Henry Hatakka

EFFECT OF HYDRODYNAMICS ON MODELLING, MONITORING AND CONTROL OF CRYSTALLIZATION

Thesis for the degree of Doctor of Science (Technology) to be presented with due permission for public examination and criticism in the Auditorium 1383 at Lappeenranta University of Technology, Lappeenranta, Finland on the 14th of December, 2010, at noon

Acta Universitatis
Lappeenrantaensis 416
Supervisors
Professor Marjatta Louhi-Kultanen
Department of Chemical Technology
Lappeenranta University of Technology
Finland

Professor Emeritus Juha Kallas
Department of Chemical Technology
Lappeenranta University of Technology
Finland,
Senior Researcher
Tallinn University of Technology
Estonia

Reviewers
Doctor Jens-Petter Andreassen
Department of Chemical Engineering
Norwegian University of Science and Technology
Trondheim
Norway

Professor Kwang-Joo Kim
Department of Chemical Engineering
Hanbat National University
Korea

Opponent
Doctor Jens-Petter Andreassen
Department of Chemical Engineering
Norwegian University of Science and Technology
Trondheim
Norway

Custos
Professor Marjatta Louhi-Kultanen
Department of Chemical Technology
Lappeenranta University of Technology
Finland

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ABSTRACT

Henry Hatakka
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Crystallization is a purification method used to obtain crystalline product of a certain crystal size. It is one of the oldest industrial unit processes and commonly used in modern industry due to its good purification capability from rather impure solutions with reasonably low energy consumption. However, the process is extremely challenging to model and control because it involves inhomogeneous mixing and many simultaneous phenomena such as nucleation, crystal growth and agglomeration. All these phenomena are dependent on supersaturation, i.e. the difference between actual liquid phase concentration and solubility. Homogeneous mass and heat transfer in the crystallizer would greatly simplify modelling and control of crystallization processes, such conditions are, however, not the reality, especially in industrial scale processes. Consequently, the hydrodynamics of crystallizers, i.e. the combination of mixing, feed and product removal flows, and recycling of the suspension, needs to be thoroughly investigated.

Understanding of hydrodynamics is important in crystallization, especially in larger-scale equipment where uniform flow conditions are difficult to attain. It is also important to understand different size scales of mixing; micro-, meso- and macromixing. Fast processes, like nucleation and chemical reactions, are typically highly dependent on micro- and mesomixing but macromixing, which equalizes the concentrations of all the species within the entire crystallizer, cannot be disregarded.

This study investigates the influence of hydrodynamics on crystallization processes. Modelling of crystallizers with the mixed suspension mixed product removal (MSMPR) theory (ideal mixing), computational fluid dynamics (CFD), and a compartmental multiblock model is compared. The importance of proper verification of CFD and multiblock models is demonstrated. In addition, the influence of different hydrodynamic conditions on reactive crystallization process control is studied. Finally, the effect of extreme local supersaturation is studied using power ultrasound to initiate nucleation.

The present work shows that mixing and chemical feeding conditions clearly affect induction time and cluster formation, nucleation, growth kinetics, and agglomeration. Consequently, the properties of crystalline end products, e.g. crystal size and crystal habit, can be influenced by management of mixing and feeding conditions. Impurities may have varying impacts on crystallization processes. As an example, manganese ions were shown to replace magnesium ions in the crystal lattice of magnesium sulphate heptahydrate, increasing the crystal growth rate significantly, whereas sodium ions showed no interaction at all. Modelling of continuous crystallization based on MSMPR theory showed that the model is feasible in a small laboratory-scale crystallizer, whereas in larger pilot- and industrial-scale crystallizers hydrodynamic
effects should be taken into account. For that reason, CFD and multiblock modelling are shown to be effective tools for modelling crystallization with inhomogeneous mixing. The present work shows also that selection of the measurement point, or points in the case of multiprobe systems, is crucial when process analytical technology (PAT) is used to control larger scale crystallization. The thesis concludes by describing how control of local supersaturation by highly localized ultrasound was successfully applied to induce nucleation and to control polymorphism in reactive crystallization of L-glutamic acid.

**Keywords:** Mixing, fluid flow, slip velocity, simulation, CFD, multiblock model, PAT, sonocrystallization

UDC 66.065.5 : 532.5
PREFACE

This study has been carried out at Lappeenranta University of Technology in the Laboratory of Separation Technology.

Financial support from the Research Foundation of Lappeenranta University of Technology, the Academy of Finland and Tekes – the Finnish Funding Agency for Technology and Innovation, and industrial partners is gratefully acknowledged.

I wish to thank my supervisors, Professor Emeritus Juha Kallas and Professor Marjatta Louhi-Kultanen for their guidance, advice and patience during this long journey. I wish to convey my warmest thanks to my previous supervisor, Professor Emeritus Seppo Hirashima, who led my first steps in the world of crystallization. I would like to express my thanks to the reviewers of this manuscript, Dr. Jens-Petter Andreassen and Professor Kwang-Joo Kim, for their valuable comments and criticism which significantly helped me to improve the thesis. Mr. Peter Jones is thanked for his help with the language of the thesis.

My sincere thanks go to all my co-authors for their productive co-operation. In particular, I am grateful to Ms. Maret Liiri, Docent Juhani Aittamaa and Professor Ville Alopaeus from Aalto University for the CFD and multiblock modelling and simulations. I wish also to thank all my colleagues and co-workers at the LUT Chemistry, especially members of the Laboratory of Separation Technology, for their support and collaboration. Dr. Hannu Alatalo deserves special appreciation for his friendship and exemplary research attitude in our co-projects over the past years. Additionally, I wish to thank Dr. Sergei Preis and Mr. Mikko Huhtanen for their friendship and support in all issues.

I would also like to express my deepest appreciation to my parents for their continuous support and care throughout my life. My warmest gratitude goes to my wife, Terhi, and my daughters, Anniina and Sandra, for all of their love, patience and understanding; without them this study would not have been possible.

Lappeenranta, December 2010

Henry Hatakka
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LIST OF PUBLICATIONS

This thesis is based on the following papers, referred to in the text with capital Roman numerals. The publications are included in this thesis.


Author’s contribution:
The author, together with other co-authors, carried out the crystallization experiments, including crystal size analyses, in papers I-III and polymorph analyses in papers II and IV-VI. He also participated in design of the experimental systems, especially aspects concerning hydrodynamics of the crystallizers. In paper III, the author was responsible for experimental verification of flow profiles and slip velocities. The author participated in preparation of all manuscripts, being the main author responsible for preparation of paper VI.

ASSOCIATED PUBLICATIONS

Some of the results introduced in this thesis are based on the associated publications, referred to in the text with lower case Roman numerals. The following associated publications are not included in this thesis.


# NOMENCLATURE

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<thead>
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<th>Symbol</th>
<th>Definition</th>
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<tbody>
<tr>
<td>( A )</td>
<td>Hamaker or van der Waals constant, ( J )</td>
</tr>
<tr>
<td>( A' )</td>
<td>constant, -</td>
</tr>
<tr>
<td>( A_{\text{het}} )</td>
<td>heterogeneous nucleation constant, ( #/(s \ m^3) )</td>
</tr>
<tr>
<td>( A_{\text{hom}} )</td>
<td>homogeneous nucleation constant, ( #/(s \ m^3) )</td>
</tr>
<tr>
<td>( A_n )</td>
<td>nucleus area, ( \text{m}^2 )</td>
</tr>
<tr>
<td>( A_1 )</td>
<td>constant, ( \text{m/s} )</td>
</tr>
<tr>
<td>( A_2 )</td>
<td>constant, -</td>
</tr>
<tr>
<td>( a )</td>
<td>coefficient or activity, -</td>
</tr>
<tr>
<td>( a_{\text{m}} )</td>
<td>mean ionic activity of solute</td>
</tr>
<tr>
<td>( a' )</td>
<td>constant, -</td>
</tr>
<tr>
<td>( a'' )</td>
<td>order of the reaction with respect to calcium, -</td>
</tr>
<tr>
<td>( B(L) )</td>
<td>particle birth function at size ( L ), ( #/(s \ m^3) )</td>
</tr>
<tr>
<td>( B' )</td>
<td>constant, -</td>
</tr>
<tr>
<td>( B_0 )</td>
<td>nucleation rate, ( #/(s \ m^3) )</td>
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<tr>
<td>( B_{0,0} )</td>
<td>nucleation rate at initial concentration, ( #/(s \ m^3) )</td>
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<tr>
<td>( B_{\text{het}} )</td>
<td>primary heterogeneous nucleation rate, ( #/(s \ m^3) )</td>
</tr>
<tr>
<td>( B_{\text{hom}} )</td>
<td>primary homogeneous nucleation rate, ( #/(s \ m^3) )</td>
</tr>
<tr>
<td>( b' )</td>
<td>constant, -</td>
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<tr>
<td>( b'' )</td>
<td>order of the reaction with respect to sulphate, -</td>
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<td>( c_{11} )</td>
<td>coefficient, ( \text{m} )</td>
</tr>
<tr>
<td>( c )</td>
<td>concentration of elementary units, ( \text{mol}/\text{m}^3 )</td>
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<tr>
<td>( c' )</td>
<td>constant, -</td>
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<tr>
<td>( c^* )</td>
<td>equilibrium concentration, ( \text{mol}/\text{m}^3 )</td>
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<tr>
<td>( c^0 )</td>
<td>concentration of potential determining ions at zero altitude, ( \text{mol}/\text{m}^3 )</td>
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<tr>
<td>( c_0 )</td>
<td>initial concentration, ( \text{mol}/\text{m}^3 )</td>
</tr>
<tr>
<td>( c_{\text{Ca}} )</td>
<td>concentration of calcium ions, ( \text{mol}/\text{m}^3 )</td>
</tr>
<tr>
<td>( c_c )</td>
<td>concentration of clusters, ( \text{mol}/\text{m}^3 )</td>
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<tr>
<td>( c_{\text{ccc}} )</td>
<td>critical coagulation concentration, ( \text{mol}/\text{m}^3 )</td>
</tr>
<tr>
<td>( c_{\text{SO}_4} )</td>
<td>concentration of sulphate ions, ( \text{mol}/\text{m}^3 )</td>
</tr>
<tr>
<td>( c_r )</td>
<td>reference concentration, ( \text{mol}/\text{m}^3 )</td>
</tr>
<tr>
<td>( \Delta c )</td>
<td>supersaturation, ( \text{mol}/\text{m}^3 )</td>
</tr>
<tr>
<td>( D )</td>
<td>distance between two plates, ( \text{m} )</td>
</tr>
<tr>
<td>( D(L) )</td>
<td>particle death function at size ( L ), ( #/(s \ m^3) )</td>
</tr>
<tr>
<td>( D_a )</td>
<td>diffusion coefficient, ( \text{m}^2/\text{s} )</td>
</tr>
<tr>
<td>( D_f )</td>
<td>turbulent diffusivity, ( \text{m}^2/\text{s} )</td>
</tr>
<tr>
<td>( d )</td>
<td>diameter of pipe, ( \text{m} )</td>
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<tr>
<td>( d'' )</td>
<td>constant, -</td>
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<tr>
<td>( d_I )</td>
<td>diameter of impeller, ( \text{m} )</td>
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<tr>
<td>( E )</td>
<td>engulfment rate coefficient, -</td>
</tr>
<tr>
<td>( E_{\text{att}} )</td>
<td>attached energy, ( \text{J} )</td>
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<tr>
<td>( E_b )</td>
<td>binding energy at a surface site, ( \text{J} )</td>
</tr>
<tr>
<td>( E_{\text{sl}} )</td>
<td>slice energy, ( \text{J} )</td>
</tr>
<tr>
<td>( e_1 )</td>
<td>activation energy, ( \text{J/mol} )</td>
</tr>
<tr>
<td>( e_C )</td>
<td>elementary charge ( 1.602 \times 10^{-19} \text{C} ), ( \text{C} )</td>
</tr>
<tr>
<td>( F_{A,t}(L) )</td>
<td>agglomeration fraction of size ( L ) at time ( t ), -</td>
</tr>
<tr>
<td>( f )</td>
<td>correction factor, -</td>
</tr>
</tbody>
</table>
\( f'' \) constant, 
\( f(\rho) \) relative shape function of both crystals, 
\( G \) growth rate, m/s 
\( G_{av} \) average crystal growth rate, m/s 
\( G_m \) median crystal growth rate, m/s 
\( G_S \) shear rate, s\(^{-1}\) 
\( \Delta G \) total enthalpy, J 
\( \Delta G_d \) surface enthalpy, J 
\( \Delta G_V \) volume enthalpy, J 
\( g \) overall growth rate order, - 
\( H \) Heaviside step function \((H(x)=1 \text{ for } x \geq 0, \quad H(x)=0 \text{ for } x < 0)\), 
\( H' \) height of liquid level, m 
\( h \) step height, m 
\( l_i \) size range i of crystals in CSD, m 
\( i' \) relative kinetic order - 
\( J_{11} \) coagulation rate, \#/\( (m^3 s) \) 
\( f \) constant, - 
\( j' \) kinetic order of suspension density - 
\( K(L_m L_n) \) agglomeration kernel, \( m^{1/3}/(\# \text{ s mol}^j) \) 
\( K_a \) activity based equilibrium coefficient - 
\( K_c \) concentration based equilibrium coefficient - 
\( K_G \) overall crystal growth coefficient, \( m^{1/3}/(\text{s mol}^j) \) 
\( K_R \) overall nucleation rate constant \( \# \text{ m}^{3(i'-1)}s^{i'-1} \text{ kg}^{-1} \text{ s}^{j'j-1} \) 
\( K_{hom} \) coefficient, - 
\( k \) Boltzmann constant, J/K 
\( k_1 \) reaction rate coefficient, \( \text{mol}^{1-a'-b'}/(\text{m}^{3(1-a'-b')}) \text{ s} \) 
\( k_d \) diffusion coefficient in crystal growth, \( \text{mol}^{1-a'-b'}/(\text{m}^{3(1-a'-b')}) \text{ s} \) 
\( k_{growth} \) mass transfer coefficient for the crystal growth, \( \text{mol}^{1-a'-b'}/(\text{m}^{3(1-a'-b')}) \text{ s} \) 
\( k_{p1} \) pre-exponential factor, \( \text{mol}^{1-a'-b'}/(\text{m}^{3(1-a'-b')}) \text{ s} \) 
\( k_r \) surface reaction coefficient in crystal growth, \( \text{mol}^{1-a'-b'}/(\text{m}^{3(1-a'-b')}) \text{ s} \) 
\( k_{ind} \) induction time coefficient, s 
\( k_V \) shape factor of volume - 
\( k' \) kinetic order of mixing - 
\( L \) crystal (nucleus) size, m 
\( \overline{L_i} \) appropriate mean size in the \( i \)th interval for calculating the \( i \)th moment, m 
\( L_m \) size of crystals of class \( m \), m 
\( L_n \) size of crystals of class \( n \) \((n \geq m)\), m 
\( M_f \) suspension density, kg/m\(^3\) 
\( m \) mole fraction - 
\( m_j \) \( j \)th moment, \( m^2/\text{mol}^j \) 
\( N \) rotation velocity of impeller, s\(^{-1}\) 
\( N_{11} \) collision rate, \#/\( (m^3 s) \) 
\( N_A \) Avogadro’s number, \#mol 
\( N_{all} \) total number of the crystals, \# 
\( N_C \) number of crystals in size range \( \Delta L \), \#/m\(^3\) 
\( N_i \) population density of crystals of size range \( i \), \#/m\(^3\) 
\( N_m \) population density of crystals of size class \( m \), \#/m\(^3\)
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N_n$</td>
<td>population density of crystals of size class $n$, $/#/m^3$</td>
</tr>
<tr>
<td>$N_P$</td>
<td>power number, -</td>
</tr>
<tr>
<td>$n$</td>
<td>population density, $/#/m^4$</td>
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<tr>
<td>$n'$</td>
<td>step density, $/#/m$</td>
</tr>
<tr>
<td>$n_0$</td>
<td>population density of nuclei $/#/m^4$</td>
</tr>
<tr>
<td>$n_{agg}$</td>
<td>population density of agglomerated particles $/#/m^4$</td>
</tr>
<tr>
<td>$n_i$</td>
<td>number of aggregates formed from $i$ primary particles #</td>
</tr>
<tr>
<td>$n_{orig}$</td>
<td>number of particles present in the original monodispersion #</td>
</tr>
<tr>
<td>$n_r$</td>
<td>number of size ranges, #</td>
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<tr>
<td>$n_t$</td>
<td>number of particles present at time $t$, #</td>
</tr>
<tr>
<td>$n_{tot}$</td>
<td>population density of all particles $/#/m^4$</td>
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<tr>
<td>$P$</td>
<td>power input from the impeller per unit mass of fluid, $W/kg$</td>
</tr>
<tr>
<td>$P_0$</td>
<td>power number, -</td>
</tr>
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<td>$P_1$</td>
<td>meeting probability, -</td>
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<tr>
<td>$P_2$</td>
<td>sticking probability, -</td>
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<tr>
<td>$Q$</td>
<td>volumetric flow rate, $m^3/s$</td>
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<td>$Q'$</td>
<td>ratio of micro- and mesomixing time constants, -</td>
</tr>
<tr>
<td>$q$</td>
<td>step flux, $#/s$</td>
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<tr>
<td>$q'$</td>
<td>parameter, -</td>
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<tr>
<td>$R$</td>
<td>ideal gas constant, $J/(mol \cdot K)$</td>
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<tr>
<td>$r$</td>
<td>agglomeration rate, $#/m^3 \cdot s$</td>
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<tr>
<td>$r'$</td>
<td>reaction growth rate order, -</td>
</tr>
<tr>
<td>$r_1$</td>
<td>reaction rate, $mol/(m^3 \cdot s)$</td>
</tr>
<tr>
<td>$r_L$</td>
<td>ratio of the upper and lower limits of size for any interval, -</td>
</tr>
<tr>
<td>$r_{vis}$</td>
<td>minimum radius at which crystal becomes visible, $m$</td>
</tr>
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<td>$S$</td>
<td>supersaturation ratio, -</td>
</tr>
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<td>$S_c$</td>
<td>Schmidt number, -</td>
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<tr>
<td>$S_h$</td>
<td>Sherwood number, -</td>
</tr>
<tr>
<td>$s_i$</td>
<td>number of the crystals in size range $I_i=[v_{i-1},v_i]$, #</td>
</tr>
<tr>
<td>$T$</td>
<td>temperature, $K$</td>
</tr>
<tr>
<td>$\bar{T}$</td>
<td>mean temperature, $K$</td>
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<td>$t$</td>
<td>time, $s$</td>
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<tr>
<td>$t^*$</td>
<td>half-time, $s$</td>
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<td>$t_G$</td>
<td>time necessary for growth to the visible crystal, $s$</td>
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<tr>
<td>$t_{ind}$</td>
<td>induction time, $s$</td>
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<tr>
<td>$t_N$</td>
<td>time necessary for nucleation, $s$</td>
</tr>
<tr>
<td>$U$</td>
<td>ratio of linear feed velocity and bulk velocity, -</td>
</tr>
<tr>
<td>$u$</td>
<td>step velocity, $m/s$</td>
</tr>
<tr>
<td>$\bar{u}$</td>
<td>local average velocity, $m/s$</td>
</tr>
<tr>
<td>$u'$</td>
<td>local velocity fluctuation causing crystals to meet, $m/s$</td>
</tr>
<tr>
<td>$V$</td>
<td>volume of fluid, $m^3$</td>
</tr>
<tr>
<td>$V_c$</td>
<td>total volume of all crystals, $m^3$</td>
</tr>
<tr>
<td>$V_s$</td>
<td>volume of solid present in a suspension, $m^3$</td>
</tr>
<tr>
<td>$V_m$</td>
<td>molar volume, $mol/m^3$</td>
</tr>
<tr>
<td>$V_n$</td>
<td>nucleus volume, $m^3$</td>
</tr>
<tr>
<td>$V_T$</td>
<td>total potential energy of interaction between surfaces, $J$</td>
</tr>
<tr>
<td>$\dot{V}$</td>
<td>volume rate of feed, $m^3/s$</td>
</tr>
<tr>
<td>$v$</td>
<td>face growth, $m/s$</td>
</tr>
<tr>
<td>$v_i$</td>
<td>$i^{th}$ size range, $m$</td>
</tr>
</tbody>
</table>
\( v_{in} \)  
particle velocity in the internal co-ordinates, \( \text{m/s} \)

\( W_{off} \)  
mass size distribution (off-line)

\( W_{on} \)  
mass size distribution (on-line)

\( x \)  
ions of species \( A \)

\( y \)  
ions of species \( B \)

\( Z \)  
surface charge density,

\( z \)  
ion valency,

**Greek Letters**

\( \alpha \)  
degree of dissociation,

\( \alpha' \)  
fraction of particles (crystals),

\( \overline{\alpha} \)  
probability that a collision leads to formation of an aggregate,

\( \bar{\alpha} \)  
probability of an effective collision,

\( \gamma \)  
activity coefficient

\( \gamma_{CL} \)  
interfacial tension, \( \text{N/m} \)

\( \delta \)  
boundary layer, film thickness, \( \text{m} \)

\( \delta(L_m) \)  
Dirac delta function,

\( \varepsilon \)  
power dissipation, \( \text{W/kg} \)

\( \varepsilon_0 \)  
permittivity of free space, \( \text{C}^2/(\text{J m}) \)

\( \varepsilon_r \)  
relative dielectric permittivity,

\( \eta \)  
viscosity, \( \text{kg/(m s)} \)

\( \theta \)  
contact angle between the nuclei and the solid-liquid interface on which the heterogeneous nucleation occurs,

\( \kappa \)  
Debye-Hückel parameter, \( \text{m}^{-1} \)

\( \lambda_b \)  
Batchelor concentration microscale, \( \text{m} \)

\( \lambda_g \)  
Taylor microscale, \( \text{m} \)

\( \lambda_K \)  
Kolmogorov microscale, \( \text{m} \)

\( \lambda_e \)  
Lagrangian microscale, \( \text{m} \)

\( \mu \)  
chemical potential \( \text{J/mol} \)

\( \Delta \mu \)  
difference of chemical potential \( \text{J/mol} \)

\( \mu_i \)  
chemical potential at the interface between the solution and the boundary layer \( \text{J/mol} \)

\( \mu_0 \)  
standard potential \( \text{J/mol} \)

\( \mu^* \)  
chemical potential of a saturated solution \( \text{J/mol} \)

\( \nu \)  
stoichiometric coefficient,

\( \nu_s \)  
kinematic viscosity, \( \text{m}^2/\text{s} \)

\( \rho \)  
crystal size ratio \( (L_m/L_n) \),

\( \sigma \)  
relative supersaturation \( (S-1) \),

\( \sigma_{act} \)  
activity-based supersaturation,

\( \tau \)  
residence time, \( \text{s} \)

\( \tau_{macro} \)  
macromixing time, \( \text{s} \)

\( \tau_{meso} \)  
mesomixing time, \( \text{s} \)

\( \tau_{micro} \)  
micromixing time, \( \text{s} \)

\( \phi \)  
affinity \( \text{J} \)
PART I: Overview of the Thesis
1. INTRODUCTION AND OBJECTIVES

1.1 Introduction

Crystallization is an important separation process and a method producing particles of a certain size distribution. It is a common unit process in industry because good purification can be attained from rather impure solutions. Crystallization, especially cooling and reaction crystallization, requires less energy than many other separation processes.

The most important phenomena in crystallization are nucleation and crystal growth, and in some cases agglomeration and crystal breakage, which affect crystal size distribution. Mainly these phenomena depend strongly on supersaturation and/or the hydrodynamics of the specific crystallizer. Supersaturation can be described as the concentration difference between the actual liquid concentration and solubility. Hydrodynamics can be described as a combination of mixing, inlet and outlet flow, and recycling of the suspension. Especially in reactive crystallization, hydrodynamics play a very important role due to high local concentration differences. If mixing and reactant feed are not well engineered, the result may be disastrous, at the very least unwanted crystal sizes and polymorphs.

Phenomena-based modelling is a powerful tool in design and development of crystallizers. However, non-uniformity of the suspension and mother liquor in the crystallizer makes simple modelling impossible in many cases. Therefore, better tools for modelling are needed. Computational fluid dynamics, CFD has developed as a major tool for modelling of crystallization in recent decades, although it makes simulation computationally demanding. Proper verification of CFD simulations is still needed, especially for turbulence models of multiphase processes.

Recently, process analytical technology (PAT) has been adopted in monitoring and control of crystallization, especially supersaturation during crystallization. However, hydrodynamics limits the value of PAT due to the non-uniformity mentioned above. The degree of non-uniformity increases dramatically when the size of crystallizer
increases to industrial scale. Good knowledge of hydrodynamics helps selection of the measurement point, or points in the case of multiprobe systems, for PAT.

1.2 Research Motivation and Objectives

In this thesis, many different industrially interesting chemicals are studied to improve understanding of crystallization processes. Different chemicals behave very differently in crystallization, due to large differences in crystallization kinetics, and therefore it is beneficial to study multiple chemical systems. However, good knowledge of crystallization kinetics is often not enough to explain all behaviours of crystallization processes, especially when the scale of the crystallizer increases, because larger scale crystallization is often highly dependent on the mixing process. Therefore, the main objective of this study is to explore the influence of hydrodynamics on the crystallization process to find the regularities between crystallization kinetics and hydrodynamics. The work focuses mainly on modelling, and PAT monitoring and control of different crystallization processes.

The introduction to the thesis discusses the theoretical background of crystallization phenomena and presents case studies related to the author's publications. These case studies are practical examples illustrating the relevance of hydrodynamics to each phenomenon.

In the thesis, study of modelling starts with kinetic study of MSMPR theory (Paper I) and development of a new discrete crystal growth method called the particle transport method (Assoc. Papers vii and viii) and ends with discussion of a combination of CFD and a multiblock model (Paper III and Assoc. Paper ix). Monitoring and control of crystallization is developed based on supersaturation monitored by ATR FTIR (Papers II, IV, V, VI and Assoc. Paper xiii). The last paper of the thesis (Paper VI), in addition to addressing monitoring and control of crystallization, studies different nucleation methods. The most effective nucleation method reviewed in the paper is power ultrasound, which may be considered as partially affecting hydrodynamics too. The background to the hydrodynamics of these cases is discussed in detail in the thesis.
2. SUPERSATURATION AND CRYSTALLIZATION KINETICS

The most important phenomena in crystallization are nucleation, crystal growth, and sometimes agglomeration and/or crystal breakage, since they all affect the size of product crystals. The first three phenomena depend strongly on supersaturation, the physical properties of the chemical concerned, and the hydrodynamics of the specific crystallizer. The last phenomenon, crystal breakage, depends on the physical properties of the chemical and the hydrodynamics of the specific crystallizer. Supersaturation is the concentration difference between the actual concentration and solubility. Hydrodynamics is a combination of mixing, inlet and outlet flow, and recycling of the suspension.

To understand supersaturation, some basic concepts of solubility and solution thermodynamics need to be clarified. A solution is formed by the addition of solid solute to the solvent. At a certain temperature a maximum amount of solute can dissolve into the solution. This maximum is called saturation, and the solute concentration is called solubility at a given condition. According to Crystallization Technology Handbook (1), thermodynamically this means that the chemical potential of species in the solute is the same as the chemical potential of species in the solid phase. The chemical potential can be described as a function of activity by the equation

\[ \mu = \mu_0 + RT \ln a \]  \hspace{1cm} (1)

If the chemical potential of the solution differs from the chemical potential of the crystal, the system is under kinetic change. When the direction of change is to the crystal, it is called the kinetic driving force of crystallization, affinity. This can be described by the equation

\[ \Phi = \Delta \mu = \mu - \mu^* = kT \ln \frac{a}{a^*} = kT \ln \frac{\chi}{\gamma^* c^*} \]  \hspace{1cm} (2)

As can be seen from Equation 2, relative activity, \( a/a^* \), and relative concentration, \( c/c^* \), correlate with affinity. The actual and equilibrium concentrations correlate with
the actual and equilibrium chemical potentials, which means that concentration difference, \( \Delta c \), can be used as the driving force of crystallization. This concentration difference is called supersaturation and can be expressed with other terms; relative supersaturation, \( \sigma \), and supersaturation ratio, \( S \). Their relationship is

\[
S = \frac{c}{c^*} = 1 + \sigma = 1 + \frac{\Delta c}{c^*}
\]

When crystals are formed from an electrolytic solution of dissociated anions and cations

\[
A_xB_y \rightleftharpoons xA^{z+} + yB^{z-}
\]

Now solubility product can be formulated with activities

\[
K_a = (a^*_A)^x(a^*_B)^y = \left( \gamma_A m_A^* \right)^x \left( \gamma_B m_B^* \right)^y
\]

or with concentrations

\[
K_c = (c^*_A)^x(c^*_B)^y
\]

The supersaturation ratio has a relationship to the equilibrium coefficient when \( x=y=1 \)

\[
S = \frac{c^*_c c^*_B}{K_c}
\]

### 2.1 Nucleation and the Metastable Zone

According to Mullin (2) nucleation can be divided into different classes as shown in Figure 1.
Secondary nucleation is divided in Handbook of Industrial Crystallization (3) into six subsections; initial breeding, polycrystalline breeding, macroabrasion, dendritic, fluid shear and contact. The presence of crystals and their interaction with the environment (crystallizer walls, impellers, etc.) is needed for secondary nucleation.

Crystals can be formed in the solution only when a number of embryos, nuclei or seeds acting as centres of crystallization exist. The kinetic processes of nucleation and crystal growth require supersaturation, which can be obtained for example by changing the solution temperature, evaporating solvent, or adding drowning-out agents or reagents. The system then attempts to achieve thermodynamic equilibrium, or the solubility limit, through nucleation and nuclei growth. If very high supersaturation, known as metastable supersaturation $\Delta c_{\text{met}}$, is obtained in the system, primary nucleation occurs. Secondary nucleation can be observed even at very low supersaturation ($\Delta c_{\text{met,sec}} < \Delta c_{\text{met,prim}}$). Figure 2 illustrates metastable zone width for different nucleation types.

In the study of crystallization, it has to be noted that the number of nuclei depends on the resolution of the analyser used for measuring the crystal size distribution; the smaller the detectable particle, the larger the number of particles registered by the analyser. Furthermore, the nucleation rate is difficult to define because the exact number of solid particles and their change with time is not easy to measure. Therefore, the crystal size distribution (CSD) in a certain size range is more important than the total number of all species. This size distribution depends primarily on
nucleation and growth rate, and these quantities are therefore used in design and scale-up of crystallizers. The CSD depends also on agglomeration, when it occurs. However, agglomeration is typically an unwanted phenomenon in crystallization and thus not used in design and scale-up of processes.

\[
\text{Metastable zone width for nucleation}
\]

Figure 2. Metastable supersaturation against temperature for several types of nucleation processes as presented in Crystallization Technology Handbook (1).

The concept of a continuous mixed suspension mixed product removal (MSMPR) crystallizer, presented by Randolph and Larson (4), has led to experimental techniques whereby crystallization kinetics (i.e., nucleation and growth rates) can be determined under conditions where both of these kinetic processes are occurring simultaneously. Such kinetics are usually correlated by semi-empirical equations of the form

\[
B_q = K_q G^m M^j N^v
\]  

(8)

In the period since the mid-1960's results of many such experimental studies have been published for a wide range of systems, as reviewed by Garside and Shah (5).
2.1.1 Primary Nucleation

Supersaturation of the solution is the only cause of nucleation in the case of primary nucleation, which can be divided into two sections as shown in Figure 1.

Randolph and Larson (4) have proposed that supersaturation is the only driving force in homogeneous nucleation, which means that there is no nucleation caused by impurities, foreign particles, or mixing. According to Crystallization Technology Handbook (1), the greater the supersaturation, the greater is the addition rate of molecules into clusters, and because addition is a random process, the more molecules in the same volume, the greater the number of collisions of the molecules, and consequently, the greater the number of additions of molecules. A large addition rate means that the number of nuclei is increasing. The free enthalpy formed by a crystal surface, $\Delta G_s$, increases with the interfacial tension, $\gamma_{CL}$ between the solid crystal surface and the surrounding solution, and also with the surface of the nuclei. The enthalpy change is to be added to the system and therefore it is positive. On the other hand, the free enthalpy formed by volume, $\Delta G_V$, is released during solid-phase formation and is thus negative. The magnitude of the free volume enthalpy $\Delta G_V$ is proportional to the volume of the nucleus and increases with increasing energy in ideal systems, $RT\ln(c/c^*)$ when the concentration $c$ of the elementary units decreases to the concentration $c^*$, the solubility concentration. The change in the total enthalpy with respect to the nucleus size passes through a maximum value, as shown in Figure 3.

A thermodynamically stable nucleus exists when the total enthalpy does not change when molecules are added or removed, in other words,

$$\frac{\partial \Delta G}{\partial \mathcal{L}} = 0 \quad (9)$$
According to Crystallization Technology Handbook (1) the primary homogeneous nucleation rate can be expressed by the equation

$$B_{\text{hom}} = A_{\text{hom}} \exp \left( \frac{-K_{\text{hom}}}{v \ln S} \right)$$  \hspace{1cm} (10)

Coefficient $K_{\text{hom}}$ is generally given for spherical nuclei as

$$K_{\text{hom}} = \frac{16 \pi}{3} \frac{\gamma_{\text{CL}}^3}{(c_s N_A)^{\frac{3}{2}} (kT)^{\frac{3}{2}}}$$  \hspace{1cm} (11)

Primary homogeneous nucleation is highly non-linear. It is very low for small values of supersaturation but becomes very high for values of supersaturation beyond critical supersaturation, corresponding to the metastable zone limit. Primary nucleation begins when supersaturation reaches the level of critical supersaturation. This is one of the fundamental differences between precipitation and ordinary crystallization because in systems where supersaturation increases smoothly, for example cooling
and evaporation crystallization, supersaturation cannot easily exceed the critical value.

According to Randolph and Larson (4), heterogeneous nucleation generally refers to new particle formation resulting from the presence of foreign insoluble material. In the presence of foreign particles, interfacial phenomena change the mechanism substantially and can form nuclei even at very low supersaturation. According to Crystallization Technology Handbook (1), nucleation kinetics is faster and the metastable zone smaller in heterogeneous primary nucleation than in homogeneous primary nucleation. The nucleation rate in heterogeneous primary nucleation can be expressed by the equation

$$B_{het} = A_{het} \exp \left( \frac{-f K_{hom}}{\nu \ln S} \right)$$

(12)

The correction factor is given by

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

(13)

### 2.1.2 Secondary Nucleation

Secondary nucleation is caused by the existence of parent crystals. Secondary nucleation is present in all existing industrial crystallizers. In precipitation of sparingly soluble substances, secondary nucleation either does not take place at all or only to a small extent because the particles formed are too small for secondary nucleation mechanisms to play an important role. The number of nuclei which are formed by secondary nucleation during precipitation is substantially lower than those resulting from primary nucleation and the contribution of secondary nucleation is thus overshadowed by primary mechanisms. Therefore, secondary nucleation need not be considered during precipitation; except in special cases such as when the initial supersaturation is low, and dendrites are formed and subsequently disintegrate, after
crystals of a sparingly soluble substance have been brought into their stable supersaturated solution, or when the crystals of the substance being crystallized reach such a size that mechanical contacts between them become important.

In a Mixed Suspension Mixed Product Removal (MSMPR) crystallizer, two possible mechanisms of secondary nucleation have been suggested. In the first mechanism crystal-impeller collisions occur as a result of impacts of crystals against the vessel walls or the rotating impeller, and the kinetic energy of the crystals is then assigned to that of the surrounding agitated fluid. Secondary nucleation can also occur following direct interaction between the parent crystals in the crystal suspension.

According to Söhnel and Garside (6) secondary nucleation may occur during precipitation with the nuclei being formed in several ways:
1. formation of nuclei on the surface of the solid phase to give structures such as dendrites, which grow on the surface of the mother crystal and subsequently break off,
2. formation of nuclei in the liquid phase due to structural changes of the liquid adjacent to a crystal or as a result of the presence of dissolved admixtures inhibiting the crystallization process,
3. formation of nuclei in the adsorption layer on the surface of the growing crystal, in the form of molecular aggregates having a crystalline structure, from where they are washed into the solution.

Numerous researchers mentioned by Clontz and McCabe (7) have shown that in the presence of crystals, nucleation occurs in a reproducible manner at moderate supersaturations. This is, however, possible only if heterogeneous nucleation does not interfere and well-formed crystals are able to grow.
2.1.3 Case Studies: Nucleation

Size-dependent crystallization kinetics of potassium sulphate in an MSMPR crystallizer where secondary nucleation was dominant was studied in Paper I. The total nucleation rate $B_0$ was expressed as an empirical power law equation (Equation 8) and parameters were found to be as follows:

$$B_0 = \left(7.698 \cdot 10^{-2}\right)G_a^{0.613}M_T^{1.164}N^{-0.901}$$
for a 10 L crystallizer (14)

and

$$B_0 = \left(5.859 \cdot 10^{-5}\right)G_a^{-1.298}M_T^{0.875}N^{-0.275}$$
for a 50 L crystallizer (15)

As can be seen from the equations, the total nucleation rate is inversely proportional to the average growth rate, probably because of the effect of the attrition rate; an increasing attrition rate causes an increasing nucleation rate and decreasing growth rate. The nucleation rate is proportional to the suspension density and impeller stirring speed, as expected. This is the same conclusion as Randolph and Rajagopal (8) presented for a potassium sulphate system. From a hydrodynamic point of view, the crystallizer used in the study was not the best possible due to the dead-zones of mixing in a cylindrical flat-bottom reactor. These dead-zones and variations in mixing may increase the size-dependency of the crystal growth rate, although cooling crystallization is not typically sensitive to slightly inhomogeneous mixing. However, the rather large difference in the power of the impeller stirring rate between the small scale (10 litres) and large scale (50 litres) in the empirical power law equation indicates increasing complication in mixing as the size of the crystallizer increases.

As a second case, polymorphism control of L-glutamic acid by sonocrystallization and seeding was studied in Paper VI. In the work, the effect of power ultrasound initiated nucleation and seeding on polymorphism in a semi-batch crystallizer was studied and polymorphs compared to those produced by spontaneous primary nucleation. As an example, the crystal size distributions of product crystals produced by three nucleation methods; power ultrasound initiated, seeded, and spontaneous nucleation, are compared in Figure 4. Power ultrasound irradiation is commonly known to induce acoustic streaming, microstreaming, and highly localized
temperature and pressure within fluids. Typically, this results in increased primary nucleation. Primary nucleation can be heterogeneous, due to cavitation (vapour bubbles), or homogeneous, due to high local temperature differences and enhanced micromixing. It is difficult to compare different nucleation phenomena when polymorphism is involved. Nevertheless, it can be seen clearly that seeding prevents or decreases primary nucleation dramatically, resulting in larger size crystals and more narrow crystal size distribution in the product. It can also be noted that the "tail" in the small size crystal range of the shown distributions is mainly caused by nucleation (secondary/primary) during the batch. Major nucleation, initiated by supersaturation (spontaneous), seeding, or ultrasound, happens at the beginning of the batch. If supersaturation is below the critical nucleation limit after major nucleation, only crystal growth occurs, especially with seeding, shown by Mullin (2), leading to large product crystals with very narrow size distribution. However, that is not the case in reactive crystallization due to high local supersaturation close to the reagent feed pipe and secondary nucleation of fragile crystals. Therefore, mixing intensity or energy dissipation rate plays also a very important role, as concluded by Åslund and Rasmusson (9), Phillips et al. (10), and Zauner and Jones (11).

Figure 4. Crystal size distributions of L-glutamic acid at the end of a semibatch process with three different nucleation methods; power ultrasound initiated (US 30%), seeded (SEED) and spontaneous (US 0) nucleation.
Hydrodynamics play a very important role in nucleation. Nucleation is extremely dependent on supersaturation and local values can be decreased by equalizing features caused by hydrodynamics. For this reason, special attention is needed in selection of mixing equipment (impeller type, baffles, draft tube etc.), feed locations, and crystallizer geometry.

2.2 Agglomeration

Agglomeration means that crystals stick together to generate a new, larger particle. Unlike nucleation and crystal growth, agglomeration is not a phenomenon occurring in all crystallization processes. Its existence depends on the crystallizing system and the operating conditions. Agglomeration during crystallization is not yet fully understood because it is usually very difficult to distinguish from crystal growth. Agglomeration study is based on measurement of the number and size of the monocrystals in an agglomerated particle.

Permanent attachment in collisions between particles in the suspension may occur if the particles are small enough for the van der Waals forces to exceed the gravitational forces. This happens usually with particles smaller than 1 μm. Smoluchowski (12) showed that the time needed to halve the number of particles in a monodisperse system can be expressed as

\[
t^* = \frac{n_i t}{n_{\text{avg}} - n_i}
\]

Agglomeration is quite common in systems that have nucleated homogeneously, where \( n_{\text{avg}} \) often exceeds \( 10^7 \) cm\(^{-3}\).

Different theoretical considerations have been developed to describe agglomeration or coagulation. Smoluchowski (12) developed early 20\(^{th}\) century theories where two types of agglomeration for colloidal particles in suspension are distinguished:
1. Perikinetic (static fluid, particles in Brownian motion)
2. Orthokinetic (agitated dispersions).
Both modes can occur in precipitation processes, but in a stirred crystallizer orthokinetic agglomeration clearly predominates. Orthokinetic agglomeration is also more important for larger particles. Usually, it begins to predominate over perikinetic agglomeration if the size of one of the particles exceeds about 0.2 μm, as shown by Gregory (13).

Derjaguin, Landau, Verwey and Overbeek, (presented by Verwey and Overbeek (14)) developed the classical standard theory of the stability of colloids in the mid 20th century. DLVO theory is based simply on the sum of the potential energies of repulsion and attraction between colloid particles. Approximate expressions of these potential energies are shown in Figure 5.

\[ V_T = V_R + V_A + V_S \]

Figure 5. Total potential energy of interaction \( V_T \), potential energies of repulsion \( V_R \) and attraction \( V_A \), and potential energy of repulsion due to the solvent layers \( V_S \), as presented by Hunter (15). \( V_S \) is assumed to be negligible until \( D < 10 \text{ nm} \).

DLVO theory was developed originally to ascertain the stability of suspensions. Particles or crystals could not agglomerate if the kinetic energy of the crystals is not sufficient to exceed the maximum of the total potential energy.

David et al. (16) showed in calculation of collision and sticking probability that the number of collisions between two particles has been found to be proportional to the concentration of particles, the total collisional cross-section, and the relative velocity
of the particles. The mechanism proposed for the encounter process differs from Smoluchowski’s theory for coagulation. The building up of a crystalline bridge between two neighbouring crystals requires that the two colliding particles stay close to each other for a length of time sufficient enough to crystallize the mass of the bridge from the supersaturated solution. Therefore, mixing effect is taken into account in collision and sticking probabilities.

David et al. (16) express the agglomeration rate as follows

\[
r = k_{\text{growth}} \Delta c^j \left( \frac{L_n + L_m}{L_m} \right)^2 f(\rho) N \, d_j \left[ 1 - \frac{(L_n + L_m)^2}{\lambda_c^2} \right] \Delta \theta
\]

(17)

David et al. (16) have made a distinction between the chemical growth regime, where the growth rate depends only on supersaturation and temperature, and the diffusional growth regime, where the growth rate depends also on the agglomerate size. In the case of chemical growth, the mass transfer coefficient for the crystal growth \( k_{\text{growth}} \) is equal to the agglomeration rate constant in the chemical growth regime \( k_A \). In diffusional growth, \( k_{\text{growth}} \) is equal to \( k'_A \, k'_D \), where \( k'_A \) means the agglomeration rate constant in the diffusional growth regime, and \( k'_D \) is the diffusional growth rate constant. The agglomeration rate constants are functions of temperature only. In diffusional growth exponent \( j \) is 1.

David et al. (16) present another form for the agglomeration rate

\[
r = K(L_n, L_m) \Delta c^j N_n \, N_m
\]

(18)

Hartel and Randolph (17) have collected equations used to calculate the agglomeration kernel, shown in Table I.
TABLE I. Agglomeration kernels as presented by Hartel and Randolph (17).

<table>
<thead>
<tr>
<th>Brownian motion</th>
<th>$K(u, v) = \frac{2eT}{3\mu} [u^{1/3} + v^{1/3}][u^{-1/3} + v^{-1/3}]$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laminar shear</td>
<td>$K(u, v) = \frac{\gamma}{S_{\theta}} [u^{1/3} + v^{1/3}]$</td>
</tr>
<tr>
<td>Turbulent diffusion</td>
<td>$K(u, v) = k_1U [u^{1/3} + v^{1/3}]$</td>
</tr>
<tr>
<td>Turbulent inertia</td>
<td>$K(u, v) = 0.2 \rho e^{3/4} \frac{v}{\mu}^{1/2}$</td>
</tr>
<tr>
<td>Gravitational settling</td>
<td>$K(u, v) = C_g E_g (u^{1/3} + v^{1/3})^2</td>
</tr>
<tr>
<td>Gravitational settling</td>
<td>$K(u, v) = C_g E_g (u^{1/3} + v^{1/3})^2</td>
</tr>
<tr>
<td>Semiempirical formulation</td>
<td>$K(u, v) = C_g E_g (v)^2/(v + u)$</td>
</tr>
</tbody>
</table>

$u^{1/3}$ and $v^{1/3}$ in the table refers to $L_m$ and $L_n$ respectively.

2.2.5 Effect of Supersaturation on Agglomeration

Agglomeration takes place parallel to crystal growth as an important size enlargement mechanism of some crystallization processes. There are various problems in determining the role of agglomeration. First, knowledge of the kinetics of agglomeration is rather limited, and therefore the choice of suitable agglomeration kernels describing agglomeration tendency is rather complicated. Moreover, it is difficult to separate agglomeration from crystal growth. Both effects are awkwardly combined when analysing particle size distributions resulting from dynamic or static experiments. Sato-Kobayashi et al. (18) proposed an empirical agglomeration fraction when the population density of the agglomerated particles and that of all particles are known

$$F_a(L) = \frac{n_{agg}(L)}{n_{tot}(L)}$$

(19)

The agglomeration fraction can be expressed in terms of separated variables.
Agglomeration is considered undesirable in industrial crystallization processes; not only because of the difficulty of controlling agglomeration in precipitation, but also because agglomeration often results in non-uniform shaped and impure crystals.

### 2.2.6 Case Studies: Agglomeration

The author studied the effect of supersaturation on agglomeration of calcium sulphate in reactive crystallization in Assoc. Paper i. The behaviour of calcium sulphate in the process studied made it possible to establish the agglomeration fraction; aggregates broke when filtrated crystals were dried at room temperature. Because the shape of calcium sulphate crystals is size-independent the agglomeration fraction, shown in Equation 19, can be calculated by the on-line and off-line mass size distributions

\[
F_{A,L}(L) = A'\Delta c^g e^{-c^g \Delta \tau} + F_{A,L-1}(L)e^{-E_{a}\frac{\Delta \tau}{\tau}}
\]  

(20)

In the study, a cylindrical tank, 10 litres in volume, with baffles and a shaped bottom, was used as a crystallizer. The impeller was a 6-flat-blade turbine. The stirring rate in all measurements was set to 400 RPM. The reagent solutions, 0.35 M aqueous calcium nitrate (Ca(NO₃)₂) and sodium sulphate (Na₂SO₄), were pumped into the crystallizer, which was initially filled with water. The feed locations of the reactants were selected in such a way that the feed streams were on opposite sides adjacent to the impeller. An example of measured and fitted on- and off-line mass size distributions and the measured supersaturation is shown in Figure 6.
Figure 6. Example of measured and fitted on- and off-line crystal size distributions (left-hand side), and the measured supersaturation (right-hand side). Sampling moments are marked in the supersaturation curve by vertical lines.

Estimation of parameters $A'$, $B'$, $C'$, $D'$ and $E'$ in Equation 20 gives the result

$$F_{A',l}(L)=h \left( \frac{L}{mm} \right)^{0.80} e^{-27000\left( \frac{L}{mm} \right)^{2.8}} + F_{A',l}(L)e^{-0.60 \frac{t_{[min]}}{t_{[min]}}}$$ (22)

The relation between the agglomeration fraction of different crystal sizes (relative difference of mass size distributions of on-line and off-line samples) and supersaturation was determined, although there was rather large average deviation in the experimental data. The error was primarily caused by the last term of Equation 22, i.e. the effect of agglomerates formed in a previous time step. The time step in the computation was not constant and short enough. However, it was concluded that the method presented is nevertheless useful, for example, in designing start-up sequences for industrial precipitation equipment. In order to avoid excessive agglomerate formation, supersaturation levels at the very beginning of operations should be maintained at the lowest levels possible.

The hydrodynamics of a 10-liter crystallizer with a shaped bottom, baffles and 6-flat-blade turbine, as used in the experiments, was suitable for the agglomeration experiments because it provides very good micro- and mesomixing in the selected feed positions. Since the scale was rather small, poor macromixing with the turbine was not critical.
Very strong aggregation was observed by the author in the beginning of batch precipitation and during start-up of continuous precipitation when high relative supersaturation is involved (Papers II, IV, V, VI, and Assoc. Papers v and vi). Massive spontaneous nucleation creates a large number of crystals which most probably collide. However, the sticking probability is low because under intensive mixing there is not enough time for the growth of bridges between particles in the aggregates.

Paper VI, for example, shows very large particles detected in the crystal size distribution of ultrasound initiated reactive crystallization of L-glutamic acid (Sample 1, immediately after nucleation). Large particles disappeared after a short period of time and detectable crystal growth is observed (Sample 2, 10 min after nucleation, and End, at the end of the batch). Such a development of CSD is shown in Figure 7.

The same phenomena were observed in Assoc. Paper vi. The median size of crystals in the start-up of reactive crystallization of barium sulphate decreases at the beginning of the crystallization and then increases in the case of short residence time and high initial concentration of the reagents, i.e. high supersaturation. The development of median crystal size in crystallization of barium sulphate from homogeneous and heterogeneous reactions of barium chloride and ammonium sulphate is shown in Figure 8.

Figure 7. Crystal size distributions of crystal samples taken during the semi-batch process of reactive sonocrystallization of L-glutamic acid. Sample 1 is taken soon after nucleation starts; sample 2 ten minutes after nucleation starts; and sample end when the semibatch crystallization ends.
2.3 Crystal Growth

In general, as soon as stable nuclei have formed in a supersaturated system, they begin to grow into crystals of visible size. This phenomenon is called crystal growth. Crystal growth in a supersaturated solution is a very complex process and has only lately become well understood. Illustrating the complexity, Mullin (2) has presented that the following processes may all be taking place simultaneously for an electrolyte crystallizing from an aqueous solution:

1. bulk diffusion of hydrated ions through the diffusion boundary layer,
2. bulk diffusion of hydrated ions through the adsorption layer,
3. surface diffusion of hydrated or dehydrated ions,
4. partial or total dehydration of ions,
5. integration of ions into the lattice,
6. counter-diffusion of released water through the adsorption layer, and
7. counter-diffusion of water through the boundary layer.

Mechanisms of crystal growth may be divided under three general categories:
1. Surface energy theories, mainly developed by Gibbs (19)
   - Crystals grow in the direction of minimum surface energy. These theories are not in much use because there is little quantitative evidence to support them.
2. Diffusion theories

- Matter is deposited continuously on a crystal surface at a rate proportional to the difference in concentration between the point of deposition and the bulk of the solution. Mathematical analysis of the process is similar to that used for other diffusion processes.

3. Adsorption-layer theories

- Crystal growth is a discontinuation process taking place by adsorption (layer by layer) on the crystal surface.

Pure diffusion-controlled growth for all sizes in a crystal population is unlikely. Turnbull (20), for example, suggests that very small crystals, nuclei should be interface-controlled and very large crystals diffusion-controlled.

In reaction crystallization, the situation is a bit more complicated. Diffusion and surface integration must happen simultaneously to two ionic species because of the electric neutrality of the crystal and the solution. Chiang and Donohue (21) proposed a model for surface integration based on chemical reaction engineering. Surface diffusion is thought not to be important in this model. Three integration mechanisms compete with volumetric diffusion of ions. These three mechanisms are as follows:

1. Individual adsorption of ions ⇒ attainment of the insoluble component in the adsorption layer ⇒ integration in the crystal lattice
2. Individual adsorption of ions ⇒ integration in the crystal lattice in ionic form
3. Ions react to the soluble intermediary component ⇒ (adsorption ⇒) integration in the crystal lattice.

Models currently used to describe crystal growth are shown in Table II. The models are briefly explained in the following sections.
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TABLE II. Growth rate models as presented in Crystallization Technology Handbook (1).

<table>
<thead>
<tr>
<th>Total growth rate</th>
<th>Mass transport</th>
<th>( m = k_d (\rho - \rho^<em>)^{\mu} ) with ( \rho - \rho^</em> = \Delta \rho )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physicochemical models</td>
<td>Only convection + diffusion</td>
<td>( m = k_d (\rho - \rho_s) )</td>
</tr>
<tr>
<td>Only surface integration</td>
<td>( m = k_e (\rho - \rho^*)^{\gamma} ) with ( k_e = k_e_0 \exp\left(-\frac{\Delta F}{RT}\right) )</td>
<td></td>
</tr>
<tr>
<td>Elimination of ( \rho_s )</td>
<td>( m = k_s (\Delta \rho - \frac{m}{k_d}) )</td>
<td></td>
</tr>
<tr>
<td>Special case ( r = 1 )</td>
<td>( m = \frac{\Delta \rho}{1/k_e + 1/k_s} )</td>
<td></td>
</tr>
<tr>
<td>Special case ( r = 2 )</td>
<td>( m = k_d \Delta \rho + \frac{k_s^2}{2k_e} - \frac{k_t^2 \Delta \rho}{k_s} )</td>
<td></td>
</tr>
<tr>
<td>Surface integration models</td>
<td>B + S model</td>
<td>( \nu_{B+S} = K_s (\Delta \rho / \rho^<em>)^{\alpha} \exp\left(-\frac{K_s \rho^</em>}{T \Delta \rho}\right) )</td>
</tr>
<tr>
<td></td>
<td>BCF model</td>
<td>( \nu_{BCF} = K_{BCF} (\Delta \rho / \rho^<em>)^{\beta} \tanh\left(\frac{K_{BCF} \rho^</em>}{T \Delta \rho}\right) ) with ( v = m/\rho_s )</td>
</tr>
</tbody>
</table>

\( m \) and \( \rho \) in the table refers to \( G \) and \( c \) respectively

2.3.1 Adsorption Layer Theories

Volmer (22) suggested early in the thirties that crystal growth is a discontinuous process, occurring by adsorption, layer by layer, on the crystal surface. This is called the adsorption layer theory. Several important modifications of the adsorption layer theory have been proposed since then.

The adsorption layer theory is based on thermodynamic reasoning. Crystallizing units are not immediately integrated into the crystal lattice when they arrive at the adsorption layer. However, they lose one degree of freedom and become free to migrate into the crystal lattice.

Burton et al. (23) developed the adsorption layer theory further. The Burton-Cabrera-Frank (BCF) relationship may be written
The BCF equation changes from a parabolic to a linear growth law as the supersaturation increases.

### 2.3.2 Kinematic Theories

Frank (24) developed a kinematic theory of crystal growth based on the movement of macrosteps of unequal distance apart (BCF theory considers a regular distribution of monoatomic steps). Figure 9 shows the step velocity \( u \) and the face growth rate \( v \) on the crystal lattice.

The step velocity can be calculated by the equation

\[
u = \frac{q}{n'}
\]  (24)

The face growth rate can be calculated by the equation

\[
v = h q = h n' u
\]  (25)

If the angle, or the slope, \( \theta \) increases, the face growth velocity increases, approaches a flat maximum and then decreases to zero. The shape of this face growth velocity curve, which is affected by the presence of impurities, is an important characteristic of the growth process.
2.3.3 Diffusion-Reaction Theories

Diffusion alone cannot explain the crystal growth mechanism. Berthoud (25) and Valeton (26), therefore, suggested that there are two sequential processes in crystallization; a diffusion process, whereby solute molecules are transported from the bulk of the fluid phase to the solid surface, followed by a first-order 'reaction' when the solute molecules arrange themselves into the crystal lattice. The overall growth rate can now be expressed as follows

\[ G = K_c \left( c - c^* \right)^\gamma = k_r \left( \Delta c - \frac{G}{k_d} \right)^\gamma \]  \hspace{1cm} (26)

Equation 26 is the most frequently used equation for crystal growth kinetics. Typically, overall growth rate order \( g \) is in the range 1 to 2 for many inorganic salts crystallized from aqueous solution. According to Tung et al. (27), also many pharmaceutical compounds exhibit simple first-order growth with no complication. However, there are some exceptions, and some of these come without explanation.

It has also been noted that Equation 26 is valid only in a narrow range of concentration. According to Kim and Myerson (28) the thermodynamically exact overall growth rate can be written as

\[ G = k_d \left( \frac{\mu - \mu^*}{RT} \right)^\gamma = k_r \left( \Delta c - \frac{G}{k_d} \right)^\gamma \] \hspace{1cm} (27)

or

\[ G = k_d \nu \ln \left( \frac{a_x}{a_{x_0}} \right) = k_r \nu \ln \left( \frac{a_x}{a_{x_0}} \right)^\gamma \] \hspace{1cm} (28)

In Paper III, Equation 28 was developed further to the form

\[ G = k_d \left( \nu \ln \left( \frac{a_x}{a_{x_0}} \right) - \frac{G}{k_d} \right)^\gamma = k_r \left( \sigma - \frac{G}{k_d} \right)^\gamma \] \hspace{1cm} (29)
2.3.4 Birth and Spread Models

Birth and spread (B+S) model are known also by other names such as nuclei-on-nuclei (NON) or polynuclear growth. These models are based on crystal surface (two-dimensional) nucleation followed by the spread of monolayers. The B+S model is the only growth model that allows a growth order, $g$, greater than 2. The face growth velocity can be calculated by the equation

$$v = A_i \sigma^{\gamma/2} \exp\left(\frac{A_i}{\sigma}\right)$$

(30)

2.3.5 Crystal Growth Rate in MSMPR

In the case of steady-state MSMPR, the crystal growth rate can be estimated from the single CSD of the product crystals. Probably the simplest method is to calculate the slope of population density versus crystal size on a normal-log scale because the population balance, as presented by Randolph and Larson (4), can be expressed as

$$n = n_0 \exp\left(-\frac{L}{G\tau}\right)$$

(31)

However, the usage of MSMPR theory is rather limited due to the assumptions underlining the theory. For example, calculation of population density is more complicated in the case of size-dependent crystal growth. Mydlarz and Jones (29) presented the following three parameter equation

$$n = n_0 \exp\left(a' L \left(\frac{\exp\left[a'(L + c')\right]}{\exp(a'c') - 1}\right)^{-\frac{L_0}{a'^{\gamma_0}}\tau}\right)$$

(32)

Parameters of Equation 32 can be solved by fitting measured population distributions to the equation. Furthermore, crystal growth rate can be calculated as a function of crystal size from the equation
\[ G(L) = G_{eq} \left[ 1 - \exp \left[ -a'(L + c') \right] \right] \]  

(33)

### 2.3.6 Case Studies: Crystal Growth

A good method to study crystal growth in practice is the use of single crystal or fluidized bed experiments. Single crystal growth was studied in the author’s assoc. paper iii. The growth of different crystal faces of magnesium sulphate heptahydrate crystals in the presence of sodium and manganese was experimentally studied and compared to growth rates found in literature. Sodium ion concentration was kept constant, i.e. the concentration ratio of sodium \( c_{Na}/c_{Mg} \) in the mother liquor was fixed at 36 weight percent. The effect of manganese on the growth rate was studied with three manganese concentrations. The concentration ratios of manganese were 0.0, 1.0 and 2.0 weight percent. The experiments were carried out at three different supersaturation levels, with three different flow velocities, and with two different crystal orientations. The growth rate both in the length and width direction of the needle-like crystals was obtained from image analysis.

Results similar to those observed by König et al. (30) with fluidized bed experiments were found in the single crystal experiments, although at a smaller supersaturation range. Figure 10 shows growth rates observed with the single crystal experiments. The results of König et al. (30) have been included in the figure. The estimated kinetic order, \( g \), from single crystal measurements was 0.8-1. The number of points (3) in the estimation was too low and the supersaturation range rather narrow for completely accurate results. Nevertheless, the magnitude of \( g \) is 1, as expected. Tai (31) showed a kinetic order 1-2 for magnesium sulphate heptahydrate with different impurities.
Figure 10. Mean linear crystal growth rate in the direction of the width (left) and length (right) of the crystal as a function of the driving force at three different initial supersaturation levels (fluidized bed measurement by König et al. (30)). Mn0ppc and Mn0ppcsw are mean linear crystal growth rates of single crystal measurements with no manganese in the mother liquor as measured in the present work. The flow velocity of mother liquor was $2 \times 10^{-2}$ m/s. Mn0ppc has crystal orientation parallel with the flow and Mn0ppcsw has crystal orientation perpendicular to the flow.

The significant advantages of single crystal growth rate measurement are the absence of crystal collisions and accurate control of fluid flow and supersaturation. However, in some cases the crystal growth rate has large deviations and statistically more valid methods, such as fluidized bed experiments, are needed. On the other hand, hydrodynamics starts to play a role in the fluidized bed (partially blocked flow, settling of crystals, etc.) and therefore, the size and number of crystals are rather limited. Hydrodynamics has an effect also on kinetics but it can be considered as minor.

The second case study was done in a MSMPR crystallizer. The size-dependent growth rate of potassium sulphate was experimentally determined in Paper I. Median growth rate $G_m$ and parameters $a^\prime$ and $c^\prime$ were estimated by fitting population density distribution to Equation 32. Then, the size-dependent crystal growth rate can be calculated from Equation 33.

The size-dependent crystal growth rate of potassium sulphate estimated in Paper I is shown in Figure 11.
Figure 11. Size-dependent crystal growth rate of potassium sulphate.

The size-dependent growth could be explained by three mechanisms:

- all crystals have the same time-averaged growth rate, but individual crystal growth rates fluctuate during growth periods
- crystals are born with a characteristic distribution of the growth rate, but individual crystals retain a constant growth rate throughout their residence in the crystallizer
- some crystals never grow or some of the nuclei are dissolved when the nuclei are created by secondary nucleation.

From the experimental research it is difficult to say which of the three mechanisms is the dominant mechanism in this system. The mechanism that the growth rate increases linearly with size for small crystal size might be because the secondary nucleation is dependent on the crystal size. The secondary nuclei are distributed within the small crystal size range and the number of nuclei created by collisions increases when the particle size is increasing because smaller nuclei are partially dissolving. When the crystal size reaches a certain size, say 10 µm, the effect of size-dependent growth will be greater and thus the growth rate increase becomes faster with crystal size.

As a third case study, the crystal growth rate was estimated by dynamic measurement of the crystal size distribution in batch crystallization. The estimation is a rather simple task. Undersize cumulative distribution is commonly used to follow $\Delta L$ in a time gap between the two distributions. However, if dynamic changes in
concentration are involved, as in batch crystallization or in the start-up of continuous crystallization, the supersaturation should be measured to establish the dependence of the growth rate on supersaturation. For example, in Paper VI, dynamic supersaturation data were available and therefore the overall crystal growth rate parameters in Equation 34 could be solved for α- and β-polymorph crystals of L-glutamic acid in the semibatch crystallization. As an example, the supersaturation level during semibatch crystallization of β-polymorph L-glutamic acid with controlled 0.7 M initial supersaturation is shown in Figure 12 (left-hand side). The supersaturation decreases during the batch crystallization due to the control strategy utilized (linear decrease as a function of added mass of sulphuric acid). The measured supersaturation (continuous line) was divided into steps by averaging (dashed line). The average growth of the crystals was assumed to be proportional to the movement of the mode of the volume based CSD between two samples taken at different times (right-hand side). The parameters $K_G$ and $g$ were solved by minimizing the square of the difference between measured $\Delta L$ and calculated $\Sigma \Delta L_i$. The change of size in each step can be calculated from the equation

$$\Delta L_i = K_G \left( \Delta c_i \right)^g \Delta t_i$$  \hspace{1cm} (34)$$

The $K_G$ values obtained were 6.0 and 660 $\mu m/(min \cdot M^g)$, and the kinetic order $g$ values were 2.6 and 9.0 for the β- and α-polymorphs, respectively. As can be seen from parameter values, the growth kinetics is much faster for the α-polymorph than the β-polymorph, mainly because of the more regular and solid shape of α-polymorph crystals. The high values of the kinetic order need, however, to be explained. Tung et al. (27) showed higher-order kinetics (2.5) with a compound solubilized by acid; the acid reaction may have effect on L-glutamic acid growth kinetics as well. A more critical point may be that the growth kinetics was determined from CSD and the effect of agglomeration was not excluded.
Figure 12. Supersaturation levels during crystal sampling for β-polymorph crystallization of L-glutamic acid.

From a hydrodynamic point of view, inhomogeneous mixing should be taken into consideration. Local differences in supersaturation and suspension density may affect the growth rate. However, measured flow patterns in the bench-scale crystallizer showed reasonably uniform flow and no large dead-zones (further details are presented in chapter 6.3.1) and therefore errors caused by hydrodynamic differences can be considered as minor.

2.4 Induction Time

A certain lapse of time is necessary for crystallization to begin on an observable level. This is called the induction time. According to Crystallization Technology Handbook (1), induction time depends on the kinetics of the different processes involved:

1. the hydrodynamics of the crystallizer (mixing),
2. the chemical reaction kinetics,
3. the nucleation rate, which leads to the formation of crystals,
4. the growth rate of the particles formed, which leads to the visibility of crystals.

The induction time can be divided into two parts in the case of rapid mixing and reaction rates

\[ t_{\text{ind}} = t_N + t_G \]  

(35)
According to Söhnel and Garside (6) three different cases of Equation 35 can be considered: (a) \( t_N >> t_G \), (b) \( t_N << t_G \) and (c) \( t_N \approx t_G \). In the case of (a) \( t_N >> t_G \), the induction time is great enough to be measurable, and it can be calculated by the equation

\[
T_{ind} = t_N = \frac{1}{B_0}
\]  

(36)

It should be noted that 1 has the dimensions of the reciprocal volume corresponding to the volume units used to describe \( B_0 \).

In the case of (b) \( t_N << t_G \) the induction time is generally too short to be measurable and will depend strongly on mixing intensity. The induction time will not contain any information about nucleation, and it can be calculated by the equation

\[
T_{ind} = \frac{r_{in}}{K_G} \left( c - c^* \right)^{\gamma}
\]  

(37)

An identical expression for the induction time, originally developed by Nielsen (32), can be defined by the intersection with the time axis of the plot of the cube root of the extent of the reaction, \( \alpha^{1/3} \), against the reaction time. Figure 13 is an example plot for \( \text{CaSO}_4 \times 2\text{H}_2\text{O} \) presented by Söhnel and Garside (6).

In the final case, (c) \( t_N \approx t_G \), the mechanisms of both nucleation and growth have to be taken into account in the model and an approximation of the induction time can be calculated by the equation

\[
T_{ind} = \left[ \frac{15}{32\sqrt{2} \pi D_{c,0}^{15/7} (e_0 V_m)^{5/7}} B_{e,0} \right]^{7/5}
\]  

(38)
2.4.1 Induction Time and Reaction Kinetics

If the reaction kinetics is limiting the overall crystal formation in a reactive crystallization process simultaneous parameter estimation of the reaction kinetics and induction time may be done. According to Levenspiel (33), a simple reaction rate equation with a coefficient obeying the Arrhenius law can be used for the reaction of compounds A and B

\[
 r_i = k_{ni} c_i \left[ -r_i \left( \frac{1}{RT} \right) \right]^{\alpha_i} c_j^\alpha_{ij} c_k^\alpha_{ik} \quad (39)
\]

An empirical equation for induction time considering concentration and temperature can be written in the form

\[
 t_{ind} = k_{ind}\left( \frac{c_i}{c_0} \right)^{\delta_i} \left( \frac{T}{T_0} \right)^{\gamma_i} \quad (40)
\]
2.4.2 Case Study: Induction Time

The author studied the induction time in Assoc. Paper ii. The paper considered simultaneous parameter estimation for the reaction kinetics and the induction time of reactive crystallization of calcium sulphate. The experimental data were measured for different temperatures (within the range 20\textdegree C - 50\textdegree C), and at different reagent concentrations (within the range 0.1 M - 0.5 M). A 10 litre stirred tank with a shaped bottom, 6-flat-blade turbine and baffles was used as the crystallizer. Calcium sulphate was precipitated by the reaction between aqueous calcium nitrate, Ca(NO\textsubscript{3})\textsubscript{2}, and sodium sulphate, Na\textsubscript{2}SO\textsubscript{4}. The equimolar and equivolume reagents were poured in the crystallizer and the suspension density was measured as a function of time by filtering and drying a sample of 25 ml solution from the crystallizer. The parameters of the reaction rate equation (Equation 39) were \( k_m = 0.68 \text{ m}^{4.83}\text{mol}^{-1.61}\text{s}^{-1} \), \( e = 96 \text{kJ/mol} \), \( a'' = 1.3 \) and \( b'' = 1.2 \). Parameters in the empirical induction time equation (Equation 40) were \( k_{\text{ind}} = 3000 \text{s} \), \( d'' = 10.0 \) and \( f'' = 2.5 \). The measured data and simulated suspension densities with the parameters shown above are presented in Figure 14. The results showed that the model agrees satisfactorily with the measured data but that there are big differences in the accuracy of fitting in the different experimental sets. It was found that most of the errors come from the sampling procedures since there were some inaccuracies in total mass balances. It was assumed that gypsum precipitates as a dihydrate. Other forms of calcium sulphate crystals may, however, be present. Moreover, the solubility of calcium sulphate is a function of the concentration of sodium nitrate. Yet, the effect of solubility is minor because of the sparingly soluble gypsum. However, nucleation and crystal growth kinetics are assumed to be much faster than reaction kinetics, which may not be the case. Therefore, the shown reaction kinetics can be considered as overall crystal formation kinetics. Nevertheless, induction time is shown to be highly dependent on initial concentration, i.e. supersaturation, and moderately dependent on temperature.
Figure 14. Suspension density of calcium sulphate in batchwise reactive crystallization experiments. The calculated suspension density from the reaction equation (supersaturation is neglected) is given as a continuous line and measured data points in diamonds.

The measured results are useful in designing start-up sequences for industrial batch or continuous reactive crystallization systems, such as the phosphoric acid process, where gypsum is precipitated as a side product.

The hydrodynamic arrangement in the experimental system was suitable due to the long induction time compared to the mixing times. Only with the highest temperature and concentration combination may the induction time be shorter than the mixing times.
2.5 Effect of Impurities on Crystallization

An impurity can be any substance other than the material being crystallized. Therefore, even the solvent from which the crystals are grown can be considered to be an impurity.

The presence of impurities or additives in a crystallization system can have a radical effect on crystal growth, nucleation, macrostep formation, agglomeration, and the uptake of foreign ions in the crystal structure. Different impurity and crystallizing chemical pairs have different effects on crystal growth; some impurities can suppress growth entirely, some may enhance growth, and some may exert a highly selective effect (acting only on certain crystallographic faces). The specific impurity may affect different crystallization chemicals differently. Impurities and additives can be divided into different groups based on their mechanism; the groups consist of metal ions, tailor-made additives, and multifunctional additives. The influence of the concentration of impurities differs very much, from very low concentrations (less than ppm) to majority concentrations, and often a reversed effect is encountered at higher concentrations. For example, the growth rate of lead nitrate increases with increase of the concentration of methylene blue up to 5 mg/L and decreases when the methylene blue concentration increases to higher concentrations.

2.5.1 Ionic Interaction

Ionic interactions in aqueous systems are of considerable importance in crystallization. According to Mullin and Garside (34), it is well known that commonly occurring ionic impurities such as Cr$^{3+}$, Al$^{3+}$ and Fe$^{3+}$ have a pronounced effect on the growth of simple inorganic salts from aqueous solution. Handbook of Industrial Crystallization (3) has listed the most common additives affecting the growth of crystals, and they are shown in Table III.
### TABLE III. Additives affecting the growth of crystals as presented in Handbook of Industrial Crystallization (3).

<table>
<thead>
<tr>
<th>Crystallizing Material</th>
<th>Additive</th>
</tr>
</thead>
<tbody>
<tr>
<td>AgBr</td>
<td>$\Gamma$, gelatin, $\text{Pb}^{2+}$, $\text{Cd}^{2+}$, urea, $\text{NH}_3$, $\text{KBr}$, dyes</td>
</tr>
<tr>
<td>AgCl</td>
<td>$\text{NH}_3$, pyridine, $\text{HgCl}_2$, dyes</td>
</tr>
<tr>
<td>AlK(SO$_4$)$_2$</td>
<td>$\text{Na}_2\text{CO}_3$, $\text{Na}_2\text{HPO}_4$, polyvinyl alcohol, $\text{HCl}$, dyes, saccharides</td>
</tr>
<tr>
<td>BaCl$_2$</td>
<td>$\text{Mn}^{2+}$, $\text{Co}^{2+}$, $\text{Ni}^{2+}$, $\text{Cu}^{2+}$, $\text{Na}$</td>
</tr>
<tr>
<td>BaCO$_3$</td>
<td>EDTA</td>
</tr>
<tr>
<td>Ba(NO$_3$)$_2$</td>
<td>Quinine, $\text{K MnO}_4$, $\text{K Fe(CN)}_6$</td>
</tr>
<tr>
<td>CaCO$_3$</td>
<td>$\text{Pb}^{2+}$, $\text{Mn}^{2+}$, $\text{Mg}^{2+}$, $\text{Co}^{2+}$, $\text{BaCl}_2$, $\text{NO}_3^-$, $\text{Sr}^{2+}$, $\text{SO}_4^{2-}$, $\text{Fe}^{2+}$, $\text{Ni}^{2+}$, $\text{Cd}^{2+}$, $\text{PO}_4^{3-}$, citrate, phosphate, alkyl aryl sulphonates</td>
</tr>
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<td>CaSO$_4$</td>
<td>$\text{H}_3\text{PO}_4$, $\text{Al}^{3+}$, $\text{Cr}^{3+}$, $\text{SO}_4^{2-}$ gel, $\text{Mn}^{2+}$</td>
</tr>
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<td>$\text{H}_2\text{SO}_4$</td>
</tr>
<tr>
<td>H$_2$BO$_3$</td>
<td>$\text{K MnO}_4$, gelatine, casein</td>
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<td>$\text{Pb}^{2+}$, fatty acids, dyes, phenol, formic, acetic, ethanoic, propionic acids</td>
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<tr>
<td>KBrO$_3$</td>
<td>$\text{NaNO}_3$, $\text{Pb}^{2+}$</td>
</tr>
<tr>
<td>KCN</td>
<td>$\text{K Fe(CN)}_6$</td>
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<tr>
<td>KCl</td>
<td>$\text{Dyes}$, $\text{HCl}$, $\text{Pb}^{2+}$, bromobenzene, phenol, $\text{MnSO}_4$, $\text{Fe}^{3+}$, $\text{Mn}^{2+}$, urea, $\text{Fe(CN)}_6^{3-}$</td>
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<td>$\text{Rb}^{+}$, $\text{Ti}$, $\text{Sn}$, $\text{Bi}$, $\text{Fe}$</td>
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<tr>
<td>KNO$_2$</td>
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</tr>
<tr>
<td>LiCl</td>
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<td>Borax</td>
</tr>
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<td>NH$_4$Br</td>
<td>$\text{Urea}$, $\text{CrO}_4^{2-}$, $\text{Fe}^{2+}$, $\text{Cu}^{2+}$, $\text{Ni}^{2+}$, $\text{Co}^{2+}$, $\text{Fe}^{2+}$, $\text{Zn}^{2+}$, $\text{Mn}^{2+}$, $\text{Cd}^{2+}$</td>
</tr>
<tr>
<td>NH$_4$ClO$_3$</td>
<td>$\text{Cd}^{2+}$, $\text{Ni}^{2+}$</td>
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<td>$\text{CuCl}_2$, $\text{CuSO}_4$, dyes, oleic acid</td>
</tr>
<tr>
<td>NaBr</td>
<td>$\text{Na}_4\text{Fe(CN)}_6$, $\text{CdBr}_2$, $\text{PbBr}_2$</td>
</tr>
<tr>
<td>NaCl</td>
<td>$\text{Na}_2\text{SO}_4$</td>
</tr>
<tr>
<td>NaCN</td>
<td>$\text{Fe}^{2+}$</td>
</tr>
<tr>
<td>NaClO$_2$</td>
<td>Polyvinyl alcohol, $\text{Fe(CN)}_6^{3-}$, $\text{Cd}^{2+}$, $\text{Pb}^{2+}$, $\text{Mn}^{2+}$, $\text{Mg}^{2+}$, $\text{Hg}^{2+}$, $\text{Fe(CN)}_6^{4-}$, $\text{urea}$, formamide, pyridine, $\text{Bi}^{3+}$, $\text{Sn}^{2+}$, $\text{Ti}^{4+}$, $\text{Fe}^{3+}$, $\text{CaCl}_2$, $\text{Cr}^{3+}$, $\text{Ba}^{2+}$, $\text{Zn}^{2+}$, acetics, $\text{CrCl}_3$, bromobenzene, phenol, aniline</td>
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<tr>
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<td>$\text{Na}_2\text{SO}_4$, $\text{Na}_2\text{SiO}_3$, $\text{SiO}_2$, $\text{Br}_2\text{O}_3$, $\text{Cr}_2\text{O}_7$, $\text{NaClO}_4$, dyes, $\text{Cu}^{2+}$</td>
</tr>
<tr>
<td>NaNO$_2$</td>
<td>$\text{Pb(NO}_3)_2$, $\text{Hg(NO}_3)_2$, $\text{C}_2$</td>
</tr>
<tr>
<td>PbCl$_2$</td>
<td>Dextrin, $\text{Mn}^{2+}$, $\text{Co}^{2+}$, $\text{Ni}^{2+}$, $\text{Cu}^{2+}$, $\text{Na}^{+}$</td>
</tr>
<tr>
<td>CH$_3$ON$_2$(urea)</td>
<td>Biuret, formamide, $\text{(NH}_3\text{H})_2\text{SO}_4$, $\text{NH}_4\text{Br}$, $\text{NH}_4\text{Cl}$, cyanuric acid</td>
</tr>
<tr>
<td>C$_3$H$_5$O$_3$N$_2$(uric acid)</td>
<td>Dyes</td>
</tr>
<tr>
<td>C$_2$H$_2$O$_2$(acetic acid)</td>
<td>Dyes</td>
</tr>
<tr>
<td>C$_3$H$_7$O$_3$(Na(sodium glutamate))</td>
<td>Lysine, $\text{CaO}$</td>
</tr>
<tr>
<td>C$_7$H$_6$O$_2$(ascorbic acid)</td>
<td>Octanoic acid, undeconoic acid, sodium dodecylbenzene-sulphonate, trimethylectadecylammonium chloride</td>
</tr>
<tr>
<td>C$_2$H$_2$O$_2$(adipic acid)</td>
<td>L-glutamic acid</td>
</tr>
<tr>
<td>C$_4$H$_7$O$_3$(potassium hydrogen phosphate)</td>
<td>CR$_3^-$, benzoic acid</td>
</tr>
<tr>
<td>C$_3$H$_5$O$_2$(saccharose)</td>
<td>Raffinose, polysaccharides, KCl, CaCl$_2$, MnSO$_4$, NH$_4$NO$_3$, CdI$_2$, glucose, betaine</td>
</tr>
<tr>
<td>C$<em>8$H$</em>{17}$N$_2$(n-parafin)</td>
<td>Diocadecylamine</td>
</tr>
<tr>
<td>Benzamide</td>
<td>Benzoic acid, o-toluamide, p-toluamide</td>
</tr>
<tr>
<td>Fructose</td>
<td>Difructose dihydroxide, glucose</td>
</tr>
<tr>
<td>L-asparginine monohydrate</td>
<td>L-glutamic acid</td>
</tr>
<tr>
<td>Sucrose</td>
<td>Raffinose, stachyose, KCl, NaBr</td>
</tr>
</tbody>
</table>
The additives in Table III are mostly metal ions, which can be purposely added but
more often are unavoidably present in the crystallizing solution. According to van
Rosmalen et al. (35), even those metal ions which only have a slight influence on
crystal growth tend to be incorporated into the host crystal. The finding is very
important in industrial practice in the uptake of divalent heavy metal ions in mineral
precipitates, e.g. for the purification of waste-water streams. The uptake can proceed
by coprecipitation of various compounds, by interstitial incorporation or by
isomorphous substitution. The uptake of foreign ions is determined by the
thermodynamics of the system, i.e. by equilibria, and the kinetics of the growth
process.

2.5.2 Tailor-Made Additives

An important class of additives (or impurities) are so called, “tailor-made” additives,
which are designed to interact in very specific ways with selected faces of crystalline
materials. These additives are designed to contain some chemical groups or moieties
that mimic the solute molecule and are thus readily adsorbed at growth sites on the
crystal surface.

Organic compounds, although more complex, lend themselves more easily for the
purpose of designing structurally-specific additives than simpler ionic compounds.
Only a few examples of tailor-made additives are known for inorganic and mineral
salts.

2.5.3 Multifunctional Additives

For ionic compounds, so called multifunctional additives are often applied to achieve
the desired effects. These kinds of additives are, for example, phosphoric acids,
polycarboxylic acids, polysulfonic acids, and many low and high molecular weight
copolymers with various acidic groups. Multifunctional additives are capable of
forming bonds with cationic species at crystal-liquid interfaces. An advantage of these
types of additives is their performance at concentrations as low as 10 to 50 ppm, the
exact dosage depending on process conditions like pH.
2.5.4 Habit Modification

Crystal habit is often used quite loosely to describe the shape and aspect ratio of crystals. From a process development and troubleshooting standpoint, the principal impact of crystal habit is on the bulk physical properties of the product. For example, crystal habit plays a part (often along with size distribution) in defining the ease and effectiveness of solid/liquid separation, bulk density, powder flow characteristics, breakage, and dustiness.

The overall shape of a growing crystal is determined by the relative rates of growth of its various faces; the slower the growth rate, the larger the face. In general, the growth rate of a surface will be controlled by a combination of structurally-related factors, such as intermolecular bonds and dislocations, and external factors, such as supersaturation, temperature, solvent, and impurity concentration. The individual crystal faces each have their own growth-rate dependence on temperature and supersaturation, so changing the temperature and supersaturation history can affect crystal habit. The extent of changes that can be induced in this way can be investigated by changing experimental conditions. As a general rule, crystals become more extreme in habit as supersaturation levels increase. Impurities operate by binding to growth sites, and thereby reducing the crystal growth rate. Since different crystal faces can have different characteristics due to the orientational order imposed by the crystal lattice, specific impurities can bind effectively to some faces, but not others. These face-specific interactions result in modification of the crystal habit, and some impurities can have significant effects even at trace levels. Comparison of crystallization from pure and impure solutions may indicate whether or not significant habit modification is caused by impurities in the test solutions.

Certain crystal habits are disliked in commercial crystals because they give the crystalline mass a poor appearance; others make the product prone to caking, induce poor flow characteristics, or give rise to difficulties in the handling or packaging of the material. A granular or prismatic crystal habit is usually desired, but there are also specific occasions when other morphologies, such as plates or needles, may be desired. Mullin (2) has listed some examples of habit modification, shown in Table IV.
The trace presence of foreign cations can exert an influence on the crystal habit of inorganic salts. Some act by simple substitution in the lattice, e.g. \( \text{Cd}^{2+} \) for \( \text{Ca}^{2+} \) in calcium salts or \( \text{Ca}^{2+} \) for \( \text{Mg}^{2+} \) in magnesium salts, as a result of similar ionic radii and charge. Trivalent cations, particularly \( \text{Cr}^{3+} \) and \( \text{Fe}^{3+} \), have a powerful effect on the morphology of salts such as ammonium and potassium dihydrogenphosphates. Complex cations, like \( \text{Fe(CN)}_6^{4-} \), have a remarkable influence on \( \text{NaCl} \), producing large, hard dendrites instead of small cubic crystals at concentrations of less than 1 ppm.

There are literally thousands of reports in the scientific literature concerning the effects of impurities on the growth of specific crystals. Comprehensive reviews of the influence of additives in the control of crystal morphology have been presented by...
van Rosmalen et al. (35), Kern (36), Boistelle (37), Davey (38), Botsaris (39), Nancollas and Zawacki (40) and Davey et al. (41).

2.5.5 Predicting the Influence of Additives

The first generally applicable quantitative measure of relative face growth rates via calculation of $E_{att}$, the attachment energy, was provided by the Hartman-Perdok technique. Calculations were simplified by reducing crystal structures to chains of strong bonds and identifying the slowest growing faces as those lying parallel to at least two bond chains. The attachment energy is then the energy released when a new layer of thickness $d_{hkl}$ is added to the crystal face. The lower the attachment energy the slower the rate at which the face is assumed to grow. According to Söhnel and Garside (6) the morphology of crystals can be calculated by attachment energy using various approximations:

* Donnay Harker. This approach makes a very simple assumption, namely that the binding energy between crystal planes is inversely proportional to the interplanar spacing. Thus, the relative growth rate of a series of faces can be assessed purely based on their structures.

* Hartman and Perdok. By examining crystal structures and identifying chains of strong bonds within them it was possible to make calculations more specific by use of available summation techniques and assuming that ions were point charges.

* Specific force fields. Initially Bennema but more recently Docherty and Roberts have attempted to make the calculations more precise by using available potential functions to describe the interactions between molecules and ions. The van der Waals and electrostatic contributions to the overall interaction energies of adjacent molecules are calculated separately by summation of the interaction $E_{ij}$ between all the individual non-bonded atoms that constitute molecules.

To find out the effect of additives or impurities, the above approximations should be extended to include the influence of additives on attachment energies and hence morphology. To do this, additive molecules are substituted for substrate molecules in the growth slice, taking each lattice site in turn. This gives new values for the slice $E_{at}$ and attachment energies $E_{att}$. The binding energy at a surface site can be calculated by the equation
\[ E_b = E_{st} + E_{at} \]  \hspace{1cm} (41)

It is now possible to calculate the change in binding energy due to the inclusion of an additive (or an impurity) in the slice. The lower the change, \( \Delta E_b \), the higher the probability that it is influenced by an additive. Without crystallographic data, these calculations can only be carried out with any certainty for tailor-made additives that are slightly modified substrate molecules. This is because the tailor-made additive molecule is assumed to have identical conformation to the substrate. The modified part of the molecule of the additive may be fixed if the molecule is rigid but may adopt a variety of conformations if, for example, free rotation about one or more bonds is possible. Docherty (42) has extended this approach to include calculations of attachment energy when a tailor-made impurity is already in a surface site.

### 2.5.6 Case studies: Influence of Impurities

Assoc. Papers iii and iv studied ionic interaction of sodium and manganese in crystallization of magnesium sulphate heptahydrate. The crystal growth rate was observed to increase in single crystal experiments when manganese concentration was increased in the range of 0-2 w-% of Mn/Mg; substantial increase was detected when manganese concentration increased from 1 to 2 w-%. As an example, the linear growth rate of magnesium sulphate heptahydrate with a flow rate 2 m/s is shown in Figure 15.

Although the concentration of sodium was constant (36 w-% of Na/Mg), no significant difference in growth rate was detected when compared to growth rates for pure magnesium sulphate found from literature (see Figure 10). Sodium did not interact with magnesium sulphate crystals and could be removed from the crystals by washing. At the same time, manganese could be only partially removed by washing, which means that a part of the manganese is substituting magnesium in the crystal lattice. An example of the effect of washing is shown in Figure 16. From the hydrodynamic point of view, not much can be done to prevent such interacting ions from acting as an impurity. The amount of non-interacting ions can be decreased by
proper design of the hydrodynamics in the crystallizer, for example, by incorporation of some backwash of product flow with low-content or no-impurity solution.

![Flow velocity 2 cm/s](image)

**Figure 15.** Mean linear crystal growth rate as a function of relative supersaturation, with three different manganese concentrations and with different crystal orientations. Abbreviations: Mn0, Mn1 and Mn2, which correspond to 0 w%, 1 w% and 2 w% of manganese in the mother liquor. The white symbols correspond to the sideway crystal orientation and the black symbols correspond to the parallel crystal orientation.

![Fraction Dissolved, -](image)

**Figure 16.** Measured sodium concentrations in crystal washing. Magnesium sulphate crystals were produced from impure mother liquor; constant sodium concentration 36 w-% of Na/Mg and different manganese concentrations.
2.6 Polymorphism in Crystallization

Some molecules are able to produce more than one crystal structure. One of the most important groups of such solid structures are called polymorphs. Each polymorph has its own unique combination of mechanical, thermal and physical properties. It is, therefore, crucial to be able to recognize and control desired polymorphs. In addition to polymorphs, Davey and Garside (43) point out that materials may also adopt other different solid forms such as solvate compounds, amorphous solids, and mesophases.

2.6.1 Polymorphism in Nucleation

The nucleation step is most critical for the production of different polymorphs due to the fact that a single crystal can grow only as one polymorph. According to Brittain (44), transformation to another polymorph involves dissolution of the polymorph and recrystallization. However, since nucleation is highly dependent on supersaturation, hydrodynamics play a very important role in polymorph control. Local supersaturation differences may lead to the production of unwanted polymorphs due to nucleation of unwanted polymorphs locally.

Primary nucleation depends on the solubility curves of polymorphs. If one polymorph has lower solubility than the other polymorph(s) throughout the entire solubility range, the polymorphs are called monotropic polymorphs. In this case, the polymorph with lower solubility is always the stable polymorph, and the other polymorph(s) is (are) unstable due to the lower free energy of the polymorph with lower solubility. However, if the solubility curves intersect at any point in the solubility range, the polymorphs are called enantiotropic polymorphs. In this case, the stable polymorph depends on temperature.

2.6.2 Case Study: Polymorphism

Polymorphism of L-glutamic acid was studied in Papers II, IV-VI and Assoc. Paper xiii. Two different polymorphs are known for L-glutamic acid, where the $\beta$-polymorph is stable and the $\alpha$-polymorph is metastable. In the author's experiments,
the habit of the β–polymorph crystals was a flake whereas the α–polymorph crystals were prismatic, as shown in Figure 17, although Encyclopedia of Chemical Technology (45) states that granular and needle habits are also known for α– and β–polymorph crystals, respectively. Raman spectroscopy was able to analyze the polymorphs since the torsion angle in the main carbon chain is significantly different in α– and β–polymorph crystals, as presented by Hirayama et al. (46), Lehmann and Nunes (47), and Ono et al. (48). A simple linear relation of the mass fraction of α–polymorph crystals with identified α– and β–polymorph spectra peaks (α–peak versus sum of α– and β–peaks) in the Raman spectroscope was used in Paper II. A more accurate polynomial relation was developed in Paper IV and used further in Papers V-VI.

Figure 17. Habit of α-polymorph crystals (> 93% purity) on the left and β-polymorph crystals (> 99% purity) on the right.

A collection of results from Papers IV-VI is shown in Figure 18. The effect of supersaturation at the nucleation point with different nucleation methods can be clearly seen. The stable β–polymorph is dominant with low supersaturation set values. High set values produce a mixture of polymorphs, and a high set value combined with controlled nucleation (seeding, ultrasound) produces mainly the α–polymorph.

Hydrodynamics has a great influence on polymorphism. Different polymorphs typically exhibit different solubilities, and hydrodynamics affect local supersaturations. The most important hydrodynamic area is the feed point of the reagent, where the nucleation takes place. Theoretically, if the nucleation of a certain polymorph can be controlled by hydrodynamic means (feed pipe/nozzle type and location, feed rate, impeller type and geometry of the crystallizer) only one
polymorph is crystallized because dissolving of one polymorph crystal and recrystallization of another is always present in polymorph transition. However, some problems appear in hydrodynamic control, especially when the scale of the crystallizer increases; dead-zones and other inhomogeneous mixing areas allow polymorph transformation, and spontaneous nucleation typically produces a mixture of polymorphs. Control of polymorphs of L-glutamic acid by different nucleation methods (spontaneous nucleation, seeding and power ultrasound initiated nucleation) was studied in Paper VI. Hydrodynamics in the crystallizer used for the experiments will be discussed later, in chapter 6.3.1.

Figure 18. Polymorph content of product crystals in semibatch crystallization of L-glutamic acid. Supersaturation was controlled with 3 different initial feedrates, mainly using feedrate 8.3 g/s (in elliptical area). Controlled nucleation (seeding and ultrasound) was used with 0.7 and 1 M set values.
3. MODELLING OF CRYSTALLIZATION

Modelling in the thesis is divided into two main parts; phenomena-based modelling of MSMPR crystallization and phenomena-based computational fluid dynamics modelling. MSMPR modelling is based on population balance and discretization, which are presented in this chapter. A new discretization method called the particle transport method (PTM) is applied to crystal growth and comparisons of different discretization methods are shown. It has to be noted that MSMPR modelling does not take into account hydrodynamics and can be applied only for small scale crystallizers. Therefore, CFD modelling is also introduced. CFD is able to take hydrodynamic effects into account but it is typically very heavy to compute due to the dense grid of the geometrical model of the crystallizer. A compartmental multiblock model is proposed for phenomena-based modelling to decrease computing due to the sparser grid needed for the geometrical model. The CFD and multiblock models are presented only briefly in this chapter because in the research the author concentrated on hydrodynamic verification of these models.

Phenomena-based modelling of MSMPR crystallization typically uses a discretized population balance due to the highly exponential decrease in the number of crystals when their size increases. The discretized population balance was originally developed by Batterham et al. (49), according to Hounslow et al. (50) and Hounslow (51).

3.1 Population Balance

Population density can be described as

\[ n = \lim_{\Delta L \to 0} \left( \frac{\Delta N_p}{\Delta L} \right) = \frac{dN_p}{dL} \]  

(42)

The population balance equation (PBE) was introduced by Hulburt and Katz (52) and developed by Randolph and Larson (4) to describe the particle size distribution in various chemical engineering problems such as crystallization, liquid-liquid/liquid-gas
dispersion, microbial cultures and polymerization. According to Randolph and Larson (4), the macroscopic population balance can be written as

\[
\frac{\partial n}{\partial t} + \nabla v_{\infty} n + \frac{nd(\log V)}{dt} = B(L) - D(L) - \sum_k \left( \frac{Q_n n_k}{V} \right) \quad (43)
\]

The internal co-ordinate properties of Equation 43 refer to those properties attached to each individual particle and, measuring quantitatively, its state independent of its position. Particle size, age, activity and energy content, and chemical composition are examples of internal co-ordinate properties. According to Randolph and Larson (4), Equation 43 can be simplified in MSMPR conditions as follows

\[
\frac{\partial n}{\partial t} + \frac{\partial (Gn)}{\partial L} + D(L) - B(L) + \frac{nd(\log V)}{dt} = \sum_k \left( \frac{Q_n n_k}{V} \right) \quad (44)
\]

According to Hounslow (51), the particle birth function due to agglomeration and nucleation can be calculated by

\[
B(L_n) = \frac{L_n^2}{2} \int_0^{L_n} K\left(\left(L_n^3 - L_m^3\right)^{\frac{1}{3}}, L_m\right) n\left(L_m^3\right) n(L_m) \frac{dL_m}{\left(L_n^3 - L_m^3\right)^{\frac{1}{3}}} \quad (45)
\]

\[
B(L_m) = B_0 \delta(L_m) \quad (46)
\]

According to Hounslow (51), the particle death function due to agglomeration can be calculated by the equation

\[
D(L_n) = n(L_n) \int_0^{L_n} K(L_n, L_m) n(L_m) dL_m \quad (47)
\]
3.2 Discretized Population Balance

According to Hounslow (51), the discretized population balance for a continuous MSMPR crystallizer at steady state can be calculated by the equation

\[
\frac{N_i - N_{i,in}}{\tau} = \left( \frac{dN_i}{dt} \right)_{\text{Batch}} = \left( \frac{dN_i}{dt} \right)_{\text{Nucleation}} + \left( \frac{dN_i}{dt} \right)_{\text{Growth}} + \left( \frac{dN_i}{dt} \right)_{\text{Agglomeration}}
\] (48)

The discretized population balance for nucleation, growth and agglomeration can now be calculated as follows

\[
\left( \frac{dN_i}{dt} \right)_{\text{Agglomeration}} = N_i \sum_{j=1}^{i+1} 2^{j-i} K(i-j,j)N_j + \frac{1}{2} K(i-1,j-1)N_{i-1}^2 - N_i \sum_{j=1}^{i+1} 2^{j-i} K(i,j)N_j - N_i \sum_{j=1}^{i+1} K(i,j)N_j
\] (49)

\[
\left( \frac{dN_i}{dt} \right)_{\text{Growth}} = \frac{2G}{(1+r)L_i} \left( \frac{r}{r^2 - 1} N_{i+1} + N_i - \frac{r}{r^2 - 1} N_{i+1} \right)
\] (50)

\[
\left( \frac{dN_i}{dt} \right)_{\text{Nucleation}} = \begin{cases} B_0 & i = 1 \\ 0 & i \neq 1 \end{cases}
\] (51)

3.3 Simplified Discretization of Agglomeration

A simplified discretization of agglomeration can be done in the following way. If the volume of a single particle is within the size range \( I = [v_0,v_n] \), then one of the size ranges can be written in normalised (maximum value 1) form

\[
v_i = 2^{(i-n_0)/\delta'}
\] (52)

The total number of crystals in the crystallizer can be calculated by
If even crystal size distribution in all size ranges is assumed, the total volume of all crystals can be calculated from the equation

\[ V_c = \sum_{i=1}^{n} s_i \left( \frac{v_{i-1} + v_i}{2} \right) = 2 \sum_{i=1}^{n} s_i v_i \]  

(54)

Coefficient \( a \) can be calculated from equation

\[ a = \frac{2^{\frac{1}{q'}} + 1}{2} \]  

(55)

If two particles of size range \( I_i \) collide, the generated particle is within the size range of \( I_{i+q'} \). If a particle of size range \( I_i \) collides with a particle of size range \( I_{i+j} \) (\( j>0 \)), the volume of the generated particle is

\[ v_i + v_{i+j} = v_{i+j} \left( 1 + 2^{\frac{1}{q'}} \right) \]  

(56)

Let the volume of the generated particle be in size range \( I_{i+m} \) and \( m \) be defined as follows

\[ v_{i+m-1} < v_i + v_{i+j} < v_{i+m} \]  

(57)

or

\[ 2^{(m-1)\frac{1}{q'}} < 1 + 2^{\frac{1}{q'}} < 2^m \]  

(58)

Now \( m \) depends only on \( j \), not on \( i \). In these size ranges, the smallest possible volume of the generated particle is
\[ v_{i-1} + v_{i+j-1} = v_{i-1} \left( 1 + 2^{\frac{j}{q}} \right) \]  

(59)

The ratio of the largest and smallest possible particle generated by collision is equal to the ratio of successive size ranges. Therefore, all particles are within the size ranges \( I_{i+m-1} \) and \( I_{i+m} \).

The fraction of the number of particles generated by collision within each size range can be calculated by a statistical volume balance. The calculated total volume \( V_c \) of the particles decreases in the collision by

\[ a(v_i + v_{i+j}) = av_i \left( 1 + 2^{\frac{j}{q}} \right) \]  

(60)

It should be noted that the coefficient \( a \) can be calculated only if the crystal size distribution is assumed to be even in all size ranges.

Let’s suppose that fraction \( \alpha' \) generates particles within the size range \( I_{i+m-1} \) and subsequently within \( I_{i+m} \). Now, the total volume \( V_c \) increases as follows

\[ a(\alpha'v_{i+m-1} + (1 - \alpha')v_{i+m}) = av_i \left( 2^{\frac{(m-1)}{q}} + (1 - \alpha')2^{\frac{m}{q}} \right) \]  

(61)

The volume \( V_c \) should be constant. Thus, the following expression may be written

\[ 1 + 2^{\frac{j}{q}} = \alpha'2^{\frac{(m-1)}{q}} + (1 - \alpha')2^{\frac{m}{q}} \]  

(62)

From which \( \alpha' \) can be solved.
3.4 Discretization of Crystal Growth

Crystals grow from one size range to another. The overall rate in size range $i$ can be defined as

$$\frac{ds_i}{dt} = \frac{ds_{in}}{dt} - \frac{ds_{out}}{dt} = \frac{G}{(r_L - 1)L_i} (r_L s_{i-1} - s_i)$$  \hspace{1cm} (63)

Randolph and Larson (4) have defined the $j^{th}$ moment as

$$m_j = \int_0^\infty L^j n(L) \, dL$$  \hspace{1cm} (64)

This must be rewritten in a discrete form

$$m_j = \sum_{i} \overline{L_i^j} s_i$$  \hspace{1cm} (65)

If crystal size distribution $n$ is divided in intervals, the $j^{th}$ moment can be calculated by the equation

$$m_j = \sum_{i}^{L_i \rightarrow L_i^j} L^j n \, dL = \sum_{i}^{L_i \rightarrow L_i^j} L^j \frac{s_i}{L_{i+1} - L_i} \, dL$$

$$= \sum_{i} \frac{s_i}{j + 1} \left( \frac{r_L^{j+1} - 1}{r_L - 1} \right) L_i^j$$  \hspace{1cm} (66)

Now equating Equation 65 with equation 66 leads to the relationship between $L_i$ and $\overline{L_i^j}$

$$\overline{L_i^j} = \frac{1}{j + 1} \left( \frac{r_L^{j+1} - 1}{r_L - 1} \right) L_i^j$$  \hspace{1cm} (67)

If a value of $r_L = \sqrt{2}$ is used, Hounslow et al. (50) suggest that
\[ L_i^j = (1.130L_j)^i = \left( \frac{1 + r_L}{2} L_i \right)^i = \left( \frac{L_i + L_j}{2} \right)^i = (L_i^j)^i \] (68)

According to Hounslow et al. (50), an alternative expression of Equation 63 can be written

\[ \frac{ds_i}{dt} = \frac{G}{L_i} \left( a' s_{i-1} + b' s_i + c' s_{i+1} \right) \] (69)

These constants can be predicted through the 0th, 1st and 2nd moments and can be written as follows

\[ a' = \frac{2r_L}{(1 + r_L)(r_L^2 - 1)} \] (70)

\[ b' = \frac{2}{1 + r_L} \] (71)

\[ c' = \frac{-2r_L}{(1 + r_L)(r_L^2 - 1)} \] (72)

Now Equation 50 can be derived from Equations 69-72.

### 3.5 Particle Transport Method

Typically, the growth term \( \frac{\partial(Gn)}{\partial L} \) in the population balance, Equation 43, causes numerical oscillation. Therefore, discretization of CSD is very important. However, this leads to the dilemma that the denser grid improves accuracy but increases computing time. A better solution is thus needed.

The Particle Transport Method (PTM) was developed by Smolianski et al. (53) and Smolianski et al. (54). It is a semi-Lagrangian explicit technique for solving convection-reaction problems. This approach belongs to the class of monotone
numerical schemes. By using an adaptivity procedure, PTM captures sharp fronts, which are typical for the problem concerned, with high accuracy. The scheme is based on the classical method of characteristics. A moving mesh system of numerical particles is used, which can be projected onto any fixed mesh with a monotone projection technique.

PTM was applied in unsteady-state modelling of crystal growth by the author in Assoc. Papers vii and viii. Paper viii concentrates on comparison of the discretization methods; linear, logarithmic and PTM. The evolution of CSD with different discretization methods (50 size classes in each method) are shown in Figure 19. The accuracy of CSD prediction with the PTM method can be clearly seen compared to spurious oscillations caused by calculation of population distribution with linear or logarithmic discretization. Paper vii concentrates on modelling of MSMPR reactive crystallization using PTM to solve crystal growth in a phenomena-based model of crystallization. The results of simulations using the model were compared to experimental results received from the start-up of continuous reactive crystallization of barium sulphate in a 300 mL vessel. Examples of calculated evolution of CSD are plotted with experimental results in Figure 20. Rather good prediction can be calculated even with the simplest kinetic models (first order reaction kinetics and simple supersaturation power equations for nucleation and crystal growth rates). Hydrodynamics in such a small scale crystallizer
with high velocity turbine mixing can be considered as ideally mixed and therefore valid for MSMPR theory.

Figure 20. Measured and calculated size distribution of BaSO₄ at time 10 min (left) and at the end of experiment (right). The feed concentrations of BaCl₂ and CuSO₄ were both 0.1 M.

Figure 21 gives an example of a simple continuous reactive crystallization flow sheet of the model. Initial values of population distribution, concentration of reactants and concentration of product are needed. Population balance equations are divided in two parts by an operator splitting method. A part calculates a population distribution projection with PTM (growth rate) and new values for nucleation, growth and reaction rates with current concentration. Simple supersaturation dependence for nucleation and growth and first order reaction kinetics were used. Concentrations for the next round are calculated in the second part, i.e. normal ODE solver.

\[
\frac{\partial n}{\partial t} - \frac{\partial \left( n \frac{\rho}{V} \right)}{\partial x} = \frac{\partial \left( \frac{\rho n}{V} \right)}{\partial x} - \frac{\rho}{V} \left[ \frac{\partial n}{\partial x} \right] - r
\]

(1)

\[\frac{\partial p}{\partial t} = \frac{\partial \left( p \frac{\rho}{V} \right)}{\partial x} - \frac{\rho}{V} \left[ \frac{\partial p}{\partial x} \right] - r
\]

(2)

\[\frac{\partial \rho}{\partial t} = -\frac{\partial \left( \rho \frac{\rho}{V} \right)}{\partial x} - \frac{\rho}{V} \left[ \frac{\partial \rho}{\partial x} \right] - r
\]

(3)

\[\frac{\partial \rho C}{\partial t} = -\frac{\partial \left( \rho \frac{\rho C}{V} \right)}{\partial x} - \frac{\rho}{V} \left[ \frac{\partial \rho C}{\partial x} \right] - r
\]

(4)

\[C = \rho \sigma \left[ \rho \right], \quad D = \rho \sigma \left[ \rho \right], \quad B_0 = k_1 \left[ \sigma \right] - \left[ \sigma \right]^{1/2}
\]

(5)

\[\sigma = k_2 \left[ \sigma \right] - \left[ \sigma \right]^{1/2}
\]

(6)

\[r = \dot{\theta} \sigma \left[ \rho \right]
\]

(7)

Figure 21. Flow sheet of a reactive crystallization MSMPR model using PTM in unsteady-state modelling of crystal growth.
The model swaps between CSD projection with PTM (algebraic) and concentration solving with ODE. The modelling platform used, ModEst 6.0, was not able to swap between ODE and the algebraic model. Therefore, full-scale modelling of crystallization was never tested, and agglomeration and breakage was not included into the model.

3.6 Computational Fluid Dynamics

Traditional MSMPR theory cannot be applied when non-ideal mixing is involved. Modelling of crystallization requires that both the fluid dynamics in the crystallizer and the crystallization phenomena are taken into account simultaneously.

Computational fluid dynamics (CFD) techniques have been developed to a level that allows complex flow situations to be modelled with a reasonable degree of detail and accuracy. In particular, multiphase systems have been the topic of extensive research in CFD in recent years. However, there is still a lack of validated, predictive models of many relevant transport phenomena, especially in the field of multiphase flows. The importance of validation, together with sophisticated modelling, is obvious when a trustworthy design basis for process equipment and its operation with multiphase systems is required.

Simultaneously occurring phenomena, such as nucleation, crystal growth, agglomeration and crystal breakage, make crystallization challenging to model. Comprehensive modelling of crystallization processes requires population balance modelling, or a representative form, coupled with advanced CFD modelling of a multiphase system.

The author studied the subject in Assoc. Paper ix where mainly crystal growth was modelled in a CFD environment. The crystal growth was based on single crystal growth applied to a suspension by predicting mass transfer film thickness from slip velocities. Robust verification methods were used, such as local temperature, local suspension density, and particle size distribution measurements. An advanced verification method based on Particle Image Velocimetry (PIV) was used and a method for slip velocity measurement developed. Qualitative agreement between the experimental results and the simulations was found in the paper. However, the
simulation was extremely heavy and time consuming due to the rather complicated geometry of the crystallizer, i.e. a bench-scale dual-impeller crystallizer with a shaped bottom and four baffles.

### 3.7 Multiblock Model

Modelling of crystallization becomes more challenging when non-ideal mixing is involved. In practice, ideal mixing can be applied only for very small-scale laboratory crystallizers. In industrial-scale crystallizers, and even in pilot- and bench-scale crystallizers, hydrodynamics should be taken into account in modelling of the process. Nowadays, CFD allows detailed modelling of crystallization including hydrodynamic characteristics. However, such detailed dynamic modelling leads to heavy and time consuming simulations. One solution for the problem is to use compartmental models, together with CFD, where the hydrodynamic effect is taken into account and the calculation time is much shorter. In compartmental models, similar hydrodynamic zones are considered as one block to decrease the number of blocks typically used in the CFD simulation. For example, in Paper III, 66 blocks and 26 crystal size classes were used to simulate crystal growth in a 100 litre crystallizer equipped with two 6-flat-blade turbines, four baffles and a W-shaped bottom. Block selection was based on CFD simulations of flow patterns. Simulated results of local suspension density, mother liquor concentration and crystal size distributions were compared to experimental measurements. Experiments were conducted in the same crystallizer by cooling the temperature from 55 °C to 20 °C. A potassium dihydrogen phosphate (KDP)-water solution was initially saturated at 55 °C temperature. Suspension samples were taken at 40, 30 and 20 °C and mother liquor samples at 45 and 25 °C. The mother liquor concentration was highest in the upper part of the crystallizer and lowest in the lower part of the crystallizer, and suspension density naturally followed an opposite pattern. Simulated suspension densities and mother liquor concentrations were reasonably well verified with the experiments, although in the upper part of the crystallizer the simulations gave a larger fraction of small crystals and narrower size distribution than found in the experiments.

In Paper III flow patterns and slip velocities of crystals simulated with CFD were also verified with PIV measurements. The verification results were satisfactory and were
published in Assoc. Paper xii. Some corrections were, however, made in the computational grid, and good agreement between the simulations and the measurements of flow patterns was found, with the exception of a minor difference in the middle part, as shown in Figure 22.

![Figure 22](image.png)

**Figure 22.** Flow patterns of the fluid with the CFD model and with the PIV measurement at 300 RPM mixing intensity; simulated flow velocities on the left-hand side and measured flow velocities on the right-hand side.

As expected, the highest flow velocities were found near the impellers. The flow velocities calculated with CFD were slightly overestimated.

The topic of verification of slip velocities will be discussed in more detail in chapter 5.4.
4. HYDRODYNAMICS IN CRYSTALLIZATION

Hydrodynamics in crystallization is a combination of mixing, inlet and outlet flow, and recycling of the suspension. One of the key factors in suspension crystallization is mixing, which provides the fluid dynamics of the crystallizer. Typically, mixing is divided into two main groups; macromixing, which represents the uniformity of the local average of the concentrations of all the species within the entire crystallizer, and micromixing, which represents molecular scale mixing. An intermediate scale, mesoscale mixing or mesomixing, was introduced by Baldyga and Bourne (55). This scale describes mixing produced by the interaction between the feed plumes and the bulk.

The definition of a perfect mixed vessel involves perfect homogeneity in all the properties inside the crystallizer. If this property is assumed, the crystallization does not depend on the space coordinates in the volume of the vessel. However, this consideration cannot be verified if the reaction or crystallization processes are fast compared to the mixing, or if there is large non-uniformity in the hydrodynamics of the crystallizer. According to Crystallization Technology Handbook (1), Beek and Miller length and time scales are typically used for mixing, shown in Table V.

<table>
<thead>
<tr>
<th>PROCESS</th>
<th>SIZE SCALE</th>
<th>TIME SCALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dispersion by the velocity field (macromixing)</td>
<td>Macroscale</td>
<td>Mixing and circulation times (1-10 s.)</td>
</tr>
<tr>
<td>Size reduction of eddies (mesomixing)</td>
<td>Taylor scale</td>
<td>Taylor time scale (0,1-1 s.)</td>
</tr>
<tr>
<td>Stretching and swirling of eddies (micromixing)</td>
<td>Kolmogorov microscale</td>
<td>Shear time scale (0,02 – 0,001 s.)</td>
</tr>
<tr>
<td>Diffusion (micromixing)</td>
<td>Batchelor microscale</td>
<td>Diffusion time (0,01 – 0,001 s.)</td>
</tr>
</tbody>
</table>

The macromixing time depends mainly on the impeller speed, whereas micromixing depends strongly on the local power input. It is important to note that the primary
nucleation process is very fast and depends greatly on the local supersaturation. In contrast, the process of crystal growth takes seconds or minutes instead of the milliseconds that are necessary for primary nucleation. Therefore, the mean supersaturation is decisive for crystal growth. Since local supersaturation is decisive for the maximum local rate of nucleation, a strong relationship exists between the median crystal size and the micromixing time.

4.1 Macromixing

Macromixing tends to average concentrations throughout the system and residence time is related to this phenomenon. Even with mechanical mixing, there are at least two different macroscopic zones in a crystallizer and three different macroscopic zones in a precipitator.

1. The first zone is close to the stirrer or circulation pump, and is a zone in which energy dissipation is much higher than average in the vessel. Breakage, agglomeration, secondary nucleation, and diffusion-controlled growth are influenced by conditions in this zone.

2. The second zone is the bulk of the vessel.

3. The third zone (for precipitation) is near the reactant feed point. This zone is more supersaturated than the rest of the vessel. Primary nucleation, in particular, will occur at a higher rate in this area.

The addition of feed streams results in concentration variations within a vessel. When the size of the crystallizer increases (up to industrial-scale) uniformity in mixing generally decreases as a result of dead zones or bypasses. The hydrodynamics can be modelled using chemical reaction engineering methodologies.

There have been many attempts to describe and model the macromixing that takes place in typical crystallizers. These efforts usually take the form of one-parameter tanks-in-series, dispersed plug flow models, or multiparameter mixed flow compartment models. The fluid flow through the reactor can also be calculated with very complex Navier-Stokes equations (CFD). Sometimes, it is easier and sufficient to characterize the hydrodynamics in a statistical way, for example, using the residence time distribution (RTD) model introduced by Danckwerts (56) in the 1950’s. The residence time, the time elapsed between entering and exiting the
crystallizer, is a distributed parameter because each group of molecules travelling together has a unique residence time.

4.1.1 Case Study: Macromixing in Dual Impeller Crystallizers

In Paper III and Assoc. Papers ix, x and xii a dual impeller crystallizer was used. Vrábel et al. (57) presented the macromixing time $\tau_{macro}$ for dual Rushton turbine mixing tanks

$$\tau_{macro} = 3.3 P_0 \frac{\sqrt{S}}{N} \left( \frac{H}{d_1} \right)^{2.43}$$

(73)

The mixing time in the dual Rushton turbine 100-liter-crystallizer used in the experiments is approximately 35 s and 29 s when the stirring rate is 250 and 300 RPM, respectively. However, the mixing time is highly sensitive to the height of the liquid level. A mere 5 cm change from the original 80 cm will cause more than 5 s change in the mixing time.

When an axial flow impeller is utilized instead of a radial flow Rushton turbine, the mixing time is decreased by a factor of 2. In the author’s experiments, a propeller was used as an axial flow impeller. The stirring rates with the propeller were 300 and 385 RPM, which gives mixing times of 15 and 11 s, respectively.

4.2 Micromixing

According to Handbook of Industrial Crystallization (3), and Baldyga and Bourne (58), the rapid non-linearity of phenomena such as nucleation has lead to more detailed study of molecular level mixing, micromixing. The importance of microscopic effects increases as the time scale of the process decreases. For instance, the progress of a chemical reaction depends on the contact possibilities of individual molecules. These contacts of molecules can only be achieved as a result of molecular diffusion on the micro scale. Such diffusion occurs in the thinning layers of liquid within the energy dissipation vortices that impose intensive elongation on the fluid elements. Concentration equalization then results from laminar convection and
molecular diffusion in these layers over length scales below turbulent eddy size, i.e. on a Kolmogorov velocity microscale $\lambda_K$

$$\lambda_K = \left( \frac{\nu^3}{\varepsilon} \right)^{0.25}$$  \hspace{1cm} (74)

The equalization is rapid at scales of the order of the Batchelor concentration microscale $\lambda_b$,

$$\lambda_b = \left( \frac{\nu^3 \cdot D_A}{\varepsilon} \right)^{0.25} = \lambda_K \cdot \text{Sc}^{-0.5} \hspace{0.5cm} \text{Sc} \gg 1$$  \hspace{1cm} (75)

For example, if $\nu = 10^{-6}$ m$^2$ s$^{-1}$, $\varepsilon = 1$ W Kg$^{-1}$ and $D_A = 10^{-9}$ m$^2$ s$^{-1}$, $\lambda_K \approx 30 \mu$m and $\lambda_b \approx 1 \mu$m.

The residence time distribution characterizes mean values of the concentration at the reactor outlet. It allows prediction of the reaction progress in the reactor only in the following two cases

(a) the reaction is a first-order reaction and the molecules decompose without any necessity of reactive collisions, and

(b) the residence time is the same for all molecules.

In both cases, all molecules in the same environment have the same mixing history, leading to simultaneous transformation of the molecules. Under all other conditions, the microscopic state in relation to local concentration fluctuations depends on the micromixing state of the reactor. The macroscopic state of the reactor characterised by the residence time distributions must also be considered.

The characteristic time constant for micromixing $\tau_{\text{micro}}$, controlled by engulfment (Sc < 4000) was described by Baldyga and Bourne (55)

$$\tau_{\text{micro}} = \frac{1}{E}$$  \hspace{1cm} (76)
where $E$ is the engulfment rate coefficient

$$E = 0.058 \sqrt{\frac{\varepsilon}{V_c}}$$  \hspace{1cm} (77)

\subsection*{4.3 Mesomixing}

Mesomixing has been much less studied than macromixing and micromixing, and it is mainly used in precipitation to describe the chemical reaction zone. The terms, mesomixing and macromixing are not always separated in the literature. This imprecision may be confusing if a reaction is stated as being macromixing-limited instead of mesomixing-limited due to fact that macromixing is related to the whole lifetime of elements in the crystallizer, whereas mesomixing describes the first moments of the reactant entering the crystallizer as a feed plume and the turbulent dispersion of the plume.

The characteristic time constant for mesomixing was defined by Baldyga and Bourne (59)

$$\tau_{\text{meso}} = \frac{\dot{V}}{u D_r} = \frac{\pi d^3}{4 D_r} U$$  \hspace{1cm} (78)

When the ratio of meso- and micromixing time constants $Q'$ is considered

$$Q' = \frac{\tau_{\text{meso}}}{\tau_{\text{micro}}} = \frac{E \dot{V}}{u D_r}$$  \hspace{1cm} (79)

the controlling mixing scale can be defined; mesomixing dominates when $Q' > 1$, micromixing dominates when $Q' < 1$, and both mechanisms have to be considered when $Q' \approx 1$. 
4.4 Effect of Hydrodynamics on the Kinetics of Crystallization

The most important crystallization processes are nucleation (primary homogeneous, primary heterogeneous and secondary) followed by crystal growth, and in some cases, agglomeration. Primary homogeneous nucleation is the fastest process among the crystallization phenomena. It is observed in the higher supersaturation range and is the main chemical process competing with the mixing process. If ideal mixing can be attained, supersaturation will be constant all over the crystallizer, leading to a low nucleation rate. However, the reality is non-uniformity in supersaturation, especially when feed of a reactant(s) and fast chemical reactions are involved. The fed reactant mixes only with a partial volume of the crystallizer before the reaction, leading to higher local supersaturation and, furthermore, a higher nucleation rate. Therefore, the location of the feed pipe has a very strong effect only on nucleation, whereas an increase in the stirring rate affects all crystallization phenomena.

4.4.1 Case Study: Effect of Feed Arrangements on Reactive Crystallization

The effect of feed arrangements on crystal size distribution in reactive crystallization of dicalcium phosphate dihydrate (DCPD) was studied in Assoc. Paper v. Three different mean residence times (10, 60 and 60 minutes), three different impeller rotation velocities (260, 300 and 400 rpm), and a constant temperature 40 °C, and pH 4 in a 10 litre crystallizer were used. DCPD was produced by the reaction of calcium hydroxide slurry, 20 percent in weight, and aqueous phosphoric acid, 10 percent in weight. Feed arrangements were: a) close together, b) at opposite sides, and c) premixed feed lines, all attached into the flat-blade type impeller discharge region. A flow sheet of the equipment used in the experiments is shown in Figure 23.

Phosphoric acid was pumped directly to the crystallizer and calcium hydroxide slurry was pumped to the crystallizer through a three-way valve. A pH controller attached to the crystallizer controlled the three-way valve. A recirculation system and a mixing system kept the concentration in the Ca(OH)₂ slurry tank constant. The product was removed by a pump, which was controlled by a level controller. The level controller firstly controlled the removing pump and in the case of an error it stopped the acid feed pump. Premixing occurred in a pipe that surrounded the two feed lines (Ca(OH)₂ and H₃PO₄). A detailed sketch is shown in Figure 24.
Figure 23. Flow sheet of the equipment used in reactive crystallization of DCPD

Figure 24. Premixing of feed lines.

Chord length distribution of crystals was monitored on-line continuously during the experiment by a MTS 3DORM laser reflection analyzer. Experiments were carried out from start-up to steady state, i.e. when the trend lines of crystal sizes were at a constant level. Off-line samples were also taken simultaneously to verify the crystal size distribution analysis with a Coulter LS 130 laser diffraction analyzer and to investigate crystal shape with a JEOL JSM-5800 scanning electron microscope.

The modes of the CSD with different operation conditions are compared in Figure 25. As can be seen, mean residence time and impeller rotation velocity did not have any significant effect on the mode of CSD when feed pipes were close together and on opposite sides. Both feed arrangements produces modes of the same size. However, increasing mean residence time decreased the mode of CSD when premixed feed was
used. Premixed feed produces larger modes due to a larger agglomeration rate, which can be seen also from the scanning electron microscope pictures in Figure 26.

Figure 25. Mode of the crystal size distribution from off-line samples of the experiments. ‘Tog’ represents the feed pipes close together, ‘opp’ the feed pipes at opposite sides and ‘mix’ usage of the premixing feed pipe.

Figure 26. SEM pictures from the off-line samples of the experiments with a 10 min mean residence time. Samples a, b and c are from experiments with an impeller rotation velocity 300 rpm and mixing arrangements close together, at opposite sides and premixed, respectively. Samples d, e and f are from experiments with premixed feed lines and mixing velocities 260, 300 and 400 rpm, respectively. 200 µm size bar is in all pictures.
According to Crystallization Technology Handbook (1), if the reactants are added into the stirrer discharge region and the feed points are close together it may lead to supersaturation peaks and high local nucleation and agglomeration rates, especially with high local specific power input. However, in this study close together and opposite side feed lines produce the same CSD, mainly because the process used is partially heterogeneous reaction crystallization, due to the low solubility of calcium hydroxide. A dissolving reactant may limit the supersaturation because nucleation is a faster process than dissolving. In the case of the premixed feed pipe, the effect of micro- and mesomixing can be better seen, although the premixing distance was constant, i.e. the premixing time was dependent on the mean residence time. The premixing time should be constant to compare results of different residence times.
5. PARTICLE IMAGE VELOCIMETRY

Measurement of flow dynamics has become an important research area of crystallization over the last decades, mainly due to the development of hydrodynamic modelling of crystallization, e.g. computational fluid dynamics, CFD. Developed models, especially turbulence models of multiphase processes, need a proper verification method. Intrusive methods are not applicable because of the disturbance to the hydrodynamics. Mavros (60) reviewed many suitable non-intrusive methods developed; Laser-Doppler Velocimetry (LDV) or Phase Doppler Anemometry (PDA), Ultrasound-Doppler Velocimetry, Simple Imaging, Flow-Followers, Color Change, Thermography, Particle Image Velocimetry (PIV), Laser Induced Fluorescence (LIF) and Tomography. Recently, PIV has been used to quickly and accurately gather quantitative information about fluid velocity fields, for example, as presented by Seybert and Evans (61), Fan et al. (62), Virdung and Rasmuson (63), and Torre et al. (64), and has been found to be a powerful tool for the study and verification of hydrodynamics. In this technique, the flow of tracer particles carried by the solution is measured by taking two photos with a short time interval. Flow directions and velocities of the tracer particles in 2-D are calculated by comparing the two consecutive photos. Use of a stereo camera system allows the flow directions and velocities of the tracer particles to be calculated in 3-D by comparing two simultaneous sets of two consecutive photos. According to Mavros (60), since PIV produces transient flow patterns, it reveals non-stationary phenomena such as flow instabilities. For this reason, several consecutive frames need to be analyzed to average the flow patterns.

PIV is an optical, non-intrusive method that is related to both flow for visualization and optical point techniques. The PIV technique can provide an accurate quantitative measure of the instantaneous flow velocity field across a planar area of a flow field. The principle is shown in Figure 27.

In the PIV method, the flow is seeded with tiny, neutrally buoyant particles called tracers, as described in DaVis manuals (65), (66) and (67). Using a light sheet, formed by passing a double pulsed laser beam through an optical arrangement including
cylindrical lenses, the particles in the flow are illuminated twice with a small time interval.

Figure 27. Principle of Particle Image Velocimetry (PIV), based on a Dantec Dynamics presentation poster.

The displacement of particles in the time between the laser pulses is recorded as either a single image exposed twice or as a pair of two single exposure images. The recorded particle displacement field is measured locally across the whole field of view of the images, scaled by the image magnification and then divided by the known pulse separation to obtain the flow velocity at each point. A camera, typically positioned perpendicular to the plane of the light sheet, is shuttered to capture the light scattered from the particles. Depending on the flow velocity and the factor of magnification of the camera lens, the delay between the two pulses is chosen such that adequate displacements of the particle image are obtained on the CCD. Velocity vectors can be calculated from the time delay between the two illuminations and the displacement of the tracers.

In evaluation of the particle images it is assumed that the tracers follow the local velocity between the two illuminations. Digital PIV recording is divided into small sub-areas called interrogation windows. Using statistical correlation techniques, one local displacement vector is determined for each interrogation window. For this reason the size of the interrogation cell is selected such that all particles within this area have moved homogeneously in the same direction and over the same distance. For good results there should be at least ten particles within one interrogation cell.

Evaluation of the particle images depends on the way these images have been recorded by the camera used. One possibility is to record the scattered light of both
illuminations in one frame, a single frame/double exposure. These pictures can be evaluated by auto-correlation. The other possibility is to record the scattered light from the first illumination in one frame and the scattered light from the second illumination in another frame. This is called a double frame / double exposure. These double frame images can be evaluated by cross-correlation.

5.1 Single Frame / Double Exposure

The scattered light from the first and second exposure of the particles is recorded in one image. The complete image is subdivided into so called interrogation windows and each window is evaluated by autocorrelation, as presented in FlowMaster Software Manual (66).

Figure 28. Evaluation of PIV recordings using auto-correlation presented in FlowMaster Software Manual (66).

The auto correlation function is characterised by two identical correlation peaks rotationally symmetrical about the highest central peak indicating zero displacement. This is a consequence of the fact that the sign of the displacement cannot be detected because it is not known which particle is illuminated by the first and which by the second laser pulse. Consequently, the information from the autocorrelation is ambiguous and not conclusive without a priori information about the observed flow. Detection of very small displacements is also a problem as the correlation peaks are then close to the central peak. Compared to cross-correlation, auto-correlation peaks are significantly smaller. High noise increases the possibility that the displacement correlation peak disappears in the background.
5.2 Double Frame / Double Exposure

The scattered light from first and second exposure of the particles is recorded in two different images. According to FlowMaster Software Manual (66), the complete image is subdivided into interrogation windows and each window is evaluated by cross-correlation.

For cross-correlation a fast double-shuttered CCD camera is typically used to record images with a “double frame / double exposure”. The minimum time delay between the two laser pulses is limited by the time necessary for the frame transfer of the camera. As the second frame cannot be shuttered, the two images have different background intensity and a suitable filter needs to be used in front of the camera lens. Compared to auto-correlation, a higher and unambiguous correlation peak is received.

![Figure 29. Evaluation of PIV recordings using cross-correlation presented in FlowMaster Software Manual (66).](image)

5.3 Features

PIV is a non-destructive technique which measures the velocity of micron-sized particles following the flow. It provides instantaneous velocity maps in a cross-section of the flow in a range from zero to supersonic.

All three velocity components may be obtained by the use of a stereoscopic arrangement. Statistics, spatial correlations and other relevant data can be obtained by using sequences of velocity vector maps.
The graphical results of PIV are quite similar to those from computational fluid dynamics, and the results of the two different approaches are therefore easy to compare. Real-time velocity maps are also in-valuable tools for fluid dynamics.

In a single camera PIV system, the third velocity component cannot be measured due to the geometry of the image. A second camera in a stereoscopic arrangement enables measurement of all three velocity components on a two-dimensional domain. Comparison of the one camera and two camera systems is illustrated in Figure 30.

![Figure 30. Stereoscopic arrangement (3D) compared to a single camera system (2D), as presented in FlowMaster Software Manual (66).](image)

5.4 Case Study: Slip Velocity Measurement

The CFD model in Paper III was used to obtain hydrodynamic information on the flow profiles, slip velocities, and classification of crystals in the crystallizer. This information was then used in a multiblock model approach for modelling crystal growth. To be able to predict the local crystal growth rates in a crystallizer it is essential to know the local conditions, including the local suspension densities, local crystal size distribution, and local slip velocities of crystals of various sizes. In addition to the effect on crystal growth rate, slip velocities affect classification of the crystals, making it even more crucial to have reliable information about the slip velocities. In Assoc. Paper xii, the author therefore developed a method for slip velocity measurement by PIV to verify the CFD model.

In Assoc. Paper xii, mixing with dual impellers was studied empirically with a stirred crystallizer 100 litres in volume. The w-shaped bottom crystallizer is shown in
Figures 31 and 32. The diameter of the crystallizer was 400 mm. Four 40 mm baffles and a pair of 135 mm 6-flat-blade turbines were used. The distance between the impellers was 400 mm. A special window system was designed to permit PIV measurements. Two glass windows were installed one above the other in a quarter sector of the crystallizer. Flat rectangular outer windows (polycarbonate) were used since the ability of the software to correct the optical distortion of cylindrical windows is limited. The space between the windows was filled with de-ionized water to minimize the shell curvature and refraction problems at the cylindrical surface of the inner window. The use of a special fluid to match the refractive index of the glass and polycarbonate, as presented by Budwig (68), was not necessary for the experimental apparatus used in this study since the large curvature radius of the vessel shell minimized refraction effects. A simple calibration was sufficient with the set-up used.

A LaVision PIV Imager PRO X2M was used with a thin sheet of light (532 nm / 50 mJ) produced by a Nd:YAG laser. Two high speed CCD cameras were used. The setup of the laser and the cameras is shown in Figures 33 and 34. Before the actual slip velocity measurements, the cameras were focused and calibrated exactly in the
same measurement area in the crystallizer using a special calibration plate. The size and distance of the marks on the calibration plate were known, and based on this information, the PIV software created the calibration model for the measurements.

A band pass filter of 532 nm light was used in the first camera to filter out other light sources except laser reflections. This allowed measurement of the flow velocities of the crystals passing by the laser sheet in the crystallizer. Two crystal size ranges, 50-100 µm and 500-710 µm, KDP crystal (99.5%, GR for analysis, Merck) were studied in this work.

A high pass filter of 540 nm light was used in the second camera to exclude other light sources except fluorescence reflections. PMMA-RhB fluorescence tracer particles of size 20-50 µm were used for measurement of the flow of the saturated KDP solution. These light tracer particles are designed to move with the fluid flow. Simultaneous and uniformly focused measurement of the flow of the crystals and the flow of the mother liquor therefore allowed calculation of the slip velocities of the crystals by simple subtraction. To improve statistical reliability, a minimum of 200 measurements were used when averaging the slip velocity results. Since a single camera was used for each phase flow, the results are presented in 2-D. Measurement of three dimensional slip velocities would need two stereo camera systems, i.e. simultaneous usage of four cameras.
The crystallizer was divided into six compartments for the PIV measurements (see Figure 35) and the measurements from these six compartments were then combined into one picture.

![Figure 35. Measured PIV compartments in the crystallizer combined to one picture.](image)

The slip velocities of the 50-100 µm and 500-710 µm KDP crystals in the aqueous saturated KDP solution (at 20 °C), measured with two different mixing intensities (250 and 300 RPM), are shown and compared with the simulated velocities in Figure 36. The verification was improved from the results presented in Assoc. Paper xii after some corrections were made in the computational grid. Now, reasonably good agreement can be found between the calculated and measured slip velocities in 2D. As expected, increasing crystal size had an increasing influence on slip velocities. For smaller crystals (with sizes of 75 µm in the simulations and 50-100 µm in the experiments) the simulations gave smaller slip velocities than found in the experiments. One reason is that the larger crystals included in the experiments have higher slip velocities than the average-sized crystals included in the simulations. Turbulence had only a negligible effect on the slip velocities of small crystals. The low slip velocities found (below 2.0 cm/s) cause the growth of small (<100 µm) KDP crystals to be in the diffusion-controlled area (see paper III for more details).
Figure 36. CFD calculations of the slip velocities in 2D compared to the measured slip velocities of KDP crystals in the crystallizer. Mixing is produced with a dual 6-flat-blade turbine.

For larger crystals (with sizes of 600 µm in the simulations and of 500-710 µm in the experiments) the simulations gave higher slip velocities than the experiments. Classification of crystals in the experiments explains the main part of the slip velocity.
differences between the upper and lower part of the crystallizer. Breakage of the crystals in the experimental vessel may also have had some effect on the results. The differences between the simulated and measured slip velocities for the large crystals are well explained by the drag correlation used in the simulations. The Schiller-Naumann drag correlation does not take into account the effect of turbulence and thus overpredicts the slip velocities for large crystals in a turbulent fluid. Relatively high slip velocities (over 2.0 cm/s in most parts of the crystallizer) cause the growth of these KDP crystals to be in the surface reaction controlled area.

Standard vector averaging for stochastic turbulence phenomena causes small errors in the measurement of slip velocities. The powerful turbulent backflow in the main flow field decreases average slip velocities locally when the direction of flow is taken into account. The velocity magnitude (directionless slip velocities) or turbulent energy dissipation may be more practical to obtain more accurate results.

Despite the slight differences between the experimental and simulated results, the method developed for measurement of the slip velocities of crystals by PIV was found to be very useful for verification of CFD calculations.
6. PROCESS ANALYTICAL TECHNOLOGY

Process analytical technology (PAT) has been defined by the United States Food and Drug Administration (FDA) as a permissible mechanism to design, analyze, and control pharmaceutical manufacturing processes through the measurement of Critical Process Parameters (CPP) which affect Critical Quality Attributes (CQA), as presented in Process Analytical Technology homepage (69).

The concept aims to understand processes by defining their CPP’s, monitoring them in a timely manner (preferably in-line or on-line), and thus providing more efficient testing while at the same time reducing over-processing, enhancing consistency, and minimizing rejects.

In order to implement a successful PAT project, a combination of the three main PAT tools is essential:

- Multivariate data acquisition and data analysis tools: usually advanced software packages which aid in design of experiments, collection of raw data, and statistical analysis of the data in order to determine the CPP.
- Process analytical chemistry (PAC) tools: in-line and on-line analytical instruments used to measure those parameters that have been defined as CPP. These mainly include near infrared spectroscopy (NIRS) but also include biosensors, Raman spectroscopy, fiber optics and others.
- Continuous improvement and/or knowledge management tools: paper systems or software packages which accumulate quality control data acquired over time for specific processes with the aim of defining process weaknesses and implementing and monitoring process improvement initiatives. These products may be the same or separate from the statistical analysis tools above.

Development in the field has been intensive in recent years. In the area of crystallization processes, for instance, several studies, for example presented by Braatz (70), Nagy et al. (71), and Khan et al. (72), have been published about spectroscopy-based monitoring and closed loop control of batch cooling
crystallization. The author used spectroscopy based closed loop control of supersaturation in semibatch reactive crystallization of glutamic acid in Papers IV-VI and spectroscopy based monitoring in Paper II and Assoc. Paper xiii. ATR FTIR spectroscopy was used in Papers IV-VI for solute concentration and simultaneous combination of Raman and ATR FTIR spectroscopy for the polymorphic state of crystals and solute concentration, respectively, in Papers II and xiii.

6.1 ATR FTIR Spectroscopy

Attenuated total reflectance (ATR) is a sampling technique used in conjunction with infrared spectroscopy which enables samples to be examined directly in the solid, liquid or gas state without further preparation. A beam of infrared light is passed through the ATR crystal in such a way that it reflects at least once off the internal surface in contact with the sample. This reflection forms the evanescent wave which extends into the sample. The penetration depth into the sample is typically between 0.5 and 2 micrometres. The author used the ATR crystal shown in Figure 37 to resolve solute concentration in the crystallizer.

![Figure 37. ATR FTIR probe used in Papers II, IV, V and VI.](image)

Fourier transform infrared spectroscopy (FTIR) is a technique used to obtain an infrared spectrum of absorption, emission, photoconductivity or Raman scattering of a solid, liquid or gas. An FTIR spectrometer simultaneously collects spectral data in a wide spectral range. The term Fourier transform infrared spectroscopy originates from the fact that a Fourier transform (a mathematical algorithm) is required to convert the
raw data into the actual spectrum. The author used the FTIR spectrometer Bomen MB155 with MID IR range and resolution of 4 cm$^{-1}$ and the ATR-probe Axiom DPR210 (modified) with AMTIR IRE to measure solute concentrations. The immersion depth of the probe was modified to 60 cm. The probe was used under a nitrogen atmosphere of an approximately 2-m light path to minimize the effect of the gas phase.

6.2 Raman Spectroscopy

According to Gardiner (73), Raman spectroscopy is a spectroscopic technique used to study vibrational, rotational, and other low-frequency modes in a system. The Raman effect occurs when light impinges upon a molecule and interacts with the electron cloud and the bonds of that molecule. For the spontaneous Raman effect, a photon excites the molecule from the ground state to a virtual energy state. When the molecule relaxes it emits a photon and returns to a different rotational or vibrational state. The difference in energy between the original state and this new state leads to a shift in the emitted photon's frequency away from the excitation wavelength. A change in the molecular polarization potential — or amount of deformation of the electron cloud — with respect to the vibrational coordinate is required for a molecule to exhibit a Raman effect. The degree of the polarizability change will determine the Raman scattering intensity. The pattern of shifted frequencies is determined by the rotational and vibrational states of the sample.

Spontaneous Raman scattering is typically very weak, and as a result, the main difficulty of Raman spectroscopy is separating the weak inelastically scattered light from the intense Rayleigh scattered laser light.

The author used off-line Raman analyses (microspectroscopy) to resolve the polymorphic state of dry L-glutamic acid crystals in Papers II, IV, V and VI. In-line Raman analyses (intrusive probe) were used to resolve the polymorphic state of crystals in suspension in Papers II and V. Horiba Jobin Yvon LabRam 300 Raman spectroscopy was used in on-line and off-line analyses except in Paper V, where a
multi-probe Raman spectrometer from the Technical Research Centre of Finland (VTT Optical Instrumentation, Oulu, Finland) was used in off-line analyses.

In the papers, characteristic peaks of dry L-glutamic acid crystals, 622 cm\(^{-1}\) and 801 cm\(^{-1}\) were selected for the \(\alpha\)- and \(\beta\)-form, respectively. Peak heights were calculated by subtracting the peak value from a reference point value. References used were 647 cm\(^{-1}\) and 789 cm\(^{-1}\) for the \(\alpha\)- and \(\beta\)-form, respectively. In paper II, two-point linear fitting was used to solve the \(\alpha\)-form fraction in the sample. More sophisticated second degree polynomial fitting, in a least squares sense, was used in the other papers. In in-line analyses, the calibration model was based on the height of the peaks at 872 and 867 cm\(^{-1}\) for the \(\alpha\)-form and the \(\beta\) form L-glutamic acid, respectively. Two-point linear fitting was used in in-line Raman spectroscopy to solve the \(\alpha\)-form fraction in the crystallizer.

### 6.3 Monitoring and Control of Crystallization

As mentioned above, two process analytical chemistry tools were used in Papers II, IV, V and VI; ATR-FTIR and Raman spectrosopes. Raman spectroscopy was used mainly to monitor the polymorphic state of L-glutamic acid crystals produced in the crystallizer. ATR-FTIR with MID-IR range was used to monitor and control the L-glutamic acid concentration in the solute of semibatch reactive crystallization of L-glutamic acid. Sulphuric acid was fed into the monosodium glutamate solution, which produced supersaturation in the crystallizer. The level of supersaturation can be controlled with the feed rate when the concentration is monitored on-line. The control loop used to compute supersaturation was based on concentration information obtained from the multivariate model of the ATR-FTIR spectrum and on the solubility obtained from polynomial fitting as a function of pH. A more detailed description of the control loop used in the experiments is given in Paper IV (pp. 2068-2070) and further in Paper V (pp. 745-746).

Previously, closed-loop process control systems have mostly been developed for batchwise cooling crystallization. Paper II and Assoc. Paper xiii applied monitoring of supersaturation using ATR-FTIR to reactive crystallization. Paper IV developed the
control structure and the control strategy was developed further in Paper V. Papers IV-VI show successful control of supersaturation with the developed control structure in semibatch reactive crystallization of L-glutamic acid.

6.3.1 Effect of Hydrodynamics

Monitoring and control make similar demands on the hydrodynamics of the crystallizer as modelling; local conditions in any point in the crystallizer should be close to average conditions in the whole crystallizer. Large deviation in local supersaturations leads to low controllability of the process; different phenomena dominate in different locations. For the above reasons, careful study of hydrodynamics was done for the laboratory- and bench-scale crystallizers used in the experiments. In industrial-scale crystallizers, uniform hydrodynamics is not a reality, and for that reason, multipoint spectroscopy was studied in Paper V. The study was based on Raman spectroscopy but multipoint spectroscopy can be applied to other PAC tools as well. Detailed knowledge of different local conditions may increase the overall controllability of the crystallization process. At a minimum, it will indicate which areas of a crystallizer need to be enhanced by mixing, geometric development of the crystallizer or other means.

Two different crystallizers were used in the author’s PAT studies (Papers II, IV-VI and Assoc. paper xiii); a 1-litre crystallizer and a 50-litre crystallizer. Both crystallizers had a similar geometry; a cylindrical body and round bottom. The effect of three different impellers, two different rotation speeds of the impellers, four different liquid volumes, and the location of the feed pipe on the flow patterns of the two crystallizers was investigated with a LaVision PIV Imager PRO X2M. The selected impeller types were a 6-flat-blade turbine and 6-pitched-blade turbine. Two different angles of pitched blades were used; 45° and -45°, to produce up-pumping and down-pumping flows. The impellers are shown in Figure 38. These turbines were selected for the experiments because of the known good micromixing effect, which is beneficial for reactive crystallization. The rotation speed of the impellers was 250 and 500 RPM in the laboratory-scale (1 liter) crystallizer and 167 RPM in the bench-scale
(50 litres) crystallizer. The tip speeds of 167 RMP in the bench-scale and 500 RPM in the laboratory-scale were constant.

Figure 38. Impellers used in 1-litre and 50-litre hydrodynamic experiments (upper row – laboratory-scale; lower row - bench-scale). The diameter of the impellers was 50% of the crystallizer diameter. From left to right, the types of impeller are flat-blade turbine, up-pumping pitched-blade turbine, and down-pumping pitched-blade turbine.

Four different liquid volumes (650, 775, 900 and 1025 in laboratory-scale, and 17.6, 20.9, 24.3 and 27.7 litres in bench-scale) were selected to investigate the effect of volume in the semibatch process with increasing volume during crystallization. The geometrical relation was kept constant in scaling.

Two feed locations were used for sulphuric acid input; one above the liquid surface and one below the surface close to the impeller in the high dissipation energy area. As expected, feed above the liquid surface resulted in more non-uniform product in the crystallizer due to large local concentration differences. Typically, controllability of crystallization decreases when local concentration differences increase.

Based on these results, an up-pumping 6-pitched-blade turbine was selected for the crystallization experiments since it provided the most uniform flow patterns in the crystallizer. The dead zone in the middle of the bottom is much smaller, as are the high flow velocity areas. Figure 39 shows flow patterns of the crystallizers with the largest measured water volume.
Figure 39. Comparison of flow patterns of two crystallizers using flat-blade, down-pumping pitched-blade and up-pumping pitched-blade turbines.
7. NUCLEATION IN CONTROLLED SUPERSATURATION

Nucleation is highly dependent on supersaturation. Therefore, accurate control of supersaturation leads to better controllability of nucleation and the whole crystallization process. Studies on spectroscopy-based monitoring and closed-loop control of batch cooling crystallization can be found in the literature, for example presented by Braatz (70), Nagy et al. (71), and Khan et al. (72). A closed control loop for semi-batch reaction crystallization of L-glutamic acid was developed in Papers IV and V. Control of supersaturation in reactive crystallization is even more critical than in cooling crystallization due to the much faster changes (the chemical reaction is commonly much faster than heat transfer). Fast changes lead also to high supersaturation values. When the crystals have different three-dimensional structures (polymorphs) the complexity of controlling the crystallization increases. Typically, different polymorphs exhibit different solubilities and thus their prevalence in the solution can be controlled by appropriate choice of the supersaturation level. However, spontaneous primary nucleation is typically difficult to control and a mixture of polymorphs may form. One well known method to increase uniformity in nucleation is seeding, as presented in Handbook of Industrial Crystallization (3). Good controllability of polymorphs is often achieved using seeding with target polymorphs, as shown by Llinàs and Goodman (74), and Dunitz and Bernstein (75). Substantial differences in crystal shape have also been achieved by ultrasonication, as shown by Guo et al. (76), Louhi-Kultanen et al. (77), and Ambrus et al. (78), although the effect is not fully understood. Ultrasound irradiation induces acoustic streaming and highly localized temperature and pressure within the fluid, which may result in local solubility changes. Typically, it will be seen as a reduction in crystal size and the inhibition of agglomeration. Because of its potential impact on solubility, and consequently on polymorphism, the effect of sonocrystallization on polymorph control in a controlled supersaturation environment was studied in Paper VI. In the study, spontaneous, seeded and ultrasound-initiated nucleation methods were compared in controlled supersaturation of semibatch reactive crystallization of L-glutamic acid. Sonocrystallization showed a clear effect on controllability of polymorphism. Ultrasound initiated nucleation in 1 M initial supersaturation produces more than 99.5 % pure α-polymorph crystals, whereas seeding produces more than 93 % pure α-polymorph crystals and spontaneous nucleation produces 40-70 % pure α-
polymorph crystals. With lower 0.7 M initial supersaturation practically all product crystals were $\beta$-polymorph.

### 7.1 Case Study: Hydrodynamics in Ultrasonication

Hydrodynamics of the crystallizer used in Paper VI was the same as discussed in more detail in chapter 6.3.1. However, power ultrasound is also known to affect hydrodynamics, mainly on local micro- and mesomixing but also on macromixing to some extent. The effect of ultrasound on the flow profiles of the mixing tank (dual Rushton turbine crystallizer) can be seen in Figure 40. An approximately 10 mm immersion probe was used in demonstration of the sonication (20 kHz, max 36 W electric power) effect. The flow profiles of the water were measured with a LaVision PIV Imager PRO X2M using a fluorescence particle to avoid disturbance of air bubbles on the measurements.

![Flow profiles with ultrasound power](image)

**Figure 40.** Effect of ultrasound power on local flow profiles. Red lines at the top of the windows indicate the position of the ultrasound probe.
The results show that with higher electric power (> 16 W) a clear effect on the flow profiles can be detected. In the system, the ultrasound probe was installed against the main flow stream. With the highest electric power, the average flow close to the tip of the probe is almost zero. This means that the flow caused by sonication is approximately equal to the average flow caused by mixing, i.e. about 0.2 m/s.

In Paper VI the impact of sonication was even more localized due to the tapered microtip (3 mm in diameter). This highly localized impact was very effective at controlling polymorphism in supersaturation-controlled semibatch crystallization of L-glutamic acid. The effect was mainly based on local heating and pressure oscillations, which provide control of the supersaturation, although it was partly based on an increase in micromixing.
8. CONCLUSIONS

The main objective of this study is to explore the influence of hydrodynamics on the crystallization process, with special emphasis on modelling, PAT monitoring, and supersaturation control. In the theoretical review of crystallization phenomena, case studies related to the author’s publications are presented and hydrodynamics discussed. The work consists of six main studies.

It was shown by examples that the hydrodynamics of a crystallizer clearly affect the crystallization phenomena. Nucleation, crystal growth and agglomeration are all dependent on supersaturation and hydrodynamics affects local supersaturation in a crystallizer. Therefore, the size and habit of the crystals produced are dependent on the hydrodynamics of the crystallizer. The size and habit of crystals can also be affected by impurities or additives. The effect of impurities and additives is, however, negligibly dependent on hydrodynamics.

MSMPR theory was shown to be feasible in modelling of small laboratory-scale crystallizers. Further development of features like the size-dependent growth rate or particle transport method (PTM) in unsteady-state modelling of the growth rate improves traditional MSMPR modelling significantly. However, with increased crystallizer size, MSMPR theory ceases to be valid, due to inhomogeneous mixing. CFD modelling with proper verification was shown to be feasible when hydrodynamic effects have to be taken into account. However, dynamic simulation with a CFD model is computationally extremely heavy and time consuming. Therefore, a multiblock model, where similar hydrodynamic zones are combined into blocks, was presented for dynamic modelling of crystal growth in a suspension. This method decreases drastically the number of blocks typically used in CFD simulations, leading to much shorter computation time. However, proper verification is needed for CFD and multiblock models. CFD and multiblock modelling were done by Maret Liiri in Helsinki University of Technology (now Aalto University) whereas the verification experiments were carried out by the author in Lappeenranta University of Technology. PIV was shown to be an effective tool for verification of flow patterns and slip velocities of crystals, although suspension density is rather limited in the
measurements. Reasonably good verification was shown, i.e. good agreement between the simulations and PIV measurements of flow patterns in a 100-liter dual turbine crystallizer. Slip velocity seems, however, to be overestimated by the model. Thus the model should be enhanced; for example, including the effect of turbulence on the drag coefficient in the simulation model may increase the accuracy of the hydrodynamics. On the other hand, PIV measurements could be improved by using the velocity magnitude (directionless slip velocities) or turbulent energy dissipation to obtain more accurate results.

PAT was successfully used to control semibatch reactive crystallization of L-glutamic acid. ATR-FTIR with MID-IR was used to monitor and control L-glutamic acid concentration in a solute using the feed pump of sulphuric acid as the actuator of the control loop. Hydrodynamics of the used crystallizer was well studied. An up-pumping 6-pitched-blade turbine produced the most uniform flow patterns of the impellers tested and it was therefore selected for the crystallizer used in the experiments. A feed nozzle position close to the impeller produced the most stable crystal size and polymorph and was therefore selected for the feed system in the experiments. Large deviation in hydrodynamics leads to local differences in supersaturation and single point monitoring is not sufficient for the control loop. Multipoint spectroscopy is shown to be feasible for control of non-uniform hydrodynamics, although such an approach will lead to the need for a complex control strategy. It would be of academic and industrial interest to develop such a multipoint control strategy.

Polymorphism of L-glutamic acid was successfully controlled by highly localized power ultrasound initiated nucleation in supersaturation controlled semibatch crystallization. The local supersaturation was affected by local heating and pressure oscillation. Increased micro- and mesomixing may have a significant role in ultrasound initiated nucleation. Vapour bubbles from cavitation and slightly modified macromixing may also affect nucleation and polymorphism, although this is not likely. The initiation method seems, however, to be promising for polymorph control and more detailed study should be undertaken.
9. REFERENCES


PART II: Publications
ERRATA FOR PUBLISHED PAPERS

Publication IV

p. 2065: The sum of the dissociation reaction of Glu (Eq. 2) and the solid–liquid equilibrium (Eq. 3) is given in equation (9). The equilibrium constant or solubility product, $K_{sp}$, for reaction equation (9) is given in equation (10). The value for the solubility product was solved from equilibrium constant of the reaction (Eq. 2) when $a$(Glu (aq)) = $c^*(Glu$ (aq,$\alpha$)).

p. 2072: Control based on the difference in the overall concentration of glutamic acid and the equilibrium value of overall concentration, Eq. 14, was successful, see Figure 16.

p. 2075: Figure captions of figures 25 and 26 are misplaced

Publication VI

p. 753: In the crystal growth kinetics study, pure polymorph results were used since no polymorph transformation took place during the semi-batch process. The production of the $\alpha$-polymorph ($i = 9$) depends more on the supersaturation than is the case for the $\beta$-polymorph ($i = 2.6$).