Design of continuous crystallization processes

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Abstract

Crystallization is an efficient thermal separation technology with low operational costs, which provides a sophisticated opportunity for purification together with the adjustment of the final product crystal size distribution (CSD). The continuous operation of the corresponding application is of interest when a large space-time-yield and constant output specifications are demanded. Nevertheless, the commonly preferred batch operation is usually simpler with respect to process design and set-up. Here, e.g. seed crystals can be utilized together with controlled cooling policies to efficiently control the final CSD. In case of a continuous process, these properties have to be adjusted by the basic crystallization mechanisms, i.e. nucleation, growth and dissolution. These mechanisms are connected to the operation conditions in a nonlinear way, which complicates the transfer of the existing batch to continuous processes. Therefore, the design of continuously operated crystallizations from solution will be the main topic of the present thesis and the following tasks will be investigated.

Besides mass balances also population balances (PBE) have to be considered for crystallization processes to capture the evolution of the solid phase. However, these PBEs contain mathematical sub-models for the relevant kinetic phenomena, which have to be quantified expensively in separate experiments for every new substance system or even for the specific experimental set-up. Hence, an efficient and universally applicable quantification method for the estimation of crystallization kinetics would be beneficial as well as the evaluation of the design of a continuous process based on these information. Consequently, a subsequent evaluation of the impact of the so quantified kinetics, e.g. the utilized mathematical approach and measurement errors, on the process design is necessary as well.

Nevertheless, complicated separation problems, like enantiomeric mixtures or substance systems with miscibility in the solid state, exist. In such cases product purity is of main interest. Fractional crystallization is one option to purify mixtures, which form solid solutions, by repeated successive steps. Nevertheless, the necessary and repetitive solid-liquid separation and the difficult solid phase transport between the corresponding crystallizations are expensive and the lack of a supporting mathematical framework complicates process design.

Therefore, the present thesis is divided into two main parts:

For the model-based design, control and optimization of crystallization processes a novel method for the estimation of the relevant kinetics is developed. This short-cut-method is based on analyzing the evolution of the crystal size distribution during a few well-planned polythermal experiments. The required information are subsequently extracted from a characteristic part of the particle collective, which allows a sequential
and therefore efficient quantification of the different kinetics. The feasibility of this method is demonstrated on the basis of systematic theoretical and experimental studies. Subsequently, three different binary substance systems are characterized with respect to their kinetics. The information of one of these is then applied for the design of a continuous process.

The second main part focuses on an innovative fractional counter-current crystallization process. The disadvantages mentioned above are avoided by means of repeated crystallization and dissolution to transport the solid phase in the dissolved, liquid state. Hence, a pseudo-continuous automated process is feasible similar to simulated moving bed chromatography or mixer-settler plants for extraction. The application of this process for substance systems exhibiting partial or total solid solutions is shown in theory and experiment. A supporting model is derived, which allows process visualization, design and optimization. This sophisticated approach consists of a simple stage-model, which comprises the data of the ternary solid-liquid equilibria. The results of this study concern the demonstration of the process principle for two selected ternary systems, which are characterized by complete miscibility in the solid state. Subsequently, the scale-up from a laboratory unit to a pilot plant with the verified model is shown. Finally, a theoretical evaluation of the feasibility of the process principle for purification of systems characterized by partial miscibility in the solid state is given.
Kurzzusammenfassung


Die Einstellung der KGV setzt inhärent Informationen über die Kinetiken der Nukleation, des Wachstums und der Auflösung voraus, die bisweilen aufwendig in separaten Experimenten, für jedes neue Stoffsysten oder jeden neuen Prozessaufbau, bestimmt werden müssen. Des Weiteren ist zu bewerten, wie sich die Kinetiken, d. h. der gewählte mathematische Ansatz, die darin enthaltenen quantifizierten Parameter, sowie evtl. Messfehler bei der Kinetikbestimmung, auf die kontinuierliche Prozessführung auswirken.


Die Arbeit gliedert sich in zwei Hauptteile:
Für die modelbasierte Auslegung der kontinuierlichen Betriebsweise soll eine neu entwickelte Methode zur Kinetikbestimmung untersucht werden. Die

Preface

Several publications were prepared in the course of this thesis and are therefore incorporated in the present manuscript. The chapters, which contain to some extend parts of these publications of the author, are listed in the following for the sake of clarity. Additionally, several students will be listed here as well, to acknowledge their assistance during the experimental works of the present thesis.

- Parts of chapter 5 were taken from [1].
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1. Introduction

Thermal separation processes are commonly operated continuously when high productivity, constant output specifications and low operational costs are demanded. Nevertheless, the corresponding batch operation is usually simpler with respect to the set-up and process design. Furthermore, it is not tailored for one specific purpose and thus, applicable for different tasks, e.g. different substance systems or for the determination of kinetic parameters. But the control of specific product properties is challenging and the dead times during charge and discharge, decrease the productivity.

For example, distillation dominates separation options for the purification of substance systems differing in boiling point [5]. This process is based on the relative volatilities of the substances involved [6]. The lower boiling component is concentrated in the vapor phase, while the higher boiling component enriches in the liquid phase in a fixed ratio for a given temperature, pressure and feed-concentration of both substances. The system tends, for a given set of state variables, to a thermodynamic equilibrium reflected by a defined distribution of the components between the liquid and the vapor phase. Nevertheless, batch distillations are in most cases insufficient to provide pure products [7]. But if the principle of the unit operation is adapted to a continuous multiple stage counter-current process, which intensifies the contact between both phases and enhances the separation efficiency, it is possible to separate fluid mixtures into all pure components. With the knowledge of the phase behavior, mass flows and stage number, a simple process design exploiting the McCabe-Thiele diagram is possible, which represents the thermodynamic equilibrium diagram of a binary rectification [6].

Similar principles as for distillation can be found for crystallization processes. Here, the separation principle is based on the thermodynamic equilibrium between a solid and a liquid phase of the involved substances. Thus for crystallizations from solution, the solubilities of the compounds have to be known for a successive purification. If the concentration of a solute in solution exceeds its solubility a crystalline solid phase may occur. Usually, these crystals consist only of one component with a defined and periodic arrangement of the elementary building units, i.e. atoms, molecules or ions, known as the crystal lattice. Thus in contrary to rectification, if the solubilities of the involved substances exhibit for given variables of state a significant difference, one substance can be crystallized in a pure manner while all others remain liquid within one batch-process.

This holds true until the elementary building units of compounds can be exchanged between their common crystal lattices. This yields solid solutions where the pure substances can be dissolved in each other in the solid state [8]. The occurring crystal phases consist of building units of different compounds in a non-stoichiometric composition, which strictly depends on the origin liquid phase or mother liquor.
composition. The quantitative distribution of the involved substances between the phases is similar to the mentioned vapor-liquid equilibrium. Thus, the separation equals the distillation and pure substances cannot be achieved within a single purification stage. Multi-stage crystallization cascades, consisting of several batch crystallizers, are utilized in this case to obtain the pure components of a system exhibiting solid solutions [9].

Several challenges arise together with this concept. First, the crystalline material has to be separated from the mother liquor and moved to another stage for further processing. Thus, the phase transport between the stages is demanding since solids cannot be pumped like liquids or gases. Furthermore, similarly the options to create a continuous and automatic process are limited. Additionally, a counter-current would be preferable, as for the rectification, to enhance the separation efficiency and reduce the loss of material.

Solid particles are characterized by a certain size and shape [10], in contrast to liquids, which are defined by their volume only, or vapors, which fill the whole space where they are contained in. The product particle size distribution is an important attribute for particulate processes since it influences e.g. the downstream processing or the applicability of the material. However, in contrast to rectifications, the crystallization process performance with respect to the particulate phase cannot be predicted based on the thermodynamic equilibrium only. Therefore, population balance equation systems (PBEs) are applied for the design, visualization and optimization of crystallization processes, which relate the process conditions to a resulting crystal size distribution (CSD). This dynamic model framework serves to predict the solid phase evolution under consideration of the corresponding process kinetics. Here, the main mechanisms are usually considered to be nucleation, growth, agglomeration, breakage and dissolution. The rates of these phenomena have a strong impact on the final process output and are related to thermodynamics and fluid dynamics in a non-linear non-intuitive way. Thus, the measurement of these rates and a subsequent parameterization of corresponding kinetic sub-models are a prerequisite for the utilization of PBEs.

However, a complex mathematical description is often unnecessary for simple batch-crystallizations. Several rules based on experience exist e.g. for the necessary seed mass or material, the cooling policy or a favorable supersaturation level, which provide feasible process design approaches without extensive calculations. Nevertheless, for continuously operated crystallizations such rules of thumb are rather rare. Furthermore, the connection and dependency of the process variables, mean residence time, supersaturation and crystallization temperature, are more complex. Thus, a model based design is necessary and preferable to achieve a steady-state operation, to avoid a periodic oscillation of the CSD as well as a complete wash-out and to obtain the demanded product quality and productivity. Hence, a simple and reliable scheme for the quantification of kinetics is desired.

The two mentioned tasks, the determination of kinetics for the design of a continuous crystallization and the efficient separation of substance systems involving solid solutions, will be the content of this work. A short-cut-method is suggested, which is based on analyzing the evolution of the crystal size distribution during a few batch-crystallization experiments. The main task is to parameterize the necessary kinetic sub-
models efficiently to predict and evaluate the performance of crystallization processes. To illustrate and explain the overall procedure and to evaluate accuracy and benefit of the approach, simulated data corresponding to hypothetical experiments, assuming predefined kinetics will be exploited. Subsequently, this method is utilized for the parameter estimation of kinetic sub-models of three different substance systems to illustrate its feasibility. The experimental procedure as well as the subsequent data analysis will be discussed. Afterwards, the quality of the parameter estimation will be evaluated by comparing the simulation results of a population balance model equipped with the parameterized kinetics with corresponding validation experiments. Finally, the obtained results will be applied to a continuously operated crystallization process and evaluated based on the experimental results.

Furthermore, a fractional crystallization process will be investigated, which transports the solid material as solutions due to innovative connection of the separation stages. Thus, the phase exchange is significantly simplified and an automated counter-current operation is feasible. A simple stage model will be derived based on the thermodynamic equilibrium of the solid and liquid phases, similar to the McCabe-Thiele theory. Afterwards, this model will be utilized to design the process for two separation problems. Corresponding experiments are carried out with a recently developed continuous counter-current crystallization plant. The subsequently obtained results will be utilized to evaluate the postulated theory as well as the general process principle.

The necessary fundamentals, required to design and optimize crystallization processes, in terms of solid-liquid equilibria and driving forces will be described in Chapter 2. Afterwards (Chapter 3), an overview of the operation modes of the different considered processes will follow. In Chapter 4 the relevant crystallization kinetics investigated in this work are defined and explained. Additionally, the utilized mathematical framework, i.e. population balance equations (PBE), is explained.

The first main part, the development of a short-cut-method for the investigation of crystallization kinetics, will be the content of the Chapter 5. This new method will be compared to commonly applied determination methods. The principle, the data analysis and the parameter estimation will be illustrated theoretically and the utilized set-up, the measurement technique and the experimental procedure will be explained.

In the following, the processed binary substance systems are introduced together with their specific data of SLE (Chapter 6). These substance systems were investigated applying the proposed short-cut-method. The results will be shown together with the quantified kinetics, which will be validated with corresponding experiments.

In Chapter 7, the estimated parameters of the utilized kinetic sub-models of one of the investigated substances are applied for the design of a continuous mixed-suspension mixed-product-removal crystallization process. Subsequently, the experimental investigations in a widely applicable continuous plant, constructed at the Max Planck Institute for Dynamics of Complex Technical Systems, are evaluated together with the corresponding model predictions.

The second main part is concerned with a novel fractional crystallization approach, which is discussed in Chapter 8. A discrete mass balance based stage model is developed for this purpose, which contains the mathematical description of SLE data. Subsequently, two different ternary substance systems, which form solid solutions, are
experimentally investigated in terms of their solid-liquid behavior. Afterwards, the introduced equilibrium stage model is equipped with the results of the solubility measurements and validated with appropriate experiments. The design of a process in a fractional counter-current crystallization plant [11] will be made based on the verified mathematical framework in Chapter 9. Dedicated experiments are carried out and evaluated with respect to the potential of the process principle together with the simple process design model. The different topics are subsequently concluded and a perspective for further works is given.
2. Solid-liquid equilibria

Solid-liquid equilibria are the basis of every crystallization or precipitation process [12]. They are defined via the thermodynamic states of 2 or more phases in equilibrium with each other. In this context, a phase is defined as a uniform kind of matter with respect to the physical and chemical properties. The knowledge of the thermodynamic conditions of a system yields the map for a certain crystallization process. It defines to a certain extend the design as well as the performance of a process. That means, appropriate ways to generate the fundamental driving force for the crystallization can be identified, occurring phases can be considered as well as the maximal yield and purity are predictable in advance. Therefore, this chapter is dedicated to solid-liquid equilibria because of its fundamental importance for the later on discussed processes and methods.

In the beginning, the supersaturation, which is the prerequisite for every crystallization, will be explained followed by the graphical representation of solid-liquid equilibria, namely phase diagrams. The last part briefly introduces methods for the determination of the necessary data.

2.1. The driving force of crystallization processes

The equilibrium is, for a certain system, the state with the lowest Gibbs energy and the highest order. It is defined by several physical conditions e.g. temperature, chemical potential or pressure. The main driving force for every process is then the distance between the state of a system to the equilibrium or stable state.

In case of crystallization, this is reflected by the difference of the chemical potentials of a substance in a certain liquid phase ($\mu_{\text{liquid}}$) and a saturated liquid phase ($\mu_{\text{sat}}$) for constant temperature and pressure [13] (eq. 2.1).

$$\Delta \mu = \mu_{\text{liquid}} - \mu_{\text{sat}} \quad (\text{eq. 2.1})$$

For crystallization from solution an equilibrium liquid phase is saturated and is defined for the present work as follows: A solution of a certain unsolvated substance, which is in equilibrium with the corresponding solid phase. Thus, the state of the system must have reached the lowest Gibbs energy for a given temperature and pressure. According to the definition of the Gibbs free energy ($\Delta G$, eq. 2.2) together with the expression of the internal energy ($\Delta U$, eq. 2.3) it follows that a change of the Gibbs free energy is connected to the amount of solute ($n$) in solution (eq. 2.4) for constant temperature and pressure.
The driving force of crystallization processes

\[ \Delta G = \Delta U + p \cdot V - T \cdot S \]  \hspace{1cm} (eq. 2.2)

\[ \Delta U = T \cdot S - p \cdot V + n \Delta \mu \]  \hspace{1cm} (eq. 2.3)

\[ \Delta G = n \Delta \mu \]  \hspace{1cm} (eq. 2.4)

Figure 2.1 illustrates for this context, the difference of the chemical potentials with respect to the amount of dissolved solute.

**Fig. 2.1:** Gibb’s energy and difference of the chemical potential of a solute dissolved in a liquid phase to the saturated state for constant temperature and pressure. *Solid line - Difference of the chemical potentials; dashed lines - Saturated state; dashed-dotted line - Gibb’s energy.*

A liquid phase with a higher amount of dissolved substance as in the equilibrium state will have a higher chemical potential. The Gibb’s free energy will be negative if a certain amount of substance solidifies (-n, eq. 2.5) and thus, crystallization will be an exergonic process for this state. In contrary, a solution, which has a lower chemical potential compared to the saturated state, will tend to dissolve more solute (n) since this decreases the Gibb’s free energy for such a system (eq. 2.6). By definition, the first state will be called super- and the latter one undersaturated.

\[ \Delta G = - n \cdot (\mu_{\text{liquid}} - \mu_{\text{sat}}) \]  \hspace{1cm} for \( \Delta \mu > 0 \)  \hspace{1cm} (eq. 2.5)

\[ \Delta G = n \cdot (\mu_{\text{liquid}} - \mu_{\text{sat}}) \]  \hspace{1cm} for \( \Delta \mu < 0 \)  \hspace{1cm} (eq. 2.6)
Hence, the difference in the chemical potential is decisive for the pathway of stability of the system. The dependency of the chemical potential on the intensive variables of a state can be derived from the first and second law of thermodynamics [14] and is given by:

\[ \mu = \mu^0(T, p) + RT \ln(a) \]  

(eq. 2.7)

Where \( \mu^0 \) describes the standard chemical potential of the liquid phase, \( R \) is the ideal gas constant and \( a \) denotes the mole fraction dependent activities of the liquid phase. Considering this definition, the thermodynamic driving force of crystallization of a pure substance according to [8, 13] for the supersaturated state is consequently:

\[ \frac{\Delta \mu}{RT} = \ln \left( \frac{a_{\text{liquid}}}{a_{\text{sat}}} \right) = \ln S_a \quad \text{for} \quad \Delta \mu > 0 \]  

(eq. 2.8)

\[ a_{\text{liquid}} = S_{\text{liquid}} \]  

(eq. 2.9)

with the molar fractions

\[ x_i = \frac{n_i}{\sum_{j} n_j} \]  

(eq. 2.10)

and the closure condition

\[ 1 = \sum_{i} x_i \]  

(eq. 2.11)

Where \( \gamma_{\text{liquid}} \) denotes the activity coefficients, \( x_{\text{liquid}} \) the mole fractions of a substance \( i \) and \( S_a \) the thermodynamic supersaturation ratio. Debye and Hückel derived in 1923 the fundamental relationship of the activity coefficient of electrolytes and their concentration in water based on the long-range interactions of the ions [15]. The concept was expanded to short-range and long-range interactions in 1973 [16-18] yielding a higher precision of the predicted activities [13]. Today, these first approaches are implemented in highly sophisticated models (e.g. eNRTL [19]), which tend to reduce the experimental effort for the determination of activity coefficients. Similar methods exist for non-electrolytes with a broad variety of different approaches [20, 21], which were already successfully applied [22, 23]. However, the exact calculation of the necessary activity coefficients is still challenging especially if real technical processes and e.g. various impurities have to be considered. Thus, these methods are up to now inconvenient for most engineering purposes.
For simplification, some assumptions according to [8, 13] are made for the technical approaches in the present study:

1) The solution is perfectly incompressible and the pressure influence on the state of the liquid phase can be neglected for ambient conditions.
2) Solutions are ideal for the considered range of concentration and thus the ratio of the activity coefficients of the liquid phase and the saturated solution, \( \gamma_{\text{liquid}} / \gamma_{\text{sat}} \), equals 1.
3) Dissociation and solvation of the substances is negligible.
4) \( \ln S = S - 1 \) for the considered range of supersaturation.

Hence, by conversion of the mole fractions also mass based concentration units can be applied for the direct calculation of the supersaturation of the system. Nevertheless, it should be mentioned that this approach leads to deviations to the thermodynamic driving force [13].

\[
S(T, x) = \frac{x_{\text{sat}}}{x_{\text{sat}}(T)} \tag{eq. 2.12}
\]

For binary systems, mole fraction, \( x \), can be applied also as mass loading, \( w \) [wt-%], in kg\text{Solute} per kg\text{Solvent} for simplification.

The description of the super- or undersaturation of a system is according to eq. 2.12 simply based on the saturated or stable state with respect to the intensive thermodynamic variable. Consequently, a general representation of the equilibrium needs to be derived in the following.

### 2.2. Phase diagrams of binary and ternary systems

The prerequisite for equilibrium of a given system are equal chemical potentials of all components in all involved phases [14].

\[
\mu_j^{(l)} = \mu_k^{(l)} \quad \text{for } j = 1 \ldots N \text{ and } l, k = 1 \ldots P \tag{eq. 2.13}
\]

It follows from eq. 2.7, that for one phase in equilibrium one (two if pressure dependencies are considered) intensive variable of state, the temperature, and N-1 molar fractions of N components are fixed. Furthermore, \( N \cdot (P - 1) \) equations are given from the equilibrium condition of P phases (eq. 2.13). Thus, \( (N - 1) \cdot P + 1 - N \cdot (P - 1) \) variables can be chosen independently without a change of the equilibrium. Generally, this relation is known as the Gibbs phase rule, which relates the degrees of freedom, \( F \), of a system to the occurring phases and components.

\[
F = N - P + 1 \tag{eq. 2.14}
\]

The rule yields the amount of intensive variables, which can be chosen arbitrarily, without a change in the amount of phases [12]. Therefore, it is considered as the
theoretical base of phase diagrams, which are the graphical representation of states and phase of a certain system with respect to temperature and the fractions of the involved components [24]. The concept of phase diagrams yields therefore the thermodynamic map for crystallization processes and will be discussed for binary and ternary systems in the next sections.

2.2.1. Binary phase diagrams

For a system of two components, e.g. substance A and B, eq. 2.14 yields a maximum of three phases, which can exist at the same time at an invariant state [12] if the pressure influence is negligible. A general representation of such a system is given in a composition-temperature diagram in figure 2.2.

![Binary phase diagram of two components A and B, which are miscible in the liquid and immiscible in the solid state. Occurring phases of A and B, important temperatures, \( T \), and compositions, \( x \), are indicated.](image)

Figure 2.2 depicts that both components are miscible in liquid state \((A+B)(l)\) and immiscible in solid state \((A(s)+B(s))\).

If a system of composition \(x_0\) is cooled down from a certain temperature solidification of component A will appear at some point. Based on the Gibbs energy [14], the first occurring solid phase has to be of component A. This specific point represents the equilibrium between the liquid phase and the occurring solid phase of A for the specific composition \((A(s)+(A+B)(l))\) if infinitely fast kinetics are assumed. The relationship, of the composition of the liquid phase and the corresponding temperature where the first solid phases can occur, yields the liquidus line of the system (line \(T_A-x_{Eu}-T_B\)). On this line, two phases are in equilibrium with each other leaving one degree of freedom for the system (eq. 2.14, pressure influence negligible). Thus, if the temperature is further decreased, the state of the system is fixed and the liquid phase composition, \(x_{liquid}\), has to tend to a new equilibrium state.
As depicted in figure 2.2, the melting points of the pure substances, \( T_A \) and \( T_B \), decrease by adding the other one until a minimum of the temperature of fusion is reached. At this point, three phases are in equilibrium with each other and thus all intensive variables are fixed. For the system shown, this invariance is named eutectic point, \( (T_{Eu}, x_{Eu}) \), and therefore the system is called eutectic system. Finally, crystals of both substances coexist in a physical mixture after total solidification.

The classification of binary systems with respect to the melting points into three fundamental types was first established by Roozeboom [25]. Among systems with one minimum of melting point, eutectic systems (Fig. 2.2), also two minima can appear \((x_{Eu,1}, x_{Eu,2}\) in Fig. 2.3 a). These systems are characterized by an additional form, which comprises the pure substances in a stoichiometric ratio [26]. In contrary to eutectic systems, both components are incorporated in one unit cell with lattice parameters different from the pure substances. Therefore, the intermediate compound or form exposes an individual melting point (dystectic), \( T_{IC} \), at the specific stoichiometric ratio and principally separates the phase diagram in two new ones.

If one substance can be replaced inside the unit cell by the other one in any ratio, complete solid state miscibility occurs (Fig. 2.3 b). Consequently, the Gibbs energy of the solid state changes with its composition [27]. Based on eq. 2.13, also the corresponding equilibrium liquid phases of these solids have to have different states with respect to the ratio of both components. Therefore, systems exhibiting solid solutions are univariant at any point on the liquidus curve. Thus, compositions of appearing solid phases strictly depend on the corresponding liquid compositions during crystallization. The solidus curve appears, except for the ideal case, as a nonlinear line connecting the melting points of both pure substances. Hence, if a liquid phase with composition \( x_0 \) is cooled to the liquidus curve, crystals with the ratio \( x_{S0} \) of \( A \) and \( B \) occur. A further decrease of the temperature leads to solidification of crystals with compositions between \( x_{S0} \) and \( x_S \) while the liquid state...
evolves according to the corresponding part of the liquidus curve. The resulting solid phase usually consists of layered crystals, which finally exhibit the overall composition $x_0$. Thus, it is practically impossible to separate substances exhibiting miscibility in solid state completely [28]. Furthermore, the underlying mechanisms of formation and dissolution of mixed crystals are yet not understood in every detail [29].

Two basic ideas exist about solid solution formation [27, 30]. If the substances have similar molecular shapes and sizes, elementary building blocks of the host crystal lattice can be replaced by molecules of the other component (miscibility due to substitution). Alternatively, interstitial miscibility is possible where host molecules are not replaced. Instead, molecules of a second component enter the interstices between the host molecules [27].

Additionally to the three general types of binary phase diagrams (Fig. 2.2 & Figs. 2.3a & b), combinations of eutectic or intermediate compound-forming systems with partial miscibility in solid state can occur. In this case, small amounts of one substance are incorporated into the nearly pure solid phase of the second one (Fig. 2.3c). Even though, eutectic and compound-forming systems mark the majority of binary melt diagrams, it should be mentioned that about 10% of all organic systems exhibit partial or total miscibility in the solid state [31].

Binary phase diagrams are not only applied for the representation of possibly appearing phases but also for the calculation of masses of crystallized material or residual liquid. Given the total and partial mass balance for a known composition $x_0$ in the 2-phase region:

$$m_i = m_{i,\text{solid}} + m_{i,\text{liquid}}$$  \hspace{1cm} (eq. 2.15)

$$m_i x_{i,0} = m_{i,\text{liquid}} x_{i,\text{liquid}}(T) + m_{i,\text{solid}} x_{i,\text{solid}}$$  \hspace{1cm} (eq. 2.16)

It follows, that the amount of liquid and solid phase at thermodynamic equilibrium for a specific temperature can be calculated, for the depicted cooling crystallization in figure 2.2, via the well-known lever rule [24]:

$$m_i (x_{i,\text{liquid}}(T) - x_{i,\text{solid}}) = ...$$ \hspace{1cm} for $T_{E_i} \leq T \leq T_A$  \hspace{1cm} (eq. 2.17)

$$m_i (x_{i,0} - x_{i,\text{solid}}) m_{\text{liquid}} + (x_{i,\text{liquid}}(T) - x_{i,0}) m_{\text{solid}}$$

$$m_i (x_{i,\text{E}} - x_{i,\text{solid}}) = (x_{i,0} - x_{i,\text{solid}}) m_{\text{liquid}} + (x_{i,\text{E}} - x_{i,0}) m_{\text{solid}}$$ \hspace{1cm} for $T < T_{E_i}$  \hspace{1cm} (eq. 2.18)

Where $x$ denotes the mass or mole fraction of a substance $i$ for the initial, liquid, solid or eutectic state and $m$ the masses or amounts of the states. Thus for the two phase area, the substance amount or mass of the phases, e.g. $m_{\text{solid}}$, for a temperature $T$ can be calculated from the overall mass of the system and the ratio between the distances $(x_{i,\text{solid}} - x_{i,0})$ and $(x_{i,\text{liquid}}(T) - x_{i,0})$. Hence, all masses and fractions can be determined in advance for a certain cooling crystallization with a given liquidus curve.
The conclusions derived from the binary melt diagrams are generally valid for binary solid-liquid equilibria. Hence, crystallizations from solution have to follow the same rules as melt crystallizations. A distinction between both processes can be made via the melting temperatures of the pure components. If they differ significantly, the substance with the lower temperature of fusion can be seen as a solvent while the other component can be called solute (Fig. 2.4 a). Even though, this distinction is not mandatory [12], the nomenclature of solute and solvent will be applied for the present work and the following sections are solely dedicated to crystallizations from solution. Furthermore, often only the solidification of the solute is of interest for crystallizations from solution. Thus, only a part of the complete binary phase diagram, which will be called solubility diagram (Fig. 2.4 b), is applied for process design or performance calculations.

From the functional relationship \( x_{A,\text{sat}} = f(T) \), which can be accessed for a single solute from solubility experiments, the driving force (eq. 2.12) for binary crystallizations from solution can be calculated.

**Fig. 2.4:** Transition of a binary phase diagram of a solvent and a solute A into a solubility diagram. a) Binary phase diagram of a solvent and a substance A (redrawn from [12]). b) Corresponding solubility diagram with the solubility curve \( (x_{A,\text{sat}} = f(T)) \), which corresponds to the liquidus curve of the substance A in the binary phase diagram.

It should be mentioned, that binary phase diagrams are usually not as simple as shown here. Polymorphism, thus the solidification of a substance in more than one crystal lattice, yields different solid phases with different properties, like e.g. temperature of fusion. Furthermore, a different kind of phase diagram can result with the formation of a new polymorph [32]. Additionally, solvent molecule incorporation into the crystal lattice can occur, yielding an intermediate compound of the solute and the solvent. These solvates are new phases with different properties similar to polymorphs. Polymorphism and solvate formation would result in a more-dimensional phase diagram where the
additional phases of both pure substances are depicted as well. A more general discussion of all these effects can be found e.g. in [33, 34].

The crystallization of a binary system is usually an ideal case. Chemical or biological syntheses yield commonly a mixture of several valuable compounds and even more impurities. A complete discussion and graphical representation of such multi component systems is usually not necessary. A feasible approach in engineering science is to combine all substances except the desired one into a merged impurity. Hence, a separation by crystallization from solution can be represented by means of a ternary mixture of a solvent and two substances. Therefore, ternary phase diagrams will be discussed in the following.

### 2.2.2. Isothermal ternary phase diagrams

Systems composed of three components yield according to eq. 2.14 a maximum of four phases, which can be in equilibrium with each other. A feasible option to illustrate the equilibrium diagrams of these systems provides the representation of the substance fractions by use of equilateral triangles. Thus, the 3rd dimension can be utilized for the depiction of a state variable dependency, e.g. temperature. The corners of the resulting prism (Fig. 2.5) reflect the pure components (A, B, Solvent) and hence, the faces the binary equilibria between the connected substances.

![Ternary phase diagram](image)

**Fig. 2.5:** Ternary phase diagram of three components A, B and Solvent, which are miscible in the liquid and immiscible in the solid state. Important temperatures, $T$, and compositions, $x_i$, are described in the text.

In figure 2.5, total miscibility in the liquid state and complete immiscibility in the solid state is assumed for the system shown. Therefore, the invariant ternary eutectic point
(T_{EU}) is connected with the binary eutectic points (T_{e1}, T_{e2}, T_{e3}) via three “eutectic lines”. Above the surfaces spanned by the points (T_{EU}, T_{e1}, T_{e2}, T_{e3}) and the temperatures of fusion (T_A, T_B, T_{Solvent}) only one liquid phase of a certain composition (x_A, x_B, x_{Solvent}) is present. The lower area is divided into two and three phase regions where pure substance can be crystallized. It is obvious then, that the whole prism (Fig. 2.5) is circuitous for practical applications and commonly not necessary. Therefore, isothermal cuts of the ternary phase diagram are utilized, which can be depicted in two dimensions as shown for a specific temperature, T, in figure 2.6.

Fig. 2.6: Isothermal cut of the ternary system A, B and Solvent together with the corresponding binary phase diagrams. Occurring phases of A, B and Solvent and important temperatures are indicated.

The binary phase diagrams of the solvent and the substances A and B yield the solubility of the pure components (x_{A,sat}(T), x_{B,sat}(T)) for the specific temperature T. Similarly, the binary melt diagram of A and B defines the corresponding eutectic composition, which is connected to the solubility of pure A and B via solubility isotherms (bold solid lines inside the triangle of Fig. 2.6).

If an evaporation crystallization is applied, a certain composition x_{i,0} of the system evolves on the line connecting the solvent corner until the solubility isotherm is passed. The system enters the 2-phase region where e.g. pure solid A is in equilibrium with a saturated liquid phase of various compositions. Further crystallization leads to depletion
Solid-liquid equilibria

of A in the mother liquor and to an increase of the ratio of B. Hence, at some point the eutectic composition is reached if A and the solvent are continuously removed from the liquid phase. Subsequently, in the three-phase domain a saturated liquid phase of eutectic composition is in equilibrium with different mixtures composed of two solid phases until the whole solvent is evaporated and the complete system is solidified. As for binary phase diagrams, the masses of each component can be calculated applying again the lever rule as explained in detail in [24].

Similarly to binary systems, in ternary solution systems, intermediate compounds can be formed (Figs. 2.7 b). Numerous examples can be found for inorganic substances e.g. salts [8, 35, 36] or alloys [24] but also for organic systems [37, 38]. In particular chiral examples like enantiomeric mixtures [26 & 39-41] (schematically shown in Fig. 2.7) attracted attention especially in case of pharmaceuticals in the recent past [42]. For both of these systems, the trajectories of the phase separation tend always to defined points in the ternary phase diagram. Based on Gibbs' phase rule, the liquid phase will end up at the eutectic composition for crystallization within the 3-phase region. Considering the point associated with the initial state also the solid composition is fixed. A similar behavior holds for the 2-phase region, where process trajectories converge either to the pure solid or the racemic compound.

Fig. 2.7: a) Ternary phase diagrams of a simple eutectic and b) an intermediate compound-forming system for two components A and B and a solvent for a temperature $T$. The number of coexisting phases is indicated.

Solid lines - solubility isotherm; dashed lines - equilibrium tie lines (conodes).

This can be exploited for separation processes based on crystallization. The composition of the system has to be changed (e.g. by cooling, evaporation) into the corresponding 2-phase region of the pure substance [43, 44]. Then the desired product can be obtained within a single crystallization process. Hence, for the commonly appearing simple eutectic and intermediate compound-forming systems several
opportunities for crystallization based separation from a solvent are known and are well investigated, e.g. processes based on applying preferential crystallization [26] [45-48] in case of enantiomers.

Besides these two more common situations, there are several systems exhibiting miscibility in the solid state (Fig. 2.8) similar to binary mixtures. For many examples formation of solid solutions over the whole range of compositions (Fig. 2.8 a) is published including inorganic systems like salts containing one common ion [8, 36, 49] or simple organic substances like amino acids [50]. For more complex organic molecules the occurrence of complete mixed crystal formation seems to be rare [26].

![Fig. 2.8: a) Ternary phase diagrams of systems with complete formation of mixed crystals for the ideal case (bold dashed line), with a solubility minimum (bold solid line) and a solubility maximum (bold dotted-dashed line). b) Ternary phase diagrams of systems with partial miscibility in the solid state at the pure components corners and c) at the intermediate compound. Bold solid lines - solubility isotherms; dashed lines - phase boundaries.](image)

However, there are more cases reported where partial solid solutions are present at the pure component side of eutectic (Fig. 2.8 b) and compound-forming systems [51]. Also the occurring compounds can exhibit miscibility in the solid state (Fig. 2.8 c) for the latter kind of solid-liquid equilibra [52]. Additionally, eventually more cases exist since partial miscibility is difficult to detect and therefore often not recognized [12].

It holds for all examples, that the Gibbs energy of solid and liquid state changes with their corresponding composition if miscibility in both phases occur as already explained for binary systems. Consequently, the tie lines below the saturation isotherm do not end at any defined component anymore and are characteristic for the solid-liquid equilibria of the particular system. In contrast, they connect specific compositions of saturated liquid phases and solid phases.
Fig. 2.9: Ternary phase diagram for a specific temperature of a system with complete formation of mixed crystals with a solubility minimum for the components A, B and a Solvent. 

- Thin solid line - solubility isotherm;
- Thin dashed lines - equilibrium tie lines (conodes);
- Bold solid line - phase separation path;
- Bold dashed line - evaporation of the solvent;
- Dots - states of the system with indicated compositions $x_i$.

If the solvent of a clear solution with the composition $x_{i0}$ is evaporated (Fig. 2.9), the state of the system evolves along the dashed line connected to the pure solvent corner until the first solid phase occurs in the supersaturated region below the solubility isotherm at $x_i$. The subsequent phase separation along the corresponding tie line (solid line in Fig. 2.9) yields a slightly enriched liquid phase, $x_{iL}$, and similarly depleted solid phase, $x_{iS}$, with respect to A. Hence, it is impossible to purify systems with miscibility in the solid state within a single crystallization step [8]. This limits the achievable purity processing such systems with regard to the crystallization methods commonly used. Especially for expensive pharmaceutical compounds this is a big economic drawback. Purification through crystallization is solely possible by periodic solidification and dissolution. Therefore, an efficient technique applying this principle will be part of the discussion in the present work.

2.3. Determination of solid-liquid equilibria

Solid-liquid equilibria are the basis of every crystallization process and therefore have to be determined as precise as possible. Small deviations from equilibrium can lead to unexpected dissolution or crystallization of an undesired phase, to erroneous performance calculations or data analysis as well as to inefficient process design. Several measurement methods are established and are well-known but none is generally outstanding [8, 12, 37, 53]. The substance system and its properties, available analytical devices as well as the desired precision of the measurements determine
amongst others the most convenient method. Generally, they can be distinguished in isothermal and polythermal approaches. Often calorimetric techniques are applied for binary melt diagrams, since they yield direct information about phase transitions. The sample is placed in an enclosed chamber and heated at a constant rate. For the example of figure 2.2 and a solid composition of $x_0$, the temperature would increase up to the point $T_{EU}$. At this invariant, the temperature would stay constant until the solid phase of B is molten completely and only crystals of A and a saturated melt remains. Subsequently, the temperature would rise again but with a different slope as before, since the occurred liquid phase possess a different heat capacity as the former solid phase. The velocity of heating changes again when the whole solid phase is molten and the liquidus curve is reached. Hence, the entire simple binary phase diagram can be constructed from these information if several compositions are investigated [37].

If more phases or components are involved, i.e. polymorphs, solvates or compounds are expected, or complex molecules have to be investigated, the temperature gradient only is often not sufficient. Therefore, a second sample of a different material with known properties is enclosed in another chamber and processed similarly. Subsequently, the heat capacity of the unknown substance can be calculated as well as the heat fluxes consumed or released by endothermic or exothermic effects by comparing the temperature evolution of both. Hence, phase changes, glass transitions, crystallinity etc. can be determined very precisely even in quantitative manner. Additionally, phase transitions with mass losses, like dehydration or desolvation can be distinguished from polymorphic changes if coupled with gravimetric measurement [12]. Several more methods exist, e.g. polythermal investigations coupled with optical or X-ray measurements, which are applied for specific tasks and can be found in literature [12].

For crystallization from solution, same principles are utilized but commonly with measuring the occurrence or disappearance of a solid phase. Samples with known composition are mixed with a defined amount of solvent to form a suspension and heated slowly. When saturation is reached, no solid phase remains and the solution becomes clear. Afterwards, the liquid phase is cooled again until the first crystals appear. In this way, solubility and metastability of a system can be investigated but suddenly occurring phases or phase transitions between solvates, hydrates or polymorphs remain usually unclear.

Isothermal methods are based upon the analysis of the phase compositions at equilibrium at a certain constant temperature. Therefore, solid and liquid phase have to be brought into contact with each other via appropriate agitation over an adequate amount of time. The equilibrium composition is then determined via the analysis of a certain physical property of the liquid phase, e.g. refractive index, conductivity, spectral analysis etc., or measured directly by chromatography or gravimetrically. Additionally, the residual equilibrium solid phase can be investigated with a carefully performed, subsequent solid-liquid separation. Here, X-ray diffraction for structural analysis, chromatography or differential scanning calorimetry can be considered.
Obviously, isothermal methods are rarely applied for solid-liquid equilibria of melts [37]. Nevertheless, for systems involving a solvent they yield most precise solubility information if performed correctly. At first, a defined amount of solvent and an appropriate amount of solute are mixed in an enclosed vessel [12]. The sample is heated until a clear solution is achieved and subsequently cooled again to the temperature of interest. After recrystallization, it is strictly required, that the solid is present in excess for the whole experiment, the vessel is uniformly heated over the entire suspension volume and the solid content is ideally distributed inside the liquid in a way that the phase contact is intensive and no sedimentation or dead zones occur. After a certain time, liquid samples should be taken periodically for concentration measurements until the liquid composition remains constant and equilibrium is achieved. Subsequently, the solid can be separated and should be analyzed as soon as possible to conserve potentially unstable polymorphs or solvates. In both cases, it is necessary to prevent nucleation of the liquid phase sample or the residual moisture on the solid phase. Hence, the whole solubility curve of a binary system can be determined if the procedure is repeated sufficiently often for the temperature range of interest. For multi-component systems, commonly more attention is directed to the solubility-composition dependency and only a few temperatures are considered. Even though the discussed method is robust and reliable, special care has to be taken if systems forming solid solutions are involved. As explained, the liquid and solid compositions depend on each other. Thus, the first occurring small crystals after recrystallizing the sample will change their composition continuously until equilibrium is reached and all particles are homogeneous [26]. Thus, the necessary time for equilibrium is dependent on solid diffusion processes inside the crystals, which are rather slow. Hence, solubility analysis should be performed with a solid content as small as possible to allow reasonable fast equilibration.

The fundamental concept of driving force of crystallization, i.e. the supersaturation, was derived in this chapter. Furthermore, the basic binary and ternary phase diagrams were introduced. In particular, the similarity between crystallization from melts and from solution was discussed as well as the special character and the purification challenges of systems forming solid solutions. The last part of this chapter was dedicated to determination options of solid-liquid equilibria and the best practice of measuring solubility curves and isotherms. The fundamentals of thermodynamics yield the basis, i.e. the phase diagrams, for every crystallization process. Hence, innumerable options of operation modes and apparatuses exist since the processes are specifically designed for the corresponding solid-liquid equilibrium. Therefore, the next chapter introduces briefly a rough framework of crystallization modes to classify the two particular processes, which are the focus of this work.
3. Operating modes for crystallization processes

Apparently, solid-liquid equilibria can become quite complex as already pointed out for simple cases in the previous chapter. Hence, the corresponding separation process has to be individually designed to meet the desired specifications. The developed crystallization instruments, operation modes or approaches are innumerable as the different substances produced by crystallization. The decision can be made based upon the mass to process, a desired crystal size distribution or shape, the necessary physical or chemical properties of the product, robustness or long-term stability of the process or on economical or ecological considerations. Commonly some of these tasks exclude each other. For example, the best performance of a crystallization process with respect to the productivity will yield most likely the worst purity of the product. If a product is produced continuously or batch-wise is in many cases a decision of the throughput and the required purity. Especially for pharmaceuticals, crop or fine chemicals a discontinuous production is favored. The corresponding product specifications are very strict with respect to the phase produced, the impurities left from the synthesis and the particle properties. Additionally, the production rate of these substances is low compared to bulk products and commonly in range of 1000 tons per year [54, 55]. However, batch production is inefficient for inexpensive products like sugar or ammonium sulfate. The operation costs would be clearly higher if only the necessary dead times for charging and discharging the crystallizer are considered [8]. On the other hand, single-stage operation is limited to systems exhibiting a simple eutectic or an intermediate compound. If the substances can form solid solutions fractional crystallization has to be applied for purification purposes.

As it can be seen from this brief discussion, all strategies have specific advantages and drawbacks and can be combined with different modes of creation of supersaturation. In order to define the tasks of the processes discussed in this work in detail and to put those into a bigger framework, a brief outline of operation modes and apparatuses applied for crystallization from solution will be given in this chapter.

3.1. Batch operation

Generally, batch operation means the charging of a vessel in the beginning of a production, the initiation of the crystallization due to generation of supersaturation together with the subsequent discharge and cleaning of the equipment. Thus, a rather simple construction of the corresponding crystallizer is sufficient since no continuous fluxes of suspension, vapor or solution have to be processed [55]. Hence, normal stirred-tanks are common, which are not tailored to any component and thus can be applied for the production of several different substances. These multi-purpose plants
are especially of interest if different polymorphs, solvates or hydrates can occur. The opportunity to clean the crystallizer between each batch prevent auto-seeding with an undesired phase. Additionally, the option to apply seed material simplifies the control of the process and improves its robustness. Since an appropriate seeding strategy serves to adjust product quality and crystal shape and ensures the solidification of the desired phase.

However, due to necessary dead-times and the process principle itself, productivity and throughput are not comparable to continuous crystallizations. Furthermore, products from different batches, which were processed under the same conditions, will vary slightly in appearance.

Additionally, the generation of supersaturation has to be adjusted to the substance system, i.e. to the solid-liquid equilibrium, the kinetics of crystallization and the physical and chemical properties of the product. For example, cooling crystallization is commonly applied if the solubility of components or mixtures varies significantly with temperature [56]. Thus, supersaturation can be adjusted precisely with an appropriate seeding strategy and heat exchange inside the reactor.

A batch crystallization from a certain start temperature, $T_0$, which is slightly supersaturated at $S_0$ is considered in figure 3.1 a). Seed crystals with a defined size distribution, $f_{\text{seed}}$, are subsequently introduced (Fig. 3.1 d) and cooling of the crystallizer content is initiated. The process output (Fig. 3.1 c) then depends on the final temperature, $T_F$, the velocity of heat exchange as well as on the cooling policy (Fig. 3.1 b, see e.g. [57, 58]). Commonly, smooth growth of the initial material and less nucleation is favored since this provides the control of the final crystal size distribution, $f$, to a certain extend. Hence, the drastically increasing supersaturation (bold line in Fig. 3.1 e) due to a natural cooling policy (NCP, bold line in Fig. 3.1 b) is undesirable. The final product (bold line in Fig. 3.1 f) is governed by fine material nucleated at the beginning of the process. Even though, linear cooling ramps (LCP) provide slightly better product qualities (dashed lines in Fig. 3.1 b, e, f), the best outcome is achieved by controlled temperature exchange (CCP dashed-dotted lines in Fig. 3.1 b, e, f). The latter one, leads to a gently increasing supersaturation, which stays constant for the rest of the process. Hence, the nucleation rate is small and most of the solidified material is formed by growth of the seed crystals.

In that way, also heat-sensitive substances can be produced under gentle conditions with defined product qualities. Furthermore, the control of occurring phases is simplified if the phase diagram is known and the initial and final crystallization temperatures as well as the seed strategy are adjusted appropriately. Nevertheless, the maximal yield of cooling crystallizations is limited to the solubility at the final process temperature.

If higher process yields are desired or if the solubility is constant over the considered temperature range, evaporation or vacuum crystallization can be applied, particularly if the solvent is volatile. Nevertheless, the boiling solution will probably spray on foreign surfaces and solidify at a different temperature and concentrations than the actual crystallizer content. Furthermore, the liquid level decreases and the residual mother liquor will solidify on the walls of the vessel. Thus, different phases can be present in this encrustation, which involves the danger of auto-seeding with e.g. an undesired polymorph [59].
The third common option is to add a second liquid, which exhibits in mixture with the solvent a lower solubility for the processed substance system. This method can be applied for substances systems where the solubility does not increase with temperature and evaporation is economically inefficient. However, high supersaturation can occur at the injection point of the anti-solvent as well as new solvates or polymorphs resulting from the added liquid phase.

Therefore, a batch cooling crystallization is often applied for the estimation of crystallization kinetics [60-63] due to the simpler control and less complex operation and is therefore considered also for the present work as the preferred operation mode.
3.2. Continuous operation

Advantageous for higher production rates are continuous processes since e.g. charging and discharging times are omitted. Hence, higher space-time-yields are achieved by continuously operated plants and therefore the operational costs are rather low. This operation mode is usually applied for mass products like e.g. sodium chloride, saccharose, acetylsalicylic acid or ammonium sulfate.

Fig. 3.2: Scheme of a continuous crystallization for different operating points. a) Steady-state operation with crystallization temperature, $T$, and steady-state supersaturation, $S_{\text{Steady}}$, as well as crystal size distribution, $f_{\text{Steady}}$. The feed is introduced from the top with the temperature $T_{\text{Feed}}$, supersaturated at $S_{\text{Feed}}$ and feed crystals distribution $f_{\text{Feed}}$. b) Scheme of the contour lines of the mean product sizes of a continuous crystallization process dependent on mean residence time, $1/F$, and initial supersaturation, $S_{\text{Feed}}$. c) Transient supersaturation of two different process variable combinations. d) Average number density distribution, $f$, produced material for the two process variable combinations.

Commonly, a saturated liquid is fed into a stirred vessel where the solvent is evaporated or vacuum is applied to simultaneously cool and concentrate the solution to generate supersaturation [64]. After a certain start-up period a dynamic steady-state is achieved if
the process variables are chosen appropriately. Afterwards, product with a constant quality can be harvested until maintenance is necessary due to fouling or encrustation. Several different types of crystallizers were developed for continuous production where the most common are the forced circulation (FC), draft tube baffle (DTB) and Oslo type crystallizer. The temperature exchange can be realized for all three apparatuses e.g. in an external circulation, which is preferred for viscous liquids or rather high temperature differences, but the mixing of the crystal phase is different. While the whole suspension is circulated in a FC crystallizer commonly only a stirrer is applied for mixing the content of a DTB vessel. Most gentle agitation is achieved with an Oslo crystallizer where the particles are suspended in a fluidized bed by recycled and concentrated mother liquor. Hence, all three are applied for the production of a certain range of crystal sizes (FC: < 0.6; DTB: < 2mm; Oslo: ≤ 4mm) since the shear forces inside the crystallizers differ drastically. However, the control of a continuous crystallization is rather complex and the process variables, e.g. mean residence time, evaporation rate or temperature difference, are correlated with the product quality in a highly non-linear way.

An abstract example of a continuous cooling crystallization is shown in figure 3.2. a). The feed, \( T_{\text{Feed}} \), and vessel temperature, \( T \), define together with the feed supersaturation, \( S_{\text{Feed}} \), and the inlet flux, \( F \), the maximal driving force for the process. If the mean residence time is too small together with a rather low supersaturation, an initial solid phase will be washed out after a certain time period (Bold black line in Fig. 3.2 b) or introduced seed crystals, \( f_{\text{Feed}} \), will not grow significantly until they are transported out of the process. Preferable is a point of operation, which leads to a coarse product with less fine material (dashed line in Fig. 3.2 d), low residual supersaturation (dashed line in Fig. 3.2 c), \( S_{\text{Steady}} \), and an appropriate mean residence time (e.g. point 1 in Fig. 3.2 b). An increase of supersaturation leads to higher growth rates but eventually also to primary nucleation. If additionally the mean residence time is decreased (point 2 in Fig. 3.2 b), i.e. the inlet flux is increased, crystals will be washed out before they become significantly large resulting in an additional increase of supersaturation. Thus, primary nucleation will increase as well until the driving force decreases again. Hence, the crystallization process will eventually oscillate with respect to product quality and supersaturation (solid line in Fig. 3.2 c). Additionally, fine material will govern the product due to primary nucleation events. The optimal process region will be complex and non-intuitive (solid lines in Fig. 3.2 b) for \( T \) and are based on the set-up and the crystallization kinetics of the substance system and therefore specific for every separation task.

Mixed suspension, mixed product removal principle

The MSMPR (mixed suspension, mixed product removal) principle is a theoretical concept, which can be applied for the acquisition of crystallization kinetics, i.e. the overall growth and nucleation rate [8, 10, 13, 56, 65]. It serves to describe the steady-state operation of a continuous crystallization based on a simplified population balance with respect to the crystal size distribution. Several assumptions have to apply for an experimental set-up and the procedure to evaluate the acquired data with the MSMPR concept. As mentioned, steady-state
operation for a given supersaturation and temperature is a prerequisite and hence
isothermal operation, a constant feed and crystallization volume as well as stable fluid
dynamics are necessary. Furthermore, an ideally mixed vessel, usually a solid free feed
flux and an isokinetic product removal are assumed. The distribution of the produced
equal shaped crystal phase can then be described by an exponentially decaying
function of the crystal size (see e.g. Fig. 3.2. d), which is logarithmized to yield a straight
monotonic decreasing line. The slope of this linear function is related inversely to the
mean residence time and the actual growth rate with respect to the process conditions.
The corresponding nucleation rate is furthermore calculated based on the intersection
point of the linear function with the ordinate. Occurring deviations from the linear
function are often the result of agglomeration or breakage of the crystals, growth rate
dispersion of the nucleated particles as well as a classifying product outlet yielding
changes of the slope or even more complex functional relationships.
To meet the constraints of the MSMPR concept, a continuous cooling crystallization in a
DTB apparatus can be utilized. Due to the draft tube baffle principle a gentle but
efficient agitation of the suspension can be realized, which provides the essential mixing
but decreases abrasion and breakage of the particles. The generation of
supersaturation due to cooling serves to avoid unnecessary encrustations resulting from
a solvent evaporation. Additionally, the agglomeration tendency can be decreased if the
solid content is kept rather low. Hence, the MSMPR concept is limited to lab scale
experiments since several of the mentioned assumptions cannot be met by industrial
crystallization processes. Nevertheless, it is applicable as a simplified approach for the
first design of a continuous crystallization process.

3.3. Fractional crystallization processes

Among simple eutectic and intermediate compound forming systems substance
mixtures with miscibility in solid state are very difficult to separate into its pure
components as pointed out in the last chapter. A few opportunities for separating solid
solution systems were reported based on a multistage process by different authors [9,
66, 67]. In all these works, the characteristic crystallization behavior of these systems is
exploited within a sequence of separation units. The fractional crystallization principle
was characterized by Matz [9] as follows: repetitive mixing of solid and liquid phases
which are not in equilibrium with each other until the phase equilibrium is reached with a
subsequent solid-liquid separation. Additionally, it is stated that a feasible process is
only possible if the solid phase is molten or dissolved in every purification stage since
the diffusive transport within a solid phase is infinitesimal compared to the liquid state.
This is of special interest for solid solutions since mixed crystals grow in layers and
have quite complex underlying phenomena of dissolution and recrystallization until the
thermodynamic equilibrium of the solid phase in presence of a certain constant liquid
phase is attained [29].
Fig. 3.3: Scheme of three cycles of a fractional crystallization to purify a system A, B and solvent, which forms solid solutions, applying a cascade of batch crystallizers. Starting from a liquid supersaturated feed in cycle one, the resulting solid phases are processed as shown in the configurations of vessels on the left side. The purification progress is depicted in triangle diagrams on the right side: solid lines - solubility isotherm at $T_2$; dashed lines - solubility isotherm at $T_1$; dashed-dotted lines - pathways of dissolution with solvent and evaporation of the solvent; double arrows - phase separation according to the thermodynamic equilibrium connection (conodes). Important partial masses, $m$, and compositions, $x_i$, are indicated.
For realization of this approach and the example shown in figure 2.9, a defined amount of feed, \( m_{\text{feed}} \), with a certain composition, \( x_{\text{feed}} \), of two dissolved substances A and B is introduced into the first stage of a fractional crystallization plant during the first cycle (left in Fig. 3.3, Cycle 1). The already at \( T_1 \) supersaturated liquid phase is cooled down to \( T_2 \) (triangle diagram in Fig. 3.3, Cycle 1) to initialize nucleation and the phase separation according to the conodes of the substance system (see double arrow in the triangle diagram in Fig. 3.3, Cycle 1). Subsequently, a liquid and a solid phase with compositions \( x_{L} \) and \( x_{S} \) are present after equilibrium is attained. Both phases with partial masses \( m_{L} \) and \( m_{S} \), which can be calculated from the phase diagram via the lever rule, are separated from each other and introduced in the next purification stages for the next cycle (liquid phase processing not shown in the figure for the sake of clearance). The solid phase is dissolved completely with pure solvent at \( T_1 \) to enhance the equilibration for the next crystallization (see dashed-dotted line in the triangle diagram in Fig. 3.3, Cycle 2). Afterwards, a part of the liquid phase is evaporated again and additionally the temperature is decreased to \( T_2 \) again to initialize the next solidification (see double arrow in the triangle diagram in Fig. 3.3, Cycle 2). The procedure of phase separation, phase transport, dissolution and recrystallization is repeated until the desired purity is reached, e.g. \( x_{3,S} \) (triangle diagram in Fig. 3.3, Cycle 3), and the product with the mass \( m_{S} \) can be harvested. It is obvious, that the transported solid phase decreases with each cycle and the final product yield will be rather low [68]. Therefore, efficient stage configurations were developed in the last century to enhance the productivity of the utilized batch crystallizer cascades [69]. However, the experimental application and validation of the specific processes are rather difficult [9, 66, 67]. The required solid-liquid separation after each recrystallization may lead to a complex process with high operational costs. Furthermore, the required transport of the crystal phase in the solid state between the crystallization units is sophisticated and thus the potential of automation is limited. Nevertheless, gradual fractional separation of two-component solid solutions in a solvent is of large interest for the production of highly purified substances since it is the only option for purification based on crystallization. Hence, there is still the potential for further improvement and a need for systematic investigations.

One opportunity for the optimization of the process is implementing a counter-current between the phases as investigated theoretically in [66]. Furthermore, the fractional crystallization principle, especially as cascades of continuous crystallizations [56, 70], is also applied for other phase systems to optimized yield or product quality and increase purification efficiency [8]. These points will be intensively discussed and an improved fractional crystallization process will be introduced in chapter 8. A subsequent proof of principle in a corresponding pilot plant will be given in chapter 9.
4. Crystallization kinetics and quantitative description

The basic kinetic mechanisms of crystallization, e.g. nucleation, growth or dissolution, are complex and yet not understood in every detail. Nevertheless, the numerical description of these fundamentals is a prerequisite for an efficient design and control of processes regardless of the operation mode or the generation of the driving force. Population balance equation systems (PBE) are applied for the description of the spatial distribution and the evolution of properties of a particulate system, e.g. a crystal collective, in a certain volume. The individuals of the population can be distinguished by a set of independent properties [10] like spatial coordinates or size and shape. These generic partial differential equations contain mathematical expressions for relevant kinetics, which reflect the actual dynamic behavior of a substance system. Consequently, the parameters comprised in the kinetic approaches applied have to be determined for every substance system or experimental set-up. Subsequently, the dynamic behavior of a particle population during a crystallization process can be described, which provides the mathematical basis for the development of control and design strategies. Therefore, this chapter is dedicated to the basic kinetic mechanisms, which alter the internal properties of a crystal phase. Subsequently, population balance systems are introduced for processes, where the control of the distribution of quantities of a particulate system is the main focus.

4.1. Basic mechanisms

Crystallization is per definition [8] the transformation from a fluid or amorphous solid phase into an ordered solid phase. The main driving force is the supersaturation, as explained in the second chapter, which will be generated mainly through temperature changes for the considered substances and processes of the present work. In an undersaturated solution present crystals will dissolve and no solidification takes place. If this solution is cooled, it will be saturated at one point according to eq. 2.12 for \( x_{\text{liquid}} = x_{\text{sat}}(T) \). The system has reached a dynamic stable state where neither crystallization nor dissolution occurs. Further temperature decrease yields a supersaturated solution and leads to growth of present crystals. Nevertheless, the formation of new crystals (i.e. nucleation) will not occur from a clear solution until a certain subcooling is attained [8, 13]. In this metastable state a reversible formation of unstable elementary building block clusters takes place, which most likely dissolve again. With increasing supersaturation these clusters will also increase in size until a
critical state is reached and the probability of dissolution and further growth of these aggregates becomes equal. At this border of metastability, rapid solidification of small crystals occurs, which can grow or agglomerate until the supersaturation is depleted. Additionally, larger particles will eventually collide with the agitation device, reactor walls or other particles and break or get abraded.

These basic mechanisms (represented in Fig. 4.1 without agglomeration and breakage), which occur during a crystallization process, will be discussed together with appropriate mathematical approaches in the following.

4.1.1. Nucleation

After a certain supersaturation is achieved spontaneous formation of crystals out of a clear solution after a finite time occurs. The state of a system between saturation and spontaneous solidification is called metastable zone. For the determination of the corresponding zone, which has a stochastic character, in the phase diagram, e.g. isothermal or polythermal methods exist as for solubility measurements, and the numerous influencing factors can be found elsewhere [8, 13, 14] and will not be discussed here.
Crystallization kinetics and quantitative description

Fig. 4.2: Principle dependency of the metastable zone width on different nucleation mechanisms [56].

Nevertheless, before macroscopic crystalline solids can develop, elementary building block clusters have to form and stabilize when the system state is at the border of the metastable zone (grey dotted line in Fig. 4.2). The classical theory for this primary homogeneous nucleation, which is mainly based upon the results of Volmer and Weber [71], Becker and Döring [72], Frenckel [73] and Farkas [74], describes the formation of an ordered structure as a series of reactions between elementary building blocks ($X_1$) with a subcritical aggregate ($X_1^{sub}$) in the absence of impurities or crystalline material.

$$X_1 + X_1 \leftrightarrow X_2 ; X_2 + X_1 \leftrightarrow X_3 ; \ldots X_{i-1} + X_i \leftrightarrow X_i$$  \hspace{1cm} (eq. 4.1)

Hence, the net rate of these spontaneous density fluctuations can be calculated based on the addition or decay of elementary building blocks. Other mechanisms, like aggregation of larger clusters, are neglected since the concentration of larger aggregates will be small compared to the concentration of single building blocks and therefore the probability of a single-step addition is much higher.

The energetic state of a growing cluster can be calculated as the sum of the creation of an interface boundary ($\Delta G_S$) and the volume excess enthalpy ($\Delta G_V$) [8, 56]. The change of the Gibbs energy due to a spherical cluster formation of $n$ elementary building blocks with radius $r$ becomes therefore:

$$\Delta G = \Delta G_T + \Delta G_S = -n\Delta \mu + A_{\text{Cluster}}(r)\gamma_S = -\frac{V_{\text{Cluster}}(r)}{\gamma_{SC}} \Delta \mu + A_{\text{Cluster}}(r)\gamma_S.$$  \hspace{1cm} (eq. 4.2)

Where $\Delta \mu$ is the driving force (eq. 2.1) per molecule, $A_{\text{Cluster}}$ and $V_{\text{Cluster}}$ are the cluster surface and volume, $V_{\text{Unit}}$ is elementary building block volume and $\gamma_{SC}$ is the surface tension of the cluster.
tension. Equation 4.2 yields the well-known correlation between the energetic barrier of nucleation and the cluster radius (Fig. 4.3).

![Figure 4.3](image.png)

**Fig. 4.3:** Change of the Gibbs energy ($\Delta G$, grey curve) depicted as the sum of the change of the surface ($\Delta G_s$, black dashed curve) and volume energy ($\Delta G_v$, black dashed-dotted curve) with respect to the cluster size ($r$) inside a supersaturated liquid phase. The critical radius or size ($r^*$) and the critical Gibbs energy ($\Delta G^*$) are indicated [8].

The change of the free energy passes through a maximum due to the different dependencies of the volume and surface energies to the cluster size, which has to be overcome to create a stable crystal. The extremum of the curve depicts the instable critical nucleus, for which the probability of dissolution or growth equals. Hence, the critical cluster size ($r^*$, eq. 4.4) can be calculated from the first derivative (eq. 4.3) of the Gibbs energy change (eq. 4.2).

$$ \frac{d\Delta G}{dr} = 0 = -\frac{4\pi r^2}{n_{\text{mol}}} \Delta \mu + 8\pi r \gamma_s $$

(eq. 4.3)

$$ r^* = \frac{2 n_{\text{mol}} \gamma_s \Delta \mu}{2 \Delta \mu} $$

(eq. 4.4)

Substitution of this expression back into equation 4.2 yields the equation of the change of the Gibbs energy for a critical cluster [8].
Crystallization kinetics and quantitative description

\[ \Delta G^* = \frac{16 \pi r^2 \gamma^2}{3} = \frac{16 \pi r^2 \gamma^2}{3 kT \ln(S)} \]  \hspace{1cm} (eq. 4.5)

Here, \( T \) denotes the temperature and \( k \) the Boltzmann constant. The probability that clusters reach the critical size due to thermal fluctuations can be described by a Boltzmann distribution [71], which yields together with a pre-exponential factor, \( k_0 \) [73, 74], an expression for the rate of primary nucleating spherical particles at steady-state conditions [8, 13].

\[ B_{\text{hom}} = k_0 \exp \left( \frac{-\Delta G^*}{kT} \right) = k_0 \exp \left( \frac{-16 \pi r^2 \gamma^2}{3 kT \ln(S)} \right) \]  \hspace{1cm} (eq. 4.6)

The classical theory describes a strong exponential increase of nucleation rate if a certain supersaturation is exceeded or temperature is increased. Even though this theory can describe frequently experimental results (see e.g. [13]), it assumes among other things a steady-state of isotropic reactions in equation 4.1, that the physical laws of a continuum can be applied to molecular aggregates as well as that contributions from the translational and rotational degrees of freedom of a cluster can be neglected [13, 56]. Hence, several modifications where applied to reduce these assumptions (e.g. the kinetic nucleation theory [75, 76] or application of statistical and quantum mechanics [77, 78]), which include additional fitting parameters or the intensive need of computational resources.

Even though, these methods elucidate the underlying mechanisms or describe experimental results precisely, the needed experimental and computational effort limit their application for engineering purposes. Therefore, frequently power-laws are applied (e.g. eq. 4.7) for the quantification of primary homogeneous nucleation rates [19].

\[ B_{\text{hom}} = k_0 (w - w_{\text{sat}})^6 \]  \hspace{1cm} (eq. 4.7)

Nevertheless, pure homogeneous nucleation is a theoretical case since foreign surfaces, e.g. from dust particles or the reactor walls, are always present. These surfaces might decrease the energy barrier for elementary building block clusters to form a critical nucleus. Apparently, no general rule exists, which surface is catalytic active for the primary nucleation of a certain substance system [8]. However, the common theory for heterogeneous nucleation relates the decrease of the energy barrier to the ratio of the surface tensions of the cluster to the foreign material and the bulk solution. The molecular aggregate can “wet” the foreign surface if this ratio is favorable and reduces the contribution of \( \Delta G_S \) to the overall change of the Gibbs energy.

\[ \Delta G^*_{\text{het}} = \phi \Delta G^* \]  \hspace{1cm} (eq. 4.8)

with
Basic mechanisms

\[ \phi = \frac{(2 + \cos(\alpha))(1 - \cos(\alpha))^2}{4} \]  
(eq. 4.9)

Where \( \Delta G^* \) is the reduced Gibbs energy for a critical cluster due to a foreign material and \( \phi \) is a number between 0 and 1 describing the activity of the surface via the angle \( \alpha \) between the cluster and the foreign solid. Consequently, heterogeneous nucleation occurs at lower supersaturations (grey dashed-dotted line in Fig. 4.2).

Commonly, batch crystallizations are initiated by seeding with appropriate material and continuous processes rely on the presence of a suitable amount of solid phase. Hence, primary nucleation is of less interest for technical applications. Additionally, there is evidence [79] that even from a clear solution only a few first particles are formed by primary nucleation while later evolving crystals originate from them by secondary nucleation.

Several studies in the last century investigated the origin and mechanisms of secondary nucleation. A comprehensive summary can be found in [13], [8] or [80]. Roughly, all mechanisms can be distinguished between apparent and true secondary nucleation based on the necessity of supersaturation.

Apparent secondary nucleation includes mechanisms, which increase the amount of crystals even in a saturated solution like dust on seed crystals, breakage of larger agglomerates or abrasion of macroscopic particles. The latter can be one of the main sources of newly generated crystals and is therefore the often investigated, e.g. [81-84]. Commonly, crystal-stirrer, crystal-crystal collisions or collisions between crystals and the reactor walls or installations are considered. The intensity of abrasion is influenced by many factors, like the stirrer geometry, the design of the crystallizer and the energy dissipation. For example, collisions with the agitation device increase e.g. with the amount of blades and their setting angle [81]. Furthermore, the probability and intensity of contact rises with the stirring speed and the place (edge or plain) where the blade hits the crystal. Obviously, also the suspension density and the particles size distribution will have an influence. Larger crystals will for example less likely follow the fluid streamlines and hence collide more often with parts of the reactor. But also the crystal shape, the mechanical properties of the crystallized material and the quality of the crystal surface [13] will change the rate of secondary nucleation.

Nevertheless, it is well-known that even low energy stress on a growing crystal, which is not sufficient for damaging the solid phase, produces new particles when supersaturation is present [13, 80, 85, 86]. The theory is based on an adsorption layer of semi-ordered, partly desolvated solute present on the surface of a growing crystal. This layer of elementary building blocks, which are in the state between bulk and crystal phase, are much more sensible to mechanical stress. Hence, a rupture of aggregates or cluster is likely even due to slight contacts, e.g. crystal-crystal collisions, which are otherwise not sufficient to abrade the crystal surface macroscopically [81]. The released aggregates in a pre-critical state need a certain driving force to evolve to a stable solid phase. Therefore, this kind of mechanism is sometimes termed true secondary nucleation [13].

The low energy contacts of crystals can become much more probable than crystal-stirrer collisions depending on the suspension density and the hydrodynamics inside the
crystallizer. Furthermore, also the shear forces between the mother liquor and the crystal surface can cause a rupture of the adsorption layer [80]. Hence, true secondary nucleation is sometimes considered to be the main source of secondary nucleation [10]. There are more theoretical mechanisms like dendrite coarsening, activation of clusters in the force field near the crystal surface or depletion of impurities by present crystals, which can explain an increase of particles due to a present solid phase. However, a significantly lower driving force is necessary to generate particles by secondary nucleation (black dashed line in Fig. 4.2) compared to the primary mechanisms but a distinction between the mentioned secondary mechanisms can hardly be made in laboratory experiments and is impossible in a real crystallizer environment. Additionally, expensive and time consuming but excellent theoretical and experimental investigations like in [81] are usually not feasible. Hence, several studies [10, 83, 87, 88] apply a power-law (eq. 4.10) consisting of the main dependencies of secondary nucleation like the stirrer speed and the suspension density, which can be measured easily.

\[ B_{\text{sec}} = k_c \omega^{p_1} \rho_{\text{susp}}^{p_2} \exp \left( -\frac{E_a}{RT} \right) (S - 1)^{p_3} \]  (eq. 4.10)

Where \( \omega \) is the stirrer speed, \( \rho_{\text{susp}} \) is the suspension density, \( E_a \) is the activation energy and \( p_1, p_2, p_3 \) are fitting parameters. The pre-factor \( k_c \) contains consequently all other effects influencing the secondary nucleation like the crystal shape dependency or geometrical aspects of the set-up, which are supposed to be constant.

Beside the mentioned mechanical influences, also supersaturation, temperature and additives can change the secondary nucleation rate. A larger driving force leads to a roughening of the surface or dendritic growth as well as to an increase of the thickness of the adsorption layer [13] and smaller critical size and hence to an increase of newly generated particles. Also a faster healing of damaged crystal edges occurs, which then serve again as an effective source for macro-abrasion [83]. In contrary, if a temperature dependency exists, it is closely related to the mechanism. Crystal-stirrer collisions are probably not altered by a temperature change if the viscosities and densities of the phases are nearly constant. An influence on the adsorption layer [10] or on the survivability of subcritical clusters is conceivable.

4.1.2. Crystal growth

If a crystal grows, solute building blocks are transported from the bulk phase to the crystal surface and are incorporated into the crystal lattice. Several theories were developed how the different steps of crystal grow proceed and how a general expression for the growth rate can be developed.

It is accepted, that at first a building block has to overcome a laminar boundary from the bulk phase to the vicinity of the crystal surface by molecular diffusion [7]. The resistance of this diffusion process is determined by the thickness of the layer, which mainly depends on the interstitial velocity between the crystal and the bulk phase, and the diffusivity of the solute, which is according to the Stokes-Einstein equation a function of temperature and viscosity.
When the building block approaches the crystal surface it will get desolvated and under certain circumstances integrated into the crystal lattice. The probability of integration of a randomly approaching solute molecule depends on the energy released during this step. Kossel and Stansky [13] evaluated different positions on a crystal surface and defined the most suitable in a perfect crystal without defect and a primitive cubic lattice as half-crystal position (or kink position). Here, the building block has 13 direct neighbors and therefore the energetically most stable position. On a crystal terrace close to a growing edge, it is conceivable that a certain surface diffusion step takes place if a solute molecule arrives at a flat crystal face in an unfavored position. Therefore, the incorporation step will not be instantaneous due the desolvation of solute building block and the surface diffusion process [89]. The boundary layer theory [8, 13] defines consequently a third, intermediate phase between the crystal surface and the bulk phase, which consists of partly desolvated semi-ordered building blocks like also suggested by some spinodal decomposition theories. Some experimental works gave evidence that this intermediate phase exists and showed its importance for secondary nucleation [85, 86, 90] as mentioned in the previous chapter. Finally the overall transport of a solute molecule from the bulk phase to the crystal surface consists of several sub-steps:

- Molecular diffusion of a building block through the laminar boundary layer (Fig. 4.4).
- Diffusion through the boundary layer and potential partial desolvation.
- Adsorption on the crystal surface eventually with a second partial desolvation.
- Surface diffusion to an energetically favored crystal lattice position for incorporation with complete or partial desolvation.
- Counter-diffusion of the solvent molecules through the boundary layer and the laminar boundary into the bulk phase.

The subsequent incorporation of a building block is dependent on the energy released during the integration. This energy is related to molecular position of attachment, i.e. if the building block attaches to a terrace, step or kink site, and on the crystal face where it is incorporated. Three different types thereof (kinked (K-faces), stepped (S-faces) or flat faces (F-faces)) can occur on a perfect “Kossel-crystal” defined by the amount of nearest neighbors. Following the definition of Hartmann and Perdok [91], these face classes are better distinguished by their orientation with respect to the strongest bonds of the crystal lattice. Here, a strong bond is defined as “a bond releasing a high amount of energy in the crystallization process.” [91] Hartmann and Perdok concluded that a F-face is parallel to two or more of these periodically repeated strongest bonds. Building blocks, which are incorporated on these faces release the lowest amount of energy. A S-face is parallel to one of the strongest bond chains and a K-face to none of them. Hence, the incorporation of a building block into a K- or S-face will release more energy and these faces will therefore expose larger growth rates. Consequently, the crystal shape and the growth process will be governed mainly by F- or slow growing S-faces.
Regarding the classical theory of Kossel and Stansky [13], crystal growth taking place only at kink positions on F-faces would lead to perfect cubic crystals with smooth surfaces and a decreasing rate of building block incorporation. However, it was already stated in the mid of the last century, that edges on a crystal surface always develop a certain amount of kink positions due to thermal fluctuations [92,93]. Additionally, real crystals contain usually lattice defects, which may form growing edges and therefore an amount of growth positions on a crystal face. Hence, even F-faces expose significant and stable growth rates at low supersaturation [8]. One common model, which describes the influence of lattice defects and thermal fluctuations on the crystal growth rate, was developed by Burton, Cabrera and Frank. The corresponding BCF model [94] is based on screw dislocations, which continuously provide an amount of growing steps forming characteristic spirals on the crystal surface [95,96]. If the driving force increases above a critical level, 2-dimensional stable nuclei can form inside the boundary layer [8, 96]. This mechanism leads to the deposition of disc-shaped monolayers of critical length, which subsequently spread over the crystal face. The geometry as well as the deposition or nucleation rate depends on the surface tension of the crystal faces forming the edges of the 2-dimensional nuclei similar to primary homogeneous nucleation [97, 98]. Obviously, the overall growth rate increases by this mechanism since numerous aggregates are formed covering the crystal faces and providing a large amount of growing edges.

At even higher driving forces, the elementary building blocks are incorporated regardless of their position. Even the attachment on a crystal face terrace yields a favorable state with respect to the free energy by this rough or dendritic growth mechanism. Recently, the group of Doherty gave a substantiated review about the three mentioned mechanisms [97, 98]. They incorporated additionally energetic calculations of the crystal faces based on the Hartmann-Perdok-rules to estimate the work necessary to form kink positions in a monolayer edge [99]. Together with the theory of Burton, Cabrera and Frank [92, 93] they were able to refine the equilibrium shape calculations of Hartmann and Perdok [100] under consideration of different growth mechanisms [98, 101, 102]. In summary, the incorporation step of building blocks is dependent on the supersaturation, which determines the growth mechanism to a certain extent, the considered crystal face and the position of incorporation with respect to the crystal lattice, which define the released energy and therewith the rate of integration. To capture all these influences several of the involved parameter of [98], e.g. for the energies of transitions states or the surface tension, are estimated with sophisticated methods. Additionally, influences of the a priori transport step, like e.g. the diffusion coefficients in the laminar or boundary layer or the layer thicknesses, complicate the determination of the overall growth process.

Therefore, a diffusion-reaction model is often applied for industrial and engineering purposes [13]. It comprises only the two rate determining general sub-steps of crystal growth: diffusive transport from the bulk phase to the crystal surface and subsequent integration (Fig. 4.4).
The transport over the laminar layer, \( \frac{dM_{\text{diff}}}{dt} \), can be quantified with equation 4.11 assuming a steady-state concentration profile (Fig. 4.4) and that the diffusion can be described via Fick’s first law.

\[
\frac{dM_{\text{diff}}}{dt} = -k_{\text{Diff}} A_{BL} (w_{\text{bulk}} - w_i)
\]

Where \( w_{\text{bulk}} \) and \( w_i \) are the concentrations in the bulk phase and at the boundary layer and \( A_{BL} \) is the surface of the boundary layer. The coefficient \( k_{\text{Diff}} \) comprises the laminar layer thickness as well as the diffusion coefficient and depends therefore on the fluid dynamics, temperature and the physical properties of the solution.

Subsequently, the building blocks arrived at the boundary layer are integrated by any of the afore mentioned mechanisms into the crystal lattice (eq. 4.12).

\[
\frac{dM_{\text{int}}}{dt} = k_r A_{CS} (w_i - w_{\text{sat}}(T))^j
\]

Where \( w_{\text{sat}} \) is the saturation concentration and \( A_{CS} \) the surface of the crystal. The coefficient \( k_r \) accounts in this case for the anisotropy of the integration and lumps all diffusion influences of boundary layer or on the surface as well as the temperature dependency of the integration step. The exponent \( j \) is related to the dominating growth mechanism [10] and is usually assumed in the limits of 1 and 2. This reflects the supersaturation dependency of the BCF model and the 2-dimensional nucleation mechanism. For low supersaturations the BCF model correlates to \( S^2 \) while for higher driving forces both, the BCF and the 2D mechanism, depend linearly on the supersaturation.

Both approaches are commonly merged to eliminate the unknown concentration at the boundary layer and the solid deposition rate, \( \frac{dM_s}{dt} \), is approximated with equation 4.13 [13].
Crystallization kinetics and quantitative description

\[ \frac{dm_c}{dt} = k'_g A_g \left( w - w_{\text{sat}}(T) \right)^g \]  \hspace{1cm} (eq. 4.13)

Where \( k'_g \) contains the influences previously captured by \( k_{\text{ori}} \) and \( k_v \). The exponent \( g \) is not clearly related anymore to the growth mechanism due to the approximation. Equation 4.13 can be rearranged to give the growth rate of a certain dimension, \( L \), for further application within the PBE framework [10].

\[ G = \frac{dl}{dt} = \frac{k_s k_v L^2}{3 \rho_s k_v L^2} w_{\text{sat}}(T) S(T) - 1]^g = k_s(T) S(T) - 1]^g \]  \hspace{1cm} (eq. 4.14)

Where \( k_s \) and \( k_v \) are the surface and volume shape factors and \( \rho_s \) is the solid density. Equation 4.14 is an entirely empirical relationship with fitting parameters \( k_g \) and \( g \) but nevertheless a widely applied growth approach [103-107]. The overall temperature dependency of equation 4.14 can be approximated with the well-known Arrhenius-approach [8, 13].

\[ k_g = k_{g,0} \exp \left( \frac{-E_{g,0}}{RT} \right) \]  \hspace{1cm} (eq. 4.15)

Even though, equation 4.14 was applied successfully to describe experimental results, two influences are neglected, which are of great importance for technical crystallization processes.

Additives, which are usually present due to the feed material or the set-up, decrease the growth rate sometimes drastically and are effective even at low concentrations [108]. Some reviews on this topic can be found e.g. in [109] or [110]. The effect of additives on crystal growth are usually anisotropic and therefore they can change the crystal shape significantly (see e.g. [111-113]). Nevertheless, the underlying mechanism is not completely elucidated up to now and is specific for every impurity. Thus, the determination of growth kinetics in a technical process will always yield only an effective rate, which is specific for experimental procedure.

Furthermore, every crystal will expose its own individual growth rate. The effect of growth rate dispersion is related to different reasons [8, 13, 114]. For example, based on the Gibbs-Thomson effect small crystals (<1\,\mu m) will have a higher solubility. Thus, they tend to grow slower than larger particles. Additionally, fluid dynamics will eventually affect the growth rate dependent on the crystal size. The interstitial velocity in a well-mixed crystallizer is probably higher for larger crystals since small particles will follow more likely the stream lines of the fluid. Hence, the thickness of the laminar layer or even the adsorption layer is reduced, which decreases the substance transport resistance. In contrary, larger particles will have more collisions with e.g. the stirrer or the reactor wall causing more abrasion and therefore exhibit a lower effective growth rate. These effects are related to the particle size and therefore sometimes misinterpreted as size-dependent growth. In addition, some intrinsic properties, like for example lattice defects, of every crystal will cause a random distribution of growth rates, which leads to the well-known broadening of unimodal crystal populations [115, 116].
Initially provided seed crystals differ with respect to their surface quality [114]. This implies a different amount of kink positions, which influence the growth rate, even though this effect decays after a certain start-up period. The number of lattice defects, which are influencing among others the BCF mechanism, is also an individual particle property [13], which is probably effective over the whole time of the process. Additionally, the growth rate dispersion can increase during the process. Stress and tension inside a crystal caused for example by collisions, seems to change the solubility of the individual particle but also the amount of lattice dislocations [81, 117]. Hence, the mechanical properties of the solid phase as well as the process conditions are decisive for a positive or negative effect on the growth rate.

Furthermore, crystals will randomly move through different regimes of supersaturation and temperature even in a well dispersed system. These local gradients, e.g. at the crystallizer walls, can lead to a broadening of the particle population even though this effect may be small. Finally, also the process conditions or the growth history of a particle will change its growth rate. A large supersaturation will lead to several imperfections on the crystal surface and will eventually decrease the actual growth rate over the process time [116, 117].

Growth rate dispersion is even more important for nucleated particles regardless on the mechanism of nucleation. It was shown that the growth rate of 70µm crystals is on average twenty times larger than the growth rate of 3µm crystals [118]. This was often misinterpreted as size-dependent growth while the reason is that the particles which become bigger are already good growing crystals and expose therefore higher growth rates. An additional conclusion is that the growth rate spread of the smallest crystals is even higher than the one from the large particles yielding a high percentage of nuclei exhibiting even negligible growth rates [117, 118]. This effect was also proven by Jones and Larson [116] who showed furthermore that the evolution of the growth rate dispersion is affected by the several process parameters as well. Strain inside the crystal lattice of secondary nuclei, which is caused by high supersaturation, pressure or temperature, leads to a decrease of the average initial growth rate and to higher dispersion. Attempts were made, e.g. by Gahn [81], to characterize the growth rate dispersion of secondary nuclei with respect to the mechanical properties of the crystalline material and the stress on the crystal lattice by stirring or other collisions of the particles. Nevertheless, also primary nucleated crystals show significant growth rate dispersion [119].

In conclusion, growth rate dispersion of nucleated particles is of great importance for continuous nucleation since it seems that only 10-15% of the nucleated particles become large enough to account for 95% of the whole mass of the crystalline product in such processes [10]. The rest of the small particles do not show significant growth and are most likely washed out of the process. Even though, many models exist to describe the dispersion for macroscopic crystals (see e.g. [10] or [115]) the description of the growth rate dispersion of nucleated particles is often based on expensive experimental observations [81, 116, 119] and efficient characterization methods as well as an elucidation of the underlying mechanisms are still missing [115].
4.1.3. Dissolution

Several crystallization processes involve the dissolution of a part of the fines content of a particle collective to alter the product quality. Hence, the kinetics of dissolution is also of interest for the design of a fines dissolution loop in a continuous crystallization or for the optimization of an alternating temperature profile after a completed batch crystallization.

Dissolution of crystals is stated to follow the same steps, surface disintegration, solvation and diffusion into the bulk phase, as the crystal growth while undersaturation is present. Nevertheless, experiments show significantly higher dissolution than growth rates for similar thermodynamic conditions [8, 120]. A common explanation is a change of the crystal shape by the occurrence of crystal faces with higher Miller indices or a surface altering leading to the disappearance of crystal edges and vertices [120], formation of dissolution pits [8] or even skeleton-shaped crystals [121]. Additionally, the fast growing faces will dominate the crystal surface in contrary to growth. In consequence, more contact surface and weak positions of elementary building blocks are exposed to the bulk face. Hence, only the diffusive transport into the bulk face should be rate determining but the microscopic substance transport, the crystallography during dissolution and the surface disintegration mechanism is still not clarified.

Additionally, temperature, the pH value and impurities influence the dissolution kinetics [122-124] similarly to growth. Nevertheless, in many cases a simple linear temperature dependent approach is sufficient to describe the dissolution rate with respect to mass [8, 123] or crystal size reduction [120] (eq. 4.16).

\[
D = \frac{dL}{dt} = k_{\alpha}(S(T) - 1)
\]

(eq. 4.16)

4.1.4. Agglomeration and breakage

For lab-scale experiments with low solid content and moderate stirring rates breakage as well as agglomeration can be neglected for larger particles [56], as it was stated in chapter 3. Specific reactor geometries (e.g. DTB or Oslo crystallizer) decrease additionally the mechanical stress applied to the crystal phase by smooth agitation. These conditions were reasonably met during the experimental investigations as it will be shown in the following chapters and therefore agglomeration and breakage are not considered for the dynamic modeling.

Nevertheless, nuclei and small crystals are significantly affected by agglomeration [8] and aggregation especially for these process conditions. These particles will follow most likely the stream lines of the fluid field leading to low shear stress. Hence, adhesive and cohesive forces will lead to clustering of these fines, which can stay together as loosely bounded aggregates. Solid bonds are formed between the individual crystals of an aggregate if the supersaturation is sufficiently high. The resulting particles are commonly termed as agglomerates, which are barely affected by the fluid shear forces anymore. For low supersaturations, aggregates are probably disintegrated by mechanical forces before solid bonds can form.
However, agglomeration and aggregation will influence the results of experiments for the estimation of nucleation rates [56]. The absolute error is not accessible but will increase with supersaturation and number of small particles.

4.2. Continuous model

Population balance equation systems (PBE) are applied to describe the dynamic behavior of a particle collective, e.g. a population of crystals, with respect to the process conditions. The individuals of the population can be distinguished by a set of independent properties [10], where external coordinates describe the spatial distribution and internal coordinates characterize inherent properties like size and shape. The particulate phase is in connection with a continuous phase, i.e. a liquid or gas, which provides the necessary mass or energy transfer for the considered process. Since the conservation laws have to be fulfilled, corresponding balances for the exchange between the particulate and the continuous phase are applied, which describe the state of the overall system time and space dependent.

All kinetics introduced in the last section, except agglomeration and breakage, are incorporated in the population balance framework for a mathematical description of the evolution of a particulate population. However, detailed information about e.g. growth, nucleation or dissolution rates of a particulate substance system are often not available. Hence, the parameters comprised in the corresponding mathematical approaches have to be determined. Therefore, a method for the quantification of crystallization kinetics is introduced in chapter 5.

PBE models are an active field of scientific investigations due to the complexity and the diversity of potential applications (e.g. [103, 106 & 125-128]). A detailed discussion can be found in [10] and [129]. Hence, the mathematical framework will be introduced in a simplified form, which is based on several following assumptions, to shorten the derivation of the utilized PBE model for a batch and a continuous MSMPR process.

4.2.1. Population balance

For this work, the applied property balance is considered for a 1-dimensional state space. The spatial distribution of the particle collective or the concentration is negligible of the population and continuous balance since an ideally-mixed system is considered. The characteristic length, $L$, is different for each substance system and will be characterized in chapter 6.

For the crystallization case, the general population balance [10] reduces to equation 4.17 if breakage, agglomeration and volume contraction due to an occurring solid phase are neglected and size independent growth is assumed.

$$\frac{\partial f(t,L)}{\partial t} = -G(S(t),T(t)) \frac{\partial f(t,L)}{\partial L} + \frac{1}{\tau} (f_s - f_\omega) + B_0(S(t),T(t)) \quad \text{for } S \geq 1 \quad (\text{eq. 4.17})$$

Here, $f$ is the number density distribution, $B_0$ is the nucleation rate and $G$ represents the growth kinetics. The nucleation rate will be expressed via the boundary conditions of the discretization of the PBE system and can therefore be neglected in the general
formulation. No particles are fed to or taken from the reactor and hence equation 4.18 results for the simulations of a polythermal batch-process.

\[
\frac{\partial f(t,L)}{\partial t} = -G(S(t), T(t)) \frac{\partial f(t,L)}{\partial L} \quad \text{for } S \geq 1 \quad \text{(eq. 4.18)}
\]

For the continuous crystallization a solid-free inlet flux is assumed as well as constant suspension volume. Additionally, the withdrawn product distribution is equal to the reactor content, which yields equation 4.19 for the numerical studies of the continuous process.

\[
\frac{\partial f(t,L)}{\partial t} = -G(S(t), T(t)) \frac{\partial f(t,L)}{\partial L} \frac{f(t,L)}{\tau} \quad \text{for } S \geq 1 \quad \text{(eq. 4.19)}
\]

The corresponding driving force for crystal growth in equation 4.17-4.19, is the supersaturation, which is defined according to equation 2.12 as the ratio between the actual concentration, \( w \), and the saturation concentration, \( w_{\text{Sat}}(T) \), at a certain temperature. It should be mentioned again that the concentration, \( w \), denotes the mass loading.

The population balances were subsequently discretized (Appendix A) applying a finite volume method together with the upwind scheme [130], since an analytical solution is generally not available for these PDE systems.

For the resulting ODE system, two initial conditions (IC) are required. The initial size distribution, \( f_{\text{Seed}} \), is assumed to be zero if primary nucleated experiments are considered. If a seeded experiment is simulated and no experimental data is available, it is assumed that the seed crystals can be characterized by a perfect Gaussian distribution (eq. 4.20) with a certain mean value, \( L_{\text{Seed}} \), and standard deviation, \( \sigma \). The initial distribution is scaled to a certain mass, \( m_{\text{Seed}} \), with equation 4.21 since the Gaussian distribution is normalized.

\[
f_{\text{Seed}}(L) = \frac{1}{\sigma \sqrt{2\pi}} \exp \left( -\frac{1}{2} \left( \frac{L - L_{\text{Seed}}}{\sigma} \right) ^2 \right) \quad \text{(eq. 4.20)}
\]

\[
f_{\text{Seed}}(L) = f_{\text{Seed}}(L) \frac{m_{\text{Seed}}}{k \rho_{\text{Seed}} \int_0^L L f_{\text{Seed}}(L) dL} \quad \text{(eq. 4.21)}
\]

The occurrence of new crystals due to nucleation is introduced as an initial condition at the crystal size \( L = 0 \) (eq. 4.24). Subsequently, all conditions are defined for the crystallization case as follows:
IC for $S \geq 1$:

$$f(t = 0, L) = 0 \quad \text{prim. nucleation (eq. 4.22)}$$

$$f(t = 0, L) = f_{\infty}(L) \quad \text{seeded experiment (eq. 4.23)}$$

$$f(t, L = 0) = \frac{R}{G} \quad \text{(eq. 4.24)}$$

The dissolution rate, $D$, replaces the growth rate, $G$, for the case of undersaturation ($S < 1$) in equations 4.17-4.19 and 4.24. Furthermore, the initial conditions have to be adjusted in the model framework (eqs. 4.26 & 4.27). Similarly, the applied upwind scheme is changed with respect to the direction for the discretization.

IC for $S < 1$:

$$f(t = 0, L) = f_0(t, L) \quad \text{(eq. 4.26)}$$

$$f(t, L = 0) = \frac{D}{D} \quad \text{(eq. 4.27)}$$

Where $f_0$ describes the crystal size distribution before the liquid phase becomes undersaturated. The initial condition for the internal coordinate (eq. 4.27) specifies the rate, $D$, of crystals with a size $L \to 0$ vanishing from the population due to dissolution. This rate can hardly be determined experimentally and is thus numerically approximated by individuals, which cross for a certain time step the border of the last element of the discretized grid at $L = 0$.

**4.2.2. Mass balance of the continuous phase**

The continuous balance describes the concentration evolution during the considered processes and is coupled with the property balances via the mass exchange of the crystal growth or dissolution. The general mass balance of the liquid phase for an ideally-mixed system can be written as follows:

$$\frac{dm}{dt} = \dot{m}_s - \dot{m}_w - \dot{m}_{conv} \quad \text{(eq. 4.28)}$$

The mass consumed due to crystal growth, $\dot{m}_{conv}$, depends on the change of the third moment of the particle distribution. For simplification, the mass loading was chosen as concentration unit in terms of $[kg\text{Solute}/kg\text{Solvent}]$. Hence, the chosen formulation of the concentration equation 4.28 can be rewritten as:
Crystallization kinetics and quantitative description

\[ \frac{d(V_{\text{vap}}, \rho_{\text{vap}}, \omega)}{dt} = V_{\text{vap}}, \rho_{\text{vap}}, \omega - \rho_{\text{vap}, \text{t}}, \rho_{\text{vap}, \text{s}}(T(t)) \omega(t) - 3k, \rho_{\text{vap}} \left[ L G(S(t), T(t)) f(t, L) \right] dL \quad \text{(eq. 4.29)} \]

It should be noted, that for the batch-case the overall solvent mass inside the reactor is assumed to be constant. Hence, the corresponding mass balance consists of the accumulation in the liquid phase and the transport of substance to the solid phase due to crystallization.

\[ \frac{dv}{dt} = -3k, \rho_{\text{vap}} G(S(t), T(t)) \left[ \frac{L f(t, L)}{V_{\text{vap}, \rho_{\text{vap}, \text{t}}}(T)} \right] dL \quad \text{(eq. 4.30)} \]

Similarly, the mass balance for the continuous process can be derived. It should be mentioned, that the water content is dynamically calculated for this case due to the operation mode.

\[ \frac{dv}{dt} = \frac{1}{\tau} \left( \frac{\rho_{\text{vap}, \omega}(T)}{\rho_{\text{vap}, \omega}(T)} \omega - w(t) \right) - 3k, \rho_{\text{vap}} G(S(t), T) \frac{L f(t, L)}{V_{\text{vap}, \omega}(w(t), T) \rho_{\text{vap}, \omega}(T)} \quad \text{(eq. 4.31)} \]

The IC for the mass balances (eqs. 4.30 & 4.31) is subsequently:

\[ w(t = 0) = w_{i} \quad \text{(eq. 4.32)} \]

The whole model framework (eqs. 4.17-4.32) was implemented in MatLab and the solutions were approximated with a preprogrammed (ode45) Runge-Kutta method 4th order [131]. It will be applied in the following chapter to evaluate batch-crystallizations for the estimation of crystallization kinetics. Furthermore, the continuous model will be applied for the design of a MSMPR crystallization in chapter 7.
5. Novel short-cut method for the quantification of crystallization kinetics

Population balance models are of high interest for the efficient design, control and optimization of crystallization processes but the comprised mathematical sub-models for the description of the relevant kinetic phenomena, such as growth, dissolution and nucleation of particles can be rather complex as shown in the previous chapter. Currently, kinetic model approaches developed in academia intend to provide an insight into the mechanisms of the underlying processes. This induces a gap between the goal to answer basic scientific questions and the industrial utilization of these models. Common problems are the lack of practicability of the developed complex and detailed mathematical descriptions, the need for expensive and challenging measurement techniques as well as time consuming experimental demands to gain necessary basic knowledge of every substance system. Nevertheless, also simple kinetic sub-models are available, which lead to a decrease of numerical complexity and therefore reduce the number of necessary parameters and computationally time. The main task for the present study is therefore not to elucidate the underlying mechanism in detail but to provide sufficient information for a process design. However, the component specific parameters, which are included in all kinetic models, have to be determined for every new substance system or even for the specific experimental set-up.

Thus, a short-cut-method will be suggested, which is based on analyzing the evolution of the crystal size distribution during a few batch-crystallization experiments. The main task is to parameterize the necessary kinetic sub-models efficiently to predict and evaluate the performance of crystallization processes. To illustrate the overall procedure and to evaluate accuracy and benefit of the approach, simulated data corresponding to hypothetical experiments, assuming predefined kinetics will be exploited. A certain dataset of experiments is created with defined kinetics. Subsequently, it will be shown that it is possible to re-estimate the kinetic parameters again with a limited data amount. Then less complex kinetic approaches will be applied together with the short-cut-method to evaluate whether the procedure is still feasible even if a different approach was taken. Afterwards, it will be investigated if the error of the estimated kinetics evolves with the amount of data utilized for the estimation routine and how experimental errors influence the precision of the short-cut-method. Finally, an MSMPR process will be designed with the estimated and the initial kinetics. The comparison of both processes show the quality of the parameter estimation even if significant experimental errors are made and a limited data set is available.
5.1. Common quantification methods

Several methods with specific assets and drawbacks are known for the quantification of crystallization kinetics. One, which is simple to apply, is to perform desupersaturation experiments [8, 132]. Isothermal seeded batch experiments are investigated with respect to the occurring decrease of the supersaturation level and are subsequently correlated with an appropriate mass balance. It is hence possible to extract the growth rate of the present seeds with the main information extracted from the precisely measured concentration.

The corresponding objective function can be constructed for the diffusion-reaction theory (eq. 4.13) from the simple correlation:

\[
k \Delta \omega = \frac{d\omega}{dt} \frac{1}{m_{\omega A}}
\]  
(eq. 5.1)

However, this method is limited to process conditions where no nucleation occurs otherwise both mechanisms are lumped within the growth kinetics. Additionally, the seed crystals have to be chosen carefully and characterized extensively before and after the growth process to calculate the mean surface area change. Furthermore, several experiments (e.g. eleven in [133]) are necessary to determine growth kinetics for a certain range of temperature and supersaturation. More recent studies try to combine this method with solid phase measurement techniques (e.g. Laser reflection measurements, Ultrasonic probes, high resolution cameras for multi-dimensional investigations) for improvement [133-135].

Homogeneous nucleation kinetics can be measured with a similar method. The set-up used for growth rate estimation is used for induction time experiments [136-137] from which nucleation rates can be extracted.

\[
t_{\text{ind}} = \left( \frac{4 \rho_s}{k_B T G} \right)^{\frac{1}{v}}
\]  
(eq. 5.2)

Here \( t_{\text{ind}} \) depicts the induction time, \( \rho_s \) the suspension density of the nucleated particles and \( k_\text{v} \) the volumetric shape factor. The growth rate is necessary in this framework to correct for the time between the real nucleation and the actual time when the crystals can be measured. Hence, growth and primary nucleation kinetics can be quantified for a crystallization design with simple investigations with an experimental set-up close to the process conditions. Although the results of the mentioned studies for nucleation and growth rate quantification are verifiable and reproducible, the effort and the limits of this procedure remain. Furthermore, secondary nucleation is the dominating mechanism during a seeded batch-crystallization. Hence, the induction time measurements and the subsequent calculations have to be carried out from seeded experiments, which will be difficult.

Another method applies various types of single crystal growth cells [13-138]. Here, a super- or undersaturated solution is pumped through an isolated and temperature controlled volume to investigate one single crystal inside this volume with a microscope.
during growth or dissolution. Thus, the length or mass change of the crystal can be correlated directly with the supersaturation level inside the cell.

\[
\frac{dL_{hkl}}{dt} = G_{hkl} \tag{eq. 5.3}
\]

Where \(dL_{hkl}\) is the change of the distance of a certain face to the crystal centre, which can be correlated with its corresponding growth rate, \(G_{hkl}\). Furthermore, the shape evolution of the seed crystal can be well observed during these processes [139-140], which serves to identify possible sub-models of the corresponding kinetics [141]. However, the conditions, especially the fluid dynamics and present surfaces, inside a single crystal growth cell and in commonly applied reactors will differ from each other. Thus, a crystallization process design based on the results of this technique can be strongly erroneous. Furthermore, the correct determination of the length change of a crystallographic face will be difficult from a 2-dimensional microscopic image. Additionally, a rather wide scattering of single crystal data is usually observed due to growth rate dispersion and hence a certain amount of experiments (e.g. 101 in [140]) per operation point are needed for statistical analysis. Thus, this technique is commonly applied for lab-scale experiments to generate data for theoretical studies [8, 13].

It is more convenient to measure the corresponding kinetics from bulk crystallizations under consideration of the liquid and solid phase evolution to neglect the effect of growth rate dispersion. It has been well investigated, that the CSD of a continuous MSMPR crystallization serve to identify both, the nucleation and growth kinetics [8] [114, 138, 142]. With the steady-state assumption equation 4.19 reduces to:

\[
0 \exp\left(\frac{L}{G_T}\right) = \exp\left(\frac{f_0}{G_T}\right) \tag{eq. 5.4}
\]

Separation of variables yields the well-known number density distribution of the product from a MSMPR process fulfilling the constraints discussed in chapter 3.2.

\[
f = f_0 \exp\left(-\frac{L}{G_T}\right) \quad \text{with} \quad f_0 = \frac{B}{G} \tag{eq. 5.5}
\]

Hence, the nucleation and growth kinetics can be quantified for the operation point e.g. from the logarithmic plot of the product CSD. However, the experimental effort will increase if the kinetics are investigated over a broad range of supersaturation, stirring speed or temperature (e.g. eleven experiments are utilized in [142] or 26 in [143], which were carried out over at least ten mean residence times) since steady-state operation is mandatory for the subsequent data analysis. Furthermore, agglomeration, breakage, a classifying product removal or growth rate dispersion alter the product distribution and complicate the data analysis. Nevertheless, the information generated with MSMPR experiments are closely related to the process conditions if a continuous crystallization should be designed subsequently within the same set-up.
In the past century, also fluidized bed crystallizers were applied for the quantification of crystal growth rates [114, 138]. A crystal population of precisely characterised mass and shape is trapped inside a tubular crystallizer, which is feded continuously with a supersaturated liquid phase. The population is then observed with imaging techniques during the experiment or weighed afterwards. The evaluation is similar to equation 5.1 for the weighing method and only a mean growth rate can be estimated. Secondary nucleation is prevented by this approach but the relative velocity, between the fluid and the particles, is limited to the floating conditions of the particles. Hence, the fluid dynamics will be different compared to a commonly applied stirred tank. Nevertheless, the real growth rate excluding any abrasion processes can be evaluated rather fast even with unsteady conditions over a broad range of supersaturation if imaging techniques and an inline concentration measurement are used. Following this idea, polythermal batch-crystallizations can be advantageous since they provide several combinations of supersaturation and temperature additionally during one experiment. If the solid phase evolution is measured simultaneously, they provide a thorough and efficient investigation of the desired kinetics over the considered range of process conditions. These information can be subsequently utilized to quantify crystallization kinetics in two general ways. The inverse method, were a full PBE model is fitted to experimental results, is one sophisticated approach often applied [144, 145]. However, the necessary parameter optimization routine can be highly time consuming depending on the discretization or model reduction of the PBE framework. Furthermore, there is a certain risk that the extracted experimental information are distributed to all kinetic sub-models applied. In other words, that a concentration reduction caused by a growth process is attributed also to the nucleation kinetics by the optimization routine. Especially for power-law approaches with highly correlated parameters, as shown in the following, this problem can have a significant influence.

Another approach separates the information from the experiments related to the corresponding kinetics. A rather detailed dissertation [146] describes the experimental set-up and data processing to calculate nucleation and growth rates during seeded cooling crystallizations with fixed supersaturation. The suspension density and mean size evolution of the crystal entity were subsequently exploited for the separate quantification of the nucleation and growth kinetics even though the measurement precision was rather limited. In this case, laser diffraction was utilized to investigate the solid phase, which can lead to errors when the crystal shape differs significantly from perfect spheres, since reflections of faceted particles and the orientation of crystals influence the result significantly [147, 148]. Furthermore, the mean length of the whole crystal size distribution (CSD) was utilized as an indicator for the growth of the particles. This eventually obscures the real growth rate, particularly if nucleation, agglomeration or breakage occurs. Nevertheless, it was mathematically shown [149] that it is possible to determine the exact growth rate by following one characteristic of the CSD during a crystallization. Borchert investigated this idea with a multi-dimensional population balance system [63]. It was possible to show in theory and experiment, that the growth of the faces of the seed population can be followed. Hence, the crystallographic face growth rates could be quantified according to [149] and verified. However, the procedure requires a detailed crystal shape model and a complex shape estimation routine [103].
Therefore, the idea of Yokota [150] will be followed where it is shown how the three parameters \((\kappa_g, 0, \frac{E_A}{g}, g)\) of a temperature-dependent power law (eqs. 4.14 & 4.15) for the crystal growth can be identified based on four precisely determined 1-dimensional CSDs of polythermal batch-crystallizations.

Nevertheless, it is rather difficult to accurately measure CSDs during an experiment. Consequently, four determined crystal size distributions may not be sufficient. Hence, the influence of experimental errors on the subsequent parameter estimates will be investigated additionally. Furthermore, the approach of [150] will be extended to identify the growth, nucleation and dissolution kinetics and the accuracy of this procedure will be evaluated by the design of a continuous crystallization process.

### 5.2. Basic idea and assumptions

The method is based on the observation of the evolution of the solid phase during cooling batch-crystallizations. Together with the solution concentrations and temperatures of a few well planned experiments, it is possible to quantify the desired crystallization kinetics considering that the crystal population moves to higher sizes due to growth \((G)\) and to smaller sizes due to dissolution \((D)\) [63, 138] (Figs. 5.1 a) and 5.1 b). Hence, it is straightforward to exploit seeded batch crystallization experiments for this purpose if size-independent growth [114] is assumed even though growth rate dispersion occurs.

![Fig. 5.1: a) & b) Movement of a seed-peak due to crystal growth (G) and dissolution (D). c) Change of the particle number (N) of the CSD due to nucleation (B0) [1]. Solid lines - Initial state; dashed lines - Evolution of the state.](image)

When the seed crystals are chosen appropriately with respect to size and shape they should be well identifiable during the crystallization with a suitable online or offline measurement technique (e.g. sieve analysis or online microscopy). Therefore, the particles should be large enough so that they can be distinguished from eventually occurring nuclei and the substance specific crystal shape should be developed completely to reduce agglomeration. These crystals will move through the state space (e.g. a characteristic length or width of the particles) during the process with a certain velocity, i.e. their growth or dissolution rate respectively. Subsequently, it is required to quantify this crystal size evolution, since it contains the information about the underlying growth or dissolution kinetics. The information can be utilized directly, in connection with the corresponding supersaturation and temperature present in the crystallizer, to estimate the necessary parameters in a kinetic sub-model for growth or dissolution without the need of a full PBE system.
A similar procedure can be applied to analyze the birth of new crystals \( (B_0) \). Here, the change of the total number of crystals, \( N \), over time is strictly connected to the nucleation kinetics if breakage and agglomeration are neglected (Fig. 5.1 c). Altogether, the proposed procedure leads to an efficient and fast quantification scheme since the essential information are extracted from the CSDs and applied individually for the parameterization of the different kinetic sub-models.

This procedure, in the following referred to as short-cut-method, has several advantages. At first, only a few experiments are necessary to estimate all basic crystallization kinetics for a large range of supersaturation and temperature since several combinations of these process variables are present during non-isothermal batch-crystallizations. Second, the numerical effort is reduced since no full PBE model is applied. Only the parameters of one postulated kinetic sub-model are fitted at once. Furthermore, this approach can be universally applied with different measurement techniques to the crystallizer, which will be utilized for a subsequent process.

5.3. Simulation study

For the evaluation of the short-cut-method, synthetic process data of batch crystallizations are generated and subsequently analyzed. A one-dimensional PBE system is used to create the required information. This ideal case reflects at first perfect concentration and temperature signals as well as an accurate measurement of the size distribution during the experiment. The model framework and all necessary process and kinetic parameters are explained in the following.

Similar to [150], temperature and supersaturation dependent power-law approaches with three parameters (eq. 5.6) are applied for the crystallization kinetics in the PBE system of chapter 4.2.

\[
K = p_1 \exp\left(\frac{-p_2}{RT}\right)(S - 1)^{p_3} \quad \text{for } K = G, D, B_0
\]  

(eq. 5.6)

Here, \( p_1 \) is the pre-exponential factor, \( k_0 \), \( p_2 \) is usually referred to as the activation energy, \( E_A \), and \( p_3 \) is the power law exponent.

The batch crystallizations were carried out as a combination of crystallization and dissolution to have information about all three kinetics considered in this study within one experiment. Hence, the crystallizer is cooled down linearly after seeding until a certain temperature difference is achieved. Subsequently, the reactor is heated up with a linear temperature ramp to the starting temperature again. Hence, also the dissolution of particles has to be considered for the case of undersaturation \( (S<1) \).

For the simulation of the process data with the model framework introduced before, substance characteristics are required such as the solubility, the physical properties and parameters for the kinetics. Potassium alum is chosen in the present study as a model substance since it is a well-known compound for which the needed data is easily accessible. The solubility curve measured in preliminary experiments was expressed with a 4th order polynomial (eq. 5.7) and fitted to own experimental results (Fig. 5.2).

\[ S = \text{soln}_i \]

(eq. 5.7)

The physical characteristics of the solid phase and the solubility parameters, \( \rho_{\text{sat},i} \), are given in table 5.1.
\[ w_{\text{sat}} = p_{\text{sat},1} + p_{\text{sat},2}\theta + p_{\text{sat},3}\theta^2 + p_{\text{sat},4}\theta^3 + p_{\text{sat},5}\theta^4 \]  
(eq. 5.7)

**Fig. 5.2:** Solubility curve of potassium aluminum sulfate dodecahydrate. Stars depict solubility measurements and the bold line illustrates the 4th order polynomial (eq. 5.7).

**Table 5.1:** Physical properties and solubility parameters of potassium alum.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid density [kg/m³]</td>
<td>$\rho_{\text{sat}}$</td>
<td>1750</td>
</tr>
<tr>
<td>Volume shape factor</td>
<td>$k_v$</td>
<td>$\sqrt[3]{2}$</td>
</tr>
<tr>
<td>Solub. Parameter 1</td>
<td>$p_{\text{sat},1}$</td>
<td>5.06</td>
</tr>
<tr>
<td>Solub. Parameter 2</td>
<td>$p_{\text{sat},2}$</td>
<td>0.23</td>
</tr>
<tr>
<td>Solub. Parameter 3</td>
<td>$p_{\text{sat},3}$</td>
<td>$7.76 \times 10^{-3}$</td>
</tr>
<tr>
<td>Solub. Parameter 4</td>
<td>$p_{\text{sat},4}$</td>
<td>$-2.43 \times 10^{-4}$</td>
</tr>
<tr>
<td>Solub. Parameter 5</td>
<td>$p_{\text{sat},5}$</td>
<td>$4.86 \times 10^{-6}$</td>
</tr>
</tbody>
</table>

Several authors investigated the crystallization kinetics of potassium alum over the past decades either with empirical approaches [150, 151] or based on thermodynamics [152]. In this section, kinetics are assumed for the model substance, which were obtained during preliminary studies on the short-cut-method with this compound [153]. The parameter values of the assumed kinetic sub-models used for the generation of synthetic process data for growth, nucleation or dissolution (eq. 5.6) are listed in table 5.2.
Table 5.2: Provided kinetic parameters (to be recovered by the short-cut-method) for growth, nucleation and dissolution of potassium alum contained in eq. 5.6. 
$p_1$ - pre-exponential factor, $k_0$; $p_2$ - activation energy, $E_A$; $p_3$ - exponent.

<table>
<thead>
<tr>
<th>Kinetics</th>
<th>$p_1$ [m/s; 1/s]</th>
<th>$p_2$ [kJ/mol]</th>
<th>$p_3$ [-]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth G</td>
<td>5·10$^7$</td>
<td>75</td>
<td>1.4</td>
</tr>
<tr>
<td>Nucleation G</td>
<td>1·10$^{15}$</td>
<td>50</td>
<td>1.5</td>
</tr>
<tr>
<td>Dissolution D</td>
<td>6.5·10$^{-6}$</td>
<td>0.1</td>
<td>1.1</td>
</tr>
</tbody>
</table>

With the now defined substance system in silico experiments can be planned and simulated. It is assumed that the kinetics should be investigated in a temperature range of 293 K to 323 K. In order to cover a large range of supersaturation, three different starting points (303 K, 313 K and 323 K) with respect to the initial temperature are chosen (table 5.3).

Table 5.3: Process conditions for the simulated batch crystallizations. All parameters were kept constant except the initial saturation temperature.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saturation temperature, $T_0$</td>
<td>303, 313, 323</td>
<td>[K]</td>
</tr>
<tr>
<td>Final temperature, $T_{end}$</td>
<td>293, 303, 313</td>
<td>[K]</td>
</tr>
<tr>
<td>Initial supersaturation, $S_0$</td>
<td>1</td>
<td>[-]</td>
</tr>
<tr>
<td>Cooling ramp</td>
<td>-5</td>
<td>[K/h]</td>
</tr>
<tr>
<td>Heating ramp</td>
<td>20</td>
<td>[K/h]</td>
</tr>
<tr>
<td>Seed mass, $m_{seed}$</td>
<td>0.57·10$^{-3}$</td>
<td>[kgSeed/kgSolvent]</td>
</tr>
<tr>
<td>Mean seed length, $L_{seed}$</td>
<td>265</td>
<td>[µm]</td>
</tr>
</tbody>
</table>

The simulations start from a solution saturated at the initial temperature since seeded batch crystallizations are necessary for the proposed method. Furthermore, the linear cooling ramp is set to -5 K/h. This provides a sufficient supersaturation, which is essential for the identification of a unique set of kinetic parameters. Crystallization experiments carried out following the saturation curve ($S = 1$) would lead to an infinite amount of undistinguishable parameter combinations in the subsequent estimation procedure. A higher cooling rate would lead to strong nucleation, complicating the evaluation of the growing seed crystals.

After a total cooling of 10 K, linear heating was initiated until the initial saturation temperature was reached in order to investigate the dissolution within the same run. To generate an appropriate undersaturation the heating ramp was set to 20 K/h since dissolution proceeds faster than crystal growth.

The CSD of the initial seeds is assumed to have a Gaussian distribution (eq. 4.21) with a mean length of 265 µm and a standard deviation of 20 µm, which corresponds to a sieve fraction between 150 µm and 400 µm. The initial mass of the crystal phase is adjusted to 0.57 $g_{seed}/kg_{solvent}$ (5% of the expected product mass on average). This ensures a good observability of the growth process while the initial crystal surface area
is not strongly limiting the attainable supersaturation. Except for the initial temperature all parameters were kept constant during all experiments. The process parameters are summarized in Table 5.3.

5.4. Simulated experimental data

With the defined model framework of Chapter 4.2 and the given parameters of Table 5.1-5.3, three batch experiments were calculated for time steps of 10s and 2000 discrete elements to have moderate numerical dispersion at reasonable computational costs. The grid was discretized equidistantly between 1 μm and 2 mm. The temperature, concentration and supersaturation for all three simulations are depicted in Figure 5.3.

Fig. 5.3: Temperature, concentration and supersaturation of the simulated batch experiments. Exp. 1 - T₀ = 303 K; Exp. 2 - T₀ = 313 K; Exp. 3 - T₀ = 323 K.

In the present study, we assume no or little a priori knowledge about the substance to test the short-cut-method. If first estimates of the crystallization kinetics exist, efficient tools [154, 155] can be utilized to improve the selection of process parameters and to enhance the accuracy of the subsequent parameter optimization by setting convenient experimental conditions. Nevertheless, Figure 5.3 shows that the process parameters were selected appropriately to have reasonable super- and undersaturation during the cooling and heating ramps, respectively. These super- and undersaturations, together with the process temperature, define the range where kinetic parameter estimations are suitable (Fig. 5.4), since only for this range experimental data is available. Furthermore, it is also the maximum range to which the estimated kinetics should be extrapolated.

In the following, the corresponding driving force, process temperature and the evolution of the solid phase from the simulated process will be used to re-estimate the underlying given crystallization kinetics.
5.5. Data processing

As explained in the beginning, the short-cut-method is based on the observation of the evolution of the particulate and continuous phase. The experimental information of the liquid phase, i.e. supersaturation and temperature, are applied together with the change of a certain crystal length characteristic to determine the growth kinetics. Additionally, the nucleation kinetics can be estimated with the same procedure, by applying the change of the particle number instead of the crystal size. Both information result from an appropriate evaluation of the observed crystal size distributions (Fig. 5.5).

However, it is usually not possible for real processes to measure the CSD inline and continuously during the entire experiments. Therefore, a discrete sampling of the solid phase is assumed, which yields only a few crystal size distributions (Fig. 5.6).
Novel short-cut method for the quantification of crystallization kinetics

Subsequently, the essential information about growth, dissolution and nucleation have to be extracted from these CSDs.

Fig. 5.6: Five sampled crystal size distributions (grey dashed lines) with labeled mean lengths of the growing seed population (Exp. 3). The underlying black solid lines illustrate the Gaussian distribution fitted to the grown seed fractions.

To characterize the growth behavior it is sufficient to follow the mean length of the growing seed fraction (eq. 5.8).

\[ L_\text{mean} = \frac{\int L f(t, L) dL}{\int f(t, L) dL} \]  

(eq. 5.8)

This mean length is a characteristic for the growth of the entire crystal population, which is not influenced by growth rate dispersion, if size independent growth is assumed. However, it is practically impossible to define the correct \( L_{\text{min}} \) and \( L_{\text{max}} \), which corresponds only to the growing seed fraction from an entire CSD as nucleation, breakage or agglomeration can be involved. Nevertheless, the distribution function, which describes the seeds initially best, should be capable to describe the growing seeds as well. It is then convenient, to fit the parameters of this function (eq. 4.21) in a way, so that it reproduces a part of the CSD, namely the leading edge, which corresponds to the grown seeds (black lines in Fig. 5.6). Hence, distortions due to nucleation, breakage or agglomeration can be attenuated. After a successful fit of the distribution function to the growing seed fraction of each CSD, a set of values for the parameters \( L_\text{mean} \) and \( \sigma \) (eq. 4.21) is obtained. This finally yields the transient evolution of the mean length of the growing seed fraction and therefore the required objective information about the growth kinetics, \( L_\text{mean}(t, S, T) \). A similar procedure can be applied during the dissolution of the crystal population, to acquire the necessary information for the corresponding dissolution kinetics.
Furthermore, the measured CSDs are integrated yielding the total particle number, \( N_{\text{exp}}(t, S, T) \). The increase of particles while the solution is supersaturated can be utilized for the determination of a specific nucleation sub-model (e.g. eq. 5.6). The simulated data of all three experiments were sampled equidistantly five times while supersaturation or undersaturation was present. Hence, small deviations with respect to time occur since the change from crystallization to dissolution differs between the experiments. The acquired CSDs were processed as described above to obtain the necessary data (Points in Fig. 5.7 and 5.8) for the subsequent parameter estimation.

**Fig. 5.7:** Sampled mean length of the growing/dissolving seed fraction from the size distributions, which serve as input information for the growth and dissolution parameter estimation.

*Points* - mean lengths of the seed fraction of the sampled CSD; *grey lines* - trends for the entire experiments.

**Fig. 5.8:** Sampled particle number evolution from integrated number density distributions, which serve as input information for the nucleation parameter estimation.

*Points* - total particle numbers of the sampled CSD; *grey lines* - trends for the entire experiments.
5.6. Optimization

At first, it will be shown that the kinetic parameters given in table 5.2 can be re-estimated with the data set discussed in section 5.4. The objective functions, applying a least squares method for the three experiments (nExp = 3) with five samples (nSamples = 5), are:

\[ OF_g = \sum_{i} \sum_{j} (T_{exp,i,j} - T_{sim,i,j})^2 \quad \text{for } S \geq 1, t < t_{S<1} \quad \text{(growth)} \quad (eq. 5.9) \]

\[ OF_n = \sum_{i} \sum_{j} (N_{exp,i,j} - N_{sim,i,j})^2 \quad \text{for } S \geq 1, t < t_{S<1} \quad \text{(nucleation)} \quad (eq. 5.10) \]

\[ OF_d = \sum_{i} \sum_{j} (T_{exp,i,j} - T_{sim,i,j})^2 \quad \text{for } S < 1, t > t_{S<1} \quad \text{(dissolution)} \quad (eq. 5.11) \]

The values \( T_{sim} \) and \( N_{sim} \) in these objectives can be calculated by:

\[ T_{sim} = T_{exp} + \int k_s \exp\left(\frac{-E_s}{RT}\right) (S-1)^\gamma dt \quad \text{for } S \geq 1, t < t_{S<1} \quad (eq. 5.12) \]

\[ N_{sim} = N_{exp} + \int k_s \exp\left(\frac{-E_s}{RT}\right) S (S-1)^\gamma dt \quad \text{for } S \geq 1, t < t_{S<1} \quad (eq. 5.13) \]

\[ \Sigma_{sim} = \Sigma_{exp} - \int k_s \exp\left(\frac{-E_s}{RT}\right) (S-1)^\gamma dt \quad \text{for } S < 1, t > t_{S<1} \quad (eq. 5.14) \]

Where \( t_{S<1} \) is the point when for first time undersaturation is present in the system. All kinetic sub-models (eqs. 5.9-5.14) were fitted to the corresponding data separately, applying a simplex algorithm [156] and a stochastic initial value generator. Therefore, three parameters are estimated at once to different data sets. The parameters minimizing all objective functions are summarized in table 5.4 (compare table 5.2).

As expected, small deviations occur between the given kinetic parameters and the re-estimates even with undisturbed simulated data due to the well-known correlation between the parameters in power laws [157, 158]. The relatively large deviation for \( p_2 \) of the dissolution kinetics is also not significant. Furthermore, numerical errors resulting from the discretization, the tolerances of the applied Runge-Kutta-method and the optimization routine as well as errors from the adaption of the seed-peak affect the parameter estimation.
Table 5.4: Values of the estimated kinetic parameters (eq. 5.6) and the corresponding average errors (eq. 5.16) for growth, nucleation and dissolution applying the data of three experiments where five samples were taken.

- $p_1$: pre-exponential factor, $k_0$
- $p_2$: activation energy, $E_A$
- $p_3$: exponent

<table>
<thead>
<tr>
<th>Kinetics</th>
<th>free parameters</th>
<th>$p_1$ [m/s; 1/s]</th>
<th>$p_2$ [kJ/mol]</th>
<th>$p_3$ [-]</th>
<th>Error average [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth G</td>
<td>3</td>
<td>Est. 4.6·10^7</td>
<td>74.8</td>
<td>1.39</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Orig.*</td>
<td>5·10^7</td>
<td>75</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Nucleation B0</td>
<td>3</td>
<td>Est. 8.9·10^14</td>
<td>49.8</td>
<td>1.49</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>Orig.*</td>
<td>1·10^13</td>
<td>50</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Dissolution D</td>
<td>3</td>
<td>Est. 5.9·10^-6</td>
<td>2.1·10^-7</td>
<td>1.11</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>Orig.*</td>
<td>6.5·10^-6</td>
<td>0.1</td>
<td>1.1</td>
<td></td>
</tr>
</tbody>
</table>

* compare table 5.2

The left side of figure 5.9 shows the corresponding logarithmic objective function for growth calculated for various pre-exponential factors and various exponents, $\log(OFG_{kg,0,g})$. The logarithmic objective growth function calculated for different pre-exponential factors and for different activation energies, $\log(OFG_{kg,0,E_A,g})$, is depicted on the right side of figure 5.9.

Fig. 5.9, left: Logarithmic dependence of the objective function on the pre-exponential factor and the exponent with constant estimated activation energy. Right: logarithmic objective as a function of the pre-exponential factor and the activation energy with constant estimated exponent (activation energy values of the abscissa are chosen to provide a good visibility of the optimum). Bold black lines - individual 95% confidence intervals.

In both cases, the objective function depicts straight contour lines in the logarithmic diagram due to the exponential correlation of the corresponding parameters. Particularly the objective function calculated for different pre-exponential factors and activation energies (Fig. 5.9, right) shows an elongated valley, which is unfavorable for parameter estimations. Additionally, this finding emphasizes that the pre-exponential factor is more sensitive to perturbations than the activation energy or the exponent. An approach to
improve the issue of correlated parameters in temperature dependent power law kinetics is given in \cite{157, 158}. It was not applied here due to the different focus of this study.

\[
Error(S,T) = \frac{|(K_{\text{est}}(S,T) - K_{\text{given}}(S,T))|}{K_{\text{given}}} \quad (\text{eq. 5.15})
\]

\[
Error_{\text{avg}} = \frac{1}{K_{1} - K_{N}} \sum_{K_{1}} \sum_{K_{N}} Error(S,T) \quad (\text{eq. 5.16})
\]

for \( K = G, B_0, D; S_k = S_{\text{min}} \ldots S_{\text{max}} \) and \( T_m = T_{\text{min}} \ldots T_{\text{max}} \).

Nevertheless, the deviation (eq. 5.15) between the estimated and the given kinetic parameters is rather small as shown in figure 5.10. The depicted errors are 0.04\% for growth, 0.1\% for nucleation and 0.16\% for dissolution on average (eq. 5.16). Thus, kinetic parameters can be re-estimated applying the short-cut-method via this optimization procedure. Furthermore, the information, extracted from the CSD, are fitted to every mechanism separately. Thus the objective function does not depend on the solution of a full population balance model. Only the nonlinear correlations in the equations 5.12-5.14 are applied, which decreases the computational effort during the parameter estimation significantly.

Fig. 5.10: Deviations (eq. 5.15) between the estimated and the given kinetic. a) growth; b) nucleation; c) dissolution.

White dashed lines - transient temperature and supersaturation of the experiments used (compare Fig. 5.4); points - sample times of the solid phase.

In the previous section, the ideal case was considered, where the structure of the “correct” rate laws is known. Commonly however, the correct kinetic mechanism is unknown when real experimental data is processed. In order to investigate the resulting error, which occurs when a wrong kinetics is assumed, the approach given by equation 5.6 is simplified and fitted to the same synthetic data as applied in the previous section. Thereby, the number of free parameters is reduced and thus, the complexity of the estimation problem is decreased. Two simplifications are chosen. In the first scenario, a linear supersaturation dependence is assumed (eq. 5.17), whereas in the second scenario temperature-independent kinetics are assumed, which are linearly dependent on the supersaturation as well (eq. 5.18).
\[ K = p \exp\left(\frac{-p}{RT}\right)(S - 1) \quad \text{for } K = G, D, B_0 \]  
(eq. 5.17)

\[ K = p_i(S - 1) \quad \text{for } K = G, D, B_0 \]  
(eq. 5.18)

The simplified kinetic sub-models (eqs. 5.17 & 5.18) were again fitted to the same synthetic data of three experiments assuming that five samples were taken to evaluate how the adapted simplified approach deviates from the original kinetics.

The error between the estimated kinetics with two free parameters (eq. 5.17) and one free parameter (eq. 5.18) is shown in Fig. 5.11 a)-c) and Fig. 5.11 d)-f), respectively. The error increases with lowering the complexity of the kinetic approach as expected (compare Fig. 5.11 a) & d). The deviation is particularly high where the kinetics is rather fast as well as at the borders of the considered supersaturation and temperature range. Furthermore, the error of the dissolution kinetics is rather low compared to the error of the nucleation and growth kinetics for both simplifications considered (eq. 5.17 & 5.18, table 5.5), which can be explained by the low supersaturation and temperature dependence of the original dissolution kinetics.

![Fig. 5.11: Deviations (eq. 5.15) between the estimated kinetics with two free parameters (eq. 5.17 and parameter in table 5.5) and the given kinetics. a) growth; b) nucleation; c) dissolution. Deviations (eq. 5.15) between the estimated kinetics with one free parameters (eq. 5.18 and parameters in table 5.5 and the given kinetic. d) growth; e) nucleation; f) dissolution. White dashed lines - transient temperature and supersaturation of the experiments used; points - sample times of the solid phase or times where CSD information is available for the parameter estimation.](image-url)

The same holds for the average deviation (eq. 5.16) of the simplified estimated kinetics. The average error (compare table 5.4 and table 5.5) increases by a factor of ten for dissolution if the supersaturation dependency is less pronounced (eq. 5.17) and by a
factor of 50 to 70 for growth and nucleation. If additionally the temperature dependence
is neglected as well (eq. 5.18), the average error doubles again for the latter two
kinetics. Consequently, the deviation of the dissolution remains nearly constant as the
temperature dependence is rather low (see table 5.2 for comparison).

Table 5.5: Values of the estimated kinetic parameters (eqs. 5.17, 5.18) and the corresponding
average errors (eq. 5.16) for growth, nucleation and dissolution with a linear temperature
dependent and independent kinetic approach. The data of three experiments where five samples
were taken was applied.

<table>
<thead>
<tr>
<th>Kinetics</th>
<th>free parameters</th>
<th>$p_1$ [m/s; 1/s]</th>
<th>$p_2$ [kJ/mol]</th>
<th>$p_3$ [-]</th>
<th>Error average [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth G</td>
<td>2</td>
<td>$6.0 \cdot 10^5$</td>
<td>61.4</td>
<td>1</td>
<td>2.9</td>
</tr>
<tr>
<td>Nucleation B0</td>
<td>2</td>
<td>$1.9 \cdot 10^{12}$</td>
<td>32.7</td>
<td>1</td>
<td>5.3</td>
</tr>
<tr>
<td>Dissolution D</td>
<td>2</td>
<td>$6.8 \cdot 10^{-6}$</td>
<td>1.3</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>Growth G</td>
<td>1</td>
<td>$1.9 \cdot 10^{-6}$</td>
<td>0</td>
<td>1</td>
<td>10.2</td>
</tr>
<tr>
<td>Nucleation B0</td>
<td>1</td>
<td>$4.9 \cdot 10^{-3}$</td>
<td>0</td>
<td>1</td>
<td>10.1</td>
</tr>
<tr>
<td>Dissolution D</td>
<td>1</td>
<td>$4.1 \cdot 10^{-6}$</td>
<td>0</td>
<td>1</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Even though, an average error of 10% for the linear approach (eq. 5.18) is rather low, a
fair evaluation is only possible if the rates approaches themselves are compared for the
considered supersaturation and temperature ranges.

As it is shown in figure 5.12 (left), the linear kinetics intersects on a single curve with the
original growth kinetics and strongly deviates otherwise. In contrary, a good description
is achieved if the temperature dependence is conserved (eq. 5.17; Fig. 5.12, right).
Hence, a model prediction with this simplified kinetic approach would also agree well
with experimental measurements.
In the following, the accuracy of the proposed short-cut-method will be investigated for measurement signals, which exhibit deviations from the perfect synthetic data.

5.7. Influence of measurement errors

In contrast to simulated data, experimental measurements have limited precision. Several distortions or errors occur due to manual mistakes during the experimental procedure, the accuracy of measurement technology or random deviations. Hence, the results of the data analysis and processing will be erroneous as well. Therefore, the error propagation for the presented short-cut-method has to be quantified. At first the amount of samples and experiments is kept constant but 2 different types of errors are assumed.

Essential for the estimation scheme are the information of the CSD as well as the concentration and temperature of the liquid phase. The precision of the entire particle size distribution is strongly dependent on the applied measurement technique. For example, the correct amount of very small particles is hardly detectable by a sieve analysis. On the other hand, reflections and scattering of big crystals will influence the accuracy of laser diffraction measurement techniques. A general and precise simulation of these errors is impossible. Thus, a generic error will be assumed for both required information of the CSD, the crystal number and the mean length evolution of the seed fraction. The transient data point will be distorted randomly with a maximal deviation of 5% of the actual value (Fig. 5.13, right).

![Fig. 5.13: Example of randomly distorted measurement signals. Left: Supersaturation signal, which was created by a stochastic fluctuation of the concentration signal in combination with a deflected saturation curve. Right: Mean length of the seed fraction of the simulated experiment 1. Black lines - maximum error, which were randomly added for the estimation scheme to the original data.](image)

Another important information for kinetic estimation methods is the super- or undersaturation. Here, the precision of the concentration measurement and the accuracy of the solubility curve are decisive. Therefore, a stochastic error is assumed
for the concentration and the temperature information for the solubility data points depicted in figure 5.2. Subsequently, a new solubility curve (eq. 5.7) was fitted to the faulty data and applied for the parameter estimation. A maximal stochastic error of 1% was chosen for the solubility analysis based on experience. Furthermore, a noise level of 1% was applied to the concentration signal. An example for the resulting distorted supersaturation signal is depicted in figure 5.13 (left).

It can be expected that also an error in the temperature information will influence the subsequently estimated kinetics. However, resistance temperature measurement devices are quite precise and the impact should be rather small in comparison to the other distorted signals considered and therefore this case will not be investigated.

It should be noted, that the errors assumed do not cover all effects which can occur during real experiments. Nevertheless, they serve as an example to investigate how robust the short-cut-method for different kinetic sub-models (eqs. 5.6, 5.17, 5.18) is. All parameters of all models were estimated ten times for different erroneous measurement information. The mean of the average errors (eq. 5.16) with respect to the original kinetics are shown together with the corresponding standard deviation in figure 5.14.

It can be seen that the correct kinetics (eq. 5.6, Fig. 5.14 a) with three free parameters is rather sensitive to measurement errors, which results in the largest increase of the average error and the highest standard deviations. Furthermore, it can be concluded that noise applied to the supersaturation signal ("S") has a higher impact compared to an error in the crystal length and number information ("L & N"). An exception is the average error of the dissolution kinetics, which is rather sensitive towards deviations in the evolution of the mean lengths of the seed fraction. It can be supposed that the large
size reduction is one reason for this fact since the dissolution is rather fast compared to
nucleation or growth. Furthermore, this relation can be found also for the other model
approaches. If the supersaturation signal and the crystal length and number information
are erroneous (Erroneous signal "Both") for the parameter estimation a simple
superimposition of the single errors can be observed.
The trends described for the model approach with three free parameters become
apparent for the other model approaches as well (Fig. 5.14 b) and c). Nevertheless, a
decreasing amount of free parameters, which have to be estimated, leads to higher
robustness if measurement errors occur. For example, the kinetic approach with two
free parameters (eq. 5.17, Fig. 5.14 b) has lower average kinetic errors and lower
standard deviations if both measurement signals are noisy.
In contrary, almost no change is observed for the growth and nucleation kinetics with
one free parameter (eq. 5.18, Fig. 5.14 c). The initial kinetics cannot be described by a
linear approach and thus, measurement errors will have a rather low influence on the
error propagation in this case. The dissolution kinetics can be reflected by a linear
approach since it has a rather low supersaturation and temperature dependence. Thus,
the effect of erroneous measurement signals is visible in that case.
The mean parameters, which were estimated with the erroneous transient
measurement signals, are listed in table 5.6 together with the estimated parameters
applying the original signals for all three model approaches. It can be seen that none of
the parameters can be re-estimated exactly except of the kinetic approach with one free
parameter. The reason is the correlation of the corresponding parameters of the applied
power laws (eqs. 5.6 and 5.17). Hence, erroneous measurement information induce a
strong shift of the global minimum of the objective function and therefore completely
different parameter combinations. Furthermore, local minima, which can occur due to
the randomized errors, have to be taken into account. Hence, the high standard
devation especially of the pre-exponential factor is obvious.
Table 5.6: Estimated kinetic parameters for growth, \( G \), nucleation, \( B \), and dissolution, \( D \). The mean values of the parameters of the three different considered approaches (eqs. 5.6, 5.17, 5.18) are given, which were estimated applying the perfect (Orig.) and the distorted (Error) measurement signals.

\( p_1 \) - pre-exponential factor [m/s; 1/s]; \( p_2 \) - activation energy [kJ/mol]; \( p_3 \) - exponent [-]; 
\( \sigma \) - absolute standard deviation.

<table>
<thead>
<tr>
<th>Free parameter</th>
<th>Kinetics</th>
<th>Signal</th>
<th>( p_1,\text{mean} )</th>
<th>( \pm \sigma )</th>
<th>( p_2,\text{mean} )</th>
<th>( \pm \sigma )</th>
<th>( p_3,\text{mean} )</th>
<th>( \pm \sigma )</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>G</td>
<td>Orig.</td>
<td>5·10^{-5}</td>
<td>2.1·10^{2}</td>
<td>6.6·10^{6}</td>
<td>62.7</td>
<td>9</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Error</td>
<td>1.9·10^{-13}</td>
<td>2.9·10^{-15}</td>
<td>4.8·10^{-11}</td>
<td>31.8</td>
<td>8.8</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>Orig.</td>
<td>1·10^{5}</td>
<td>50</td>
<td>1.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Error</td>
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<td>3.3·10^{-4}</td>
<td>7.3</td>
<td>5.9</td>
<td>0.8</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>Orig.</td>
<td>6·10^{-4}</td>
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<td>1.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Error</td>
<td>1.9·10^{-4}</td>
<td>3.3·10^{-4}</td>
<td>7.3</td>
<td>5.9</td>
<td>0.8</td>
<td>0.3</td>
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<tr>
<td>2</td>
<td>G</td>
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<td>6·10^{-5}</td>
<td>1.3·10^{2}</td>
<td>4·10^{-15}</td>
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<td>14.9</td>
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<tr>
<td></td>
<td></td>
<td>Error</td>
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<td>9.1·10^{-15}</td>
<td>2.9·10^{-11}</td>
<td>27.3</td>
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<td>B</td>
<td>Orig.</td>
<td>6.8·10^{-6}</td>
<td>2.1·10^{4}</td>
<td>3.1·10^{-7}</td>
<td>5.8</td>
<td>5.7</td>
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</tr>
<tr>
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<td>Error</td>
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<td>1.5·10^{-7}</td>
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<td>3.8·10^{4}</td>
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<tr>
<td></td>
<td>D</td>
<td>Orig.</td>
<td>4.1·10^{-6}</td>
<td>4.2·10^{-6}</td>
<td>4·10^{-7}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Error</td>
<td>1.9·10^{-4}</td>
<td>1.5·10^{-7}</td>
<td>4.9·10^{-6}</td>
<td>3.8·10^{4}</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* compare table 5.2
** compare table 5.5

However, a higher accuracy of the estimated rates can be expected if more information are provided for the short-cut-method. Hence, the impact of the amount of experiments and CSD samples was investigated as well. Therefore, the evolution of the average error (eq. 5.16) between the given and the estimated kinetics is investigated with respect to an increasing amount of experimental data. Figure 5.15 a) shows, that at least three experiments and three CSD samples are necessary for a kinetic approach with three free parameters (eq. 5.6) to achieve a low average error. However, a further increase of CSD samples does not necessarily result in a better estimate. It can be seen that even with twelve CSD samples a worse estimate is possible compared to the case where four CSD samples are applied.

Regarding this fact, there is evidence that four samples of one single experiment is in general not sufficient for the estimation of kinetics as suggested by Yokota et al. [150], if the precision of the measured quantities is not high enough.
In contrast, a kinetic approach with two free parameters (Fig. 5.15 b) shows already a good fit if only two experiments and at least two CSD samples are provided. Furthermore, the kinetic approach with one free parameter (Fig. 5.15 c) will not give a much better result regardless how much information is provided. It should be mentioned, that the conclusions drawn above are distinct for the specific randomized errors considered. The results will differ significantly if, e.g. static or oscillating errors, are considered as well.

Fig. 5.15: Average deviations (eq. 5.16) between the estimated growth kinetics and the given kinetics applying different sub-models and different amounts of experiments and CSD samples. a) Estimated growth approach with three free parameters (eq. 5.6). b) Estimated growth approach with two free parameters (eq. 5.17). c) Estimated growth approach with one free parameter (eq. 5.18).

The concept of the short-cut-method is to apply the least amount of experiments and CSD samples to reduce the effort for the quantification of the relevant rates. However, a general conclusion cannot be stated since the necessary amount of experimental information depends on the complexity of the original kinetics, the precision of the measurement technology and the amount of parameters of the applied model approach which have to be determined. For the specific constellation considered it can be stated that two experiments with three CSD samples are sufficient to determine the parameters of the growth, nucleation and dissolution kinetics if a model approach with two free parameters is assumed. This would yield an average error of 5\% with respect to the original kinetics and the considered range of supersaturation and temperature (eq. 5.16).

However, in general the average deviations and the precision of the parameters are not of major interest. Crucial for the short-cut-method is the efficient quantification of kinetics to design or optimize processes. Hence, the effect of the discussed deviations will be evaluated with respect to the performance of a simulated crystallization process in the following.

5.8. Applying kinetic parameters for the design of a crystallization process

The parameterized sub-models of the nucleation and growth kinetics are applied to predict the performance of a crystallization process. Hence, a conclusion is feasible how the deviations to the original initial values influence the result of an overall crystallization
process. Therefore, the model framework derived in chapter 4.2 for a continuous crystallization (eqs. 4.19 and 4.31) will be applied. If the original kinetics for growth and nucleation (Table 5.2) are applied, the product quality, e.g. the mean size (eq. 5.8), and the outlet concentration can be calculated for various combinations of supersaturation, $S$, temperature, $T$, and mean residence time, $\tau$. Figure 5.16 illustrates these calculations with respect to the mean product crystal size. The bold black lines depict in the $\tau$-$S$-plane the mean product levels for the considered supersaturations and mean residence times and a constant temperature. Whereas, the $S$-$T$-plane depicts the mean product levels for the considered supersaturations and temperatures and a constant mean residence time. It can be seen for the considered range of the process variables, that the influence of the crystallization temperature is higher than the effect of supersaturation and mean residence time due to the strong temperature dependency of the growth and nucleation approach. Furthermore, smooth and undisturbed curves result for the contours of the product quality for the simple power-law kinetics chosen.

Additionally, if the total crystal mass inside the reactor drops below the initial seed mass no steady-state is achievable as the crystallizer would run out of solid material. This assumption is necessary since the secondary nucleation approach yields positive values independent of the process conditions. Thus, even if the mean residence time approaches zero and the supersaturation approaches one, a continuous crystallization would be possible, which is not feasible.

Three different combinations of temperature, supersaturation and mean residence time are chosen leading to different steady-states, which serve for the comparison (Table 5.7, black dots in Fig. 5.16). Considering the trajectories of the batch experiments (Fig. 5.16 right) these combinations are in the range of the observed supersaturation and temperature. Nevertheless, for point two and three the highest deviations are expected as they are near the border where the estimated kinetics were assumed to be valid. For every combination of process parameters, the continuous crystallization was simulated for a span of ten mean residence times to ensure that a steady state is reached.

Subsequently, the model approaches with three, two and one free parameters (eqs. 5.6, 5.17, 5.18) were applied and the mean product sizes as well as the outlet supersaturation are compared to the original kinetics. It should be mentioned, that the different parameter combinations resulting from the ten randomly erroneous supersaturation and CSD information were applied and not their mean values (Table 5.6).

| Table 5.7: Tested process variables combinations of the different steady-states. |
|------------------|------|------|------|
| $T$ [K] | $S$ [-] | $\tau$ [h] |
| P1 | 300 | 1.027 | 0.42 |
| P2 | 300 | 1.053 | 0.83 |
| P3 | 322 | 1.027 | 0.83 |
Fig. 5.16. **Left:** Mean product size (eq. 5.8) of a continuous crystallization process applying the original kinetic parameters and the kinetic approach of eq. 5.6. **Bold black lines** - contour lines of the mean product size with some indicated values; **red dashed line** - assumed border of achievable steady-states with respect to the process variables. **Right:** Tested process parameter combinations for the evaluation of the quality of the kinetics in context with the trajectories of the simulated batch experiments. **Points** - indications of tested process parameter combinations for the evaluation of the quality of the kinetics, which were estimated applying distorted measurement signals.

Table 5.8 summarizes the results of the continuous crystallization simulations for the three operating conditions and the different model approaches. The comparison between the original and the estimated kinetics shows that the outlet supersaturation and the mean product size are well predictable with the model approaches consisting of two and three free parameters (eqs. 5.6, 5.17). The differences of the mean crystal size (product quality) are 3.9% and 1.8% on average. Furthermore, the predictions of the final supersaturations and concentrations (not shown in table 5.8) exhibit an average error of 0.1%. Thus, the estimated kinetic parameters are applicable to predict and analyze the considered continuous crystallization process even though the parameter estimation was done with faulty measurement signals. The linear model approach deviates the most with around 1% regarding the outlet supersaturation and with nearly 25% with respect to the product mean size. In summary, all kinetic approaches are able to predict the final liquid composition of the steady-states rather precisely. With respect to the product quality the deviations are higher with the linear approach but much lower with the more complex models.
Table 5.8: Result of the continuous crystallization simulations for three different process variable combinations. Depicted are the mean supersaturation and the mean product size (eq. 5.8) from the steady-state using the original and the estimated kinetics, which were optimized (eqs. 5.6, 5.17, 5.18) with different distorted measurement signals (compare Table 5.6).

<table>
<thead>
<tr>
<th>Set point</th>
<th>Free parameter</th>
<th>$S_{\text{crit}}$</th>
<th>$\pm \sigma$ [-]</th>
<th>$\mu_{\text{end}}$ [µm]</th>
<th>$\pm \sigma$ [µm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1 Orig.</td>
<td>1.025</td>
<td>39.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.024</td>
<td>0.002</td>
<td>40.8</td>
<td>7.8</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1.024</td>
<td>0.001</td>
<td>43.8</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.019</td>
<td>0.001</td>
<td>57.5</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>P2 Orig.</td>
<td>1.025</td>
<td>76.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.023</td>
<td>0.006</td>
<td>75.9</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1.021</td>
<td>0.002</td>
<td>76.8</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.015</td>
<td>0.001</td>
<td>86.2</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>P3 Orig.</td>
<td>1.008</td>
<td>102.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.008</td>
<td>0.003</td>
<td>100.1</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1.006</td>
<td>0.001</td>
<td>102.9</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.014</td>
<td>0.001</td>
<td>80.6</td>
<td>1.5</td>
<td></td>
</tr>
</tbody>
</table>

5.9. Summary

The presented short-cut-method is capable of quantifying growth, nucleation and dissolution rates for the generic systems presented. The physical and kinetic properties of potassium alum served as an example substance in this context. It could be shown that a sporadic sampling of the solid phase is sufficient to follow the evolution of the crystal phase with respect to the total number and the enlargement of the seed crystal fraction. In the following, the original kinetic parameters were re-estimated with this sparse information with a high precision. Since the original kinetics and its complexity are usually unknown for new substances, simplifications of the initial kinetics were compared. It can be stated that a simplification of the kinetic approach is appropriate if the main dependencies are conserved. An oversimplification will lead to rather high deviations between the model prediction and measured quantities. The proposed short-cut-method serves here to acquire the data needed for a subsequent quantification. Subsequently, several kinetic sub-models can be evaluated efficiently since the computational effort of the estimation routine is rather low.

Afterwards, the synthetic data was distorted randomly to simulate measurement errors as well as to quantify the error propagation for the estimation procedure. It was found that, especially a precise supersaturation signal is essential for a correct fit of the kinetics. Furthermore, it could be shown that the more complex model approach was rather sensitive to erroneous input signals. Eventually, if all measurement errors were considered together, the model approaches with two and three free parameters exhibited the same quality.
Furthermore, the data amount, which is provided for the optimization routine, is also decisive for the resulting accuracy if erroneous measurement signals are involved. It was shown, that for the considered situation at least three experiments for the model approach with three free parameters and two experiments for the model approach with two free parameters together with three CSD samples are necessary to achieve a good estimation result.

A continuous crystallization was designed with the different sets of estimated parameters since the main focus of the short-cut-method is to efficiently evaluate crystallization process performances. Three different process variable combinations, which led to three different steady-states, were chosen to evaluate the quality of the estimated rates in case of faulty measurement signals. Even though, the estimated kinetics with three and two free parameters deviated from the original kinetics on average by 8%, the deviation from the expected steady-state condition was only 0.1% with respect to the liquid phase and 3-4% with respect to the product quality. This is only one possible application where the short-cut-method serves to parameterize the overall process model. Generally, the proposed method can be applied for every one-dimensional model of crystallization processes. It should be emphasized, that the seed population serves as a benchmark for the whole crystal entity. A different growth behavior due to growth rate dispersion e.g. exposed by nucleated particles will not be detected. Furthermore, the characteristic length of the particles is among other things mainly defined by the CSD measurement technique. A Laser diffraction of a certain population will yield a different size distribution than a sieve analysis. Hence, the kinetic investigations have to be carried out with one and the same technique with the characteristic length defined by the measurement principle.

The short-cut-method is capable for the estimation and quantification of kinetics applying various model approaches and synthetic experiments. Additionally, the numerical effort is reduced because every kinetic approach is estimated separately and no full population balance model is used. However, also experiments are carried out for the validation of the proposed method. The experimental set-up and procedure as well as the results are part of the next chapter.
6. Substances and investigations of SLE and kinetics

The binary model substance systems for the investigated short-cut-method and continuous crystallization and the experimental methods will be explained in the following. Furthermore, the results of the solubility measurements as well as the crystallization kinetics will be given.

6.1. Substances

Three binary model substance systems were utilized for the experimental validation of the short-cut-method, namely potassium aluminum sulfate dodecahydrate (potash alum, KAL), potassium dihydrogen phosphate (KDP) and ortho aminobenzoic acid (oABA), dissolved in water. A MSMPR process, which is part of chapter 7, was subsequently designed with the basic information of the solubility and the crystallization kinetics for the system KDP-water.

Potash alum (KAl(SO₄)₂·12H₂O, KAL) was purchased from Applichem with a purity of >99.5%. It crystallizes from water and ambient conditions as a dodecahydrate in a cubic lattice with the space group Pa3. The crystal shape is dominated by the slow growing {111} faces but sometimes also the {100} and {110} faces were observed (Fig. 6.1). A correlation between the occurrences of the faces with the process conditions was not found.

Fig. 6.1: Typical crystal shapes of potassium aluminum sulfate (KAL) from different experiments.
The shape was assumed to be a perfect octahedron even though (100) and (110) faces were frequently observed. The characteristic length, \( L \), was chosen to be the edge length of the base of the octahedron (second largest elongation) since this would be the measured mesh size of a sieve analysis (Fig. 6.2). Therefore, the volumetric shape factor, \( k_V \), can be calculated with simple geometrical equations to \( \sqrt[3]{2/3} \) (Table 6.1).

Fig. 6.2: Assumed shape of KAL for the calculation of the shape factor \( k_V \).

The transition temperature of the hydrate in the solid state from the 12·H\(_2\)O to 3·H\(_2\)O is reported to be 358.99K [159]. Information about polymorphs were not found. The solutions utilized during the investigations had a pH value of around 3.02 (±0.08) and the purity of the crystallized material as well as the solidified phase were frequently validated via ion chromatography and XRPD. Nevertheless, the material was always purchased from the same batch and company to have a constant impurity matrix. This was a necessary constraint since recrystallization of the whole utilized material (~100 kg) was not feasible and several additives affect, even on a not detectable level, the crystallization kinetics [108] and lead to different crystal shapes [160].

**Potassium dihydrogen phosphate (KH\(_2\)PO\(_4\), KDP)** was purchased from Carl Roth with a purity of >98%. The substance crystallizes as an anhydrate with a tetragonal lattice at room temperature and belongs to the space group I-42d. Two polymorphs are known below -150°C and above 190°C [161], which should not affect the experiments at ambient conditions carried out in this work. The substance crystallized from water forms prisms ([100] faces) with pyramidal ends ([101] faces). The growth and dissolution kinetics of these phases depend drastically on temperature, the supersaturation level and present impurities. Figure 6.3 shows KDP crystals grown from different supersaturations, where the left particle reflects the highest and the right one the lowest driving force, to illustrate this fact.
The corresponding volume shape factor is consequently dependent on the process conditions as well. Hence, this substance serves for the proposed short-cut-method to investigate the accuracy of the estimated kinetics with respect to shape changes of the substance of interest since the task is to parameterize simple 1-dimensional PBE models. Similar to KAL the distributor and the corresponding batch of the bought KDP had to be one and the same to ensure a constant impurity matrix of the initial material. The volume of a KDP crystal consists of the volume of two pyramids and one cuboid (Fig. 6.4).

![Crystal shapes of potassium dihydrogen phosphate grown from different conditions.](image)

**Fig. 6.3:** Crystal shapes of potassium dihydrogen phosphate grown from different conditions.

The heights of the pyramidal ends are related to the edge length of the cross section of the cuboid via equation 6.1.

$$h_{pyr} = \frac{c}{2a} L_2$$  \hspace{1cm} (eq. 6.1)

Where $c$ and $a$ are the tetragonal lattice parameters of KDP (I-42d) [162]. Thus, the volume of a KDP crystal can be calculated via:
Therefore, the shape factor is dependent on two dimensions and cannot be calculated based on the second biggest dimension alone. Hence, online microscopy was applied to evaluate a high amount of particles with respect to $L_1$ and $L_2$ (eq. 6.2). As for KAL, the pH value of the utilized solutions was measured (4.12 ±0.11) and the purity of the crystallized material as well as the solidified phase were frequently validated via ion chromatography and XRPD.

Ortho aminobenzoic acid ($\text{C}_7\text{H}_7\text{NO}_2$, oABA) was bought from VWR with a purity of >99%. The kinetics of this substance were investigated for the design of fluidized bed crystallization experiments carried out in a different study [163]. Three different polymorphs from oABA are known [164-166]. Form I, which is stable at ambient conditions up to 81°C, crystallizes with an orthorhombic lattice (P2_1cn) and was the only phase observed throughout all experiments even though the crystal shape differs from other studies [167, 168]. The appearance of brownish rhombic plates (Fig. 6.5), in contrary to the normal colorless prismatic habit, could not be clarified in detail but an insoluble impurity, which was observed during the experiments, can be a possible reason.

Fig. 6.5: Typical crystal shapes of ortho aminobenzoic acid from different experiments.

Nevertheless, a perfect rhombic plate with the length $L$ (Fig. 6.6) was assumed for the calculations of the shape factor.

Fig. 6.6: Assumed shape of oABA for the calculation of the shape factor $k_V$. 

$$V_{\text{expr}} = V_{\text{obs}} + 2V_{\text{pr}} = L_1^2L_2 \frac{2c}{3a} L_1^3$$

(eq. 6.2)
Several crystals were investigated with an offline microscope to determine the ratio of both dimensions (length, thickness) as well as the angles of the rhomboid. The large angle was found to be 110° (±1.13) and the ratio between the characteristic length \( L \) and the crystal thickness determined to be 0.28 even though the standard deviation is relatively large (±0.05). Hence, the volume of the oABA crystals can be calculated via:

\[
V_{\text{oABA}} = 0.28 \frac{L^3}{\sin(110^\circ)}
\]

(eq. 6.3)

The solvent for all three solutes utilized for the experimental validation of the short-cut-method is deionized water. All substance characteristics are summarized in table 6.1.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>KAL (hydr.)</th>
<th>KDP</th>
<th>oABA</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid density</td>
<td>1750</td>
<td>2340</td>
<td>1380</td>
<td>[kg/m³]</td>
</tr>
<tr>
<td>Volume shape factor</td>
<td>2/3</td>
<td>0.75 (avg.)</td>
<td>0.28(±0.05)</td>
<td>[-]</td>
</tr>
<tr>
<td>Molar mass</td>
<td>474.39</td>
<td>136.09</td>
<td>137.14</td>
<td>[g/mol]</td>
</tr>
<tr>
<td>Purity</td>
<td>≥99.5%</td>
<td>≥98%</td>
<td>≥99</td>
<td>[%]</td>
</tr>
<tr>
<td>Distributor</td>
<td>Applichem</td>
<td>Carl Roth</td>
<td>VWR</td>
<td></td>
</tr>
<tr>
<td>Shape</td>
<td>octahedron</td>
<td>prismatic</td>
<td>rhombic plates</td>
<td></td>
</tr>
<tr>
<td>Space group</td>
<td>Pa3 [159]</td>
<td>I-42d [162]</td>
<td>P2_1cn [164]</td>
<td></td>
</tr>
<tr>
<td>pH (sat. sol.)</td>
<td>3.02 (±0.08)</td>
<td>4.12 (±0.11)</td>
<td>n. d.</td>
<td>[-]</td>
</tr>
</tbody>
</table>

6.2. Solid-liquid equilibria

The SLE of all systems were determined applying the isothermal technique as described in chapter 2.3. The utilized measurement techniques and the results are described in the following.

6.2.1. Analysis and procedures

The saturation curves of potassium dihydrogen phosphate (KDP) and potassium alum (KAL) in water were analyzed gravimetrically in the temperature range of 10°C - 70°C. Three different suspensions (25 ml) were prepared in closed glass vials for each substance and three samples of each liquid phase were withdrawn and analyzed after equilibration (at least 24 h). An ion chromatography system (Dionex, ICS 1100, Thermo Scientific, conditions in table 6.2) was applied for frequently performed purity analysis of the solid phases and the respective liquid phases after solid-liquid separation. The solid phases were analyzed after solid-liquid separation with respect to the occurring phases. X-ray powder diffraction (XRPD) was therefore utilized applying an X'Pert Pro
Diffractometer (PANalytical GmbH, Germany) in a 2-Theta range between 20 and 80°, with a step size of 0.008° and a step time of 120s.

Table 6.2: Conditions of the applied chromatographic methods.

<table>
<thead>
<tr>
<th>Kations</th>
<th>Anions</th>
<th>oABA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Column</td>
<td>Ion Pac CS16, 3x250mm</td>
<td>Ion Pac AS22, 4x250mm</td>
</tr>
<tr>
<td>Eluent</td>
<td>30mM methanesulfonic acid</td>
<td>4.5mM sodium carbonate / 1.4mM sodium hydrogen</td>
</tr>
<tr>
<td>Flow</td>
<td>0.4 ml/min</td>
<td>1.2 ml/min</td>
</tr>
<tr>
<td>Injection volume</td>
<td>50 µL</td>
<td>50 µL</td>
</tr>
<tr>
<td>Temperature</td>
<td>40 °C</td>
<td>-</td>
</tr>
</tbody>
</table>

The solubility of the ortho aminobenzoic acid (oABA) was determined in [163] applying the same isothermal method as for the salt systems in a range of 20°C - 60°C. In contrary to the simple salt systems, an HPLC analysis (Dionex HP 1200, Thermo Scientific, conditions in table 6.2) was applied for the determination of the saturation concentration since the solubility of oABA is rather low. The XRPD parameters were adjusted to 3 and 40° (2-Theta), 0.017° (step size) and 50s (step time) for the evaluation of the residual solid phases.

6.2.2. Results

Concentration analyses were performed as described above and subsequently a polynomial expression (eq. 6.4) is fitted to the solubility data of the three binary substance systems. The determined saturation curves of KAL, KDP and oABA are depicted in figure 6.7 together with data from literature [8, 163].

\[ w_{sat} = p_{sat,1} + p_{sat,2} \theta + p_{sat,3} \theta^2 + p_{sat,4} \theta^3 + p_{sat,5} \theta^4 \]  \hspace{1cm} (eq. 6.4)

Fig 6.7: a) Measured solubilities in comparison with literature data [8] of potassium alum and b) potassium dihydrogen phosphate together with the corresponding polynomial expression (eq. 6.4). c) Solubility of ortho aminobenzoic acid taken from [163] together with the polynomial expression.
The corresponding parameters are listed in Table 6.3. All solubility lines increase strictly monotonic without discontinuities giving no evidence for an unrecognized phase change for the temperature range of interest. With these information, the crystallization experiments of the next section applying the short-cut-method were planned and carried out.

**Table 6.3:** Solubility parameters of KAL, KDP and oABA corresponding to eq. 6.4.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>KAL((SO_4)_2)</th>
<th>KH(_2)PO(_4)</th>
<th>oABA</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>(p_{sat,1})</td>
<td>5.06</td>
<td>15.24</td>
<td>5.48 (\times) 10(^{-1})</td>
<td>wt-%</td>
</tr>
<tr>
<td>(p_{sat,2})</td>
<td>0.23</td>
<td>2.06 (\times) 10(^{-1})</td>
<td>-1.93 (\times) 10(^{-2})</td>
<td>wt-%/°C</td>
</tr>
<tr>
<td>(p_{sat,3})</td>
<td>7.76 (\times) 10(^{-3})</td>
<td>1.01 (\times) 10(^{-2})</td>
<td>7.90 (\times) 10(^{-4})</td>
<td>wt-%/°C(^2)</td>
</tr>
<tr>
<td>(p_{sat,4})</td>
<td>-2.43 (\times) 10(^{-4})</td>
<td>-1.45 (\times) 10(^{-4})</td>
<td>0</td>
<td>wt-%/°C(^3)</td>
</tr>
<tr>
<td>(p_{sat,5})</td>
<td>4.86 (\times) 10(^{-6})</td>
<td>1.23 (\times) 10(^{-5})</td>
<td>0</td>
<td>wt-%/°C(^4)</td>
</tr>
</tbody>
</table>

### 6.3. Crystallization kinetics

The short-cut-method described theoretically in chapter 5 is utilized to quantify experimentally the nucleation, growth and dissolution kinetics of three different binary substance systems, which were introduced in the beginning of this chapter. Potash alum (KAL) was chosen as a model substance to verify the overall procedure since it is well investigated with respect to its kinetics in the literature. Potassium dihydrogen phosphate (KDP) is reported to change the crystal shape with changing supersaturation [63]. Therefore, the substance served to study qualitatively the influence of a crystal shape change on the accuracy of the utilized 1-dimensional quantification scheme. Furthermore, a continuous MSMPR experiment is designed and carried out on the basis of the estimated kinetics. The ortho-aminobenzoic acid (oABA) had to be investigated to support the design and the modeling of a fluidized bed crystallizer for a different project [163]. Due to its low solubility, a strong agglomeration tendency and an insoluble impurity content in the feed stock, it is close to a realistic example of commercially produced components. The experimental procedure, the applied set-up as well as the results are given in the following together with specific validation experiments to verify the estimated kinetics.

#### 6.3.1. Experimental strategy

The experiments are started from a slightly supersaturated solution, which is cooled further after the seeds are added. Samples are taken during the experiment to analyze the CSD with an appropriate measurement technique. Nucleation will take place and the initial crystals will grow as long as supersaturation is present. Subsequently, the mean length (\(\bar{L}\)) of the growing seed fraction is extracted from the CSDs as input information for the parameter estimation of the growth kinetics (G). The supersaturation (S) during the crystallization process is calculated based on the temperature (T) and the measured concentration, together with a preliminarily determined solubility curve.
All present crystals in the CSD samples are evaluated to observe the change of the total amount of particles \((N)\) during the crystallization. Afterwards, the parameters of a nucleation \((B_0)\) sub-model are fitted to this data.

The same procedure described for the growth kinetics was applied to quantify the dissolution rate \((D)\) as well while undersaturation is present (e.g. due to heating). Thus, the necessary information are the transient temperature and concentration as well as the crystal size distribution, which can be recorded by various measurement techniques. The specific set-up chosen is presented in the next section. Nevertheless, the short-cut-method is not limited to any measurement technique as long as the necessary information are provided with an appropriate accuracy.

**6.3.2. Set-up**

The reactor utilized for the experimental investigations is a double jacket draft tube baffle crystallizer with an inner volume of 25 L (Fig. 6.8). It is equipped with a refractive index probe (RI (PR-23, K-Patents) in Fig. 6.8) and a Pt100 (T in Fig. 6.8) for the inline analysis of the concentration and temperature of the liquid phase. Additionally, the liquid concentration is determined offline after periodic sampling with a gravimetric or an HPLC analysis (HP 1200, Dionex) to verify the inline measurement. An appropriate mixing of the solid and liquid phase is ensured by a propeller stirrer.

![Fig. 6.8: Scheme of the utilized experimental set-up (For the detailed instrumentation diagram see chapter 7). The 25 L crystallizer is equipped with temperature (T) and concentration (refractive index probe, RI) measurement devices for the liquid phase analysis. An online microscope and a non-classifying bottom outlet can be used to investigate the solid phase.](image-url)
Two different options for the analysis of the CSD are present at the utilized set-up. One is an online microscope (QicPic, Sympatec) connected to the crystallizer via thermostated tubes and a peristaltic pump (IP 65, Ismatec). The unclassified suspension is withdrawn from the crystallizer and introduced into a flow-through-cell of 2 mm width. The microscope records up to 25 images per second of the suspension in a field of view of 5-by-5 mm. All images are evaluated automatically with the image processing toolbox pre-programmed in Matlab (Mathworks) and a modified algorithm described in [169] with respect to the observed single crystals. Thus, the CSD is measured without any further treatment of the suspension.

Even though, this technique is precise and reliable, crystals which are bigger than 1.0 - 1.5 mm cannot be investigated due to sedimentation inside the flow-through-cell. Furthermore, the saturation temperature limit for the device is 35°C - 40°C since the cell cannot be tempered and blockage of the suspension flow can occur. Thus for the second option, the bottom outlet is utilized to analyze the solid phase when higher concentrated solutions are present or bigger crystals have to be investigated. The suspension is withdrawn unclassified from the crystallizer via the pneumatic valve and subsequently washed, filtered and dried appropriately. A sieve analysis is utilized afterwards to determine the CSD of the sample.

6.3.3. Analysis

The refractive index (RI) probe was used to investigate the solution concentration of both salt systems during the experiments. Since the refractive index depends on the temperature as well, a 2-dimensional calibration was performed over a temperature range of $0°C...60°C$ and a concentration ($\frac{g\text{ Solute}}{g\text{ Solvent}}$) range of $w = 0...c_{\text{Sat}}(60°C)$. A polynomial function ($w = f(\text{RI, } 0°C)$) was fitted to the corresponding data and subsequently applied to reconstruct the solution concentration from the continuous measurement signal.

The ortho aminobenzoic acid concentration could not be measured precisely with the refractive index probe. Thus, samples were taken during the experimental investigations and analyzed with the same HPLC method (Table 6.2) already applied for the SLE measurements of this substance.

Necessary CSD information were extracted from the recorded images of the online microscope and from the sieve analysis. The latter one is a rather old and well known technique often used for particle analysis. It is assumed, that the second biggest dimension of the crystals defines the mesh size of the sieve, which it can pass. Thus, this dimension is the basis for the measured CSD.

Suspension samples taken during the process, are filtered, washed and dried appropriately. The solid phases were subsequently sieved using 23 sieves (Analytical sieves, Retsch) with mesh sizes from 63 µm to 2000 µm placed on a mechanical shaker (AS200 digit, Retsch), which was set for 15 min to a frequency of 60 Hz. The sieve fractions were weighed afterwards yielding the corresponding mass distribution.

Microscopic investigations are more complex with respect to the CSD analysis. The evaluation of the recorded images from the online device is roughly divided into 3 steps: image enhancement, thresholding and region filling as well as particle identification and measurement [63]. Important
is, that only single crystals are evaluated for the CSD. Agglomerates and air bubbles are excluded automatically to a certain extent. For comparison with the sieve analysis, the minimal Ferret-diameter was utilized for the size evaluation of the observed particles.

The solid phases were additionally analyzed with respect to the occurring phases by X-Ray Powder Diffraction applying the methods for the corresponding substance described in chapter 6.2.1.

6.3.4. Experimental procedure

The seeded batch-crystallizations were carried out with the set-up described in section 6.3.2. At first, solutions of the corresponding substances, saturated at the indicated temperatures, T_{Sat}, were created (see Table 6.4 and Fig. 6.9). The mass of initial material, m_{Solute}, is mixed for 30 min with the solvent, m_{H2O}, at 10 K above the saturation temperature to ensure complete dissolution. Before the seeds are added (t_0 in Fig. 6.9), all solutions are subcooled by 1 K (T_0 in Fig. 6.9).

Subsequently, different linear cooling and heating ramps (ΔT/Δt in Table 6.4) are applied to generate the corresponding driving force for the crystallization. The stirring rate was in all cases 300 rpm.

Fig. 6.9: Illustrations of the different temperature scenarios, which are applied for the investigations of the three substance systems. a) Linear cooling with subsequent linear heating to investigate growth and dissolution of the seed fraction (G/D in Table 6.4). b) Simple linear cooling to investigate only growth of the seed fraction (G in Table 6.4) or primary nucleation (Pri. nuc. in Table 6.4). c) Simple linear heating to investigate dissolution of the seed fraction (D in Table 6.4).

It is essential for the short-cut-method to generate sufficient supersaturation during the experiments to be able to observe an appropriate growth of the seed crystals (for the dissolution kinetics vice versa). Nevertheless, extremely high supersaturation should be avoided as well, since strong nucleation complicates the evaluation of the growing seed fraction. Thus, the cooling rates were chosen accordingly for every substance. Furthermore, for the three substance systems, slightly different experimental procedures were applied, which are detailed in the following.

Potassium alum was investigated with the online microscope (exp. KAL_{-7}–KAL_{+4}) and offline, using the sieve analysis (exp. KAL_{-8}–KAL_{+4}).
KAL4), cooling rates of -5 and -10 K/h as well as 100 g of seed crystals with a mean size of 250 µm were chosen. This procedure provided a good tracking of the seed fraction and enough supersaturation to investigate growth together with the secondary nucleation behavior. A subsequent heating ramp of 15 K/h was applied to additionally investigate the dissolution within the same experiment (Fig. 6.9 a) and G/ D in Table 6.4). The cooling ramp was stopped at T_{min} (see Table 6.4 and Fig. 6.9) when either the seed crystals grew too large and thus, started to settle inside the flow-through cell, or crystallization inside the cell blocked suspension flow. The final temperature of the experiments (T_{final} in Table 6.4 and Fig. 6.9) was chosen to ensure a complete dissolution of the seed crystals.

For the offline investigation of the CSD evolution (exp. KAL5- KAL 11), sufficient solid material had to be provided for a precise sieve analysis. Thus, an average suspension volume of 300 ml was withdrawn via the bottom valve and processed as described in section 6.3.3. The volume reduction due to the sampling must not change the fluid dynamics inside the draft tube crystallizer significantly. Thus, only a limited amount of samples was taken during one experiment. Therefore, the growth and secondary nucleation kinetics had to be investigated separately from the dissolution kinetics during a different set of experiments (Fig. 6.9 b) and c) when the sieve analysis was applied. Additionally, the seeding strategy had to be adjusted to the resolution of the sieve analysis. For the growth experiments, 400 g of crystals with a mean length of 550 µm were used. Due to the initially higher crystal surface, the cooling rate was increased to -15 K/h to generate enough supersaturation. For the dissolution experiments, seed crystals with a mean length of 1 mm were used. The initial mass was calculated to create a saturated solution after the final temperature (T_{final}).

Even though, the experimental effort for the sieve analyses was higher than for the online microscopy, higher temperatures as well as larger crystals could be investigated. The procedure for the investigation of potassium dihydrogen phosphate (KDP1- KDP4) was similar to the experiments with KAL where the online microscope was used. It is known, that the shapes of KDP crystals strongly depend on supersaturation during crystallization [63]. Thus, the cooling and heating rates were increased for the KDP experiments to additionally investigate the impact of the shape change on the results of the short-cut method. Similar to the (KAL1- KAL4) experiments, 100 g of seed crystals with a mean length of 250 µm were used.

The general investigation of the ortho aminobenzoic acid (oABA1-oABA5) was carried out in a similar way as the KDP experiments with a seeding strategy adapted to the low solubility of the substance. Only 1.6 g to 16 g of seed crystals with a mean length of 77 µm are provided to ensure a good visibility of the growth of these crystals. Furthermore, experiments from clear solutions were carried out (temperature profile Fig. 6.9 b) for this substance to investigate the primary nucleation behavior (Pri. nuc. in Table 6.4). For every substance system, a validation experiment (KAL_{valid}, KDP_{valid}, oABA_{valid} in table 6.4) was performed, which was not utilized during the parameter estimation. The comparison between the measured quantities of these experiments and a model prediction with the quantified kinetic rates will serve as an evaluation of the short-cut-method and the estimates.

The observations of selected experiments from table 6.4 as well as the results of the parameter estimations will be discussed in the following.
Table 6.4: Experimental procedures for the substances potassium alum (KAL), potassium dihydrogen phosphate (KDP) and orthoaminobenzoic acid (oABA). The investigated kinetics (primary nucleation (Pri. nuc.), growth (G), and dissolution (D)) are listed together with the cooling and heating ramps, the initial saturation temperature and the corresponding substance masses. Marked experiments are presented and intensively discussed in the following.

<table>
<thead>
<tr>
<th>Sampling method</th>
<th>Exp.</th>
<th>Investigated kinetics</th>
<th>$\Delta T / \Delta t$ [K/h]</th>
<th>$T_{sat}$ [K]</th>
<th>$T_{min}$ [K]</th>
<th>$T_{final}$ [K]</th>
<th>$m_{H_2O}$ [kg]</th>
<th>$m_{solute}$ [kg]</th>
<th>$m_{seeds}$ [kg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Online microscopy</td>
<td>KAL$_{1}$</td>
<td>G/ D</td>
<td>-5/ +15</td>
<td>303</td>
<td>296</td>
<td>306</td>
<td>21</td>
<td>3.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Online microscopy</td>
<td>KAL$_{2}$</td>
<td>G/ D</td>
<td>-10/ +15</td>
<td>303</td>
<td>296</td>
<td>306</td>
<td>21</td>
<td>3.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Online microscopy</td>
<td>KAL$_{3}$</td>
<td>G/ D</td>
<td>-5/ +15</td>
<td>308</td>
<td>299</td>
<td>314</td>
<td>20</td>
<td>4</td>
<td>0.1</td>
</tr>
<tr>
<td>Online microscopy</td>
<td>KAL$_{4}$</td>
<td>G/ D</td>
<td>-10/ +15</td>
<td>308</td>
<td>295</td>
<td>314</td>
<td>20</td>
<td>4</td>
<td>0.1</td>
</tr>
<tr>
<td>Online microscopy</td>
<td>KAL$_{valid}$</td>
<td>G/ D/ G</td>
<td>-10/ +15/ -5</td>
<td>308</td>
<td>299</td>
<td>299</td>
<td>20</td>
<td>4</td>
<td>0.1</td>
</tr>
<tr>
<td>Online microscopy</td>
<td>KDP$_{1}$</td>
<td>G/ D</td>
<td>-10/ 20</td>
<td>303</td>
<td>296</td>
<td>309</td>
<td>21</td>
<td>5.9</td>
<td>0.1</td>
</tr>
<tr>
<td>Online microscopy</td>
<td>KDP$_{2}$</td>
<td>G/ D</td>
<td>-16/ 20</td>
<td>303</td>
<td>295</td>
<td>310</td>
<td>21</td>
<td>5.9</td>
<td>0.1</td>
</tr>
<tr>
<td>Online microscopy</td>
<td>KDP$_{3}$</td>
<td>G/ D</td>
<td>-5/ 20</td>
<td>303</td>
<td>297</td>
<td>310</td>
<td>21</td>
<td>5.9</td>
<td>0.1</td>
</tr>
<tr>
<td>Online microscopy</td>
<td>KDP$_{4}$</td>
<td>G/ D</td>
<td>-16/ 20</td>
<td>308</td>
<td>300</td>
<td>314</td>
<td>21</td>
<td>6.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Online microscopy</td>
<td>KDP$_{valid}$</td>
<td>G/ D/ G/ D</td>
<td>-10/ 20/ -5/ 20</td>
<td>308</td>
<td>300</td>
<td>314</td>
<td>21</td>
<td>6.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Online microscopy</td>
<td>oABA$_{1}$</td>
<td>Pri. nuc.</td>
<td>-10</td>
<td>308</td>
<td>292.5</td>
<td>292.5</td>
<td>23</td>
<td>0.17</td>
<td>0</td>
</tr>
<tr>
<td>Online microscopy</td>
<td>oABA$_{2}$</td>
<td>G/ D</td>
<td>-10/ 11</td>
<td>308</td>
<td>292.6</td>
<td>312</td>
<td>23</td>
<td>0.17</td>
<td>16·10$^{-3}$</td>
</tr>
<tr>
<td>Online microscopy</td>
<td>oABA$_{3}$</td>
<td>Pri. nuc.</td>
<td>-11</td>
<td>308</td>
<td>292.6</td>
<td>292.6</td>
<td>23</td>
<td>0.17</td>
<td>0</td>
</tr>
<tr>
<td>Online microscopy</td>
<td>oABA$_{4}$</td>
<td>G</td>
<td>-5</td>
<td>312</td>
<td>292.6</td>
<td>292.6</td>
<td>23</td>
<td>0.2</td>
<td>16·10$^{-4}$</td>
</tr>
<tr>
<td>Online microscopy</td>
<td>oABA$_{5}$</td>
<td>G/ D</td>
<td>-7.5/ 11</td>
<td>312</td>
<td>292</td>
<td>314</td>
<td>23</td>
<td>0.2</td>
<td>16·10$^{-4}$</td>
</tr>
<tr>
<td>Online microscopy</td>
<td>oABA$_{valid}$</td>
<td>Pri. nuc.</td>
<td>alternating</td>
<td>313</td>
<td>293</td>
<td>293</td>
<td>23</td>
<td>0.21</td>
<td>0</td>
</tr>
</tbody>
</table>
6.3.5. Results

In the following the data analysis, parameter estimation as well as the model validation will be discussed in detail for potassium alum. For the other substances only the parameter estimates and the model prediction in comparison with the measurements of the validation experiments are given to avoid unnecessary repetitions.

6.3.5.1. Data analysis

Figure 6.10 shows, as an example, the measurements of experiment KAL1 where a linear cooling ramp of -5 K/h and a linear heating ramp of 15 K/h was used (see Table 6.4).

![Figure 6.10: Measured data of the experiment KAL1. a) Temperature. b) Concentration trajectory determined from the refractive index probe. c) Calculated transient supersaturation. d) Observed CSD evolution depicted as a mass density distribution, $q_3$ (eq. 6.5).](image)

After seeding at $t = 0$, the concentration starts to decrease as expected (Fig. 6.10 b). The decrease of the liquid phase concentration accelerates once the cooling is initiated.
The transient supersaturation depicted in figure 6.10 c) was calculated using the temperature profile (Fig. 6.10 a), the concentration and the corresponding solubility curve (Fig. 6.7 a). It can be seen that due to cooling, a maximum of 5 % supersaturation in the crystallization region and as a result of the subsequent heating a minimum of 2 % undersaturation in the dissolution region is reached.

The measured CSD evolution from the recorded images of the online microscopy is shown in figure 6.10 d) as a mass density distribution, \( q_3 \) (eq. 6.5). During cooling, the seed crystals grow to a final size of around 550 \( \mu m \) until undersaturation is present (\( t = 1.4 \) h). Subsequently, the crystals dissolve and the average crystal length decreases.

\[
q_3(L) = \frac{\int_0^L f(L)dL}{\int_0^\infty f(L)dL}
\]

(eq. 6.5)

Additionally, secondary nucleation occurs in the crystallization region at \( L < 100 \) \( \mu m \) (Fig. 6.10 d). Apparently, these new crystals exhibit a much lower growth rate than the initial seeds. This behavior can be caused by growth rate dispersion as already discussed in chapter 4.1.2.

Furthermore, outliers are visible (small peaks at \( L > 500 \) \( \mu m \)), which are most likely caused by agglomerates or air bubbles which passed the image processing routine. Especially secondary nucleation, breakage, agglomeration and outliers are challenging for the quantification of the growth rate since the short-cut-method is based on an accurate calculation of the mean size of the seed fraction. Therefore, the procedure described in chapter 5.5. is applied yielding an objective mean length of the growing seed fraction (eq. 5.8), which is not influenced by other effects.

This procedure is explained using two observed CSDs as an example (Fig. 6.11 a). The left distribution depicts the initial seeds (grey dashed line), which can be described best with a Gaussian distribution (black solid line). It can be seen from the right CSD that, agglomerates (small shoulder at \( L = 500 \) \( \mu m \)), secondary nuclei and outlier can be isolated from the seed fraction when the distribution function is fitted appropriately. All observed CSDs are processed as described yielding the evolution of the mean length (black dashed lines in Fig. 6.11 b) of the seed fraction.
The calculated evolution of the trend of the mean lengths, $\bar{L}$, of the seed fraction for experiment KAL1 is depicted in figure 6.12 a). Additionally, all measured objects are counted, which yields the total particle number evolution (Fig. 6.12 b). These transient solid phase quantities are the basis for the subsequent parameter estimation, which will be explained in the next section.

Fig 6.12: a) Evolution of the seed mean length, $\bar{L}$, and b) the total particle number of the experiment KAL1, after processing the observed CSDs.

Similar data can be extracted from sieve analysis as well (Fig. 6.13). Even though this technique is limited in precision, the movement of the seed fraction is clearly visible for the crystallization case (Fig. 6.13 a) and for the dissolution case (Fig. 6.13 b). Thus, the procedure explained for the online microscopy is applied for the sieve analysis as well, which yields the evolution of the mean lengths of the seed fraction. Nevertheless, it was
not possible to precisely determine the overall particle amount from the sieve fraction weights. Thus, no nucleation rate can be estimated from this data.

**Fig 6.13:** Sieve analysis of all samples taken during the experiments KAL7 (a) and KAL9 (b) with indicated directions of growth and dissolution.

### 6.3.5.2. Parameter estimation

As shown in figure 5.5 in chapter 5, the recorded data from the seeded batch crystallizations, with exception of the validation experiments, was processed and then used for the parameter estimation. The driving force (e.g. super- or undersaturation) and the temperature signal are applied together with appropriate sub-models to yield the model predictions for the different kinetics ($I_m$ and $N_m$). The parameters comprised in the sub-models are then varied to match the transient seed fraction mean length and particle number evolution ($I_m$ and $N_m$). It is important to notice, that no full population balance model was applied for the parameter estimation and all kinetic sub-models were fitted separately to their corresponding data set. Additionally, no mass balance was involved in the fitting procedure as well. The objective functions applied together with a least squares method were introduced in chapter 5.6 (eqs. 5.9 - 5.11).

A temperature dependent power-law, as already introduced in chapter 5.3, was chosen to describe the kinetics of growth and nucleation (eq. 6.6). Additionally, a sub-model, which depends on the solid content, $M$, in the crystallizer (eq. 6.7), was applied as well since it accounts for the secondary nucleation. For the validation experiments the sub-model was chosen, which gave the best fitting result with respect to the objective function during parameter estimation. Also the amount of parameters was reduced in all kinetic approaches, if the simplification leads to a similar or even better quality.

$$K = p_e \exp \left(-\frac{P_e}{RT} \right) (S - 1)^\nu \quad \text{for } K = G, D, B_0 \quad \text{(eq. 6.6)}$$

$$B_0 = p_e (S - 1)^\nu M^-\nu \quad \text{for secondary nucleation} \quad \text{(eq. 6.7)}$$
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with

\[ M = \frac{(w_{\infty}(T_{\infty} - 273.15K) - w) m_{\infty} + m_{\infty}}{P_{\infty}} \]  

(eq. 6.8)

With these sub-models, the values of \( L_{\text{sim}} \) and \( N_{\text{sim}} \) in the objectives can be calculated by eqs. 5.12 - 5.14. A similar equation is utilized for the secondary nucleation approach (eq. 6.9):

\[ N_{\text{sim}} = N_{\text{nuc}} + \int k_{nuc}(S-1) M \, dt \quad \text{for} \ S \geq 1 \]  

(eq. 6.9)

The best fitting result (parameters in table 6.5) achieved for potassium aluminum sulfate is shown exemplarily for experiment KAL1 in figure 6.14.

Fig. 6.14: Fitting results for the evolution of the seed mean length, \( L \), and the total particle number exemplary shown for the experiment KAL1. Dots and squares - experimental observations; Dashed lines - predictions of the temperature dependent sub-models (eq. 6.6) for the different kinetics.

A power-law with three parameters (eq. 6.6) is found to describe nucleation and growth best whereas a linear, temperature independent approach is sufficient for dissolution kinetics. Nevertheless, it can be seen from the estimated parameter values in table 6.5 that the temperature dependence for nucleation and growth is almost negligible.
Table 6.5: Kinetic parameter values of the power-law sub-model (eq. 6.6) estimated for potassium aluminum sulfate applying the CSD results from online microscopy and the sieve analysis.

<table>
<thead>
<tr>
<th>Sampling method</th>
<th>Exp.</th>
<th>Kinetics</th>
<th>$p_1$ [m/s; 1/s]</th>
<th>$p_2$ [kJ/mol]</th>
<th>$p_3$ [-]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Online microscopy</td>
<td>KAL$_1$-KAL$_4$</td>
<td>Growth G</td>
<td>$1.7 \cdot 10^{-6}$</td>
<td>$5.7 \cdot 10^{-11}$</td>
<td>1.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nucleation B$_0$</td>
<td>$12.3 \cdot 10^{5}$</td>
<td>$5.2 \cdot 10^{-11}$</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dissolution D</td>
<td>$4.3 \cdot 10^{-6}$</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Sieve analysis</td>
<td>KAL$<em>5$-KAL$</em>{11}$</td>
<td>Growth G</td>
<td>$6 \cdot 10^{-6}$</td>
<td>$4.5 \cdot 10^{-7}$</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dissolution D</td>
<td>$4.5 \cdot 10^{-6}$</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
6.3.5.3. Model validation for Potassium alum

For evaluation of the quantified kinetics, a validation experiment, KAL\textsubscript{Valid} (Table 6.4), was carried out, which did not serve as additional input information during the parameter estimation procedure. It consisted of several cycles of crystallization and dissolution to have a qualitative difference to the experiments, which were utilized for the quantification of the kinetics. Additionally, a model prediction of the validation experiment was carried out with the estimated kinetic parameters and a full 1-dimensional population balance (chapter 4.2). The measured temperature profile, the initial concentration and the seed distribution served as the input for the simulation. The measurements from the validation experiment of potassium alum of the temperature, concentration and the CSD are given in figure 6.15 together with the corresponding model predictions where the estimated parameters of table 6.5 were applied.

![Fig. 6.15: Measured quantities of the validation experiment KAL\textsubscript{Valid} in comparison to the model equipped with the estimated parameters from table 6.5. a) Temperature. b) Measured and simulated concentration profile. c) Observed CSD (online microscopy). d) Predicted solid phase evolution applying the obtained parameters.](image-url)
Two different kinetic parameter sets were utilized for the simulations. The first set for growth, nucleation and dissolution, results from the online microscopic measurements (Fig. 6.15 b), Simulation (online microscopy)). A complete model parameterization is not possible with the results of the sieve analysis since nucleation cannot be determined with a suitable degree of accuracy. Instead, the quantified nucleation rate obtained from the online microscopy is applied to validate the estimated growth and dissolution parameters from the sieve analysis (Fig. 6.15 b), Simulation (sieve analysis)).

It is clearly visible that the model prediction is in a very good agreement with the measured concentration signal (Fig. 6.15 b), even though the temperature profile (Fig. 6.15 a) is rather complex. Furthermore, almost the same simulation output is obtained when the estimated parameters for growth and dissolution of the sieve analysis are applied. Small deviations occur only after seeding (t = 0...0.5 h) where the actual growth of the initial crystals is faster than the predicted one or attached dust is growing as well. Also the simulation of the solid phase evolution (Fig. 6.15 d) agrees well with the measurements of the online microscopy (Fig. 6.15 c). The predicted final size of the seed fraction (560 µm applying the kinetics resulting from the online microscopic investigations; 570 µm utilizing the quantified kinetics from the sieve analysis) only deviates by about 20-30 µm from the observations (590 µm).

Fig. 6.16: Comparison of growth kinetics of potassium alum from own measurements with references at T = 302.6 K.
Solid line - growth rate quantified with online microscopy applying eq. 6.6 and parameters of table 6.5; dashed line - growth rate quantified with sieve analysis applying eq. 6.6 and parameters of table 6.5; dashed-dotted line - growth rate according to [170] applying a linear approach (eq. 6.6 with p2 = 0 & p3 = 1); dotted line - growth rate according to [171] applying a linear approach (eq. 6.6 with p2 = 0 & p3 = 1).
Nevertheless, the nucleated particles are much more present in the simulation results. Either, a higher nucleation rate is predicted or the newly born crystals exhibited due to growth rate dispersion not the same growth rate as the seed crystals during the experiment, an observation which was made during the experiments KAL_{11} as well.

The quantified growth kinetics are in a good agreement with data from different references \[170, 171\] as shown in figure 6.16 for a temperature of 29.4°C. Nevertheless, various studies exist, which quantified completely different growth rates (for a comprehensive summary see e.g. \[172\]). Thus, it should be stressed again, that numerous parameters influence the quantification of kinetics like e.g. the method itself, the experimental set-up, present impurities and available measurement techniques.
6.3.5.4. Model validation for Potassium dihydrogen phosphate

Potassium dihydrogen phosphate is chosen as model substance since the shape of the crystals depends significantly on the applied process conditions. If only one crystal dimension (e.g. crystal length or width) is followed during the experimental investigations, a simulation utilizing the subsequently estimated parameters, describes just this dimension. Consequently, an error will occur if another dimension is predominant for certain crystallization conditions. Thus, the impact of a changing morphology on the precision of the quantified kinetic rates utilizing the short-cut-method can be investigated. The experimental analysis and the parameter estimation for KDP were carried out in the same way as for KAL.

Fig. 6.17: Measured quantities of the validation experiment KDP$^{\text{valid}}$ in comparison to the model equipped with the estimated parameters from table 6.6. a) Temperature and observed crystal shapes. b) Measured and simulated concentration profile. c) Observed CSD (online microscopy). d) Predicted solid phase evolution applying the kinetics from the online microscopy.
The images recorded during the validation experiment for KDP (KDP_valid) show that the crystal shape is changing remarkably (Fig. 6.17 a). Nevertheless, the predicted concentration profile (Fig. 6.17 b) agrees well with the experimental values. This model prediction was carried out applying a power law combined with an Arrhenius approach (eq. 6.6) for growth, a solid content dependent secondary nucleation sub-model (eq. 6.7) and a linear temperature independent approach for the dissolution. The kinetic parameters obtained during the previous analysis of the experiments (KDP1 - KDP4) are given in table 6.6.

Table 6.6: Kinetic parameters estimated using the power-law sub-model (eq. 6.6) for growth and dissolution and the parameters for the solid content dependent nucleation sub-model (eq. 6.7) for potassium dihydrogen phosphate applying the CSD results from the online microscopy.

<table>
<thead>
<tr>
<th>Sampling method</th>
<th>Exp.</th>
<th>Kinetics</th>
<th>p1 [m/s, 1/s]</th>
<th>p2 [kJ/mol, -]</th>
<th>p3 [-]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Online microscopy</td>
<td>KDP1-KDP4</td>
<td>Growth G</td>
<td>5.1·10^5</td>
<td>70</td>
<td>1.26</td>
</tr>
<tr>
<td>Nucleation B</td>
<td>5.2·10^-2</td>
<td>1</td>
<td>5.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dissolution D</td>
<td>7.0·10^-2</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Even though the concentration can be well predicted, deviations in the solid phase evolution between experiment and simulations occur since the volumetric shape factor, \( k_V \), is constant in the calculations. The chosen \( k_V \) of 0.75, which is an average of all observed single crystals during the experiments KDP1-KDP4, best describes crystals with prismatic shapes (Fig. 6.17 a), \( t = 0.8 \) h but not the bi-pyramidal (Fig. 6.17 a), \( t = 0.1 \) h or needle like shapes (Fig. 6.17 a), \( t = 3.8 \) h. Thus, the deviations of the seed fraction mean length between simulation and experiment increases from 5 µm (experiment: 530 µm, simulation: 535 µm) after the first crystallization cycle (\( t = 1 \) h) to 90 µm (experiment: 440 µm, simulation: 530 µm) after the second cycle (\( t = 3 \)). Nevertheless, the overall trend of the experiment can be predicted with a good agreement applying the determined kinetics.

The comparison with literature data (Fig. 6.18) yields again a good agreement with particular references [173] but only a fair agreement with recent studies carried out in the Max-Planck-Institute Magdeburg [63]. Again, one concrete reason for the found deviations cannot be specified similar to the results of potash alum.
Fig. 6.18: Comparison of growth kinetics of KDP from own measurements with the growth rates of the \{100\}-faces of different references at $T = 303.15$ K.

Solid line - growth rate quantified with online microscopy applying eq. 6.6 and parameters of table 6.6; dashed line - growth rate according to [63] applying a temperature independent power-law (eq. 6.6 with $p_2 = 0$); dashed-dotted line - growth rate according to [173] applying a temperature independent power-law (eq. 6.6 with $p_2 = 0$).
6.3.5.5. Model validation for ortho aminobenzoic acid

In contrary to the well soluble and well growing substances KDP and KAL, oABA is a case close to pharmaceuticals. The solubility in water is limited to 1 wt-% for the investigated temperature range. Furthermore, a part of the crystal phase is floating on the liquid surface during crystallization/dissolution experiments due to the low solid density. Additionally, a lot of air bubbles were mixed into the suspension due to these floating crystals. Present crystals exhibited a strong agglomeration tendency regardless whether the process was seeded or not. Also some insoluble impurities were present in the raw material, which lead, together with the other facts mentioned, to a rather strong scattering of the CSD data acquired with the online microscope.

![Fig. 6.19: Measured quantities of the validation experiment oABAValid in comparison to the model equipped with the estimated parameters from table 6.6.](image)

- a) Temperature.
- b) Measured and simulated concentration profile.
- c) Observed CSD (online microscopy).
- d) Predicted solid phase evolution applying the kinetics from the online microscopy.

The liquid phase composition was not measured continuously in this case since the substance seems to decompose in solution over time with a noticeable change of the...
liquid color from yellow to brown. Thus, the concentration was determined by sampling and offline analysis applying HPLC as described in section 6.3.3. Nevertheless, the same data analysis procedure as described above for KAL was applied to the experiments oABA1–oABA5. The estimated parameters of the applied temperature independent power-laws are listed in table 6.7.

<table>
<thead>
<tr>
<th>Sampling method</th>
<th>Exp.</th>
<th>Kinetics</th>
<th>$p_1$ [m/s; 1/s]</th>
<th>$p_2$ [kJ/mol; -]</th>
<th>$p_3$ [-]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Online microscopy</td>
<td>oABA1–oABA5</td>
<td>Growth G</td>
<td>$3.37 \cdot 10^{-7}$</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nucleation Bₙ</td>
<td>$1.39 \cdot 10^{-5}$</td>
<td>0</td>
<td>2.62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dissolution D</td>
<td>$5.63 \cdot 10^{-1}$</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

It should be noted that in the case of oABA also crystallizations from clear solutions were performed (Table 6.4) and exploited during the parameter estimation since secondary nucleation could not be observed sufficiently. Therefore, also the validation experiment was performed without seed material to evaluate the quantified nucleation kinetics. The experimental results from this run are depicted in figure 6.19. Furthermore, the solid phase was confirmed to be the stable polymorph [167] as expected.

It can be stated, that the model prediction for the concentration agrees with the experimental observations (Fig. 6.19 b) even for this challenging case. Nevertheless, the deviations are higher than for the other two substances as expected. Especially the predicted dissolution is slightly faster in comparison to the experimental results. The mentioned scattering of the CSD data can be seen in figure 6.19 c). This fact covers the primary nucleation of the validation experiment. Here, the solid phase evolution is observable after 2 h at first. After this period the trend of the experiment agrees with the model prediction (Fig. 6.19 d). Nevertheless, the measured mean product size is 420 µm (t = 8 h) and deviates by about 70 µm from the simulation (mean size 350 µm). Even though, the precision of the predictions is much lower than for the other substances, the quantified rates would be sufficient and necessary for a first process design since no information about the different kinetics can be found in literature.

6.3.6. Conclusions regarding the potential of the short-cut-method

The application of the short-cut-method for the quantification of kinetics, which are necessary for 1-dimensional population balance models, was demonstrated for three different substance systems. The experimental procedure, data analysis and the estimation routine was discussed in detail. It could be shown, that the crystallization kinetics can be determined precisely for substances like potassium alum with four simple seeded batch experiments. Nevertheless, it was observed that the quantified growth rates of the seed crystals are not necessarily valid for particles, which nucleate during the process. However, the estimated growth exponents are in a range between
one and two for all three substances, which is in agreement with the literature [8] for the chosen growth approach (eq. 4.14). Low activation energies were found for the potash alum kinetics of nucleation and growth (Table 6.5) and thus temperature-independency can be concluded for the corresponding rates at least in the investigated temperature range. The nucleation exponent is close to one for this substance, which is reasonable if a secondary nucleation mechanism is dominating.

The activation energy of the growth kinetics of KDP (Table 6.6) indicates an integration limited mechanism. However, a justified interpretation is difficult due to the correlation of the fitted parameters of eq. 6.6. The secondary nucleation approach (eq. 6.8) described the particle number evolution best for this substance. Here, the large exponent accounts for a strong solid content-dependency.

The kinetics of oABA (Table 6.7) were described best with temperature-independent approaches. Event though, unseeded experiments were utilized for the parameter estimation of the nucleation approach, a rather small exponent was found. Hence, there is evidence that eventually primary and secondary nucleation were observed together. Furthermore, it can be stated from the results generated by the simulation study in chapter 5, that eventually less experiments are necessary than used here and that the accuracy of the estimated kinetic rates increases with higher precision of the measurements of the CSD and the concentration.

Additionally it could be shown, that growth and dissolution kinetics can be quantified utilizing a simple sieve analysis with a sufficient degree of accuracy compared to the more sophisticated method employing an online microscope. If the substance of interest exhibits a drastic morphological shape change during the process, deviations between the model predictions and the experimental measurements occur. This was demonstrated for potassium dihydrogen phosphate when assuming a constant volume shape factor. It is possible to determine the growth rates of all occurring crystal faces to overcome this problem [63]. Nevertheless, currently this procedure cannot be applied for more complicated crystal shapes. Thus, a first approach would be to correlate at least the volumetric shape factor with the process conditions.

The short-cut-method was also applied to the complicated case of ortho amino benzoic acid, which led to the highest deviations between simulation and experimental observations. The properties of the crystal phase of this substance complicate a precise CSD determination. Furthermore, an inline concentration measurement was not possible in this case. Thus, errors, which are made during the offline analysis of the solution, will influence the precision of the estimates as well. Nevertheless, it could be shown that the concentration during the process can be predicted with an acceptable accuracy and that at least the trend of the solid phase evolution can be described even for an unseeded experiment.

In summary, the short-cut-method can be applied to quantify fast and reliable kinetic rates, which can be applied for design of batch processes. The parameterized approaches were validated with independent experiments and are in a good agreement with literature data for KDP and KAL. Hence, the estimates should be applicable for the
Crystallization kinetics

optimization of temperature profiles for example. However, the successful design of a
continuous crystallization is more complex due to e.g. growth rate dispersion and
therefore discussed in the next chapter.
7. Application of the quantified kinetics - continuous crystallization

For binary systems or pseudo binary systems, e.g. a main component with negligible impurities, purification can be commonly achieved within one crystallization step. Hence, the adjustment of the product quality and the continuous production can be the main focus. Nevertheless, a reliable design method for e.g. processes applying the MSMPR principle is still missing. Fundamental concepts were established in the late past century by e.g. Randolph, Larson, Mullin, Nyvlt and Jones [10, 13, 65, 174 & 175-177]. Afterwards, several attempts were made regarding the dynamic control and stability of continuously operated crystallizers [125, 126] or to apply new modeling tools (e.g. CFD modeling [178, 179]) to generate insights in the fluid mechanics and particle-fluid interactions inside the corresponding reactor. However, satisfactory and efficient design methods based on previously quantified crystallization kinetics are not available. In the recent past, interest in continuously operated crystallizer is rising again due to the high space-time yield as well as the constant product quality and new studies were carried out to improve the optimization and design of these processes [127]. Therefore, the opportunity to design a continuous MSMPR crystallization with the kinetics quantified in Chapter 6 is evaluated theoretically and experimentally in the present work. Practical works will be carried out in a continuously operated plant, which was constructed over three years in the MPI for Complex Technical Systems. Before, the kinetics of potassium dihydrogen phosphate (KDP) will be applied to determine proper regions of operation with respect to the achievable mean crystal size and suspension density. The comparison with the experimental results and the applicability of the short-cut-method introduced in chapter 5 for the design of continuous crystallizations will be discussed in the end of this chapter.

7.1. Dynamic modeling and operating conditions

The population balance for a continuous crystallization (eq. 4.19) is utilized together with the corresponding mass balance (eq. 4.31) to investigate possible steady-states with respect to the resulting product quality and achievable overall crystal mass. It will be shown, how different kinetic approaches and changing growth and nucleation kinetics influence the quantities of interest.

Two different nucleation approaches will be applied for the MSMPR simulations since the generation of new particles is the most critical mechanism for a continuous crystallization. Hence, next to the suspension density related secondary nucleation kinetics (eq. 6.7), a power-law (eq. 6.6) was utilized as well and parameterized with the
same data as applied in chapter 6. The estimated set of kinetic parameters utilized in this chapter is listed in table 7.1.

**Table 7.1:** Estimated kinetic parameters applying a power-law sub-model (eq. 6.6) for nucleation for potassium dihydrogen phosphate applying the CSD results from the online microscopy, together with the parameters of the solid content dependent nucleation sub-model (eq. 6.7) and the chosen growth approach of chapter 6.3.5.

<table>
<thead>
<tr>
<th>Kinetics</th>
<th>$p_1$ [m/s, 1/s]</th>
<th>$p_2$ [kJ/mol, -]</th>
<th>$p_3$ [-]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth G</td>
<td>5.1·10$^6$</td>
<td>70</td>
<td>1.26</td>
</tr>
<tr>
<td>Sec. nuc. $B_0$</td>
<td>5.2·10$^{-2}$</td>
<td>1</td>
<td>5.8</td>
</tr>
<tr>
<td>Nuc. (Power-law)</td>
<td>3.5·10$^{21}$</td>
<td>77</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Figure 7.1 depicts the simulation of the validation experiment KDP$_{\text{valid}}$ with both nucleation approaches in comparison with the measured concentration. Both simulations agree well with these experimental results even though the secondary nucleation approach fits slightly better as expected. Also the evolution of the particulate phase can be described well with both mechanisms. Hence, the different nucleation approaches are applied to investigate different steady-states to identify suitable process parameter combinations for subsequent experiments.

Fig. 7.1: Measured concentration of the validation experiment KDP$_{\text{valid}}$ from chapter 6 in comparison to the model equipped with the estimated parameters from table 7.1 and 2 different nucleation approaches.

The initial conditions are chosen according to the previous batch-experiments, which were carried out with KDP. The crystallization temperature will be in the range of 30-35°C since the kinetics were quantified for these values. Different initial supersaturations, which are the ratios between the saturation concentration at feed temperature to the saturation concentration at crystallization temperature, will be tested beginning from 1 to 1.14, which is the maximal driving force observed during the seeded
batch-experiments. According to the experimental set-up, which will be shown in the following, feed flow rates up to 3 l/min can be applied. Nevertheless, the consequential mean residence time of 8.33 min is very low for a crystallization process. Thus, the feed addition will be limited from 0.1 l/min to 1 l/min yielding mean residence times from 250 to 25 min. Furthermore, 100 g of seed crystals with a mean length of 250 µm will be simulated to start the overall process. Subsequently, the dynamic simulations are carried out over at least 10 mean residence times to ensure steady-state for every combination of chosen process conditions (table 7.2). The initial numerical variables like tolerances, grid size or step sizes are kept constant as explained in chapter 4.

Table 7.2: Simulated process conditions for different continuous crystallizations.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feed temperature</td>
<td>( T_{\text{Feed}} )</td>
<td>309.7</td>
<td>[K]</td>
</tr>
<tr>
<td>Crystallization temperature</td>
<td>( T )</td>
<td>302.75-309.6</td>
<td>[K]</td>
</tr>
<tr>
<td>Initial supersaturation</td>
<td>( S_0 )</td>
<td>1...1.14</td>
<td>[-]</td>
</tr>
<tr>
<td>Mean residence time</td>
<td>( \tau )</td>
<td>25-250</td>
<td>[min]</td>
</tr>
<tr>
<td>Shape factor</td>
<td>( k_V )</td>
<td>0.75</td>
<td>[-]</td>
</tr>
<tr>
<td>Seed mass</td>
<td>( m_{\text{Seed}} )</td>
<td>0.1</td>
<td>[kg]</td>
</tr>
</tbody>
</table>

7.1.1. Steady-state prerequisites

It is well known, that nonlinear oscillations can occur during a continuous crystallization [126]. If a high amount of the crystal phase is discharged from the process either by product removal or fines destruction, supersaturation rises until strong nucleation takes place. A similar effect can be observed if the crystal growth is retarded by e.g. impurities resulting in fluctuations of the product quality with respect to the mean size. Even though, these oscillations are of interest for developments in control strategies, a more fundamental question is: if a steady-state crystallization is possible with the chosen process conditions. A wash-out, i.e. a complete loss of solid material, occurs if e.g. the supersaturation is too low or the mean residence time too short. This case cannot be reflected by the utilized PBE model or by the chosen kinetic approaches, which were discussed in chapter 6. Hence, it is assumed that no steady-state is achievable if the total crystal mass inside the reactor drops below the initial seed mass. The calculated steady-state masses of the overall crystal phase for the quantified kinetics of KDP (table 7.1) and the chosen process conditions (table 7.2) are depicted in figure 7.2 to reflect this constraint.

The total crystal mass for the different simulated steady-states increase with increasing supersaturation and mean residence time for both nucleation approaches tested. Furthermore, a strong influence of the mean residence time is visible only up to 50...100 min depending on the supersaturation. Afterwards, the system approaches asymptotically equilibrium conditions. Hence, if the product crystal size distribution is not of interest, a process with the highest yield will require conditions at the upper border of
the figure but best productivity requires conditions corresponding to the lower right corner. Furthermore, it is shown that several combinations of initial supersaturations and mean residence times would lead to a wash-out of the solid content according to the introduced constraint (process conditions left from the bold solid line in Fig. 7.2).

It can be seen, that the power-law approach for nucleation (Fig. 7.2, right) yields even for the lowest supersaturations and small mean residence times a certain solid content in contrary to the secondary nucleation approach (Fig. 7.2, left). Thus, the latter mechanism yields more realistic trends in this range of process parameter combinations. Furthermore, the process parameter range for attainable steady-states is significantly smaller.

**Fig. 7.2:** Total crystal mass of different steady-states for the process conditions listed in table 7.2 and the quantified kinetics of KDP (table 7.1). **Left:** Secondary nucleation approach. **Right:** Power-law approach. 
*Bold solid line* - contour line equivalent to the initial seed mass; *solid lines* - steady-state mass of the solid content with indicated values in [kg].

### 7.1.2 Influence of kinetics

The mean product crystal size as well as the steady-state crystal mass depend nonlinearly on the process conditions corresponding to the chosen kinetic approaches. Figure 7.3 shows the product quality of different steady-states (table 7.2) together with the wash-out constraint as introduced above. Furthermore, also the experimentally investigated process parameter combinations are depicted (crosses in Fig. 7.3, section 7.3).

The simulation with the secondary nucleation approach (Fig. 7.3, left) yields the largest mean crystal sizes on the left hand side of the steady-state criterion. Only a few particles are present in this range, which prevents strong nucleation and promotes growth of the present particles. Practically, a wash-out would occur. The mean crystal size decreases strongly with increasing supersaturation due to the increasing overall solid content whereby nucleation becomes dominant.
Simulations carried out with the power-law approach (Fig. 7.3, right) evolve contrarily as expected since only supersaturation and temperature influencing the nucleation rate. Hence, the mean crystal size increases with increasing driving force and mean residence time.

**Fig. 7.3:** Product quality of different steady-states for the process conditions listed in table 7.2 and the quantified kinetics of KDP (table 7.1). **Left:** Secondary nucleation approach. **Right:** Power-law approach. *Bold solid line* - contour line equivalent to the initial seed mass; *solid lines* - mean product crystal size with indicated values in [mm]; *crosses* - experimentally investigated process parameters.

Even though, the estimated kinetic rates applying the short-cut-method are capable to describe independent experiments with a good precision, derivations between the measurements and simulations are visible (Fig. 7.1) and thus small uncertainties remain. Hence, the growth and nucleation rates are varied for ± 20% to get an idea about the sensibility of the calculated product qualities of the different steady-states. Regarding the secondary nucleation approach only small changes for the resulting mean crystal sizes of the different process variable combinations are observed (Fig. 7.4, left). An increasing growth rate gives initially a faster increasing suspension density and therefore also a higher nucleation rate for the states on the right hand side of the stability criterion. In contrary, by decreasing both kinetics fewer particles are generated due to nucleation and more supersaturation is consumed by the similarly retarded growth process. In summary, the variations of the kinetics almost cancel out for this specific case. Nevertheless, the boundary of attainable steady-states is shifted significantly (bold dotted lines in Fig. 7.4, left) towards lower supersaturations by increasing the kinetics.
Fig. 7.4: Product quality of different steady-states for the process conditions listed in table 7.2 and varied nucleation and growth rate in comparison with the originally kinetics of figure 7.3. Left: Secondary nucleation approach. Right: Power-law approach.

Bold solid line - contour line equivalent to the initial seed mass; solid lines - mean product crystal size with indicated values in [mm].

The change of the product quality by altering the crystallization rates is higher for the power-law nucleation approach for the area of interest (Fig. 7.4, right). This becomes clear especially for the contour of the mean crystal size of 0.15 mm, which is shifted to lower supersaturations and residence times. The growth of the particles consumes more of the excess of dissolved material for the specific mean residence time “leaving” less supersaturation for nucleation, which is a possible reason for the observations. Nevertheless, the data basis for the short-cut-method with respect to higher driving forces is rather limited and therefore simulation results for high supersaturations are arguable. In contrary to the secondary nucleation approach, the boarder of attainable steady-states is almost constant and therefore its variation not shown in figure 7.4 (right) for the sake of clarity.

Three different process parameter combinations are chosen for the experimental investigations of the continuous crystallization (crosses in Fig. 7.3, table 7.3). Points two and three should yield steady-states according to the prediction. They were chosen to stress the generic stability criterion introduced in section 7.1.1, to produce distinct mean crystal sizes and to have reasonable experimental times. In contrary, the first point was chosen to investigate the applicability of the different nucleation approaches. In the following the experimental set-up for the continuous crystallization is explained and subsequently the results of the three points are discussed.

Table 7.3: Tested process variables combinations of the planned steady-states.

<table>
<thead>
<tr>
<th></th>
<th>T [K]</th>
<th>S_0 [-]</th>
<th>τ [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>306.75</td>
<td>1.06</td>
<td>52</td>
</tr>
<tr>
<td>P2</td>
<td>306.75</td>
<td>1.06</td>
<td>85</td>
</tr>
<tr>
<td>P3</td>
<td>304.75</td>
<td>1.11</td>
<td>52</td>
</tr>
</tbody>
</table>
7.2. Set up of a MSMPR-plant

The core of the MSMPR plant is the 25 L draft tube baffle crystallizer already mentioned in chapter 6, where it was utilized for the estimation of crystallization kinetics. It was intensively studied via CFD-DEM simulations [180, 181] to investigate the fluid and particle pathways as well as the mechanical stress applied on the crystal phase. In summary, it was found that theoretically a smooth and almost perfect distribution of the particulate phase can be achieved with moderate stirring rates. It should be mentioned, that additionally intensive effort was made to validate the carried out CFD simulations with a small-scale geometry of the 25 L reactor with innovative measurement technologies [182].

Additionally, two 80 L tanks serve for supplying the feed solution and one 3 L tank as a hold-up for the product suspension. All vessels are connected by a framework comprised of thermostat-controlled pipes, pumps and valves, which ensure together with numerous measurement devices a well controllable and robust continuous process. The complete flow-chart is depicted in figure 7.5 and important parts will be explained in segments together with the experimental start-up procedure in the following.
Fig. 7.5: Flow chart of the 25 L MSMPR plant for continuous crystallization processes.
The initial feed solution is prepared in the stirred feed tanks B1 and B2 (individually manufactured vessels, material B1: polyvinylidene difluoride, material B2: stainless steel), which are temperature-controlled via two thermostats (HX1, RK 20 KP, Lauda, Germany; HX2, Integral RK 20 KP, Lauda, Germany; Fig. 7.6) connected to Pt100 (TIC05, TIC58, Fig. 7.6) inside the vessels. The exchange of solution between the B1 and B2 is achieved via a gear pump (P4, 3030-110, Scherzinger, Germany; Fig. 7.6) and an electrically heated steel pipe. To control the liquid level inside the tanks two capacitive liquid level probes (LIC89 & LIC57, Liquicap FMI, Endress+Hauser Messtechnik GmbH+Co. KG, Germany; Fig. 7.6) are utilized, which are connected to P4.

![Fig. 7.6: Feed tank segment of the MSMPR plant.](image)

A suitable option to ensure a constant feed concentration during the continuous experiments is to prepare a suspension of the processed component in B1 and a clear saturated solution in B2, both kept at saturation temperature during the experiment. The solution of B2 is subsequently utilized for processing and the suspension for refreshment of the depleted mother liquor from the crystallization. This demands a precise and fast temperature adjustment especially in B1 since the feed-back of the crystallizer will cause temperature disturbances. However, the polymeric material of tank B1 prevents an efficient heat exchange and induces a control time constant of over 1h.

Hence, initially a certain amount of substance and solvent are weighed and mixed in B1 to create a defined and clear solution. B1 is then kept at a high temperature (10-20 K
above saturation temperature) during the experiment to ensure a fast dissolution of the processed suspension of the crystallizer. The hot solution is transported to B2 via P4 where it is cooled to 5 K above saturation. A filter candle inside B1 prevents the transport of small particles. Thus, the initial concentration of the feed solution in B2 is almost maintained even during long-term experiments.

The feed solution is subsequently transported with a gear pump (P1, 3030-110, Scherzinger, Germany; Fig. 7.6) to the 25 L crystallizer C1 (BASF, material: borosilicate glass). All devices as well as the tubing are isolated and thermostat-controlled to prevent blockades inside the connecting pipes, damaging of pumps and measurement devices and to ensure saturation temperature at the entrance of C1 (TIC81, Fig. 7.7). Therefore a trace heating from the feed tanks to C1 is established consisting of copper pipes fed by thermostat HX6 (Lauda, Proline RP 845c, Germany), which is controlled by the Pt100 TIC81.

The flux to the reactor and the density of the solution is recorded by a coriolis mass flow meter (FI08, ADI08, TI08, Cori-flow™, Bronkhorst, Netherlands; Fig. 7.7). A capacitive liquid level probe (LIC25, Liquicap FMI, Endress+Hauser Messtechnik GmbH+Co. KG, Germany; Fig. 7.7) connected to the gear pump P1 ensures a constant volume inside the crystallizer C1 during the experiments. Here, the solution is cooled (thermostat HX4, Lauda, Integral XT 550 Wc, Germany) to crystallization temperature and the concentration as well as the temperature are measured via inline probes (AI24, refractive index probe, PR-23, K-Patents, Finland; Pt 100 TIC26; Fig. 7.7).

The product is released from the crystallizer via a periodically opened pressure-controlled valve (YI29, Fig. 7.7). Subsequently, the product suspension is send to the hold-up tank B3 or offline samples are taken from a three-way valve.
Finally, the suspension is pumped back from B3 to the first feed tank B1 utilizing a peristaltic pump (P3, Ismatec, Flowmaster FMT 300, Germany; Fig. 7.7). Again, to prevent blockades all tubes and vessel B3 is kept at 10-20 K above saturation temperature via thermostat HX8 (Lauda, Proline RP 845c, Germany).

In the beginning of the experiment, clear solution is fed into the crystallizer without cooling to initialize the liquid circulation from the feed tanks to the crystallizer and back. Subsequently, the cooling of the crystallizer and the feed pipes is initiated until the demanded temperature regime is established. A subsequent seeding represents the actual start of the continuous crystallization.

It should be mentioned, that the maximal temperature reduction from B2 to C1 is 3 - 5 K for moderate process temperatures (5 - 80°C) depending on the flow rate of P1. Furthermore, a maximal supercooling of 15 - 20 K dependent on the feed flow rate and feed temperature can be achieved inside the crystallizer due to the limited cooling surface and occurring encrustations.

Hence, preliminary water tests of the plant are recommended to determine the achievable temperatures inside the different vessels and tubings dependent on the flow rates of the different pumps (P1 - P4) since the feedback between the different parts of the plant can be complex and non-intuitive.

A fines dissolution loop was constructed as depicted in figure 7.8 but not utilized during the experiments of the present study even though its functionality was demonstrated. Suspension can be removed from the crystallizer via a sedimentation tube and pump P2 (3030-110, Scherzinger, Germany; Fig. 7.8). The tube is placed in the upward flow field of the crystallizer in the outside section of the draft tube. Hence, the particle cut size can be well controlled with the adjusted flow rate of P2. An effective heating and therefore dissolution of the fines is ensured with a steel spiral located inside the thermostat HX5 (Lauda, Proline RP 855, Germany; Fig. 7.8), which serves as a heat exchanger with a defined residence time.

A similar construction is utilized for the reflux to C1 where the solution is cooled to crystallization temperature (HX7, Lauda, Proline RP 855, Germany; Fig. 7.8). Again, a trace heating of the pipes connected to the corresponding thermostats prevents blockades and the mass flux is recorded via a coriolis mass flow meter (FI85, ADI85, TI85, Cori-flow™, Bronkhorst, Netherlands; Fig. 7.8).
7.3. Experimental results

The process is started as described in the previous section to test the process variable combinations listed in Table 7.3. The conditions were kept constant until a steady-state was identifiable, the concentration probe or the online microscope was blocked or a wash-out occurred. Subsequently, the crystallizer was heated again 10 K above saturation temperature for 30 min to ensure dissolution of remaining crystalline material before the next process conditions were tested.

Figure 7.9 and 7.10 depict the results of the process variable combinations P1 (T = 306.75 K, S_0 = 1.06, \( \tau = 52 \) min) and P2 (T = 306.75 K, S_0 = 1.06, \( \tau = 85 \) min). It is obvious, that the concentration (Fig. 7.9 a) and 7.10 a) decreases after seeding but raises again after circa one mean residence time to the initial value in both cases. In contrary, the simulated data depict a much larger concentration and supersaturation (Fig. 7.9 b) and 7.10 b) degradation and at least for the point P2 a stable steady-state. The recorded images from the online measurements were evaluated after the experiment with respect to the CSD (Fig. 7.9 d) and 7.10 d) and particle amount (Fig. 7.9 c) and 7.10 c). Similar to the concentration, the total crystal number decreases after one mean residence time almost to the initial value before seeding. Hence, it has to be concluded that the process variable combinations P1 and P2 do not yield a steady-state, which was predicted by the simulations with the secondary nucleation approach as well.

The recorded CSDs show, that the initial seeds start to grow before they are discharged from the crystallizer. Furthermore, the amount of small particles inside the reactor remains almost constant, which implies that no significant nucleation takes place. In contrary, the simulated CSD evolution (Fig. 7.9 e) and 7.10 e) depicts a larger growth of the seed crystals, which simultaneously appear to remain longer inside the crystallizer. Furthermore, strong nucleation is visible in contrary to the experimental distributions.
Additionally, the small particles exhibit a significant enlargement up to 300-400 µm at t = 1.6 h. This was not observed during the experiment where only a small fraction of the nucleated crystals was growing to larger sizes.

Fig. 7.9: Experimental results of the process variable combination P1 (T = 306.75 K, S₀ = 1.06, τ = 52 min) in comparison with the simulated trends. a) Concentration signal; b) Supersaturation; c) Particle density; d) Experimental CSD; e) Simulated CSD.
Experimental results

Fig. 7.10: Experimental results of the process variable combination P2 ($T = 306.75$ K, $S_0 = 1.06$, $\tau = 85$ min) in comparison with the simulated trends. a) Concentration signal; b) Supersaturation; c) Particle density; d) Experimental CSD; e) Simulated CSD.

In contrary to P1 and P2, the process variable combination P3 (Fig. 7.11) led to a steady-state with respect to the concentration and the crystal size distribution. Nevertheless, the degradation of the driving force is again not comparable to the model prediction independently of the nucleation mechanism (Fig. 7.11 c). However, the particle amount remained almost constant after a transient oscillation subsequent to seeding. The visible peaks at around $t = 4$ h are the result of a blockade of the online microscope.

Furthermore, the simulation yields a larger particle amount and thus much higher suspension densities regardless of the nucleation approach. An immediate increase of small crystals can be seen by applying the power-law submodel (dashed-dotted line in Fig. 7.11 d). In contrary, the secondary nucleation approach yields first a decrease of particles subsequent to seeding with a sharp increase in the following (dashed line in Fig. 7.11 d) after the initial crystals were grown to an appropriate size.

Figure 7.11 e) and f) depict the normalized final particle distribution and the transient mean particle length of the experiment in comparison with the theoretical data. The product distribution is in a good agreement with the simulations for larger crystal sizes. However, the fine content differs due to the finite resolution of the online microscope and dust as well as other impurity particles, which could not be removed during the evaluation of the image data and are especially present for the size classes between 20 and 100 µm.

The simulated transient mean lengths are smaller over the entire time as expected due to the significantly higher nucleation rates. Nevertheless, the observed and calculated CSD evolution (Fig. 7.11 g) & h) appears to be qualitatively in good agreement apart from the high nucleation peak in the beginning of the simulation.
Fig. 7.11: Experimental results of the process variable combination P3 (T = 304.75 K, S₀ = 1.06, τ = 52 min) in comparison with the simulated trends. a) Concentration signal; b) Temperature; c) Supersaturation; d) Particle density; e) Normalized seed and product distribution; f) Mean particle size; g) Experimental CSD; h) Simulated CSD applying the secondary nucleation mechanism.
In summary, the theoretical calculations cannot predict the measured quantities in general, which implies that the transfer of the kinetics determined in previous batch-experiments to a continuous process is difficult. The kinetics can be exploited to illustrate the different regions of product quality and possible steady-states as shown in section 7.1. Thus, at least trends are identifiable, which process variable has a major or minor influence on the process result. Additionally, it can be shown not every process variable combination leads to a stable process and that the impact of small changes is complex and non-intuitive, which was also proven experimentally.

The obvious mismatch of the transient quantities can be the consequence of a measurement error during the determination of the saturation curve. However, the solubility experiments were done twice by different experimenters with similar results, which are in good agreement with literature data (see Chapter 6, Fig 6.7 b). The transient concentration during all experiments was additionally evaluated with offline samples gravimetrically, which supported the measured concentration from the inline RI probe. Furthermore, the two Pt100 inside the crystallizer recorded similar and logical values. Thus, measurement errors of the temperature or the concentration and a therewith calculated eventually faulty supersaturation are improbable reasons for the observed differences between the model and the experiments. Also, the utilized seed crystals were from the same lot and thus the same quality as applied for the previous batch-experiments.

Eventually, the fluid dynamics influenced the outcome of the continuous experiment in terms of non-ideal mixing or a preferred discharge of a specific crystal size. However, there was no evidence found for this during intensive CFD studies. A smooth and efficient agitation was shown e.g. in [180] and even though several dead zones exist an almost ideal mixing can be assumed. Furthermore, the PBE model, which was applied for the dynamic simulations, can comprise mistakes or wrong approaches. Nevertheless, it was successfully applied for the batch experiments and only extended with simple terms for the continuous process.

A probable reason are the previously quantified kinetics, even though they could be validated with an independent batch experiment. A stable continuous crystallization relies on the secondary nucleation. Hence, small errors of the determined nucleation rate would have a significant impact and the choice of the kinetic sub-model is decisive as shown in section 7.1.

Another uncertainty factor is the in chapter 4 already mentioned growth rate dispersion. The quantified growth rates from chapter 6 applied seeded batch experiments, which means well growing, already macroscopic crystals. In several studies [116, 117, 119] it was shown, that the growth rates of nucleated particles are on average much smaller than the ones of larger particles. Additionally, the present work illustrated this fact as well (compare fines in Fig. 6.15 c) & d). This implies, that every quantification method, which apply seed crystals will eventually determine growth rates, which do not account for nucleated crystals. Already Randolph and Larson [10] mentioned the importance of this fact for the continuous crystallization. They stated, that “only 10-15% of the number of nuclei formed...account for 95% of the mass of the crystalline product” of a continuous crystallization. “The growth rate of the other 85-90% of the number is too low to produce appreciable mass during their residence time in the crystallizer.” Hence, the
experimental results and the mismatch to the theoretical calculations can be interpreted as follows: The initial seeds grow well and serve for secondary nucleation. The generated nuclei grow only partly to a significant size. Thus, the secondary nucleation rate decreases with time since less crystal surface is present, which leads in the end to the observed low particle amount and low supersaturation degradation. The great importance of a growth rate dispersion quantification method would be thus obvious. Nevertheless, also impurities can be a possible cause of low growth and nucleation rates. The continuous experiments shown were the first performed in the recently constructed plant. Thus, it cannot be excluded that impurities were present in the tubes and tanks, which were not removed during the cleaning procedure. However, there are many possible reasons for the deviations between the simulations and the experiment. The identification of the most probable cause would have required more experiments with different constraints and conditions, which were not realizable. During the work, the initially bought KDP was not available anymore with the same quality. Material, which was purchased from a different distributor, exhibited significantly different kinetics with which even the batch-experiments could not be reproduced. Thus, there is evidence that the impurity matrix of the KDP had changed since this substance is highly sensitive to present additives even in very low concentrations [120]. Nevertheless, an ICP-OES analysis (see Appendix B) of the materials yielded no noticeable difference.

7.4. Summary

The task of this chapter was to introduce a continuous crystallization, which was performed in a recently constructed MSMPR plant. In the beginning different nucleation approaches were applied to evaluate the stability and the resulting product quality of different process variable combinations. It could be shown, that the corresponding correlations are rather complex. Kinetic information can be applied here to elucidate feasible and suitable operation points. Subsequently, three different process variable combinations were evaluated experimentally. The results showed that a simple transfer from the kinetics from seeded batch experiments to a continuous process is difficult. However, the deviations between the simulated and measured quantities could not be clarified in detail but different interpretations of the results were given. Nevertheless, the constructed plant was applied for a successive continuous crystallization over 24 h. Thus, the experimental framework for a final clarification of the open questions is given. Furthermore, the prediction of the steady-state is complicated with the applied model as it was shown in section 5.8. In this context it should be mentioned, that especially the growth rate dispersion is of great importance for the considered process and that a corresponding efficient quantification method would be highly beneficial. Nevertheless, for challenging separations, like the purification of substance mixtures with miscibility in the solid state, other processes and operating modes have to be applied. An example of a fractional counter-current crystallization is discussed in the next chapter.
8. Counter-current crystallization - separation of solid solution systems

The present chapter is dedicated to the improvement of the fractional crystallization process (Fig. 3.3) introduced in section 3.3. Several applications for melts crystallizations show that a counter-current serves to improve the overall separation efficiency, which was also stated in [66] for crystallizations from solution. The counter-current principle is widely applied for thermal separation processes to intensify contact between phases, which enhances the substance transport and therefore the efficiency. Familiar continuous process examples are mixer-settler devices for extraction, the simulated-moving-bed principle in chromatography and rectification columns. Application fields for crystallization are commonly found for the purification of melts [8] or for crystallization cascades [56].

Solidification of melts on a cooled surface, e.g. dynamic solid layer crystallization on various types of heat exchangers, yields a variation of heat transfer coefficients as the solid crystal layer grows. Hence, the heat transfer will decrease if the temperature gradient is not controlled appropriately. Therefore, columns can be applied like in rectification where the feed is introduced e.g. at the top [8]. The crystals are formed in suspension on their way downwards the apparatus and the nearly pure material is partly molten at the bottom. This decreases the impurity content of the liquid phase and mostly pure melt is transported upwards to intensify the purification effect. Additionally, a commonly applied sweating step of e.g. solid layer crystallization [183] can be avoided. However, these types of columns require a significant difference of the densities of melt and crystals for the gravimetric movement. Other concepts involve a screw gear to provide a forced convection of the solid material in counter-current to the liquid phase. The purification efficiency can be additionally intensified and also solid solutions can be separated if a combination with partial melting and recrystallization is realized, like established in Brodie purifiers [8].

Besides purification, counter-current operation is additionally applied for the adjustment of the crystal size distribution [56]. For solution crystallizations, cascades of continuous crystallizers are connected via the liquid input and the suspension output fluxes. The concentrated feed is introduced in the first stage, partially depleted and subsequently transported to the second stage. Hence, the supersaturation present in each crystallizer can be adjusted precisely due to different temperature regimes in the stages and strong nucleation can be avoided. The necessary seed crystals for the whole cascade are produced in the last stage where the suspension is classified and transported to the stage before. Thus, coarse crystals with low fine content and a high purity can be produced continuously due to the growth in defined supersaturation steps.
A few applications of counter-current crystallization columns exist for the separation of mixed crystal forming systems from solution [66, 184]. Nevertheless, the purification efficiency and productivity seems to be limited. Since no repeated dissolution and recrystallization is applied, the equilibration time is based on the diffusion processes within the solid phase. Furthermore, the operation is complicated and specified to a certain separation problem.

A few attempts were made with sequences of batch-crystallizers [185] following e.g. the Upjohn-scheme [186]. However, the characteristic solid-liquid equilibrium of a system involving solid solutions could not be represented correctly and a complete counter-current was not achieved in this study. Another work [67] discusses theoretically a continuous crystallization cascade, which reflects correctly a successive counter-current. Nevertheless, the necessary solid-liquid separation and the required solid transport were neglected and the experimental validation carried out as a series of manual batch-crystallizations. Hence, an efficient and universal approach for separating systems involving solid solutions (Fig. 2.9) based on fractional crystallization (chapter 3.3, Fig. 3.3) will be discussed in the following.

At first, an equilibrium stage model of a counter-current fractional crystallization process is derived, which is sufficient to describe a purification based on discrete time steps and purification stages. Afterwards, the SLE of two different ternary substance systems is investigated, which serve to validate the equilibrium stage model and the process principle. The validated model is then applied in chapter 9 to design and illustrate a semi-continuous separation utilizing a recently developed fractional crystallization plant.

8.1. Development of a discrete equilibrium model

The application of PBE systems (chapter 4) is complex since the kinetics have to be quantified and the equation system has to be discretized and solved numerically. For processes where the evolution of the individuals is not of interest and only a global purification is desired, reduced equilibrium-controlled models can be applied. For example, rectification columns, mixer-settler devices or stationary chromatographic simulated moving bed processes can be described with cell or Craig models [187] to a certain extend.

The approach discussed in the following is based on the thermodynamic phase relations of a ternary substance system involving solid solutions. A simplified mathematical description of the related phase diagrams in Cartesian coordinates will be the focus of the first part. Subsequently, it is incorporated into an efficient cell model, which reflects a sequence of separation units, to model a counter-current fractional crystallization cascade with a system of nonlinear algebraic equations for an efficient design, illustration or optimization.

8.1.1. Description of ternary phase diagrams involving solid solutions

To simplify the mathematical description of systems forming solid solutions the next part will focus first for illustration on chiral systems with complete miscibility in the solid phase as introduced in chapter 2 (Fig. 2.9).
The occurrence of complete miscibility in the solid phase is shown in the ternary phase diagram in figure 8.1 for a system of two components A and B. These components can be for example two enantiomers. In this case the phase diagrams will be symmetrical around the axis characterized by 50:50 mixtures of those two [26]. Below the solubility isotherm two homogeneous phases, a saturated liquid and a solid solution of the particular composition of the two compounds A and B, are in equilibrium with each other (Fig. 8.1).

**Fig. 8.1:** Illustration of a ternary phase diagram for a solid solution forming system containing two enantiomers A and B. $x_i$, specifies the mass fractions of the components A, B and the Solvent and $z_1$, $z_2$, corresponding Cartesian coordinates. Points $x_{A, sat}$ and $x_{B, sat}$ specify the pure component solubilities.

*Bold solid line* - solubility isotherm.

The mass or mole fractions of the ternary phase diagram, $x_i$, are transformed into two Cartesian coordinates $z_1$ and $z_2$. This is done via the geometrical rules valid for equilateral triangles.

$$z_1 = x_i - 0.5 \cdot x_{Solvent} \quad \text{(eq. 8.1)}$$

$$z_2 = x_{Solvent} \sin\left(\frac{\pi}{3}\right) \quad \text{(eq. 8.2)}$$

After this transformation, the functional correlations for the liquidus and solidus isotherms can be formulated in Cartesian coordinates as well. A suitable simple empirical function, $a(z_{1,2})$, is chosen, which is capable to reflect the results of solubility measurements. For the illustration given in figure 8.1, a quadratic expression (N=2) for
Development of a discrete equilibrium model

Equation 8.4 connects the solubilities of the two pure substances in the liquid phase \((x_{A,sat} and x_{B,sat} in Fig. 8.1)\), which are specified by the Cartesian coordinates \(z_1(x_{A,sat})\) and \(z_1(x_{B,sat})\).

Below the solubility isotherm, two specific states in the solid and liquid phases coexist in equilibrium with each other connected by conodes (only one shown as dashed line in Fig. 8.2).

\[ \alpha(z_{1,L}) = \alpha(z_{1,i}) \quad \text{for} \quad z_{1,L} = z_1(x_{A,sat}) \ldots z_1(x_{B,sat}) \quad (eq. 8.3) \]

\[ \alpha(z_{1,i}) = \lambda_1 + \lambda_2 z_{1,i} + \lambda_3 z_{1,i}^2 + \ldots + \lambda_n z_{1,i}^n \quad \text{for} \quad z_{1,L} = z_1(x_{A,sat}) \ldots z_1(x_{B,sat}) \quad (eq. 8.4) \]

The comprised parameters, \(\lambda_0 - \lambda_n\), of equation 8.6 have to be determined empirically based on experimental results. Subsequently, all points on the solubility isotherm are

\[ \beta(z_{1,i}) = \beta(z_{1,i}) \quad \text{for} \quad z_{1,L} = z_1(x_{A,sat}) \ldots z_1(x_{B,sat}) \quad (eq. 8.5) \]

\[ \beta(z_{1,i}) = \kappa_1 + \kappa_2 z_{1,i} + \kappa_3 z_{1,i}^2 + \ldots + \kappa_n z_{1,i}^n \quad \text{for} \quad z_{1,L} = z_1(x_{A,sat}) \ldots z_1(x_{B,sat}) \quad (eq. 8.6) \]
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connected with one specific point on the solidus curve (schematically shown in Fig. 8.3 as dashed lines).

\[ \beta(z_i) \]

is related to the courses of the conodes and defines the separation behavior of the related SLE. Figure 8.4 a) depicts the function \( \beta(z_i) \) for the generic ternary phase diagram of figure 8.3. The ideal separation behavior is shown as dashed line for which fractional crystallization is not applicable as purification process. The extensions of the conodes would merge in the pure solvent corner (grey dashed lines in Fig. 8.4 b) and the liquid and solid phase ratio of the involved substances A and B would be equal after a crystallization of a certain liquid phase.

For the generic case of figure 8.3, two different separation behaviors are visible in figure 8.4 a) disconnected by the 50:50 ratio of both substances. An A-enriched liquid phase and an A-depleted solid phase would be present for an initial state on the A side of the ternary diagram. For a B-enriched state of the initial solution this behavior is inversed. Hence, in between an alyotropic point is present where similar to the ideal system a separation of both substances is not possible.
Fig. 8.4: a) Separation function $\beta(z_{1,i})$ for the generic solid solution example of figure 8.3 (solid line). It can be seen, that the depicted system exposes an alyotropic point. Dashed line - ideal system, which cannot be separated via fractional crystallization at this temperature.

b) Ternary phase diagram with the conodes reflected by figure 8.4 a). Solid lines - separation behavior of the generic system of figure 8.3; grey dashed lines - ideal separation behavior.

For the crystallization of systems involving solid solutions as illustrated in figure 8.3 (point $(z_1(x_{i,0}), z_2(x_{i,0}))$) equation 8.4 and 8.6 can be used to calculate the thermodynamic equilibrium state for the phase separation of a given non-equilibrated starting composition $x_{i,0}(z_{1,0}, z_{2,0})$.

\[
\begin{align*}
\chi \beta \chi &= \chi \alpha \\
\chi \alpha &= \chi \alpha
\end{align*}
\]  
(eq. 8.7)

\[
\begin{align*}
z_{1,i} &= z_{1,i} + \chi (z_{1,i} - z_{1,i}) = \beta(z_{1,i}) + \chi (z_{1,i} - \beta(z_{1,i})) \\
z_{1,i} &= \chi z_{1,i} = \chi \alpha (z_{1,i}) \quad \text{for } z_{1,L} = z_{1}(x_A, sat) \ldots z_{1}(x_B, sat)
\end{align*}
\]  
(eq. 8.8)

Thus, two unknown variables, the height on the corresponding condode, $\chi$, and the $z_1$ coordinate on the solubility isotherm, remain. For polynomials of higher order of $y(z_1)$ and $\alpha(z_1)$ it is difficult to solve this equation system explicitly and a numerical algorithm, e.g. a Newton algorithm, has to be applied. The corresponding objective function can be formulated as follows:

\[
r(z_{1,i}) = 0 = \left( \beta(z_{1,i}) + \frac{z_{1,i}}{\alpha(z_{1,i})} (z_{1,i} - \beta(z_{1,i})) \right) - z_{1,i}
\]  
(eq. 8.9)

Hence, the Cartesian coordinates of the phases, which are in equilibrium after a complete crystallization of a liquid with the composition $x_i$, can be determined. Subsequently, the Cartesian coordinates are transformed back into mass fraction again for calculations based on mass balances.
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It should be mentioned, that the solubility and the courses of the conodes will change for different temperatures. Hence, the functions $\alpha(z_{1,\ell}, T)$ and $\beta(z_{1,\ell}, T)$ yield surfaces, which can be determined completely only if sufficient data is available. For the fractional crystallizations considered in this work solely two process temperatures are considered and thus a complete parameterization of $\alpha(z_{1,\ell}, T)$ and $\beta(z_{1,\ell}, T)$ was not the focus. Furthermore, the deposited solid phase will reflect the actual state of the solution, which is changing during the crystallization and hence crystals will grow in layers with varying composition and will not be completely homogeneous [29]. Nevertheless, to describe the phase separation for such a system thermodynamic equilibrium between both phases is assumed, which is sufficiently accurate as long as the deposited mass is significantly smaller than the residual liquid mass.

In summary, it is possible to efficiently implement the empirically determined solid-liquid equilibria of a substance system characterized by solid solutions due to the transformation of the phase diagram into Cartesian coordinates. It serves subsequently to calculate the equilibrium states of a solid and liquid phase after a crystallization step. Thus, the model can be utilized within the mass balances of a particular crystallization cascade as discussed in the next section.

8.1.2. Stage model for counter-current fractional crystallization

As already pointed out, a complete separation of a system forming mixed crystals is difficult to achieve with the commonly applied single-stage crystallization processes. The fractional crystallization introduced in chapter 3 can be utilized amongst other processes for the separation of substances forming solid solutions. For such a case, several crystallizers or process stages and several batch-crystallizations or cycles are necessary and the process design is based on a demanded purity. Nevertheless, the required solid-liquid separation after each crystallization and the necessary transport of the solid phase leads to a complex process, which is difficult to automatize. In 2009, the company HAPILA GmbH (Gera, Germany) developed an automated crystallization plant [11], which was already applied for the production of highly purified pharmaceuticals [188] and can be adapted for the separation of solid solution systems.

The transport of solid phases between different batch crystallizers is avoided by periodically performed dissolution steps. Periodic realization of suitable temperature changes and arranging specific connections between the various crystallizers provide the opportunity to move the solid phases as solutions in the desired direction. Hence, the process can be automatized easily. Furthermore, the impurity content of the crystals grown in layers, which are characteristic for solid solution systems, can be efficiently reduced due to the repeated dissolution. In every stage a new equilibrium is attained in contrary to column processes, where the solid phase is transported in counter-current to the liquid phase.

The scheme of this periodically working counter-current cascade, which will be discussed in detail in the following, is shown in figure 8.5.
Fig. 8.5: Principle of the counter-current crystallization cascade. The direct transport of a solid phase is avoided due to the specific liquid transport and periodical dissolution.

Every process cycle of the cascade contains different sub-steps, i.e. transport of the liquid phases, crystallization and dissolution, which are performed simultaneously in all separation-stages. The periodically repeated individual sub-steps of a cycle \( k \) can be explained considering three neighboring stages \( j-1, j \) and \( j+1 \) (Fig. 8.6), which are initially filled with a certain suspension from a previous crystallization.

Fig. 8.6: Three stages \((j-1, j, j+1)\) of the crystallization cascade at time steps \( k \) and \( k+1 \). Solid lines - transport of the dissolved solid masses, \( m_s \), with the mass fractions, \( x_{i,s} \), of the substances \( i \) (i = A, B, Solvent); dashed lines - transport of the liquid masses, \( m_l \), with the compositions, \( x_{i,l} \), of the substances \( i \).

The crystallization leads to saturated liquid phases in equilibrium with corresponding solid phases in all vessels. The liquid phases are then separated from the solid phases using inline filters and transported two stages forward in the “liquid phase direction” towards product outlet 1 (Stage 2, Fig. 8.5). Thus, the liquid phase of stage \( j+1 \) is
transported into stage \( j-1 \) (Fig. 8.6). The suspensions, which contain the retained solid phases and the transferred liquid phases, are heated for dissolution to create clear solutions. They are subsequently transported to the neighboring vessels in the “solid phase direction” towards product outlet 2 (Stage \( J \), Fig. 8.5), i.e. from stage \( j-1 \) to stage \( j \) (Fig. 8.6). Thus, a counter-current operation is simulated since all solid phases are moved one stage towards product outlet 2 and all liquid phases are transferred one stage towards product outlet 1 within one cycle \( k \). After the completed transport, supersaturation is generated in a next cycle \((k+1)\) by cooling or solvent evaporation, to initiate crystallization in all stages. After a few number of cycles the pure product 2 is recovered from the last stage \( J \) in direction of the solid phase transport. Only fresh solvent is added here to the process for the last purification step. The most enriched mother liquor is removed out of the second stage as product 1. The substance determined as product 1 or 2 depends on the enrichment behavior of substance A and B and thus on the solid-liquid equilibrium of the system. The procedure described can be carried out over many steps in a cascade of an arbitrary number of stages. A PBE model, which describes the complete particle collective for every sub-step as introduced in the chapter 4 is hence unnecessary and would be computationally very expensive. The sub-steps can be combined in a mass balance considering both phases (liquid: \( l \), solid: \( s \)) in all stages and sub-steps. Evaluating a random stage \( j \) in a cascade of \( J \) crystallizers provides for steady state conditions the following overall mass balance for two consecutive time steps \( k \) and \( k+1 \) out of a sequence of \( K \) steps:

\[
m_{l,j}^k + m_{s,j}^k = m_{l,j}^{k+1} + m_{s,j}^{k+1}
\]

(eq. 8.10)

Additionally to the transport steps, three additional sub-steps have to be considered for a feasible process. Eventually, the liquid phase, which is present in a certain stage \( j+1 \), is not capable to dissolve the solid present in stage \( j-1 \) completely. Thus, solvent is added in order to provide a saturated solution for the subsequent crystallization, \( m_{\text{Solv}}^j \) (not shown in Fig. 8.6).

Furthermore, a certain start-up phase of the cascade will be observable. During this period the cascade is consequently filled starting from the feed stage towards the product outlets. Hence, eventually no mother liquor is present from a random stage \( j+1 \) for a stage \( j-1 \). For these initial steps present solid phases are dissolved in pure solvent as well.

The plant utilized for the experimental validation, applies evaporation and cooling to generate supersaturation for the subsequent crystallization. Thus, a corresponding term for the solvent removal has to be included in the overall mass balance, \( m_{\text{Evap}}^j \).

For some process options it can be advantageous to introduce the feed, \( m_{\text{Feed}}^j \), at any stage \( j \) or even in more than one stage. Thus, equation 8.10 is rearranged in the following form:

\[
m_{l,j}^k + m_{s,j}^k + m_{\text{Solv}}^j + m_{\text{Feed}}^j = m_{l,j}^{k+1} + m_{s,j}^{k+1} + m_{\text{Evap}}^j
\]

(eq. 8.11)
The corresponding partial mass balance comprising the mass fractions for three components \( i \) (\( i = A, B \) and Solvent) in the solid, \( x^s_{i,j} \), and liquid phase, \( x^l_{i,j} \), can be formulated in analogy to the overall mass balance (eq. 8.11).

\[
\begin{align*}
& m^j_{i,Sol} x^s_{i,j} + m^j_{i,Sol} x^l_{i,j} + m^j_{i,Feed} x^s_{i,j,Feed} + m^j_{i,Exp} x^l_{i,j,Exp} = \\
& m^j_{i,j,Sol} + m^j_{i,j,Exp} \\
& \text{eq. 8.12}
\end{align*}
\]

The feed mass and composition, \( m^j_{i,Feed} \) and \( x^l_{i,j,Feed} \), is assumed to be known as initial conditions as well as that vapor and solvent fluxes contain only solvent (\( x^s_{i,Sol,j,Evap} = x^s_{i,Sol,j} \)). Furthermore, solvent incorporation in the crystal phase will be neglected (\( x^s_{i,Sol,j} = 0 \)). For simplification, \( \epsilon^j \) as the ratio of the liquid phase mass, \( m^j_{i,l} \), to the total mass, \( m^j_{i} \), in a stage \( j \) is introduced.

\[
\epsilon^j = \frac{m^j_{i,l}}{m^j_{i}} = \frac{m^j_{i}}{m^j_{i,l} + m^j_{i,j}} \quad \text{eq. 8.13}
\]

Thus, the partial mass (eq. 8.12) balance can reformulated:

\[
\begin{align*}
& \epsilon^j_i (m^j_{i,j,Sol} x^s_{i,j} + (1-\epsilon^j_i) m^j_{i,j,Exp} x^s_{i,j,Exp} + m^j_{i,Feed} x^s_{i,j,Feed} + m^j_{i,Exp} x^l_{i,j,Exp} = \\
& \epsilon^j_i m^j_{i,j,Sol} x^s_{i,j} + (1-\epsilon^j_i) m^j_{i,j,Exp} x^s_{i,j,Exp} = \\
& \text{eq. 8.14}
\end{align*}
\]

for \( i = A, B, \) Solvent; \( k = 1…K \) and \( j = 1…J \).

The model is initiated by specifying starting values for the masses \( (m^j_{i}, m^j_{i,Feed}) \), mass fractions \( (x^l_{i,j,Feed}, x^l_{i,j,Exp}) \) and solid contents \( (\epsilon^j_i) \) of all stages \( j \) \( (1 \leq j \leq J) \) for the first cycle \( (k = 1) \).

Considering a case where all stages are empty and only one is filled in the first cycle with a mass of e.g. solid feed of certain composition \( (P_{Feed}, \text{Fig. 8.7 left}) \). Consequently, a particular mass of pure solvent according to the solubility curve has to be introduced for dissolution. The needed solvent can be calculated easily applying the lever rule (eq. 2.17):

\[
m^j_{i,Sol} = m^j_{i,Feed} \frac{P_{Feed}}{P_{Sol}} = m^j_{i,Feed} \left( \frac{x^l_{i,j,Feed} - x^l_{i,j,Exp}}{x^l_{i,j,Exp} - x^l_{i,j,Sol}} \right) \quad \text{for } i = \text{Solvent} \quad \text{eq. 8.15}
\]

Subsequently, supersaturation is generated, e.g. due to evaporation, to provoke crystallization (Fig. 8.7 right). The degree of evaporation, \( \delta^j \), is a design parameter, which can be chosen arbitrarily for any stage and cycle.

\[
\delta^j_i = \frac{m^j_{i,Exp}}{m^j_{i,j}} \sum_i \left( m^j_{i,Feed} x^s_{i,j,Feed} + m^j_{i,Sol} x^s_{i,j,Sol} \right) \quad \text{for } i = \text{Solvent} \quad \text{eq. 8.16}
\]
Counter-current crystallization - separation of solid solution systems

Fig. 8.7: Scheme of three sub-steps of the counter-current crystallization cascade - Feed addition, dissolution with pure solvent and evaporation.

Dashed line - linear connection of the considered composition \((P_{\text{Feed}}, P_{\text{sat}}, P_0)\) to the pure solvent corner, \(P_{\text{solv}}\).

Hence, the necessary mass fractions, \(x_{i,l}^{2}\) and \(x_{i,l}^{3}\), as well as the phase ratio \(\epsilon_{i}^{(l+1)}\) after the subsequent crystallization need to be calculated. They depend generally on the compositions the entering solid and liquid fluxes (eq. 8.14) and on the degree of evaporation (eq. 8.16). For the example shown in figure 8.7, all necessary masses and compositions are known since no solid and liquid masses of a previous separation step have to be considered. The starting composition of the crystallization \((P_0)\) is transferred into Cartesian coordinates and the corresponding conode is identified according to equation 8.9.

Fig. 8.8: Scheme of separation step and any arbitrary cycle of the counter-current crystallization cascade.

Dashed line - linear connection of the considered composition \((P_{\text{mix}}, P_{\text{sat}})\) to the pure solvent corner, \(P_{\text{solv}}\); solid line with arrows - crystallization of a solid phase according to the phase diagram; solid line - mixing line of two phases.
Thus, the composition and the masses (acc. to $P_{j,l}$ and $P_{j,s}$) after the separation can be calculated (Fig. 8.8 left). However, due to the following solid-liquid separation certain residual moisture has to be considered as well. The corresponding ratio of liquid mass after the crystallization and withdrawn liquid mass is given as follows:

$$
\phi_j = \frac{m_{j,l}^2}{m_{j,s}^2}
$$

(eq. 8.17)

This value is characteristic for the experimental set-up and has to be determined in advance. Hence, the compositions and masses of the neighboring stages for the next cycle can be calculated.

$$
m_{j,s+1,l}^i = \phi_j m_{j,l}^i, \text{ with } x_{j,s+1,l}^i = x_{j,l}^i
$$

(eq. 8.18)

$$
m_{j,s+1,s}^i = (1-\phi_j) m_{j,l}^i + m_{j,s}^i, \text{ with } x_{j,s+1,s}^i = \frac{(1-\phi_j) m_{j,l}^i x_{j,l}^i + m_{j,s}^i x_{j,s}^i}{(1-\phi_j) m_{j,l}^i + m_{j,s}^i}
$$

(eq. 8.19)

for $i = A, B, \text{Solvent}$

Finally, all specific input values for the next cycle ($k = 2$) are defined (Fig. 8.8 right, feed addition not shown) and the nonlinear algebraic system of mass balances (eq. 8.14) can be solved step-wise in order to calculate the progress of separations in the counter-current cascade. The required input is the solubility isotherm (eq. 8.4) and the separation behavior (eq. 8.6) of a certain substance system, which can be determined by SLE measurements and will be discussed in section 8.3.

8.2. Substances

Two generic ternary systems will be utilized for the verification of the feasibility of a separation of systems involving solid solutions with a counter-current fractional crystallization plant developed by the company Hapila [11].

The substance systems consisting of potassium chloride-potassium bromide-water and ammonium sulfate-potassium sulfate-water are known [189] to form solid solutions over a large compositions range and were therefore chosen for as model compounds for the counter-current crystallization plant. The determination of a shape factor was omitted since the separation of these substances was the main focus.

$(\text{NH}_4)_2\text{SO}_4/K_2\text{SO}_4$ crystallize in an orthorhombic lattice (Pnam) [190, 191] of which two ranges of different solid solutions are reported [192]. In contrary, it is reported that KCl/KBr form complete solid solutions in a cubic crystal lattice (Fm-3m) [193]. Furthermore, hydrates are not known in the considered range of temperatures for these systems and deionized water was utilized as solvent for both cases. The characteristics of the purchased pure substance are summarized in table 8.1.
Table 8.1: Substance characteristics of the investigated ternary systems.

<table>
<thead>
<tr>
<th>Substance characteristics of the investigated ternary systems.</th>
<th>Symbol</th>
<th>(NH₄)₂SO₄</th>
<th>K₂SO₄</th>
<th>KCl</th>
<th>KBr</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid density</td>
<td>ρₜₜₜₜ</td>
<td>1770</td>
<td>2662</td>
<td>1984</td>
<td>2750</td>
<td>[kg/m³]</td>
</tr>
<tr>
<td>Molar mass</td>
<td>M</td>
<td>132.14</td>
<td>174.27</td>
<td>74.56</td>
<td>119.00</td>
<td>[g/mol]</td>
</tr>
<tr>
<td>Purity</td>
<td>Pr</td>
<td>≥99.5%</td>
<td>≥98%</td>
<td>≥99</td>
<td>≥99.5</td>
<td>[%]</td>
</tr>
<tr>
<td>Distributor</td>
<td></td>
<td>Carl Roth</td>
<td>Carl Roth</td>
<td>Applichem</td>
<td>Carl Roth</td>
<td></td>
</tr>
<tr>
<td>Space group</td>
<td></td>
<td>Pnam</td>
<td>Pnam</td>
<td>Fm-3m</td>
<td>Fm-3m</td>
<td></td>
</tr>
</tbody>
</table>

8.3. Solid-liquid equilibria

SLE measurements were carried out for both systems at 30°C and 80°C to verify the published thermodynamic data [49] of the selected ternary systems ((NH₄)₂SO₄/ K₂SO₄; KCl/ KBr). Similarly, to the measurement of KDP and KAL isothermal solubility experiments are carried out.

Different compositions of the salt systems were filled in closed glass vials and dissolved in 10 ml of water. The excess mass of the applied solids were kept as low as possible to ensure a complete and fast equilibration between both phases. After at least 48 h of equilibration time, samples of the saturated liquid phases were taken with syringes equipped with filters (10-16 µm pore size) and analyzed subsequently by ion chromatography. The residual crystals were washed and investigated by XRPD analysis and the corresponding compositions determined via ion chromatography. The measurement methods and conditions were the same for IC (table 6.2) and XRPD as used for KAL and KDP described in chapter 6.2.1.

The measured SLE data of the system KCl / KBr / H₂O is illustrated in figure 8.9, where isothermal tie lines for 30°C and liquidus lines for 30°C and 80°C are shown in the ternary phase diagram (Fig. 8.9 a). It can be seen that the solubility of KCl and KBr rises with increasing temperature, as well as with increasing amounts of KBr in KCl / KBr mixtures. Similar to the in silico example (Fig. 8.4), the equilibrium behavior represented by the depicted conodes can also be expressed by means of a distribution diagram as shown in figure 8.9 b). In contrary to the applied Cartesian coordinates, the equilibrium distribution of KCl in the solid and liquid phase is plotted, analogous to the McCabe-Thiele diagram commonly used to present vapor-liquid equilibria [6], for better comparison with the ternary phase diagram. A solvent free fraction of KCl, $x_{KCl, l^*}$, was calculated to allow a better comparison with the solid phase composition for this purpose.

$$x_{KCl, l} = \frac{x_{KCl}}{x_{KCl} + x_{KBr}}$$  \hspace{1cm} (eq. 8.20)

KCl can be enriched in the liquid phase for small fractions of this component, while for larger amounts of KCl, enrichment is achievable in the solid phase. At the intersection
point of the KCl distribution curve and the ideal distribution line (dashed line in Fig. 8.9 b), the liquid and solid phases have the same composition. This point, which is called azeotrope when dealing with VLE, was designated alyotrope for SLE systems [194]. Hence, only one component can be obtained in a pure manner from this specific ternary system depending on the location of the starting composition compared to the alyotrope.

A mathematical description is necessary to utilize the measured data together with the derived cell model of the fractional counter-current crystallization plant. Polynomial expressions 3rd order, as introduced in the previous part (eqs. 8.4 & 8.6), were fitted to the measured equilibrium connections (dots in Fig. 8.9 b) and liquidus curves (dots shown for the 30°C liquidus isotherm in Fig. 8.9 a). The parameters, which yield a good agreement between the predicted phase diagram and the experimental results (Fig. 8.9 a), are listed in table 8.2. It should be mentioned, that the connections between the equilibrated solid and liquid phases (conodes) were split in two sections (1st section: \( x_{KCl,l^*} = 0 \ldots 0.37 \); 2nd section: \( x_{KCl,l^*} = 0.37 \ldots 1 \)) and subsequently described with two different polynomials.
Table 8.2: Parameters used for the modeling of the SLE of the system KCl / KBr / H₂O in Cartesian coordinates.

<table>
<thead>
<tr>
<th></th>
<th>λ₀</th>
<th>λ₁</th>
<th>λ₂</th>
<th>λ₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>30°C</td>
<td>0.4478</td>
<td>2.0857</td>
<td>-5.8279</td>
<td>4.2786</td>
</tr>
<tr>
<td>80°C</td>
<td>0.6760</td>
<td>-0.2566</td>
<td>-0.4128</td>
<td>0.4071</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>χ₀</th>
<th>χ₁</th>
<th>χ₂</th>
<th>χ₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st section</td>
<td>0</td>
<td>1.9227</td>
<td>-1.2013</td>
<td>2.2786</td>
</tr>
<tr>
<td>2nd section</td>
<td>0</td>
<td>12.8854</td>
<td>-19.4347</td>
<td>10.9691</td>
</tr>
</tbody>
</table>

The XRPD pattern of the equilibrated solid phases from the solubility measurements are summarized in figure 8.10. The pure KBr and KCl pattern are plotted at the top and bottom where in between the XRPD patterns of equilibrium mixtures containing both components are shown. It becomes clear, that the characteristic reflexes steadily shift from the KBr to the KCl 2-Theta values with increasing amount of KCl in the mixture. This proofs the formation of solid solutions over the whole range of tested compositions and also ensures well equilibrated solubility measurements.

Fig. 8.10: XRPD analysis of pure KCl and pure KBr, as well as of equilibrated mixtures of both components.

The same empirical description was applied to quantify the SLE for the system K₂SO₄ / (NH₄)₂SO₄ / H₂O as depicted in figure 8.11. Literature data was utilized to describe the liquidus isotherm at 30°C and the corresponding conodes due to the good data basis of [49]. Nevertheless, the liquidus isotherm at 80°C was determined by own measurements and additionally solubility experiments were performed also at 30°C to support the published data of [49]. As expected, the solubility increases with increasing...
temperature, as well as with increasing amount of (NH₄)₂SO₄ in K₂SO₄ / (NH₄)₂SO₄ mixtures. In contrary to the KCl / KBr / H₂O system, the distribution diagram (Fig. 8.11 b) does not show an alyotropic point and K₂SO₄ is always enriched in the solid phase, i.e. a complete separation of both compounds from any feed composition is possible. Similar to KCl / KBr / H₂O a parameter optimization was performed to describe the measured data (dashed and dotted lines in Fig. 8.11, parameter summarized in table 8.3).

![Figure 8.11](image)

Fig. 8.11: a) Ternary phase diagram for K₂SO₄ / (NH₄)₂SO₄ / H₂O in comparison with the modeled data. Dashed lines - liquidus isotherms of 30°C [49] (upper) and 80°C (lower), using eq. 8.4; solid line - tie lines of [49]; dotted lines - regressed tie lines, using eq. 8.6. b) Distribution diagram for K₂SO₄ plotted in mass fractions K₂SO₄ in the solid phase, xK₂SO₄,s, against the solvent free liquid phase composition, xK₂SO₄,l. Dots - K₂SO₄ distribution [49]; dashed-dotted line - ideal distribution; dotted line - regressions of the 1st section (xK₂SO₄,l = 0…0.39) and 2nd section (xK₂SO₄,l = 0.39…1) describing the separation behavior.

Table 8.3: Parameters used for the modeling of the SLE of the system K₂SO₄ / (NH₄)₂SO₄ / H₂O in Cartesian coordinates.

<table>
<thead>
<tr>
<th>Solubility isotherm (function n(z₁,z₂); eq. 8.4)</th>
<th>λ₀</th>
<th>λ₁</th>
<th>λ₂</th>
<th>λ₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>30°C</td>
<td>0.4053</td>
<td>4.42107</td>
<td>-11.4782</td>
<td>7.6234</td>
</tr>
<tr>
<td>80°C</td>
<td>0.6925</td>
<td>1.7453</td>
<td>-5.8033</td>
<td>4.0502</td>
</tr>
<tr>
<td>Separation behavior (function μ(z₁,z₂); eq. 8.6)</td>
<td>k₁</td>
<td>k₂</td>
<td>k₃</td>
<td>k₄</td>
</tr>
<tr>
<td>1st section</td>
<td>7.4097</td>
<td>218.1671</td>
<td>-143.6822</td>
<td>7.6234</td>
</tr>
<tr>
<td>2nd section</td>
<td>73.2387</td>
<td>-235.4358</td>
<td>325.3984</td>
<td>260.0689</td>
</tr>
</tbody>
</table>
The XRPD analysis of K$_2$SO$_4$ / (NH$_4$)$_2$SO$_4$ mixtures of the own measurements at 30°C revealed a similar peak shifting as the system KCl / KBr. Consequently, also for this system solid solutions were present over the entire range of compositions. The reported range of a second form of solid solutions could not be verified.

![Fig. 8.12: XRPD analysis of pure K$_2$SO$_4$ and pure (NH$_4$)$_2$SO$_4$, as well as of the mixtures of both components.](image)

The ternary SLE were successfully described with empirical functions in Cartesian coordinates. In the following they are applied to design and visualize the experiments to validate the introduced counter-current fractional crystallization principle and the equilibrium stage model.

**8.4. Validation of the stage model**

To verify the described stage model of the process (eq. 8.14), sequentially performed counter-current vacuum crystallization experiments were carried out manually. A rotary evaporator (Rotavapor R-114, Büchi, Switzerland) was used, consisting of a thermostated water bath, a condenser and a 500ml flask for the solution. The evaporator was connected to a vacuum pump (MB8NT Vacuubrand, Germany) for pressure control. Temperatures were followed by a resistance thermometer (Alden 2290-8 Ahlborn, Germany).

The manual counter-current experiment is done according to the multi-step process principle described in the previous chapter. Figure 8.13 shows the concrete configurations used for the lab-scale experiment, which is adapted to the principle of the pilot-scale plant introduced in chapter 9. To simplify the figure, details of the transport of the liquids and the dissolution of solid phases are not considered. Instead, the final
Validation of the stage model

result of the transport steps are depicted, with the liquid moving at each step one stage towards product outlet 1 and the solid moving one stage towards the product outlet 2 (compare Fig. 8.5). Based on figure 8.13, the experimental procedure will be described in the following.

For the lab-scale experiment the system KCl / KBr / H₂O was utilized. Every single experiment performed in the evaporator symbolizes a stage at a specific step \( k \) (Fig. 8.13, left). Altogether, six experiments \((k = 1; j = 1; k = 2; j = 1, 2; k = 3; j = 1, 2, 3)\) were done sequentially in the same vessel with manually performed transport steps. According to the process scheme, the flask was filled with saturated liquid phase and/or solid phase originating from the previous time step. The run representing the first crystallizer in the counter-current process \((j = 1, \text{ feed stage})\) received additional feed \((50:50 \text{ composition } \text{KCl:KBr})\). For all experiments the flask was filled with a specific amount of solvent, which was determined using the SLE data and the model to create saturated solutions at the upper process temperature (80°C). Afterwards the suspensions were heated to 80°C to get a clear saturated solution. For the subsequent crystallization, the heater was turned off, but the flask was kept in the water bath. Due to
the gentle cooling, the temperature of the solution could be closely followed by the temperature of the water bath.

With decreasing temperature a stepwise reduction of the pressure was realized based on the vapor pressure of water in presence of the specific composition of KCl / KBr to initiate crystallization. In this way a rather constant water evaporation rate could be achieved. After the final temperature of 30°C was reached, evacuation was stopped and the mass of the flask was weighted in order to calculate the degree of evaporation $\delta$ applying equation 8.16.

After solid-liquid separation the compositions of both phases were measured with ion chromatography and solid phase analysis was done by XRPD. The residual moisture of the solid was determined by weighing the crystal phase before and after drying. These information were incorporated in the calculations for comparison with the experimental results.

The ternary phase diagrams depicted in figure 8.14 are utilized to illustrate the results of the rotary evaporator experiments in comparison with the model calculations for stages $j = 1, 2, 3$ and time steps $k = 1, 2, 3$ (compare Fig. 8.13). At the beginning of every time step, feed (50:50 wt-% KCl:KBr) is introduced in stage 1 to create a saturated solution at 80°C with an appropriate amount of solvent. Afterwards, a vacuum evaporation was performed to provoke crystallization. The mass of solvent loss is determined by weighing and the resulting composition is calculated based on equation 8.16 and incorporated in the model (open dots below the solubility isotherms in Fig. 8.14).

The experimental results of the crystallization triggered by temperature reduction down to 30°C and the solvent removal are illustrated by solid lines in figure 8.14. The corresponding tie lines calculated applying the equilibrium model are represented by dotted lines.

Regarding the first stage and the first step an enrichment of KCl in the solid phase can be observed (Fig. 8.14, $k = 1$). Furthermore, it can be seen, that the experimental tie line is not exactly located on the calculated starting composition. The mismatch is probably caused by a final crystallization temperature lower than 30°C, which leads to an inaccurate prediction of the tie line, and an overestimation of the enrichment of KCl in the solid phase. The residual crystal phase is separated from the liquid phase and utilized for the next crystallization at time step 2 in stage 2. Similarly to step one, solvent is added to this crystal slurry to create a saturated solution at 80°C. The same procedure was applied for the residual crystal phases of time step 2, which were further processed in time step 3 corresponding to figure 8.13.

In contrast to step 1 and stage 1, the experimental and calculated tie lines of all stages are in good agreement for steps 2 and 3 (Fig. 8.14, $k = 2, 3$). Stage $j = 2$ is filled first in $k = 2$ with the previous solid phase of $j = 1, k = 1$. For the time steps 2 and 3, stage 2 provides further enrichment of KCl in the solid phase, which agrees well with the distribution diagram (Fig. 8.9 b) and the model predictions.

The third stage ($j = 3$) is filled during step $k = 3$ with the previous solid phase of $j = 2, k = 2$. A further enrichment of KCl takes place, up to a final composition of 95 wt-% KCl in the solid phase, which can be calculated also by the model.
8.5. Summary

In the beginning, the mathematical description of ternary phase diagrams involving solid solutions in Cartesian coordinates was explained. The core information are the solubility isotherm for the crystallization temperature and the corresponding separation behavior. This description serves to calculate the masses and compositions of the components of interest after crystallization from solution. An equilibrium stage model was derived and applied for the mathematical simulation of the process.

Fig. 8.14: Results of the lab-scale experiments of the process step $k = 1, 2, 3$ for the stages $j = 1, 2, 3$ (see Fig. 8.13).

Dashed lines - liquidus isotherms of 30°C (upper) and 80°C (lower), using eq. 8.4; solid lines - observed equilibria; dotted lines - calculated equilibria; dashed-dotted line - feed composition; unfilled dots - calculated phase compositions; dots - measured phase compositions.
Two generic salt systems (KCl/ KBr/ H₂O; (NH₄)₂SO₄/ K₂SO₄/ H₂O) were characterized, empirically described and subsequently used for experimental investigations. Lab-scale experiments carried out for the first system (KCl/ KBr/ H₂O) in a rotary evaporator, served as a first verification of the configuration and the model.

It can be stated, that the experiments proved the general applicability of the counter-current process and the equilibrium model. According to the distribution diagram (Fig. 8.9 b), an enrichment of KCl in the solid phases was expected for a feed composition of 50 wt-% KCl / 50 wt-% KBr. Within three steps, the feed mixture was purified up to 95 wt-% KCl. The observed compositions of the solid and liquid phases after crystallization were in a good agreement with the predictions by the model for all steps and stages. Pilot-scale experiments are planned and described with the verified model and carried out pseudo-continuously for the second ternary system ((NH₄)₂SO₄/ K₂SO₄/ H₂O) in chapter 9. Additionally, a simulation study of a ternary system forming partial solid solutions is discussed to show the applicability of the principle to a broader range of separation problems.
9. Application of the stage model - fractional counter-current crystallization

Since the equilibrium model was successfully validated in the previous chapter, a fractional crystallization is carried out in an existing pilot plant developed by the company HAPILA located in Gera (plant HAPIpur, Fig. 9.1, [11]). The plant is operated pseudo-continuously, similar to simulated moving bed chromatography, due to its automation and the process principle discussed in section 8.1.2, which enhances the productivity and yields constant product specifications after a dynamic start-up phase.

Fig. 9.1: Scheme of the automatic multi-stage pilot plant HAPIpur, which was used for the experimental investigations of the pseudo-continuous fractional crystallization (compare Fig. 8.5).

1 - condensers; 2 - solvent reservoir; 3 - heat exchangers; 4 - filter frits; solid lines - transport of the dissolved solid phase; dashed lines - transport of liquid phase (mother liquor); dashed-dotted lines - solvent dosing; dotted lines - vapor transport; grey solid lines - heat exchange medium; Pressure system and measurement equipment are not shown.
The plant consists of four identical 2 L crystallizers (St. 1…St. 4) and an additional 2 L buffer tank (Bu), connected by silicon tubes with integrated valves. Connections are arranged appropriately to realize the process principle described in chapter 8.1.2. Filter frits (4) are mounted at the end of the mother liquor transport pipe for internal solid-liquid separation. A “waste” vessel (Prod. 1) connected with St. 1 and a product vessel (Prod. 2) ensured the collection of the outgoing mass flows. Electromagnetic stirrers are utilized for mixing and the temperature inside the crystallizers is followed by PT100 temperature sensors. Heat exchangers inside the crystallizers connected with a thermostat are used for heating. Active cooling is realized by evaporation of the solvent and can be controlled via a vacuum pump and defined pressure programs. The generated pressure difference is also utilized for the transport of the liquid phases. The buffer tank and the crystallizers can be opened during the experiments to add manually feed or additional solvent. Every crystallizer is connected with a condenser (1) to liquefy and collect the solvent in a reservoir (2).

9.1. Design and realization

Applying this set-up, pilot-plant experiments are carried out utilizing four crystallizers (Fig. 9.1) according to the scheme depicted in figure 9.2, which is similar to the lab-scale experiments. The system K₂SO₄ / (NH₄)₂SO₄ / H₂O is processed in this case since KCl is highly corrosive for metal parts of the reactors. To enable manual sampling of all process steps, a semi-automatic operation mode is chosen i.e. mass transport and phase separation are done automatically, but feed and solvent are added manually. The necessary masses of feed and solvent were pre-calculated for every stage \( j \) and time step \( k \) applying the component mass balances (eq. 8.14) combined with the specific SLE behavior to ensure the correct operating conditions of the pseudo-continuous process.
Fig. 9.2: Experimental set-up and procedures (steps $k$ and stages $j$) of the pilot-scale experiment with the second stage as feed stage. Solid line - solid phase; dashed line - liquid phase; dotted line - solvent; dashed-dotted line - feed. Evaporation streams are not shown.

Furthermore, the evaporation degree $\delta$ (eq. 8.16) has to be specified for the experimental set-up as an input parameter in advance as well. It depends on the operating conditions and is specific for every crystallizer as well as for every composition of $K_2SO_4 / (NH_4)_2SO_4$ present during the process. Hence, preliminary experiments are carried out as follows: the steady-state compositions of the chosen process configurations are calculated based on the equilibrium model. The determined mixtures of $K_2SO_4 / (NH_4)_2SO_4 / H_2O$ are prepared specifically for every crystallizer heated to 80°C to get saturated solutions. A first pressure profile calculated based on a
substance specific Magnus equation \([195]\) is applied and iteratively adapted to achieve the final temperature (30°C) without a high bubble formation, which can cause encrustations. This procedure of heating and vacuum evaporation is repeated four times to match the desired evaporation degree of roughly 27.5%. Subsequently, a solid-liquid separation is performed and the masses of the phases are weighed to calculate the specific \(d\) for each crystallizer. Simultaneously, the specific residual moisture (eq. 8.17) is determined as well by drying and weighing the resulting crystal slurries. Hence, all plant parameters and operation conditions are quantified exploiting the equilibrium stage model and the specific SLE. To initialize the process, feed and solvent were added to the second stage \(j = 2\) and the described pressure reduction was used to provoke crystallization. Samples of the saturated liquid phase at 80°C before evaporation, as well as samples of the suspension at 30°C after evaporation were taken manually by syringes with silicon hoses. Solid and liquid phases were analyzed by ion chromatography and XRPD. It should be mentioned that stage 1 is a special case in this configuration (Fig. 9.1) because no feed and no solid is added here and only the mother liquor of stage 2 is processed to enhance the overall yield.

With the given initial conditions of the equilibrium model (feed composition 75 wt-% \(\text{K}_2\text{SO}_4\) / 25 wt-% \((\text{NH}_4)_2\text{SO}_4\) and adapted evaporation degrees \(d\)), a calculation of the pilot-scale process (Fig. 9.2) is performed for comparison with the measured data. This comparison is shown for the steps \(k = 1, 3, 5\) and for all four stages in figure 9.3. A higher enrichment of \(\text{K}_2\text{SO}_4\) in the solid phase can be seen for the first cycle \((k = 1)\). This deviation is most likely caused by the final crystallization temperature, which was not reached during the experiment (compare black and unfilled dot at the 30°C solubility isotherm). Furthermore, the evaporation degree differs slightly as well between the calculation and the experiment (compare black and unfilled dot below the 80°C solubility isotherm). Nevertheless, purification up to 99.9% is already achieved after the first three time steps (Fig. 9.3 \(k = 3\)) in stage 4 since all tie lines tend strongly to higher compositions of \(\text{K}_2\text{SO}_4\) in the solid phase. As it can be seen, the deviations between the model and the results are reduced for this cycle since the experimental conditions (final temperature, evaporation degree) match the calculated ones.
Application of the stage model - fractional counter-current crystallization

In contrary, the model mismatch is higher for the 5th time step again due to the mentioned reasons. Nevertheless, it can be stated that a separation of systems involving solid solutions is possible with the fractional counter-current crystallization plant and highly pure product can be harvested. Additionally, the recycle of the liquid phase simplifies the purification (all tie lines shift to pure K$_2$SO$_4$ from time step 3 to 5) and therefore a higher yield can be expected. A table with all mass fractions of the five time steps for the four separation stages can be found in appendix C.

Subsequently, to get an overall view on the process, the compositions of the leaving streams were compared with the composition of the incoming feed for all cycles. The saturated liquid phase after crystallization of stage 1 represents the stream which is discarded (product 2). For comparison with the feed mixture, the “waste” composition in figure 9.4 was corrected for the solvent fraction.
Due to the process configuration it takes one process step, until the first liquid phase is transported out of the process from stage 1. Compared to the feed composition (25 wt-% (NH$_4$)$_2$SO$_4$ / 75 wt-% K$_2$SO$_4$), (NH$_4$)$_2$SO$_4$ is enriched in the waste. However, this enrichment decreases during the process due to the change of the composition in the feed crystallizer (stage 2), which tends to higher amounts of K$_2$SO$_4$. This is a result of the recycle of K$_2$SO$_4$ enriched liquid phase from stage 3. It can be concluded, that the model is capable to predict the transient state of the feed stage and also the decreasing enrichment of the waste stream with respect to (NH$_4$)$_2$SO$_4$.

The composition of the product stream is shown in figure 9.5. Due to the studied process configuration, three stages have to be filled to reach the product outlet. Consequently, the first product leaves the process at step 3, which is as predicted by the model, almost pure K$_2$SO$_4$ (Purity > 99.9 wt-%).
Application of the stage model - fractional counter-current crystallization

Fig. 9.5: Composition of the product (solid phase of stage 4) over all steps.
Open symbols - calculated compositions; Filled symbols - measured composition (symbols overlapping).

For industrial applications, the yield plays a key role. Here, the yield of a component \( i \), \( Y^i \), is defined by the sum of the product masses of the component to the sum of the feed masses of this component for all time steps \( k \).

\[
Y^i = \frac{\sum_{k=1}^{K} m_{prod,i}^k}{\sum_{k=1}^{K} m_{feed,i}^k}
\]  
(eq. 9.1)

Figure 9.6 depicts the experimentally obtained and calculated yields of \( \text{K}_2\text{SO}_4 \) over all steps. Since the first product leaves the process during the third step, the yield stays zero for the first and the second step. Afterwards it increases up to 14% after five stages. Compared with the predicted data, a gap between the calculated and measured yields becomes evident. The appearance of an unknown impurity in the experimental set-up is seen as the main reason. The origin of this impurity, which blocked the silicone tubes, could not be clarified within the frame of this study. This blocking led to a reduced transport of substance to the product 1 outlet and therefore to a reduced yield.

The modeled yield is with 25% still low after five steps. However, at this point the process has not yet reached its periodic stationary state. In addition, a significant amount of feed is required to initially fill the four stages. A simulation study showed that the stationary state of the process will be reached after approximately 30 steps reaching a maximum yield of 64%. The yield is limited by the unavoidable loss of \( \text{K}_2\text{SO}_4 \) at the waste outlet.
The verified equilibrium stage model (chapter 8.1.2) supported the identification of suitable operating parameters for the fractional counter-current crystallization plant and was utilized for the experimental design and visualization. Three points have to be addressed regarding the comparison between the calculated and measured quantities to explain the observed deviations: The SLE of K₂SO₄/ (NH₄)₂SO₄ was adapted to literature data [189] measured at 25°C due to the beneficial data basis. Nevertheless, small deviations will occur due to the crystallization at 30°C even though the results were not significantly different to own solubility measurements at 30°C.

Secondly, the evaporation degrees had to be determined and fixed in advance. It was shown (Fig. 9.3) by sampling of liquid and solid phase for each time step, that the masses of evaporated solvent change for each cycle and every stage. A direct measurement or control of this important parameter would be beneficial. Similar deviations were observed for the final crystallization temperature (30°C) as well. Hence, an active temperature control for each stage adapted to the contained suspension or solution volume is necessary.

Nevertheless, a successful purification of K₂SO₄ (Purity > 99.9 wt-%) and an enrichment of (NH₄)₂SO₄ could be achieved. Complete simultaneous purification of K₂SO₄ and (NH₄)₂SO₄ would be feasible if more separation stages are considered. Hence, the fractional crystallization plant is applicable for the separation of systems involving mixed crystals. However, more common cases are the formation of partial solid solution at the pure component corner of the ternary phase diagram or near an intermediate compound (Fig. 2.8). Therefore, a theoretical study will be shown for such a system in the following to proof the applicability of the discussed processes for these SLE.
9.2. Model based separation analysis of systems with partial solid solutions

Similar shapes and sizes of the molecules of the components are of key importance for the formation of solid solutions [27]. Full miscibility in the solid state is only probable in case the differences are small. Therefore this phenomenon is particularly rare for organic substances. For example, only 1% of all chiral organic systems show complete solid solutions [26]. More frequent and much more common is partial miscibility in solid state and therefore of special interest.

![Fig. 9.7: Ternary phase diagram of the chiral system of the ethanolamine salt of 3-chloromandelic acid in ethanol [196] together with the simulation results for three stages (j = 1, 2, 3) of the fractional counter-current pilot-plant during the third process step (k = 3). Dashed-lines - Solubility isotherm for 30°C and 40°C; grey areas - areas of non-miscibility, providing the two solid states (Mix 1 and Mix 2); dashed-dotted line - feed composition (82:18); dotted lines - simulated tie lines; dots - composition before and after phase separation.](image)

The model used above to quantify the separation of systems with full miscibility (eq. 8.14), is also able to handle systems characterized by partial solid solutions. For illustration purposes a simulation study was performed considering the chiral system of
the two ethanolamine salts of 3-chloromandelic acid (E3CIMA), which forms a eutectic system with miscibility at solid state over a wide range of compositions [196]. Recently published SLE data for this system were integrated into the model described in chapter 8.1.2 (eq. 8.14). Figure 9.7 shows the ternary phase diagram of the system with solubility isotherms at 30°C and 40°C. Partial miscibility is found at compositions below ~25 wt-% and above ~75 wt-% (S)-E3CIMA. Crystallization in between these regions would lead to a saturated liquid phase containing the two salts in a 50:50 composition and a mixture of mixed crystals of the composition ~25 wt-% (S)-E3CIMA / ~75 wt-% (R)-E3CIMA (Mix 1) and ~75 wt-% (S)-E3CIMA / ~25 wt-% (R)-E3CIMA (Mix 2).

For the theoretical study of the counter-current process, a feed composition of 82 wt-% (S)-E3CIMA / 18 wt-% (R)-E3CIMA is assumed. The simulation was performed using the process configuration of the lab-scale experiment (Fig. 9.2), i.e. three stages were calculated. The feed was introduced into the first stage ($j = 1$) and the simulation was carried out over a series of steps. Crystallization was initiated for the calculation by cooling from 40°C down to 30°C as well as by evaporation. Figure 9.7 illustrates the results for the third step in the phase diagram. The given simulated tie lines indicate that the initial mixture can be purified with the counter-current process efficiently within three stages to a purity of 99.8 wt-% (S)-E3CIMA. The results demonstrate that the process concept is capable to handle systems with partial miscibility in the solid state as well. It should be mentioned, that the calculations were carried out with little information about the solid-liquid equilibrium in the range of the partial solid solutions. Hence, a linear distribution close to the ideal behavior was assumed, which reflects a "worst-case" scenario. Even though, the applicability of the cascade can be shown theoretically.

9.3. Summary

Counter-current separation processes are attractive in general. However, for processes exploiting solid-liquid equilibria, problems arise associated with the transport of solid phases. A novel fractional multi-stage counter-current crystallization process configuration was investigated, which can separate e.g. systems forming solid solutions. The innovative configuration uses a periodic dissolution of the crystallized solids and their subsequent transport as liquids. The corresponding sub-steps are automatized in the utilized plant, which was developed by the HAPILA GmbH and operated in Gera. The verified equilibrium stage model of chapter 8.1.2 was utilized to design and to run a pilot-plant. A feed mixture of 75 wt-% K$_2$SO$_4$ / 25 wt-% (NH$_4$)$_2$SO$_4$ was successfully purified within three stages to provide 99.9 wt-% K$_2$SO$_4$. By adding an additional stage for a further purification of the "waste" component, an enrichment of (NH$_4$)$_2$SO$_4$ up to 55 wt-% was achieved. All compositions could be predicted satisfactorily by the model. Improved yields and purities are possible, when the number of steps is increased since the losses during the start-up of the process have to be counterbalanced.

The results of an additionally carried out simulation study for the chiral system of the two ethanolamine salts of 3-chloromandelic acid further demonstrate the applicability of the process and the model for systems characterized by partial miscibility in the solid phase.
Conclusions and outlook

Crystallization as a highly efficient thermal separation technique is widely applied in industry for purification of substances as well as for particle design of solid products. A process layout exploiting the thermodynamic basis, the phase relations, is state of the art and commonly sufficient. Nevertheless, for demanding separations like the isolation of enantiopure substances or the resolution of mixtures involving solid solutions new approaches have to be found. Furthermore, model-based design of crystallization processes applying population balance equations became more important for industrial purposes in recent years due to commercially available software and academic elucidation of the mathematical fundamentals. Nevertheless, the demanded kinetic information of a substance system, which are the connection of the theoretical mathematical framework and the actual problem, are still complicated to quantify. Several methods exist with different advantages and drawbacks but most are dedicated to specific cases. Hence, especially for a complex process design, e.g. for the transfer of a batch into a continuous crystallization, where sophisticated models are necessary, the applicability of a priori simulation studies and numerical optimization schemes are limited.

The present work focused on investigating two different main tasks. First, a novel approach for the quantification of crystallization kinetics was conceived, which is widely applicable and yields reliable parameter estimates. Furthermore, a robust continuous crystallization plant utilizing the MSMPR principle was designed and constructed to evaluate the transferability and utilization of the quantified kinetics. Secondly, a sophisticated fractional crystallization process was explained, which can be applied for an efficient separation of challenging substance systems involving solid solutions. The mathematical basis of the process descriptions was introduced and validated with corresponding experiments.

In the first part of the thesis, the proposed short-cut-method for the quantification of crystallization kinetics was explained, theoretically studied and applied experimentally. This method aimed for improvement of the efficiency of the quantification of kinetic rates at the expense of precise mechanism identification. Nevertheless, it is not limited to a specific set-up or measurement technology and is therefore widely applicable preferably directly at the crystallization process of interest. A model-based investigation confirmed that the extraction of the characteristic data of the kinetics of nucleation, growth and dissolution is feasible from simple, 1-dimensional CSD measurements with the utilization of the seed distribution function. The application of polythermal experiments reduces the information required to quantify the desired
rates for a given range of operating conditions. Furthermore, it can be stated that the developed optimization routine, utilizing a stochastic generator for the initial guess without the application of a full PBE model, yields time-efficient precise parameter estimates if perfect data is available. An attempt to quantify the minimal data amount and the impact of different measurement errors was made.

The short-cut-method was applied to three different binary substance systems, namely potassium aluminum sulfate dodecahydrate-water, potassium dihydrogen phosphate-water and ortho aminobenzoic acid-water. The estimated rates utilizing data from few well planned experiments were validated afterwards with independent measurements.

Subsequently, the quantified kinetics were applied, to study theoretically the stability and product quality of different process parameter combinations of a continuous crystallization. It could be shown, that different regions of process stability and product size distribution exist, which are non-linearly connected to the system conditions. Corresponding continuous crystallizations were carried out and compared with the theoretical calculations. The kinetics quantified in batch experiments could not describe the measurements in every detail. There is evidence, that especially nucleation kinetics or growth rate dispersion are key factors for a better understanding of this process. Here, the short-cut-method could be extended to also capture the latter effect to enhance corresponding predictions.

The second part was dedicated to study a counter-current fractional crystallization process patented by HAPILA in 2009, which avoids the difficult solid transport by dissolution of the solidified material after each separation step. A novel cell model, which is based primarily on the phase relationship of the ternary system of interest, was developed to describe an equilibrium controlled pseudo-continuous crystallization. This model comprises a geometrical description of the corresponding phase diagrams to efficiently calculate compositions and masses after each separation step, which is especially complicated for systems involving solid solutions due to their specific thermodynamic properties. Nevertheless, the cell model can be utilized also for multi-component systems independent of the general phase behavior, i.e. eutectic, compound forming or solid solution system, due to the geometrical approach.

The derived cell-model together with the characteristic SLE of two specific ternary systems (potassium chloride-potassium bromide-water and ammonium sulfate-potassium sulfate-water), which were characterized over the course of this work, could be applied to describe results of preliminary experiments, which mimicked the process of interest. Hence, the verified cell model was utilized for further investigations and to design and visualize a complete process in an industrial pilot-scale plant. The applicability of this pseudo-continuous crystallization for the production of pure components from a substance system involving solid solutions was proven with the experimental results.

Even though, main topics of this thesis were studied successfully, open questions remain. An efficient quantification of the growth rate dispersion of nucleated particles is seen as one open task for future work. This demands more sophisticated measurement technologies on the one hand but also reasonable procedures to extract the necessary information following the idea of the short-cut-method. The implementation of the growth
rate dispersion can possibly improve the applicability of the kinetics determined with the invented method to continuous crystallizations. Nevertheless, a process optimization of seeded batch-processes is one possible application of the estimates since they could be verified with corresponding experiments.

Sophisticated control strategies for fluidized bed applications exist, which can be utilized without information about kinetics to adjust product particle size distribution. The MSMPR plant constructed in the course of this thesis, which provides sufficient online and inline measurement data, can be exploited to verify several of these theoretical strategies for the field of crystallization.

The transfer of the pseudo-continuous into a continuous process is one possible improvement for the investigated counter-current crystallization plant. This option is already suggested by the process scheme in figure 8.5 based on continuous dissolution tanks in between the separation stages.

Furthermore, different process configurations and crystallizer connections should be studied with respect to productivity, yield and for the resolution of solid solution systems exhibiting an alyotropic point. Especially the temperature dependency of the SLE is a major point of interest for this case to identify suitable conditions for the production of pure components. A continuous multi-stage process with sophisticated crystallizer connections would be beneficial and could resolve almost all difficult separation problems.
Symbols and abbreviations

Latin symbols

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Unit</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>m²</td>
<td>Surface</td>
</tr>
<tr>
<td>Avg. error</td>
<td>-</td>
<td>Average error</td>
</tr>
<tr>
<td>a</td>
<td>-</td>
<td>Activity</td>
</tr>
<tr>
<td>abs</td>
<td>-</td>
<td>Absolute value</td>
</tr>
<tr>
<td>B₀</td>
<td>[1/s]</td>
<td>Nucleation rate</td>
</tr>
<tr>
<td>b</td>
<td>-</td>
<td>Nucleation exponent</td>
</tr>
<tr>
<td>D</td>
<td>[m/s]</td>
<td>Dissolution rate</td>
</tr>
<tr>
<td>d</td>
<td>-</td>
<td>Dissolution exponent</td>
</tr>
<tr>
<td>Eₘ,i</td>
<td>[J/Kmol]</td>
<td>Activation energy for the different kinetic approaches</td>
</tr>
<tr>
<td>Error</td>
<td>-</td>
<td>Deviation</td>
</tr>
<tr>
<td>F</td>
<td>-</td>
<td>Degrees of freedom</td>
</tr>
<tr>
<td>F</td>
<td>[m³/s]</td>
<td>Volumetric flow</td>
</tr>
<tr>
<td>f</td>
<td>[1/m]</td>
<td>Number density distribution/ function</td>
</tr>
<tr>
<td>G</td>
<td>[J; m/s]</td>
<td>Gibbs energy; Growth rate</td>
</tr>
<tr>
<td>g</td>
<td>-</td>
<td>Growth exponent</td>
</tr>
<tr>
<td>i</td>
<td>-</td>
<td>Exponent of the Arrhenius approach (i = g, b, d)</td>
</tr>
<tr>
<td>K</td>
<td>[m/s; 1/s]</td>
<td>Kinetics G, B₀ or D</td>
</tr>
<tr>
<td>kₐ</td>
<td>-</td>
<td>Surface correlation factor</td>
</tr>
<tr>
<td>kᵥ</td>
<td>-</td>
<td>Volume shape factor</td>
</tr>
<tr>
<td>kᵢ</td>
<td>[m/s; 1/s]</td>
<td>Rate constant for i = g, b, d</td>
</tr>
<tr>
<td>k</td>
<td>-</td>
<td>Boltzmann constant</td>
</tr>
<tr>
<td>L</td>
<td>[m]</td>
<td>Property coordinate</td>
</tr>
<tr>
<td>L</td>
<td>[m]</td>
<td>Mean length</td>
</tr>
<tr>
<td>log₁₀</td>
<td>-</td>
<td>Logarithm to the base 10</td>
</tr>
<tr>
<td>M</td>
<td>[g/ mol; kg/ m³]</td>
<td>Molar mass; Suspension density</td>
</tr>
<tr>
<td>m</td>
<td>[kg]</td>
<td>Mass</td>
</tr>
<tr>
<td>N</td>
<td>[-; #]</td>
<td>Number of components; Crystal number</td>
</tr>
<tr>
<td>n</td>
<td>[mol]</td>
<td>Amount</td>
</tr>
<tr>
<td>OF</td>
<td>[m; 1]</td>
<td>Objective function</td>
</tr>
<tr>
<td>P</td>
<td>[-]</td>
<td>Number of phases/ Point</td>
</tr>
<tr>
<td>Pr</td>
<td>[%]</td>
<td>Purity</td>
</tr>
<tr>
<td>p</td>
<td>[Pa; -]</td>
<td>Pressure; Parameters for the solubility correlation and kinetic approaches</td>
</tr>
<tr>
<td>qₒ(0, 1, 2, 3)</td>
<td>[1/ m]</td>
<td>Relative size distribution with respect to the dimension 0 (amount), 1 (length), 2 (surface), 3 (volume or mass)</td>
</tr>
<tr>
<td>R</td>
<td>[J/Kmol]</td>
<td>Ideal gas constant</td>
</tr>
<tr>
<td>r</td>
<td>[m]</td>
<td>Radius</td>
</tr>
<tr>
<td>S</td>
<td>[J/K; -]</td>
<td>Entropy; Relative Supersaturation</td>
</tr>
<tr>
<td>T</td>
<td>[K]</td>
<td>Temperature in Kelvin</td>
</tr>
<tr>
<td>t</td>
<td>[h]</td>
<td>Time</td>
</tr>
<tr>
<td>tₛ&lt;₁</td>
<td>[h]</td>
<td>First time of undersaturation during the experiments</td>
</tr>
<tr>
<td>U</td>
<td>[J]</td>
<td>Internal energy</td>
</tr>
</tbody>
</table>
Symbols and abbreviations

**Symbols**

\( V \) \([\text{m}^3]\)  
Volume

\( w \) \([-\text{]}\)  
Concentration (mass loading, \([\text{g Solute/g Solvent}]\))

\( \chi \) \([-\text{]}\)  
Mass or mole fraction

\( \gamma \) \([\%]\)  
Yield

\( z \) \([-\text{]}\)  
Cartesian coordinate

**Greek symbols**

\( \alpha \) \([\text{°}]\)  
Wetting angle; Function for solubility isotherms

\( \beta \) \([-\text{]}\)  
Function for separation behavior

\( \delta \) \([-\text{]}\)  
Evaporation degree

\( \varepsilon \) \([-\text{]}\)  
Free liquid ratio

\( \gamma \) \([-; \text{J/m}^2]\)  
Activity coefficient; Surface tension

\( \kappa \) \([-\text{]}\)  
Parameters for the description of the separation behavior of ternary systems

\( \lambda \) \([-\text{]}\)  
Parameters for the description of solubility isotherm

\( \mu \) \([\text{J/mol}]\)  
Chemical potential

\( \nu \) \([\text{m}^3/\text{mol}]\)  
Molar volume

\( \omega \) \([\text{rpm}]\)  
Stirrer rotation speed

\( \phi \) \([-\text{]}\)  
Wetting efficiency; Residual moisture

\( \rho \) \([\text{kg/m}^3]\)  
Density

\( \sigma \) \([\text{m}]\)  
Standard deviation

\( \tau \) \([\text{h}]\)  
Mean residence time

\( \theta \) \([\text{°C}]\)  
Temperature in degree Celsius

\( \chi \) \([-\text{]}\)  
Height equivalent in a ternary phase diagram

**Superscripts**

\( (l),(k) \)  
Number of phases in eq. 2.13

\( * \)  
Critical cluster property

\( k \)  
Time steps for the fractional crystallization

\( 0 \)  
Standard conditions

**Subscripts**

A, B, Solvent  
Substances

average  
Average

a  
Activity based supersaturation

BL  
Boundary layer

Bulk  
Bulk phase

Cluster  
Molecular cluster

CS  
Crystal surface

Cryst  
Crystal

cub  
Cube

Diff  
Diffusion

Exp  
Experiment

Eu  
Eutectic

Evap  
Evaporation

\( e_{1...3} \)  
Binary eutectic points
end    Final
est    Estimated
exp    Experimental
Final    Final
given    Given/ original
het    Primary heterogeneous nucleation
hom    Primary homogeneous nucleation
IC    Intermediate compound
i    Component i = A, B, Solvent
in    Inlet stream
Int    Integration
j    Stage number of the fractional crystallization
K    Kinetics G, B0 or D
L/ liquid    Liquid phase
l*    Solvent free liquid composition
max    Maximum value
mean    Mean value
min    Minimum value
mix    Mixed phases
out    Outlet stream
pri    Primary nucleation
Prod    Product
pyr    Pyramid
Reactor    Reactor
S    Surface
sample    Sample
sat    Saturation
sec    Secondary nucleation
Seeds    Seed
sim    Simulated
S/ solid    Solid phase
solute    Solute
Solv/ solvent    Solvent
Steady    Steady-state
Susp    Suspension
Unit    Elementary building unit
V    Volume
0    Initial value/ Particles with size $\rightarrow 0$
Bibliography


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between the impeller blades and the crystals on the secondary nucleation rate of the potash-alum system", *International Chemical Engineering*, vol. 21, no. 2, pp. 269-275, 1981.


[98] Lovette, M. A.; Doherty, M. F., "Predictive Modeling of Supersaturation-Dependent


Appendix A - Discretization of the population balance equations

The general population balance from chapter 4.2.1 for the continuous crystallization serves to explain the discretization scheme.

\[ \frac{\partial f(t, L)}{\partial t} = -G(S, T) \frac{\partial f(t, L)}{\partial L} - \frac{f(t, L)}{\tau} \quad \text{for } S \geq 1 \]  
(\text{eq. A.1})

Eq. A.1 is discretized via the finite volume method together with the initial conditions (eqs. A.2 - A.4) for crystallization.

IC for crystallization ($S \geq 1$):

\[ f(t=0, L) = 0 \quad \text{prim. nucleation} \]  
(eq. A.2)

\[ f(t=0, L) = f_{\text{seed}}(L) \quad \text{seeded experiment} \]  
(eq. A.3)

\[ f(t=L=0) = \frac{R}{G} \]  
(eq. A.4)

An equidistant grid with finite distances \(\Delta L\) and \(n\) sections as well as a section-wise constant population density function are assumed. The upwind scheme as well as the Leibnitz-rule is applied to derive the eqs. A.5 - A.7 for a section \(i = -n \ldots 1 \ldots n\).

The sections with negative indices are utilized to smoothen the disappearance of crystals in case of dissolution since no physically based vanishing rate can be determined.

\[ \frac{df(t)}{dt} = \frac{1}{\Delta L} \left( G f(t) - B_i \right) - \frac{f(t)}{\tau} \quad \text{for } i = 1 \]  
(eq. A.5)

\[ \frac{df(t)}{dt} = \frac{G}{\Delta L} \left( f(t) - f_{\text{seed}}(t) \right) + \frac{f(t)}{\tau} \quad \text{for } i = 2 \ldots n \]  
(eq. A.6)
The direction of the upwind scheme is reversed in case of dissolution to derive the eqs. A.10 - A.12 considering the adapted initial conditions (eqs. A.8 & A.9).

IC for dissolution (S < 1):

\[ f(t = 0, L) = f_s(t, L) \quad \text{(eq. A.8)} \]

\[ f(t, L = 0) = \frac{D_0}{D} \quad \text{(eq. A.9)} \]

Dissolution (S < 1):

\[ \frac{df(t)}{dt} = \frac{D}{\Delta L} (f_s(t) - f_s(t)) - \frac{f(t)}{\tau} \quad \text{for } i = 1 \ldots n-1 \quad \text{(eq. A.10)} \]

\[ \frac{df(t)}{dt} = 0 \quad \text{for } i = 1 \quad \text{(eq. A.11)} \]

\[ \frac{df(t)}{dt} = \frac{D}{\Delta L} (f_s(t) - f_s(t)) \quad \text{for } i = -1 \ldots -n \quad \text{(eq. A.12)} \]

The rate \( D_0 \) is not accessible by measurements. An second grid is applied with negative indices where the dissolving particles, which cross \( L_1 = 0 \) (Fig. A.1), are “stored” to avoid numerical problems. These sections do not contribute to the mass balance or any other population related effects. All values are erased if crystallization takes place again.

The equation system A.4 - A.6 and A.10 - A.12 was implemented together with the mass balance (eq. A.13) for the corresponding simulations.

\[ \frac{dw}{dt} = \frac{1}{\tau} \left( \frac{\rho_{\text{soln}}(T)}{\rho_{\text{sol}}(T)} w_s - w \right) - \frac{3k \rho_{\text{sol}} G(S,T)}{V_{\text{sol}}(w,T) \rho_{\text{sol}}(T)} \int L \cdot f(L) dL \quad \text{(eq. A.13)} \]

IC for the mass balance:

\[ w(t = 0) = w_i \quad \text{(eq. A.14)} \]
Appendix B - Analysis of different feed materials of KDP

The ICP-OES analyses (performed at the university Rostock, SPECTROBLUE ICP-OES, SPECTRO Analytical Instruments GmbH, Germany) of different potassium dihydrogen phosphate feed stocks from different manufacturers with the same purity (≥98) is shown in Table B.1. Different samples were prepared from 10 wt-% solutions [g_{solution}/ g_{water}] and the results are given in [mg_{element}/ kg_{dry solid}]. The sample letter specifies the manufacturer (A - Carl Roth GmbH + Co. KG; B - AppliChem GmbH; C - Grüssing GmbH Analytika) where the KDP purchased from Carl Roth GmbH + Co. KG was utilized for the determination of the crystallization kinetics in chapter 6.

Table B.1: ICP-OES analysis of different potassium dihydrogen phosphate feed stocks.
A - Carl Roth GmbH + Co. KG; B - AppliChem GmbH; C - Grüssing GmbH Analytika; numbers - sample number

<table>
<thead>
<tr>
<th>Element/ wavelength</th>
<th>Ultrapure water</th>
<th>A - 1</th>
<th>B - 1</th>
<th>B - 2</th>
<th>B - 3</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al 396.152</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
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## Appendix C - Data of the fractional crystallization pilot-plant

Table C.1: IC analyses of the compositions of the occurred phases during the separation experiment of section 9.1 for all stages and all time steps in [wt-%]. Additionally, the masses of the introduced feed and the harvested product are given.

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**Curriculum Vitae**

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**Profession**

| 07/2010 - Present | Max Planck Institute for Dynamics of Complex Technical Systems - Scientific coworker within the „International Max Planck Research School“. Research is located in the field of crystallization within the group of Physical and Chemical Foundations supervised by Prof. Andreas Seidel-Morgenstern and Prof. Heike Lorenz. |

Thesis topic: *Design of continuous crystallization processes*

**Education**

| 08/1995 - 03/2004 | “Werner-von-Siemens-Gymnasium”, Magdeburg, University-Entrance Diploma |
| 10/2009          | Student Research Project (Mark: 1.7) |
| 06/2010          | Diploma - Thesis (Mark: 1.0) |

**Military service**

| 04/2004 - 12/2004 | Army, Augustdorf |

**Internships**

| 09/2005 - 10/2005 | Metall-Elektro-Bau GmbH, Magdeburg, Germany |
| 08/2006 - 09/2006 | Basic internship on metal working |
| 11/2008 - 04/2009 | Intelli Energy GmbH, Barleben, Germany |

- Development of a natural gas engine for energy production

Magdeburg, 01. April 2016