Estimation of the scaling of the nucleation time with volume when the nucleation rate does not exist

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Abstract

Recent experimental [Diao *et al., J. Am. Chem. Soc.* **2011** *133*, 3756.] and simulation results [Sear, *J. Phys. Cond. Matt.* **2012** *24*, 052205.] are not consistent with a nucleation rate that is in the thermodynamic limit. This has consequences, if the rate is not in the thermodynamic limit, the time for nucleation will not necessarily scale as one over system size. Here, I show how to analyse data for nucleation times to test for the existence of a well defined nucleation rate. I also show how to estimate the scaling of the nucleation time with the number of nucleation sites. The prediction is that the farther the system is from the thermodynamic limit, the more rapidly the nucleation time varies with system size. To make this prediction, I use extreme-value statistics. I also show how nucleation data can be analysed to extract information on the heterogeneity in the surfaces nucleation is occurring on.

Introduction

It is often assumed that the rate of nucleation is well defined for a solution at a given temperature, supersaturation etc., and that this rate is proportional to either the volume or the surface area. Here

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we study systems where the nucleation rate is not well defined. There are experimental results,[1–6] computer simulation results,[7] and model calculation results[8–10] that are inconsistent with a well-defined nucleation rate that is the same for all members of a set of nominally identical samples. If the rate is the same for all members of a set of samples, then the fraction where nucleation has not occurred must decrease exponentially with time, this is not the case.[1–7]

When I say that the nucleation rate does not exist, I mean that the rate is far from the thermodynamic limit.[11] Properties of a crystallising droplet, such as the heat capacity, viscosity, etc, are in the thermodynamic limit.[12] These properties do not vary from one sample at the same concentration and temperature, to another. Also, properties such as the heat capacity are proportional to the volume. By contrast, it appears that the nucleation rate may vary by orders of magnitude from one nominally identical sample to another, and then it may not be proportional to the volume.

Nucleation may be much faster in one nominally identical sample than in another because of differing impurities in the sample.[8–10] Nucleation is almost always heterogeneous, i.e., it occurs at a surface,[13,14] and the nucleation barrier is extremely sensitive to details of the surface.[8,15–23] Then, simply by chance one crystallising droplet may have a particularly good nucleation site and so nucleation is fast, whereas another droplet does not, and so nucleation is much slower.[11]

Here I introduce a simple model, and show how to estimate the variation with droplet volume, of the typical time until nucleation occurs. I show that it is related to the variability in the nucleation sites, and that this variability can be estimated from experiments. Throughout this paper, I define the nucleation time as the time until the first nucleus forms in the droplet or simulation system. I assume that the time to equilibrate at a particular temperature, supersaturation, etc, is much smaller than the nucleation time, and so can be neglected. I do the same for the time the crystal takes to grow from the microscopic nucleus to a crystal large enough to be observed.

Because the effective nucleation rate varies so widely from one sample to another, defining a typical nucleation rate or time is not trivial. However we do need a measure of the average nucleation time. I choose the median time until nucleation, τ_{MED}. The median is most convenient, because in experiment, a small fraction of the samples may never crystallise,[1–4,6] which prevents

the use of the arithmetic mean.

Prior work

Deviations from the behaviour expected in the thermodynamic limit have been found for a single system size in work by Diao *et al.*[1–4] This is for aspirin and similar molecules crystallising from solution. Kabath *et al.*[5] and Murray *et al.*[6] have also found similar behaviour. Their work studied the freezing of droplets of water.

There has been a significant amount of modelling work on systems where nucleation is determined by an impurity which varies from droplet to droplet.[8–10] This is motivated by work on ice nucleation, and mostly considers not nucleation times but the temperatures at which water droplets freeze on cooling at a fixed cooling rate. The limit in which the nucleation temperature is determined by the impurity in the droplet, and where this impurity varies from droplet to droplet is called the "singular" limit.[8] In this limit, the nucleation rate does not exist, in the sense defined in the Introduction. I am not aware of any attempts to predict the scaling with volume in this limit.

Diao and coworkers worked with sets of droplets, where each droplet was a crystallising solution of either aspirin or paracetamol,[1] of the molecule ROY,[3] etc.. The molecule ROY is named after its red, orange and yellow crystals, i.e., it has a number of polymorphs of different colours. They plotted the fraction of these droplets that had not crystallised, $P(t)$, as a function of time t. Note that $P(t)$ is what is called a cumulative probability, it is the cumulative probability that nucleation has not occurred at any time less than t. They then fitted a stretched exponential

$$P(t) = \exp[-(t/\tau)^{\beta}] \tag{1}$$

to the data.[3,4] Here β is an exponent, and $\beta \leq 1$ for a stretched exponential. Also τ is a characteristic timescale. In a number of cases (but not in all) the fit was good. I have also calculated $P(t)$ in computer simulations of nucleation in the presence of quenched disorder, and found that the stretched exponential is an excellent fit to the calculated $P(t)$. Note that the stretched exponential

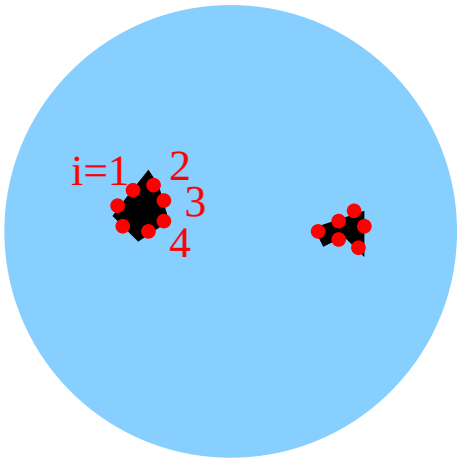

Figure 1: Schematic of a droplet (blue) containing two impurities (black), each with many nucleation sites (red discs). I have labelled sites $i = 1$ to 4. This schematic is not to scale, a droplet will typically contain many impurities, which will mostly be microscopic, and each impurity will have a very large number of nucleation sites.

distribution is also the Weibull distribution in extreme-value statistics.[24]

As noted earlier,[7] a value of $\beta < 1$ is incompatible with the nucleation rate being the same in all the samples studied. A $\beta < 1$ means the rate *must* vary widely from one nominally identical droplet to another. If the rate is the same in all samples, the fraction must decay as a simple exponential, i.e., $\beta = 1$, whereas a stretched exponential with $\beta < 1$ is symptomatic of a range of rates.[25] This breakdown in the thermodynamic limit is, in the language of statistical physics, a breakdown in self-averaging, and the variability from site to site is a form of what is called quenched disorder. This has been extensively studied in other contexts, and previously applied to nucleation.[11]

Model

The systems I have in mind are systems like those of Diao and coworkers,[1–4] where crystallisation is occurring in small droplets. These rapidly reach thermal equilibrium, so the thermal-equilibration time is unimportant, and only a single nucleation event is required for crystallisation. Also, the time for the crystals to grow is much smaller than the typical nucleation times, and so can be neglected.

The model for the freezing of droplets is simple. I make the following assumptions:

1. Each droplet contains surfaces that have a total of N nucleation sites. This is illustrated in Figure 1. I expect N to scale with the number of impurities and/or surface area of material added to provide heterogeneous nucleation sites.[1,26] I will assume $N \gg 1$, and that the fluctuations in N between one droplet and in the next is negligible, so that we can use the same N for all droplets.

2. At each nucleation site $i = 1, N$, there is a characteristic time for nucleation, t_i, that varies very widely from one site to another. I treat each nucleation site as independent, so the t_i are independent random variables.

3. Only one nucleation event is required to induce crystallisation of the droplet, and the time for growth of the crystal to be large enough to be observable is negligible in comparison with the time for nucleation. Then the time for crystallisation, t_X, is well approximated by the minimum of the N nucleation times, i.e.,

$$t_X(N) = \min(t_1, t_2, \ldots, t_N) \tag{2}$$

Assumption 3 allows us to use what are called extreme-value statistics. See, for example Kotz and Nadarajah's book[24] for an introduction to these statistics. Also, there are simple models for variability in which assumption 3 is seen to be satisfied.[11,26]

Extreme value statistics

We will now use extreme value statistics to determine the scaling of the median nucleation time, τ_{MED}, with the number of nucleation sites, N. First, I write the cumulative probability that nucleation has occurred on none of N sites, in terms of the reduced variable $x = t/\tau$

$$G(x) = \exp\left[-x^{\beta}\right] \tag{3}$$

Within extreme value statistics, $G(x)$ must obey the stability postulate, which here is[24]

$$[G(x)]^s = G(a_s x) \tag{4}$$

where a_s is a constant that depends on s but not x, and s is a scale factor. For example, $s = 2$ implies that we double the size of system, from N to $2N$. Physically speaking, this equation follows from two assumptions.

The first is that in the large N limit, scaling up by a factor of s cannot change the functional form, i.e., if for N sites the cumulative probability distribution is a stretched exponential with a given value of β, then after, for example, doubling N, the cumulative probability distribution function is still a stretched exponential, with the same value of β. However, the timescale for nucleation is scaled by some s-dependent factor a_s. This is why on the right hand side we write the cumulative probability as $G(a_s x)$. The second assumption is that as the sites are independent, increasing the system size by a factor of s changes the cumulative probability from $G(x)$ to $[G(x)]^s$, because of course independent probabilities are multiplicative.

Substituting eq (3) in eq (4), we get

$$\exp[-sx^\beta] = \exp[-(a_s x)^\beta] \tag{5}$$

so

$$a_s = s^{1/\beta} \tag{6}$$

and the timescale for nucleation, τ, scales with scale factor s, as

$$\tau(sN) = \tau(N)s^{-1/\beta} \tag{7}$$

$$\tau_{MED}(sN) = \tau_{MED}(N)s^{-1/\beta} \tag{8}$$

where in the second line we used that fact that for a stretched exponential the median nucleation time, τ_{MED}, is related to τ by $\tau_{MED} = (\ln 2)^{1/\beta}\tau$. The median time for crystallisation scales with

the number of nucleation sites as the power law $s^{-1/\beta}$. The exponent β is obtainable from a fit to the nucleation times in a set of crystallising samples at one system size. This is the main result of this paper.

Second derivation

I will now show how to relate $P(t)$, which is accessible from fits in experiments, to the probability distribution function of the nucleation times at individual nucleation sites, $\sigma(t_i)$, which is not accessible. This will allow us to use experimental data to learn about the distribution of microscopic nucleation sites.

The stretched exponential $P(t)$ of eq (1) can be derived if we assume a power-law form for $\sigma(t_i)$

$$\sigma(t_i) \sim \beta \frac{t_i^{\beta-1}}{\tau_1^{\beta}} \tag{9}$$

Here τ_1 is a parameter (with dimensions of time), of the distribution σ of nucleation times at individual sites. These nucleation times, t_i, are random variables sampled from the distribution σ. Note that eq (9) is the small t_i tail of the distribution. As it is the smallest of many nucleation times that we are interested in, the small t_i part is the only part of the distribution we care about.

The cumulative probability that the nucleation time is t_i or greater is then

$$\Sigma(t_i) \sim 1 - (t_i/\tau_1)^{\beta} \tag{10}$$

The probability $P(t)$ that crystallisation has *not* occurred at a time t is simply the probability that all N t_i's are greater than t, which as the nucleation sites are independent is simply

$$P(t) = \Sigma(t_1 = t)\Sigma(t_2 = t)\ldots\Sigma(t_N = t) = [\Sigma(t)]^N \tag{11}$$

We can use eq (10) in eq (11),

$$P(t) = \left[1 - (t/\tau_1)^\beta\right]^N \simeq \exp\left[-N\,(t/\tau_1)^\beta\right] = \exp\left[-(t/\tau_N)^\beta\right] \tag{12}$$

with

$$\tau_N = \tau_1/N^{1/\beta} \tag{13}$$

which recovers the stretched exponential of eq (1), and the scaling of τ with system size, of eq (8). Note that the derivation relies on the system being in the $N \gg 1$ limit, and so not only is N large but $(t/\tau_1)^\beta \ll 1$, in the region of interest where P is not very close to 0.

So, the exponent β in the stretched exponential is related to the exponent of the power law in the small time tail of the distribution of nucleation times at the individual nucleation sites. A smaller β in the stretched exponential, is a result of the the exponent, $(\beta - 1)$ of the power law being more negative, closer to -1. A smaller $(\beta - 1)$ comes from a σ that curves up faster as time decreases. So, the more σ curves up at small times, the farther from exponential is the fraction not crystallised, $P(t)$. Or the flatter is σ, the closer $P(t)$ is to exponential; when $\beta = 1$, σ is flat and $P(t)$ is a simple exponential.

Test

To test the model, I use previously published simulation data[7] for nucleation rates at randomly varying nucleation sites. These sites are clusters produced via a diffusion-limited-aggregation like process. See Sear[7] for details. I use a large set of 270,000 of these sites (clusters), and for the nucleation rates I use the fit to nucleation rates obtained at a supersaturation given by the lattice model parameter $h/kT = 0.03$.

To model an experiment on a set of M droplets I take M systems, each with N nucleation sites. Then I calculate the nucleation rate, R, for each one of the M systems by summing the N site rates. The nucleation time of each model droplet is then a random number drawn from an exponential distribution with mean of $1/R$. Having obtained the M nucleation times, I then plot the fraction

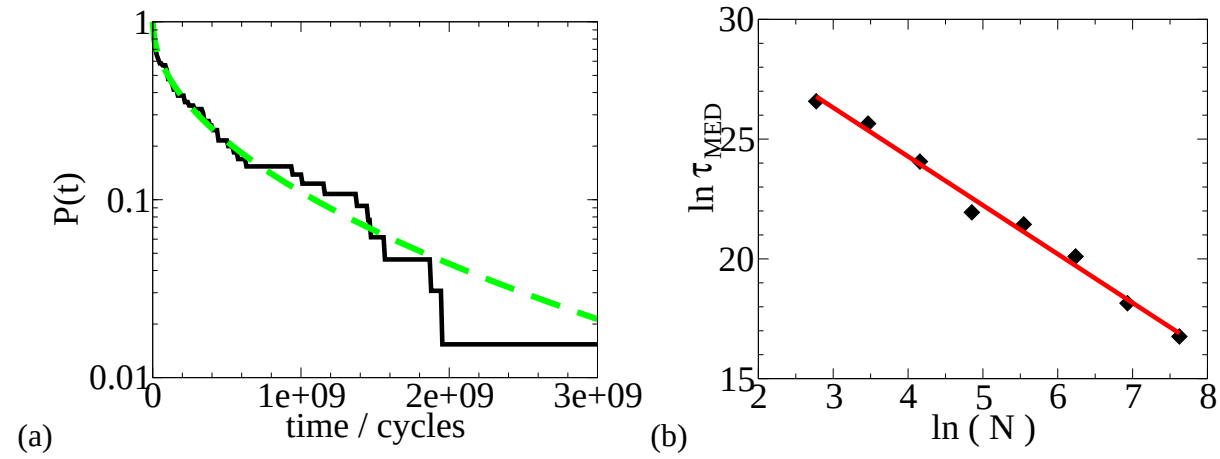

Figure 2: (a) Plot of the fraction of $M = 65$ samples where nucleation has *not* occurred, as a function of time t. The time is in units of simulation cycles. The black curve uses data from Sear,[7] and the green dashed curve is a Weibull fit. For the black curve each of the 65 systems has $N = 1024$ nucleation sites, and the fit is $\exp\left[-(t/2.12\times10^8)^{0.508}\right]$. (b) Plot of the log of the median time for nucleation to occur, τ_{MED}, as a function of the log of the number of nucleation sites, N, in the system, at a fixed supersaturation. The black diamonds use rate data from Sear,[7] and the red line is a fit of $\ln\tau_{MED}(N) = 32.43 - 2.04\ln(N)$ to this data.

that have not nucleated as a function of time, $P(t)$.

A plot of $P(t)$ for $M = 65$ systems, each with $N = 1024$ nucleation sites, is shown in Figure 2(a). It is the black curve. A stretched exponential fit to this data is shown as a dashed green curve; the fit is $P(t) = \exp\left[-(t/2.12\times10^8)^{0.508}\right]$, so $\beta = 0.508$. I have fit to other sets of sites, and other sizes N and get comparable values for β, i.e., values around 0.5. The mean and standard deviation for fits of $P(t)$ to 4 independent sets of $M = 65$ systems each with 1024 sites, is 0.555 ± 0.029.

To test if the β values obtained from fits to data at a single system size can predict the scaling with size, I also calculate the median time to nucleate, τ_{MED}, as a function of N. The results are shown in Figure 2(b).

I start with a small system, with $N = 16$. I sum the N rates to get a total nucleation rate R. The nucleation time is then a random number sampled from an exponential distribution of mean $1/R$. I do this for $M = 65$ independent systems, and then find the median of these 65 nucleation times. This is our estimate for t_{MED} at $N = 16$. I repeat this for $N = 32$, 64, ..., 2048, to obtain the median time to nucleate as a function of the number of nucleation sites. The times are plotted in Figure

2(b), together with a power law fit of the form $\tau_{MED} = aN^b$. The best-fit exponent $b = -2.04$.

Thus, from the fits to the systems at a fixed size in Figure 2(a) I obtain β values. Our extreme-value-statistics theory predicts that τ_{MED} scales with N as $-1/\beta$, which if I take the mean value for $N = 1024$, is predicted to be -1.8. This value is close to the value $b = -2.04$ of the best fit to τ_{MED} as a function of N. Thus in this case we can test our theory, and this test is successful.

Applications

Having tested the theory, I use it to make predictions. Diao *et al.*[3] studied the crystallisation of ROY from solution. They did so with nothing added, and so where nucleation presumably occurs on impurities, and with the addition of poly(ethylene glycol) diacrylate (PEGDA) hydrogel particles. With the PEGDA hydrogel particles their fit to the surviving fraction of liquid drops yielded a best-fit value of $\beta = 0.25$, so I predict that on scaling the exposed surface area A of hydrogel, the median time to observe crystallisation will scale as A^4. Without the hydrogel particles, the best-fit value was found to be $\beta = 0.37$, and so at constant impurity concentration and assuming the impurities are in the bulk of the liquid drop bulk (not at the surface) I predict a scaling with droplet volume, V, of $V^{2.7}$. We should note that the data of Diao *et al.*[3] are not perfectly fit by the stretched exponential function, and so there is probably considerable uncertainty in the exact value of the exponent. However, I expect the prediction of a power-law scaling of median nucleation time, with an exponent that is not the trivial thermodynamic one, to be robust.

An exponent of $\beta = 0.37$ implies that in the small time tail, the probability distribution of nucleation times at the individual nucleation times varies as $\sigma(t_i) \sim t_i^{-0.63}$. The smaller β exponent in the presence of PEGDA particles implies that then $\sigma \sim t_i^{-0.75}$, and so curves up more rapidly at small times, i.e., the distribution of nucleation times is more heavily skewed to small times.

There are also systems which have nucleation rates in the thermodynamic limit. Duft and Leisner[27] studied the nucleation of ice in ultra-pure water droplets. This was at very low temperatures, around -36°C. They showed that the fraction remaining unfrozen decreases exponentially with time. Dalnoki-Veress and coworkers[28,29] have performed similar studies, but studied the crys-

tallisation of polymer droplets (of both poly(ethylene oxide) and polyethylene). They also found exponentially decaying fractions. Jiang and ter Horst[30] also present crystallisation data, most of which is well fit by an exponential function. Their data is on the crystallisation from solution of the molecules *m*-aminobenzoic acid (*m*-ABA) and L-histidine (L-His). Thus, most of this data[27–30] is consistent with well defined nucleation rates that are in the thermodynamic limit. It appears that these rates may scale either with volume[27,28] or with surface area.[29]

When the nucleation rate is proportional to the volume, this is consistent with nucleation on impurities with surfaces that are relatively uniform, i.e., with the t_i being narrowly distributed. This assumes that the concentration of impurities is constant. It is also consistent with homogeneous nucleation. When the rate scales with the surface area this is consistent both with nucleation on impurities concentrated at the droplet surface that are relatively uniform, and with heterogeneous nucleation at a clean surface.

Finally, it should be noted that the stability postulate of extreme value statistics, eq (4), implies that the fraction of samples that have crystallised at a fixed time decreases exponentially as system size (here s) increases. If droplets are prepared, and then the fraction of them that have crystallised after a fixed time determined (as it often is in protein crystallisation[31]), then this fraction should decrease exponentially with droplet volume. Unfortunately I am not aware of studies which quantify the effect of varying the volume. Any deviations from exponential behaviour would be clear evidence for time dependent phenomena, such is irreversible reactions (e.g., oxidation) of the molecules.

Conclusion

Nucleation can be dominated by one or a few sites[26] even in systems with Avogadro's number of molecules. So, even for macroscopic systems the nucleation rate may not have reached the thermodynamic limit.[7] For crystallising droplets although properties such as their heat capacity may be in the thermodynamic limit, the nucleation rate is not. Thus whereas the heat capacity will

scale linearly with the volume, the nucleation rate may have a different scaling. Here, I have made the physically reasonable assumption that nucleation occurs at the site where the barrier is lowest and so the local rate is highest. Then we can use extreme-value statistics.[24] This allows us to make predictions about the form of $P(t)$, the fraction of samples that have not crystallised as a function of time, and about the scaling of the median time until nucleation, τ_{MED}, with volume. The median time is a power law function of size, but with an exponent, $-1/\beta \leq -1$. This exponent can be estimated by fitting to the fraction of a set of samples that have not crystallised, as a function of time. Thus data at one volume can be used to predict the median nucleation times at larger and smaller crystallisation volumes.

The scaling of the nucleation rate with the volume or with the amount of added impurities is important. It is typically a straightforward parameter to vary in experiments, and in manufacturing we often wish to scale up to larger volumes. In these cases the result of this paper could be used to estimate how crystallisation times scale with volume.

Crystallisation has also been studied in systems with microscopic volumes, down to a few nanometres across (zeptolitre volumes). For example, Tester *et al.*[32] looked at calcium carbonate crystallisation in vesicles, around 100 nm across. Cooper and coworkers[33,34] have studied crystallisation (of glycine and other molecules, and of graphene) in microemulsions, where nucleation is believed to occur in microemulsion droplets of order 10 nm across. Ward and coworkers, and others, have studied crystallisation in nanoscale pores,[35] including, for example, glycine in nanoscale diameter cylindrical pores.[35,36] These systems may be too small for the approach introduced here to work, they may even be sufficiently small for homogeneous nucleation to be occurring. Future theoretical work could look at how this small-volume limit is approached. Before this is understood future experimental work should be aware of the uncertainty involved in extrapolating from bulk measurements on heterogeneous nucleation on impurities, to what may be homogeneous nucleation in these microscopic volumes.

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Estimation of the scaling of the nucleation time with volume when the nucleation rate does not exist

Richard P. Sear

Synopsis

Some recent experiments are not consistent with a nucleation rate that is in the thermodynamic limit, and this may turn out to be common in the nucleation of crystals. Here, I predict that the farther a system is from the thermodynamic limit, the more rapidly the nucleation time varies with volume. To make this prediction, I introduce the use of extreme-value statistics to modelling nucleation.