A thermodynamic framework for the modeling and optimization of crystallization processes

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A THERMODYNAMIC FRAMEWORK FOR THE MODELING AND OPTIMIZATION OF CRYSTALLIZATION PROCESSES

A Dissertation

Submitted to the Graduate Faculty of the Louisiana State University and Agricultural and Mechanical College in partial fulfillment of the requirements for the degree of Doctor of Philosophy in

The Gordon A. and Mary Cain Department of Chemical Engineering

by

David John Widenski
B.ChE., University of Minnesota, 2002
M.S., Louisiana State University, 2010
May 2012
This dissertation is dedicated

to the memory of my grandfathers,

Edward John Russell

and

John Stanley Widenski.
ACKNOWLEDGEMENTS

Foremost I thank my research advisor, Professor Jose A. Romagnoli, for his guidance during my doctoral studies. I also thank him for allowing me to tailor my research as I saw fit, and allowing me to take additional classes to enrich my educational experience.

I thank Dr. Ali Abbas for the immense amount of work that he did for me during my doctoral studies. His feedback was essential in helping me publish the number of papers that I did. I also thank him for hosting me at the University of Sydney from April 2008 to October 2008. I was able to learn a lot about crystallization theory and how to perform experiments from Dr. Abbas and his other graduate students. I also want to thank the National Science Foundation and the Australian Academy of Science for funding my research in Australia.

I thank the members of my committee, Professors Karsten Thompson, James Spivey, Francisco Hung, and my Dean’s Representative, Professor Sukhamay Kundu for their helpful feedback during my studies.

I thank all of my current and former labmates for providing helpful research advice. In particular, Ombretta Foddi whom with I learned crystallization theory and gPROMS during my first year, Daira Aragon and Miguel Estrada for helping me learn and debug gPROMS programs, Omar Galan for helping refine my experimental procedure, Gregory Robertson and Paritosh Sharma for giving helpful presentation feedback and for giving general life advice, and Giuseppe Cogoni who helped perform experiments and data analysis.

I thank the administrative staff of the chemical engineering department. In particular, I want to thank Rob Willis for computer application and hardware support, Darla Dao for financial reimbursement and supply ordering support, and Melanie McCandless and Melissa Fay for administrative support.
I thank the undergraduate lab instructor, Dr. Harry Toups, and the undergraduate lab manager, Bob Perkins, for allowing the use departmental laboratory equipment. I also thank Karsten Thompson and Pradeep Battad for providing laboratory equipment, and fellow graduate students Nimesh Poddar and Franz Ehrenhauser for providing invaluable laboratory equipment purchase and operating advice.

I thank my rigorous education from the University of Minnesota. The education prepared me well for graduate school, and allowed me to become a very successful graduate student and researcher. I thank all of my professors, in particular Professors Christopher Macosko and George Psihos for writing letters of recommendation, which were necessary to gain acceptance to Louisiana State University.

Lastly, I thank my family for being supportive while I pursued my degree. In particular I want to mention, my mother Jane, my father Richard, and my sister Jill who were extremely supportive during my studies, and who I know are extremely proud of my accomplishment.
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ABSTRACT

Crystallization is a widely used chemical engineering separation unit operation process. Since this technique can produce high purity products it is used for the industrial production of many chemical compounds, such as pharmaceuticals, agrochemicals, and fine chemicals. The production of these products is a multi-million dollar industry. Any methods to improve the production of these products would be highly valued. Thus, the main objective of this work is to target model-based optimal strategies for crystallization operations specifically targeting crystal size and crystal size distribution (CSD). In particular, take the knowledge gained and translate it into an economically and practically feasible implementation that is utilizable by the pharmaceutical industry.

To achieve this, a comprehensive crystallization modeling framework is developed. This framework predicts the CSD while taking into account temperature, seeding variables, and antisolvent feed rates. In addition, this framework takes into account the recent proliferation of predictive thermodynamic solubility models. These solubility models have the potential to greatly reduce the need for experimental data, thus, improving the crystallization model’s predictive ability. Finally, these crystallization models are implemented into the gPROMS modeling software and are used for model-based optimization.

The crystallization modeling framework is developed for several different scenarios. One framework consists of a full thermodynamic crystallization model for potassium chloride. This modeling framework when combined with model-based optimization is proven to be superior to heuristic methods. Another framework, which utilizes several different predictive thermodynamic solubility models, evaluates their use to predict crystallization behavior and to determine optimal operating conditions, cooling profiles, and antisolvent feed profiles. It is
shown that these models can be used to determine optimal operating conditions and cooling profiles, but they are not sufficiently accurate to be used to determine optimal antisolvent feed profiles. The last crystallization framework is developed for the non-isothermal antisolvent crystallization of sodium chloride. This framework shows that for systems whose solute solubility is relatively independent of temperature, adding temperature control as a second degree of freedom is beneficial. In particular, it allows for the production of crystal mean sizes unattainable at other temperatures, and for the joint control of particle mean size and dispersion.
1. INTRODUCTION

1.1 Literature Review

1.1.1 Crystallization Overview

Crystallization is a powerful production and separation process. It can mass-produce products with purities that are difficult to achieve using other production processes. Due to this reason, crystallization is the preferred way to manufacture pharmaceuticals and proteins that are subject to United States Food and Drug Administration (FDA) purity regulations. It also is used for the manufacture of agrochemicals and fine chemicals. The driving force for crystallization is the change in chemical potential between the liquid and solid phases. Since chemical potential is hard to measure, supersaturation is commonly used instead. Supersaturation occurs when the solution concentration is higher than the equilibrium concentration. There are several different crystallization techniques currently used to generate supersaturation necessary for crystallization. The most common techniques are cooling, evaporation, and antisolvent addition. All of these techniques cause crystallization due to changes in equilibrium solubility. The appropriate technique to use depends on the solubility behavior of the compound to be crystallized. Cooling crystallization is used when the equilibrium solubility changes with temperature. For these compounds the change in temperature will generate supersaturation. Some examples where cooling crystallization has been used are: ammonium sulphate [Tadayon et al., 2002; Nowee et al., 2007], paracetamol [Fujiwara et al., 2002; Worlitschek and Mazzoti, 2004; Nagy et al., 2008a], and potassium sulphate [Jagadesh et al., 1999].

Cooling crystallization is not applicable when either the compound is temperature sensitive, or if the compound’s equilibrium solubility does not change significantly with temperature. When the previous limitations occur, another crystallization method is needed.
Often this can be done by adding a second solvent to the system. Normally, for crystallization the compound is highly soluble in the original solvent. If it isn’t sufficiently soluble, crystal yield will be poor. The second solvent, called an antisolvent, is a solvent where the compound is less soluble, and as the second solvent is added to the initial solvent the compound’s solubility decreases in the solution. This is also known as drowning out crystallization because the antisolvent “drowns” the solute out of solution. Some examples of antisolvent crystallization are sodium chloride [Nowee et al., 2008] and paracetamol [Zhou et al., 2006; Trifkovic et al., 2008].

Sometimes the solubility of a compound is significantly affected by both temperature and addition of an antisolvent. In this case it is beneficial to apply both techniques. This technique has been performed recently for lovastatin [Nagy et al., 2008b] and acetylsalicylic acid [Lindenberg et al., 2009]. The biggest advantage to joint cooling-antisolvent crystallization is crystal yield. This technique can produce more product per batch than either individual cooling or antisolvent crystallization. Since crystallization is used for the production of high-valued pharmaceuticals, any way to increase the profitability of the process is valuable.

1.1.2 Crystallization Modeling

Like many chemical engineering processes, modeling is being done to better understand and utilize crystallization processes. However, crystallization modeling is more complicated than many chemical engineering processes for several reasons. First, it is often operated at unsteady state due to the batch nature of crystallization processes. Second, in addition to the standard mass and energy balances, a population balance is also needed. This population balance incorporates many different types of phenomena such as nucleation, growth, agglomeration, and attrition. The
end-result is that the crystallization model is a system of algebraic, partial differential, and ordinary differential equations.

The population balance technique which was first developed by Hulburt and Katz [1964], allows for the tracking of particulates as they form and grow during the process. The population balance model has been used to model emulsion polymerizations [Thompson and Stevens, 1977; Crowley at al., 2000] in the field of chemical engineering. Ramkrishna [2000] wrote a book describing how the population balance can be used for particulate systems in chemical engineering. Before the advent of modern computers the population balance had not reached its full potential because it can only be solved analytically for several arbitrary scenarios. Due to that limitation, Randolph and Larson [1988] developed an ingenious way to solve the population balance. Their method, the method of moments, converts the partial differential equation population balance into a small system of ordinary differential equations. This method allows for the calculation of moments of the distribution such that descriptors such as mean size and coefficient of variation can be determined. The disadvantage of this technique is that unique crystal size distributions cannot be determined. Now that computer software can easily solve the partial differential population balance equation, the equation can be solved using methods that allow for the creation of a crystal size distribution. These methods consist of using finite differences, finite elements, wavelets, etc. Another way to portray the crystal distribution is to use the Fokker-Plank Equation [Galan et al., 2010; Grosso et al., 2010]. Assuming a unimodal distribution an extremely simple way to model the CSD is to use a probability density function, and logistically model the mean and variance over time. While this approach can effectively model these parameters, the phenomenological aspects of the system are lost. We believe that the ideal way to represent a particulate distribution is with a population balance.
In addition to a population balance several other models are needed to complete the overall crystallization model. These models represent common crystallization phenomena such as nucleation, growth, agglomeration, attrition, as well as traditional mass and energy balances. Nucleation encompasses a broad range of subtypes of primary and secondary nucleation. Primary nucleation is when crystals are formed without the presence of already formed crystals, while secondary nucleation is the converse. Primary nucleation consists of homogenous nucleation and heterogeneous nucleation. Homogeneous nucleation is when crystals are formed in a pure solution, and heterogeneous nucleation is when crystals are formed due to impurities in the solution. Homogeneous nucleation has been modeled thermodynamically [Mersmann, 2001; Mullin, 2001; Zhou et al., 2006], and heterogeneous nucleation has been modeled thermodynamically [Mersmann, 2001]. Empirical primary nucleation models generally do not distinguish between homogeneous and heterogeneous mechanisms and have been modeled [Nowee et al., 2007, 2008]. Secondary nucleation can be caused by contact, shear, and surface mechanisms. These have been modeled by [Mersmann, 2001; Worlitschek and Mazzotti, 2004].

The second crystallization phenomenon is crystal growth. Crystal growth is when dissolved solute is used to grow preexisting crystals instead of creating new ones. Akin to catalysis, crystal growth can be diffusion or surface integration limited [Mullin, 2001]. When diffusion limited, crystal growth can be modeled with a mass transfer coefficient, and is linearly related to supersaturation. When surface integration limited, crystal growth can be modeled with an Arrhenius formulation, and is nonlinearly related to supersaturation. Growth kinetics have been modeled thermodynamically [Worlitschek and Mazzotti, 2004] and empirically [Nowee et al., 2007, 2008]. The population balance can be greatly simplified by making two growth assumptions. First, the assumption that crystal growth is independent of crystal size, which
means that crystal growth follows McCabe’s Law. The second assumption is that crystal growth can be characterized by one primary size axis. This reduces the three-dimensional population balance to a one-dimensional population balance.

Agglomeration and attrition are other crystallization phenomena that can occur. Agglomeration is when crystals join together to form larger crystals, and attrition is when crystals break into smaller fragments by colliding with each other, the crystal impeller, or other elements of the crystallizer. These are usually assumed to be negligible, but aggregation and attrition have been modeled [Mersmann, 2001].

Other models needed for the crystallization model are mass and energy balances. The mass balance accounts for mass that is transferred from dissolved solute either to form new crystals or to grow preexisting crystals. Generally explicit energy balances are not needed unless temperature control is required. The energy balance can then describe the relationship between the crystallizer jacket temperature and the internal crystallizer temperature.

### 1.1.3 Crystallization Optimization

Crystallization optimization techniques have been around for decades. Initially, the optimal operation of crystallization processes was based on thumb rules and industrial knowledge. In the early 1970’s optimal profiles for cooling crystallization were designed to suppress nucleation [Mullin and Nyvlt, 1971; Jones, 1974; Jones and Mullin, 1974]. They were able to decrease the amount of nucleation occurring using programmed cooling curves. Later the importance of seed mass and seed size in minimizing nucleation was showed [Jagadesh et al., 1999]. Since then, many others have developed crystallization models that allow for joint cooling profile and seed mass optimization [Chung et al., 1999; Sarker et al., 2006; Nowee et al., 2007].
These optimizations consist of single objective optimizations such as maximization of weight mean size [Chung et al., 1999], minimization of coefficient of variation (COV) [Chung et al., 1999], minimization of the nucleation to seed ratio [Chung et al., 1999], maximization of volume mean size [Nowee et al., 2007], and minimization of the variance [Nowee et al., 2007]. The multi-objective optimizations consist of maximization of weight mean size and minimization of nucleation; maximization of weight mean size and minimization of time, and maximization of weight mean size and minimization of time and COV [Sarker et al., 2006].

Several authors also developed optimal antisolvent feed profiles for different objective functions [Nowee et al., 2008; Sheikhzadeh et al., 2008; Trifkovic et al., 2008]. Single objective optimizations of maximization of volume mean size, minimization of total nucleation, and specified final volume mean size were done [Nowee et al., 2008]. Other authors did both single objective and multiple objective optimizations [Sheikhzadeh et al., 2008; Trifkovic et al., 2008]. Single objective optimizations consisted of minimizing the nucleation to growth rate, and minimizing the nucleation to seed ratio [Sheikhzadeh et al., 2008; Trifkovic et al., 2008]. The multi-objective optimization consisted of a joint optimization of both single objective functions and minimization of the COV [Sheikhzadeh et al., 2008; Trifkovic et al., 2008].

Joint cooling-antisolvent optimizations have also been performed [Nagy et al., 2008b; Lindenberg et al., 2009]. Single objective optimizations of minimization of COV, minimization of nucleation to seed mass ratio, maximization of number mean size, and maximization of weight mean size were done [Nagy et al., 2008b]. The authors state that the best performance for each objective was fulfilled by joint cooling-antisolvent operation [Nagy et al., 2008b]. A multi-objective optimization of joint minimization of process time and nucleation using a weighting function was also done [Lindenberg et al., 2009].
1.1.4 Solubility Modeling

In order to calculate the equilibrium concentration needed to calculate supersaturation a solubility model is needed. Solution concentration can then be related to supersaturation, which is the driving force used in most crystallization models. Supersaturation exists when the solution concentration is larger than the equilibrium concentration. Nucleation is usually modeled with relative supersaturation ($S$), which is the ratio of solution concentration over equilibrium concentration. Absolute supersaturation ($\Delta C$), which is the difference between solution concentration and equilibrium concentration, is usually used as the driving force for growth. In order to calculate supersaturation, equilibrium concentration needs to be known. If solubility data has already been determined, then a solubility model can be made. This can either be done empirically using exponential models [Romero et al., 1996], polynomial models [Zhou et al., 2006; Lindenberg et al., 2008], artificial neural networks [Nagy et al., 2008b], etc. The experimental data can also be used to fit the binary interaction parameters of correlative thermodynamic models such as van Laar, NRTL, UNIQUAC, or Wilson [Worlitschek and Mazzotti, 2004; Widenski et al., 2010].

However, if experimental solubility data is not known, then either the solubility will need to be measured or estimated. Accurately measuring the equilibrium solubility can be a time-consuming process using techniques such as gravimetry [Granberg and Rasmuson, 1999] or chemometrics [Hojjati and Rohani, 2006]. One way around this is to use predictive solubility models. Predictive solubility models are generalized models with parameters for solutes and solvents. One just needs to find the corresponding parameters for the solute and solvent(s) desired, and use the model to determine equilibrium solubility. Examples of predictive solubility models are NRTL-SAC [Chen and Song, 2004], eNRTL-SAC [Chen and Song, 2005],

The disadvantages to predictive solubility models are that the parameters may not have been determined for new solutes, and that due to their nature they can have varying accuracy predicting the equilibrium solubility. Even with these limitations, the question is: can predictive solubility models be successfully used for modeling and the subsequent optimization of crystallization processes?

1.2 Dissertation Motivation

As described earlier, crystallization models can be extremely useful for the optimization and control of crystallization processes. However, these crystallization models require an extensive amount of experimental data. First, experimental solubility data is required to create a solubility model. This solubility model is used to calculate supersaturation, which is needed for the crystallization model. Second, crystallization data is needed to determine the parameters for the crystallization kinetic model. This experimental data need can be incredibly cumbersome to obtain if it is not already present in the literature.

One way to reduce this experimental burden is via first-principles thermodynamic modeling. The first application of this is to use predictive thermodynamic solubility modeling. Predictive solubility models allow one to predict the solubility of a solute in pure or mixed solvents. This is extremely useful for antisolvent crystallization, but can also be used for evaporative or cooling crystallization. Predictive solubility models also have the potential to be used as a solvent-antisolvent screening tool to pick optimal pairs. In addition, these have the
potential to be used to determine optimal operating conditions for many different crystallization processes. Also, if sufficiently accurate, these predictive thermodynamic solubility models can be used for dynamic optimization of cooling and antisolvent crystallization.

The second way to use first-principles thermodynamic modeling is for modeling the nucleation and growth kinetics. If these kinetic parameters for the desired crystallization systems are not available in the literature, they will need to be determined by performing numerous crystallization experiments. Instead of performing these experiments, the kinetic parameters can be approximated using thermodynamic models.

Finally, optimizing the formulation of antisolvent crystallization processes towards the manufacture of tailored materials is the final motivation of this project. Consequently, subsequent to the validation step, the model will be used within an optimization framework towards the development of a general method for reproducible production of crystals with prespecified size and distribution. Based on the previous modeling and optimization studies an advanced model-based strategy could be envisaged for implementation of optimal operational strategies. Within the dynamic optimization proposed here, the aims are to determine the time horizon, the values of the time-invariant parameters, and the time variation of the control variables over the entire period in such a way as to minimize (or maximize) the objective function (specific crystal size and distribution). This will be the first time that this approach will be used for the non-isothermal antisolvent crystallization of solutes with temperature insensitive solubility.

1.3 Aims and Contributions of This Dissertation

The research undertaken herein has the main objective of contributing towards model-based optimal strategies for crystallization operations specifically targeting crystal size and CSD
control. A secondary objective is to validate the theoretical propositions experimentally. The ultimate aim of this research is to take the knowledge gained and translate it into an economically and practically feasible implementation that is utilizable by the pharmaceutical industry. This means to develop skills and tools that allow the production of crystalline materials of desired crystal size. It is anticipated that eventually this will lead to consumer requests of an end product with a specific CSD (and morphology) being fulfilled by a highly automated optimal model-based crystallization framework.

Our investigations of the state-of-the-art in this field, together with our experimental/modeling/networking efforts, have addressed the following key problems:

1. A comprehensive and coherent framework for modeling crystallization systems was developed and implemented. In this regard, batch and semi-batch crystallization models for prediction of CSD taking into account effects of temperature, seeding variables, and feeding rates of antisolvents were developed. The availability of such models creates opportunities not only for finding optimal operating policies but also to investigate a number of issues related to the crystallization activities of this project. Specifically, in this research:

   - The modeling framework is used to determine optimal seed mass and cooling profiles. By comparing the results from the seed chart and model-based optimization, the advantages of model-based optimization were demonstrated. The proposed approach eliminates the need of using an arbitrary cooling curve or an arbitrary seed size as required when using seed charts. Model-based optimization has an unlimited range of cooling profiles and seed sizes to choose from compared to the fixed range of those in the seed chart.
   - The modeling framework is used to investigate the applicability of predictive thermodynamic solubility models in crystallization modeling. Specifically, we have
implemented and analyzed the feasibility of these thermodynamic models to determine optimal operating conditions for evaporative, cooling, isothermal antisolvent, and non-isothermal antisolvent crystallization. This contribution opens the door for these predictive solubility models to be used as an antisolvent screening mechanism to quickly determine the most appropriate solvent(s) for a given application. Furthermore, it will eventually eliminate the need for experimental solubility data as in the case of empirical approaches currently used in crystallization modeling, and will contribute towards generic models to be used over a range of conditions and systems.

- In another front, the modeling framework is used also to investigate and analyze the use of thermodynamic growth kinetic models as opposed to simplistic empirical approaches to model the crystal growth mechanisms. The availability of such kinetic growth models will reduce the need for crystallization models to be trained to experimental data for each specific system studied. Unfortunately, to create such generalized models, a multitude of experiments needs to be performed if the data (dielectric constants, activity coefficients, diffusivities, etc.) is not already listed in the literature. This experimental burden is still larger than the one needed to estimate the parameters of an empirical growth model for typical crystallization systems.

2. Optimizing crystallizer performance is the ultimate aim of this project. Specifically, in crystallization, the over-riding objectives of such an optimizing scheme are to obtain a product with desired crystal size characteristics. Our approach relies on the idea of relating the consumer requirements to the operational parameters. Various objective functions have been sought. A novel mathematical formulation of the CSD has been developed for the purpose of optimization and control set-pointing. A model-based dynamic optimization solution has been
developed for this problem that identifies optimal crystallization operational conditions including temperature, seeding variables, and antisolvent feed rate. Our research and experience suggests that the investigations of this project are well proposed to fill the gap in this area of research. Evidence of this is that there has, in general, been a lack of work carried out in the field of model-based crystallization optimization and specifically a lack in the optimization of the functional form of the CSD of the end-product.

3. Finally, experimental work is conducted to validate the simulated optimization results. Both parameter estimation and dynamic optimization studies will utilize crystallization facilities which were designed to have a wide-range of operational flexibility/controllability allowing a wide-range of parametric studies to be undertaken within tightly controlled regions. The facilities exceptionally undertake this model and optimization validation work, and with their unique design features will facilitate research towards novel optimal crystallization solutions.

1.4 Structure of the Dissertation

The following paragraphs detail how the dissertation is structured. Although each chapter is self-contained some details are not repeated in subsequent chapters. The first chapter highlights the motivation for the dissertation, generalizes the different thermodynamic frameworks utilized in the dissertation, and gives a brief literature background of crystallization modeling.

In the second chapter a full crystallization model is developed from equations and parameters found in the literature. In particular, full thermodynamic nucleation models for homogeneous, heterogeneous, and surface nucleation kinetics are used, as well as a thermodynamic mass-transfer-based growth kinetic formulation. This model is then used to
create an “experimental” seed chart. Optimization via heuristic methods such as the seed chart is then compared to model-based optimization. It is shown that model-based optimization is superior to heuristic methods, and the focus of experimental work should be for the development of crystallization models not to develop heuristics.

The third chapter shows the effect of using predictive thermodynamic solubility models in cooling crystallization modeling. Predictive thermodynamic models, MOSCED, NRTL-SAC, and UNIFAC; correlative thermodynamic models, van Laar, Wilson, and NRTL; and an empirical model are compared to each other with respect to predicted solubility accuracy of paracetamol in ethanol from 10-55 °C. The predictive models are then compared to each other to see how each model affects cooling crystallization for two different cooling profiles. Lastly, the use of predictive models to generate an optimal seed loading and cooling profile is investigated.

The fourth chapter continues the work started in chapter 3, but the focus has been shifted from cooling crystallization to isothermal antisolvent crystallization. In this chapter the Jouyban-Acree predictive solubility model, an empirical model, and the previously mentioned predictive thermodynamic solubility models are compared to each other with respect to the solubility accuracy of paracetamol in a water-acetone mixture at 16 °C. It is shown that only the empirical, Jouyban-Acree, and NRTL-SAC models give solubility results usable for crystallization modeling. These models are then compared to each other for antisolvent crystallization modeling using several fixed antisolvent flow rates. Akin to chapter 3, the use of these models to create optimal antisolvent profiles is examined.

The fifth chapter uses the same predictive solubility models used in chapters 2 and 3, but in a slightly different context. In this chapter, these models are used to determine the optimal operating conditions for the evaporative, cooling, isothermal antisolvent, and non-isothermal
antisolvent crystallization of paracetamol in an acetone-water mixture. Before this is investigated, the importance of the determination of these parameters is shown for three systems: potassium chloride-water-ethanol, paracetamol-water-acetone, and paracetamol-water-isopropanol. Then each solubility model is compared to each to evaluate how effectively they determine optimal operating conditions for each crystallization method.

The sixth chapter shows the development of a non-isothermal antisolvent crystallization model for sodium chloride. This chapter shows the benefit of manipulating temperature in systems where the solute has temperature insensitive solubility. Specifically, that it allows for the joint control of crystal mean size and coefficient of variation. In addition, this non-isothermal model is shown to be superior to pre-existing isothermal sodium chloride crystallization models when operated isothermally.

The seventh chapter concludes the dissertation, and lists possible future work. Information regarding the publication of each chapter is listed below:

A book chapter about the modeling of crystallization processes was coauthored with my advisor Jose Romagnoli and Ali Abbas from the University of Sydney for the Dynamic Process Modeling Volume of Process Systems Engineering. The detailed reference is listed below:


1.5 References


Crowley T.J., Meadows E.S., Kostoulas E., Doyle III J., Control of particle size distribution described by a population balance model of semibatch emulsion polymerization, Journal of Process Control, 2000, 10:5, 419-432


2. A MODEL-BASED NUCLEATION STUDY OF THE COMBINED EFFECT OF SEED PROPERTIES AND COOLING RATE IN COOLING CRYSTALLIZATION*

2.1 Introduction

Crystallization is a widely used chemical engineering unit operation for the production of high purity products for the pharmaceutical, fertilizer, and fine chemical industries. Crystallization can be operated under various modes including cooling, evaporation, or drowning out. One of the most commonly used techniques is cooling, the technique considered in this chapter. A predetermined temperature profile is invoked in cooling crystallization causing the generation of supersaturation, which in turn causes both the formation and growth of crystals. Historically, cooling crystallization was originally performed using a natural cooling profile. The crystallizer temperature follows Newton’s Law of Cooling where the temperature decreases quickly at first then slowly reaches the bath, jacket, or ambient temperature. The advantage of natural cooling is that no temperature control is needed and hence it alternatively has been dubbed as “uncontrolled cooling”. However, the disadvantage of natural cooling is that in the beginning of the batch the supersaturation increases sharply which may cause excessive primary nucleation to occur resulting in broad or even bimodal crystal size distributions (CSD).

In order to prevent excessive nucleation from occurring, it is important to maintain the solution’s supersaturation below the primary nucleation metastable limit. The metastable limit is the supersaturation value that if exceeded, causes spontaneous nucleation to occur in the solution. For this to occur, crystal growth must be able to keep up with the generation of supersaturation. If supersaturation increases too quickly and surpasses the metastable limit, uncontrollable primary nucleation will occur. An alternative temperature profile implemented to

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improve on natural cooling was linear cooling [Ayerst and Phillips, 1969]. In linear cooling the
temperature is decreased at a constant cooling rate from its initial supersaturation temperature to
a specified final temperature. This profile generally produces a lower supersaturation peak than
natural cooling, but like natural cooling, primary nucleation still occurs. In the early 1970s,
Mullin and Nyvlt [1971] proposed another profile they called “programmed cooling”. The
cooling rate in programmed cooling is calculated mathematically. It is slow at first but increases
towards the end of the batch. Unfortunately, the final CSD still observed bimodality. Mullin and
Jones [1974], later included nucleation kinetics to further improve the programmed cooling
profile. Since those early studies, numerous other authors used various optimization techniques
to find optimal cooling profiles for various crystallizing systems. The resultant profiles are
usually similar to the convex shape of the original programmed cooling profile by Mullin and
Nyvlt [1971].

Another way to minimize nucleation is to seed the crystallizer with preexisting crystals. Seed
crystals minimize nucleation by consuming any supersaturation generated during the
crystallization run, thus decreasing the probability of excessive supersaturation from occurring.
The addition of seed no longer requires the crystallizer to operate beyond the metastable limit in
order to form crystals. This prevents uncontrollable primary nucleation from occurring, however,
it is imperative to add the correct initial amount of seed to the crystallizer in order to get
sufficiently grown crystals. If the seed loading is too large, the seed will not grow sufficiently
and on the other hand if it is too low, there will not be enough seed to suppress primary
nucleation. Therefore there is an optimum amount of seed that should be added, and often this
optimal amount is found through trial and error [Bohlin and Rasmuson, 1992]. Jagadesh et al.
[1996] investigated the effect of seeding on the final CSD profile. They successfully showed that
a suboptimal cooling profile such as natural cooling can be utilized to produce unimodal CSD’s for the potash alum system. They introduced the seed chart for the determination of the seeding parameters, namely seed size and seed mass. Once either one of these seeding parameters is fixed, the seed chart can be used to read the other parameter that will maximize seed growth. Kubota et al. [2001] did further studies producing a seed chart for potassium sulphate. They showed that using an optimum amount of potassium sulphate seed, a unimodal CSD can be produced even using suboptimal natural cooling which was something previous investigators [Jones, 1974; Jones and Mullin, 1974] could not achieve with programmed cooling for the same system. Other authors [Chung et al., 1999; Choong and Smith, 2004; Sarker et al., 2006; Nowee et al., 2007], investigated how either the seed size, seed loading, seed surface area, and/or the cooling profile affected the resultant CSD. Since then other authors [Matthew and Rawlings, 1998; Xie et al., 2001; Lung-Somarriba et al., 2004; Hojjati and Rohani, 2005] have performed optimization studies to find joint optimal temperature and seed profiles for various systems while Worlitschek and Mazzotti [2004] only optimized the cooling profile.

In this chapter, a detailed model of the potassium chloride (KCl) crystallization process, founded on population balance theory, is first presented. This model is then used for simulation and analysis through which a theoretical seed chart for combined seeded-cooling crystallization is developed. The analysis here illustrates how model-based optimization of seed mass, seed size, and the temperature profile gives superior results over the current trends of experimentally optimizing the seed. This test system was chosen because for the detailed nucleation and growth models developed in this chapter, many chemical properties are required. This allowed for the development of a crystallization model from known parameters, which minimized the need to approximate parameter values.
2.2 Modeling of the Crystallization Process

2.2.1 Primary Nucleation

Primary nucleation occurs when nuclei form in the absence of already formed crystals. This can occur through two different mechanisms, homogenous and heterogeneous nucleation.

2.2.1.1 Homogeneous Nucleation

Homogeneous nucleation is the process where nuclei are formed spontaneously from a supersaturated solution that has crossed the metastable limit. An equation derived from classical nucleation theory for homogeneous nucleation [Mersmann, 2001] is used:

\[
B_{\text{hom}} = 1.5 \times D_{AB} (C N_A)^{7/3} \sqrt{\frac{\gamma_{CL}}{kT C_c N_A}} \exp \left(- \frac{16 \pi}{3} \frac{\gamma_{CL}}{kT} \left(\frac{1}{C_c N_A} \right)^2 \frac{1}{(v \ln S)^2}\right)
\]

(2.1)

where \(D_{AB}\) is the diffusion coefficient, \(C\) is the solute concentration, \(N_A\) is Avogadro’s number, \(\gamma_{CL}\) is the interfacial tension of the solution, \(k\) is Boltzmann’s constant, \(C_c\) is the molar density of the solute, \(v\) is the ion correction factor, and \(S\) is the relative supersaturation. The diffusion coefficient is calculated from the Einstein-Stokes equation (Equation 2.2), and the interfacial tension is calculated from a correlation (Equation 2.4) proposed by Mersmann [1990]. The values of these parameters and all future parameters are listed in Section 2.8.

\[
D_{AB} = \frac{kT}{2\pi\eta d_m}
\]

(2.2)

\[
d_m = \frac{3}{\sqrt{C_c N_A}}
\]

(2.3)

\[
\gamma_{CL} = kTK (C_c N_A)^{2/3} \ln \left(\frac{C_c}{C^*}\right)
\]

(2.4)
where $\eta$ is the dynamic viscosity of water, $K$ is a constant, and $C^*$ is the equilibrium concentration.

### 2.2.1.2 Heterogeneous Nucleation

The other type of primary nucleation considered is heterogeneous nucleation, a phenomenon that occurs when dissolved solute begins to adsorb on the surface of foreign substances in the solution or on crystallizer surfaces generating nuclei. Heterogeneous nucleation is dominant over homogeneous nucleation when the supersaturation is below the metastable limit. For heterogeneous nucleation, Equation 2.5 derived from classical nucleation theory by Mersmann [2001] is used:

$$
B_{het} = \left( \frac{1}{2\pi} a_{for} d_m HE_{ad} (CN_A)^{\frac{7}{3}} \sqrt{\frac{f Y_{CL}}{kT}} V_m \right) \times \\
\left( \frac{D_{surf} \sin \theta}{r_c} HE_{ad} d_m (CN_A)^{\frac{1}{3}} + 3\pi D_{AB} (1 - \cos \theta) \right) \exp \left( - \frac{4}{3} \pi f \frac{Y_{CL}}{kT} r_c^2 \right)
$$

(2.5)

where $a_{for}$ is the surface area of foreign particles in the solution, $HE_{AD}$ is an adsorption constant that correlates how strongly the solute is held to the surface of the foreign particles, $f$ is a geometric correction factor, $V_m$ is the molecular volume of the solute, $\theta$ is the contact angle of the solute adsorbing onto the foreign particles, $r_c$ is the critical nucleus radius, and $D_{surf}$ is the surface diffusion coefficient. $D_{surf}$, $r_c$, and $f$ are described by the following equations:

$$
r_c = \frac{2M_W Y_{CL}}{\rho_c R T v \ln S}
$$

(2.6)

$$
f = \frac{(2 + \cos \theta)(1 - \cos \theta)^2}{4}
$$

(2.7)
There are some simplifying assumptions that were used in these nucleation models. The models were derived from classical nucleation theory using isothermal conditions for non-ionic species. This is adequate for the purposes of this current study primarily aiming to analyze qualitative behavior.

2.2.2 Secondary Nucleation

Secondary nucleation refers to the formation of nuclei in the presence of already formed crystals. This can occur through several different mechanisms, namely surface, contact, fracture, shear, and attrition mechanisms.

2.2.2.1 Surface Nucleation

The first type of secondary nucleation considered is surface nucleation. Surface nucleation occurs when new nuclei are formed by growths detaching from the surface of already formed crystals. Equation 2.9 derived from classical nucleation theory by Mersmann [2001] for surface nucleation is used:

\[
B_{surf} = 9E \frac{D_{AB} d_m^4}{d_m^4 L_{32}} \varphi_T \exp \left( -\pi \frac{(y_{CL} d_m^2 / kT)^2}{v \ln S} \right) 
\]

where \(L_{32}\) is the Sauter mean diameter, and \(\varphi_T\) is the crystal holdup.

2.2.2.2 Attrition

The other type of secondary nucleation considered is nucleation caused by attrition. Attrition occurs when crystals collide with each other or with the impeller inside the crystallizer.
Mersmann [2001] also derived an equation to predict attrition-based secondary nucleation:

$$B_{\text{attrit}} = 7 \times 10^{-4} \varphi_T \frac{H_V^5}{\mu^3} \left( \frac{\Gamma}{K} \right)^{-3} \frac{\pi^2 \rho_c \bar{\varepsilon} N_v N_{a, eff}}{2k_v P_o} \frac{N_{a, tot}}{\tilde{N}^3 \eta_g}$$  \hspace{1cm} (2.10)

where $H_V$ is Vicker’s hardness, $\mu$ is the shear modulus, $\Gamma/K$ is the fracture resistance, $\bar{\varepsilon}$ is the mean specific power input, $N_v$ is the flow number, $P_o$ is the power number, $k_v$ is the volumetric shape factor, $\eta_g$ is the geometry target efficiency, $\eta_w$ is the velocity target efficiency, and $N_{a, eff}/N_{a, tot}$ is the fraction of crystal fragments that can grow. There are several assumptions that were used in the development and use of this nucleation model. The first assumption is that every particle that is lost to attrition is able to grow to larger sizes. The second is that the mass of the original particle does not change upon attrition. This is due to the assumption that nuclei have zero size, hence they also have zero mass. In practice, not every particle that breaks off will grow, and normally the attrition fragments will have a distribution of sizes and will not be monodisperse.

These four nucleation models are assumed to be the dominant nucleation types and thus are the only ones considered in this study. Other nucleation types such as contact, shear, and fracture secondary nucleation as well as agglomeration were not considered. The total nucleation is then taken to be the sum of the four types of nucleation considered:

$$B_{\text{tot}} = B_{\text{hom}} + B_{\text{het}} + B_{\text{surf}} + B_{\text{attrit}}$$  \hspace{1cm} (2.11)

### 2.2.3 Growth

Crystal growth can be limited by surface integration or by diffusion, phenomena analogous to those occurring in catalysis reactions. In the case of growth limited by surface integration, crystal growth can be described using an Arrhenius relationship analogous to an $n^{th}$ order reaction. However, if the limiting step is diffusion of the solute across the crystal’s
boundary layer to the crystal’s surface, then it is analogous to reactions that are diffusion limited. In this case, crystal growth is modeled as a mass transfer process. The growth of potassium chloride is reported to be diffusion limited, so crystal growth is modeled as a mass transfer process using a mass transfer coefficient [Lopes and Farelo, 2006]:

\[ G = \frac{k_d}{3\rho_c} \Delta C \]  \hspace{1cm} (2.12)

where \( \Delta C \) is absolute supersaturation and \( k_d \) is a mass transfer coefficient estimated using the following correlation [Perry, 1997]:

\[ k_d = \frac{D_{AB}}{L} \left( 2 + 0.8 \left( \frac{\bar{L}\rho_s^3}{\eta^3} \right)^{1/5} Sc^{1/3} \right) \]  \hspace{1cm} (2.13)

where \( Sc \) is the Schmidt number, \( \bar{L} \) is a median crystal size, and \( \rho_s \) is the density of the solution.

### 2.2.4 Temperature Dependent Solubility and Density

In order to accurately simulate the supersaturation profile, a temperature dependent relationship for the solubility of KCl in water is required. Tabulated experimental data for the solubility of KCl in water [Lide, 2006] was correlated using a quadratic equation (Equation 2.14) over a temperature range of 0-100 °C.

\[ C^* = \rho_s(27.76 + 0.3206T - 3.452 \times 10^{-4}T^2) \]  \hspace{1cm} (2.14)

where \( T \) is the temperature in Kelvin, and \( \rho_s \) is the density of the saturated solution. The empirical fit is plotted against the data points in the right subfigure of Figure 2.1. The density of the aqueous solution was assumed to be that of saturated KCl. Density data for KCl [Mullin, 2001] was correlated to a third order polynomial (Equation 2.15) over a temperature range of 0-90 °C. The empirical fit is plotted against the data points in the left subfigure of Figure 2.1. The solubility and density correlations had adjusted \( R^2 \) values of 1.0000 and 0.9995 respectively.
\[ \rho_s = 3.069 \times 10^{-8} T^3 - 9.522 \times 10^{-6} T^2 + 1.211 \times 10^{-3} T + 1.153 \]  \hspace{1cm} (2.15)

**Figure 2.1:** Temperature dependent KCl solubility (left) and saturated density (right) in water.

### 2.3 Population Balance

Since crystallization is a particulate process, a population balance is used to account for the number of crystals during the batch. The population balance for a constant volume batch crystallizer with negligible agglomeration and where crystal growth follows McCabe’s Law is:

\[
\frac{\partial n(L,t)}{\partial t} + G \frac{\partial n(L,t)}{\partial L} - B_{tot} = 0
\]  \hspace{1cm} (2.16)

where \( G \) is the growth rate, \( B_{tot} \) is the nucleation rate, \( L \) is the length, and \( n(L,t) \) is the crystal number distribution. The nucleation rate represents birth or generation of crystals in the first size range, from which it follows that:

\[ B = B_0 \delta(L) \]  \hspace{1cm} (2.17)

where \( B_0 \) is the nucleation rate and \( \delta(L) \) is the Dirac delta function. Two common methods for solving population balances are the method of moments and the method of discretization. The method of moments solves the population balance by calculating the individual moments of the
crystal distribution. The method of moments is a system of $\Phi+1$ ordinary differential equations where $\Phi$ is usually equal to 4. The method of moments is described by Equation Set 2.18:

$$\begin{align*}
\frac{d\mu_0}{dt} &= B \\
\frac{d\mu_i}{dt} &= i\mu_{i-1}G \quad i = 1 \ldots \Phi
\end{align*}$$

where $\mu_i$ is the $i$th moment of the distribution.

The method of moments requires less computational time than the discretization method, but the disadvantage of the method of moments is that a unique CSD cannot be recovered from the different moments. Since the modeling of the CSD is important, the discretization method is used. In order to make the simulation results independent of the grid size, 1000 discretization intervals was sufficient to minimize the discretization error to an acceptable level. A larger number of intervals showed minimal gains at the expense of much longer computational times. For 1000 discretization intervals, the computational time required to execute a crystallization simulation was less than 3 minutes using a 2.8 GHz Pentium 4 computer. The population balance is discretized in a backward finite difference manner because it has been shown to be more stable than a central finite difference [Abbas, 2003]. Since the population balance is a partial differential equation (PDE), discretization turns the PDE into a system of ordinary differential equations (ODE) with initial and boundary conditions listed in Equation Set 2.19:

$$\begin{align*}
\frac{dn_1}{dt} &= B - G \frac{n_1}{2\delta_1} \\
\frac{dn_i}{dt} &= G \left( \frac{n_{i-1}}{2\delta_{i-1}} - \frac{n_i}{2\delta_i} \right) \quad i = 2 \ldots \zeta \\
n_i(t = 0) &= n_{i,0} \quad i = 1 \ldots \zeta \\
L_0(t) &= 0.1 \mu m \quad L_\zeta(t) = 1000 \mu m
\end{align*}$$

(2.19)
where $\zeta$ is the number of discretization intervals, \( n_{i,0} \) is the seed distribution, and $\delta$ is the length of each discretization interval given by:

$$
\delta_i = L_i - L_{i-1} \quad i = 1 \ldots \zeta
$$

(2.20)

The individual discretization lengths are chosen using an equally distributed series, defined by:

$$
L_i = L_0 b^i \quad i = 0 \ldots \zeta
$$

(2.21)

$$
b = \left( \frac{L_{\text{max}}}{L_0} \right)^{\frac{1}{\zeta}}
$$

(2.22)

where $L_0$ is the nucleate size and $L_{\text{max}}$ is the maximum crystal size used in the discretization.

Even though the method of moments is not used to solve the population balance, it is important to calculate the individual moments because not only do they give important statistical information about the crystal batch properties, as seen in Table 2.1, but they also serve in determining the mass balance and the surface nucleation kinetic parameters. The integral and discretized moment definitions can, respectively, be written as:

$$
\mu_i = \int_0^\infty L^i n(L, t) \, dL
$$

(2.23)

$$
\mu_i = \sum_{j=0}^\zeta L_j^n_j(L, t)
$$

(2.24)

<table>
<thead>
<tr>
<th>Moment</th>
<th>Physical meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu_0$</td>
<td>Total number of crystals</td>
</tr>
<tr>
<td>$\mu_1$</td>
<td>Total length of crystals</td>
</tr>
<tr>
<td>$\mu_2$</td>
<td>Total area of crystals</td>
</tr>
<tr>
<td>$\mu_3$</td>
<td>Total volume of crystals</td>
</tr>
<tr>
<td>$\mu_1/\mu_0$</td>
<td>Number-weighted mean crystal size</td>
</tr>
<tr>
<td>$\mu_3/\mu_2$</td>
<td>Area-weighted (Sauter) mean crystal size</td>
</tr>
<tr>
<td>$\mu_4/\mu_3$</td>
<td>Volume-weighted mean crystal size</td>
</tr>
</tbody>
</table>

Table 2.1: Statistical meaning of moments.
2.3.1 Grid Dependency Analysis

This finite difference discretization technique is a simple straightforward technique compared to other discretization techniques in the literature. To test the grid dependency of the model, all the variables were fixed except for the grid interval lengths. The size axis was fixed from 0.05-1000 microns, and the interval lengths were varied by varying the number of intervals from 10-2000. In investigating the grid dependency, four crystallization variables were reported; absolute supersaturation, number-weighted mean size, volume-weighted mean size, and final number percent CSD.

Figure 2.2: Supersaturation dependency.

Supersaturation is the most important variable in crystallization processes, and dictates the growth and nucleation mechanisms. It is thus the first variable analyzed. It is imperative that
supersaturation not be a function of interval length. Otherwise the growth and nucleation results will be incorrect. Due to the fact that the supersaturation profile crosses several orders of magnitude, supersaturation is plotted on a semi-log plot so that the interval dependency can be more easily examined. Figure 2.2 illustrates the dependency of the supersaturation profile on the discretization intervals. At low discretization interval numbers such as 10 or 20, the supersaturation profile is slightly larger than the supersaturation profile for the higher interval number discretizations. However, increasing the number of discretization intervals past 110 does not significantly increase the accuracy of the results as can be seen in the inset of Figure 2.2.

Figure 2.3: Number mean size dependency.
The next important variable analyzed is the average size of the crystals. One way to represent the average size is through the number-weighted mean size. By looking at Figure 2.3, it can be seen again that the lower intervals of 10 and 20 slightly underestimate the number mean size. It appears that 110 discretization intervals would again be adequate, and by looking at the inset of Figure 2.3 there is slight improvement in the number mean size by increasing the number of intervals from 110 to 2000. The number mean size increases a micron from 111 to 112 microns. Using 110 discretization intervals introduces less than 1% error in the number mean size average than if 2000 discretization intervals were used.

Figure 2.4: Volume mean size dependency.
The third variable analyzed is the volume-weighted mean size. Figure 2.4 shows that there is a greater interval dependency of this variable than the previous two variables. Using intervals less than 400 results in overestimated volume mean sizes. The zoomed inset in Figure 2.4 shows that using 400 intervals is not sufficient. 800 intervals are required to reasonably approach the accuracy afforded by 2000 intervals.

![Figure 2.4: Effect of interval number on number percent CSD.](image)

**Figure 2.4:** Effect of interval number on number percent CSD.

The last variable analyzed is the number percent CSD. Since the magnitude of the number percent is a function of the number of intervals, each distribution was normalized for comparative purposes. Figure 2.5 shows why the low interval numbers were so bad at estimating the previous variables. The distributions representing 10 and 20 discretization intervals are
extremely poor estimations of the CSD. Once the number of discretization intervals approaches 110, the CSD starts resembling the higher interval number CSD’s. Figure 2.5 shows that further increasing the number of intervals from 110 to 800 results in the interval dependency becoming less sensitive. It can also be seen why the volume mean size is more sensitive to the number of discretization intervals than the number mean size. This is due to the width of the distribution. Even though there is the same amount of crystals both above and below the mean, the total volume of crystals is not the same. The higher volume of crystals larger than the number mean size results in a bias in the volume mean size to larger sizes because they have much larger volumes than the smaller sizes.

2.3.2 Interval Effect on Computational Time

To ensure the most accurate results, one would use the highest number of intervals possible. Why not then use more than 2000 intervals such as 5000 or 10000? This can be explained by looking at Figure 2.6. As the number of intervals increase the computational time penalty becomes more severe. To be able to estimate the computational time required for using more than 2000 intervals, the number of discretization intervals versus computational time was fit to a second order polynomial with a $R^2$ value of 0.999 shown in the equation below:

$$t = 4.98 \times 10^{-05}\zeta^2 + 8.48 \times 10^{-02}\zeta + 6.27$$

(2.25)

For example, the estimated computational time to use 5000 intervals would be almost 30 minutes, while 100 minutes would be needed for 10000 intervals. The time required to use more than 2000 intervals is not worth the computational time required for minimal improvements in the simulation results. In addition, simulation engines occasionally have stability problems with intervals more than 2000.
The number of intervals required to give accurate results depends on several factors. First, is the distance between the largest and smallest size. The potassium chloride discretization was done from 0.05 to 1000 microns which resulted in an interval length dependent only on the number of intervals. If the size limits are changed, then the grid will become coarser or finer than what it was previously. If the maximum size increased from 1000 to 2000 microns then the number of intervals would be doubled to ensure the same interval length. Likewise, if the maximum size became 500 microns then the number of intervals could be halved which would decrease the computational time required. This means that carefully chosen size limits can make the simulation more computationally efficient. Second, the number of intervals depends on what variables are of importance. If only the supersaturation and number mean size variables are important to report, then a coarser grid can be used than that would have been required if the volume mean size is the variable of interest. Since the volume mean size is often a reported
variable it would follow that at least 800 discretization intervals should be used for appropriate accuracy.

2.4 Results and Analysis

2.4.1 Temperature Profiles and Seed Initial Conditions

Three different temperature profiles shown in Figure 2.7 are considered in this work to investigate their effects on the crystallization process. These three profiles represent three popular cooling regimes; linear, quench, and programmed cooling. For each temperature profile the temperature was decreased from 55 °C to 10 °C over 30 minutes. The 50 L crystallizer at the University of Sydney has a maximum cooling rate of 3 K/min which was used as the maximum cooling rate allowable for the three cooling profiles.

Figure 2.7: Temperature profiles used in the simulation analysis. Linear cooling (Profile A), Quench cooling (Profile B) and Programmed cooling (Profile C).

To investigate the effect of the size of the seed, three different seed sizes 75, 250, and 500 microns were evaluated with various seed mass loadings. The seed loadings were carefully chosen to be where the critical seed loading would be for each different seed size. Since it has
been proven by Kubota et al. [2001] that the critical seed loading is dependent on the seed size, the seed loadings were specified differently for each seed size. The 75, 250, and 500 micron seed loadings ranged from 0.1-1, 1-40, and 10-100 g of KCl per kg of H₂O respectively. The simulation was setup such that it represented the addition of seed before cooling was initiated, thus acting as an initial condition. Stochastic experimental simulations comprised of 25 seed loadings were subsequently carried out in gPROMS (Process Systems Enterprise, UK) for each unique size and temperature profile combination.

2.4.2 Seed Chart Results

By organizing the data into a seed chart, as shown in Figure 2.8, it can be seen that the simulations produced results very similar to the experimental seed charts published in the literature [Jagadesh et al., 1999; Kubota et al., 2001]. This seed chart shows that the smaller seed sizes grow more compared to their initial size and require less loading than the larger seeds. It also shows that the temperature profile does not have an effect on the final crystal size until the seed loading approaches the critical seed amount for that profile. Crystal growth follows the ideal growth line until the seed loading becomes insufficient and nucleation occurs. This causes the deviation of the curves away from the ideal growth line. Since this deviation is dependent on the temperature profile, it follows that the critical seed amount is a function of the temperature profile. This is because some cooling profiles are superior than others at maximizing the final crystal mean size. Thus, if the operator’s goal is to maximize the growth of the crystals, then both the temperature profile and the seed loading are important. In addition, the operator can sacrifice some final crystal size by seeding an amount that is higher than the critical seed amount.
which will decouple the system from the temperature profile. For this case, minimal or no temperature control will be required.

Figure 2.8: Seed Chart of KCl. (Red lines represent quench cooling, blue lines represent programmed cooling, and black lines represent linear cooling. The left cluster represents the 75 micron seed, the middle cluster represents the 250 micron seed, and the right cluster represents the 500 micron seed).

While inspecting the seed chart, it may seem that it is always better to seed small sizes. This is not always true. It is true that small seed sizes will grow more than the larger seed sizes due to the limited amount of solute mass available in the solution. However, if the objective is to make large crystals, it may be necessary to seed moderate to high seed sizes at the expense of higher seed loading. For example, the 75 micron seed was only able to grow to 330 microns before the temperature profile affected the size. However, the 250 and 500 microns seed sizes were able to grow to 425 and 630 microns respectively regardless of the temperature profile. The
following subfigures in Figure 2.9 depict how the volume mean size is dependent on the seed loading for each temperature profile.

For the 75 micron seed, the linear cooling profile is able to grow the largest crystals, followed by the programmed and quench cooling profile. At seed loadings greater than $4 \times 10^{-4}$ kg, the crystal size is independent of the temperature profile. This shows that there is a substantial benefit to optimizing the temperature profile to maximize the crystal size. The right subfigure of Figure 2.9 displays the volume percent CSD of the seed loading that generates the largest size for each individual temperature profile. Volume percent CSD rather than number percent CSD was examined because most laboratory instruments that measure size distributions measure volume percent, not number percent.

It can be noticed that the distributions are not unimodal. All three distributions show slight bimodality with the linear and programmed cooling profiles showing a second peak at 350 and 50 microns respectively. The quench cooling curve shows an almost imperceptible peak around 225 microns. The 250 micron seed shows similar behavior. The linear cooling profile grows the largest crystals followed by the quench and programmed cooling profiles. At seed loadings greater than 0.01 kg, crystal size is independent of the temperature profile. Again, there is an advantage to optimizing the temperature profile to maximize the crystal size. By inspecting their corresponding CSD’s, it can be seen that two of the profiles produce bimodal distributions. The linear profile has a second peak around 150 microns, and the programmed profile has a peak around 50 microns. The quench cooling profile does not have a perceptible second peak.

The 500 micron seed shows the exact same behavior as the 250 micron seed. Again the linear cooling profile grows the largest crystals followed by the quench and programmed cooling profiles. At seed loadings greater than 0.04 kg the crystal size is independent of the temperature
As for the other two seed sizes, there is an advantage to optimizing the temperature profile. By inspecting their corresponding CSD’s there are almost imperceptible peaks under 100 microns. For all practical purposes, they can be considered unimodal distributions.

<table>
<thead>
<tr>
<th>Seed Size (µm)</th>
<th>L_{43}</th>
<th>Volume Percent CSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td><img src="image1" alt="Volume Mean Size" /></td>
<td><img src="image2" alt="Volume Percent CSD" /></td>
</tr>
<tr>
<td>250</td>
<td><img src="image3" alt="Volume Mean Size" /></td>
<td><img src="image4" alt="Volume Percent CSD" /></td>
</tr>
<tr>
<td>500</td>
<td><img src="image5" alt="Volume Mean Size" /></td>
<td><img src="image6" alt="Volume Percent CSD" /></td>
</tr>
</tbody>
</table>

**Figure 2.9:** Volume mean size and CSD plots.
Table 2.2 displays the actual values for the maximum volume-weighted mean crystal size for each seed size and temperature profile. For the 75 micron seed, the linear cooling profile produces crystals that are 41% larger than the ones produced from the quench cooling profile and 36% larger than those produced under the programmed cooling profile. For the 250 micron seed, the linear cooling profile creates crystals that are 35% larger than the ones produced by the programmed profile and 15% larger than the quench cooling profile. For the 500 micron seed, the linear profile creates crystals that are 20% larger than the crystals produced from the programmed cooling profile and 4% larger than the quench cooling profile. The greatest benefit to maximizing the crystal size by optimizing the temperature profile is with the smaller seed sizes. The larger seed sizes do not get as much of a benefit.

<table>
<thead>
<tr>
<th>Seed size (microns)</th>
<th>Linear profile</th>
<th>Quench profile</th>
<th>Programmed profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>474</td>
<td>336</td>
<td>349</td>
</tr>
<tr>
<td>250</td>
<td>572</td>
<td>489</td>
<td>425</td>
</tr>
<tr>
<td>500</td>
<td>761</td>
<td>734</td>
<td>631</td>
</tr>
</tbody>
</table>

### 2.4.2.1 Supersaturation Profiles

Inspection of the supersaturation subfigures in Figure 2.10 shows that the supersaturation profile is a function of the seed loading and of the temperature profile. For a given seed size, as the seed loading is decreased, the maximum of the supersaturation curve will increase, which is expected. When an insufficient seed loading is used, the supersaturation curve will spike and cause nucleation to occur causing the crystal’s mean size to decrease. This represents the solution concentration surpassing the metastable boundary for surface nucleation. Due to the nucleation kinetics used in the model, surface nucleation is the primary cause for excessive
nucleation when seed is present. Primary homogeneous or heterogeneous nucleation never has the chance to occur. In systems where surface nucleation is not as strong, homogenous or heterogeneous nucleation may be the dominant nucleation mechanism. By inspecting these supersaturation profiles, the level of supersaturation required for excessive nucleation to occur can be determined. Consequently, this supersaturation level can then be programmed as a
control system set-point. When supersaturation begins to approach this peak, the control system can either adjust the temperature or indicate what amount of seed crystals should be added to the system to lower the supersaturation level. From careful examination of the supersaturation profiles, it can be seen whether a profile is growth or nucleation dominant. If the profile reaches a maximum and quickly decreases, then the profile is nucleation dominant. On the other hand, if the supersaturation reaches a maximum but does not quickly return to zero, then the profile is primarily growth dominant. A comparison of the supersaturation plots for each cooling profile for the 75 micron seed explains why the linear cooling profile generates the largest crystals. It is the only profile where the supersaturation is able to remain constant for the longest period of time. This allows for more consistent crystal growth than the other temperature profiles thus producing the largest crystals.

2.4.2.2 Seed Efficiency

Crystal yield is constant for each cooling profile because the initial and final temperatures are the same. Even though the yield does not vary with seed size or temperature profile, the seed efficiency does. The seed efficiency, $Y_E$, is defined as the total mass of KCl that is crystallized per batch divided by the initial seed mass. A seed efficiency value of 1 indicates that the seed did not grow. Likewise, a seed efficiency value of five means that the produced crystal mass is five times the initial seed mass. The seed efficiency increases when either the seed size or loading is decreased. This is because the larger seed sizes require a higher seed loading to prevent nucleation from occurring, and there is a limited amount of solute that can be crystallized from solution. The seed efficiency is also dependent on the temperature profile because the optimum temperature profile will require less seed loading which will maximize seed efficiency. Table 2.3
shows the dependence of the seed efficiency on the cooling profile. For the 75 micron seed, the linear cooling profile has a seed efficiency that is 3.5 times greater than that for the quench cooling profile and 2.35 times greater than the programmed cooling case. For the 250 micron seed, the linear cooling profile has a seed efficiency that is 2.00 times greater than the programmed cooling profile and 2.07 times greater than the quench cooling profile. For the 500 micron seed, the linear cooling profile has a seed efficiency that is 1.84 times greater than the programmed cooling profile, and 1.18 times greater than the quench cooling profile.

<table>
<thead>
<tr>
<th>Seed size (microns)</th>
<th>Seed efficiency at maximum crystal sizes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Linear cooling</td>
</tr>
<tr>
<td>75</td>
<td>$Y_E=280$</td>
</tr>
<tr>
<td>250</td>
<td>$Y_E=15.6$</td>
</tr>
<tr>
<td>500</td>
<td>$Y_E=3.78$</td>
</tr>
</tbody>
</table>

This shows that there is a substantial benefit in optimizing the temperature profile for seed efficiency. Analogous to the discussion of the crystal mean size, if the operator’s primary goal is to maximize the seed efficiency then the temperature profile and seed size are important. However, if the operator is willing to settle for less than optimal seed efficiency then it will be independent of the temperature profile.

2.5 Joint Seeding and Cooling Optimization

As discussed earlier there are benefits to optimizing the temperature profile, namely larger crystal size and less seed loading. In this section, we utilize the model developed in Sections 2.2-2.3 in a dynamic optimization exercise solved in gPROMS gOPT facility. The selected objective function is the minimization of the zeroth moment (Equation 2.26). This is the
same as minimizing the total amount of particles at the end of the experiment. This both minimizes the initial seed loading to maximize seed efficiency, and minimizes nucleation to maximize growth. Assuming a unimodal seed distribution, successful optimization of this objective function should ensure a unimodal distribution. Three constraints are used: the desired final crystal size (end point constraint), the initial ($T_0$) and final ($T_f$) temperatures (initial and end point constraints), and the maximum cooling rate (path constraint). An explicit metastable limit constraint is not required, because it is an implicit part of the nucleation model.

$$\text{min } \mu_0 \quad \text{subject to}$$

$$a \leq \frac{L_{43}}{L_{43,\text{seed}}} \leq b$$

$$T_0 = 55 ^\circ C$$

$$T_f = 10 ^\circ C$$

$$-0.05 \leq \frac{dT}{dt} \leq 0 ^\circ C/s$$

(2.26)

The optimization determines two control variables, the initial seed loading and the temperature profile. The temperature profile was discretized with 30 one-minute control intervals. The three optimized temperature profiles for the 75, 250, and 500 micron seeds are displayed in the left subfigure of Figure 2.11. All three profiles are very similar in shape. They all have a quench cooling section initially followed by linear cooling. The initial quench cooling has the effect of quickly raising the supersaturation to the metastable limit of approximately 0.22 kg/m$^3$, whereas the subsequent linear cooling keeps it at that limit until the end of the batch. This ensures maximum growth over the batch.

The optimal cooling profiles are concave instead of the convex profiles typically reported [Jones, 1974; Jones and Mullin, 1974; Chung et al., 1999; Xie et al., 2001; Choong and Smith, 2004; Worlitschek and Mazzotti, 2004; Hojjati and Rohani, 2005; Sarker et al., 2006; Nowee et al., 2007], because the Surface Nucleation Efficiency Factor ($E$) used had a value of 0.001. Since this parameter is not known, only knowing it ranges between 0 and 1, it had to be estimated. A
much smaller $E$ value of $1 \times 10^{-20}$ was tested and it produces a convex temperature profile. Worlitschek and Mazzotti [2004] used a similar secondary nucleation model with a value of $E$ equal to $2.4 \times 10^{-20}$ that also resulted in a convex cooling profile. The important result of this optimization is that the temperature profile succeeds in maximizing the supersaturation available for growth, yet avoids nucleation.

**Figure 2.11:** Optimized temperature (CP) and supersaturation (SS) profiles (left), and optimized volume percent CSD (right).

All three seed sizes were able to grow to larger sizes with the optimized temperature profiles than with the previous profiles used in generating the seed chart. In addition, all three final volume percent CSD’s shown in the right subfigure of Figure 2.11 have unimodal distributions which show that nucleation was successfully suppressed. Due to the optimized temperature profiles, less seed loading was required which also increased the efficiency of the process. These optimization studies show the benefit of optimizing the temperature profile and the seed conditions, and that joint optimization of the seed loading and temperature profile is superior to the seed chart in creating unimodal distributions of large mean size.
Table 2.4: Optimization results.

<table>
<thead>
<tr>
<th>Seed size (microns)</th>
<th>Seed loading (kg)</th>
<th>( L_{43} ) (microns)</th>
<th>( a \leq \frac{L_{43}}{L_{43,Seed}} \leq b )</th>
<th>( \frac{L_{43}}{L_{43,Seed}} )</th>
<th>( Y_E )</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>1.26 x 10^{-4}</td>
<td>505</td>
<td>6.60-7.00</td>
<td>6.73</td>
<td>306</td>
</tr>
<tr>
<td>250</td>
<td>2.71 x 10^{-3}</td>
<td>617</td>
<td>2.40-2.50</td>
<td>2.47</td>
<td>15.1</td>
</tr>
<tr>
<td>500</td>
<td>1.11 x 10^{-2}</td>
<td>822</td>
<td>1.60-1.65</td>
<td>1.64</td>
<td>4.45</td>
</tr>
</tbody>
</table>

When the seed chart was introduced in the late 1990’s it was a very useful tool. However, recent advances in modeling tools, crystallization modeling, and computational horsepower are overshadowing the usefulness of the seed chart. The disadvantage of the seed chart is that it does not optimize the temperature profile, and it requires many experiments to generate the required data. If another temperature profile is desired, then more experiments would be needed to add that temperature profile data to the seed chart. This is clearly laborious and resource consuming. However, an accurate crystallization model developed from carefully planned experiments alleviates these limitations. Such experiments derived from model-based experimental design are optimally designed for operating conditions that can be used to calculate the crystallization model parameters with as few experiments as possible. These experiments may differ greatly than the ones used to create a seed chart. In addition, the crystallization model will work for any temperature profile or seed size. The advantage of the crystallization model is that it can be used to optimize both the seed loading and the temperature profile for any objective function. Experimental time spent creating a seed chart is better spent toward the development of a crystallization model via model-based experimental design.

2.6 Generalization to Other Chemical Systems and Implementation

This model-based approach can be generalized for other systems. The approach would depend on several factors. First, is the data available in the literature for the needed parameters?
If the value is not known, does one have the necessary resources to calculate these parameter values? If not, or if performing the necessary experiments would be time inefficient then a lumped parameter approach modeling the dominant nucleation mechanism should be used. Third, in order to validate either the detailed or lumped parameter model, crystallization experimental data will be needed. This data should consist of the seed loading, the temperature profile; and concentration, crystal size and size distribution measurements at different times during the experiment.

All models will have some uncertainty in the values of their parameters. Before implementing a crystallization model into a production environment it is essential to do several tests of the model. First, sensitivity testing of the model must be done to slight changes in initial and operating conditions for the calculated optimal conditions. If these changes do not affect the results significantly, then the model is robust enough to be implemented. However, if the results do change significantly then the model will have to be reevaluated. Also, to help protect against model uncertainty, the optimum seed loading can be increased which will combine the seed chart’s robustness with the model’s ability to create superior optimum cooling curves.

2.7 Conclusions

The simulations based only on theoretical crystallization kinetics, confirm the initial results of Jagadesh et al. [1999] and Kubota et al. [2001] that seeding is the dominant parameter for cooling crystallization. The amount of seed dictates how much the seed can grow. The temperature profile determines if the seed will be able to achieve that size. The simulations showed that if a sufficient amount of seed is used then the final crystal properties are the same regardless of the temperature profile implemented. However, once the critical seed loading is
reached the temperature profile becomes the dominant parameter, and crystallization begins to operate more as an unseeded crystallization process. The temperature profile in seeded crystallization is important for maximization of the final crystal size or total crystal yield. Maximizing the amount of seed growth is desired for maximum end-product crystal sizes and is achieved more reliably through the joint optimization of cooling profile and seeding characteristics. The model-based optimization is crucial for identifying the limits for operating the crystallization process. The model-based optimization was shown in this work to produce superior results than a seed chart. The seed chart has been a very useful tool for crystallization processes, but the advantages in crystallization modeling and optimization make it the preferred method for future work in this field.

2.8 Nomenclature

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
<th>Value</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$a_{for}$</td>
<td>Area of Foreign Substance</td>
<td>$2.5 \times 10^5$</td>
<td>$m^2/m^3$</td>
</tr>
<tr>
<td>$B_{attrit}$</td>
<td>Attrition Secondary Nucleation</td>
<td></td>
<td>Crystals/ $m^3$ s</td>
</tr>
<tr>
<td>$B_{hom}$</td>
<td>Homogeneous Nucleation</td>
<td></td>
<td>Crystals/ $m^3$ s</td>
</tr>
<tr>
<td>$B_{het}$</td>
<td>Heterogeneous Nucleation</td>
<td></td>
<td>Crystals/ $m^3$ s</td>
</tr>
<tr>
<td>$B_{surf}$</td>
<td>Surface Nucleation</td>
<td></td>
<td>Crystals/ $m^3$ s</td>
</tr>
<tr>
<td>$B_{tot}$</td>
<td>Total Nucleation</td>
<td></td>
<td>Crystals/ $m^3$ s</td>
</tr>
<tr>
<td>$C$</td>
<td>Solution Concentration</td>
<td></td>
<td>kg/ $m^3$</td>
</tr>
<tr>
<td>$C_c$</td>
<td>Molar Density of KCl</td>
<td></td>
<td>kmol/ $m^3$</td>
</tr>
<tr>
<td>$C^*$</td>
<td>Equilibrium Concentration</td>
<td></td>
<td>kg/ $m^3$</td>
</tr>
<tr>
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<td>$3.966 \times 10^{-10}$</td>
<td>m</td>
</tr>
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<td>Diffusion Coefficient</td>
<td></td>
<td>m$^2$/s</td>
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<tr>
<td>$D_{surf}$</td>
<td>Surface Diffusion</td>
<td></td>
<td>m/s</td>
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<tr>
<td>$E$</td>
<td>Surface Nucleation Efficiency</td>
<td>0.001</td>
<td>Dimensionless</td>
</tr>
<tr>
<td>$f$</td>
<td>Geometric Correction Factor</td>
<td>0.0580583</td>
<td>Dimensionless</td>
</tr>
<tr>
<td>$G$</td>
<td>Growth</td>
<td></td>
<td>m/s</td>
</tr>
<tr>
<td>$HE_{AD}$</td>
<td>Adsorption Constant</td>
<td>$9.0 \times 10^{-9}$</td>
<td>Dimensionless</td>
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<tr>
<td>$H_Y$</td>
<td>Vicker’s Hardness</td>
<td>$9.1 \times 10^7$</td>
<td>N/ $m^2$</td>
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<tr>
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<td>Boltzmann Constant</td>
<td>$1.38048 \times 10^{-23}$</td>
<td>J/K</td>
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<tr>
<td>$k_d$</td>
<td>Mass Transfer Coefficient</td>
<td></td>
<td>m/s</td>
</tr>
<tr>
<td>$k_v$</td>
<td>Volumetric Shape Factor of KCl</td>
<td>1</td>
<td>Dimensionless</td>
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<td>Symbol</td>
<td>Definition</td>
<td>Value</td>
<td>Units</td>
</tr>
<tr>
<td>--------</td>
<td>------------</td>
<td>---------------</td>
<td>------------------</td>
</tr>
<tr>
<td>$K$</td>
<td>Interfacial Tension Correlation Constant</td>
<td>0.085</td>
<td>Dimensionless</td>
</tr>
<tr>
<td>$L$</td>
<td>Characteristic Crystal Size</td>
<td></td>
<td>m</td>
</tr>
<tr>
<td>$L_{32}$</td>
<td>Sauter Mean Size</td>
<td></td>
<td>m</td>
</tr>
<tr>
<td>$L_{43}$</td>
<td>Volume Mean Size</td>
<td></td>
<td>m</td>
</tr>
<tr>
<td>$L_i$</td>
<td>Discretized Crystal Length</td>
<td></td>
<td>m</td>
</tr>
<tr>
<td>$L_0$</td>
<td>Smallest Discretized Crystal Size</td>
<td>$5 \times 10^{-8}$</td>
<td>m</td>
</tr>
<tr>
<td>$L_{max}$</td>
<td>Largest Discretized Crystal Size</td>
<td>0.001</td>
<td>m</td>
</tr>
<tr>
<td>$M_w$</td>
<td>Molecular Weight of KCl</td>
<td>74.551</td>
<td>kg/kmol</td>
</tr>
<tr>
<td>$n$</td>
<td>Number Density</td>
<td></td>
<td>Crystals</td>
</tr>
<tr>
<td>$n_j$</td>
<td>Discretized Number Density</td>
<td></td>
<td>Crystals</td>
</tr>
<tr>
<td>$N_a$</td>
<td>Avogadro’s Number</td>
<td>$6.0223 \times 10^{26}$</td>
<td>Particles/kmol</td>
</tr>
<tr>
<td>$N_{a,eff}$</td>
<td>Effective Attrition Fragments</td>
<td></td>
<td>Crystals</td>
</tr>
<tr>
<td>$N_{a,tot}$</td>
<td>Total Attrition Fragments</td>
<td></td>
<td>Crystals</td>
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<td>Optimization Objective Function</td>
<td>Varies</td>
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<td>Power Number</td>
<td>0.36</td>
<td>Dimensionless</td>
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<tr>
<td>$r_c$</td>
<td>Nuclei Critical Radius</td>
<td></td>
<td>m</td>
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<tr>
<td>$R$</td>
<td>Gas Constant</td>
<td>8314.39</td>
<td>J/kmol K</td>
</tr>
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<td>$S$</td>
<td>Relative Supersaturation</td>
<td></td>
<td>Dimensionless</td>
</tr>
<tr>
<td>$Sc$</td>
<td>Schmidt Number</td>
<td></td>
<td>Dimensionless</td>
</tr>
<tr>
<td>$t$</td>
<td>Time</td>
<td></td>
<td>s</td>
</tr>
<tr>
<td>$T$</td>
<td>Temperature</td>
<td></td>
<td>K</td>
</tr>
<tr>
<td>$V_m$</td>
<td>Molecular Volume of KCl</td>
<td>$6.239 \times 10^{-29}$</td>
<td>m$^3$/Particle</td>
</tr>
<tr>
<td>$\delta_i$</td>
<td>Discretization Interval Length</td>
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<td>m</td>
</tr>
<tr>
<td>$\Delta C$</td>
<td>Absolute Supersaturation</td>
<td></td>
<td>kg/ m$^3$</td>
</tr>
<tr>
<td>$\bar{\varepsilon}$</td>
<td>Mean Specific Power Input</td>
<td>0.27</td>
<td>W/m$^3$</td>
</tr>
<tr>
<td>$\eta$</td>
<td>Dynamic Viscosity of Water</td>
<td></td>
<td>Pa s</td>
</tr>
<tr>
<td>$\eta_g$</td>
<td>Geometric Target Efficiency</td>
<td>0.03</td>
<td>Dimensionless</td>
</tr>
<tr>
<td>$\eta_w$</td>
<td>Velocity Target Efficiency</td>
<td>0.8</td>
<td>Dimensionless</td>
</tr>
<tr>
<td>$\gamma_{CL}$</td>
<td>Surface Tension</td>
<td></td>
<td>J/ m$^2$</td>
</tr>
<tr>
<td>$\Gamma/K$</td>
<td>Fracture Resistance</td>
<td>12.9</td>
<td>J/ m$^2$</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Shear Modulus</td>
<td>$9.44 \times 10^9$</td>
<td>N/m$^2$</td>
</tr>
<tr>
<td>$\mu_i$</td>
<td>$i^{th}$ Moment</td>
<td></td>
<td>m$^i$</td>
</tr>
<tr>
<td>$\nu$</td>
<td>Ion Correction factor</td>
<td>2</td>
<td>Dimensionless</td>
</tr>
<tr>
<td>$\varphi_T$</td>
<td>Crystal Holdup</td>
<td></td>
<td>Solution</td>
</tr>
<tr>
<td>$P_c$</td>
<td>Density of KCl Crystal</td>
<td>1984</td>
<td>kg/ m$^3$</td>
</tr>
<tr>
<td>$P_s$</td>
<td>Solution Density</td>
<td></td>
<td>kg/ m$^3$</td>
</tr>
<tr>
<td>$\theta$</td>
<td>Contact Angle</td>
<td>45</td>
<td>Degrees</td>
</tr>
<tr>
<td>$\zeta$</td>
<td>Number of Intervals</td>
<td>1000</td>
<td>Dimensionless</td>
</tr>
</tbody>
</table>
2.9 References


3. USE OF PREDICTIVE SOLUBILITY MODELS FOR COOLING CRYSTALLIZATION MODELING AND OPTIMIZATION*

3.1 Introduction

Crystallization is a traditional and widely used industrial process for the production of particulates. These particulates may include agrochemicals, biological proteins, fine chemicals, and pharmaceuticals. A key advantage of utilizing crystallization as a separation process is its role in the production of high purity products, important for specialized industries. Making the crystallization process more relevant is the United States Federal Drug Administration’s strict regulations on the required purity for biological proteins and pharmaceuticals.

The thermodynamic driving force for crystallization is the difference in the chemical potential between the solute and the solution. Since chemical potential is difficult to quantify, solution supersaturation, a more readily measurable quantity, is used conveniently as an approximation. The trajectory the supersaturation follows affects the final crystal’s size, crystal size distribution (CSD), habit (shape), and purity. Not only can the crystal’s size and habit affect the particle product’s performance, as in the case of the biological availability/activity of pharmaceuticals, but the production of inadequately sized particles can block filters downstream causing operational problems.

Traditionally, industrial crystallizers were run either on a trial and error basis, or by utilizing ‘rules of thumb’. These methods commonly produced suboptimal recipes which resulted in failed batches and economic losses. In addition, these methods often proved to be less reliable when used during scale-up. There has recently been increased interest in the development of crystallization models to predict operating conditions that produce crystals with desirable

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characteristics. [Nagy et al., 2007; Nowee et al., 2007ab] The use of crystallization models allows the development of optimal recipes without the use of excessive laboratory time or resources. In addition, the crystallizer model in combination with the recent availability of robust in situ crystallization instrumentation can be implemented into a model-based control scheme to keep the crystallizer operating on the correct trajectory [Fujiwara et al., 2005].

In this work, the cooling crystallization of acetaminophen in ethanol is investigated. Acetaminophen, also known as paracetamol, is the active ingredient in a commonly used painkiller, Tylenol®. Acetaminophen has chemical formula, C₈H₉NO₂, with the chemical structure shown in Figure 3.1. Acetaminophen is advantageous to use because not only is it inexpensive, it also has been studied heavily in the literature. The temperature dependent solubility of acetaminophen in ethanol was investigated by Romero et al. [1996], Fernandez [1999], Granberg and Rasmuson [1999], and Worlitschek and Mazzotti [2004]. Its thermodynamic properties were studied by Hojjati and Rohani [2006]. Although the cooling crystallization of acetaminophen was previously studied by several groups including Hendrickson and Grant [1998] and Fujiwara et al. [2002], very few works such as that by Worlitschek and Mazzotti [2004] looked into simulating the crystal size distribution (CSD), or used a thermodynamically-based solubility model. However, the latter workers did not evaluate the effect of different solubility models on the CSD prediction, leaving an open question as to which of the available solubility models is most appropriate. This chapter compares the use of empirical, thermodynamic, and generalized predictive thermodynamic solubility models to evaluate how these affect the resultant supersaturation profile and consequently the CSD, and then details how to make the crystallization model more robust against solubility model error. In
addition, the effect of these solubility models on the predicted optimal profile and the sensitivity of a validated crystallization model to these solubility models’ optimal profiles will be evaluated.

Figure 3.1: Molecular structure of acetaminophen.

3.2 Solubility Models

3.2.1 Supersaturation

The driving force for crystallization is the difference in chemical potential between the solid and liquid phases, expressed as:

$$\exp\left(\frac{\Delta\mu_{cp}}{RT}\right) = \frac{f_l}{f_s} = \frac{\gamma_l c}{\gamma_{l,eq} c_{eq}} = S$$

(3.1)

where $S$ is the relative supersaturation, $\Delta\mu_{cp}$ is the difference in chemical potential, $f_l$ is the fugacity of the liquid phase, $f_s$ is the fugacity of the solid phase, $c_{eq}$ and $\gamma_{eq}$ respectively are the concentration and activity coefficient of the liquid phase at equilibrium, and $\gamma$ and $c$ are the actual concentration and activity coefficient of the solution, respectively. As an approximation, the ratio of activity coefficients is brought to unity, leading to the practical description of the relative supersaturation defined as the ratio of the solution concentration to the equilibrium concentration:

$$S = \frac{C}{C_{eq}}$$

(3.2)
The absolute supersaturation is also commonly used and is defined as the difference between the solution concentration and the equilibrium concentration (Equation 3.3), and is typically defined in units of g solute/kg solvent.

\[ \Delta c = c - c_{eq} \]  

(3.3)

Supersaturation can be generated by one of three primary methods, namely evaporation, cooling, and antisolvent addition. In evaporative crystallization, the solution is heated which causes the solvent to evaporate. This loss of solvent from the solution makes the solution more concentrated which simultaneously causes the generation of supersaturation. Cooling crystallization is reliant on the fact that most solutes experience a decrease in solubility as temperature decreases. Finally, in antisolvent crystallization, supersaturation is generated by the addition of a carefully chosen antisolvent that reduces the solubility of the solute in the solvent mixture. This antisolvent may either be a liquid, gas, or a supercritical fluid. Two or more of these mentioned techniques can be combined in the same operation enabling enhanced results. For instance, adding antisolvent to a cooling crystallization operation provides that operation with an extra degree of freedom, where a calculated antisolvent addition can work as a seeding mechanism.

A good solubility model accurately predicts how the equilibrium concentration of the solute changes over the course of the crystallization batch. This accurate solubility prediction is required for a crystallization model to in turn become accurate in predicting crystal product properties such as size. Solubility models can be based on either empirical or thermodynamic foundations. An empirical solubility model is an equation fitted to experimental solubility data, and typically has no underlying physical meaning, while on the other hand, a thermodynamic solubility model both fits the data and has physical meaning. Common types of thermodynamic
models include those based on excess Gibbs energy such as Wilson, NRTL, or UNIQUAC. In addition, predictive thermodynamic models can also be used such as MOSCED, NRTL-SAC, or UNIFAC. The advantage of these predictive models is that no new experimental data is needed to calculate activity coefficients.

3.2.2 Empirical and Correlative Models

The simplest of solubility models are empirical models. These are simply mathematical equations fitted to experimental data. Empirical models relate solubility to a measured experimental variable. These experimental variables can be temperature, solvent composition, density, conductivity, absorbance, etc.

The next class of solubility models is correlative models. Correlative thermodynamic solubility models are models that have thermodynamic meaning and are fit to experimental data. The most common of these models, are excess Gibbs energy models, which are further simplified to activity coefficient models. All of these models have binary interaction parameters that are fit to experimental data.

Several different solubility models were used for the purpose of evaluating the effect of these models on the predicted final crystal properties. The first on the list is an empirical correlation solubility model developed by Fernandez [1999] for acetaminophen in ethanol:

$$c_{eq} = C_1 \exp(C_2 T)$$  \hspace{1cm} (3.4)

where $c_{eq}$ is in kg acetaminophen/kg solvent, $C_1 = 2.955 \times 10^{-4}$ kg/kg, and $C_2 = 2.179 \times 10^{-2}$ K$^{-1}$.

We next evaluate excess Gibbs energy models, in activity coefficient form. These activity coefficient models considered are van Laar, Wilson, and NRTL. In these correlative models the
solvent and solute are components 1 and 2 respectively. The simplest of the three is the van Laar model [Prausnitz et al., 1999] depicted in Equation 3.5:

\[
\ln \gamma_2 = \frac{B_{VL}}{1 + \frac{B_{VL}}{A_{VL}x_j}} 1 = x_1 + x_2
\]  

(3.5)

where \(A_{VL}\) and \(B_{VL}\) are the binary interaction parameters, \(x_2\) is the mole fraction of solute, and \(x_1\) is the mole fraction of solvent. The disadvantage of the van Laar model is that there is no explicit temperature dependence of the activity coefficient. Unlike the van Laar model, the Wilson and NRTL activity coefficient models [Prausnitz et al., 1999] both carry temperature dependencies and are given by Equation Sets 3.6 and 3.7 respectively.

\[
\ln \gamma_2 = -\ln(x_2 + \Lambda_{21}x_1) - x_1\left(\frac{\Lambda_{12}}{x_1 + \Lambda_{12}x_2} - \frac{\Lambda_{21}}{\Lambda_{21}x_1 + x_2}\right)
\]

\[
\Lambda_{12} = \frac{v_2}{v_1} \exp\left(-\frac{\Delta \lambda_{12}}{RT}\right) \quad \Lambda_{21} = \frac{v_1}{v_2} \exp\left(-\frac{\Delta \lambda_{21}}{RT}\right) \quad 1 = x_1 + x_2
\]  

(3.6)

\[
\ln \gamma_2 = x_1 \left[\tau_{12} \left(\frac{G_{12}}{x_2 + x_1 G_{12}}\right)^2 + \left(\frac{\tau_{21} G_{21}}{(x_1 + x_2 G_{21})^2}\right)\right]
\]

\[
G_{12} = \exp(-\alpha \tau_{12}) \quad G_{21} = \exp(-\alpha \tau_{21}) \quad \tau_{12} = \frac{\Delta g_{12}}{RT} \quad \tau_{21} = \frac{\Delta g_{21}}{RT} \quad 1 = x_1 + x_2
\]  

(3.7)

where in the Wilson model, \(v_1\) and \(v_2\) are the molar volume of components 1 and 2, and \(\Delta \lambda_{12}\) and \(\Delta \lambda_{21}\) are the binary interaction parameters. In the NRTL model, \(\Delta g_{12}\) and \(\Delta g_{21}\) are the binary interaction parameters, and \(\alpha\) is the nonrandomness parameter.

### 3.2.3 Predictive Models

Predictive thermodynamic models are generalized models used to predict solubility behavior of different compounds. These models are developed from extensive experimental data for many different chemical systems. The parameters for these models are correlated depending
on the chemical structure or properties of the compounds. With the database of parameters, solubility data can be predicted for systems not used to create the model.

The first predictive thermodynamic model considered is the MOSCED (Modified Separation of Cohesive Energy Density) model. The MOSCED model is a thermodynamic model used to calculate infinite-dilution activity coefficients. The advantage of the MOSCED model is that no experimental data is needed to calculate the infinite-dilution activity coefficients. The MOSCED model further calculates temperature dependent infinite-dilution activity coefficients, such that a temperature-dependent activity coefficient model is not required. The MOSCED model was originally developed for binary liquid solutions, but was later extended to liquid-solid systems by Drauker et al. [2007]. The MOSCED model is shown in Equation Set 3.8 as modified by Lazzaroni et al. [2005].

\[
\ln \gamma_{i,j}^\infty = \frac{v_i^0}{RT} \left[ (\lambda_j - \lambda_i)^2 + \frac{q_j^2 q_i^2 (\tau_j - \tau_i)^2}{\psi_j} + \frac{(\alpha_j - \alpha_i)(\beta_j - \beta_i)}{\xi_j} \right] + d_{ji}
\]

\[
d_{ji} = \ln \left( \frac{v_i^0}{v_j^0} \right)^{aa} + 1 - \left( \frac{v_i^0}{v_j^0} \right)^{aa}
\]

\[
\alpha_j = \alpha_j^0 \left( \frac{293}{T(K)} \right)^{0.8}, \quad \beta_j = \beta_j^0 \left( \frac{293}{T(K)} \right)^{0.8}, \quad \tau_j = \tau_j^0 \left( \frac{293}{T(K)} \right)^{0.4}
\]

this representation of the MOSCED model is used to find the \( j \)-th substance infinite-dilution activity coefficient in substance \( i \). Similarly, the model can be used to find the infinite-dilution
activity coefficient for substance \( i \) in \( j \) by switching the subscripts \( i \) and \( j \) around. The MOSCED model contains five adjustable parameters: \( \lambda, \alpha, \beta, q, \tau \) corresponding to dispersion, hydrogen bond acidity, hydrogen bond basicity, induction, and polarity. Molar volume, \( v \), is not an adjustable parameter except for the special case of water. Details on these parameters and their correlated values for acetaminophen (Table 3.1) are given in Lazzaroni et al. [2005].

<table>
<thead>
<tr>
<th>MOSCED Parameter</th>
<th>( v^0 )</th>
<th>( \lambda )</th>
<th>( \tau^0 )</th>
<th>( q )</th>
<th>( \alpha^0 )</th>
<th>( \beta^0 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>58.6</td>
<td>14.37</td>
<td>2.53</td>
<td>1.0</td>
<td>12.58</td>
<td>13.29</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>105.4</td>
<td>18.45</td>
<td>2.67</td>
<td>0.9</td>
<td>16.19</td>
<td>13.18</td>
</tr>
</tbody>
</table>

Once the two infinite-dilution activity coefficients are calculated from the MOSCED model, they can be substituted into an excess Gibbs energy model to find the binary interaction parameters for that system. With the MOSCED model no experimental data is needed to calculate these binary interaction parameters.

<table>
<thead>
<tr>
<th>NRTL-SAC Parameters</th>
<th>Ethanol</th>
<th>Acetaminophen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrophobicity (X)</td>
<td>0.256</td>
<td>0.498</td>
</tr>
<tr>
<td>Polarity (Y-)</td>
<td>0.081</td>
<td>0.487</td>
</tr>
<tr>
<td>Polarity (Y+)</td>
<td>0</td>
<td>0.162</td>
</tr>
<tr>
<td>Hydrophilicity (Z)</td>
<td>0.507</td>
<td>1.270</td>
</tr>
</tbody>
</table>

The next predictive thermodynamic model considered is the NRTL Segment Activity Coefficient model (NRTL-SAC) developed by Chen and Song [2004]. The NRTL-SAC model is derived from the polymer NRTL model with similar segment theory. The NRTL-SAC model breaks down each molecule into three different segments: hydrophobicity (X), polarity (\( Y_-, Y_+ \)),
and hydrophilicity (Z). The NRTL-SAC model as developed by Chen and Song [2004] is described by Equation Set 3.9:

\[
\ln \gamma_i = \ln \gamma_i^C + \ln \gamma_i^R
\]

\[
\ln \gamma_i^C = \ln \frac{\phi_i}{x_i} + 1 - r_i \sum_j \frac{\phi_j}{r_j}
\]

\[
\ln \gamma_i^R = \sum_m r_{m,i} (\ln \Gamma_m^{lc} - \ln \Gamma_m^{lc,i})
\]

\[
\ln \Gamma_m^{lc} = \frac{\sum_j x_j G_{jm} \tau_{jm}}{\sum_k x_k G_{km}} + \sum_m \frac{x_m G_{m,m'}}{\sum_k x_k G_{km}} \left( \tau_{mm'} - \frac{\sum_n x_n G_{nm} \tau_{nm}}{\sum_k x_k G_{km}} \right)
\]

\[
\ln \Gamma_m^{lc,i} = \frac{\sum_n x_n G_{nm} \tau_{nm}}{\sum_k x_k G_{km}} + \sum_m \frac{x_m G_{m,m'}}{\sum_k x_k G_{km}} \left( \tau_{mm'} - \frac{\sum_n x_n G_{nm} \tau_{nm}}{\sum_k x_k G_{km}} \right)
\]

\[
x_n = \frac{\sum_j x_j r_{n,j}}{\sum_i \sum_m x_i r_{m,i}} \quad x_{n,i} = \frac{r_{n,i}}{\sum_m r_{m,i}} \quad r_i = \sum_m r_{m,i} \quad \phi_i = \frac{r_i x_i}{\sum_j r_j x_j} \quad G_{km} = e^{-\kappa_{km} \tau_{km}}
\]

where \(\gamma_i^C\) and \(\gamma_i^R\) are the combinatorial and residual contributions to the activity coefficient of component \(i\). \(k, l, m, m',\) and \(n\) are the segment indices, \(i\) and \(j\) are the component indices, \(x_n\) is the segment-based mole fraction of segment species \(n\), \(x_i\) is the mole fraction of component \(i\), \(x_{n,i}\) is the segment fraction of segment species \(n\) in component \(i\), \(\Gamma_m^{lc}\) is the activity coefficient of segment species \(m\), \(\Gamma_m^{lc,i}\) is the activity coefficient of segment species \(m\) in component \(i\), \(r_{m,i}\) is the number of segment species \(m\) in component \(i\), \(r_i\) is the total segment number of component \(i\), and \(\phi_i\) is the segment mole fraction of component \(i\). \(\tau_{km}\) and \(\alpha_{km}\) are the NRTL-SAC binary interaction parameter and nonrandomness parameter between segments \(n\) and \(m\) respectively. These parameters are tabulated in Chen and Crafts [2006] for each segment pair. Further details about the development of the NRTL-SAC model can be found in Chen and Song [2004] and
Chen and Crafts [2006]. The NRTL-SAC model parameters for ethanol and acetaminophen as correlated by Chen and Crafts [2006] are in Table 3.2.

The last predictive thermodynamic model considered is the UNIFAC model developed by Fredenslund, Jones, and Prausnitz [1975]. The UNIFAC model, though similar to the UNIQUAC model has one important difference. The UNIQUAC model is a correlative model that has adjustable parameters that are unique for each binary system, and the UNIFAC model is a predictive model that has two different parameters for each functional group. Some examples of functional groups are CH$_3$, OH, and CHO. Each functional group has an area and volume structural parameter. Also, each functional group pair has two unique binary interaction parameters associated to that pair. Predicting activity coefficients with the UNIFAC model is easy. All that is needed is to decompose the chemicals into their substituent groups, and look up the group parameters in the literature. The UNIFAC model is described by Equation Set 3.10:

$$
\ln \gamma_i = \ln \gamma_i^C + \ln \gamma_i^R \\
\ln \gamma_i^C = \ln \frac{\Phi_{i,U}}{x_i} + \frac{z}{2} q_i \ln \frac{\theta_i}{\Phi_{i,U}} + l_i - \frac{\Phi_{i,U}}{x_i} \sum_j x_j l_j \\
\ln \gamma_i^R = \sum_k u_k^{(i)} (\ln \Gamma_k - \ln \Gamma_k^{(i)})$$

$$
\ln \Gamma_k = \ln \Gamma_k^{(i)} = Q_k \left[ 1 - \ln \left( \sum_m \Theta_m \psi_{km} \right) - \sum_m \Theta_m \psi_{nm} \right] \\
l_i = \frac{z}{2} (r_{i,U} - q_{i,U}) - (r_{i,U} - 1) \\
\theta_i = \frac{q_{i,U} x_i}{\sum_j q_{j,U} x_j} \quad \Phi_{i,U} = \frac{r_{i,U} x_i}{\sum_j r_{j,U} x_j} \quad \Theta_m = \frac{Q_m X_m}{\sum_n Q_n X_n} \quad \psi_{mn} = e^{(-\frac{a_{mn}}{T})} \\
r_{i,U} = \sum_k u_k^{(i)} R_k \quad q_{i,U} = \sum_k u_k^{(i)} Q_k$$
where $\gamma_i$ is the activity coefficient of component $i$, $\gamma_i^C$ and $\gamma_i^R$ are the combinatorial and residual parts of the activity coefficient of component $i$, $\Gamma_k$ is the residual activity coefficient of group $k$, $\Gamma_k^{(i)}$ is the residual activity coefficient of group $k$ in a reference solution containing only groups of type $i$, $z$ is the coordination number, $r_{i,U}$ is the volume structural parameter of component $i$, $r_{i,U}$ is the area structural parameter of component $i$, $\theta_i$ is the area fraction of component $i$, $\Phi_i$ is the volume fraction of component $i$, $\Theta_m$ is the area fraction of group $m$, $Q_k$ is the volume structural parameter of group $k$, $R_k$ is the area structural parameter of group $k$, $v_k^{(i)}$ is the number of $k$ groups in component $i$, $x_i$ is the mole fraction of component $i$, $X_m$ is the mole fraction of group $m$ in the mixture, $\Psi_{mn}$ is the group interaction parameter between $m$ and $n$, and $a_{mn}$ is the measure of interaction between groups $m$ and $n$. The UNIFAC parameters for ethanol and acetaminophen the molecules were calculated from the individual functional group parameters found in Poling, Prausnitz, and O’Conell [2000] and are displayed in Table 3.3. Since the acetaminophen aromatic NH functional group was not listed it was approximated as an aromatic NH$_2$ functional group in the same manner of Hojjati and Rohani [2006].

<table>
<thead>
<tr>
<th>UNIFAC Parameters</th>
<th>Ethanol</th>
<th>Acetaminophen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area Structural Parameter ($r_{i,U}$)</td>
<td>2.5755</td>
<td>5.7528</td>
</tr>
<tr>
<td>Volume Structural Parameter ($q_{i,U}$)</td>
<td>2.5880</td>
<td>4.5840</td>
</tr>
</tbody>
</table>

In order to calculate an equilibrium solute concentration, an activity coefficient model is solved simultaneously with the solid solubility model (Equation 3.11) to calculate both the mole fraction and the activity coefficient of the solute.

$$\ln \left( x_2 y_2 \right) = \frac{\Delta H_{\text{fusion}}}{R} \left( \frac{1}{T_{\text{melt}}} - \frac{1}{T} \right) \frac{\Delta C_p}{R} \left( \ln \left( \frac{T_{\text{melt}}}{T} \right) - \frac{T_{\text{melt}}}{T} + 1 \right)$$  \hspace{1cm} (3.11)
where \( x_2 \) is the mole fraction of the solute, \( \gamma_2 \) is the activity coefficient of the solute, \( T_{\text{melt}} \) is the solute’s melting temperature, \( \Delta H_{\text{fusion}} \) is the solute’s enthalpy of fusion, and \( \Delta C_p \) is the solute’s change in heat capacity from the solid to liquid phase. Utilizing differential scanning calorimetry, Hojjati and Rohani [2006] measured the thermal properties of acetaminophen to be \( T_{\text{melt}} = 442.2 \text{ K} \), \( \Delta H_{\text{fusion}} = 28.1 \text{ kJ/mol} \), and \( \Delta C_p = 99.6 \text{ J/mol K} \).

### 3.2.4 Estimation of Interaction Parameters

The computer package gPROMS (Process Systems Enterprise Ltd, London) with its parameter estimation facility gEST was used to estimate the optimal values of the binary interaction parameters for each activity coefficient model. The maximum likelihood function (Equation 3.12) used in the gEST facility, describes the highest probability of the model predicting the real data.

\[
\Phi(k, \theta) = \frac{M}{2} \ln(2\pi) + \frac{1}{2} \min_{k,\theta} \left\{ \sum_{i=1}^{\alpha} \sum_{j=1}^{\beta_i} \sum_{k=1}^{\gamma_{ij}} \left[ \ln(\sigma_{ijk}^2) + \frac{(\hat{Y}_{ijk} - Y_{ijk})^2}{\sigma_{ijk}^2} \right] \right\} 
\]  

(3.12)

where \( M \) is the total number of measurements taken, \( \alpha \) is the number of experiments, \( \beta_i \) is the number of variables measured in the \( i \)th experiment, and \( \gamma_{ij} \) is the number of measurements of the \( j \)th variable in the \( i \)th experiment. \( \sigma_{ijk}^2 \) is the variance of the \( k \)th measurement of variable \( j \) in experiment \( i \). A constant variance error model (homoscedastic) was assumed. These measurement errors are assumed to be independent and normally distributed with zero mean. This transforms the error from \( \sigma_{ijk}^2 \) to \( \omega_{ijk}^2 \) where \( \omega \) is the constant standard deviation of the measurement error. This assumption as well as assuming independent measurements transforms the problem from a maximum likelihood objective function to the least squares objective function (Equation 3.13):
\[
\Phi(k, \theta) = \min_{k, \theta} \left\{ \sum_{i=1}^{N} \sum_{j=1}^{M} \left[ \ln\left( \sigma_{ik}^2 \right) + \left( \frac{Y_{jk} - Y_{jk}}{\sigma_{jk}} \right)^2 \right] \right\}
\]

(3.13)

Experimental data from Worlitschek and Mazzotti [2004] for the solubility of acetaminophen in ethanol from 10-55 °C were used to carry out the parameter estimation. This data combined with the appropriate activity coefficient model and the solid solubility equation was used in gEST to calculate the binary interaction parameters. The parameter estimation resulted in the binary interaction parameters displayed in Table 3.4.

<table>
<thead>
<tr>
<th>Solubility Model</th>
<th>Binary Interaction Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Laar</td>
<td>(\alpha) 184.2, 0.2128</td>
</tr>
<tr>
<td>Wilson</td>
<td>1858 J/mol K, -1181 J/mol K</td>
</tr>
<tr>
<td>NRTL</td>
<td>0.3777, 2403 J/mol K, -1351 J/mol K</td>
</tr>
</tbody>
</table>

With the newly calculated binary interaction parameters, the prediction of the different models can now be compared. This is done graphically in Figure 3.2 against literature experimental data. The empirical model and each of the activity coefficient models all appear to provide good fits to the experimental data while the MOSCED model systematically underestimates the solubility over the entire temperature range of interest.

An analysis of variance test (ANOVA) was then carried out for each model’s prediction compared to the experimental data and is shown in Table 3.5. The NRTL and the Wilson activity coefficient models provide the best fit for the data with corresponding p-values of 1.00. The fit of the NRTL model is not significantly better than the Wilson model, even though the NRTL model has one more adjustable parameter. The simpler van Laar activity coefficient model is the worst activity coefficient model, but it is still better than the empirical model having a slightly higher
p-value of 0.967 to 0.939. The MOSCED models provide a very poor fit to the solubility data with p-values much smaller than the others, between 0.0669-0.0785. This means that there is a large statistical difference between the correlative thermodynamic models and the MOSCED models. The MOSCED model combined with the Wilson model produces results that are slightly better than using the MOSCED model with either the NRTL or van Laar model. In between are the UNIFAC and NRTL-SAC models which have p-values of 0.654 and 0.467 respectively. This statistically shows that the fit for these two models is better than the MOSCED model, but not as good as the empirical and correlative models.

![Equilibrium solubility curves](image)

**Figure 3.2:** Equilibrium solubility curves for the different solubility models compared to experimental data from Worlitschek and Mazzotti [2004].

The F-statistics for each model follow the same pattern as the p-values did. This is expected because the p-values are calculated from the F-statistics. The empirical and correlative
models have F-statistics much lower than the critical F-statistic of 4.49 (using \( \alpha=0.05 \)). These models have solubility predictions that are not significantly different from the experimental data. The MOSCED models have F-statistics (3.53-3.87) that are close to the critical value which shows that the MOSCED models’ predictions have the most significant deviation from the data followed by the NRTL-SAC model’s F-statistic of 0.555 and UNIFAC model’s F-statistic of 0.209. The UNIFAC model was the best predictive model but its F-statistic is more than the empirical or correlative models.

\[
\begin{array}{ccc}
\text{Solubility Models} & \text{p-value} & \text{F-statistic} \\
\text{Empirical Model} & 0.939 & 6.03 \times 10^{-03} \\
\text{NRTL} & 1.00 & 3.54 \times 10^{-07} \\
\text{Van Laar} & 0.967 & 1.77 \times 10^{-03} \\
\text{Wilson} & 1.00 & 1.74 \times 10^{-08} \\
\text{MOSCED and NRTL} & 0.0669 & 3.87 \\
\text{MOSCED and van Laar} & 0.0765 & 3.58 \\
\text{MOSCED and Wilson} & 0.0785 & 3.53 \\
\text{NRTL-SAC} & 0.467 & 0.555 \\
\text{UNIFAC} & 0.654 & 0.209 \\
\end{array}
\]

The parity plot in Figure 3.3 supports this conclusion. All three of the correlative thermodynamic models as well as the empirical model data points are scattered across the diagonal. This means that the predicted solubility closely matches the experimental solubility. However, the three MOSCED models’ data points are scattered below the diagonal and show the same under-prediction systematic bias seen in Figure 3.2. The NRTL-SAC and UNIFAC models have similar errors compared to the experimental data. Above 20 °C both models over predict the solubility and below 20 °C both models under-predict the solubility, but the UNIFAC model predicts values that are slightly better than the NRTL-SAC model predictions.
The reason for the poor fit of the MOSCED model is because it is a generalized model. The tabulated MOSCED parameters are averaged over a wide variety of solvents in order to make the model as applicable to as many systems as possible. In the case where experimental solubility data is not available, the MOSCED model gives a first estimate to the solubility. However, if experimental data is available, it is preferable to fit binary interaction parameters of an activity coefficient model to get a more accurate solubility prediction.

3.3 Crystallization Model

Since crystallization is a particulate process, a population balance is used to account for the number and size of crystals during the batch. The population balance for a constant volume
batch crystallizer with negligible agglomeration and attrition, and where crystal growth follows McCabe’s Law is written as [Randolph and Larson, 1988]:

\[
\frac{\partial n(L,t)}{\partial t} + G \frac{\partial n(L,t)}{\partial L} - B = 0
\]  

(3.14)

where \( n(L,t) \) is the crystal distribution, \( G \) is the growth rate, \( B \) is the nucleation rate and \( L \) is the crystal length. The population balance is typically solved through the method of moments or via discretization. The method of moments requires less computational time than the discretization method, but the disadvantage of the method of moments is that a unique CSD cannot be recovered. If the number of size intervals is chosen properly, the computational penalty in using the method of moments is reduced. In this work we use the discretization method with 250 size intervals. This lead to a solution computational time of less than 30 seconds using a 3.4 Ghz Pentium D computer. A backward finite difference discretization is used as this was previously shown to be more stable than a central finite difference [Abbas and Romagnoli, 2007]. The discretization converts the partial differential equation (PDE) population balance into a system of ordinary differential equations (ODE) with initial and boundary conditions shown in Equation Set 3.15:

\[
\frac{d n_i}{d t} = B - G \frac{n_i}{2\delta_i}
\]

\[
\frac{d n_i}{d t} = G \left( \frac{n_{i-1}}{2\delta_{i-1}} - \frac{n_i}{2\delta_i} \right) \quad i = 2..\zeta
\]

\[n_i(t = 0) = n_{i,0} \quad i = 1..\zeta \]

\[L_0(t) = 0.1 \, \mu m \]

\[L_\zeta(t) = 1000 \, \mu m \]

where \( \zeta \) is the number of discretization intervals, and \( \delta \) is the length of each discretization interval given by:
\[ \delta_i = L_i - L_{i-1} \quad i = 1 \ldots \zeta \]  

The individual discretization lengths are chosen using a geometric series:

\[ L_i = L_0 b^i \quad i = 0 \ldots \zeta \]  

\[ b = \left( \frac{L_{\text{max}}}{L_0} \right)^{\frac{1}{\zeta}} \]  

\( L_0 \) is the nucleate size and \( L_{\text{max}} \) is the maximum crystal size used in the discretization. As seen in the population balance, crystallization is dictated by growth and nucleation mechanisms. However, there are additional mechanisms that can occur in crystallization such as attrition and agglomeration. Attrition refers to the collision of crystals with other crystals or with the crystallizer components to form smaller crystals, while agglomeration is when crystals collide to form larger crystals. As stated before, these two mechanisms are assumed to be negligible and are not considered in the model.

Crystal growth will occur when the solution’s relative supersaturation is greater than one. In order for crystal growth to occur, the dissolved solute molecules must dissolve through the crystal’s boundary layer where they will attach to the crystal’s surface. The opposite of growth, dissolution, is when the crystal begins to dissolve in the solution, and occurs when the solution’s relative supersaturation is less than one. Depending on the nature of the system, growth can either be diffusion or surface reaction controlled, while dissolution is normally diffusion controlled. Worlitschek and Mazzotti [2004] modeled acetaminophen crystal growth as being surface reaction limited with an Arrhenius function, while dissolution was modeled as a diffusion limited process. Equation 3.21 represents these two mass transfer phenomena conditional to supersaturation:
where \( c_c \) is the molar density of acetaminophen, \( k_d \) is a mass transfer coefficient, and \( E_a, k_g, \) and \( g \) are adjustable parameters. \( E_a \) is the activation energy necessary for growth, \( k_g \) is the Arrhenius pre-exponential factor, and \( g \) is the crystal growth exponent.

When operated at supersaturations smaller than the metastable limit, secondary nucleation is the dominant nucleation mechanism. Secondary nucleation is caused by the presence of suspended particles in solution through several different mechanisms. It can occur due to the solvent washing away weakly held surface crystals (fluid shear), due to severe crystal collisions (attrition), or due to weak collisions with crystallizer equipment or other crystals (contact nucleation). The secondary nucleation kinetic is adopted after Worlitschek and Mazzotti [2004]:

\[
B = \begin{cases}
\frac{k_a \mu_2 D}{d_m^2} \exp \left[ -\pi \left( \frac{\gamma_{sl} d_m^2}{kT} \right)^2 \frac{1}{\ln S} \right] & S > 1 \\
0 & S \leq 1
\end{cases}
\]  

(3.22)

where \( k_a \) is the crystal shape factor, \( D \) is the diffusion coefficient, \( d_m \) is the molecular diameter of acetaminophen, \( k \) is the Boltzmann constant, \( \mu_2 \) is the second moment, and \( E \) and \( \gamma_{sl} \) are adjustable parameters. \( E \) represents the fraction of nuclei that are detached from the surface of the crystals which has a value between 0 and 1. \( \gamma_{sl} \) represents the solutions interfacial tension. Even though there are interfacial tension correlations available, Worlitschek and Mazzotti [2004] suggest using an adjustable parameter for interfacial tension due to the limited accuracy of those correlations. Another method for modeling secondary nucleation is to model it with the breakage kernel of the population balance instead of using a separate nucleation model [Ulbert and
Lakatos, 2007]. The molecular diameter, diffusion coefficient, and mass transfer coefficient are calculated using the following equations:

\[
d_m = \sqrt[3]{\frac{1}{c_c N_a}} \tag{3.23}
\]

\[
D = \frac{kT}{2\pi \eta_1 d_m} \tag{3.24}
\]

\[
k_d = \frac{D}{L} \left(2 + 0.8 \left(\frac{\epsilon \bar{L}^4 \rho_1^3}{\eta_1^3}\right)^{1/5} \text{Sc}^{1/3}\right) \tag{3.25}
\]

where \(N_a\) is Avogadro’s number, \(\eta_1\) in the Stokes-Einstein equation is the dynamic viscosity of the solvent, \(\bar{L}\) is a characteristic crystal size, \(\rho_1\) is the density of the solvent, \(\text{Sc}\) is the Schmitt number, and \(\epsilon\) is the mean specific power input.

Worlitschek and Mazzotti [2004] subsequently conducted parameter estimation with experimental data to estimate values of the adjustable parameters for the above kinetic equations. That exercise led to the following values: \(E = 7.0 \times 10^{20}\), \(\gamma_{sl} = 2.5 \times 10^{-3}\) J/m\(^2\), \(k_g = 21\) m/s (m\(^3\)/kmol)\(^{1.9}\), \(g = 1.9\), and \(E_a = 4.16 \times 10^4\) kJ/kmol. However they used an incorrect value for \(d_m\) in their nucleation equation. They used \(7.18 \times 10^{-10}\) m instead of the correct value of \(5.79 \times 10^{-10}\) m which is calculated from Equation 3.23. Using the correct value for \(d_m\) changes the values of \(E\) and \(\gamma_{sl}\) to \(E = 2.4 \times 10^{-20}\) and \(\gamma_{sl} = 3.8 \times 10^{-3}\) J/m\(^2\).

The mass balance of the solute in solution for constant volume batch cooling crystallization is:

\[
\frac{dc}{dt} = -\frac{3\rho_c k_v}{m_s} \int_0^\infty G L^2 n(L, t) dL \tag{3.26}
\]

where \(c\) is the solute concentration (kg solute/kg solvent), \(k_v\) is the volumetric shape factor of the crystal, \(\rho_c\) is the solid density of the crystal, and \(m_s\) is the mass of the solvent. For
acetaminophen: $k_v$, $k_a$, and $\rho_c$ are 0.866, 5.196, and 1296 kg/m$^3$ respectively. No energy balance was explicitly specified in the crystallization model. It is assumed that the control system maintains the reactor temperature at the set-point specified.

3.4 Results and Discussion

3.4.1 Seeding

The crystallization kinetics presented above only considers secondary nucleation, while primary nucleation is neglected. This implies that each crystallization batch must be seeded with crystals for either crystal growth or nucleation to occur. From CSD data in Worlitschek and Mazzotti [2004], the seed was approximated to be log-normally distributed with a mean size of 190 microns and standard deviation of 30 microns. However, they did not specify the amount of seed used for their experiments. An optimum seed amount found through stochastic simulations is $1.15 \times 10^{11} \mu m^2$, corresponding to a seed mass of 0.224 kg, which provides the supersaturation data fit of Figure 3.4 for the linear cooling (left) and step cooling (right).

Using the same seed amount for the other temperature profiles resulted in a good fit to the supersaturation data, as illustrated in the case under step cooling shown in Figure 3.4. It was thus assumed that the seed loading was constant for the crystallization runs performed in Worlitschek and Mazzotti [2004].

In order to evaluate the effect of the different solubility models on the final crystallization results, six of the nine previously evaluated equations were selected; (a) NRTL, (b) van Laar, (c) Empirical, (d) UNIFAC, (e) NRTL-SAC, and (f) MOSCED model combined with the Wilson model. The NRTL model was chosen because it was the most accurate activity coefficient model, and should give the best representation to actual experimental data. The other models
were chosen to depict how the magnitude of error in the solubility model affects the final CSD. These six models were compared under two different cooling regimes, namely linear cooling and step cooling, used in Worlitschek and Mazzotti [2004]. Figure 3.5 shows the implemented linear and step cooling profiles.

**Figure 3.4:** Relative supersaturation for linear cooling (left), and relative supersaturation for step cooling (right). Simulated profile using the NRTL model (line) is plotted against experimental data (crosses) from Worlitschek and Mazzotti ([2004]).

**Figure 3.5:** Linear and step cooling temperature profiles.
3.4.2 Linear Cooling Simulation

The upcoming figures either depict one of two things. They either show the relative supersaturation profile for a simulated batch, or show the final volume percent crystal size distribution (CSD) produced at the end of the simulated batch.

There is a large difference between several of the solubility models under linear cooling as seen in the two top subfigures in Figure 3.6. The MOSCED model greatly overestimates the initial relative supersaturation due to the model’s bias for under-predicting the equilibrium solubility. The van Laar model slightly overestimates the initial equilibrium solubility which causes a lower initial relative supersaturation. However, after 15000 seconds, the van Laar, NRTL, and empirical models are almost indistinguishable from each other while the MOSCED model provides a poor prediction throughout the batch.

The reason for the slight differences in the first peak for the NRTL, empirical, and van Laar models shown in the two bottom subfigures of Figure 3.6 is due to the relative supersaturation curve peaking at a higher value than the others causing increased secondary nucleation. The MOSCED model predicts that there will be a large peak of small crystals due to excessive secondary nucleation in the beginning of the batch. This is due to the high initial supersaturation which causes the large amount of secondary nucleation. Since the MOSCED model predicts secondary nucleation earlier than the other five models, and peaks at a higher relative supersaturation value than the others, it also should predict that the first peak’s maximum should have a larger crystal size than the others. However, this is not the case because the growth kinetic rate was modeled as being a function of absolute supersaturation. For a fixed relative supersaturation, the absolute supersaturation can have varying values depending on the value of the equilibrium concentration. Since the MOSCED model under-predicts the solubility...
of acetaminophen, it will have a corresponding absolute supersaturation that is lower than the other models. This lower absolute supersaturation causes less growth of the crystals. The two other predictive models, NRTL-SAC and UNIFAC, give results that are between the others.
They predict a supersaturation profile that is closer to the correlative models with the exception that it peaks a little higher than the others. This is what causes the larger first peak. The errors between the different solubility models do not result in large differences in the final CSD except for the MOSCED model which only is qualitatively accurate.

3.4.3 Step Cooling Simulation

The same observations from linear cooling can be observed in the two top subfigures of Figure 3.7 for step cooling between each models predicted initial relative supersaturation. The NRTL and empirical models are almost indistinguishable from each other, the MOSCED model overpredicts, while the van Laar, UNIFAC, and NRTL-SAC models under-predict the initial relative supersaturation. The van Laar, UNIFAC, and NRTL-SAC models are able to recover to the other models predictions at around 7500 seconds, but the MOSCED model never fully recovers to the other models prediction.

Just as in the linear cooling case, the empirical, van Laar, and NRTL models approximately predict the same final CSD (Figure 3.7). However, the MOSCED model predicts the same CSD (Figure 3.7) as for the linear cooling case. This is again due to the excessive initial supersaturation causing excessive nucleation in the beginning which dominates the batch throughout the batch. For the linear cooling case, it was just a coincidence that the MOSCED model’s CSD resembled the other models predictions. The UNIFAC and NRTL-SAC models give a better prediction than the MOSCED model, but are not much better in their prediction. These two cooling profiles show that small errors in the solubility model do not affect the final CSD significantly, as in the case of the empirical, NRTL, and van Laar models. Moderate errors can affect the final CSD, but its effect is dependent on the cooling profile used. The UNIFAC
Figure 3.7: Relative supersaturation and volume percent CSD for step cooling (top left: empirical and correlative models, top right: predictive models (NRTL model is shown for comparison), bottom left: empirical and correlative models, bottom right: predictive models (NRTL model is shown for comparison)).

The UNIFAC and NRTL-SAC models give a good prediction for the linear cooling profile, but their prediction is not as good for the step cooling profile. However, if there are large errors in the solubility model as in the case of the MOSCED model, the model will deliver a poor fit to the
data. Especially, if the solubility model under-predicts the equilibrium solubility which will cause false amounts of initial nucleation.

3.5 Robustness against Solubility Model Errors

Since crystallization models are often used to predict or to find optimal cooling profiles, it would be advantageous to make the model more robust against solubility model errors or biases. Solubility models are rarely perfect models and have some uncertainty or error inherent to their use. This is especially true for predictive thermodynamic models like the MOSCED model. These models are developed over a wide range of solvents and are not always very accurate. For the acetaminophen in ethanol case the MOSCED model has a systematic bias of under-predicting the equilibrium concentration. One way to make the model more robust is to specify the initial supersaturation condition instead of an initial solution concentration. This will remove the solubility’s model effect on the initial supersaturation. As seen earlier, the crystallization model is sensitive to the initial conditions. If the initial solute concentration is specified, the initial supersaturation will be dependent on the solubility’s model equilibrium prediction. An incorrect equilibrium prediction will thus cause an incorrect initial supersaturation which may cause the crystallization CSD prediction to diverge from the correct one. Thus by specifying the initial supersaturation, the solubility model no longer affects the crystallization initial conditions. It is reasonable to be able to specify the initial supersaturation because that will be known when doing crystallization experiments. It is typically desired to start the crystallization either at saturated or slightly undersaturated conditions before the cooling profile is initiated. For seeded crystallization, the relative supersaturation is usually kept small to stay within the metastable region. If the relative supersaturation is too high and the metastable region
is exceeded, uncontrollable nucleation will occur. When the initial supersaturation is specified, each solubility model does a much better job at predicting the relative supersaturation profiles for both linear and step cooling depicted in the four subfigures of Figure 3.8.

**Figure 3.8:** Relative supersaturation for linear and step cooling with a fixed initial relative supersaturation: top left: linear - empirical and correlative models, top right: linear - predictive models (NRTL model is shown for comparison), bottom left: step - empirical and correlative models, bottom right: step - predictive models (NRTL model is shown for comparison).
For both cooling profiles, the MOSCED model does a much better job at matching the other solubility models. It still has slightly higher relative supersaturation peaks than the other models, but now the model predicts the final CSD much better. Even though the MOSCED
model’s solubility curve is similarly shaped to the correlative solubility model curves seen in Figure 3.2, there are small variations in the inflection which causes the slightly different supersaturation curves in the right subfigures of Figure 3.8. The NRTL-SAC and UNIFAC models do not show much improvement for the linear profile case (top left subfigure in Figure 3.8), but show improvement for the step cooling case (bottom right subfigure in Figure 3.8). They are now almost indistinguishable from the NRTL model.

All of the predictive models can now predict the CSD for both linear and step cooling much more accurately than before which is shown in the right subfigures of Figure 3.9. The NRTL-SAC and UNIFAC model predictions for step cooling have greatly improved. The MOSCED model’s prediction is significantly improved for both temperature profiles. However, the secondary nucleated crystals do not grow as much in the MOSCED model’s prediction as in the other predictions for both cooling profiles. A further modification is made to further the model’s robustness and that is to make the growth kinetics a function of relative supersaturation instead of absolute supersaturation. Thus the absolute supersaturation can be rewritten as:

$$\Delta c = c_{eq}^{ref} (S - 1)$$

(3.27)

where $c_{eq}^{ref}$ is a reference equilibrium concentration and $S$ is the relative supersaturation. In order to make this change of variables, a reference equilibrium concentration needs to be chosen. Since the crystallization cooling batches go from 30 °C to 10 °C the reference equilibrium concentration was taken to be 176 g Acetaminophen/kg solvent at 20 °C. Substituting this into the growth kinetic equation resulted in the CSD profiles shown in Figure 3.10.

The MOSCED model now achieves a much better prediction of the final CSD. The grown secondary nucleates now have approximately the same size distribution for each solubility model for each corresponding cooling profile. This showed that making the growth kinetics a
function of relative supersaturation instead of absolute supersaturation, the crystallization model is much more robust against solubility model errors. The reason for these improved CSD results can be seen in the supersaturation subfigures of Figure 3.10. The MOSCED model does much better at predicting the correct relative supersaturation at the beginning of the batch. The effect of this improvement is that the relative supersaturation prediction is slightly worse at the end of the
batch. Since the crystallization phenomena predominantly occurs near the beginning of the batch, the superior supersaturation prediction at the beginning helps the predicted CSD more than the inferior prediction later that works to disadvantage the CSD prediction.

**Figure 3.11**: Volume percent CSD for linear and step cooling with \( G = f(S) \): top left: linear - empirical and correlative models, top right: linear - predictive models, bottom left: step - empirical and correlative models, bottom right: step - predictive models (NRTL model is shown for comparison).
However, this robustness adjustment has a detrimental effect on the other solubility models. It causes the NRTL-SAC and UNIFAC models to overestimate the supersaturation at the beginning of the batch for both the linear and step cooling profiles shown in the right subfigures of Figure 3.10. This over-prediction of the relative supersaturation causes more secondary nucleation to occur which can be seen in the right subfigures of Figure 3.11. The secondary nucleation peak is much larger than it was before the growth kinetics was modified.

The growth kinetic change greatly helps the MOSCED model, but it disadvantages both the NRTL-SAC and UNIFAC predictions for both cooling profiles. This change also affects the empirical and correlative models as shown in Figure 3.11. It causes the relative supersaturation to be overestimated at the beginning of the batch, and underestimated at the end compared to the NRTL model with standard growth kinetics. As before, this causes more secondary nucleation which affects the predicted CSD. Modifying the growth kinetic should only be done when the model’s solubility prediction is known or hypothesized to be far from the actual value. If this growth kinetic correction is not needed, it may do more harm than good.

### 3.6 Optimization

Next, the effect of using predictive solubility models on cooling crystallization optimization is compared. The optimization objective is to maximize the volume mean size (Equation 3.28). There is a maximum cooling rate constraint, and upper and lower bound constraints on the temperature. In addition, the solution is initially saturated per each model’s prediction. This dynamic optimization was done through joint optimization of the cooling profile and the seed loading. The initial seed size was set at a volume mean size of 155 microns. The
optimization run was discretized into 14 equal 5000 second intervals. The calculated optimal cooling profiles for each solubility model are shown in Figure 3.12

\[
\begin{align*}
\max D_{43} & \quad \text{subject to} \quad 10 \, ^\circ C \leq T \leq 30 \, ^\circ C \\
-0.05 \leq \frac{dT}{dt} \leq 0 \, ^\circ C/s \\
\end{align*}
\]

\[c_i = c_{eq}\]  \hspace{1cm} (3.28)

As seen in Figure 3.12, each of the four profiles appears very similar. Each profile has almost the same beginning and ending. Each model’s profile cools quickly at the beginning and the end of the experiment. Between 5000 seconds and 55000 seconds is where the solubility profiles differ. NRTL-SAC and UNIFAC have the most aggressive cooling profile resembling a concave cooling profile and MOSCED-Wilson utilizes more of a linear cooling profile in this period. There is a larger discrepancy between each of the seed loadings. The MOSCED-Wilson
model has the largest seed loading followed by the NRTL, NRTL-SAC, and UNIFAC models. Since the MOSCED-Wilson model’s optimal profile has a seed loading larger than the base case (NRTL), it is assumed that this model would be able to produce desirable results when implemented in a real system. However, the NRTL-SAC and UNIFAC models both have seed loadings less than the base case, so they may produce unfavorable results when implemented in a real system.

![Graph showing volume mean size sensitivity to different optimal profiles.](image)

**Figure 3.13:** Volume mean size sensitivity to different optimal profiles.

### 3.6.1 Optimization Sensitivity Analysis

Next, each optimal profile was implemented into the crystallization model using the NRTL solubility model. The NRTL model was chosen because it best matched the experimental data. Thus, it should best approximate what would happen if these other profiles were implemented into an actual crystallizer. The first variable analyzed is the objective variable,
volume mean size. As can be seen in Figure 3.13 the NRTL and the MOSCED-Wilson optimal profiles grew the seed the most. The MOSCED-Wilson profile almost grew particles the same size as the NRTL profile. This difference can be attributed to the seed loading. The MOSCED-Wilson profile had a larger seed loading. Since there are more crystals in suspension they will not be able to grow as large. Both the NRTL-SAC and UNIFAC volume mean size profiles quickly increased then began to decrease. These decreases are attributed to secondary nucleation creating many fines which decrease the mean size.

![Size (Microns)](image)

**Figure 3.14:** Volume percent CSDs for each optimal profile.

The next variable looked into is the volume percent CSD shown in Figure 3.14. Both the NRTL and MOSCED-Wilson models produce unimodal profiles. However, both the NRTL-SAC and UNIFAC models produce bimodal distributions. This is due to the secondary nucleation that
caused the decrease in crystal mean size. Looking at Figure 3.14, it clearly can be seen why the mean size decreased for the NRTL-SAC and UNIFAC models in Figure 3.13.

The last variable analyzed is relative supersaturation. Looking at the relative supersaturation profiles in Figure 2.15 can help understand what happened in both the volume mean size and volume percent CSD figures. For both the NRTL-SAC and UNIFAC model profiles, the supersaturation was much higher between 5000 and 25000 seconds. This larger supersaturation value caused the occurrence of secondary nucleation for these two profiles. The NRTL and MOSCED-Wilson models have much lower supersaturation levels. This is most likely attributed to these model’s higher seed loadings which enhances the seed’s ability to consume solute and keep the supersaturation from becoming too large.

![Supersaturation profiles for each optimal profile.](image)

**Figure 3.15:** Supersaturation profiles for each optimal profile.
This analysis shows that predictive models can be used for cooling crystallization optimization if certain conditions are met. They can be used if the predictive model’s seed loading is larger than the nominal optimum case. This increase in seed loading reduces the model’s sensitivity to the cooling profile. However, if the seed loading is much less than the nominal optimum case then the results will be poor. One way around this problem, is to use multiple predictive models, and use the model which produces the largest optimal seed loading.

3.7 Conclusion

Different models for solubility were presented and evaluated within a population balance crystallization model. The effect of the error of solubility models on the crystallization final CSD predictions was evaluated using seven different solubility models. It was shown that minor solubility model errors do not greatly affect the final CSD. However, large errors in the solubility model can be detrimental to the prediction as in the use of the MOSCED model. However, there are two ways to modify the MOSCED model to make it more robust against solubility errors. By specifying the initial relative supersaturation and by making the crystallization growth kinetics a function of relative supersaturation, the crystallization model is much more robust against solubility model errors. With these changes to the model, the generalized MOSCED model can predict the final CSD more accurately. However, the growth kinetic change has to be carried out cautiously for other predictive models, because it may cause the model to make a worse prediction. It was also shown that predictive models can be successfully used for cooling optimization given the predictive model’s optimal seed loading is larger than the optimal nominal value, and the predictive model’s optimal cooling profile does not differ much from the optimal nominal value.
### 3.8 Nomenclature

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<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
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<td>UNIFAC Interaction Parameter between Groups $m$ and $n$</td>
<td></td>
<td>$K^{-1}$</td>
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<td>$aa$</td>
<td>MOSCED Parameter</td>
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<td>van Laar Binary Activity Coefficient</td>
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<td>Discretization Parameter</td>
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<td>Crystal Growth</td>
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<td>m/s</td>
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<td>(J/cm$^3$)$^{0.5}$</td>
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<td>i^{th} Moment</td>
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3.9 References


4. USE OF PREDICTIVE SOLUBILITY MODELS FOR
ISOTHERMAL ANTISOLVENT CRYSTALLIZATION
MODELING AND OPTIMIZATION

4.1 Introduction

Crystallization is a chemical engineering unit operation that is widely used for the production of high purity products in the pharmaceutical, agrochemical, and fine chemical industries. Since these are multimillion dollar industries, any methods to improve the production of these products would be highly valued.

Crystallization phenomena of nucleation and growth are driven by supersaturation. Supersaturation can be induced by several methods namely cooling, evaporation, and antisolvent addition. Antisolvent crystallization is advantageous when the solute is temperature sensitive, or if its solubility is weakly temperature dependent. For these cases, the crystallization methods of cooling and evaporation cannot be used. In antisolvent crystallization, a second solvent which can be either a liquid or a supercritical gas is used to reduce the solubility of the solute, hence the use of term “antisolvent”. When an antisolvent is added to the solution, the equilibrium is altered to generate the required supersaturation. This supersaturation causes the solute to nucleate and growth of crystals subsequently follows. In this chapter we look exclusively at isothermal antisolvent crystallization considering constant temperature conditions throughout the crystallization operation.

It has been shown that optimal crystallization operation is best achieved using a modeling approach [Worlitschek, 2004; Nowee et al., 2007; 2008a/b; Lindenberg, 2009]. This crystallization model, typically based on population balances, requires a companion solubility

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model. The solubility prediction is a fundamental aspect of any crystallization model because its prediction is required for the calculation of supersaturation, which in turn is used for determining nucleation, growth, and other crystallization phenomena. Supersaturation is defined as the difference between the solution concentration and the equilibrium concentration (absolute supersaturation), or the ratio of the two (relative supersaturation).

Empirical solubility models have been extensively used in crystallization modeling [Zhou et al., 2006; Nagy et al., 2007; Nowee et al., 2008ab]. It is of interest to understand how predictive solubility models such as the MOSCED, NRTL-SAC, UNIFAC, and Jouyban-Acree models, can be incorporated into crystallization models and how their accuracy predicting the solubility profiles influences the crystallization model prediction and optimal profile calculation. The outcome of combining predictive solubility modeling with the crystallization model is expected to reduce the need for solubility experimental data and consequently streamline the optimization of the crystallization process. In Chapter 3, we investigated the effect of predictive models for the cooling crystallization of acetaminophen and found that predictive solubility models can successfully be used for modeling cooling crystallization [Widenski et al., 2010].

Although there has been extensive work done in the area of crystallization control and optimization [Braatz, 2002; Zhou et al., 2006; Nowee et al., 2008; Sheikhzadeh et al., 2008], as far as we are aware there is no study that has investigated the use of predictive solubility models in developing optimal antisolvent feed profiles. This chapter investigates (a) the extent these solubility models affect antisolvent crystallization predictions of relative supersaturation and volume mean size profiles and (b) the effects different solubility models have on the optimization of antisolvent crystallization. Both the effect of the solubility model on the predicted optimal profile and the sensitivity of a validated crystallization model to these
solubility models’ optimal profiles will be evaluated. Specifically, we examine the effect on the supersaturation, mean size, and volume percent crystal size distribution (CSD) profiles.

The chapter is structured as follows: Section 4.2 reviews and describes the relevant solubility models. Section 4.3 evaluates the implementation of the various solubility model formulations into the crystallization model. These models are then evaluated against each other using fixed antisolvent feed rates. Section 4.4 evaluates the effect of solubility models on creating optimal profiles. Section 4.5 presents an optimization sensitivity analysis of the optimal profiles produced from each model. Section 4.6 finally concludes.

4.2 Solubility Models

Several predictive solubility models were considered for this study namely the MOSCED, UNIFAC, NRTL-SAC, and Jouyban-Acree models. Each of these models is capable of predicting solute equilibrium without additional solubility data, except for the Jouyban-Acree model. The Jouyban-Acree model requires two solubility data points, the solubility of the solute in the pure solvent and the solubility of the solute in the pure antisolvent. The ternary acetaminophen-acetone-water system is used as the model system in this study at an isothermal operating temperature of 16 °C.

The MOSCED model [Lazzaroni et al., 2005], generates infinite-dilution activity coefficients. In order to obtain a non-infinite-dilution activity coefficient, another activity coefficient model is required. The van Laar, Wilson, and NRTL models were each combined with the MOSCED model to evaluate which would give the best prediction to known experimental data. Formulations for the van Laar, Wilson, and NRTL models are listed in Widenski et al. [2010] and Chapter 3. The MOSCED model is described by Equation Set 4.1:
\[
\ln \gamma_{i,j}^\infty = \frac{v_i^0}{RT} \left[ \lambda_j - \lambda_i \right]^2 + \frac{q_j^2 q_i^2 (\tau_j - \tau_i)^2}{\psi_j} + \frac{(\alpha_j - \alpha_i)(\beta_j - \beta_i)}{\xi_j} \bigg] + d_{ji}
\]

\[
d_{ji} = \ln \left( \frac{v_i^0}{v_j^0} \right)^{aa} + 1 - \left( \frac{v_i^0}{v_j^0} \right)^{aa} \]

\[
\alpha = \alpha_j^0 \left( \frac{293}{T(K)} \right)^{0.8}, \quad \beta = \beta_j^0 \left( \frac{293}{T(K)} \right)^{0.8}, \quad \tau = \tau_j^0 \left( \frac{293}{T(K)} \right)^{0.4}
\]

\[
\xi_j = 0.68(POL - 1) + \left[ 3.24 - 2.4e^{-0.002687(\alpha_j^0 \beta_j^0)^{1.5}} \right]^{293/\left( T \right)^2} + 1
\]

\[
POL = q_j^0 \left[ 1.15 - 1.15e^{-0.002337(\tau_j^0)^3} \right] + 1
\]

---

**Table 4.1: MOSCED model parameters for acetaminophen, acetone, and water.**

<table>
<thead>
<tr>
<th>MOSCED Parameter</th>
<th>MOSCED Parameter</th>
</tr>
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<tr>
<td>$v^0$</td>
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</tr>
<tr>
<td>Acetaminophen</td>
<td>105.4</td>
</tr>
<tr>
<td>Acetone</td>
<td>73.8</td>
</tr>
<tr>
<td>Water</td>
<td>36.0</td>
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</table>

This representation of the MOSCED model is used to find substance $j$’s infinite-dilution activity coefficient in substance $i$. Similarly, the model can be used to find the infinite-dilution activity coefficient for substance $i$ in $j$ by switching the subscripts $i$ and $j$. The MOSCED model contains five adjustable parameters: $\lambda$, $\alpha$, $\beta$, $q$, and $\tau$ corresponding to dispersion, hydrogen bond acidity, hydrogen bond basicity, induction, and polarity respectively. The sixth parameter, $v$, molar volume is adjustable only for the special case of water. Details on these parameters and their correlated values for various compounds are given in Lazzaroni et al. [2005]. Specifically,
the MOSCED parameter values at 273.15 K for acetaminophen, acetone, and water are listed in Table 4.1.

The next solubility model considered is the UNIFAC model [Anderson and Prausnitz, 1978]. The UNIFAC model predicts activity coefficients based on group contributions, and is described by Equation Set 4.2:

\[
\ln \gamma_l = \ln \gamma_l^C + \ln \gamma_l^R
\]

\[
\ln \gamma_l^C = \ln \frac{\Phi_{i,U}}{x_i} + \frac{z}{2} q_i \ln \frac{\theta_i}{\Phi_{i,U}} + l_i - \frac{\Phi_{i,U}}{x_i} \sum \theta_j l_j
\]

\[
\ln \gamma_l^R = \sum_k \psi_k^{(i)} \left( \ln \Gamma_k - \ln \Gamma_k^{(i)} \right)
\]

\[
\ln \Gamma_k = \ln \Gamma_k^{(i)} = Q_k \left[ 1 - \ln \left( \sum_m \theta_m \psi_{mk} \right) - \sum_m \frac{\theta_m \psi_{km}}{\sum \theta_n \psi_{nm}} \right]
\]

\[
l_i = \frac{z}{2} (r_{i,U} - q_{i,U}) - (r_{i,U} - 1)
\]

\[
\theta_i = \frac{q_{i,U} x_i}{\sum_j q_{j,U} x_j}, \quad \Phi_{i,U} = \frac{r_{i,U} x_i}{\sum_j r_{j,U} x_j}, \quad \theta_m = \frac{Q_m X_m}{\sum_n Q_n X_n}, \quad \psi_{mn} = e^{(-\alpha_{mn} / T)}
\]

\[
r_{i,U} = \sum_k \psi_k^{(i)} R_k, \quad q_{i,U} = \sum_k \psi_k^{(i)} Q_k
\]

where \( \gamma_l \) is the activity coefficient of component \( i \), \( \gamma_l^C \) and \( \gamma_l^R \) are the combinatorial and residual parts of the activity coefficient of component \( i \), \( \Gamma_k \) is the residual activity coefficient of group \( k \), \( \Gamma_k^{(i)} \) is the residual activity coefficient of group \( k \) in a reference solution containing only groups of type \( i \), \( z \) is the coordination number, \( r_{i,U} \) is the volume structural parameter of component \( i \), \( r_{i,U} \) is the area structural parameter of component \( i \), \( \theta_i \) is the area fraction of component \( i \), \( \Phi_i \) is the volume fraction of component \( i \), \( \theta_m \) is the area fraction of group \( m \), \( Q_k \) is the volume structural parameter of group \( k \), \( R_k \) is the area structural parameter of group \( k \), \( \psi_k^{(i)} \), is the number
of $k$ groups in component $i$, $x_i$ is the mole fraction of component $i$, $X_m$ is the mole fraction of group $m$ in the mixture, $\Psi_{mn}$ is the group interaction parameter between $m$ and $n$, and $a_{mn}$ is the measure of interaction between groups $m$ and $n$. The UNIFAC parameters for water, acetone, and acetaminophen molecules were calculated from the individual functional group parameters found in Poling, Prausnitz, and O’Conell [2000]. Since the acetaminophen aromatic NH functional group was not listed, it was approximated as an aromatic NH$_2$ functional group in the same manner as Hojjati and Rohani [2006]. The UNIFAC structural parameters for acetaminophen, acetone, and water are listed in Table 4.2. The MOSCED and UNIFAC models predicted equilibrium profiles for acetaminophen in acetone and water are shown in Figure 4.1.

![Figure 4.1: MOSCED and UNIFAC solubility predictions.](image-url)
Table 4.2: UNIFAC parameters for acetaminophen, acetone, and water.

<table>
<thead>
<tr>
<th></th>
<th>Acetaminophen</th>
<th>Acetone</th>
<th>Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area Structural Parameter $(r_i,U)$</td>
<td>5.7528</td>
<td>2.5735</td>
<td>0.9200</td>
</tr>
<tr>
<td>Volume Structural Parameter $(q_i,U)$</td>
<td>4.5840</td>
<td>2.336</td>
<td>1.4000</td>
</tr>
</tbody>
</table>

The MOSCED models all give very poor solubility predictions. They all greatly underestimate the solubility. The MOSCED-NRTL and MOSCED-Wilson combination models give better estimates to the shape of the solubility curve than the MOSCED-van Laar combination model does. The UNIFAC model is the worst of the models both greatly overestimating the solubility and weakly representing the shape of the curve.

The next solubility model considered is the NRTL-SAC model [Chen and Song, 2004; Chen and Crafts, 2006]. The NRTL-SAC model is a NRTL activity coefficient model that they modified using segment theory in a similar way as the polymer NRTL model. The NRTL-SAC model is described by Equation Set 4.3:

\[
\ln \gamma_i = \ln \gamma_i^C + \ln \gamma_i^R
\]

\[
\ln \gamma_i^C = \ln \frac{\phi_i}{x_i} + 1 - \sum_j \frac{\phi_j}{r_j}
\]

\[
\ln \gamma_i^R = \sum_m r_{m,i} (\ln \Gamma_m^{lc} - \ln \Gamma_m^{lc,i})
\]

\[
\ln \Gamma_m^{lc} = \frac{\sum_j x_j G_{jm} \tau_{jm}}{\sum_k x_k G_{km}} + \sum_{m'} \frac{x_{m'} G_{mm'} \tau_{mm'}}{\sum_k x_k G_{km'}} \left( \frac{\tau_{mm'}}{\sum_k x_k G_{km'}} - \frac{\sum_n x_n G_{nm'} \tau_{nm'}}{\sum_k x_k G_{km'}} \right)
\]

\[
\ln \Gamma_m^{lc,i} = \frac{\sum_n x_{n,i} G_{nm} \tau_{nm}}{\sum_k x_{k,i} G_{km}} + \sum_{m'} \frac{x_{m',i} G_{m'm'} \tau_{m'm'}}{\sum_k x_{k,i} G_{km'}} \left( \frac{\tau_{m'm'}}{\sum_k x_{k,i} G_{km'}} - \frac{\sum_n x_{n,i} G_{nm'} \tau_{nm'}}{\sum_k x_{k,i} G_{km'}} \right)
\]

\[
x_n = \frac{\sum_j x_j r_{n,j}}{\sum_i \sum_m x_i r_{m,i}}
\]

\[
x_{n,i} = \frac{r_{n,i}}{\sum_m r_{m,i}}
\]

\[
r_i = \sum_m r_{m,i}
\]

\[
\phi_i = \frac{r_i x_i}{\sum_j r_j x_j}
\]

\[
G_{km} = e^{-x_{km} \tau_{km}}
\]
where $\gamma_i^c$ and $\gamma_i^p$ are the combinatorial and residual contributions to the activity coefficient of component $i$. $k, l, m, m'$, and $n$ are the segment indices, $i$ and $j$ are the component indices, $x_n$ is the segment-based mole fraction of segment species $n$, $x_i$ is the mole fraction of component $i$, $x_{n,i}$ is the segment fraction of segment species $n$ in component $i$, $\Gamma_m^{li}$ is the activity coefficient of segment species $m$, $\Gamma_m^{le,j}$ is the activity coefficient of segment species $m$ in component $i$, $r_{m,i}$ is the number of segment species $m$ in component $i$, $r_i$ is the total segment number of component $i$, and $\phi_i$ is the segment mole fraction of component $i$. $\tau_{km}$ and $\alpha_{km}$ are the NRTL-SAC binary interaction and nonrandomness parameters between segments $k$ and $m$ respectively. These parameters are tabulated in Chen and Crafts [2006] for each segment pair. The specific parameter values for acetaminophen, acetone, and water are listed in Table 4.3. Further details about the development of the NRTL-SAC model can be found in Chen and Crafts [2006] and Chen and Song [2004].

<table>
<thead>
<tr>
<th>Table 4.3: NRTL-SAC parameters for acetaminophen, acetone, and water.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
</tr>
<tr>
<td>Hydrophobicity (X)</td>
</tr>
<tr>
<td>Polarity (Y-)</td>
</tr>
<tr>
<td>Polarity (Y+)</td>
</tr>
<tr>
<td>Hydrophilicity (Z)</td>
</tr>
</tbody>
</table>

Furthermore, another solubility model considered is the Jouyban-Acree Model [Jouyban et al., 2006]. The Jouyban-Acree model is a semi-empirical model developed to predict the solubility of pharmaceuticals in organic solutions. This model requires the solubilities of both pure components in a binary solute-solvent system, and predicts the solubility of a solute in a solvent mixture. The Jouyban-Acree model is described by Equation 4.4:
\[
\log x_{2,mix} = f_1 \log x_{2,1} + f_3 \log x_{2,3} + f_1 f_3 \left[ \frac{C_0}{T} + \frac{C_1 (f_1 - f_3)}{T} + \frac{C_2 (f_1 - f_3)^2}{T} \right]
\] (4.4)

where \( f_i \) is the solute-free volume fraction of the solvent, \( f_3 \) is the solute-free volume fraction of the antisolvent, \( x_{2,1} \) is the solubility of the solute in pure solvent, \( x_{2,3} \) is the solubility of the solute in pure antisolvent, \( x_{2,mix} \) is the solubility of the solute in the solvent mixture. \( C_0, C_1, \) and \( C_3 \) are constants equal to 724.21, 485.17, and 194.41 respectively.

The last solubility model considered is an empirical model generated from data from Granberg and Rasmuson [2000] by Zhou et al. [2006]:

\[
C^* = -5.01902 \times 10^{-12} w^6 + 1.69767 \times 10^{-9} w^5 - 2.46765 \times 10^{-7} w^4 + 2.19262 \times 10^{-5} w^3 - 1.27018 \times 10^{-3} w^2 + 3.42614 \times 10^{-2} w + 7.96086 \times 10^{-2}
\] (4.5)

where \( C^* \) is the equilibrium concentration (kg paracetamol/kg solvents), and \( w \) is the solute-free mass percent of water. The Jouyban-Acree, NRTL-SAC, and empirical model solubility predictions are shown in Figure 4.2.

![Figure 4.2: Empirical, Jouyban-Acree, and NRTL-SAC solubility predictions.](image)
The NRTL-SAC and Jouyban-Acree solubility models both predict the equilibrium solubility much better than the MOSCED or UNIFAC models did. The empirical model fits the data very well and will be considered as the standard solubility model for benchmarking.

An ANOVA statistical analysis of the solubility models’ predicted solubilities against the experimental data was carried out. As seen in Table 4.4, only the empirical, Jouyban-Acree, and NRTL-SAC models had F-statistics lower than the critical F-statistic of 4.20(α = 0.05). Each MOSCED combination and the UNIFAC model had F-statistics much larger than the critical F-statistic. This means that these models provide extremely bad fits to the experimental data.

Since the UNIFAC and MOSCED models gave statistically significant poor solubility predictions, only the NRTL-SAC and Jouyban-Acree models will be compared against the empirical model for further crystallization studies.

<table>
<thead>
<tr>
<th>Table 4.4: Statistical evaluation of the solubility models.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solubility model</td>
</tr>
<tr>
<td>Empirical</td>
</tr>
<tr>
<td>Jouyban-Acree</td>
</tr>
<tr>
<td>MOSCED - NRTL</td>
</tr>
<tr>
<td>MOSCED - van Laar</td>
</tr>
<tr>
<td>MOSCED - Wilson</td>
</tr>
<tr>
<td>NRTL-SAC</td>
</tr>
<tr>
<td>UNIFAC</td>
</tr>
</tbody>
</table>

4.3 Crystallization Model and Simulation

In order to evaluate the effect of the solubility model on the predicted crystal properties a crystallization model is needed. The crystallization model is comprised of a population balance with corresponding crystallization kinetics, a mass balance, and a solubility model [Nowee et al.,
2008a/b]. The population balance considered was for a crystallization system with size-independent crystal growth, and with negligible attrition and agglomeration.

\[
\frac{\partial n(L, t)}{\partial t} + \frac{n(L, t)}{V} \frac{dV}{dt} + G \frac{\partial n(L, t)}{\partial L} = 0
\]  

(4.6)

where \( n(L, t) \) is the crystal density (no. of particles/m\(^4\)), \( V \) is the volume (m\(^3\)), \( G \) is the growth rate (m/s), \( B \) is the nucleation rate (no. of particles/ s m\(^3\)), \( n_i \) is the initial crystal density (no. of particles/m\(^4\)), and \( L_0 \) is the nuclei size (m).

The population balance was solved using the method of lines discretization technique. This technique converts the partial differential equation into a system of ordinary differential equations with corresponding boundary and initial conditions shown in Equation Set 4.7.

\[
\frac{dn_1}{dt} = B_0 - G \frac{n_1}{2\delta} - \frac{n_1}{V} \frac{dV}{dt}
\]

\[
\frac{dn_i}{dt} = G \left( \frac{n_{i-1}}{2\delta_{i-1}} - \frac{n_i}{2\delta_i} \right) - \frac{n_i}{V} \frac{dV}{dt} \quad i = 2..\zeta
\]

\[
n_i(t = 0) = 0 \quad i = 1..\zeta
\]

\[
n(L = 0, t) = 0
\]

\[
n(L = \infty, t) = 0
\]

where \( \zeta \) is the number of discretization intervals, and \( \delta \) is the length of each discretization interval given by:

\[
\delta_i = L_i - L_{i-1} \quad i = 1 .. \zeta
\]  

(4.8)

The individual discretization lengths are chosen using a geometric series:

\[
L_i = L_0 b^i \quad i = 0..\zeta
\]  

(4.9)

\[
b = \left( \frac{L_{\text{max}}}{L_0} \right)^{\frac{1}{\zeta}}
\]  

(4.10)
where $L_0$ is the nucleate size defined earlier and is given a value of 0.1 $\mu$m and $L_{\text{max}}$ is 1000 $\mu$m, the maximum crystal size used in the discretization.

The mass balance of the solute in solution for feed-batch antisolvent crystallization is:

$$\frac{d(Cm_s)}{dt} = -3\rho_c k_v V \int_0^{\infty} GL^2 n(L, t) dL$$

(4.11)

where $C$ is the solute concentration (kg solute/kg solvents), $k_v$ is the volumetric shape factor of the crystal, $\rho_c$ is the solid density of the crystal, and $m_s$ is the mass of the solvent. For acetaminophen: $k_v$, and $\rho_c$ are 0.866, and 1296 kg/m$^3$ respectively.

No energy balance was explicitly specified in the crystallization model. It is assumed that the control system maintains the reactor temperature at the set-point specified.

Acetaminophen in acetone with water as the antisolvent is used in this study as the antisolvent crystallization system. The antisolvent crystallization kinetics were taken from Zhou et al. [2006]. The authors developed their kinetics from previous crystallization data performed by Granberg et al. [1999, 2001].

$$B_0 = 8.56080 \times 10^8 \exp \left\{ -1.22850 \times 10^{-3} \frac{\ln^3 \left( \frac{\rho_c}{C^* \rho_s} \right)}{\ln^2 \left( \frac{C}{C^*} \right)} \right\}$$

(4.12)

$$G = k_g (C - C^*)^g$$

(4.13)

$$k_g = 4.01067 \times 10^{-8} w^2 - 1.76198 \times 10^{-6} w + 5.78135 \times 10^{-5}$$

(4.14)

$$g = -4.22536 \times 10^{-3} w + 1.77428$$

(4.15)

where $B_0$ is the nucleation rate (no. of particles/m$^4$ s) for the discretized population balance, $\rho_s$ is the density of the slurry (kg/m$^3$), $C^*$ is the equilibrium concentration defined previously, $G$ is the crystal growth rate (m/s), and $w$ is the solute-free mass percent of antisolvent (water) in the solution. The growth kinetic depends on the solvent composition, and is only valid for solute-free
water mass percent values greater than 30%. The crystallization kinetics are dependent on the solubility model, because the solubility model will affect both absolute and relative supersaturation.

The simulations were executed using the gPROMS modeling package (Process Systems Enterprise, UK). The general process modeling system (gPROMS®) is an equation-oriented high-level declarative modeling, simulation, and optimization package. It allows the development of hierarchical models of arbitrary depth involving a range of process models including distributed systems and process with discontinuities. gPROMS directly supports simulation, parameter estimation, and optimization activities as well as, following the CAPE-OPEN standards, provides an open environment and can be used in real-time applications.

The population balance was solved by backward finite difference discretization using 250 geometrically spaced intervals across the size axis from 0.5-1000 microns. The model solution was checked for numerical dependence and there was found to be a minimal benefit to using more than 250 discretization intervals. To evaluate the effect of using different solubility sub-models on the predicted crystallization results two different antisolvent feed rates were used, specifically 25 and 400 g/min. Both antisolvent simulations were done isothermally at 16 °C. The initial antisolvent solute-free mass fraction of water was 0.3 and the antisolvent feed rate was added until the solute-free mass fraction of water reached 0.8. The initial solvent mass was 1 kg, and the amount of acetaminophen added was equal to the equilibrium value of the solubility model used. After the antisolvent feed was stopped, the simulation was continued for 10 minutes to consume any remaining supersaturation, and allow the solution to reach equilibrium.

The left subfigure in Figure 4.3 shows the predicted relative supersaturation profiles for the 25 g/min antisolvent feed rate for the different solubility models. The Jouyban-Acree and
empirical models result in similar profiles while the NRTL-SAC model deviates significantly. The variation in the NRTL-SAC supersaturation profile is due to the divergence of the NRTL-SAC equilibrium profile past 0.3 solute-free mass fraction of water from the experimental data. The NRTL-SAC model predicts that the solubility of acetaminophen in the mixture does not decrease at the same composition that the empirical and Jouyban-Acree models decrease. It actually predicts a slight increase in equilibrium solubility which causes the decrease in relative supersaturation. The right subfigure in Figure 4.3 shows the relative supersaturation profile for the 400 g/min feed rate. It shows the same behaviour as the lower feed rate with the exception that the profiles peak higher. This is expected because the higher feed rate should cause more nucleation due to excessive supersaturation.

![Relative Supersaturation Profile](image)

**Figure 4.3:** Relative supersaturation profile for antisolvent feed rates of 25 g/min (left), and 400 g/min (right).

The end product volume mean sizes (taken at time = 95 minutes) for the 400 g/min feed rate are, as expected, smaller than those for the 25 g/min feed rate. Figure 4.4 illustrates this situation, using the empirical model as a basis. The 400 g/min feed rate results in a volume mean size of 156 microns, but under a feed rate of 25 g/min, the volume mean size increases to 192
microns. These figures also show that the NRTL-SAC model over-predicts, while the Jouyban-Acree model under-predicts the volume mean size for both feed rates. In addition, the figures show that the prediction is more dependent on the solubility model for the 25 g/min feed rate than the 400 g/min feed rate. The volume percent CSD plots in Figure 4.5 show the same results. There is a larger discrepancy between the predicted size distributions for the 25 g/min feed rate than for the 400 g/min feed rate. Intermediate feed rates between 25 and 400 g/min were then simulated with results displayed in Table 4.5.

**Figure 4.4:** Volume mean size profile for antisolvent feed rates of 25 g/min (right) and 400 g/min (left).

**Figure 4.5:** Volume percent CSD for antisolvent feed rate of 25 g/min (left) and 400 g/min (right).
Table 4.5: Predicted end product volume mean size for each solubility model.

<table>
<thead>
<tr>
<th>Antisolvent Feed Rate (g/min)</th>
<th>Empirical</th>
<th>Jouyban - Acree</th>
<th>% Error</th>
<th>NRTL- SAC</th>
<th>% Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>192</td>
<td>167</td>
<td>13.0</td>
<td>247</td>
<td>28.6</td>
</tr>
<tr>
<td>50</td>
<td>170</td>
<td>150</td>
<td>11.8</td>
<td>205</td>
<td>20.6</td>
</tr>
<tr>
<td>100</td>
<td>158</td>
<td>142</td>
<td>10.1</td>
<td>180</td>
<td>13.9</td>
</tr>
<tr>
<td>200</td>
<td>154</td>
<td>141</td>
<td>8.4</td>
<td>166</td>
<td>7.8</td>
</tr>
<tr>
<td>400</td>
<td>156</td>
<td>144</td>
<td>7.7</td>
<td>160</td>
<td>2.6</td>
</tr>
</tbody>
</table>

4.4 Optimization

The effect of different solubility models on model generated optimal profiles was evaluated next. The first optimization objective (O-1) was to minimize the total amount of nucleated crystals by minimizing the zeroth moment while creating a maximum final volume mean crystal size ($D_{43}$) of 200 microns. The optimization constraints were to end with a solute-free antisolvent mass percent of water of 88%, an isothermal operating temperature of 16 °C, and the mass feed rate of water could range between 0 and 400 g/min. The final solute-free antisolvent mass percent of water was chosen to be 88% for the following reason. Since the initial concentration of water is 40% and the initial solution is saturated, water concentrations greater than 88% will cause formed crystals to dissolve. This is not a multi-objective optimization problem because the mean size requirement was added as a constraint to the optimization objective function. The duration of the experiment was fixed at 4200 seconds. The control interval was discretized into 10 fixed 360 second intervals where the antisolvent flow rate could be adjusted in a piecewise constant manner. The final 600 seconds had a fixed antisolvent flow rate of zero. This was done to ensure that all remaining supersaturation is consumed at the end of the run. The number of intervals chosen was to lessen the grid dependency of the optimization. The optimizations were implemented using the gPROMS package (Process System
Enterprise, UK) using the gOPT entity. The objective function used is defined in Equation 4.16 subject to initial conditions in Equation 4.17.

\[
\begin{align*}
\min \mu_0 \quad \text{subject to} \quad & \left\{ \begin{array}{l}
D_{43} = 200 \mu m \\
w_f = 88% \\
0 \leq \frac{dW}{dt} \leq 400 \text{ g/min Water}
\end{array} \right.
\end{align*}
\tag{4.16}
\]

\[
T = 16 ^\circ C \quad w_i = 40\% \quad n_i(L, 0) = 0 \quad C_i = C_i^*
\tag{4.17}
\]

This optimization was carried out using the crystallization model in Section 3.3 separately with each of the empirical, Jouyban-Acree, and NRTL-SAC solubility models. The MOSCED and UNIFAC models were not considered because when those models were incorporated into the crystallization model they did not predict any crystallization phenomena such as nucleation or growth.

4.4.1 Optimal Antisolvent Feed Profiles for O-1.

Each solubility model resulted in an optimal profile (Figure 4.6). The empirical and Jouyban-Acree models generated similar optimal profiles (denoted Profile A.1 and Profile B.1 respectively) with a small initial flow rate at the beginning of the experiment, moderate flow rate in the middle, and higher flow rate at the end. In contrast, the NRTL-SAC model calculates an optimal profile (denoted Profile C.1) that has a moderate initial flow rate followed by a high flow rate in the middle, and no flow at the end.

4.4.2 Optimal Antisolvent Feed Profiles for O-2.

The second multi-objective optimization objective (O-2) was to create a larger final volume mean size \((D_{43})\) of 400 microns while again minimizing the total amount of nucleated
crystals by minimizing the zeroth moment. The objective function formulation for O-2 was the same as for O-1 with the exception that $D_{43}$ now is set to 400 microns.

![Graph of optimal antisolvent feed profiles for OR1.](image)

**Figure 4.6:** Optimal antisolvent feed profiles for O-1.

Each solubility model resulted in a new optimal profile for O-2 (Figure 4.7). The empirical and Jouyban-Acree models again generated similar optimal profiles (denoted Profile A.2 and Profile B.2 respectively) with a small initial flow rate at the beginning of the experiment, a high flow rate in the middle for A.2, and a high flow rate at the end for B.2. In contrast, the NRTL-SAC model calculates an optimal profile (denoted Profile C.2) that has a moderate initial flow rate followed by a low flow rate in the middle, and a moderate flow rate at the end.
4.5. Optimization Sensitivity Analysis

The crystallization model was executed for each generated optimal feed profile (A.1-C.2) using the empirical solubility model. The empirical model is used as the benchmark since it showed very close agreement to experimental solubility data. This should predict what these optimal profiles would actually produce in a real crystallizer. Results are shown in the next sections.

4.5.1 Optimal Profiles for O-1 Evaluation

When the optimal profiles are implemented into the empirical solubility model there are several observed differences in the simulated supersaturation profiles (Figure 4.8) under profiles...
A.1, B.1, and C.1. The NRTL-SAC optimal profile (C.1) causes the supersaturation to peak earlier than the other two models, while the supersaturation caused by the Jouyban-Acree profile (B.1) is shown to be similar in shape to the empirical profile (A.1), but with a delay. Next, the effect on the volume mean crystal size is shown in Figure 4.9.

**Figure 4.8:** Relative supersaturation profiles for each optimal antisolvent feed profile for O-1.

**Figure 4.9:** Volume mean size profiles for each optimal antisolvent feed profile for O-1.
The NRTL-SAC optimal profile’s (C.1) supersaturation profile only has one large early supersaturation peak which is associated with the first primary increase in crystal size, and a second peak which is associated with the subsequent increase in crystal size. The empirical optimal profile’s (A.1) generated supersaturation profile has four peaks which is associated with four increases in crystal size. Likewise, the supersaturation profile for the Jouyban-Acree optimal profile (B.1) is also associated with four increases in \( D_{43} \). In all of these \( D_{43} \) profiles, the first size increase is most likely associated with the supersaturation effect on the \( B/G \) term of the population balance boundary condition. The other growth increases are most likely associated with the effect of the supersaturation profile on regular growth kinetics. Using the empirical solubility model, the empirical optimal profile (A.1) satisfies its objective of 200 microns, the Jouyban-Acree optimal profile (B.1) is higher at 242 microns, and the NRTL-SAC optimal profile (C.1) is lower at 169 microns. Both predictive models optimal profiles did not meet the optimization objective, but are within 21% of the desired value.

**Figure 4.10:** Volume percent CSD for each optimal antisolvent feed profile for O-1.
Figure 4.10 shows the volume percent CSD for each optimal profile. All three optimal profiles give similar distributions with the NRTL-SAC optimal profile (C.1) distribution having a lower mean size than the others, and the Jouyban-Acree optimal profile (B.1) distribution having a larger mean size. All three optimal profiles generated distributions with similar width.

For this objective function (O-1) only the empirical model’s optimal profile (A.1) was able to satisfy the objective to create a volume mean size of 200 microns, but the predictive models’ profiles (B.1 and C.1) were able to be within 20% of the desired value. Also, all three profiles were able to produce unimodal profiles by successfully reducing subsequent nucleation from occurring once crystals were present in suspension.

4.5.2 Optimal Profiles for O-2 Evaluation

The next objective function considered is the 400 volume mean size objective function (O-2). As seen in Figure 4.11, the generated supersaturation profiles follow the same trend as for the first objective function (O-1). The NRTL-SAC optimal profile (C.2) generates a supersaturation profile that is nearly identical to the supersaturation profile that C.1 generated for O-1. The empirical optimal profile (A.2) generates a supersaturation amount that is above 1.02 from 500 to 2500 seconds. The Jouyban-Acree optimal profile (B.2) generates a supersaturation peak that is similar to (A.2) but not as high of a supersaturation amount.

The Jouyban-Acree (B.2) and NRTL-SAC (C.2) optimal profiles both generated a much smaller mean size because they did not generate the required supersaturation. The Jouyban-Acree optimal profile (B.2) generated a volume mean size of 271 microns and the NRTL-SAC optimal profile (C.2) generated a volume mean size of 162 microns. Both predictive solubility models’ optimal profiles do not satisfy O-2 as well as they satisfied O-1.
Figure 4.11: Relative supersaturation profiles for each optimal antisolvent feed profile for O-2.

Figure 4.12: Volume mean size profiles for each optimal antisolvent feed profile for O-2.
Figure 4.13 shows the volume percent CSD for each optimal profile for O-2. For this case, there is a larger difference between the three profiles. Clearly, the Jouyban-Acree (B.2) and NRTL-SAC (C.2) optimal profiles did not satisfy the optimization objective. In addition, the distribution width had more variation between the three profiles. The empirical profile (A.2) had the lowest distribution width, followed by the Jouyban-Acree (B.2) and the NRTL-SAC (C.2) model had the largest distribution width.

Just as for the first case (O-1), only the empirical model’s optimal profile (A.2) was able to satisfy the objective (O-2) to create a volume mean size of 400 microns. Both predictive model profiles (B.2 and C.2) produced a much smaller volume mean size. The Jouyban-Acree profile (B.2) produced particles 32% smaller, and the NRTL-SAC profile (C.2) produced particles 60% smaller. Even though they did not produce the proper volume mean size, all three profiles were successfully able to reduce nucleation to produce unimodal profiles.

Figure 4.13: Volume percent CSD for each optimal antisolvent feed profile for O-2.
4.5.3 Optimization Evaluation

The reason why the optimal flow rates are similar for both the empirical and Jouyban-Acree model is that the slopes of both solubility curves are very similar. Since the slope of the solubility curve is what dictates the supersaturation profile, it would be expected to give similar supersaturation profiles. The NRTL-SAC model has a different slope in its solubility profile, which causes the larger deviation in these reported results. In order for a predictive solubility model to produce predictive optimal profiles it must be both quantitatively and qualitatively accurate.

Only the optimal profiles (A.1, A.2) generated from the empirical solubility model were able to satisfy both optimization objectives. When other optimal profiles were used the final volume mean size was as much as 60% under-predicted and 21% over-predicted when implemented into the empirical solubility model. The deviation from the objective criteria increased as the targeted volume mean size increased.

<table>
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<th>Optimal Feed Profile</th>
<th>Final Volume Mean Size and Percent Error</th>
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<tr>
<td></td>
<td>O-1 (200)</td>
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<tr>
<td>NRTL-SAC</td>
<td>169</td>
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</table>

It is important to mention that the optimal profiles generated are not guaranteed global optima; they are most likely local optima. Although there may be better local optima for each optimization, the overall result is what is important. Generated optimal profiles for one solubility profile do not reproduce the same results when implemented into another solubility profile.
4.6 Conclusions

Several predictive solubility models were considered for this study namely the MOSCED, UNIFAC, NRTL-SAC, and Jouyban-Acree models. The MOSCED and UNIFAC models were very poor predictors of the equilibrium solubility. However, the Jouyban-Acree and NRTL-SAC predictions showed closer agreement to experimental data.

The models’ predictions of relative supersaturation and volume mean size were shown to be significantly influenced by the solubility predictions’ errors, even for the better Jouyban-Acree and NRTL-SAC models, thus highlighting that caution is needed in selecting the right solubility formulation. As the antisolvent feed rate decreased, the solubility model error had a greater effect on the predicted volume mean size. The solubility model can also predict delayed nucleation phenomena, such as determined by the NRTL-SAC model. The solubility model did have an effect on the optimal profile, and generated a unique optimal antisolvent feed profile. The use of the predictive solubility models’ optimal profiles did not satisfy the original objective function, which means that the use of an incorrect solubility model will create a sub-optimal antisolvent feed profile that will not satisfy its intended crystallization optimization objectives in a real system. This underpins the significance of the solubility profile in crystallization optimization work.

4.7 Nomenclature

<table>
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<th>Symbol</th>
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### Symbol Description Value Units

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### 4.8 References


5. USE OF PREDICTIVE SOLUBILITY MODELS TO DETERMINE OPTIMAL OPERATING CONDITIONS TO MAXIMIZE CRYSTAL YIELD FOR EVAPORATIVE, COOLING, AND ANTISOLVENT CRYSTALLIZATION

5.1 Introduction

Crystallization is a unit operation separation process that has been used for several decades. It is used for the production of pharmaceuticals, fine chemicals, and fertilizers. Temperature and solvent composition are key variables that can be manipulated to control crystallization processes. Depending on the physicochemical properties of the crystallizing compound, one or both of these variables can be used. The evaporative mode of crystallization can be used in cases where the compound (solute) does not decompose at the solvent’s boiling temperature. If the solute decomposes at or near the boiling temperature, but its solubility is strongly temperature dependent, then the cooling mode of crystallization can be selected. In some other cases where the solubility of the solute is strongly dependent on solvent composition, antisolvent crystallization is a more appropriate option. The manipulated variable for antisolvent crystallization is the antisolvent feed rate. For compounds that have solubilities that depend on both temperature and solvent composition, cooling and antisolvent modes can be operated together. This combined technique has been recently used for lovastatin [Nagy et al., 2008a], acetylsalicylic acid [Lindenberg et al., 2009], and sodium chloride [Widenski et al., 2012].

The combined technique was shown to improve crystal yield, crystal size, and crystal size distribution over the use of the single modes of cooling or antisolvent crystallization [Nagy et al., 2008a; Lindenberg et al., 2009]. However, there has been minimal investigation to evaluate how
different temperatures and initial compositions affect the crystal yield of individual antisolvent or cooling crystallization processes. For example, paracetamol has a solubility that is maximized in binary aqueous solutions [Romero et al., 1996; Granberg and Rasmuson, 2000; Hojjati and Rohani, 2006], but current work has been done in pure solvents [Fujiwara et al., 2002; Worlitschek and Mazzotti, 2004; Nagy et al., 2008b]. Proper determination of this binary mixture could increase yield significantly for cooling or evaporative crystallization. Operating antisolvent crystallization at an improper temperature can cause zero product to be formed while product can be formed at a different operating temperature. Also, due to the dilution effect of antisolvent crystallization, adding too much antisolvent can cause crystals to dissolve and disappear. It follows that it is possible to optimize yield with proper determination of the operating temperature and composition range.

This paper presents the use of crystallization models for the optimization of crystallization yield for the different modes of operation, namely evaporative, cooling, isothermal antisolvent, and non-isothermal antisolvent. Instead of using empirical solubility models, the use of predictive solubility models to aid in determining optimal operating conditions is investigated. In particular, the MOSCED, UNIFAC, NRTL-SAC, and Jouyban-Acree models are selected. This is motivated by the possibility of successfully using predictive solubility models as an antisolvent screening mechanism to accurately determine optimal operating parameters, and thus accurately calculating yield. This is significant because it allows rapid preliminary screening of various solvent-antisolvent mixtures without the need for experimental solubility data.

The chapter is structured as follows. Section 5.2 is a systematic overview of how each crystallization mode of operation affects crystallization yield. Section 5.3 presents the predictive
solubility models investigated in this chapter as well as a benchmark empirical model. Section 5.4 gives the model-based optimization results for each solubility model, and Section 5.5 concludes the chapter.

5.2. Crystal Yield

Yield is an important crystallization property because it dictates the quantity of product crystals that can be produced in a crystallizer. A low-yield process will need either a much larger crystallizer or multiple crystallizers to produce the same throughput as a high-yield process. Yield is a state variable so it does not depend on the operating path of the crystallizer; it just depends on the initial and final conditions. Crystal shape, size, and distribution are not state variables and depend on the operating path. Since these properties cannot be determined by solubility data these properties will not be considered. For some operations these properties might have more importance than yield.

5.2.1 Crystallization Systems and Solubility Analysis

Evaporation, cooling, isothermal antisolvent, and non-isothermal antisolvent methods will be compared for two model compounds. The model compounds chosen are potassium chloride (KCl) and paracetamol. Potassium chloride is used as a fertilizer, and as a sodium chloride salt substitute. Paracetamol, also known as acetaminophen, is used as a pain reliever and is the active ingredient in Tylenol®. Both compounds solubilities are affected by temperature and an antisolvent so they are good compounds to use for this study. The ternary systems considered are: potassium chloride – water – ethanol (EtOH) (system KCL), paracetamol – water – acetone (system P-A), and paracetamol – water – isopropanol (system P-IPA). Three
temperatures were chosen for each compound. The temperatures were chosen to be the highest temperature and lowest temperature tabulated in each reference, as well as an intermediate temperature. The solubility data for system KCL is from Pinho and Macedo [2005], and is shown for 25, 50 and 75 °C in the left subfigure of Figure 5.1. The solubility data for system P-A is from Granberg and Rasmuson [2000], and is plotted for 0, 15, and 30 °C in the right subfigure of Figure 5.1. Lastly the solubility data for system P-IPA is from Hojjati and Rohani [2006], and is plotted for 5, 25, and 40 °C in the right subfigure of Figure 5.1. These two figures show how different antisolvents can affect the systems. The left subfigure of Figure 5.1 shows that the solubility decreases faster, for a given composition change, as the temperature is increased. The right subfigure of Figure 5.1 shows that paracetamol solubility is affected more by water in the acetone-water system than the isopropanol-water system. Thus, the acetone-water system should have a higher antisolvent crystallization yield. For consistency all of the yields calculated in this paper are for the saturated compound in an initial basis of 100 g of solvent(s). All solvent mass fractions reported are on a solute-free basis.

**Figure 5.1:** KCl-water-ethanol solubility (left), and paracetamol solubility for water-isopropanol and water-acetone systems (right).
5.2.2 Evaporative Crystallization Yield

The yield from evaporative crystallization was assumed to be equal to that of a saturated solution at 75 °C for KCl, 30 °C for P-A, and 40 °C for P-IPA, and is calculated using Equation 5.1:

\[ Y = C_s(T, w) \]  

(5.1)

where \( Y \) is the crystal yield and \( C_s \) is the saturation concentration at temperature (\( T \)), \( w \) is the solute-free ethanol percent for system KCl, and \( w \) is the solute-free water percent for the paracetamol systems. As seen in the left subfigure of Figure 5.2, the KCl system yield is maximized in pure water and decreases exponentially as ethanol is added. For the paracetamol systems, shown in the right and bottom subfigures of Figure 5.2, the maximum yield occurs at a specific mixture of water and the organic solvent. These systems show that the maximum yield recoverable does not always occur with a pure solvent.

5.2.3 Cooling Crystallization Yield

For cooling, two different starting temperatures were used for each system. The initial solution was at a condition equivalent to saturation of 100 g of solvent and was then cooled to either one of two final temperatures. The cooling yield is calculated using Equation 5.2:

\[ Y = C_s(T_0, w) - C_s(T_f, w) \]  

(5.2)

where \( C_s \) is the saturation concentration at the initial (\( T_0 \)) and final (\( T_f \)) temperatures. The cooling yields for each system are displayed on the same subfigures of Figure 5.2 as they were for evaporation. Three trends can be observed for all three systems. First, evaporative crystallization has a much higher yield than for cooling. This difference can be decreased by decreasing the value of the final temperature, i.e. by application of further cooling capacity. The second trend is
that for equal temperature changes, the yield will usually be highest for the highest starting temperature. This is because solubility usually increases exponentially with temperature. Since the

solubility increases exponentially, the solubility will be highest at the highest temperature. For example, for paracetamol in 100 g of 30% water / 70% acetone solution, the solubility of paracetamol is 49.46, 38.42, and 30.59 g at 30, 15, and 0 °C respectively. The yield from 30-15 °C cooling is 11.04 g, and from 15-0 °C cooling is 7.83 g. The yield for 30-15 °C cooling is 41% greater than for 15-0 °C cooling. Third, the maximum cooling yield occurs at or near the

Figure 5.2: Cooling and evaporative yields for KCl-water-ethanol (left), paracetamol-water-isopropanol (right), and paracetamol-water-acetone (bottom).
composition with the highest solubility for a given temperature. The maximum cooling yield for KCl is 13.50 g in pure water. The same trend happens for paracetamol. The maximum yield is 19.63 g in system P-IPA, and 18.87 g in system P-A.

5.2.4 Isothermal Antisolvent Crystallization Yield

The next crystallization method considered is isothermal antisolvent crystallization. Crystal yield for antisolvent crystallization is calculated using Equation 5.3, where \( m_s \) is the mass of solvents (kg), and \( w_o \) and \( w_f \) are initial and final solute-free antisolvent compositions.

\[
Y = C_o(T, w_0) - C_s(T, w_f) \left( \frac{m_s}{0.1} \right)
\]

(5.3)

Yield for isothermal antisolvent crystallization shows some interesting behavior. For all three systems, the yield is dependent on both the temperature and starting composition. For the KCl system, displayed in the left subfigure of Figure 5.3, the maximum yield at a given isothermal operating temperature occurs as antisolvent is added to an initial composition of pure water, but as the fraction of ethanol increases in the initial solvent composition, the maximum attainable yield at a given isothermal operating temperature decreases. Also, the maximum yield at a given initial solvent composition increases as the isothermal operating temperature increases. For example, the yield is 9 g higher at 75 °C than it is at 25 °C when starting in pure water and adding ethanol until the final solution is 90% ethanol. Paracetamol shows more interesting behavior. For paracetamol, only certain starting compositions will produce crystals. For example, the bottom subfigure of Figure 5.3 shows that if the antisolvent crystallization was started in pure acetone at 0 °C, when the fraction of water reached 0.3, 40 g of solute would need to be added to reattain saturation conditions. Moreover, the curve never crosses zero so this starting composition will never produce crystals using this antisolvent. However, if antisolvent
crystallization is added to an initial acetone solvent fraction of 0.3 or greater, then a positive crystal yield will be produced. Importantly, a period of undersaturation is not seen for these initial solvent compositions.

**Figure 5.3:** Isothermal antisolvent yields for KCl-water-ethanol (left), paracetamol-water-isopropanol starting at pure water and 40% water (right), and paracetamol-water-acetone at 0 °C starting at different initial solvent compositions (bottom).

5.2.5 Non-Isothermal Antisolvent Crystallization Yield

Both cooling and antisolvent methods can be combined to improve crystal yield. This can be done using various different paths, but the two extreme methods are to cool first then add the
antisolvent, or first add the antisolvent and then cool the solution. The crystal yield is independent of the specific path chosen. It just depends on the initial and final temperature and composition, and is calculated with Equation 5.4:

\[
Y = C_s(T_0, w_0) - C_s(T_f, w_f) \left( \frac{m_s}{0.1} \right)
\]  

(5.4)

Figure 5.4: Non-isothermal antisolvent yields for KCl-water-ethanol (left), paracetamol-water-isopropanol (right), and paracetamol-water-acetone (bottom). Each line represents the crystal yield for a given initial solvent composition.

These plots were made assuming that cooling occurs first, and antisolvent is added afterwards. If one looks carefully at the subfigures of Figure 5.4, it can be seen that the yield
curves for each initial solvent composition rise out of the cooling yield curve for each solute’s maximum temperature change.

The non-isothermal antisolvent yields for KCl shown in the left subfigure of Figure 5.4 are similar to the isothermal antisolvent yields. However, they differ in an important way. The cooling was fixed from 75-25 °C, and the initial composition was varied. The addition of cooling shifts the yield up proportionally with cooling amount. If done in an initial composition of zero ethanol then the maximum attainable yield by adding ethanol antisolvent is 49.4 g. However, if the initial composition of ethanol is 0.4 then the maximum attainable yield by adding antisolvent ethanol is 15 g. The same trend is followed for P-IPA and P-A in the right and bottom subfigures of Figure 5.4 respectively. For the P-IPA system, if the initial solvent fraction of water is 0, the maximum attainable crystal yield is 6 g. However, if the initial solvent fraction of water is 0.4 then the maximum attainable crystal yield is 27 g. For the P-A system, if the initial antisolvent fraction is 0, then adding antisolvent cannot increase the crystal yield. The maximum attainable yield at a water solvent mass fraction of 0 is from sole cooling crystallization with a yield of 5 g. However, if the initial solvent fraction of water is 0.3, then the maximum attainable crystal yield by adding an antisolvent is 40 g. In this case adding antisolvent is incredibly beneficial because at this initial solvent composition the cooling yield is 20 g less. This reiterates the point that to maximize yield for antisolvent crystallization the initial solvent composition is important. In conclusion, by comparing Figure 5.4 to Figure 5.3 it is seen that adding cooling to antisolvent is beneficial. At any given initial solvent composition, no matter how much antisolvent is added, the yield will be higher for non-isothermal antisolvent crystallization than for isothermal antisolvent crystallization. This is the benefit of adding cooling. The maximum yield for KCl increased to 49.1 g, increased to 39.1 for P-A, and increased to 27.3 for P-IPA.
5.2.6 Comparison of Methods

As seen, the crystallization yield depends on many factors, the crystallization method, operating temperature, degree of cooling, initial solvent composition, and addition of an antisolvent. Table 5.1 shows the maximum yields attainable using evaporation (E), cooling (C), isothermal antisolvent (I-AS), and non-isothermal antisolvent (NI-AS). For the KCl system, disregarding evaporation, the maximum yield was for non-isothermal antisolvent with 49.1 g, followed by isothermal antisolvent with 44.6 g, and last was cooling with 13.5 g. There is a large decrease from isothermal antisolvent to cooling which suggests that this compound is more sensitive to the antisolvent than to temperature. For both paracetamol systems, again disregarding evaporation, the non-isothermal antisolvent method had the largest yields of 39.1 g for system P-A and 27.3 g for system P-IPA. For system P-A, the best cooling and isothermal antisolvent methods had similar yields of 18.9 and 21.1 g respectively. However, for system P-IPA, the isothermal antisolvent method had a much smaller yield than for cooling, 7.5 g to 19.6 g. Adding either cooling or antisolvent was equally beneficial for system P-A, but adding antisolvent to system-IPA was much less beneficial.

5.2.7 Other Considerations

Even though adding antisolvent crystallization to an existing cooling crystallization process improves the yield, there are consequences in doing so. Antisolvent crystallization results in a solvent mixture at the end of the batch. The solvent must either be disposed of or separated. This can add significantly to the crystallizer operating costs. These operating costs may outweigh the increased yield of adding antisolvent to the process. However, the reverse is extremely beneficial. Adding cooling to an antisolvent process may not significantly increase the
operating costs of the process, but can significantly increase the yield. In addition, if the antisolvent crystallization process is not operated at an optimal temperature, finding the optimal temperature and operating the crystallizer at that temperature can significantly increase the yield.

<table>
<thead>
<tr>
<th>System</th>
<th>Maximum Yields (g/100 g) for Each Crystallization Method for Each System</th>
<th>E</th>
<th>C</th>
<th>I-AS</th>
<th>NI-AS</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCl-H$_2$O-ETOH</td>
<td></td>
<td>49.4</td>
<td>13.5</td>
<td>44.6</td>
<td>49.1</td>
</tr>
<tr>
<td>Best Conditions</td>
<td></td>
<td>75-25 °C @ 0% EtOH</td>
<td>0-90 % EtOH</td>
<td>75-25 °C</td>
<td></td>
</tr>
<tr>
<td>P - H$_2$O - A</td>
<td></td>
<td>49.5</td>
<td>18.9</td>
<td>21.1</td>
<td>39.1</td>
</tr>
<tr>
<td>Best Conditions</td>
<td></td>
<td>30% H$_2$O @ 30 °C</td>
<td>30-85% H$_2$O @ 15 °C</td>
<td>30-85% H$_2$O @ 30-0 °C</td>
<td></td>
</tr>
<tr>
<td>P - H$_2$O - IPA</td>
<td></td>
<td>34.9</td>
<td>19.6</td>
<td>7.5</td>
<td>27.3</td>
</tr>
<tr>
<td>Best Conditions</td>
<td></td>
<td>30% H$_2$O @ 40-5 °C</td>
<td>40-90% H$_2$O @ 5 °C</td>
<td>40-90% H$_2$O @ 40-5 °C</td>
<td></td>
</tr>
</tbody>
</table>

5.2.8 Model-Based Yield Optimization

As seen there are advantages to finding optimal operating parameters for each crystallization method. However, instead of using discrete data to make the decisions, the data can be used to create a solubility model. This solubility model can then be used to find optimal points that are not dependent on the discrete data.

5.3 Solubility Models

Several predictive solubility models were considered for this study namely the MOSCED, UNIFAC, NRTL-SAC, and Jouyban-Acree models. Except for the Jouyban-Acree model, each of these models is capable of predicting solute equilibrium without additional solubility data. The Jouyban-Acree model requires two solubility data points, the solubility of the solute in the pure solvent and the solubility of the solute in the pure antisolvent. The ternary
acetaminophen-acetone-water system is used as the model system in this crystallization study operating between 30 and 0 °C.

The MOSCED model [Lazzaroni et al., 2005], generates infinite-dilution activity coefficients. In order to obtain a non-infinite-dilution activity coefficient, another activity coefficient model is required. For this analysis, the Wilson model was combined with the MOSCED model. The Wilson model formulation is listed in Widenski et al. [2010]. The MOSCED model is described by Equation Set 5.5.

\[
\ln \gamma_{i,j}^\infty = \frac{v_i^0}{RT} \left[ (\lambda_j - \lambda_i)^2 + \frac{q_i^2 q_j^2 (\tau_j - \tau_i)^2}{\psi_j} + \frac{(\alpha_j - \alpha_i)(\beta_j - \beta_i)}{\xi_j} \right] + d_{ji}
\]

\[
d_{ji} = \ln \left( \frac{v_i^0}{v_j^0} \right)^{aa} + 1 - \left( \frac{v_i^0}{v_j^0} \right)^{aa}
\]

\[
aa = 0.953 - 0.002314[(\tau_i)^2 + \alpha_i \beta_i]
\]

\[
\psi_j = POL + 0.002629 \alpha_j \beta_j
\]

\[
\xi_j = 0.68(POL - 1) + \left[ 3.24 - 2.4e^{-0.002687(\alpha_j \beta_j)^{1.5}} \right]^{(\frac{293}{T})^2}
\]

\[
POL = q_j^4 \left[ 1.15 - 1.15e^{-0.002337(\tau_j)^3} \right] + 1
\]

\[
\alpha_j = \alpha_j^0 \left( \frac{293}{T(K)} \right)^{0.8}, \quad \beta_j = \beta_j^0 \left( \frac{293}{T(K)} \right)^{0.8}, \quad \tau_j = \tau_j^0 \left( \frac{293}{T(K)} \right)^{0.4}
\]  

(5.5)

This representation of the MOSCED model is used to find substance j’s infinite-dilution activity coefficient in substance i. Similarly, the model can be used to find the infinite-dilution activity coefficient for substance i in j by switching the subscripts i and j. The MOSCED model contains five adjustable parameters: \(\lambda\), \(\alpha\), \(\beta\), \(q\), and \(\tau\) corresponding to dispersion, hydrogen bond acidity, hydrogen bond basicity, induction, and polarity respectively. The sixth parameter, \(v\), molar
volume is adjustable only for the special case of water. Details on these parameters and their correlated values for various compounds are given in Lazzaroni et al. [2005], and the MOSCED parameter values for acetaminophen, acetone, and water are listed in Widenski et al. [2011].

The next solubility model considered is the UNIFAC model [Anderson and Prausnitz, 1978]. The UNIFAC model predicts activity coefficients based on group contributions, and is described by Equation Set 5.6:

\[
\ln \gamma_i = \ln \gamma_i^C + \ln \gamma_i^R
\]

\[
\ln \gamma_i^C = \ln \frac{\Phi_{i,U}}{x_i} + \frac{z}{2} q_i \ln \frac{\theta_i}{\Phi_{i,U}} + l_i - \frac{\Phi_{i,U}}{x_i} \sum_j x_j l_j
\]

\[
\ln \gamma_i^R = \sum_k v_k^{(i)} (\ln \Gamma_k - \ln \Gamma_k^{(i)})
\]

\[
\ln \Gamma_k = \ln \Gamma_k^{(i)} = Q_k \left[ 1 - \ln \left( \sum_m \frac{\theta_m \Psi_{mk}}{\sum_n \theta_n \Psi_{nm}} \right) - \sum_m \frac{\theta_m \Psi_{km}}{\sum_n \theta_n \Psi_{nm}} \right]
\]

\[
l_i = \frac{z}{2} (r_{i,U} - q_{i,U}) - (r_{i,U} - 1)
\]

\[
\theta_i = \frac{q_{i,U} x_i}{\sum_j q_{j,U} x_j}, \quad \Phi_{i,U} = \frac{r_{i,U} x_i}{\sum_j r_{j,U} x_j}, \quad \theta_m = \frac{Q_m x_m}{\sum_n Q_n x_n}, \quad \Psi_{mn} = e^{\left( -\frac{a_{mn}}{P} \right)} \quad (5.6)
\]

\[
r_{i,U} = \sum_k v_k^{(i)} R_k, \quad q_{i,U} = \sum_k v_k^{(i)} Q_k
\]

where \(\gamma_i\) is the activity coefficient of component \(i\), \(\gamma_i^C\) and \(\gamma_i^R\) are the combinatorial and residual parts of the activity coefficient of component \(i\), \(\Gamma_k\) is the residual activity coefficient of group \(k\), \(\Gamma_k^{(i)}\) is the residual activity coefficient of group \(k\) in a reference solution containing only groups of type \(i\), \(z\) is the coordination number, \(r_{i,U}\) is the volume structural parameter of component \(i\), \(r_{i,U}\) is the area structural parameter of component \(i\), \(\theta_i\) is the area fraction of component \(i\), \(\Phi_i\) is the volume fraction of component \(i\), \(\Theta_m\) is the area fraction of group \(m\), \(Q_k\) is the volume
structural parameter of group $k$, $R_k$, is the area structural parameter of group $k$, $v_k^{(i)}$, is the number of $k$ groups in component $i$, $x_i$ is the mole fraction of component $i$, $X_m$ is the mole fraction of group $m$ in the mixture, $\Psi_{mn}$ is the group interaction parameter between $m$ and $n$, and $a_{mn}$ is the measure of interaction between groups $m$ and $n$. The UNIFAC structural parameters for acetaminophen, acetone, and water are listed in Widenski et al. [2011].

The next solubility model considered is the NRTL-SAC model [Chen and Song, 2004; Chen and Crafts, 2006]. The NRTL-SAC model is a NRTL activity coefficient model that they modified using segment theory in a similar way as the polymer NRTL model. The NRTL-SAC model is described by Equation Set 5.7:

$$
\ln \gamma_i = \ln \gamma_i^C + \ln \gamma_i^R
$$

$$
\ln \gamma_i^C = \ln \frac{\phi_i}{x_i} + 1 - r_i \sum \frac{\phi_j}{r_j}
$$

$$
\ln \gamma_i^R = \sum r_{m,i} (\ln \Gamma_m^{lc} - \ln \Gamma_m^{lc,i})
$$

$$
\ln \Gamma_m^{lc} = \frac{\sum_j x_j G_{jm} \tau_{jm}}{\sum_k x_k G_{km}} + \sum_{m'} \frac{x_{m'} G_{mm'}}{\sum_k x_k G_{km'}} \left( \tau_{mm'} - \frac{\sum_n x_n G_{nm'} \tau_{nm'}}{\sum_k x_k G_{km'}} \right)
$$

$$
\ln \Gamma_m^{lc,i} = \frac{\sum x_{n,i} G_{nm} \tau_{nm}}{\sum_k x_{k,i} G_{km}} + \sum_{m'} \frac{x_{m',i} G_{mm'}}{\sum_k x_{k,i} G_{km'}} \left( \tau_{mm'} - \frac{\sum_n x_n G_{nm'} \tau_{nm'}}{\sum_k x_{k,i} G_{km'}} \right)
$$

$$
x_n = \frac{\sum_j x_j \tau_{n,j}}{\sum_i \sum_m x_i r_{m,i}} \quad x_{n,i} = \frac{\tau_{n,i}}{\sum_m r_{m,i}} \quad r_i = \sum_m r_{m,i}
$$

$$
\phi_i = \frac{\tau_i x_i}{\sum_j \tau_j x_j}, \quad G_{km} = e^{-\alpha_{km} \tau_{km}}
$$

(5.7)

where $\gamma_i^C$ and $\gamma_i^R$ are the combinatorial and residual contributions to the activity coefficient of component $i$. $k$, $l$, $m$, $m'$, and $n$ are the segment indices, $i$ and $j$ are the component indices, $x_n$ is the segment-based mole fraction of segment species $n$, $x_i$ is the mole fraction of component $i$, $x_{n,i}$
is the segment fraction of segment species \( n \) in component \( i \), \( \Gamma_{m}^{n} \) is the activity coefficient of segment species \( m \), \( \Gamma_{m}^{1c} \) is the activity coefficient of segment species \( m \) in component \( i \), \( r_{m,i} \) is the number of segment species \( m \) in component \( i \), \( r_{i} \) is the total segment number of component \( i \), and \( \phi_{i} \) is the segment mole fraction of component \( i \). \( \tau_{km} \) and \( \alpha_{km} \) are the NRTL-SAC binary interaction and nonrandomness parameters between segments \( k \) and \( m \) respectively. These parameters are tabulated in Chen and Crafts [2006] for each segment pair, and the specific parameter values for acetaminophen, acetone, and water are listed in Widenski et al. [2011]. Further details about the development of the NRTL-SAC model can be found in Chen and Crafts [2006] and Chen and Song [2004].

Furthermore, another solubility model considered is the Jouyban-Acree Model [Jouyban et al., 2006]. The Jouyban-Acree model is a semi-empirical model developed to predict the solubility of pharmaceuticals in organic solutions. This model requires the solubilities of both pure components in a binary solute-solvent system, and predicts the solubility of a solute in a solvent mixture. The Jouyban-Acree model is described by Equation 5.8:

\[
\log x_{2,mix} = f_1 \log x_{2,1} + f_3 \log x_{2,3} + f_1 f_3 \left[ \frac{C_0}{T} + \frac{C_1 (f_1 - f_3)}{T} + \frac{C_2 (f_1 - f_3)^2}{T} \right]
\]  

(5.8)

where \( f_1 \) is the solute-free volume fraction of the solvent, \( f_3 \) is the solute-free volume fraction of the antisolvent, \( x_{2,1} \) is the solubility of the solute in pure solvent, \( x_{2,3} \) is the solubility of the solute in pure antisolvent, \( x_{2,mix} \) is the solubility of the solute in the solvent mixture. \( C_0, C_1, \) and \( C_3 \) are constants equal to 724.21, 485.17, and 194.41 respectively. The Jouyban-Acree model can be made temperature dependent by using temperature dependent \( x_{2,1} \) and \( x_{2,3} \) terms. For this work, Equations 5.9-5.10 were used to make the Jouyban-Acree model usable between 30-0 °C.
\[ x_{2,1} = 8.315 \times 10^{-5} \exp(0.002067T) \]  \hspace{1cm} (5.9)

\[ x_{2,3} = 2.648 \times 10^{-7} \exp(0.002946T) \]  \hspace{1cm} (5.10)

The last solubility model considered is an empirical model generated from data from Granberg and Rasmuson [2000]. Four different 5th order polynomials were generated for temperatures in ten degree increments from 30-0 °C. The polynomial coefficients are listed in Table 5.2 for Equation 5.11.

\[ C_s = a_0 w^5 + a_1 w^4 + a_2 w^3 + a_3 w^2 + a_4 w + a_5 \]  \hspace{1cm} (5.11)

where \( C_s \) is the equilibrium concentration (g paracetamol/kg solvents), and \( w \) is the solute-free mass percent of water.

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>( a_0 )</th>
<th>( a_1 )</th>
<th>( a_2 )</th>
<th>( a_3 )</th>
<th>( a_4 )</th>
<th>( a_5 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.966e-07</td>
<td>-8.503e-05</td>
<td>0.01415</td>
<td>-1.06344</td>
<td>29.74149</td>
<td>54.25003</td>
</tr>
<tr>
<td>10</td>
<td>1.925e-07</td>
<td>-8.114e-05</td>
<td>0.013723</td>
<td>-1.07448</td>
<td>31.52038</td>
<td>69.22067</td>
</tr>
<tr>
<td>20</td>
<td>2.389e-07</td>
<td>-9.000e-05</td>
<td>0.01444</td>
<td>-1.13318</td>
<td>34.28747</td>
<td>88.68038</td>
</tr>
<tr>
<td>30</td>
<td>2.745e-07</td>
<td>-9.431e-05</td>
<td>0.014549</td>
<td>-1.16558</td>
<td>36.98468</td>
<td>113.3252</td>
</tr>
</tbody>
</table>

In order to calculate an equilibrium solute concentration, the activity coefficients determined from the MOSCED, NRTL-SAC, and UNIFAC models are solved simultaneously with the solid solubility model (Equation 5.12) to calculate the mole fraction of the solute.

\[
\ln \left( x_2 \gamma_2 \right) = \frac{\Delta H_{\text{fusion}}}{R} \left( \frac{1}{T_{\text{melt}}} - \frac{1}{T} \right) - \frac{\Delta C_p}{R} \left( \ln \left( \frac{T_{\text{melt}}}{T} \right) - \frac{T_{\text{melt}}}{T} + 1 \right) \]  \hspace{1cm} (5.12)

where \( x_2 \) is the mole fraction of the solute, \( \gamma_2 \) is the activity coefficient of the solute, \( T_{\text{melt}} \) is the solute’s melting temperature, \( \Delta H_{\text{fusion}} \) is the solute’s enthalpy of fusion, and \( \Delta C_p \) is the solute’s change in heat capacity from the solid to liquid phase. Hojjati and Rohani [2006] measured the thermal properties of acetaminophen to be \( T_{\text{melt}} = 442.2 \) K, \( \Delta H_{\text{fusion}} = 28.1 \) kJ/mol, and \( \Delta C_p = 99.6 \) J/mol K.
Figure 5.5: Solubility model predictions for the paracetamol – water – acetone system at different temperatures.

The empirical model, MOSCED and Wilson, NRTL-SAC, Jouyban-Acree, and UNIFAC models are plotted against the experimental data for 0, 10, 20, and 30 °C in Figure 5.5. As can be seen in the subfigures, the UNIFAC model greatly overestimated the solubility for each temperature. The second worst model is the MOSCED and Wilson model combination. It underestimated the solubility at 10, 20, and 30 °C, and also predicted an unusually large
solubility in pure water at 0 °C. The three models that performed the best were the empirical, Jouyban-Acree, and NRTL-SAC models. The empirical model was an extremely good fit to the data at each temperature. The Jouyban-Acree model slightly underestimated the solubility, and the NRTL-SAC model matched the data well up to 40% water, then slightly overestimated the solubility for higher mass percent values.

5.4 Optimization

Each of these solubility models will be used to create optimal operating conditions that will maximize crystallization yield (Equation 5.13) for different crystallization modes of operation. The crystallization methods investigated are evaporation, cooling, isothermal antisolvent, and non-isothermal antisolvent. The specific manipulated variables from the set of \( \{w_o, w_f, T_o, T_f\} \) depend on the crystallization method used. The optimization constraints are that the temperature must be between 10 and 30 °C, the solute-free water percent must be between 0 and 100, and that the solution is initially saturated.

\[
\max_{w_o, w_f, T_o, T_f} \ Y \quad \text{subject to} \quad \begin{cases} 
10 \, ^\circ\text{C} \leq T \leq 30 \, ^\circ\text{C} \\
0 \leq w \leq 100 \\
c_i = c_{eq}
\end{cases} \tag{5.13}
\]

5.4.1 Evaporation

To maximize crystal yield two parameters were optimized, the initial saturation temperature, and the initial solvent composition. The optimal operating conditions for evaporation are listed in Table 5.3. Each model with the exception of the MOSCED model selected the upper bound of 30 °C. Since solubility generally increases with temperature this result is expected. The MOSCED model’s selection of the lower temperature bound of 0 °C was
unusual. This is most likely because the MOSCED model loses accuracy at temperatures away from standard conditions. The difference between the other models is that each model selected different solvent compositions. The empirical model selected a water percent of 27.1%, the Jouyban-Acree model selected a water percent of 25.9%, the NRTL-SAC selected a water percent of 46.6%, the UNIFAC model selected a water percent of 59.7%, and the MOSCED model selected a water percent of 100%. The Jouyban-Acree model most closely matched the empirical selection. With these operating parameters the empirical model predicted a yield of 49.7 g, Jouyban-Acree predicted 36.3 g, NRTL-SAC predicted 56.4 g, UNIFAC predicted 107.0 g, and MOSCED predicted 65.1 g.

![Graph](image)

**Figure 5.6:** Predicted (left) and actual (right) yields for evaporation (diamonds) and cooling (circles) modes of operation.

If each model’s optimal conditions were implemented none of them would exactly match the empirical model’s predicted yield. The closest models were the Jouyban-Acree and NRTL-SAC selected conditions that resulted in yields that were 99.9% and 80.1% of the maximum. The worst models were the UNIFAC and MOSCED models that selected conditions being 18.1% and
22.4% of the maximum yield. For evaporative crystallization the Jouyban-Acree model is able to be used successfully to predict optimal operating conditions.

<table>
<thead>
<tr>
<th>Table 5.3: Optimal operating conditions for evaporation and cooling modes.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evaporation</strong></td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td><em>w</em></td>
</tr>
<tr>
<td><em>T</em>₀ (°C)</td>
</tr>
<tr>
<td>Predicted Yield (g)</td>
</tr>
<tr>
<td>Actual Yield (g)</td>
</tr>
<tr>
<td><strong>Cooling</strong></td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td><em>w</em></td>
</tr>
<tr>
<td><em>T</em>₀ (°C)</td>
</tr>
<tr>
<td><em>T</em>ᵣ (°C)</td>
</tr>
<tr>
<td>Predicted Yield (g)</td>
</tr>
<tr>
<td>Actual Yield (g)</td>
</tr>
</tbody>
</table>

**5.4.2 Cooling**

To maximize cooling yield three operating parameters were optimized, the initial temperature, the final temperature, and the operating solvent composition. The optimal operating conditions for cooling are listed in Table 5.3. As expected, each model selected initial and final temperatures that were at the lower and upper temperature constraints, 10 and 30 °C. As in evaporation, they all selected different solvent compositions. The empirical model selected a water percent of 38.9%, the Jouyban-Acree model selected a water percent of 25.7%, the NRTL-SAC model selected a water percent of 18.6%, the UNIFAC model selected a water percent of 52.8%, and the MOSCED model selected a water percent of 100%. The predicted crystal yield was 198.0 g for the empirical model, 164.2 g for the Jouyban-Acree model, 284.0 g for the NRTL-SAC model, 195.5 g for the UNIFAC model, and 17.3 g for the MOSCED model.

As for evaporation, none of the predictive models could match the empirical yield. Again, the best models were the Jouyban-Acree, UNIFAC, and NRTL-SAC models whose selected
conditions had actual yields of 90.0%, 89.9%, and 78.5% of the maximum. The worst model was the MOSCED model which had selected conditions that had an actual yield of 28.3% of the maximum. For cooling, the Jouyban-Acree and UNIFAC models can be successfully used to predict optimal operating conditions.

5.4.3 Isothermal Antisolvent

To maximize crystal yield for isothermal antisolvent operation, two parameters were optimized, the initial and final solvent composition. This was performed at four different temperatures, 0, 10, 20, and 30 °C. By looking at Table 5.4 it can be seen that the optimal antisolvent compositions were significantly different for each model, and also were dependent on the operating temperature. For example, the selected initial solvent composition for the empirical model varied from 24.5% water at 0 °C to 34.5% water at 30 °C. Likewise, the selected final solvent composition for the Jouyban-Acree model varied from 84.1% water at 0 °C to 80.3% water at 30 °C. The selected conditions and their predicted yields are shown in the left subfigure of Figure 5.7. The horizontal lines in each subfigure of Figure 5.7 graphically represent the maximum yield attained at each operating temperature as well as its corresponding optimal initial and final solvent compositions. The MOSCED and UNIFAC models are not displayed because they did not select a change in solvent composition. As seen in the left subfigure of Figure 5.7, both the Jouyban-Acree and NRTL-SAC models predicted that increasing the isothermal operating temperature would increase crystal yield. However, the empirical model shows that the maximum crystal yield is relatively unaffected by the isothermal operating temperature.
As before none of the predictive models selected conditions that are able to match the empirical model’s actual yield. This is displayed in the right subfigure of Figure 5.7. At 0 °C, the Jouyban-Agree, and NRTL-SAC models had selected conditions that had yields that were 97.6% and 57.1% of the maximum. At 10 °C, the Jouyban-Agree, and NRTL-SAC models had selected conditions that had yields that were 95.3% and 62.7% of the maximum. At 20 °C, the Jouyban-Agree, and NRTL-SAC models had selected conditions that had yields that were 91.4% and 66.7% of the maximum. At 30 °C, the Jouyban-Agree, and NRTL-SAC models had selected conditions that had yields that were 80.7% and 67.0% of the maximum. It is interesting to note that the Jouyban-Agree model did better as the operating temperature decreased, and the NRTL-SAC model did slightly better as the temperature increased. In conclusion, the Jouyban-Agree model can be used successfully to find the optimal operating conditions for isothermal antisolvent crystallization.

*Figure 5.7:* Predicted (left) and actual (right) yields for isothermal antisolvent operation at 30 °C (black), 20 °C (blue), 10 °C (red), and 0 °C (green).
### Table 5.4: Optimal isothermal antisolvent operating conditions.

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Empirical</th>
<th>NRTL-SAC</th>
<th>Jouyban-Acree</th>
<th>UNIFAC</th>
<th>MOSCED</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>0 °C</strong></td>
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<tr>
<td>$w_0$</td>
<td>24.5</td>
<td>48.1</td>
<td>28.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$w_f$</td>
<td>86.1</td>
<td>86.6</td>
<td>84.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predicted Yield (g)</td>
<td>20.9</td>
<td>17.6</td>
<td>11.6</td>
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<td>12.0</td>
<td>20.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>10 °C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$w_0$</td>
<td>26.8</td>
<td>48.9</td>
<td>28.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$w_f$</td>
<td>86.4</td>
<td>87.4</td>
<td>81.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predicted Yield (g)</td>
<td>21.3</td>
<td>21.5</td>
<td>13.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actual Yield (g)</td>
<td>N/A</td>
<td>13.4</td>
<td>20.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>20 °C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$w_0$</td>
<td>30.1</td>
<td>50.2</td>
<td>28.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$w_f$</td>
<td>86.7</td>
<td>88.5</td>
<td>80.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predicted Yield (g)</td>
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<td>26.4</td>
<td>15.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actual Yield (g)</td>
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<td>19.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>30 °C</strong></td>
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<td></td>
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<tr>
<td>$w_0$</td>
<td>34.5</td>
<td>52.6</td>
<td>28.6</td>
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<tr>
<td>$w_f$</td>
<td>87.1</td>
<td>90.1</td>
<td>80.3</td>
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</tr>
<tr>
<td>Predicted Yield (g)</td>
<td>20.6</td>
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<td>18.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actual Yield (g)</td>
<td>N/A</td>
<td>13.8</td>
<td>16.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 5.4.4 Non-Isothermal Antisolvent

For non-isothermal antisolvent operation, four operating conditions were optimized, initial and final temperature, and initial and final solvent composition. The resultant optimal conditions are listed in Table 5.5. The subfigures of Figure 5.8 graphically show the optimal non-isothermal antisolvent yield for each solubility model as well as each model’s optimum initial and final solvent compositions tabulated in Table 5.5. As for cooling, each model selected initial and final temperatures that were at the upper and lower temperature constraints of 30 and 10 °C. Also, as for the isothermal antisolvent case, both the UNIFAC and MOSCED models did not change the solvent composition; the result was the same as for cooling. The predicted yields
were 39.2, 45.3, and 28.1 g for the empirical, NRTL-SAC, and Jouyban-A cree models. The actual yields for the Jouyban-A cree and NRTL-SAC model were 98.0% and 75.7% of the maximum. The MOSCED and UNIFAC models had actual yields that were 45.4% and 14.3% of the maximum. For non-isothermal antisolvent operation the Jouyban-A cree model did an excellent job at predicting optimal operating conditions.

**Figure 5.8:** Predicted (left) and actual (right) yields for non-isothermal antisolvent operation.

<table>
<thead>
<tr>
<th>Table 5.5: Optimal non-isothermal antisolvent operating conditions.</th>
</tr>
</thead>
<tbody>
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<tr>
<td>$w_0$</td>
</tr>
<tr>
<td>$w_f$</td>
</tr>
<tr>
<td>$T_0$ (°C)</td>
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<tr>
<td>$T_f$ (°C)</td>
</tr>
<tr>
<td>Predicted Yield (g)</td>
</tr>
<tr>
<td>Actual Yield (g)</td>
</tr>
</tbody>
</table>

**5.4.5 Comparison of Different Modes of Operation**

Figure 5.9 displays the optimal predicted and corresponding actual yields for each mode of crystallization operation. The best overall model was the Jouyban-A cree model which had actual yields closer to the empirical model for each crystallization mode of operation. The
The NRTL-SAC model gave acceptable results for each crystallization mode of operation. The UNIFAC model was only acceptable for the cooling mode of operation, and the MOSCED model gave extremely poor results for each crystallization mode of operation.

**Figure 5.9:** Comparison of predicted (left) and actual (right) yields for cooling (circles), evaporation (diamonds), isothermal antisolvent (filled-circle lines), and non-isothermal antisolvent (open-circle lines) modes of operation.

### 5.5 Conclusions

Each of the three crystallization methods has its advantages and disadvantages. Evaporation provides highest yields, but requires extensive energy to evaporate the solvent. Both cooling and antisolvent yields depend on temperature, starting composition, and the properties of the compound. In order to optimize the yield of a given crystallization process, extensive solubility data is needed. A temperature-composition solubility model can be used to determine the optimal operating conditions for each crystallization method. The use of predictive solubility models can be used to predict optimal operating conditions for each crystallization method, but their results are inconsistent. The best performing models were the Jouyban-Acree and NRTL-SAC models, while the MOSCED and UNIFAC models performed poorly. The use of these
models would be extremely advantageous because this would lessen the need for the extensive experimental solubility data required to create empirical solubility models. More systems and solvent-pairs need to be tested to see if there is a specific model that consistently outperforms the others. Then, those predictive solubility models may be used to screen solvent-antisolvent pairs, finding ones that will maximize the yield of the process.

5.6 Nomenclature

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Value</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$a_i$</td>
<td>Empirical Solubility Model Coefficients ($i=1:5$)</td>
<td>Table 5.2</td>
<td>g/kg Solvents</td>
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<tr>
<td>$a_{mn}$</td>
<td>UNIFAC Interaction Parameter between Groups $m$ and $n$</td>
<td></td>
<td>K$^{-1}$</td>
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<tr>
<td>$aa$</td>
<td>MOSCED Parameter</td>
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<td>$C$</td>
<td>Solution Concentration</td>
<td>kg/kg solvent</td>
<td></td>
</tr>
<tr>
<td>$C_s$</td>
<td>Equilibrium Solution Concentration</td>
<td>kg/kg solvent</td>
<td></td>
</tr>
<tr>
<td>$C_i$</td>
<td>Initial Solution Concentration</td>
<td>kg/kg solvent</td>
<td></td>
</tr>
<tr>
<td>$C_0, C_i, C_2$</td>
<td>Jouyban-Acree Constants</td>
<td>724.21, 485.17, 194.41</td>
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</tr>
<tr>
<td>$d_{ii}$</td>
<td>MOSCED Parameter</td>
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<td>Solute-Free Volume Fraction of Solvent</td>
<td></td>
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</tr>
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<td>$f_3$</td>
<td>Solute-Free Volume Fraction of Antisolvent</td>
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<td>Mass of Solvent</td>
<td>kg</td>
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<td>MOSCED Induction Parameter</td>
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<td>$Q_k$</td>
<td>UNIFAC Volume Structural Parameter of Group $k$</td>
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<td>POL</td>
<td>MOSCED Parameter</td>
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<td>Total Segment Number of Component $i$</td>
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<td>Dimensionless</td>
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<tr>
<td>$r_{i,U}$</td>
<td>UNIFAC Volume Structural Parameter of Component $i$</td>
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<td>Dimensionless</td>
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<tr>
<td>$r_{m,i}$</td>
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<td>$R_k$</td>
<td>UNIFAC Area Structural Parameter</td>
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<td>Dimensionless</td>
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<td>$T$</td>
<td>Temperature</td>
<td>K</td>
<td></td>
</tr>
<tr>
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<td>Initial Temperature</td>
<td>K</td>
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</tr>
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<td>$T_f$</td>
<td>Final Temperature</td>
<td>K</td>
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<tr>
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<td>Description</td>
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<td>$Y$</td>
<td>Crystal Yield</td>
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<td>$\alpha$</td>
<td>NRTL Nonrandomness Parameter</td>
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<td>$\beta$</td>
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5.7 References


6. A THERMODYNAMIC MODELING APPROACH FOR THE NON-ISOTHERMAL ANTISOLVENT CRYSTALLIZATION OF A SOLUTE WITH WEAK TEMPERATURE DEPENDENT SOLUBILITY*

6.1 Introduction

Crystallization is a chemical engineering unit operation utilized in several industries for the production of fertilizers, pharmaceuticals, and fine chemicals. Crystallization is the result of supersaturation changes which are the result of changes in solubility equilibrium. Several ways to change equilibrium solubility include: cooling, evaporation, and addition of an antisolvent. This chapter investigates the use of an antisolvent to generate supersaturation. Antisolvent crystallization has been modeled for many systems [Woo et al., 2006; Zhou et al., 2006; Nowee et al., 2008a/b; Sheikhzadeh et al., 2008; Trifkovic et al., 2008], and cooling has been combined with antisolvent crystallization for several systems [Nagy et al., 2008; Lindenberg et al., 2009]. The organic systems, paracetamol and acetyl-salicylic acid, used in the aforementioned two papers have solubilities that change significantly with temperature. For these cases, it is beneficial to incorporate cooling with antisolvent crystallization because it can significantly increase crystallization yield. The question is then, for crystallizing systems where solubility is weakly dependent on temperature, can manipulating the temperature be beneficial?

It is hypothesized that, for systems with solubility weakly dependent on temperature, it is possible to impart significantly improved control over both the distribution mean size and coefficient of variation by manipulating temperature together with antisolvent feed rate. This strategy allows a second degree of freedom (cooling) to be used to control the crystallization process. This degree of freedom would typically be neglected for systems with weakly

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temperature dependent systems. However, the growth kinetics may carry temperature dependence which would lead to size distribution changes. For these systems it is the kinetics and not the equilibrium which would be neglected. This chapter incorporates these temperature dependent kinetics and quantifies their contribution to the product mean size and coefficient of variation.

Specifically, this chapter tests this hypothesis through investigations in the non-isothermal antisolvent crystallization of sodium chloride (NaCl), the solubility of which is practically independent of temperature. A composition-temperature dependent crystallization model is developed for the non-isothermal crystallization of sodium chloride. This is comprised of a population balance model with thermodynamic nucleation and growth kinetic equations. This model is solved and compared to preexisting isothermal sodium chloride crystallization models [Nowee et al., 2008a/b]. Lastly, the developed model is used to determine two optimal profiles to control the particle size to two specified values while minimizing the coefficient of variation.

6.2 Experimental Procedure

6.2.1 Experimental Setup

In order to validate the model and evaluate the effect of temperature on sodium chloride antisolvent crystallization, nine experiments at different temperature (10 °C, 20 °C, and 30 °C) and antisolvent feed rate (0.8 mL/min, 1.5 mL/min, and 3.0 mL/min) combinations were performed.

The experiments were performed using the following experimental procedure. First, an initial solution containing 34.0 g of 99.5% pure NaCl (Sigma, United States) and 100.0 g of
deionized H$_2$O was placed in a 1000 mL Erlenmeyer flask. The flask was then immersed into a larger glass reservoir containing water. Stirring of the solution was done via a magnetic stirrer bar placed within the Erlenmeyer flask. The temperature of the flask was controlled via a refrigerated circulator connected to cooling coils inside the glass reservoir. The antisolvent, 190 proof ethanol (PHARMCOAAPER, United States), was added via a peristaltic pump (Cole Palmer, United States) that was calibrated prior to each experiment. The solution was stirred before the run was started for at least 30 minutes to allow the NaCl to completely dissolve.

During the experimental run, 8 mL samples of crystals in suspension were withdrawn with the aid of a syringe at regular intervals and were then vacuum filtered using 5 µm filter paper. The filter paper sample was set aside to dry for at least 24 hours before further examination.

6.2.2 Crystal Size Measurement

Light microscopy was used to measure the size of the crystals. A stereo light microscope (Wild-Heerbrugg, Switzerland) was used which connected to a digital camera (Amscope Model MD500, United States). Several images were taken with the camera for each sample and analyzed using the AmScope software (iScope, United States). The software allows for the measurement of the length or area of particular crystals in units of pixels. Using a supplied calibration slide, these lengths and areas can be converted to a micron length scale. For the 2.5x magnification objective the conversion factor is 0.78 microns/pixel. The number of crystals measured varied for each sample and was fixed by a stabilization criterion of ±2.5% of the mean. Figure 6.1 shows how the mean size varies with the number of crystals measured. Both horizontal lines represent the final mean size ±2.5%. As the number of crystals increases the
accuracy of the mean size estimation improves. This is supported by the Central Limit Theorem that states as the size of the random sample increases, the sample mean will converge to the population mean.

![Example mean size convergence of a measured data sample.](image)

**Figure 6.1:** Example mean size convergence of a measured data sample.

### 6.2.3 Experimental Crystal Size Distribution

In order to use the experimental data for parameter estimation of a proposed model, two characteristics of the distribution are needed; one describing the mean size, and one describing the variance of the distribution. The data was assumed to be one of two distributions, either normal or log-normal. The probability density functions for both normal and log-normal distributions are shown below:

\[
pdf = \frac{1}{\sqrt{2\pi s^2}} \exp\left(-\frac{(x - \mu)^2}{2s^2}\right) \tag{6.1}
\]

\[
pdf_{LN} = \frac{1}{x\sqrt{2\pi s_{LN}^2}} \exp\left(-\frac{(\ln x - \mu_{LN})^2}{2s_{LN}^2}\right) \tag{6.2}
\]
where $\mu$ and $s^2$ are the mean and sample variance of the normal distribution, and $\mu_{LN}$ and $s^2_{LN}$ are the logarithmic sample mean and logarithmic sample variance of the log-normal distribution.

The logarithmic mean, logarithmic variance, linear mean, and linear variance can be calculated from each other using the following relationships:

$$\mu = \exp(\mu_{LN} + 0.5s^2_{LN})$$

$$s^2 = [\exp(s^2_{LN} + 2\mu_{LN})][\exp(s^2_{LN}) - 1]$$

$$\mu_{LN} = \ln \mu - 0.5 \ln \left(1 + \frac{s^2_{LN}}{\mu^2_{LN}}\right)$$

$$s^2_{LN} = \ln \left(1 + \frac{s^2_{LN}}{\mu^2_{LN}}\right)$$

**Table 6.1:** Number of experimental samples that passed normality (N) or log-normality (LN) test.

<table>
<thead>
<tr>
<th></th>
<th>0.8 mL/min</th>
<th>1.5 mL/min</th>
<th>3.0 mL/min</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>LN</td>
<td>N</td>
<td>LN</td>
</tr>
<tr>
<td>10 °C</td>
<td>3/9</td>
<td>8/9</td>
<td>3/9</td>
<td>7/9</td>
</tr>
<tr>
<td>20 °C</td>
<td>2/9</td>
<td>7/9</td>
<td>3/9</td>
<td>7/9</td>
</tr>
<tr>
<td>Overall</td>
<td>7/27</td>
<td>19/27</td>
<td>8/27</td>
<td>19/27</td>
</tr>
</tbody>
</table>

The Shapiro-Wilk normality test with an alpha value of 0.05 was used to test the data for normality or log-normality. The data passed the Shapiro-Wilk log-normality test 61% of the time which was more than the normality test pass-rate of 27% so the data was modeled as a log-normal distribution with a corresponding log-normal mean and variance. Table 6.1 shows the number of samples from each run that passed either the normality (N) or log-normality (LN) test. One unique feature of the log-normal distribution is that the linear mean, linear median, and linear mode are not equal to each other unlike the normal distribution. For a log-normal distribution the mean is larger than the median which is larger than the mode. Figure 6.2 shows
the log-normal fit for an example data sample. The histogram columns represent the experimental data sorted into 25 micron bins while the grey dashed line represents the smoothed log-normal approximation.

![Diagram](image)

**Figure 6.2:** Example smoothed log-normal fit to experimental data for the 10 °C 0.8 mL/min experimental condition taken at 2 hours.

### 6.3 Model Development

#### 6.3.1 Population, Mass, and Energy Balances

The typical method of modeling crystallization processes is to use population balances, enabling the tracking of a distribution of particles as they grow in suspension. Traditionally, a complete population balance crystallization model is comprised of a population balance with corresponding crystallization kinetics, mass balance, and solubility model. The population balance considered here is for a crystallization system with size-independent crystal growth, and with negligible attrition and agglomeration. The population balance is described by Equation 6.7:

$$\frac{\partial n(L, t)}{\partial t} + \frac{n(L, t)}{V} \frac{dV}{dt} + G \frac{\partial n(L, t)}{\partial L} - B = 0$$  \hspace{1cm} (6.7)
where \( n(L,t) \) is the crystal density (no. of particles/m\(^4\)), \( V \) is the volume (m\(^3\)), \( G \) is the growth rate (m/s), and \( B \) is the nucleation rate (no. of particles/ s m\(^4\)).

The population balance was solved using the method of lines discretization technique. This technique converts the partial differential equation into a system of ordinary differential equations with corresponding boundary and initial conditions shown in Equation Set 6.8:

\[
\frac{dn_1}{dt} = B - G \frac{n_1}{2\delta_1} - \frac{n_1 dV}{V dt}
\]

\[
\frac{dn_i}{dt} = G \left( \frac{n_{i-1}}{2\delta_{i-1}} - \frac{n_i}{2\delta_i} \right) - \frac{n_i dV}{V dt} \quad i = 2..\zeta
\]

\[
n_i(t = 0) = 0 \quad i = 1..\zeta
\]

\[
n_1(L_0, t) = 0
\]

\[
n_\zeta(L_\zeta, t) = 0
\]

where \( \zeta \) is the number of discretization intervals, and \( \delta \) is the length of each discretization interval given by:

\[
\delta_i = L_i - L_{i-1} \quad i = 1...\zeta
\]

The individual discretization lengths are chosen using a geometric series:

\[
L_i = L_0 b^i \quad i = 0..\zeta
\]

\[
b = \left( \frac{L_{\text{max}}}{L_0} \right)^{\frac{1}{\zeta}}
\]

where \( L_0 \) is the nucleate size and \( L_{\text{max}} \) is the maximum crystal size used in the discretization.

The mass balance of the solute in solution for antisolvent crystallization is:

\[
\frac{d(Cm_s)}{dt} = -3\rho_c k_v V \int_0^\infty GL^2 n(L, t) dL
\]

where \( C \) is the solute concentration (kg solute/kg solvents), \( k_v \) is the volumetric shape factor of the crystal, \( \rho_c \) is the solid density of the crystal, and \( m_s \) is the mass of the solvent. For sodium
chloride: \( k_v \) and \( \rho_c \) are 1, and 2165 kg/m\(^3\) respectively. No energy balance was explicitly specified in the crystallization model. It is assumed that the control system maintains the reactor temperature at the set-point specified.

### 6.3.2 Solubility Model

A solubility model is necessary for a crystallization model because it is used to calculate the equilibrium concentration needed to determine the absolute and relative supersaturation used in the kinetic equations. The solubility data for sodium chloride in binary ethanol water mixtures in Galleguillos et al. [2003] was fit to a quadratic polynomial with an \( R^2 \) value of 0.9905.

\[
C^* = \begin{cases} 
 c_1 w^2 + c_2 w + c_3 & w \leq 0.849 \\
 0 & w > 0.849 
\end{cases}
\]  

(6.12)

where \( c_1=20.678 \), \( c_2=-59.294 \), and \( c_3=35.43 \) over solute-free ethanol mass fractions less than 0.849. Solute-free ethanol mass fractions greater than 0.849 were set to an equilibrium solubility of zero. There is no temperature dependence on the solubility of sodium chloride because it is weakly temperature dependent over the range of temperatures used in our experiments. The percent change in solubility for NaCl in water of a 20 degree temperature change from 30 °C to 10 °C is 1.1% [Mullin, 2001].

### 6.3.3 Nucleation Modeling

The nucleation rate is modeled after the one used by Zhou et al. [2006]:

\[
B = b_0 \exp \left( -b_1 \frac{\log^3 \left( \frac{\rho_c}{C^* \rho_s} \right)}{\log^2 (S)} \right)
\]  

(6.13)

where \( b_0 \) and \( b_1 \) are nucleation parameters. \( B \) is the nucleation rate defined earlier, \( \rho_c \) is the crystal density of sodium chloride (kg/m\(^3\)), \( C^* \) is the equilibrium concentration (kg NaCl/kg
solvents), $\rho_s$ is the suspension density (kg/m$^3$), and $S$ is the relative supersaturation. For the nucleation kinetic, there is no explicit temperature or antisolvent composition dependences. A nucleation model was tried that varied $b_1$ with temperature, but the mean size results were not as good as the nucleation model shown above in Equation 6.13.

6.3.4 Growth Modeling

6.3.4.1 Thermodynamic Growth Modeling

Potassium chloride (KCl) is reported to be mass transfer limited, so NaCl is assumed to behave similarly. Thus, the growth kinetic can be represented thermodynamically utilizing a mass transfer coefficient shown in Equation 6.14:

$$G = k_d \Delta C$$  \hspace{1cm} (6.14)

where $\Delta C$ is absolute supersaturation and $k_d$ is a mass transfer coefficient estimated using the following mass transfer correlation [Perry, 1997]:

$$k_d = \frac{D_{AB}}{L} \left( 2 + 0.8 \left( \frac{\bar{\varepsilon} L \rho_s^3}{\eta_s^3} \right)^{1/5} Sc^{1/3} \right)$$  \hspace{1cm} (6.15)

where $Sc$ is the Schmidt number, $\bar{L}$ is a median crystal size (m), $\bar{\varepsilon}$ is the mean specific power input, and $\rho_s$ is the density of the solution (kg/m$^3$), and $D_{AB}$ is a diffusion coefficient (m$^2$/s). For many compounds the Stokes-Einstein equation can be used to estimate the diffusion coefficient. However, since sodium chloride produces an electrolyte solution, an ionic-based diffusion coefficient is preferred. A semi-empirical equation derived by Gordon [Poling et al., 1988], that estimates the diffusivity of sodium chloride in a saturated water-ethanol solution is shown in Equation 6.16:
\[ D_{\text{NaCl},1,3} = D_{\text{NaCl},1,3}^0 \left( \frac{1}{\rho_{1,3} \bar{V}_{1,3}} \right) \left( \frac{\eta_{1,3}}{\eta_s} \right) \left\{ 1 + m \left[ \frac{\partial (\ln \gamma_{x\pm})}{\partial m} \right] \right\} \]  

(6.16)

where \( D_{\text{NaCl},1,3} \) is the diffusivity of NaCl in a saturated water-ethanol solution (m\(^2\)/s), \( D_{\text{NaCl},1,3}^0 \) is the infinite-dilution diffusivity of the solute-free solution (m\(^2\)/s), \( \rho_{1,3} \) is the molar density of the solute-free solution (mol/m\(^3\)), \( \eta_{1,3} \) is the viscosity of the solute-free solution (Pa s), \( \eta_s \) is the viscosity of the suspension (Pa s), \( \bar{V}_{1,3} \) is the partial molar volume of the solute-free solution (m\(^3\)/mol), \( m \) is the molarity of the suspension (mol/kg), and \( \gamma_{x\pm} \) is a molality-based mean activity coefficient. The infinite-dilution diffusivity of the mixture is calculated using the mixing rule of Perkins-Geankoplis [Perkins and Geankoplis, 1969]:

\[ D_{\text{NaCl},1,3}^0 = \frac{x_1 D_{\text{NaCl},1}^0 \eta_1^{0.8} + x_3 D_{\text{NaCl},3}^0 \eta_3^{0.8}}{\eta_{1,3}^{0.8}} \]  

(6.17)

where \( x_1 \) is the mole fraction of water, \( x_3 \) is the mole fraction of ethanol, \( \eta_1 \) is the viscosity of water (Pa s), \( \eta_3 \) is the viscosity of ethanol (Pa s), \( D_{\text{NaCl},1}^0 \) is the infinite-dilution diffusivity of NaCl in water (m\(^2\)/s), and \( D_{\text{NaCl},3}^0 \) is the infinite-dilution diffusivity of NaCl in ethanol (m\(^2\)/s).

The infinite-dilution diffusivities in pure water and ethanol are calculated by the Nernst-Haskell equation:

\[ D_{\text{NaCl}}^0 = 17.862 \times 10^{-10} \left( \frac{\lambda_{\text{Na}^+} \lambda_{\text{Cl}^-}}{\lambda_{\text{Na}^+} + \lambda_{\text{Cl}^-}} \right) T \]  

(6.18)

where \( T \) is temperature (K), and \( \lambda_{\text{Na}^+} \) and \( \lambda_{\text{Cl}^-} \) are limiting ionic conductances found in Harned and Owen [1958].

To calculate the mean activity coefficient the Pitzer-Simonson model was used [Pitzer and Simonson, 1986]. This model is preferred over the original Pitzer model [Pitzer, 1973] when the solute has high but finite solubility in the solvent. For most crystallization systems the solute will be highly soluble in the solvent at the beginning of the run, thus this is an ideal model to use.
for electrolyte solutions. The Pitzer-Simonson model uses a molality-based mean activity coefficient that is comprised of short-range and long-range force terms:

\[
\ln \gamma_{X_\pm} = \ln \gamma_{X_\pm}^S + \ln \gamma_{X_\pm}^{DH} \tag{6.19}
\]

The short-range and long-range interactions can be calculated using Equations 6.20 and 6.23 for a mixture of two neutral series with a strong 1:1 MX electrolyte such as NaCl. In particular, the short-range interactions can be calculated using Equation 6.20:

\[
\ln \gamma_{X_\pm}^S = \frac{x_1 x_3}{f^2} \left\{ (1 - f^2)w_{13} + 2(x_1 - x_3) \frac{1 - f^2}{f} u_{13} + [(1 - 2x_i)f^2 - 1]Z_{13MX} \right\} \\
+ \frac{f^2 - 1}{f} (x_1 W_{1MX} + x_3 W_{3MX}) \\
+ \frac{x_1}{3f^2} [f^3 (2 - 2x_1 + x_i) + x_1 f^2 (3x_1 + x_3) - 2x_3]U_{1MX} \\
+ \frac{x_3}{3f^2} [f^3 (2 - 2x_3 + x_i) + x_1 f^2 (3x_3 + x_1) - 2x_1]U_{3MX} \tag{6.20}
\]

\[
f = 1 - x_i \tag{6.21}
\]

\[
x_i = 1 - x_1 - x_3 \tag{6.22}
\]

where \(\gamma_{X_\pm}^S\) is the short-range interaction activity coefficient, \(x_i\) is the mole fraction of solute, \(f\) is the mole fraction of solvents, \(u_{13}\) and \(w_{13}\) are parameters for the binary solvent system, \(W_{innx}\) and \(U_{innx}\) are parameters for the solvent \(i\) and MX electrolyte, and \(Z_{13MX}\) is a triple interaction parameter. Values for \(u_{13}, w_{13}, W_{innx}, U_{innx}\), and \(Z_{13MX}\) at various temperatures for the water-ethanol-NaCl ternary system are tabulated in Lopes et al. [2001].
The long-range interactions can be calculated using Equation 6.23:

\[
\ln \gamma_{x \pm}^{\text{PH}} = -A_x \left[ \frac{2}{\rho} \ln \left( 1 + \rho \sqrt{I_x} \right) + \frac{(1 - 2I_x)\sqrt{I_x}}{1 + \rho \sqrt{I_x}} \right] + x_x B_{MX} g \\
- x_x x_M B_{MX} \left[ \frac{g}{2I_x} + \left( 1 - \frac{1}{2I_x} \right) \exp \left( -\alpha \sqrt{I_x} \right) \right]
\]  

(6.23)

where \( \gamma_{x \pm}^{\text{PH}} \) is the long-range interaction activity coefficient, \( A_x \) is a mole-fraction based Debye-Hückel coefficient for the osmotic function, \( B_{MX} \) is a long-range interaction parameter, \( \rho \) is a parameter equivalent to the distance of closest approach, \( a \), of the Debye-Hückel theory, \( \alpha \) is a parameter equal to 13 [Pitzer and Simonson, 1986], and \( I_x \) is the mole-fraction-based ionic strength of the solution. \( A_x, \rho, I_x, \) and \( g \) are defined using Equations 6.24 [Pitzer, 1991], 6.25 [Pitzer, 1991], 6.26 [Lopes et al., 2001], and 6.27 [Lopes et al., 2001]:

\[
A_x = \frac{1}{3} \sqrt{\frac{2\pi N_a \rho_s}{M_{mol}}} \left( \frac{e^2}{D_{le} k_b T} \right)
\]  

(6.24)

\[
\rho = 2150 \sqrt{\frac{\rho_s}{D_{le} T}}
\]  

(6.25)

\[
I_x = x_M + x_x
\]  

(6.26)

\[
g = \frac{2\left[ 1 - (1 + \alpha \sqrt{I_x}) \exp \left( -\alpha \sqrt{I_x} \right) \right]}{\alpha \sqrt{I_x}^2}
\]  

(6.27)

where \( \rho_s \) is the density of the suspension defined earlier, \( D_{le} \) is the dielectric constant of the solution mixture, \( e \) is the electronic charge, \( k_b \) is Boltzmann’s constant, \( N_a \) is Avogadro’s number, \( M_{mol} \) is the average molecular weight of the solvent (mol/kg), and \( x_M \) and \( x_x \) are the mole fractions of the cation and anion of solute MX.

The molality-based activity coefficient can be converted to a molar-based activity coefficient using Equation 6.28:
\[ \gamma_{X\pm} = \gamma (1 + 0.002M_{\text{mol}}m) \quad (6.28) \]

The molality of the solution can be calculated using Equation 6.29:

\[ m = \frac{1000w_2}{MW_2} \frac{1}{w_1 + w_3} \quad (6.29) \]

To be able to use this model several material properties are needed. First, the dielectric constant needs to be known for various solution compositions as well as for various temperatures. Second, the partial molar volume needs to be known. Third, the viscosity of both the solute-free solution and the suspension need to be known. Fourth, the density of the suspension needs to be known. Lastly, if the individual parameters for the Pitzer-Simonson model are not known, further experiments will be needed to calculate them. This method requires an enormous amount of experimental data to be known or determined. In addition, there is no guarantee that this will accurately predict crystallization behavior. In fact, when this growth model was combined with the previous nucleation model the predicted crystallization mean size results were very poor. To be able to use this thermodynamic growth kinetic model, some of the model parameters would need to be re-estimated. Since the thermodynamic growth model has a very large parameter set it would be difficult to determine which specific parameters should be adjusted. Due to these downsides, an empirical model instead was used for the growth kinetic relationship.

**6.3.4.2 Empirical Growth Modeling**

The empirical growth model formulation is shown in Equation 6.30:

\[ G = \left[ g_0 - g_1 (1 + w)^{g_2} \right] g_3 \exp\left( -\frac{g_4}{RT} \right) \Delta C^{g_5 + g_6 w} \quad (6.30) \]
where $g_0, g_1, g_2, g_3, g_4, g_5,$ and $g_6$ are adjustable growth parameters. $G$ is the crystal growth rate defined earlier, $w$ is the solute-free mass percent of antisolvent (ethanol) in the solution, $R$ is the ideal gas constant, $T$ is temperature (K), and $\Delta C$ is absolute supersaturation (kg/m$^3$). The growth kinetic is explicitly dependent on both temperature and antisolvent composition. The parameter $g_0$ represents the default growth rate, and parameters $g_1$ and $g_2$ represent the reduction in growth rate due to antisolvent addition. Parameter $g_3$ represents the growth rate temperature dependence, $g_4$ is the base supersaturation growth rate exponent, and $g_5$ is the dependence of the growth rate exponent on antisolvent addition. The growth kinetics were modeled this way because it was shown that the growth rate of potassium chloride in aqueous ethanol mixtures decreased sharply as the percentage of ethanol increased [Lopes and Farelo, 2006]. Thus, it is hypothesized that crystal growth approaches zero at a certain critical ethanol composition for the similar sodium chloride compound.

### 6.4 Kinetic Parameter Estimation

The kinetic parameters of the model $[b_0, b_1, g_0, g_1, g_2, g_3, g_4, g_5, g_6]$ were estimated using the gPROMS entity gEST which uses a maximum likelihood approach. Each of the nine experiments was used for parameter estimation. Since the crystallization data was log-normal, the data’s log-normal mean and log-normal standard deviation were used to represent the data’s crystal size distribution. Since the crystal size measurement technique used has a higher probability of choosing the larger crystals in the image to measure, the Sauter mean size ($D_{32}$) was used as the representative mean size, and an area based coefficient of variation was used. Coefficient of variance (COV) is useful because it can be calculated from the moments generated from the population balance.
where $\mu_4$, $\mu_3$, and $\mu_2$ are the fourth, third, and second moments of the crystal distribution. The coefficient of variation can be expressed in terms of the log-normal variance in the following way:

$$COV = \sqrt{\left(\frac{\mu_4\mu_2}{\mu_3^2} - 1\right)}$$  \hspace{1cm} (6.31)

This allows for the comparison between the experimental data and the model-generated data for the parameter estimation solver. The generated optimum set of parameters, as well as their confidence intervals, and $t$-statistics are listed in Table 6.2. Although, this model had the best objective function value of 505.2, every parameter but $g_4$ had $t$-statistics smaller than the critical value which suggests that the model is over-parameterized. Parameters that have $t$-statistics smaller than the critical value suggest that the parameter is not statistically different from zero.

**Table 6.2:** Model nucleation and growth kinetic parameters with corresponding confidence intervals.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>95% Confidence Interval (±)</th>
<th>90% Confidence Interval (±)</th>
<th>99% Confidence Interval (±)</th>
<th>t-statistic</th>
<th>$t_{c,a=0.10}$=1.656</th>
<th>$t_{c,a=0.05}$=1.977</th>
<th>$t_{c,a=0.01}$=2.852</th>
</tr>
</thead>
<tbody>
<tr>
<td>$(b_0 \cdot 10^7)$</td>
<td>0.1182</td>
<td>0.1555</td>
<td>0.1303</td>
<td>0.2054</td>
<td><strong>0.7598</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$(b_1 \cdot 10^4)$</td>
<td>8.172</td>
<td>31.76</td>
<td>26.60</td>
<td>41.96</td>
<td><strong>0.2573</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$g_0$</td>
<td>0.5557</td>
<td>2.566 x $10^5$</td>
<td>2.149 x $10^5$</td>
<td>3.390 x $10^5$</td>
<td><strong>2.165 x 10^{-06}</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$g_1$</td>
<td>0.001705</td>
<td>803.6</td>
<td>673.0</td>
<td>1062</td>
<td><strong>2.121 x 10^{-06}</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$g_2$</td>
<td>10.04</td>
<td>144</td>
<td>120.6</td>
<td>190.2</td>
<td><strong>0.06971</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$g_3$</td>
<td>1.139</td>
<td>4.709 x $10^5$</td>
<td>3.944 x $10^5$</td>
<td>6.220 x $10^5$</td>
<td><strong>2.418 x 10^{-06}</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$g_4$</td>
<td>24460</td>
<td>5292</td>
<td>4432</td>
<td>6990</td>
<td>4.623</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$g_5$</td>
<td>0.8683</td>
<td>1.903</td>
<td>1.594</td>
<td>2.514</td>
<td><strong>0.4562</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$g_6$</td>
<td>0.7169</td>
<td>1.550</td>
<td>1.550</td>
<td>2.047</td>
<td><strong>0.4626</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Bold values are $t$-statistics that are less than the 95% critical $t$-statistic.*
Table 6.3: Different non-isothermal nucleation and growth kinetic model formulations, number of adjustable parameters, objective function values, and statistical validity.

<table>
<thead>
<tr>
<th>Model</th>
<th>Model Formulation</th>
<th>Number of Adjustable Parameters</th>
<th>Objective Function Value</th>
<th>All Parameters have 95% t-statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>$B = b_0 \exp \left( -b_1 \frac{\log^3 \left( \frac{\rho_c}{C_s \rho_s} \right)}{\log^2 (S)} \right)$</td>
<td>6</td>
<td>505.8</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>$G = [1 - 0.001(1 + w)]^{g_2} \exp \left( -\frac{g_4}{RT} \right) \Delta C^{g_5 + g_6 w}$</td>
<td>6</td>
<td>505.8</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>$B = b_0 \exp \left( -0.0001 \frac{\log^3 \left( \frac{\rho_c}{C_s \rho_s} \right)}{\log^2 (S)} \right)$</td>
<td>5</td>
<td>506.0</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>$G = [1 - 0.001(1 + w)]^{g_2} \exp \left( -\frac{g_4}{RT} \right) \Delta C^{g_5 + g_6 w}$</td>
<td>5</td>
<td>506.1</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>$B = b_0 \exp \left( -0.0001 \frac{\log^3 \left( \frac{\rho_c}{C_s \rho_s} \right)}{\log^2 (S)} \right)$</td>
<td>4</td>
<td>506.1</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>$G = [1 - 0.001(1 + w)]^{g_2} \exp \left( -\frac{g_4}{RT} \right) \Delta C^{1 + g_6 w}$</td>
<td>4</td>
<td>506.1</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>$B = b_0 \exp \left( -0.0001 \frac{\log^3 \left( \frac{\rho_c}{C_s \rho_s} \right)}{\log^2 (S)} \right)$</td>
<td>3</td>
<td>513.2</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>$G = [1 - 0.001(1 + w)]^{g_2} \exp \left( -\frac{g_4}{RT} \right) \Delta C$</td>
<td>3</td>
<td>513.2</td>
<td>Yes</td>
</tr>
</tbody>
</table>

6.5 Model Refinement

Since the model was believed to be over-parameterized, the model was reduced from a 9 adjustable parameter model to four different models with numbers of adjustable parameters varying from 3 to 6. For each of the models, the previous parameters $g_0$, $g_1$, and $g_3$ were set to 1, 0.001, and 1 respectively. The resultant 6 parameter model, Model 2, had an objective value of 505.75 with more reasonable confidence intervals on the parameters. However, since $b_1$ still had a large confidence interval another nucleation model was considered which set $b_1$ to a fixed...
value. This 5 parameter model, Model 3, had an objective value of 506. Another growth model was considered which set $g_5$ to a fixed value of 1. Since potassium chloride growth is reported to be mass-transfer limited, it is expected that the supersaturation exponent also should be near 1 for sodium chloride. This model, Model 4, has a slightly higher objective value of 506.1, but now all of the parameters have good confidence interval limits. Another model, Model 5, was tried that set $g_6$ to zero. This model had an objective value of 513.2, and was not as good as Model 4.

### Table 6.4: Nucleation and growth kinetic parameters with corresponding confidence intervals for models 2-5.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Model Number</th>
<th>Parameter Value</th>
<th>95% Confidence Interval (±)</th>
<th>90% Confidence Interval (±)</th>
<th>99% Confidence Interval (±)</th>
<th>t-Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>$(b_0 \cdot 10^7)$</td>
<td>2</td>
<td>11.43</td>
<td>5.138</td>
<td>6.135</td>
<td>8.103</td>
<td><strong>1.863</strong></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>11.72</td>
<td>5.053</td>
<td>6.034</td>
<td>7.967</td>
<td><strong>1.942</strong></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>11.78</td>
<td>3.096</td>
<td>3.697</td>
<td>4.881</td>
<td>3.186</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>11.47</td>
<td>3.065</td>
<td>3.658</td>
<td>4.831</td>
<td>3.134</td>
</tr>
<tr>
<td>$(b_1 \cdot 10^4)$</td>
<td>2</td>
<td>11.96</td>
<td>0.6942</td>
<td>0.8289</td>
<td>1.095</td>
<td><strong>14.42</strong></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>12.05</td>
<td>0.6920</td>
<td>0.8265</td>
<td>1.091</td>
<td><strong>14.58</strong></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>12.09</td>
<td>0.6706</td>
<td>0.8007</td>
<td>1.057</td>
<td><strong>15.1</strong></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>13.15</td>
<td>0.6272</td>
<td>0.7485</td>
<td>0.9886</td>
<td><strong>17.57</strong></td>
</tr>
<tr>
<td>$g_2$</td>
<td>2</td>
<td>24605</td>
<td>4386</td>
<td>5237</td>
<td>6916</td>
<td><strong>4.699</strong></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>24538</td>
<td>3149</td>
<td>3760</td>
<td>4965</td>
<td><strong>6.526</strong></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>24253</td>
<td>593.5</td>
<td>708.7</td>
<td>935.8</td>
<td><strong>34.22</strong></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>24742</td>
<td>569.2</td>
<td>679.3</td>
<td>897.1</td>
<td><strong>36.43</strong></td>
</tr>
<tr>
<td>$g_5$</td>
<td>2</td>
<td>0.9901</td>
<td>0.4344</td>
<td>0.5187</td>
<td>0.6850</td>
<td><strong>1.909</strong></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.9752</td>
<td>0.2159</td>
<td>0.2577</td>
<td>0.3403</td>
<td><strong>3.784</strong></td>
</tr>
<tr>
<td>$g_6$</td>
<td>2</td>
<td>0.7274</td>
<td>0.1984</td>
<td>0.2369</td>
<td>0.3128</td>
<td><strong>3.071</strong></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.7521</td>
<td>0.1651</td>
<td>0.1971</td>
<td>0.2602</td>
<td><strong>3.816</strong></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0.7385</td>
<td>0.1614</td>
<td>0.1928</td>
<td>0.2545</td>
<td><strong>3.831</strong></td>
</tr>
</tbody>
</table>

Bold values are t-statistics that are less than the 95% critical t-statistic.

Table 6.3 lists the parameters for each model as well as their confidence intervals and t-statistics. Table 6.4 lists the model, its number of adjustable parameters, the objective function
value, and whether all of the parameters had t-statistics greater than the 95% t-statistic. Only Models 4 and 5 had parameters with sufficiently large t-statistics to make each parameter statistically different from zero. Since Model 4 had a lower objective function value than Model 5; it was chosen as the best model formulation to continue working with.

\[
\Sigma = \begin{bmatrix}
0.035 & -0.0237 & -64.6 & 0.0138 \\
-0.0237 & 0.164 & 30.8 & -0.0103 \\
-64.6 & 30.8 & 1.29 \times 10^5 & -29.3 \\
0.0138 & -0.0103 & -29.3 & 0.00951
\end{bmatrix}
\]

\[
\rho = \begin{bmatrix}
1 & -0.312 & -0.964 & 0.759 \\
-0.312 & 1 & 0.212 & -0.262 \\
-0.964 & 0.212 & 1 & -0.838 \\
0.759 & -0.262 & -0.838 & 1
\end{bmatrix}
\]

The variance-covariance and correlation matrix for Model 4 are shown above. The variances and covariances related to parameter \( b_0 \) are scaled in the same manner as shown in Table 6.4. The correlation matrix shows that several parameter pairs are correlated. Parameter pairs \( b_0-g_4 \) and \( g_4-g_6 \) are highly negatively correlated, and parameter pair \( b_0-g_6 \) is highly positively correlated. Thus, if \( b_0 \) increases, \( g_4 \) will decrease and \( g_6 \) will increase. Likewise, if \( g_4 \) increases \( g_6 \) will decrease.

Model 4’s confidence ellipsoids for each parameter pair are shown in Figure 6.3. The optimal point and the 90%, 95%, and 99% confidence ellipsoids are displayed. The 99% confidence ellipsoid is the largest ellipsoid followed by the 95% and 90% ellipsoids. None of the confidence ellipsoids cross either the x or y axes. Thus, no parameter pair has a parameter value equal to zero. The confidence ellipsoids show the strong positive correlation between \( b_0 \) and \( g_6 \), and the strong negative correlation between \( b_0 \) and \( g_4 \), and \( g_4 \) and \( g_6 \).
Figure 6.3: Confidence ellipsoids for Model 4 nucleation and growth kinetic parameters.
Figures 6.4-6.6 show how the CSD model predictions compare to the raw histogram experimental data and the smoothed data approximation used for parameter estimation. Each run shows the samples taken at 30 minutes, 2 hours, and the final sample taken which time depends on the specific experimental run. Figure 6.4 shows the three different flow rates for 10 °C. Likewise, Figures 6.5 and 6.6 show 20 °C and 30 °C. For all three operating temperatures, the model does a good job of matching both the smoothed data and the raw data histograms for each flow rate. Figure 6.7, shows how the predicted mean size grows for each operating condition pair. The model predicts the data well overall, but there are some conditions where the model prediction is not good. In particular, the model under-predicts the mean size for the first 200 minutes of 20 °C 0.8 ml/min, slightly under-predicts the mean size for 20 °C 1.5 ml/min, and slightly over-predicts the mean size for 20 °C 3.0 ml/min. These results also show the effect of temperature on the final product mean size. For a given antisolvent feed rate, the crystals are larger at 30 °C than at 10 °C. This quantitatively shows the benefit of using the temperature degree of freedom to influence the final product mean size. Similarly for a given temperature, the final product mean size is larger for the slowest feed rate of 0.8 mL/min compared to the fastest feed rate of 3.0 mL/min. This also quantitatively shows the benefit of using the antisolvent degree of freedom to influence the final product mean size. Thus, one is able to use either temperature or antisolvent feed rate to achieve a desired crystal size.

Table 6.5 lists the mean absolute deviation (MAD) of the mean size for each temperature and feed rate combination. For example, the MAD for the low temperature and low feed rate combination was 5.38 microns. Including every sample for each experimental run, the MAD of the mean size was 7.18 microns. This may seem like a large deviation, but this needs to be compared to the confidence intervals on the experimental data points. To calculate the confidence
Figure 6.4: Model-data fits for selected samples of the 10 °C experimental runs.

Table 6.5: Mean absolute deviation of model predicted to experimentally measured mean size for each experimental run.

<table>
<thead>
<tr>
<th>Feed Rate (mL/min)</th>
<th>10 °C</th>
<th>20 °C</th>
<th>30 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.8</td>
<td>5.38</td>
<td>8.86</td>
<td>8.14</td>
</tr>
<tr>
<td>1.5</td>
<td>3.75</td>
<td>9.87</td>
<td>8.26</td>
</tr>
<tr>
<td>3.0</td>
<td>3.29</td>
<td>11.3</td>
<td>5.00</td>
</tr>
</tbody>
</table>
Figure 6.5: Model-data fits for selected samples of the 20 °C experimental runs.

Table 6.6: 95% confidence limits of experimentally measured mean size for each experimental run.

<table>
<thead>
<tr>
<th>Feed Rate (mL/min)</th>
<th>10 °C</th>
<th>20 °C</th>
<th>30 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.8</td>
<td>7.90</td>
<td>9.75</td>
<td>9.20</td>
</tr>
<tr>
<td>1.5</td>
<td>10.7</td>
<td>11.6</td>
<td>11.2</td>
</tr>
<tr>
<td>3.0</td>
<td>8.50</td>
<td>8.30</td>
<td>10.6</td>
</tr>
</tbody>
</table>
Figure 6.6: Model-data fits for selected samples of the 30 °C experimental runs.

Table 6.7: Mean absolute deviation of model predicted to experimentally measured standard deviation for each experimental run.

<table>
<thead>
<tr>
<th>Flow Rate (mL/min)</th>
<th>10 °C</th>
<th>20 °C</th>
<th>30 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.8</td>
<td>3.77</td>
<td>5.06</td>
<td>2.45</td>
</tr>
<tr>
<td>1.5</td>
<td>4.77</td>
<td>4.05</td>
<td>4.88</td>
</tr>
<tr>
<td>3.0</td>
<td>3.51</td>
<td>5.54</td>
<td>2.90</td>
</tr>
</tbody>
</table>
Figure 6.7: Mean size model-data fits for the nine experimental runs.

interval, the average standard deviation and average number of particles measured are needed. The average standard deviation of each sample was 47.62, and an average number of crystals measured was 126. The 95% confidence interval on the mean size is ±9.66 microns. This is slightly larger than the model. Thus, the model’s predictions are within the 95% confidence intervals of the data. The specific 95% confidence intervals for each experimental run are listed in Table 6.6. The MAD of the standard deviation for each run is shown in Table 6.7. Including
every sample for each experimental run, the MAD of the standard deviation of the mean size was 4.11 microns.

**Figure 6.8:** Crystal size distributions, mean size, temperature, and antisolvent feed rate for the validation run.

### 6.6 Validation

Before the model can be used for optimization studies, it needs to be validated with a different operating condition than what was used for model creation. The validation run used had operating conditions that changed throughout the run. In particular, the temperature began at 20 °C, and was cooled to 12 °C. The antisolvent feed rate began at 3.0 mL/min and was reduced to 1.8 mL/min through several step changes. Figure 6.8, shows the implemented antisolvent and temperature profiles, the model-predicted mean size, and the model-predicted CSD for selected
times. The model does a good job at matching the predicted mean size to the data throughout the run, but the model predicts a slightly narrower CSD than the data.

6.6.1 Validation of Model to Previous Sodium Chloride Data

Nowee et al. [2008a] developed a sodium chloride model for the isothermal antisolvent crystallization of sodium chloride at 25 °C. The authors proposed four different models shown in Table 6.8. Two models having four adjustable parameters, and two models having seven adjustable parameters. These models will be compared to the four parameter model (Widenski Model 4) developed earlier.

As before, the gPROMS entity gEST was used for parameter estimation for Widenski Model #4. Volume mean size data for three different antisolvent flow rates of 49.4 mL/hr, 98.6 mL/hr, and 194 mL/hr were used to fit the model. The parameter values for Widenski Model #4 are \( \{b_0, g_2, g_4, g_6\} = \{2.2639e6, 17.2094, 23588, 2.00\} \). The parameter values for each Nowee model are listed in Nowee et al., 2008a. The sum of the residuals between the data and model was compared between the models in Nowee et al., 2008a and the new model is shown in Table 6.9. As can be seen, Widenski Model #4 has the lowest residual for each experimental condition. Thus, this model formulation is superior to either of the Nowee model formulations. Figure 6.9, shows each model’s fit to the three experimental conditions used for parameter estimation. It can be seen visually that Widenski Model #4 is significantly better at each experimental condition. The model was then validated with three different optimal profiles provided in Nowee et al., 2008b. The optimization objectives were to maximize volume mean size, minimize nucleation, and to create particles with 100 micron volume mean size. Widenski Model #4 does a good job of
Figure 6.9: Nowee et al., 2008a/b vs. Widenski model comparison.
matching the volume mean size prediction to the data points for each run. Thus, this model was successfully validated for this system.

**Table 6.8:** Widenski Model #4 and Nowee et al. sodium chloride model comparison.

<table>
<thead>
<tr>
<th>Model</th>
<th>Model Formulation</th>
<th>Number of Adjustable Parameters</th>
</tr>
</thead>
</table>
| Nowee #1    | \( B = k_b \Delta C^b M_T \)  
\( G = k_0 \Delta C^{g_0} \) | 4                              |
| Nowee #2    | \( B = k_b \Delta C^b M_T \)  
\( G = k_0 (\frac{\Delta C \cdot g_0}{C^*}) \) | 4                              |
| Nowee #3    | \( B = k_b \Delta C^b M_T \)  
\( G = (k_0 + k_1 w_3 + k_2 w_3^2) \Delta C^{g_0 + g_1 w} \) | 7                              |
| Nowee #4    | \( B = k_b \Delta C^b M_T \)  
\( G = (k_0 + k_1 w_3 + k_2 w_3^2) (\frac{\Delta C \cdot g_0 + g_1 w}{C^*}) \) | 7                              |
| Widenski #4 | \( B = b_0 \exp \left( -0.0001 \frac{\log^3 \left( \frac{\rho_c}{C^* \rho_s} \right)}{\log^2 (S)} \right) \) | 4                              |
|             | \( G = [1 - 0.001 (1 + w)^{g_0}] \exp \left( \frac{-g_1}{RT} \right) \Delta C^{1 + g_6 w} \) |                                 |

**Table 6.9:** Sum of the residuals between the predicted and experimentally measured mean size of each model for the different experimental conditions.

<table>
<thead>
<tr>
<th>Flow Rate (mL/min)</th>
<th>Nowee Model 1</th>
<th>Nowee Model 2</th>
<th>Nowee Model 3</th>
<th>Nowee Model 4</th>
<th>Nowee Model 4</th>
<th>Widenski Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>49.4</td>
<td>6064</td>
<td>2230</td>
<td>365</td>
<td>435</td>
<td>343</td>
<td></td>
</tr>
<tr>
<td>98.6</td>
<td>7478</td>
<td>2051</td>
<td>773</td>
<td>838</td>
<td>597</td>
<td></td>
</tr>
<tr>
<td>194</td>
<td>4491</td>
<td>3207</td>
<td>581</td>
<td>1188</td>
<td>315</td>
<td></td>
</tr>
<tr>
<td>Sum</td>
<td>18033</td>
<td>7488</td>
<td>1719</td>
<td>2471</td>
<td>1255</td>
<td></td>
</tr>
</tbody>
</table>

**6.7 Optimization**

Now that the model has been successfully validated it can be used to create optimal profiles for various optimization objectives. As shown in Section 6.5, both the temperature and
antisolvent feed rate can be used to produce different final product mean sizes. Now these two degrees of freedom will be combined to control both the crystal mean size and coefficient of variation by specifying two different objectives. The two objectives will be to create two specific crystal mean sizes, specifically 145 and 165 microns while minimizing the final coefficient of variation. The optimal profiles for each objective were determined using the gPROMS entity gOPT.

\[
\begin{align*}
\text{min } COV & \quad \text{subject to } \\
10 & \leq T \leq 30 \\
0.8 & \leq \frac{dV}{dt} \leq 3.0 \\
D_{32} & = \{145 \text{ or } 165\}
\end{align*}
\] (6.33)

The optimization formulation was the minimization of the coefficient of variation while satisfying either the 145 or 165 micron mean size constraint (Equation 6.33). The temperature was limited between 10 and 30 °C, and the antisolvent flow rate was limited between 0.8 and 3.0 mL/min. This was to keep each variable within the bounds used to create the model. The time of the experiment was fixed at 480 minutes, with 24 equally-spaced 20 minute control intervals. The generated optimal antisolvent and temperature profiles for each objective are shown in Figure 6.10.

![Optimal Profile for D_{32} = 145](image1)

![Optimal Profile for D_{32} = 165](image2)

**Figure 6.10:** Optimal antisolvent and temperature profiles.
Figure 6.11: Mean size and crystal size distribution model-data fits for the two implemented optimal profiles.
The optimal antisolvent and cooling profiles were implemented for the two objective functions. The results for the mean size are shown in Figure 6.11. For the 145 micron size objective, the experimental mean size tracks the model prediction very well. The only outlying experimental data point is at four hours which is slightly lower than the data estimate. The data tracks the model prediction for the 165 micron size objective good as well. For this objective, the experimental data is slightly larger than the model prediction for the first 2 hours of the experimental run; after that, the experimental data tracks the model prediction accurately. The CSDs are shown at 30 minutes, 2 hours, and 8 hours. The model CSD fits the experimental data very well when the mean size is accurately predicted. For example, the mean size is smaller at the 30 minute sample time for the 165 micron size objective; thus, the predicted CSD is skewed to the left when compared to the experimental data. For the other shown times, the predicted CSD does a good job at matching the experimental data.

These results show the benefit to manipulating both temperature and antisolvent feed rate. Using the model we were able to successfully control the particle size while at the same time optimizing the coefficient of variation. Specifically, we were able to control the particle size to either 145 or 165 microns while also minimizing the coefficient of variation. This shows that by utilizing both degrees of freedom, temperature and antisolvent feed rate, one is able to control not only the crystal mean size, but also the coefficient of variation.

6.8 Conclusion

A thermodynamic growth framework was developed for the sodium chloride-water-ethanol ternary electrolyte system. Due to the amount of experimental data needed to successfully create the growth model, and because it gave poor results when joined with a
population balance, the thermodynamic growth model was eschewed in favor of an empirical model. Future researchers may investigate which parameters are appropriate to be adjusted for the thermodynamic growth model. The resultant model gave extremely good results and was validated for both non-isothermal and isothermal antisolvent systems. It was shown that both temperature and antisolvent feed rate affect the final product mean size. The final product mean sizes were larger as the temperature increased and as the antisolvent feed rate decreased. This showed that even for solutes with temperature insensitive solubility, crystal size can be significantly affected by temperature as well as by the antisolvent feed rate. The model was then used to develop optimal profiles for two specified mean sizes of 145 and 165 microns while minimizing the coefficient of variation. These optimal profiles were successfully validated; both optimizations had good data-model matches. Thus, the original hypothesis that it is possible to control both product mean size and coefficient of variation by utilizing both temperature and antisolvent feed rate degrees of freedom has been confirmed. Adjusting the temperature affects the growth rate kinetic which allows the user to direct the formation of small or large size particles while jointly controlling for the coefficient of variation.

### 6.9 Nomenclature

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Value</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_x$</td>
<td>Debye-Hückel Coefficient</td>
<td>Dimensionless</td>
<td></td>
</tr>
<tr>
<td>$b$</td>
<td>Discretization Parameter</td>
<td>Dimensionless</td>
<td></td>
</tr>
<tr>
<td>$b_i$</td>
<td>Widenski Model Nucleation Adjustable Parameters ($i=0\ldots1$)</td>
<td>Varies</td>
<td></td>
</tr>
<tr>
<td>$B$</td>
<td>Nucleation Rate</td>
<td>Crystals/s m$^3$</td>
<td></td>
</tr>
<tr>
<td>$B_{MX}$</td>
<td>Pitzer-Simonson Long-Range Interaction Parameter</td>
<td>dimensionless</td>
<td></td>
</tr>
<tr>
<td>$C$</td>
<td>Solution Concentration</td>
<td>kg/ kg Solvent</td>
<td></td>
</tr>
<tr>
<td>$C_1, C_2, C_3$</td>
<td>Solubility Model Adjustable Parameters 21.0678, -59.294, 35.43</td>
<td>Varies</td>
<td></td>
</tr>
<tr>
<td>$C^*$</td>
<td>Equilibrium Solution Concentration</td>
<td>kg/ kg Solvent</td>
<td></td>
</tr>
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<td>Symbol</td>
<td>Description</td>
<td>Value</td>
<td>Units</td>
</tr>
<tr>
<td>--------</td>
<td>-------------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>COV</td>
<td>Area Based Coefficient of Variation</td>
<td></td>
<td>Dimensionless</td>
</tr>
<tr>
<td>D&lt;sub&gt;32&lt;/sub&gt;</td>
<td>Sauter Mean Size</td>
<td></td>
<td>µm</td>
</tr>
<tr>
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<td>m&lt;sup&gt;2&lt;/sup&gt;/s</td>
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<td>m&lt;sup&gt;2&lt;/sup&gt;/s</td>
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<td>m&lt;sup&gt;2&lt;/sup&gt;/s</td>
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<td>Mole Fraction Of Solvents</td>
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<td>Widenski Model Adjustable Growth Parameters</td>
<td>(i=0…6)</td>
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<td>G</td>
<td>Crystal Growth</td>
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### 6.10 References


7. CONCLUSIONS AND RECOMMENDATIONS

This doctoral dissertation has focused on the development of an applicable and generic model-based framework for the advanced operation of crystallization processes. The present work systematically addressed the problems of modelling a number of crystallization processes through analysis, optimization, and experimental validation. Strategies have been devised, that can be used in industry, to maximize the overall process performance.

The proposed strategy combined tools from different disciplines - specifically in the areas of kinetic and dynamic modeling, process optimization, and parameter estimation. The main conclusions are outlined in the following:

1. A comprehensive and coherent framework for modeling crystallization systems was developed and implemented. In this regard, batch and semi-batch crystallization models for prediction of CSD taking into account effects of temperature, seeding variables, and feeding rates of antisolvents were developed. By implementing these models into the gPROMS modeling and simulation software, these models were able to be successfully used to derive optimal operating policies, analyze predictive solubility models, estimate kinetic parameters, analyze different model formulations, and investigate a number of other crystallization issues. Specifically, the following was showed:

- The modeling framework was used to determine optimal seed mass and cooling profiles for a specified seed size. By comparing the results from the seed chart and model-based optimization the advantages of model-based optimization over heuristics were demonstrated. One advantage is that this approach eliminates the need of using arbitrary cooling curves and arbitrary seed sizes as required when using seed charts. This allows for superior optimization performance, resulting in increased crystallizer efficiency. A
second advantage is that model-based optimization has an unlimited range of cooling profiles and seed sizes to choose from compared to the fixed range of those in the seed chart. This allows for increased operational flexibility.

- The modeling framework was used to investigate the applicability of predictive thermodynamic solubility models in crystallization modeling. Specifically, we have implemented and analyzed the feasibility of these thermodynamic models to determine optimal operating conditions for evaporative, cooling, isothermal antisolvent, and non-isothermal antisolvent crystallization. The advantage of this finding is that it opens the door for these predictive solubility models to be used as an antisolvent screening mechanism to quickly determine the most appropriate solvent(s) for a given application. In addition, the applicability of these thermodynamic predictive models to dynamic optimization was analyzed for two cases. For the cooling crystallization case, several predictive models successfully located the optimal cooling trajectory. However, for isothermal antisolvent crystallization dynamic optimization these models were not sufficiently accurate to be used over an empirical model to determine optimal antisolvent feed profiles. Nevertheless, as these predictive models continue to improve they will eventually eliminate the need for experimental solubility data as in the case of empirical approaches currently used in crystallization modeling and will contribute towards generic models to be used over a range of conditions and systems.

- Another aspect of the modeling framework was the investigation and analysis of thermodynamic growth kinetic models as opposed to simplistic empirical approaches to model the crystal growth mechanisms. The availability of such kinetic growth models will reduce the need for crystallization models to be trained to experimental data for each
specific system studied. Unfortunately, to create such a generalized model a multitude of experiments need to be performed if the data (dielectric constants, activity coefficients, diffusivities, etc.) is not already available in the literature. This experimental burden is still larger than the one needed to estimate the parameters of an empirical growth model for typical crystallization systems. However, as thermodynamic growth models continue to improve this approach may prove be a feasible alternative in the future.

2. The optimization of crystallizer performance was the primary aim of this project. Specifically, in crystallization, the over-riding objectives of such an optimizing scheme are to obtain a product with the desired crystal size characteristics. Our approach relied on the idea of relating the consumer requirements to the operational parameters. Various objective functions have been sought. A novel mathematical formulation of the CSD was developed for the purpose of optimization and control set-pointing. A model-based dynamic optimization solution has been developed for this problem that identifies optimal crystallization operational conditions including temperature, seeding variables, and antisolvent feed rate. In particular, control of crystal mean size was achieved while jointly optimizing the crystal dispersion.

3. Finally, experimental work was conducted to validate the simulated optimization results. Experimental data obtained from several experiments at various different operating conditions was combined with a proposed crystallization model in gPROMS. Within gPROMS, kinetic parameter estimation was performed to determine kinetic parameter values as well as each parameter’s confidence interval. After careful statistical analysis, the proper crystallization model formulation was chosen. This work showed how beneficial it is to manipulate both the antisolvent feed rate and the crystallizer temperature for the case where the solute has temperature insensitive solubility. In particular, this experimental work showed that
temperature can be used as a second degree of freedom to obtain mean crystal sizes unattainable at other temperatures, and more importantly for joint control of crystal mean size and dispersion.

7.1 Future Work

There are several ways that future research can extend this dissertation research:

1. Evaluation of predictive thermodynamic solubility models for antisolvent screening. This would be the final step in the evaluation of predictive thermodynamic solubility models in crystallization modeling. Even though these models have not been perfectly accurate in previous studies, they may be sufficiently accurate for use in screening potential solvent-antisolvent pairs from poor solvent-antisolvent ones. They will reduce the solvent-antisolvent test pool, and may select solvent-antisolvent pairs that would not have been selected.

2. Combining the non-isothermal crystallization model framework with online image analysis, producing a crystallization monitoring and control framework. This would incorporate the crystallization model framework into a model-predictive control one. The model-predictive controller would use the model to forecast the mean size set-point trajectory throughout the process. Online image analysis would take pictures via an in situ image acquisition setup, and analyze these pictures to determine the crystal mean size. If there is substantial variation between the measured mean size and the set-point, the controller would either adjust the antisolvent feed rate or temperature to create a new set-point trajectory.

3. Testing whether antisolvent composition purity affects crystallization behavior. Our group noticed different crystallization behavior when using 200 proof (100%) ethanol vs. 190 proof (95%) ethanol. The 200 proof ethanol created much smaller particles than the 190 proof
ethanol. It is hypothesized that this is due to higher local supersaturation levels caused by the 200 proof ethanol, not by the larger amount of ethanol added. To test this theory and the importance on crystallization behavior, several experiments can be performed varying the ethanol purity while keeping the amount of ethanol added by varying the antisolvent feed rate.

4. Expanding the crystallization modeling and optimization framework. Expanding the framework can be done by adding further manipulated variables, testing lumped parameter thermodynamic growth and nucleation models, adding model complexity, and adding further constraints to the optimization process. Further manipulated variables such as seed size, seed loading, and seed crystal size distribution allow one to further customize the crystal CSD by seeding crystals with a specified mean size and variance. The use of lumped parameter thermodynamic growth and nucleation models allows one to model the crystallization process using chemical engineering principles while allowing the model to account for non-idealities. Model complexity can be increased by incorporating size-independent growth along multiple growth directions, or by adding agglomeration and attrition terms to the population balance equation. Lastly, the addition of further parameters and constraints to the optimization process can determine optimum conditions that will maximize profit while satisfying product quality constraints (mean size and coefficient of variation). This can be accomplished by adding product prices, raw material prices, process operating costs, equipment costs, procurement costs, personnel costs, separation costs, waste disposal costs, company minimum profitability requirements, environmental regulations, etc. These can help the user to determine which crystallization process is appropriate and how to best operate it.
APPENDIX A: LETTERS OF PERMISSION

Title: A model-based nucleation study of the combined effect of seed properties and cooling rate in cooling crystallization

Author: D.J. Widenski, A. Abbas, J.A. Romagnoli

Publication: Computers & Chemical Engineering

Publisher: Elsevier

Date: Nov 11, 2010

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Licensed content author D.J. Widenski, A. Abbas, J.A. Romagnoli
Licensed content date December 2010
Licensed content volume number 49
Title: Use of Predictive Solubility Models for Isothermal Antisolvent Crystallization Modeling and Optimization

Author: David J. Widenski et al.

Publication: Industrial & Engineering Chemistry Research

Publisher: American Chemical Society

Date: Jul 1, 2011

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APPENDIX B: AUTHOR’S CONTRIBUTIONS


12. Cogoni G., **Widenski D.**, Grosso M., Baratti R., Romagnoli J. Comparison between population balances and stochastic models for crystallization processes (*in preparation*)
VITA

David Widenski was born in Menomonee Falls, Wisconsin, in 1980. He graduated from Martin Luther High School in Greendale, Wisconsin. After which he enrolled at the University of Minnesota in August 1998, and graduated with a Bachelor of Chemical Engineering with a minor in chemistry in May 2002.

David traveled to Louisiana in August 2006 where he enrolled as a doctoral student in chemical engineering at Louisiana State University. There he joined Professor Jose Romagnoli’s Process Systems Engineering Research Group in December 2006. In March 2008, he received a Donald W. Clayton Graduate Excellence Award. In December 2010, he received a Master of Science Degree in Chemical Engineering from Louisiana State University. He expects to receive the Doctor of Philosophy Degree in Chemical Engineering in May 2012. To date he is the author of nine peer-reviewed journal articles, book chapters, and conference proceedings. His research has also been presented at three major national and international conferences. He is also a member of the Honor Society of Phi Kappa Phi.

David also received a National Science Foundation EAPSI Fellowship Award in 2008 which gave him the opportunity to study with Dr. Ali Abbas at the University of Sydney from April 2008 - October 2008. While in Australia he received a PADI SCUBA Open Water Diver Certification and was able to experience the underwater beauty of the Great Barrier Reef.

While performing his graduate studies David achieved many personal accomplishments. As an avid golfer, he scored his second career eagle at Copper Mill Golf Club holing out a 7 iron from 170 yards. He also became an accomplished ballroom dancer, learned how to ride a horse, obtained his motorcycle license endorsement, became a skilled landscape photographer, and became a wine connoisseur.