

Insights into phase transition kinetics from colloid science

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Colloids display intriguing transitions between gas, liquid, solid and liquid crystalline phases. Such phase transitions are ubiquitous in nature and have been studied for decades. However, the predictions of phase diagrams are not always realized; systems often become undercooled, supersaturated, or trapped in gel-like states. In many cases the end products strongly depend on the starting position in the phase diagram and discrepancies between predictions and actual observations are due to the intricacies of the dynamics of phase transitions. Colloid science aims to understand the underlying mechanisms of these transitions. Important advances have been made, for example, with new imaging techniques that allow direct observation of individual colloidal particles undergoing phase transitions, revealing some of the secrets of the complex pathways involved.

Figure 1 illustrates three types of phase diagram. The first (Fig. 1a) is a simple system of hard spheres. Introducing attractions results in three-phase equilibria, as in atomic systems such as argon (Fig. 1b). With shorter-range attractions the gas–liquid (or fluid–fluid) equilibrium becomes metastable (Fig. 1c). This is often observed in protein systems. One might assume equilibrium diagrams show the complete picture, with perhaps the initial distance from the phase boundary (indicative of the distance to equilibrium) controlling the speed with which the equilibrium phases are attained; however, this is the exception rather than the rule.

Hard-sphere colloids suspended in a solvent provide an excellent illustration of the difficulties involved in understanding the equilibrium states and the mechanisms by which systems evolve. Entropy considerations predict that these systems will form crystals if the volume fraction is increased. Above the ‘freezing’ volume fraction, $\phi_f = 0.494$, it is entropically favourable if some spheres are in a crystal, but above the ‘melting’ volume fraction, $\phi_m = 0.545$, all spheres should be in a crystal (Fig. 1a). However this is not always the situation found experimentally, either because the conditions the theory assumes (low polydispersity, for example) are not satisfied, or the dynamics of the system have dictated a different structure (note that we cannot say that this structure is the equilibrium structure—if entropy favours crystal formation then a crystal will form eventually, however the system may remain in the less-favoured state for a significant amount of time). This crystallization process is often interpreted within the familiar framework of nucleation and growth. There has been renewed interest in this mechanism recently, both with simulations¹ and experimentally^{2,3}: by monitoring the individual particles undergoing the transition it is possible to evaluate and improve the model.

The classical theory predicts that the free energy cost, ΔG , of forming a nucleus of radius r is:

$$\Delta G = \frac{4\pi r^3 \rho \Delta\mu}{3} + 4\pi r^2 \gamma$$

where γ is the surface free energy, ρ is the density of the bulk liquid, and $\Delta\mu$ is the chemical potential difference between the bulk solid and bulk liquid. For a large enough radius the (favourable) volume term begins to dominate the (unfavourable) surface term, the nucleus becomes stable, and may grow.

Directly observing crystal nucleation is difficult, often because once crystal nuclei are big enough to be seen they are well beyond the critical stage. Extensive simulation work has been done but there are still discrepancies, for example, in the prediction of the nucleation rate. Today, advances in microscopy and computational technology mean that particles in crystallizing samples can be tracked, effectively letting us run time ‘backwards’ from the large, growing crystals to the earlier, critical times to examine the critical nuclei^{2,3}. This allows assumptions and predictions from simulations and experiments to be compared (Fig. 2). One premise that may be disputed is that of a spherical nucleus. The critical nucleus may be anisotropic with different free energy costs associated with different faces (this would have repercussions on the growth rate as different faces are likely to grow at different rates). Using confocal microscopy, Gasser *et al.*³ have observed elliptical nuclei (Fig. 2b). A second discrepancy between simulations and experiment occurs in the value of the surface tension: it is almost seven times lower³ than found by simulations¹. However, a small amount of charge in the system of ref. 3 means that the freezing and melting transitions are observed at $\phi_f = 0.38$ and $\phi_m = 0.42$, so it would be interesting to determine whether this small charge can also affect the surface tension.

The packing of the spheres within the crystal also requires attention. Although the most stable is face-centred cubic packing⁴ (f.c.c.), the Ostwald rule of stages states that the transition from one

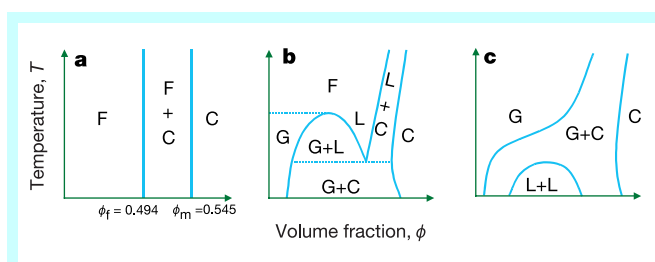


Figure 1 A wide range of phase diagrams occurs naturally. **a**, For a purely hard-sphere system the phase diagram shows only fluid (F) and crystal (C) phases. **b**, Atomic systems are often modelled by hard spheres with long-range attractions. This leads to equilibrium between gas (G), liquid (L) and crystal phases. **c**, In cases where the attraction is short-range, as in protein systems (important in physiology), equilibrium between gas and crystal is found, but the liquid–liquid transition becomes metastable.

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phase to another proceeds via the intermediate metastable states. Alexander and McTague⁵ argued that the first step would be body-centred cubic packing (b.c.c.), but this is rarely seen, even as an intermediate. Instead, the crystal usually shows random hexagonal close-packing (h.c.p.), even in the most ideal conditions⁶, although the degree of randomness appears to depend on growth rate⁷. This anneals to the more stable f.c.c., but because the energy difference between the h.c.p and f.c.c. structures is small, the driving force is also small and the step may be slow, depending also on factors such as crystal size⁸.

Pusey and van Megen⁹ clearly observed that above a certain volume fraction ($\phi_g = 0.58$) an amorphous glassy phase appeared that did not crystallize over several months. The kinetic arrest found in glass formation occurs in many systems^{10,11} and its understanding is an important scientific goal. Important in understanding the glass transition is the notion of spatial heterogeneities in the sample, that is, distinct relaxing domains or regions where particles move cooperatively. Microscopy has proven invaluable in looking directly at particle movement in colloidal samples, allowing characterization of the dynamics and structure in glassy systems^{12–15}. Until 1997 it was generally thought that $\phi_g = 0.58$ was an intrinsic glass transition volume fraction for hard-sphere colloidal suspensions, but then samples with high volume fractions, which fail to crystallize even after a year on Earth, were seen⁶ to crystallize fully in less than two weeks in microgravity (order of magnitude, $10^{-6}g$). This has also

been corroborated in experiments on centrifuged samples¹⁶ and indicates that even a small amount of a uniaxial stress can jam a system such that crystallization is not observed, as illustrated in Fig. 3.

These findings illustrate the complications found in the simple case of entropy-driven crystallization of hard spheres, where the phase diagram is a straightforward crystal–fluid equilibrium, but the complementary techniques of microscopy and computer simulation have led to advances in the understanding of this phase transition. This also aids the interpretation of the same mechanism in less straightforward systems.

Colloid–polymer systems

The fluid–solid transition can be complicated, but transitions involving three-phase equilibria or metastable states, as found in more familiar atomic and molecular systems, can be even more tortuous, as can be inferred from the increased complexity of the phase diagrams. An analogous situation can be produced in colloidal systems where the addition of polymer is used to produce an attraction between the particles (Fig. 4a). Depending on the relative sizes of the polymer and the colloid, such systems not only show the gas–crystal coexistence described above, but also gas, liquid and crystal coexistence, leading to remarkable phase behaviour.

The depletion interaction that is induced by adding polymer to a colloidal system effectively widens the region over which phase separation is expected (illustrated in Fig. 4b, c). An advantage of these systems is that the range and depth of the potential are controlled by the size and volume fraction of the polymer respectively. For a given colloid size, two distinct situations can be resolved, depending on the polymer size (Fig. 4b, c). The polymer concentration C_p is akin to inverse temperature: compare Fig. 4b, c with Fig. 1b, c (which illustrate predictions for atomic and protein systems). Because the range of the interaction can be tuned, a variety of phase diagrams can be realized. This allows the study of transitions both in systems with long-range attractions and those with very short-range attractions where the phase diagrams predict intriguing metastable states.

Although it is possible to predict the equilibrium phases of such systems, they also show frustrating behaviour; for many systems a colloidal crystal is expected but not achieved. In some instances not even the colloid-rich phase is attained, the system being trapped in a

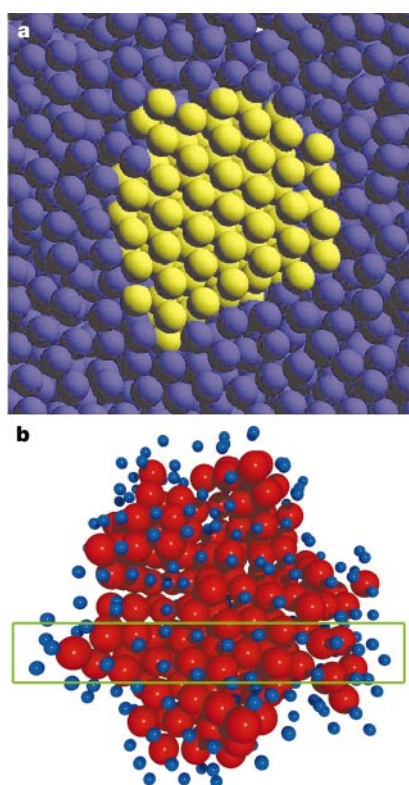


Figure 2 Nucleation events in simulations and in experiments. **a**, Simulations provide insights into the structure, shape and packing of critical nuclei, as this image from the work of Auer and Frenkel¹ illustrates. Until recently, this was the main technique with which such events could be observed; however, advances in imaging technology now allow critical nuclei to be imaged in three dimensions. **b**, The crystallization of poly-methyl methacrylate colloids was followed in real time by Gasser *et al.*³, and crystal nuclei were identified, allowing comparisons to be made with the results of simulations and theory. Reproduced with permission from ref. 3. Copyright (2002) American Association for the Advancement of Science.

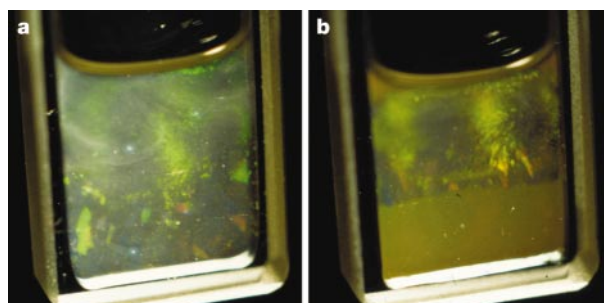


Figure 3 Suppression of crystallization by a small amount of uniaxial stress¹⁶. The samples both show poly-methyl methacrylate spheres in a solvent where there is only a very small density difference between colloid and solvent. The sample in **b**, however, shows for fewer crystal regions than the sample in **a**. This difference in degree of crystallization was caused by applying a small amount of stress (by centrifuging the sample) to the sample in **b**. Although the stress was applied only for a period of hours and the samples were then left to crystallize for over a year, the experiment demonstrates how dramatically stress can jam a system. Reproduced with permission from ref. 16. Copyright (2000) American Chemical Society.

gel-like phase instead. Much depends on the initial conditions, in this case, polymer concentration and colloid volume fraction. Although slightly changing one condition may not alter which equilibrium phases are expected, it may significantly affect whether or not they are reached (Fig. 4d). Thus, to predict the transition mechanisms of both colloid and colloid–polymer systems reliably is difficult.

Predictions from phase diagrams and free energy

One illustration of the importance of the kinetics and mechanisms to an actual experiment is recent work on the diffusive growth of crystals from polydisperse spheres¹⁷. The essence is that because smaller spheres move fastest, they arrive at the crystal surface first and the resulting crystal has more small particles than one might otherwise expect. Although it is predicted that polydisperse systems will fractionate in order to form crystals^{18–20}, with the simplest case comprising a crystal and coexisting fluid with different size distributions and thus different polydispersities, this is a thermodynamic route to fractionation; the fractionation via diffusive growth, described above, is a dynamic route. (We note that the thermodynamic fractionation requires the crystals to be made up of the larger particles.) Recent work indicates that polydispersity can greatly affect the crystal nucleation rate because of the increase in the crystal–fluid surface free energy²¹, leading to intriguing predictions concerning, for example, the variation in the density of the critical nucleus²². Polydispersity may also play a part in the slowing of the kinetics on the approach of the glass transition²³.

Predictions of the kinetics often come from free-energy diagrams, from which the unstable and metastable regions and the commonly associated mechanisms of spinodal decomposition and nucleation and growth can be delineated. In spinodal decomposition, almost any fluctuation in the order parameter (here, colloid volume fraction) lowers the free energy and is commonly modelled by the Cahn–Hilliard theory using a coarse-graining approach (that is, considering length scales large compared to the colloid) to examine the change in volume fraction. However, the possibilities are more numerous than this. In the 1960s Cahn²⁴ described how free energy curves can predict which nucleation events are possible. In an extension of this work, Evans *et al.*²⁵ show that for a given position in the phase diagram several mechanisms may occur simultaneously and, equally important, some mechanisms may not be possible. Both gas nucleation and crystal nucleation are seen to occur concurrently²⁶; the kinetics in that part of the phase diagram will be very different to those where only crystal nucleation is feasible. Although examples have focused on work on colloid–polymer mixtures²⁷, the method by which possible mechanisms are identified depends only on the free-energy curves and is equally applicable to atomic, colloidal or protein systems.

Evans *et al.*²⁵ predict that for a small region of the phase diagram, the only mechanism of phase separation is by the nucleation of the solid phase (kinetic region E, in their terminology). Protein crystallographers have long been aware that the structures obtained depend sensitively on the initial conditions and this region, close to the phase boundary, seems to be that often giving the best crystals in both colloid and protein crystallization. Globular proteins and colloids have similar global phase diagrams but there are several differences. Proteins are neither perfectly spherical, nor isotropic. Surface groups often result in proteins having orientational order in the crystal and this aetiological (orientation-dependent) interaction is likely to result in more complex mechanisms²⁸, while leaving the global phase diagram relatively unchanged.

Aggregation behaviour

The narrow window of crystallization (see Fig. 4d) mentioned above seems, at first, counter-intuitive. The drive to phase-separate increases on going further from the phase boundary, so we might assume that the rate of separation and crystal formation would also increase. In fact, although change is fast in such regions, the mechanism of change itself obstructs the pathway to crystallization and often crystals are not formed—a good demonstration of the proverb ‘more haste, less speed’.

Different mechanisms can indeed be seen as the interaction

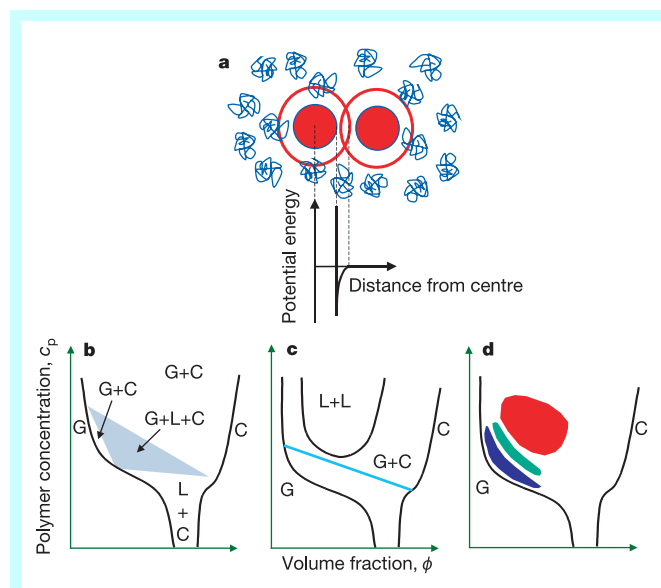


Figure 4 The depletion interaction and its phase diagrams, a concept that was introduced by Asakura and Oosawa⁷⁵ in 1954 and later by Vrij⁷⁶. **a**, A volume exists around each sphere into which the centre of the polymer coil cannot penetrate. On approach these ‘excluded volumes’ overlap and the total volume available to the polymers increases, increasing their entropy (at the expense of some colloidal entropy). Statistical mechanics predict the partitioning into colloid-rich and polymer-rich phases. For a given colloid size the phase diagrams are sensitive to the polymer size: **b**, large polymer; **c**, small polymer. The polymer can partition into different phases, so the lines indicating coexisting phases are not necessarily horizontal. Phase diagrams are similar to those in Fig. 1, but are inverted, as polymer concentration plays the role of inverse temperature. **b** is similar to an atomic system, having regions of three-phase equilibria (shaded area). **c** is similar to systems found for some proteins, with two-phase coexistence and a metastable liquid–liquid region. **d**. The situation often found experimentally, for short polymers. The blue area indicates a region where crystals are formed; the green area indicates aggregation; and the red area indicates gelation. Thus, only in the narrow region close to the phase boundary are the equilibrium phases reached.

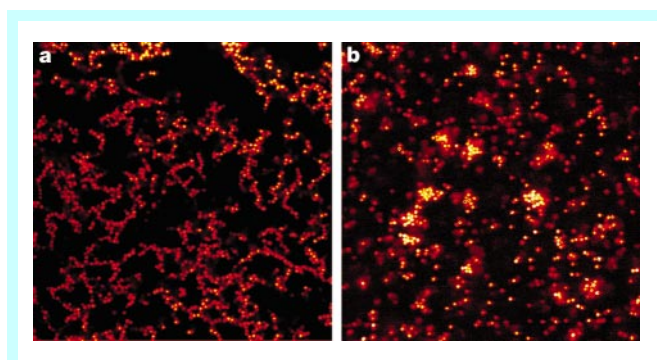


Figure 5 Confocal microscopy imaging at phase separation in colloid–polymer mixtures³⁵. Different pathways to phase separation are observed in different parts of the phase diagram. **a**, Open, stringy structures are observed deep within the phase-separation region where the dominant mechanism is aggregation. **b**, Closer to the binodal, the mechanism appears more like that of nucleation and growth: compact clusters appear after a significant delay time.

between particles increases (Fig. 5). Deep in the phase diagram, aggregation occurs. This is best described on a particle level. The first model was formulated at the beginning of the twentieth century by Schmoluchowski²⁹. Making the assumption that particles ‘stick’ immediately and permanently on contact, he successfully described the time evolution of the particle size distribution.

Since then there has been a large volume of work on aggregation using a number of different assumptions^{30–36}. Those above describe an extreme of aggregation: evolution is limited by the time taken for particles or clusters to diffuse and encounter one another and is thus termed diffusion-limited cluster aggregation (DLCA). Experiments and simulations have revealed that this results in a monodisperse cluster-size distribution, the clusters having a fractal dimension, $d_f = 1.8$. An alternative situation is that particles do not stick immediately because of an energy barrier: here, the rate-limiting step is to overcome the barrier and this is termed reaction-limited cluster aggregation (RLCA). RLCA produces more compact clusters ($d_f = 2.1$) and a polydisperse cluster-size distribution.

Light-scattering experiments have revealed growth laws and surprising similarities with spinodal decomposition^{32,34,37–40}. Although spinodal decomposition has been seen in systems with a stable gas–liquid equilibrium⁴¹ and one could argue that aggregation and spinodal decomposition are similar in that there appears to be no barrier to phase separation, it is less easy to see how the coarse-graining model of Cahn and Hilliard applies to aggregating fractals. Thus the extent of similarity and its interpretation is of interest^{34,37}. Because of the fractal nature of the clusters, aggregation can result in a gel, where a cluster spans the sample. Simulations provide many predictions of the aggregate structure and intriguing insights into the effects of different interactions. Work by Tanaka and Araki⁴², for example, indicates that hydrodynamic interactions between particles may lead to more open, stringy structures.

Samples often show behaviour intermediate between RLCA and DLCA. If the assumption of sticking permanently is invalid, as it must be if the samples are to reach the equilibrium phases, further evolution is quite involved^{30,43–46}. Pure rearrangements (rotations of side-arms, for example), changes in aggregation mechanism and particle detachment may all occur, possibly concurrently. Thus the routes by which the equilibrium phase is formed are complex. In a system where the particles are likely to stick immediately they are, by the same token, less likely to detach again and surrounding particles caging in a central one may restrict particle movement⁴⁷. So for a particle to leave a site and move to one more favourable will take longer than in a system where the depth of attraction is less, but where the attraction is less the phase separation will probably have been dominated by a nucleation and growth mechanism which already favours crystal formation. Thus, despite the large driving force, the road to crystallization is hindered all the way and samples will take a long time to reach equilibrium.

Gelation is a frequent result of aggregation. Such gels are often quite weak and their rheology and evolution is of interest^{44,46,48–51}. Several groups have examined transient gels^{41,52–55}, which maintain a relatively robust structure for a certain time before collapsing. Dynamic light scattering indicates that the kinetic behaviour at the colloid–gel transition is remarkably similar to that at the colloid–glass transition^{50,51}. This suggests that the jamming observed in gelation in colloidal suspensions could be related to the jamming responsible for glass formation. In turn, this led to the proposal⁵⁶ that gelation and the glass transition may be manifestations of more general jamming transitions⁵⁷ where, depending on the system, the controlling factor may be temperature, applied stress, interaction energy or volume fraction.

Aggregation, in many guises, is also seen in protein systems. Intriguingly, these reveal there may be another mechanism of growth hitherto unseen in colloidal systems, that is, growth of protein crystals via attachment (to the crystal) of single proteins

(monomers) or intermediate dimers or oligomers. Whether or not this occurs is a subject of great debate^{58–61}, but the kinetics of the aggregation and crystallization would be greatly affected.

The effect of metastable states

It was shown in Fig. 4 that as the range of attraction is reduced the fluid–fluid transition becomes metastable. Indeed, in long-range, three-phase systems, as the range is decreased and the stable fluid–fluid region almost disappears, the structure of the equilibrium fluid phase appears to change⁶². As illustrated in Fig. 6 even in the stable region the proximity of a fluid–fluid critical point may have a significant effect on the dynamics owing to the appearance of critical fluctuations, which may enhance crystal nucleation^{63,64}. The nucleus can also be enveloped by a fluid layer—this coating would alter the surface tension and thus the nucleation and growth process⁶⁵.

Within the metastable region the Ostwald rule implies that fluid–fluid phase separation would precede the fluid–crystal transition. Whether crystals are best grown inside or outside the metastable region is a matter of debate^{65–68}. If fluid–fluid separation occurs first, nucleation may be enhanced but growth will be determined by the now-high volume fraction and could produce less-well-ordered crystals. Outside the region, even with a fluid coating, growth is still determined by the average density. The fluid–fluid phase separation is not seen in colloidal systems, rather, as described above, it is usually pre-empted by a gelled state^{69,70}. In contrast, in protein systems, which have similar global phase diagrams, the transition is observed^{71–74}. This implies that there are subtle differences affecting the phase-separation pathways, and long-range forces may be important⁷⁰.

Thus phase transitions present us with a variety of bewildering pathways to phase separation, and although many are beginning to be well understood it is perhaps in those routes which lead to the non-equilibrium states—glasses or gels—where future surprises may be found. □

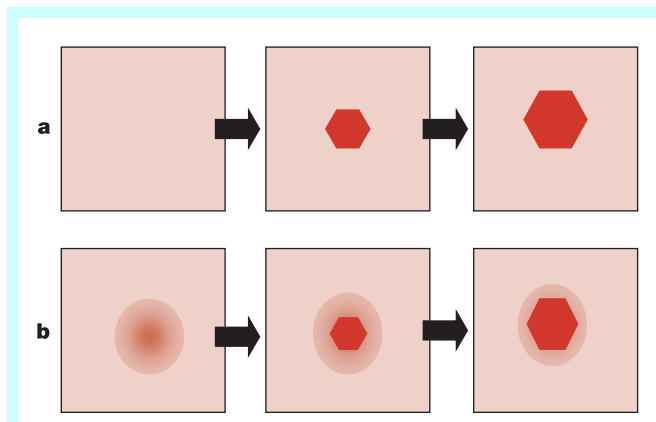


Figure 6 Nucleation mechanisms around the metastable critical point. **a**, The traditional picture of a crystal nucleating and growing in the original fluid. In order to get reasonable nucleation rates the initial concentration may have to be quite high, resulting in rapidly growing (owing to the large thermodynamic driving force) and thus more-disordered crystals, or aggregates. **b**, A two-step mechanism is suggested to occur around the metastable critical point. In this case, the initial step is the formation of a fluid droplet, either through phase separation⁶⁸ or the presence of critical fluctuations⁶³. The high density of this droplet increases the nucleation rate. As the crystal grows, a covering film of fluid acts like a buffer between the original fluid and the growing crystal. In protein systems this fluid layer aids growth because it means monomers are always available for the growth steps and they have ample time within the film to find the proper orientation for bonding. Thus the nucleation is increased because of the effect of metastable states on the dynamics, rather than by an increase in the thermodynamic driving force.

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