Chapter 1

Introduction

Crystallisation is one of the oldest forms of phase separation used by humanity [1], put simply, it is the formation and growth of a new structured phase within a disordered bulk phase. This has applications in a number of industries such as pharmaceuticals [2], food production [3], and electronics [4]. Where the extraction of dilute materials can help improve product quality while keeping production costs low. Modern crystallisation methods involve manipulating the solubility of the target chemical (aka the solute) in order to encourage the formation of a separate phase that can be easily extracted [2]. This is simple enough to understand on a macro scale when the concentration can be assumed as a time-dependent variable; but at a micro level the crystallisation process is not merely subject to solubility but also due to the inter-molecular forces that can inhibit or enhance the formation of a new phase. Theories attempting to describe the phenomena but none have proven viable to explain the various pathways available [5].

Crystallisation can be subdivided into two stages: The first stage - nucleation - is the formation of a brand new phase within the bulk solution, while nucleation can occur readily in most solutions it is difficult to predict if a nucleus will remain stable within the solution or if it will be dissolve. The latter stage - crystal growth - is focused instead on how an already stable nucleus grows into its final shape depending on the conditions of the surrounding fluid, understanding how and where deformities occur within the crystal structure are of extreme importance to several industries [2, 4].

This chapter will outline our current understanding of nucleation, where there is

a gap in the literature, and why there is still a need for local control of nucleation events. Furthermore, it will also highlight recent developments involving the use of optical tweezers (and other *in situ* methods) in order to develop our understanding of nucleation. Lastly we highlight the connection between optical tweezer's ability to probe fluid viscosity via rotational motion, and the known link between nucleation and fluid flow, to propose a novel potential method of creating localised nucleation events.

1.1 Nucleation

Nucleation is an example of a binary phase separation, where a dilute phase is miscible in a bulk phase, more often called the solute and solvent respectively. When a small amount of solute is added to the solvent the solute will diffuse throughout the solvent, reaching an equilibrium concentration throughout the solution. Because of molecular interactions, the two can only remain in equilibrium while below a specific concentration (C_{eq}) - below which the chemical potential μ for a single phase is greater than the potential required to separate the two. Once C_{eq} is exceeded there is a chemical potential difference driving the solution to separate the two phases. This does not mean that nucleation will occur immediately once C_{eq} is exceeded, only that there is a chemical potential supporting nucleation.

Since different combinations of solute and solvent will have different equilibrium concentrations, researchers often instead measure the ratio between the solute and solvent by using 'supersaturation' [6]:

$$S(T) = \frac{C_{sol}}{C_{eq}(T)} \tag{1.1}$$

Where C_{sol} is just the solute concentration, and $C_{eq}(T)$ is the equilibrium concentration of the solute at temperature T based on the main solvent. While the solution remains supersaturated there is a chemical potential driving the solute to coalesce and separate from the solution as an ordered solid, the first formation of the crystal is referred to as the nucleus and understanding its formation has been the focus of researchers for decades now. Typically, for an industrial crystallisation process the

working principle is based on controlling and manipulating the supersaturation of the system.

1.1.1 Primary & Secondary nucleation

nucleation process be broadly categorised into either primary or secondary nucleation. The former describes the formation of an initial nucleus within the bulk phase, absent of any external surfaces. Primary nucleation is dependent only on the local concentrations of the solute which can fluctuate unpredictably, as such it is often modelled at a large scale as a stochastic process. The only reliable factor being that higher supersaturations will result in more nucleation events to occur sooner.

An important metric for crystallisation procedures is the nucleation rate of the solution, a measure of the total volume or mass of crystalline material produced for a given set of initial conditions. At an industrial scale this metric is a contribution of both primary and secondary nucleation events. At a small scale one can estimate the contribution of the primary nucleation pathway by making repeated measurements of sample solutions and seeing how many have nucleated after a given time, giving us a Poisson probability distribution.

$$P(t) = 1 - exp\left[-JV(t - t_g)\right] = \frac{M^*(t)}{M} \tag{1.2}$$

Where J is the nucleation rate, t_g is the 'growth time' which accounts for the initial delay due to the stochastic nature of primary nucleation, V is the volume of the individual samples, and $M^*(t)$ & M are the number of nucleated samples and the total number of samples used respectively. While (1.2) is useful for studying the effects of different parameters at a small scale, for industrial applications there are to many external factors for primary nucleation to be measured accurately. Overall while the primary nucleation rate is significant when studying solutions for small volumes, the contributions of secondary nucleation is far more significant when considering nucleation rate for an industrial crystalliser.

Secondary nucleation is the result of a initial seed crystal inducing further nucle-

ation within the bulk solution [7]. The seed crystals are often prepared ahead of time and added to a supersaturate solution. Due to interactions with the surrounding fluid and the container walls it is possible for the seed crystals to act as a surface for further nucleation [8]. However this is just one possible way in which a seed crystal can enhance the nucleation rate, depending on the conditions of the crystalliser there are multiple mechanism by which the seed crystal can contribute to the nucleation rate of the system. Control of secondary nucleation events are crucial for ensuring reliable industrial crystalliser performance. Fig. 1.1 depicts an attempt of classifying every possible mechanism that could lead to secondary nucleation.
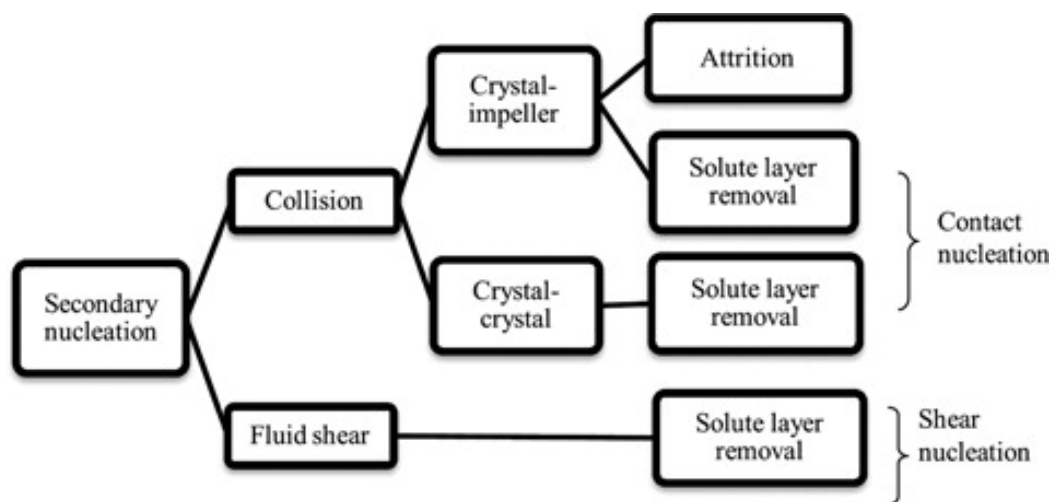

Figure 1.1: Secondary Nucleation mechanisms, classified by Agrawal and Paterson [9]

This is not a universal classification system, there are a variety of opinions on how best to characterise different phenomena. It is heavily dependent on the theory used to describe nucleation events, this is accurate for both secondary and primary nucleation.

1.2 Nucleation Theories

In order to predict the nucleation rate of a given solution we need a solid understanding of how the individual molecules interact such that they transition from an unordered phase to a ordered phase. Over the years several theories have been proposed to explain how nucleation events occur, so far there has yet to be a standout candidate that reliably

predicts the systems behaviour. Either they fail to accurately predict nucleation rates or more generally cannot describe new experimental results.

1.2.1 Classical Nucleation Theory (CNT)

Sometimes referred to as 'Gibbs Nucleation Theory' the original theory was first formed from the works of Volmer and Weber, and Frenkel [10, 11]. While initially it was more focused on describing droplet formation in condensing vapours it was extrapolated to describe crystallisation. The central premise of classical theory is that nucleation occurs stochastically due to collisions between individual solute molecules, ions, or atoms. At the same time the bulk phase is resistant to the formation of a new phase. The competition between these random collisions and the bulk solution can be used to predict the probability of a newly formed nucleus.

Consider a supersaturated solution, at some time individual sub units collide rapidly, one after another, forming a nucleus of volume $4\pi r^3/3$. The newly formed phase has a lower chemical potential than the surrounding solution, reducing the free energy of the system. Simultaneously, the formation of a new interface is resited by the bulk phase due to surface tension. The net free energy of the system for a nucleus of radius r is given as [12]:

$$\Delta G = \frac{-4\pi r^3}{3v} k_B T \ln(S) + 4\pi r^2 \sigma_{inf} \tag{1.3}$$

Where S is the supersaturation from eq. (1.1) v is the approximate volume of an individual molecule, k_B is the Boltzmann constant, and σ_{inf} is the interfacial tension of the bulk solution. This assumes that the nucleus will have a spherical morphology so that the surface tension σ_{inf} is a scalar value. Looking at (1.3) suggests that there must be some critical size r where the free energy gain from the nucleus exceeds the surface tension of the surrounding fluid. This is reflected in fig. 1.2 where we plot the free energy of the system against nucleus size. This reveals a critical size above which the gain in free energy exceeds the interfacial tension. Furthermore fig. 1.2 shows how increasing the supersaturation of the system reduces said barrier.
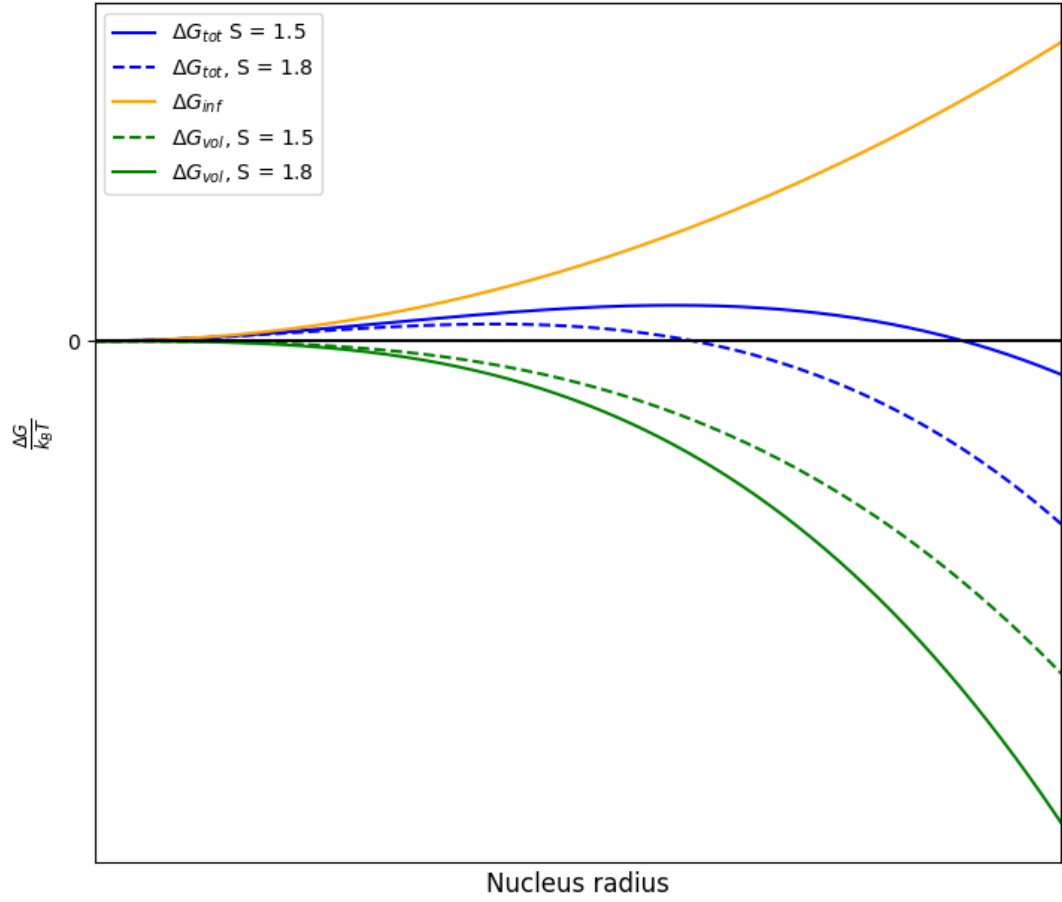
Figure 1.2: Free energy diagram of a newly formed nucleus according to the Classical Nucleation Theory. The total free energy (blue) is due to the competition between the volume free energy gain (green) and the interfacial free energy cost (orange). Dotted lines are for a higher supersaturation than the solid lines, the interfacial energy cost is independent of supersaturation. Diagram was constructed in python using a naive assumption of $v = 1 \times 10^{-12} \ m^3$ and $\sigma_{inf} = 0.0001 \ J/m^2$

The maximum value of ΔG_{tot} is the free energy barrier that any newly formed nucleus needs to overcome in order to stabilise. The nucleation rate (the volume of new crystalline material formed per unit time), is therefore commonly defined as being dependent on the energy barrier ΔG^*:

$$J = A \ exp \left[-\frac{\Delta G^*}{k_B T} \right] \tag{1.4}$$

Where A is a pre-factor that can be fine tuned to the exact demands of the system, the free energy barrier can be found by finding the stationary point of ΔG_{tot}.

CNT is often regarded as a good description of the macro system, its obvious that for all crystallization systems there is an inherent energy barrier that dictates the nucleation rate. Where it falters is in its predictive ability, both in estimating nucleation rates [13, 14], and in the structure of newly formed nuclei [15, 16]. Recent studies suggest classical nucleation is merely one of many possible pathways that can be taken to produce an ordered crystalline phase. Prompting the development of alternative theories to better describe the nucleation process.

1.2.2 Two Step Nucleation

The two step nucleation theory is an extension to the CNT that suggests that prior to nucleation, the solute will form precursor structures. The CNT assumes that solute structures below the critical radius should be unstable within the solution due to interfacial forces trying to dissolve the solute. This assumption is based on the idea that any interactions between solute molecules are much weaker than that between solute and solvent molecules. If instead the solute molecule interactions are significant then it stands to reason that subcritical liquid-like structures are stable.

The first observation of a liquid-like structure was in $CaCO_3$ solutions, initially it was assumed that polymers were a necessary additive to create a precursor structure [17, 12]. This is not the case when the solution is above its critical temperature, allowing the solution to be in the binodal region of the phase diagram. This would result in the formation of two liquid phases, one being rich in solute, the other being solute poor [12, 5]. Several papers later reported the presence of stable liquid-like clusters that formed prior to nucleation [18, 19, 20].

The formation of these clusters can be understood by Oswald's rule; which says that any crystallising system does not immediately take the path to the lowest possible energy state but instead first transitions to the state with the smallest free energy barrier [21]. Oswald's rule was assumed to be applicable for crystal polymorphs but can be generalised to describe the nucleation process also. Further phase transitions
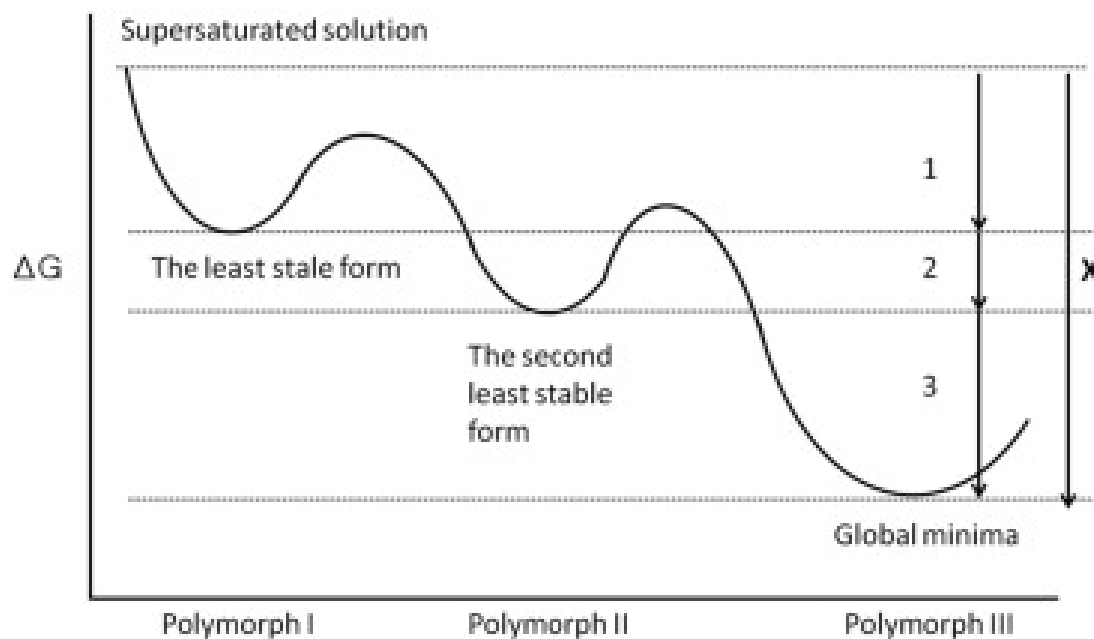
Figure 1.3: Free energy diagram of Oswald's rule for a crystal with three possible polymorphs. The diagram shows that there exist local minima in the free energy that represent the different polymorphic forms. A similar free energy diagram can be used to describe the two-step nucleation mechanism.

can still occur but the pathway taken should always minimises the overall free energy cost. It is assumed that between the amorphous phase and the crystalline phase the solute undergoes dehydration while changing structurally into a more ordered phase, though there is some discussion whether the process merely undergoes dehydration, or if there is a more complex chemical reaction [12].

With regards to liquid-precursors, there is still a lot of discussion about the relationship between the solution conditions and the the precursors. The size and rate at which these precursors agglomerate based on the degree of saturation would provide invaluable information on the kinetics of two-step nucleation [5]. In some cases it has even been shown that 'ageing' solutions is a necessary step in order to detect the presence of stable amorphous clusters [22]. This was in solutions that were supersaturated and yet after the formation of precursors spontaneous nucleation was not seen even after several days of observation [22]. This suggests that in some cases the precursors are metastable and require an external trigger to induce crystallisation. The presence of metastable

structures and other phenomena has lead to development of a more universal theory, namely non-classical nucleation.

1.2.3 Non-classical Nucleation

Two-step nucleation is based on the idea that between the bulk solution and the final crystalline phase there exists and intermediate stage. While this is broadly an accepted concept, research has shown that in some cases the intermediate stage can be subdivided into multiple states. This has been shown to be the case with metals in both solid and liquid conditions [23, 24] and colloidal simulations have indicated that the precursors undergo structural change over time [25]. While in some cases it has been possible to directly monitor the structural change in the amorphous clusters, many organic compounds have not received such treatment due to the difficulty of characterising and monitoring the pre nucleation stage [5]. This is often why two-step nucleation is simply referred to as multi-step nucleation.

There are also a myriad of other unique nucleation events that deviate significantly from both the classical and two-step nucleation theories. A review paper discussing recent advances in non-classical crystallisation highlighted that depending on the collision kinetics of the system and the molecular interactions could result in drastically different reaction kinetics. In the former case, unstable subcritical nuclei have been shown to collide and coalesce into a supercritical nucleus, but only in conditions where subcritical nucleation are plentiful despite a low degree of supersaturation [26]. The latter case is more prevalent for dipole solute molecules, the anisotropic attraction results in nuclei with non-spherical geometries, this results in varying kinetics for agglomeration dependent on the orientation of each molecule [16]. Phenomena such as the above examples has been collectively refereed to as non classical nucleation, it is known that they must be related to both CNT and multi-step nucleation but the connection is not clear based on the current literature.

As such, much of the research into nucleation theory is focused on developing *in situ* techniques that can monitor and characterise the pre nucleation stage, this would glean information on cases when both classical and non-classical nucleation is a possibility

[12].

1.3   In situ techniques for studying nucleation

There are several different phenomena [5, 12] that are not well described by any individual theoretical framework (CNT or multi-step nucleation for example). There is an increasing interest in probing the pre-nucleated solution.

One of the key conclusions is the need for the development of better *in situ* techniques for characterizing and imaging the nucleation pathways. Understanding which specific pathway is unfolding under a certain set of experimental parameters would allow one to develop a map of the thermodynamic landscape available to a pre-nucleation system. The challenge therein lies in developing experimental methods by which one can reproduce similar nucleation events and in turn use characterisation techniques to identify the pathway taken. The method not only needs to be repeatable for a single set of system parameters, but also needs to be flexible enough to replicate results regardless of the system parameters (i.e. varying supersaturation, temperature, and solute choice). There have been several different methods deployed to try and observe crystallisation at a microscopic scale.

1.3.1   Computer Simulations

While not a direct observation of nucleation events, computer simulations have proved an invaluable tool for studying and testing predictions about the pre-nucleated solution. By comparing the simulative nucleation rate to the expected rate given by current models, researchers can test newly developed theories and glean information about the microscopic parameters of a system.

The main challenge facing computer simulations is the issue of limited scope. Molecular dynamic simulations are constrained by their choice of time and length scale, for example simulations in a canonical ensemble face issues where the chemical potential is depleted to the point that the driving force for crystallisation is halted [27, 28], this can be addressed but requires an extensive increase in computational resources to

maintain the chemical potential equilibria. Like wise in most cases the choice of time scale is a crucial factor, shorter time scales provide a more accurate evolution of the solution; however, in some cases the time scale magnitude for crystallisation is often far greater than the time scale used in the simulation. This has led to more advanced sampling techniques that allow for longer time scales which has provided insights into the pre-nucleation solution stage and formation of pre-nucleated clusters [28].

The study of the pre-nucleated solution and the evolution of precursors has been aided greatly by the use of simulative studies. Early on it was shown in colloidal crystallisation that the structure of the precursor was time dependent; colloidal simulations showed that regardless of the molecular interactions between colloids the atomic packing pattern was predominately hexagonal centred, over time the packing became dominated by body centred packing in the case where the interactions were longer reaching [25]. They also confirmed that precursor formation was driven not by local density variations, but instead was driven by the local bond order of the colloidal precursors [25], providing strong evidence that the colloidal pre-nucleation clusters undergo rearrangement prior to nucleation. Further developments in $NaCl$ simulations have shown that by varying the density fluctuations the precursor structure could either be amorphous, the classical rock-salt structure, or a new structure similar to wurtzite. While this result is difficult to confirm it provides a important conclusion, that simulations can hint at new nucleation pathways that have not been confirmed experimentally. This means that computer simulations can not be merely used to confirm theories, but can be used to examine and search for novel results.

Overall computer simulations make up a core area of research in the study of nucleation. The technique is however limited, often struggling to examine nucleation over longer time scales or larger number of particles. While sampling methods and enhanced simulation techniques has alleviated this somewhat they are still far from being able to describe the behaviour of larger molecules undergoing nucleation.

1.3.2 Transmission Electron Microscope (TEM)

One of the more well known techniques used for direct observations of crystallisation dynamics is using transmission electron microscopy (TEM). The basic working principle involves creating a focused beam of electrons that are directed onto a target sample. Due to the wave-particle duality, the electrons can be treated as a unified beam of light, whose wavelength is dependent on the kinetic energy of the electrons. The wavelength of an individual electron is given by [29]:

$$\lambda_e = \frac{h}{\sqrt{2mE(1 + \frac{E}{2mc^2})}} \tag{1.5}$$

When incident on a sample the wave is scattered by the sample and can then be detected by an imaging screen that measures the difference in intensity between the scattered and transmitted beams. The advantage of TEM is that one can bypass the diffraction limit imposed by visible light, the maximum resolution that can be achieved by a microscope is given by [30]:

$$d = \frac{\lambda}{2NA} \tag{1.6}$$

where NA is the numerical aperture of the objective lens, and λ is the wavelength of light used to illuminate a sample. For a visible light LED with an average wavelength of 550 nm, the upper limit for an objective lens (NA of 1.2) is around 230 nm whereas a similar lens focusing an electron beam with an average kinetic energy of 100 keV will have a maximum resolution of just over 4 pm [30]. There is an upper limit to the maximum resolution possible as electron lens are far inferior to what modern optics can achieve [30] so there is a trade off between quality and resolution.

TEM technology has proven invaluable to the study of nucleation at an atomic level. The samples are often only a few hundred atoms thick in order to optimise the imaging results. Much of the supporting evidence for non-classical nucleation has been demonstrated via TEM [24]. For example when Cao *et al* observed the formation of amorphous atomic cluster using $\gamma-$Fe,Au, and Re; all three of which underwent

continuous transformation before eventually reaching an final ordered state [23]. The amorphous cluster did not immediately transition to an ordered structure, instead fluctuating somewhat randomly until eventually settling into a crystalline structure [23]. This was confirmed both in solid growth and liquid growth conditions [23, 31], suggesting that the non-classical nucleation path dominates in all cases of metal crystal formation [24]. Confirmation is necessary for different solute choices, as in the case of organic solids it is believed that non-classical nucleation only dominates in low supersaturations whereas classical nucleation is dominate at higher supersaturations.

TEM analysis has not been extended to the study of organic crystals, proteins, or simple salts at an atomic level however. The main reason being that organic materials can be damaged by the electron beam and therefore need to be frozen prior to being imaged [30]. This was used to study the polymorphic time dependence of glycine crystals, by varying the time prior to freezing Broadhurst *et al* showed that β glycine dominates initially but α- glycine is more stable after a longer period, γ-glycine was only found when allowed to dry over an hour on a glass slide [32]. While this was invaluable for showing the time scales with which polymorphs form, it doesn't provide much information on the kinetics of crystal growth as these were snap shots and not direct observations of the nucleation process.

Overall TEM analysis is invaluable for the study of atomic crystal growth, the secondary scattering from electron beams also allows for chemical and structural information to be gleaned from the target. This has given strong evidence for the non-classical nucleation theory, particularly in metal crystal formation. Due to the high energy of the electrons, organic materials have not received the same focus outside of cryoTEM analysis. Non-invasive methods are therefore necessary to gain an understanding of the crystal growth and formation of organic crystals, particularly when both classical and multi-step nucleation can occur.

1.3.3 Laser induced nucleation

From as early as 1996 it has been known that laser irradiation using a Gaussian beam is a viable method of inducing nucleation within a supersaturated solution [38]. The first

reported case was notable as it used a 1.064 μm laser, the glycine solutions would appear transparent to such a laser which would suggest there was no photo-chemical reaction. Later studies into this phenomena found that the laser polarisation can influence the polymorph produced. With circularly polarised light producing α-glycine and linearly polarised light forming γ-glycine [39]. Future research has found nucleation can be induced by 1 of 3 routes.

1.3.3.1   Non-Photochemical Laser Induced Nucleation

Non-photochemical laser induced nucleation (NPLIN) involves irradiating a solution with a pulsed laser [38, 39, 40]. The laser itself does not have to be heavily focused, instead irradiating a large region of the solution all at once. The choice of laser is of particular importance; with nucleation probability changing depending on the wavelength. A study of KCl solutions found that for lower intensities it was found that nucleation was favoured for lower wavelengths but above a peak intensity of $5 MW/cm^2$ the wavelength independence disappeared [41]. Measurements of the intensity prior and after irradiation confirmed this wavelength dependence was not due to any photo-chemical interactions [41].

Additionally, the choice of solute will effect the setup, not only because some solute's are unaffected, but also because there is a minimum laser threshold before nucleation is observed [39]. Several papers have debated the exact mechanism that induces NPLIN [39, 42]. A suggested theory to this is an optical Kerr effect: For anisotropically charged solute molecules the electric field can reorient them to match the propagation direction [39]. If enough molecules are co-aligned the free energy barrier is reduced to allow for ambient nucleation [42]. An alternative theory is the dielectric polarisation effect, in conditions that are unfavourable to cluster formation the polarising effect can stabilise the clusters [43]. As the cluster concentration rises so does the likelihood of nucleation [14].

Both theories are similar to one another but where the optical Kerr theory is limited to anisotropic solute molecules, the direct polarisation theory is more flexible. Regardless both theories struggle to explain why the phenomena is not observed in all

nucleation systems [44], such as acetamide which is similar to urea which does nucleate when irradiated [45]. One of the benefits of NPLIN is that since the pulses are relatively low in their intensity they can be fired off quickly in succession, allowing for continuos crystallisation set ups. Overall, the NPLIN phenomena needs further research to properly describe its effects. The mean pulse intensity needs to be kept relatively low (on the order of $0.1 - 0.01 GW/cm^2$), as high intensity pulses lead to a completely different nucleation mechanism.

1.3.3.2   High Intensity Laser Induced Nucleation

High intensity laser induced nucleation (HILIN), where the pulse intensity is on the order of several PW/cm^2 is far simpler a mechanism to explain in comparison to NPLIN. The production of nuclei can be wholly associated to a cavitation process within the target solution, where the laser focus results in thermo- cavitation and the subsequent pressure wave leads to a nucleation event around the focus of the laser [46, 47, 48].

What remains in question is both how the physical properties (size, polymorph, etc) are influenced by the cavitation process, and how the pressure change triggers nucleation. The former has already been investigated; by adjusting the focal position Ikeda *et al* could control the polymorph of indomethacin [49], this is not a universal method however, as it has also been shown that laser power can influence the crystal polymorph [50]. The latter is a tricky task to address due to the fact that these cavitation bubbles form and collapse in less than 100 μs. Using fluorescence dyed proteins, researchers were able to observe a sudden spike in fluorescence just as the cavitation bubble began to collapse, they suggested that due to the collapse of the cavitation bubble the protein clusters are brought together at the lasers focal point. However, while the fluorescence imaging indicates a local concentration increase it is difficult to quantify this change depending on the size of the bubble [44]. It has been suggested that in theory any solution can undergo HILIN [44], but proving such a theory requires a clear understanding of the phenomena both before and after cavitation occurs. Current research aims to combine experimental research with computer simulations to develop a universal theory, with the hope that this could also be related to NPLIN.

1.3.3.3 Trapping Induced Nucleation

Lastly, there is trapping induced nucleation, this is where optical tweezers come into play (see below). Due to the radiation pressure created by the focused beam, it is possible to manipulate the solute, this was demonstrated with amino acids such as glycine [51]. Whether or not a crystal forms is due to the location of the laser focus. When focusing on the cover slip, supersaturated solutions of glycine and D_2O were shown to create a dense liquid droplet of glycine and water [52, 53]. The dipole moment of the glycine molecules is too small to be influenced by the optical trap, as such it would suggest that larger aggregates are being manipulated. Applying dynamic light scattering analysis to the dense liquid region showed that it was populated by clusters that would consolidate together upon being focused by the optical trap [54]. Molecular simulations of glycine solutions showed that these clusters are unstable when using pure glycine below the saturation point suggesting that the clusters are formed due to glycine reaction products [55]. When the optical trap is moved from the cover slip to the air-solution interface, nucleation would occur before a dense liquid region could form [52]. Repeated experiments where the laser is focused on the air-solution interface have lead to a variety of different nucleation events. In some instances the nucleation occurs spontaneously after a short period of time [52]. Whereas allowing a solution to age results in the formation of amorphous precursors that when irradiated will nucleate immediately [22]. The precursors are only seen when the solution is irradiated by an optical tweezer and the growth rate can be controlled somewhat by varying the laser power [22]. The reason why nucleation is only seen at the air-solution interface is due to the limited molecular mobility close to the interface. Often tweezing experiments will use a hydrophilic coating to minimise the height of the solution droplet and further limit the molecular mobility [53, 54].

Walton and Wynne discussed a plausible model for how the tweezer focus could result in a nucleation event. Put simply, when the laser is focused at the solution the radiation pressure draws in solute material, creating a concentrated region of solute. This also creates a depleted region around the focus and raises the local temperature. When the laser is turned off the depleted region around the focus quickly cools back

to the ambient temperature. This sudden cooling allows for nucleation to occur just outside the focus.

Laser induced nucleation has the potential to be a viable method for *in-situ* studying of nucleation events. Using high numerical aperture lens one can localise the nucleation event to a specific region of the solution. The current issue is that the mechanism behind laser induced nucleation is not fully understood, as such it is rather difficult to modify the laser for different solution parameters. Instead it may be more effective to manipulate the solution using trapped particles. One way would to generate an optical torque on a trapped particle and therefore shear the surrounding fluid, a method that is already in common use for micro-rheological studies [56, 57].

1.4 Optical Tweezers

1.4.1 Background

Optical tweezing has been a field of applied optics ever since the 1980s when Ashkin [33] first showed that focused light was capable of trapping micron sized particles due to light exerting 'radiation pressure'. The working principle was that a light source such as a laser could trap small objects within a 2D plane, as long as the light source had an approximately Gaussian profile (colloquially called a Gaussian beam). Soon after, Ashkin showed that the introduction of a microscope objective would allow one to focus the light source to a diffraction limited point that would stably trap small objects within a confined volume [34]. This allowed Ashkin and others to study individual biological cells as the overall force was on the order of 10^{-12} N while being non-invasive to the internal structure. Later it would be used to probe microscopic properties such as the formation of colloidal aggregates [35] to the drag forces exerted by a pure vacuum [36, 37]. Due to the predictable behaviour of light, optical tweezers have become essential for measuring and exerting precise forces on the magnitude of pico-newtons allowing one to probe the material properties of the smallest materials.

1.4.2 Optical Torque and rotation

Electromagnetic fields can transfer both linear and angular momentum [58]; more accurately the field is said to have both orbital and spin momentum. Though there is some debate on how to decompose the total momentum into these two components [59, 60], for this project we do not need to calculate the exact quantities and will instead look at the broader effects of both components. Orbital angular momentum arises from the shape of the wavefront of the particular field in question; for simple Gaussian beams the wavefronts are uniform and equally spaced resulting in the typical radiation pressure that Ashkin and co demonstrated [34]. However, higher order modes of a Gaussian beam (for example: Laguerre-Gaussian modes) have non-uniform wave fronts meaning the orbital momentum has both angular and linear components; depending on the relative size of the target particle one can induce rotation, or orbiting [59, 61].

Spin angular momentum (SAM) is attributed to the spin density of the field, early research has shown that the spin density is non- zero for any beam despite the fact that the total SAM transferred to a medium is 0 [60, 62]. This has sparked debate if SAM is even a physical quantity as it does not aid in the transport of energy directly [62] and so cannot be directly observed in some cases despite being non-zero. This paradox is resolved by representing the wave as an array of spin momentum loops that cancel one-another out when the medium is homogeneous.Spacial inhomogeneities cause these spin loops to no longer be equal, resulting in non-zero spin density, anisotropic mediums (such as birefringent crystal lattices) experience a transfer of spin angular momentum, imparting an optical torque.

Birefringence is a material property often seen in crystalline materials, where the crystal lattice has a different structure dependent on its orientation. Since light is composed of waves that propagate in orthogonally to one another, a birefringent material will refract light differently depending on the light's polarisation. Therefore it can be said that the material has two separate refractive indices. For circularly polarised light this inhomogeneity results in a high degree of SAM being transferred to the target object [63, 64]. The greater the difference between the two refractive indices the greater the angular momentum transfer.

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The ability to transfer angular momentum has been exploited to rotate microspheres as fast as 1000 Hz while suspended in a bulk medium [64] as well as a means of measuring the local temperature and shear response of said medium [65, 66]. Calculating the optical torque applied to a birefringent material is given via:

$$
\begin{aligned}
\tau_{opt} = & -\frac{\epsilon}{2\omega_{laser}} E_0^2 sin(kd(\Delta n)) cos2\theta sin2\phi \\
& + \frac{\epsilon}{2\omega_{laser}} E_0^2 (1 - cos(kd(\Delta n)) sin2\phi)
\end{aligned}
\tag{1.7}
$$

Where Δn is the difference between the two refractive indices, θ is the angle between the particle's long axis and the polarisation vector of the local EM field, and ϕ is the phase shift in the EM field. The first term represents the 'orientational' torque which aligns the long axis of the particle with the electric field, when aligned $\theta = 0$ meaning the entire term is negligible for particle's with a stable orientation. The second term is due purely to the polarisation of the laser, for circularly polarised light $\phi = \pi/4$ thus maximising the torque transferred to the target particle. Eq. (1.7) is only applicable for particles with a known birefringence, but there are other mechanisms that result in optical torque.

A common example is shape induced birefringence. If a particle has an anisotropic shape, it is more susceptible to being polarised along its longer axis than its shorter axis. Consider, for example, an ellipsoid elongated along one of its primary axis' ($r_z > r_x = r_y$). In a plane polarised beam such a particle will align with the polarisation vector. Therefore, the particle will rotate as angular momentum is transferred along its long axis. One common feature, regardless of shape, is that a particle with shape birefringence will rotate when it lies perpendicular to the direction of propagation. This is seen most evidently with spherical dimers [36, 67] but even for elliptical particles rotational motion is only detected when their long axis is not aligned with the direction of propagation [68, 69].

Often the optical torque experienced is far greater than similar spherical particles that are birefringent [59]. Currently spherical dimers are being rotated in vacuums to measure quantum forces and torques [36, 67]. There are some alternative cases where

particles are rotated while not being aligned in the plane of the polarisation. However in these cases their shape is often specifically engineered to scatter light in such a way that the net momentum change always occurs in one direction regardless of the laser polarisation [70].

Other examples of optical torque is when an anisotropic particle is aligned with the beam's direction of propagation (in which case $\theta = \pi/2$ and the first term disappears). This is analogous to an optically trapped sphere, where alongside a restoring force the particle also experiences a restoring torque. This seemingly random rotational motion is referred to as libation [59],often in typical suspension trapping situations (where the particle is suspended in a fluid) the rotational motion is washed out by the translational motion. As such, many experiments elect to trap in low pressure environments to precisely measure the optical torque being exerted by the optical trap [36]. This has lead experiments to try and achieve '0 kelvin' motion, where by trapping a silica dimer they were able to restrict its motion using 3 optical traps simultaneously. Despite this, they found that the dimer's rotational motion about its long axis could not be controlled leading to the undesired rotational modes [71].

The detection and measurement of optical torque is still a field of intense research, not only does it have potential to understand quantum fluctuations in a particle's motion but also allows for the creation of more effective micro-rotors. The latter being especially pertinent for understanding the behaviour of fluids experiencing localised shearing.

1.4.3 Characterisation of rotational motion

Rotational motion about a single axis is easiest to account for. When the power spectra of elliptical polystyrene particles was fitted by Yogesh *et al* [72], they assumed that the rotational motion was purely in the transverse plane. As such they did not have to account for any variance in the trapping strength due to orientation nor did they need to consider non-periodic rotational behaviour. In the case where rotational motion is stochastic the problem is more complex. For example, when an optical fibre trap characterisation technique was implemented by Saffron *et al* [73, 74], they were able

to use dynamic light scattering to characterise both the axial and lateral trap stiffness acting on microspheres. The only drawback admitted to in their work was that the technique was constrained to isotropic scatters as their theoretical model for describing the auto-correlation function was predicated on the fact that any variations in the signal are due to the particles translational motion within the confines of a cylindrical trap [73]. Where the upper limit of the cylindrical trap is given by the Rayleigh range ($z_R = n\omega_0/NA$). However, as demonstrated by the results from Chapter 4.1, the axial traps of spherical aggregates is often situated far beyond the Rayleigh range (for a 1.2 NA laser this is $\pm 5.985\mu m$).

1.5   Shear induced Nucleation

It has long been known that fluid shear rate plays a role in influencing nucleation; however, the exact relationship between shear rate and nucleation rate has only been recently understood for specific solutions. Theoretical research into shear induced nucleation suggests that there should be a slight increase in the nucleation rate at low shear rates, reaching a maximum increase in nucleation rate, and then at higher shear rates the nucleation rate begins to drop off.

This has been shown theoretically for both simple colloidal [75, 76, 77] and ice crystal formation [78]; however, no experimental work into these systems has been conducted to confirm these theories. There is some experimental evidence for this phenomena in simple salt and protein solutions - though the authors emphasise that mechanical agitation cannot be ruled out - there has not been a exhaustive study into the shearing effects apart from in glycine solutions. In [76] it was found that a shear rate of around 3000 s^{-1} was the maximum shear rate that would yield the highest nucleation rate. Using the theoretical model established in [75, 79] which modifies the CNT to account for the effects of a nucleus undergoing shearing, accounting for the fact that a nucleus' growth is undergoing competition between flow-mediated molecular transport and the strain applied by the flow field which inhibits the growth of the nucleus. There central conclusion (from both the theoretical and experimental results) is that there is

an optimal shear rate in which the nucleation rate is maximised.

However, a question that arises from this result, if there is a optimal shear rate in which molecular transport is maximised and strain is minimised, then surely there should also be a shear rate in which the molecular transport and strain are equal - allowing one to suspend a nucleus at a constant radius. In this scenario, the molecular transport would prevent the nucleus from dissolving, but the strain would prevent the nucleus from growing. This however would require one to be able to apply a continuous shear rate to a targeted nucleus with high precision, there is also no model for an individual nucleus in a continuous fluid field.

1.6   Significance of Thesis

As I have hoped to make clear in the above introduction, the current state of nucleation theory is rather cumbersome at a micro-level. Models such as CNT and multi-step nucleation are not sufficient for describing the myriad of potential pathways nucleation can go down. As suggested by some review articles, the best way to address this is by developing *in-situ* methods that can study the pre nucleation phase in greater detail [5]. Furthermore, the ability to localise nucleation allows for better characterisation of the kinetics of crystal growth. Laser induced nucleation stands to be an ideal method to study the nucleation of organic compounds, as the laser output can be concentrated to a small area [44] while not altering the organic compound - as is the case with TEM. However, laser induced nucleation in itself is also poorly understood, meaning trying to study the nucleation kinetics is difficult if the effect of the laser. With this in mind we suggest that we instead utilise another application of optical tweezers, manipulation of micro-scale particles to induce nucleation around a small localised area. The most common method for manipulating a fluid is by localised fluid shearing, which has been shown to directly influence nucleation rates [76]. One challenge lies in the fact that its clear that the local fluid properties have a direct influence on the likelihood of laser induced nucleation from occurring [44, 45, 53, 22].

A way around this would be to try and induce the local fluid without directly relying

on the electromagnetic field. Optical tweezers can reliably do so already by applying an optical torque to a trapped particle in order to induce fluid flow [56, 57]. It's already well documented that shearing will enhance nucleation events at a macro-level [76]. Micro-rheological studies using optical tweezing have been more interested in probing the local viscosity rather than try and use it as a means of shearing the fluid to induce crystal growth.

1.7 Overview

Overall the aim of the PhD is to study viability of using micro-rotors to generate localised fluid flow around the beam focus. The results are reported in chapter 3, this is then followed by experimental work where we use a galvano- mirror to move the beam and hence generate shear flow. While overall unsuccessful the addition of a moving beam focus showed that the growth of a nucleus can be localised around the trap focus. This presents a new insights for controlling and studying the growth of a newly formed nucleus by precise movement of the trapping focus.

The latter chapters cover computer simulations into the behaviour of microscopic spherical dimers in an optical trap. Prior research into dimers using back focal plane interferometry has mostly considered their trapping behaviour to be similar to a single sphere but with a difference in trapping strength. Computer simulations reveal a host of new behaviours dependent on the dimer's size, orientation, proximity to the trapping focus, and even the polarisation of the trapping beam. The latter in particular suggests that multi-spherical particles can act as sophisticated micro-rotors.

However, this raises a its own host of experimental challenges, namely how do we characterise the behaviour of an arbitrary particle. Relying on current characterisation techniques is not possible as they are predicated on the trapping object to behave like an isolated sphere. Two novel methods of measuring rotational motion are discussed in chapter 5; firstly via a novel detection fibre method that allows for instantaneous measurements of the orientational behaviour of optically trapped ellipsoids/dimers; and secondly we create a simulative quadrant photo diode that replicates laboratory results,

utilising linear regression techniques we measure the change in orientation in order to measure the optical torque applied to a non-birefringent particle.

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