Classical nucleation theory for the nucleation of the solid phase of spherical particles with a short-ranged attraction

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Abstract
Classical nucleation theory is used to estimate the free-energy barrier to nucleation of the solid phase of particles interacting via a potential which has a short-ranged attraction. Due to the high interfacial tension between the fluid and solid phases, this barrier is very large, much larger than in hard spheres. It is divergent in the limit that the range of the attraction tends to zero. We predict an upper limit on nucleation in good agreement with the results of experiments on the crystallisation of proteins.

1 Introduction
It is difficult to crystallise globular proteins yet it is important to do so as X-ray crystallography can be performed on crystalline proteins and the full structure of the protein in its native state determined. Knowing the structure of a protein is crucial to understanding its function. Proteins are of course vital to all life. Crystallising a protein is difficult as there seem to be only a few conditions under which a protein solution crystallises but many under which the solution is either stable on all accessible time scales or useless amorphous aggregates form. This is in sharp contrast to the simpler system of hard-sphere-like colloids. The crystallisation of these is routine. Here we will examine the first stage of crystallisation: nucleation. We will do so using classical nucleation theory. Although not a quantitative theory, it has the merit of simplicity and incorporates the essential features of nucleation. These are that nucleation is a large amplitude, localised, fluctuation which forms a microscopic crystallite of the crystalline phase.

Because of their phase diagram, it has been suggested that the interaction between globular protein molecules can be approximated by a steeply repulsive core, which prevents two protein molecules interpenetrating, and an attraction with a range that is much less than the diameter of the protein; the surfaces of two protein molecules have to be within a tenth or less of their diameter for there to be a significant attraction. Here we will study a simple model potential of this type. In fact, the interactions between protein molecules are complex and include quite specific, non-spherically symmetric interactions, thus it should be borne in mind that our model potential is extremely simplified.

Classical nucleation theory requires as input the chemical potential of the metastable fluid phase from which the crystal forms, the chemical potential of the crystalline phase and the surface tension. The last of these three, the surface tension, often poses a problem as the surface tension is known for only a very few model potentials. Indeed even for the simplest potential, the hard-sphere potential, accurate values for the surface tension have only been calculated recently. However, recently the author has calculated the surface tension for a potential consisting of a hard core and a very short-ranged attraction.

In the next section we will define our model potential and describe its phase behaviour. We will give the required expressions for the chemical potential in the fluid and solid phases. Then in the third section we will obtain the classical nucleation theory predictions for our model. The fourth section compares our theory with experiment and the fifth is a conclusion.

2 Model and bulk phase diagram
First, we define the hard-sphere+square-well potential. It is the spherically symmetric pair potential \( u(r) \) defined by

\[
    u(r) = \begin{cases} 
        \infty & r \leq \sigma \\
        -\epsilon & \sigma < r \leq \sigma(1+\delta) \\
        0 & r > \sigma(1+\delta) 
    \end{cases},
\]

where \( \sigma \) is the hard-sphere diameter, and \( r \) is the separation between the centres of the spheres. The potential depends on one parameter, \( \delta \), the ratio of the range of the attraction to the hard-sphere diameter. We will always consider
this range to be small: $\delta \ll 1$. The first person to consider very short-ranged attractions was Baxter\cite{Baxter1972} who considered a potential with zero range, $\delta = 0$, and with a well-depth $\epsilon/kT$ adjusted so that the second virial coefficient was of order unity. $T$ is the temperature and $k$ is Boltzmann’s constant. This model is often termed the sticky-sphere model. Within it the second virial coefficient is used as a temperature-like variable. However, Stell\cite{Stell1972} showed that the sticky-sphere model was pathological, its fluid phase is unstable at all non-zero densities. Therefore, we will not consider this model but instead will follow Stell when we take the limit $\delta \to 0$, thus obtaining his $\beta_0$ model\cite{Stell1972, Stell1973, Stell1975}.

The bulk phase behaviour of the $\beta_0$ model is described in Refs.\cite{Stell1972, Stell1973, Stell1975} and \cite{Stell1974}, and is displayed in Fig. 1. If the double limit $\delta \to 0$ and $kT/\epsilon \to 0$ is taken such that $T > T_{\text{coll}}$ then the equilibrium phase behaviour is identical to that of hard spheres. If $T < T_{\text{coll}}$ then the behaviour is radically different: a close-packed solid coexists with a fluid phase of zero density. The temperature $T_{\text{coll}}$ is\cite{Stell1972, Stell1973, Stell1975}

$$\frac{kT_{\text{coll}}}{\epsilon} = \frac{2}{\ln(1/\delta)}$$

(2)

The close packed density is $2^{1/3} \sigma^{-3}$ which corresponds to a volume fraction $\eta$ occupied by the hard cores of $\eta = 2^{1/3} \pi / 6 \approx 0.74$. At close packing there is an inessential solid-solid transition.\cite{Stell1972} The bulk phase behaviour of hard spheres with a short-range square well attraction, $0.06 \geq \delta > 0$, is qualitatively similar.\cite{Stell1972} It is essentially Fig. 1 but with the corners rounded off and the horizontal (vertical) lines no longer horizontal (vertical) but sloping, see Refs.\cite{Stell1972, Stell1973, Stell1975} and \cite{Stell1974}. The coexisting densities no longer change discontinuously but only rapidly near $T_{\text{coll}}$. For $\delta > 0.06$ there is no solid–solid transition but there is no vapour-liquid transition until considerably larger values of $\delta$.

2.1 Phase coexistence for nonzero $\delta$

At temperatures significantly below $T_{\text{coll}}$, the density of the fluid phase which coexists with the solid phase is very low (zero in the $\delta \to 0$ limit). So, we will approximate the chemical potential of the fluid phase by that of an ideal gas. Around the temperature $T_{\text{coll}}$ the density of the fluid phase which coexists with the solid rapidly increases (in the $\delta \to 0$ limit it is horizontal, see Fig. 1). So the accuracy of the approximation will rapidly worsen as the temperature reaches $T_{\text{coll}}$. The chemical potential, $\mu_f$, of an ideal gas

$$\mu_f = kT \ln \rho,$$

(3)

where $\rho$ is the fluid’s number density of spheres times $\sigma^3$ to render it dimensionless. We have neglected a term $\ln(\Lambda/\sigma^3)$, where $\Lambda$ is the integral over the momentum degrees of freedom.

At low temperature, the Helmholtz free energy per particle, $a_s$, of the solid phase can be calculated by using a cell theory,\cite{Stell1972} and assuming that the attractions are strong enough so that they force the lattice constant to be small enough so that each sphere is within the range of the attractive interaction of all twelve of its nearest neighbours.\cite{Stell1972} This fixes the energy per particle at $-6\epsilon$ and the lattice constant at $\sigma(1 + c\delta)$, where $c$ is a constant a little less than one, see Ref.\cite{Stell1972}. Then the Helmholtz free energy per particle $a_s$ is\cite{Stell1972, Stell1973, Stell1975}

$$\frac{a_s}{kT} = - \ln q_p$$

(4)

where $q_p$ is the partition function of a single particle trapped in a cage formed by its twelve neighbours fixed at their points in a perfect lattice. This lattice is either face-centred cubic or hexagonal close-packed, in each a particle has the same arrangement of nearest neighbours so it does not matter which. As the lattice constant is sufficiently small, throughout the cage the particle attracts all twelve neighbours and so its energy is constant at $-6\epsilon$. The partition function is then just the volume available to the centre of mass of the particle times $\Lambda^{-1} \exp(6\epsilon/kT)$, where $\Lambda^{-1}$ is the integral over the momentum degrees of freedom. The volume is of the order of $(c\delta\sigma)^3$, i.e., the cube of the difference between the lattice constant and the hard-sphere diameter. The particle at its lattice position is $\sigma(1 + c\delta)$ away from each of its neighbours and cannot move within $\sigma$ of them due to the hard-sphere interaction. Thus, it can move a distance $c\delta\sigma$ in the direction of each of its neighbours. Actually, the volume to which the particle is restricted is quite complicated, see Ref.\cite{Stell1974} but it is not far from $(c\delta\sigma)^3$. We will approximate it by $(c\delta\sigma)^3$; an approximation which becomes increasingly accurate as $\delta$ decreases.\cite{Stell1972} Then, we have for $q_p$,

$$q_p = (c\delta\sigma)^3 \Lambda^{-1} \exp(6\epsilon/kT)$$

(5)

Inserting this expression for $q_p$ into Eq. (4),

$$\frac{a_s}{kT} = - \ln (\delta^3) - 6\epsilon/kT = \frac{\mu_s}{kT}$$

(6)

where we have neglected a term $\ln(\Lambda/\sigma^3)$. The chemical potential $\mu_s = a_s + p_s/\rho$ where $p_s$ is the pressure and $\rho$ is the density. At coexistence the pressure is very low, note that the gas density is zero in Fig. 1. Therefore, $p_s/\rho$ contributes a negligible amount to the chemical potential for the $\beta_0$ model. This enables us to equate $a_s$ and $\mu_s$ as we have done in Eq. (4). For the $\beta_0$ model all temperatures below $T_{\text{coll}}$ in the $\delta \to 0$ limit are low in the sense that the solid is close-packed and so no different from the solid at zero temperature. When $\delta$ is nonzero the accuracy of our low temperature approximation, Eq. (4), will rapidly worsen as $T_{\text{coll}}$ is approached from below.

Equating the chemical potentials of the fluid, Eq. (3), and solid, Eq. (4), phases yields an equation relating the density of the coexisting fluid to the temperature of coexistence, at a given value for $\delta$. We can rearrange the equation
to give the temperature of coexistence, $T_{co}$, as a function of the density of the coexisting fluid phase, $\rho_f$,
\[
\frac{kT_{co}}{\epsilon} = \frac{6}{3\ln(1/\delta) - \ln \rho_f}.
\]
(7)

As we cool a fluid phase of density $\rho_f$, then, at equilibrium, the solid phase appears at the temperature $T_{co}$ of Eq. (7). Using Eq. (2) for $T_{coll}$ we can express $T_{co}$ as a fraction of $T_{coll}$
\[
\frac{T_{co}}{T_{coll}} = \frac{1}{1 - \ln \rho_f / [3\ln(1/\delta)]}.
\]
(8)

As $\delta$ is small the ratio $T_{co}/T_{coll}$ is near one for a very wide range of $\rho_f$. For example, when $\delta = 0.05$, $T_{co}/T_{coll} = 0.80$ and 0.66 for $\rho_f = 0.1$ and 0.01, respectively.

2.2 The second virial coefficient

For the square-well potential of Eq. (4) with $\delta \ll 1$, the second virial coefficient is
\[
B_2 = B_{2s}^s - 2\pi\sigma^3 \delta \exp(\epsilon/kT) - 1,
\]
(9)
where $B_{2s}^s = (2\pi/3)\sigma^3$ is the second virial coefficient of hard spheres. Generally we will be working at sufficiently large values of $\epsilon/kT$ that we can neglect the $-1$ term in parentheses in Eq. (8). Therefore, we will neglect this term from now on. From the second virial coefficient Baxter defined the $\tau$ parameter
\[
\tau = \frac{1}{4(1 - B_2/B_{2s}^s)},
\]
(10)
which has been described as an effective temperature although it is not a simple reduced temperature as it is not a simple ratio of the thermal energy, $kT$, to an energy. It can be written directly in terms of the temperature and the range $\delta$
\[
\tau = \frac{1}{12\delta \exp(\epsilon/kT)}.
\]
(11)

Straightaway, we can find $\tau$ at the temperature $T_{coll}$, $\tau_{coll}$, by substituting Eq. (2) into Eq. (3).
\[
\tau_{coll} = \frac{1}{12\delta^{1/2}},
\]
(12)

thus as $\delta$ tends to zero, $\tau_{coll}$ diverges. $\tau_{coll}$ is the value of $\tau$ at $T_{coll}$, when the fluid–solid transition widens from the relatively narrow coexistence region of hard spheres to coexistence between a dilute gas and a near close-packed solid.

The experiments measure the strength of the attractive interaction by measuring the second virial coefficient via scattering whereas we measure it via the ratio of the well-depth to the thermal energy, $\epsilon/kT$. Thus we consider here the problem of relating $B_2$ and $\tau$ to $\epsilon/kT$. For nonzero $\delta$, $B_2$ and hence $\tau$ is a well-behaved single-valued function of temperature and so it is possible to uniquely map each value of $B_2$ or $\tau$ to a temperature $T$ and vice-versa. However, if $\delta = 0$ then $B_2$ is not a well-behaved function of temperature. If we take the double limit $\delta, kT/\epsilon \to 0$ then
\[
\frac{B_2}{B_{2s}^s} = \begin{cases} 
1 & T > T_{B20} \\
-\infty & T < T_{B20}
\end{cases},
\]
(13)
where $T_{B20}$ is given by
\[
\frac{kT_{B20}}{\epsilon} = \frac{1}{\ln(1/\delta)}.
\]
(14)

All temperatures above $T_{B20}$ map onto a second virial coefficient equal to $B_{2s}^s$, and all values below $T_{B20}$ map onto $-\infty$. Conversely, all nonzero and non-infinite values of $(B_2 - B_{2s}^s)/B_{2s}^s$, and hence of $\tau$, correspond to the temperature $T_{B20}$, see the discussion of Stell. Which is why $\tau$ is useless to describe the phase diagram of spheres with an attraction of zero range.

Away from the double limit, where $\delta$ is small but nonzero, the variation of $\tau$ with temperature depends strongly on the range $\delta$. We plot $\tau$, Eq. (11), against the reduced temperature $kT/\epsilon$ in Fig. 2. At any given reduced temperature, $kT/\epsilon$, $\tau$ varies as $\delta^{-1}$. Determining $\epsilon$ from scattering data for $\tau$ thus requires an accurate knowledge of $\delta$. This is not available for globular proteins, see section 4.

2.3 The metastable fluid phase

Nucleation occurs from a metastable phase, i.e., a phase which is not the equilibrium phase. We cannot obtain the nucleation rate in a metastable phase without making assumptions about this phase. We will assume that the metastable phase is close to an ideal gas. Justification for this assumption is provided by the fact that the densities we will consider will be quite low that the metastable phase is close to an ideal gas. Justification for this assumption is provided by the fact that the densities we will consider will be quite low and that the second virial coefficient of the leading order correction to the ideal gas is useless to describe the phase diagram of spheres with an attraction of zero range. However, assuming ideal gas behaviour will not be correct if the attractive interactions are strong enough to cause non-equilibrium effects such as gelation or in the vicinity of a metastable fluid–fluid transition. Both gelation and a metastable fluid–fluid transition have been observed in experiment.

3 Classical nucleation theory

Classical nucleation theory assumes that the nucleus of the solid phase has a free energy $\Delta F$ which is the sum of a bulk term and surface term. See the book of Debenedetti for an excellent introduction to classical nucleation theory. The bulk term is equal to the number of spheres in the nucleus, $n$, times the chemical potential difference
\[\Delta \mu = \mu_{eq} - \mu_m,\] where \(\mu_{eq}\) is the chemical potential of the coexisting equilibrium fluid and solid phases, and \(\mu_m\) is the chemical potential of the metastable fluid phase which contains the nucleus. Our Eq. (3) gives the chemical potential of the solid phase at coexistence \(\mu_s\) which is equal to \(\mu_{eq}\). The surface term is the surface area of the nucleus times the surface tension \(\gamma\) of the bulk interface between the coexisting solid and fluid phases, i.e., any difference between the spherical interface between the solid nucleus and the surrounding metastable fluid phase, and the flat interface between the coexisting solid and fluid phases is ignored. The interfacial tension of an interface between a solid phase and a fluid phase depends on the orientation of the interface with respect to the lattice of the solid. To get around this problem, either some orientationally averaged interfacial tension or the interfacial tension with the interfacial tension of the flat interface with respect to the lattice of the solid. To get around this problem, either some orientationally averaged interfacial tension or the interfacial tension with the 

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We will see below that its value is irrelevant and so we do not attempt to estimate it. Then the surface area of the nucleus is \(n^{2/3}(18\pi)^{1/3}(1+c\delta)^2\sigma^2\). So, 

\[\Delta F(n) = n\Delta \mu + n^{2/3}(18\pi)^{1/3}(1+c\delta)^2\sigma^2.\] (15)

The first term in \(\Delta F\) is the bulk term, which is negative and decreases linearly with \(n\), and the second term is the surface term which is positive and increases as \(n^{2/3}\). Thus \(\Delta F\) passes through a maximum, denoted by \(\Delta F^*\), at some value of \(n\), denoted by \(n^*\). The nucleus with \(n^*\) spheres is called the critical nucleus. This is the nucleus of the solid phase at the size at which its free energy is greatest. As the frequency with which a fluctuation occurs scales as \(\exp(-\text{free energy cost}/kT)\), the formation of the fluctuation with the highest free energy cost is the rate limiting process. Thus, classical nucleation theory predicts that the nucleation rate is proportional to \(\exp(-\Delta F^*/kT)\) where \(\Delta F^* = \Delta F(n^*)\) is the maximum in the free energy of Eq. (15). Taking the derivative of Eq. (15) with respect to \(n\) and equating to zero yields the number of spheres in the cluster at the top of the barrier 

\[n^* = \frac{16\pi(1+c\delta)^2\sigma^2}{3|\Delta \mu|^3},\] (16)

and inserting this value of \(n\) in Eq. (15)

\[\Delta F^* = \frac{8\pi(1+c\delta)^2\sigma^2}{3|\Delta \mu|^2}.\] (17)

Now, the interfacial tension, \(\gamma_{111}\), for an interface in the 111 crystal plane, between the coexisting close-packed solid phase and infinitely dilute gas phase of the \(\beta_0\) model is given by 

\[\gamma_{111} = 3^{1/2}\epsilon\sigma^{-2}, \quad \delta = 0.\] (18)

Which, like our expression for the chemical potential, Eq. (3), is a low temperature approximation also valid when \(0 < \delta \ll 1\), but which breaks down, when \(\delta\) is nonzero, as \(T_{coll}\) is approached from below. Other lattice planes have slightly higher tensions, e.g., the 100 plane has a surface tension \(\gamma_{100} = 2\epsilon\sigma^{-2}\). We will approximate \(\gamma\) for all small values of \(\delta\) by the surface tension of the 111 plane \(\gamma_{111}\), which will vary with \(\delta\). The tension \(\gamma_{111}\) is the energy penalty due to the broken bonds at the surface of the solid. Therefore, it scales as one over the square of the lattice constant, \((1+c\delta)\sigma\). So, for all small values of \(\delta\) we have 

\[\frac{\gamma(1+c\delta)^2\sigma^2}{kT} = \frac{3^{1/2}}{2}\epsilon = \frac{3^{1/2}}{2}\ln(1/\delta) \left(\frac{T_{coll}}{T}\right),\] (19)

where the second equality was obtained using Eq. (2). In Ref. [5] it was shown that the gas-solid interface is narrow, only one sphere wide, and so the assumption of classical nucleation theory that the interface is narrow [22–24] is fully justified.

Then, the free-energy barrier to nucleation, \(\Delta F^*\), expressed as a function of temperature and the excess chemical potential over that at equilibrium, is 

\[\frac{\Delta F^*}{kT} = \frac{3^{1/2}}{2}\pi\ln(1/\delta)^3 (T/T_{coll})^{-3}.\] (20)

The corresponding expression for \(n^*\) is 

\[n^* = \frac{3^{1/2}2\pi\ln(1/\delta)^3 (T/T_{coll})^{-3}}{|\Delta \mu/kT|^3}.\] (21)

Equations (20) and (21) are valid below and not too close to \(T_{coll}\). From them we see that at fixed chemical potential difference, \(\Delta \mu/kT\), and ratio of the temperature to \(T_{coll}\), as \(\delta\) decreases both the free-energy barrier and the size of the critical nucleus increase as \(\ln(1/\delta)^3\). The increasing surface tension, Eq. (19), as \(\delta\) decreases is increasing the barrier to nucleation.

We would like to express \(\Delta F^*\) and \(n^*\) purely in terms of temperature, density of the metastable fluid phase, \(\rho_f\), and \(\delta\). To do this we need to know \(\Delta \mu = \mu_s - \mu_m\). Now, \(\mu_s\) is given by Eq. (3). This leaves the effective chemical potential of the metastable fluid phase. We will estimate this by assuming that the metastable fluid phase closely resembles an ideal gas, see Section 2.3. This is an accurate approximation near coexistence. So, with this assumption, \(\mu_m\) is given by Eq. (3) with \(\rho = \rho_f\), and so \(\Delta \mu\) is 

\[\frac{\Delta \mu}{kT} = 3\ln(1/\delta) - 6\frac{\epsilon}{kT} - \ln(2\pi)\]

\[= 3\ln(1/\delta) - 6\frac{\epsilon}{kT}.\] (22)
If we use Eq. (1) to obtain a value for $T_{co}$ at the given value for $\rho_f$ then we can define a reduced temperature $t = T/T_{co}$; a function of $T$ and $\rho_f$. The reduced temperature $t$ is the temperature as a fraction of the coexistence temperature at the same value of the fluid density. In terms of $t$, Eq. (24) can be rewritten as

$$\frac{\Delta \mu}{kT} = 3\ln(1/\delta)[1 - t^{-1}] \left[ 1 - \frac{\ln \rho_f}{3 \ln(1/\delta)} \right].$$

(23)

This is the excess chemical potential of a metastable fluid phase at a density $\rho_f$ and at a fraction $t$ of the temperature at which a fluid of this same density $\rho_f$ coexists with the solid phase. $\Delta \mu$ is of order $kT$ when $(T_{co} - T)/T_{co} = 1 - t \approx 1/\ln(1/\delta)$. To achieve a chemical potential in the metastable fluid which is of order $kT$ higher than at equilibrium we need only go a small fraction of $T_{co}$ below $T_{co}$. When the temperature difference $(T_{co} - T)/T_{co}$ is finite, $\Delta \mu$ diverges in the $\delta \to 0$ limit.

We can substitute Eq. (23) for $\Delta \mu$, and Eq. (3) for $T_{coll}$ into Eq. (24) to obtain the free energy barrier to nucleation as a function of temperature and the range of the attraction, $\delta$,

$$\frac{\Delta F^\ast}{kT} = \frac{3^{-3/2} \pi \ln(1/\delta) (1 - \ln \rho_f/[3 \ln(1/\delta)])}{t(1-t)^2}.$$

(24)

Which is the free energy barrier to the nucleation of the solid phase in a metastable fluid phase at a density $\rho_f$ and at a fraction $t$ of the temperature at which a fluid of this same density $\rho_f$ coexists with the solid phase. At a given fraction, $t$, of the phase transition temperature, the free energy barrier to nucleation increases as $\ln(1/\delta)$, as the range, $\delta$, decreases. The corresponding expression for $n^\ast$ is very simple,

$$n^\ast = \frac{3^{-5/2} \pi}{(1-t)^3},$$

(25)

which is not a function of the range $\delta$ at fixed $t$. It is the number of spheres in the critical nucleus in a metastable fluid phase at a density $\rho_f$ and at a fraction $t$ of the temperature at which a fluid of this same density $\rho_f$ coexists with the solid phase. Our Eqs. (24) and (25) for $\Delta F^\ast$ and $n^\ast$, respectively, rely on our approximations for $\gamma$ and $\Delta \mu$ being accurate, which they are provided we are not too close to $T_{coll}$ when $\delta$ is nonzero, and provided the metastable phase is not too unlike an ideal gas. Also, the free energy is derived by assuming that we can treat it as the sum of a bulk part and an interfacial part. This is reasonable if $n$ is large but breaks down when it is small. Thus, classical nucleation theories break down when $n^\ast$ drops below about twenty. From Eq. (25), $n^\ast = 20$ when $t = 0.73$. Thus below $t \simeq 0.7$ the critical nucleus is so small that classical nucleation theory can no longer be expected to be reliable.

The free energy barrier $\Delta F^\ast/kT$ and the number of spheres $n^\ast$ at the top of the barrier are plotted in Figs. 3 and 4, respectively, for three different ranges $\delta = 0.1, 0.05$ and 0.01. At any value of $t$ the shorter the range the larger is $\Delta F^\ast/kT$. This is true even though as the range decreases $\Delta \mu/kT$, Eq. (23), increases. $\Delta F^\ast/kT$ varies as $(\gamma \sigma^2/kT)^2/(\Delta \mu/kT)^2$ and as both the surface tension $\gamma$ and $\Delta \mu/kT$ vary as $\ln(1/\delta)$, then $\Delta F^\ast/kT$ varies as $\ln(1/\delta)$, Eq. (24). But the number of spheres at the top of the barrier is independent of range, see Fig. 4. Thus we predict that when the attraction is very short-ranged, the free energy barrier to nucleation is larger than it is when the attraction is longer-ranged but the number of spheres at the top of the free energy barrier, $n^\ast$, is the same. As both the free-energy barrier and $\Delta \mu/kT$ increase with decreasing range then the free-energy barrier will only be small enough for nucleation to occur when $\Delta \mu/kT$ is very large.

4 Comparison with protein nucleation

We have specified the state of our model system by the density $\rho$ and the reduced temperature $kT/\epsilon$, which is the ratio of the thermal energy to the attractive energy. For protein solutions the attraction is a free energy not an energy, and so its strength $\epsilon$ is a function of temperature, salt concentration and other variables. The dependence on temperature is then rather complex. For example, adding polymer induces a depletion attraction which is proportional to temperature and to the concentration of polymer. All this makes a direct determination of the ratio of the thermal energy to the attraction free energy all but impossible in experiment. What can often be measured in experiment is the second virial coefficient. George and Wilson use the second virial coefficient $B_2$ as a measure of the strength of the attraction, and Rosenbaum et al. use Baxter’s $\tau$ parameter. The second virial coefficient, Eq. (23), is a function of $\epsilon/kT$ and $\delta$. Thus to convert a temperature into $\tau$ or vice versa we need to know the range of the attraction between protein molecules. We do not know this range, also we do not know the extent to which it varies from protein to protein. Rosenbaum et al. study lysozyme, effective diameter 3.4nm and STA, effective diameter 1.3nm. Only if the range of the attraction scales with the size of the protein will the range of the attraction be the same in each case. In the absence of an estimate for the range of the attraction between protein molecules we have performed calculations for a few values of the range, $\delta$.

Rosenbaum et al. plot the values of Baxter’s $\tau$ parameter for which a number of globular proteins crystallise. They conclude that “crystallising conditions occur for $0.06 < \tau < 0.15$”. In order to compare the results of classical nucleation theory with experiment we rewrite the free-energy barrier, Eq. (17), in terms of $\tau$. To do this we use Eq. (11) to substitute $\tau$ for $\epsilon/kT$ in Eqs. (14) and (22) and then we substitute the resulting expressions for $\gamma$ and
We have plotted $\Delta F^*/kT$ as a function of $\tau$ in Fig. 5.

For $\delta = 0.1$ and 0.05, the free-energy barrier is a very sharply varying function of $\tau$. A little below $\tau = 0.15$ and 0.2, for $\delta = 0.1$ and 0.05, respectively, the free-energy barrier increases to huge values. The sharply varying free energies and the fact that the nucleation rate depends exponentially on the free-energy means that there will be a well defined upper limit to the value of $\tau$ at which nucleation occurs during a given time scale. Our prediction, for very reasonable ranges $\delta = 0.05$ and 0.1, of an upper limit to nucleation at $\tau$ around 0.15 is in good agreement with experiment. Despite the crudity of our theory this agreement may not be fortuitous. We do not know the range $\delta$ that best corresponds to the interaction potential of any globular protein and our calculation of the free energy barrier may be out by tens of $kT$. However, when the range is of the order of a few % of the hard-sphere diameter then changing the range by a factor of two or more and adding or subtracting several tens of $kT$ to $\Delta F^*$ do not alter our prediction that nucleation cannot occur above $\tau = 0.15 \pm 0.05$.

Because of the nucleation rate's exponential dependence on the distance into the metastable regime it is common to observe a well-defined threshold beyond which nucleation is not observed. Thus our finding of a well-defined upper limit on nucleation is not surprising. However, the fact that this upper limit occurs at a value of $\tau$ which depends very weakly on the range of the attraction, $\delta$, is more interesting. It is a possible explanation of why many different proteins have approximately the same upper limit even though the effective interaction potential may differ from protein to protein.

If we compare Figs. 3 and 5 we see that when the barrier height is plotted as a function of $t$, the shorter the range the steeper the curve followed by the barrier height, whereas when the barrier height is plotted as a function of $\tau$ it is the other way around. Changing variables from $t$ to $\tau$ reverses the trend in the change of the free-energy barrier with $\delta$. This is a consequence of the increasingly rapid variation of $\tau$ with temperature as $\delta$ decreases. It suggests caution in interpreting $\tau$ as a temperature-like variable.

Although the interaction between globular proteins is complex and poorly understood, there is an experimental system with a known, short range. This is hard-sphere-like colloidal particles with added non-adsorbing polymer with a radius of gyration much less than the diameter of the particles. Then the polymer induces a depletion attraction with a range $\delta$ approximately equal to the radius of gyration divided by the diameter of the colloidal particles. Ilett et al. studied a system with a range $\delta$ of approximately 0.08. However, as the coexistence densities were not determined accurately we cannot compare our theoretical predictions with these experiments. Qualitatively, they find that crystallisation only occurs if they are not too far into the metastable regime, if $t$ is not too small. If $t$ is too small then a gel forms. As for proteins there is a window within which crystallisation takes place.

5 Conclusion

We have calculated the free-energy barrier to nucleation, within classical nucleation theory, for spherically symmetric potentials consisting of a hard-core and a short-range attraction. A simple model potential for globular proteins and some colloidal systems. The short-range attraction makes nucleation more difficult: the surface tension, Eq. (14), is larger than for many other systems, e.g., hard spheres, which means that at the same value of $\Delta \mu/kT$ the free energy barrier to nucleation is higher when there is a short-ranged attraction than for hard spheres. The surface tension for hard spheres is, from density-functional theory, $0.3kT\sigma^{-2}$ whilst with an attraction of range 10% of the diameter of the particle, $\delta = 0.1$, at a temperature $(2/3)T_{coll}$, it is $5.9kT\sigma^{-2}$. The surface tension for hard spheres is an order of magnitude smaller and the nucleation rate is very sensitive to the surface tension, it varies as $\exp[-(\gamma\sigma^2/kT)^3]$ at constant $\Delta \mu/kT$.

The large barriers to nucleation predicted by classical nucleation theory are certainly consistent with the difficulty experienced in crystallising proteins and the non-equilibrium behaviour observed for colloidal particles with a short-ranged attraction. However, the uncertainty surrounding the interaction between protein molecules makes comparison with theory, which is for a specific model potential, very difficult. Experimental results for the location of the onset of nucleation for colloidal systems for which the the interaction potential potential and phase coexistence boundaries are both known would be very useful in understanding protein crystallisation and in testing theoretical predictions.

The barrier to nucleation decreases as the temperature drops more and more below the transition temperature $T_{co}$, i.e., as $t$ decreases, and we move further into the metastable region of the phase diagram. Thus we can lower the free energy barrier by moving deeper into the metastable regime. However, by doing so we may encounter difficulties such as the fluid becoming sufficiently cold to form a gel-like state in which the dynamics are at least partly arrested, preventing the formation of the crystalline phase. Ten Wolde and Frenkel have suggested that a metastable fluid-fluid transition may offer a way round this problem.

An interesting prediction of classical nucleation theory is that the critical nucleus at a given value of the free-energy barrier shrinks as the range of the attraction, $\delta$, decreases. Thus under the conditions in which the free-energy barrier is small enough to permit nucleation on a reasonable time scale the nucleus becomes smaller and smaller as $\delta$.
decreases. Indeed it becomes so small that classical nucleation theory breaks down, even when $\Delta F^*$ is still large, of order tens of $kT$.

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Figure 1: The phase diagram of the $\beta_0$ model. The solid lines denote the coexisting densities at the fluid-solid and solid-solid transitions. The density difference between the coexisting phases at the solid–solid transition is zero on this scale. The letters denote the fluid (F) and solid (S) phases, and the two-phase region of fluid-solid coexistence is marked with the number 2. The dashed lines are tie lines connecting coexisting fluid and solid phases.
Figure 2: Baxter’s $\tau$ parameter, Eq. (11), plotted as a function of the ratio of the thermal energy to the well depth, $kT/\epsilon$. The solid, dashed, and dotted curves are for ranges $\delta = 0.1, 0.05$ and 0.01, respectively. $kT_{b20}/\epsilon = 0.43$ and 0.22 for $\delta = 0.1$ and 0.01, respectively.

Figure 3: The free energy barrier $\Delta F^*/kT$ is plotted as a function of $t = T/T_{co}$ for three ranges: $\delta = 0.1$ (solid curve), $\delta = 0.05$ (dashed curve) and $\delta = 0.01$ (dotted curve). For $\delta = 0.1, 0.05$ and 0.01, $kT_{co}/\epsilon = 0.65, 0.53$ and 0.37, respectively.
Figure 4: The number of spheres at the top of barrier, $n^*$, as a function of $t = T/T_{co}$. The one curve plotted is for any (short) range $\delta$.

![Figure 4](image)

Figure 5: The free energy barrier $\Delta F^*/kT$ is plotted as a function of Baxter’s $\tau$ parameter for three ranges: $\delta = 0.1$ (solid curve), $\delta = 0.05$ (dashed curve) and $\delta = 0.01$ (dotted curve). All three curves are plotted down to $\tau = 0.1$ but in the case of $\delta = 0.01$ the size of critical nucleus, $n^*$, drops below twenty at $\tau = 0.2$ and so the dotted curve from $\tau = 0.1$ to 0.2 is really out of the range of applicability of classical nucleation theory.

![Figure 5](image)