Robust Optimization in Nanoparticle Technology Exemplified by Means of a Residence Time Reactor

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Abstract

Knowledge-based determination of the best-possible experimental setups for nanoparticle design is highly challenging and currently often out-of-reach. Although production processes do not follow idealized lab conditions, it is necessary that quality requirements are met in order to receive high-quality end products. However, in particular large-scale processes in chemical engineering are accompanied by noticeable uncertainty, for instance in physico-chemical material properties, but also temperature profiles and residence time distributions. Therefore, production needs to be protected against uncertainties that are inherent in the process. Robust mathematical optimization can help determining such best possible processes that are hedged against uncertainties. The latter guarantees that quality requirements are met regardless of how the uncertainties manifest themselves within predefined ranges. As an example, in this work we model a particle synthesis process with seeded growth by population balance equations and study different growth kinetics. The optimization task consists of determining the mean residence time that maximizes the product mass subject to a guaranteed yield. The resulting model is a nonlinear optimization problem (NLP). Protecting against uncertainties is a crucial task in this context, since the total mass necessarily has to be disposed if the particles grow too large for further use. We hedge against uncertain growth rates and derive an equivalent and algorithmically tractable reformulation for the robust counterpart of the NLP. In particular the latter amounts to solving a convex optimization problem that can efficiently be solved to global optimality. We evaluate our optimization approach for the seeded growth synthesis of zinc oxide quantum dots. We demonstrate computationally that a guaranteed yield is indeed met for all growth rates that manifest themselves within previously defined regions. The protection against uncertainties only reduces the maximum amount of product that can be obtained by a negligible margin, i.e. the "price of robustness" is affordable.

Keywords: particle design, robust optimization, process optimization, reformulation

1. Introduction

The optimal design of nanoparticles consists of many challenging tasks that include the establishment of appropriate experimental setups and processes for fabricating the desired end products. Formulating particle synthesis as a model based optimization problem and solving it via appropriate methods is an important step towards efficient processes that can be implemented in production. For example, the approach can decide how to produce the maximum possible mass of particles within a given target size, while at the same time quality requirements such as a minimal yield – a defined amount of coarse or fine fractions, are met.

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only name a few (see e.g. [3, 4] and [5]). Many of these parameters influence the thermodynamic driving force for particle formation and growth, i.e. supersaturation. Ignoring uncertainties in nanoparticle design, their impact can be so severe that finally the end products are not of the desired quality and need to be discarded completely. In case of smallest nanoparticles, this aspect is particularly pressing due to the fact that structure-property relationships are often so pronounced that smallest changes in dispersity have a tremendous effect on the product performance (see [6, 7, 8, 9] and [10]). For instance, in case of quantum confined semiconductor nanoparticles, so-called quantum dots, smallest changes in size or a slight increase in dispersity can have a tremendous effect on the position of the band gap or the photoluminescence quantum yield, or both [11]. In particular for such systems, mathematical optimization offers the unique possibility to establish optimized processes in such a way that the end products are of the required quality, even under uncertainty. Their influence is intensified when we aim at up-scaling a process from idealized laboratory conditions to industrial production. Then, inaccuracies in set parameters and analytical measurement uncertainties potentiate and the challenge arises to keep the quality requirements even in an up-scaled process.

In order to overcome these challenges, in this work, we use and develop methodologies from the active research field of mathematical optimization under uncertainty, in particular from robust optimization. We demonstrate the value of robust optimization for the very first step in the nanoparticle design chain, namely particle synthesis. We investigate seeded growth synthesis in reactors considering their residence time distributions, i.e. the distribution of the times the particles remain in the reactor. The goal is to maximize the mass of particles with the quality requirement that the particle size is within a given size range, i.e. maximize the yield for an application-dependent size range. To this end, we consider two different scenarios and distinguish between reaction-limited and diffusion-limited growth. A change of only a few degrees in temperature may change the growth kinetics in such a way that the end products are no longer particles within the desired size range. For example, if the growth rate is higher or lower than expected, the particles may either be too large or too small. To overcome these limitations and provide a guaranteed yield even under uncertain growth conditions, we focus on protecting against uncertainties during particle growth. However, methodologies and mathematical concepts from robust optimization could be applied to other problems in chemical engineering as well, e.g. nucleation, coating processes or drying.

Main paradigms for optimization with uncertain parameters consist in stochastic optimization, see for example [12], and robust optimization, see [13]. Stochastic optimization problems contain probabilistic quantities like probability, expected value or higher moments of random variables. It protects against uncertainties with a certain probability and in expectation, see e.g. [14], [12] and [15]. In case of nanoparticle design we need to guarantee quality requirements not only with high probability but with certainty. Hence, robust optimization is required. During robust optimization, one defines beforehand against which uncertainties protection is sought, which means in our case against deviations in the growth rates. The goal is to determine a synthesis process with the highest yield, while at the same time guaranteeing that the particles are within a certain size range for all considered realizations of the uncertain growth rates. The robust optimization model developed here is algorithmically tractable and is able to obtain globally optimal solutions. Robustness usually comes with a cost that has to be paid in order to guarantee uncertainty protection, the so-called “prize of robustness”. For synthesis, it may lead to a reduced yield during reaction at larger scale in comparison to what is the maximum achievement at ideal lab conditions. In our study, however, we can show computationally that the price of robustness of our protected solution is very low, while maintaining purity requirements even in a worst-case scenario that might cause high losses when no protection against uncertainties is implemented.

In Section 2 we survey relevant literature in optimization. We introduce the optimized particle synthesis process in Section 3. To this end, we describe the evolution of the particles within the reactor using different choices of residence time distributions (RTD), namely a laminar flow tube RTD and an experimentally determined RTD of a microfluidic setup. In Section 4 the approach is extended so that the process is protected against uncertain growth laws in a robust fashion. It is shown that the resulting model can be reformulated to a standard convex optimization problem that can quickly be solved to global optimality by modern available software. Computational results for the different settings, that differ in the growth kinetics (diffusion-limited and reaction-limited) are addressed in Section 5. In our computational evaluations, we show that – for the considered settings – robust synthesis is not costly. Indeed, the price of robustness is only a few percents from the maximum yield of idealized lab experiments, whereas in the non-robust setting a significant portion of the end product does not satisfy the quality requirements. We conclude by discussing more generally robust optimization of nanoparticle processes in Section 6.

2. Robust mathematical optimization

Ignoring uncertainties at first, suppose we are given a general standard nominal optimization problem, i.e. we ask for a solution vector $x \in \mathbb{R}^n$ that optimizes some objective function $f$. In a synthesis process, such an objective function can for example model the mass of particles of the desired size with respect to a certain reactor length $x$. Let $f : \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}$ and $\bar{u}$ be a typical realization of the input parameters. In addition, the solution $x$ needs to satisfy constraints $g(x, \bar{u}) \leq 0$, where $g : \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}^k$. 


In our context, these constraints model necessary quality requirements on the end product. In formulas, the optimization problem reads

\[
\max_{x \in \mathbb{R}^n} \min_{u \in U} \quad f(x, u) \\
\text{s.t.} \quad g(x, u) \leq 0.
\]

Let us now ask how the situation changes if not all input parameters are known exactly or if their values vary. In robust optimization, we hedge against parameter realizations \(u\) that are contained in an a priori defined uncertainty set \(U \subseteq \mathbb{R}^m\) that usually is assumed to be a convex region. A solution \(x\) is called robust feasible if it satisfies the constraints regardless of how the uncertainties \(u\) manifest themselves within \(U\). A solution \(x\) is called robust optimum if it attains the best guaranteed objective function value among all robust feasible solutions. The robust optimum solves the corresponding robust counterpart

\[
\max_{x \in \mathbb{R}^n} \min_{u \in U} \quad f(x, u) \\
\text{s.t.} \quad g(x, u) \leq 0 \quad \forall u \in U.
\]

Due to the fact that there may be infinitely many constraints and in addition the problem has a max-min structure, it is usually both, computationally and analytically, much harder to solve than the original problem. In general no generic solution approaches exist for such semi-infinite problems. However, for several relevant classes of optimization problems, it is possible to nevertheless develop efficient solution approaches. Then, the robust counterpart is called algorithmically tractable.

One method to obtain a tractable problem is to reformulate the robust counterpart so that the resulting task is a 'standard' finite optimization model that yields correct solutions for the robust counterpart. Along these lines, in Theorem 4.2 we provide such an equivalent reformulation for optimized synthesis processes. One of the first publications on robust linear problems is [16]. If some duality results hold for the occurring optimization problems, the derivation of an equivalent robust counterpart is often achieved by duality arguments from linear or more general nonlinear convex optimization as in [17], and [18], respectively. Geometries for the uncertainty set that are commonly used for a robust protection are polyhedral and ellipsoidal sets. For more details about the possible combinations of constraint function classes together with different geometries, we refer the reader to [19]. Seminal sources for robust optimization consist of, among many others, [20] for discrete problems and [13] for continuous tasks. Key publications about robust protection of more different kinds of optimization problems were published, e.g. [21] on convex optimization. For more general nonconvex robust optimization problems deriving an equivalent reformulation is hardly possible because duality arguments usually do not hold and in general nonconvex problems are difficult. Some recent approaches are for example robust local search methods [22, 23] or decomposition methods like in [21] motivated by outer approximation of semi-infinite problems [25]. The authors of [26] survey nonlinear robust optimization to a great extend. The paradigm of robust optimization has been successfully applied in various applications such as logistics [27, 28] or robust energy networks [29, 30].

We end the literature overview by mentioning that a robust protection against uncertainties can cause some loss in the objective value, i.e., the objective value of the robust solution is typically smaller than the nominal objective which corresponds to (unprotected) idealized lab conditions. Such a loss can be accepted as long as it is either not too large or it must be accepted because a robust protection is crucial for the application, e.g. thermal uncertainties in nuclear power plants. For a measure of this loss, we define the price of robustness as the percentage of loss compared to the optimal objective value of the nominal, i.e., idealized, problem. Robustness always comes with the benefit that an obtained solution can for sure be implemented in practice and leads to the best possible guaranteed output, as long as the uncertainty manifests itself within the given uncertainty set.

3. Mathematically optimized synthesis: Sketch of the problem

In this section, we describe the mathematical model for particle synthesis, in particular particle growth.

![Illustration of a typical continuous growth process. Upper panels: Seeds that grow in a residence time reactor to the target product; lower panels: Initial PSD and product PSD with the target size range highlighted gray](image)

Figure 1: Illustration of a typical continuous growth process. Upper panels: Seeds that grow in a residence time reactor to the target product; lower panels: Initial PSD and product PSD with the target size range highlighted gray.

Figure 1 illustrates a typical continuous growth process in particle technology like described in [31, 32] and [33]. In the upper part, a flow tube is shown where on the left side there are small particles at the start of the process. In the lower part, an initial particle size distribution (PSD) is shown, e.g. after passing a previous nucleation zone. Basically, it describes the distribution of the various particle sizes within the feed. Obviously, the feed consists of small particles that should grow within the flow tube reactor to a set size. For this process, the combination of the
axial and radial temperature profile that the particles are exposed to over time, i.e. depending on the RTD, is decisive. While ideally all fluid elements experience the same residence time in the reactor, in a real process, the occurrence of an RTD cannot be avoided. At this point it must be mentioned that, strictly speaking, also the temperature distribution would vary, both radially and axially. However, in the following, we will only focus on RTD and assume isothermal conditions. If we assume such conditions, i.e. constant temperature throughout the whole growth reactor, the RTD defines how long the fluid elements and thus the feed particles stay within the growth zone and thus the dispersity of the end product. Finally, the particles that leave the reactor are grown, as shown on the right side in the upper part. Here, the particles within the "allowed size range" are colored in black. However, due to pronounced RTD in a technical process, there will also be particles that are too small or too large. These particles are highlighted in gray in Figure 1. The size distribution of the particles within the end product is on right side below in Figure 1. Thus, the task for robust optimization is to maximize the product mass while it is guaranteed that the yield of our end product meets a certain bound, e.g. 90%.

3.1. Modeling Particle Synthesis

The basis of modeling the particle growth as part of a synthesis process is the linear population balance equation (PBE). In formulas: 

\[ \partial_t q(t, x) + \partial_x (G_g(x)q(t, x)) = 0 \quad \forall t > 0, x > 0, \]  

\[ q(0, x) = q_0(x) \quad \forall x > 0. \]  

\[ q(t, 0) = 0 \quad \forall t > 0. \] 

Here, \( x \in \mathbb{R}_{>0} \) denotes the particle size, \( t \in \mathbb{R}_{>0} \) the process time and \( G_g : \mathbb{R}_{>0} \rightarrow \mathbb{R}_{>0} \) describes the size dependent growth kinetics parameterized by a growth factor \( g \in \mathbb{R} \). Furthermore, \( q : \mathbb{R}_{>0} \times \mathbb{R}_{>0} \rightarrow \mathbb{R}_{>0} \) is the PSD inside the reactor and \( q_0 : \mathbb{R}_{>0} \rightarrow \mathbb{R}_{>0} \) the initial PSD, i.e. the PSD for \( t = 0 \). The partial derivative with respect to size and time is denoted by \( \partial_x \) and \( \partial_t \), respectively. We note that all PSDs considered here are number-weighted in general. Since we will later need two indices, for the sake of clarity we here omit an additional index for the weighting.

In general, growth kinetics depend on the concentrations or equivalently on the solution in a nonlocal way [34, Subsec. 1.2]. The main simplification in the proposed model is, that these concentration effects are neglected. For growth kinetics which depend on the concentration in a multiplicative way (as e.g. modeled in [35, Def. 1.1]), this simplification is "only" a rescaling of the process time. Thus, considering the simplified model still gives insight into how uncertainties in the process conditions will affect the product quality. We are aware that also supersaturation or solubility influence the growth kinetics and are prone to uncertainty. Thus, in practice it is important to hedge against them as well. However, then the growth kinetics in formula (2a) itself is a solution of a partial differential equation. Thus, the PBE (2) is in general not solvable analytically. Therefore, we assume that the growth rate fluctuates independently from other parameters within a predefined interval that is predefined in the input (see Section 4). Considering other parameters and more difficult PBEs is left for future research.

Equation (2a) is a partial differential equation modeling the evolution of the particle number density over time supplemented with initial values (2c) for \( t = 0 \) and zero boundary condition at \( x = 0 \) stated in (2b). As there is no source term on the right hand side of Equation (2a) and zero boundary condition for \( x = 0 \) in (2c), no new particles nucleate.

By taking the residence time \( \tau \) into account, the particles are distributed by the PSD:

\[ q_{g, \tau}(x) := \int_0^\infty E_\tau(t)q_g(t, x)dt, \]  

\[ \text{where } q_g \text{ solves the PBE } (2) \text{ (for an illustration see final PSD in Figure 1). We recall that these PSDs describe the probability density of particles of one-dimensional size } x \in \mathbb{R}_{>0} \text{ inside the reactor at process time } t \geq 0. \]  

Further, the probabilistic behavior of the residence time, is modeled by the RTD \( E_\tau(t) \). \( \tau \in \mathbb{R}_{>0} \) denotes the mean residence time.

Since Equation (2a) is a linear balance law, there exists a unique solution for \( q_0 \in L^1(\mathbb{R}_{>0}) \) and \( G_g \in L^\infty(\mathbb{R}_{>0}) \) locally Lipschitz [34]. The PBE can be solved analytically for a broad class of growth kinetics \( G_g(x) \) via the method of characteristics.

As PSDs often exhibit lognormal shape (see e.g. [36]), we consider the initial PSD as being a log-normal distribution. In practice, the seeds are often characterized by their mean particle size and relative standard deviation that can be determined through experiments (see [37] and [38]). Thus, for given mean value \( \mu \in \mathbb{R}_{>0} \) and standard deviation \( \sigma \in \mathbb{R}_{>0} \) the log-normal \( q_0 \) considered in the remainder of this article is for all \( x > 0 \) defined by:

\[ q_0(x) = \frac{1}{\sqrt{2\pi \ln(\frac{x^2}{\sigma^2} + 1)}} \cdot \exp \left( -\frac{\ln(x) - \ln(\mu / \sqrt{\frac{x^2}{\sigma^2} + 1})}{2 \ln(\frac{x^2}{\sigma^2} + 1)} \right)^2 \]  

see e.g. [39].

In the following Section 3.1.1 we specify two relevant growth kinetics \( G_g \) for which a solution can be obtained analytically: reaction-limited [40] and diffusion-limited growth [41] [40]. In Section 5 we investigate the impact of the specific growth kinetics on the optimal mean residence
time \( \tau \). Noteworthy, the considerations in the present section are valid for both growth kinetics. For the remainder of this article, this allows us to simply denote the density of the PSD for a fixed growth rate \( g \) by \( q_g \) without the need to specify \( g \) in every instance.

### 3.1.1. Growth Kinetics

First, we consider reaction-limited growth kinetics, i.e. \( G_g(x) = g \), where we assume, that the particles grow constantly over time regardless of their size. We apply the method of characteristics to solve (2) and obtain the unique solution for a given initial datum \( q_0 \) by:

\[
q_g(t,x) = \begin{cases} 
  q_0(x-gt), & \text{if } x-gt > 0, \\
  0, & \text{otherwise}.
\end{cases}
\]

The second considered growth kinetics in this contribution is diffusion-limited growth, i.e. \( G_g(x) = \frac{x}{2} \). In this case the particles grow with decreasing speed for increased sizes. The resulting PBE provides the following solution:

\[
q_g(t,x) = \begin{cases} 
  \frac{x}{\sqrt{x^2-2gt}}q_0(\sqrt{x^2-2gt}), & \text{if } x^2-2gt > 0, \\
  0, & \text{otherwise}.
\end{cases}
\]

### 3.1.2. Residence time in flow reactors

The RTD is dependent on \( \tau \), which can be controlled with regard to its mean value by changing the reactor’s length for a given flow rate. In a longer reactor, the particles need more time to pass through, i.e. \( \tau \) is bigger. This results in larger particles at the end of the reactor since the particles have more time to grow. Therefore, by controlling the reactor’s length, one controls the mean residence time and with that consequently the resulting particle sizes. Noteworthy, our mathematical framework also lays the foundation for considering a flow-rate dependent change in the shape of the RTD and thus in the width of the resulting PSD as well. In the following, we will consider two different RTDs to compare their impact on the optimization of \( \tau \).

At first, there is the analytical RTD of a laminar flow tube. With that we assume the reagent moves linearly through the tube without being mixed or stopped:

\[
E_{\tau}(t) = \begin{cases} 
  \frac{t^2}{2\tau}, & \text{if } t > \frac{\tau}{2} \\
  0, & \text{otherwise}
\end{cases}
\]

The laminar flow RTD is a standard simplification of reality, e.g. as described in \([42] \) or \([43] \). However, using this RTD in our model implies, that due to zero velocity at the wall even after a long process time some particles still remain in the reactor and grow. As the considered linear model does not involve reduction of supersaturation the resulting model is unrealistic for long process times. In the subsequent optimization problem this leads to extremely large particles, that limit the feasibility of the problem to very low guaranteed yields. Thus, we decided to not further discuss the simplified laminar flow RTD in this paper.

In contrast to the laminar flow RTD, one can also determine an RTD through experiments, e.g. \([42] \) Sec. 6, Fig. 10(a)). The experiments therein were based on a microfluidic setup for continuous nanoparticle synthesis and led to the following RTD:

\[
E_{\tau}(t) = \begin{cases} 
  \frac{1}{\sqrt{2\pi\sigma_E(t-\tau)}} \exp\left(-\frac{(\ln(t-\tau) - \mu_E)^2}{2\sigma_E^2}\right), & t-\tau > 0 \\
  0, & \text{otherwise}
\end{cases}
\]

For this RTD, we fitted the parameters \( \mu_E \) and \( \sigma_E \) to the log-normal distribution on the experimentally determined datapoints from \([42] \). In the remainder of this article we focus on this RTD, which is more realistic as it describes real experiments where all fluid elements leave the reactor in a reasonable time frame.

### 3.2. Optimization of Particle Synthesis

To set up a suitable optimization problem for robust growth during nanoparticle synthesis, we first need to define a range of quantities:

- **Total mass**: Mass of all particles produced through the growth process
- **Product mass**: Mass of all particles that are situated in the target size interval \([x_1, x_2]\), where \(0 \leq x_1 < x_2\) are given
- **Yield**: Ratio of product mass to total mass
- **Loss**: Difference of 1 and Yield.

As optimization task, we maximize the product mass while ensuring that a lower bound on the yield \( P_{\min} \in [0, 1] \) is satisfied. The latter is given, e.g., by quality and economical requirements from industry like a certain yield that must be produced to make the process economically feasible. Among the different variables that could be optimized, e.g. temperature, flow rate or reactor dimensions, we concentrate on the mean residence time \( \tau \). The reason for our choice is that we can realize an optimal \( \tau \) by building a reactor of the corresponding length or adjusting its flow speed accordingly. As we consider the mass of the synthesized particles as yield, we multiply \( q_{g,\tau}(x) \) with \( x^3 \) and neglect constants as the optimum solution of the optimization problem is invariant of. We obtain the following objective function:

\[
J_g(x_1,x_2,\tau) = \int_{x_1}^{x_2} x^3 \int_0^\infty E_{\tau}(t)q_g(x,t)dt dx.
\]

The objective is to find the optimal mean residence time \( \tau \) such that the mass of particles that reach the end of the reactor with a size \( x \in [x_1, x_2] \) is maximized, i.e. we maximize \( J_g(x_1,x_2,\tau) \) (which is proportional to the aimed mass) with respect to \( \tau > 0 \).

Since we assume that there is no post-synthetic classification step, although approaches like chromatography are
coning in reach like described in [44] and [45], the yield at the end of the reactor can either be taken or rejected as a whole but not partially. Thus, we demand that a purity of at least $P_{\text{min}}$ has to be met to guarantee a certain share of particles within the right size. Since the yield can be denoted by $J_y(x_1, x_2, \tau)$, we obtain as a purity constraint:

$$J_y(x_1, x_2, \tau) \geq P_{\text{min}}.$$

Thus, we formulate the problem for optimizing the synthesis process as:

$$\begin{align*}
\max_{\tau > 0} & \quad J_y(x_1, x_2, \tau), \\
\text{s.t.} & \quad J_y(x_1, x_2, \tau) \geq P_{\text{min}}.
\end{align*}$$

(7a, 7b)

Problem (7) is a continuous nonlinear optimization problem (NLP). Commonly, one determines a first-order optimal solution with the help of local search methods like interior point methods [46]. A detailed overview of numerical methods for NLPs can be found in [47]. Such local optimization solvers typically only determine locally but not necessarily globally optimal solutions. Although the computational effort is relatively low, convergence of local solvers is in general not guaranteed and depends heavily on the chosen initial value. In addition, local solutions can be much worse, when compared to the global solution. An additional difficulty is posed by the integration terms. For specifying the uncertainty set, let the nominal value $g$ and $\tau$ be considered as variations of $g$ against which we want to hedge against and define the uncertainty set as the interval $[g_0 - \Delta g_0, g_0 + \Delta g_0]$. A robust optimum solution $\tau^*$ is feasible for every realization of $g$ within the uncertainty set, i.e., $g \in [g_0 - \Delta g_0, g_0 + \Delta g_0]$ and maximizes the guaranteed product mass. In formulas, we have:

$$\begin{align*}
\max_{\tau > 0} \quad & \min_{g \in [g_0 - \Delta g_0, g_0 + \Delta g_0]} J_y(x_1, x_2, \tau) \\
\text{s.t.} & \quad \frac{J_y(x_1, x_2, \tau)}{J_y(0, \infty, \tau)} \geq P_{\text{min}}
\end{align*}$$

(8a, 8b)

Problem (8) is a robust Nonlinear Program with nonlinear objective and semi-infinite constraints due to the for-all constraint. For this problem class, no general solution approach exists. In order to nevertheless be able to solve it efficiently, we exploit the problem structure as follows. By numerical evidence, the product mass as well as the yield are quasiconcave not only in $\tau$ but also quasiconcave in $g$ within the considered intervals. We formulate the quasiconcavity with respect to $g$ as follows:

**Assumption 3.2 (Quasiconcave objective functional and constraint).** The functions $J_y(x_1, x_2, \tau)$ and $\frac{J_y(x_1, x_2, \tau)}{J_y(0, \infty, \tau)}$ are quasiconcave in $\tau$ for fixed $0 \leq x_1 < x_2$.

This implies that the smallest objective value is attained at the boundaries of the feasible set, if the latter is convex. This allows us to establish the convexity of the feasible set.

**Lemma 3.3.** Under Assumption 3.2, the feasible set $S := \{ \tau > 0 : \frac{J_y(x_1, x_2, \tau)}{J_y(0, \infty, \tau)} \geq P_{\text{min}} \}$ is convex.

**Proof.** Denote the constraint function as $h(\tau) := \frac{J_y(x_1, x_2, \tau)}{J_y(0, \infty, \tau)}$. For $\tau_1, \tau_2 \in S$ with $\tau_1 \neq \tau_2$, due to quasiconcavity $h(\tau_1, 1 - \lambda) \leq \min \{ h(\tau_1), h(\tau_2) \} \geq P_{\text{min}}$ holds for every $\lambda \in [0, 1]$. As this is true for all values $\tau_1, \tau_2 \in S$ the claim is proven.

The quasiconcavity of the objective function and the convexity of the feasible set establish that, like in a classical convex optimization problem, every local solution of (7) is also globally optimal like shown in Section 4. Thus, Problem (7) can be solved to global optimality with available standard solvers for NLPs, e.g. IPOPT [48], CONOPT [49] or matlab [50] intern FMINCON.
Under Assumption 3.2, the minimum of \( J(x_1, x_2, \tau) \) is attained either at \( g = g_0 - \Delta g_0 \) or at \( g = g_0 + \Delta g_0 \). Furthermore, due to quasiconcavity, if a solution to Problem (7) is feasible for the largest and for the smallest growth rate, it is feasible for all growth rates in between. This leads to the following convex reformulation of (7) that is solvable efficiently by available software:

**Theorem 4.2.** Under Assumptions 3.2 and 4.1 Problem (8) can be reformulated as the following convex optimization model:

\[
\begin{align}
\max_{\tau, z > 0} & \quad z \\
\text{s.t.} & \quad J_{g_0 - \Delta g_0}(x_1, x_2, \tau) \geq z, \quad (9a) \\
& \quad J_{g_0 + \Delta g_0}(x_1, x_2, \tau) \geq z, \quad (9b) \\
& \quad J_{g_0 - \Delta g_0}(x_1, x_2, \tau) \geq P_{\min}, \quad (9c) \\
& \quad J_{g_0 + \Delta g_0}(x_1, x_2, \tau) \geq P_{\min}. \quad (9d)
\end{align}
\]

**Proof.** First, we rewrite the objective \( \min_{\tau, z > 0} J(x_1, x_2, \tau) \) for each \( \tau \) is either attained at \( g = g_0 + \Delta g_0 \) or at \( g = g_0 + \Delta g_0 \). Thus, we introduce an additional variable \( z \) with \( z \leq J_{g_0 - \Delta g_0}(x_1, x_2, \tau) \) and \( z \leq J_{g_0 + \Delta g_0}(x_1, x_2, \tau) \). A maximal \( z \) satisfying these constraints therefore correctly attains the minimum of the objectives evaluated at the limits of the considered \( g \) interval. Next, we reformulate the yield constraint:

\[
\frac{J_g(x_1, x_2, \tau)}{J_g(0, \infty, \tau)} \geq P_{\min} \quad \forall g \in [g_0 - \Delta g_0, g_0 + \Delta g_0]
\]

which implies a transition to so-called 'narrow' PSDs [38], [51] and [3]. Therefore, the uncertainty set is chosen as \( g \in [0.18 \text{ nm}, 0.22 \text{ nm}] \).

We solve Problem (7) and Problem (9) for the two growth kinetics defined in Section 3. Since the choice of the growth kinetics has a huge impact on the PSD at the reactor’s end, not every yield can be reached with every configuration, thus \( P_{\min} \) has to be different for different growth kinetics. We always set it to the highest value for which it was possible to find a robust feasible solution. Interestingly, we will see later that from all chosen models, we can robustly guarantee the highest yield for the physically most realistic modeling of the RTD and growth kinetics.

First, we use the measured RTD from [32], see Section 5.1, with reaction-limited growth and obtain an optimal solution for a minimal yield of 75%. The second configuration is the more realistic one for small particles and the robust counterpart can be solved for a minimal yield of 90%. If the problem is feasible for such a large \( P_{\min} \), high quality regarding the desired particle size of the total mass can be guaranteed.

We solve Problem (7) and Problem (9) with a standard notebook within seconds. For optimizing the nonlinear optimization problems, we use the Matlab intern optimization toolbox **fmincon** [50]. The evaluation of occurring integral expressions is executed with the function **int**.

We further evaluate the robust solutions by computing their price of robustness. Let \( z_{\text{nom}} \) be an optimal solution

\[
\text{Lemma 3.3 and obtain that the feasible set of (9) is convex. Since the new objective is linear and thus concave, we immediately obtain that every locally optimal solution of Problem (9) is also globally optimal.}
\]

The main benefit of Theorem 4.2 is that the reformulated problem is a standard convex optimization problem for which the same standard solvers as for Problem (7) determine global optima.

5. Computational Results

In this section we present numerical results for the robust process optimization of ZnO nanoparticle synthesis. Based on [32], we assume as initial PSD (seed) \( q_0 \) a log-normal distribution with mean size \( \bar{\mu} = 1.8 \text{ nm} \) and a relative standard deviation of \( \bar{\sigma} = 10 \% \). Through (4), as shown in Figure 1, this leads to an initial PSD of:

\[
q_0(x) = \frac{1}{\sqrt{0.02\pi x}} \exp\left(-\frac{\ln(x) - 0.58^2}{0.02}\right).
\]

This PSD is used for the initial condition \( [2] \) in (2). We demonstrate our approach in an exemplary manner for a target particle size interval \( [x_1, x_2] \), where \( x_1 = 3.0 - 0.3 \text{ nm} \) and \( x_2 = 3.0 + 0.3 \text{ nm} \). These particles shall grow with a nominal growth rate \( g_0 \) of 0.2 \( \text{nm/s} \). For the deviation in the growth rate we chose 10% as this indicates a transition to so-called ‘narrow’ PSDs [38], [51]

We solve Problem (7) and Problem (9) for the two growth kinetics defined in Section 3. Since the choice of the growth kinetics has a huge impact on the PSD at the reactor’s end, not every yield can be reached with every configuration, thus \( P_{\min} \) has to be different for different growth kinetics. We always set it to the highest value for which it was possible to find a robust feasible solution. Interestingly, we will see later that from all chosen models, we can robustly guarantee the highest yield for the physically most realistic modeling of the RTD and growth kinetics.

First, we use the measured RTD from [32], see Section 5.1, with reaction-limited growth and obtain an optimal solution for a minimal yield of 75%.

The second configuration is the more realistic one for small particles and the robust counterpart can be solved for a minimal yield of 90%. If the problem is feasible for such a large \( P_{\min} \), high quality regarding the desired particle size of the total mass can be guaranteed.

We solve Problem (7) and Problem (9) with a standard notebook within seconds. For optimizing the nonlinear optimization problems, we use the Matlab intern optimization toolbox **fmincon** [50]. The evaluation of occurring integral expressions is executed with the function **int**.

We further evaluate the robust solutions by computing their price of robustness. Let \( z_{\text{nom}} \) be an optimal solution

\[
\text{Lemma 3.3 and obtain that the feasible set of (9) is convex. Since the new objective is linear and thus concave, we immediately obtain that every locally optimal solution of Problem (9) is also globally optimal.}
\]

The main benefit of Theorem 4.2 is that the reformulated problem is a standard convex optimization problem for which the same standard solvers as for Problem (7) determine global optima.
of Problem (1) and $\tau_{\text{rob}}$ an optimal solution for the robust Problem (1). The *price of robustness* is determined as:

$$\frac{z_{\text{nom}} - z_{\text{rob}}}{z_{\text{nom}}}.$$  

(11)

If this value is limited, the process can be implemented efficiently in practice. If its value cannot be accepted in practice, the question arises which uncertainties largely influence it, and whether it can be reduced, e.g., by incorporating additional measurements.

### 5.1. Results for Reaction-Limited Growth Kinetics

In this setting, the RTD $E_r(t)$ is log-normally distributed with $\mu_E$ and $\sigma_E$ fitted to the data from [32].

As growth kinetics we consider reaction-limited growth $G_g(x) = g$ and derive $q_g$ by inserting this growth rate to the linear PBE (2) with the above initial PSD $q_{t0}$ as described in Section 3.1.1. In this setting, there is no robust solution that guarantees a yield $P_{\text{min}}$, i.e., a ratio of particles in the desired size range, of 80 %. However, it is $\tau_{\text{nom}} = 6.28$ and $\tau_{\text{rob}} = 5.88$ for $P_{\text{min}} = 0.75$. From (Figure 2) it becomes clear that the density distributions do not have significant tails. As the parabolas are still broader than the desired size interval, no yield greater or equal to 80 % could be reached for any realization of growth rates $g \in \{0.18 \, \text{nm min}, 0.2 \, \text{nm min}, 0.22 \, \text{nm min}\}$. One observes that with increasing values of $g$ the parabola is shifted to the right. Thus, the nominal optimal total mass with $g = 0.22 \, \text{nm min}$ again becomes infeasible. The graphs of the densities with $\tau_{\text{rob}}$ are shifted to the left and flattened, when compared to $\tau_{\text{nom}}$. We determined the yields for $g_0 - \Delta g_0$, $g_0$ and $g_0 + \Delta g_0$ with $\tau_{\text{nom}}$ and $\tau_{\text{rob}}$ and summarized them in Table 1.

<table>
<thead>
<tr>
<th>(g)</th>
<th>(g_0 - \Delta g_0)</th>
<th>(g_0)</th>
<th>(g_0 + \Delta g_0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>yield, nominal</td>
<td>0.84</td>
<td>0.80</td>
<td>0.64</td>
</tr>
<tr>
<td>yield, robust</td>
<td>0.79</td>
<td>0.83</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Figure 3 illustrates the product mass, the total mass and the yield with respect to the growth rate. The graph of the optimal product mass obtained in the nominal setting is a parabola with a maximum at $g_0$, whereas in the robust case the maximum is attained between $g_0$ and $g_0 + \Delta g$ and remains quite high. The graph of the yields is also a parabola. However, as ensured by the robust model (9), the robust yield remains feasible for all considered growth rates, whereas the nominal yield falls below 0.75 at a certain point of the interval $[0.205 \, \text{nm min}, 0.206 \, \text{nm min}]$. Using the robust mean residence time $\tau_{\text{rob}}$, a yield of 75 % is en-
sured regardless of how the growth rate manifests itself within the uncertainty interval. Compared to an idealized process under lab conditions the robust process, i.e. with \( \tau_{\text{rob}} \), produces 3.5 % less product mass. From Figure 3 we observe that for \( \tau = \tau_{\text{nom}} \) and a growth rate larger than \( 0.207 \, \text{nm}^{-1} \), the yield falls below \( P_{\text{min}} \). Then, the total mass needs to be disposed completely. If we assume a uniformly distributed uncertainty in \( g \), we would produce a useless end product in about 32.5 % of all processes. The robust solution avoids such violation of quality requirements, only by the low cost of loosing 3.5 % in mass.

In the following Section 5.2 reaction-limited growth will be replaced by the, at least for fast precipitating nanoparticles, more realistic diffusion-limited growth (see \[4\] and \[52\]). However, the exact particle formation mechanism of quantum dots is still not unravelled and rather likely might become more complex than expected (see \[53\], \[54\] and \[55\]).

### 5.2. Results for Diffusion-Limited Growth Kinetics

In this subsection we derive \( \bar{q} \) by using the RTD (3) determined with data from \[32\] and the diffusion-limited growth kinetics \( G_g(x) = \frac{1}{2} \), see Section 3.1.1. Both, the PSD at the start and the RTD are assumed to follow log-normal distributions with the same parameters as in the last section. We solved the nominal problem (7) and the robust problem (9) with a guaranteed yield of \( 90 \% \).

For a higher yield the robust problem is infeasible which implies that regardless of how the growth rate manifests itself within the uncertainty set, it is not possible to determine a mean residence time so that quality requirements of the end product are met.

With a guaranteed yield of 90 %, we obtained \( \tau_{\text{nom}} = 16.04 \) for the nominal and \( \tau_{\text{rob}} = 14.97 \) for the robust problem. In Figure 4 the volume PSDs \( x^q \tau_{g} \) for \( g \in \{ g_0 - \Delta g_0, g_0, g_0 + \Delta g_0 \} \) and \( \tau \in \{ \tau_{\text{nom}}, \tau_{\text{rob}} \} \) are shown.

![Figure 4: PSDs at the reactor outlet derived for different growth rates and the nominal (solid curves) and the robust (dashed curves) optimal \( \tau \). The areas under the curves are proportional to the respective masses](image-url)

As in Section 5.1, the densities at the reactor outlet have one maximum but in the current model the width of the distribution is much smaller and thus clearly more favorable with regard to typical applications of quantum dots like light emitting diodes with high emission (compare steepness and peak height with Figure 2). With regard to optimization, narrow distributions are key to guarantee a high yield since more volume is contained in the desired size interval \([x_1, x_2]\).

With increasing growth rate the peak shifts to the right and the whole graph is stretched. We observe that on the one hand for nominal optimal \( \tau \) the maximum value is larger than for robust optimal \( \tau \). On the other hand if \( g = g_0 + \Delta g_0 = 0.22 \, \text{nm}^{-1} \), the graph exceeds \( x_2 \) widely and the yield requirement can not be satisfied anymore. Conversely, in the robust optimal case one observes again, that all three graphs mostly lie within the desired size range. Compared to Section 5.1 we consequently expect the same pattern of values except for a higher yield. Table 2 confirms this expectation.

<table>
<thead>
<tr>
<th>growth rate</th>
<th>( g_0 - \Delta g_0 )</th>
<th>( g_0 )</th>
<th>( g_0 + \Delta g_0 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>yield nominal</td>
<td>0.98</td>
<td>0.93</td>
<td>0.77</td>
</tr>
<tr>
<td>yield robust</td>
<td>0.99</td>
<td>0.97</td>
<td>0.90</td>
</tr>
</tbody>
</table>

If the particles grow at a rate of \( g_0 + \Delta g_0 \), the nominal optimal \( \tau \) violates the requirements since 0.77 < 0.9, whereas the robust optimal \( \tau \) meets the requirements for all considered growth rates.

As in the previous sections, we illustrate the product mass and the total mass as well as the yield with respect to \( g \) in Figure 5. The nominal product mass increases slowly for \( g < 0.2 \, \text{nm}^{-1} \) and then decreases fast, whereas the robust total mass increases fast for \( g < 0.22 \, \text{nm}^{-1} \) and then decreases slowly. The nominal yield is a quickly decreasing function and falls below 0.9 in the interval \([0.206 \, \text{nm}^{-1}, 0.22 \, \text{nm}^{-1}]\). The robust yield is decreasing much slower and remains feasible.

As in Section 5.1, we have to pay a price of robustness (11). However this time, we only have to pay 2.3 %. From Figure 5 we observe that for \( \tau = \tau_{\text{nom}} \) and a growth rate > 0.206 \( \text{nm}^{-1} \), the corresponding total mass has to be disposed. If we again assume a uniformly distributed uncertainty in \( g \), we have to dispose the end product in about 35.0 % of the processes. Eventually, we suffer an even smaller loss of 2.3 % as price of robustness compared to the higher share of 35.0 % of the synthesis processes that become infeasible for the nominal optimal \( \tau \).

### 5.3. Properties of the robustification

In general, for optimizing the product mass, large particles within the desired size range are preferred over small ones, which corresponds to larger values of \( \tau \). However, we noticed that the yield for the nominal optimal product mass with respect to \( g_0 \) is strictly greater than \( P_{\text{min}} \). Thus, \( \tau \) could be increased without obtaining an infeasible solution for the nominal growth rate \( g_0 \). But surprisingly...
this leads to a decrease in the objective value instead of a further increase. The reason for this effect is the following: By increasing $\tau$, the graph of the density shifts to the right and the particles grow larger, but also a significant share of the particles grows too large. Thus, the best value for $\tau$ is given by a trade-off between increasing the product mass through larger particles and loosing product mass if the particles grow too large. Hence, the ideal location of the PSD for maximizing the product mass does not necessarily coincide with a location that satisfies the yield constraint exactly.

In the robust case we observe this effect only for reaction-limited growth. In case of diffusion-limited growth, the product mass further increases for growing $\tau$ but is limited by the yield constraint which is fulfilled with equality for the worst-case scenario $g = g_0 + \Delta g_0$.

Let us now elaborate on the feasibility of the solutions in both models. The nominal optimal graph of the mass-weighted PSD $x^2g_{\tau_{\text{nom}}}$ shifts to the right with growing $g$. Thus, setting $g = g_0 + \Delta g_0 = 0.22 \text{ mm}$ pushes the main volume below the graph out of the desired size interval $[x_1, x_2]$ and leads to a violation of the yield constraint (see e.g. Figure 4). If we set $g = g_0 - \Delta g_0 = 0.18 \text{ mm}$, the graph shifts to the left, remains inside of $[x_1, x_2]$ and thus is still feasible.

As robustification aims to guarantee feasibility also for the considered interval limits $g_0 + \Delta g_0$, the graphs of the densities are shifted to the left and therefore, the robust optimal $\tau$ is always smaller than the nominal optimal one, i.e. $\tau_{\text{rob}} = \tau_{\text{nom}}$. This indicates that reactors should be built shorter than under idealized lab conditions ensuring that the yield constraint is met for every uncertain $g \in [g_0 - \Delta g_0, g_0 + \Delta g_0]$.

In summary, it can be said that the nominal idealized model is feasible for $g \in [g_0 - \Delta g_0, g_0]$ but gets infeasible above a certain $g \in [g_0, g_0 + \Delta g_0]$. In contrast, robust optimal solutions are feasible for every $g \in [g_0 - \Delta g_0, g_0 + \Delta g_0]$ as was illustrated in Figure 3 and Figure 5.

The price of robustness is about 3.5 % in Subsection 5.1 and 2.3 % in Subsection 5.2. Since in Subsection 5.1 we would dispose 32.5 % and in Subsection 5.2 35.0 % of our outcomes in the nominal case. Thus, this is certainly a price worth paying.

6. Conclusions and Outlook

In this work, we have observed that robust protection against uncertainties is very valuable for synthesis in reactors modeled by RTDs. In particular, we considered a synthesis process, whose initial, time-dependent PSD is derived from a PBE with different growth kinetics. We distinguish between two behaviors of the particles within the reactor, both dependent on their mean respective residence time. On the one hand, we assume a laminar flow tube, on the other hand, we fit the RTD to measured values from [32]. Consequently, the particle sizes at the end of the reactor are distributed with the convolution of the above PSD and RTD over time.

For these different growth kinetics and RTDs we established a mathematical optimization problem that computes the optimal mean residence time maximizing the product mass of the process, while guaranteeing a given minimal yield of the end product. We then extended this optimization problem to be able to deal with uncertainties in the growth rate. Here, we applied methods from robust optimization to compute an optimal mean residence time – a residence time that maximizes the product mass for the worst realization of uncertainty and simultaneously ensures that the yield constraints are met for every realization of uncertainty within the considered uncertainty set.

Subsequently, we demonstrate this approach at the example of ZnO nanoparticle synthesis and a uncertainty of 10 % in the growth rate. For example, one observes that if the process is modeled by diffusion-limited growth behavior combined with an RTD stemming from [32], our optimization can guarantee a purity of 90 % of the resulting yield. Furthermore, the loss of 2.3 % of the mass in product compared to a model that does not protect against uncertainties and thus potentially disposes entire charges of end product, is acceptable.
Finally, we want to stress possible extensions of our approach. Although we only considered the case of uncertain growth, we suppose that the method could also be beneficial for uncertainties caused by temperature, inaccuracies in the flow rate or even pulsation, or measurement errors during derivation of material properties. Furthermore, also in other processes, that are strongly dependent on the RTD such as chromatography, parameters are varying and uncertainties have a huge impact on the outcome. Thus, the concept of robust protection might be key to establish a more general methodology to deal with uncertainties in the context of nanoparticle design, for example also in particle separation and characterization, or in their suitable combination. We believe that in particular in the context of disperse systems, robust optimization will play a key role in bringing new materials and technologies into the market.

In future work, the nonlinearity of the PBE 24 - the nonlocal dependency of the growth rate on the solution due to conservation of mass, see e.g. [35, Def. 1.1] - needs to be taken into account. By this, uncertainties in e.g. temperature and solubility can directly be considered. Further, uncertainties in the initial PSD is of great interest.

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References


