Solutions to inversion problems in preferential crystallization of enantiomers—part I: Batch crystallization in a single vessel

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HIGHLIGHTS

\begin{itemize}
\item Focus on analytical methods for control of preferential crystallization.
\item Orbital flatness can be excluded for preferential crystallization moment models.
\item Dynamic inversion for realization of desired final crystal size distributions.
\item Idealizing assumptions can be justified which greatly simplify dynamic inversion.
\item Numerical example using a detailed process model.
\end{itemize}

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ABSTRACT

In this series of two papers, we investigate inversion techniques for models describing the crystallization of conglomerate forming enantiomers, with application for preferential crystallization. Here, in Part I, a simple batch process in one vessel is considered. In Part II, the results will be extended to a technically important setup consisting of two coupled crystallizers. The research presented here builds on prior work on the use of orbital flatness concepts for trajectory planning and control of single-substance crystallization. Based on a known necessary condition for flatness, we show that moment models for crystallization of enantiomers typically do not exhibit the orbital flatness property. However, we show that a scaling of time introduced in our prior work is still useful. We present inversion results for the realization of prescribed final-time crystal size distributions (CSDs). Due to the lack of orbital flatness, these results involve integration of a zero dynamics. A number of idealizations of the process model are investigated and shown to be suitable for appropriate problem settings. We present a numerical example which demonstrates the exact as well as the simplified inversion procedures, and also justifies application of the simplified techniques.

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1. Introduction

Preferential crystallization is an attractive way for the separation of enantiomers, chiral substances, which share many physical and chemical properties, but may differ, e.g., in their metabolic effects. The crystallization is out of a solution, and its principle is similar to that of crystallization of a single substance, where mass is transported from the liquid phase, i.e., the solution, to the solid phase, i.e., the crystalline material. Growth of existing crystals, and nucleation of new crystals, are the main phenomena, which influence, over time, a population of crystals. We do not consider here other effects such as conglomeration and breakage. There are a number of ways to influence, or control, the crystallization process. Frequently, the temperature of the slurry inside a tank is considered as a manipulated variable. This makes sense as often the dynamics of the temperature transfer is much faster than that of the crystallization. Also, a low-level controller can help in tracking a temperature reference, provided that the temperature in the slurry (consisting of solution and crystals) can be measured. A common way to speed up crystallization and make the process more reproducible consists in the addition of seed crystals.

Here, in contrast to single substance crystallization, two species of enantiomers, $E_1$ and $E_2$, are present in the system. Instead of one concentration in the liquid phase, two mass fractions are now defined, one for each enantiomer, along with two supersaturations, and so on. The sub-processes corresponding to the crystallization of enantiomers $E_1$ and $E_2$, respectively, may be coupled via their liquid and solid phases.

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Most chiral substances can be classified into one of two types (Lorenz et al., 2006). In this work we focus on conglomerates. "For conglomerates, there exists an attractive possibility to directly crystallize pure enantiomers from a racemic solution" (Lorenz et al., 2006). This means that, under equilibrium conditions, pure $E_1$ crystals and pure $E_2$ crystals can coexist with a racemic (50%/50%) solution. Rather than of mixed crystals, the solid material consists of a mixture of individually pure crystals. For the other type, compound forming enantiomers, it is only possible "[... ] to obtain pure solid enantiomers, once a certain minimum enrichment is available" (Lorenz et al., 2006).

Crystallization of conglomerates becomes preferential by adding seed crystals for only one enantiomer, the preferred enantiomer, into a vessel containing the solution (which may be racemic) and operating in the so-called metastable region. The latter is usually referred to as a certain range of temperature and mass fractions, where, qualitatively, growth and secondary nucleation are predominant, and primary nucleation is negligible. At the beginning of the process, only the seed crystals will grow, and nuclei of the same species as the seed crystals will form by secondary nucleation. Crystallization will thus be in favor of the preferred enantiomer. At some time nucleation of the other, counter enantiomer becomes significant, and the process has to be stopped in order to avoid unacceptable impurification. The qualitative idea of a metastable region with sharp boundaries is not sufficient for adequate prediction of this time instant, and, more generally, for control of the system. Rather than that, an accurate mathematical description of the effects of growth and nucleation is required.

Fig. 1 illustrates a simple batch process for preferential crystallization in a stirred tank. Elsner et al. (2005a,b, 2009) have described two modes of operation for the technical realization of separation of conglomerates by preferential crystallization, with the goal of obtaining pure fractions of both kinds. The cyclic mode can be thought of as a sequence of simple batch processes. Before each batch, seed crystals of either $E_1$ or $E_2$ are added. After the batch this enantiomer is harvested, and the solution is replenished (e.g., by adding a racemic mixture of $E_1$ and $E_2$). In the subsequent batch, the roles of $E_1$ and $E_2$ are interchanged, and so on. In a coupled mode, two vessels, $A$ and $B$, are operated simultaneously. In one crystallizer, pure $E_1$ shall be produced, and pure $E_2$ in the other one. Crystal free liquid is exchanged between the vessels. Simply speaking, this measure increases the amount of time during which the two processes can be kept in the metastable region. Of course, the batch can be repeated over and over, as long as enough racemate to replenish the solution and enough seed crystals are provided.

Control and optimization of (continuous and batch) crystallization processes has gained a lot of attention since the 1970s. Modeling and solution methods dealing with the reconstruction of the evolution of crystal size distributions (CSDs), or of CSD properties, are an essential prerequisite for many of the developed feedforward and feedback schemes. Population balance equations (PBEs) are frequently used to describe the dynamics of particulate processes (e.g., Randolph and Larson, 1988; Ramkrishna, 2000). Discretization-based methods can be used to compute directly the evolution of CSDs, such as finite difference schemes (e.g., Kumar and Ramkrishna, 1996) or high resolution finite volume schemes (e.g., Gunawan et al., 2004). On the other hand, it was recognized early (Hulburt and Katz, 1964) that, for suitable PBE models, a closed set of a finite number of ordinary differential equations (ODEs) can be derived via the so-called (standard) method of moments, which describes the evolution of the principal moments of the CSD. It should be noted that reconstructing a CSD from a finite number of its moments is not unique (John et al., 2007).

Features of more detailed population balance equations, such as conglomeration and breakage, or growth rates depending on particle size, prevent the derivation of closed ODE models based on the (standard) method of moments. A number of methods have been suggested to overcome this problem, e.g., the quadrature method of moments (McGraw, 1997). Certain techniques allow the derivation of approximate low-order ODE models. These include, for example, the method of weighted residuals (Rawlings et al., 1992; Singh and Ramkrishna, 1977; Ramkrishna, 2000), or approaches which have recently been suggested by Qamar et al. (2009, 2010, 2011) and Bajcinca et al. (2011).

Trajectory planning and optimal control of batch crystallizers, starting with classical contributions such as, e.g., Mullin and Nyvlt (1971), Ajinkya and Ray (1974), Jones (1974), still remains an active topic (e.g., Ma et al., 2002; Sarkar et al., 2006; Aamir et al., 2009; Bajcinca et al., 2011; Bajcinca and Hofmann, 2011). For example, in Aamir et al. (2009), the quadrature method of moments is combined with the method of characteristics to simulate the evolution of CSDs in a batch crystallization process with size-dependent growth rate. This feedforward simulation technique is subsequently used within a dynamic optimization scheme aiming at approximately achieving specified target CSDs under additional constraints, such as process duration; in this scenario, temperature is considered as the controlled variable. PBEs with growth rate depending on particle size are also considered in Bajcinca et al. (2011). There, transformation of time and length coordinates enables efficient computation of temperature profiles for realization of specified CSDs.

With the realization that particulate processes are prone to significant uncertainties and disturbances, a lot of recent work puts much emphasis on using advanced feedback control schemes. For example, based on geometric control theory, a nonlinear output feedback controller is designed for a continuous crystallizer in Chiu and Christofides (1999). This approach involves a systematic model reduction technique based on the combination of the method of weighted residuals and approximate inertial manifolds. An extended Luemberger-type observer is used to estimate immeasurable state variables. In subsequent papers, model uncertainty (Chiu and Christofides, 2000) and actuator constraints (El-Farra et al., 2001) are explicitly considered.

In Vollmer and Raisch (2002), Motz et al. (2003), a continuous crystallizer model involving size-dependent growth, attrition, fines dissolution and reflux of undersaturated solution is considered, which shows oscillatory behavior. The fines dissolution rate is considered as the manipulated variable. The controller design, which aims at stabilizing an unstable steady state, follows a late lumping approach: an H∞ robust performance problem is solved based on the linearized infinite-dimensional model, and the controller is subsequently approximated by a finite-dimensional transfer function.

Inversion of a moment model for batch crystallization is employed in the feedforward part of a two-degree-of-freedom control scheme suggested in Kleinert et al. (2010). Given a
prescribed temporal evolution of the crystal mean size or supersaturation, the inversion results in trajectories of several variables, including the slurry temperature. Notably, nucleation is neglected in the underlying design model. The computed trajectories serve as setpoints for a cascaded feedback part. An extended Kalman filter is used for observation of the crystal mean size, when only temperature and concentration measurements are available.

Model predictive control (MPC) and related techniques have also been actively investigated for crystallizer control (e.g., Nagy and Braatz, 2003; Zhang and Rohani, 2003; Shi et al., 2005, 2006; Nagy, 2009). For example, in the MPC approach in Shi et al. (2005), an optimal control problem for a temperature-controlled batch crystallizer is repeatedly solved. The aim is the maximization of the volume-averaged crystal size under additional constraints regarding, e.g., temperature, supersaturation and also nucleation rate. An extended Luenberger-type observer generates the required estimates of the current state of a standard moment model, using only concentration and temperature measurements. In subsequent work (Shi et al., 2006), MPC is investigated for both continuous and batch particulate processes. In the continuous case, closed-loop asymptotic stabilization of an unstable steady state can be guaranteed by using a mixed strategy with switching between MPC and bounded Lyapunov-based control. In the batch case, the optimal control goal now consists in minimizing the total volume of fines (i.e., the third moment of the CSD part corresponding to grown nucleated crystals), while a minimum desired volume of grown seed crystals poses one of the constraints. Controller design is again based on standard moment models.

Control of preferential crystallization processes, on the other hand, is a relatively new field. For example, Wang and Ching (2006) have performed trajectory planning with the aim of controlling critical supersaturation in batch preferential crystallization. In Angelov et al. (2006), initial conditions of an isothermally operated, cyclic operation mode (see above) have been optimized. Later, in Angelov et al. (2008), the temperature profile was optimized for batch preferential crystallization. The aim consisted in maximizing the amount of the preferred enantiomer while avoiding inadmissible impurification with the counter enantiomer. Likewise, Bhat and Huang (2009) have performed optimization of the process in a more complex, multi-objective setting. In Hofmann et al. (2011), constant supersaturation control is combined with process stopping based on a worst-case impurity estimate.

Work has also been done in fields, which can be seen as related to preferential crystallization. For example, for selective crystallization of one of the polymorphic forms of $\gamma$-glutamic acid in Kee et al. (2009), supersaturation profiles are followed by using concentration feedback control.

This paper and its companion (Hofmann and Raisch, submitted for publication) focus on the solution of feedforward control problems. In particular, the problem of realizing prescribed final-time CSDs shall be extended from single-substance crystallization processes (Vollmer and Raisch, 2006) to preferential crystallization of enantiomers. Here, in Part I, as we restrict ourselves to a simple batch process, this can be illustrated by means of Fig. 2: the final-time CSD of one of the two enantiomers in the tank is specified, and the temperature profile which has to be applied in order to achieve the specification is to be determined. Note that the analysis could be repeated a number of times for subsequent batches in cyclic mode. Then, in general, every batch will start with different initial conditions, which result from the previous batch and some discrete actions, such as product removal and addition of new racemate and seed crystals.

Vollmer and Raisch (2003) have shown that a moment model for crystallization of a single substance in a single crystallizer is orbitally flat, i.e., the model is differentially flat, or just flat, in a transformed time. These concepts will be summarized in Section 3. Note that flatness can be seen as a property which makes inversion of the system a straightforward problem, namely a purely algebraic one. Based on an appropriate time scaling of a partial differential equation (PDE) population balance model, as well as of a moment model, it is then possible to realize prescribed forms for the nucleated part of a CSD. Also other tasks, namely the efficient computation of optimal control profiles, as well as feedback control, can then be solved in a (nearly) analytic way (Vollmer and Raisch, 2003, 2006).

In Raisch et al. (2005), these results were related to control problems in preferential crystallization of enantiomers, including the cyclic and coupled modes of operation. It was hypothesized that, due to different growth rates of the two enantiomer species, transformation of moment models into flat systems is no longer possible. However, as one general goal of the suggested separation schemes is to keep the crystallized mass of the counter enantiomer as low as possible, neglecting nucleation of this species was suggested as a reasonable idealization; this may allow transforming a subsystem describing only crystallization of the preferred enantiomer into a flat system.

The work in this paper and its companion (Hofmann and Raisch, submitted for publication) is twofold: first, we will show how the inversion results (Vollmer and Raisch, 2003, 2006) can be extended to the case of crystallization of enantiomers, where moment models are not orbitally flat. Inversion for these models is still possible, but not as efficient as in the orbitally flat case. Consequently, we will investigate a number of idealizing assumptions. Here, in Part I, we will consider neglecting nucleation terms. As just stated, this especially makes sense if it is done for the counter enantiomer only. Of course, in this case, inversion can only be performed w.r.t. the preferred enantiomer (when, for example, a final-time CSD is specified), but will be greatly simplified. Alternatively, we will neglect nucleation of the preferred enantiomer only, motivated by the idea that growing seed crystals outweigh nucleation, both in terms of product properties and of feedback inside the model. In Part II, which will be focused on the coupled mode of operation, we will introduce restrictions and idealizations pertaining to the growth and nucleation rates, and to the technical realization of the coupling, i.e., the exchange of liquid between two crystallizer vessels.

This paper is organized as follows: in Section 2, the population balance and moment models are given for the process of crystallization of two conglomerate forming enantiomers in a single crystallizer vessel. Section 3 contains a brief recapitulation of some basic concepts and conditions relating to (orbital) flatness. In Sections 4.1 and 4.2, we show how parts of the results by Vollmer and Raisch (2003, 2006) can be used in the process of system inversion that is necessary to realize prescribed final-time CSDs.
In Section 4.3, we show that, normally, moment models for crystallization of enantiomers are not orbitally flat. Despite this, in Section 4.4, we solve the problem of inverting a moment model, which completes the task of realizing a prescribed final-time CSD of one of the two enantiomer species. This step involves solution of differential equations. In Sections 5.1 and 5.2 we present simplified solutions for the cases when nucleation of the counter enantiomer or the preferred enantiomer, respectively, is neglected. In the former case, the resulting simplified system is orbitally flat.

In a numerical example in Section 6, we compare the idealized and non-idealized solution methods. We also investigate the results when temperature trajectories obtained using the idealized models are used as inputs to the non-idealized models.

2. Model

We assume only the basic mechanisms of growth and nucleation to take place, no other effects, such as conglomeration and breakage.

Population balance equations (PBEs) are frequently used to describe the dynamics of particulate processes (Randolph and Larson, 1988; Ramkrishna, 2000). In the enantiomer context, two PBEs are required to describe the evolution of the involved crystal populations. The PBE for one enantiomer, e.g., $E_1$, is given by

$$\frac{df_{E_1}(L,t)}{dt} = \frac{\partial \left( \rho G_{E_1}(L) f_{E_1}(L,t) \right)}{\partial L},$$

(1a)

with boundary and initial conditions

$$f_{E_1}(0, t) = \frac{B_{E_1}(t)}{G_{E_1}(0, t)},$$

(1b)

$$f_{E_1}(L, 0) = f_{E_1, \text{seed}}(L),$$

(1c)

where $t$ represents time and the scalar $L$ crystal length, $f_{E_1}$ is a number density function, the so-called crystal size distribution (CSD), and $G_{E_1}(L, t)$, $B_{E_1}(t)$ are growth and nucleation rates of $E_1$, respectively. Note that newly nucleated crystals are assumed to initially have size zero ($L=0$). We assume size-independent growth rates, so that instead of $G_{E_1}(L, t)$, we can just write $G_{E_1}(t)$. Note that the time-varying character of $G_{E_1}$ and $B_{E_1}$ may result from dependencies on other process variables. This will in the following often be denoted by writing $G_{E_1}(\cdot)$, $B_{E_1}(\cdot)$. The equations and definitions are totally analogous for enantiomer $E_2$, and the complete model then includes both sets of equations. The right side of Fig. 2 illustrates the involved crystal populations at final time $t_f$. The picture looks qualitatively the same at any time $t > 0$. Note that the CSD belonging to $E_1$, $f_{E_1}$, has been split into two parts. One represents growing seed crystals, $f_{E_1,a}$, and the other one, $f_{E_1,s}$, represents growing nucleated crystals. In the following, these two parts will be referred to as the seed CSD, and the nucleated CSD, respectively. In this scenario, $E_1$ represents the desired enantiomer, therefore $E_2$ is not seeded, and $f_{E_1,s}$ is identically zero. Note that in a cyclic mode of operation, the roles of $E_1$ and $E_2$ change from batch to batch.

For a single substance crystallization process with size-independent growth, a closed moment model can be derived (e.g., Hulburt and Katz, 1964; Myerson, 2002). In the preferential crystallization context, more than one population is involved. In analogy to a single substance crystallization process, it is possible to derive a moment model that describes the evolution of the principal moments of all relevant CSDs, i.e., that of enantiomers $E_1$ and $E_2$. As will be seen later, a closed model can be obtained which includes only the first four moments of each enantiomer (assuming that nucleation terms do not depend on higher moments). In total, we then arrive at a model consisting of 8 first order ODEs

$$\dot{\mu}_{E_1} = iG_{E_1}(\cdot)\mu_{E_1-1}(\cdot), \quad i = 1 \ldots 3,$$

(2a)

$$\dot{\mu}_{E_2} = B_{E_2}(\cdot),$$

(2b)

$$\dot{\mu}_{E_3} = iG_{E_3}(\cdot)\mu_{E_3-1}(\cdot), \quad i = 1 \ldots 3,$$

(2c)

$$\dot{\mu}_{E_4} = B_{E_4}(\cdot).$$

(2d)

where the moments are defined as

$$\mu_{E_1}(t) = \int_{0}^{\infty} L^i f_{E_1}(L, t) dL, \quad i = 0 \ldots 3,$$

(3a)

$$\mu_{E_2}(t) = \int_{0}^{\infty} L^i f_{E_2}(L, t) dL, \quad i = 0 \ldots 3,$$

(3b)

The associated initial conditions are

$$\mu_{E_1}(0) = \mu_{E_1, \text{seed}} = \int_{0}^{\infty} L^i f_{E_1, \text{seed}}(L) dL, \quad i = 0 \ldots 3,$$

(4a)

$$\mu_{E_2}(0) = \mu_{E_2, \text{seed}} = \int_{0}^{\infty} L^i f_{E_2, \text{seed}}(L) dL, \quad i = 0 \ldots 3.$$

(4b)

Note that, when the application is preferential crystallization, and $E_1$ is the preferred enantiomer, then $\mu_{E_2, \text{seed}} = 0$. As far as a moment model is concerned, the analysis in the remainder of this paper, and the numerical example in Section 6, will be based on (2).

The expressions for the growth and nucleation rates are critical for the ability of the model to represent the real crystallization process. In the literature, one can find equations for the process of crystallization of a single substance of various complexity (e.g., Miller and Rawlings, 1994; Mullin, 2001; Mersmann, 2001). For the enantioseparation process, accurate models are expected to become even more complex, as there are potential cross-couplings between various liquid and solid phases of the respective enantiomers. We have used increasingly detailed models (Elser et al., 2005a, 2011; Angelov et al., 2008; Eicke et al., 2010; Hofmann et al., 2011).

To account for the current model structure, and for future model developments, investigations in the main part of this paper will be based on generic functional dependencies of the growth and nucleation rates

$$G_{E_1}(\cdot) = G_{E_1}(T, \omega_{E_1}, \omega_{E_2}, \omega_{E_3}),$$

(5a)

$$G_{E_2}(\cdot) = G_{E_2}(T, \omega_{E_1}, \omega_{E_2}, \omega_{E_3}),$$

(5b)

$$B_{E_1}(\cdot) = B_{E_1}(T, \omega_{E_1}, \omega_{E_2}, \omega_{E_3}, \omega_{E_4}, \omega_{E_5}, \omega_{E_6}, \omega_{E_7}, \omega_{E_8}),$$

(5c)

$$B_{E_2}(\cdot) = B_{E_2}(T, \omega_{E_1}, \omega_{E_2}, \omega_{E_3}, \omega_{E_4}, \omega_{E_5}, \omega_{E_6}, \omega_{E_7}, \omega_{E_8}).$$

(5d)

The temperature of the slurry, also called the crystallization temperature, is denoted by $T$. It is sufficient to consider the mass fractions $\omega_{E_1}$, $\omega_{E_2}$ in (5), since the mass of solvent (frequently water) $m_W$ in the tank is constant, and thus a unique algebraic relationship exists between $\omega_{E_1}$, $\omega_{E_2}$ and the dissolved masses

$$m_{E_1}, m_{E_2},$$

(6a)

$$m_{E_1} = m_{E_1} + m_{E_2} + m_W,$$

(6b)

$$m_{E_2} = m_{E_1} + m_{E_2} + m_W.$$
moments of their size distributions. Note that (5) allows a cross-coupling between the enantiomer species emanating from their solid phases.

Additional differential equations describe the evolution of the liquid mass in the single crystallizer

\[ m_{1,E_1} = -3G_{E_1}(\cdot)\rho_s k_{c} \mu_{2E_1}, \]  
\[ m_{1,E_5} = -3G_{E_5}(\cdot)\rho_s k_{H2E_5}, \]  

where \( \rho_s \) is the density of the crystals, and \( k_c \) is a volume shape factor. Here, as no substance is exchanged with the environment during the batch, (7) can be replaced by algebraic mass balance equations

\[ m_{1,E_1} = m_{0,E_1} - \rho_s k_{c}(\mu_{2E_1} - \mu_{2E_1}(0)), \]  
\[ m_{1,E_5} = m_{0,E_5} - \rho_s k_{c}(\mu_{2E_5} - \mu_{2E_5}(0)). \] 

Consequently, \( \rho_s k_{c} \) and \( m_{i,E} \) need not be part of the state.

We will now pose basic assumptions on the growth and nucleation rate terms, i.e., on \( G_{E_1}(\cdot), G_{E_5}(\cdot), B_{E_1}(\cdot), B_{E_5}(\cdot) \), and also on the ratios \( (B_{E_1}/G_{E_1})(\cdot), (B_{E_5}/G_{E_5})(\cdot) \), which will enable us to establish existence and uniqueness of solutions to the proposed inversion problem, without referring to specific kinetics and parameters.

We require these assumptions to hold for all values of the state, i.e., the moments, and the input, i.e., the temperature, in a certain physically meaningful domain \( D \), where \( D \) is an open connected set.

We assume that, within \( D \), when \( G_{E_1}(\cdot), G_{E_5}(\cdot), B_{E_1}(\cdot), B_{E_5}(\cdot) \) are regarded as functions of all their non-constant arguments, they are continuously differentiable, i.e., all partial derivatives w.r.t. the arguments exist and are continuous at every point in \( D \). Also, the functions must be positive in \( D \). The latter implies that also any function defined as a ratio of rate expressions will be continuously differentiable within \( D \). This can be seen by noting that a function of several variables is continuously differentiable at a point, if all partial derivatives exist and are continuous at that point (Khalil, 2001). If the denominator of the quotient of two functions is non-zero, the quotient rule for functions of a single variable can be used to compute all the partial derivatives, and it guarantees their existence and continuity.

For the results in Section 4.3, we require \( G_{E_1}(\cdot), G_{E_5}(\cdot), B_{E_1}(\cdot), B_{E_5}(\cdot) \) to be continuously differentiable twice w.r.t. the temperature input \( T \).

Furthermore, we assume that the derivative of at least one of the ratios \( (B_{E_1}/G_{E_1})(\cdot) \) and \( (B_{E_5}/G_{E_5})(\cdot) \), with respect to the temperature input \( T \), is nowhere equal to zero. From continuity of these derivatives, it then follows that the respective one is either everywhere positive or negative.

The first part of the above assumptions only poses basic differentiability properties, which are not too restrictive. Also, requiring that the growth and nucleation rates be positive is no additional restriction, since the model itself is not valid otherwise. Only the strict monotonicity assumption between \( T \) and \( (B_{E_1}/G_{E_1})(\cdot) \), respectively \( (B_{E_5}/G_{E_5})(\cdot) \), may pose a real restriction. Frequently, in crystallization systems, there are competing mechanisms governing the rates: for example, supersaturation, as a driving force, decreases with increasing temperature, while an Arrhenius law can pose a positive influence of increasing temperature on the respective rate. Consequently, there might be two distinct temperature values resulting in the same rate ratio. One possible way to handle this is to suitably partition \( D \) into subsets where the relevant functions are strictly monotonic.

3. Flatness and orbital flatness

In the following, we briefly recapitulate the notions of differential flatness and orbital flatness (e.g., Fliess et al., 1995a, 1999). (Differential) flatness is a property of dynamic systems. A simple criterion (Rothfuß et al., 1997; Fliess et al., 1995a) states that, if a system

\[ \dot{x}(t) = f(x(t), u(t)), \quad x(t) \in \mathbb{R}^n, \quad u(t) \in \mathbb{R}^m \]  

is differentially flat, this is equivalent to the existence of a so-called flat output,

\[ y(t) = h(x(t), u(t), \ldots, u^{(p)}(t)), \quad y(t) \in \mathbb{R}^m, \]  

which satisfies the following properties:

1. The output \( y(t) \) can be expressed as a function of the system state \( x(t) \) and input \( u(t) \) and finitely many time derivatives of the input.
2. The system state and input can be expressed as functions of the output \( y(t) \) and finitely many of its time derivatives

\[ x(t) = y^p_1(y(t), y(t), \ldots, y^{(p)}(t)), \]  
\[ u(t) = y^p_2(y(t), y(t), \ldots, y^{(p+1)}(t)). \] 

The flat output \( y(t) \) and its derivatives therefore algebraically parametrize the system state and input. Thus, given a sufficiently smooth output trajectory, inversion (i.e., determination of \( u(t) \)) is possible without solving any differential equations. The above condition is a way to verify flatness, when a flat output candidate is already known. Note that, as stated in (10), a flat output must have the same dimension as the system input (Fliess et al., 1999).

For SISO systems in the following control affine form:

\[ \dot{x} = f(x) + g(x)u, \]  
\[ y = h(x), \] 

another way to characterize flatness is to state that the relative degree \( v \) of the system must be equal to \( n \), implying that the system must not have an internal (zero) dynamics (Khalil, 2001; Isidori, 1995). The relative degree is defined as the least positive integer \( v \), s.t.

\[ L_v T^{-1} h \neq 0, \]  

where the differential operator \( L_v \) denotes the \( k \)-th order Lie-derivative along a vector field \( \gamma \), defined in the usual way. Related concepts exist for MIMO systems (Isidori, 1995).

Given a suitable output \( y \), verification of flatness may be straightforward. However, proving that a system is non-flat is more involved. For SISO systems, a necessary and sufficient condition can be stated requiring involutivity of a certain distribution of vector fields (Khalil, 2001; Isidori, 1995; Nijmeijer and van der Schaft, 1990). However, the required computation of repeated LIE-Brackets may become intense for higher system dimensions.

For MIMO systems, a necessary condition for flatness can be given by the ruled manifold criterion (Sluis, 1993; Rouchon, 1994; Fliess et al., 1995b; Martin et al., 1997; Sira-Ramírez, 2004; Lévine, 2009). It states (Martin et al., 1997): “Assume \( x = f(x, u) \) is flat. The projection on the \( p \)-space of the submanifold \( p = f(x, u) \), where \( x \) is considered as a parameter, is a ruled submanifold for all \( x \). The criterion just means that eliminating \( u \) from \( x = f(x, u) \) yields a set of equations \( F(x, x) = 0 \) [i.e., an implicit representation of the system] with the following
property: for all \((x,p)\) such that \(F(x,p) = 0\), there exists \(g \in \mathbb{R}^n\), \(g \neq 0\) such that
\[
\forall \lambda \in \mathbb{R}, \quad F(x,p + \lambda g) = 0.
\] (15)

Note that for input-affine systems this condition always holds.

A system is orbitally flat (Fliess et al., 1995a; Respondek, 1998; Guay, 1999) if it can be turned flat by an appropriate state and input dependent time scaling

\[
[t_0,t_f] \rightarrow [\tau_0,\tau_f].
\] (16a)

\[
\frac{dt}{d\tau} = s(x(t),u(t)), \quad \tau(t_0) = \tau_0,
\] (16b)

\[0 < s(x(t),u(t)) < \infty \quad \forall \tau.
\] (16c)

The last condition ensures that \(t\) is strictly increasing in \(\tau\), and therefore guarantees that the time scaling is invertible. In scaled time, the system differential read

\[
\frac{d}{d\tau} x(\tau) = s(x(\tau),u(\tau)) \cdot f(x(\tau),u(\tau)).
\] (17)

### 4. Analysis of the single crystallizer configuration

#### 4.1. Time scaling of the population balance equation

To realize prescribed final-time CSDs, the first step taken by Vollmer and Raisch (2003, 2006) is to scale time with the growth rate of the population balance model. This turns the population balance PDE into a simple linear transport equation. Using this transport equation, the trajectory of the output \(\mu_1(\tau)\), which realizes a given final-time CSD \(f(L,\tau_f)\) can be directly computed. Moreover, \(\mu_1(\tau)\) was shown to be a flat output of a moment model in the same transformed time \(\tau\).

In the enantiomer context, we can scale time either with the growth rate of \(E_1\) or \(E_2\). Without loss of generality, we assume that the growth rate of enantiomer \(E_1\) is chosen, and denote the resulting scaled time \(\tau_{E_1}\), i.e.,

\[
d\tau_{E_1} = G_{E_1}(\cdot) dt.
\] (18)

Then, the population balance equation for enantiomer \(E_1\) becomes

\[
\frac{\partial f_{E_1}(L,\tau_{E_1})}{\partial \tau_{E_1}} = - \frac{\partial f_{E_1}(L,\tau_{E_1})}{\partial L},
\] (19a)

with boundary and initial conditions

\[
f_{E_1}(0,\tau_{E_1}) = \frac{B_{E_1}(\tau_{E_1})}{G_{E_1}(\tau_{E_1})},
\] (19b)

\[
f_{E_1}(L,0) = f_{E_1,seed}(L).\] (19c)

As in Vollmer and Raisch (2003), the characteristic curves that describe the solutions become straight lines, see Fig. 3, and the required final-time shape of the nucleated part of the CSD \(f_{E_1}(L,\tau_{E_1,f})\), \(L \in [0, L_{\text{max}} = \tau_{E_1,f}]\), can trivially be converted to a temporal evolution of the boundary condition, i.e.,

\[
\frac{B_{E_1}(\tau_{E_1})}{G_{E_1}(\tau_{E_1})} = f_{E_1}(\tau_{E_1,f} - \tau_{E_1},\tau_{E_1,f}), \quad \tau_{E_1} = 0, \ldots, \tau_{E_1,f}.
\] (20)

Note that the part of the final-time CSD \(f_{E_1}(L,\tau_{E_1,f})\) with \(L > \tau_{E_1,f}\) is merely a shifted version of the CSD of seed crystals, and can therefore not be freely prescribed

\[
f_{E_1}(L,\tau_{E_1,f}) = f_{E_1,seed}(L-\tau_{E_1,f}), \quad L > \tau_{E_1,f}.
\] (21)

This shows that \(\tau_{E_1}\) corresponds to the gain in length of crystals belonging to the seed distribution.

#### 4.2. Time scaling of the moment model

Following the procedure given by Vollmer and Raisch (2003), the transformation (18) is applied to the moment model (2a) and (2b) for enantiomer \(E_1\). The result is

\[
\frac{d}{d\tau_{E_1}} \mu_{E_1}^i = \mu_{E_1}^{i-1}, \quad i = 1 \ldots 3,
\] (22a)

\[
\frac{d}{d\tau_{E_1}} \mu_{E_1}^3 = \frac{B_{E_1}(\tau_{E_1})}{G_{E_1}(\tau_{E_1})}.
\] (22b)

This represents a linear time-invariant system with input signal \(B_{E_1}/G_{E_1}\). In fact, it is a simple chain of integrators (see Fig. 4), and it is immediately clear that the third moment \(\mu_{E_1}^3\) is a flat output of this part of the overall system.

According to Section 4.1, the profile of \(B_{E_1}/G_{E_1}\) in scaled time is determined by the desired final-time CSD for \(E_1\). By integrating this profile, one obtains the temporal evolution of the moments

\[
\mu_{E_1}^0, \ldots, \mu_{E_1}^3.
\]

For this, the initial conditions of the moments must be taken into account. Normally, if \(E_1\) is the preferred enantiomer, these are the moments of the CSD of the seed crystals, whereas if \(E_1\) is the counter enantiomer they are zero. Note that, when a desired final-time CSD is in a suitable functional form (e.g., a
parametrization by splines), then closed form solutions may be found for \( (22) \).

To simplify notation, we will define the state vector of the overall model by

\[
\mathbf{x}^T = [\mathbf{\mu}^T_{\text{SE}}, \ldots, \mathbf{\mu}^T_{\text{EE}}, \mathbf{\mu}^T_{\text{EE}}, \ldots, \mathbf{\mu}^T_{\text{EE}}],
\]

(23)

and denote the temperature, which serves as the input, \( u \), i.e.,

\[
u = i \quad T. \tag{24}\]

Hence, in original time \( t \), the moment model reads as

\[
\begin{align*}
\mathbf{x}_i &= (4-i)\mathbf{G}_E_i (\mathbf{x}, u) \mathbf{x}_{i+1}, & i &= 1 \ldots 3, \\
\mathbf{x}_4 &= \mathbf{B}_E (\mathbf{x}, u), \\
\mathbf{x}_5 &= (8-i)\mathbf{G}_E_i (\mathbf{x}, u) \mathbf{x}_{i+1}, & i &= 5 \ldots 7, \\
\mathbf{x}_6 &= \mathbf{B}_E (\mathbf{x}, u).
\end{align*} \tag{25a-c}\]

For some of the following analysis, we require an input-affine model. To achieve this, we consider temperature as another state variable, and its derivative as a new input \( \pi \), i.e.,

\[
\mathbf{x}_9 \doteq T, \\
\pi \doteq \frac{d}{dt} \mathbf{x}_9 = \frac{1}{\mathbf{G}_E (\mathbf{x})} \frac{d}{dt} \mathbf{x}_9. \tag{26}
\]

The input \( \pi \) is defined to give simpler equations when the model is transformed into the time scaled according to \( \mathbf{G}_E (\cdot) \), i.e., \( \tau_{E_i} \).

4.3. Lack of orbital flatness

Based on the ruled manifold criterion \( \text{(Sluis, 1993; Rouchon, 1994; Fliess et al., 1995b; Martin et al., 1997; Sira-Ram\'irez, 2004; Lévine, 2009)} \), see Section 3, we will argue that, typically, the model \( (25) \) is not orbitally flat. Roughly speaking, we show that no strictly monotonic time scaling can simultaneously “align” more than two of the right hand sides of \( (25) \), which are nonlinear in \( u \).

In Appendix A, we derive a general test to exclude orbital flatness of a given single input system, \( \mathbf{x} = f(\mathbf{x}, u) \).

To exclude orbital flatness of a system in the form of \( (25) \), the local conditions \( (A.12) \) have to be checked. More precisely, we can choose some \( (\mathbf{x}_a, \mathbf{u}_a) \) and verify, for every one of the right hand sides of \( (25) \), one after the other, that, when this function takes the role of \( f_a \), two of the remaining functions can take the roles of \( f_b \) and \( f_c \), so that \( (A.12) \) is the case. Recall that, according to the basic assumptions in Section 2, the system differential equations are continuously differentiable twice w.r.t. \( u \).

In the following, the procedure is demonstrated for a very basic example of growth and nucleation rate functions in crystallization of enanitomers, suggesting that practical models for such processes are not orbitally flat. The model is overly simplistic in that, e.g., only secondary nucleation is considered. It is therefore presumed that, at time \( t = 0 \), crystals of both enantiomer species are already present

\[
\begin{align*}
G_E (\cdot) &= k_0 (\mathbf{w}_E, v - 1) \delta, \\
B_E (\cdot) &= k_0 (\mathbf{w}_E, v - 1) \delta \mathbf{\mu}_{\text{SE}}, \\
B_E (\cdot) &= k_0 (\mathbf{w}_E, v - 1) \delta \mathbf{\mu}_{\text{EE}},
\end{align*} \tag{28a-c}\]

where

\[
u = \frac{1}{\mathbf{w}_{\text{eq}(u)}} \quad \mathbf{w} \doteq \mathbf{w}_{\text{eq}(T)}. \tag{29}\]

In this simple example, we assume an equilibrium mass fraction, \( \mathbf{w}_{\text{eq}(T)} \), which is a static, invertible function of temperature \( T \), and which is common for both enantiomers.

This makes it possible to analyze system \( (25) \) and \( (28) \), with \( v \) as the input, instead of system \( (25), (28), (29) \), with \( u = T \) as the input. In fact, noting that “\( [a] \) system \( \mathbf{x} = f(\mathbf{x}, u) \) is flat if, and only if, the closed loop system \( \mathbf{x} = f (\mathbf{x}, \pi(u)) \) is flat with \( u = \pi(u) \) being an invertible feedback, i.e., \( \pi = \mathbf{h}(\mathbf{x}, u) \) with \( u = \pi(u) \)” \( \text{(Sira-Ram\'irez, 2004)} \), we see that system \( (25) \), \( (28), (29) \) being orbitally flat would imply that system \( (25) \) and \( (28) \) also be orbitally flat. Knowing a suitable time scaling function \( s(u) \), one could substitute \( u \) by the inverse of \( (29) \) in both \( \mathbf{s}(\mathbf{u}) \) and \( f (\mathbf{x}, u) \) and arrive at a system (with input \( v \) which would still be flat.

To verify that system \( (25) \) and \( (28) \) is not orbitally flat, we choose \( (\mathbf{x}_a, \mathbf{u}_a) \) s.t. \( (\mathbf{w}_{E_i}, \mathbf{w}_{E_j}, \mathbf{w}_{E_k}) = (0.12, 0.11, 0.1) \), \( \mathbf{\mu}_{\text{EE}} \neq 0 \), \( i = 0 \ldots 3 \) and \( \mathbf{\mu}_{\text{EE}} \neq 0 \), \( i = 0 \ldots 3 \). Note that these are reasonable values, which could be encountered during normal operation of the process. Computing the expressions in \( (A.12) \), with \( (\cdot) = d/dv(\cdot) \) \( (\cdot) = d^2/dv^2(\cdot) \), where, one after the other, each of the eight time derivative functions in \( (25) \), \( (28) \) substituted, takes the role of \( f_a \), and each time two of the remaining functions are appropriately chosen as \( f_b \) \( f_c \), one can exclude orbital flatness, as long as \( b \neq g, b \neq f \neq g \), and \( b \neq f \neq g \). By conducting another test, e.g., with \( (\mathbf{w}_{E_i}, \mathbf{w}_{E_j}, \mathbf{w}_{E_k}) = (0.13, 0.12, 0.1) \), the last three cases can be ruled out as well, so that only in the case \( b = g \) orbital flatness cannot be excluded.

Note that, when the system would consist only of \( (25) \) and \( (25) \) \( (25) \) and \( (25) \) are considered as constant parameters, then it would be easy to see that, regardless of \( (\mathbf{x}_a, \mathbf{u}_a) \), and which of the four right hand sides, respectively, are assigned to \( f_a \) \( f_c \), at least one equation of \( (A.12) \) is zero. This is due to the common way \( u \) enters in the functions \( (25a) \), via \( \mathbf{G}_E (\mathbf{x}, u) \). The argument is analogous for a system \( (25c) \) and \( (25d) \). This is not surprising, since these submodels have the same structure as a moment model for single substance crystallization, which was shown to be orbitally flat by Vollmer and Raisch \( \text{(2003)} \). Following these ideas, in Section 5.1, we will introduce an idealized model with the same property.

4.4. Dynamic inversion

In this section, we show how inversion of the complete, non-idealized, moment model for enantioseparation in a single crystallizer is possible. Although the model is not orbitally flat, the time scaling process in Sections 4.1 and 4.2 still contributes decisively to the solution.

There exist two growth rates, namely \( \mathbf{G}_E (\cdot) \) and \( \mathbf{G}_E (\cdot) \), which are, in general, not equal. Suppose we are primarily interested in one of the enantiomers, say \( E_1 \). We will therefore use the time transformation \( (18) \)

\[
dT = \mathbf{G}_E (\cdot) dt. \tag{30}\]

In accordance with Section 4.3, we will show that, if this time transformation is applied to the complete, non-idealized model, the third moment of enantiomer \( E_1 \), is not a flat output. However, we will demonstrate that inversion of the system with this output,

\[
y = \pi x_1 \tag{31}\]

is still possible, but involves the solution of differential equations. The existence of a solution then depends also on the zero dynamics.
When the time transformation (30) is applied to (25)–(29), the resulting set of ODEs is
\[
\frac{d}{dt_{E_i}} x_i = (4-i) x_{i+1}, \quad i = 1 \ldots 3, \tag{32a}
\]
\[
\frac{d}{dt_{E_i}} x_4 = \frac{B_{E_i}}{G_{E_i}} (x_1, \ldots, x_8, x_9), \tag{32b}
\]
\[
\frac{d}{dt_{E_i}} x_i = (8-i) \frac{G_{E_i}}{G_{E_i}} (x) x_{i+1}, \quad i = 5 \ldots 7, \tag{32c}
\]
\[
\frac{d}{dt_{E_i}} x_8 = \frac{B_{E_i}}{G_{E_i}} (x_1, \ldots, x_8, x_9), \tag{32d}
\]
\[
\frac{d}{dt_{E_i}} x_9 = x_9. \tag{32e}
\]

The expressions \( B_{E_i}/G_{E_i}(x) \), \( G_{E_i}/G_{E_i}(x) \) and \( B_{E_i}/G_{E_i}(x) \) denote nonlinear functions determined by the respective growth and nucleation rates.

Note that (31) and (32) is in control affine form (13), with
\[
f(x) = \begin{bmatrix} 3x_2, 2x_3, x_4, \frac{B_{E_i}}{G_{E_i}} (x), 3 \frac{G_{E_i}}{G_{E_i}} (x)x_6, 2 \frac{G_{E_i}}{G_{E_i}} (x)x_7, \frac{G_{E_i}}{G_{E_i}} (x)x_8, \frac{B_{E_i}}{G_{E_i}} (x), 0 \end{bmatrix}^T, \tag{33}
\]
\[
g(x) = [0, 0, 0, 0, 0, 0, 0, 1], \tag{34}
\]
\[
h(x) = x_1. \tag{35}
\]

Therefore,
\[
L_0^1 h = x_1; \quad L_0^4 L_0^1 h = 0; \tag{36a}
\]
\[
L_0^2 h = 3x_2; \quad L_0^4 L_0^2 h = 0; \tag{36b}
\]
\[
L_0^3 h = 6x_3; \quad L_0^4 L_0^3 h = 0; \tag{36c}
\]
\[
L_0^4 h = 6x_4; \quad L_0^4 L_0^4 h = 0; \tag{36d}
\]
\[
L_0^5 h = \frac{B_{E_i}}{G_{E_i}} (x); \quad L_0^4 L_0^5 h = 6 \frac{\partial}{\partial x_9} \left( \frac{B_{E_i}}{G_{E_i}} (x) \right). \tag{36e}
\]

With regard to the assumptions presented in Section 2, the partial derivative of \( B_{E_i}/G_{E_i} \) with respect to temperature, i.e., \( x_9 \), must not be equal to zero within the physically meaningful domain \( D \). Therefore,
\[
L_0^4 L_0^5 h \neq 0. \tag{37}
\]

Consequently, the relative degree of the system is \( v = 5 < n = 9 \), and \( y \equiv x_1 \) is not a flat output. Note that the system has strong relative degree \( v = 5 \), because (36) and (37) hold in the entire domain of definition, \( D \).

Nevertheless, inversion of the system is still possible. We can transform the system into a normal form (Khalil, 2001; Isidori, 1995) by introducing a new state \( z \)
\[
z_1 = y = L_0^5 h(x) = x_1, \tag{38a}
\]
\[
z_2 = \frac{d}{dt_{E_i}} y = L_0^1 h(x) = 3x_2, \tag{38b}
\]
\[
z_3 = \frac{d^2}{dt_{E_i}^2} y = L_0^2 h(x) = 6x_3, \tag{38c}
\]
\[
z_4 = \frac{d^3}{dt_{E_i}^3} y = L_0^3 h(x) = 6x_4, \tag{38d}
\]

\[
z_5 \equiv \frac{d^4}{dt_{E_i}^4} y = L_0^5 h(x) = \frac{B_{E_i}}{G_{E_i}} (x), \tag{38e}
\]
\[
z_i \equiv x_{i-1}, \quad i = 6 \ldots 9. \tag{38f}
\]

To obtain the inverse transformation, the state variables \( x_1 \) to \( x_4 \) and \( x_5 \) to \( x_9 \) can be found trivially. For obtaining \( x_9 \), (38e) must be inverted, i.e., the solution of
\[
6 \frac{B_{E_i}}{G_{E_i}} (x_1, \ldots, x_4, x_5, \ldots, x_8, x_9) = z_5, \tag{39}
\]

respectively
\[
6 \frac{B_{E_i}}{G_{E_i}} (z_1, \frac{1}{3} z_2, \frac{1}{5} z_3, \frac{1}{6} z_4, \frac{1}{5} z_5, \frac{1}{3} z_6, z_7, z_8, z_9) = z_5. \tag{40}
\]

must be computed. Under the assumptions in Section 2, a unique solution exists when operation is in the physically meaningful domain \( D \), i.e., \( x_9 \) can be written as a function of \( z \), which, slightly abusing notation, we denote as
\[
x_9 = \left( \frac{B_{E_i}}{G_{E_i}} \right)^{-1} \left( z_1, \frac{1}{3} z_2, \frac{1}{5} z_3, \frac{1}{6} z_4, \frac{1}{5} z_5, \frac{1}{3} z_6, z_7, z_8, z_9 \right). \tag{41}
\]

The resulting system is
\[
\frac{d}{dt_{E_i}} z_i = z_{i+1}, \quad i = 1 \ldots 4, \tag{42a}
\]
\[
\frac{d}{dt_{E_i}} z_5 = L_0^5 h(x) + L_0^4 L_0^5 h(x) \cdot \pi, \tag{42b}
\]
\[
\frac{d}{dt_{E_i}} z_6 = 3 \frac{G_{E_i}}{G_{E_i}} (x) z_7, \tag{42c}
\]
\[
\frac{d}{dt_{E_i}} z_7 = 2 \frac{G_{E_i}}{G_{E_i}} (x) z_8, \tag{42d}
\]
\[
\frac{d}{dt_{E_i}} z_8 = \frac{G_{E_i}}{G_{E_i}} (x) z_9, \tag{42e}
\]
\[
\frac{d}{dt_{E_i}} z_9 = \frac{B_{E_i}}{G_{E_i}} (x). \tag{42f}
\]

where \( x \) can be substituted by the inverse transform. Note that (42) is in Byrnes–Isidori normal form (Kravaris and Kantor, 1990; Isidori, 1995), since \( \pi \) only enters (in an affine way) in (42b).

Using
\[
L_0^5 h = 6 \frac{\partial}{\partial x} \left( \frac{B_{E_i}}{G_{E_i}} (x) \right) f(x), \tag{43}
\]
and (36), Eq. (42b) reads
\[
\frac{d}{dt_{E_i}} z_5 = 6 \frac{\partial}{\partial x} \left( \frac{B_{E_i}}{G_{E_i}} (x) \right) f(x) + 6 \frac{\partial}{\partial x} \left( \frac{B_{E_i}}{G_{E_i}} (x) \right) \cdot \pi. \tag{44}
\]

In the Byrnes–Isidori normal form, (42c)–(42f) constitute the zero dynamics. Because \( z_6, \ldots, z_9 \) correspond to \( x_5, \ldots, x_8 \), this dynamics can be directly identified as the dynamics of the counter enantiomer subsystem.

When a desired, sufficiently smooth, output trajectory \( y(\tau_{E_i}) \), \( \tau_{E_i} \in [0, T_{E_i}] \) is specified, then \( z_1 \) to \( z_5 \), respectively \( x_1 \) to \( x_4 \) and \( B_{E_i}/G_{E_i} \), are directly determined as functions of \( \tau_{E_i} \), and also their initial conditions are uniquely determined, i.e., their trajectories are determined by the trajectories of the respective derivatives of the output, (38a)–(38e). We require that \( y \) be continuously differentiable five times with respect to \( \tau_{E_i} \), so that these functions, including \( B_{E_i}/G_{E_i} = \frac{d^5}{d\tau_{E_i}^5} y \), are all continuously differentiable w.r.t. \( \tau_{E_i} \). For the realization of a specified final-time CSD for \( E_i \), \( B_{E_i}/G_{E_i} \) and \( x_1 \) to \( x_4 \) are determined according to Sections
4.1 and 4.2; the specified CSD must be continuously differentiable w.r.t. \( L \).

For obtaining the trajectory of the remaining part of the state, the zero dynamics, \((42c) - (42f)\), has to be integrated. Therefore, in \((42c) - (42f)\), the explicit time-dependent functions \( x_1(\tau_{E1}) \) to \( x_4(\tau_{E1}) \) can be directly substituted. For \( x_0 \), the solution \((41)\) can be substituted (involving the explicit time-dependent function \( z_0(\tau_{E1}) \)). Under the basic assumptions in Section 2, in the physically meaningful domain \( D \), \((41)\) is continuously differentiable w.r.t. all its arguments. This can be seen using the implicit function theorem (e.g., Khalil, 2001), noting in particular that, w.r.t. all its arguments. This can be seen using the implicit solution must leave any compact subset \( V \). When \( \delta_0(\tau_{E1}) \), the input \( u(\tau_{E1}) \) can be computed using \((42b)\). This step is optional, since the “real” input is \( u(\tau_{E1}) = \delta(\tau_{E1}) = x_0(\tau_{E1}) \).

For establishing existence and uniqueness of solutions, it can be first checked whether the trajectories of the state variables \( x_1 \) to \( x_4 \) (known as explicit \( \tau_{E1} \)-time dependent functions) do not violate \( D \). Then, existence and uniqueness of solutions of \((42c) - (42f)\) (with all substitutions made) has to be checked. Using the product rule and the quotient rule for differentiation, and noting that \( G_E(\cdot) > 0 \), it can be seen that, inside \( D \), the functions in these differential equations are continuously differentiable, and therefore locally Lipschitz, in the state variables, and in the “time” \( \tau_{E1} \). Thus, a unique local solution exists from any given initial condition inside \( D \) (Khalil, 2001), on a maximal open time interval \([0, \tau_{E1,max}]\). If \( \tau_{E1,max} > \tau_{E1,f} \) (the specified final time), then a unique solution has been found. If \( \tau_{E1,max} \leq \tau_{E1,f} \), then no solution exists, and one can conclude that the prescribed output profile, respectively final-time CSD, is not realizable.

When computing solutions, it can be hard to check whether \( \tau_{E1,max} > \tau_{E1,f} \) or not. However, the fact that, if \( \tau_{E1,max} \) is finite, a solution must leave any compact subset \( W \) of \( D \) (Khalil, 2001) shows a practical way to check if an output profile (respectively final-time CSD) can be realized: one chooses a compact set \( W \), whose boundary keeps a certain safety distance from the boundary of \( D \). Then, if a solution can be computed which leaves \( W \), while still remaining in \( D \), one can at least conclude that the specification cannot be realized while keeping the safety distance from the boundary of \( D \).

Having found the profile \( x_0(\tau_{E1}) = T(\tau_{E1}) \), the inverse time transformation,

\[
I(\tau_{E1}) = \int_0^{\tau_{E1}} \frac{1}{c_E(x(\tau_{E1}))} dt_{E1},
\]

must be performed to arrive at the physically implementable (e.g., by means of a temperature tracking controller) profile \( T(t) = T(\tau_{E1}) \circ T_{E1}(t) \), where \( T_{E1}(t) \) denotes the inverse of \((45)\). Fig. 5 illustrates the main steps in the complete inversion scheme, involving results from Sections 4.1, 4.2 and 4.4, in the case when a desired final CSD for enantiomer \( E_1 \) shall be realized.

To reconstruct the final-time CSD of the other enantiomer species, e.g., \( E_2 \), we can proceed as follows: by applying the inverse time transformation \((45)\) to the known signals \( G_{E_2}(\tau_{E1}) \) and \( B_{E_2}(\tau_{E1}) \), we obtain the respective temporal growth and nucleation rate profiles, \( G_{E_2}(t) \) and \( B_{E_2}(t) \). We can then scale time according to \( dt_{E2} = G_{E_2}(t) dt \) and, obtain, in particular, the profile \( (B_{E_2}/G_{E_2})(\tau_{E1}) \). The corresponding CSD is then easily determined by \((20)\) and, if seed crystals were added for the respective enantiomer species, \((21)\); if necessary, one has to substitute \( E_1 \) by \( E_2 \) in these equations. This argument shows that the non-specified final-time CSD is completely determined by the specified one. Following these ideas, it is not hard to adapt the results to the pure forward (i.e., simulation) problem: given the temperature profile, determine the final-time CSDs of both enantiomer species.

Note that, especially in the enantiomer context, the existence of solutions for the proposed inversion problem cannot be taken for granted. Due to different liquid mass fractions of the two enantiomer species, the temperature required to realize a certain nucleation rate (respectively, nucleation to growth rate ratio) of one enantiomer may drive supersaturation of the other enantiomer below one. However, this would imply dissolution of crystals of that enantiomer, and is not covered by the model introduced in Section 2. Such a situation is indeed relevant in practice, for example in the cyclic operation mode. There, every batch starts with excess liquid mass fraction of the preferred enantiomer.

### 5. Analysis using idealizing assumptions

In this section, we discuss the implications on the inversion problem for a single crystallizer, when nucleation of one enantiomer species is neglected. Inversion shall of course be performed for the enantiomer species for which nucleation is not neglected. Otherwise, one could only specify how much the seed crystals shall grow. This problem would not have a unique solution.

Depending on the actual problem setting, one of the idealizations illustrated in Fig. 6 can make sense. In Fig. 6(a), nucleation of the counter enantiomer, \( E_2 \), is neglected, and the nucleated part of the respective CSD, \( f_{E_2,n} \), vanishes. As no seed crystals are added for \( E_2 \), this means that no crystallization of \( E_2 \) occurs. In Section 5.1, we show how this leads to an idealized system which is orbitally flat (i.e., flat in a scaled time \( \tau_{E1} \)), and thus easily

---

**Fig. 5.** Complete inversion scheme for realization of a desired final-time CSD, \( f_{E_1,des} \), for enantiomer \( E_1 \).

**Fig. 6.** Idealizations: (a) neglecting crystallization of the counter enantiomer; (b) neglecting nucleation of the preferred enantiomer.
invertible, effectively describing single substance crystallization of the preferred enantiomer, \( E_1 \). An application of this scenario may arise when a product (preferred enantiomer) with a strictly defined CSD must be achieved.

In Fig. 6(b), nucleation of the preferred enantiomer, \( E_1 \), is neglected, so that \( \hat{f}_{E_1,n} \) vanishes. The CSD of \( E_1 \) is then fully described by the seed distribution and the gain in length of the seed crystals, \( t_E \). The final CSD of the counter enantiomer, \( E_2 \), is specified, and an appropriate temperature profile is sought. This will be discussed in Section 5.2. Compared to Section 4.4, the inversion will be simplified in that the zero dynamics can be written in terms of one state only.

When applying one of these idealizations, one of course has to check whether it is justified for the specific problem, possibly a posteriori, i.e., after a temperature trajectory \( T(t) \) has been obtained. This will be demonstrated for a numerical example in Section 6.

5.1. Neglecting nucleation of the counter enantiomer

Here, it is assumed that no crystallization occurs for the counter enantiomer species, \( E_2 \), as illustrated in Fig. 6(a). This means that no seed crystals have been added for this species, and, on the other hand, (primary) nucleation is neglected.

When the results for the system inversion in Sections 4.1, 4.2 and 4.4 are adopted to this scenario, with the targeted enantiomer being \( E_1 \), then what remains of Eqs. (42) is

\[
\begin{align*}
\frac{d}{dt} z_i &= z_{i+1}, \quad i = 1 \ldots 4, \quad (46a) \\
\frac{d}{dt} z_5 &= L_f^5 h(x_1, \ldots, x_6, 0, \ldots, 0, x_9) \\
&\quad + L_f^5 h(x_1, \ldots, x_6, 0, \ldots, 0, x_9) \cdot \Pi, \quad (46b)
\end{align*}
\]

where the definitions of \( x \) and \( z \) follow (23), (26), (38), (41).

In particular,

\[ x_9 = x_9 = \left( \frac{B_{E_2}}{C_{E_2}} \right)^{-1} \left( z_1, \frac{1}{2} z_2, \frac{1}{2} z_3, \frac{1}{2} z_4, \frac{1}{2} z_5, 0, 0, 0 \right). \]  

(47)

This system is of dimension \( p = 5 \), and it has essentially the same structure as the one treated by Vollmer and Raisch (2003). Under the basic assumptions on growth and nucleation rates in Section 2, it can be easily verified to be flat: the relative degree is \( r = 5 = p \). Of course, for complicated rate expressions, inversion solutions may be more demanding than in Vollmer and Raisch (2003). Specifically, it may be necessary to solve (47) numerically. However, unlike in Section 4.4, no differential equations must be solved.

5.2. Neglecting nucleation of the preferred enantiomer

It can be shown in a fashion analogous to Section 4.3 that the moment model resulting from this idealization is not orbitally flat. In this case, in (25), treat the constant \( x_4 \) as a parameter, substitute it into (25a), (25c), (25d), and remove (25b).

Here, as nucleation of the preferred enantiomer is neglected, the goal is to realize a specified final CSD of the counter enantiomer, \( E_2 \). The solution of this inversion problem is analogous to the procedure described in Sections 4.1, 4.2 and 4.4. However, time must now be scaled with the growth rate of the counter enantiomer

\[ d t_{E_2} = C_{E_2}(\tau) \, d \tau. \]  

(48)

It still makes sense to define \( \tau_{E_1} \), i.e., the gain in length of the seed crystals of the preferred enantiomer, as a state variable. In fact, in the absence of nucleation, the CSD of \( E_1 \) is merely a shifted version of the CSD of the seed crystals, where the value of the shift is \( \tau_{E_1} \). It is easy to show that its moments are fully determined by polynomial expressions, in terms of \( \tau_{E_1} \)

\[
\begin{align*}
\mu_{BE_1}(\tau_{E_1}) &= \mu_{BE}(0) = \text{const.}, \quad (49a) \\
\mu_{1E_1}(\tau_{E_1}) &= \mu_{BE}(0) \tau_{E_1} + \mu_{2E_1}(0), \quad (49b) \\
\mu_{2E_1}(\tau_{E_1}) &= \mu_{BE}(0) \tau_{E_1}^2 + 2 \mu_{1E_1}(0) \tau_{E_1} + \mu_{2E_1}(0), \quad (49c) \\
\mu_{3E_1}(\tau_{E_1}) &= \mu_{BE}(0) \tau_{E_1}^3 + 3 \mu_{1E_1}(0) \tau_{E_1}^2 + 3 \mu_{2E_1}(0) \tau_{E_1} + \mu_{3E_1}(0). \quad (49d)
\end{align*}
\]

Note that the final gain in length of the seed crystals, \( \tau_{E_1,f} \), is not part of the specification, and, due to differing growth rates of \( E_1 \) and \( E_2 \), it will, in general, be different from the final scaled time, \( \tau_{E_1,f} \).

By setting \( B_{E_2}(\tau) = 0 \), and substituting the polynomial expressions (49) into the remaining growth and nucleation rate functions, the results from Section 4.4 can be adopted for the idealized system of this section, resulting in a simpler zero dynamics, i.e., one involving less states. When \( \Pi, x \) and \( z \) are now defined as

\[
\begin{align*}
\Pi &\triangleq \frac{d}{dt} \frac{C_{E_2}(\tau)}{C_{E_2}(\tau)} \frac{d}{dt} T, \quad (50) \\
x^I &\triangleq \left[ \mu_{BE_2}, \mu_{2E_2}, \mu_{BE_1}, \mu_{BE_1}, \tau_{E_1}, T \right], \\
\end{align*}
\]

(51)

and

\[
\begin{align*}
\Pi^I &\triangleq \left[ \mu_{BE_2}, 3 \mu_{2E_2}, 6 \mu_{BE_1}, \mu_{BE_1}, \frac{B_{E_2}}{C_{E_2}}(x), \tau_{E_1} \right]. \\
\end{align*}
\]

(52)

respectively, one arrives at the following system in normal form:

\[
\begin{align*}
\frac{d}{dt} z_i &= z_{i+1}, \quad i = 1 \ldots 4, \quad (53a) \\
\frac{d}{dt} z_5 &= L_f^5 h(x) + L_f L_f^5 h(x) \cdot \Pi, \quad (53b) \\
\frac{d}{dt} z_6 &= \frac{C_{E_2}}{C_{E_2}}(x), \quad (53c)
\end{align*}
\]

where

\[
\begin{align*}
L_f^5 h(x) &= 6 \frac{\partial}{\partial x} \left( \frac{B_{E_2}}{C_{E_2}}(x) \right) f(x), \quad (54) \\
L_f L_f^5 h(x) &= 6 \frac{\partial}{\partial x} \left( \frac{B_{E_2}}{C_{E_2}}(x) \right). \quad (55)
\end{align*}
\]

6. Numerical example

6.1. Detailed model

The equations and parameters used in the following case study are based on ongoing work for modeling the crystallization of \( l \)/d-threonine in the PCF group (Andreas Seidel-Morgenstern) at the Max Planck Institute in Magdeburg. For an explanation of modeling background, assumptions, equations and determination of parameters see Elsner et al. (2011). The following model is a result of further modifications and adjustments of parameters. Notably, a new (empirical) term has been added (e.g., Eicke et al., 2010) to describe the effect of heterogenous primary nucleation, where different enantiomer species in the tank influence the nucleation rates of each other via their solid phases. Essentially the same version of the model that we use in the following has also been employed by Hofmann et al. (2011). However, as opposed to this contribution, we do not consider size-dependent
growth here. Therefore, the model can be obtained from Hofmann et al. (2011) by setting \( \gamma(L) \equiv 1 \).

In the following, \( \alpha \)-threonine corresponds to \( E_1 \), and \( \beta \)-threonine to \( E_2 \). The supersaturation of an enantiomer, for example \( E_1 \), is given by:

\[
S_{E_1} = \frac{W_{E_1}}{W_{E_1,E_1}}, \quad \text{with} \quad W_{E_1,E_1} = a_1(T-273.15) + a_0,
\]

where \( T \) is the temperature of the slurry, i.e., the so-called crystallization temperature. The growth rate expression is

\[
G_{E_1}(\cdot) = k_{g,0,E_1} \exp \left( \frac{-E_{g,E_1}}{R_g T} \right) (S_{E_1}(\cdot)-1)^\varphi,
\]

with

\[
k_{g,0,E_1} = k_{g,01,E_1} \cdot \omega \nu^\gamma_v.
\]

Here, \( \omega \) denotes the stirrer speed. For each enantiomer, the nucleation rate is a sum of contributions from primary and secondary nucleation. For example, for \( E_1 \),

\[
B_{E_1}(\cdot) = B_{\text{prim},E_1}(\cdot) + B_{\text{sec},E_1}(\cdot).
\]

By primary nucleation, nuclei of an enantiomer species can be formed, even without the presence of existing crystals of that species in the tank. The following expression is based on work by Mersmann (2001):

\[
B_{\text{prim},E_1} = k_{b,\text{prim},E_1} T \exp \left( -\frac{K_{T,\text{visc}}}{T} \right) \cdot \exp \left( -\frac{W_{E_1} + W_{E_1,E_1}}{K_{W,\text{visc}}} \right) \cdot \ln \left( \frac{\rho_s}{\rho_{E_1,E_1}} \right) \cdot (S_{E_1,E_1})^{2/3}
\]

- \exp(-k_{\text{prim},\log}(\frac{\ln(\rho_s/C_{eq,E_1})}{\ln(S_{E_1})})) \cdot (1+A_1\mu_{E_1}^2).

The empirical term \((1+A_1\mu_{E_1}^2)\) was introduced as a means to describe the effect of heterogenous primary nucleation. The equilibrium concentration in the tank for enantiomer \( E_1 \), \( C_{eq,E_1} \), is given by

\[
C_{eq,E_1} = \rho_{\text{sol}} W_{E_1,E_1}.
\]

The density of the aqueous solution in the tank is given by

\[
\rho_{\text{sol}} = 1000 \cdot (\rho_{\text{water}} + K_w(W_{E_1} + W_{E_1,E_1})),
\]

and

\[
\rho_{\text{water}} = \sqrt{(K_1 + K_2(T-273.15)^2)}.
\]

Secondary nucleation of \( E_1 \) is induced by existing crystals of \( E_1 \) (Mersmann, 2001):

\[
B_{\text{sec},E_1} = k_{b,\text{sec},E_1} \exp \left( -\frac{E_{b,\text{sec},E_1}}{R_g T} \right) \cdot (S_{E_1} - 1)^\varphi \cdot (\rho_{E_1,E_1})^\gamma_v.
\]

The kinetics of \( E_2 \) are analogous to (56)–(65), and are obtained simply by exchanging the indexes for \( E_1 \), \( E_2 \). Parameters which have an index of \( E_1 \) or \( E_2 \) may differ between the enantiomer species. However, in this case study, these pairs are equal, i.e., parameters are symmetric w.r.t. the two enantiomer species.

Table 1 lists the values of the parameters and initial conditions. Note that in this numerical example stirrer speed \( \omega \) is assumed constant.

### Table 1
Parameters and initial conditions used in the numerical example.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Symbol</th>
<th>Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density of enantiomer crystals</td>
<td>( \rho_s )</td>
<td>1250</td>
<td>(kg m(^{-3}))</td>
</tr>
<tr>
<td>Volume shape factor</td>
<td>( k_v )</td>
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<td>(-)</td>
</tr>
<tr>
<td>Constants for solution density</td>
<td>( K_1 )</td>
<td>1.00023</td>
<td>(m(^3) kg(^{-1}))</td>
</tr>
<tr>
<td></td>
<td>( K_2 )</td>
<td>4.68088 \times 10^{-6}</td>
<td>(m(^3) kg(^{-1}) K(^{-2}))</td>
</tr>
<tr>
<td></td>
<td>( K_3 )</td>
<td>3.652</td>
<td>(kg m(^{-1}))</td>
</tr>
<tr>
<td>Solubility constants</td>
<td>( a_1 )</td>
<td>3.983</td>
<td>(K(^{-1}))</td>
</tr>
<tr>
<td></td>
<td>( a_0 )</td>
<td>-3.4505 \times 10^{-2}</td>
<td>(-)</td>
</tr>
<tr>
<td>Universal gas constant</td>
<td>( R_g )</td>
<td>8.314472</td>
<td>(J K(^{-1}) mol(^{-1}))</td>
</tr>
<tr>
<td>Stirrer speed</td>
<td>( \omega )</td>
<td>2π \times 250</td>
<td>(min(^{-1}))</td>
</tr>
<tr>
<td>Crystal growth</td>
<td>Growth rate coefficient</td>
<td>( k_{b,01,E_1} )</td>
<td>2.7493 \times 10^7</td>
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<td></td>
<td>Exponent for stirrer speed (growth)</td>
<td>( n_g )</td>
<td>0.4573</td>
</tr>
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<td>Activation energy for crystal growth</td>
<td>( E_{b,g,E_1} )</td>
<td>75.549 \times 10^3</td>
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<td>Growth exponent</td>
<td>( g )</td>
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<td>(-)</td>
</tr>
<tr>
<td>Primary nucleation</td>
<td>Nucleation coefficient (primary nucleation)</td>
<td>( k_{b,\text{prim}} )</td>
<td>2.35657 \times 10^{-5}</td>
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<td>Parameter for temperature dependence</td>
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<td></td>
<td>Parameter for mass fraction dependence</td>
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<td>Constant for exponential law (primary nucleation)</td>
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<td></td>
<td>Heterogenous primary nucleation constant</td>
<td>( A_1 )</td>
<td>6.5608 \times 10^{-4}</td>
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<tr>
<td>Secondary nucleation</td>
<td>Nucleation coefficient (secondary nucleation)</td>
<td>( k_{b,\text{sec},E_1} )</td>
<td>3.2635 \times 10^{10}</td>
</tr>
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<td>Exponent for stirrer speed (secondary nucleation)</td>
<td>( n_{b,sec} )</td>
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<td>Activation energy (secondary nucleation)</td>
<td>( E_{b,sec,E_1} )</td>
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<td>Exponent for secondary nucleation</td>
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<td></td>
<td>Nucleation exponent (secondary nucleation)</td>
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<td>Initial conditions</td>
<td>Mass of solvent (water)</td>
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</tr>
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<td>Initial liquid (dissolved) masses</td>
<td>( m_{E_1,E_1}(0) )</td>
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</tr>
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<td>Initial (seed) moments of the preferred enantiomer CSD</td>
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<tr>
<td></td>
<td></td>
<td>( \mu_{E_2}(0) )</td>
<td>7.8331</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( \mu_{E_3}(0) )</td>
<td>4.7793 \times 10^{-3}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( \mu_{E_4}(0) )</td>
<td>3.2733 \times 10^{-6}</td>
</tr>
<tr>
<td></td>
<td>Initial moments of the counter enantiomer CSD</td>
<td>( \mu_{E_1}(0) )</td>
<td>0</td>
</tr>
</tbody>
</table>
6.2. Scenario one: final-time CSD of the preferred enantiomer specified

In this case study, we concentrate on inversion results when the final CSD of one of the involved nucleated crystal populations (distinguished by the enantiomer species) is specified. First, we consider inversion of the model for realization of a prescribed final-time CSD of the preferred enantiomer, i.e., the seeded enantiomer, \( E_1 \). We compare the exact solution, Sections 4.1, 4.2 and 4.4, to the one based on orbital flatness of the system resulting from neglecting the nucleation of the counter enantiomer, see Section 5.1.

The specified (desired) final-time CSD for the preferred enantiomer, \( E_1 \), follows an exponential prototype CSD:

\[
F_{E_1,\text{des}}(L) = \begin{cases} 
\mu_{f, n, \text{des}} \cdot \exp \left( \frac{-20(L - L_{\text{max}})}{L_{\text{max}}} \right), & L \in [0, L_{\text{max}}] \\
\int_{L_{\text{seed}}}^{L_{\text{max}}} \exp \left( \frac{-20(L - L_{\text{max}})}{L_{\text{max}}} \right) \, dL, & L > L_{\text{max}}.
\end{cases}
\] (66)

Recall that the upper CSD part is merely a shifted version of the CSD of the seed crystals. The free parameters \( \mu_{f, n, \text{des}} \) and \( L_{\text{max}} \) determine the resulting third moment of the lower (i.e., nucleated) part of the specified final CSD, and the maximum length of crystals belonging to that part, respectively. They are chosen as

\[
\mu_{f, n, \text{des}} = 10.0 \, \text{[cm}^3\text{]}, \quad L_{\text{max}} = 0.5 \, \text{[mm]}.
\] (67)

Comparison between exact and simplified solutions is conducted in the following manner: the input (temperature) profiles computed by the exact and simplified solution techniques, respectively, are compared. Furthermore, the temperature profile corresponding to the simplified solution is applied as an input to the original model, and the resulting deviations of the final-time CSD from the specification are shown. In addition to plots of CSDs of final crystal populations, plots of mass density functions (MDFs) are shown, which may be more appropriate to judge errors. To obtain these CSDs, respectively MDFs, the forward (i.e., simulation) problem is solved.

Figs. 7–11 show numerical results obtained for scenario one. The plots labeled “exct. inv.” correspond to the exact inversion. The temperature profile obtained using the flatness-based idealized solution is used as an input to simulate the original model,
and the resulting trajectories and CSDs (MDFs) are labeled “flat inv.”. In the plots of the third moments, these moments are split into parts from nucleation (index \( n \)) and growing seeds (index \( s \)). For example, \( \mu_{3E_1} = \mu_{3E_1,n} + \mu_{3E_1,s} \). This splitting is, of course, only relevant for the preferred enantiomer species, for which seed crystals are initially added.

Note that the choice of model equations, parameters and specifications for the case study cannot represent all circumstances in which the proposed exact as well as idealized solution techniques are potentially helpful. Nevertheless, the numerical results may be an orientation when using different equations, parameters or problem settings. We think that, for problems concerning mainly the preferred enantiomer in a single crystallizer, the idealized, flatness-based approach is very well suited. Note that an a posteriori justification of the idealizing assumption can be given as follows: after a temperature profile has been obtained, in can be checked in a single simulation of the original (non-idealized) model that crystallization of the counter enantiomer is sufficiently low, and, as a consequence, the degradation of the specified final CSD is acceptably small. The numerical results of scenario one, Figs. 7–11, demonstrate how well this approach can work, even when the amount of crystalline material (third moment) of the preferred enantiomer produced by nucleation is comparable to the amount produced by growing seeds (see Fig. 9), and also the resulting third moment of the counter enantiomer is not considerably lower. The dashed and corresponding solid lines in these figures virtually coincide.

6.3. Scenario two: final-time CSD of the counter enantiomer specified

Here, we compute the solution which realizes a prescribed final-time CSD of the counter enantiomer, \( E_2 \). The specification follows an exponential prototype CSD:

\[
 f_{E_{2,\text{des}}}(L) = \begin{cases} 
 \mu_{3E_{2,\text{des}}} \cdot \exp \left( \frac{-20L}{L_{\text{max}}} \right) & \text{for } 0 \leq L \leq L_{\text{max}} \\
 0, & \text{for } L > L_{\text{max}}
\end{cases}
\]

(68)

with

\[
 \mu_{3E_{2,\text{des}}} = 0.001 \text{ [cm}^3\text{]; } L_{\text{max}} = 0.59 \text{ [mm].}
\]

(69)

The numerical results are shown in Figs. 12–17. We compare the exact solution, Sections 4.1, 4.2 and 4.4, to the one involving a
simplified zero dynamics, resulting from neglecting the nucleation of the preferred enantiomer, see Section 5.2. The temperature profile obtained in the latter case is used as an input to simulate the original model, resulting in the plots labeled “no p.-nuc. inv.”.

Scenario two demonstrates that the relation between the final CSDs of the two enantiomer species may not be straightforward. This time, the specification consists of the counter enantiomer CSD. The same exponential CSD shape as in scenario one is used, but with smaller “amplitude”. Fig. 12 shows that a relatively high amount of nucleation of the preferred enantiomer results, i.e., the ratio of nucleation of the preferred enantiomer over nucleation of the counter enantiomer is much higher than in scenario one. Still, when compared to the growth of the seeds (see Fig. 14) the resulting amount of nucleation of the preferred enantiomer is low enough for applicability of the idealized solution from Section 5.2. The resulting errors, though noticeable (see Figs. 13 and 15), are reasonably small. In fact, in Figs. 12, 16 and 17, the dashed lines and the corresponding solid lines are virtually indistinguishable.

7. Conclusion

In this paper, we have considered population balance and moment models describing crystallization of two enantiomer species in one vessel. We have summarized the concepts of differential flatness and orbital flatness, which are properties of nonlinear systems that greatly facilitate analysis and control. Based on a well known necessary condition for flatness, we have derived a test to exclude orbital flatness of typical moment models for preferential crystallization. Note that this test could be useful for a wider class of single input systems. We then have presented a technique for inversion of the system, when a given, final crystal size distribution belonging to either one of the enantiomer species must be achieved in a batch process. In a technical application, one species, the preferred enantiomer, is seeded, while nucleation of the other species, the counter enantiomer, shall be kept suitably low.

Exact inversion involves the numerical solution of differential equations. This computational burden is certainly adequate when feedforward control profiles for realization of specified CSDs are sought. The most relevant application in practice may be the achievement of a product (i.e., the preferred enantiomer) with a tightly specified CSD. In this context, two general requirements seem important. First, the nucleated CSD of the preferred enantiomer, for which, within certain bounds, any shape can be realized, should represent a significant share of its total CSD (e.g., in terms of the associated third moment). Second, after obtaining the solution, it has to be checked if the purity requirement is met, i.e., if the crystalline mass of the counter enantiomer is sufficiently low.

When (only) the preferred enantiomer is targeted by the specification, a simplified inversion technique, which is based on orbital flatness of an idealized model (i.e., one where nucleation of the counter enantiomer is neglected), can be applied to solve the inversion problem. However, the computational advantage seems even more important for the solution of optimal control problems concerning properties of the final CSD of the preferred enantiomer. One could adopt the method proposed by Vollmer and Raisch (2003): by parametrizing the final CSD of the preferred enantiomer the whole evolution of the state is then algebraically parametrized, and the dynamic optimization problem is converted to a (nonlinear) static optimization problem.

A different approach, frequently used in practice, to obtain a well defined product CSD, is to rely mainly on the growth of seed crystals (i.e., the product then mainly consists of a shifted version of the CSD of the seed crystals). Especially for substances for
which nucleation (in particular, secondary nucleation) is generally low relative to growth optimization of properties of the nucleated CSD of the preferred enantiomer is then a less vital task. Therefore, entirely neglecting nucleation of the preferred enantiomer makes increased sense in that case, and a second type of simplified solution presented in this paper can be applied. In this case, as nucleation of the counter enantiomer is neglected, a dynamic optimization scheme can be most useful for the actual separation problem. For example, one could maximize the purity of the product.

In future work, the extension of the developed ideas to a wider class of models should be investigated. For example, our analysis is based on closed moment models for preferential crystallization, which cannot be obtained when PBE models are more complex. This can, e.g., be due to size-dependent growth rates. However, it may be possible to follow the proposed ideas and derive inversion schemes on the basis of approximate ODE models, using concepts brought up in the literature review in Section 1. Furthermore, it was assumed in this work that growth and nucleation rate functions are continuously differentiable. In particular, it was required that the process is operated under conditions, where the growth (and nucleation) rates of both enantiomer species are positive; this may not be the case in certain applications. Moreover, while not explicitly considered in this paper, the developed methods may also be useful in areas related to preferential crystallization, such as selective crystallization of polymorphs, or fractional crystallization. Transfer of the results should be particularly simple, if the system at hand is compatible with the model structure and the basic assumptions given in Section 2.

The developed feedforward control schemes should also be complemented by appropriate feedback control. Our treatment naturally suggests the use of methods from geometric control theory, such as exact, respectively input–output linearization. The efficient flatness-based inversion schemes enabled by the use of idealized design models, or optimal control solutions based on this, may also be useful in the context of model predictive control.

In Part II, the inversion results of this paper will be extended to a setup consisting of two coupled crystallizer vessels. This setup enables simultaneous production of pure fractions of two enantiomer species, one in each vessel, whereby the exchange of crystal free liquid helps in reducing the driving force for nucleation of the counter enantiomers. We will show the effect of additional idealizations motivated by the design of the process. In particular, we will show how the above mentioned, simplified solutions can be combined with these new idealizations.

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Appendix A. Test for lack of orbital flatness

Here, based on the ruled manifold criterion (Sluis, 1993; Rouchon, 1994; Fliess et al., 1995b; Martin et al., 1997; SiracRamírez, 2004; Lévêne, 2009), we derive a test to exclude orbital flatness of a SISO system \( \dot{x} = f(x,u) \), with \( \dim x = n \geq 3 \), and \( \dim u = m = 1 \). The test requires checking conditions on \( f \) and its derivatives w.r.t. \( u \).

Consider three out of the \( n \) system differential equations, combined with a time scaling function \( s(\cdot) \); in the following, \( \dot{x} \) denotes the derivative of \( x \) w.r.t. scaled time

\[
\dot{x}_a = s(x,u) \cdot \dot{f}_a(x,u),
\]

(A.1a)

\[
\dot{x}_b = s(x,u) \cdot \dot{f}_b(x,u),
\]

(A.1b)

\[
\dot{x}_c = s(x,u) \cdot \dot{f}_c(x,u),
\]

(A.1c)

where \( a,b,c \in \{1, \ldots, n\} \). Further, consider a triple \( (p,x_p,u_p) \), which satisfies (A.1)

\[
p_a = s(x_p,u_p) \cdot \dot{f}_a(x_p,u_p),
\]

(A.2a)

\[
p_b = s(x_p,u_p) \cdot \dot{f}_b(x_p,u_p),
\]

(A.2b)

\[
p_c = s(x_p,u_p) \cdot \dot{f}_c(x_p,u_p).
\]

(A.2c)

The function \( f(\cdot) \) is supposed to be continuous in its arguments, and continuously differentiable twice w.r.t. \( u \), at least in a certain neighborhood of \((x_p,u_p)\).

The ruled manifold criterion states that, if a system is flat, there must exist, at any \( x_p \), a vector \( g \in \mathbb{R}^n \), \( g \neq 0 \), s.t. a line \( p +/- g \) is contained in the manifold of all possible values \( x \) for the left hand sides of the system differential equations; in this regard, \( x = x_p \) is considered a fixed parameter.

Assume that we have chosen an appropriate candidate time scaling function \( s(\cdot) \), and want to check if it can turn the system flat. By appropriate we mean, on the one hand, that the values of \( s(\cdot) \) must be positive. On the other hand, we also suppose that, at \((x_1,u_1)\), \( s(\cdot) \) is continuously differentiable twice w.r.t. \( u \). In the following, we investigate whether, after scaling time according to \( s(\cdot) \), the ruled manifold criterion can be satisfied locally, at \((x_p,u_p)\). In this context, \( p \), \( x_p \), and \( u_p \) are constants. Note that \( p \) depends on the value of \( s(x_p,u_p) \), so that \( (p,x_p,u_p) \) is only fully determined once the value of the time scaling function is known. By locally we mean that we allow the domain of \( u \) to be restricted to some small neighborhood of \( u_p \). By varying \( u \) within that neighborhood, it must then be possible to vary \( x \) on a local (i.e., a small open) segment of a straight line containing \( p \).

Assume that, for given \((x_p,u_p)\), \( u \) could be eliminated (at least locally) from the time-scaled system differential equations, i.e., \( x = x_p + uf(s_x) \). This assumption will be justified at the end of this section. More specifically, it will be seen that if the conditions of the test, which will be developed in the following, are satisfied, this implies that after choosing any appropriate time scaling function it is always possible to solve (locally) one of the system differential equations (say, the \( i \)th one) for \( u \). In other words, \( u \) can be written as a function of \( x \), denoted as \( u = (s_x)^{-1}(x) \). Knowing this, it is clear that when trying to verify the ruled manifold criterion only straight lines with \( g_x \neq 0 \) have to be taken into consideration. Otherwise the projection of the (local segment of the) line onto the \( x_i \)-space would be a point \((p_i)\), which gets mapped by \((s_x)^{-1}(\cdot)\) onto a point \((u_p)\) in the input-space. That point cannot get mapped by \( s(\cdot) \) to (the local segment of a) straight line. On the other hand, the projection of an open segment of a straight line containing \( p \), with \( g_x \neq 0 \), onto the \( x_i \)-space is an open interval containing \( p \). The inverse image, w.r.t. the continuous function \( s(\cdot) \), of this open set is an open set containing \( u_p \). Furthermore, because \( s(\cdot) \) does have an inverse function, this open set is equal to the respective forward image of the inverse function \((s_x)^{-1}(\cdot)\) (see, e.g., Apostol, 1974, Definition 4.21), which is a connected set (because continuous functions map connected sets onto connected sets). In conclusion, in order to vary \( x \) on a local segment of a straight line, \( u \) must take on all values in an open interval containing \( u_p \), i.e., a neighborhood of \( u_p \).

In the following, we investigate input deviations characterized by \( \Delta u = u - u_p \). The goal is to derive local conditions, at \((p,x_p,u_p)\),
for the value of the time scaling function \( s(\cdot) \) and its derivatives w.r.t. \( u \). In view of the above considerations, we can now state the conditions of the ruled manifold criterion in the context of the explicit system representation (A.1): given any \((p, x_p, u_p)\), which satisfy (A.2), there must exist a \( g \neq 0 \), s.t.

\[
p_a + \lambda g_a = s(x_p, u_p + \Delta u - f_a(x_p, u_p + \Delta u)),
\]

\[ (A.3a) \]

\[
p_b + \lambda g_b = s(x_p, u_p + \Delta u - f_b(x_p, u_p + \Delta u)),
\]

\[ (A.3b) \]

\[
p_c + \lambda g_c = s(x_p, u_p + \Delta u - f_c(x_p, u_p + \Delta u))
\]

\[ (A.3c) \]

is satisfiable (a solution \( \lambda \in \mathbb{R} \) exists) for all values of \( \Delta u \), at least in a neighborhood of zero.

According to the ruled manifold criterion, not all components of \( g \) are allowed to be zero. Suppose therefore that \( g_a \neq 0 \). Taking two of the equations of (A.3), (A.3a), (A.3b), \( \lambda \) can be eliminated

\[
\frac{dg_a}{du} = \frac{s(x_p, u_p + \Delta u - f_a(x_p, u_p + \Delta u) - g_a}{p_a - g_a}.
\]

\[ (A.4) \]

Recall that, at \((x_p, u_p, f_a(\cdot)) \), \( i \in \{1, \ldots, n\} \), and \( s(\cdot) \) are supposed to be continuously differentiable twice w.r.t. \( u \), and that (A.4) must be fulfilled for all \( \Delta u \) in a neighborhood of zero. It is therefore justified to take the first and second derivatives of (A.4) w.r.t. \( \Delta u \). In the following, brevity, we omit the dependencies \((x, u)\) of the functions, and we denote \((\gamma) := d/d\Delta u(\cdot) = d/d\Delta u(\gamma(\cdot)) \), \( \gamma := d^2/d\Delta u^2(\cdot) = d^2/d(\Delta u^2(\cdot)) \). The first derivative w.r.t. \( \Delta u \) of (A.4) then reads

\[
\frac{dg_a}{du} (s' f_a + f s_a) = s f'_a + f s_a.
\]

\[ (A.5) \]

In the same way, (A.3a) and (A.3c) can be compared. We now denote \( k_1 := g_1 / g_a, k_2 := g_2 / g_a \). Taking derivatives up to order two, w.r.t. \( \Delta u \), yields the following set of equations:

\[
 s(k_1 f'_a - f_b) + s'(k_1 f_a - f_b) = 0,
\]

\[ (A.6a) \]

\[
 s(k_2 f'_a - f_b) + s'(k_2 f_a - f_b) = 0,
\]

\[ (A.6b) \]

\[
 s(k_3 f'_a - f_b) + s'(k_3 f_a - f_b) = 0,
\]

\[ (A.6c) \]

\[
 s(k_4 f'_a - f_b) + s'(k_4 f_a - f_b) = 0.
\]

\[ (A.6d) \]

Note that (A.7) are simply the derivatives, w.r.t. \( \Delta u \), of (A.6). In order for \( s(\cdot) \) to be an appropriate time scaling, the solution for \( s \) must be non-trivial. For such a solution to exist in (A.6), the respective determinant must be zero

\[
f_a f'_a - f_b f'_a + k_1 (f_a f'_a - f_b f'_a) - k_2 (f_a f'_a - f_b f'_a) = 0.
\]

\[ (A.8) \]

Suppose that, at \((x_p, u_p)\), we have checked that \( f_a f'_a - f_b f'_a \neq 0 \). Then

\[
k_2 = \frac{f_a f'_a - f_b f'_a + k_1 (f_a f'_a - f_b f'_a)}{f_a f'_a - f_b f'_a}.
\]

\[ (A.9) \]

From (A.6a), we also deduce \( k_1 f_a f'_a - f_b f'_a \neq 0 \), since, due to the assumption \( f_a f'_a - f_b f'_a \neq 0 \), the opposite would imply \( k_1 f_a f'_a - f_b f'_a \neq 0 \), immediately leading to the trivial solution \( s = 0 \). We can then solve (A.6a) for \( s' \)

\[
s' = -k_1 f_a f'_a - f_b f'_a.
\]

\[ (A.10) \]

After substituting the expressions for \( k_2 \) and \( s' \) into (A.7), we again arrive at a system of equations, which is linear in the two unknowns \( s \) and \( s' \), when \( k_1 \) is considered as an additional (unknown) parameter. We do not show the lengthy equations here. For a non-trivial solution, i.e., \( s \neq 0 \), to exist, the determinant of this two by two system, which takes a rather simple form, must again be zero

\[
\frac{k_1 f_a f'_a - f_b f'_a}{k_2 f_a f'_a - f_b f'_a}.
\]

\[ (A.11) \]

Assume we have checked that, at \((x_p, u_p)\), where also \( f_a f'_a - f_b f'_a \neq 0 \), the second factor of (A.11) is non-zero. Then the determinant cannot be zero (the condition \( k_2 f_a f'_a - f_b f'_a \neq 0 \) was established above). We conclude that, given \((x_p, u_p)\),

\[
f_a f'_a - f_b f'_a \neq 0,
\]

\[ (A.12a) \]

and

\[
f_a f'_a - f_b f'_a \neq 0,
\]

\[ (A.12b) \]

together, exclude the existence of any appropriate time scaling function \( s(x, u) \), which would allow a ruling, with \( g_a \neq 0 \), of the manifold of possible (scaled) time derivatives \( x \), at the resulting triple \((p, x_p, u_p)\). To exclude orbit flatness of a given system \( x = f(x, u) \), one can select a suitable \((x_p, u_p)\), and verify (A.12) for every possible choice of \( f_a \) among the \( n \) components of \( f(\cdot) \). Therefore, each time, two of the remaining components must be appropriately assigned to \( f_a, f_b \).

Recall that in our argument, it was supposed that, at the point \((x_p, u_p) \), \( s(\cdot) \) is continuously differentiable twice w.r.t. \( u \). In other words, we have only ruled out all time scaling functions, which are continuously differentiable twice w.r.t. \( u \) at that point, as candidates for turning the system flat. This condition can be relaxed by noting that, due to continuity of \( f(\cdot) \) and its first and second derivatives, the verified inequalities (A.12) will hold not only at \((x_p, u_p) \), but also in a certain neighborhood of that point. This means that any time scaling function which is continuously differentiable twice w.r.t. \( u \) anywhere in that neighborhood can be ruled out as well. In conclusion, by saying that the system is not orbitally flat, we mean that no time scaling function which is continuously differentiable twice w.r.t. \( u \) anywhere in a certain neighborhood of \((x_p, u_p)\) permits the ruled manifold necessary condition to be locally satisfied.

If the conditions of the test described above are satisfied, then \( f_a f'_a - f_b f'_a \neq 0 \) is true for at least one pair \((a, b) \), \( a, b \in \{1, \ldots, n\} \). Using this inequality, it can also be easily seen that no appropriate time scaling function can cause the derivatives, w.r.t. \( u \), of \( s(f_a(\cdot)) \) and \( s(f_b(\cdot)) \) to be simultaneously zero. Then, by the implicit function theorem, at least one of \( s(f_a(\cdot)) \) or \( s(f_b(\cdot)) \) can (at least locally) be solved for \( u \), confirming that \( u \) can be eliminated from the time-scaled system differential equations. Also, no appropriate time scaling function can cause all derivatives of the system differential equations, w.r.t. the transformed time, to be simultaneously zero.

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