A dynamical theory of homogeneous nucleation for colloids and macromolecules

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Homogeneous nucleation is formulated within the context of fluctuating hydrodynamics. It is shown that for a colloidal system in the strong damping limit the most likely path for nucleation can be determined by gradient descent in density space governed by a nontrivial metric. This is illustrated by application to low-density/high-density liquid transition of globular proteins in solution where it is shown that nucleation process involves two stages: the formation of an extended region with enhanced density followed by the formation of a cluster within this region.

This description has several shortcomings. The surface tension is generally not constant and, especially for small clusters, can depend strongly on the size of the cluster. There is also no reason that the density within the cluster should be constant or, even if it were, that it should be equal to the bulk density for all cluster sizes. A more detailed picture can be developed using Density Functional Theory (DFT) from which provides models of the free energy of the cluster as a function of its radius can be calculated giving a quantitative picture of homogeneous nucleation.

The fundamental difficulty underlying these and other equilibrium, free-energy based approaches is that the physical description is incomplete since homogeneous nucleation is a fundamentally nonequilibrium, fluctuation-driven process. This raises several questions about the classical description such as whether the free energy plays such a central role and whether it is necessary that the growing cluster actually pass through the critical cluster. The solution is to develop a nonequilibrium, dynamical description of homogeneous nucleation and this is the goal here. The following development is based on Brownian Dynamics wherein molecules move according to Newton’s laws while being subject to a frictional force as well as fluctuating forces. This is a simple model for colloids and the important case of macromolecules in solution in which case the friction and the fluctuations come from the bath/solvent.

Theory The system consists of a collection of molecules of unit mass with positions and momenta $q_i, p_i$ interacting via a potential $V$. Additionally, the particles interact with a bath/solvent of light particles and this is described via a frictional drag and a fluctuating force

$$\dot{q}_i = p_i, \quad \dot{p}_i = -\frac{\partial V}{\partial q_i} - \gamma p_i + f_i(t)$$

where all components of the fluctuating force are Gaussian and independent,

$$\langle f_i(t)f_j(t') \rangle = 2\gamma k_BT\delta_{ij}\delta(t-t')$$

Defining the local density and momentum density respectively as

$$\begin{align*}
\rho(r; t) &= \sum_i \delta(r - q_i) \\
\mathbf{j}(r; t) &= \sum_i p_i \delta(r - q_i)
\end{align*}$$
one sees that these satisfy the exact equations
\[
\frac{\partial \bar{\rho}(\mathbf{r}; t)}{\partial t} = -\nabla \cdot \mathbf{j}(\mathbf{r}; t) = -\nabla \cdot \left( \sum_i \mathbf{p}_i \delta(\mathbf{r} - \mathbf{q}_i) - \sum_i \frac{\partial V}{\partial \mathbf{q}_i} \delta(\mathbf{r} - \mathbf{q}_i) \right)
\]
\[
- \gamma \mathbf{j}(\mathbf{r}; t) + \sqrt{2\gamma k_BT} \bar{\rho}(\mathbf{r}; t) \mathbf{F}(\mathbf{r}; t)
\]
with
\[
\langle \mathbf{F}(\mathbf{r}; t) \mathbf{F}(\mathbf{r'}; t') \rangle = \delta(t-t') \delta(\mathbf{r} - \mathbf{r'}) \mathbf{1}
\]
Coarse graining in space and assuming local equilibrium leads to a mesoscopic description of fluctuations in terms of fluctuating hydrodynamics. Neglecting temperature fluctuations gives
\[
\frac{\partial \rho(\mathbf{r})}{\partial \mathbf{t}} + \nabla \cdot \mathbf{j}(\mathbf{r}) = 0
\]
\[
\frac{\partial \mathbf{j}(\mathbf{r})}{\partial \mathbf{t}} + \nabla \cdot \mathbf{j}(\mathbf{r}) \mathbf{j}(\mathbf{r})/\rho(\mathbf{r}) + \rho(\mathbf{r}) \nabla \frac{\delta F[\rho]}{\delta \rho(\mathbf{r})} + \nabla \cdot \Pi(\mathbf{r}) = -\gamma \mathbf{j}(\mathbf{r}) + \sqrt{2\gamma k_BT} \bar{\rho}(\mathbf{r}) \xi(\mathbf{r}; t)
\]
where \( \rho(\mathbf{r}) \) and \( \mathbf{j}(\mathbf{r}) \) are the coarse-grained local density and momentum density, \( F[\rho] \) is the coarse-grained free energy and \( \Pi \) is the dissipative part of the stress tensor which has both a deterministic and a fluctuating contribution. The free energy term is a representation of the local pressure and has been discussed extensively in the DFT literature: its use here can be viewed as a local equilibrium approximation. The quantity \( \xi(\mathbf{r}; t) \) is the noise due to the Brownian dynamics and is white and delta-correlated in space and time. Note that this is just the natural generalization of Landau and Lifshitz’s fluctuating hydrodynamics taking account of the Brownian forces. Assuming that the velocity will always be small due to the damping, the convective term can be neglected so that the second equation becomes linear in the momentum density. Eliminating the momentum current then gives
\[
\frac{\partial^2 \rho(\mathbf{r})}{\partial t^2} + \gamma \frac{\partial \rho(\mathbf{r})}{\partial t} - \nabla \cdot \left( \rho(\mathbf{r}) \nabla \frac{\delta F[\rho]}{\delta \rho(\mathbf{r})} \right) + \nabla \cdot \sqrt{2\gamma k_BT} \bar{\rho}(\mathbf{r}) \xi(\mathbf{r}; t) = 0
\]
In the following, the second-time derivative, the so-called inertial term, will be neglected, as is usual in the small-damping approximation. Then, when the density is low, in the ideal gas limit, the first term on the right becomes \( \gamma^{-1} \bar{k_B T} \nabla^2 \rho(\mathbf{r}) \) so that \( D \equiv \gamma^{-1} \bar{k_B T} \) can be identified as the diffusion constant.

The use of fluctuating hydrodynamics as basis for studying nucleation is similar to the approach developed by Langer. The primary difference here is that the emphasis is on understanding the time-evolution of the formation of the critical cluster whereas previous work focused on the nucleation rate. This development differs from more phenomenological approaches which are couched entirely in terms of order parameters, such as based on nonequilibrium thermodynamics or phase field theory, in that nonlinearities of the transport coefficients and colored noise occur naturally and play an important role. One of the goals below is to relate the hydrodynamic description to one involving order parameters.

In order to characterize the generic properties of the process of nucleation, we focus here on the most likely path (MLP) where a “path” is understood as a function \( \rho(\mathbf{r}; t) \) connecting the initial state of pure metastable phase and the final state of pure stable phase. When the noise amplitude is small (as in the strong damping limit), most systems should go through a nucleation pathway close to this generic result. In general, determining the MLP is complex. However, without the inertial term, Eq. (7) is a gradient-driven, diffusive dynamics which obeys a fluctuation-dissipation relation. By a straightforward generalization of [14], it can be shown that for this type of dynamics the MLP connecting metastable states does indeed pass through the critical point and that it coincides with either the forward-time or backward-time deterministic trajectory in density space. The MLP can therefore be determined by starting at a local minimum and moving along the deterministic path
\[
\frac{\partial \rho(\mathbf{r})}{\partial t} = \pm \nabla \cdot \left( \rho(\mathbf{r}) \nabla \frac{\delta F[\rho]}{\delta \rho(\mathbf{r})} \right)
\]
where the sign is chosen according to the direction one wishes to move.

Equation (8) is the primary theoretical result of this paper. It superficially resembles the usual Dynamic Density Functional Theory (DDFT) equation but in fact considerably more general. It says that the most likely path can be determined by following the DDFT dynamics when that dynamics does indeed connect the desired states such as in passing from a high-energy to a low-energy state with no barrier separating them. (An example of this would be spinodal decomposition.) However, DDFT cannot describe the crossing of a free energy barrier as it specifically pertains to the ensemble-averaged density. In essence, it is the result of averaging Eq. (7) (without the inertial term) over the noise. In contrast, Eq. (8) also describes the MLP when this means following the sign of the gradient or, equivalently, by following the time-reversed dynamics. It can therefore be viewed as an extension of DDFT to barrier-crossing problems, given the various assumptions set out above. This simple result is strongly dependent on the existence of the fluctuation-dissipation relation in Eq. (4) and on the assumption of weak noise (compared to the thermodynamic driving force). It will not be exact if either of these
case it becomes analogous to the vapor/liquid transition can be modeled using an effective pair-potential in which the phase and a high density liquid-like phase. This behavior is assumed to be spherical and only parameter is the size of the cluster: more generally, a minimal set would include some measure of the density inside the cluster and the width of the interface as well. In the present formalism, the order parameters must somehow be related to the spatial density since it is the fundamental quantity describing the evolution. We therefore imagine that the density profile is approximated by some test function of the form \( \rho(r, t) = f(r; x(t)) \) where \( x(t) \) stands for the set of order parameters. It is possible to give an exact equation for the evolution of the parameters based on an analysis of the MLP but here a more heuristic method is used. First, Eq. (8) is integrated over a spherical volume of radius \( r \) giving

\[
\frac{\partial m(r; x(t))}{\partial t} = \pm D \int \rho(r') \left( \frac{\partial}{\partial r'} \frac{\delta \beta F[m]}{\delta \rho(r')} \right) dS \quad (9)
\]

where \( m(r; x(t)) \) is the mass in the spherical shell of radius \( r \) and the notation indicates a surface integral over that shell. Then, spherical symmetry is assumed and Eq. (9) is multiplied by \( r^{-2} \rho^{-1}(r) \frac{\partial m(r)}{\partial x_a} \) and integrated over \( r \) to get

\[
g_{ab} \frac{dx_b}{dt} = \pm D \frac{\partial \beta \Omega}{4\pi \partial x_a} \quad (10)
\]

where the metric is

\[
g_{ab} = 4\pi \int_0^\infty \frac{1}{r^2} \frac{\partial m(r)}{\partial x_a} \frac{\partial m(r)}{\partial x_b} dr \quad (11)
\]

and where \( \Omega = F - \mu N \) is the grand potential which arises due to an integration by parts. This becomes exact if the parametrization is complete in the sense that \( f(r; x(t)) \) is able to represent any well-behaved function arbitrarily closely (e.g. an expansion in a complete set of basis functions). The exact minimization of the action for the case of a finite number of order parameters and its relation to this approximation will be discussed elsewhere.

**Application to low density/high density liquid transition in globular proteins** Many proteins in solution exhibit a phase transition between a low density gas-like phase and a high density liquid-like phase. This behavior can be modeled using an effective pair-potential in which case it becomes analogous to the vapor/liquid transition in simple fluids. Calculations were performed for the ten Wolde-Frenkel model potential for globular proteins having hard-core diameter \( \sigma \) and energy scale \( \epsilon \) using the squared-gradient free energy model,

\[
F[\rho] = \int \left( f(\rho(r)) + \frac{1}{2} K (\nabla \rho(r))^2 \right) dr \quad (12)
\]

where \( f(\rho) \) is the bulk free energy per unit volume, calculated using thermodynamic perturbation theory, and the coefficient \( K \) was calculated using a recently-derived approximation. Equation (8) was integrated (assuming spherical symmetry) by discretizing the right hand side using Eq. (10) and the method of piece-wise linear profiles (equivalent to a variable grid method). At a temperature of \( k_B T = 0.375 \epsilon \) and with a pressure supersaturation of 1.159, the exact excess energy barrier was found to be \( \Delta \beta \Omega = 75.8 \) with 1158 molecules in the cluster while the discretization with 19 parameters gives a value of 77.1 and 1175 molecules. The MLP was then determined by starting near the at the critical cluster and perturbing in the direction of the negative eigenvalue and integrating Eq. (10) numerically. In tracing the backwards part of the path, the calculations were terminated when \( \beta \Delta \Omega = 1k_B T \) since the weak noise approximation is not applicable for lower energies.

Figure 1 shows the evolution of the excess number of particles, excess free energy and of the central density. The independent variable is the natural reaction coordinate which is distance along the nucleation pathway as calculated using the metric, Eq. (11). When the cluster is large, the path is similar to that which would be obtained using typical heuristic methods. However, for smaller droplets, the results are quite nonclassical. Figure 2 gives the spatial size of the droplet according to two different measures: the equimolar radius as calculated

![Figure 1](image1.png)

**FIG. 1.** The excess particle number, excess free energy and central density relative to their values in the critical cluster as functions of the natural reaction coordinate, \( s \), where \( s=0 \) corresponds to the initial vapor phase and the final liquid phase occurs for \( s = \infty \). The vertical line marks the transition between the two growth regimes (see text).
Conclusions  A description of nucleation applicable to colloids and macromolecules in solution based on fluctuating hydrodynamics has been developed. It was shown that under assumptions of strong dissipation and weak noise the most likely path could be determined by gradient descent on the free energy surface and that it necessarily passes through the critical point, thus providing justification for more heuristic methods based solely on free energy considerations[6]. It is also interesting to note that Eq.(10) can be seen to justify more phenomenological treatments of nucleation in which a set of order parameters is assumed to evolve stochastically as $\frac{dx}{dt} = L \frac{\delta F}{\delta x} + \xi$ with a fluctuation-dissipation relation determining the amplitude of the noise. The same approach can be applied to other nucleation phenomena such as heterogeneous nucleation, nucleation in confined systems and even, conceivably, to transitions in granular fluids.

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