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# Communication: 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. © 2011 American Institute of Physics. [doi:10.1063/1.3657400]

## INTRODUCTION

Homogeneous nucleation is a fundamental physical process of importance in fields as diverse as chemistry, materials science, biology, and cosmology. Our basic understanding of it goes back to Gibbs.<sup>1</sup> The physics is governed by the fact that the excess free energy of a liquid cluster relative to the vapor has a negative contribution that scales as the volume and a positive contribution due to surface tension that scales as the surface area. In classical nucleation theory (CNT) it is assumed that the cluster is spherical, its interior is in the bulk liquid state, and the surface tension is the same as for the co-existing liquid and vapor so that the free energy of the cluster as a function of its radius can be calculated giving a quantitative picture of homogeneous nucleation.<sup>1</sup>

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) which provides models of the free energy as a functional of the density profile (see, e.g., Refs. 2 and 3). One can describe the density according to some parametrization (such as a hyperbolic tangent) which will involve at least three parameters: the central density, the radius, and the interfacial width, and proceed by choosing a reaction coordinate – such as the radius of the cluster – and minimizing the free energy while holding the reaction coordinate constant. This does indeed lead to finite interfacial widths and size-dependent central densities, as expected (for recent examples, see Refs. 4 and 5).

Despite being physically reasonable, there are significant conceptual problems with this approach, such as the arbitrariness of the reaction coordinate. As described, the nucleation pathway will consist of a monotonically increasing radius with the other parameters determined by the minimization. However, one could just as well choose the

number of molecules in the cluster as the reaction coordinate in which case – in principle – the radius need not increase monotonically along the pathway since the mass of the cluster can increase by increasing the width while, at the same time, decreasing the radius.<sup>5</sup> Even the excess mass is not a good reaction coordinate in general and imposing more complex constraints can, at least for some models, lead to spurious divergences.<sup>6</sup>

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 passes 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  $\mathbf{q}_i, \mathbf{p}_i$  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:

$$\dot{\mathbf{q}}_i = \mathbf{p}_i, \quad \dot{\mathbf{p}}_i = -\frac{\partial V}{\partial \mathbf{q}_i} - \gamma \mathbf{p}_i + \mathbf{f}_i(t), \quad (1)$$

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

$$\langle \mathbf{f}_i(t) \mathbf{f}_j(t') \rangle = 2\gamma k_B T \mathbf{1} \delta_{ij} \delta(t - t'). \quad (2)$$

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Defining the local density and momentum density, respectively, as

$$\begin{Bmatrix} \widehat{\rho}(\mathbf{r}; t) \\ \widehat{\mathbf{j}}(\mathbf{r}; t) \end{Bmatrix} = \sum_i \begin{Bmatrix} 1 \\ \mathbf{p}_i \end{Bmatrix} \delta(\mathbf{r} - \mathbf{q}_i), \quad (3)$$

one sees that these satisfy the exact equations

$$\begin{aligned} \frac{\partial \widehat{\rho}(\mathbf{r}; t)}{\partial t} &= -\nabla \cdot \widehat{\mathbf{j}}(\mathbf{r}; t), \\ \frac{\partial \widehat{\mathbf{j}}(\mathbf{r}; t)}{\partial t} &= -\nabla \cdot \sum_i \mathbf{p}_i \mathbf{p}_i \delta(\mathbf{r} - \mathbf{q}_i) - \sum_i \frac{\partial V}{\partial \mathbf{q}_i} \delta(\mathbf{r} - \mathbf{q}_i) \\ &\quad - \gamma \widehat{\mathbf{j}}(\mathbf{r}; t) + \sqrt{2\gamma k_B T \widehat{\rho}(\mathbf{r}; t)} \mathbf{F}(\mathbf{r}; t) \end{aligned} \quad (4)$$

with

$$\langle \mathbf{F}(\mathbf{r}; t) \mathbf{F}(\mathbf{r}'; t') \rangle = \delta(t - t') \delta(\mathbf{r} - \mathbf{r}') \mathbf{1}. \quad (5)$$

Coarse graining in space and assuming local equilibrium leads to a mesoscopic description of fluctuations in terms of fluctuating hydrodynamics. Neglecting temperature fluctuations gives

$$\begin{aligned} \frac{\partial \rho(\mathbf{r})}{\partial t} + \nabla \cdot \mathbf{j}(\mathbf{r}) &= 0, \\ \frac{\partial \mathbf{j}(\mathbf{r})}{\partial t} + \nabla \cdot \mathbf{j}(\mathbf{r}) \mathbf{j}(\mathbf{r}) / \rho(\mathbf{r}) + \rho(\mathbf{r}) \nabla \frac{\delta F[\rho]}{\delta \rho(\mathbf{r})} \\ + \nabla \cdot \Pi(\mathbf{r}) &= -\gamma \mathbf{j}(\mathbf{r}) + \sqrt{2\gamma k_B T \rho(\mathbf{r})} \boldsymbol{\xi}(\mathbf{r}; t), \end{aligned} \quad (6)$$

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.<sup>7</sup> 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.<sup>2,8-10</sup> The quantity  $\boldsymbol{\xi}(\mathbf{r}; t)$  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

$$\begin{aligned} \frac{\partial^2 \rho(\mathbf{r})}{\partial t^2} + \gamma \frac{\partial \rho(\mathbf{r})}{\partial t} - \nabla \cdot \left( \rho(\mathbf{r}) \nabla \frac{\delta F[\rho]}{\delta \rho(\mathbf{r})} \right) \\ + \nabla \cdot \sqrt{2\gamma k_B T \rho(\mathbf{r})} \boldsymbol{\xi}(\mathbf{r}; t) &= 0. \end{aligned} \quad (7)$$

In the following, the second-time derivative, the so-called inertial term, will be neglected, as is usual in the strong-damping approximation. Then, when the density is low, in the ideal gas limit, the first term on the right becomes  $\gamma^{-1} k_B T \nabla^2 \rho(\mathbf{r})$  so that  $D \equiv \gamma^{-1} k_B T$  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.<sup>11</sup> 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 nonequilibrium thermodynamics<sup>12</sup> or phase field theory,<sup>13</sup> 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 the 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 a pure metastable phase and the final state of a 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 Ref. 14, it can be shown that *for this type of dynamics the MLP connecting metastable states does indeed pass through the saddle point* and that it coincides with either the forward-time or backward-time deterministic trajectory in density space.<sup>15</sup> The MLP can therefore be determined by starting at a local minimum and moving along the deterministic path

$$\frac{\partial \rho(\mathbf{r})}{\partial t} = \pm D \nabla \cdot \left( \rho(\mathbf{r}) \nabla \frac{\delta \beta F[\rho]}{\delta \rho(\mathbf{r})} \right), \quad (8)$$

where the sign is chosen according to the direction one wishes to move.<sup>14,15</sup>

Equation (8) is the primary theoretical result of this communication. It superficially resembles the usual dynamic density functional theory (DDFT) equation<sup>2,7,9,10</sup> but is, 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.<sup>9</sup>) 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 going uphill against the free energy gradient. In that case, it says that the MLP can be obtained by reversing the sign of the gradient or, equivalently, by following the time-reversed dynamics.<sup>14,15</sup> 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. (7) and on the assumption of weak noise (compared to the thermodynamic driving force). It will not be exact if either of these conditions are violated and, in particular, the much more complicated strong-noise result will be discussed in at a later time. Finally, it is important to note that Eq. (8) is simply a mathematical means of identifying the MLP and that it does not imply in any sense that the actual (strongly dissipative) dynamics is time-reversal invariant.

In principle, Eq. (8) could be integrated directly to determine the MLP or some other technique, such as the string method, used to determine the path. However, the goal here is to generalize previous descriptions of nucleation which are based on a set of order parameters characterizing the system. In CNT, the cluster is assumed to be spherical and the 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  $\rho(r, t) = f(r; \mathbf{x}(t))$ , where  $\mathbf{x}(t)$  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

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

where  $m(r; \mathbf{x}(t))$  is the mass inside 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  $r^{-2} \rho^{-1}(r) (\partial m(r)/\partial x_a)$  and integrated over  $r$  to get

$$g_{ab} \frac{dx_b}{dt} = \pm D \frac{1}{4\pi} \frac{\partial \beta \Omega}{\partial x_a}, \quad (10)$$

where repeated indices are summed and the metric is

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

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  $f(r; \mathbf{x}(t))$  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 (for information on the phase behavior of proteins, see, e.g., Refs. 16 and 17). 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<sup>18</sup> model potential for globular proteins having hard-core diameter  $\sigma$  and energy scale  $\epsilon$  using the squared-gradient free energy model,

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

where  $f(\rho)$  is the bulk free energy per unit volume, calculated using thermodynamic perturbation theory, and the coefficient

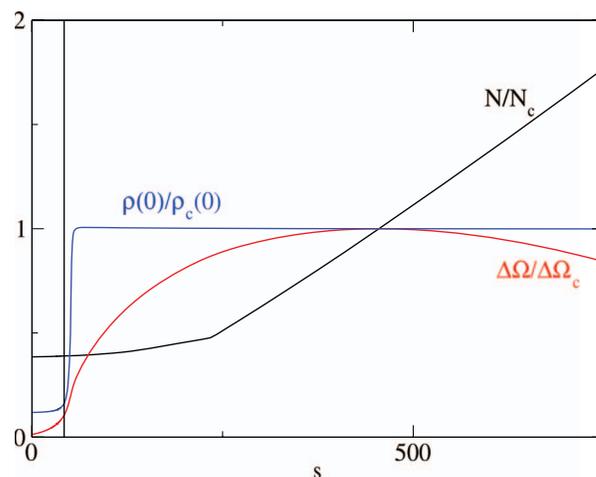


FIG. 1. The excess particle number, excess free energy, and central density relative to their values in the critical cluster as functions of the natural reaction coordinate,  $s$ , where  $s = 0$  corresponds to the initial vapor phase and the final liquid phase occurs for  $s = \infty$ . The vertical line marks the transition between the two growth regimes (see text).

$K$  was calculated using a recently derived approximation.<sup>5</sup> Equation (8) was integrated (assuming spherical symmetry) by discretizing the right hand side using Eq. (10) and the method of piece-wise linear profiles<sup>5</sup> (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 critical cluster and perturbing in the direction of the negative eigenvalue<sup>19</sup> and integrating Eq. (10) numerically.<sup>20</sup> 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.<sup>21</sup>

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 the 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 based on the central density and the (model-dependent) total spatial extent of the droplet (in this model, the droplet always has a well-defined finite support). Combining the information in these two figures, it is seen that the MLP begins with a spatially extended disturbance having very low density but a fixed excess number of molecules (in the present case, about 450).

The interpretation of these results is not as different from the usual picture of nucleation as they might at first appear. At short times, during which the equimolar radius is nearly constant, a small increase in density forms over a spatially extended volume. From Fig. 1, it is apparent that, despite its spatial extent, the excess energy of this density fluctuation

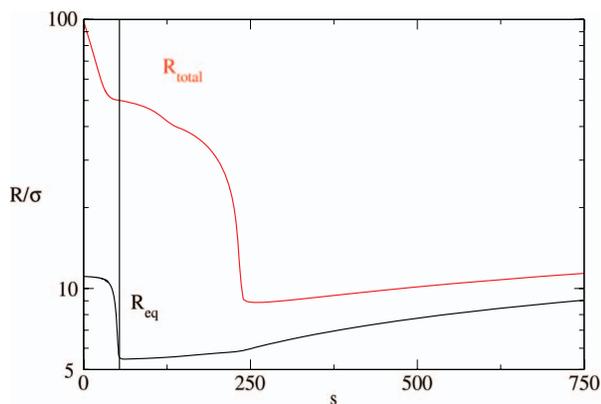


FIG. 2. The same as Fig. 1, but showing the equimolar radius,  $R_{eq}$ , and the total spatial extent,  $R_{total}$ , along the path. The vertical line marks the same point as in Fig. 1.

is quite small so that its formation is not improbable. The second part of the process is the formation of a cluster within this region of enhanced density. That nucleation would preferentially take place in a region of enhanced density, which therefore already contains some of the excess mass needed to form a cluster, is quite reasonable. Indeed, having the necessary excess mass present locally allows the cluster to form more rapidly than if matter had to diffuse in from the surrounding bulk. What does appear strange is the directed nature of process with the density fluctuation appearing to contract to form the nucleus. This is partly a result of insisting on spherical symmetry and partly due to a well-known property of the MLP wherein it typically involves a system crossing a barrier in the shortest number of steps possible with no back-tracking or variation.<sup>21</sup> The MLP is of course an abstraction: an actual realization of the processes will involve fluctuations around it and will not appear so deterministic (see, e.g., Ref. 21). Finally, because mass is conserved, any dynamical process of cluster formation is going to give the appearance of drawing in mass from the boundaries of the system.

## 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.<sup>6</sup> 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  $dx/dt = L(\delta F/\delta x) + \xi$  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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- <sup>1</sup>D. Kashchiev, *Nucleation: Basic Theory with Applications* (Butterworth-Heinemann, Oxford, 2000).
- <sup>2</sup>R. Evans, *Adv. Phys.* **28**, 143 (1979).
- <sup>3</sup>D. W. Oxtoby and R. Evans, *J. Chem. Phys.* **89**, 7521 (1988).
- <sup>4</sup>S. Ghosh and S. K. Ghosh, *J. Chem. Phys.* **134**, 024502 (2011).
- <sup>5</sup>J. F. Lutsko, *J. Chem. Phys.* **134**, 164501 (2011).
- <sup>6</sup>J. F. Lutsko, *Europhys. Lett.* **83**, 46007 (2008).
- <sup>7</sup>P.-H. Chavanis, *Physica A* **387**, 5716 (2008); **390**, 1546 (2011).
- <sup>8</sup>D. S. Dean, *J. Phys. A: Math. Gen.* **29**, L613 (1996).
- <sup>9</sup>A. J. Archer and R. Evans, *J. Chem. Phys.* **121**, 4246 (2004).
- <sup>10</sup>A. J. Archer and M. Rauscher, *J. Phys. A: Math. Gen.* **37**, 9325 (2004).
- <sup>11</sup>J. S. Langer, *Ann. Phys.* **54**, 258 (1969); J. S. Langer and L. A. Turski, *Phys. Rev. A* **8**, 3230 (1973).
- <sup>12</sup>G. Nicolis and C. Nicolis, *Physica A* **323**, 139 (2003).
- <sup>13</sup>A. Shiryayev and J. D. Gunton, *J. Chem. Phys.* **120**, 8318 (2004).
- <sup>14</sup>E. Vanden-Eijnden and M. Heymann, *J. Chem. Phys.* **128**, 061103 (2008).
- <sup>15</sup>See supplementary material at <http://dx.doi.org/10.1063/1.3657400> for a proof.
- <sup>16</sup>P. G. Vekilov, *Cryst. Growth Des.* **4**, 671 (2004).
- <sup>17</sup>J. D. Gunton, A. Shiryayev, and D. L. Pagan, *Protein Condensation: Kinetic Pathways to Crystallization and Disease* (Cambridge University Press, Cambridge, England, 2007).
- <sup>18</sup>P. R. ten Wolde and D. Frenkel, *Science* **77**, 1975 (1997).
- <sup>19</sup>D. Wales, *Energy Landscapes* (Cambridge University Press, Cambridge, England, 2003).
- <sup>20</sup>The Intel ODE solver was used, see <http://software.intel.com/en-us/articles/intel-ordinary-differential-equations-solver-library/>.
- <sup>21</sup>M. Bier, I. Derényi, M. Kostur, and R. D. Astumian, *Phys. Rev. E* **59**, 6422 (1999).