Nucleation of colloids and macromolecules: does the nucleation pathway matter?

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(Dated: 7 February 2012)

A recent description of diffusion-limited nucleation based on fluctuating hydrodynamics that extends classical nucleation theory predicts a very non-classical two-step scenario whereby nucleation is most likely to occur in spatially-extended, low-amplitude density fluctuations. In this paper, it is shown how the formalism can be used to determine the maximum probability of observing any proposed nucleation pathway, thus allowing one to address the question as to their relative likelihood, including of the newly proposed pathway compared to classical scenarios. Calculations are presented for the nucleation of high-concentration bubbles in a low-concentration solution of globular proteins and it is found that the relative probabilities (new theory compared to classical result) for reaching a critical nucleus containing $N_c$ molecules scales as $e^{-N_c/3}$ thus indicating that for all but the smallest nuclei, the classical scenario is extremely unlikely.

I. INTRODUCTION

Nucleation - whether homogeneous or heterogeneous - is a paradigmatic example of self assembly. It occurs when a physical system can be in two or more states that are separated by free-energy barriers. If the system is initially in one of the metastable states, thermal fluctuations can drive it over the free energy barrier and into a more stable state. Because the energy needed to overcome the barrier scales with the spatial size of the system, the process occurs locally via the formation of a finite sized cluster or nucleus. In many processes of interest such as the crystallization of proteins from solution\textsuperscript{1,2}, the formation of snowflakes\textsuperscript{3} and the crystallization of polymorphic solids\textsuperscript{4} the system may pass through one or more intermediate metastable states before arriving at the final, stable state. In fact, the heuristic known as Ostwald’s rule of stages specifically states that a system will pass in turn from one state to another having the next lowest free energy until it reaches the minimal energy state. Various arguments can be given in support of this rule\textsuperscript{5} and they can be grouped into two classes: either it arises because the barriers separated “similar” states are smaller than those separating disparate states or it arises due to the kinetics of the transition. The former reason is an application of another heuristic known as the Stranski-Totomanow conjecture which states that the observed transition will be the one corresponding to the minimal energy barrier\textsuperscript{6}. The latter is more difficult to characterize as it may depend on microscopic details of the various states and the dynamics of the system. Recent work on model systems indicates that, depending on the free energy landscape and the dynamics, either Ostwald or Stranski-Totomanow or both may be correct or none.

The common issue at question is the description of the nucleation pathway. Clearly, a theoretical description for the nucleation pathway that goes beyond the empirical heuristics mentioned above must be based on a dynamical description of the nucleation including the role of thermal fluctuations, mass and energy transport and the structure of the various phases. A framework for such a dynamical formulation of nucleation has recently been described\textsuperscript{7}. For large clusters, it was shown to reproduce classical nucleation theory (CNT) in the weak-noise limit. For a diffusion-limited nucleation - appropriate for the description of colloids and macromolecules in solution - it was shown that the relative probability of different nucleation pathways could be easily calculated and that the most likely path (MLP) could be determined by steepest-descent on the free energy surface. This framework can be contrasted with numerous proposals for determining the nucleation pathway based solely on the properties of the free energy surface with no dynamical input, see e.g.\textsuperscript{8} -\textsuperscript{16}. As discussed below, because of the heuristic nature of the latter, evaluating their relative merits has proven difficult.

The purpose of this paper is to illustrate the comparison of different candidate nucleation pathways by means of their relative probability. The particular example investigated is the formation of high concentration droplets in a low-concentration solution of globular proteins. This process is analogous to the vapor-liquid transition in simple fluids and, while being of intrinsic interest as part of the process of crystallization in globular proteins, has the practical advantage of allowing for a relatively simple theoretical description as described in Ref. 8 and 9 and below. For this problem, the recently developed dynamical theory of nucleation predicts a very different nucleation pathway than do the older DFT-based theories. The new prediction is that the process of droplet nucleation involves two steps: first, a long-wavelength density fluctuation forms and then a nucleation event takes place within this fluctuation. The older, classical view is that nucleation begins with a spatially localized cluster that grows monotonically. From a point of view focused on the comparison of the theories, it is therefore of interest...
to compare the relative likelihood of these two pathways so as to determine whether the difference between them is qualitative or quantitative. More broadly, in the context of the general theory of nucleation this allows us to address the question of how important it is to choose the “right” path when there are multiple possible paths that pass through the (unique) critical cluster. Note that a feature of the heuristic rules is that they are phrased entirely in terms of the free energy maxima (the barriers) and minima (the states) and, hence, the provide no guidance on this question. In this sense, they are in accord with the common intuition that all that matters in nucleation are the free-energy extrema which, in addition to their use in choosing pathways, are also the only relevant quantities entering the Classical Nucleation Theory (CNT) for nucleation rates. Here, it will be shown that even paths beginning and ending on the same states and passing over the same barriers can have wildly different probabilities of occurrence. The paths compared will be the most likely path as determined from the dynamical theory and a path determined from one of the non-dynamical, free-energy methods which, by means of direct comparison to simulation, is known to give a very accurate description of the free energy barrier for nucleation in proteins. Since this method has also recently been applied to the study of nucleation of wetting films on curved substrates and of ordered phases of block copolymers, where multiple candidate pathways were found, it is of particular interest to use as a test-case. This paper therefore serves two purposes: (i) to introduce a method of comparing the likelihood of candidate nucleation pathways, however they are arrived at; and (ii) to use this method to determine whether the proposed non-classical pathway is significantly different (more probable) than a “classical” alternative.

In Section II, the elements of the theoretical description are reviewed. Section III describes the application to the nucleation of protein-rich droplets in solution, including a detailed comparison of the different candidate pathways and a computation of their relative probabilities. The paper ends with a brief discussion of our conclusions.

II. THEORY

The present theoretical development is concerns a collection of particles - molecules or colloidal particles - that interact with one another via a prescribed pair potential and which are also subject to random, Brownian forces. This is a simple model for large particles in a bath of small particles wherein the effect of the bath or solution is incorporated via the effective interaction between the large particles and random (Brownian) forces acting on the large particles. As such, the bath is not explicitly represented except through the amplitude of the random noise which in turn determines the (low-concentration) diffusion constant for the large particles. For this reason, the concentration of the large particles is equivalent to their density and the two terms will be used interchangeable in the following. Further details of the microscopic model can be found in Ref. The fundamental quantity with which the phase transition is characterized is then the local concentration (or number density), \( \rho(\mathbf{r}) \). The density/concentration is commonly assumed to be spherically symmetric and this assumption will be used throughout the present development. The initial, metastable, system is characterized by a uniform density \( \rho(r) = \rho_l \) where \( \rho_l \) is a minimum of the bulk free energy. The new phase is also characterized by a uniform density, \( \rho(r) = \rho_f \), where \( \rho_f \) is the global minimum of the bulk free energy. We assume throughout the existence of a Helmholtz free energy functional, \( F[\rho] \), so that, e.g., in the grand canonical ensemble the appropriate free energy is \( \Omega[\rho] = F[\rho] - \mu N \) where \( N = \int \rho(\mathbf{r}) \, d\mathbf{r} \) is the total number of particles. For a uniform density the free energy becomes an ordinary function, \( F[\rho(\mathbf{r}) = \rho_l] \equiv F(\rho_l) \), and the conditions for the uniform phases to be minima are the usual relations \( \frac{\delta F(\rho_l)}{\delta \rho(\mathbf{r})} = 0 \),

\[
\frac{\delta \Omega[\rho]}{\delta \rho(\mathbf{r})} = 0. \tag{1}
\]

There are generally two approaches to representing the density function. One is to simply discretize space by introducing a lattice of points \( r_i = i \Delta \) so that one works with a series of values \( \rho_l \equiv \rho(\Delta) \). An alternative is to use parametrized functional form such as a hyperbolic tangent,

\[
\rho(r) = \rho_0 + \frac{\rho_\infty - \rho_0}{1 + \exp \left( \frac{2 r - w}{w} \right)} \tag{2}
\]

or an exponential form

\[
\rho(r) = \left[ \rho_0 - \frac{\rho_0 - \rho_\infty}{2} \exp \left( \frac{r - R}{w} \right) \right] \Theta(R - r) \tag{3}
\]

\[
+ \left[ \rho_\infty + \frac{\rho_0 - \rho_\infty}{2} \exp \left( \frac{R - r}{w} \right) \right] \Theta(r - R)
\]

where, in both cases, there are four parameters: a radius, \( R \), a width, \( w \), the interior density, \( \rho_0 \) that characterizes the central density for large \( (R \gg w) \) clusters and the density far from the cluster, \( \rho_\infty \). It is easy to show that in the thermodynamic limit the latter must be a minimum of the free energy so that we will normally have
that it is equal to the initial density \( \rho_\infty = \rho_i \). The advantage of the first method, discretization, is that it is clear that one can approach the continuum limit by decreasing the lattice spacing whereas the advantage of the second method, parametrization, is that one can hope to get good results with relatively few parameters. In fact, the two methods can be viewed as two different approaches to parametrization and other possibilities - such as representation in terms of Fourier components or projection onto some other set of basis functions - have the same characteristic. We can therefore without loss of generality assume that the density field is represented by a collection of \( N \) parameters denoted generically as \( x_i \) so that \( \rho (r) = f (r; x) \), for some function \( f \). The change in the density profile as a function of time therefore becomes a change in the parameters so that more generally we have \( \rho (r; t) = f (r; x (t)) \). Thus, specification of the evolution of the parameters, \( x (t) \), corresponds to the prescription of a path in density space. The same notion holds when the path is parametrized by some other quantity rather than time - e.g. the equivalent of a reaction coordinate.

To give a concrete illustration, Ghosh and Ghosh use the exponential profile with the radius acting as the reaction coordinate. They determine the other parameters by minimizing the free energy while holding the radius constant thus parametrize the path by the radius. However, this is not a unique prescription since one could equally well parametrize by the excess number of particles in the cluster,

\[
\Delta N \equiv \int (\rho (r) - \rho_\infty) \, dr
\]

and, as pointed out previously, these need not be the same since one could increase \( \Delta N \) while holding the radius constant and increasing the width. This ambiguity is the fundamental problem with methods based solely on free energy considerations: there is no obvious method to determine which approach is preferable (or more pertinently, which is chosen by Nature).

Previously, it was shown that under the assumptions listed above, the MLP can be determined by gradient descent on the free energy surface. This means that first the saddle point is located and then one solves

\[
\frac{dx_i}{dt} = \pm g_{ij}^{-1} (x) \frac{\partial \Omega}{\partial x_j}
\]

where the sign is chosen according to whether one is moving uphill from the initial state, \( \rho_i \), to the saddle point (plus sign) or downhill from the saddle point to the final state, (minus sign). Alternatively, one can start at the saddle point and solve this equation with the minus sign to determine the two halves of the path. The information about dynamics is contained in the matrix of kinetic coefficients, \( g_{ij}^{-1} \), which are calculated as the inverse of

\[
g_{ij} (x) = \int_0^\infty \frac{1}{4 \pi^2 r^2 \rho (r; x)} \frac{\partial m (r; x)}{\partial x_i} \frac{\partial m (r; x)}{\partial x_j} \, dr
\]

where the cumulative mass is

\[
m (r; x) = 4 \pi \int_0^r \rho (r') r'^2 \, dr'.
\]

Another interpretation of Eq.(3) is that the MLP is determined by steepest descent on the free energy surface with the matrix \( g_{ij} \) playing the role of a Riemannian metric. In general, the probability density for any path, \( \rho (r; x (t)) \) for \( 0 \leq t \leq T \), is given by

\[
P [x] = \mathcal{N} \exp \left( -\frac{1}{2} S [x] \right)
\]

where the action is

\[
S [x] = \int_0^T \mathcal{L}(x, \dot{x}) \, dt,
\]

the Lagrangian is

\[
\mathcal{L}(x, \dot{x}) = \frac{1}{2} \frac{\partial \Omega}{\partial x_j} g_{ij} \frac{\partial \Omega}{\partial x_k}
\]

and where the normalization constant, \( \mathcal{N} \), is independent of the path but otherwise unknown. Given two paths, \( x (t) \) and \( y (t) \), their relative probability can be calculated using these expressions provided they are parametrized in the same way. Note that Eq.(3) gives the probability density and not the probability of the path. The latter would actually be \( P [x] / Dx \) where \( Dx \) is the path measure. For example, if time were discretized using \( M + 1 \) values \( t_i = i (T/M) \) and if the parameters are then given by \( x_{ij} \equiv x_i (t_j) \) then the measure would be

\[
Dx = \prod_{i=1}^{N} \prod_{j=0}^{M} dx_{ij}.
\]

This factor is irrelevant for computing the relative probability of two paths described by the same parametrization since it would drop out of the ratio leaving the ratio of the probability densities, \( P [x] / P [y] \). On the other hand, it is clear that one cannot meaningfully compare two paths based on different parametrization schemes since the measure, and the normalization factor, would in general be different.

It may still be possible to compare the paths in an approximate manner by approximately translating one parametrization scheme into another. For example, a path based on a discretization of the density on a set of \( N \) lattice points, \( r_i \), cannot be directly compared to one based on a discretization over \( 2N \) lattice points, \( r_i' \). However, one can translate either parametrization into the language of the other by, e.g., using cubic-spline interpolation over the \( N \)-point profiles to evaluate the density at the lattice positions of the \( 2N \)-point discretization.

Another question is whether there is any way to compare the probabilities of pathways that are not determined from the dynamical model? In particular, one would like to be able to evaluate the utility of the large number of existing heuristic approaches for the determination of nucleation pathways which typically give a path
in terms of a reaction coordinate, which will be called $s$, rather than the time? For example, if the path is determined by minimizing the free energy at constant excess particle number, $N$, for different values of $N$ ranging from zero to the mass of the critical cluster, then the reaction coordinate, $s$, would be $N$. It would seem that the only physical meaning of such a path is that a real system would follow it in the course of time so that if the path $x(s)$ goes from the initial state at $s = 0$ to the saddle point at $s = s_{\text{max}}$ then, this must mean that the physical relation provides the desired expression for the system begins at $\rho(r; t = 0) = \rho(r; x(s = 0))$ and ends at the saddle point at $\rho(r; t = T) = \rho(r; x(s = s_{\text{max}}))$. Since both time and the reaction coordinate vary monotonically during this processes, it must be that they are related so that we can write

$$\frac{dp}{dt} = ds \frac{dp}{ds} \equiv v(s) \frac{dp}{ds}$$

with $v(s) \equiv ds/dt$ being the speed along the path. Writing substituting this into the expression for the path probability we get

$$P[\rho] = N \exp \left(-\frac{1}{4} \int_{s_{\text{max}}}^{s_{\text{max}}} \left(v(s) \frac{dx_i}{ds} - g_{ij}^{-1} \frac{\partial \Omega}{\partial x_j} \right) g_{il} \left(v(s) \frac{dx_l}{ds} - g_{lk}^{-1} \frac{\partial \Omega}{\partial x_k} \right) v^{-1}(s) ds \right)$$

We can now maximize the probability with respect to variations in $v(s)$ to find that

$$\frac{dx_i}{ds} g_{il} \frac{dx_l}{ds} - \frac{\partial \Omega}{\partial x_j} g_{k}^{-1} \frac{\partial \Omega}{\partial x_k} (v(s))^{-2} = 0$$

or

$$\sqrt{\frac{\partial x_i}{\partial s} g_{il} \frac{dx_l}{ds} \frac{\partial x_i}{\partial s} g_{lj}^{-1} \frac{\partial x_j}{\partial s}} = v^{-1}(s)$$

This relation provides the desired expression for the speed the system advances along the proposed path. Direct evaluation of the second functional derivative of the path probability density shows that this is indeed a maximum. The explicit form of the induced dynamics is

$$\frac{dx_i}{dt} = \sqrt{\frac{\partial \Omega}{\partial x_j} g_{k}^{-1} \frac{\partial \Omega}{\partial x_k} \frac{dx_i}{ds} g_{lm} \frac{dx_l}{ds} ds}$$

The probability density itself becomes

$$P[\rho] = N \exp \left(-\frac{1}{2} \int_{s_{\text{max}}}^{s_{\text{max}}} \left[ \sqrt{\frac{dx_i}{ds} g_{il} \frac{dx_l}{ds} \sqrt{\frac{\partial \Omega}{\partial x_j} g_{kj}^{-1} \frac{\partial \Omega}{\partial x_k} - \frac{dx_i}{ds} \frac{\partial \Omega}{\partial x_i}} ds \right] ds \right)$$

which, with the time eliminated, gives a method to compare the probabilities for parametrized paths. Notice that this expression is invariant under a reparametrization of the reaction coordinate, e.g. $ds \rightarrow u(s') ds'$, so that it is a purely geometric quantity. In fact, if we further introduce the gradient force

$$b_i = g^{-1}_{ij}(x) \frac{\partial \Omega}{\partial x_j}$$

it can be written as

$$P[\rho] = N \exp \left(-\int_{s_{\text{max}}}^{s_{\text{max}}} \left| \mathbf{b} \right| \sin \left(\theta \left(\frac{dx}{ds}, \mathbf{b}\right) \right) \right) ds$$

where $|\mathbf{b}| = \sqrt{b_i g_{ij} b_j}$ and where $\theta \left(\frac{dx}{ds}, \mathbf{b}\right)$ is the angle between $\frac{dx}{ds}$ and $\mathbf{b}$. This form emphasizes the purely geometric nature of the optimized path. In particular, the parametrization-invariance means that the result is independent of the value of the upper limit, $s_{\text{max}}$, so that any convenient rescaling is allowed.

### III. APPLICATIONS

The dynamical theory on which these results are based is applicable to, e.g., globular proteins in solution which can be modeled at the crudest level as spherical molecules interacting via a short-ranged effective potential and subject to Brownian forces due to the solvent. Here, the model potential of ten Wolde and Frenkel consisting of a hard core and short-ranged attraction,

$$V(r) = \left\{ \begin{array}{ll} \frac{4}{3 \alpha} \left(\frac{1}{(\frac{r}{\sigma})^6} - \alpha \left(\frac{1}{(\frac{r}{\sigma})^6}\right)ight), & r < \sigma \\ \infty, & r \geq \sigma \end{array} \right.$$
FIG. 1. The spherically-symmetric concentration (density) distribution at various points along the classical path, as determined from Eq. (20). The initial state has uniform concentration, \( \rho(r) = 0.075 \), and the value of the concentration at the origin increases monotonically along the nucleation pathway.

will be used. The energy scale is set by \( \epsilon \) and the hard-core radius is \( \sigma \) while the parameter \( \alpha \) determines the distance of the attractive minimum from the hard core: the typical value for globular proteins of \( \alpha = 50 \) will be used. The bulk free energy is approximated using thermodynamic perturbation theory.

In CNT, it is assumed that the material in the interior of a cluster is in the bulk state: e.g., if a liquid phase is being nucleated from a gas then it is assumed that the density inside the cluster is always that of the bulk liquid and the cluster grows simply by increasing its radius from zero. More detailed non-classical results allow for the possibility of the interior density to vary from the bulk value and the typical behavior, as shown in Fig. 1, is for the density to begin at that of the background gas and to increase as the radius increases until eventually reaching that of the bulk when the cluster is very large. This is associated with the fact that in contrast to CNT the interface between the cluster and the gas is of finite extent so that when the cluster is small, all molecules may be considered to be in an intermediate, interfacial region. Recently, it has been shown that solving the equations for the MLP yields an unexpected result: the cluster does not begin with a small, localized increase in density but rather it starts as a spatially extended density fluctuation with the actual nucleation event occurring within this structure. The initial radius is infinite and the excess mass is finite so that the density is that of the vapor. The first part of the process involves the gradual decrease in the radius with the excess mass remaining nearly constant so that the density increases slowly. This represents the formation of a density fluctuation containing excess mass relative to the background. The second stage of the process is the formation of a nucleus within this region of slightly enhanced density. The excess mass within the density fluctuation is the basis for the formation of the cluster which then goes on to grow as in the classical scenarios.

In order to make a quantitative comparison of these different pathways, calculations of the most likely path

FIG. 2. Some aspects of the nucleation pathway as determined using a typical DFT method, left panel, and determined from the dynamical theory, right panel. The figures show the central density, \( \rho(r = 0) \), excess particle number, \( N \), and excess free energy, \( \Delta \Omega \), as functions of distance along the nucleation pathway. The left panel, labeled “Classical”, is the result of the heuristic theory, Eq. (20), whereas the right panel shows the most likely path (MLP), as described in the text. All quantities, including the ordinate, have been scaled by their values at the critical cluster. (Note that despite the differences in the paths, the critical cluster is uniquely determined by the free energy and so is the same for both paths.)

FIG. 3. The same as Fig. 2 but showing the equimolar radius, \( R_{eq} \) and the “total” radius, \( R_{total} \), as a function of distance along the nucleation pathway for the path determined from DFT gradient descent, left panel, and from the dynamical theory, right panel.
for the nucleation of high-concentration droplets in a low-concentration protein solution were performed as described in Ref. 9 and using a “classical” method which is known to give a good quantitative description of constrained clusters. The determination of the MLP amounts to the solution of Eq. (5). The classical calculation takes a very similar form to the MLP calculation despite the fact that it was proposed on purely heuristic grounds prior to the MLP method: it involves gradient descent on the free energy surface

\[
\frac{dx_i}{ds} = -\frac{1}{\sqrt{\frac{\partial^2 \Delta \Omega}{\partial x_i^2}} \tilde{g}_{ij}^{-1} \frac{\partial \beta \Delta \Omega}{\partial x_j}},
\]  

(20)

but with a heuristic metric given by

\[
\tilde{g}_{ij}(x) = \int \frac{\partial \rho(r; x)}{\partial x_i} \frac{\partial \rho(r; x)}{\partial x_j} dr.
\]  

(21)

Note that the first of these equations is equivalent to Eq. (4), but with distance along the path used as the independent variable rather than “time” (since, in the classical theories, there is no dynamics and so no natural concept of time). The similarity between these two calculations is striking and one of the advantages of the dynamical approach is that it shows that gradient descent on the free energy surface does indeed characterize the nucleation pathway provided the correct metric is used. The “correct” metric is basically defined in terms of mass differences rather than density differences which can be traced to the fact that the underlying theory is based on fluctuating hydrodynamics in which mass is conserved. In contrast, the heuristic metric was simply guessed based on the criterion of simplicity and a prejudice towards the use of local density as the fundamental variable and, so, no physical meaning can be attached to the paths derived from it.

In all calculations, spherical symmetry was assumed so that the configuration at any given instant is characterized by the variation of density as a function of distance from the origin. Figure 4 shows the density distribution taken from a sequence of points along the classical pathway. The concentration begins as a constant, equal to the concentration of the solution. The formation of a cluster involves a monotonic increase in density near the origin until a density close to that of the bulk high-concentration solution is obtained. Beyond this point, the cluster grows via a monotonic increase in its radius.

For the MLP it is known that the path probability (using either Eq. (8) or Eq. (10)) is simply given by

\[
P_{MLP} = N e^{-\beta \Delta \Omega}
\]  

(22)

where \(\Delta \Omega\) is the difference in free energy between the beginning and end points. Numerical evaluation of Eqs. (8)- (10) confirms this relation to a high degrees of numerical accuracy. The “classical” model gives the sequence of profiles shown in Fig. 1. The log of the path probability generated by this ansatz is shown in Figure 2.

![Figure 4](image)

**FIG. 4.** The action for the classical and MLP nucleation pathways shown as a function of excess free energy. Note that in both cases, the path probability density is related to the action by \(P \sim e^{-S}\). Also, both paths end at the critical cluster which is the same for all paths. The curve for the MLP is trivial as one knows that \(S_{MLP} = -\Delta \Omega\).

The energy barrier in these calculations is \(\beta \Delta \Omega \approx 88\) so that \(P_{MLP} \approx N e^{-88}\). In contrast, the probability of the heuristic path is \(P_{classical} \approx N e^{-480}\) so that it is as if the energy barrier were \(480k_B T\) rather than \(88k_B T\). The relative probability is

\[
P_{classical} = e^{-398} P_{MLP}
\]  

(23)

so that the heuristic path is very unlikely compared to the MLP. This simple comparison illustrates the fact that the path probability is quite sensitive to the path and is not determined solely by the free energy barrier.

Finally, the variation of the relative path probabilities as a function of the supersaturation is illustrated in Fig. 5 which shows the difference in the action as a function of size of the critical cluster. At least for the range of cluster-sizes shown in the figure, there is an almost linear relation which implies the relation

\[
P_{classical} \approx e^{-N_{critical}/3} P_{MLP}.
\]

IV. CONCLUSIONS

Based on the recently proposed dynamical approach to nucleation, a method has been derived for determining the maximum probability of observing any given nucleation pathway. The method is applicable to all pathways without regard to how they are constructed. This allows one to then ask whether heuristically-derived pathways are reasonable approximations to the most likely pathway. The formalism has been illustrated for the problem of the nucleation of high-concentration droplets from a low-concentration solution of globular proteins. It was shown that the probability for a “classical” nucleation pathway, which begins with a small, localized cluster,
FIG. 5. The difference in action between the classical path and the MLP, $\Delta S = S_{\text{classical}} - S_{\text{MLP}}$, for different values of supersaturation corresponding to different critical cluster sizes. The relative path probability for the two paths is $P_{\text{classical}}/P_{\text{MLP}} = e^{-\Delta S}$. A linear fit to the calculated points gives $\Delta S \approx 0.34 N_c$.

compared to that of the most likely path, which invokes a two-step mechanism whereby nucleation begins with a spatially-extended, small-amplitude density fluctuation, scales like $e^{-N_{\text{critical}}/3}$ so that for all but the smallest clusters, it is extremely small. This comparison serves to show that classical paths, even though intuitively appealing, can have very low probability of occurrence. Contrary to the expectation that all that matters for nucleation is the free energy barrier, these results show that there is a dramatic quantitative difference in the likelihood of observing the classical scenario compared to the non-classical one. Of course, only one family of “classical” pathways has been investigated here and there are many alternatives such as those found in Refs. 10, 13, 14 and 16. It is possible that some of these compare more favorably with the non-classical Most Likely Path, but this can only be resolved by direct calculations.

ACKNOWLEDGMENTS

This work was partially supported in part by the European Space Agency under contract number ESA AO-2004-070 and by FNRS Belgium under contract C-Net NR/FVH 972.

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