This document contains the **post-print pdf-version** of the referred paper:

**“ Assessment of the parameter identifiability of population balance models
for air jet mills”**

by **Satyajeet S. Bhonsale, Bard Stokbroekx, Jan F. Van Impe**

which has been archived on the university repository Lirias of the KU Leuven
(<https://lirias.kuleuven.be/>).

The content is identical to the content of the published paper, but without the final
typesetting by the publisher.

When referring to this work, please cite the full bibliographic info:

Bhonsale, S., Stokbroekx, B., Van Impe, J.F., 2020. Assessment of the parameter
identifiability of population balance models for air jet mills. *Computers & Chemical
Engineering*, Art. No. 107506

The journal and the original published paper can be found at:

<https://doi.org/10.1016/j.compchemeng.2020.107056>

The corresponding author can be contacted for additional info.

Conditions for open access are available at: <http://www.sherpa.ac.uk/romeo/>

Assessment of the parameter identifiability of population balance models for air jet mills

Satyajeet S. Bhonsale^{a,b}, Bard Stokbroekx^b, Jan Van Impe^{a,*}

^a*BioTeC+, Department of Chemical Engineering, Technology Campus Ghent, KU Leuven, Gebroeders de Smetstraat 1, 9000 Ghent, Belgium*

^b*Crystallisation Technology Unit, Pharmaceutical Development and Manufacturing Sciences, Janssen Pharmaceutica, Turnhoutseweg 30, 2340 Beerse, Belgium*

Abstract

Air jet mills are ubiquitous breakage devices not only in the pharmaceutical industry, but also in food and the toner manufacturing industry. The popularity of air jet mills arises due to its self-classifying, non-contaminating, and non-degrading operation while also maintaining a narrow particle size distribution. A popular approach towards mathematically modelling comminution devices like the jet mill is the population balance model framework. Population balance model for breakage is a semi-empirical framework in which several parameters are estimated from the experimental data. In many cases the experimental data available is insufficient, or of bad quality to guarantee the estimation of unique parameters. Thus it is imperative to assess the identifiability of such models to ensure that the chosen model structure is identifiable, both structurally and practically. In this study, we analyse

---

Abbreviations: PSD, Particle Size Distribution; API_m Active Pharmaceutical Ingredient; PBM, Population Balance Model; CI, Confidence Interval

*Corresponding author

Email addresses: `satyajeetsheetal.bhonsale@kuleuven.be` (Satyajeet S. Bhonsale), `bstokbro@its.jnj.com` (Bard Stokbroekx), Tel: +32 16 32 14 66, email: `jan.vanimpe@kuleuven.be` (Jan Van Impe)

the identifiability of the population balance model developed for the air jet mill. The identifiability analysis is carried out on basis of in-silico data generated by assuming certain parameter values to represent the true process. Based on several scenarios tested with data containing variety of information, it is shown that the model is practically non-identifiable for the situations in which the particle size measurement is available only at the end of the milling. The model becomes identifiable once continuous time measurements are available. The same holds for a reduced model with only the five breakage parameters.

Keywords: population balance model, air jet mill, profile likelihood, model identifiability

---

1. Introduction

Particle size distribution (PSD) is an important quality attribute of an active pharmaceutical ingredient (API). For Biopharmaceutical Class System II drugs (e.g., Glibenclamide used for treating type 2 diabetes, Bicalutamide used for treating prostate cancer, etc.), the PSD dictates the dissolution rate, and hence the bioavailability of the APIs (Liversidge & Cundy, 1995; Vogt et al., 2008). In terms of processing, powders with finer particles tend to flow poorly (Liu et al., 2008), while large particles can have a detrimental effect on the tablet strengths (McKenna & McCafferty, 1982). Moreover, as the size and shape of the seed particles affects the morphology and crystal size control in the crystallizer (Palis & Kienle, 2014; Yu et al., 2016), the seed particles are often milled to desired properties. The high importance of the PSD on processing and final development of a drug product makes

control of particle size via milling an important processing step within the pharmaceutical manufacturing industry. Such precise control requires well-identified process models which can predict the output quality attribute with a high certainty.

Due to its robustness and reliability, spiral jet mills are popular micronization devices in the industry. In spiral jet mills, compressed gas is pushed through a number of tangential nozzles into the cylindrical (or elliptical) milling chamber to create a vortex. The input material is fed to a vacuum injector which delivers the particles to the vortex in the milling chamber. The centrifugal forces in the vortex retain the particles in the mill where they undergo breakage due to particle particle collisions. As the particles reduce in size (x), the drag ($\sim x^2$) decreases slower than the centrifugal force ($\sim x^3$), until a point where the drag force exceeds the centrifugal force and the particles are pulled through the outlet in the centre of the mill. Depending on mill design, the particles may be collected directly via a filter or through a combined vane-less axial entry reverse flow cyclonic separator. The absence of any moving parts makes jet mills particularly attractive. The particle-particle collision driven breakage, and absence of any moving parts leads to a non-contaminating operation. Moreover, the jet stream from the nozzles expands into the milling chamber leading to a good thermal regulation making spiral jet mills attractive for temperature sensitive APIs. Figure [1](#) shows a schematic of the the air jet mills. It has to be noted that although the schematic depicts the mill to be cylindrical, elliptical mills are also available on the market. The change in the geometry affects the performance of the mill, but the underlying principle remains the same.

The Quality by Design paradigm adopted by the Food and Drugs Authority in the United States, and European Medicines Agency in the European Union calls for an improved process understanding based on mechanistic or semi-mechanistic models. To this extent, various modelling approaches have been used to describe micronization processes. However, despite its widespread use, modelling studies on air jet mills specifically are relatively scarce. One of the earliest studies on jet mills hypothesized that the output particle cut size could be estimated by balancing the opposing centrifugal and drag force (Dobson & Rothwell, 1969). MacDonald et al. (2016) used such a force balance approach, while considering the mill geometry to derive a cut size equation. Following the same rationale, researchers have applied computational fluid dynamics (CFD) approach to study the jet mill. As CFD approach does not account for the particle phase in the system, a coupled CFD - Discrete Element Models (DEM) approach is used. DEMs use numerical solution of Newtonian kinematics along with contact mechanics to determine particle trajectories (Cundall & Strack, 1979). Some of the studies focusing on jet mills are tabulated in Table I. Apart from these mechanistic approaches, variety of empirical models have also been used (Midoux et al., 1999; Teng et al., 2010).

As the mechanistic CFD-DEM models are constrained by computational and memory costs, and empirical models are too limited in their predictive capabilities, a semi-mechanistic model is normally well suited for engineering purposes. A common approach to model particulate processes is the population balance (PBM) approach (Ramakrishna, 2000; Naik & Chaudhuri, 2015). PBM is a semi-empirical framework in which breakage is described

as a rate process (Austin, 1971). Although its common to represent breakage as a first order process (Austin, 1971; Capece et al., 2014), some studies have confirmed the non-linear nature of breakage (Capece et al., 2011, 2015, 2018). As a full description of a PBM leads to a complex integro-differential equation which needs to be solved numerically (Bhonsale et al., 2019), it is not uncommon to simplify the framework to and write a discretized PBM. For a time continuous, size-discrete, well mixed batch milling process, the PBM can be described as

$$\frac{dM_i}{dt} = -S_i M_i + \sum_{j=1}^{i-1} b_{ij} S_j M_j \quad (1)$$

$$N \geq i \geq j \geq 1$$

In the above equation, i and j are the size class indices which run from class 1 which contains the largest particles, to class N which contains the smallest. M_i is the mass in the size class i . S_i is the specific rate of breakage. b_{ij} is the breakage distribution function which describes the distribution of particles formed in class i when a particle in class j breaks. To ensure conservation of mass, the following constraints need to be ensured.

$$S_N = 0, \quad \sum_{i=j+1}^N b_{ij} = 1, \quad b_{ii} = 0 \quad (2)$$

Gommeren et al. (1996) used a compartmentalized PBM to model the spiral jet mill. However, detailed simulations are not provided and estimation of the multitude of parameters in the model is not mentioned. In Starkey et al. (2014a) a steady state PBM was developed for air jet mills whose parameters were then related to the material properties in Starkey et al.

(2014b). Recently, Rodnianski et al. (2019) developed a multiscale CFD-DEM-population level model for a jet mill in which the parameters at the population scale were obtained via the CFD-DEM simulations. However, such a coupling requires extensive computational effort at multiple operating conditions to develop the so called machine function.

The parameters in the PBM can be determined through “direct measurement methods” which need extensive experimental work involving mono-sized feeds (Austin & Bhatia, 1972; Austin & Luckie, 1972). An alternative is to fit the parameters of the PBMs directly to experimental data using non-linear optimization techniques (Capece et al., 2011).

The accuracy of parameter estimates obtained via non-linear optimization (non-linear parameter estimation) depends on the quality of the experiments, and on the model structure itself. If the parameters are not estimated with a reasonable accuracy, the errors propagate through the model and lead to significant loss of certainty in the predictions (Bhonsale et al., 2018). Often, some parameters in a model cannot be estimated uniquely, while some parameters are only estimated with a degree of precision and accuracy (which is evident from the width of the confidence intervals (Walter & Pronzato, 1997)). The issue of non-uniqueness and precision of a parameter estimate is addressed by its *identifiability*. A parameter is said to be non-identifiable if it cannot be uniquely estimated. Identifiability can be assessed at two levels: structural identifiability and practical identifiability. When the input-output behaviour of a model is not affected by even large changes in the model parameters, the model is said to be structurally non-identifiable (Walter & Pronzato, 1997). Structural non-identifiability arises due to selection of poor

model structure e.g., by excessive parametrisation, or inclusion of structures which cannot be determined experimentally (Nimmegeers et al., 2017). Although structurally non-identifiable models can be used for simulations, no sensible interpretation of the parameter estimates can be made (Lauwers, 2015). Practical identifiability addresses the issue of precision and accuracy of the parameter estimate. A parameter is practically non-identifiable if it is characterized by excessively large confidence intervals. Practical non-identifiability can be resolved by improving the quality and/or the quantity of the experimental data. Structural identifiability is a necessary condition for practical identifiability. For a structurally non-identifiable model, no numerical algorithm can provide reliable parameter estimates. Given the stringent quality requirements in a pharmaceutical product, models on which the prediction and control are based need to be extremely accurate. Thus, the models used to describe processes such as milling need to be not only structurally identifiable, but also practically identifiable with narrow confidence intervals on the parameters.

Various approaches exist to assess the identifiability of models and model parameters. For linear time invariant systems, methods based on Laplace transforms (Cobelli et al., 1979) or the Markov parameter (Grewal & Glover, 1976) are commonly used. In some cases, non-linear equations can be transformed into the linear invariant form for the analysis (Dochain, 1995). Grewal & Glover (1976) showed that if the linearized invariant of the non-linear model is identifiable, then the non-linear model is also identifiable. However, non-identifiability of the linearized version does not mean non-identifiability of the non-linear model (Vajda et al., 1989). For non-linear models, struc-

tural identifiability can be assessed by investigating the coefficients of the Taylor series (Pohjanpalo, 1978), or using differential algebra based methods (Saccomani et al., 2003; Boulrier & Lemaire, 2009), etc. The differential algebra based methods can quickly get very involved and complex for large scale models. For large-scale models, the identifiability problem can be reformulated as an observability problem by considering the parameters as non-varying states (Sedoglavic, 2002; Karlsson et al., 2012). Local algebraic observability is a sufficient condition for local structural identifiability (Hermann & Krener, 1977; Diop & Wang, 1983). Moreover, a number of software tools which implement some of the above methods are also available (Bellu et al., 2007; Chi et al., 2011; Meshkat et al., 2014). However, according to Jiménez-Hornero et al. (2008), there is no general technique can be applied to all models and it is impossible to determine a priori which technique to apply for a given model.

Practical identifiability can be assessed via the sensitivity matrix. The sensitivity matrix (S) is a $n_t n_y \times n_\theta$ dimensional matrix (where n_t, n_y, n_θ represent the number of sampling points, measured variables ($\mathbf{y}$), and parameters (θ) respectively) whose elements are composed of individual sensitivities

at each time

$$S = \begin{bmatrix} \frac{\partial y_1(t_0)}{\partial \theta_1} & \dots & \frac{\partial y_1(t_0)}{\partial \theta_{n_\theta}} \\ \vdots & \ddots & \vdots \\ \frac{\partial y_{n_y}(t_0)}{\partial \theta_1} & \dots & \frac{\partial y_{n_y}(t_0)}{\partial \theta_{n_\theta}} \\ \vdots & \ddots & \vdots \\ \frac{\partial y_1(t_{n_t})}{\partial \theta_1} & \dots & \frac{\partial y_1(t_{n_t})}{\partial \theta_{n_\theta}} \\ \vdots & \ddots & \vdots \\ \frac{\partial y_{n_y}(t_{n_t})}{\partial \theta_1} & \dots & \frac{\partial y_{n_y}(t_{n_t})}{\partial \theta_{n_\theta}} \end{bmatrix} \quad (3)$$

Linear dependencies in S indicate parameter correlations. By building a correlation matrix from the columns of S , parameters can be ranked from least identifiable to most identifiable (Jacquez & Greif, 1985). Similarly, the orthogonal method iterates over the columns of S to determine independence (Yao et al., 2003). In Quaizer & Mönnigmann (2009), an algorithm to detect the non-identifiable parameters is presented based on the eigenvalues of the Hessian matrix $\mathcal{H} = S^\top S$. A model is identifiable if the smallest eigenvalue is larger than a predefined threshold. Degenring et al. (2004) define three criteria based on principle component analysis to achieve a parameter ranking. The sensitivities are computed at a nominal value of the parameter and thus characterize the local practical identifiability of the model in the immediate vicinity of the nominal parameter values.

Another approach to assess the practical identifiability is by performing parameter estimations on in silico data and analysing the quality of the parameter estimates. Using a maximum likelihood estimator, the parameter and its associated covariance can be estimated. The covariance is used to quantify the uncertainty on the parameter via the *asymptotic* confidence

intervals. The width of the confidence intervals provides an indication on the sensitivity of model response to small parameter changes. Practically identifiable parameters are characterized by narrow confidence intervals. As calculating the exact covariance matrix is computationally expensive, it is approximated using the Fischer Information Matrix (FIM) or by a Monte Carlo sampling approach. The FIM combines the information on measurement errors (described by the measurement covariance matrix $\mathbf{Q}$) with the sensitivity of the model output to infinitesimal changes in the parameters ($S(\theta)_{ti}$ as defined in Eq. (3) for a sampling point ti). The FIM is defined as

$$\mathcal{F}(\theta) = \sum_{ti=0}^{n_t} S(\theta)_{ti}^T \cdot \mathbf{Q}^{-1} \cdot S(\theta)_{ti} \quad (4)$$

Under specific assumptions on the noise, the maximum likelihood estimator is a consistent estimator with the covariance ($\mathbf{C}$) bounded below by the Cramer-Rao bound:

$$\mathbf{C} \geq \mathcal{F}^{-1}(\theta) \quad (5)$$

If a large number of measurements are available (i.e., $n_t \rightarrow \infty$), the Cramer-Rao bound becomes an equality and the FIM can be used as an approximation for the covariance matrix. In the Monte Carlo approach, a parameter profile is built using a large number of measurement realizations which are then used to derive the covariance of the parameter estimates. Higher values of the off-diagonal terms in the covariance matrix indicate a high degree of correlation between the parameter pair, i.e., change in a parameter can be offset by a change in the other. Issues pertaining to practical non-identifiability can be resolved by improving the quality of experimental data

obtained. Apart from improving the sensor quality, designing input profiles which sufficiently excite the process provides with informative data. Such inputs are designed using optimal experiment design (OED) (Telen et al., 2012; Nimmegeers et al., 2020). OED calculates the inputs profiles by solving a dynamic optimization with a scalar metric based on the FIM as the objective. Some commonly used information metrics are mentioned in Table 2.

The asymptotic confidence intervals are exact only if the output $\mathbf{y}$ linearly depends on θ . In cases where the model response has non-linear dependencies, the use of asymptotic confidence intervals may be misleading (Joshi et al., 2006). Moreover, as the covariance matrix is positive semi-definite, the asymptotic confidence intervals are always finite. An alternative method to assess both the structural and practical identifiability is based on detecting the flatness of the profile likelihood (Raue et al., 2009). The identifiability is characterised by the *finite sample* confidence intervals which is known to perform better when limited data is available (Neale & Miller, 1997). Being a data driven approach, the profile likelihood based method has the advantage of not imposing any restrictions on the algebraic form of the model (Raue et al., 2014). Due to this, the profile likelihood approach has been widely used in systems biology (Gross & Blüthgen, 2020; Lee et al.; Coulibaly et al., 2019; Kendrick et al., 2019) wherein the large biological networks lead to complex mathematical models which cannot be assessed via analytical methods. Recently, this approach has seen use in studying identifiability of large scale or complex models for (bio)chemical processes like a lithium-ion battery (Zhou et al., 2020), and the fluidized bed agglomeration process (Golovin et al.,

2018). However, the use of profile likelihood approach requires some a priori understanding of the process and the knowledge of the nominal parameters. Process insight is required to determine parameter ranges within which the likelihood is calculated. Moreover, the repeated parameter estimations required can be computationally expensive.

The aim of this paper is to assess the identifiability of the parameters involved in the PBM of the air jet mill. The analysis of the PBM of a jet mill is carried out using in-silico data. Different experimental situations are simulated to generate the data which is used for the analysis. The article is organized as follows. First, the PBM describing the jet mill is presented along with the nominal parameters used for the simulation. Next the concept of identifiability based on profile likelihood is elaborated. Finally, the method is used to assess the jet mill PBM for the different experimental conditions.

2. Theoretical and numerical methods

2.1. Population balance model of air jet mill

A common expression for the breakage rate is a power law which takes into the consideration the effect of particle size on breakage (Austin, 1971).

$$S_i = \alpha \left(\frac{x_i}{x_1} \right)^\lambda \quad (6)$$

where, x_i is the particle size representing the class i . The parameter α represents the extent or the rate of breakage and depends on machine and material properties. λ determines the size dependency of breakage rate and can be considered to be solely the function of material properties (Gommeren et al., 1996). An empirical model for describing how mother particles break

is given by

$$B_{i,j} = \phi \left(\frac{x_{i-1}}{x_j} \right)^\gamma + (1 - \phi) \left(\frac{x_{i-1}}{x_j} \right)^\beta \quad (7)$$

$$b_{i,j} = B_{i,j} - B_{i+1,j}, \text{ and } b_{N,j} = B(N,j) \quad (8)$$

Due to the self-classifying nature of the jet mill a classification curve is defined. This curves gives the probability with which the particles in a particular size class will exit the mill. Following (Gommeren et al., 1996), a log-normal curve is used to define the classification probability.

$$P_i = 1 - \frac{1}{2} \left[\operatorname{erf} \left(\frac{\log(x_i) - \mu_c}{\sqrt{2}\sigma_c} \right) \right] \quad (9)$$

Where erf is the error function, μ_c represents the mean of the log-normal classification curve and σ_c is related to the width of the curve. By assuming the jet mill to operate in a semi-continuous mode, the PBM in Eq. (1) is now extended to include the inlet ($\dot{M}_{i,\text{in}}$) and outlet terms ($\dot{M}_{i,\text{out}}$) as

$$\begin{aligned} \frac{dM_i}{dt} &= \dot{M}_{i,\text{in}} - \dot{M}_{i,\text{out}} - S_i M_i + \sum_{j=1}^{i-1} b_{ij} S_j M_j \\ \dot{M}_{i,\text{in}} &= f_{i,\text{in}} \dot{m}_s, \quad \dot{M}_{i,\text{out}} = P_i M_i \end{aligned} \quad (10)$$

where, f_{in} is the PSD of the feed material, $\dot{m}_s$ is the mass feed rate into the mill. The fully described model in Eq. (10) consists of 7 parameters which have to be estimated: 5 breakage parameters ($\alpha, \lambda, \phi, \gamma, \beta$), and 2 classification parameters (μ_c, σ_c). The nominal values of all the 7 parameters used for the data generation are reported in Table 3. The feed PSD is assumed to be a normally distributed with a given mean and standard deviation and is generated in Matlab using its “normcdf” function. The mean (μ) and the standard deviation (σ) for the input PSD are also mentioned in Table 3.

2.2. Parameter Estimation

The parameter estimation is carried out by minimizing the sum of squared errors, which serves as an indicator for goodness of the model fit. For a hypothetical model $y = f(\theta)$, the objective is defined as:

$$L^2(\theta) = \sum_{i=1}^m \sum_{t=1}^{N_t} \left(y_{\text{meas}}^{i,t} - f(\theta) \right)^2 \quad (11)$$

where, $y_{\text{meas}}^{i,t}$ is the measured value of output i at a discrete time point t . The estimates of the parameter θ are given as

$$\hat{\theta} = \arg \min [L^2(\theta)] \quad (12)$$

For data with normally distributed independent noise, the least squares estimator corresponds to the maximum likelihood estimator and thus L^2 can be used interchangeably with likelihood.

The parameter estimate $\hat{\theta}$ is associated with a certain confidence interval (CI) $[\theta_-, \theta_+]$ at a confidence level α which signifies that the range contains the true value of the parameter θ with a probability α . One way of calculating the CI is to use the likelihood based confidence region as defined by

$$\{\theta \mid L^2(\theta) - L^2(\hat{\theta}) < \Delta_\alpha\} \quad \text{with} \quad \Delta_\alpha = \chi^2(\alpha, \#df) \quad (13)$$

where $\chi^2(\alpha, \#df)$ is the α quantile of the χ^2 distribution with $\#df$ degrees of freedom. The boundary of this region denotes the confidence interval of the parameters (Meeker & Escobar, 1995). The profile likelihood based CIs are considered better than the asymptotic CIs normally used (Neale & Miller, 1997). The asymptotic CIs are calculated based on the estimation of the covariance matrix. As mentioned earlier, the covariance matrix is,

under specific assumptions, estimated from the FIM or using the Monte Carlo sampling approach. Without computing the sensitivities, the FIM can be obtained from the curvature of the likelihood function, i.e., the second derivative of the Hessian of the likelihood function evaluated at the maximum likelihood estimates $\left(\mathcal{H} = \nabla^\top \nabla (\mathbb{L}^2(\hat{\theta}))\right)$ is the observed FIM (Pawitan, 2013). The covariance can then be used to calculate the asymptotic CIs as

$$\theta_{\pm} = \hat{\theta} \pm \sqrt{\chi^2(\alpha, \#df) \cdot C_{ii}} \quad (14)$$

2.3. Identifiability analysis

As mentioned previously, structural non-identifiability is linked to the model structure, while practical non-identifiability is linked to the data. A formal definition of identifiability can be given based on an idealized model framework, $\mathcal{M}(\theta)$ where: (i) it is the perfect representation of the process, (ii) the measurement is noise free, (iii) the input excitation can be chosen at will, and (iv) sampling frequency can be chosen at will.

Definition 2.1. Global Structural Identifiability. A parameter θ is globally structurally identifiable if under the idealised conditions and for almost any parameter value $\theta^* \in N_{\theta}$, the input-output behaviour is identical for the estimated parameter values $\hat{\theta} \in N_{\theta}$ as for θ^* (Walter & Pronzato, 1997), i.e.,

$$\mathcal{M}(\hat{\theta}) = \mathcal{M}(\theta^*) \implies \hat{\theta} = \theta^* \quad (15)$$

The definition of global structural identifiability can be extended to the entire model. A model is globally structurally identifiable if all its parameters are globally structurally identifiable. In many cases when the global identifiability can be difficult to establish, it might be sufficient to prove a local identifiability.

Definition 2.2. Local Structural Identifiability. A parameter θ is locally structurally identifiable *if under the idealised conditions and for almost any parameter value $\theta^* \in N_\theta$, there exists a neighbourhood V such that the input-output behaviour is identical for the estimated parameter values $\hat{\theta} \in V$ as for θ^** (Walter & Pronzato, 1997), i.e.,

$$\mathcal{M}(\hat{\theta}) = \mathcal{M}(\theta^*), \quad \hat{\theta} \in V \implies \hat{\theta} = \theta^* \quad (16)$$

A model is locally structurally identifiable if all its parameters are locally structurally identifiable.

Structural non-identifiability arises from excessive parametrization of the model, or by choice of a completely wrong structure. Structural identifiability can only be resolved by manipulating the model such that non identifiable parameters are either removed or lumped together. The confidence interval of a structurally non-identifiable parameter extends to infinity in both upper and lower limits.

Structurally identifiable models can still be practically non-identifiable. Practical non-identifiability arises from lack of good quality experimental data. The confidence intervals of practically non-identifiable parameter extends to infinity only in one direction and is characterized by a shallow likelihood. A practically non-identifiable parameter can be rendered identifiable by adding more informative data to the parameter estimation.

Correlated parameters are not identifiable. If the relationship between the parameters does not depend on the control variables, the parameters are structurally non-identifiable. While if a functional relationship exists, the correlated parameters will be practically non-identifiable (Li & Vu, 2013). In the latter case, the correlations can be relaxed by a proper experiment design

(Versyck et al., 1997; Steiert et al., 2012).

In this study we follow the approach described in Raue et al. (2009). The idea of Raue’s approach is to follow the likelihood to detect where it flattens out. To this extent, the concept of profile likelihood is used. The profile likelihood for any parameter is defined as

$$L_{\text{PL}}^2(\theta_i) = \min_{\theta_{j \neq i}} \left[L^2(\theta) \right] \quad (17)$$

The profile likelihood of a parameter θ_i is calculated at by reoptimizing $L^2(\theta)$ with respect to all parameters except θ_i . By varying the parameter θ_i and reoptimizing, the profile likelihood curve can be calculated. Based on the desired confidence, a threshold Δ_α is defined. The profile likelihood of a structurally non-identifiable parameter is characterized by a flat profile extending in both directions, while practical non-identifiability is represented by a profile likelihood that has a minimum, but does not exceed the threshold in either one of the directions. An identifiable parameter on the other hand is characterize by a profile likelihood which extends above the threshold in both directions and has a clear minima (Raue et al., 2009). Figure 4 depicts a schematic of profile likelihoods for the non-identifiable and identifiable parameters where in the star represents the true parameter value.

3. Numerical results and discussion

For generation of the data, parameter estimation, and the identifiability analysis the particle size classes for the PBM are defined from $700\mu\text{m}$ as the class 1 to $0.0995\mu\text{m}$ as class 70 which is the smallest. The number of classes and the size range is chosen based on the laser diffraction

measurements commonly available in the laboratories. Figure 3 shows the simulated output for the nominal parameters. With 70 classes, the model consists of a system of 70 differential equations describing the evolution of particle mass each size bin within the milling chamber and 70 algebraic equations describing the particle mass in each size bin in the output stream. In the current manuscript, unless explicitly mentioned, experiment refers to an in-silico simulation of the described PBM. Two experimental situations are considered: (i) semi-continuous operation in which the product is assumed to be collected at the outlet and the sample taken only at the end of 200s experiment, and (ii) continuous operation for 200s where data is assumed to be measured online at an interval of 1s. Such a continuous operation is not uncommon in the industry, especially with online PSD measurement devices like the Insitex. The in-silico data is generated by solving the ODEs by the *ode15s* solver in MATLAB. *ode15s* is a variable step, variable order method based on numerical differentiation formulas well suited for stiff differential equations. The data is then used for parameter estimation using the *lsqnonlin* function in MATLAB. *lsqnonlin* uses an interior trust region approach to solve the least squares objective. The profile likelihood points are generated at 100 points between the parameter boundaries. The choice of parameter boundaries requires insight into the process and the model. The parameter α describes the rate of breakage and cannot be negative. It is thus lower bound by 0, while the upper bound is chosen to be a reasonably high rate. Given the nature of size dependence of breakage, the power law exponent is constrained between 0 and 1. Similarly, the breakage distribution function exponents are constrained between 0 and 10, while the weight ϕ lies between

0 and 1. The parameters of the classification curve are chosen based on the output PSD that is expected. In total building a profile likelihood for one parameter requires 100 calls to the optimization routine which further requires multiple calls to the integrator. As the aim of the paper is to discuss the applicability of the method to the PBM of an air jet mill, no particular heed is paid to the efficiency of the optimization or the integration routines. With proper structured programming and using state of the art integrators and optimization routines, the computation can be made more efficient.

3.1. Parameter identifiability for PBM with semi-continuous milling

In most cases the only PSD measurement available is after the entire product batch has been milled. Considering this data for the parameter estimation, the profile likelihoods of the parameters are depicted in Figure 5. The red dot marks the ‘true’ value of the parameter, and the black dotted line represents the threshold value set at 95% confidence interval. As can be seen from the figure, almost all profiles are extremely flat. The only exceptions are the classification parameters. The classification parameters show a flat profile until a sudden jump in the likelihood after a particular parameter value is reached. In a log-normal classification curve, the parameter μ_c represents the log of the median of the distribution. As this value gets higher, the cut off for the particles escaping the mill increases exponentially. A very high value of μ_c would mean no particles leave the mill. The fact that there is a measured output means that at least few particles have left the mill. Thus, the profile likelihood shows a drastic increase after a certain value. However, within an operable range of parameters, the profile likelihood can be considered to be flat.

For a parameter to be identifiable, the profile likelihood should cross the threshold line on both sides of the nominal parameters value. Flat profiles mean that changes in parameter value have no effect on the likelihood of the model, and the confidence interval associated with the parameter is effectively infinite. Although the flatness of the profile likelihood indicates structural non-identifiability, this would not be the case in this situation. Zooming into the profile likelihoods of all the parameters around the nominal ‘true’ values shows a slight curvature in the profiles with a clear minima at the nominal parameter value. This indicates that although the parameters are structurally identifiable, the parameters are practically non-identifiable.

Air jet milling is a combination of two processes: milling and classification. Both these processes occur in the same geometric space and are affected by the same input parameters. As the only measurement available is at the end of the milling process, the measured PSD is of the particles broken *and* classified. To be able to identify all the parameters, the breakage kernel has to be deconvoluted from the classification kernel.

A solution to distinguish breakage from classification would be to measure particles that are broken but not classified (i.e., measure the PSD inside the milling chamber) along with particles that are broken and classified. Physically, such a measurement can be obtained by performing a crash test; the pressure and the feed rate are switched off instantaneously, the mill is carefully opened, and all the material inside the milling chamber is collected, sampled and measured. The profile likelihood for this scenario is depicted in Figure 6. It can be seen that identifiability of the breakage rate kernel has improved significantly, but the breakage distribution parameters remain

practically non-identifiable.

Another possible solution to achieve the deconvolution of the kernels is to determine the classification independently of the breakage kernel or vice versa. Breakage rate can be determined independently of classification by carrying out independent breakage only studies. However, as the breakage rate is heavily dependent on the mode of breakage, the experiments need to be carried out on the same equipment as being modelled. As mentioned previously, such breakage only experiments are almost impossible to carry out on the jet mill as the outlet consists of particles broken as well as classified. On the other hand, classification parameters depend on the mill geometry and the particle size, and can be determined via CFD simulations (Rodnianski et al., 2013) without need for extensive experimentation. Thus for the current simulation study, assuming availability of the classification parameters is more practical than assuming availability of the breakage parameters. Fixing the two parameters of the classification curve, only five parameters need to be determined from the PSD. Figure 7 shows the profile likelihoods of the five breakage parameters. The clear observation is that the identifiability is not affected. Although the breakage rate α becomes identifiable, all the other parameters still have profile likelihoods which do not cross the threshold limit in either directions. Again, even if these profile likelihoods seem completely flat, close inspection reveals a small degree of curvature indicating practical non-identifiability. If a PSD measurement is available from within the milling chamber, the identifiability of the breakage rate parameters improves significantly while the breakage distribution parameters remain non-identifiable. This is depicted in Figure 8.

3.2. Parameter identifiability for PBM with continuous milling

The increasing focus of the FDA on the Process Analytical Technology (PAT) has been influential in the availability of in-, on-, at-line instruments for real time measurements [Chan et al., \(2008\)](#). With the availability of in-line sampling and measurements devices like the Malvern Insitec® or the Sympatec Twister®, it is now possible to have a continuous measurement of drying milled PSD available [\(Silva et al., 2013\)](#). Such measurements give information on the time evolution of the PSD leaving the mill [\(Harvill et al., 1995\)](#). In this section, the identifiability of the PBM parameters is assessed assuming availability of such dynamic data. It is assumed that a PSD measurement is available every 1 s. This is not unrealistic as in-line sensors have high sampling rates (e.g., Malvern Insitec has a maximum frequency of 4 Hz.)

For the first case, time evolution of the PSD of the particles leaving the mill is considered for the parameter estimation with all PBM parameters considered unknown. Figure [9](#) depicts the profile likelihood of all the 7 parameters. The dynamic information available in the time evolution of the PSD, it can clearly be seen that all the parameters in the PBM can now be identified. The Figures [9d-9e](#) are identical except with two different values of the minima. This occurs due to the nature of the breakage distribution function. The breakage distribution function as given by [8](#) consists of two exponents and a weight parameter which varies between 0 and 1. However, this means that the parameters γ and β are interchangeable depending upon whether the weight is above or below the 0.5 value.

Once the parameters are identifiable, addition of more information for the

parameter estimation will lead to better estimates, i.e., parameters estimate with high confidence (small interval). This can be noticed in Figure 10. The solid line depicts the profile likelihoods of all the parameters in a case where along with continuous output PSD, the PSD of material inside the milling chamber is measured at the end of the milling routine. It can be noticed that the curvature of the profile likelihood increases with addition of this information leading to a more convex profile likelihood plot than the previous case (illustrated by the faint line). An increase in curvature of the profile likelihood indicates an increase in the confidence on the parameters.

4. Conclusions

Identification of the parameters of the PBM for a jet mill is not trivial. As the PBM leads to complex integro-differential equations with highly non-linear terms, classical identifiability tests cannot be used. Profile likelihood approach provides a data-driven framework which can be used for any model structure. Using the profile likelihood approach, it is shown that for the given breakage kernels it is almost impossible to identify all the parameters for the semi-continuous case. Unfortunately, this is the most common case in an industrial or laboratory setting. Continuous measurement devices like In-sitec although available, are by no means widespread for milling operations. Although the profile likelihood curves look flat in the figures, the existence of a slight degree of curvature in the profile likelihood indicates a practical non-identifiability rather than a structural non-identifiability. A solution to such a non-identifiability is to reduce the model or to collect more informative data. Both these cases are discussed. The PBM for the semi-continuous

case remains non-identifiable even when the model is reduced by fixing the classification parameters. Although the addition of information by extra measurement within the mill leads to an improvement in the identifiability, it does not eliminate the issue. Given that in most cases the non-identifiable parameters belonged to the breakage distribution function, it might be useful to eliminate these parameters during the model reduction and describe new breakage distribution functions with less parameters.

For the case with continuous PSD measurement, the dynamic information added leads to a completely identifiable system. Further addition of information to this scenario (by internal measurements at the end of milling or theoretically even continuous internal measurements) leads to a increased confidence in the parameter estimates. However, the identifiability depends on the rate of breakage. If the dynamics of the breakage are extremely fast, the information available in the dynamic region might not be rich enough to guarantee identifiability. This fortifies the importance of continuous and fast online PSD measurement in particulate processes. The results also show the limitations of the parameter estimation approach for identifying breakage kernels in the PBM. An alternative approach is to systematically perform breakage tests and derive the breakage kernels mechanistically for individual materials.

Acknowledgements

This work was supported by Center of Excellence OPTEC-Optimization in Engineering of the KU Leuven Research Council, project G086318N of the Fund for Scientific Research-Flanders. SB holds a IWT Baekeland grant

IWT150715 for his PhD research.

Austin, L. (1971). Introduction to the mathematical description of grinding as a rate process. *Powder Technol.*, 5, 1 – 17.

Austin, L., & Bhatia, V. (1972). Experimental methods for grinding studies in laboratory mills. *Powder Technol.*, 5, 261 – 266.

Austin, L., & Luckie, P. (1972). Methods for determination of breakage distribution parameters. *Powder Technol.*, 5, 215 – 222.

Bellu, G., Saccomani, M. P., Audoly, S., & D'Angi, L. (2007). Daisy: A new software tool to test global identifiability of biological and physiological systems. *Comput. Meth. Prog. Bio.*, 88, 52 – 61.

Bhonsale, S., Telen, D., Stokbroekx, B., & Van Impe, J. (2018). An analysis of uncertainty propagation methods applied to breakage population balance. *Processes*, 6.

Bhonsale, S. S., Telen, D., Stokbroekx, B., & Impe, J. V. (2019). Comparison of numerical solution strategies for population balance model of continuous cone mill. *Powder Technol.*, 345, 739 – 749.

Bnà, S., Ponzini, R., Cestari, M., Cavazzoni, C., Cottini, C., & Benassi, A. (2020). Investigation of particle dynamics and classification mechanism in a spiral jet mill through computational fluid dynamics and discrete element methods. *Powder Technol.*, 364, 746–773.

Boulier, F., & Lemaire, F. (2009). Differential algebra and qssa methods

- in biochemistry. *IFAC Proceedings Volumes*, 42, 33 – 38. 15th IFAC Symposium on System Identification.
- Brosh, T., Kalman, H., Levy, A., Peyron, I., & Ricard, F. (2014). DEMCFD simulation of particle comminution in jet-mill. *Powder Technol.*, 257, 104 – 112.
- Capece, M., Bilgili, E., & Dav, R. (2014). Insight into first-order breakage kinetics using a particle-scale breakage rate constant. *Chem. Eng. Sci.*, 117, 318 – 330.
- Capece, M., Bilgili, E., & Dave, R. (2011). Identification of the breakage rate and distribution parameters in a non-linear population balance model for batch milling. *Powder Technol.*, 208, 195 – 204.
- Capece, M., Dav, R., & Bilgili, E. (2015). On the origin of non-linear breakage kinetics in dry milling. *Powder Technol.*, 272, 189 – 203.
- Capece, M., Dav, R., & Bilgili, E. (2018). A pseudo-coupled DEMnon-linear PBM approach for simulating the evolution of particle size during dry milling. *Powder Technol.*, 323, 374 – 384.
- Chan, L. W., Tan, L. H., & Heng, P. W. S. (2008). Process analytical technology: Application to particle sizing in spray drying. *AAPS PharmSciTech*, 9, 259–266.
- Chi, O., Banga, J. R., & Balsa-Canto, E. (2011). GenSSI: a software toolbox for structural identifiability analysis of biological models. *Bioinformatics*, 27, 2610–2611.

- Cobelli, C., Lepschy, A., & Jacur, G. (1979). Identifiability results on some constrained compartmental systems. *Math. Biosci.*, *47*, 173 – 195.
- Coulibaly, A., Bettendorf, A., Kostina, E., Figueiredo, A. S., Velsquez, S. Y., Bock, H.-G., Thiel, M., Lindner, H. A., & Barbarossa, M. V. (2019). Interleukin-15 signaling in HIF-1 α regulation in natural killer cells, insights through mathematical models. *Frontiers in Immunology*, *10*, 2401.
- Cundall, P., & Strack, O. (1979). Discrete numerical model for granular assemblies. *Geotechnique*, *29*, 47–65.
- Degenring, D., Froemel, C., Dikta, G., & Takors, R. (2004). Sensitivity analysis for the reduction of complex metabolism models. *J. Process Control*, *14*, 729–745.
- Diop, S., & Wang, Y. (1983). Equivalence between algebraic observability and local generic observability. In *Proceedings of 32nd IEEE Conference on Decision and Control*. IEEE.
- Dobson, B., & Rothwell, E. (1969). Particle size reduction in a fluid energy mill. *Powder Technol.*, *3*, 213 – 217.
- Dochain, D. (1995). Structural identifiability of biokinetic models of activated sludge respiration. *Water Res.*, *29*, 2571–2578.
- Golovin, I., Strenzke, G., Dürr, R., Palis, S., Bück, A., Tsotsas, E., & Achim Kienle (2018). Parameter identification for continuous fluidized bed spray agglomeration. *Processes*, *6*, 246.

- Gommeren, H., Heitzmann, D., Kramer, H., Heiskanen, K., & Scarlett, B. (1996). Dynamic modeling of a closed loop jet mill. *Int. J. Miner. Process.*, *44-45*, 497 – 506. Comminution.
- Grewal, M., & Glover, K. (1976). Identifiability of linear and nonlinear dynamical systems. *IEEE T. Automat. Contr.*, *21*, 833–837.
- Gross, T., & Blüthgen, N. (2020). Identifiability and experimental design in perturbation studies. *bioRxiv*, .
- Han, T., Kalman, H., & Levy, A. (2002). DEM simulation of particle comminution in jet milling. *Particul. Sci. and Technol.*, *20*, 325–340.
- Harvill, T. L., Hoog, J. H., & Holve, D. J. (1995). In-process particle size distribution measurements and control. *Part. Part. Syst. Char.*, *12*, 309–313.
- Hermann, R., & Krener, A. (1977). Nonlinear controllability and observability. *IEEE Trans. Autom. Control*, *22*, 728–740.
- Jacquez, J. A., & Greif, P. (1985). Numerical parameter identifiability and estimability: Integrating identifiability, estimability, and optimal sampling design. *Math. Biosci.*, *77*, 201–227.
- Jiménez-Hornero, J. E., Santos-Dueñas, I. M., & Garcia-Garcia, I. (2008). Structural identifiability of a model for the acetic acid fermentation process. *Math. Biosci.*, *216*, 154–162.
- Joshi, M., Seidel-Morgenstern, A., & Kremling, A. (2006). Exploiting the

- bootstrap method for quantifying parameter confidence intervals in dynamical systems. *Metab. Eng.*, 8, 447–455.
- Karlsson, J., Anguelova, M., & Jirstrand, M. (2012). An efficient method for structural identifiability analysis of large dynamic systems. *IFAC Proceedings Volumes*, 45, 941–946.
- Kendrick, F., Evans, N. D., Berlanga, O., Harding, S. J., & Chappell, M. J. (2019). Parameter identification for a model of neonatal fc receptor-mediated recycling of endogenous immunoglobulin g in humans. *Frontiers in Immunology*, 10, 674.
- Lauwers, J. (2015). Advanced methods for the structural and practical identification of large-scale non-linear biochemical systems. application to anaerobic digestion models.
- Lee, D., Jayaraman, A., & Kwon, J. S.-I. (). Identification of cell-to-cell heterogeneity through systems engineering approaches. *AIChE J.*, (p. e16915).
- Levy, A., & Kalman, H. (2007). Numerical study of particle motion in jet milling. *Particul. Sci. Technol.*, 25, 197–204.
- Li, P., & Vu, Q. D. (2013). Identification of parameter correlations for parameter estimation in dynamic biological models. *BMC Syst. Biol.*, 7, 91.
- Liu, L., Marziano, I., Bentham, A., Litster, J., E.T.White, & Howes, T. (2008). Effect of particle properties on the flowability of ibuprofen powders. *Int. J. Pharm.*, 362, 109 – 117.

- Liversidge, G. G., & Cundy, K. C. (1995). Particle size reduction for improvement of oral bioavailability of hydrophobic drugs: I. absolute oral bioavailability of nanocrystalline danazol in beagle dogs. *Int. J. Pharm.*, *125*, 91 – 97.
- MacDonald, R., Rowe, D., Martin, E., & Gorringer, L. (2016). The spiral jet mill cut size equation. *Powder Technol.*, *299*, 26 – 40.
- McKenna, A., & McCafferty, D. F. (1982). Effect of particle size on the compaction mechanism and tensile strength of tablets. *J. Pharm. Pharmacol.*, *34*, 347–351.
- Meeker, W. Q., & Escobar, L. A. (1995). Teaching about approximate confidence regions based on maximum likelihood estimation. *The American Statistician*, *49*, 48–53.
- Meshkat, N., Kuo, C. E.-z., & DiStefano III, J. (2014). On finding and using identifiable parameter combinations in nonlinear dynamic systems biology models and combos: A novel web implementation. *PLOS ONE*, *9*, 1–14.
- Midoux, N., Hoek, P., Pailleres, L., & Authelin, J. (1999). Micronization of pharmaceutical substances in a spiral jet mill. *Powder Technol.*, *104*, 113 – 120.
- Naik, S., & Chaudhuri, B. (2015). Quantifying dry milling in pharmaceutical processing: A review on experimental and modeling approaches. *J. Pharm. Sci.*, *104*, 2401 – 2413.
- Neale, M. C., & Miller, M. B. (1997). The use of likelihood-based confidence intervals in genetic models. *Behav. Genet.*, *27*, 113–120.

- Nimmegeers, P., Bhonsale, S., Telen, D., & Impe, J. V. (2020). Optimal experiment design under parametric uncertainty: A comparison of a sensitivities based approach versus a polynomial chaos based stochastic approach. *Chem. Eng. Sci.*, 221, 115651.
- Nimmegeers, P., Lauwers, J., Telen, D., Logist, F., & Impe, J. V. (2017). Identifiability of large-scale non-linear dynamic network models applied to the ADM1-case study. *Math. Biosci.*, 288, 21–34.
- Palis, S., & Kienle, A. (2014). Discrepancy based control of particulate processes. *J. Process Control*, 24, 33–46.
- Pawitan, Y. (2013). *In All Likelihood*. Oxford University Press.
- Pohjanpalo, H. (1978). System identifiability based on the power series expansion of the solution. *Math. Biosci.*, 41, 21 – 33.
- Quaiser, T., & Mönnigmann, M. (2009). Systematic identifiability testing for unambiguous mechanistic modeling – application to JAK-STAT, MAP kinase, and NF- κ b signaling pathway models. *BMC Syst. Biol.*, 3, 50.
- Ramakrishna, D. (2000). *Population Balances*. Elsevier Inc.
- Raue, A., Karlsson, J., Saccomani, M. P., Jirstrand, M., & Timmer, J. (2014). Comparison of approaches for parameter identifiability analysis of biological systems. *Bioinformatics*, 30, 1440–1448.
- Raue, A., Kreutz, C., Maiwald, T., Bachmann, J., Schilling, M., Klingmüller, U., & Timmer, J. (2009). Structural and practical identifiability analysis

- of partially observed dynamical models by exploiting the profile likelihood. *Bioinformatics*, *25*, 1923–1929.
- Rodnianski, V., Krakauer, N., Darwesh, K., Levy, A., Kalman, H., Peyron, I., & Ricard, F. (2013). Aerodynamic classification in a spiral jet mill. *Powder Technol.*, *243*, 110 – 119.
- Rodnianski, V., Levy, A., & Kalman, H. (2019). A new method for simulation of comminution process in jet mills. *Powder Technol.*, *343*, 867 – 879.
- Saccomani, M. P., Audoly, S., & D’ Angiò, L. (2003). Parameter identifiability of nonlinear systems: the role of initial conditions. *Automatica*, *39*, 619–632. doi:[10.1016/s0005-1098\(02\)00302-3](https://doi.org/10.1016/s0005-1098(02)00302-3).
- Sedoglavic, A. (2002). A probabilistic algorithm to test local algebraic observability in polynomial time. *J Symb Comput*, *33*, 735–755.
- Silva, A. F., Burggraeve, A., Denon, Q., der Meeren, P. V., Sandler, N., Kerkhof, T. V. D., Hellings, M., Vervaet, C., Remon, J. P., Lopes, J. A., & Beer, T. D. (2013). Particle sizing measurements in pharmaceutical applications: Comparison of in-process methods versus off-line methods. *Eur. J. Pharm. Biopharm.*, *85*, 1006–1018.
- Starkey, D., Taylor, C., Morgan, N., Winston, K., Svoronos, S., Mecholsky, J., Powers, K., & Iacocca, R. (2014a). Modeling of continuous self-classifying spiral jet mills part 1: Model structure and validation using mill experiments. *AIChE J.*, *60*, 4086–4095.
- Starkey, D., Taylor, C., Siddabathuni, S., Parikh, J., Svoronos, S., Mecholsky, J., Powers, K., & Iacocca, R. (2014b). Modeling of continuous

- self-classifying spiral jet mills part 2: Powder-dependent parameters from characterization experiments. *AIChE J.*, *60*, 4096–4103.
- Steiert, B., Raue, A., Timmer, J., & Kreutz, C. (2012). Experimental design for parameter estimation of gene regulatory networks. *PLoS ONE*, *7*, e40052.
- Telen, D., Logist, F., Derlinden, E. V., Tack, I., & Impe, J. V. (2012). Optimal experiment design for dynamic bioprocesses: A multi-objective approach. *Chem. Eng. Sci.*, *78*, 82–97.
- Teng, S., Wang, P., Zhang, Q., & Gogos, C. (2011). Analysis of fluid energy mill by gas-solid two-phase flow simulation. *Powder Technol.*, *208*, 684 – 693.
- Teng, S., Wang, P., Zhu, L., Young, M.-W., & Gogos, C. G. (2009). Experimental and numerical analysis of a lab-scale fluid energy mill. *Powder Technol.*, *195*, 31 – 39.
- Teng, S., Wang, P., Zhu, L., Young, M.-W., & Gogos, C. G. (2010). Mathematical modeling of fluid energy milling based on a stochastic approach. *Chem. Eng. Sci.*, *65*, 4323 – 4331.
- Vajda, S., Rabitz, H., Walter, E., & Lecourtier, Y. (1989). Qualitative and quantitative identifiability analysis of nonlinear chemical kinetic models. *Chem. Eng. Commun.*, *83*, 191–219.
- Versyck, K., Claes, J., & van Impe, J. (1997). Practical identification of unstructured growth kinetics by application of optimal experimental design. *Biotechnol. Progr.*, *13*, 524–531.

- Vogt, M., Kunath, K., & Dressman, J. B. (2008). Dissolution enhancement of fenofibrate by micronization, cogrinding and spray-drying: Comparison with commercial preparations. *Eur. J. Pharm. Biopharm.*, *68*, 283 – 288.
- Walter, E., & Pronzato, L. (1997). *Identification of Parametric Models from Experimental Data*. Springer-Verlag London.
- Yao, K. Z., Shaw, B. M., Kou, B., McAuley, K. B., & Bacon, D. W. (2003). Modeling ethylene/butene copolymerization with multi-site catalysts: Parameter estimability and experimental design. *Polym. React. Eng.*, *11*, 563–588.
- Yu, Z.-Q., Yeoh, A., Chow, P. S., & Tan, R. B. H. (2016). Particle size control in batch crystallization of pyrazinamide on different scales. *Org. Process Res. Dev.*, *20*, 2100–2107.
- Zhou, W., Huang, R., Liu, K., & Zhang, W. (2020). A novel interval-based approach for quantifying practical parameter identifiability of a lithium-ion battery model. *Int. J. Energy Res.*, *44*, 3558–3573.

Tables

Table 1: Modelling studies on air jet mills

Modelling approach	Study	Main findings
	Levy & Kalman (2007)	• Euler-Lagrangian simulation for particle flow • some large particles escape the mill due to being carried by fine particles and not by their aerodynamic properties
CFD	Teng et al. (2009)	• breakage occurs in a thick layer near the wall • mean gas velocity in this layer is affected considerably by the grinding pressure, but less significantly by the feed pressure

Rodnianski et al.

(2013)

- cut size as a function of spin number (i.e., ratio of tangential velocity to radial velocity)
- empirical correlations between flow parameters, and mill geometry on the spin number

---

Han et al. (2002)

- analysis using 2D coupling and including breakage.

CFD-DEM

Teng et al. (2011)

- particles form a circulating layer at the peripheral wall
- Feed pressure does not contribute to breakage
- at higher operating pressures, a wider particle velocity distribution is observed

Brosh et al. (2014)

- simulations including van der Waals forces showed better comparability with experimental results
- adding van der Waals forces made simulation more efficient

Bnà et al. (2020)

- fine particles prefer to move along the wall
- fluid deceleration due to powder hold up has major influence on classification
- drag is the most important force acting on particles less than $50\text{ }\mu\text{m}$

CFD-DEM-PBM

Rodnianski et al.
(2019)

- CFD-DEM is used to formulate a machine function without considering breakage
- machine functions and material functions are combined eventually to describe breakage

Table 2: Optimal Experiment Design Criteria (Walter & Pronzato 1997, Telen et al. 2012)

Information Criterion	Mathematical representation	Interpretation
A Criterion	$\min \left[\text{trace}(\mathcal{F})^{-1} \right]$	minimise the mean of the parameter estimation errors
D Criterion	$\max \left[\det(\mathcal{F}) \right]$	minimise the volume of the joint confidence region
E Criterion	$\min \left[\lambda_{\min}(\mathcal{F}) \right]$	minimise the largest parameter error
Modified E Criterion	$\min \left[\frac{\lambda_{\max}(\mathcal{F})}{\lambda_{\min}(\mathcal{F})} \right]$	achieve circular joint confidence interval
M Criterion	$\max \left[\min(\mathcal{F}_{ii}) \right]$	minimise the uncertainty of the most uncertain parameter (θ_i) directly

Table 3: Nominal parameter values and simulation conditions

Parameter Type	Parameter	Value
Breakage Rate	α	5
	λ	0.9
Breakage Distribution	ϕ	0.22
	γ	1.5
	β	5
Classification	μ_c	1.5
	σ_c	2
Feed Characteristics	$\dot{m}_s$	0.244 g/s
	μ	150 μm
	σ	50
Time	T_{end}	200 s

Figures

Figure 1: A schematic representation of the jet mills with (a) side view and (b) top view. FR represents the feed rates and shows where the particles would enter the grinding chamber. GP represents grinding pressure and shows the location of nozzles. The symbol of tge eye represents the measurement position.

(a) Breakage Rate

(b) Breakage Distribution Function

(c) Classification Probability

Figure 2: Breakage and classification functions at nominal parameter values.

(a) Production rate and feed rate of mill simulated at nominal parameters (b) Particle Size Distributions in the feed, output and mill hold up

Figure 3: Simulated output of the jet mill at nominal parameter values.

Figure 4: Schematic of profile likelihood for structurally and practically non-identifiable parameters, and identifiable parameter. The dashed red line shows the confidence band

Figure 5: Profile likelihoods for the 7 parameters in the PBM considering only output measurements at end of the milling

Figure 6: Profile likelihoods for the 7 parameters in the PBM considering the output measurement at end of the milling along with the PSD inside the milling chamber.

Figure 7: Profile likelihoods for the 5 parameters in the PBM considering only output measurements at end of the milling

Figure 8: Profile likelihoods for the 5 parameters in the PBM considering the output measurement at end of the milling along with the PSD inside the milling chamber.

Figure 9: Profile likelihoods for the 7 parameters in the PBM considering the output measurements continuously with a sampling interval of 1 s.

Figure 10: Profile likelihoods for the 7 parameters in the PBM considering the output measurements continuously with a sampling interval of 1 s along with a measurement in the milling chamber at the end of milling.