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Recent advances in the monitoring, modelling and control of crystallization systems

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ABSTRACT

Crystallization is one of the most important unit operations used for the separation and purification of crystalline solid products. Appropriate design and control of the crystallization process is paramount to produce crystalline products with tailor-made-properties. This paper provides an overview of selected recent developments in the modelling, monitoring and control of crystallization processes. We consider the topics discussed in this review to be enabling technologies for the development of the next generation of crystallization processes with significantly improved predictability, robustness and controllability.

Keywords: Population balance modelling; Process analytical technologies; Crystallization modelling; Crystallization monitoring; Crystallization control; Crystallization review

1. Introduction

Crystallization is one of the oldest unit operations used for the separation and purification of solid products. It is a widely used process across the vast majority of industries, including pharmaceutical, food, microelectronics and bulk and fine chemicals. The production process of the majority of all solid products includes at least one crystallization step during the synthesis and/or purification of intermediates and/or the final product. Since crystallization is often the first step when the pure solid product is separated from the liquid solution it represents a crucial process to tailor the solid properties, such as crystal size distribution (CSD), shape, polymorphic form and purity. Since these characteristics have a strong effect on the final product properties (e.g. dissolution behaviour, bioavailability, shelf-life, etc.), as well as on the efficiency of the downstream processes (such as filtration, drying etc.), the proper design and control of crystallization processes can have a significant effect on the overall efficiency of the solid production process and the quality of the final product as discussed in previous review articles on the topic of crystallization process monitoring and control (Rawlings et al., 1993; Braatz, 2002; Yu et al., 2007; Nagy and Braatz, 2012).

During the past two decades significant research effort has been concentrated on the better understanding of the mechanisms that govern crystallization processes (nucleation, growth, polymorphic transformation) (Erdemir et al., 2007, 2009; Towler et al., 2004) as well as on the modelling and control of crystallization systems, with significant progresses enabled by the development and broader applications of process analytical technology (PAT) tools and increase in computing power. The key developments have occurred in four broad categories: (i) modelling, (ii) monitoring, (iii) control, and (iv) novel crystallization concepts. In the modelling area major developments occurred in the use of multi-dimensional population balance models for morphological modelling of crystallization processes, as well as in the better understanding of crystallization in impure media. Developments in the monitoring of crystallization processes can be attributed to the introduction of the concepts of process analytical technologies

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and the motivation within the pharmaceutical and fine chemical industries to manufacture high quality crystalline products with improved consistency in shorter time. Key developments in the monitoring include advances in imaging hardware and software as well as the application of advanced chemometrics and statistical process control concepts. The advances in the modelling and monitoring of crystallization processes have also led to significant progress in the development and application of advanced control concepts. The requirements to apply crystallizations in the case of increasingly complex systems (e.g. multicomponent and impure system, large organic molecules such as proteins and biopharmaceuticals) as well as the recent advances in the paradigm shift from batch to continuous manufacturing in the pharmaceutical industries have also motivated the development of novel crystallization designs.

2. Population balance modelling of crystallization systems

2.1. The current context of PBM

A large number of natural or industrial processes deal with dispersed phase systems: cells, droplets, particles, for example. Among these systems, solids elaboration processes and, notably, crystallization operations take an important place. As a mathematical tool of choice, the formalism of population balance equations (PBE) is more and more frequently used in both academic and industrial research for the dynamic modelling of crystallization systems. PBEs were developed about 50 years ago by Hulbert and Katz (1964) and mathematically analyzed in a remarkable and extensive way by Ramkrishna in his famous reference book (Ramkrishna, 2000). The early pioneers in the application of PBEs for the modelling of crystallization processes were Randolph and Larson (1971). The mathematical formalism of PBEs arises from the very basic principle of the continuity of the mass of dispersed individual objects. Many mathematical expressions of this principle can be found in the literature, some of them are rather abstruse. Among others, the following expression that accounts for growth, agglomeration and breakage phenomena can be found in (Bück et al., 2012), it expresses the time variation of a given number density function $n(t, x,\xi)$ under consideration:

$$\frac{\partial n}{\partial t} + \sum_{k=1}^{3} \frac{\partial (G_{x,k} n)}{\partial x_k} + \sum_{i=1}^{n} \frac{\partial (G_{\xi,n} n)}{\partial \xi_i} = \dot{n}_{in} - \dot{n}_{out} + p \quad (1)$$

where ξ denotes a vector of particle properties and x the vector of external coordinates (i.e. spatial position), G_x and G_ξ are the transport velocities along the coordinates, $\dot{n}_{in}$ and $\dot{n}_{out}$ denote the inlet and outlet particle fluxes and p is a lumped expression of the overall rate of appearance (or disappearance) of particles in the system. According to the process under consideration, such production input may have multiple causes: agglomeration, breakage, dissolution, chemical reaction, melting, and others.

From a physical viewpoint, many aspects of Eq. (1) are not that obvious and the equation can be considered as a mathematical formula only. For process engineers, such a way of approaching PBM is not very satisfactory as it obviously lacks physical understanding. In order to make PBEs easier to understand, the general equation can be simplified assuming that the particles under consideration can be characterized through the definition of one single size variable (e.g. diameter of spherical particles). Assuming well-mixed homogeneous systems the PBE can be simplified even further, as follows:

$$\begin{aligned} &\frac{dn(L,t)}{dt} + G(t)\frac{dn(L,t)}{dL} = 0 \\ &n(L,0) = 0 \\ &n(0,t) \approx n(L^*,t) \approx \frac{R_N(t)}{G(t)} \end{aligned} \quad (2)$$

where $R_N(t)$ is the overall rate of nucleation expressed in # $s^{-1}\,m^{-3}$ (e.g. the sum of primary and secondary nucleation events), L is a single characteristic particle size which usually results from a very rough approximation of the real particle shape, and $G = dL/dt$ is the growth rate (in $m\,s^{-1}$). The initial condition in Eq. (2) above assumes that no particles are initially present in the crystallizer.

A wide range of population balance modelling (PBM) applications was reported during the past 20 years, together with the development of more accurate and powerful techniques dedicated to their numerical resolution (Qamar and Warnecke, 2007; Kariwala et al., 2012; Gunawan et al., 2004). For simulating complex crystallization phenomena (i.e. in a multivariable context and/or in the presence of agglomeration, aggregation, breakage phenomena), as well as for the advanced modelling of challenging specific systems such as preferential crystallization, phase transition processes, shape evolutions, etc.), one has to deal with the numerical solution of the complex partial–integral–differential equations arising from Eq. (1), which, due notably to their hyperbolic features, raise significant solving difficulties.

During the past 10 years, the use of PBMs to understand complex dispersed processes has reached a new level of refinement as more variables characterizing individual particles – such as particle shape or phase composition, structure of agglomerates, growth rate distributions, etc. – were included in the models to enhance their predictive features (Nopens et al., 2009). Such progresses have been made possible thanks to the availability of frequent, accurate and reliable experimental data. Sensors are indeed the key for developing and validating advanced PBM. Provided appropriate measurements technologies be available, an additional step to crystallization modelling lies in the possibility of simulating new particle features, including crystals end-use and quality properties. Among possible advanced applications, one can mention for example controlling the bio-availability of active pharmaceutical ingredients (APIs), improving the chemical purity of crystals, mastering the textural properties of additives, ensuring the polymorphic stability of crystals on storage, etc.

As emphasized in a following part of this paper, many hopes have thus been placed in the development of process analytical technologies (PATs). However, despite the many progresses accomplished during the past 20 years, monitoring the development of crystallization processes and the time evolutions of the various solid and liquid phases in presence remains an open and complex problem. Meanwhile, even though the development of advanced simulation models is not as crucial to industrialists as developing new measurement technologies, the need for sensors is one of the strongest hyphens between academic and industrial concerns. Unless it is absolutely necessary, the primary need for industrialists is clearly not to obtain nice and intellectually seductive models but to take benefit from research advances in their

current production practice. Such a gap between theoretical issues and process development objectives does not prevent however innovative modelling applications to highlight and suggest valuable industrial progresses. An account on the use of PBMs from industrial point of view (as perceived by BASF SE) is presented by Gerstlauer et al. (2006).

During the past 15 years, the joint use of in-line in situ sensors and PBM has allowed, on the one hand, to analyse and describe the transient behaviour of important crystallization systems; on the other hand, data and modelling tools being available enabled the identification of the kinetic and physical parameters involved for predictive purposes (i.e. nucleation, growth, breakage, agglomeration parameters, etc.) (Nagy et al., 2008; Gherras and Fevotte, 2012; Ma and Braatz, 2003; Schöll et al., 2007). PBM parameter identification should allow a significant advancement in crystallization understanding. As a remarkable example, the irruption of undesirable polymorphic transitions in pharmaceutical production has been a major traumatism which compelled scientists and engineers to focus an important activity on polymorphic systems and on phase transition dynamics. After the famous Ritonavir case in 1998, researchers had to pay more attention on the time of development of drug products, and on a better understanding of the dynamics of phase transition phenomena. Meanwhile, modelling and identifying phase transition processes was made possible by the development of new sensing strategies (e.g. in situ ATR-FTIR spectroscopy, Raman spectroscopy, in situ video acquisition, FBRM, etc.) That is how several research groups in the world reported the application of PAT to monitoring polymorphic transition systems, and few groups presented PB Models of solvent-mediated phase transition phenomena (e.g. Codan et al., 2013; Févotte et al., 2007; Ono et al., 2004).

2.2. PBM and significant current research topics

Many recent trends can be distinguished in the open literature regarding the development of new PBM applications to crystallization processes. Without the sake of completeness, the following three typical subjects of interest can be considered as rather exemplary:

- Modelling the dynamics of 2D and 3D particle sizes is undeniably one of the most challenging and promising current research theme in crystallization: Gaining understanding in the transient behaviour of several crystal characteristic sizes should allow designing new operating and control policies for mastering the shapes of particles and, consequently, the properties related to both the size and shape distribution. As already outlined, completing such a task requires significant improvements in sensing technologies, which, until today, can ill provide the reliable and relevant time varying data required by morphological PB Models.
- Modelling the many breakage and agglomeration phenomena resulting from multi-particle interactions is obviously a key issue for understanding and controlling crystals shape and CSD in real dispersed media and, in particular, during crystallization processes occurring under stirring. As almost every fundamental phenomena involved in crystallization, it is clear that agglomeration and breakage are not merely a question of crystal size distribution. Indeed, the physical complex couplings between basic crystallization phenomena are so strong that agglomeration and breakage can also have a crucial effect on almost all crystallization governing processes. For example, nucleation and growth can significantly be affected by the creation of solid/liquid interfaces exhibiting new surface properties.
- Modelling the crystallization and the separation of optically active molecules is clearly an increasingly important topic, notably for pharmaceutical R&D purposes. To speak only of pharmaceutical applications, it is well-known that the resolution of racemic compounds represents a major therapeutic, economic and industrial issue.

In parallel with the development of new PBM applications, providing predictive features to PB Models requires that a research effort should be focused on advanced parameter identification and state observation techniques (Rawlings and Bakshi, 2006; Bakir et al., 2006). From this latter point of view, it should be underlined that as partial differential systems (i.e. infinite dimensional nonlinear and non-stationary systems), PBEs raise specific and complex mathematical difficulties. As outlined by (Nopens et al., 2009), due to the need of getting appropriate physicochemical, kinetic or thermodynamic data, the availability of experimental information (i.e. thanks to the use of PATs) paves the way of proper model identification, experimental design, and thus allows solving problems related to model predictions. However, the development of specific parameter identification techniques remains a rather "poor relation" in the field, even though theoretical and/or applicative papers have already been published showing the concern of accounting for specific dynamic features of crystallization systems (Nagy et al., 2008; Ma and Braatz, 2003; Ramkrishna and Mahoney, 2002; Mersmann et al., 2002; Marchal et al., 1988; David et al., 1995; Gherras and Fevotte, 2012; Ma and Wang, 2012; Schöll et al., 2007; Cornel et al., 2009; Bück et al., 2012).

2.3. Morphological PBE modelling of particles

Before the appearance of powerful sensing technologies about 20 years ago almost all reported papers have been devoted to modelling the time variations of mono-dimensional crystal size distributions (CSD). In such a framework, it is clear that crystals are improperly reduced to ideal spherical or cubic particles. Putting aside crystal shapes in PBM should now be outperformed because the shape of particles has a large impact on their end-product quality and functionality, as well as on their downstream processing (Lovette et al., 2008).

Morphological modelling is just starting to emerge in PBM. Modelling the time variations of crystal shapes is however a major challenging issue which raises outstandingly tough technological and theoretical problems. "Old" unidimensional CSD models were obviously unable to account for dynamic variations of crystal shapes, and it makes no doubt that modelling particle morphologies will allow significant innovations and improvements for controlling properties of manufactured dispersed solids (Variankaval et al., 2008). An increasing number of studies have been published that can be considered as preliminary steps towards morphological PBM. In most cases, the size and/or shape measurement strategy is based on image analysis (see e.g. Wang et al., 2008; Grof et al., 2011; Ferreira et al., 2011). However, the cart should not be put before the horse: even in the mono-dimensional and 2D cases, measuring particle size is far from being straightforward, especially when the suspension solids content exceeds 8–10%. The difficulty in dealing with concentrated suspensions is

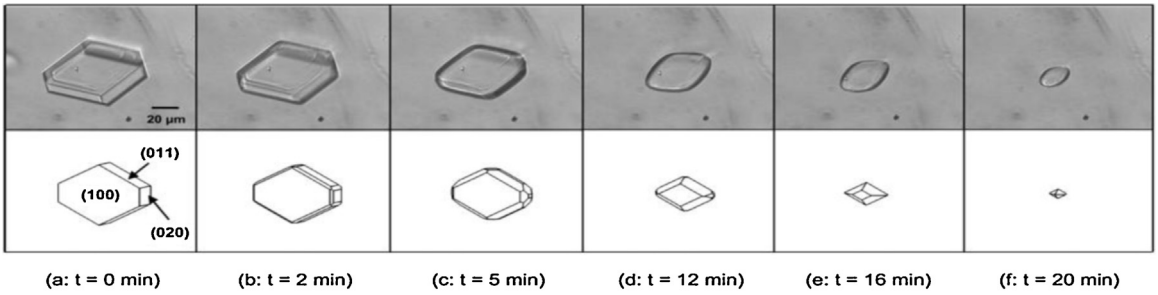

Fig. 1 – Comparison of experimental observations (top) and model predictions (bottom) for *b*-succinic acid dissolving in water (from Snyder et al., 2008).

clearly a severe limitation of most size measurement techniques and, in particular, imaging technologies (Larsen and Rawlings, 2009; Ahmad et al., 2012; Zhou et al., 2009; Simon et al., 2012). Roughly speaking, at least two main difficulties have to be overcome before computing 2D CSDs from video pictures. First, even advanced image processing algorithms hardly identify overlapping, stuck or aggregated crystals; second, it remains difficult to extract "real sizes" of particles from picture where they are necessarily randomly projected on the 2D focal plan (Larsen et al., 2007; Wang et al., 2008; Larsen and Rawlings, 2009; Zhou et al., 2009; Schorsch et al., 2012).

In addition to major technological difficulties, modelling the dynamics of crystal shape during crystallization processes requires a significant and difficult mathematical work. New appropriate mathematical formalisms still have probably to be developed before they can be incorporated in multivariate PBEs; such a very difficult task is still at the dawn even though promising models are already available. For example, the pioneering work presented by Lovette and Doherty (2012) and Lovette et al. (2008) describe the relative perpendicular distances of each crystal face H_i (with $i = 1$ to N) from an origin inside the crystal subject to growth (or dissolution) rate G_i:

$$\frac{dH_i}{dt} = G_i, G_i \in \mathbb{R}, \quad i = 1, \ldots, N \tag{3}$$

The resulting N differential equations are adimentionalized with respect to a reference face H_{ref}. Such change of coordinates allows defining relative growth rates with $x_i = H_i/H_{ref}$ and $R_i = G_i/G_{ref}$ (taken in a broad sense: $x_i < 0 \Leftrightarrow$ dissolution process). Doherty and coworkers then define "warped" times for growth according to the following expression:

$$d\xi = \frac{G_{ref}}{H_{ref}} dt \tag{4}$$

The change of coordinates results in the following "normalized" system derived from Eq. (1):

$$\frac{dx_i}{d\xi} = R_i - x_i, \quad i = 1 \ldots N - 1 \tag{5}$$

The application of known crystallographic data to the new coordinate system allowed reconstructing the crystal shapes in various process conditions (Snyder et al., 2008; Lovette et al., 2012; Lovette and Doherty, 2012; Zhang et al., 2006. As an example, Snyder et al. (2008) designed a purely predictive model in the case of the dissolution of β-succinic acid dissolving in water. The model was compared to the experimental observations. Even though the paper is not the most recent published by the group, Fig. 1 is an impressive illustration of the potential of morphological PBM.

2.4. PBM of crystallization processes with additives or impurities

Trying to see beyond actual research concerns, it may seem surprising that some problems essential to improving crystallization understanding and practice still remain outside the scope of PBM. To take but one example, among the many challenging PBM issues, modelling the inhibiting or promoting effects of impurities or additives on nucleation and crystal growth has not received attention in so far as it is important to fundamental, industrial, environmental and biological crystallization dynamics. This is all the more surprising that impurities are known to have a major impact on the development of industrial, as well as natural crystallization systems. In the case of industrial crystallization even trace amounts of impurities can significantly inhibit or promote crystal growth rates and, consequently, have a significant impact on the sizes and shape distributions of the solid products. It is therefore reasonable to assume that in the near future the effect of impurities or additives should be incorporated in crystallization PBM, because in the "true industrial world", impurities are quite unavoidable.

Most past reported experimental studies dealing with impurities in solution rely on the use of experimental devices allowing measurements of the growth rate of single crystals placed in very specific and restrictive operating conditions (e.g. constant supersaturation, observation of single mono-crystals an others). Such studies cannot account for the complexity and the "non-ideality" of industrial processes. In particular they do not allow investigating the many dynamic couplings between crystallization phenomena (nucleation, growth, etc.) occurring in stirred suspensions of individual particles during batch operations. Thanks to the availability of new sensing PATs the time is right now for the design of PBM accounting for the effects of impurities (or additives).

Inhibition of crystal growth in the presence of impurities is widely reported in the literature (Heijna et al., 2008; Martins et al., 2011; Sangwal, 2007). A common effect of growth reduction is the cessation of the growth rate at the end of batch processes (i.e. when low supersaturation levels are obtained). This effect obviously reduces the yield of solid. Impurities are also undesirable because growth rate inhibitions reduce the productivity of industrial operations. Several inhibition models were proposed in the past, most of them assume that the growth process is hindered by the adsorption

of impurity species on growing crystal faces (Cabrera and Vermilyea, 1958; Kubota, 2001; Martins et al., 2011; Sizemore and Doherty, 2009). For example, Kubota–Mullin model quantify the growth inhibition mechanism through the following ratio Γ between the step velocities in pure (u_0) and impure (u) solvents (Kubota et al., 1997):

$$\Gamma = \frac{u}{u_0} \approx \frac{G}{G_0} = 1 - \alpha\theta^* \tag{6}$$

where α is an overall parameter characterizing the efficiency of impurities to hinder the crystal growth ($\alpha \propto 1/\sigma$), σ the relative supersaturation, θ^* the steady-state coverage fraction by adsorbed impurities of active growing crystal surface can be estimated thanks to Langmuir adsorption theory (in the following K is the Langmuir adsorption constant and C_i is the concentration of impurity):

$$\theta^* = \frac{K C_i}{1 + K C_i} \tag{7}$$

A remarkable early paper was published about the investigation of the precipitation of barium sulfate in the presence of additives (PMA–PVS = polymaleic acid–polyvinylsulfonic acid), that does not seem to have received the attention it deserved (Van Drunen et al., 1996). The study, based on a rather simple PB Model showed that nucleation is enhanced by PMA–PVS. Assuming Langmuir adsorption of the additive on the crystal surface was not found to allow for a reasonable description of the kinetics.

Ferreira et al. (2011) presented a study of the solution crystallization kinetics of 6-aminopenicillanic acid (APA) in the presence of PenG (penicillin G) and PAA (coproduct phenylacetic acid). The kinetic parameters of APA crystallization were determined; the results allowed concluding that the APA crystal growth rates were not changed by adding PenG and PAA in concentrations of 0.55 and 1.13 mM.

Vetter et al. (2011) presented a population balance model of the crystallization of ibuprofen inhibited by the dissolution of polymeric additive pluronic F127. In order to isolate and observe the growth rate, desupersaturation experiments were performed. The latter were seeded by well-characterized sieved crystals. The crystallization process was monitored thanks to the use of ATR-FTIR spectroscopy and FBRM. The kinetic parameters of the crystallization were estimated using "standard" nonlinear optimization techniques fitting the PBM predictions to the experimental data. The joint use of advanced PAT monitoring and PBM was thus shown to open invaluable perspectives for the control of solution crystallization operations using tailor-made additives.

The inhibitory effect of a polymer additive HPMC (hydroxypropylmethyl cellulose) on the nucleation and growth in water of amorphous felodipine was investigated by Abbou Oucherif et al. (2013). PBM showed that HPMC was able to inhibit nucleation and growth at very low polymer concentrations. The inhibitory impact was much greater on nucleation as opposed to growth: HPMC reduces the nucleation of felodipine by a factor up to eight orders of magnitude while it only decreases the rate of crystal growth by a factor of 2.

The above mentioned studies assume steady-state adsorption of impurities while several reported studies have shown that the dynamics of the adsorption on the crystal surface cannot always be neglected (Guzman et al., 1997; Kubota, 2001; Martins et al., 2011). This is the reason why, as a first phenomenological approximation, the transient behavior of the coverage process (i.e. the time variations of θ) was suggested to obey a first-order dynamics with a time constant τ:

$$G(t) = G_0(t)\left(1 - \alpha\frac{K C_i}{1 + K C_i}\left[1 - \exp\left(-\frac{(t-\nu)}{\tau}\right)\right]\right), \tag{8}$$

where $(t-\nu)$ is the time spent by a particle in the presence of impurities. Applying the impurity adsorption model to PBE (even in the mono-dimensional case described by Eq. (2)) is not straightforward as it changes the dimension of the problem: the time $(t-\nu)$ spent by the growing crystals in contact with impurities should now be accounted for. Indeed, even though they are exposed to the same supersaturation, two crystals present in suspension at time t do not necessarily exhibit the same growth rate because their coverage by the impurity differs (i.e. they don't have the same "history"). A new resolution method of characteristics allowing solving this problem was proposed by Févotte and Févotte (2010). In the case of unsteady-state impurity adsorption (Fevotte and Gherras, 2012) studied the crystallization of ammonium oxalate in water in the presence of nickel sulfate. The nucleation, growth and inhibition parameters involved were estimated using experimental supersaturation and CSD data acquired thanks to ATR-FTIR spectroscopy and in situ video imaging, respectively. The PB inhibition model showed that multiple nucleation bursts were made possible by the unsteady-state features of the inhibiting adsorption process (also called pinning mechanism). This phenomenon was suggested to explain the "historical" problem of multiple nucleation bursts in batch crystallization (Mullin, 2001). An extension of the approach has been proposed by Majumder and Nagy (2013) who used a 2D-PBM in conjunction with the growth kinetic model (8) to describe the evolution of the crystal shape distribution in the presence of growth modifiers. The authors also proposed a feedback control approach that manipulates the concentration of the growth modifier in the system to achieve a desired mean aspect ratio of the crystals.

To the best of our knowledge, no more than the five above-mentioned studies dealing with the PB Modelling of the effect of impurities can be found in the open literature. These studies clearly demonstrate how important the effect of impurities or additives is and how it should be further explored in the near future, in particular in the field of pharmaceutical processes.

3. Crystallization monitoring systems

3.1. *Process analytical technology (PAT)*

Process analytical technology (PAT) is a term mainly used in the context of pharmaceutical crystallization processes; however, the associated terms and methods apply to practically all crystallization systems. PAT is defined by the U.S. Food and Drug Administration (FDA) as "a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality" (FDA, 2004). The application of PAT is the key enabler for the implementation of the quality-by-design (QbD) concepts and for advanced crystallization control approaches (Yu et al., 2003; Barrett et al., 2005; Braatz et al., 2002).

The monitoring techniques of the crystallization processes is generally differentiated based on whether the information

obtained is related to the properties of the liquid or the solid phase. The properties of interest of the solution phase are provided by the solution temperature, supersaturation, and concentration, whereas crystal size distribution (CSD) and morphology provide information about the dispersed solid phase. Monitoring the liquid-phase concentration provides information about the degree of supersaturation, hence the driving force of the crystallization, as well as the potential yield. Monitoring the solid phase provides quantitative information about size and shape distribution, polymorphic content, and indicates the existence of agglomeration or breakage as well as provides a direct indication how the operating conditions affect the system and the solid product. The measurement of the liquid- and solid-phase variables is required to (i) develop better understanding of the dominating mechanisms and effect of operating conditions on the crystallization product properties; (ii) design the experiments and obtain data for identification of the crystallization kinetics; (iii) design controllers to maximize product quality and minimize operating costs; (iv) operate the process within the required performance indicators using suitable feedback control. Often PAT techniques are used in conjunction with solid state analyses to provide better understanding of crystallization processes (Abu Bakar et al., 2011; Howard et al., 2009).

The real-time process information provided by the PAT tools can be integrated into the control algorithm to provide an optimal control strategy. PAT focuses on the utilization of real-time measurement tools but also incorporates chemical, physical, microbiological, and statistical analysis such as chemometrics conducted in an integrated manner (Yu et al., 2003). Chemometrics is typically applied in the interpretation of the multivariate data provided by in situ process monitoring devices. In addition to constructing calibration models for sensors, chemometrics can be used to derive mathematical relationships between the desired product properties, such as the CSD, and the various contributing variables, such as the solute concentration. The mathematical relationships can be constructed using multivariate data analysis methods such as multiple linear regression (MLR), principal component analysis (PCA), principal component regression (PCR), partial least squares (PLS), and variations of these approaches. One of the key areas where significant developments have been achieved in the past decade is in the imaging and image analysis based monitoring of crystallization processes.

3.2. *Imaging sensors*

Imaging sensors have received significant attention in the last 20 years due to the capability of monitoring individual crystal features e.g. two or three dimensional size and because images represent an intuitive source of information. A review by Verma and Shlichta (2008) discusses that crystal size and growth monitoring using optical, electromagnetic and acoustic imaging has attracted significant interest for convection, temperature and solute concentration monitoring around a growing crystal.

An early work which deals with optical imaging based crystallization process monitoring – flow-through cell placed below a microscope – is the contribution of Patience and Rawlings (2001). Optical imaging sensor developments have been started more than 10 years ago by companies such as DuPont, USA (Scott et al., 2001), Lasentec/Mettler Toledo, Switzerland (Kempkes et al., 2008), MTS-Düsseldorf, Germany (Qu et al., 2006), Perdix, The Netherlands (Li et al., 2008), PS Prozesstechnik GmbH, Switzerland and Sartorius Stedim Biotech, Germany (Bluma et al., 2009), which propose probe based solutions. Recently, also universities have been involved in the design of optical imaging probes (Presles et al., 2010; Khalil et al., 2010; Khalil et al., 2011) and evaluation of low-cost PAT sensors such as endoscopes (Simon et al., 2009a). The fast adoption of the endoscopy concept in the industrial environment at Lonza AG, Visp, Switzerland has demonstrated that low-cost PAT tools can be used for crystallization monitoring (Simon et al., 2012). Furthermore, the SOPAT GmbH spin-off grounded in 2012 from the TU Berlin (www.sopatec.com) also proposes an endoscopic imaging hardware for process monitoring, so that the interest for this sensor is confirmed. Another in situ imaging probe, which is for example regularly used for crystallization process development at BASF SE is the MV-i sensor from Microvision Instruments, France.

Other imaging sensors are the flow-through cell imaging devices (Ferreira et al., 2011; Kempkes et al., 2010b) such as the XPT-C from PS Prozesstechnik GmbH, Switzerland (Arnold et al., 2011), Malvern Sysmex FPIA 3000 and Qicpic from Sympatec, Germany (Borchert and Sundmacher, 2011). A non-contact external monitoring solution was developed at GSK to measure particle size (De Anda et al., 2005a,b). Abu Bakar et al. (2010) proposed an image analysis approach that used images obtained from hot stage microscopy to identify polymorphic transformations. Using a similar approach, crystal growth and nucleation rates have been extracted from hot-stage microscopy pictures by Stapley et al. (2009). The in-situ imaging probes have also been used for crystallization process scale-up in skid configuration next to refractive index, particle size and liquid concentration measurements (Kadam et al., 2012). Furthermore, experimental setups which use three-dimensional imaging techniques constitute an emerging field of research (Wang et al., 2008; Kempkes et al., 2009, 2010a; Darakis et al., 2010; Khanam et al., 2011; Sandler, 2011; Soppela et al., 2011; Chakraborty et al., 2012; Singh et al., 2012; Schorsch et al., 2012).

3.3. *Image analysis strategies*

The image analysis methods encountered in the field of crystallization process monitoring can be classified in two major classes: those which aim at the crystal boundary detection and those which monitor changes of image descriptors. In the image analysis literature the first class is referred to as blob or object detection/segmentation while the second class is mainly classified as texture analysis. The information obtained upon image segmentation is the presence of crystals in images (nucleation detection), two or three-dimensional size (crystal growth, dissolution, shape change associated with polymorphic transformation) (De Anda et al., 2005b; Sarkar et al., 2009; Zhang et al., 2011) and the number of crystals in the image (secondary nucleation, attrition or breakage). The crystal size information is typically used to validate population balance models (Caillet et al., 2007; Ma et al., 2007; Puel et al., 1997).

During a regular crystallization process the solid concentration can reach as much as 20–30% w/w% so that the information extraction from such images is more challenging due to out of focus and overlapping crystals. Therefore, several research projects have presented results which tackle this latter issue (Larsen et al., 2006; Korath et al., 2007; Ahmad et al., 2012). A recent contribution from Zhang et al. (2011) performs a wavelet transformation on the images and then use

fuzzy C-means clustering for particle segmentation. Furthermore, multivariate statistical concepts can be used on image texture descriptors to perform segmentation (Sarkar et al., 2009). Another way of identifying crystal shape in images is to match partial crystal features with shape templates defined a priori—this is referred to as model based object recognition (Larsen et al., 2007). Object identification can also be used to perform nucleation detection and to decide whether new crystals appear in images (Simon et al., 2009a). The particular feature of this application is that the image background or reference image is constant—the clear liquid is the background and the reference is dynamically updated. This implies that performing a background subtraction – the previous image is subtracted from the current – the appearance of the crystals can be identified. The updating of the reference provides additional robustness and is needed to compensate for external (e.g. light conditions in the lab) or internal (due to the lamp) changes of illumination intensity. Sensitive nucleation detection methods can be used for the accurate determination of induction times thus nucleation mechanism, metastable zone and can significantly improve the crystallization process control when the direct nucleation control method is implemented. In this latter application early nucleation detection allows the controller to drive the measured FBRM counts faster and with less overshoots or heating/cooling cycles to the specified setpoint (Abu Bakar et al., 2009; Saleemi et al., 2012a,b).

The reliability to infer particle size distributions from images with overlapping particles can be assessed using a dimensionless number as discussed by Larsen and Rawlings (2008), while Zhou and co-workers have concluded that monosodium glutamate crystal size can be tracked within 8% error (Zhou et al., 2009). In order to perform the automated tuning of the segmentation algorithms, the crystal size determination can be posed as a non-linear optimization problem which is solved with a gradient-free method such as the simplex routine (Zhou et al., 2011).

The image texture based methods derive process information in form of specific image descriptors e.g. image intensity or brightness, scaling exponent of fractality (Velazquez-Camilo et al., 2010a,b) or fractal dimension (Zhang et al., 2013). For concentrated slurries with overlapping particles an alternative to segmentation is to use image feature or texture descriptors. The time series trends based on these descriptors can be linked to various process states (calibration) or conclusions can be drawn based on trend evolution so that process transitions can be detected. In this category belongs also the bulk video imaging concept since no crystal property is monitored, and rather the bulk reflective properties are recorded (Simon et al., 2009b). In previous works it was shown that nucleation onset determination and solid-concentration change associated with polymorphic transformation, growth and dissolution as well as mixing changes can be monitored using image intensity or image histogram mean trends (Simon et al., 2009b, 2010a) the information behind these two concepts are equivalent as discussed by Simon et al. (Simon et al., 2010b). Recently, it was shown that image intensity trends can be used to measure dissolution curves (Silva et al., 2013).

The use of image intensity trends is analog with the concept of the widely spread turbidity meter which can be calibrated to slurry properties such as particle size and solid concentration, and it is used to monitor nucleation, crystal growth, breakage and dissolution. Since both the endoscope and turbidity sensors are in the low-cost category future investigations and systematic comparison works are relevant to identify the similarities and differences between turbidity measurements and intensity trends derived from images; first steps in this direction have already been reported (Caciano de Sena et al., 2011; Simon et al., 2011).

From industrial point of view non-contact externally placed sensors are of particular interest. Such sensors are the FT-Raman, FT-NIR and imaging systems (Simon et al., 2009b; De Anda et al., 2005a; Brown and Ni, 2011a; Brown and Ni, 2011b, 2012). Particularly in pilot and production facilities, these show inherent advantages which can be translated into low implementation costs e.g. installation, minimum maintenance as fouling does not occur and avoidance of sensor damage due to corrosive low pH environments encountered in the case of many reaction-precipitation systems.

3.4. *Challenges in crystallization monitoring*

The breadth of analytical methods which are suitable to be used as PAT is extremely broad. Much of the recent attention has been on spectroscopic methods which include IR, NIR, UV and Raman techniques. An important challenge is related to the fact that most techniques have been used in single component crystallisation systems, whereas in practice crystallisation most often occurs in the presence of other species. The development of robust monitoring approaches for multi-component crystallisation systems is a key enabler for the widespread adoption of these approaches. This often requires the development of nonlinear deconvolution approaches, and results in complex calibration methods. However, the complexity of the chemometric approaches required may hinder the broad industrial application of the techniques. Hence a challenge is to develop simplified and/or automated calibration approaches or methodologies based on the direct interpretation of the signals. The reliable measurement of components in low concentrations is also key challenge which would allow the direct control of the purity of the crystals and enable the use of low concentrations of growth and nucleation modifiers for better crystal shape control. This requires developments both in the sensor technologies (e.g. specially coated optical windows) and the calibration/chemometric methods.

While highly accurate in situ concentration monitoring approaches have been developed, the monitoring of the solid state properties is still a challenge. The currently available techniques generally provide mean properties or work only for solid concentration much lower than typically found in crystallisation systems. Attempt to overcome these problems have been proposed by the in line use of the approaches in measurement systems with complex dilution loops, which however may affect the properties of the samples. Recent advances in the application of holography based imaging approaches can provide high quality size and shape information in slurries however the problems related to high solid concentrations are yet to be resolved.

3.5. *Emerging topics in crystallization monitoring*

The development of new cost effective PAT tools is of increasing importance. Various in situ low-cost sensors have been proposed for process monitoring: di-electric constant measurements (He et al., 2010, 2012), refractive index, acoustic methods (Pertig et al., 2011; Stelzer et al., 2013) and acquisition of optical images (Simon et al., 2012). Recently, an exposed core optical fiber sensor has been proposed for scale formation monitoring (Boerkamp et al., 2013). Furthermore, it is

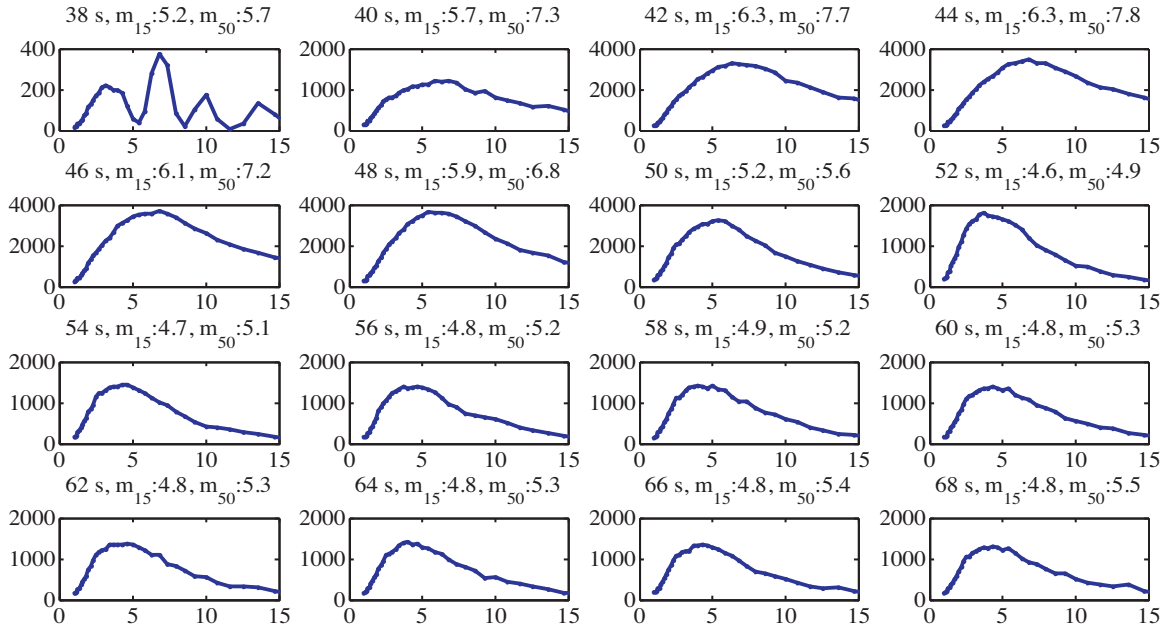

Fig. 2 – Chord-length distributions before and after nucleation (Simon and Myerson (2011)); x: cld size, y: counts/s. Nucleation detected at 40 s. m_{15} is the unweighted mean CLD size on the 1–15 μm interval; m_{50} refers to the unweighted mean on the 1–50 μm range.

considered that non-contact sensors will receive significant attention in future e.g. external imaging (Simon et al., 2009b) and external acoustic monitoring (Gherras et al., 2012).

Another emerging field for the application of PAT sensors is in the context of continuous crystallization monitoring. As of today FBRM implementations (Simon and Myerson, 2011; Ferguson et al., 2012) and on-line imaging (Borchert and Sundmacher, 2011) have already been reported. Fig. 2 shows the chord-length distributions recorded during the anti-solvent precipitation in a plug-flow flow crystallizer equipped with a Kenics static mixer.

As shown by recent contributions, it is also expected that the PAT sensors will play an important role in the monitoring and control of co-crystallization processes e.g. ATR-FTIR (Gagniere et al., 2009; Yu et al., 2010, 2011; Gagniere et al., 2012) and FT-NIR spectroscopy (Lee et al., 2013).

Generally industrial crystallization occurs in impure media when often multiple species may crystallize out. Nevertheless most crystallization studies focus on the recrystallization of single pure components. Very few studies have been performed for the monitoring and design of multi-component crystallization systems (Saleemi et al., 2012d).

Calibration-free process monitoring is another promising class of methods which facilitate the implementation of PAT. In this area two major categories have been proposed: the first is the *model based* calibration-free monitoring e.g. monitoring of liquid concentration and solid concentration of polymorphic forms (Cornel and Mazzotti, 2008)—this method is a remarkable extension of the early work of Maeder and Zuberbuehler (1990); Puxty et al., 2006). Using the same concept it was also shown that crystal growth rates can be monitored by fitting directly the ATR-FTIR and Raman spectra (Cornel and Mazzotti, 2009). In the second class of calibration and model-free methods belongs the supersaturation monitoring concept using ATR-FTIR (Barrett et al., 2010) and Raman spectroscopy (Hao et al., 2010); these monitor spectra intensity changes in relation to spectra intensity corresponding to the equilibrium solubility.

A key area is definitely the development of in situ measurement techniques for crystal size and shape which can work in high solid concentration. Despite the fact that various PAT techniques are often used simultaneously to monitor crystallization processes, the resulting information is very rarely combined and applied for decision making or control in real time. More recently the concept of crystallization process informatics system has been introduced, which is based on the use of a so-called composite sensor array (CSA), or composite PAT array, for monitoring multiple process and quality properties at the same time, rather than one at a time (Nagy and Braatz, 2012). The concept of CSA is based on considering the combination of signals from various PAT measurements as a single bundle of complex information, which allows using simultaneously all signals from all measurement devices for automated decision support and feedback control of the crystallization process. Fig. 3 shows an illustration of the first implementation of the crystallization process informatics system (CryPRINS) concept with a CSA that consists of a focused beam reflectance measurement (FBRM), a particle vision and measurement (PVM), an ATR-UV/Vis and a Raman probe, developed at Loughborough University, UK. The complementary and redundancy in the acquired

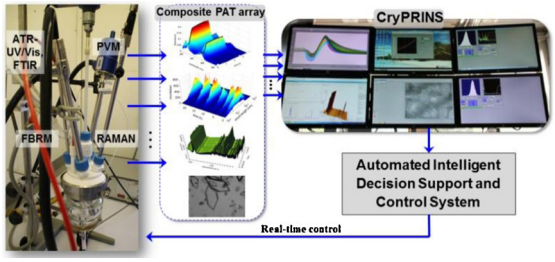

Fig. 3 – Picture and diagram of a crystallization system with a composite sensor array (CSA) and crystallization process informatics systems (CryPRINS).

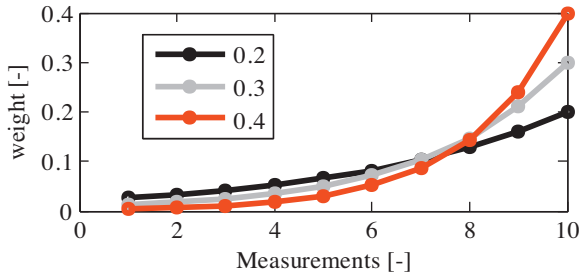

Fig. 4 – EWMA weights as function of lambda for a moving window of size 10.

information provided by the CSA allow the implementation of robust crystallization control strategies. This system must also provide a generic communication interface based on industry standard protocols such as OPC (OLE – object linking and embedding – for Process Control) or ethernet, to allow the communication between various PAT technologies provided by different vendors and the distributed control system (DCS) to implement the proposed control actions. The combination of the signals can be performed using model-based approaches or by applying chemometrics using simultaneously all signals from all measurement devices, with a system that automatically determines the most relevant combination of signals for a particular process or control objective. For the broader adoption of this information integration concept and the use of PAT tools in feedback control it is paramount that sensor vendor companies recognize the importance of providing industry standard communication features within their software system that allow real-time connection with control technologies, rather than using the instruments as simple stand-alone monitoring tools.

4. Statistical process monitoring concepts for crystallization systems

Traditionally the concept of statistical process monitoring (SPM) has been developed and proposed for the monitoring of steady-state processes. These methods are built on time series measurements and are used to signal unwanted departures from steady-state conditions. Thus these approaches are readily applicable in the monitoring of continuous crystallization systems.

The purpose of statistical monitoring tools is to discriminate between random events and systematic changes of the process. The percentage of tolerated Type I monitoring error – the process is considered out of control, when actually is not – is typically 5% or 1%, which implies that out of 100 measurements 5 or 1 may be *randomly* out of the control limits. It is important to highlight that when consecutive measurements are out of control it is a sign of autocorrelation and then the process indeed can be considered as changed.

Frequently used statistical monitoring methods are the control charts e.g. Shewhart (1925), cumulative sum and exponentially weighted moving average (EWMA) (Hunter, 1986). These control charts are built on stationary time series and assume normal distribution and independence between measurements. These charts differ from each other by applying different weighting to past data samples: e.g. the Shewhart chart weights only the last observation, the CUSUM chart assigns equal weights to all observations and the EWMA applies an exponentially decaying weighting (Fig. 4) according to the following equations:

$$y_{t+1} = \sum_{s=0}^{t} w_s y_s \tag{9}$$

where y_s is the observation at time t, y_{t+1} is the EWMA prediction and w_s are the weights.

$$w_s = \lambda(1-\lambda)^{t-s} \tag{10}$$

where λ is the memory factor [–] which usually takes values between 0.15 and 0.4. Note that when lambda is one only the weight of the most recent measurement is 1 and the rest 0, which corresponds to the Shewhart chart. To decrease the false alarms rate the control charts are used in combination with control rules.

In order to investigate the autocorrelation patterns in the frequency domain frequency plots or periodograms are used and the autocorrelation extent is evaluated by using autocorrelation charts. The autocorrelation of a time series ρ_k at lag k is unknown in practice but it can be estimated for a stationary process:

$$\rho_k = \frac{\gamma_k}{\gamma_0}, \quad k = 0, 1, 2, \ldots \tag{11}$$

where γ_k is the autocovariance function defined as

$$\gamma_k = \frac{1}{N}\sum_{t=1}^{N-k}(y_t - \bar{y})(y_{t+k} - \bar{y}), \quad k = 0, 1, 2, \ldots \tag{12}$$

where y is the time series and $\bar{y}$ is the sample mean. The 95% confidence interval is defined by two standard deviation limits $\pm 2(\mathrm{Var}(\rho_k^2))^{\frac{1}{2}}$ where Var is the variance of ρ_k assuming that the true autocorrelations beyond some lag u are zero (Box et al., 2008):

$$Var(\rho_k) \approx \tfrac{1}{N}(1 + 2(\rho_1^2 + \cdots + \rho_u^2)), \quad u = k - 1 \tag{13}$$

An alternative to periodograms is the Durbin–Watson (Durbin and Watson, 1950) autocorrelation test.

Highly auto-correlated time series occur when an imaging sensor systematically captures reflections due to moving parts e.g. reflections from the stirrer in a stirred vessel. Since the batch crystallization vessels are mixed this issue inherently needs attention (Simon et al., 2010a). The reason why autocorrelation needs to be addressed is that it causes false alarms or Type I errors. In order to remove the cyclic patterns often digital filters are designed in the frequency domain and the filter is convoluted with the measurements. Another option is to use control charts which take into account the autocorrelation and modify the control limits accordingly (Lu and Reynolds, 1999). A further approach is to fit a time series model that models the autocorrelation and then use the residuals for monitoring.

To test for normal distribution several normality tests can be used such as: Lillefors or modified Kolmogorov–Smirnov, Cramer von Misses, Anderson–Darling, χ^2 goodnes of fit, Shapiro–Wilk and Jarque–Bera. Fig. 5 shows the Fourier spectra of a time series which contains oscillations at 1.66 Hz (the images contain reflections from a stirrer rotating at 100 rpm) and the spectra of a random and normally distributed trend. Note that in the latter case no dominating frequency can be identified and the power is approximately equal at all frequencies—this is often also referred as Gaussian white noise.

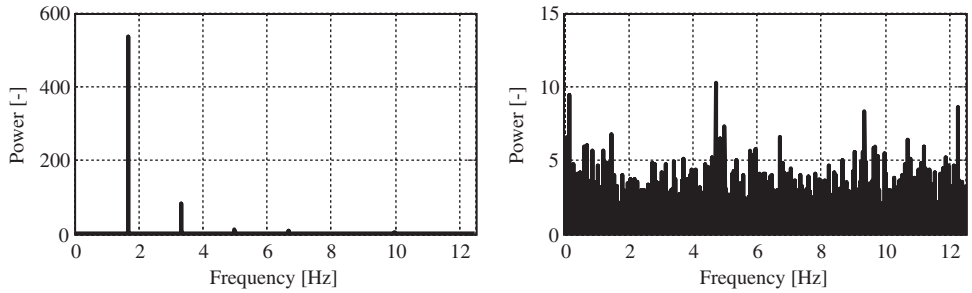

Fig. 5 – Power density plots of autocorrelated (left) and of randomly, normally distributed time series (right), 25 Hz sampling.

Control chart applications for crystallization process monitoring include nucleation detection using ATR-FTIR spectra (Pollanen et al., 2006) and imaging data (Simon et al., 2010a). When multivariate data is available and the variables are correlated – not to be confused with the autocorelation of time series – e.g. spectra, the use of multivariate control charts e.g. dynamic principal component analysis is one choice as shown by Thirunahari et al. (2011). Works published by Simoglou et al. (2004, 2005) discuss the comparison of batch dynamic principal component analysis, moving window principal component analysis, batch observation level analysis, time-varying state space modelling (TVSS) for the monitoring of sugar crystallization. The authors have found that TVSS is the most effective in handling varying batch lengths and the presence of serial correlation (autocorrelation) among data. Two recent works discuss the implementation of multivariate control charts on the FT-Raman and FT-NIR spectra to monitor the polymorphic transformation of Carbamazepine and Piroxicam (Rocha and Poppi, 2010, 2011).

A further use of the control charts is not only to indicate deviation from desired process states or product characteristics but also serve as a switching mechanism. The implementation of such concept for the switching from nucleation to seed conditioning is discussed by Simon et al. (2010b). In this regard the control charts can be seen as the simplest feedback control structures and can be designed on time series generated by any sensor e.g. turbidity, FBRM counts or on the intensity trend of the first principal component (T1) of colour images, as shown in Fig. 6.

It is foreseen that with the advent of continuous manufacturing and continuous crystallization the application of statistical process monitoring methods will experience a revival since it is of utmost importance to ensure that the crystals properties are constant.

5. Crystallization control approaches

In the majority of industrial crystallization systems, typical feedback control strategies (e.g. PID, cascade) are designed to follow simple heuristic operating policies (e.g. a linear temperature profile or an antisolvent addition or evaporation rate) (Rawlings et al., 2002).

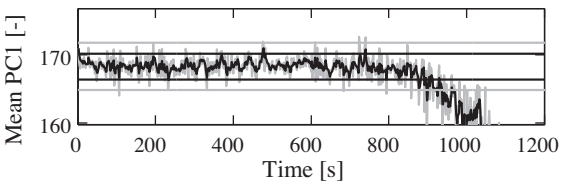

Fig. 6 – Shewhart (gray) and EWMA (black) SPCs of mean T1 images: the decreasing trend is due to negative loadings (Simon et al., 2010a).

The most important driver for the implementation of crystallization control strategies has been the development of the in situ sensors, which have become available in the last decade of the previous century and enabled real-time precise measurement of the solute concentration (e.g. via ATR-FTIR, ATR-UV/VIS), and the characteristics of the crystal size distribution such as mass, size, shape and morphology. This recent emergence of modern sensor technologies and advances in crystallization modelling and control have enabled more advanced control strategies to be increasingly applied (e.g. Braatz, 2002; Fujiwara et al., 2005; Mesbah et al., 2011b; Nagy, 2009). Generally speaking, two main classes of control approaches can be differentiated for crystallization processes: (i) model-based and (ii) model free control techniques (Fig. 7). However more recently hybrid control approaches have also been developed that use a combination of model-based and model-free control techniques for crystallization design and control. For example simplified model-based CSD estimators have been developed and used for crystallization design and control, which are based on the assumption that the crystallization process is controlled at a constant supersaturation level, achieved using model-free (supersaturation) control approaches (Aamir et al., 2009, 2012; Nagy and Aamir, 2012). Additionally, model-free control approaches can be used to selectively trigger crystallization mechanisms by designing intelligent controlled experiments (e.g. growth dominated process versus growth with nucleation) that will provide experimental data that can significantly enhance the estimation of parameters for crystallization models.

5.1. *Model-based control approaches*

Model based control strategies range back to the early seventies when pioneering work of Mullin and Nyvlt (1971) and Jones and Mullin (1974) showed the benefits of a programmed off line calculated cooling profile. Since then, especially in the last decades, major advances have been made the model based optimal control of various aspects of the product quality (Nagy and Braatz, 2012). The model-based optimization is subject to a set of constraints due to equipment limitations (e.g. maximum and minimum temperature values, maximum and minimum cooling rates, maximum volume, limits on antisolvent addition rate). The crystallization must also satisfy a productivity constraint that ensures a desired yield at the end of the batch. Quality constraints can also be included in the optimization (e.g. Worlitschek and Mazzotti, 2004; Corriou and Rohani, 2008; Sarkar et al., 2006). The main advantage of the model-based approaches is that in principle

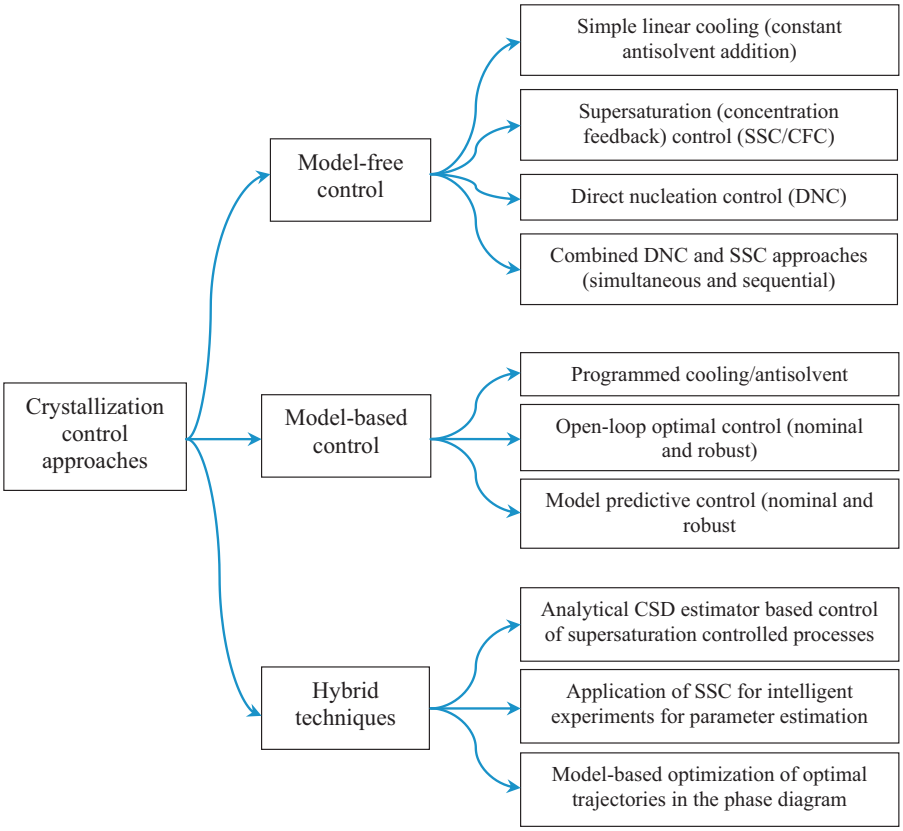

Fig. 7 – Generic breakdown of crystallization control approaches.

they can provide the theoretically optimal recipe or operating conditions and generally require smaller number of experiments for identification, especially when properly designed, than for statistical experimental design of crystallization conditions. Model-based techniques also have the benefits of increased process understanding, and the possibility of incorporating the effects of non-ideal mixing via computational fluid dynamics (e.g. Woo et al., 2006). However these advantages also impose several challenges and require the solution of a series of scientific problems.

Nagy and Braatz (2012) pointed out in their review a number of problems in the general model based control work:

1. There is a strong emphasis on the optimization of the temperature profile without taking into account the growth characteristics of the nuclei or seed crystals (e.g. growth rate dispersion).
2. There is on overwhelming use of the mean crystal size and coefficient of variation as the main control objective, which can still result in a large number of fines particles.
3. Failure to take into account the uncertainty in the kinetic models, which can lead to very poor performance of the controller when applied in practice.
4. Lack of attention to the operational constraints of the supersaturation during operation, which is defined by the metastable zone for primary or secondary nucleation.

Different model-based control approaches are possible ranging from programmed cooling using a simple tracking controller to enforce a predefined cooling profile in the crystallizer up to multi-variable non-linear optimal control (such as nonlinear model predictive control), which requires a real-time simulation and dynamic optimization of the input trajectories. The main components for a model-based control strategy are:

(i) The process model, which describes the product quality and process performance of the crystallization process with the required accuracy. The model is used either in real-time or off-line to achieve the desired performance or product quality. The model can be a detailed non-linear process model, describing all the details of the crystallization process and mass transfer in the crystallizer; however often a simplified, reduced or linearized model is used to enable real-time optimization of the trajectories. In most cases the process model consists of the population balance equation, material and enthalpy balances and constitutive kinetic models for the crystallization kinetics. The model should give a robust and accurate description of the crystallization process in the current crystallizer and therefore always requires parameter estimation and validation steps before it can be applied in the controller design. In addition to be used for the calculation of the optimal operating profile a process model is required in the observer in the case of real-time model based control for state and parameter estimation.

(ii) A dynamic observer can be used to prevent that the states in the process model drift away from the real states in the process. This is a crucial component of the model-predictive control scheme to achieve robust offset-free control. It is important to note that even if in the case of crystallization processes often full state-feedback can be achieved by using appropriate measurements (measuring concentration, CSD, temperature, etc.), the use of state estimation is still crucial to deal with model-plant mismatch and achieve robust control performance.

The states in the model are continuously updated on the basis of the real-time measured process variables and corrected for process disturbances, model/plant mismatch and uncertain initial conditions. The observer is also used to estimate unmeasurable process variables. Different types of observers have been used in crystallization control. In combination with the moment model in many cases the extended (non-linear) Luenberger type of observer is used (Kalbasenka et al., 2007; Mesbah et al., 2011a). Other types are available and Mesbah et al. (2011a) have recently performed a comparison between the different types of observers and concluded that both the extended as well as the unscented Kalman filters can give better performance than the deterministic extended Luenberger observer.

(iii) A dynamic optimizer is used to determine the optimal trajectory to reach the desired state of the process at the lowest possible costs. The possibility to formulate constraints represents an important advantage of the model-based control approaches. The efficiency and robustness of the optimiser plays an important role in the design of the control system. Mesbah et al. (2011b) compared three different non-linear optimization strategies, i.e. single shooting, multiple shooting, and simultaneous optimization, in a real-time implementation of the model-based control approach. The results indicated that the three optimization strategies perform similarly in terms of optimal process operation. However, the single shooting strategy is computationally more expensive.

Hu et al. (2005) studied the optimal control of a batch cooling process, maximizing final-time seed size and minimizing the mass ratio between the nucleated and the grown seed crystal using the cooling profile. Chung et al. (1999) proposed a seed distribution design approach using model-based optimization of the shape of the seed CSD. Although optimal control gave some improvement of the objective function, hardly any effect was found on the product CSD. Kalbasenka et al. (2007) studied the growth behaviour in seeded batch evaporative crystallisation experiments using narrow seed distributions of grinded crystals and reported a strong dispersion in the growth rates and even dissolution of part of these seed crystals, which resulted in a strong broadening of the CSD of the product crystals and in a lack of batch to batch reproducibility. Pre-treatment by ageing of the seeds crystals and a high relative supersaturation in the crystallizer at the initial growth phase of the seed crystal were found to be essential to remove the batch to batch variability of the crystal size and to lower the width of the distribution. Aamir and coworkers confirmed the importance of the quality of seed crystals (Aamir et al., 2010). From a combined model-based and experimental evaluation, they concluded that depending on the pre-treatment of the seed crystals, initial breeding, ripening and agglomeration can drastically influence the performance of the seeds, stressing the importance of the use of well-defined seed preparation techniques. They also proposed a model-based recipe optimization approach that allowed very good tailoring of the product CSD by combining the right amount of sieved seed fractions (Aamir et al., 2010a). Mesbah et al. (2011b, 2012) performed closed-loop model based control studies on a semi industrial batch evaporative crystallizer. In these dynamic optimization studies the growth rate was maximized below a predefined constrained value after the initial phase of the batch by manipulation of the heat input to the crystallizer. The results showed that the model-based growth control approach was able to achieve a substantial increase, i.e. 30%, in the amount of crystals produced in the batch at constant product quality (Mesbah et al., 2007, 2010, 2011b, 2012). Although no attempts were reported to improve on the product quality the feasibility of the model-based control approach was clearly demonstrated both based on the reduced (moment model) as well as using the full population balance models.

Nagy and Aamir (2012) continued on this line and designed a simpler controller based on the idea that if the supersaturation is properly controlled at a sufficiently low level using a supersaturation control approach, the seeded batch process will be dominated by growth only. For such a case an analytical CSD estimator has been derived, which directly relates the seed CSD to the product CSD with only two degrees of freedom, i.e the supersaturation level and the batch time (Nagy and Aamir, 2012; Aamir et al., 2012). An off-line optimization can then determine the temperature profile needed to achieve the desired CSD. Experimental evaluation of the method showed a remarkable ability to generate a predefined shape of the product CSD (Aamir et al., 2012). Zhang et al. (2012) continued this line of research and extended it to include both primary and secondary nucleation in unseeded batches using a discretised process model. First of all the reachability of the desired product CSD is determined taking into account model uncertainty, especially for the nucleation parameters (Zhang et al., 2012). Due to the strong impact of the uncertain nucleation parameters on the crystallization process, leading to infeasible control the authors propose to add an additional control law based on the moments of the distribution, which can be obtained using a state estimator from the concentration measurements. Nagy (2009) proposed a robust control scheme consisting of a tracking controller for the temperature and concentration to drive the system to the desired location in the phase diagram and a robust supervising controller to adapt these trajectories in the case of changing process conditions or process disturbances (Nagy, 2009). Several of the proposed techniques have used controlled dissolutions for the elimination of unwanted fine particles (Nagy et al., 2011). Samad et al. (2013) used the simplified analytical estimator developed by Nagy and Aamir (2012) and proposed a systematic framework for the design of process monitoring systems for crystallization processes.

5.2. *Challenges*

The main challenges in the control of crystallisation are mainly related to the large variations in the solution thermodynamics and kinetics, which can be induced by impurities or other components in the crystallizer, the complex nonlinear dynamics with non-ideal mixing, and various disturbances characteristic to these systems, made often more complex due to multiple polymorphic phase transformations and complex shapes (e.g. in the case of large organic molecules). These complex processes are often characterized by different spatial and time scales. Challenges are also related to the increased difficulty in modelling some of the practical objectives (e.g. filterability, purity, tablet stability, dissolution behaviour), and the significant time and engineering effort required for the model development. Additionally, the performance of the model-based approach depends on the model accuracy although the robustness of the model-based control

approaches can be improved by incorporating linear or nonlinear robustness analysis into the optimization (Nagy, 2009).

5.3. Scientific issues

Current scientific issues are related to the (i) modelling aspects (ii) efficiency of the control and optimisation approaches (iii) availability of reliable sensor technologies. Since generally various mechanisms at different scales are relevant for the properties of the crystalline products it is important to use appropriate multi-scale modelling approaches for the analysis, design and control of crystallization processes. The model-based control approaches often require the solution of one or more population balance equations (PBEs), hence the development of efficient numerical solution approaches is crucial for real-time model predictive control. For shape and polymorphic control, or when dissolution is also considered a system of two- (or multi-) dimensional PBEs must be solved. The incorporation of better mechanistic models in the PBE, which describe nucleation, growth, agglomeration and breakage based on first-principles as well as the effect of hydrodynamics, would significantly enhance the prediction ability and robustness of the model-based control techniques. With these increases in the model complexity the development of efficient numerical approaches for the solution of the model equations as well as for the optimisation problem becomes increasingly important. Efficient model-based estimation approaches which can use the information available from different sensors at different time scales and provide the parameters and consistent initial conditions required for the model prediction must be developed for the feasible real-time application of the crystallisation control approaches.

5.4. Emerging topics

Emerging topics for model-based control include the development of novel control approaches that allow more freedom in designing simultaneously the crystal shape, polymorphic form and CSD. For example the use of growth and nucleation modifying agents as manipulating inputs can provide extra degrees of freedom for better manipulation of the crystal properties. The simultaneous optimisation of different supersaturation generation approaches (e.g. cooling and antisolvent addition) can significantly enhance the efficiency of the crystallisation processes (Nagy et al., 2008b). The application of dynamic seeding has recently proved to be an efficient new control approach to improve the CSD control (Nagy and Aamir, 2012; Woo et al., 2011). Model-based approaches also enable the design and control of crystallization processes as integrated unit operations, taking into account downstream processing units, and considering final product properties as control objectives. These integrated product and process engineering approaches will need to combine advanced sensor technologies using information fusion, as well as model-based and model-free control techniques to design products with tailor-made properties (Fig. 8). Control of continuous crystallisation processes is of increasing interest in particular in the pharmaceutical industries. The current aim in developing crystallisation control approaches is the implementation of a new generation of integrated and intensified crystallisation systems with drastically improved flexibility, predictability, stability and controllability. New directions of developing control systems for crystallization include the use of hybrid first-principles and data-driven (e.g. statistical, artificial neural networks, response surface methods, etc.) modelling approaches, multi-objective nonlinear model predictive control techniques, as well as the development of robust and intelligent adaptive control methodologies. These approaches will enable the crystallisation as an integrated, intensified and intelligent process, which can react and adapt to changing operating conditions to guarantee the sustainable production of consistent high quality final solid products.

5.5. Model-free control approaches

Model-free control approaches are based on the direct use of PAT-based measurements in feedback control of crystallization processes. Model-free control approaches include: (i) the simple control using linear cooling (or constant antisolvent addition), (ii) supersaturation control (SSC) or often called concentration feedback control (CFC) approaches (Gutwald and

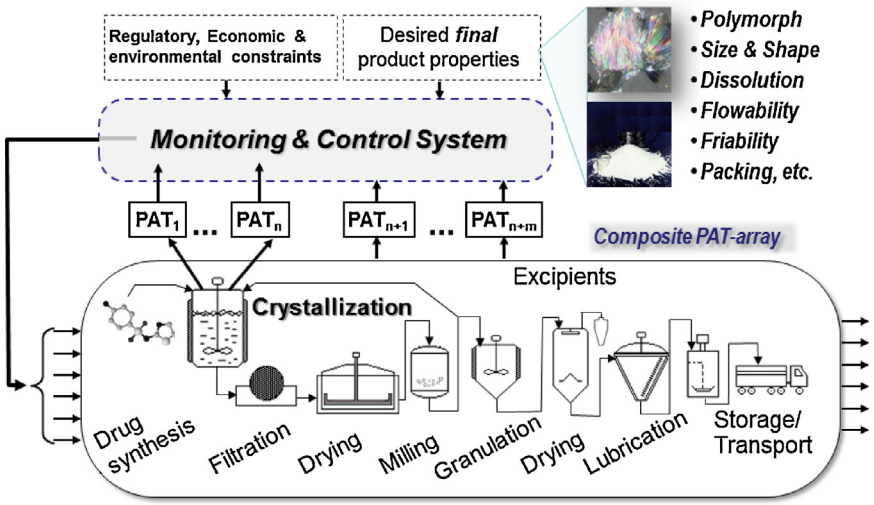

Fig. 8 – A systems view of the integrated crystallization and product formulation process chain for end-point particle property control. Crystallization is the key unit operation between drug synthesis and the formulation and the process where the key solid properties can be manipulated first.

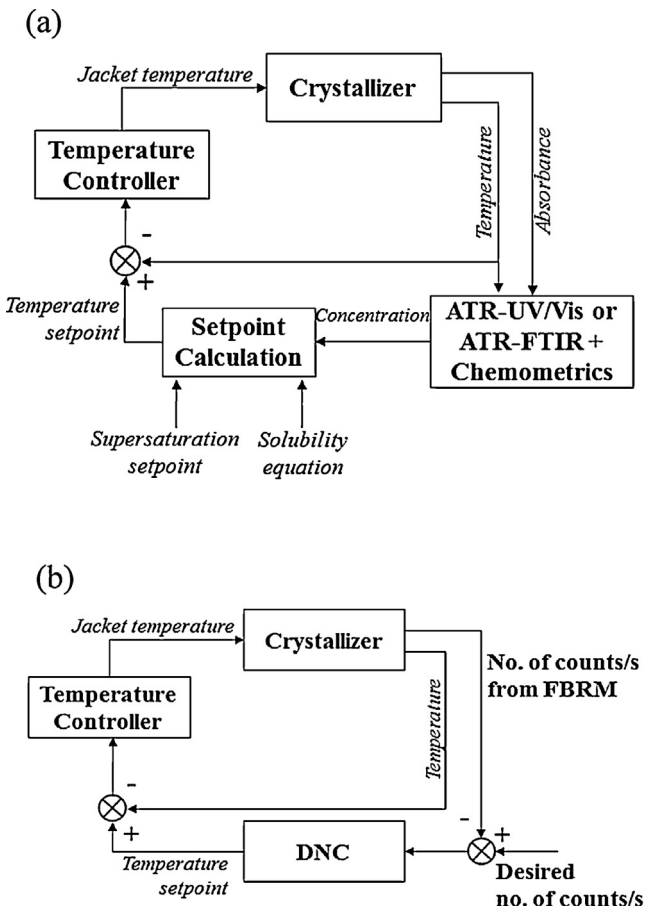

Fig. 9 – Schematic representation of the two main model-free control approaches: (a) supersaturation control (SSC) and (b) direct nucleation control (DNC).

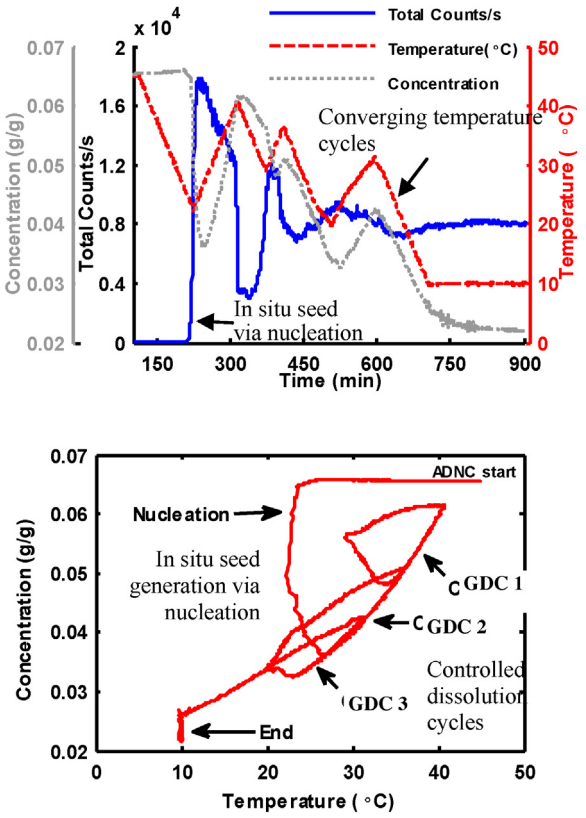

Fig. 10 – Sample results using direct nucleation control (DNC) as a rapid crystallization design approach for a cardiovascular drug (adapted from Saleemi et al., 2012c).

Mersmann, 1990; Fujiwara et al., 2005; Nagy et al., 2008a; Gron et al., 2003; Zhou et al., 2006), (iii) direct nucleation control (Abu Bakar et al., 2009; Saleemi et al., 2012a,b,c) and (iv) combined DNC–SSC approaches. Whilst the first category of traditional open-loop control approaches are model free, they are often discussed separately from the other model-free techniques, which in fact represent major novel development in crystallization control as opposed to the standard linear cooling or constant antisolvent addition techniques. Supersaturation control is based on the idea to control the crystallization process by following a desired operating curve in the phase diagram. To determine the current state of the crystallization process in the phase diagram it is necessary to measure concentration and temperature (solvent/antisolvent ratio), and the process is controlled by manipulating the temperature (solvent/antisolvent ratio), to follow the desired concentration (supersaturation) trajectory in the phase diagram. The approach provides the advantage that the operating curve can be defined based on detailed understanding of the crystallization process, to avoid triggering unwanted mechanisms, such as nucleation or polymorphic transformation and often can result in close to optimal crystallization performance after only a few experiments. In the majority of applications constant supersaturation (absolute or relative) is used for setpoint although the approach conceptually allows to specify more complex trajectories in the phase diagram for example in the case of systems with complicated phase behaviour, e.g. with multiple forms (polymorphs, hydrates, solvates etc). The schematic representation of the SSC approach is shown in Fig. 9(a). The SSC approach controls the crystallization process in the phase diagram, thus it is a more direct approach than controlling the process by following temperature trajectories defined in time. Nevertheless, the solid properties are not controlled directly and it is possible for two crystallization batches controlled at the same supersaturation to produce largely different products, due to disturbances, e.g. accidental seeding, attrition, agglomeration or others.

The main characteristic of the direct nucleation control (DNC) approach is that it directly measures and controls properties of the solid particles. The original approach was developed to control the number of particle counts per second provided by FBRM measurement, based on the concept that the number of particles in the system is in correlation with the CSD that can be achieved. If a smaller number of particles is maintained the resulting mean size of the product will be larger and vice versa. The approach detects directly the increase and decrease in the number of particles (or a measure related to this) and increases or decreases the supersaturation or creates dissolution to control the measured number of particles around the desired value, as shown in Fig. 9(b). The controlled growth and dissolution cycles (GDCs) are achieved by cooling/heating or anitsolvent/solvent addition cycles (or a combination of the two). The GDCs have proved to have numerous benefits in achieving better crystalline product properties. DNC can be used for consistent in situ seed generation, elimination of agglomeration, elimination of fine particles, to provide more uniform and larger particle size, elimination of problems with solvent inclusion, better polymorphic purity. Additionally the GDCs have an effect of slow surface dissolution and regrowth, which can significantly increase crystal purity by decreasing the amount of foreign molecules that can be incorporated in the crystal lattice. Amongst the many other benefits GDCs can also improve the aspect ratio of needle-shaped particles.

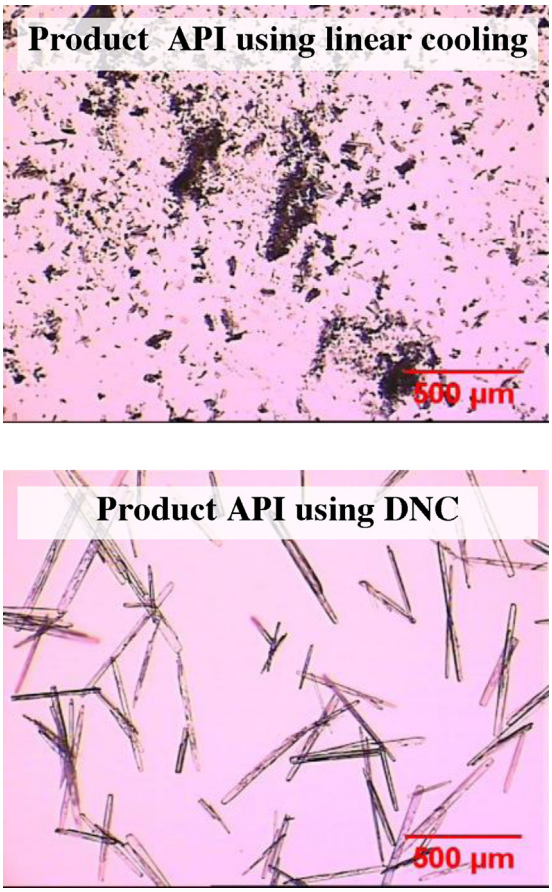

Fig. 11 – Microscopic pictures of a cardiovascular API product obtained using linear cooling and DNC respectively. DNC produces large, crystals with no agglomeration and eliminated problems with solvent inclusion (adapted from Saleemi et al., 2012c).

Fig. 10 shows sample results (Saleemi et al., 2012c) of using DNC for the design and control of the quality of an active pharmaceutical ingredient (an antiarrhythmic cardiovascular drug). It can be seen that DNC automatically resulted in three GDCs, which have led to the elimination of agglomeration (and solvent inclusion) problem, providing a very rapid crystallization development approach through feedback control. The distinguishing feature of DNC, to provide converging temperature cycles, as opposed to traditional temperature cycling that generally uses same initial and final temperature can also be observed (Saleemi et al., 2012c). The DNC yielded high quality crystals with no agglomeration and eliminated the problems related to solvent inclusion (Fig. 11).

Although the original DNC approach is based on controlling the number of counts per second resulting from the FBRM other properties can be used in the control algorithm, such as number of counts within certain size ranges or other statistics of the distribution, e.g. standard deviation, as well as combination of statistics. Additionally, other PAT tools can be used in similar feedback control approach to generate GDCs to control different signals provided by the measurement device (e.g. turbidity).

6. Conclusions

The paper provided a critical overview of selected topics related to the major developments in crystallization research over the past couple of decades. One of the main developments occurred in the application of population balance modelling tools for simulation of crystal shape evolution, polymorphic systems as well as crystallization in the presence of impurities and multi-components systems (e.g. chiral crystallization). Another important topic described in the paper includes advances in the monitoring of crystallization processes including considerable new developments in the sensing hardware and processing algorithms (e.g. chemometrics, image analysis). Statistical process control approaches are presented as a relatively unexplored collection of tools that can be used for improved monitoring and control of crystallization processes. The development and application of advanced feedback control approaches represent the third major area where crystallization research has witnessed significant progress. Most of the developments described in the paper have reached a relatively mature stage for batch crystallization systems with one of the key current and future set of activities being targeted towards extending and adapting advanced modelling, monitoring and control concepts for continuous crystallization processes.

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References

Aamir, E., Nagy, Z.K., Rielly, C.D., 2010a. Optimal seed recipe design for crystal size distribution control for batch cooling crystallization processes. Chem. Eng. Sci. 65, 3602–3614.

Aamir, E., Nagy, Z.K., Rielly, C.D., Kleinert, T., Judat, B., 2009. Combined quadrature method of moments and method of characteristics approach for efficient solution of population balance models for dynamic modelling and crystal size distribution control of crystallization processes. Ind. Eng. Chem. Res. 48 (18), 8575–8584.

Aamir, E., Rielly, C.D., Nagy, Z.K., 2010. Evaluation of the effect of seed preparation method on the product crystal size distribution for batch cooling crystallization processes. Cryst. Growth Des. 10 (11), 4728–4740.

Aamir, E., Rielly, C.D., Nagy, Z.K., 2012. Experimental evaluation of the targeted direct design of temperature trajectories for growth-dominated crystallization processes using an analytical crystal size distribution estimator. Ind. Eng. Chem. Res. 51 (51), 16677–16687.

Abbou Oucherif, K., Raina, S., Taylor, L.S., Litster, J.D., 2013. Quantitative analysis of the inhibitory effect of HPMC on felodipine crystallization kinetics using population balance modeling. Cryst. Eng. Commun. 15, 2197–2205.

Abu Bakar, M.R., Nagy, Z.K., Saleemi, A.N., Rielly, C.D., 2009. The impact of direct nucleation control on crystal size distribution in pharmaceutical crystallization processes. Cryst. Growth Des. 9, 1378–1384.

Abu Bakar, M.R., Nagy, Z.K., Rielly, C.D., 2010. A combinational approach of differential scanning calorimetry–hot-stage microscopy with image analysis in the investigation of sulfathiazole polymorphism. J.Therm. Anal. Calorim. 99 (2), 609–619.

Abu Bakar, M.R., Nagy, Z.K., Rielly, C.D., Dann, S.E., 2011. Investigation of the riddle of sulfathiazole polymorphism. Int. J. Pharm. 414, 86–103.

Ahmad, O.S., Debayle, J., Gherras, N., Presles, B., Fevotte, G., Pinoli, J.-C., 2012. Quantification of overlapping polygonal-shaped particles based on a new segmentation

method of in situ images during crystallization. J. Electron. Imaging 21, 021115–21121.
Arnold, Y.E., Imanidis, G., Kuentz, M.T., 2011. Advancing in-vitro drug precipitation testing: new process monitoring tools and a kinetic nucleation and growth model. J. Pharm. Pharmacol. 63, 333–341.
Bakir, T., Othman, S., Fevotte, G., Hammouri, H., 2006. Nonlinear observer of crystal-size distribution during batch crystallization. AIChE J. 52, 2188–2197.
Barrett, P., Smith, B., Worlitschek, J., Bracken, V., O'Sullivan, B., O'Grady, D., 2005. A review of the use of process analytical technology for the understanding and optimization of production batch crystallization processes. Org. Process Res. Dev. 9, 348–355.
Barrett, M., McNamara, M., Hao, H., Barrett, P., Glennon, B., 2010. Supersaturation tracking for the development, optimization and control of crystallization processes. Chem. Eng. Res. Des. 88, 1108–1119.
Bluma, A., Höpfner, T., Rudolph, G., Lindner, P., Beutel, S., Hitzmann, B., Scheper, T., 2009. Adaptation of in-situ microscopy for crystallization processes. J. Cryst. Growth 311, 4193–4198.
Boerkamp, M., Lamb, D.W., Lye, P.G., 2013. An intrinsic exposed core optical fibre sensor as a quantitative surface crystallization monitoring sensor. Sens. Actuators, B 177, 964–969.
Borchert, C., Sundmacher, K., 2011. Crystal aggregation in a flow tube: image-based observation. Chem. Eng. Tech. 34, 545–556.
Box, G.E.P., Jenkins, G.M., Reinsel, G.C., 2008. Time Series Analysis, fourth ed. John Wiley & Sons, Inc, Hoboken, NJ.
Braatz, R.D., 2002. Advanced control of crystallization processes. Annu. Rev. Control 26, 87–99.
Braatz, R.D., Fujiwara, M., Ma, D.L., Togkalidou, T., Tafti, D.K., 2002. Simulation and new sensor technologies for industrial crystallization: a review. Int. J. Mod. Phys. B 16, 346–353.
Brown, C.J., Ni, X.-W., 2012. Determination of metastable zone width, mean particle size and detectable number density using video imaging in an oscillatory baffled crystallizer. Cryst. Eng. Commun. 14, 2944–2949.
Brown, C.J., Ni, X.-W., 2011a. Online evaluation of paracetamol antisolvent crystallization growth rate with video imaging in an oscillatory baffled crystallizer. Cryst. Growth Des. 11, 719–725.
Brown, C.J., Ni, X.-W., 2011b. Evaluation of growth kinetics of antisolvent crystallization of Paracetamol in an oscillatory baffled crystallizer utilizing video imaging. Cryst. Growth Des. 11, 3994–4000.
Bück, A., Klaunick, G., Kumar, J., Peglow, M., Tsotsas, E., 2012. Numerical simulation of particulate processes for control and estimation by spectral methods. AIChE J. 58, 2309–2319.
Cabrera, N., Vermilyea, D., 1958. Growth of crystals from solution. Growth Perfection Cryst., 393–408.
Caciano de Sena, R., Soares, M., Pereira, M.L.O., Cruz Domingues da Silva, R., Ferreira do Rosario, F., Cajaiba da Silva, J.F., 2011. A simple method based on the application of a CCD camera as a sensor to detect low concentrations of barium sulfate in suspension. Sensors 11, 864–875.
Caillet, A., Rivoire, A., Galvan, J.M., Puel, F., Fevotte, G., 2007. Crystallization of monohydrate citric acid. 1. In situ monitoring through the joint use of Raman spectroscopy and image analysis. Cryst. Growth Des. 7, 2080–2087.
Chakraborty, J., Sarkar, D., Singh, A., Bharti, A.K., 2012. Measuring the three-dimensional morphology of crystals using regular reflection of light. Cryst. Growth Des. 12, 6042–6049.
Chung, S.H., Ma, D.L., Braatz, R.D., 1999. Optimal seeding in batch crystallization. Can. J. Chem. Eng. 77, 590–596.
Codan, L., Eckstein, C.F., Mazzotti, M., 2013. Growth kinetics of S-mandelic acid in aqueous solutions in the presence of R-mandelic acid. Cryst. Growth Des. 13, 652–663.
Corriou, J.P., Rohani, S., 2008. A new look at optimal control of a batch crystallizer. AIChE J. 54, 3188–3206.
Cornel, J., Lindenberg, C., Mazzotti, M., 2009. Experimental characterization and population balance modeling of the polymorph transformation of L-glutamic acid. Cryst. Growth Des. 9, 243–252.
Cornel, J., Mazzotti, M., 2008. Calibration-free quantitative application of in situ Raman spectroscopy to a crystallization process. Anal. Chem. 80, 9240–9249.
Cornel, J., Mazzotti, M., 2009. Estimating crystal growth rates using in situ ATR-FTIR and Raman spectroscopy in a calibration-free manner. Ind. Eng. Chem. Res. 48, 10740–10745.
Darakis, E., Khanam, T., Rajendran, A., Kariwala, V., Naughton, T.J., Asundi, A.K., 2010. Microparticle characterization using digital holography. Chem. Eng. Sci. 65, 1037–1044.
David, R., Marchal, P., Marcant, B., 1995. Modelling of agglomeration in industrial crystallization from solution. Chem. Eng. Technol. 18, 302–309.
De Anda, J.C., Wang, X.Z., Lai, X., Roberts, K.J., Jennings, K.H., Wilkinson, M.J., Watson, D., Roberts, D., 2005a. Real-time product morphology monitoring in crystallization using imaging technique. AIChE J. 51, 1406–1414.
De Anda, J.C., Wang, X.Z., Roberts, K.J., 2005b. Multi-scale segmentation image analysis for the in-process monitoring of particle shape with batch crystallisers. Chem. Eng. Sci. 60, 1053–1065.
Durbin, J., Watson, G.S., 1950. Testing for serial correlation in least squares regression. I. Biometrika 37, 409–428.
Erdemir, D., Lee, A.Y., Myerson, A.S., 2009. Nucleation of crystals from solution: classical and two step models. Acc. Chem. Res. 42, 621–629.
Erdemir, D., Lee, A.Y., Myerson, A.S., 2007. Polymorph selection: the role of nucleation, crystal growth and molecular modeling. Curr. Opin. Drug Discovery Dev. 10, 746–755.
FDA, 2004, PAT Guidance for Industry—A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance. ⟨http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070305.pdf⟩.
Ferguson, S., Morris, G., Hao, H., Barrett, M., Glennon, B., 2012. In-situ monitoring and characterization of plug flow crystallizers. Chem. Eng. Sci. 77, 105–111.
Ferreira, A., Faria, N., Rocha, F., Teixeira, J.A., 2011. Using an online image analysis technique to characterize sucrose crystal morphology during a crystallization run. Ind. Eng. Chem. Res. 50, 6990–7002.
Févotte, F., Févotte, G., 2010. A method of characteristics for solving population balance equations (PBE) describing the adsorption of impurities during crystallization processes. Chem. Eng. Sci. 65, 3191–3198.
Févotte, G., Alexandre, C., Nida, S.O., 2007. A population balance model of the solution-mediated phase transition of citric acid. AIChE J. 53, 2578–2589.
Fevotte, G., Gherras, N., 2012. On multiple nucleation bursts during solution crystallization in pure and impure solvent. Cryst. Growth Des. 12, 3407–3417.
Fujiwara, M., Nagy, Z.K., Chew, J.W., Braatz, R.D., 2005. First-principles and direct design approaches for the control of pharmaceutical crystallization. J. Process Control 15, 493–504.
Gherras, N., Fevotte, G., 2012. On the use of process analytical technologies and population balance equations for the estimation of crystallization kinetics. A case study. AIChE J. 58, 2650–2664.
Grof, Z., Schoellhammer, C.M., Rajniak, P., Štěpánek, F., 2011. Computational and experimental investigation of needle-shaped crystal breakage. Int. J. Pharm. 407, 12–20.
Gron, H., Borissova, A., Roberts, K.J., 2003. In-process ATR-FTIR spectroscopy for closed-loop supersaturation control of a batch crystallizer producing monosodium glutamate crystals of defined size. Ind. Eng. Chem. Res. 42, 198–206.
Gunawan, R., Fusman, I., Braatz, R.D., 2004. High resolution algorithms for multidimensional population balance equations. AIChE J. 50, 2738–2749.
Gutwald, T., Mersmann, A., 1990. Batch cooling crystallization at constant supersaturation: technique and experimental results. Chem. Eng. Technol. 13, 229–237.

Guzman, L.A., Maeda, K., Hirota, S., Masaaki, Y., Kubota, N., 1997. Unsteady-state impurity effect of chromium(III) on the growth rate of potassium sulphate crystal in aqueous solution. J. Cryst. Growth 181, 272–280.

Gagniere, E., Mangin, D., Puel, F., Bebon, C., Klein, J.-P., Monnier, O., Garcia, E., 2009. Cocrystal formation in solution: in situ solute concentration monitoring of the two components and kinetic pathways. Cryst. Growth Des. 9, 3376–3383.

Gagniere, E., Puel, F., Mangin, D., Valour, J.P., Rivoire, A., Galvan, J.M., Monnier, O., Klein, J.P., 2012. In situ monitoring of cocrystallization processes—complementary use of sensing technologies. Chem. Eng. Technol. 35, 1039–1044.

Gerstlauer, A., Gahn, C., Zhou, H., Rauls, M., Schreiber, M., 2006. Application of population balances in the chemical industry—current status and future needs. Chem. Eng. Sci. 61, 205–217.

Gherras, N., Serris, E., Fevotte, G., 2012. Monitoring industrial pharmaceutical crystallization processes using acoustic emission in pure and impure media. Int. J. Pharm. 439, 109–119.

Hao, H., Su, W., Barrett, M., Caron, V., Healy, A.-M., Glennon, B., 2010. A calibration-free application of Raman spectroscopy to the monitoring of mannitol crystallization and its polymorphic transformation. Org. Proc. Res. Dev. 14, 1209–1214.

He, G., Hermanto, M.W., Tjahjono, M., Chow, P.S., Tan, R.B.H., Garland, M., 2012. Comparison of dielectric constant meter with turbidity meter and focused beam reflectance measurement for metastable zone width determination. Chem. Eng. Res. Des. 90, 259–265.

He, G., Tjahjono, M., Chow, P.S., Tan, R.B.H., Garland, M., 2010. In situ determination of metastable zone width using dielectric constant measurement. Org. Proc. Res. Dev. 14, 1469–1472.

Heijna, M.C.R., Van Enckevort, W.J.P., Vlieg, E., 2008. Growth inhibition of protein crystals: a study of lysozyme polymorphs. Cryst. Growth Des. 8, 270–274.

Howard, K.S., Nagy, Z.K., Saha, B., Robertson, A.L., Steele, G., 2009. Combined PAT-solid state analytical approach for the detection and study of sodium benzoate hydrate. Org. Proc. Res. Dev. 13 (3), 590–597.

Hu, Q., Rohani, S., Jutan, A., 2005. Modelling and optimization of seeded batch crystallizers. Comput. Chem. Eng. 29 (4), 911–918.

Hulbert, H.M., Katz, S., 1964. Some problems in particle technology: A statistical mechanical formulation. Chem. Eng. Sci. 19, 555–574.

Hunter, J.S., 1986. The exponentially weighted moving average. J. Qual. Technol. 18, 203–210.

Jones, A.G., Mullin, J.W., 1974. Programmed cooling crystallization of potassium sulphate solutions. Chem. Eng. Sci. 29 (1), 105–118.

Kadam, S.S., Vissers, J.A.W., Forgione, M., Geertman, R.M., Daudey, P.J., Stankiewicz, A.I., Kramer, H.J.M., 2012. Rapid crystallization process development strategy from lab to industrial scale with PAT tools in skid configuration. Org. Proc. Res. Dev. 16, 769–780.

Kalbasenka, A.N., Spierings, L.C.P., Huesman, A.E.M., Kramer, H.J.M., 2007. Application of seeding as a process actuator in a model predictive control framework for fed-batch crystallization of ammonium sulphate. Part. Part. Syst. Char. 24 (1), 40–48.

Kariwala, V., Cao, Y., Nagy, Z.K., 2012. Automatic differentiation-based quadrature method of moments for solving population balance equations. AIChE J. 58, 842–854.

Kempkes, M., Darakis, E., Khanam, T., Rajendran, A., Kariwala, V., Mazzotti, M., Naughton, T.J., Asundi, A.K., 2009. Three dimensional digital holographic profiling of micro-fibres. Opt. Express 17, 2938–2943.

Kempkes, M., Eggers, J., Mazzotti, M., 2008. Measurement of particle size and shape by FBRM and in situ microscopy. Chem. Eng. Sci. 63, 4656–4675.

Kempkes, M., Vetter, T., Mazzotti, M., 2010a. Measurement of 3D particle size distributions by stereoscopic imaging. Chem. Eng. Sci. 65, 1362–1373.

Kempkes, M., Vetter, T., Mazzotti, M., 2010b. Monitoring the particle size and shape in the crystallization of Paracetamol from water. Chem. Eng. Res. Des. 88, 447–454.

Khalil, A., Puel, F., Chevalier, Y., Galvan, J.-M., Rivoire, A., Klein, J.-P., 2010. Study of droplet size distribution during an emulsification process using in situ video probe coupled with an automatic image analysis. Chem. Eng. J. 165, 946–957.

Khalil, A., Puel, F., Cosson, X., Gorbatchev, O., Chevalier, Y., Galvan, J.-M., Rivoire, A., Klein, J.-P., 2011. Crystallization-in-emulsion process of a melted organic compound: in situ optical monitoring and simultaneous droplet and particle size measurements. J. Cryst. Growth, 6th National Congress on Industrial Crystallization (CRISTAL-6) 342, 99–109.

Khanam, T., Rahman, M.N., Rajendran, A., Kariwala, V., Asundi, A.K., 2011. Accurate size measurement of needle-shaped particles using digital holography. Chem. Eng. Sci. 66, 2699–2706.

Korath, J.M., Abbas, A., Romagnoli, J.A., 2007. Separating touching and overlapping objects in particle images—a combined approach. Chem. Eng. Trans. 11, 167–172.

Kubota, N., 2001. Effect of impurities on the growth kinetics of crystals. Cryst. Res. Technol. 36, 749–769.

Kubota, N., Yokota, M., Mullin, J.W., 1997. Supersaturation dependence of crystal growth in solutions in the presence of impurity. J. Cryst. Growth 182, 86–94.

Larsen, P.A., Patience, D.B., Rawlings, J.B., 2006a. Industrial crystallization process control. IEEE Control Syst. Mag. 26 (4), 70–80.

Larsen, P.A., Rawlings, J.B., 2008. Assessing the reliability of particle number density measurements obtained by image analysis. Part. Part. Syst. Char. 25, 420–433.

Larsen, P.A., Rawlings, J.B., 2009. The potential of current high-resolution imaging-based particle size distribution measurements for crystallization monitoring. AIChE J. 55, 896–905.

Larsen, P.A., Rawlings, J.B., Ferrier, N.J., 2006b. An algorithm for analyzing noisy, in situ images of high-aspect-ratio crystals to monitor particle size distribution. Chem. Eng. Sci. 61, 5236–5248.

Larsen, P.A., Rawlings, J.B., Ferrier, N.J., 2007. Model-based object recognition to measure crystal size and shape distributions from in situ video images. Chem. Eng. Sci. 62, 1430–1441.

Lee, M.-J., Chun, N.-H., Wang, I.-C., Liu, J.J., Jeong, M.-Y., Choi, G.J., 2013. Understanding the formation of indomethacin-saccharin cocrystals by anti-solvent crystallization. Cryst. Growth Des. 13, 2067–2074.

Li, R.F., Penchev, R., Ramachandran, V., Roberts, K.J., Wang, X.Z., Tweedie, R.J., Prior, A., Gerritsen, J.W., Hugen, F.M., 2008. Particle shape characterisation via image analysis: from laboratory studies to in-process measurements using an in situ particle viewer system. Org. Proc. Res. Dev. 12, 837–849.

Lovette, M.A., Browning, A.R., Griffin, D.W., Sizemore, J.P., Snyder, R.C., Doherty, M.F., 2008. Crystal shape engineering. Ind. Eng. Chem. Res. 47, 9812–9833.

Lovette, M.A., Doherty, M.F., 2012. Predictive modelling of supersaturation-dependent crystal shapes. Cryst. Growth Des. 12, 656–669.

Lovette, M.A., Muratore, M., Doherty, M.F., 2012. Crystal shape modification through cycles of dissolution and growth: attainable regions and experimental validation. AIChE J. 58, 1465–1474.

Lu, C.W., Reynolds, M.R., 1999. EWMA control charts for monitoring the mean of autocorrelated processes. J. Qual. Technol. 31, 166–188.

Ma, C.Y., Wang, X.Z., 2012. Model identification of crystal facet growth kinetics in morphological population balance modelling of L-glutamic acid crystallization and experimental validation. Chem. Eng. Sci. 70, 22–30.

Ma, C.Y., Wang, X.Z., Roberts, K.J., 2007. Multi-dimensional population balance modeling of the growth of rod-like

L-glutamic acid crystals using growth rates estimated from in-process imaging. Adv. Powder Technol. 18, 707–723.
Ma, D.L., Braatz, R.D., 2003. Robust identification and control of batch processes. Comput. Chem. Eng. 27, 1175–1184.
Maeder, M., Zuberbuehler, A.D., 1990. Nonlinear least-squares fitting of multivariate absorption data. Anal. Chem. 62, 2220–2224.
Majumder, A., Nagy, Z.K., 2013a. Prediction and control of crystal shape distribution in the presence of crystal growth modifiers. Chem. Eng. Sci. 101, 593–602.
Majumder, A., Nagy, Z.K., 2013b. Fines removal in a continuous plug flow crystallizer by optimal spatial temperature profiles with controlled dissolution. AIChE J., http://dx.doi.org/10.1002/aic.14196, in press.
Marchal, P., David, R., Klein, J.P., Villermaux, J., 1988. Crystallization and precipitation engineering—I. An efficient method for solving population balance in crystallization with agglomeration. Chem. Eng. Sci. 43, 59–67.
Martins, P.M., Rocha, F., Damas, A.M., Rein, P., 2011. Unsteady-state inhibition of crystal growth caused by solution impurities. Cryst. Eng. Commun. 13, 1103–1110.
Mersmann, A., Braun, B., Loffelmann, M., 2002. Prediction of crystallization coefficients of the population balance. Chem. Eng. Sci. 57, 4267–4275.
Mesbah, A., Huesman, A.E.M., Kramer, H.J.M., Van den Hof, P.M.J., 2011a. A comparison of nonlinear observers for output feedback model-based control of seeded batch crystallization processes. J. Process Control 21 (4), 652–666.
Mesbah, A., Huesman, A.E.M., Kramer, H.J.M., Nagy, Z.K., Van den Hof, P.M.J., 2011b. Real-time control of seeded batch crystallization processes. AIChE J. 57, 1557–1569.
Mesbah, A., Kalbasenka, A.N., Huesman, A.E.M., Kramer, H.J.M., Jansens, P.J., Van den Hof, P.M.J., 2007. Real-time dynamic optimization of crystal yield in fed-batch evaporative crystallization of ammonium sulphate. In: Proc. of the 14th International Workshop on Industrial Crystallization (BIWIC), Delft, The Netherlands, pp. 81–88.
Mesbah, A., Landlust, J., Huesman, A.E.M., Kramer, H.J.M., Jansens, P.J., Van den Hof, P.M.J., 2010. A model-based control framework for industrial batch crystallization processes. Chemical Eng. Res. Des. 88, 1223–1233.
Mesbah, A., Nagy, Z.K., Huesman, A.E.M., Kramer, H.J.M., Van den Hof, P.M.J., 2012. Nonlinear model-based control of a semi-industrial batch crystallizer using a population balance modeling framework. IEEE Trans. Control Syst. Technol. 20, 1188–1201.
Mullin, J.W., 2001. Crystallization. Butterworth-Heinemann, Boston.
Mullin, J.W., Nyvlt, J., 1971. Programmed cooling of batch crystallizers. Chem. Eng. Sci. 26 (3), 369–377.
Nagy, Z.K., 2009. Model based robust control approach for batch crystallization product design. Comput. Chem. Eng. 33, 1685–1691.
Nagy, Z.K., Aamir, E., 2012. Systematic design of supersaturation controlled crystallization processes for shaping the crystal size distribution using an analytical estimator. Chem. Eng. Sci. 84, 656–670.
Nagy, Z.K., Aamir, E., Rielly, C.D., 2011. Internal fines removal using a population balance model based control of crystal size distribution under dissolution, growth and nucleation mechanisms. Cryst. Growth Des. 11, 2205–2219.
Nagy, Z.K., Braatz, R.D., 2012. Advances and new directions in crystallization control. Annu. Rev. Chem. Biomol. Eng. 3, 55–75.
Nagy, Z.K., Chew, J.W., Fujiwara, M., Braatz, R.D., 2008a. Comparative performance of concentration and temperature controlled crystallizations. J. Process Control 18, 399–407.
Nagy, Z.K., Fujiwara, M., Braatz, R.D., 2008b. Modelling and control of combined cooling and antisolvent crystallization processes. J. Process Control 18, 856–864.
Nagy, Z.K., Fujiwara, M., Woo, X.Y., Braatz, R.D., 2008. Determination of the kinetic parameters for the crystallization of paracetamol from water using metastable zone width experiments. Ind. Eng. Chem. Res. 47, 1245–1252.
Nopens, I., Briesen, H., Ducostec, J., 2009. Celebrating a milestone in population balance modeling. Chem. Eng. Sci. 64 (4), 627.
Ono, T., Kramer, H.J.M., ter Horst, J.H., Jansens, P.J., 2004. Process modeling of the polymorphic transformation of L-glutamic acid. Cryst. Growth Des. 4, 1161–1167.
Patience, D.B., Rawlings, J.B., 2001. Particle-shape monitoring and control in crystallization processes. AIChE J. 47, 2125–2130.
Pertig, D., Buchfink, R., Petersen, S., Stelzer, T., Ulrich, J., 2011. Inline analyzing of industrial crystallization processes by an innovative ultrasonic probe technique. Chem. Eng. Tech. 34, 639–646.
Pollanen, K., Hakkinen, A., Reinikainen, S.P., Rantanen, J., Minkkinen, P., 2006. Dynamic PCA-based MSPC charts for nucleation prediction in batch cooling crystallization processes. Chemom. Intell. Lab. Syst. 84, 126–133.
Presles, B., Debayle, J., Fevotte, G., Pinoli, J.C., 2010. Novel image analysis method for in situ monitoring the particle size distribution of batch crystallization processes. J. Electron. Imaging 19 (3), 031207.
Puel, F., Marchal, P., Klein, J., 1997. Habit transient analysis in industrial crystallization using two dimensional crystal sizing technique. Chem. Eng. Res. Des. 75, 193–205.
Puxty, G., Maeder, M., Hungerbuhler, K., 2006. Tutorial on the fitting of kinetics models to multivariate spectroscopic measurements with non-linear least-squares regression. Chemom. Intell. Lab. Syst. 81, 149–164.
Qamar, S., Warnecke, G., 2007. Numerical solution of population balance equations for nucleation, growth and aggregation processes. Comput. Chem. Eng. 31, 1576–1589.
Qu, H.Y., Louhi-Kultanen, M., Kallas, J., 2006. In-line image analysis on the effects of additives in batch cooling crystallization. J. Cryst. Growth 289, 286–294.
Ramkrishna, D., 2000. Population Balances: Theory and Applications to Particulate Systems in Engineering. Academic Press, New York.
Ramkrishna, D., Mahoney, A.W., 2002. Population balance modeling, promise for the future. Chem. Eng. Sci. 57, 595–606.
Randolph, A.D., Larson, M.A., 1971. Theory of Particulate Processes: Analysis and Techniques of Continuous Crystallization, first ed. Academic Press, New York.
Rawlings, J.B., Miller, S.M., Witkowski, W.R., 1993. Model identification and control of solution crystallization processes: a review. Ind. Eng. Chem. Res. 32, 1275–1296.
Rawlings, J.B., Bakshi, B.R., 2006. Particle filtering and moving horizon estimation. Comput. Chem. Eng. 30, 1529–1541.
Rawlings, J.B., Sink, C.W., Miller, S.M., 2002. Control of crystallization processes. In: Myerson, A.S. (Ed.), Handbook of Industrial Crystallization. , second ed. Butterworth-Heinemann, Boston.
Rocha, W.F.d.C., Poppi, R.J., 2010. Multivariate control charts based on net analyte signal (NAS) for characterization of the polymorphic composition of piroxicam using near infrared spectroscopy. Microchem. J. 96, 21–26.
Rocha, W.F.d.C., Poppi, R.J., 2011. Multivariate control charts based on net analyte signal (NAS) and Raman spectroscopy for quality control of carbamazepine. Anal. Chim. Acta 705, 35–40.
Saleemi, A.N., Rielly, C., Nagy, Z.K., 2012a. Automated direct nucleation control for in situ dynamic fines removal in batch cooling crystallization. Cryst. Eng. Commun. 14, 2196–2203.
Saleemi, A.N., Rielly, C.D., Nagy, Z.K., 2012b. Comparative investigation of supersaturation and automated direct nucleation control of crystal size distributions using ATR-UV/Vis spectroscopy and FBRM. Cryst. Growth Des. 12, 1792–1807.
Saleemi, A.N., Steele, G., Pedge, N., Freeman, A., Nagy, Z.K., 2012c. Enhancing crystalline properties of a cardiovascular active pharmaceutical ingredient using a process analytical technology based crystallization feedback control strategy. Int. J. Pharm. 430, 56–64.
Saleemi, A.N., Rielly, C.D., Nagy, Z.K., 2012d. Monitoring of the combined cooling and antisolvent crystallization of mixtures

of aminobenzoic acid isomers using ATR-UV/Vis spectroscopy and FBRM. Chem. Eng. Sci. 77, 122–129.
Samad, N.A.F.A., Sin, G., Gernaey, K.V., Gani, R., 2013. A systematic framework for design of process monitoring and control (PAT) systems for crystallization processes. Comput. Chem. Eng. 54, 8–23.
Sandler, N., 2011. Photometric imaging in particle size measurement and surface visualization. Int. J. Pharm. 417, 227–234.
Sangwal, K., 2007. Additives and Crystallization Processes: From Fundamentals to Applications. Wiley-Blackwell (John Wiley & Sons Ltd), Hoboken, NJ.
Sarkar, D., Doan, X.-T., Ying, Z., Srinivasan, R., 2009. In situ particle size estimation for crystallization processes by multivariate image analysis. Chem. Eng. Sci. 64, 9–19.
Sarkar, D., Rohani, S., Jutan, A., 2006. Multi-objective optimization of seeded batch crystallization processes. Chem. Eng. Sci. 61, 5282–5295.
Schorsch, S., Vetter, T., Mazzotti, M., 2012. Measuring multidimensional particle size distributions during crystallization. Chem. Eng. Sci. 77, 130–142.
Schöll, J., Lindenberg, C., Vicum, L., Brozio, J., Mazzotti, M., 2007. Precipitation of α L-glutamic acid: determination of growth kinetics. Faraday Discuss. 136, 247–264.
Scott, D.M., Sunshine, G., Rosen, L., Jochen, E., 2001. Industrial applications of process imaging & image processing, In: McCann, H.; Scott, D. M. (Eds), Process Imaging for Automatic Control, vol. 4188, pp. 1–9.
Shewhart, W.A., 1925. The application of statistics as an aid in maintaining quality of a manufactured product. J. Am. Soc. Stat. Assoc. 20, 546–548.
Silva, A.d.P.M.D., de Oliveira, P.B., Bandini, T.B., Barreto Junior, A.G., de Sena, R.C., Silva, J.F.C.D., 2013. Low-cost system based on image analysis to determine solubility curves. Sens. Actuators B 177, 1071–1074.
Simoglou, A., Georgieva, P., Martin, E.B., Morris, A.J., Feyo de Azevedo, S., 2004. On-line multivariate statistical monitoring of a fed-batch sugar crystallisation process. Comput.-Aided Chem. Eng. 18, 817–822.
Simoglou, A., Georgieva, P., Martin, E.B., Morris, A.J., Feyo de Azevedo, S., 2005. On-line monitoring of a sugar crystallization process. Comp. Chem. Eng. 29, 1411–1422.
Simon, L.L., Nagy, Z.K., Hungerbuhler, K., 2009a. Endoscopy-based in situ bulk video imaging of batch crystallization processes. Org. Process Res. Dev., Special Issue on Polymorphism and Crystallization 13, 1254–1261.
Simon, L.L., Nagy, Z.K., Hungerbuhler, K., 2009b. Comparison of external bulk video imaging with focused beam reflectance measurement and ultra-violet visible spectroscopy for crystallization nucleation detection and metastable zone identification in food and pharmaceutical crystallization processes. Chem. Eng. Sci. 64, 3344–3351.
Simon, L.L., Abbou Oucherif, K., Nagy, Z.K., Hungerbuhler, K., 2010a. Bulk video Imaging based multivariate image analysis, process control chart and acoustic signal assisted nucleation detection. Chem. Eng. Sci. 65, 4983–4995.
Simon, L.L., Abbou Oucherif, K., Nagy, Z.K., Hungerbuhler, K., 2010b. Histogram matching, hypothesis testing, and statistical control-chart-assisted nucleation detection using bulk video imaging for optimal switching between nucleation and seed conditioning steps. Ind. Eng. Chem. Res. 49, 9932–9944.
Simon, L.L., Reinlein, S., Hungerbuhler, K., 2011. Turbidity and endoscopy assisted monitoring of pseudopolymorphic transformation of citric acid. In: 18th International Symposium on Industrial Crystallization (ISIC 18), ⟨www.aidic.it/isic18/webpapers/199Simon.pdf⟩.
Simon, L.L., Myerson, A.S., 2011. Continuous antisolvent plug-flow crystallization of a fast growing API. In: 18th International Symposium on Industrial Crystallization (ISIC 18), ⟨www.aidic.it/isic18/webpapers/250Simon.pdf⟩.
Simon, L.L., Merz, T., Dubuis, S., Lieb, A., Hungerbuhler, K., 2012. In-situ monitoring of pharmaceutical and specialty chemicals crystallization processes using endoscopy-stroboscopy and multivariate image analysis. Chem. Eng. Res. Des. 90, 1847–1855.
Singh, M.R., Chakraborty, J., Nere, N., Tung, H.-H., Bordawekar, S., Ramkrishna, D., 2012. Image-analysis-based method for 3D crystal morphology measurement and polymorph identification using confocal microscopy. Cryst. Growth Des. 12, 3735–3748.
Sizemore, J.P., Doherty, M.F., 2009. A new model for the effect of molecular imposters on the shape of faceted molecular crystals. Cryst. Growth Des. 9, 2637–2645.
Snyder, R.C., Veesler, S., Doherty, M.F., 2008. The evolution of crystal shape during dissolution: predictions and experiments. Cryst. Growth Des. 8, 1100–1101.
Soppela, I., Airaksinen, S., Hatara, J., Raikkonen, H., Antikainen, O., Yliruusi, J., Sandler, N., 2011. Rapid particle size measurement using 3D surface imaging. AAPS Pharmscitech 12, 476–484.
Stapley, A.G.F., Himawan, C., MacNaughtan, W., Foster, T.J., 2009. A computational method for extracting crystallization growth and nucleation rate data from hot stage microscope images. Cryst. Growth Des. 9, 5061–5068.
Stelzer, T., Pertig, D., Ulrich, J., 2013. Ultrasonic crystallization monitoring technique for simultaneous in-line measurement of liquid and polid Phase. J. Cryst. Growth 362, 71–76.
Thirunahari, S., Chow, P.S., Tan, R.B.H., 2011. Quality by Design (QbD)-based crystallization process development for the polymorphic drug tolbutamide. Cryst. Growth Des. 11, 3027–3038.
Towler, C.S., Davey, R.J., Lancaster, R.W., Price, C.J., 2004. Impact of molecular speciation on crystal nucleation in polymorphic systems: the conundrum of glycine and molecular 'self poisoning'. J. Am. Chem. Soc. 126, 13347–13353.
Van Drunen, M.A., Merkus, H.G., Scarlett, B., van Rosmalen, G.M., 1996. Barium sulfate precipitation: crystallization kinetics and the role of the additive PMA–PVS. Part. Part. Syst. Char. 13–5, 313–321.
Variankaval, N., Cote, A.S., Doherty, M.F., 2008. From form to function: crystallization of active pharmaceutical ingredients. AIChE J. 54, 1682–1688.
Velazquez-Camilo, O., Bolanos-Reynoso, E., Rodriguez, E., Alvarez-Ramirez, J., 2010a. Characterization of cane sugar crystallization using image fractal analysis. J. Food Eng. 100, 77–84.
Velazquez-Camilo, O., Bolanos-Reynoso, E., Rodriguez, E., Alvarez-Ramirez, J., 2010b. Fractal analysis of crystallization slurry images. J. Cryst. Growth 312, 842–850.
Verma, S., Shlichta, P.J., 2008. Imaging techniques for mapping solution parameters, growth rate, and surface features during the growth of crystals from solution. Prog. Cryst. Growth Charact. Mater. 54, 1–120.
Vetter, T., Mazzotti, M., Brozio, J., 2011. Slowing the growth rate of ibuprofen crystals using the polymeric additive Pluronic F127. Cryst. Growth Des 11 (9), 3813–3821.
Wang, X.Z., Roberts, K.J., Ma, C., 2008. Crystal growth measurement using 2D and 3D imaging and the perspectives for shape control. Chem. Eng. Sci. 63, 1173–1184.
Woo, X.Y., Tan, R.B.H., Braatz, R.D., 2011. Precise tailoring of the crystal size distribution by controlled growth and continuous seeding from impinging jet crystallizers. Cryst. Eng. Commun. 13, 2006–2014.
Woo, X.Y., Tan, R.B.H., Chow, P.S., Braatz, R.D., 2006. Simulation of mixing effects in antisolvent crystallization using a coupled CFD–PDF–PBE approach. Cryst. Growth Des. 6, 1291–1303.
Worlitschek, J., Mazzotti, M., 2004. Model-based optimization of particle size distribution in batch-cooling crystallization of paracetamol. Cryst. Growth Des. 4, 891–903.
Yu, L.X., Lionberger, R.A., Raw, A.S., D'Costa, R., Wu, H., Hussain, A.S., 2003. Applications of process analytical technology to crystallization processes. Adv. Drug Delivery Rev. 56, 349–369.
Yu, Z.Q., Chew, J.W., Chow, P.S., Tan, R.B.H., 2007. Recent advances in crystallization control—an industrial perspective. Chem. Eng. Res. Des. 85, 893–905.

Yu, Z.Q., Chow, P.S., Tan, R.B.H., 2010. Operating regions in cooling cocrystallization of caffeine and glutaric acid in acetonitrile. Cryst. Growth Des. 10, 2382–2387.

Yu, Z.Q., Chow, P.S., Tan, R.B.H., Ang, W.H., 2011. Supersaturation control in cooling polymorphic co-crystallization of caffeine and glutaric acid. Cryst. Growth Des. 11, 4525–4532.

Zhang, B., Abbas, A., Romagnoli, J.A., 2011. Multi-resolution fuzzy clustering approach for image-based particle characterization for particle systems. Chemom. Intell. Lab. Syst. 107, 155–164.

Zhang, K., Nadri, M., Xu, C.-Z., 2012. Reachability-based feedback control of crystal size distribution in batch crystallization processes. J. Process Control 22 (10), 1856–1864.

Zhang, B., Abbas, A., Romagnoli, J.A., 2013. Automatic image-based estimation of texture analysis as a monitoring tool for crystal growth. Chemom. Intell. Lab. Syst. 121, 42–51.

Zhang, Y., Sizemore, J.P., Doherty, M.F., 2006. Shape evolution of 3-dimensional faceted crystals. AIChE J. 52, 1906–1915.

Zhou, G.X., Fujiwara, M., Woo, X.Y., Rusli, E., Tung, H., Starbuck, C., Davidson, O., Ge, Z., Braatz, R.D., 2006. Direct design of pharmaceutical antisolvent crystallization through concentration control. Cryst. Growth Des. 6, 892–898.

Zhou, Y., Lakshminarayanan, S., Srinivasan, R., 2011. Optimization of image processing parameters for large sets of in-process video microscopy images acquired from batch crystallization processes: integration of uniform design and simplex search. Chemom. Intell. Lab. Syst. 107, 290–302.

Zhou, Y., Srinivasan, R., Lakshminarayanan, S., 2009. Critical evaluation of image processing approaches for real-time crystal size measurements. Comput. Chem. Eng. 33, 1022–1035.