A Mechanistic Model for Particle Breakage within Agitated Crystallization Systems

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Abstract

Throughout the field of particulate processing the application of modelling techniques to predict, optimize, or otherwise enhance processes is widespread. Perhaps the most common technique when it comes to modelling particulate populations themselves and how they interact with the physical systems they are contained in is the Population Balance concept formalized by Randolph and Larson (1971). Through this concept it is possible to formalize mathematical models of general particulate mechanisms such as dissolution, growth, nucleation, agglomeration, and breakage. However, while the mathematical formalization of the general models is well understood in terms of their functional forms (Hounslow, Pearson and Instone (2001); Kumar (2006); Kumar and Kumar (2013); Qamar and Warnecke (2007); Qamar et al. (2009), for example) a challenge remains in developing robust physical models for each mechanism that can accurately describe experimental observations.

Presented in this work is a new breakage kinetic that incorporates fundamental hydrodynamic factors of the agitation vessel itself, and material response characteristics of the crystal materiel undergoing agitation. Combined, these factors provide a realistic breakage model for pharmaceutical particulate processes involving typical agitation techniques. Ultimately, this kinetic serves to expand the state-of-the-art for modelling agitated crystallization processes, and provides the foundations for further understanding in crystal-crystallizer interactions.

For the hydrodynamic factors, the role of boundary layer effects on particle trajectories and impact rates was investigated (Tyrrell et al. 2018). Through the use of shadowgraphy imaging it was shown that there exists a critical Reynolds threshold, below which collision between particles and an
impeller blade is unlikely. Furthermore, those particles that do collide experience only a fraction of the nominal impeller tip-speed. Thus, this gives credit to the presence of a squeeze film boundary layer cushioning impacts at the impeller and around probes/baffles. As a result, the actual impact rate of particles with a typical crystallization system is often much lower than expected as the hydrodynamic conditions serve to protect the crystals from collision events.

For the material response factors, the breakage characteristics of crystals when impacting a target surface, such as a stainless steel impeller blade, were investigated (Tyrrell and Frawley, 2018). Crystals were accelerated towards a target and impacted at various speeds and across a range of crystal sizes. This allowed construction of a failure probability heatmap, outlining the probability of damage occurring to the crystal after an impact had occurred. From this, the probability of failure for any crystal size and velocity pair was extracted and compared to theoretical forms for the expected failure probability distributions. Good agreement was found between the proposed failure model and the observed failure rates.

Lastly, the hydrodynamic and material response characteristics were combined using a physically relevant rate expression based on the characteristic circulation time of the system. The resulting expression forms a new breakage model for particulate processing. To validate this model, Particle Size Distributions (PSDs) of three Active Pharmaceutical Ingredients (APIs) were gathered after two separate agitation experiments. A Genetic Algorithm (GA) was then used to investigate if the proposed hydrodynamic and material response factors could accurately explain the process outputs. Overall, it was found that the model performed well in parameterizing for the output PSDs, returning realistic parameters for both the hydrodynamic and material response terms in the model.
List of Publications


Acknowledgements

To my parents, family, and friends.
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## Nomenclature

### Latin Letters

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
<th>Unit</th>
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<tbody>
<tr>
<td>( b(x, x') )</td>
<td>Fragment distribution of sizes in ( x ) produced from breakage of size ( x' )</td>
<td>( m^{-3} )</td>
</tr>
<tr>
<td>( C^* )</td>
<td>Saturation concentration</td>
<td>( kg/m^3 )</td>
</tr>
<tr>
<td>( C_D )</td>
<td>Particle coefficient of drag</td>
<td>–</td>
</tr>
<tr>
<td>( C_{\infty} )</td>
<td>Bulk supersaturation</td>
<td>( kg/m^3 )</td>
</tr>
<tr>
<td>( C_I )</td>
<td>Crystal-liquid interface supersaturation</td>
<td>( kg/m^3 )</td>
</tr>
<tr>
<td>( E_{c,t} )</td>
<td>Crystal (c) or target (t) (Elastic) Young’s Modulus</td>
<td>–</td>
</tr>
<tr>
<td>( E_a )</td>
<td>Activation energy for crystal growth</td>
<td>( J/mol )</td>
</tr>
<tr>
<td>( f_c )</td>
<td>Vessel circulation frequency</td>
<td>( Hz )</td>
</tr>
<tr>
<td>( F_{cr} )</td>
<td>Critical failure load associated for crack propagation during collision event</td>
<td>( N )</td>
</tr>
<tr>
<td>( F_I )</td>
<td>Impeller flow number</td>
<td>–</td>
</tr>
<tr>
<td>( G )</td>
<td>Growth rate of internal particle size coordinate</td>
<td>( m/s )</td>
</tr>
<tr>
<td>( I )</td>
<td>Integer value of total number of discrete numerical cells such that ( 1 \leq i \leq I )</td>
<td>–</td>
</tr>
<tr>
<td>( k )</td>
<td>Hertzian indentation constant</td>
<td>–</td>
</tr>
<tr>
<td>( k_{d,s,g} )</td>
<td>Growth kinetic coefficients for diffusion (d) and surface integration (s) steps, and general power-law growth (g)</td>
<td>( m/s )</td>
</tr>
<tr>
<td>( K_{IC} )</td>
<td>Material fracture toughness</td>
<td>( Pa.m^{1/2} )</td>
</tr>
<tr>
<td>( L_{\text{break}}^\pm )</td>
<td>Population Balance breakage operator</td>
<td>–</td>
</tr>
<tr>
<td>( m )</td>
<td>Weibull modulus for CDF of Weibull distribution</td>
<td>–</td>
</tr>
<tr>
<td>( \hat{n}_i )</td>
<td>Numerical approximation of averaged cell-centred density function ( n_i )</td>
<td>( -, m^{-3} )</td>
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<tr>
<td>( N )</td>
<td>Impeller RPM</td>
<td>( rev/min )</td>
</tr>
<tr>
<td>( n, n(t, x) )</td>
<td>Population Balance density function</td>
<td>( -, m^{-3} )</td>
</tr>
<tr>
<td>( N_0 )</td>
<td>Complement of particle breakage selection function</td>
<td>–</td>
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**Nomenclature**

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<thead>
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<th>Description</th>
<th>Units</th>
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<tr>
<td>$p_k^i$</td>
<td>Discretization integral limits for breakage equation</td>
<td>$x^3$</td>
</tr>
<tr>
<td>$Q$</td>
<td>System circulation (pumping) capacity</td>
<td>$m^3/s$</td>
</tr>
<tr>
<td>$q$</td>
<td>Numerical mesh refinement parameter for smallest size ranges</td>
<td>–</td>
</tr>
<tr>
<td>$R$</td>
<td>Ideal gas constant</td>
<td>$J/mol.K$</td>
</tr>
<tr>
<td>$R_i$</td>
<td>Population impact rate</td>
<td>$Hz$</td>
</tr>
<tr>
<td>$Re$</td>
<td>Particle Reynolds number</td>
<td>–</td>
</tr>
<tr>
<td>$S$</td>
<td>Particle breakage selection function</td>
<td>–</td>
</tr>
<tr>
<td>$S(x)$</td>
<td>Final breakage selection rate of the system for each particle size $x$</td>
<td>$Hz$</td>
</tr>
<tr>
<td>$Stk$</td>
<td>Particle Stokes number</td>
<td>–</td>
</tr>
<tr>
<td>$u_f$</td>
<td>Particle velocity corresponding to $1 - 1/e = 63.2%$ probability of failure for given particle size</td>
<td>$m/s$</td>
</tr>
<tr>
<td>$v_{ortho}$</td>
<td>Component of particle impact velocity orthogonal to impacting surface, i.e. target-normal velocity.</td>
<td>$m/s$</td>
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**Greek Letters**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Units</th>
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<tbody>
<tr>
<td>$\alpha_{1,2}$</td>
<td>Exponential Correction indices for critical failure load modification</td>
<td>-</td>
</tr>
<tr>
<td>$\alpha_r$</td>
<td>Growth kinetic solution saturation dependency term</td>
<td>-</td>
</tr>
<tr>
<td>$\beta_{1,2}$</td>
<td>Exponential Correction coefficients for critical failure load modification</td>
<td>$N$</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>Interfacial tension for primary homogeneous nucleation</td>
<td>$J/m^2$</td>
</tr>
<tr>
<td>$\eta_0$</td>
<td>Reynolds threshold value for hydrodynamic efficiency</td>
<td>–</td>
</tr>
<tr>
<td>$\eta_{Re}$</td>
<td>Reynolds coefficient for hydrodynamic efficiency</td>
<td>–</td>
</tr>
<tr>
<td>$\Theta$</td>
<td>$n$-dimensional parameter vector for optimization algorithm</td>
<td>–</td>
</tr>
<tr>
<td>$\Lambda$</td>
<td>Continuous numerical domain space</td>
<td>–</td>
</tr>
<tr>
<td>$\mu_f$</td>
<td>Lognormal Fragment distribution centre location</td>
<td>$m^3$</td>
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<td>$\mu_k$</td>
<td>$k^{th}$ order moment of population balance density function</td>
<td>–</td>
</tr>
<tr>
<td>$\nu(y)$</td>
<td>Total number of fragments generated by particle of size $y$ after a breakage event</td>
<td>#</td>
</tr>
<tr>
<td>$\nu_{c,t}$</td>
<td>Crystal (c) or target (t) Poisson’s Ratio</td>
<td>–</td>
</tr>
<tr>
<td>Symbol</td>
<td>Description</td>
<td>Unit</td>
</tr>
<tr>
<td>--------</td>
<td>-------------</td>
<td>------</td>
</tr>
<tr>
<td>( \rho_c )</td>
<td>Crystal material density</td>
<td>( \text{kg/m}^3 )</td>
</tr>
<tr>
<td>( \sigma_f )</td>
<td>Lognormal Fragment distribution standard deviation</td>
<td>( \text{m}^3 )</td>
</tr>
<tr>
<td>( \sigma_{\text{rel}} )</td>
<td>Relative supersaturation: ( \frac{C - C^<em>}{C^</em>} )</td>
<td>–</td>
</tr>
<tr>
<td>( \tau )</td>
<td>Particle relaxation time</td>
<td>( \text{s} )</td>
</tr>
<tr>
<td>( \phi_{\text{hydro}} )</td>
<td>System hydrodynamic efficiency</td>
<td>–</td>
</tr>
<tr>
<td>( \psi(\Theta) )</td>
<td>Fitness function returning an indication of solution quality for given parameter vector ( \Theta )</td>
<td>–</td>
</tr>
<tr>
<td>( \psi_{\text{circ}} )</td>
<td>System circulation efficiency</td>
<td>–</td>
</tr>
<tr>
<td>( \omega_{1,2} )</td>
<td>Fragment distribution weights for modes 1 and 2</td>
<td>–</td>
</tr>
<tr>
<td>( \Omega_i )</td>
<td>Discrete sub-region of ( i^{th} ) space such that ( \Omega_i \in \Lambda )</td>
<td>–</td>
</tr>
<tr>
<td>( \omega_{i}^b )</td>
<td>Discretization weight for breakage birth operator in cell ( i )</td>
<td>–</td>
</tr>
<tr>
<td>( \omega_{i}^d )</td>
<td>Discretization weight for breakage death operator in cell ( i )</td>
<td>–</td>
</tr>
</tbody>
</table>
Nomenclature
1

Introduction

In this introductory chapter an outline of pharmaceutical crystallisation is presented alongside the main research aims and objectives of the completed work. Finally, the thesis outline is detailed on a per-chapter basis. Subsequent literature reviews and theoretical discussions on the methods and analysis will be carried out in chapters 2, 3, and 4. Chapters 5 and 6 detail the experimental and numerical results obtained and their discussion therein.

1.1 Crystallisation

Throughout the pharmaceutical industry a crucial step in the production of any solid form “Active Pharmaceutical Ingredient” (API) is crystallization. This step effectively allows us to yield a highly pure form of the desired API while also allowing the tailoring of crystal size and morphology. Having control over these aspects becomes important for downstream processes such as isolation, drying, packaging, and bio-availability/dissolution in the body. However, there exists a number of mechanisms at play during any crystallization step that often serve to make difficult the task of controlling the resulting product and its Particle Size Distribution (PSD). In order to better understand the roots of these complications it is necessary to cover some introductory aspects of crystallization.

Firstly, one may think of crystallization as a transformative process whereby one seeks to extract specific dissolved substances from a solution in order to obtain the purest solid form of that dissolved substance. Often, it is a pure solid dosage form of
desired API molecule that is of interest. In order to do this, one can saturate some solvent with the desired molecule and subsequently provide some means to coax the API molecules out of solution into their solid form. This may be enabled through various means, such as cooling or anti-solvent addition, in either seeded or unseeded crystallization systems [Myerson and Ginde, 2002]. The goal of any crystallization method is therefore to provide some pathway for the solid form of the API molecule to precipitate out of a supersaturated solution in a controlled manner. Importantly there exists two fundamental crystallization mechanisms when considering how a solute molecule may reach a solid form: nucleation, and growth.

Crystal growth is a relatively straightforward process whereby solute molecules adhere to pre-existing clusters/crystals in the system, thus providing a pathway to its solid form. Growth is a well studied mechanism with a wealth of literature describing theoretical and empirical growth rate laws for common systems (discussed in section 2.1). Nucleation is a much broader pathway with multiple proposed mechanisms of action, discussed further in section 2.2. However, nucleation and growth only describe how the solute molecules may crystallize out of solution into their solid form. The conditions crystals experience in their solid form thereafter is yet to be discussed. Considering that the crystallisation vessels need to be stirred or otherwise agitated in order to ensure good mixing of the system it become apparent that crystals may experience collision with the crystallizer itself, with probes, baffles, or neighbouring crystals themselves. These collisions may then result in the manifestation of agglomeration or breakage of crystals for certain operating conditions. The result of this is that the modelling of crystallization systems is often compounded by the simultaneous action of several mechanisms serving to confuse the appropriate choice of kinetics for each mechanism at play.

A useful way to interpret the problem at hand is to consider a crystallization system in terms of a mass or volume conservation. Consider that there is no net volume flux in terms of inlet/outlets to the system volume. Growth, nucleation, agglomeration, and breakage can then be conceptualized in terms of their effect on the volume-based particle size distribution. Considering the case of pure growth in a non-nucleating system it is expected only that the PSD shift rightward as in fig.1.1. In this way, growth is seen to act in a distinctly advective sense on the PSD. Of course then for a
1.1 Crystallisation

system in pure growth one may quite easily predict its behaviour, however, in reality crystallization processes often present with some degree of crystal breeding in addition to growth. This breeding phenomenon may arise from primary/secondary nucleation mechanisms, or may also be the result of some attrition/breakage occurring in the reactor.

Referring back to the volume conservation concept, nucleation may be considered as a source term; taking mass from solution and adding it to the crystal population’s mass in the solid phase. Breakage may be treated as a sink-source term with no effect on the solute concentration in solution, only serving to re-distribute the solid phase’s mass along its size coordinate. In this way, the system is effectively a number of mass conservation laws to uphold with regards as to how mass is proportioned in the system as the crystallization process goes on. Immediately, one might recognise that tracking these sink-source terms accurately may become quite an intensive task for complex systems with multiple growth, nucleation, breakage, and/or agglomeration pathways. This is particularly important when considering that secondary nucleation and crystal breakage are essentially two possible mechanisms of the same generalized crystal breeding pathway, i.e. both contribute to a source term in the overall volume conservation. As such, for systems where crystal breeding may result in undesirable PSDs or more generally an unpredictability in the system it would be useful to have a tool to identify what mechanism is responsible for breeding these new crystal nuclei.

A commonly held assumption is that crystal breeding can be appropriately modelled using attrition-based secondary nucleation kinetics [Evans et al. 1974; PSE 2015]. These effectively state that new nuclei are formed at a rate proportional to some collision rate in the system. However, recently it has been proposed that a surface-shear mechanism may be responsible for generating nuclei at a surprising rate [Anwar et al.]
1. INTRODUCTION

Further to this, experimental observations have clearly shown that in the absence of breakage the rate of secondary nuclei generation within the system remains independent of agitation rates \cite{DeSouza2016}. Indicating that a surface breeding mechanism was favoured over traditional attrition breeding pathways. It is clear then that there exists some gap in knowledge as to particle breakage behaviour within crystallization processes for pharmaceutical products. As such the aim of this work is to quantitatively describe this behaviour and investigate how crystal breeding through breakage/attrition pathways may be an unreliable model for a majority of crystallization systems.

Taking the example of a seeded batch crystallization, crystal breeding may be explained through fluid shearing yet also seemingly through attrition nucleation. For a seeded batch crystallization, start with some supersaturated solution where the solvent fluid is laden with solute molecules of our desired API that are essentially waiting for some opportunity to form an ordered crystalline solid of said API. In order to kick-start this ordering processes, “seed” crystals are added that the dissolved solute molecules adhere to and result in the overall growth of our initial seed population. The seed population is itself the desired crystalline form of the API, as such the resulting population from the crystallization-growth reaction will be of the same form as the initial seed. Using the assumption of surface nuclei shearing \cite{Anwar2015, DeSouza2016, Threlfall2016} it is stipulated that the rate at which new nuclei are born into the system is some function of how many crystals experience enough fluid shear to separate any weakly bound nuclei on their surface. On the contrary, one could also argue that new crystals may be born into the system at some rate proportional to the rate of attrition or collisions in the system. Both theories seem to make intuitive sense, but which one is accurate? In order to answer this question, it makes sense to investigate if there exists a test that may disprove one (or both) of the statements. Since there exists literature supporting the theory of a surface shearing mechanism, it therefore makes sense to investigate whether crystal breeding may also be explained via breakage/attrition pathways. In doing this the work may clarify the case for a surface shearing model. In addition, a robust methodology for modelling the behaviour of particle breakage in the context of pharmaceutical processes is provided, an area that has escaped rigorous investigation to date.
1.1 Crystallisation

Additionally, crystal breakage is not only a concern for when the isolation of nucleation or breeding mechanisms is of interest. The production and development of solid-form pharmaceutical drug products is invariably burdened by the issue of unwanted or uncontrollable crystal breakage. Active Pharmaceutical Ingredients (APIs) must not only satisfy purity standards, but also crystal shape and size specifications, with the final Particle Size Distribution (PSD) of the product staying within acceptable measures. These are often stated as various characteristic size limits such as the Sauter Mean Diameter ($D_{3,2}$), or De Brouckere / Volume Mean Diameter ($D_{4,3}$). Additionally, percentile limits such as $D_{10}$, $D_{50}$, and $D_{90}$ may be imposed in order to limit the population in the 10th, 50th, and 90th percentiles of a distribution, respectively. In cases of large-scale crystal breakage any or all of these measures may be violated as, while breakage inherently conserves mass, it redistributes crystal mass about lower size classes throughout the process.

Production of a desired API typically requires crystallization, isolation, and drying steps. Each of these processes may then bring with it a set of harsh mechanically abrasive environments. The resulting time-evolution of the PSD will therefore depend on not only accurate kinetics for mechanisms such as growth and nucleation, but also on reliable kinetics for crystal breakage. Moreover, as breakage itself essentially forms new crystal nuclei as fragmentation occurs this process may serve to compound crystal nucleation growth kinetics (De Souza et al., 2016; Evans et al., 1974; Srisanga et al., 2015), increasing unpredictability in the system. Furthermore, as modelling methods such as Population Balances (Randolph and Larson, 1971) are often used to predict process outcomes given changes in operating conditions or for optimization exercises it becomes clear now that developing reliable breakage kinetics is paramount for accurate process control and optimization.

Typically, modelling methods for crystal breakage include various types of functional forms for breakage kinetics, as reported by multiple authors (Hounslow, Pearson and Instone, 2001; Rachah et al., 2016; Szilágyi et al., 2015). Formally these functions describe selection and distribution functions that govern the number of particles that may break and their subsequent fragmentation distributions. There exists a number of methods for the determination of these functions and their parameters. Optimization/minimization techniques, such as those employed by Bari and Pandit (2018) and
1. INTRODUCTION

Pohar and Likozar (2014), are a very robust method for extraction of process kinetics and model validation. However, they require advance knowledge of the system and rarely serve to explain mechanisms mechanistically as high-dimensional parametrization may not always provide a realistic interpretation of the mechanisms at work. Recent studies utilizing a combination of numerical and experimental methods to determine the breakage characteristics of Silicon Carbide (SiC) particles have been carried out (Hadavi et al., 2016). While a powerful method, pharmaceutical materials have yet to be investigated to such an extent. Repeated impacts of pharmaceutical crystals have also been studied (Biscans, 2004; Marrot and Biscans, 2001), yielding information about how crystal mass progresses during fragmentation, however the failure probabilities of these crystals was not reported. Investigations of crystal velocity profiles approaching a target wall have been carried out by Tyrrell et al. (2018). However the study was concerned primarily with the boundary layer effects near the target plane in a liquid-based system, and did not yield any detailed data on any observed fragmentation. Further numerical and experimental studies determining the expected impact velocities and frequencies of crystals in a stirred vessel (Derksen, 2003; Kee and Reilly, 2004) have provided valuable information on the environment crystals often encounter during crystallization processes. Empirical size-velocity relationships for breakage selection functions and fragmentation distributions of pharmaceutical powders have been reported (Kwan et al., 2004; Meier et al., 2008), and provide useful data on the observed breakage probabilities for range of crystal materials. Experimental breakage rate parameters have been extracted successfully by Bao et al. (2006), however these kinetics tell us little about the fundamental mechanism of breakage occurring. Simplified binary breakage mechanisms used to model crystallization of high and low-aspect ratio crystals have also been proposed (Borsos and Lakatos, 2014; Lu and Wang, 2006). However, this two-body equal-volume method is typically not accurate for the vast majority of realistic breakage and fragmentation in pharmaceutical processes. Ghadiri and Zhang (2002); Zhang and Ghadiri (2002) proposed a theoretical model of chipping for crystalline particles, illustrating underlying mechanisms that may be incorporated into the construction of mechanistic section functions. Furthermore, Vogel and Peukert (2003) described a model for the prediction of breakage selection functions of limestone, glass spheres, and various polymers. It was shown that if the material properties are known it may be possible to theoretically determine any failure probability from fundamental
material properties. However, it remains to be investigated how well this theory can be applied to pharmaceutical materials as the scale of these particles introduces significant variability in breakage characteristics, as will be demonstrated here.

1.2 Industrial Scale Processes

A naive methodology for industrial scale crystallisation might follow the lines of trial and error. Small tweaks are made to the crystallisation process in order to iteratively tailor the final Particle Size Distribution (PSD). This trial and error solution can be costly and aside from the financial aspect, it is simply an inefficient solution to the problem. A much more elegant solution would be to develop a model for the process that could take various initial conditions and monitor the resultant PSD as an output. Fortunately, the Population Balance (PB) equations developed by Randolph and Larson (1971) provide a platform for modelling particulate systems such as these. However, the problem does not in-fact lie with the mathematical description of the problem, rather in the development of accurate growth and crystal breeding kinetics that govern the final PSD.

The mechanisms of crystal breeding are an area of great interest and provide the basis of this thesis. A major issue with large scale operations is the requirement for scale-independent models: kinetics that can take into account the vast difference in scale between lab and plant reactors. Developing kinetics based on the fundamental breeding mechanisms occurring during crystallization processes serves to address the issue of scale, as ideally any fundamental or mechanistic kinetic would have good scalability due to its generality. Through this it is possible to design kinetics that fit the actual physical phenomena rather than regressing data and inferring kinetics based on representative samples of the final product. Being able to accurately predict the PSD of a given crystallisation process would vastly increase the efficiency of industrial scale operations and greatly reduce the cost of scale-up from lab-to-plant processes.

1.3 Research Objectives

The goal of this thesis is to investigate the influence of attrition/breakage on crystal breeding during crystallization processes. This will be reasoned via experimental
1. INTRODUCTION

observations and further supported by the development of a robust numerical model for solving the PB equations for a stirred batch reactor with attrition/breakage. As such, it will formulate the limiting conditions required for breakage and discuss their implications in attrition breeding models. Further to this, the mathematical model will provide a theoretical approach to illustrating the behaviour of particle breakage within crystallization systems. As such, the result will be both an empirical description for particle breakage with a theoretical model for predicting breakage behaviour. The research objective can be broken down thus:

- Investigate the relevant factors for crystal breakage within crystallization systems, considering both local hydrodynamics and physical material characteristics.

- Identify if crystal breakage may be responsible for the generation of large numbers of new crystal nuclei, i.e. crystal breeding.

- Investigate the hydrodynamic response of particle-fluid interactions and report driving factors with regards to collision events.

- Develop realistic breakage kinetics that can successfully predict the probability of crystal failure for a given collision event.

- Construct a sensible kinetic rate expression to convert experimental observations into useful kinetic parameters for PB breakage modelling.

- Develop a robust model for solving the PB equations for a stirred batch reactor concerning crystal breeding via attrition/breakage.

- Develop a methodology for parametrizing predictive models with experimental data.

- Implement the new PB model and evaluate its performance in explaining crystal breeding phenomena.

- Comment on the expected breakage trends versus the observed and predicted trends, thereby closing the discussion on crystal breeding through attrition/breakage pathways.
1.4 Thesis Outline

The remaining chapters of this thesis are as follows:

*Chapter Two* presents the theoretical background to the breakage model developed in this thesis. Additionally, an review on the remaining mechanisms of interest during a crystallisation process is given, namely: Growth, Nucleation, & Agglomeration. While breakage is the primary concern here, the other mechanisms have been covered for the sake of completeness.

*Chapter Three* outlines existing numerical methods and describes the finite volume method used to solve the PB equations used in Chapter 6. The MATLAB code for this model is given in *Appendix A*.

*Chapter Four* presents the experimental methods used in order to identify and describe the governing factors for the breakage model. Thus, the goal of this chapter is to introduce the methodology by which particle breakage may be studied in order to ascertain information on these parameters. This includes nano-indentation, shadow-imaging, and data analysis techniques. The Python scripts for data processing are given in *Appendix B*.

*Chapter Five* describes the experimental data collected and development on the breakage model’s hydrodynamic and material response factors. Additionally, it is outlined how these parameters may be implemented in the above PB solver to model breakage processes within crystallization systems, and perhaps for generalized comminution within particulate processing steps. Results validating the theoretical basis given in *Chapter 2* are illustrated and discussed.

*Chapter Six* implements the new PB breakage model in a Finite Volume Scheme (FVS). Model validation and optimization algorithm choices are given here with detail discussion on model construction and its performance with experimental data. MATLAB code for the numerical data is given in *Appendix A*.
1. INTRODUCTION

Chapter Seven provides conclusions and summarizes the work carried out in this thesis and provides an outlook to potential future work.

A series of documents detailing the MATLAB and Python code used in this work have been included in the Appendix section of this thesis. For environmental and compactness reasons, the code itself is not printed, but given in the accompanying CD and USB drives. The directories are as such:

- **Appendix A** presents all MATLAB code used for the numerical model presented in Chapter 2 and Chapter 6. All experimental data files are contained in the attached directory. Model solution optimization files are given with both the capability to parse for direct results, or can be run again directly if desired.

- **Appendix B** presents all Python scripts used to process shadowgraphy data. The histogramming and Kernel Density Estimate scripts are given. Data classification scripts are provided for each algorithm discussed in this work.
2

Crystallization Kinetics

A review of crystallization theory is presented in the following chapter. Topics are broken down into distinct classes and discussed accordingly. The main focus of this section is to outline briefly the various mechanisms present within a crystallization system - in general; nucleation, growth, breakage, and agglomeration - before outlining the Population Balance framework in the subsequent chapter. While the work in this thesis primarily deals with particle breakage effects it is important to at least provide a broad interpretation of the adjoining mechanisms typically found within the field of crystallization. Therefore, the purpose of this chapter is to understand the context of breakage/attrition within crystallization systems as a whole. As such, mechanisms will be discussed in terms of their well-known mathematical expressions and overall physical theories, as opposed to reviewing their explicit derivations from first principles. In doing this, a better mathematical formalization is gained as to how these mechanisms may be used within modelling frameworks such as Population Balance (PB) models. Lastly, this section will hopefully provide a greater understanding of the challenges in constructing reliable crystallization kinetics and their importance in industrial and scientific advancement.

2.1 Growth

In the case of seeded batch reactions, crystal growth is a relatively straight-forward process; molecules of solute will continue to crystallise out of solution and onto the seed surface until solution equilibrium occurs, i.e. until a supersaturation ratio of 1.0
has been reached. The characteristic dimension that a growth operator may affect can realistically be chosen as any internal coordinate of the particle itself. However, from McCabe’s $\Delta L$ Law [McCabe, 1929] it is often convenient to employ a linear dimension such as the volume equivalent sphere diameter, as opposed to particle mass or volume itself. For the purposes here the concept of growth is discussed in terms of the equivalent spherical diameter for ease of illustration. The growth rate ($G$) of crystals in a stirred vessel is essentially the velocity component of the corresponding internal coordinate vector, $\mathbf{x}$; in this case the equivalent diameter. As such it can be described formally as:

$$G = \frac{\partial x}{\partial t}$$  \hspace{1cm} (2.1)

The physical mechanisms behind crystal growth may be broken down into two distinct types: normal and lateral. Normal growth corresponds to those mechanisms that increase the crystal size normal to the growth face itself; these include spiral dislocation growth and adhesive growth via nucleation. Lateral mechanisms serve to grow in a direction parallel to the crystal face, such as step growth. Importantly, the normal and lateral mechanisms are both required in order to fully explain crystal growth.

**Normal Growth** Also termed adhesive growth, normal growth provides mechanisms by which steps on the crystal surface may arise. These steps are then the basis for lateral growth of that crystal surface. Two main theories surround the origin of these steps. The first, and perhaps most widely accepted theory, relies on naturally occurring screw...
dislocations in the crystal lattice that result in a portion of the crystal face displacing upwards, normal to the original surface. This dislocation creates a step by which a spiral growth pattern can emerge, growing both normally and laterally. This is a fundamental mechanism in the Burton, Cabrera, and Frank (BCF) model of growth \cite{Burton1951}. Stated briefly, the rate of advancement of the step is proportional to the distance from the centre of the dislocation. This results in the outer edge of the dislocation step growing faster than the centre, causing the dislocation to grow in a spiral pattern. If the growth rate is dependent on orientation, this results in the formation of a growth pyramid as illustrated in fig. 2.2. Alternatively, it has been suggested that steps may form from 2-dimensional nucleation on the surface of a crystal \cite{Burton1951, Myerson2002}. In a supersaturated environment, solute molecules may cluster on a pre-existing surface of a crystal. Upon reaching a critical size, the cluster becomes stable and will most likely grow indefinitely \cite{Uwaha2015}. This mechanism can be thought of as the nucleation of a new layer on the crystal surface, providing new steps for lateral growth. Figure 2.3 depicts how this new layer, sometimes referred to as an island, forms on the crystal surface.

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure22.png}
\caption{Illustration of a screw dislocation and the resulting spiral growth pattern. \cite{Uwaha2015}}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure23.png}
\caption{Growth via 2D nucleation. A new island is formed on the crystal surface, with the stepped face providing lateral growth of that layer. \cite{Uwaha2015}}
\end{figure}
2. CRYSTALLIZATION KINETICS

Lateral Growth  Lateral growth requires the presence of a stepped surface. As discussed previously, these stepped surfaces can arise from screw dislocations or 2D nucleation. Additionally, it has been shown that for temperatures above absolute zero, thermal fluctuations in the crystal’s environment ensures its surface will have a degree roughness (Burton et al., 1951; Uwaha, 2015). This provides the surface with a number of steps, each with a high concentration of kinks by which the step can advance across the crystal surface via growth. In this sense there are three mechanisms by which a stepped surface may arise, and subsequently grow. Figure 2.4 illustrates a kink in a stepped crystal surface.

![Figure 2.4: Presence of a kink in a stepped crystal surface.](Burton et al., 1951)

Adsorbed solute molecules on the crystal surface will tend to diffuse towards these stepped faces. Molecules are incorporated into the step, and may subsequently diffuse along the step in order to find a kink site; the most energetically favourable position (Burton et al., 1951). In modelling scenarios, functional forms for growth are often assumed to follow two-step diffusion-integration mechanisms or empirical power-law relations that provide parametrizable forms for the above physical mechanisms (Garside et al., 2002).

2.1.1 Two-Step Growth

Two-step theory stipulates that growth occurs in two distinct steps: mass transfer, and surface integration. These steps are representative of the mechanisms for initial solute deposition onto the seed surface, and subsequent growth of the seed face. Firstly, crystal
growth is dominated by a diffusion mechanism whereby solute molecules are deposited onto the crystal surface at a rate proportional to (Garside et al., 2002, 1976):

\[ G_d = k_d \frac{(C_\infty - C_I)}{\rho_c} \]  

(2.2)

Whereby the diffusion-controlled growth rate \( G_d \) is dependent on the mass-transfer coefficient \( k_d \), the crystal density \( \rho_c \), and the concentration driving force between the bulk concentration \( C_\infty \) and crystal-liquid interface concentration \( C_I \); concentrations are given in units \( kg/m^3 \) of solute per solvent. A worthwhile note about this approach is that it allows for straightforward inclusion of dissolution kinetics in addition to growth. As dissolution may be treated as a negative mass transfer step, \( C_I \) in eq 2.2 can be replaced by the saturation concentration \( C^* \) yielding a kinetic expression for dissolution via mass-transfer (PSE, 2015; Uchin et al., 2017). Following the mass-transfer step of growth, the surface integration step of growth can be given as:

\[ G_s = K_s \left( \frac{C_I - C^*}{\rho_c} \right)^{\alpha_r} \]  

(2.3)

Where there is now a surface integration rate coefficient \( K_s \), and the driving force utilizes the interface concentration \( C_I \) instead of the bulk concentration \( C_\infty \). An additional term, \( \alpha_r \), is also apparent and describes the solution saturation dependency on the crystal growth rate. Furthermore, the rate coefficient in eq 2.3 can be broken down further to incorporate their temperature dependency and is written as:

\[ K_s = k_s \exp \left( -\frac{E_a}{RT} \right) \]  

(2.4)

The final rate coefficients for growth can be be read as functions of Activation Energy \( E_a \), the ideal gas constant \( R \), and solution temperature \( T \) with the new rate coefficients for diffusion and integration given as \( k_d \) and \( k_s \). Sherwood correlations can provide an estimate for \( k_d \) (Uchin et al., 2017) and for crystals larger than 60\( \mu \)m these yield:

\[ k_d^{(e)} = \frac{D_{AB}}{x} \left[ 2 + 0.8 \left( \frac{\bar{\varepsilon} x^4}{\nu^3} \right)^{1/5} \left( \frac{\nu}{D_{AB}} \right)^{1/3} \right] \]  

(2.5)
2. CRYSTALLIZATION KINETICS

Subsequently, for crystal smaller than 60µm an addition relation can be implemented (Levins and Glastonbury, 1972):

\[
k_d^{(e)} = \frac{D_{AB}}{x} \left[ 2 + 0.47 \left( \frac{\varepsilon^{1/3} x^{4/3}}{\nu} \right)^{0.62} \left( \frac{d_s}{d_t} \right)^{0.17} \left( \frac{\nu}{D_{AB}} \right)^{0.36} \right]
\] (2.6)

where \( \nu \) is the kinematic viscosity of solution, \( d_s \) and \( d_t \) represent the stirrer and tank diameters respectively, \( \varepsilon \) is the energy dissipation rate, and \( D_{AB} \) represents the diffusion coefficient of the solute in the liquid given by the Stokes-Einstein relation:

\[
D_{AB} = \frac{\alpha kT}{6\pi \eta d_m^2}
\] (2.7)

Where \( \alpha \) is a relaxation factor applied in order to account for eq.2.6 and 2.7 formally being closer to approximations for near-neutral buoyancy particles in a low Reynolds number flow. Solution temperature is given by \( T \) in Kelvin, \( k \) is the Boltzmann constant, \( \eta \) is the dynamic viscosity of solution, and \( d_m \) is the molecular diameter of the solute. Equations 2.5, 2.6, and 2.7 allow for the determination of \( k_d^{(e)} \), forming a theoretical basis for handling mass-transfer steps in growth and also dissolution.

2.1.2 Power-Law Growth

A simpler approach to this two-step model is often employed via the empirical power-law relationships previously mentioned. The power-law growth kinetic can be thought as more of a more high-level description of growth, capturing mass-transfer and integration steps all in one expression. Using the absolute saturation (\( \Delta C = C_\infty - C^* \)), it is simply stated as:

\[
G = k_g \exp \left( -\frac{E_a}{RT} \right) \left( \frac{\Delta C}{\rho_c} \right)^{\alpha_g}
\] (2.8)

or alternatively formulated using the relative supersaturation (\( \sigma_{rel} = \frac{C_\infty - C^*}{C^*} \)):

\[
G = k_g \exp \left( -\frac{E_a}{RT} \right) \sigma_{rel}^{\alpha_g}
\] (2.9)

As is clear, eq.2.8 is similar in form to eqs. 2.2 and 2.3. This power-law approach provides a simplistic way to estimate growth rates while utilizing parameters based in
physical mechanisms. The rate and order terms, $k_g$ and $\alpha_g$, can be used to parametrize for overall rate dependencies on driving force and mass-transfer/integration rate coefficients found in the two-step approach.

### 2.1.3 Growth Rate Dispersion

It is important to briefly discuss Growth Rate Dispersion (GRD) before finishing the discussion on growth kinetics. GRD is an important phenomenon in the general perception of how growth operates across a population and affects how the growth operator will be treated in modelling efforts. Most recently, GRD has been shown to have a significant effect on racemization reactions whereby complete chiral resolution can be obtained through subtle differences in each chiral populations growth rates (Uchin et al., 2017). There exists three pertinent models for capturing the effects of GRD (Srisanga et al., 2015):

- **Growth Diffusivity (GD) Model** (Randolph and White, 1977): all crystals grow at the same time-averaged growth rate. However, at any time the individual crystal growth rate may fluctuate randomly about the overall average rate.

- **Constant Crystal Growth (CCG) Model** (Berglund and Larson, 1982): individual crystals in a population have their own inherent growth rate that is constant over a given set of conditions and different to the growth rate of others in the population.

- **Common History (CH) Model** (White et al., 1998): if the nuclei that produced the crystal population nucleated at the same instant, under the same conditions, and experienced the same conditions since nucleation then the PSD of the crystals will be proportional to the distribution of the inherent crystal growth rates. This model is closely linked to the CCG model and is arguably an extension that allows for excellent CCG modelling of GRD when nucleation is negligible.

A key aspect of GRD is how it may masquerade under the guise of Size Dependent Growth (SDG). However, McCabe’s $\Delta L$ Law (McCabe, 1929) states that growth is typically independent of crystal size, with literature stating size-dependent growth only being observed below the 1µm scale (Myerson and Ginde, 2002). As such, most
2. CRYSTALLIZATION KINETICS

reactions are assumed to be size-independent with respect to observed growth kinetics for process models.

What is important to note here is that the application of eq\[2.8\] in evaluating crystal growth rates effectively employed the CH model for GRD. As long as nucleation can be said to remain negligible from the early time-steps in the process, this approach provides a valid estimate for the population’s growth rate. Furthermore, this allows for the simplification of the growth advecter for modelling efforts as it does not need to be treated specially when formulating the Population Balance Equations (PBEs). However, this will be discussed in more detail in Chapter 3.

2.2 Nucleation

There are two main categories when concerning nucleation during pharmaceutical processes: Primary and Secondary. Primary Nucleation is associated with the spontaneous formation of new crystal nuclei in highly supersaturated systems without any prior crystalline surface present. The mechanism enabling this is typically cited as arising from the ordered clustering of individual solute molecules in solution reaching a critical cluster size whereby it becomes “stable” and can be considered as a new crystal nucleus (Myerson and Ginde, 2002). Secondary Nucleation results from the formation of new crystal nuclei breeding from the parent crystallizing material itself or from interactions between the parent crystal and its environment (crystallizer walls, neighbouring crystals, probes, impellers, etc.).

2.2.1 Primary

Homogeneous

Primary Homogeneous Nucleation is stated to occur due to local fluctuations in concentration giving rise to these ordered solute clusters that may eventually become stable crystal nuclei (Garside et al., 2002; Myerson and Ginde, 2002). It is considered an additive mechanism whereby addition of new solute molecules to the parent cluster occurs until a critical size is reached. However, if the cluster cannot maintain stability for a sufficient period it may also break down and diffuse back into solution. The rate
2.2 Nucleation

Figure 2.5: Structure of Nucleation mechanisms (Myerson and Ginde (2002))
2. CRYSTALLIZATION KINETICS

at which new nuclei are formed due to homogeneous nucleation is, in general, given by an Arrhenius rate expression:

\[ B_0 = A \exp \left( -\frac{\Delta G_{cr}}{kT} \right) \] (2.10)

Whereby the rate of generation of new nuclei is proportional to a pre-exponential factor \((A)\), free energy of formation for critically sized nuclei \((\Delta G_{cr})\), the Boltzmann constant \((k)\), and solution temperature \((T)\). The free energy of formation for critical nuclei can also be found via minimization of free energy over the particle radius. The derivation of this can be found in Myerson and Ginde (2002), and is given as:

\[ \Delta G_{cr} = \frac{16\pi\gamma^3\nu_f^2}{3(kTlnS)^2} \] (2.11)

where \(\nu_f\) represents the fluid kinematic viscosity, \(S\) the supersaturation ratio \((C_\infty/C^*)\), and \(\gamma\) the interfacial tension in \(J/m^2\) between the newly forming crystal surface and supersaturated solution in which it is located Mullin (2001).

Heterogeneous

In a similar fashion to homogeneous nucleation, heterogeneous nucleation involves the creation of new crystal nuclei prior to the existence of any solid crystalline material in the system. However, the key difference here is that heterogeneous nucleation occurs when any foreign substance in the supersaturated solution accelerates the nucleation process. This can be explained by the fact that such “impurities” only serve to reduce the required free energy of formation. It was found by Volmer (1939) that in-fact the presence of foreign substances other than the crystallizing material serves to affect the free energy of formation via:

\[ \Delta G_{hom} = \phi \Delta G_{het} \] (2.12)

\[ \phi = \frac{1}{4}(2 + \cos \theta)(1 - \cos \theta)^2 \] (2.13)

Where the factor \(\phi\) is given as a function of the wetting angle \((\theta)\) of the foreign solid phase. Therefore, heterogeneous nucleation is often observed more readily, as a lower supersaturation is required when compared to homogeneous systems. Values for
2.2 Nucleation

Primary nucleation rates can be obtained by substituting eq 2.12 or eq 2.11 into eq 2.10 to obtain Primary Nucleation kinetics.

2.2.2 Secondary

While Primary nucleation does not require any prior crystalline seed material, Secondary nucleation is entirely characteristic of the presence of pre-existing crystal nuclei. From fig 2.5 it is clear that for Secondary nucleation there exists a number of mechanisms to consider. This is in essence why Secondary nucleation is often difficult to control or predict, as there exists multiple pathways of explanation.

Initial / Dust Breeding

This mechanism stipulates that secondary nuclei can arise from small pre-existing crystallites on the seed crystal itself which, when introduced into a supersaturated solution, serve as additional nucleation sites. This may be commonly observed in batch processes where the addition of unwashed seed material may result in such secondary nuclei, as reported by De Souza et al. (2016).

Polycrystalline Breeding

For high levels of supersaturation, polycrystalline aggregates may be formed. Fragmentation of these aggregates can result in the formation of seemingly new crystal nucleation sites. However, this mechanism is not considered to be likely in industrial applications or where fragmentation may not be likely (Myerson and Ginde, 2002).

Macroabraison

As crystals collide with either the crystallizer itself (probes, impellers, baffles, etc.) or with neighbouring crystals, there is a chance that the more energetic collisions will result in the formation of new crystal nuclei via macroabraison of the crystal surface. This mechanism is driven by the chipping and minor fragmentation of crystals during processing and is typical of highly agitated systems, or those with high solids loading. The generation of secondary nuclei via this mechanism is highly dependent on
2. CRYSTALLIZATION KINETICS

the two-way coupling between crystal-fluid interactions. Crystal material properties influence the fragmentation behaviour, while the suspending fluid and solids loading plays a large role in the collision frequencies, impact speeds, and angles of collision. As this mechanism relies on particle collisions, however, this work will demonstrate that abrasion-based theories may only work for highly agitated systems where particle collisions are more likely and energetic.

Dendritic

At high levels of supersaturation, needle or dendritic breeding may also occur. At higher supersaturations crystallization often results in high aspect ratio crystals with dendritic structures forming as growth continues. These in-turn may fragment in solution and again form new crystal nuclei over time, similar to the macroabrasion mechanism.

Fluid Shear

In a similar manner to macroabrasion and dendritic breeding, fluid shear can influence the generation of secondary nuclei. The shearing of small surface nuclei not yet fully incorporated into the crystal structure results in a substantial increase in the total particle count. As these nuclei are sheared from the parent surface, they in-turn serve as new nucleation sites (Anwar et al. 2015; De Souza et al. 2016). This mechanism is therefore somewhat auto-catalytic as each crystal and each new nucleus has the potential to generate more and more secondary nuclei as the population grows larger in number.

Contact Nucleation

Nuclei can be generated simply from contact between crystals and another surface such as crystal-crystallizer or crystal-crystal interactions. Of course, with this mechanism macroabrasion is known to generate new nuclei, however with contact nucleation there is no requirement for damage to the parent crystal if nuclei are formed from the absorbed solute layer near the crystal surface. Therefore, while there may be no abrasion or fragmentation after contact with another surface, the parent crystal may still generate a number of secondary nuclei (Agrawal and Paterson 2015).
Perhaps most interestingly throughout secondary nucleation mechanisms is the recurring theme of crystal fragmentation responsible for the generation of new crystal nuclei. In general, it would serve to broaden the scope of kinetic models for secondary nucleation mechanisms incorporating some comminution-based concept. As such, the next section will discuss how one might incorporate crystal fragmentation into process modelling approaches, with the aim of explaining secondary nucleation and the generation of fine particles as a whole.

2.3 Agglomeration

The occurrence of agglomeration is typically only observed at high supersaturations and high solids loading. This can be reasoned mathematically by investigating the Smoluchowski Coagulation equation \cite{Filbet2004} for systems of colliding particles such as the Mumtaz agglomeration kernel \cite{Mumtaz1997}. Essentially this states that the rate at which particles can agglomerate in the system is dependent on the level of supersaturation available to form a bonding surface between them, the fluid dynamic shear rate in the vessel, and the individual particle sizes. These factors represent the propensity for particles to collide in the system and then their subsequent chances of forming an agglomerative bond.

When considering how agglomeration occurs between pre-existing crystals in solution, one must first provide a reasonable mechanism by which particles may collide and form agglomerates. It was first shown by von Smoluchowski \cite{Smoluchowski1917} how these collision rates can be given as a function of fluid shear within the system. Additionally, fluid acceleration effects arising from discrepancies in particle relaxation times can also result in particles colliding. This is due to particles with shorter relaxation times being able to respond to changes in the fluid velocity field more easily than those with larger relaxation times \cite{Hollander2001}. In general, if there is a sufficient velocity gradient between particles, and their paths intersect or overlap to some degree, this will result in one of the three archetypal collisions illustrated in fig.2.6.

As PB modelling is typically applied on the macro-scale a simplification is usually made whereby the fluid shear dependency is approximated by a volume-averaged energy dissipation expression \cite{Andreassen2004, Hounslow2004}.
2. CRYSTALLIZATION KINETICS

![Diagram of three archetypal particle collision mechanisms](image)

**Figure 2.6:** A simplified illustration of the three archetypal particle collision mechanisms due to a velocity gradient between particles caused by fluid shear within the system.

Barrick and Bramley [2001] [Muntaz et al., 1997]. This is reflected by the Smoluchowski’s collision rate given in terms of energy dissipation ($\varepsilon$) and fluid kinematic viscosity ($\nu_f$) as [PSE 2015]:

$$
\beta_{\text{coll}} = \sqrt{\frac{8\pi\varepsilon}{15\nu_f d_{3.0}^3}}
$$

Where the volume-number mean crystal size in the system ($d_{3.0}$) is used in order to obtain an averaged result. However, in order to take into account of the fact that not all collisions will result in a bond strong enough to sustain the agglomerate, the Muntaz kinetic [Muntaz et al., 1997] introduced an efficiency term to eq.2.14 such that:

$$
\beta_{\text{agg}} = \Psi \beta_{\text{coll}}
$$

The agglomeration efficiency ($\Psi$) in eq.2.15 is taken to be an average across the entire system. From Hounslow, Mumtaz, Collier, Barrick and Bramley (2001) it can be given as:

$$
\Psi = \frac{(M(\varepsilon)/M_{50})^\gamma}{1 + (M(\varepsilon)/M_{50})^\gamma}
$$

with fitting parameter $0.5 \leq \gamma \leq 0.8$. The dimensionless strength of the joining
2.3 Agglomeration

bond \((M)\) is given as:

\[
M(\varepsilon) = \frac{\sigma^* \mu_f^{1/2} G^2}{\rho_f^{3/2} \bar{d}_{3,0}^2 \varepsilon^{3/2}}
\]  \(2.17\)

Where \(\rho_f\) denotes the fluid density, \(\mu_f\) is the fluid dynamic viscosity, \(G\) is taken as the linear growth rate such as that from section \(2.1\) and \(\sigma^*\) is the apparent yield stress of the material. The value of \(M_{50}\) is that for which \(\Psi = 0\). In familiar terms the value \(M\) can be seen as the ratio of the neck’s strength to the applied stress. In this way it illustrates how successful an agglomeration event is likely to be, with \(\Psi\) yielding the overall agglomeration efficiency as a result. Furthermore, in order to more easily utilize this kinetic the simplification:

\[
\Psi = \frac{(A_{50} G)/(\varepsilon \rho d_{3,0}^2)}{1 + (A_{50} G)/(\varepsilon \rho d_{3,0}^2)}
\]  \(2.18\)

is often implemented, with \(A_{50}\) and \(M\) defined as:

\[
M = \frac{L \sigma^* G}{\varepsilon \rho d_{3,0}^2}
\]  \(2.19\)

\[
A_{50} = \frac{L \sigma^*}{M_{50}}
\]

Where \(L\) denotes the length of the contact line between agglomerating crystals, \(\sigma^*\) as the apparent yield strength, and \(M_{50}\) as a dimensionless strength corresponding to an efficiency of 0.5. In this way \(A_{50}\) can be viewed as a representation of factors associated with vessel geometry, contact points between agglomerating crystals, and material strength (PSE, 2015). Furthermore, since it is difficult to determine the effects of these factors independently, this implementation allows \(A_{50}\) to be parametrized through some optimization method.

As a note, recent literature (Hollander et al., 2001) has proposed a more mechanistic insight into how reactor hydrodynamics affect agglomeration rates by coupling a Monte Carlo scheme for particle size distribution modelling and a Lattice Boltzmann scheme to simulate the local flow field. It was shown that in order to adequately represent particle collisions for agglomeration, detailed knowledge of local hydrodynamics is required. However, obtaining this information requires large computational resources and parametrizable formulations for macro-scale kinetics may be preferable. Therefore, the ...
2. CRYSTALLIZATION KINETICS

Muntaz kinetic was outlined above in order to illustrate a typical agglomeration kernel used in process modelling. There are also various other agglomeration kernels used, such as the sum \( \beta_{agg} = x + x' \), product \( \beta_{agg} = xx' \), or constant \( \beta_{agg} = \beta_0 \) kernels. However, these usually for analytical purposes as they are gross oversimplifications of the physical agglomeration process.

2.4 Breakage

Finally, the primary subject of study in this thesis is presented. The theoretical basis provided in the following sections extends the work carried out in Tyrrell et al. (2018) and Tyrrell and Frawley (2018). Hydrodynamic and material response factors are combined in order to provide a realistic breakage model. Furthermore, breakage is intrinsically linked to secondary nucleation as fine fragments may in-turn serve as new nucleation sites throughout the process. Therefore, the breakage kinetic developed here provides new insight into the modelling and control of fines distributions in pharmaceutical processes.

Breakage in a Population Balance (PB) framework consists of two key factors: selection functions, and distribution functions. The former governs what portion of crystals in a population will break given a set of conditions, while the latter dictates the size-distribution of fragments formed from each of these “selected” crystals. Using these two functions it is possible to determine the amount of breakage occurring and where the crystal mass is being re-distributed after fragmentation. Determination of the functional forms for these factors is a challenge for pharmaceutical materials as there exists little information on physical material properties, and fragmentation studies detailing selection and distribution functions.

2.4.1 Selection Functions

There exists numerous forms that can be chosen for the breakage selection function. Uniform, binary, and exponential functions have been proposed by Bao et al. (2006); Hounslow, Pearson and Instone (2001); Qamar et al. (2009) are amongst the most commonly used forms for the selection of crystal breakage rates. However, perhaps the most widely used of these is the well-established Weibull distribution (Weibull 1951).
In general, Weibull statistics are useful for survivability modelling. As such, it has been used extensively in literature when conducting studies on particle breakage and comminution (Meier et al., 2008; Salman et al., 1995; Vogel and Peukert, 2003) and is given as (Salman et al., 1995):

$$N_0 = 100e^{[-(\frac{v}{c})^m]} \equiv 1 - \hat{S}(x) \quad (2.20)$$

Whereby $N_0$ yields the percentage of the population which remains unbroken after an impact with a boundary at velocity $v$ and Weibull Modulus $m$. Formally, eq. (2.20) is the Cumulative Distribution Function (CDF) of the Weibull distribution and represents the complement of the breakage selection function, $\hat{S}(x)$. The shape of eq. (2.20) is influenced by parameters $c$ and $m$ in the exponent. Thus, eq. (2.20) can be used to inform experimental work as to which physical variables may be of importance. Parameter “$m$” is known as the Weibull Modulus and is a parameterized constant for each crystal material. Parameter “$c$” is a function of the critical failure velocity ($u_f$) at which $1 - \frac{1}{e} = 63.2\%$ of particles will fail, and the impact angle of the particle ($\alpha$), it is given as:

$$c = \frac{u_f}{\sin\alpha} \quad (2.21)$$

Substituting eq. (2.21) into eq. (2.20), the following expression is obtained in the exponent:

$$\frac{v}{c} = \frac{v \sin \alpha}{u_f} = \frac{v_{ortho}}{u_f} \quad (2.22)$$

Therefore, parameter “$c$” ensures the exponent of eq. (2.20) is effectively the ratio of the critical failure velocity ($u_f$) to the orthogonal component of the impact velocity ($v_{ortho}$). Investigating further it can be seen that $u_f$ is itself a function of various crystal properties. Maxim et al. (2003) detailed this relationship as:

$$u_f = \left[ \frac{F_{cr}}{2R^2} \left( \frac{3k^2}{\pi E^2 \rho} \right) \right]^{\frac{1}{2}} \quad (2.23)$$

It is now clear from eq. (2.23) that $u_f$ is not only a function of particle radius ($R$), but various other material properties. The critical failure load ($F_{cr}$), Young’s Modulus ($E$),
bulk density ($\rho$), and Hertzian indentation constant ($k$) all play a role in the failure velocity of a given crystal. Laugier (1984) developed an expression for $k$ given as:

$$k = \frac{9}{16} \left[ (1 - \nu_c^2) + (1 - \nu_t^2) \frac{E_c}{E_t} \right]$$ (2.24)

Where the Poisson’s Ratio ($\nu$) and Young’s Modulus ($E$) for the crystal and impacting surface (or “target”) are denoted by suffixes $c$ and $t$, respectively. Furthermore, Bearman (1999) described a relationship between a material’s fracture toughness ($K_{IC}$) and critical failure load ($F_{cr}$), simplified here for spherical particles:

$$F_{cr} = \frac{K_{IC}(D^2)^{\frac{3}{4}}}{26.56}.$$ (2.25)

Eq.2.25 indicates that the critical failure load is directly proportional to particle size. However, as observed in this work and reported by Kendall (1978) there exists a critical limit whereby impacts no longer cause fracture and instead result in plastic ductile yielding and prior to this the failure load rises rapidly as particle sizes decrease. Accounting for this, a proposed modification of eq.2.25 is given:

$$F_{cr} = \frac{K_{IC}(D^2)^{\frac{3}{4}}}{26.56} (\beta_1 e^{\alpha_1 x} + \beta_2 e^{\alpha_2 x})$$ (2.26)

The additional terms $\beta$ and $\alpha$ can then be used to incorporate the sharp inflection of $F_{cr}$ at smaller scales. Their successful application in modelling crystal breakage at this scale is demonstrated by Tyrrell and Frawley (2018). Although it may be argued that these parameters provide a somewhat non-physical representation, they provide an initial attempt to explain the variability of the required failure load with decreasing particle sizes. Their inclusion allows for an extension of this theory towards more applicable pharmaceutical-scale particle sizes. Furthermore, as these parameters are solely functions of particle size, their application and parametrization serves to explain only if variability with particle size can account for any discrepancies between the theoretical and empirical approaches. Combined, eqs. (2.20), (2.21), (2.23), (2.24) and (2.26) provide a theoretical basis for determining breakage populations of any given sample, provided the fundamental physical material properties can be determined.
2.4 Breakage

2.4.2 Rate Expressions

In order to fully utilize eq. 2.20, \( S(x) \) must be converted to a rate-based equation for useful implementation as a kinetic expression (refer back to the Arrhenius expression in eq. 2.10). In order to obtain this rate expression a physical interpretation of breakage within the reactor is required. As such, the following is a theoretical construction for the determination of a breakage selection rate, \( S(x) \), for use in a Population Balance framework. The parameters of which may be optimized in order to determine if the presented theory can effectively explain experimental data, in a similar manner to the methods presented by Rumpf (1973); Szilágyi and Nagy (2018); Vogel and Peukert (2003).

Consider first that breakage will affect the entire population evenly, i.e. reflecting the assumption of an perfectly mixed, homogeneous population as is typical of modelling approaches. Knowing this, it is reasonable then to assume that the breakage rate within a reactor is acting over some fraction of the total fluid volume whereby all particles contained in this volume are considered to encounter a breakage mechanism of some kind. This volume is representative of regions near the impeller, probes, baffles, and also small volumes of high solids loading where crystal-crystal interactions may be frequent. This way it is assumed that the generation of new crystal nuclei comes from a fraction of the fluid volume contained within the system and is dependent on how this volume is circulated throughout the system. Figure 2.7 gives a schematic example of the total vessel volume, the total fluid volume (or fill volume), and the impeller region’s volume. What will now be detailed is how a breakage frequency can be determined via the rate at which the total fluid volume can be circulated through the impeller region.

The total fluid volume can be determined with relative ease if the vessel dimensions are known and the experimental fill height is recorded; in this way the fluid volume may also be referred to as the fill volume. The volume pertaining to crystal-crystals collisions resulting in breakage should be negligible for low solids loadings, and for populations dominated by smaller particle sizes where the fluid interaction itself may inhibit or cushion crystal-crystal collisions (Marble, 1964). Lastly, the impeller volume is treated in a slightly different way: the impeller volume itself is not required, but rather the rate at which the impeller can circulate the total fluid volume per-second. This will yield a rate indicating what fraction of the total fluid volume passes through
2. CRYSTALLIZATION KINETICS

Figure 2.7: A simplified volume schematic of generic closed system for agitated crystallization. Dimensions other than volume are not required as the system is considered in a macroscopic sense.

the impeller region. To do this, a similar method to that in Kee and Reilly (2004) is adopted whereby the impeller volume is assumed to have a circulation frequency with which fluid elements pass through it, denoted $f_c$:

$$ f_c = \frac{FlN D^3}{V} \quad (2.27) $$

This describes the rate at which fluid elements from the total fluid volume ($V$) can be circulated as a function of Flow Number ($Fl$), agitation RPM ($N$), and agitator diameter ($D$). Breaking this down further, it can be seen that eq.2.27 is fundamentally a ratio of circulating capacity ($Q$) to fluid volume ($V$) (Paul et al., 2004):

$$ Q = FlN D^3 \quad (2.28) $$

$$ \Rightarrow f_c = \frac{Q}{V} = \frac{1}{t_c} \quad (2.29) $$

Where $t_c$ denotes the characteristic circulation time of the vessel. This circulation frequency is then taken to be proportional to the impact frequency in the vessel. To this extent, it is possible to relate an impact rate ($R_i$) describing the frequency of particle impacts via two efficiency factors given by:

$$ R_i = f_c \psi_{circ} \phi_{hydro} \quad (2.30) $$
2.4 Breakage

Above, $\psi_{\text{circ}}$ is taken as the circulation efficiency and $\phi_{\text{hydro}}$ as the hydrodynamic efficiency. The circulation efficiency is a parameterized proportionality constant relating the circulation frequency to the particle impact frequency. This is rationalized via the assumptions of a well-mixed, and homogeneous particle population in the system. The hydrodynamic efficiency stems from the interaction between particles and the flow field near the colliding surface, however this is to be discussed further in chapter 5 for the sake of clarity and structure. In short, $R_i$ should be interpreted as the number of particle impacts that occur in each size class per-second. It is determined by the circulation capacity of the impeller, the total fluid volume being circulated, and the circulation and hydrodynamic efficiencies of the system. Combined, these factors gather the relevant operating conditions and hydrodynamic interactions that govern particle impact rates within an agitated crystallization system.

The above rate-expression indicates that the impact frequency in a vessel should remain constant for a given RPM and steady state operating conditions where the hydrodynamic factors are also constant. However, the rate of breakage itself within this volume may vary over time due the re-distribution of mass into lower size classes. It is stipulated that this is due to smaller particles becoming more Stokesian in advection (discussed in chapter 5) and less prone to fragmentation as size decreases owing to (Kendall, 1978):

$$\sigma_{cr} \propto \frac{1}{\sqrt{d_c}}$$  \hspace{1cm} (2.31)

Whereby the crystal material's crack propagation stress ($\sigma_{cr}$) is inversely proportional to the root of particle/crystal size ($d_c$). Therefore, the time-independent selection function from eq 2.20 can be combined with the particle impact rate within the system (eq 2.30) to provide an estimate for the fraction of broken particles being produced per-second; i.e. the selection rate $S(x)$. Taking into consideration that not all impact result in fragmentation, the final selection rate is defined as:

$$S(x) = R_i \hat{S}(x)$$  \hspace{1cm} (2.32)

Eq 2.32 effectively states that if the impact rate ($R_i$) is known then it is possible to determine what fraction of these impacts will result in fragmentation based on the earlier selection function in eq 2.20. This ensures that crystal strength characteristics are taken into account for each collision, with collision rates themselves being predicted on the basis of hydrodynamic factors in the system.
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2.4.3 Distribution Functions

It is not merely enough to know the extent of the population that is broken, it is also required that the distribution of fragments arising from these broken particles is determined. The overall general trend of natural size-distributions to follow well defined probability distributions may also be rationalized by investigating some fundamental statistical theorems. The asymptotic behaviour of size-distributions near their maxima and minima, i.e. largest and smallest sizes, follows the Generalized Extreme Value theorem also known as the Fisher-Tippett-Gnedenko theorem (Fisher, 1930). This effectively gives reason to the observation of low particle counts in both the upper and lower extremes of particle sizes, and formalizes that distributions typically converge to one of three generalized extreme value distributions: Gumbel (type I), Frchet (type II), or Weibull (type III). A caveat of this should be noted that samples within the population should be independent and identically distributed, as is the case for only a single random variable in particle size. Additionally, from the Central Limit theorem one may generally ascertain that independent and identically distributed variables such as particle size measurements will tend toward some attractor distribution. This equates to stating that the observable fragment size distributions from particulate processes such as breakage will always tend towards some well-known fundamental probability distribution approximated by, but not limited to, a normal distribution or the lognormal distribution in a log domain.

While it is now clear as to why particulate populations tend to be well-approximated by some set of known probability distribution, there remains a decision in choosing which distribution is most appropriate. From the Principle of Maximum Entropy it is known that the probability distribution that would best represent some observed data is one that has the maximum information entropy (Jaynes, 1957a, b). Therefore, from both the Generalized Extreme Value and Central Limit theorems it is expected that size-distribution functions such as the overall volume PSD of a population, or the fragment size distribution for breakage processes will follow some set of known distribution families. As previously noted, the Weibull (Rosin-Rammler) and lognormal distributions are popular choices for PSDs and fragment distributions, respectively. Knowing these distribution families of interest, one may then chose the maximum entropy probability distribution of this family according to the Principle of Maximum

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2.4 Breakage

Entropy. This serves to minimize the distribution’s bias and it follows that physical systems tend towards maximum entropy configurations over time. Importantly, both the lognormal and Weibull distributions are the maximum entropy distributions of their respective classes. As such, is it clear now perhaps as to why these distributions tend to fit experimental data quite well. Below in eq.2.33 is an the normalized lognormal distribution for daughter fragments with location and scale parameters given by \( \mu_f \) and \( \sigma_f \), respectively (Hounslow, Pearson and Instone, 2001).

\[
b(x, x') = \frac{1}{x} \sqrt{\frac{\pi}{2 \ln \sigma_f}} \exp \left[ - \left( \frac{\ln x / \mu_f}{\sqrt{2 \ln \sigma_f}} \right)^2 \right] \frac{1}{1 + \text{erf} \left[ \frac{\ln x'/\mu_f}{\sqrt{2 \ln \sigma_f}} \right]} \tag{2.33}
\]

This distribution provides a lognormal function normalized on \( x \in [0, x'] \) as particles of size \( x \) are generated from parent particles of size \( x' \). As such the lognormal distribution must be scaled to these bounds. Additionally, the leading term of \( x'/x \) is required to convert the distribution into a mass-conservative one for the internal size coordinate given in terms of particle volume (\( m^3 \)). Multiple choices for this distribution function can be taken, beta distributions, Gaussian, uniform, constant kernels, etc. The choice of function depends on the system being modelling and is compound specific. Although, from the above these distributions tend to centre around log-normal/Weibull distributions, so-called “attractor” distributions.

Additionally, multi-modal or attrition-fragmentation distributions may often occur (Hounslow, Pearson and Instone, 2001; Kwan et al., 2004; Salvatori and Mazzotti, 2018). In these cases a weighted combination of lognormal, gamma, or beta distributions could effectively capture such behaviour. However for the sake of simplicity in this work, the weighted bi-modal sum is defined as:

\[
b(x, x') = \omega_1 b_1(x, x') + \omega_2 b_2(x, x') \tag{2.34}
\]

Where the weights must sum to unity in order to conserve the first and second order moments, i.e. total particle counts and volume. By adjusting the weights in eq.2.34 the model can accurately capture any bi-modality inherent in comminution events. Values for \( \mu_f \) and \( \sigma_f \) should also be chosen to represent the characteristic modes of the resulting experimental PSDs.
2. CRYSTALLIZATION KINETICS

2.5 Summary

From this chapter the main mechanisms of crystallization processes have been detailed. While each mechanism outlined may not be the subject of direct study here, they have served to broaden the context in which a new breakage/attrition model is relevant. As an example, when considering a process with a high degree of breakage it might then also be prudent to consider how this affects GRD, or how it may conflict with agglomeration in the system, even as far as impacting nucleation rates for mechanisms such as dust breeding or driving macroabrasion mechanisms for secondary nucleation. Even from a rudimentary understanding of the entirety of expected crystallization mechanisms, it is possible to more appropriately study one in isolation; as is the case for crystal breakage in this thesis.

A theoretical description of the new breakage kinetic developed as part of this thesis is given. A fundamental circulation frequency of the system is defined, with the overall breakage rate posed as a function of this fundamental rate. The concept of a hydrodynamic efficiency governing the rate at which particles can collide has been introduced. This term is detailed as a function of particle Reynolds number and enables the model to capture the combined effects of fluid viscosities and agitation conditions such as impeller RPM and type. A breakage model is also defined in terms of an established two-term Weibull distribution. This incorporates the crystal material properties into the breakage kinetic and generalizes the model over various crystal materials.

The next chapter will outline how particulate systems may be modelled with a Population Balance approach. This will serve to detail the modelling framework in which the breakage kinetic may be used, with reference to the selection and distribution functions given in section 2.4.
3

Population Balances

The following chapter formally introduces the Population Balance (PB) concept developed by [Randolph and Larson (1971)] and its application to crystal breakage modelling. Moment and discretization methods are discussed in the context of solving the Population Balance Equations (PBEs) for various systems. Lastly the Finite Volume Scheme used for solving the system of PBE is outlined. A discussion on its conservation of total particle counts and volume is given, in addition to how the breakage rate-expression from Chapter 2 may be treated as independent of time in order to provide a speed-up in computation times.

3.1 The Population Balance Concept

Formalized by [Randolph and Larson (1971)], the Population Balance (PB) framework is based on the concept of a particle phase space. This space consists of the least number of independent coordinates required to completely define a particle distribution function, \( n = n(t,x) \). This space typically divided into two subregions: internal and external particle coordinates. The key in realizing the power of population balances lay in the physical meaning of these coordinates. For the set of external coordinates, this is relatively straightforward as they simply represent the spatial distribution of the particles. These may be used in systems with low homogeneity or anywhere that the spatial distribution of particles is an important decision variable. However, it is typical to apply the assumption of a well-mixed process whereby the spatial distribution may be neglected.
3. POPULATION BALANCES

For internal coordinate properties, these quantitatively represent any number of states that may be associated with a particle. In pharmaceutical processing, individual particle size is illustrative of a well-known internal coordinate; as are particle growth rates, chemical activity, elastic moduli, or particle age. Using the PB framework, it is possible to provide a mathematical description of the evolution of these internal and external coordinates over time. It is clear then, why PB modelling may permeate a large number of particulate processes fields, with its ability to effectively model any system that can be represented in a particle phase space.

3.1.1 Governing Equations

For the PB model used here, focus is given solely to particle breakage rates and the subsequent generation of fines in crystal processing. The system is a stirred vessel, with no volume flux, and the assumptions of a well-mixed and homogeneous particle population can be made for steady-state conditions. The governing PBE is therefore given as (Randolph and Larson, 1971):

\[
\frac{\partial n}{\partial t} + \nabla \cdot \mathbf{v}_i n = B - D \tag{3.1}
\]

Whereby \(n = n(t, x)\) represents the population density of particle sizes in \(x\), \(B\) and \(D\) form any birth and death functions of particles, \(\mathbf{v}_i\) represents the internal velocity coordinates in phase-space with a gradient operator (\(\nabla\)) across all specified internal coordinates. This operator allows one to incorporate particle growth mechanisms along internal dimensional property coordinates such as particle volume or linear diameter. However, in order to study breakage more effectively this growth operator is assumed to be negligible and may be dropped from the model in order to isolate breakage itself. This has repercussions in the experimental aspect of model validate, however careful choice of suspension fluid for the particle system allows for negligible growth. If the fluid has a low or zero net solubility for the particle population of interest, growth may confidently be neglected as per the definitions in section 2.1. Equation 3.1 can now be rewritten as:

\[
\frac{\partial n}{\partial t} = \mathcal{L}^\pm \tag{3.2}
\]
3.1 The Population Balance Concept

with the \( k^{th} \)-moment given by:

\[ \mu_k = \int_0^\infty x^k n(t, x) dx \tag{3.3} \]

Importantly, the model here considers the internal coordinate \((x)\) in terms of individual particle volume. As such, the zeroth \((k = 0)\) and first \((k = 1)\) order moments generated by eq.3.3 represent the total particle numbers and volume, respectively. For breakage, it is imperative that these values be properly conserved over time as breakage solely serves to re-distribute volume, and increase total particle numbers. Therefore, the Mass Conserving Number Preserving (MCNP) discretization for breakage PBEs developed by Saha et al. (2016) is used. This will ensure that the first order moment (total volume) remains constant over time, and that the zeroth moment (total numbers) is not affected by spurious generation of new particles in the model domain.

3.1.2 Incorporating Breakage

In this work, the birth and death of particles are governed by the mechanistic breakage kernel developed outlined in Section 2.4. Therefore, \( \mathcal{L}^\pm \) must be formally described in terms of a rate equation. The equation for \( \mathcal{L}^\pm \) which has been used by a number of authors (Hounslow, Pearson and Instone, 2001; Kumar, 2006; Kumar and Kumar, 2013; Qamar et al., 2009; Szilágyi and Nagy, 2018) is given by:

\[ \mathcal{L}^\pm_{\text{break}} = \int_x^\infty b(t, x, x') S(x') n(t, x') dx' - S(x) n(t, x) \tag{3.4} \]

The selection and distribution functions, \( S(x') \) and \( b(x, x') \), describe the rate at which particles of size \( x' \) are selected to break and their subsequent daughter fragment distributions in size \( x \). These functions are akin to probability distributions that act on the number density function \( (n(t, x)) \), as such they should be defined on the interval \([0,1]\) for conservation. The functional forms of \( S(x) \) and \( b(x, x') \) have been covered previously in section 2.4, it is now clear from eq.3.4 where these kinetics are implemented in modelling environments. The second term on the RHS of eq.3.4 represents the breakage death function, describing the rate at which particles depart size class \( x \). Additionally, the integral term accounts for the net birth rate of particles from the
3. POPULATION BALANCES

combined effect of breakage of all particle sizes larger than \( x \). It is important to note here that eq.3.4 is typically considered to model particle sizes \( x \) in terms of spherical volumes, i.e. \( x = k_vL^3 \) for \( L \) given as a linear particle dimension such as the spherical diameter, and \( k_v \) denoted as the particle shape factor \( \text{(Nývlt and Matuchová, 1976)} \). This is largely due to the requirement of any solution to eq.3.4 to be conservative in mass, at the very least. Therefore, any form of eq.3.4 that can be said to conserve the first moment of a volume-discretized density function will inherently be mass conservative also. A semi-discrete (in volume space only) scheme was developed by Saha et al. (2016) that allows direct discretization of eq.3.4 while conserving both the zeroth and first order moments, i.e. total particle numbers and total volume. The implementation of this discretization will be outlined in the following sections on typical solution methods to PBEs.

3.2 Solution Methods

3.2.1 Moment Based Methods

Moment based methods are widely implemented strategies for solving a system of PBEs due to its simplicity and low computational cost. These methods only require that the moments of the resulting distribution \( n(t, x) \) be tracked. This has its benefits and drawbacks insofar as while computational times are low, the exact population density function is lost and must be reconstructed if required at any time. However, explicit conservation of the density function is not always required. For well-conditioned systems the density function may follow a known form and can easily be recovered via methods such as Moment Surfaces \( \text{(Hutton et al., 2012)} \) to determine centre and scale parameters for density distribution functions. However, as more independent variables are incorporated into the distribution function the number of moments required to reconstruct it also increases. Typically it would be computationally inexpensive to track the first 6 moments in order to enhance accuracy, with higher order moments adding an increasing number of components to the solution array. Furthermore, an advantage of the high computational efficiency garnered from moment based methods is their ability to be incorporated into larger simulation frameworks such as CFD-coupled solvers \( \text{(Akroyd et al., 2011)} \).
3.2 Solution Methods

In summary, a number of moment based methods exist, with the choice largely being made by computational efficiency versus, number of moments required, and operators to be considered (growth, nucleation, breakage, and/or agglomeration). For example, the Standard Method of Moments (SMoM) is unable to handle generalized growth rate dispersion, breakage, or agglomeration kinetics (Hulburt and Katz, 1964). Simplified linear kernels can be used in order to ensure the moment equation can be closed, i.e., its evaluation requires a finite number of moments or mathematical operations. However, when incorporating generalized mechanisms the moment equations cannot be formulated in a closed-form expression. As such, the equations are impossible to solve numerically with only the lower order moments and often requires a priori knowledge of the distribution type in order for reconstruction (Mitchell, 2012; Omar and Rohani, 2017). Methods such as the Quadrature Method of Moments (QMoM) (McGraw, 1997) and Extended Method of Moments (EMoM) (Falola et al., 2013) were developed in order to address this issue and to develop methods for recovering the population density function. The key to these methods is the ability to recover solutions to the moment equation (eq. 3.3) using efficient numerical integration schemes such as quadrature or trapezoidal rules (Omar and Rohani, 2017). This circumvents the closure problem as any $n^{th}$ order moment can be recovered at will and independently of all other moments. However, these methods still suffer from the requirement of a priori knowledge of the population density function’s distribution form; something that is explicitly conserved in more discretization schemes or “class” based methods.

3.2.2 Discretization Methods

The major attraction to discretization based methods is the ability to solve PBEs without further reformulations, such as is required in the moment based methods. By doing this, the density function is explicitly conserved across the integration step and subsequently this approach can yield more detailed information. However, this comes at the cost of relatively large computational overhead as the number of scalars to be solved is drastically increased proportional to the required discretization domain. Although the moment based methods require a PBE to be solved for each individual moment, a discretization scheme requires a PBE to be solved for each discretization cell.
3. POPULATION BALANCES

As population balances here are typically modelled on the internal coordinates of size or volume, this often results in discretization methods requiring large number of scalars to be solved at each time step in order to obtain accurate result. Conversely, moment based methods must solve for the number of moments required to reconstruct the distribution; typically on the order of 6 to 10 moments depending on the distribution being applied. More generally, discretization methods must scale proportionally with the domain size and required accuracy, while moment based methods are less dependent on the required size/volume domain as they rely on the number of lower and higher order moments required to reconstruct the population’s density function (Falola et al., 2013).

Numerous discretization methods have been developed over time, with most focusing around discretization of the internal coordinate. However, fully discretized Finite Volume Methods (FVMs) akin to Direct Numerical Simulation (DNS), such as that in Szilágyi and Nagy (2018), allow for both internal coordinate discretization as well as temporal discretization. Such a method is useful for parallel operations whereby time-step control may be used to align solutions of combined crystal populations. Fixed pivot methods provide an powerful method that can incorporate comminution and agglomeration mechanisms with relative ease (Iggland and Mazzoti, 2011; Kumar and Ramkrishna, 1996). Additionally, characteristic-based methods may be used to track individual particle internal coordinates (Hounslow and Reynolds, 2006). This method allows for a much more simplistic implementation of growth and nucleation kinetics, principally the ability to easily model growth rate dispersion as each particle can be given unique growth rates akin to the Common History model for GRD as discussed in section 2.1.

The computational overhead associated with discretization scheme is weighted against their ability to more accurately capture mechanisms such as growth rate dispersion, breakage, and agglomeration of particles over time. This is due to these mechanisms requiring explicit knowledge of the population’s density function at each solution time, as is evident in section 3.1.2 above describing the mathematical form for breakage modelling. For this reason, the work here has centred around the use of a semi-discrete finite volume scheme discretized in particle volume and integrated across time; enabling conservation of the density function for breakage modelling.
3.2.3 Other Methods

Monte Carlo (MC) methods provide an alternative to the aforementioned techniques and provide a framework for spatially inhomogeneous solutions (He et al., 2015; Zhao and Zheng, 2013). Owing to their inherently stochastic nature, they are well suited to modelling various growth, nucleation, agglomeration, and breakage kinetics. MC methods rely on an underlying methodology in how the PB equations are treated. Two common MC implementations are constant-number and constant-volume (Omar and Rohani, 2017). Constant-number methods expand or contract the simulation volume in order to maintain a constant number of particles. Constant-volume methods start with a known particle volume, and increases or decreases the number of particles in the system according to the events occurring between each simulation step. Overall, these methods rely on the fact that upon generating a set of solutions from a set of random inputs, the real solution (or solutions) will appear more often. By running a large number of MC simulations, the actual solution can be converged upon (Omar and Rohani, 2017).

Lattice Boltzmann (LB) formulations have also been developed for multi-dimensional PB systems (Majumder et al., 2012a,b). This method provides an extremely powerful tool for modelling PB systems where advection (growth) may be dominant, and at least an equivalent method to those such as finite volumes for processes involving nucleation, agglomeration, and breakage. Additionally, LB methods are well-suited to large scale parallelization for solving their governing equations; an attractive characteristic of any modelling framework.

3.3 The Finite Volume Method

Finite Volume Methods (FVMs) are well suited to solving a wide array of Partial Differential Equations (PDEs), such as the set of hyperbolic PDEs that are the Population Balance equations. A finite volume method breaks a domain, denoted here as the continuous space \( \Lambda \), into a number of discrete sub-regions denoted here as \( \Omega \). The solution to the desired PDE (in this case, eq.3.12) can then be evaluated within each cell in the domain for each time-step required. This evaluation will return the numerical approximation for the \( i^{th} \) cell as \( \tilde{n}_i \), given by eq.3.6. Figure 3.1 illustrates how the domain
space can be broken up into cells, with each cell containing a discrete solution or output to eq.3.12. This is similar to the more general finite differencing method, however ones must be careful to provide a mass-conservative approach and hence a finite volume scheme.

![Discretized particle size domain](image)

**Figure 3.1**: Discretized particle size domain, \( N_i \) representing the cell-averaged value of the population density function in the \( i^{th} \) discretization cell (\( \Omega_i \)) within the numerical domain (\( \Lambda \)).

Like most discretization methods, FVMs can be semi or fully discrete. Fully discrete schemes provide explicit time-step control by discretizing over time as well as discretization over the abscissa; which in this case is the internal size coordinate \( (x) \), given in particle volume. For this work, a semi-discrete scheme is used as explicit time-step control was not required and the use of standard time-integrator functions, such as MATLAB’s ODE15s, provided adequate time-integration. Re-stating the general PB expression from eq.3.1 for crystallization processes, with zero net volume flux, and size-independent growth, this yields:

\[
\frac{\partial n(x,t)}{\partial t} + G \frac{\partial n(x,t)}{\partial x} = L^+_{\text{nuc}} + L^\pm_{\text{agg}} + L^\pm_{\text{break}} \tag{3.5}
\]

The sink-source terms \( (L^\pm) \) for nucleation, agglomeration, and breakage may take various forms depending on the specific mechanisms being implemented for each. What
must be done now is to formulate the aforementioned cell-averaged value in each discretization cell. This is given by the cell-centred average ($\tilde{n}_i$):

$$\tilde{n}_i = \frac{1}{\Delta x_i} \int_{\Omega_i} n(x, t) dx \quad (3.6)$$

Integration of eq.3.5 over the $i$th discretization cell ($\Omega_i$) and rearranging for $n(x, t)$ will result in a finite volume conservation for that cell of the form:

$$\frac{\partial}{\partial t} \int_{\Omega_i} n(x, t) dx = \int_{\Omega_i} L^+_{\text{nuc}} dx + \int_{\Omega_i} L^+_{\text{agg}} dx + \int_{\Omega_i} L^\pm_{\text{break}} dx - G \int_{\Omega_i} \frac{\partial n(x, t)}{\partial x} dx \quad (3.7)$$

Using the cell-average value for $n(x, t)$ from eq.3.6, and similarly for $L^+_{\text{nuc}}$, this yields:

$$\frac{\partial \tilde{n}_i}{\partial t} = \tilde{L}^+_{\text{nuc},i} + \int_{\Omega_i} L^\pm_{\text{agg}} dx + \int_{\Omega_i} L^\pm_{\text{break}} dx - G \int_{\Omega_i} \frac{\partial n(x, t)}{\partial x} dx \quad (3.8)$$

Equation 3.8 represents a general format of the FVM for PB applications in crystallization processes. The remaining step is to provide suitable numerical integration rules for the discrete integrals over $\Omega_i$ for each expression. Growth kinetics are governed via the growth operator $G$, here assumed to be size-independent; although size-dependent models can be incorporated if the operator is considered within the discretization integral. For the growth integral, straightforward differencing rules such as upwind or central differences can be used. Alternatively high-resolution flux limited schemes can be implemented for higher degrees of accuracy if desired (Koren, 1993; Qamar and Warnecke, 2007; Qamar et al., 2009). Nucleation kinetics are also relatively straightforward to implement with simple quadrature rules (such as midpoint or Gaussian) for integration of the equivalent cell average (eq.3.6) for $L^+_{\text{nuc}}$. However, the governing equations for breakage and agglomeration are expressed in terms of integral equations over the domain space. Breakage has been introduced in eq.3.4 and agglomeration is given by the Smoluchowski equation:

$$L^\pm_{\text{agg}} = \frac{1}{2} \int_0^x \beta_{\text{agg}}(x', x-x') n(x^*) n(x-x') dx' - n(x) \int_0^\infty \beta_{\text{agg}}(x, x') n(x') dx' \quad (3.9)$$

In agglomeration, particles of size $x'$ merge with those of size $x'$ to form new agglomerates of at a rate according to the agglomeration kernel $\beta_{\text{agg}}(x, x')$. This provides
the death mechanism by which particles of sizes $x$ or $x'$ may leave their respective size classes by merging with another particle to form size $x + x'$. Complementary to this, particles are borne into the size class $x$ at a rate according to $\beta_{agg}(x', x - x')$, providing the birth mechanism into size $x$ for $x' \in (0, x)$. As integral takes into account the agglomeration of all sizes less than $x$ that may agglomerate to form a new particle in $x$, and the agglomeration kernel is assumed to be symmetric ($\beta_{agg}(x, x') = \beta_{agg}(x'x)$), the integral must be halved in order to avoid doubling up over the domain. Thus, the forms used for the agglomeration ($L_{agg}^{\pm}$) and breakage ($L_{break}^{\pm}$) processes, present a larger challenge due to their inherent integro-differential nature of the PBE for these mechanisms.

Recent finite volume schemes have introduced weighted discretizations of the agglomeration (Forestier-Coste and Mancini, 2012) and breakage equations (Saha et al., 2016). These result in volume and number preserving finite volume formulations of the PB integro-differential equations without the need to additional reformulation of the breakage and agglomeration integrals (Filbet and Laurençot, 2004; Qamar et al., 2009). These forms avoid the requirement for any reformulation of equations 3.4 and 3.9 and provide discrete forms for the agglomeration ($\int_{\Omega_i} L_{agg}^{\pm} dx$) and breakage ($\int_{\Omega_i} L_{break}^{\pm} dx$) integral expressions. An outline of the discrete breakage equation is given in section 3.3.2. However, as agglomeration is only included here for the sake of a general PBE description the reader is referred to the work of Forestier-Coste and Mancini (2012) for details on the discrete formulation of agglomeration in a finite volume scheme. An outline of this formulation would require extensive discussion only serving to distract from the main focus of this work. Suffice to say that eq.3.8 provides the basis for any PB-FVM with the integral domain expression over $\Omega_i$ for each mechanism requiring consideration unique to the intended PB application and chosen kernels. The following section will now deal with the domain discretization itself and how the evaluation grid illustrated in fig.3.1 is constructed.

3.3.1 Domain Discretization

In order to discretize the full internal property domain space ($\Lambda$) across a given range there exists two common approaches to generating the solution domain intervals (Qamar et al., 2009): regular/uniform grids, and geometric grids. This grid will then
provide the cell definitions, according to required solution interval, that the numerical solution to the PBEs will be evaluated upon. While regular grids are often easier to implement, a geometric grid ensures the solution accurately capture gradients at small scales. Therefore, a geometric grid will allow more accurate modelling of breakage processes as the fragment size distribution is more properly captured in the smallest size scales; where solution gradients are most likely to be highest.

**Figure 3.2:** Detailed illustration of a discretization cell ($\Omega_i$) from fig.3.1. The FVM produces values at each $i_{th}$ cell centre, with $\tilde{n}_i$ representing the cell-averaged value, with the indices of each cell given below. The flux in each cell is determined via the finite volume formulation of the governing differential equations of the problem at hand.

**Geometric Grid** Taking $I$ as a large integer representing the total number of cells, and define $(x_{i-\frac{1}{2}})_{i=1,...,I+1}$ as the partitions of $[x_{\text{min}}, x_{\text{max}}]$ whereby $x_{\text{max}}$ and $x_{\text{min}}$ represent the maximum and minimum values of the property variable. Therefore, in order to generate the grid itself, define for $i = 1, 2, ..., I$:

\[
\begin{align*}
  x_{\frac{1}{2}} &= x_{\text{min}}, & x_{I+\frac{1}{2}} &= x_{\text{max}} \\
  x_{i+\frac{1}{2}} &= x_{\text{min}} + 2^{(i-1)/q}(x_{\text{max}} - x_{\text{min}}) 
\end{align*}
\]  

(3.10)

where parameter $q$ is used to control the extent of grid refinement at the smaller size ranges. The corresponding cell nodes are then given by:

\[
\begin{align*}
  x_i &= \frac{x_{i-\frac{1}{2}} + x_{i+\frac{1}{2}}}{2}, & \Delta x_i &= x_{i+\frac{1}{2}} - x_{i-\frac{1}{2}} 
\end{align*}
\]  

(3.11)

For this work, 400 grid points were used for all simulations. This number was chosen as it provided a balance of performance in evaluation and fidelity in the model results.
3. POPULATION BALANCES

The grid refinement parameter was chosen as \( q = 10 \), providing sufficient resolution at the lower size classes, where solution gradients are highest. This ensured that the generation of fine particles from breakage could be accurately modelled over a fine grid; accurately capturing the fragment size distributions for breakage.

3.3.2 Numerical Integration Scheme

While eq.3.5 represents a general crystallization PB model, the focus of this work considers breakage in isolation. As such, the growth, nucleation, an agglomeration integrals can be omitted. Thus, the resulting PBE for a stirred batch reactor for pure breakage eqns.3.2 and 3.4 can be recalled as:

\[
\frac{\partial n}{\partial t} = \int_{x}^{\infty} b(t, x, x') S(x') n(t, x') dx' - S(x) n(t, x) \tag{3.12}
\]

Equation 3.12 must now be discretized along the internal property coordinate of interest. As previously noted, in order to more appropriately model breakage events it is prudent to discretize along the crystal volume coordinate. A semi-discrete scheme is used here whereby the system is discretized only in the volume dimension. A fully discrete scheme \( \text{(Szilágyi and Nagy, 2018)} \) was not used as there is no requirement for explicit time-stepping control. The model can be numerically integrated over time with the use of common ODE solvers, such as MATLAB’s ODE suite. As previously outlined, the FVM for a breakage PB defines the solution as:

\[
\frac{\partial \hat{n}_i}{\partial t} = \int_{\Omega_i} E^\pm_{\text{break}} dx = \int_{x_{i-1/2}}^{x_{i+1/2}} \int_{x}^{\infty} b(t, x, x') S(x') n(t, x') dx' dx - \int_{x_{i-1/2}}^{x_{i+1/2}} S(x) n(t, x) dx \tag{3.13}
\]

By reversing the order of integration in eq.3.13 and providing discretization weights to ensure proper conservation of the fragmentation distribution, a mass conserving number preserving (MCNP) discrete formulation of the Finite Volume Scheme for eq.3.13 can be found. It is given as \( \text{(Saha et al., 2016)} \):

\[
\frac{\partial \tilde{n}_i}{\partial t} = \frac{1}{\Delta x_i} \sum_{k=1}^{I} \omega_k^b S_k \tilde{n}_k \Delta x_k \int_{x_{i-1/2}}^{x_{i+1/2}} b(x, x_k) dx - \omega_i^d S_i \tilde{n}_i \tag{3.14}
\]
where the weights $\omega^b_k$ and $\omega^d_i$ are defined by:

$$\omega^b_k = \frac{x_k [\nu(x_k) - 1]}{\sum_{j=1}^{k-1} (x_k - x_j) \int_{x_{j-1/2}}^{p_{kj}} b(x, x_k) dx}$$ (3.15)

$$\omega^d_i = \frac{\omega^b_i}{x_i} \sum_{k=1}^{i} x_k \int_{x_{k-1/2}}^{p_{ki}} b(x, x_i) dx$$ (3.16)

The integral limit $p_{ki}$ is defined:

$$p_{ki} = \begin{cases} x_i, & \text{if } k = i \\ x_{i+1/2}, & \text{if } k \neq i \end{cases}$$ (3.17)

and the term $\nu(y)$ denotes the total number of fragments a particle of size $y$ generates upon breakage, and is given by:

$$\nu(y) = \int_{0}^{y} b(x, y) dx$$ (3.18)

Lastly, note that $\hat{n}_i$ is to be taken as the numerical approximation of the average number density function $n_i(x, t)$ for:

$$n_i(x, t) = \frac{1}{\Delta x_i} \int_{\Omega_i} n(x, t) dx$$ (3.19)

For an appropriately proportioned domain mesh that ensures a sufficiently smooth number density function across the domain, it can be said that $n_i(t, x)$ and $n(t, x)$ are identical up to an order of $\Delta x^2$ (Saha et al., 2016). The weights in eqs. (3.15) and (3.16) essentially ensure that the system will conserve both the zeroth and first moments of the system by weighting the interaction between selection and re-distribution so that the system remains conservative for arbitrary choices of breakage functions. Additionally, at $i = 1$ and $i = I$ one may use simple forward and backward differencing formulas respectively in order to easily maintain boundary conditions.

As a matter of efficiency, if the solution grid and $b(x, x')$ integrands in eqs. (3.14) to (3.16) can be said to be time-independent these terms may be evaluated outside of the time-integration step and stored in memory. This vastly reduces the number of
computations required in each numerical integration step, resulting in solution times on the order of seconds. A time-dependent selection function has been applied in literature by Hounslow, Pearson and Instone (2001), however, it is stipulated here that the selection rate is a function of hydrodynamic parameters and material constants. Therefore, if the system is said to be operating at isothermal, steady-state conditions any time-dependence on selection function may be misinterpreted size-dependence as the population evolves towards smaller sizes over time due to comminution. Therefore, this apparent breakage function time-dependence is rather an artefact of the population density’s time-evolution. This can also be reasoned from Kapur and Agrawal (1970) and the approach of a power series to solve for the population density over time. This seemingly time-dependent behaviour is a direct consequence of the selection function’s variation with size coupled with the fact that the numbers of particles in each size is changing over time as breakage occurs. Therefore, by providing a form for this selection function based on physical constants it would be expected that the two approaches behave similarly, as it has already been shown that Kapur’s approach is valid for at least short time scales (Raman et al. 2011; Xiouras et al. 2018).

Utilizing eqs. (2.20), (2.23), (2.24), (2.26), (2.33) and (3.14), the solution to equation 3.12 can be found with an appropriate time-based ODE solver. For this work MATLAB’s ODE15s solver was used; this function returns a variable-step variable-order (VSVO) solver to integrate the PBE with respect to time using numerical differentiation formulas (NDFs) (Shampine and Reichelt 1997; Shampine et al. 1999).

3.4 Summary

The numerical model and solution method have been outlined above. A finite volume scheme for pure breakage in a Population Balance framework has been formalized and discussed in the broader context of population balance solution methods. A discussion on the preservation of total particle numbers and conservation of volume has been carried out, and the importance of these factors in regards to accurate breakage modelling is highlighted. For the model to properly conserve mass, it is a requirement that the zeroth and first order moment be conserved when using particle volume as the internal coordinate in the Population Balance framework. The Mass Conserving Number Preserving (MCNP) discretization developed by Saha et al. (2016) is detailed with regards
3.4 Summary

to its use in providing the numerical solution for breakage via eq. 3.4. Lastly, the kinetic expressions for the breakage mechanisms in this scheme have been discussed in terms of their general implementation and required parameters. This serves to clarify the roles of the selection function \( S(x) \) and fragment distribution function \( b(x, x') \) detailed in section 2.4. Overall, this section provides the mathematical background to the Finite Volume Population Balance model, the result of which are presented in chapter 6.
3. POPULATION BALANCES
Experimental Apparatus & Methods

In this chapter the experimental apparatus and methods used to obtain the results in both Chapter 5 and Chapter 6 are detailed. The shadowgraphy technique is outlined in brief, and discussed with regards to its use in determining the hydrodynamic factors associated with particle collision with a flat surface; such as an impeller blade during a typical agitated crystallization process. This technique is also used in conjunction with a post-processing script written in Python (see Appendix 7.3) to determine the critical failure velocities of each crystal material and to determine the relationship between failure probability, crystal size, and impact velocity. These experimental methods are used to provide quantitative evidence of hydrodynamic and material response boundaries that must be overcome in order to result in crystal breakage, as seen in Chapter 5.

A crystal nano-indentation technique is also detailed, and its application in determining the required elastic moduli for each crystal material is discussed. Challenges in sample preparation due to the delicate nature of crystals and their sensitivity to solvents used in typical mounting media, such as epoxy or acrylic resins, are also outlined.

Lastly, the two experimental agitation vessels for providing Particle Size Distributions (PSDs) of pure breakage processes are illustrated. The Malvern Hydro 3000 Particle Size Analysis (PSA) apparatus is discussed in terms of its use in providing...
in-situ PSA within a surrogate crystallization vessel capable of high agitation rates (2500RPM) without vortex formation of the suspension fluid’s free-surface. A similar vessel is detailed for the lower agitation rates (500RPM), in addition to an offline Malvern Morphologi PSA technique. Importantly, these two agitation systems provide two unique hydrodynamic environments for each crystal material and provide valuable comparative datasets for the Population Balance model results presented in Chapter 7. The material properties for each crystal material tested are given at the end of this chapter in tables 4.2, 4.3, and 4.4.

4.1 Shadowgraphy Imaging

A shadowgraphy imaging technique was used to track particle sizes and velocities as they approach and collide with a target surface. This provides an experimental surrogate for crystal-crystallizer collisions over a range of crystal sizes and inlet velocities. In order to generate consistent velocities for particle impact testing, a bespoke testing apparatus was developed. An enclosed test section with good optical access enables the formation and observation of a controlled impinging fluid column.

Two variations of the impactor were developed in order to deal with both air and liquid transport phases. Tests carried out in air form the datasets for the material response characteristics as in this scenario the hydrodynamic factors are mitigated. This is due to air having a much lower absolute viscosity and as such any boundary layer effects will be negligible, as discussed in Tyrrell et al. (2018) and Marble (1964). Tests carried out in the liquid transport phase were used to determine the effects of hydrodynamic factors associated with particle-surface collisions. Therefore, the two variations serve to complement each other in determining the hydrodynamic and material response factors as each topic can be studied in isolation.

**Liquid System** For the liquid-based method, a pressurized air reservoir was used in order to develop the required inlet liquid flow velocity. This provided a relatively inexpensive and straightforward method for producing a consistent inlet velocity, ensuring viscous drag does not slow the particle to its terminal velocity before measurement can begin. In addition to this, the inlet nozzle was kept at a constant 10mm distance from
the target plane in order to ensure an approximately constant flow velocity normal to
the target surface. Therefore, any measured particle deceleration is solely attributable
to the squeeze film boundary layer interaction between the particle and target surface.
The testing mechanism utilized a particle-fluid solution held at a desired pressure and
released through a nozzle into the test chamber. A high-speed control valve allowed the
inlet velocity of particles to be controlled accurately. Direct measurement of particle
impact velocities can then be gained from the Shadowgraphy imaging technique.

Crystals of paracetamol (A5000 Acetaminophen) were suspended in a saturated
solution of deionised water as the use of solvents, or indeed non-solvent suspension
fluids, was seen to be unnecessary under the assumption that dimensionless parameters
such as Reynolds and Stokes numbers can be correlated regardless of the choice of
liquid phase. A stainless steel target was used in order to accurately represent a typical
industrial-scale impeller blade, however the material properties of the target surface
have a very minimal effect on the magnitude of the cushioning effect. The inlet flow
angle was maintained at a constant 90° to the target surface in order to more easily
quantify particle velocities. More oblique angle of impact would merely result in greater
deflection of incoming particles. Therefore, the conditions under which the impacts were
carried out are representative of the most aggressive conditions a particle could come
4. EXPERIMENTAL APPARATUS & METHODS

to expect in practice. Thus if breakage remained unseen in these cases, it could easily be stipulated that it would also not occur under the majority of similar crystallization processes. Crystals used here are within a nominal range of $100 \rightarrow 400\mu m$, with inlet flow velocities between $1 \rightarrow 10m/s$.

**Air System** For the air-based impact tester, the fluid column could be held at a specified inlet velocity set by a programmable Mass Flow Controller (MFC). Introduction of particles into the flow was controlled via a venturi tube inlet system that ensured crystals were accelerated along a straight track, avoiding any potential pre-stressing. Prior to loading crystals into the particle feed hopper, the MFC is allowed to reach steady-state flow before measurement begins. This allowed any inlet velocity fluctuations to settle, reducing potential systematic error. Once the inlet velocity had reached steady-state, the capture sequence was initiated, crystals were loaded into the venturi feed, and flow carried the crystals into the measurement volume at a pre-determined inlet velocity. Direct measurement of particle impact velocities was then gained from the Shadowgraphy imaging technique.

![Air-based impact testing schematic](Tyrrell and Frawley, 2018)

A stainless steel target was used in both cases in order to minimize any influence of the target’s material properties on crystal breakage results, i.e. the Young’s Modulus of each material satisfies $E_{target} \gg E_{crystal}$. As previously mentioned, impact angles
were maintained at 90°. This allows for the simplification of \( c = u_f \) from \( \sin \frac{\pi}{2} = 1 \); making experimental measurements easier to process and interpret.

### 4.1.1 Shadowgraphy Processing

Crystal velocities and equivalent spherical diameters are measured through a shadowgraphy particle tracking technique, similar to that in [Hadavi et al. (2016a)](#). This method images individual particles as they approach a target surface. Particle tracking is enabled via a peak-searching algorithm tailored to identify specific particle sizes and shapes. The observation window is uniformly backlit and the resulting particle silhouettes are tracked through an image inversion process. Particle velocity vectors and sizes can be determined and tracked through the entire capture sequence. Images are acquired via long-range microscopy coupled with a high-speed camera capable of capturing images at up to 125,000 Hz, providing excellent temporal resolution for particles velocity calculations. Using this method it is possible to track particles down to 1 µm in resolution, allowing precise measurement of the parent crystal’s size and velocity upon collision with the target surface.

As the raw image being captured is of particle silhouettes, a high-quality background image must first be taken in order for an image inversion process to yield a photographic negative that transforms particle shadows to light-intensities; this process is outlined in fig.4.3. Through this inversion, a peak-searching algorithm can then identify particle boundaries, and calculate sizes and velocities between sequential frames.

![Reference Acquired Inversion](image)

**Figure 4.3:** Sample image inversion process; two captured particles become light intensities after subtracting a reference image.
4. EXPERIMENTAL APPARATUS & METHODS

The inverted image is then searched for pixels that match a global light-intensity threshold. For example, it might only consider a pixel to be part of a crystal if its intensity is above 50% of the maximum intensity of the whole image. The global threshold value is set by the operator in order to provide the best match to the visible silhouette. Figure 4.4 outlines this Global Threshold for a first pass in identifying all possible particles.

![Figure 4.4: Shadowgraphy global segmentation (particle identification)](image)

However, factors such as imperfections in target surfaces, pixel noise, background image noise, and out-of-focus particles can lead to spurious or unwanted particle representations. Therefore, it is imperative that images are thoroughly processed in order to eliminate any such error as derived velocities can be affected by misrepresented particles. Filtering of particle noise is controlled via a series of user-defined limits associated with maximum and minimum light intensities and their respective spatial distributions. Fig 4.5 shows an example of how a specific particle can be filtered using high and low-pass filters. In this case the particle is either above or within the high and low-pass bands, i.e. the particle is sufficiently focused. The limits of these high and low-pass filters are tuned manually and should be fixed at a point where, ideally, all background particles are neglected and only the particle of interest is tracked.

As an additional step, image noise is reduced by normalising the camera sensor before each capture sequence, and background noise is reduced by averaging a background reference image over 10 images in order to yield a more uniform background.
image. Specific particle sizes can also be filtered to eliminate any remaining micron-scale noise being misrepresented as particles and affecting subsequent image calculations. Furthermore, particles can be filtered by area, minimum or maximum diameter, circularity, and velocity in order to filter out any unwanted data. Individual particle velocities are found quite readily as each particle’s location is known between frames and the time-step value is fixed by the image capture rate known to the system. It is in this way that the shadowgraphy method provides an excellent platform for the measurement of $u_f$ over a range of crystal sizes and velocities. Figure 4.6 illustrates the resulting images from the shadowgraphy technique. The approaching crystal’s sizes and velocity can be measured directly throughout approach and collision with the target surface.

**Figure 4.5:** Shadowgraphy secondary segmentation (particle filter)

**Figure 4.6:** Sample processed shadowgraphy image with particle size ($D_c$) and velocity ($V_i$) overlay
4. EXPERIMENTAL APPARATUS & METHODS

4.2 Crystal Nano-Indentation

In order to determine the mechanical properties of the Darunavir Ethanolate crystals a nano-indentation technique was employed, yielding data on the Young’s Modulus ($E_c$). Estimates for these properties are seldom reported in literature due the delicate nature of pharmaceutical crystals, however there does exists some data for a small number of compounds (Varughese et al., 2013). The application of nanoindentation specific to crystal engineering is relatively new and there exists some literature detailing how this method can be used to generate elastic moduli, hardness, and fracture toughness values (Ju. et al., 2007; Liu et al., 2008; Varughese et al., 2013). Importantly, nano-indentation requires samples to have a low surface roughness and a stable mounting medium to hold the crystals while the indentation is carried out, usually over a number of hours. Both of these requirements present their own set of difficulties as such small and delicate crystals need to be handled carefully. Furthermore, due to their soluble nature they often prove troublesome to set in hard-set resins or similar mounting methods. Therefore, not only are samples a challenge to mount for indentation, but also require very careful grinding and polishing in order to result in a sufficiently smooth surface for indentation.

For the work presented here, crystals were placed into cylindrical moulds to form pucks of the approximate shape and size required for the translation stage in the nano-indentation system. A fast-setting acrylic-based resin was then poured in to fill the mould and secure the crystals in place once set. The pucks were then released from their moulds and ground down to expose the mounted crystals within. They were further polished to a sufficient surface finish in order to enable accurate indentation results. Once secured in the indentation platform, the system is given

![Continuous Stiffness Measurement (CSM) technique](Li and Bhushan, 2002)
4.2 Crystal Nano-Indentation

...a set of user-defined indentation locations and instructed to carry out the indentations at its discretion. Small fluctuations in displacement may cause the indentation to fail, therefore the system waits for these to drop below acceptable limits while the automated tests are carried out. Thermal variations and environmental vibrations are major sources of surface drift. As such, the system is kept in a temperature-controlled room within a vibration isolating stage in order to minimize any external perturbations.

The Continuous Stiffness Measurement (CSM) technique was used here to calculate the elastic modulus, chosen for its ability to continuously track the resulting modulus; allowing data to be captured for even incomplete indentation attempts (Li and Bhushan, 2002). This technique utilizes harmonic loading force superimposed over the nominally increasing indentation load \( P \), illustrated in fig.4.7. The in-phase and out-of-phase displacement responses resulting from this harmonic loading can then be resolved to determine a contact stiffness \( S \) as a continuous function of depth. The advantage of this method lies with the ability to continuously measure the contact stiffness throughout loading, in contrast to the quasi-static method whereby stiffness may only be determined during unloading. Not only does this enable tracking of depth-dependent properties, but it is also less sensitive to thermal drift (Asif and Pethica, 1996), enabling greater ease of use. Furthermore, the continuous measurement of properties allows for complete data recovery even if indentation fails at some point before or during loading/unloading. This may be useful in designing more reliable experiment procedures and evaluating the performance of materials where failure may occur before unloading.

In order to determine the sample’s contact stiffness, a spring and dash-pot system is used to model the response of the sample. Figure 4.8 illustrates the model system that is typically used to determine the required relationships between the applied load and resulting displacement. The indenter support spring constant \( K_s \), stiffness of the indenter frame \( K_f = C_f \), frame load compliance \( C_f \), and indenter mass \( m \) are known constants for any given testing apparatus. As such, the dynamic response of the model can be written in terms of the desired contact stiffness value \( S \), and the damping coefficient \( C \) due to air gaps in the sensing capacitors. Considering that the applied load is a forced harmonic at a frequency \( \omega \) and is of the form \( P = P_0 e^{i\omega t} \)
4. EXPERIMENTAL APPARATUS & METHODS

Figure 4.8: Material response model for CSM stiffness determination, reproduced from Li and Bhushan (2002)

with amplitude $P_0$, and the indenter displacement response is $h(\omega) = h_0 e^{i(\omega t + \phi)}$ with amplitude $h_0$ and phase angle $\phi$, the contact stiffness can be evaluated as:

$$\left| \frac{P_0}{h(\omega)} \right| = \sqrt{\left(\left(S^{-1} + K_f^{-1}\right)^{-1} + K_S - m\omega^2\right)^2 + \omega^2C^2}$$  \hspace{1cm} (4.1)

The phase angle between the applied force and the resulting displacement signals can be given as:

$$\tan(\phi) = \frac{\omega C}{\left(S^{-1} + K_f^{-1}\right)^{-1} + K_S - m\omega^2}$$  \hspace{1cm} (4.2)

Rearranging eqs. (4.1) and (4.2) for the stiffness ($S$) and damping ($\omega C$) one obtains:

$$S = \frac{1}{\frac{P_0}{h(\omega)} \cos \phi - (K_S - m\omega^2) - K_f^{-1}}$$  \hspace{1cm} (4.3)

$$\omega C = \frac{P_0}{h(\omega)} \sin \phi$$  \hspace{1cm} (4.4)

The contact stiffness of the sample can now be determined from the load-displacement relationships above. The elastic modulus can be extracted via Li and Bhushan (2002), Oliver and Pharr (1992), Sneddon (1965):

$$S = 2\beta \sqrt{\frac{A}{\pi}E_r}$$  \hspace{1cm} (4.5)
4.3 Agitated Vessels & Particle Size Analysis

Where $\beta$ is a constant that depends on the indenter geometry, $A$ is the contact area, and $E_r$ is the reduced elastic modulus that accounts for deformation in both the sample and the indenter. $E_r$ is given by:

$$
E_r = \frac{1 - \nu_s^2}{E_s} + \frac{1 - \nu_i^2}{E_i}
$$

(4.6)

Where the Poisson’s ratio ($\nu$) and elastic modulus ($E$) of both the sample and the indenter, denoted by subscripts $s$ and $i$, are required. Therefore, eqns. (4.3) and (4.4) combined with eqns. (4.5) and (4.6) provide a means to extract the sample’s elastic modulus via the CSM nano-indentation technique.

4.3 Agitated Vessels & Particle Size Analysis

Darunavir Ethanolate (Prezista), Acetaminophen (Paracetamol), and Pregabalin (Lyrica) were each subject to a mechanically intensive stirring process over the course of several hours. This resulted in a total of 5 experimental PSDs, providing the test sets for the proposed model in estimating the hydrodynamic and material response parameters. Each experiment was carried out in a non-solvent to avoid growth and nucleation concerns. This also ensured that evaporation of the suspension fluid was not a factor, something that may be an issue in typical solvent-based systems. As a result, the experimental data is effectively the representation of the proportion of breakage in an agitated vessel; the ideal validation dataset for the proposed model.

The experimental datasets consist of two major subsets: those conducted with PSA in-situ, and those conducted in a overhead stirred crystallization analogue with external offline PSA. The in-situ experiments were conducted in order to obtain the higher RPM limit at 2500 where breakage is considered to be dominant, and provided extrema for model validation. The high-RPM studies can be used to parameterize the material response characteristics, principally those in eq. (2.26) in a scenario where breakage can be considered as the dominant mechanism, i.e. crystal breakage in isolation from any other mechanism. As the breakage model parameters in eq. (2.26) for Prezista have been determined previously (Tyrrell and Frawley 2018), the 2500RPM dataset was not required for this API. Therefore, these sets are only required for the two remaining compounds: Paracetamol and Pregabalin.
Figure 4.9: Shown again for clarity, the simplified volume schematic of generic closed system for agitated crystallization. Dimensions for each agitation system are given in Table 4.1.

For the crystallization analogues, the vessels were agitated at a nominal RPM of 500 in order to represent the higher limit of typical stirred crystallization vessels; past 500 RPM the free-surface of the suspension medium formed a severe vortex and as such no experimental data was taken past this condition for the sake of maintaining similarity to typical crystallization systems. The resulting datasets then provide a benchmark as to the models accuracy in describing breakage processes via the proposed model.

**Table 4.1:** Vessel dimensions for each agitation experiments.

<table>
<thead>
<tr>
<th>Experimental Setup</th>
<th>Vessel Height</th>
<th>Vessel Diameter</th>
<th>Impeller Height</th>
<th>Impeller Diameter</th>
<th>Impeller Flow Number</th>
<th>Fill Height</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>137.5mm</td>
<td>75.0mm</td>
<td>5.75mm</td>
<td>28.85mm</td>
<td>0.50</td>
<td>50.0mm</td>
</tr>
<tr>
<td>2</td>
<td>55.0mm</td>
<td>88.5mm</td>
<td>6.5mm</td>
<td>56.0mm</td>
<td>0.70</td>
<td>55.0mm</td>
</tr>
</tbody>
</table>

A Malvern Mastersizer 3000 Hydro Particle Size Analysis (PSA) instrument was used in order to obtain the in-situ PSDs, while a Mastersizer Morphologi instrument was used for offline PSA with the crystallization analogue. The use of the Malvern Morphologi instrument for the crystallization analogues ensured that no additional breakage occurred after samples were taken from as any additional stirring may contaminate the process output PSD. However, for the case of in-situ measurements this effect is negligible as the measurement vessel serves dually as the stirring vessel itself. Furthermore, the decision to use vegetable oil as a suspension fluid during the in-situ
4.4 Summary

Discussed above are the methodologies for tracking particle sizes and impact velocities using the Shadowgraphy technique, determining crystal elastic moduli via nanoindentation, and the experimental flow for obtaining breakage dominant PSDs for each compound and RPM pair.
4. EXPERIMENTAL APPARATUS & METHODS

Shadowgraphy imaging provides the experimental method for identifying the behaviour of particles near a colliding surface when submersed in a liquid solution and forms the basis of evidence for the hydrodynamic parameters. The shadowgraphy technique was also employed in determining the breakage probabilities of crystals impacting a target surface when the hydrodynamic factors were negligible (in air). These datasets provided the particle sizes and collision velocities that result in breakage, and were used to demonstrate the validity of the selection function theory described in section 2.4.1.

A crystal nanoindentation technique was used to determine the elastic moduli for each API; a fundamental characteristic constant for the material response parameters of each crystal. Lastly, the Malvern Mastersizer and Morphologi PSA techniques were used to provide the experimental PSD validation sets for the proposed breakage model. These sets are representative of two agitation vessels: one at 2500RPM in rapeseed oil, and the other at 500RPM in cyclohexane. The use of two different suspension fluids and RPMs provides a test as to the models ability to parameterize for various hydrodynamic conditions. The use of three separate APIs provides a test for the parameterization of material response factors. The results of this parametrization (determination of $F_{cr}$) can also be compared to those determined experimentally, via the shadowgraphy method, for Prezista.
Crystal-Crystallizer Interactions

In this chapter the area of crystal-crystallizer interactions will be investigated with regards to crystal breakage. Specifically those concerned with crystal-impeller collisions as they represent the harshest mechanical environment a crystal may experience during a stirred batch crystallization. As shown in Tyrrell et al. (2018), the role of an impeller squeeze film boundary layer is investigated in detail here with quantitative data presented on how this phenomenon can effectively protect crystals from breakage effects at the impeller. Thus demonstrating the role of hydrodynamics in governing fundamental crystal collision frequencies.

The role of crystal material characteristics in determining crystal breakage probabilities is then discussed. As demonstrated by Tyrrell and Frawley (2018), for a given crystal elastic modulus and fracture toughness, the likelihood of breakage can be determined via established comminution laws (Salman et al., 1995). Therefore, if a collision frequency and impact velocity can be determined from hydrodynamic factors, this breakage probability will result in the fraction of the population to undergo breakage. Combined, these factors provide the basis for a new crystal breakage model for agitated crystallization experiments.

5.1 Squeeze Film Boundary Layer - Tyrrell et al. (2018)

The theoretical foundations for predicting the cushioning-effect of squeeze films has been well documented in literature (Clark, 1995; Clark and Burmeister, 1992, 2004; Clark and Hartwich, 2001; Uddin et al., 2004; Wenglarz, 1982). The squeeze film
boundary layer can be considered as a volume of fluid that must “escape” the volume trapped between an approaching particle and the target surface. Illustrated in fig. 5.1 is this control volume trapped between the target surface and the approaching particle, with an equivalent cylinder used to simplify the definition of the control volume.

Looking at fig. 5.1 it is clear that the displacement of fluid from this control volume will extract a considerable amount of work from the approaching particle, thus reducing its velocity. Furthermore, considering that the suspension phase here is liquid water the assumption of constant density is implicit. Therefore, with compressibility effects negated, the particle must be slowed to allow for the fluid to escape from the squeeze film in time. A clear way to interpret this effect is to apply a mass conservation to the control volume:

\[-\pi R^2 V_p = 2\pi Rh V_{av}\]  \hspace{1cm} (5.1)

Evidently the rate at which a particle can approach a target surface \((V_p)\) is directly linked to the average rate at which fluid can escape the bounded cavity between them \((V_{av})\). The solution for \(V_p\) above can be found from Clark and Burmeister (1992). However, given briefly the extent to which particle-plane collisions are softened by this squeeze film is inversely proportional to the particle-fluid density ratio and freestream particle Reynolds number. Therefore, by simultaneously measuring particle sizes and
velocities it would be possible to determine the link between particle Reynolds numbers and squeeze film particle arrest experimentally.

### 5.1.1 Particle Size Effect

As is evidenced in fig 5.2, the velocity gradient proved to be largely independent of particle size. Particles of 400 $\mu m$ to 100 $\mu m$ for initial velocities of 2 m/s and 6 m/s are presented here for comparison yet it is only within approximately 500 $\mu m$ of the target surface that a difference in particle sets manifests itself in either a collision event or particle arrest. This is highly characteristic of a squeeze film boundary layer effect cushioning particles in close proximity to the target surface. Furthermore, if additional factors such as Stokes drag were to play a significant role in particle arrest there would be a more observable particle size dependency between sets.

![Figure 5.2: The effect of particle size on velocity profiles near the boundary wall for particle sizes of 100 – 400 $\mu m$](image)

Qualitatively, a driving factor in whether or not a particle will collide is thought to be its inertia, whereby particles with a larger inertia have a much stronger tendency to penetrate the squeeze film boundary layer. However, a direct link to a measure of particle inertia such as the Stokes number is difficult to quantify as the characteristic
flow length, $l_0$, and particle relaxation time, $\tau$, in

$$Stk = \frac{V_p \tau}{l_0}$$ (5.2)

need to be appropriately defined in order to accurately represent the ultra-Stokesian flow regime here where $Re \gg 1$. Furthermore, particle geometry likely plays a large role in determining if surface collision will result. Particles with similar masses yet different geometries will present different areas to the target surface; thereby increasing or decreasing the magnitude of the retardant force with area. Therefore, a more readily available method for discriminating between particle collision or arrest is the freestream particle Reynolds number. A threshold between contact and non-contact particles could then be defined through an associated critical freestream particle Reynolds number.

### 5.1.2 Particle Trajectories

Now, in order to determine a critical Reynolds number outlining the threshold between surface contact and particle arrest, nominal particle sizes of 100, 200, 300, and 400µm were used in conjunction with those velocities representative of blade tip-speeds ($1 \rightarrow 10$ m/s). Starting with the 300 & 400µm particle sizes in fig.5.3 collision was evident in all cases, with particles seen to retain approximately 10% of their initial velocity upon collision. However, with such small impact velocities there was no observable crystal fragmentation suggesting that the squeeze film can effectively prevent direct mechanical breakage in these cases. Furthermore, this then lends credit to a particle fatiguing mechanism suggested by [De Souza et al. (2016)](deSouza2016) for extremely long time-scale processes as these low-velocity collisions may build up stress over time in the crystal structure and cause micro-attrition over time.

However, the data in fig.5.3 is unable to identify the threshold between contact and arrest as all particles are seen to impact the target surface ($y = 0$) with some small residual velocity. Therefore, in order to determine a critical Reynolds number for arrest, particle sizes were reduced to the effect of reducing their associated Reynolds number. Thus, at this lower spectrum of Reynolds numbers the point at which particle arrest will occur can be more easily determined. Furthermore, a formal definition for cases of complete particle arrest is now required. A sensible definition for this point
is the freestream particle Reynolds number for which a particle only \textit{just} collides with the surface, i.e. those freestream particle Reynolds numbers for which \( V_0 \approx 0 \) at \( h = 0 \).

Following this, the velocity profiles of 100, 200, and 300\,\mu m particle sizes shown in fig.5.4 are indicative of the limiting behaviour of a squeeze film effect near the target surface. It is evident that the particles’ normal velocities are approaching zero at some finite distance, \( \delta \), from the target surface. The 300\,\mu m particle is seen to collide some small residual velocity, while the 200\,\mu m particle is arrested before collision; indicating a threshold has been crossed whereby collision is no longer probable. From here, the freestream Reynolds numbers of each case can then be seen in fig.5.5 plotted alongside \( \delta \); the distance from the target at which the particle’s normal velocity component approaches zero. It is evident now, that particle’s with Reynolds numbers above 250 can be expected to contact the target surface with a finite residual velocity. Those particles below this threshold are then observed to arrest and redirect with the flow.
as they approach the target plane. Following this, the formal definition of a critical Reynolds number can then be given as:

$$Re_c = \frac{\rho V_c d_c}{\mu} = 250$$

(5.3)

Where $V_c$ and $d_c$ represent the critical freestream velocity and particle diameter, above which contact is likely to occur. Therefore, at some given freestream velocity there will be an associated critical particle diameter, below which particles will be fully arrested by the squeeze film boundary layer. Conversely, the same is true that for a given PSD there exists some critical freestream velocity, or tip-speed, below which particle arrest will occur.

As a matter of interest, the particle Stokes number were investigated despite the inherent trouble in defining the particle relaxation time ($\tau$) as previously stated. A functional form for this relaxation time is given in terms of particle density ($\rho_p$), particle diameter ($d_p$), and fluid dynamic viscosity ($\mu$) (Lau and Nathan 2016):

$$\tau = \frac{\rho_p d_p^2}{18\mu}$$

(5.4)
5.1 Squeeze Film Boundary Layer - Tyrrell et al. (2018)

Figure 5.5: Reynolds Numbers at particle inlet plotted against the particle’s distance to the target surface as its velocity approaches zero, i.e. $\delta \geq 0$ implies no collision.

It is important to note here that eq.5.4 corresponds to a Stokesian flow regime that has special consideration for how the coefficient of drag ($C_D$) varies with Reynolds number. For eq.5.4, it must be said that $C_D \propto \frac{1}{Re}$ which is typically only accurate for $Re < 1$. Therefore, the presented Stokes numbers here for larger Reynolds numbers will tend to underestimate the Stokesian drag, and hence overestimate the Stokes number itself. Essentially, this amounts to the drag acting on a particle not being fully represented in the non-Stokesian regime. In order to correct for this a non-Stokes drag correction factor was introduced by Israel and Rosner (1983) and results in the effective Stokes number:

$$Stk_{eff} = \psi(Re_p)Stk$$  \hspace{1cm} (5.5)

where the Stokes efficiency, and particle Reynolds number are given by:

$$\psi(Re_p) = \frac{24}{Re_p} \int_0^{Re_p} \frac{1}{C_D(Re')Re'}dRe'$$  \hspace{1cm} (5.6)

$$Re_p = \frac{\rho V_p d_p}{\mu}$$  \hspace{1cm} (5.7)

The remaining step is to determine an appropriate correlation for $C_D(Re')$ in the integrand denominator for eq.5.6. This effectively corrects for the error introduced by implementing eq.5.4 for those cases where $Re \gg 1$. This correlation was investigated
5. CRYSTAL-CRYSTALLIZER INTERACTIONS

with two proposed models: the Schiller-Neumann formula \cite{Kelbaliyev2011}, and the Hölzer-Sommerfeld correlation \cite{HölzerSommerfeld2008}. As an additional point of clarity: Reynolds numbers are used here in a general sense, however, in the context of this work the most useful definition is that pertaining to the particle velocity and size, i.e. the particle Reynolds number as defined by eq.\ref{eq:5.7}.

**Schiller-Naumann** From \cite{Kelbaliyev2011}, it can be stated that for \( Re \leq 500 \) the relationship between Reynolds number and drag coefficient can be given in a general format of:

\[
C_D = \frac{24}{Re} (1 + ARe^n) \tag{5.8}
\]

The above represents standard drag curve for solid spherical particles \cite{BagchiBalachandar2003,Cliftetal2005}. The Schiller-Naumann formula sets these parameters at \( A = 0.15 \) and \( n = 0.687 \), derived from experimental data in \cite{SchillerNaumann1933}.

**Hölzer-Sommerfeld** \cite{HölzerSommerfeld2008} developed a correlation for \( C_D \) based on extensive experimentation and is essentially a linear combination of the non-Stokesian and Stokesian models:

\[
C_D = \frac{8}{Re} \frac{1}{\sqrt{\varphi}} + \frac{16}{Re} \frac{1}{\sqrt{\varphi}} + \frac{3}{\sqrt{Re}} \frac{1}{\varphi_\parallel} + 0.4210^{0.4(-\log \varphi)^{0.2}} \frac{1}{\varphi_\perp} \tag{5.9}
\]

where the terms \( \varphi \), \( \varphi_\parallel \), and \( \varphi_\perp \) effectively represent the various shape factors associated with particle orientation. From \cite{HölzerSommerfeld2008} these are formally defined as:

\[
\varphi = \frac{\text{Area}_{\text{sphere}}}{\text{Area}_{\text{particle}}} \quad \varphi_\perp = \frac{\text{CSA}_{\text{sphere}}}{(\text{Projected Area})_{\text{particle}}} \quad \varphi_\parallel = \frac{\text{CSA}_{\text{sphere}}}{2} - (\text{Projected Longitudinal CSA})_{\text{particle}}
\]

A comparison between the Schiller-Neumann and Hölzer-Sommerfeld models can be seen in fig.\ref{fig:5.6}. In order to obtain a useful comparison, the Hölzer-Sommerfeld model is given two sets of shape factors. It is clear that some first-pass parametrization of the shape factors above, it is possible to roughly mimic the Schiller-Naumann model through eq.\ref{eq:5.9}.
5.1 Squeeze Film Boundary Layer - Tyrrell et al. (2018)

Figure 5.6: Comparison between Schiller-Neumann and Hölzer-Sommerfeld models for evaluating $C_D(Re)$.

For this reason, the Hölzer-Sommerfeld (HS) model was chosen as the most appropriate drag model as it incorporated non-spherical effects and may more rigorously describe the Reynolds-drag relationship. The remaining portion of this analysis is to evaluate the integral itself in eq. 5.6 in order to determine a more accurate Stokes number via eqs. (5.2), (5.4) and (5.5). Figure 5.7 shows clearly how the effective Stokes number for increasing Reynolds numbers is affected via the Stokes efficiency.

Figure 5.7: Stokes efficiency factor ($\psi(Re)$) with increasing Reynolds numbers. Note that $\psi(Re) \to 1$ as $C_D \to 24/Re$.

Applying this updated formulation for the particle Stokes number, it can be seen in fig.5.8 that according to the prescribed drag laws (HS) all particles below $\sim 1,600 \mu m$
should be able to effectively follow the flow streamlines. Additionally, the naive Stokes number without consideration for any drag law tends to underestimate the drag on a particle and thus provides a lower limit of $\sim 600 \mu m$. However, this is not the full picture as while particles may be able to advect with the flow efficiently there still remains the consideration for the role of the squeeze film boundary layer. Essentially, those particles with lower Reynolds numbers are seen to be unable to penetrate this boundary layer; resulting in a complete arrest of their incoming orthogonal velocity component in accordance with literature (Clark and Hartwich, 2001).

![Particle Reynolds & Stokes numbers with increasing size.](image)

From this, it is stipulated that the impact rate of particles within an agitated vessel be a function of both Stokes and Reynolds numbers. While Stokes numbers indicate that the majority of particles are capable of slowing to approximately 10% of their initial approach velocity, the Reynolds number of each particle serves as an indication of its ability to penetrate the surface squeeze film boundary layer and result in a collision event. Therefore, the proceeding section will detail a proposed probabilistic model for predicting collision events based on particle Reynolds numbers with collision speeds.
5.1 Squeeze Film Boundary Layer - Tyrrell et al. (2018)

given via the approximate 10% rule given from the Stokes number analysis for this system.

5.1.3 Impact Efficiency

From chapter 2 the notion of an impact frequency \( f_i \) and an associated hydrodynamic efficiency \( \phi(x, v_x) \) have been discussed. Effectively, this hydrodynamic efficiency represents the conditional probability of collision with a surface for a given particle size and velocity knowing that the system is contained in a hydrodynamic environment. From the preceding sections it has become clear that the determination of whether or not a particle will collide may indeed be some weighted function of both particle size and velocity for a given system. This is reflected by eq.5.3 whereby a critical collision threshold is represented by a critical particle Reynolds number: itself a function of both particle size, velocity, and indeed fluid kinematic viscosity. Additionally, qualitative considerations about particle Stokes numbers again fortifies the assumption that any impact probability will be a function of particle size and velocity.

Taking this into account, an appropriate size-velocity model must be determined. As the observable data here is a binary result, either collision occurred or it did not, a logistic model was chosen in order to accurately represent predictor variables. This method provides a means to evaluate a continuous probability based on discrete binary observations and provides a method to explain the binary dependent variable in terms of a set of related real-valued independent variables (Strano and Colosimo 2000; Walker and Duncan 1967). Therefore, the conditional probability of impact given particle size and velocity \( \phi(x, v_x) \) can be well-represented by the logistic regression model of the form:

\[
\phi(x, v_x) = \frac{1}{1 + e^{-(\eta_0 + \eta_{Re}Re_x)}}
\]

(5.10)

Fitting parameters \( \eta_0 \), and \( \eta_{Re} \) result in the Reynolds dependency of the impact probability within a hydrodynamic field. These parameters represent a function of the hydrodynamic factors associated with particle sizes and velocities. Parameter \( \eta_0 \) governs the location of the dashed line in fig.5.9 allowing parameterization of the critical Reynolds number demonstrated in eq.5.3 and fig.5.5. Parameter \( \eta_{Re} \) describes the width, or slope, of the sigmoid curve centred around \( \eta_0 \). Combined, these parameters allow full control
over the location and width of the hydrodynamic threshold. What this has enabled now is a dimensional approach to determining the important parameters influencing crystal impact rates within a reactor. The remaining step is to evaluate in a similar fashion the fraction of this frequency that will result in any form of comminution.

![Graph](image)

**Figure 5.9:** Logistic efficiency function for the crystal Reynolds number with dashed lines representing the controllable bounds over how sensitive the model is around the critical value of $Re = 250$. Parameter $\eta_0$ controls the threshold centre (central dashed red line), while parameter $\eta_{Re}$ determines the slope of the curve about this centre.

### 5.2 Crystal Failure Velocities - [Tyrrell and Frawley (2018)]

Presented here is a methodology that allows for the determination of robust mechanistic breakage selection functions for pharmaceutical products, with insight into the prevailing forms of fragment distributions. Shadowgraphy imaging was used to image individual crystals with a post-processing methodology developed in Python, enabling visualization and extraction of crystal breakage probabilities and modal distributions. Using Python’s built-in bi-variate histogram functionality it was possible to discern what population of crystals may break across gives size ranges and impact velocities. Furthermore, a Kernel Density Estimation (KDE) is performed on the data in order to generate a smooth, continuous function of breakage; enabling the extraction of selection functions across any desired sizes and velocities. Further to this, a crys-
tal nano-indentation study was performed in order to determine the crystal Young’s Modulus ($E_c$), hereto previously unknown for this compound and integral in theoretical fragmentation equations. Using this data the observed selection functions can be compared against a breakage model described by [Salman et al., 1995] in order to determine its effectiveness in pharmaceutical process modelling. This model is fundamentally parametrized by a size-velocity relationship based on the widely implemented Weibull statistics. Additionally, insight into the modes of fragmentation crystals undergo as their size and impact velocities vary is enabled by establishing 3 characteristic breakage modes. This allows us to simultaneously visualize the progression of the numbers of broken crystals in a population and also how crystal fragments are generated upon failure.

5.2.1 Breakage Modes

It is important to define breakage modes which are representative of the observed types of crystal breakage. For this work, three distinct breakage modes were considered: intact, chipping, and splitting/disintegration. By dividing breakage into classifications it is possible to infer something about not only the numbers of particles being broken but also the distribution of breakage modes across a range of crystal sizes and velocities. Outlined in fig [5.10] are the three modes of macroscopic breakage used. Mode I represents an intact or undamaged crystal after impact, with Modes II and III indicating progressive failure towards complete disintegration of the parent crystal after impact. While the probability of fragmentation can be determined without the description of these last two modes, as breakage is a somewhat binary choice insofar as a crystal is seen to fragment or it is not, they do provide a useful description of possible fragmentation distributions. Based on the distributions of each characteristic mode, one may be able to more appropriately chose the probability distributions for the resulting fragment sizes.

The intact Mode I is relatively easy to identify as there are no visible fragments formed during or after collision with the target surface. Discrimination between Mode I and the other modes is therefore straightforward. Focus is turned to discerning particles of Mode II (chipped) versus Mode III (split/disintegrated). For extreme cases where the parent crystal is entirely disintegrated it can be easily identified as Mode
III. However, there existed a small number of cases whereby a crystal that may not be entirely disintegrated may lay in either Mode II or III and as such it is important that one can consistently and accurately discriminate between each mode.

For the method presented here, Modes II and III are characterized firstly by the identification of any damage to the parent crystal. From here, the extent of damage is then considered: Formally, Mode II can be identified when there is no perceptible change in the projected area when viewed by the observer, i.e. the projected area re-
mains approximately constant over the collision. Mode III is therefore characterized by any collision resulting in damage to the parent crystal whereby the projected area cannot be said to remain constant over the collision. Figure 5.11 gives an example of particle failure characteristic to Mode III. Additionally figure 5.12 demonstrates how the projected area of a crystal identified as Mode II remains approximately constant, allowing for small fluctuations according to crystal rotation effects after collision. Inspecting the data for Mode III it is clear that there exists a characteristic large decrease in projected area after collision. Furthermore, there also exists some key qualitative characteristics aiding in the identification of each mode based on their fragmentation behaviour. Throughout experimentation it was evident that failure in Mode III typically resulted in an observable increase in the number of larger fragment sizes. This behaviour is in line with that of typically brittle materials whereby catastrophic failure results in larger portions fragmenting as opposed to a general increase in small/chipped fragments, with the distribution being observably bi-modal (Hounslow, Pearson and In-stone, 2001; Pearson et al., 2001). This is contrasted by the more uniformly distributed fragment sizes observed for Mode II as chipping favoured small, numerous, and more uniform fragments. In this way each breakage mode can be identified with relative ease and speed while maintaining a high level of accuracy and consistency throughout.

Figure 5.12: Illustration of projected areas from two different crystals after damage has been identified. Captured images of the crystal before and after impact are shown above.
5. CRYSTAL-CRYSTALLIZER INTERACTIONS

However, a drawback of this method is that due to the narrow depth of field of the long-distance microscopy technique used to image particles, the exact fragment size distributions resulting from each impact are extremely difficult to capture. After particle impact the resulting fragments are typically out of frame or outside of the focal plane, therefore size and velocity calculations would be highly unreliable. Although this may be remedied with the use of a wider depth of field, higher capture rates, increased sensor resolution, and the possible implementation of an in-line laser diffraction technique for particle size analysis.

5.2.2 Experimental Conditions

Crystals of Darunavir Ethanolate within a nominal range of 100 − 500\(\mu m\), representative of a typical PSD for this API product, were used throughout the experimental testing. Inlet velocities were nominally ranged from 1 → 10\(m/s\) and are limited by the capture frequency of the high-speed camera at a given resolution. Table 5.1 outlines the particle sizes and velocities used in this section. The range of velocities used here is representative of typical velocities crystals may encounter in processes such as stirred crystallizations, powder transport systems, and isolation/drying operations. Crystals were sieved into their respective size classes (100, 200, 300, 400, 500\(\mu m\)) as testing the samples otherwise resulted in a large number of fines, making it difficult to isolate individual crystals.

<table>
<thead>
<tr>
<th>Crystal Material</th>
<th>Sizes [(\mu m)]</th>
<th>Velocities [(m/s)]</th>
<th>Target Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darunavir Ethanolate</td>
<td>100 → 500(\mu m)</td>
<td>1 → 10(m/s)</td>
<td>Stainless Steel</td>
</tr>
</tbody>
</table>

Using the crystal-nanoindentation technique outlined in section 4.2, the Young’s Modulus could be determined for Darunavir Ethanolate crystals. A total of 5 indentation datasets were recovered for this API. Figure 5.13 illustrates the captured datasets and the resulting moduli. Furthermore, crystals typically exhibit a noticeable degree of anisotropy between difference crystal faces, leading to small variations in the observed nanoindentation responses. Therefore, the resulting datasets here have been averaged to give a more easily interpreted value. A value of \(\nu_c = 0.3\) has been assumed for
an approximate crystal Poisson’s ratio for brittle materials [Varughese et al., 2013],
with a shape factor approximated by the average aspect ratio of the crystals observed
($k_v \approx \frac{d_{\text{min}}}{d_{\text{max}}}$). Furthermore, an approximate crystal density was calculated via the sam-
ple bulk density. A void fraction of $\phi \approx 10\%$ was applied in order to correct for the
packing of crystals as a typical value [Larry L. Augsburger, 2008]. All noteworthy
material properties for both the crystal and target can be seen in table 5.2.

![Figure 5.13](image)

**Figure 5.13:** Resulting elastic modulus determinations from nano-indentation tests (left)
and the averaged moduli (right). Values are averaged over the indicated
Area of Interest (AOI) in the left figure.

**Table 5.2:** Crystal Physical Properties

<table>
<thead>
<tr>
<th>Material</th>
<th>Poisson’s Ratio ($\nu$)</th>
<th>Young’s Modulus ($E$)</th>
<th>Density ($\rho$)</th>
<th>Shape Factor ($k_v$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darunavir Ethanolate</td>
<td>0.3</td>
<td>1.021 GPa ± 0.242</td>
<td>850.84 kg/m$^3$ ± 7.73</td>
<td>0.58 ± 0.0316</td>
</tr>
<tr>
<td>Stainless Steel</td>
<td>0.27</td>
<td>197.5 GPa ± 7.5</td>
<td>7,970 kg/m$^3$ ± 100</td>
<td>-</td>
</tr>
</tbody>
</table>

### 5.2.3 Data Collection, Robust Statistics, & Error Analysis

Prior to exporting the raw velocity, position, and crystal size data for the determination
of failure parameters the data was manually inspected for any potential sources of error
and/or outliers for each dataset. Each set of images is inspected in order to ensure
5. CRYSTAL-CRYSTALLIZER INTERACTIONS

crystals are tracked accurately and the images are of sufficient quality, i.e. in focus, low noise, and clean particle tracking. Import, processing, and export of final data is handled through a python script written specifically for this work.

A key aspect to this processes lies with the ability to track crystal size and velocity over a finite distance before collision. This affords an opportunity to perform some statistical analysis on the captured data as multiple measurement points exist for each crystal as it passes through the measurement section. As such, average values for crystal size and velocity are gathered for each collision to be used as the representative value of each dataset. However, as with any experimental method there exists inherent sources of random and systematic error within the captured data. The latter is an internal property of the experimental method and as such is very hard to detect or correct for and may affect both the precision and accuracy of measurements. To this extent the experimental apparatus is calibrated for particle sizing before each use and good optical clarity into the test section ensures the image capture is as error-free and repeatable. The high-speed capture rate of 125,000 frames-per-second also ensures sufficient temporal resolution between concurrent frames for accurate velocity calculations. Further to this the use of a programmable MFC ensures inlet velocity set-points can be maintained reliably and repeated with little variance. The challenge then lies with ensuring the captured measurements are of sufficient accuracy in order to generate reliable averages, i.e. minimization of random error.

Particle noise and environmental interference play a role in creating sources of random error. As crystals may not be completely isolated from their neighbours in each captured frame throughout the collision sequence, this may lead to spurious size and velocity calculations. Additionally as crystals impact the target surface there was a chance that the crystal size calculations would take surface shadows, reflections, or imperfections as part of the parent crystal. Finally, as crystals may not be free of any solid-body rotation as they approach the target, there will be a natural variance in observed diameters as difference faces of the crystal are presented. Therefore, each dataset may not only potentially incorporate a small number of erroneous data points but also data points outside of the average that represent a longer or shorter axis being observed. The key then is to identify highly improbable and unrealistic values, or outliers, that may be excluded in order to reduce the error of each measurement while
maintaining true datapoints. To do this, three key aspects were examined for each size-velocity dataset: modified z-scores, mean vs. median, and the standard deviation error. The first two analyses can be used to provide robust statistics and detect potential outliers in the data (Rousseeuw and Hubert 2011), while the third provides a quantitative method for rejecting datasets with high error. What is important to note here is that these robust statistics provide tools to find a fit close to the data that would have been obtained without outliers. It is then possible to identify potential outliers based on their deviation from this fit.

5.2.4 Modified Z-Scores

From Rousseeuw and Hubert (2011) and Iglewicz and Hoaglin (1993) the method of modified z-scores is implemented here in order to identify potential outliers in the measured velocity and size data. Outliers in this data may be attributed to the sources of error and variance outlined previously. It is important that points found using this method are not immediately discarded as outliers can often be an interesting part of the data itself as opposed to entirely erroneous data. It is only after careful consideration in relation to the resulting population that outliers maybe discarded or neglected.

The classical z-scoring method uses the standard deviation and mean of the set in order to determine a z-score, a measure of how far a point is from the mean in terms of standard deviations. However, as the mean and standard deviation are highly sensitive to contamination in the dataset, i.e. easily thrown by the presence of outliers, more robust indicators must be used. The modified z-scores are calculated by replacing the mean with median and standard deviation with Median Absolute Deviation (MAD). Using more robust statistical indicators such as the population median and MAD, this modified z-scoring method provides a more reliable indication of outliers in the data; as the median and MAD are not easily perturbed by contamination/ outliers in the original dataset. These indicators are characterized by bounded influence functions (Hampel et al. 1986), a measure of its resilience to one outlier, and a high breakdown value (Hampel 1971), a measure of its ability to resist change due to a number of
outliers. The modified z-score is calculated as:

\[ z_i = \frac{x_i - \text{median}(x_j)}{\text{MAD}} \]  

where,

\[ \text{MAD} = 1.483 \frac{\text{median}_{i=1,\ldots,n} \left| x_i - \text{median}_{j=1,\ldots,n}(x_j) \right|}{n} \]  

The leading constant of 1.482 ensures that the MAD is unbiased over a normal distribution. Following the calculation of z-scores for each datapoint, all those scores above a certain threshold are then considered to be outliers. For the work presented here, a relatively high z-score of \( |z_i| \geq 3.5 \) was considered to indicate the datapoint in question is highly likely to be an outlier. This ensured that any points identified as outliers were most certainly a large multiple of standard deviations from the mean.

![Sample of Z-Scoring method from eq.5.11](image)

Figure 5.14: Sample of Z-Scoring method from eq.5.11. Raw Velocity data is presented against the particle’s distance to target, where the average velocity is used as the nominal impact velocity (steady-state flow). Modified z-scores are calculated and the thresholds are outlined in the shaded regions.
Figure [5.14](#) illustrates how this modified z-scoring method can identify potential outliers in order reduce potential error in the data. The same method was applied to the particle size analysis with care taken during the data capture step to ensure as many erroneous size measurements as possible are eliminated prior to this outlier detection. The next step was then to discern whether or not these flagged outliers and their removal serve to shift the data towards its "true" or uncontaminated set.

**Mean vs. Median**

As the z-scoring method served to only identify potential outliers there was a possibility that it may yield a number of false positives, i.e. flagging real data as outliers. Following this, in order to then determine the effect of removing any outliers from a dataset, the median of the original and corrected datasets was compared against their respective mean values. Owing to the medians higher breakdown value and bounded influence function, it will be a more robust indicator of the uncontaminated dataset when compared against a set with outliers (Rousseeuw and Hubert, 2011). Therefore by investigating how the mean progresses towards the median before and after any outliers are isolated, one may determine how their removal may affect the accuracy of the dataset. In this way the method ensures that removal of any outlier only serves to increase accuracy and precision of the data to be used in generating results by way of removing only wholly erroneous data.

The method proceeds as follows: the raw data was compared against it’s corrected set and focus is given to how the mean varies with respect to the median between each set. If a positive association was found, i.e. the mean tends towards the median or vice-versa, the corrected set was kept. If there was a negative association, i.e. drift between either mean or median, the flagged outliers were kept and the original dataset was used. This method was enabled by tracking the absolute value of their ratios given by:

\[
\left| \frac{\bar{x} - \text{median}(x)}{\bar{x} - \text{median}(x)} \right|_{\text{original}} \geq 1.0 \tag{5.13}
\]
5. CRYSTAL-CRYSTALLIZER INTERACTIONS

While eq. 5.13 remains above unity it can be said that the result of removing the identified outliers serves to correct the dataset towards its true values. Figure 5.15 illustrates the final datasets and their correction ratio according to eq. 5.13. In this way it was ensured that no “true” data was eliminated as a result of outlier detection and only those highly improbably or unrealistic datapoints were neglected.

![Figure 5.15](image-url)

**Figure 5.15:** Correction ratio from eq. 5.13 displayed for each dataset. Note that all final sets maintain ratio ≥ 1.0.

### Standard Deviation Error

After the measurements themselves in each dataset have been inspected, it is prudent to ensure the overall sets themselves are of sufficient quality, i.e. low error or variance. In order to ensure datasets with high global error or variance were not incorporated into the usable data for heatmap generation, each set’s standard deviation was recorded and matched against a maximum allowable threshold. The ratio of standard deviation ($\sigma$) to the average measured value ($\bar{x}$) - be it size or velocity - was monitored and all those sets with

$$\frac{\sigma}{\bar{x}} > 15\%$$

were considered to be outside acceptable error limits and were removed from the data used to generate failure probabilities. An error ratio of 15% indicates that the standard deviation cannot be more than 15% of the observed value. Using this threshold
the total average error between all sets was inspected. It resulted that at a threshold of 15% the average standard deviation error per dataset did not exceed 6.55% in velocity measurements and 3.39% in size measurements. The average standard deviation error taken over all sets resulted at 6.05% and 2.60% for velocity and size measurements respectively. By limiting those sets with excessive error a more accurate depiction of particle breakage is enabled. Furthermore, after consideration of the discrepancy in error between size and velocity measurements it was concluded that as crystals may rotate and have non-ideal geometries as they are transported in the fluid jet, there may be fluctuations in the observed velocities throughout their approach to the target plane. In this way, the measured velocities appear to contain a larger margin of error. However it is argued that this is simply an artefact of the crystal’s natural advection. Additionally, inspecting fig. 5.16 it can be seen that error margins appear to be within the approximate population boundaries of each mode; indicating a satisfactory level of accuracy.

**Figure 5.16:** Datasets used for damage mapping: points with transparent centre represent sets kept for analysis. Discarded sets remain as solid markers.
5. CRYSTAL-CRYSTALLIZER INTERACTIONS

5.2.5 Construction of Failure PDF

As previously discussed, the determination of a critical failure velocity ($u_f$) as a function of crystal size presents a challenge wherein $u_f$ is not solely a function of crystal size. Factors such as orientation to the target, surface imperfections, lattice defects, and de-agglomeration masquerading as parent crystal breakage will cause variations in the failure velocity of two similarly sized crystals. Therefore in order to more accurately capture the quasi-stochastic nature of breakage at this scale, a density function representing the discrete probability of crystal failure at a given size and velocity is presented here as a measure of crystal breakage.

In order to determine such a density function, a large experimental dataset with various impact velocities and crystal sizes was required in order to populate a bi-variate histogram function. In order to reduce the number of experiments required, some \textit{a priori} knowledge can be used to focus the crystal sizes and velocities to be examined. From the discussion in section 2.4.2 it is known that the crack propagation stress ($\sigma_{cr}$) becomes \textit{inversely} proportional to the square-root of a crystal’s diameter ($d_c$) at smaller particle sizes; from eq.2.31:

$$\sigma_{cr} \propto \frac{1}{\sqrt{d_c}}$$

Applying this, the range in which breakage measurements are required can be focused to specific regions. Consider that a crystal of size $x$ is seen to fail at a velocity of 5\textit{m/s}; the assumption can then be made that crystals of size \textit{greater than} $x$ will also break at this velocity. Therefore, all crystal sizes \textit{greater than} $x$ need only be tested with impact velocities $\leq 5\text{m/s}$. A similar logic can also be used to say those crystals of size \textit{less than} $x$ need only be tested with impact velocities $\geq 5\text{m/s}$. Using this “reduction” method, the number of experiments can be cut dramatically as reliable inferences can be made about the data outside of experimental bounds, i.e. missing data can be inferred with appropriate use of the previous logic. This logic can be expressed using pseudo-code as:

\begin{align*}
\text{if } \text{Fail}(d_x, v_x) = \text{True} & \Rightarrow \text{Fail}(d \geq d_x, v_x) = \text{True} & \text{if } \text{Fail}(d_x, v_x) = \text{False} & \Rightarrow \text{Fail}(d \leq d_x, v_x) = \text{False} \\
\text{or } \text{Fail}(d_x, v \geq v_x) = \text{True} & \Rightarrow \text{Fail}(d_x, v \leq v_x) = \text{False}
\end{align*}
This reduction method allows the experimental data collection to focus on regions where breakage becomes more stochastic in nature, i.e., a transition region where a combination of breakage modes may be seen. However, as the “broken” meshpoints essentially reflect all points outside of Mode I, this in turn does not provide sufficient resolution between Modes II and III. Therefore, although use of the broken meshpoints still allows accurate determination of the overall failure distribution, it does not provide usable data on the progressing of the failure Modes, principally Modes II and III. As such, experimental data is still required in this region if the re-distribution of fragments is to be investigated fully. Outlined in fig. 5.17 is a sample of gathered data along this transition region with the overlay of meshpoints generated using the reduction method discussed previously. Furthermore, the illustrated mesh region was in-fact investigated however it was seen to encompasses the region where solely Mode I was observed, as was expected. As such data collection here was not required and the area was populated with intact meshpoints in order to generate a more accurate density function. A total of 394 experimental datasets, each an individual crystal impact, were used to construct the damage map given in fig. 5.18 with a total of 6,415 processed size-velocity datapoints.

Figure 5.17: Raw data (a) collected in area of interest with mesh applied from outlined reduction method (b). Meshpoints indicate inferred values. Gridlines represent histogram bins.
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The data in fig 5.17(b) can then be binned into a bi-variate histogram in order to determine a density function of breakage per size class per impact velocity. Furthermore, taking this discrete density value and dividing by the overall number of measurements it is possible to determine a discrete failure probability as:

$$P(fail|D_c, V_i) = \frac{n_{M_{II}} + n_{M_{III}}}{n_{Mode_{I}} + n_{Mode_{II}} + n_{Mode_{III}}}$$ (5.17)

<table>
<thead>
<tr>
<th>$V_i$</th>
<th>Crystal Impact Velocity [m/s]</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_c$</td>
<td>Crystal Size [µm]</td>
</tr>
<tr>
<td>$n_{M_{I}}$</td>
<td># of intact crystals (Mode I)</td>
</tr>
<tr>
<td>$n_{M_{II}}$</td>
<td># of chipped crystals (Mode II)</td>
</tr>
<tr>
<td>$n_{M_{III}}$</td>
<td># of split/disintegrated crystals (Mode III)</td>
</tr>
</tbody>
</table>

The resulting probability density function is a representation of the discrete probability that a crystal of size $d_x$ will fail for a given impact velocity $v_y$, according to the abscissa and ordinate axes. Figure 5.18 shows the discrete failure probability with a Gaussian-smoothed heat-map projection of the bi-variate histogram for $P(fail|D_c, V_i)$. Using this heatmap, the selection functions for particle breakage may now be directly inferred from the visualized failure probability. However, firstly the specific failure velocities ($u_f$) of each size class must be determined. Following this, the associated failure probability of each size class in fig 5.18 can be determined.
5.2 Crystal Failure Velocities - Tyrrell and Frawley (2018)

Density Function

Figure 5.18: Discrete probability of crystal failure for a range of crystal sizes and impact velocities

5.2.6 Calculation of Failure Velocities

Taking the theory outlined above in section 2.4.1 and the experimentally determined material properties in table 5.2 it is now possible to compare the observed data to predicted values for $u_f$. Extracting values for size and velocity corresponding to a failure probability of 63.2% as per eq\[2.21\] it is possible to parametrize for values of $\beta$ and $\alpha$ in eq\[2.26\]. Successful parametrization of these size-dependency constants will indicate whether or not the current theory can indeed explain crystal breakage at this scale and provides a predictive method for determining breakage selection functions through eq\[2.20\].

Re-drawing fig.5.18 with an overlay of $P(\text{fail}|D_c, V_i = u_f) = 63.2\%$, as per the definition in eq\[2.21\], yields a somewhat jagged curve for $u_f$, seen in fig.5.19(left). Therefore, an additional comparative method is implemented via the determination of a Kernel
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Density Estimate (KDE). KDEs provide a method to estimate the continuous PDF of the given data and provides a smooth interpretation of the failure map in fig. 5.18 for comparison. For this, a Gaussian kernel is used with a rule-of-thumb bandwidth selection given by Scott’s Rule (Scott, 1992). The resulting KDE is illustrated in fig. 5.19(right) and is shown to yield a much smoother function for the 63.2% failure isoline with good agreement to the original discrete density function.

![Kernel Density Estimate vs Density Function](image)

*Figure 5.19: Original PDF (left) and calculated Kernel Density Estimate (right) with corresponding isolines for \( P(\text{fail}) = 63.2\% \).*

From here, a least-squares minimization exercise can be carried out for parameters in eq. 2.26 in order to determine if the presented theory can explain the observed data for \( u_f \). This method is carried out for both the original density function and KDE shown. Figure 5.20 shows the fits obtained for \( u_f \) by parametrizing against the isoline data acquired from both the PDF and KDE methods with a fracture toughness taken as \( K_{IC} = 0.03 \text{MPa} \sqrt{\text{m}} \) as an approximate figure in line with literature on pharmaceutical crystals (Varughese et al., 2013). The resulting parameters can be seen in table 5.3.
5.2 Crystal Failure Velocities - Tyrrell and Frawley (2018)

Figure 5.20: Fits obtained via the discrete probability density (left) and Kernel Density Estimation (right). Original heatmap functions transparency overlays given as a guide to the eye.

Table 5.3: Theoretical Parameters

<table>
<thead>
<tr>
<th>Method</th>
<th>$\alpha_1$</th>
<th>$\alpha_2$</th>
<th>$\beta_1$</th>
<th>$\beta_2$</th>
<th>$R^2$</th>
<th>Adjusted $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDF</td>
<td>$-877.79 \pm 758.36$</td>
<td>$0.63 \pm 0.36 \times 10^6$</td>
<td>$15.01 \pm 4.07$</td>
<td>$8.54 \pm 30.23 \times 10^3$</td>
<td>0.9797</td>
<td>0.9527</td>
</tr>
<tr>
<td>KDE</td>
<td>$550.34 \pm 31.04$</td>
<td>$-69.57 \pm 1.79 \times 10^6$</td>
<td>$16.10 \pm 0.162$</td>
<td>$30.03 \pm 0.606 \times 10^3$</td>
<td>0.9850</td>
<td>0.9651</td>
</tr>
</tbody>
</table>

As is evident above, the PDF and KDE are in good agreement. The resulting parametrizations are shown to be more reliable for the KDE method as it provides a larger sample set due to its continuous function, rather than the PDF method’s discrete sampling histogram. Figure 5.20 illustrates the fits of both methods overlaid with the original failure heatmap projects for each method. It is again clear from this that the KDE method provides an accurate representation of the PDF and shows good agreement between methods. Furthermore, the KDE parametrization resulted in lower standard deviation bounds for each parameter; again demonstrating a more reliable description of breakage. A key point illustrated here is the ability of eq. (2.26) to perform well in describing the variance of $u_f$ with size; owing to the inclusion of the size-exponent modification. From a more physical standpoint it is suggested that this
additional term may be linked to the exponential variance of mass / kinetic energy when compared with a linear dimension such as the equivalent spherical diameter. Although further work remains in determining the physical relationships for the terms in eq.2.26.

5.2.7 Selection Function Extraction

The final step in determining the breakage selection functions for each size class is to implement predictions for \( u_f \) into eq.2.20 for a range of sizes and compare these to the functions extracted from the KDE. This is a relatively straightforward exercise as the failure heatmap obtained from the KDE method provides a smooth density function that can be evaluated over any given range. Figure 5.21 illustrates how selection functions may be extracted from the KDE method by visualizing the data with its entire z-coordinate surface projection.

**Figure 5.21:** Failure map shown with z-coordinate and extracted failure contours (black curves) for \( d_c = 100, 200, 300, 400, 500, 600 \mu m \)

Theoretical predictions can be obtained by substituting values of \( u_f \) into eq.2.21 for each size class, resulting in a value for \( N_0 \equiv 1 - S(x) \), also as a function of particle size. The Weibull Modulus \( (m) \) was obtained via an Nelder-Mead minimization technique,
5.2 Crystal Failure Velocities - Tyrrell and Frawley (2018)

searching for a minimum of:

\[ \psi(m) = \sum_{i=1}^{n_S} \sum_{j=1}^{n_{m,i}} (y_{i,j} - \hat{y}_{i,j})^2 \]  \hspace{1cm} (5.18)

Where \( n_S \), and \( n_{m,i} \) denote the number of selection function datasets and number of samples in the \( i \)th set, respectively. The values \( y_{i,j} \) and \( \hat{y}_{i,j} \) represent the observed and predicted values for the \( i \)th selection function and \( j \)th sample point. Therefore a minimum of \( \psi(m) \) in eq.5.18 ensures that the resulting modulus parameter provides the best fit across all extracted section distributions according to a least-squares estimation, and yielded a value of \( m = 2.20 \). Theoretically, this value could be refined even further by parametrizing across the continuous distribution for \( S(x) \) given by the KDE in fig.5.19(right), however this was deemed unnecessary for the purposes of illustration.

![Figure 5.22: Selection functions extracted from KDE method, with theoretical models given via eq.2.20](image)

It is clear from fig.5.22 that the given model can effectively predict failure probabilities for particles in excess of \( \sim 200\mu m \) (fig.5.23), however below this threshold the theoretical description rapidly diverges from reality. However from fig.5.20 \( u_f \) can be seen to be in good agreement with theoretical values across the entire size range. It
can then be reasoned that the critical failure load \( (F_{cr}) \) from eq.2.26 is of the right approximate form with the included size-exponent modification. Therefore, it must be the functional form for \( N_0 \) in eq.2.20 that is resulting in this divergence. This is in-line with the expected performance of the damage model as the Weibull CDF was not expected to be able to appropriately model data when the probability of failure approaches an asymptote before unity.

![Figure 5.23: Objective function (\( \psi \)) error for each extracted size coordinate. Note the rapid divergence as sizes decrease below \( \sim 200 \mu m \). Solid line is given as a guide to the eye](image)

It is speculated that in these cases the Weibull modulus \( (m) \) effectively results in a gross error between observed and predicted data. In order to remedy this, a more complex model that has the capability to reflect a high degree of variability between the required failure stresses and particle sizes is required. Importantly, it must be able to reflect the critical threshold at which the failure load becomes an exponentially-based function of particle size, as opposed to linearly proportional, with an additional measure to capture the point at which yielding may occur in place of fragmentation. A Flexible Weibull Distribution (FWD) in El-Desouky et al. (2017) illustrates how the Weibull distribution may be modified to more accurately capture the asymmetry over particle
sizes of problems such as this. Furthermore, it is expected that similar divergence behaviour will likely be observed for any distribution function whose integral is bound at unity on the desired limits as the subsequent CDF will be unable to account for the asymptotic behaviour of the observed data. However, the description of such is the subject of ongoing work and is not described here.

5.3 Breakage Modes: Mapping & Classification

5.3.1 Probability Mapping

It is also possible to draw some inferences about the distribution of breakage modes over various size classes and impact velocities. Taking a similar approach to the previous section and breaking each mode into its own distribution via the modal probability:

\[
P(M_X|D_c, V_i) = \frac{n_{M_X}}{n_{M_I} + n_{M_{II}} + n_{M_{III}}} \quad (5.19)
\]

It is then possible to construct a similar density function for each modal region, allowing us to track how the breakage modes vary across a range of crystal sizes and impact velocities. In this way it is possible to visualize how different types of breakage result across a range of crystal sizes and impact velocities. Looking first at Mode I in fig.5.24, it is clear that smaller crystal sizes and lower impact velocities tend to remain intact upon collision. Looking at the sub-100\(\mu m\) scale, it can be seen that the intact Mode I becomes the dominant mode below \(\sim 50\mu m\); outlining that crystal breakage is highly unlikely below this threshold. As discussed previously, this is further indication of crystal sizes approaching \(d_{crit}\), the critical diameter characterizing the brittle-ductile transition for particulate systems as suggested by Kendall (1978) and Roberts (1991).

Furthermore, as crystal size increases the probability of Mode I decreases. The breakage mode is shifting from Mode I to Mode III over some transition zone whereby there may exist a mixture of each mode throughout the breakage population. However, dealing firstly with Mode III in order to determine the upper bounds of this transition zone fig.5.25 outlines the distribution of this bounding mode.

It is evident that Mode III becomes more dominant as crystal size and impact velocity increase. It is suggested that this may be due to a larger crystal’s structure.
being unable to undergo ductile deformation, resulting in brittle failure. In addition, higher impact velocities yield greater impact energies whereby crystals can no longer sustain ductile deformation and disintegrate under the load. Finally, the transition from Modes I to III can be seen in the distribution for Mode II in fig. 5.26. This chipping mode is indicative of crystals undergoing minor failure, however at the lower impact velocities there is not enough energy to cause catastrophic failure of the crystal structure, i.e. Mode III.

Note that in this region there does not exist a point at which crystals were seen to only fragment in Mode II at these size ranges. This transition period reveals the highly stochastic nature of breakage; similar particles with similar initial conditions can result in various degrees of breakage. Although these functions do not provide the exact fragmentation size-distributions themselves, it is clear that they provide an extremely useful guide to the choice of re-distribution functions. The proportions of each mode inform us of at least the distribution forms, and provide insight into the choice of uniform versus multi-model fragment distributions based on the prevalence of
chipping, splitting, and combinations thereof. Up to now this choice has been mostly one of “best-fit”, whereas now it can be bolstered by experimental observations, helping to guide the process of predictive modelling.

Interestingly, it is clear that Mode II becomes dominant as sizes increase in excess of 500 µm. One might expect this to occur where larger particle sizes are able to absorb impacts more efficiently. However, the data indicates that the smaller particles are clearly seen to have a higher fragmentation tolerance, yielding somewhat of a contradiction. A resolution to this is found in the relationship between failure loads and particle sizes. While smaller particles are indeed seen to be more resilient to fragmentation there is an approaching reversal of this as particle sizes increase; as also reported by Kendall (1978). Looking again at fig.5.19 it is suggested that the value for $u_f$ between 400 and 600 µm size ranges is approaching some further point at which $u_f$ becomes linearly proportional with particle size. As discussed, this is certainly not a new phenomenon (Bearman, 1999) however it does serve to illustrate the requirement for a more inclusive breakage model, accounting for such a transition.
5. CRYSTAL-CRYSTALLIZER INTERACTIONS

5.3.2 Modal Classification

As a matter of convenience it is desirable to transform the above probabilistic heatmaps into deterministic bounds on each breakage mode. In this section, statistical classification algorithms are utilized in order to provide quantitative and consistent methods to evaluate where the boundaries between each mode would be expected to lie. Additionally, through this more rigorous approach the modal probabilities maps presented above may be refined. However, it is prudent to first introduce some important aspects of classification in general and a brief discussion on each algorithm implemented.

The overarching goal of any classification exercise is to identify key groups within the data and determine which data belongs to which group by searching for some well-defined boundary separating each group. A classifier may use any one of a number of mathematical formulations to define this boundary between data groups. A typical example of classification would be through the use of a linear classification boundary, i.e. there exists some straight line separating data groups (linearly separable). Figure 5.27 illustrates how such a boundary may be constructed, and is reminiscent of how

**Figure 5.26**: Mode II: discrete probability across crystal size classes and impact velocities
linear regression seeks to find the best fit of a straight line through some given data. However, in this case the algorithm seeks to find a straight line which maximizes the distance between each data group. In this way, the resulting line can be said to represent the decision boundary of that algorithm.

**Figure 5.27**: Structure of a typical linear classification boundary calculated via a Support Vector Machine (SVM).

The process of how the decision boundary in fig.5.27 is calculated varies depending on the functional form of the boundary itself. For this example a simple linear boundary is presented, which may be formulated in terms of Linear Discriminant Analysis (LDA), first described by Fisher (1936), or via machine learning algorithms such as Support Vector Machines (SVMs) (Cortes and Vapnik, 1995; Cristianini and Shawe-Taylor, 2000) or Artificial Neural Networks (ANNs) (Warren, 1994; Wasserman, 1998). The latter are capable of implementing a wide range of boundary functions for both linear and non-linear classifications. For the sake of brevity and to maintain the scope of this work the details of such algorithms are only referred to in the literature above.

Three main classification methods were investigated for the data here: Quadratic Discriminant Analysis (QDA), Support Vector Machine (SVM), and a Multi-layer Perceptron (MLP) classifier. Below, a brief description of each method is provided in
5. CRYSTAL-CRYSTALLIZER INTERACTIONS

order to provide some background information on each algorithm. Additionally, each
method here should be considered as a *supervised learning* method where each algo-

rithm is given some set of inputs (size and velocity coordinates) and instructed to map
these to some set of known outputs, in this case Modes I, II, and III. Therefore, each
case is a fitting exercise to “learn” the most likely classification boundary. The algo-

rithms update their parameters in order to best match the given set of targets, provided
by the supervisor. In this case, the breakage mode of each size-velocity datapoint is
know from experimental observation and is provided to each method prior to learning.

It is also noted here that the MLP model performed best and as such its discussion
will be more lengthy that the others in order to more properly cover the applied method.
Discussions on QDA and SVM are kept brief for reasons previously stated.

**Quadratic Discriminant Analysis - QDA** Essentially an extension of Fisher’s Lin-
ar Discriminant Analysis (LDA). However, boundaries between datasets in Quadratic
Discriminant Analysis (QDA) are assumed to be a quadric surface rather than a linear
one. This classifier is robust in defining most low-dimensional datasets that do not have
a high degree of non-linearity. This is one of the simplest classification algorithms, and
performs well on the dataset provided here.

However, as the boundary is assumed to be some quadratic function it may be
accurate on the truncated space between our maximum and minimum size-velocity
coordinates yet it would likely not perform well extended far outside the provided
dataset. Essentially this translates to a larger model bias than other methods that
may be more robust in classifying non-linear datasets. Examining the form of \(2.26\), a
quadric surface may not be the ideal classification boundary as it would be unable to
effectively capture the non-linearity of the failure velocity \(u_f\) with varying particle
size and velocity.

**Support Vector Machine - SVM** A highly robust method for classification, re-
gression, and outlier detection. In terms of purely classification, SVMs are capable of
using various decision boundary functions, with a wide range of linear and non-linear
algorithms. Typically these are referred to as Support Vector Classifiers (SVCs) when
using an SVM methodology to classify data. Overall, this method provides a more general format for implementing various classification algorithms.

For the data presented here, an SVC with a Radial Basis Function (RBF) kernel was used to determine the decision boundaries between each mode. Both polynomial and logistic kernels were also considered, however the polynomial classifier is quite similar to QDA and a logistic kernel inherently results in a linear decision boundary. Therefore, using an RBF kernel this may more accurately represent non-linearities in the classification boundary.

In order to determine the learning/convergence rate of an SVM, a penalty factor \( C \) and kernel coefficient \( \gamma \) must be parametrized. The former governs the regularization of the classifier and provides a way to trade-off between the boundary margin size (see fig. 5.27) and classification accuracy. Larger values of \( C \) encourage a narrower margin if the classifier can correctly classify each input, while lower values encourage a larger margin and simpler decision boundary at the cost of classification accuracy. For the RBF kernel, \( \gamma \) governs the radius of the kernel’s influence and intuitively can be understood as a measure of how “far” a single training datapoint can influence the decision boundary location from.

**Multi-Layer Perceptron - MLP** This method uses an Artificial Neural Network (ANN) with an input/output layer and multiple hidden layers in order to generate a decision boundary from some given training dataset. The network utilizes back-propagation to adjust individual neuron weights in the hidden layers in order learn the underlying transformation that maps given inputs to known outputs (supervised learning). This method seeks to minimize the cross-entropy log-loss function that indicates how accurate a resulting classification is to the known classification for that set of inputs. Expressed mathematically, the network attempts to solve for weighting values \( w \) for some given inputs \( x \) that map to a known set of outputs \( z(x) \) via:

\[
    z(x) = b_k + \sum_{j=1}^{n_h} w_{j,k} \varphi \left( b_h + \sum_{i=1}^{n_x} w_{i,h} x_i \right)
\]  

(5.20)

If the error is high, the ANN is provided with new weights through the Limited-memory Broyden-Fletcher-Goldfarb-Shanno (LBFGS) optimization algorithm and the
process repeats until the network can effectively predict the correct class for each training datapoint to a sufficient accuracy. For the data here, optimization is terminated after the change in the error function drops below a tolerance of $1e^{-4}$ for at least 10 consecutive iterations.

This method is capable of handling highly non-linear data and learns where each datapoint belongs in an iterative fashion. The rate at which the ANN can “learn” where the decision boundaries are is governed by the learning rate hyperparameter, $\epsilon$. The value of this hyperparameter is factored with the magnitude of the loss function gradients, and yields a balance between computational efficiency and higher model accuracy. However, with decreasing learning rates the potential for overfitting increases.

In order to combat overfitting, L2-regularization can be implemented. The L2-regularization hyperparameter, typically denoted $\alpha$, is factored with the magnitude of the weights found during backpropagation. The value of $\alpha$ can steer the network towards larger or smaller weight values. Small values of $\alpha$ may increase accuracy and reduce overfitting at the cost of computational speed as, while larger values provide faster results but with larger model bias (underfitting). Tuning the L2-regularization term and learning rate should be done via thorough cross-validation in order to ensure the resulting values provide a stable model with minimal overfitting.

**Figure 5.28:** Artificial Neural Network structure with two inputs $(X_1, X_2)$, three outputs $(I, II, III)$, and a single hidden layer of size $n = 100$. 
The preferred method of cross-validation here is a nested approach where the hyperparameters are tuned using an exhaustive grid search that will evaluate the model across a given set of possible hyperparameters, with the input datasets being generated through k-fold cross-validation. This CV method takes the entire dataset and subdivides it into $k = 5$ subsets of randomly shuffled x-y pairs. An exhaustive grid search is then run on each of the 5 sets, using $k - 1$ datasets to train the model and validating the results on the remaining data set; approximating a leave-one-out CV method. The scores generated then for each CV dataset are the mean accuracy scores that represent the fraction of the data that the model labelled correctly. Furthermore, the inner CV score is compared against an outer CV method whereby each run of the grid search inner loop is cross-validated again using 5-fold validation. This process is represented graphically in fig.5.30.

By cross-validating the data that is fed into the grid search for tuning hyperparameters (which itself is cross-validated again), an indication of the model’s sensitivity to the data when tuning hyperparameters is determined. Effectively, the model cross-validates the grid search for the ideal hyperparameters (outer CV) that itself is using
cross-validation to chose the final hyperparameter values (inner CV). The results of this approach are demonstrated in figure 5.31 whereby it is evident that the models are stable and may be reliably parametrized. The CV scores shown are those for the inner and outer validations, essentially representing how sensitive the model is to perturbations in the data. A stable model should result in a low discrepancy between the inner and outer cross-validations, as well as low variance across iterations.

**Figure 5.30:** Nested Cross-Validation illustration of how datasets are handled.

**Figure 5.31:** (Top) MLP, SVM, and QDA Classifiers cross-validation scores, inner CV yields higher scores in general. (Bottom) Inner vs. Outer CV score differences for each classifier.
Figure 5.32 illustrates the optimized classification models for the dataset presented in fig.5.17(b). The input data is scaled in order to ensure large numerical values of size and/or velocity do not govern the learning process. This processes ensures the resulting data has a mean at zero and a variance of unity, allowing the algorithms to perform more efficiently. Without scaling the data, some ranges for large sizes such as the 600µm datapoints might have a controlling interest in the learning process as the lower sizes would be numerically insignificant. In this way, care should always be taken to account for the scalability of the classification algorithm; in particular with any neural network as their weighting function are sensitive to this phenomenon. Fortunately, these scaling processes is easily reversible after classification has been carried out. Additionally, classifier output labels for Modes I, II, and III are transformed to numeric values of −1, 0, and 1 for simplicity.

Figure 5.32: QDA, SVM, and MLP Classifiers after cross-validation optimization for hyperparameters.

From fig.5.32 evidence is again seen on the expansion of the chipping mode (Mode II) as particle sizes increase, as previously discussed in section 5.3.1. Furthermore, the classification methodology provides a way to collapse the probabilistic values for each mode in figs. 5.24 to 5.26 into deterministic boundaries between each mode. This allows for a far more simplistic interpretation of the data not only for qualitative understanding but also for usage in particulate modelling as one may trade model bias in exchange for faster results. Additionally, one may inspect the model probabilities for each mode show in fig.5.33.
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![Figure 5.33:](top to bottom) MLP, QDA, and SVM probability values for each classification type (i.e. mode). In each sub-figure, the heatmap indicates the probability that an observation belongs to the respective mode of that figure. This gives an indication as to the likelihood of observing each mode independently across all sizes and velocities.

By visualizing the classification probabilities the accuracy that each model has in determining the bounds for each mode or class may be investigated. Thus yielding an indication of how well each model is performing. In fig. 5.33 it can be seen that the boundary of Mode 1 (no observable fragmentation) is quite well defined, as is the lower boundary for Mode 2 as a direct result. What causes some uncertainty, however, is the spread of Mode 3 and its somewhat stochastic nature when only discussed in terms of particle sizes and impact velocities. It is argued that the variance of Mode 3 here is, at least in part, due to the inherent anisotropy of crystalline structures (Liu et al., 2008; Varughese et al., 2013) affecting crack propagation and resulting fragmentation behaviour. Therefore, as individual particles may impact the same target but with
5.3 Breakage Modes: Mapping & Classification

different crystal faces one might expect that similarly sized particles at similar impact velocities would result in some degree of uncertainty when predicting the occurrence of Mode 3. From the data presented here it is stipulated that this variance only exists in a narrow band across the transition zone between Modes 2 and 3, with Mode 3 becoming clearly dominant as velocities increase. As an additional step, the classification probability can be reckoned in terms of the failure probabilities illustrated in fig[5.21]. Taking the probability of failure as $1 - P(\text{Mode I})$, where $P(\text{Mode I})$ is the classification prediction probability from fig[5.33], this provides an additional format for visualizing selection functions based solely on the determination of each classification model’s decision boundary for Mode I; as illustrated for each model in fig[5.34].

![Figure 5.34](image_url)

**Figure 5.34:** (left to right) MLP, QDA, and SVM probabilities for $1 - P(\text{Mode I})$; yielding an equivalent method for the determination of a continuous function for the failure PDF discussed previously.

5.3.3 Combining Hydrodynamics & Material Response

From section[5.1.2] it is noted that in liquid-based systems there exists a critical Reynolds number that provides a limiting factor for particle contact with a target surface such as an impeller blade in the case of crystallization applications. Plotting the isoline for $Re_c$ with the Mode I decision boundaries in fig[5.35] particle breakage in such begins...
5. CRYSTAL-CRYSTALLIZER INTERACTIONS

to become demystified.

Figure 5.35: Mode I decision boundaries for each classifier, with those values of size \(x\) and velocity \(y\) corresponding to \(Re_c = 250\) shown alongside.

What fig.5.35 illustrates is the fact that colliding with a surface is only the first of two hurdles. It is clear to see that even if impact may occur, the particle still has to impact with enough velocity to overcome the Mode I boundary in order to result in any measurable degree of fragmentation. This provides a quantitative illustration of the hydrodynamic and material response factors in governing particle breakage in agitated systems, i.e. proof-of-concept for the breakage model presented in section 2.4. Furthermore, this method also allows for those particles that do overcome this modal boundary to be quantified in terms of their expected breakage mode. This, in turn, informs the choice of daughter distribution function as it is possible to characterize each mode by small, uniform fragments in Mode II and essentially bi-model fragments of both large and small fragments in Mode III. Similar to a method proposed in Hounslow, Pearson and Instone (2001), these boundaries could provide information as to a weighted sum of fragmentation distributions akin to:

\[
b(x, x') = w_2b_2(x, x') + w_3b_3(x, x')
\]

where the subscripts 2 and 3 denote the characteristic fragmentation distributions of breakage Modes II and III. These characteristic modes may be quite similar for some compounds, and may indeed be appropriately modelled using a single distribution function for both. However, this method allows for a combination of fragmentation modes with their relative weights summing to unity. For example, a material might present in breakage with two distinct chipping (Mode II) and splitting (Mode III) distributions. In this case, one could use a lognormal distribution for both modes,
however Mode II would have smaller centre ($\mu_g$) and scale ($\sigma_g$) values than Mode III. Thereby creating a bimodal distribution function based on weighting functions determined from an analysis such as that resulting in fig 5.32 for a specific compound.

5.4 Summary

The work presented in this chapter consists of two major contributions: the determination of hydrodynamic and material response boundaries. Firstly, the role of vessel hydrodynamics on particle impact probabilities is outlined. It was shown that a squeeze film boundary layer between crystals and the impeller can drastically reduce the likelihood of a collision occurring. A Reynolds threshold can be defined that provides a parametrizable hydrodynamic term governing the rate of collisions occurring in a vessel. As such the comparison between the cyclohexane and rapeseed oil datasets discussed in chapter 4 will serve to highlight the role of vessel hydrodynamics in chapter 6. Additionally, the squeeze film boundary layer was shown to reduce collision speeds to approximately 10% of the initial particle approach speed. Importantly, this has implications in the breakage response of the crystals as reduced impact velocities will result in reduce breakage probabilities.

Secondly, it was shown that the breakage model theory presented in chapter 2 can successfully be applied to modelling crystal breakage events. Coefficients for the critical failure load ($F_{cr}$) in eq. 2.26 were shown to be parametrizable for the Prezista API, as confirmed via experimental data gathered via the shadowgraphy technique. It is then stipulated that these coefficients are, in general, parametrizable terms of the breakage model. Their determination requires either a breakage dominant process in order to extract the values for a given material, or explicit shadowgraphy testing. Thus, it will be shown in Chapter 6 that the 2500 RPM datasets provided for both Paracetamol and Pregabalin can serve as the material response parametrization sets.

Using a data classification technique it was possible to locate a quantitative breakage boundary, below which one can assume negligible crystal breakage. Additionally, the hydrodynamic Reynolds threshold provides a secondary boundary, below which crystals are not expect to collide at all. The quantification of clear hydrodynamic and material response boundaries to crystal breakage have been presented in a graphical
5. CRYSTAL-CRYSTALLIZER INTERACTIONS

manner (fig. 5.35), providing clarification as to their relevance in governing collisions and breakage over particle sizes velocities. The hydrodynamic response also illustrates that attrition in crystallization systems may be suppressed entirely if fluid viscosities are high, or agitation rates are low enough such that the hydrodynamic boundary overtakes the material response boundary. In these cases, it can be said that collisions are highly unlikely, and that the small fraction of collisions that may occur will not be energetic enough to overcome the material response boundary. Thus the model provides a thorough description of crystal-crystallizer interactions that can accurately account for both vessel hydrodynamics and crystal material characteristics.
6

Breakage Modelling - Finite Volume

The proposed hydrodynamic and material response concepts dealt with in the previous chapter are implemented here in a Finite Volume Population Balance model in order to fully explore the usefulness of the work. The population balance model for pure breakage outlined in chapter 3 is restated here for clarity:

\[
\frac{\partial n}{\partial t} = \int_{x}^{\infty} b(t, x, x') S(x') n(t, x') dx' - S(x) n(t, x)
\]

with its discretized form given from eq.3.14 as:

\[
\frac{\partial \hat{n}_i}{\partial t} = \frac{1}{\Delta x_i} \sum_{k=i}^{I} \omega_k^b S_k \hat{n}_k \Delta x_k \int_{x_{i-1/2}}^{r_k} b(x, x_k) dx - \omega_d^b \hat{S}_i \hat{n}_i
\]

Expressions for the RHS terms of the PBE above have been discussed in Chapter 3. Outlined below is the formal definition of these expressions and the optimization algorithm used to determine the model’s performance in predicting a realistic API production step. Firstly, the required terms and parameters are re-stated in section 6.1. The experimental conditions for each PSD to be tested against the model are then detailed in section 6.2, both the agitation conditions and material constants obtained from crystal nanoindentation are given. Section 6.3 then discusses how the model is parametrized against these datasets, with a focus on using a Genetic Algorithm in comparison to a Particle Swarm Optimization. Attention is also given to the topic of
6. BREAKAGE MODELLING - FINITE VOLUME

constrained multiobjective optimization, and Pareto Optimality. Lastly, the model results are detailed in section 6.4. Model performance in parameterizing realistic failure load curves and hydrodynamic efficiency factors is discussed. The topic of model overfitting is also discussed in relation to the overall accuracy of the model when compared to experimental data.

6.1 Constructing The Breakage Kinetics

Using eqs. (2.20), (2.21) and (2.23) to (2.26) an expression for the breakage selection rate, $S(x)$, for any crystal size can be formulated. From section 2.4 the general breakage rate function is given as:

$$S(x) = R_i \hat{S}(x) \quad (2.32)$$

Equation 2.32 gives the fraction of the population in size $x$ that is expected to undergo some comminution mechanism per-second, i.e. %s$^{-1}$ of size $x$ undergoing breakage. Breaking each component on the RHS into its functional dimensions:

$$R_i = R_i(Fl,N_{imp},D_{imp},V_{sys},\psi_{cic},\phi_{hydro}) \quad (6.1)$$

$$\phi_{hydro} = \phi_{hydro}(\eta_0,\eta_{Re},Re_x) \quad (6.2)$$

$$\hat{S}(x) = \hat{S}(x,v_x,m,K_{IC},E_{c,t},\rho_c,\gamma_{c,t},\alpha_{1,2},\beta_{1,2}) \quad (6.3)$$

Above, eqs. (6.1) to (6.3) represent the governing equations for determining the breakage selection rate, $S(x)$. Additionally, the daughter distribution, $b(x,l)$, on a normalized log-normal distribution is defined as:

$$b(x,x') = \left( \frac{x'}{x} \right) \frac{1}{x \sqrt{2\pi} \ln \sigma_f} \exp \left[ -\left( \ln \frac{x}{\mu_f} \right)^2 \right] \frac{1 + \text{erf} \left( \frac{\ln \frac{x}{\mu_f}}{\sqrt{2} \ln \sigma_f} \right)}{1 + \text{erf} \left( \frac{\ln \frac{x'}{\mu_f}}{\sqrt{2} \ln \sigma_f} \right)} \quad (6.4)$$

with weights,

$$b(x,x') = \omega_1 b_1(x,x') + \omega_2 b_2(x,x') \quad (6.5)$$

Above, fragments of size $x$ are formed from a parent crystal of size $x'$. The numerator in eq. (6.4) is the log-normal probability density function defined on $x \in [0, \infty]$. In order to normalize the distribution on $x \in [0, x']$, the log-normal CDF is given in the denominator; this ensures the probability distribution function is truncated along the
6.2 Experimental Conditions

length of the required discretization domain and that resulting values will be scaled accordingly. Furthermore, the leading term \(\frac{F}{x}\) ensures that the density function is scaled according to volume and will provide a conservative form for the daughter distribution (Hounslow, Pearson and Instone [2001]), given \(x\) corresponds to particle volume.

Finally, parameters given in **bold** are the optimization dimensions of the system; coming to a total of 13 parameters, counting subscripts and omitting the complementary parameters for fragment distribution weights satisfying \(\omega_2 = 1 - \omega_1\). Table 6.1 gives an overview of the optimization parameters. These may be estimated by an appropriate non-linear optimization algorithm such as Particle Swarm Optimization (PSO) or a Genetic Algorithm (GA). Other methods such as gradient descents, interior points, simplex, etc. may quickly encounter issues as their inherent linearity will tend to settle on local minima for non-convex minimization functions (Rockafeller [1993]). This is avoided in PSO or GA optimizations as the global solution is considered amongst throughout optimization and the optimal solution is an informed minimum that considers the best available point across potentially numerous local minima (Hassan et al. [1993]).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Units</th>
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<tbody>
<tr>
<td>(\psi_{circ})</td>
<td>Circulation efficiency</td>
<td>-</td>
</tr>
<tr>
<td>(\eta_0)</td>
<td>Critical Reynolds number for hydrodynamic threshold</td>
<td>-</td>
</tr>
<tr>
<td>(\eta_\rho)</td>
<td>Width parameter of hydrodynamic threshold</td>
<td>-</td>
</tr>
<tr>
<td>(m)</td>
<td>Weibull Modulus</td>
<td>-</td>
</tr>
<tr>
<td>(\alpha_{1,2})</td>
<td>Failure Load size-exponent</td>
<td>-</td>
</tr>
<tr>
<td>(\beta_{1,2})</td>
<td>Failure load pre-exponent</td>
<td>(N)</td>
</tr>
<tr>
<td>(\mu_{f(1,2)})</td>
<td>Location parameter of fragment distributions, numeric subscript denotes individual mode</td>
<td>(\mu m)</td>
</tr>
<tr>
<td>(\sigma_{f(1,2)})</td>
<td>Scale parameter of fragment distributions, numeric subscript denotes individual mode</td>
<td>(\mu m)</td>
</tr>
<tr>
<td>(\omega_{1,2})</td>
<td>Fragment distribution weights, (\omega_2 = 1 - \omega_1)</td>
<td>-</td>
</tr>
</tbody>
</table>

### Table 6.1: Model parameter descriptions for global optimization algorithm.

6.2 Experimental Conditions

The material properties for each API used are outlined in table 6.2. As discussed in chapter 4, a nanoindentation technique was used to obtain the elastic modulus of each
6. BREAKAGE MODELLING - FINITE VOLUME

API. Crystal densities are given as the sample bulk density with an approximate void fraction of 10% \cite{L. Augsburger 2008}. Values for crystal Poisson’s Ratios are taken as 0.3 for brittle materials. Table 6.3 outlines the experimental conditions for each of the PSD results used in the model, redrawn from \textit{chapter} 4 for clarity.

\textbf{Table 6.2:} Material Physical Properties

<table>
<thead>
<tr>
<th>Material</th>
<th>Poisson’s Ratio ((\gamma))</th>
<th>Young’s Modulus ((E))</th>
<th>Density ((\rho))</th>
<th>Shape Factor ((k_v))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prezista</td>
<td>0.3</td>
<td>1.021 ± 0.24 GPa</td>
<td>850.84 kg/m(^3)</td>
<td>0.58</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>0.3</td>
<td>10.6 ± 0.62 GPa</td>
<td>1334 kg/m(^3)</td>
<td>0.866</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>0.3</td>
<td>3.20 ± 0.36 GPa</td>
<td>900 kg/m(^3)</td>
<td>0.70</td>
</tr>
<tr>
<td>Stainless Steel</td>
<td>0.27</td>
<td>200 GPa</td>
<td>7,970 kg/m(^3)</td>
<td>-</td>
</tr>
</tbody>
</table>

\textbf{Table 6.3:} Experimental conditions and datasets.

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>Crystal Material</th>
<th>RPM</th>
<th>Suspension Medium</th>
<th>Residence time</th>
<th>PSA technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Paracetamol</td>
<td>2500</td>
<td>Rapeseed Oil</td>
<td>9 hrs</td>
<td>Mastersizer</td>
</tr>
<tr>
<td>1b</td>
<td>Pregabalin</td>
<td>2500</td>
<td>Rapeseed Oil</td>
<td>5 hrs</td>
<td>Mastersizer</td>
</tr>
<tr>
<td>2a</td>
<td>Paracetamol</td>
<td>400</td>
<td>Cyclohexane</td>
<td>4 hrs</td>
<td>Morphologi</td>
</tr>
<tr>
<td>2b</td>
<td>Prezista</td>
<td>500</td>
<td>Cyclohexane</td>
<td>4 hrs</td>
<td>Morphologi</td>
</tr>
<tr>
<td>2c</td>
<td>Pregabalin</td>
<td>500</td>
<td>Cyclohexane</td>
<td>4 hrs</td>
<td>Morphologi</td>
</tr>
</tbody>
</table>

6.3 Optimization Algorithm

A formal definition of the optimization algorithm used to estimate the kinetic parameters outlined above is given here. The algorithm must perform well in high-dimensional, non-linear optimizations, with multiple minimization objectives. To this regard, both the Genetic Algorithm (GA) and Particle Swarm Optimization (PSO) methods were investigated. These are both subsets of evolutionary computation methods that use metaheuristics to solve optimization problems. These methods take inspiration from natural phenomena such as natural selection (GA) and swarm intelligence (PSO) to converge on solutions with the highest measure of optimality according to some user-defined metric.
Genetic Algorithm

Genetic Algorithms (GAs) are a well known global optimization technique developed on the basis of Darwinian Theory and natural selection [Deb et al., 2002; Fisher, 1930]. Optimization exercises require some method for determining the population of potential solutions, with typical gradient decent or simplex methods such as Nelder-Mead or nonlinear minimizations often providing good results for low-dimensional problems. However, for cases of high nonlinearity or high-dimensional search spaces with multiple potential local minima, evolutionary methods can provide more reliable results [Hassan et al., 1993]. Table 6.4 details the relevant GA parameters used for the work here, while the following discussion will provide an overview of Genetic Algorithms in the context of optimization.

A Genetic Algorithm crates a population of potential solution vectors (Θ) and ranks each objective function returned. These vectors are often refereed to as “chromosomes” in an evolutionary sense, with the parameters within referred to as “genes”. In practical terms, they are a vector in D-dimensional space that contains the adjustable parameters of the optimization problem to hand. Figure 6.1 illustrates the parameter vector itself, containing up to D parameters for optimization. Vectors are selected from the previous generation (parents) via a scaling and ranking method that sorts solutions by optimality. Select genetic operations are then performed on the selected vectors in order to produce the next generation (children). In this case the genetic operators are
elitist, crossover, and mutation operations. Elitist children are those preserved from the previous generation, these ensure that a sufficient number of acceptable solutions remain after each generation. Crossover children are the product of the combination of two elite parents, the new parameter vector (child) is a combination of the two parents according to a user-defined crossover method; these provide new solutions from the pre-existing population. Mutation children are the result of a mutation operation performed on an elite parent, the result of which may change the solution entirely from the parent’s state; these serve to provide a degree of diversity to the search space.

![Figure 6.2: Genetic operations for crossover and mutation. Parents are chosen via the selection function and are assigned in generating crossover children or may have individual genes altered by slight random variations to introduce mutation.](image)

Importantly, each crossover and mutation operation is done so as to maintain any constraints on the parameter bounds. In this way the Genetic Algorithm can more effectively search the entire feasible parameter space, ensuring only those realistic or expected parameters are chosen at each generation. Additionally, each parameter vector (or chromosome) can be evaluated in parallel provided the fitness function allows for parameterization. In the case here, each individual is a single PBE model that can be evaluated independent of the others; thus this optimization can take advantage of massive parallelization up to the scale of the chromosomal population size itself.
6.3 Optimization Algorithm

Table 6.4: Genetic operations and parameters used in GA optimization technique

<table>
<thead>
<tr>
<th>Operations</th>
<th>Method</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elite</td>
<td>5% guaranteed selection</td>
<td>Ensures 5% of the previous population are carried over into the next generation as elite children</td>
</tr>
<tr>
<td>Crossover</td>
<td>Arithmetic Mean</td>
<td>Weighted arithmetic mean of two elite parents. Weights are randomly generated over (0, 1). Crossover fraction is set at 80% of the previous generation, excluding elite children.</td>
</tr>
<tr>
<td>Mutation</td>
<td>Adaptive Feasible</td>
<td>Generates random changes for each gene (parameter) while ensuring constrains are not violated. Mutation fraction is determined as $1 - \text{Crossover Fraction} = 20%$.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population Size</td>
<td>200</td>
<td>Total number of chromosomes (parameter vectors) used to search the parameter space.</td>
</tr>
<tr>
<td>Max. Generations</td>
<td>100</td>
<td>Total number of generations before GA terminates.</td>
</tr>
<tr>
<td>Stall Generations</td>
<td>10</td>
<td>Total number of generations before GA terminates if change in objective function is below function tolerance.</td>
</tr>
<tr>
<td>Function Tolerance</td>
<td>1e−3</td>
<td>Minimum relative change in objective function required for GA stall criteria.</td>
</tr>
<tr>
<td>Pareto Fraction</td>
<td>0.35</td>
<td>Fraction of population to remain intact from previous Pareto front while GA searches for updated sets.</td>
</tr>
</tbody>
</table>

Particle Swarm Optimization

Similar in effect to how GAs search the parameter space, Particle Swarm Optimization (PSO) sets out an initial population of parameter vectors (or particles) and uses swarm behaviour to determine the updates to each particle upon each iteration (Eberhart and Kennedy, 1995; Wang et al., 2018). Again, inspired by natural phenomenon PSO attempts to mimic swarm behaviour, such as that in flocking birds, and harnesses this to determine global minima in high-dimensional search spaces. PSO is used here as a comparative method, and as such is discussed phenomenologically as its implementation was not required in the final model.

PSO can be thought of as each particle attempting to find its own minimum while also being influenced by the leading particles that have found the best minimum so far. In this way each particle is allowed to search its own neighbourhood effectively, while always travelling towards a global minimum over time. Figure 6.3 illustrates how a population may evolve over time to avoid settling in local minima. As the algorithm iterates, each particle updates its best position and attempts to move towards it and the overall global minimum. The more particles that locate the global minimum, the larger its influence on those that have yet to arrive at it. Utilizing this behaviour, the updates for each parameter vector can be obtained for each particle in the swarm and a global minimum can be located.
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![Figure 6.3](image)

**Figure 6.3:** Illustration of how the swarm population tends to evolve towards the global minimum (blue) even in the presence of local minima (red, purple). Each particle is searching its neighbourhood for a minimum while constantly being “attracted” to the latest global minimum by all those particles that have settled upon it.

PSO literature often refers to velocity ($V$) and position ($X$) (Eberhart and Kennedy, 1995; Wang et al., 2018). However, in order to maintain consistency within this document the notation of position is referred to as the parameter vector $\Theta$; i.e. $X \equiv \Theta$ and is directly analogous to the chromosomal representation in a Genetic Algorithm. Consider that the $i^{th}$ particle has a position vector $\Theta_i = (\theta_{i1}, \theta_{i2}, \ldots, \theta_{id}, \ldots, \theta_{iD})$ defined in D-dimensional space. Each particle has a corresponding velocity vector $V_i = (v_{i1}, v_{i2}, \ldots, v_{id}, \ldots, v_{iD})$. Additionally, the vector $P_i = (p_{i1}, p_{i2}, \ldots, p_{id}, \ldots, p_{iD})$ containing the most optimal particle position that has been visited so far is retained throughout optimization. Following these definitions, the formal mathematical iteration of particle $i$, at time $t$, for parameter $d$, with velocity $v_{i,t}^d$ is given as:

$$v_{i,t+1}^d = \omega v_{i,t}^d + c_1 u_1 (p_{i,t}^d - \theta_{i,t}^d) + c_2 u_2 (p_{g,t}^d - \theta_{i,t}^d) \quad (6.6)$$

The inertial ($\omega$), cognitive ($c_1$), and social ($c_2$) weights are set prior to optimization and govern how the particle’s position is updated at each iteration, as previously illus-
6.3 Optimization Algorithm

The values of $u_1$ and $u_2$ are taken as uniformly distributed random number on $(0, 1)$, and introduce a small degree of variability in the swarm’s movement owing to the cognitive and social vectors. PSO provides a method by which to adjust the velocity vector itself, and subsequently provide the updated position vector by $\theta = \theta + v_\theta$ (Eberhart and Kennedy 1995, Wang et al. 2018). In this way, PSO attempts to mimic intelligent swarm behaviour and harness this in narrowing down on global minima while avoiding local minima. The particle update procedure is illustrated graphically in fig. 6.4 Adjusting the weights of the inertial, cognitive, and social factors will fundamentally alter the swarm’s behaviour. A large social weighing will tend to attract all particles strongly to the global minimum found so-far. However by allowing social and inertial factors, the parameter space can be explored more thoroughly by the rest of the swarm. Combined, PSO provides a method by which to avoid local minima and focus on global solutions, while maintaining a degree of exploration in the search space.

Figure 6.4: Schematic illustration of the factors affecting individual particle movement. By adjusting the inertial, cognitive, and social weights, the algorithm can control the swarm’s behaviour (Wang et al. 2018).

6.3.1 GA vs. PSO - Synthetic Comparison

In order to ascertain which optimization strategy may be most efficient in parametrizing the PB model presented in chapter 3, a synthetic test was carried out for both GA and PSO optimizations. Model parameters were set at some physically realistic initial values, outlined in table 6.5. The model output at these was recorded and saved to memory as the synthetic target of each optimization approach. The optimization target
6. BREAKAGE MODELLING - FINITE VOLUME

for each method is set to parametrize for a minimum squared error between the target volume PSD and the model output volume PSD. In a similar fashion to eq. 5.18 the objective function \( \psi \) is defined as:

\[
\psi(\Theta) = \sum_{j=1}^{n_{m,i}} (y_j - \tilde{y}_j)^2
\]

(6.7)

whereby \( \Theta \) is the input parameter vector of dimension 10, with the synthetic comparison parameters outlined in table 6.5. Both PSO and GA optimizations arrived at optimal solutions in each case, as is clear from fig 6.5.

![Comparison of GA and PSO optimizations in parametrizing for the target distribution](image)

**Figure 6.5:** Comparison of GA and PSO optimizations in parametrizing for the target distribution

**Table 6.5:** Initial and target Parameters for synthetic optimization test between PSO and GA.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>( \alpha_1 )</th>
<th>( \alpha_2 )</th>
<th>( \beta_1 )</th>
<th>( \beta_2 )</th>
<th>Weibull Modulus, ( m )</th>
<th>( \mu_f )</th>
<th>( \sigma_f )</th>
<th>( \psi_{irc} )</th>
<th>( \eta_0 )</th>
<th>( \eta_{ho} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>530 (x10^3)</td>
<td>-69.57 (x10^3)</td>
<td>61.1</td>
<td>30.03 (x10^3)</td>
<td>2.2 (150μm)^3</td>
<td>2.25</td>
<td>0.5</td>
<td>225</td>
<td>1 x 10^-2</td>
<td></td>
</tr>
<tr>
<td>Target</td>
<td>300 45.57 (x10^3)</td>
<td>35 25.03 (x10^3)</td>
<td>1.5</td>
<td>150μm)^3</td>
<td>4.0</td>
<td>0.75</td>
<td>300</td>
<td>2 x 10^-2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**GA Results**

| Initial | 530 45.57 (x10^3) | 35 25.03 (x10^3) | 1.5         | 150μm)^3 | 4.0 | 0.75 | 300 | 2 x 10^-2 |
| Target  | 300 45.57 (x10^3) | 35 25.03 (x10^3) | 1.5         | 150μm)^3 | 4.0 | 0.75 | 300 | 2 x 10^-2 |

**PSO Results**

| Initial | 530 45.57 (x10^3) | 35 25.03 (x10^3) | 1.5         | 150μm)^3 | 4.0 | 0.75 | 300 | 2 x 10^-2 |
| Target  | 300 45.57 (x10^3) | 35 25.03 (x10^3) | 1.5         | 150μm)^3 | 4.0 | 0.75 | 300 | 2 x 10^-2 |
6.3 Optimization Algorithm

Considering that both GA and PSO are capable of providing a stable optimization model that can reproduce its outputs, attention is turned to which method may be most efficient in doing so. Inspection of the GA and PSO evaluation performance results in some deciding factors as to the choice of optimization algorithm. Tracking the total fitness function evaluations, the iterations required for convergence, and time to find an acceptable solution - in this case $\psi(\Theta) \leq 0.001$ - one can quickly determine the most suitable algorithm for the problem at hand.

Comparing the Genetic Algorithm to the Particle Swarm Optimization in fig. 6.6, it is clear that the GA outperformed PSO in both number of fitness function evaluations required and total iterations until convergence. Moreover, the GA optimizer took 22.2385 hours to converge while the PSO approach took 38.7452 hours. To summarize, the Genetic Algorithm converged 1.7 times faster, required 1.4 times fewer function evaluations, and converged in only 9 iterations compared to 30 for PSO. The Genetic Algorithm is also more readily suited to multi-objective optimization problems; a key factor in parametrizing high-dimensional problems with multiple output optimization requirements.

6.3.2 Multi-objective Optimization

For any optimization procedure, it is typically required that a “fitness” or “objective” function be defined similar to eq. 6.7. This function returns a value describing the optimality of the solution resulting from the parameters chosen by the optimization algorithm. This function may return single or multiple values each representative of a different, but not necessarily independent, optimization objective that informs the
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optimization algorithm as to the closeness of its solution to the pre-defined target solution.

In terms of pharmaceutical processing, the resulting volume-size distribution of particles is often used as a release specification and is therefore considered here as a primary optimization objective. The objectives for the optimization algorithm are therefore given as representation of this PSD over three size brackets chosen to represent the characteristic modes of the target PSD. One objective is given for the fines distribution, another for the remainder of the size domain, and the last represents the overall PSD itself. By providing focus on the fines distribution and the remainder of the population, the optimization algorithm is forced to consider only the solutions that accurately explain the experimental observations in both of these size classes. Thus, the model considers the smaller size classes in equal importance to the larger size classes and the optimization objective is a more even representation of the entire PSD. Each objective is given by means of a weighted Euclidean $L^p$-norm whereby:

$$
\psi_i(\Theta) = w_i \left( \sum_{j=1}^{n_{m,i}} (y_{i,j} - \tilde{y}_{i,j})^2 \right)^{1/2}
$$

subject to $\Theta \in S$

Above, the $i^{th}$ objective to minimize ($\psi_i(\Theta)$) is considered as a weighted sum over the number of sample points ($n_{m,i}$) in the experimental ($y_{i,j}$) and model domains ($\tilde{y}_{i,j}$), with the weighting of each objective ($w_i$) indicating their relative importance. This method searches the feasible decision variable space ($S$) for values of the decision vector ($\Theta$) that return a minimum of this function. However, a drawback of this method is the high sensitivity to the weighting function ($w_i$) (Hu and Eberhart, 2002) as resulting squared error values for large numerical objective functions will dominate the evaluation of $\psi(\Theta)$ leading to higher model bias. To alleviate this, the inputs to eq[6.8] are scaled and normalized by a z-scoring method in order to ensure a mean of zero and a standard deviation of unity. This type of data scaling is commonplace in data-driven applications for avoiding bias when considering a large spread of numeric values. The objective function returned is a vector of length three, where each component represents one of the three PSD MSE objectives.
6.3 Optimization Algorithm

The concept of Pareto Optimality is then used in order to ensure that the final set of solutions found by an optimization algorithm lay on the Pareto frontier for that problem. This frontier represents the set of solutions, referred to as the Pareto set, that ensure any further parametrization serves only to improve the optimality of each objective. In this case, where one objective cannot be improved without degrading another objective, the solution is termed non-dominated. This may be represented graphically in fig.6.7.

Figure 6.7: (a) The feasible decision variable space (X). (b) An illustrative Pareto frontier and feasible objective space (S) representing the variation of two conflicting objective functions $\psi_1$ and $\psi_2$. Reproduced from Miettinen (1998a).

In fig.6.7b the set of feasible objective function values is bounded by the region $S$. This region contains the resulting set of feasible objective function values after evaluation of each objective function across the feasible set of decision variables ($x_i \in \Theta \in X$), seen in fig.6.7a. In order for a solution to be termed “Pareto optimal” there must exist no feasible solution that dominates them, i.e. where $\psi_1$ or $\psi_2$ in fig.6.7 return a more optimal solution. The thickened boundary line in fig.6.7 above represents all those objective function values that can be said to be non-dominated in this way. Therefore, any solution that is a member of the set of solutions along this line is termed Pareto optimal and is referred to as being on the “Pareto frontier” for that set.

Furthermore, it is conceivable that there exists multiple optimal solutions each with various degrees of optimality for each objective, as is evident from 6.7b. In these cases, there must be a method that can decide which optimal solution is best for the
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purposes of the problem at hand. This amounts to seeking the most preferred solution of the Pareto optimal solutions. Thus, an intelligent choice must be made as to which optimal solution is best when considering that some objectives may be more important than others, and requires some input from an external decision maker (DM) as to which solution is most preferred. This DM is taken to be a person with some “expertise” in the most preferred objectives and will decide upon the final Pareto optimal solution. There exists four key philosophies in determining this most optimal solution: No-Preference, Interactive, A Priori, and A Posteriori methods. Each is covered only briefly here as these are extensively documented (Miettinen, 1998a).

No Preference

Utilized when there is no explicit instruction as to which objective is most preferred. A typical example of this is the Method of Global Criterion (Miettinen, 1998b), which scalarizes the multi-objective function into a single criterion requiring a minimum of:

\[
\min \left( \sum_{i=1}^{n_{ob}} \left| f_i(\Theta) - z_i^{ideal} \right|^p \right)^{1/p}
\]

subject to \( \Theta \in X \)

for which \( z^{ideal} \) is the ideal objective vector, \( f(x) \) is the evaluated objective vector, and the set \( X \) is the feasible set of parameters. Eq.6.9 measures the distance of the current objective vector to some reference or ideal vector according to a choice of distance metric. In this case the \( L_p \) norm has been implemented above which can be stated formally for a vector \( x \) as:

\[
||x||_p = (|x_1|^p + |x_2|^p + \cdots + |x_n|^p)^{1/p}
\]

with choices for \( p \) resulting in various distance metrics. For example, for \( p = 1 \) this yields the rectilinear norm: \( ||x||_1 = |x_1| + |x_2| + \cdots + |x_n| \), also known as “Manhattan distance”. However, choosing \( p = 2 \) yields the standard Euclidean norm: \( ||x||_2 = \sqrt{|x_1|^2 + |x_2|^2 + \cdots + |x_n|^2} \). Furthermore, for any \( L^p - norm \) with \( 1 \leq p < \infty \) the resulting solution is guaranteed to be Pareto optimal (Miettinen, 1998a).
This method poses a problem in that if $z^{\text{ideal}}$ is unknown, some reference point must be selected. If not carefully selected, the feasibility of this ideal point may be in question; potentially resulting in a failure to determine solutions. Furthermore, this method treats each objective function equally and as such the resulting solution will be a neutral compromise of all Pareto optimal solutions in the set and it is up to the DM to choose an appropriate metric for eq.6.9.

**Interactive**

This is an iterative method analogous to supervised learning models for deep learning algorithms. A set of solutions is presented at each iteration, and the decision maker provides preferences for each set, informing the next iteration. This process repeats until some optimal solution is found that satisfies the decision maker. The main advantage of this method is that it provides iterative information to the decision maker as the solution progresses. This then allows the DM to consider the feasibility of their preferences as the solution progresses and can concentrate on solutions that may be most interesting or provide greater insight into the problem domain or constraint choices.

**A Priori**

This method requires that some preferences as to the importance of each objective is supplied prior to function evaluation. Typical a priori methodologies include linear scalarization, $\epsilon$-constraint methods, value functions, and lexicographic ordering (Miettinen, 1998a). In brief, these methodologies take some prior information about the quality, provided by the DM, of each Pareto optimal solution and return the best solution among the given Pareto optimal set. A difficulty with this again is that encoding what is meant by “quality” prior to evaluation of the Pareto front is complicated and the DM may not have explicit knowledge as to the most preferred solution until the Pareto optimal set is presented. Furthermore, the feasibility of the DM’s preferences may affect the outcome in a similar fashion to the distance metric in no-preference methods.

**A Posteriori**

This method provides either all Pareto optimal solutions, or a representative set thereof that may be then presented to the decision maker who selects the most preferred
solution out of the set. An advantage to this method is its ability to be encoded in evolutionary algorithms (such as NSGA-II in Deb et al. (2002)) whereby the Pareto optimal solutions are generated on the basis of the fittest individuals in a population, thus generating representative Pareto sets of solutions at each iteration. Therefore, these methods allow computation of an approximate entire Pareto front allowing the DM to chose from a wider selection of Pareto optimal solutions at his/her will. However, as only a representative set is provided in most cases due to computational complexity of high-dimensional multi-objective optimization exercises, the DM can only be assured that their choice dominates the others in the set. Therefore, the Pareto optimality is only guaranteed between the computed sets and as such the population size must be sufficient in order to satisfy at least an approximate global optimality.

In summary, the aim of this multi-objective approach is to force the model to consider the combined weight of all required objectives. In order to reduce computation times and ensure the optimization algorithm settles on a realistic minimum, three objective are specified here: minor, major, and global. Each objective corresponds to a bounded region in the final PSD whereby the minor mode is the model representation of the fine particulates, the major mode is the intermediate sizes, and the global mode considered the entire PSD as a whole. In this way the resulting Pareto front will represent how well the model can explain the generation of various sizes due to breakage and serves to enforce realistic constraints by only considering a solution optimal if it can accurately explain each objective. The resulting parameters are therefore an equal consideration for the PSD according to eq.6.8 \( \forall w_i = 1 \). The resulting final solution can then be chosen at will from the set of all Pareto Optimal sets returned from the algorithm.

6.4 Numerical Results

It has been shown in chapter 5 that there exists deterministic hydrodynamic and material response boundaries to breakage. Shown in this section is its application in explaining the behaviour of crystal suspensions subject to harsh mechanical agitation such as that in an overhead stirred container at a range of impeller RPMs across three distinct crystal materials. Utilizing the mathematical model above, in conjunction with a multi-objective Genetic Algorithm for determining the most likely parameters for the material
and hydrodynamic coefficients, the performance of the proposed breakage model can be evaluated. The initial and final PSDs of each experiment were recorded and the model was parametrized over each dataset in order to determine if it could successfully determine the outcome. It can be seen that good agreement between experiential data and model predictions was obtained. Thus indicating that the proposed mathematical description of the hydrodynamic and material response boundaries is indeed a realistic one.

6.4.1 Model Parameters

Material Parameters  Seen in figure 6.8 are the parameterized failure load characteristics for each material. As might be expected, the curves are arranged in order of increase elastic modulus; Prezista (1.021GPa) → Pregabalin (3.2GPa) → Paracetamol (10.6GPa).

![Figure 6.8: $F_{cr}/d_c$ for each material, parametrized via a bounded multiobjective Genetic Algorithm](image)

Each material exhibits similar behaviour towards a critical limit for comminution of small particles as reported in literature \cite{Anwar2015, Kendall1978}. This response is constant for any given material in its elastic range the model can be said to be general for most materials. As such it may serve API production and processing
6. BREAKAGE MODELLING - FINITE VOLUME

in optimization or design tasks in reducing the number of experimental exploration exercises as predictions, either qualitative or quantitative, can be made solely on the basis of these fundamental material characteristics.

**Hydrodynamic Parameters** Additionally, one may inspect the parameterized hydrodynamic efficiency term ($\phi_{\text{hydro}}$) for both the oil and Cyclohexane systems. This term accounts for the combined role of both suspension fluid properties, such as density and viscosity, and the effect of the impeller type itself. It is stipulated that the Reynolds intercept ($\eta_0$ in eq. [5.10]) will vary with fluid and impeller choices. Fundamentally this is due to the complex interactions between particles and a colliding surface, larger or smaller presented areas of the impeller may cause variation in the observed impact rate, while fluid properties will affect how particles behave within the flow patterns near the colliding surface. These effects can be seen in fig 6.9.

![Figure 6.9](image)

**Figure 6.9:** $\phi_{\text{hydro}}$ for each material and system case. The oil cases are given as dashed lines, while the cyclohexane cases are solid lines.

For the denser and more viscous oil, it can be seen that even the largest particles are far more protected from collisions, while in the considerably thinner cyclohexane only the smallest particles may avoid collision. Looking at the ratio of dynamic viscosities given by

$$\frac{\mu_{\text{oil}}}{\mu_{\text{cyclohexane}}} = 69.67$$
the case for hydrodynamic factors influencing fundamental impact rates, and thus comminution as a whole within a system, can be made clear. In effect, the approximately 70x more viscous fluid can more effectively protect against collisions occurring for a wider range of particle sizes. In general then, the hydrodynamic properties of the system can be said to a primary influencer of the fundamental collision rate for each particle. An additional discussion on these terms is carried out after presenting the PSDs for each experiential setup, as these will provide the required context.

6.4.2 Particle Size Distributions

2500RPM in Oil  Figures 6.10 and 6.11 below illustrate the ability of the model developed here in accurately modelling breakage dominant processes. Both the material parameters and hydrodynamic parameters given in the above section are reliably able to provide a realistic interpretation of the system here, capturing both various material and fluid properties.

![Figure 6.10: Particle Size Distribution & SEM of starter material for Paracetamol in oil at 2500RPM after 9 hours](image)

Although the agitation rate of 2500RPM is quite high, the highly viscous suspension fluid (rapeseed oil) provides a hydrodynamic boundary to breakage. While breakage still occurs, the rate at which crystals break is evidently very low. For each case it took a number of hours to see even a small change in the product PSD. This is indicative of
6. BREAKAGE MODELLING - FINITE VOLUME

![Particle Size Distribution & SEM of starter material for Pregabalin in oil at 2500RPM after 5 hours](image)

**Figure 6.11**: Particle Size Distribution & SEM of starter material for Pregabalin in oil at 2500RPM after 5 hours

A reduced collision rate directly resulting from an increased hydrodynamic boundary. This will be further discussed after presenting the 500RPM sets, however, as this will allow for a more inclusive discussion of both experimental sets.

**500RPM in Cyclohexane** The low RPM sets are more representative of a typical crystallization process. From figures 6.12 and 6.13 the model appears to perform quite well. There remains some discrepancy at the lowest size ranges, however, this is arguably an artefact of dust/initial breeding when considering batch seeded crystallization systems. This indicates that the model is well developed against overfitting as it is unable to provide a solution to these artefacts without compromising the results of the other PSD objectives.

It is clear from figure 6.14 and that in the case of Pregabalin the presence of initial fines may obscure how the PSD evolves over time. While it seems that the model could successfully predict this behaviour, the circulation efficiency ($\psi_c$) is on the order of $10^{-6}$, indicating that the model solution is to reduce the breakage frequency to almost zero. In fact, the results in fig. 6.14 were not obtained via any parametrization method as the GA consistently returned a zero-breakage solution, proof that the model has minimal tenancy to overfit.
6.4 Numerical Results

Figure 6.12: Particle Size Distribution for Paracetamol in cyclohexane at 400RPM after 4 hours.

Figure 6.13: Particle Size Distribution for Prezista in cyclohexane at 500RPM after 4 hours.
Therefore, from the combined perspective of both the mathematical model and experimental observations it is reasonable then that the increase in fine particles seen in fig.6.14 is indeed not a breakage phenomenon and is mostly likely due to initial breeding; a phenomenon common in batch seeded processes.

6.4.3 Location of Hydrodynamic Boundaries

Comparing the 2500RPM and 500RPM datasets from above, the hydrodynamic boundaries for the Paracetamol and Pregabalin experiments can be seen in fig.6.15. It is clear that the oil-based experiments have a much higher hydrodynamic boundary, as was pointed out in section 6.4.1. However, even though the hydrodynamic boundary appears to exceed the material boundary, some breakage is still observed.

This is a result of the hydrodynamic function in fig.6.9 approaching zero but never vanishing completely, as illustrated in fig.6.16. If fig.6.15 is redrawn with the lower curve as $\phi_{\text{hydro}} \rightarrow 0$, a lower hydrodynamic limit can be seen where the probability of collision is extremely small but still non-zero. This is demonstrated in fig.6.17 for the case of paracetamol, and explains why the 9 hour residence time resulted in minimal breakage when compared to the 500RPM experiments in cyclohexane.
6.4 Numerical Results

Figure 6.15: Illustration of hydrodynamic boundaries (dashed lines) and material boundaries (solid lines) for Paracetamol and Pregabalin. It is clear that the hydrodynamic boundary for oil-based experiments exceeds the material boundary, thus results in less breakage.

It is important to note that the hydrodynamic efficiency term can be reduced to zero, however the Reynolds coefficient parametrized by the GA ensured that there remained some small chance of collision over time. This behaviour is also evident from the PSDs in figures 6.10 and 6.11, and is arguably the reason each experiment took several hours to produce noticeable breakage of the initial population, while the cyclohexane-based experiments resulted in a large degree of breakage over a shorter residence time. The hydrodynamic boundary overtaking the material boundary therefore served to drastically reduce the propensity for particle collisions, and thus reduced the overall breakage rate in the system. While breakage may not be entirely inhibited, its effects over shorter time scales are negligible as the collision rates within the system are close to zero. This phenomenon is a function of vessel hydrodynamics, with factors such as fluid viscosity, agitation rate, and impeller type dictating the rate at which crystal-crystallizer collisions can occur.
Figure 6.16: Hydrodynamic boundaries for Paracetamol and Pregabalin illustrating the non-zero hydrodynamic efficiency term as particle Reynolds numbers decrease.

Figure 6.17: Hydrodynamic boundaries (dashed lines) and material boundaries (solid lines) for Paracetamol in oil at 2500RPM. As the hydrodynamic efficiency approaches zero, the hydrodynamic boundary provides a slight opportunity for crystals to collide.
6.5 Summary

The elastic modulus for each of the APIs was obtained from crystal nanoindentation experimentation, and are reported in table 6.2. To-date, these values have not been reported in literature. Using these material constants, failure load curves (fig 6.8) were parameterized via a Genetic Algorithm for Paracetamol and Pregabalin. In comparison to the profile for Prezista obtained from direct experimentation (table 5.3 from chapter 5), the profiles obtained via the GA are in-line with expectations. Paracetamol, with the highest elastic modulus, yields the highest failure load. Pregabalin is shown to be higher than Prezista, as would be expected from the decreasing elastic modulus. Thus the GA has parametrized the materials failure loads in order of decreasing elastic modulus, as would be expected. This demonstrates the exceptional ability of the multiobjective GA to parameterize the material response parameters over a breakage dominant process, without the need for additional shadowgraphy experimentation.

Hydrodynamic parameters obtained for each agitation vessel were also seen to be in expected ranges. The hydrodynamic boundary decreases with decreasing fluid viscosity, a factor directly linked to the particle Reynolds number. Although the agitation rate was significantly higher in the oil-based experiments, the increased fluid viscosity was enough to drive the overall collision probabilities for each particle size close to zero. This effect accounts for the relatively small change in PSDs even over extended residence times as collisions are far less likely overall. Importantly, material parameters were determined by the 2500RPM datasets and re-used in the 500RPM datasets in order to avoid overfitting. By allowing the model to control the location of the hydrodynamic boundary, via the hydrodynamic efficiency term ($\phi_{\text{hydro}}$), it was able to successfully parametrize both the cyclohexane and oil-based experiments.

The ability of the proposed hydrodynamic and material response parameters in modelling the breakage behaviour of three unique APIs in two unique suspension vessels and fluids has been successfully demonstrated in this chapter. It is concluded that the proposed model has been successful in providing a mechanistic approach to describing breakage in pharmaceutical processes; providing a new model for predictive capabilities.
6. BREAKAGE MODELLING - FINITE VOLUME
Summary, Conclusions, and Recommendations

7.1 Summary

Beginning from chapter 2, various important mechanisms at work during a typical crystallization process have been outlined. Existing theories of crystal growth, nucleation, and agglomeration were all reviewed. These provide context to the development of a new breakage kinetic, as described by this work. More explicitly, if the generation of new nuclei within crystallization systems is to be accurately described, it is important that the mechanisms of breakage and nucleation can be separated. An example of this lay in attrition-based secondary nucleation mechanisms (Evans et al., 1974). If crystal collision mechanisms are more fully understood, both breakage and such attrition-based secondary nucleation mechanisms will benefit from this advancement. Focusing then on breakage within agitated fluid systems, a new kinetic model for breakage was proposed that can account for both the material characteristics of API crystals and their behaviour during the interaction at a colliding surface such as an impeller blade. Two major parameter sets were identified: hydrodynamics and material response. These factors provide the collision probabilities for crystals within agitated vessels, and the breakage probabilities given a collision has occurred. Thus providing both a mechanistic collision model, and a comminution model for crystal failure.

Chapter 3 describes how this new kinetic may be implemented in a mathematical sense. A Population Balance model for breakage was outlined in detail, and solution
methods discussed. A zeroth and first order moment conserving Finite Volume formulation of the pure breakage PBE was detailed with discussion on various solution methods for typical PBEs.

The determination of limiting hydrodynamic factors during a crystal collision event are reported in chapter 5. It was shown that collision velocities are drastically reduced due to the presence of cushioning squeeze film boundary layers between approaching crystals and the colliding surface. Furthermore, it was determined that the particle Reynolds number could effectively provide a measure of the collision probability, with a logistic representation of this threshold used for the mathematical model. Overall, this work served to substantiate a mechanism by which crystal-crystallizer collision can be mitigated due to the particle-fluid interaction during collision events. The repercussions of this extend past breakage modelling, as attrition-based nucleation mechanisms (Evans et al., 1974) will also need to be revisited if crystal collisions are now seen to be unlikely for certain hydrodynamic conditions.

Subsequently, factors governing the material response due to any particle collision were detailed. Given a collision velocity and particle size, it is was possible to determine a probability of failure once the material’s elastic modulus and critical failure load behaviour is known. In conjunction with a realistic particle impact rate based on a characteristic frequency of the crystallization vessel, this probability can be used to determine the fraction of impacts per-second that are will result in breakage. Combined, the material parameters and the hydrodynamic factors provide the basis of the new kinetic model for crystal breakage in agitated fluidized systems.

In order to validate the developed kinetic, a pure breakage PBE was implemented in the Finite Volume scheme mentioned previously. Experimental data was gathered for Paracetamol, Pregabalin, and Prezista APIs at both 2500RPM in oil and 500RPM in cyclohexane. These provided datasets to validate the breakage model, the results of which can be seen in the preceding chapter. Overall, the model was seen to provide a highly accurate breakage model capable of parameterizing for various APIs and operating conditions. Importantly, the parameters returned from the Genetic Algorithm optimization technique were seen to be physically realistic in a qualitative sense.
and provide accurate quantitative results, i.e. the model has a low tendency to overfit. Therefore, it can be concluded that the proposed model in this work successfully demonstrates each of the research objectives outlined in Chapter 1, and has expanded the state-of-the-art in particulate modelling for pharmaceutical processes.

7.2 Conclusions

A new breakage kinetic was developed in order to accurately describe breakage phenomena within agitated crystallization vessels. Key physical aspects of the crystal-crystallizer iteration during breakage processes were investigated, namely hydrodynamics and material response. It was found that the collision rates within a system due to agitation can be accurately described by a logistic function of particle Reynolds number and a characteristic circulation frequency of the agitating system. Combined, these capture the system hydrodynamics and provide the probability of collision with the impeller for any given particle size, and the rate at which these collisions are expected to occur (section 5.1).

Given these collision probabilities for each size, and the approximate collision velocity of \( \sim 0.1V_{tip} \), the two-term Weibull model in eq. 2.20 can then be used to determine the probability of fragmentation for each collision; providing the material response model for breakage. It was found that the breakage characteristics of each crystal material can be parameterized for once physical constants such as the Young’s modulus, crystal density, and fracture toughness are known. This parameterization method was validated on experimental data in section 5.2 alongside a novel technique for classifying particle breakage from experimental data using Artificial Neural Networks (ANNs).

By combining vessel hydrodynamics and established particle comminution laws, this work provides a general breakage model capable of handling various API materials and hydrodynamic conditions. Implementation of the model in a Population Balance (PB) framework demonstrated its successful application to modelling particle breakage in crystallization experiments. Additionally, parameterization of the model via a Genetic Algorithm (GA) resulted in the illustration of sensible physical relationships between the hydrodynamic and material response factors in the model. It was demonstrated that for highly viscous fluids, the hydrodynamic boundary to particle collisions results
in a very low probability of breakage due to collisions being unlikely for most particle sizes. Conversely, for less viscous fluids the effect is reversed and the boundary to breakage is dominated by the material response of the crystal material; i.e. collisions are more frequent but the crystals may be strong enough to survive impact without any significant breakage occurring. Overall, this work has contributed a new mathematical model for breakage of pharmaceutical materials by adaptation of proven statistical models for comminution. Due to this, the model is said to be general and capable of handling a range of additional particulate processing steps such as isolation, drying, and milling.

The following conclusions were made during the course of this thesis:

- Breakage within crystallization vessels can often make it difficult to determine the extent of nucleation rates. This is due to how breakage serves to increase the number of fines in the population, something that nucleation mechanisms are also responsible for. As such, isolating the mechanisms at play during crystallization requires well-defined models for nucleation and breakage.

- The shadowgraphy imaging technique can provide a powerful experimental tool in the observation of crystal-crystallizer interactions. Used here, it provided meaningful insight into squeeze film boundary layers, and the breakage characteristics of APIs.

- Crystal nanoindentation, while a difficult task, can provide extremely useful physical property data on pharmaceutical compounds. In this work it was used to determined reliable elastic moduli for each of the APIs investigated. Literature on these values is rare, yet breakage laws are heavily reliant on these material properties.

- The Finite Volume Method (FVM) provides a powerful solution method to the Population Balance Equations (PBEs) for breakage. Explicit conservation of the PSD is ensured, and thus the time-evolution of breakage processes may be tracked.

- A distinct hydrodynamic boundary can be identified for liquid-based crystallization systems. This boundary may protect the crystal population from collisions.
with the crystallizer, drastically reducing the rate of breakage in the vessel. Additionally, this boundary may support surface-shear secondary nucleation over attrition-based pathways.

- A hydrodynamic efficiency term can be used to describe a threshold Reynolds number, below which the probability of collision drops dramatically. This efficiency term is parametrized as a sigmoid curve, and accounts for the vessel’s impeller type and fluid characteristics. This term provides a mathematical interpretation of the squeeze film boundary layer in a Population Balance framework. The hydrodynamic parameters can be determined via parameterization for each impeller/fluid combination (chapter 6).

- It was found that an Artificial Neural Network can provide a robust tool in data processing for crystallization processes. Using a Multi-Layer Perceptron classification techniques it was possible to quantify a material response boundary, elucidating the role of crystal material characteristics in breakage processes. Through the use of such data-driven tools it was possible to extract information about breakage selection functions and fragmentation distributions, without the need for extensive experimentation.

- Crystals that collide with the agitation impeller will only experience approximately 10% of the impeller’s tip-speed. This is a direct result of the squeeze film boundary layer. It is stipulated that the magnitude of this effect depends on the system specific hydrodynamics, such as impeller types and fluid viscosity.

- Crystal collision rates can be determined from a fundamental vessel circulation frequency under the assumption of spatial homogeneity, i.e. well-mixed vessels. Factored with the hydrodynamic efficiency term, a collision rate of the system can be described theoretically. This collision efficiency should be thought of as a macroscopic interpretation of reactor hydrodynamics, and is therefore well-suited to Population Balance modelling.

- Crystal collision rates can be converted to breakage rates through the use of an established comminution law (Weibull statistics). Particle size and impact velocity are taken as inputs and the probability of breakage is returned. Therefore, if the rate of impacts per-second is known, the overall breakage rate in the vessel
7. SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

can be determined. The only prerequisite is that the elastic modulus and fracture

toughness of the crystal material must be determined (via nanoindentation in this 

case). The breakage model coefficients for a given material can then be determined 

eperimentally (section 5.2) or parametrized from process data (chapter 6). 

- For certain crystallization systems the hydrodynamic boundary may overtake 

the material boundary. In such cases, the collision rate of the system drops 

substantially. This lowers the overall breakage rate of the system and provides 

a mechanism by which crystal breakage may be mitigated. Although breakage 

may not always be fully inhibited by this mechanism, the rate is low enough that 

breakage will only occur over greatly extended time-periods.

- A Genetic Algorithm provides a robust multiobjective optimization tool for model 

parameterization. This method can handle highly non-linear parameter spaces, 

and is shown to provide little model bias in overfitting. Pareto optimality must 

also be considered when dealing with multiobjective optimization. This will en-

sure that all solution objectives are minimized to the greatest extent possible, 

while ensuring that no objective is worsened as a result of another being im-

proved. These methods provide a robust parameter extraction technique for the 

numerical PB model.

- The breakage kinetic developed here provides extremely accurate results when 

compared to the experimental data in chapter 6. This new kinetic further serves 

to clarify the role of reactor hydrodynamic in not only breakage, but also attrition-

based nucleation mechanisms, and general collision-based kinetics on the whole. 

The model also performed well in the presence of initial breeding, with the GA 

effectively reducing the breakage rate to zero

To conclude, the relevant factors for crystal breakage with crystallization systems 

have been identified: hydrodynamics and material responses. Mathematical descrip-

tions of these factors were provided, and implemented in a numerical model for crystal 

breakage in agitated systems. It was shown that the model performed extremely well 

in parametrizing realistic values for both the hydrodynamic and material response as-

pects. The model parameters allowed in-depth explanations of the physical breakage
process, and provided clear mechanisms governing the changes seen between experimental datasets. It was further shown that crystal breakage can be dramatically inhibited if the hydrodynamic collision boundary is sufficiently high. This aspect extends not only to breakage processes, but also to collision-based mechanisms in general. If crystal collisions can be said to be negligible for some systems, as demonstrated here, this supports growing research into alternative breeding mechanisms such as surface-shearing and initial breeding (Anwar et al. 2015; De Souza et al. 2016; Yousuf and Frawley 2018).

### 7.3 Recommendation for Future Work

Recent work on secondary nucleation mechanisms suggests that initial breeding in conjunction with surface-shearing of small crystallites on the surface of seed crystals may be the leading cause of secondary nuclei generation during crystallization processes (Anwar et al. 2015; De Souza et al. 2016; Yousuf and Frawley 2018). Taking the hydrodynamic factors from this work in isolation, it is suggested that the reduced collision rates due to the squeeze film boundary layer does indeed support this view. It is reasoned that if the hydrodynamic boundary can alleviate crystal-crystallizer interactions, the pathways to attrition-based secondary nucleation are inhibited. Therefore, in these cases there must exist an alternative pathway to secondary nucleation.

It is stipulated that if the PB model used here were to incorporate crystal growth, a similar rate-expression could be used to model secondary nucleation as a surface-shearing mechanisms. The PB model for breakage would remain unchanged in eq.3.4, however, the selection and distributions functions would be modified to represent the rate at which particles generate new nuclei, and their subsequent size-distributions. This makes mathematical sense as the breakage equation is fundamentally a mass-conservation law. Therefore, if growth is responsible for the incorporation of new mass onto the existing population, the breakage equation can be used to model the detachment of surface nuclei as a “breakage” event and would re-distribute the mass to the lower size classes. In this way, one can see how breakage and secondary nucleation are linked at a fundamental level. Such a model may serve to provide a general mathematical form for surface-shear secondary nucleation mechanisms hereto unseen in literature.
The methodology applied here in constructing the breakage rate-expression in chapter 2 could also be applied to downstream processes such as isolation and drying steps where there may be mechanically intensive agitation involved. Additionally, milling steps are commonly used in order to reach a desired PSD via intentional breakage. As the breakage selection functions are based on a general comminution law (Weibull) it stands to reason that in order to apply this model to other processes, only the appropriate collision rate need be determined for each additional process, while the need to parametrize for each material only arises once; indeed a wider study on a range of APIs could be carried out in order to determine their breakage characteristics. Once complete, any industrial process need only determine the rate at which particles are expected to undergo a collision event, and apply the pre-defined breakage model for that crystal material. In this way, the model developed here may be generalized across pharmaceutical processes as a whole.

Additionally, application of the model in 2-dimensional Population Balances could provide a predictive model for particle shape control in comminution steps. Extension of the 1D fragmentation equation into 2D would require further study into the role of aspect ratio on fragmentation generation, with consideration for how the breakage selection function may vary with orientation in high-aspect ratio particles. However, numerous sources of literature exist for 2D PB breakage model (Salvatori and Mazzotti 2018; Szilágyi et al. 2015; Szilágyi and Lakatos 2017; Szilágyi and Nagy 2018) and further development of a generalized breakage model into multi-dimensional Population Balances would surely enhance the state-of-the-art in particulate processing.
Appendix A

MATLAB code for Population Balances

As mentioned during the introduction, the code itself is not printed here for both compactness and environmental reasons. However, the attached CD drive contains all pertinent files located in Appendix A.
Appendix B

Python code for Shadowgraphy processing

As mentioned during the introduction, the code itself is not printed here for both compactness and environmental reasons. However, the attached CD drive contains all pertinent files located in Appendix B.
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