chem. Phys.* 124:024102
83. Valeriani C, Sanz E, Frenkel D, 2005. Rate of homogeneous crystal nucleation in molten NaCl. *J. Chem. Phys.* 122:194501
84. Sanz E, Valeriani C, Frenkel D, Dijkstra M, 2007. Evidence for out-of-equilibrium crystal nucleation in suspensions of oppositely charged colloids.
Whitelam and Jack

85. Mladek BM, Fornleitner J, Martinez-Veracoechea FJ, Dawid A, Frenkel D, 2012. Quantitative prediction of the phase diagram of DNA-functionalized nanosized colloids. Phys. Rev. Lett. 108:268301
86. Abascal JLF, Vega C, 2005. A general purpose model for the condensed phases of water: TIP4P/2005. J. Chem. Phys. 123:234505
87. Ouldridge TE, Louis AA, Doye JPK, 2010. DNA nanotweezers studied with a coarse-grained model of DNA. Phys. Rev. Lett. 104:178101
88. Auer S, Frenkel D, 2001. Prediction of absolute crystal-nucleation rate in hard-sphere colloids. Nature 409:1020–1023
89. Whitelam S, Tamblyn I, Haxton TK, Wieland MB, Champness NR, et al., 2014. Common physical framework explains phase behavior and dynamics of atomic, molecular, and polymeric network formers. Phys. Rev. X 4:011044
90. Miller WL, Cacciuto A, 2010. Exploiting classical nucleation theory for reverse self-assembly. J. Chem. Phys. 133:234108
91. Jankowski E, Glotzer SC, 2012. Screening and designing patchy particles for optimized self-assembly propensity through assembly pathway engineering. Soft Matter 8:2852–2859
92. Klotsa D, Jack RL, 2013. Controlling crystal self-assembly using a real-time feedback scheme. J. Chem. Phys. 138:094502
93. De Yoreo JJ, Vekilov PG, 2003. Principles of crystal nucleation and growth. Reviews in mineralogy and geochemistry 54:57–93
94. Zhang F, Zocher G, Sauter A, Stehle T, Schreiber F, 2011. Novel approach to controlled protein crystallization through ligandation of yttrium cations. Journal of Applied Crystallography 44:755–762
95. Oxtoby DW, 1992. Homogeneous nucleation: theory and experiment. J. Phys.: Condens. Matt. 4:7627
96. Sear RP, 2007. Nucleation: theory and applications to protein solutions and colloidal suspensions. J. Phys.: Condens. Matt. 19:033101
97. Ryu S, Cai W, 2010. Validity of classical nucleation theory for Ising models. Phys. Rev. E 81:030601
98. Winter D, Virnau P, Binder K, 2009. Monte Carlo test of the classical theory for heterogeneous nucleation barriers. Phys. Rev. Lett. 103:225703
99. Romano F, Sciortino F, 2012. Patterning symmetry in the rational design of colloidal crystals. Nat. Commun. 3:975
100. Romano F, Sciortino F, 2011. Two dimensional assembly of triblock Janus particles into crystal phases in the two bond per patch limit. Soft Matter 7:5799–5804
101. Vekilov PG, 2005. Two-step mechanism for the nucleation of crystals from solution. Journal of crystal growth 275:65–76
102. Chung SY, Kim YM, Kim JG, Kim YJ, 2009. Multiphase transformation
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and Ostwald’s rule of stages during crystallization of a metal phosphate. *Nat. Phys.* 5:68–73

103. Liu H, Kumar SK, Douglas JF, 2009. Self-assembly-induced protein crystallization. *Phys. Rev. Lett.* 103:018101

104. Hedges LO, Whitelam S, 2011. Limit of validity of Ostwald’s rule of stages in a statistical mechanical model of crystallization. *J. Chem. Phys.* 135:164902

105. Duff N, Peters B, 2009. Nucleation in a Potts lattice gas model of crystallization from solution. *J. Chem. Phys.* 131:184101

106. Shneidman VA, 2003. On the lowest energy nucleation path in a supersaturated lattice gas. *J. Stat. Phys.* 112:293–318

107. Villar G, Wilber AW, Williamson AJ, Thiara P, Doye JP, *et al.*, 2009. Self-assembly and evolution of homomeric protein complexes. *Phys. Rev. Lett.* 102:118106

108. Hagan MF, 2014. Modeling viral capsid assembly. *Adv. Chem. Phys.* 155:1–68

109. Williamson AJ, Wilber AW, Doye JP, Louis AA, 2011. Templated self-assembly of patchy particles. *Soft Matter* 7:3423–3431

110. Haxton TK, Whitelam S, 2013. Do hierarchical structures assemble best via hierarchical pathways? *Soft Matter* 9:6851–6861

111. Zaccarelli E, 2007. Colloidal gels: equilibrium and non-equilibrium routes. *J. Phys.: Condens. Matt.* 19:323101

112. Meakin P, 1983. Formation of fractal clusters and networks by irreversible diffusion-limited aggregation. *Phys. Rev. Lett.* 51:1119–1122

113. Clouet E, Laé L, Épicier T, Lefebvre W, Nastar M, Deschamps A, 2006. Complex precipitation pathways in multicomponent alloys. *Nature Materials* 5:482–488

114. Wu KT, Feng L, Sha R, Dreyfus R, Grosberg AY, *et al.*, 2013. Kinetics of dna-coated sticky particles. *Phys. Rev. E* 88:022304

115. Nguyen TD, Glotzer SC, 2010. Reconfigurable assemblies of shape-changing nanorods. *ACS Nano* 4:2585–2594

116. Whitelam S, Rogers C, Pasqua A, Paavola C, Trent J, Geissler PL, 2009. The impact of conformational fluctuations on self-assembly: Cooperative aggregation of archaeal chaperonin proteins. *Nano Letters* 9:292–297

117. Gebauer D, Vökel A, Cölfen H, 2008. Stable prenucleation calcium carbonate clusters. *Science* 322:1819–1822

118. Wallace AF, Hedges LO, Fernandez-Martinez A, Raiteri P, Gale JD, *et al.*, 2013. Microscopic evidence for liquid-liquid separation in supersaturated CaCO₃ solutions. *Science* 341:885–889

119. Gliko O, Pan W, Katsonis P, Neumaier N, Galkin O, *et al.*, 2007. Metastable liquid clusters in super-and undersaturated protein solutions. *J. Phys. Chem. B* 111:3106–3114
120. Sleutel M, van Driessche AE, 2014. Role of clusters in nonclassical nucleation and growth of protein crystals. Proc. Natl. Acad. Sci. USA 111:E546–E553
121. Hänggi P, Talkner P, Borkovec M, 1990. Reaction-rate theory: fifty years after kramers. Rev. Mod. Phys. 62:251
122. ten Wolde PR, Ruiz-Montero MJ, Frenkel D, 1996. Numerical calculation of the rate of crystal nucleation in a lennard-jones system at moderate undercooling. J. Chem. Phys. 104:9932–9947
123. Van Wylen GJ, Sonntag RE, Wylen GJ, 1973. Fundamentals of classical thermodynamics. Wiley New York
124. Hagan MF, Elrad OM, Jack RL, 2011. Mechanisms of kinetic trapping in self-assembly and phase transformation. J. Chem. Phys. 135:104115
125. Lechner W, Dellago C, Bolhuis PG, 2011. Role of the prestructured surface cloud in crystal nucleation. Phys. Rev. Lett. 106:085701
126. Sear RP, 2012. The non-classical nucleation of crystals: microscopic mechanisms and applications to molecular crystals, ice and calcium carbonate. International Materials Reviews 57:328–356
127. Maibaum L, 2008. Phase transformation near the classical limit of stability. Phys. Rev. Lett. 101:256102
128. Ryu S, Cai W, 2010. Numerical tests of nucleation theories for the Ising models. Phys. Rev. E 82:011603
129. Agarwal V, Peters B, 2013. Solute precipitate nucleation: A review of theory and simulation advances. Adv. Chem. Phys. 155
130. Fusco D, Charbonneau P, 2013. Crystallization of asymmetric patchy models for globular proteins in solution. Phys. Rev. E 88:012721
131. Lutsko J, 2010. Recent developments in classical density functional theory. Adv. Chem. Phys. 144:1–92
132. Sanders DP, Larralde H, Leyvraz F, 2007. Competitive nucleation and the ostwald rule in a generalized potts model with multiple metastable phases. Phys. Rev. B 75:132101
133. Binder K, Stauffer D, 1976. Statistical theory of nucleation, condensation and coagulation. Adv. Phys. 25:343–396
134. Zlotnick A, Johnson JM, Wingfield PW, Stahl SJ, Endres D, 1999. A theoretical model successfully identifies features of Hepatitis B virus capsid assembly. Biochemistry 38:14644–14652
135. Knowles TPJ, Waudby CA, Devlin GL, Cohen SIA, Aguzzi A, et al., 2009. An analytical solution to the kinetics of breakable filament assembly. Science 326:1533–1537
136. Miller WL, Cacciuto A, 2009. Hierarchical self-assembly of asymmetric amphiphatic spherical colloidal particles. Phys. Rev. E 80:021404
137. Jack RL, Hagan MF, Chandler D, 2007. Fluctuation-dissipation ratios in the dynamics of self-assembly. Phys. Rev. E 76:021119
138. Grant J, Jack RL, 2012. Quantifying reversibility in a phase-separating lattice gas: An analogy with self-assembly. *Phys. Rev. E* 85:021112

139. Mezzenga R, Schurtenberger P, Burbidge A, Michel M, 2005. Understanding foods as soft materials. *Nature Mat.* 4:729–740

140. Fortini A, Sanz E, Dijkstra M, 2008. Crystallization and gelation in colloidal systems with short-ranged attractive interactions. *Phys. Rev. E* 78:041402

141. Royall CP, Malins A, 2012. The role of quench rate in colloidal gels. *Faraday Discuss.* 158:301–311

142. Teece LJ, Faers MA, Bartlett P, 2011. Ageing and collapse in gels with long-range attractions. *Soft Matter* 7:1341–1351

143. Scarlett RT, Ung MT, Crocker JC, Sinno T, 2011. A mechanistic view of binary colloidal superlattice formation using DNA-directed interactions. *Soft Matter* 7:1912–1925

144. Trinkaus H, 1983. Theory of the nucleation of multicomponent precipitates. *Phys. Rev. B* 27:7372–7378

145. Schmelzer JWP, Abyzov AS, Möller J, 2004. Nucleation versus spinodal decomposition in phase formation processes in multicomponent solutions. *J. Chem. Phys.* 121:6900

146. Whitelam S, Hedges LO, Schmit JD, 2014. Self-assembly at a nonequilibrium critical point. *Phys. Rev. Lett.* 112:155504

147. Sollich P, Wilding NB, 2011. Polydispersity induced solid-solid transitions in model colloids. *Soft Matter* 7:4472–4484

148. Sear RP, 1998. Phase separation and crystallisation of polydisperse hard spheres. *EPL (Europhysics Letters)* 44:531

149. Lee E, Kim JK, Lee M, 2009. Reversible scrolling of two-dimensional sheets from the self-assembly of laterally grafted amphiphilic rods. *Angew. Chem. Int. Ed.* 48:3657–3660

150. Lutsko JF, 2012. A dynamical theory of nucleation for colloids and macromolecules. *J. Chem. Phys.* 136:034509