

An alternating optimization approach for robust optimal control in chromatography

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Abstract Chromatographic separation plays a vital role in various areas, as this technique can deliver high-quality products both in lab- and industrial-scale processes. Economical and also ecological benefits can be expected when optimizing such processes with mathematical methods. However, even small perturbations in the operating conditions can result in significantly altered results, which may lead to the disposal of the whole product.

In this paper, we propose an algorithmic approach for the robust optimization of chromatographic processes. In our approach we combine techniques from optimization with partial differential equation (PDE) models with techniques from distributionally robust optimization in an alternate manner. Specifically, we split the nominal optimization of the separation process from

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the robustification of the fractionation times, i.e., the time window where the eluting mass is collected. We thus avoid solving computationally intractable robust mixed-integer optimal control problems constrained by PDEs.

We apply our proposed methodology to a realistic case study where a single component is to be separated from two enclosing impurities. We show that our approach indeed generates optimized controls and fractionation times that lead to a robust separation, requiring only a small number of iterations. As this algorithmic approach is quite general, it can be used for various experimental settings, thus making it a versatile method.

Keywords Chromatography · Optimal control · Distributionally robust optimization

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1 Introduction

Chromatography is a foundational separation technology employed across various industries, including pharmaceuticals, biotechnology, food processing, and chemical manufacturing, see Schmidt-Traub et al. (2012). This technology enables the selective separation of structurally similar compounds, such as chiral molecules (Subramanian 2006), protein variants (Carta and Jungbauer 2020), and nanoparticles (Supper et al. 2023a), which makes chromatography indispensable for producing high-quality pharmaceutical ingredients, food additives, and specialty chemicals.

A central challenge in chromatography is the determination of optimal fractionation times—the intervals during which target components elute from the chromatography column with sufficient purity, see, e.g., Cebulla et al. (2025) and Dienstbier et al. (2020). These time windows are critical, as their choice influences not only product purity but also process performance metrics like yield, productivity, and eluent consumption. However, accurately optimizing these intervals is complex due to the sensitivity of elution times to variations and uncertainties in operating conditions, such as mobile phase composition, pH, temperature, changes in column performance, fluctuations in retention times, and flow rate, see, e.g., Schmidt-Traub et al. (2012). Even small perturbations can shift elution profiles and degrade product quality.

Robustness is therefore essential to ensure high-purity separations despite the aforementioned uncertainties. Implementing robust chromatographic approaches is essential to meet stringent regulatory standards and to ensure the reliability and efficiency of production processes (Supper et al. 2023b). Mathematically, this leads to challenging robust nonlinear optimization problems—often involving integer decisions—for which no general, efficient solution methods currently exist.

1.1 Contribution

We propose a novel algorithm that addresses the robust optimization of both fractionation decisions as well as (further) process controls in chromatographic separation processes. Our approach can be applied to a variety of experimental conditions and is thus versatile. We also note that our algorithm is efficient in the sense that the computational intractability of a fully integrated robust mixed-integer optimal control problem with partial differential equation constraints is mitigated by a decomposition approach, where we alternately solve optimal control problems with fixed fractionation times and a finite-dimensional robust optimization problem to determine suitable, robust fractionation times.

We study the proposed methodology in a computational case study, where we investigate a hypothetical chromatographic separation process, using realistic parameters. We show that our approach yields robust and high-quality control solutions as well as optimized fractionation times. While global optimality of the obtained solutions cannot be proven, they indeed satisfy required quality constraints. Furthermore, the (robust) yield value, i.e., the considered objective function value, improves slightly during the initial iterations and then stabilizes, suggesting that the robustification introduces only minor costs of robustness.

1.2 Related Work

Robust Optimization Robust optimization (RO) replaces uncertain constraints by counterparts that must hold for all parameter realizations within a defined uncertainty set. If the underlying optimization model is convex as well, foundational results show that convex uncertainty sets yield tractable convex reformulations. This forms the basis for solving many engineering applications in a robust way. For a textbook focusing on continuous models, see, e.g., Ben-Tal et al. (2009), Bertsimas and den Hertog (2022). However, approaches are also available for some non-convexities, such as discrete decisions, see, e.g., Kouvelis and Yu (1997), Goerigk and Hartisch (2024). If no direct reformulation is available, particularly if convexity does not hold, decomposition methods or, alternatively, approximation methods are applied. For nonlinear process models, approximate robust counterparts based on sensitivity-derived penalty terms are applied by, e.g., Diehl et al. (2006). Recent surveys on nonlinear RO (Leyffer et al. 2020) provide approaches that remain computationally tractable even for larger problem sizes. In contrast, stochastic programming accounts for uncertainty in a probabilistic sense by modeling randomness via known probability distributions and associated risk measures. An introductory textbook is given by Birge and Louveaux (2006).

When statistical information is incomplete, distributionally robust optimization (DRO) considers ambiguity sets of distributions, optimizing against the worst case within them (Rahimian and Mehrotra 2022; Lin et al. 2022).

Robust Optimization for Chromatography In the context of chromatography, robustness is of particular importance since the purity requirements on the product must be satisfied even when faced with perturbations in the operating conditions, see Section 1. Consequently, a range of methodological approaches has been proposed to address robustness in chromatography.

Jakobsson et al. (2005) use a factorial experimental design approach to investigate how certain deviations in selected operating conditions affect yield and purity of the product. A pooling strategy, i.e., a determination of fractionation times, is set up by Jakobsson et al. (2007) to ensure a sufficient purity level of a product component, which is to be separated from a single impurity.

Using a sampling-based approach, Westerberg et al. (2010), Westerberg et al. (2012), and Borg et al. (2012) determine robust fractionation times by investigating the effects of variations in process conditions and model parameters on yield and purity of a product component. They set up concentration-dependent fractionation times by manually choosing and parameterizing suitable functions representing said times.

Holmqvist et al. (2015) solve an approximate robust counterpart formulation to robustly determine fractionation times and optimal process controls simultaneously. The approximation of the robust counterpart formulation arises from linearization of the state perturbations stemming from uncertain controls.

A sampling-based strategy where robust optimization is performed to determine both an optimal fractionation strategy and control of buffer salt concentration is described by Cebulla et al. (2025). There, variations in the model parameters and their effect on yield and purity of a product component are considered. A mixed-integer optimal control problem is set up to fulfill the purity requirement for the product even in the presence of parameter variations.

A different approach to enhance process robustness, particularly for continuous chromatographic processes, is by application of closed-loop optimal control, i.e., where the control scheme is adapted online to counteract measured deviations in the state space, see, e.g., Grossmann et al. (2010) and Behrens et al. (2014).

Dienstbier et al. (2023) and Dienstbier et al. (2025) proposed a tractable reformulation for continuous DRO problems with nonconvex indicator functions, transforming them into mixed-integer formulations solvable by standard algorithms. Their approach, applied to analytical chromatography using polyethylene glycol systems described by Supper et al. (2022), provides robust safe approximations of the original DRO model.

To our knowledge, available robust approaches either ignore dynamic control decisions or, if the control problem is solved, it cannot be guaranteed that obtained solutions are mathematically robust, particularly when the nonlinear process behavior has to be taken into account. Indeed, solution approaches would have to solve robust mixed-integer optimal control problems for which general and efficient approaches are still out of reach. In our work, we aim at contributing to filling this gap in the context of chromatographic separation processes.

2 Optimal Control and Robustification for Chromatographic Processes

2.1 Motivation

In column liquid chromatography, a liquid solvent (mobile phase) is pumped through a column that is typically packed with porous particles (particle / stationary phase). Separation of a mixture is achieved by exploiting the different retention times of each substance. The longer a substance remains in the stationary phase, the lower is its average velocity and it takes more time until this substance leaves the column ('elutes') compared to a substance that barely remains in the stationary phase.

We motivate the importance of safeguarding against uncertainties with an example that is shown in Figure 1. In the left picture, we observe the result of an optimized hypothetical chromatographic process in perfect lab conditions where all input is known and fixed, also called *nominal process*, see Section 2.2.2 and (7). The goal is to separate the product (middle peak) from the others so that its *yield* is maximized while its *purity*, i.e., the percentage of desired product contained in all collected material is at least 95%; see (6) for formal definitions of yield and purity. It can be seen that the peaks are clearly separated from each other and when applying the depicted fractionation times, the product purity is 95% and its yield is 100%.

On the other hand, the right picture of Figure 1 shows realistic lab conditions where uncertainties are present. The latter are modeled via additional 200 concentration profiles for each component. They are obtained by perturbing the model parameters and (piecewise constant) salt inlet control, see (1) and (2), with normally distributed errors with 2% relative standard deviation. We observe that these small errors in the parameters and the controls result in significant peak shifts and distortions. Evaluating the leftmost and right-

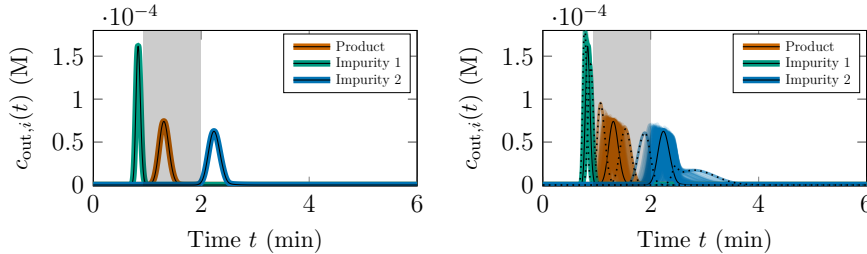


Fig. 1 Example for a chromatographic separation process. The gray-shaded area signifies the fractionation interval, i.e., the time interval where the material is collected. Left: After (nominal) optimization neglecting uncertainties, see Section 2.2.2, the components are successfully separated and the product component is fully retrieved with the desired 95% purity level. Right: For each component, 200 additional concentration profiles are generated by slightly perturbing the model parameters and salt inlet control. We observe significantly shifted peaks (dotted lines signify leftmost and rightmost peaks for each component) and the product purity may fall below 50% for these extreme profiles.

most peaks for each component, the product yield, see (6), remains at more than 99.6%, but its purity drops down to approximately 47% in the respective extreme cases.

This example shows that even small perturbations can lead to significantly different results and it may even mean that the produced product has to be discarded, as it does not satisfy quality requirements. It is thus important to determine optimized processes that are protected against uncertainties.

Our algorithmic approach for the robust optimization of chromatographic processes, described in Section 3, is composed of two main ingredients that are performed alternately: an optimal control framework for the nominal optimization of chromatographic processes and a strategy for process robustification. The process robustification aims to determine robust fractionation times and keeps all other process controls fixed, whereas the optimal control framework optimizes all other controls while keeping the fractionation decision fixed. This idea is also illustrated in Figure 2. We thus first describe in Section 2.2 the employed framework for optimal control, followed by a presentation of the robustification strategy in Section 2.3.

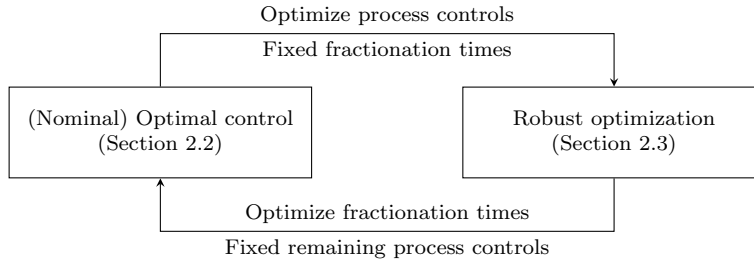


Fig. 2 Simplified illustration of the proposed algorithmic approach described in Section 3. Two subproblems are solved alternately. The optimal control framework fixes the fractionation times and optimizes (a subset of) the remaining controls. The (distributionally) robust optimization framework optimizes the fractionation times, while keeping all other degrees of freedom fixed.

2.2 An Optimal Control Framework for Chromatographic Processes

The following description of the framework for optimal control of chromatographic separation processes is extracted from Cebulla et al. (2025) and is summarized here for ease of presentation. We first describe a mathematical model for a column liquid chromatography process. Afterwards, we introduce a mixed-integer optimal control problem (MIOCP) formulation where the yield of a single product component is maximized under given purity restrictions. We refer to this formulation as the nominal problem, which is one of the two problems being solved in our alternating optimization approach, see Section 3.

2.2.1 Equilibrium-Dispersive Model (EDM)

We consider an equilibrium-dispersive model (EDM), see Schmidt-Traub et al. (2012, Section 6.2.4.1), to describe the following phenomena occurring in column chromatography processes: transport of the substances within the column, axial dispersion, and adsorption processes. We remark, however, that also other models, such as lumped rate and general rate models, see Schmidt-Traub et al. (2012, Section 6.2), can be used as underlying models for the process optimization described in Section 2.2.2, see, e.g., Cebulla et al. (2023).

The EDM is combined with a multi-component Langmuir isotherm model with mobile phase modulator, see Melander et al. (1989) and Nilsson and Andersson (2017). This adsorption model can be used to describe various chromatography techniques, such as ion exchange chromatography, hydrophobic interaction chromatography, and reversed-phase chromatography.

Given a time horizon $[0, t_f]$, with finite process duration t_f , and a column length L_c , the EDM in combination with the Langmuir isotherm model describes the concentration profiles of all components i along the axial position $x \in (0, L_c)$ of the column for a given time $t \in (0, t_f)$,

$$\frac{\partial c_{m,i}}{\partial t}(t, x) = -\frac{v_{\text{sup}}}{\varepsilon_t} \frac{\partial c_{m,i}}{\partial x}(t, x) + \tilde{D}_{\text{app},i} \frac{\partial^2 c_{m,i}}{\partial x^2}(t, x) - \frac{1 - \varepsilon_t}{\varepsilon_t} \frac{\partial q_i}{\partial t}(t, x), \quad (1a)$$

$$\begin{aligned} \frac{\partial q_i}{\partial t}(t, x) = k_{\text{kin},i} \Big[& K_{0,i} q_{\text{max},i} \exp(\gamma_{\text{salt},i} c_{m,\text{salt}}(t, x)) c_{m,i}(t, x) \\ & \left(1 - \sum_{j=1}^{n_{\text{comp}}} \frac{q_j(t, x)}{q_{\text{max},j}} \right) - q_i(t, x) \Big], \end{aligned} \quad (1b)$$

$$\frac{\partial q_{\text{salt}}}{\partial t}(t, x) = 0. \quad (1c)$$

The states in the EDM (1) are the concentrations in the mobile phase $c_{m,i}$ and the adsorbed phase q_i , respectively. With 'salt' we denote the mobile phase modulator that affects the adsorption process. We remark that (1a) holds for all components $i \in \{1, \dots, n_{\text{comp}}\} \cup \{\text{salt}\}$, whereas (1b) holds for $i \in \{1, \dots, n_{\text{comp}}\}$.

Model parameters occurring in (1) are the total porosity ε_t , the modified apparent dispersion coefficient $\tilde{D}_{\text{app}}$, as well as adsorption-related and component-dependent parameters k_{kin} , K_0 , γ_{salt} , and q_{max} . Lastly, v_{sup} is the superficial flow velocity, which is typically computed from a prescribed volumetric flow rate $\dot{V}$.

The partial differential equation (PDE) model (1) is completed with suitable boundary and initial conditions. We use Danckwerts' boundary conditions (Danckwerts 1953) that read for $i \in \{1, \dots, n_{\text{comp}}\} \cup \{\text{salt}\}$ and $t \in [0, t_f]$

$$\frac{\partial c_{m,i}}{\partial x}(t, 0) = \frac{v_{\text{sup}}}{\varepsilon_t \tilde{D}_{\text{app},i}} (c_{m,i}(t, 0) - c_{\text{in},i}(t)), \quad \frac{\partial c_{m,i}}{\partial x}(t, L_c) = 0. \quad (2)$$

Here, $c_{\text{in},i}(\cdot)$ is the inlet concentration of component i , a time-dependent control degree of freedom. We highlight that the inlet concentration for the

modifier (salt) component plays a crucial role in the adsorption process and thus in the optimization process as well.

As initial conditions we have, for $x \in [0, L_c]$ and $i \in \{1, \dots, n_{\text{comp}}\}$,

$$c_{m,i}(0, x) = 0, \quad q_i(0, x) = 0, \quad c_{m,\text{salt}}(0, x) = c_{\text{salt,init}}, \quad q_{\text{salt}}(0, x) = 0, \quad (3)$$

which corresponds to an equilibrated column, meaning that no mixture is present in the column. The salt concentration is initially set to $c_{\text{salt,init}}$, which is a time- and space-independent control degree of freedom.

2.2.2 An Optimal Control Problem for Chromatographic Processes

Typical quantities of interest in the context of optimizing chromatographic separation processes are yield and purity of the product(s), batch-cycle times, and productivity of the separation process, see Schmidt-Traub et al. (2012, Chapter 7). In our case study we aim to maximize the yield of a single product component subject to a purity constraint. To define yield and purity, here until some time $t \in (0, t_f]$, we first introduce

$$c_{\text{out},i}(t) := c_{m,i}(t, L_c) \quad (4)$$

as the concentration of component i leaving the column and

$$\text{coll} \in \{v \in L^\infty([0, t_f], \mathbb{R}) \mid v(t) \in \{0, 1\} \text{ for almost all } t \in [0, t_f]\},$$

which is a binary-valued function that signifies whether the eluate is collected or not. We highlight that this control will later be fixed in the algorithm described in Section 3, but for the sake of completeness we include this control in the following presentation. Note that L^∞ denotes the set of measurable functions that are essentially bounded.

With these quantities we can define the injected and collected amount of substance. The latter are, for $t \in [0, t_f]$, given by

$$m_{\text{in},i}(t) = \dot{V} \int_0^t c_{\text{in},i}(\tau) \, d\tau, \quad m_{\text{coll},i}(t) = \dot{V} \int_0^t c_{\text{out},i}(\tau) \, \text{coll}(\tau) \, d\tau, \quad (5)$$

which are later realized by additional ordinary differential equation (ODE) states. Lastly, the volumetric flow rate $\dot{V}$ remains fixed in our case.

The yield of a component i is the fraction of collected material from all injected material. The purity is the fraction of collected material of the desired component i from the sum of all collected components. In formulas, we have

$$\text{Yield}_i(t) = \frac{m_{\text{coll},i}(t)}{m_{\text{in},i}(t)}, \quad \text{Purity}_i(t) = \frac{m_{\text{coll},i}(t)}{\sum_{j=1}^{n_{\text{comp}}} m_{\text{coll},j}(t)}. \quad (6)$$

Note that $\text{Yield}_i(t) \in [0, 1]$ and $\text{Purity}_i(t) \in [0, 1]$ for all $i \in \{1, \dots, n_{\text{comp}}\}$ and $t \in (0, t_f]$, provided the respective denominators are not zero, but we often state yield and purity as percentages.

The overall goal is to maximize the yield of a specific product component, here denoted by $\star$, that also satisfies a prescribed degree of purity. Using a rather high-level problem formulation, the optimization problem reads

$$\begin{aligned} & \sup_{\substack{\text{coll}(\cdot), c_{\text{in,salt}}(\cdot), \\ c_{\text{salt,init}}}} \text{Yield}_\star(t_f) - \text{control regularization terms} \quad (8) \\ \text{s.t. } & \text{Purity}_\star(t_f) \geq R, \quad (7) \\ & + \text{PDE constraints (1)–(3) and ODE constraints (5),} \\ & + \text{further control constraints (9).} \end{aligned}$$

We first note that this formulation can be generalized to a mixture of multiple product components by, e.g., replacing the yield and purity by sums of yields and purities of the respective components. Doing so, the product purity holds for the collected mixture, but not necessarily for the single components.

Furthermore, depending on the underlying mathematical model used to describe a chromatographic separation process, further controls may also be subject to optimization.

The main goal in (7) is to maximize the yield of the product while ensuring a certain degree of purity. We also include control regularization terms in the objective function for the sake of well-posedness, particularly in the sense of uniqueness of a solution. We also add further control constraints to reflect a typical chromatographic (bind-and-elute) process.

As control regularization terms we use L^1 norms for discrete controls, as this choice preserves a possible bang-bang behavior for these (optimized) controls, and L^2 norms for continuous controls. We thus have

$$\begin{aligned} \text{control regularization terms} = \\ \zeta_{\text{coll}} \int_0^{t_f} |\text{coll}(t) - \text{coll}_{\text{ref}}| dt + \zeta_{c_{\text{in,salt}}} \int_0^{t_f} (c_{\text{in,salt}}(t) - c_{\text{in,salt,ref}})^2 dt, \quad (8) \end{aligned}$$

where the $\zeta_{\circ}$ are suitable weights and $\circ_{\text{ref}}$ are the regularization values for $\circ \in \{\text{coll}, c_{\text{in,salt}}\}$.

We highlight that the choice of regularization values can strongly affect the outcome, in particular when it comes to protection against uncertainty. For example, using $\text{coll}_{\text{ref}} = 0$ typically leads to a single, short fractionation interval, whereas $\text{coll}_{\text{ref}} = 1$ leads to longer and multiple fractionation intervals. In the former case, this typically means that less yield is obtained when investigating variations in the concentration profiles, while the purity requirement is not strongly violated. In the latter case, since the eluate is collected on multiple and longer time intervals, the yield often remains very high, but the purity level drops significantly.

The control constraints in (7) are chosen to reflect an experiment with two phases (related to a 'bind-and-elute' experiment). In the first phase, the mixture is injected into the system for a prescribed amount of time $t_{\text{inj}} \in (0, t_f)$ and with given sample concentrations $c_{\text{load},i}$, the latter being additional model parameters. During this time period, the buffer composition cannot be changed

and hence the salt inlet concentration remains fixed at the initially chosen value $c_{\text{salt,init}}$. In the second phase, the sample injection is stopped and the salt inlet is free for optimization to eventually elute the product.

Mathematically, we obtain the following constraints for almost all (a.a.) $t \in [0, t_f]$:

control constraints:

$$\begin{aligned} c_{\text{in},i}(t) &= \begin{cases} c_{\text{load},i}, & \text{if } 0 \leq t \leq t_{\text{inj}}, \\ 0, & \text{if } t > t_{\text{inj}}, \end{cases} \quad \text{for } i \in \{1, \dots, n_{\text{comp}}\}, \\ c_{\text{in,salt}}(t) &\in [\underline{c}_{\text{in,salt}}, \overline{c}_{\text{in,salt}}], \\ c_{\text{in,salt}}(t) &= c_{\text{salt,init}}, \quad \text{for a.a. } t \in [0, t_{\text{inj}}], \\ \text{coll}(t) &\in \{0, 1\}. \end{aligned} \tag{9}$$

Here, $\underline{c}_{\text{in,salt}}$ is a lower bound and $\overline{c}_{\text{in,salt}}$ is an upper bound on the salt inlet concentration.

We note that (7) is a nonconvex and nonlinear MIOCP with PDE and ODE constraints and thus belongs to a challenging problem class. Particularly, we cannot expect to determine global minimizers of such a problem within short computing time. This is even more true if additionally decisions shall be protected against uncertainties. To solve the nominal MIOCP (7) numerically, we employ a direct 'first discretize, then optimize' approach. We only summarize the most important steps and refer to, e.g., Bock et al. (2021) for further details.

First, we apply the method of lines approach, i.e., the PDE model (1) is spatially semi-discretized using a suitable scheme. We thus obtain an MIOCP solely constrained with ODEs. Afterwards, we perform partial outer convexification and relaxation, see Sager (2005), which yields a continuous optimal control problem (OCP), i.e., no mixed-integer controls are present. Lastly, we transform the continuous OCP into a nonlinear program (NLP) with the direct single shooting approach, see Stoer and Bulirsch (2002). To this end, we introduce a control grid

$$\mathcal{G}^C = \{0 = t_0^C < t_1^C < \dots < t_{N_C}^C = t_f\}, \quad N_C \in \mathbb{N}, \tag{10}$$

which we identify by its $N_C + 1$ grid points. Then, on each control interval $[t_j^C, t_{j+1}^C)$, $0 \leq j < N_C$, a finite-dimensional representation for the respective control function, such as polynomials, is chosen.

After solving the obtained NLP with a suitable method, the optimized relaxed controls do not necessarily satisfy the original mixed-integer (here: binary) constraints. Hence, a suitable rounding scheme needs to be applied. In our case, we would apply the so-called sum-up rounding (SUR) procedure, see Sager et al. (2012), as it can construct δ -feasible and δ -optimal controls (on a possibly finer rounding grid), see Kirches et al. (2020).

We highlight that if the eluate collection control $\text{coll}(\cdot)$ is fixed, which is the case in our novel algorithmic framework presented in Section 3, then (7)

is already a continuous OCP. Thus, we do not need to perform partial outer convexification and relaxation, and we also do not have to apply a reconstruction scheme such as SUR. However, the MIOCP formulation (7) can be solved once beforehand to obtain a good starting point for the robustification strategy. Furthermore, we would apply the relaxation and rounding approach when other discrete controls than the eluate collection enter the problem formulation, e.g., a discrete pH inlet control, see Bock et al. (2021).

2.3 (Distributionally) Robust Optimization

We now investigate the robust optimization step that follows the methodology of Dienstbier et al. (2023). We aim to find robust optimal fractionation times that maximize yield while protecting against uncertainty in concentration profiles so that the product always meets the prescribed purity constraints.

Conceptually, the robustification approach proceeds in four stages. First, uncertain process parameters induce uncertain concentration profiles. Second, these concentration profiles are interpreted as probability measures describing uncertain retention times. Third, ambiguity sets for each component are constructed from characteristic statistical properties of these measures. Fourth, the resulting semi-infinite program is safely approximated by a MIP developed in Dienstbier et al. (2023).

Considering the EDM, see (1), (2), and (3), we fix all time-dependent and time-independent controls excluding the eluate collection control. We thus obtain a predetermined, nominal concentration profile $c_{\text{out},i}^0(\cdot)$, see (4), with a 'typical' scenario of uncertainty. Consequently, to account for fluctuations in the nominal concentration profile induced by uncertain model parameters we define a simplified model for the distributionally robust optimization problem (DROP).

For clarity of notation, nominal quantities are henceforth indicated with a superscript 0, whereas quantities arising from a certain scenario are indexed by the corresponding fluctuation $p \in P$. The uncertainty set P captures all uncertain scenarios including the nominal case.

A fractionation interval $[t_-, t_+] \subseteq [0, t_f]$ is identified by the binary eluate collection control $\text{coll}(\cdot)$ and can be represented as an indicator function $\mathbb{1}_{[t_-, t_+]}(\cdot)$. The retention time, i.e., the amount of time a component $i \in \{1, \dots, n_{\text{comp}}\}$ is expected to remain in the column, is modeled as a random variable $t_i \in [0, t_f]$. In order to define the corresponding probability distribution for t_i , it is necessary to define a time-dependent function for the eluted mass $m_{\text{out},i}^p(\cdot)$.

Denoting a scenario of uncertainty by $p \in P$, the eluted mass is given by

$$m_{\text{out},i}^p(t) = \dot{V} \int_0^t c_{\text{out},i}^p(\tau) d\tau, \quad p \in P. \quad (11)$$

Consequently, the concentration profile $c_{\text{out},i}^p(\cdot)$ induces a probability distribution $\mathbb{P}_i^p \in \mathcal{M}_+([0, t_f])$ with

$$d\mathbb{P}_i^p(t) = \frac{\dot{V}}{m_{\text{out},i}^p(t_f)} c_{\text{out},i}^p(t) dt, \quad (12)$$

where $\mathcal{M}_+([0, t_f])$ denotes the space of non-negative Radon measures on $[0, t_f]$. Thus, for some $[t_-, t_+] \subseteq [0, t_f]$, the expected fractionated mass of component i with retention time t_i is given by

$$\begin{aligned} m_{\text{out},i}^p(t_f) \mathbb{P}_i^p(t_i \in [t_-, t_+]) &= m_{\text{out},i}^p(t_f) \int_{\mathbb{R}} \mathbb{1}_{[t_-, t_+]}(t_i) d\mathbb{P}_i^p(t) \\ &= \dot{V} \int_{t_-}^{t_+} c_{\text{out},i}^p(t) dt. \end{aligned}$$

In this way, scenario p translates directly into probability measure $\mathbb{P}_i^p$ for each component $i \in \{1, \dots, n_{\text{comp}}\}$. Accurately capturing all realistic scenarios in an ambiguity set while keeping computational tractability is notoriously challenging. Thus, we first replace the family of probability measures $\mathcal{P}_i$ induced by the uncertain concentration profiles by an outer description characterized through statistical properties of the profiles $\{c_{\text{out},i}^p\}_{p \in P}$. These resulting convex, moment-based ambiguity sets $\mathcal{P}_i$ are constructed as follows.

First, we establish that each $\mathbb{P}_i \in \mathcal{P}_i$ is a nonnegative Radon measure with total mass 1 on $[0, t_f]$, i.e., a probability measure, see (13a)–(13b). Then, we allow to incorporate prior knowledge on the moments of the fluctuations in order to tighten the description. To this end, formulas (13c)–(13e) restrict its first and second central moments by given lower and upper bounds, i.e. $\underline{\mu}_i, \bar{\mu}_i$ and Σ_i , respectively. The final class of constraints (13f) assumes that information on confidence sets is available. We assume that the probability of the retention time t_i being contained in an interval is bounded by some predefined function $\rho_i(\cdot)$, which we call envelope function. It is constructed as an envelope above all uncertain probability distributions $\mathbb{P}_i$ for each component i . In mathematical terms, for each $\mathbb{P}_i \in \mathcal{P}_i$ we require

$$\mathbb{P}_i \in \mathcal{M}_+([0, t_f]), \quad (13a)$$

$$\int_{\mathbb{R}} d\mathbb{P}_i(t) = 1, \quad (13b)$$

$$\int_{\mathbb{R}} t d\mathbb{P}_i(t) \geq \underline{\mu}_i, \quad (13c)$$

$$\int_{\mathbb{R}} t d\mathbb{P}_i(t) \leq \bar{\mu}_i, \quad (13d)$$

$$\int_{\mathbb{R}} \left(t - \int_{\mathbb{R}} t d\mathbb{P}_i(t) \right)^2 d\mathbb{P}_i(t) \leq \Sigma_i, \quad (13e)$$

$$(t_{j+1}^M - t_j^M) \rho_i(t_j^M) \geq \mathbb{P}_i(t_i \in [t_j^M, t_{j+1}^M]) \quad \forall j \in \{0, \dots, N_M - 1\}, \quad (13f)$$

where we use a measurement grid $\mathcal{G}^M \subseteq [0, t_f]$ with

$$\mathcal{G}^M = \{0 = t_0^M < t_1^M < \dots < t_{N_M}^M = t_f\}, \quad N_M \in \mathbb{N}, \quad (14)$$

which will later be used to discretize the time domain for the solution of DROP, see (17).

We define the ambiguity set for each component $i \in \{1, \dots, n_{\text{comp}}\}$ as

$$\mathcal{P}_i := \{\mathbb{P}_i \in \mathcal{M}_+([0, t_f]) : \mathbb{P}_i \text{ satisfies (13a) -- (13f)}\}. \quad (15)$$

These ambiguity sets may include distributions that are not physically realized and may therefore lead to conservative solutions. Nonetheless, our computational results show that this description yields high-quality outcomes. Developing tighter ambiguity sets that offer the right level of protection remains an active research area and an interesting direction for future work.

In the robust optimization step, we require that the fractionated mass of the target component $\star$ collected over the interval $[t_-, t_+]$ attains at least the prescribed purity level $R \in [0, 1]$ with respect to the total fractionated mass of all components, for all admissible probability measures contained in the ambiguity sets $\mathcal{P}_i$, $i \in \{1, \dots, n_{\text{comp}}\}$. We note that $m_{\text{out},i}^p(t_f)$, i.e., the total eluted mass for each component i and scenario $p \in P$, may vary along different scenarios. In order to simplify the DROP, we neglect these (typically minor) changes and consider the nominal masses $m_{\text{out},i}^0(t_f)$ in the computation of the purities. This gives rise to the following semi-infinite family of distributionally robust purity constraints:

$$\begin{aligned} m_{\text{out},\star}^0(t_f) \mathbb{P}_\star(t_\star \in [t_-, t_+]) &\geq \\ R \sum_{i=1}^{n_{\text{comp}}} m_{\text{out},i}^0(t_f) \mathbb{P}_i(t_i \in [t_-, t_+]), &\text{ for all } \mathbb{P}_i \in \mathcal{P}_i. \end{aligned} \quad (16)$$

We now present the full model DROP which maximizes the fractionated mass of the target component under robust purity guarantees:

$$\max_{t_-, t_+ \in [0, t_f]} m_{\text{out},\star}^0(t_f) \mathbb{P}_\star^0(t_\star \in [t_-, t_+]) \quad (17a)$$

$$\text{s.t. (16) where } \mathcal{P}_i \text{ satisfies (15).} \quad (17b)$$

To solve (17), we apply the approach from Dienstbier et al. (2023), where smooth approximations of the indicator functions in (16), for which conic duality holds, have been used in order to reformulate the model. In summary, (17) is reformulated into a semi-infinite program (SIP) containing finitely many variables, but infinitely many constraints. However, by discretizing the time horizon on a measurement grid $\mathcal{G}^M$ and continuity and compactness arguments, an algorithmically tractable safe approximation based on a mixed-integer linear problem (MIP) is derived. Although MIPs are NP-hard in general, they can be solved to global optimality with available modern software, even for large instances. The resulting MIP constitutes a safe approximation of the original problem (17). This means that, depending on the discretization size of $\mathcal{G}^M$,

a solution of the original problem may be missed; however, every solution obtained is guaranteed to be feasible for (17) and hence robust.

An advantage of (17) consists in the fact, that the ambiguity set is solely parametrized by upper and lower bounds of the mean, the variance, and the envelope function which can be derived from a meaningful scenario set of simulated as well as experimental concentration profiles, see Section 3, making it easily applicable in practice.

3 Algorithmic Approach

3.1 Uncertainty Quantification

As exemplarily shown in Section 2.1, perturbing some or all of the model parameters, as well as certain controls, leads to significantly different outcomes in the chromatographic process. In the following, we show how the information obtained from the concentration profiles can be applied to define appropriate ambiguity sets $\mathcal{P}_i$ for each component i , see (13). Assume we have a nominal concentration profile $c_{\text{out},i}^0(\cdot)$, which represents the expected uncertainty manifestation, we follow the subsequent steps:

1. **Uncertainty space exploration.** Sampling-based exploration of, e.g., the model parameter or control space to generate a collection of concentration profiles.
2. **Extreme-case quantification.** Identifying the most critical concentration profiles among the sampled realizations.
3. **Ambiguity set definition.** Specification of the ambiguity set based on statistical information from the most critical concentration profiles.

In the following, these steps are explained in more detail.

3.1.1 Step 1: Uncertainty Space Exploration

Starting from a nominally optimized chromatographic process, as described in Section 2.2.2, we generate a collection of $s \in \mathbb{N}$ concentration profiles for each component. These profiles can be obtained, e.g., by perturbing some or all of the model parameters as well as certain controls. We summarize all these samples in the finite set of uncertainty scenarios P^s . Then, the resulting set of sampled concentration profiles, i.e. uncertainty realizations, is formally defined as

$$\mathcal{C}^s := \{c_{\text{out},i}^p(\cdot)\}_{i \in \{1, \dots, n_{\text{comp}}\}, p \in P^s}. \quad (18)$$

3.1.2 Step 2: Extreme-case Quantification

Sampling-based exploration of the uncertainty space enables the identification of extreme-case realizations—here, the most extreme shifts in concentration profiles. This analysis forms the basis for constructing the ambiguity sets $\{\mathcal{P}_i\}_{i=1}^{n_{\text{comp}}}$. Since concentration profiles tend to follow a (potentially tailed) Gaussian shape, as can be seen in Figure 1, the worst-case realizations can be determined by the most extreme temporal shifts of the concentration profiles. Accordingly, we define three representative realizations:

- a *nominal* realization, i.e., the concentration profiles from the nominally optimized setting $c_{\text{out},i}^0(\cdot)$,
- a *rightmost* realization, i.e., the concentration profiles $c_{\text{out},i}^+(\cdot)$, where the component i decays latest below a threshold $\phi > 0$, and
- a *leftmost* realization, i.e., the concentration profiles $c_{\text{out},i}^-(\cdot)$, where the component i reaches a threshold $\phi > 0$ earliest.

We define

$$C^e := \bigcup_{i \in \{1, \dots, n_{\text{comp}}\}} \{c_{\text{out},i}^0(\cdot), c_{\text{out},i}^+(\cdot), c_{\text{out},i}^-(\cdot)\} \subset C^s \quad (19)$$

as the set of extreme-case realizations. We note that the extreme-case profiles may not originate from the same uncertainty realization, i.e., the leftmost (rightmost) profiles for two different components i and j may not originate from the same realization. This construction intentionally yields a conservative approximation, including possibly non-physical combinations to ensure robustness against a broad range of variations.

3.1.3 Step 3: Ambiguity Set Definition

The ambiguity sets $\{\mathcal{P}_i\}_{i=1}^{n_{\text{comp}}}$ are obtained by specifying (13) using the information contained in C^e above. First, we note that an ambiguity $\mathbb{P}_i^k$ for $k \in \{0, +, -\}$ is well defined by the uncertain scenarios $\{0, +, -\} \subset P$ following formula (12). Now, for each component i the bounds on the mean, $\underline{\mu}_i$ and $\bar{\mu}_i$, are determined by the mean values of the leftmost and rightmost realizations, $c_{\text{out},i}^-(\cdot)$ and $c_{\text{out},i}^+(\cdot)$, respectively. We remark that these means tend to coincide with the minimal / maximal observed means in Step 1. In mathematical formulas we set

$$\begin{aligned} \underline{\mu}_i &= \int_{\mathbb{R}} t \, d\mathbb{P}_i^-(t), \\ \bar{\mu}_i &= \int_{\mathbb{R}} t \, d\mathbb{P}_i^+(t). \end{aligned}$$

Furthermore, the upper bound Σ_i on the variance is given by a conservative approximation of variances from previously identified extreme-case realizations. To enhance readability we denote the variance regarding an uncertain

probability distribution $\mathbb{P}_i^p$ as

$$\text{Var}_{\mathbb{P}_i^p}(t) = \int_{\mathbb{R}} \left(t - \int_{\mathbb{R}} t d\mathbb{P}_i^p(t) \right)^2 d\mathbb{P}_i^p(t)$$

and set $\Sigma_i = \max_{j \in \{-, 0, +\}} \text{Var}_{\mathbb{P}_i^j}(t)$ as a valid upper bound.

After dualization of (16) we obtain an SIP which in turn can then be discretely approximated using methods described by Dienstbier et al. (2023). The fractionation times in the resulting MIP are now restricted to the measurement grid $\mathcal{G}^M$. Moreover, Dienstbier et al. (2023) prove validity of these bounds when tested on a concrete application. In summary, the above design ensures that the fractionation times are conservatively safeguarded against the worst observed shifts in peak location and peak width.

Finally, we specify constraint (13f). The envelope function $\rho_i(\cdot)$ bounds the uncertain concentration profile $c_{\text{out},i}(\cdot)$ within a subset of the convex hull of the three extreme realizations. Outside $[\underline{\mu}_i, \bar{\mu}_i]$, it follows the maximum of the nominal, leftmost, and rightmost profiles, while within this interval it remains constant at the global maximum concentration of component i . Formally,

$$\rho_i(t) = \begin{cases} \max\{c_{\text{out},i}^0(t), c_{\text{out},i}^+(t), c_{\text{out},i}^-(t)\}, & \text{if } t \notin [\underline{\mu}_i, \bar{\mu}_i], \\ \max_{t' \in [\underline{\mu}_i, \bar{\mu}_i]} \{c_{\text{out},i}^0(t'), c_{\text{out},i}^+(t'), c_{\text{out},i}^-(t')\}, & \text{otherwise.} \end{cases} \quad (20)$$

Thus, the three sampled concentration profiles are guaranteed to lie within the envelope function, ensuring that their induced probability measures are implicitly contained in $\{\mathcal{P}_i\}_{i=1}^{n_{\text{comp}}}$ and treated as potential realizations against which the fractionation is protected.

3.2 Algorithmic Integration

The algorithm alternately determines the optimal control and robust fractionation times while ensuring that the collected eluent meets the required purity even under uncertain probability distributions of the retention times. The approach proceeds iteratively through the following three key steps:

1. **Control optimization** by solving (7) to determine the optimal salt inlet profile¹ under nominal conditions, while keeping the fractionation times, i.e., binary control $\text{coll}(\cdot)$, fixed.
2. **Uncertainty quantification**, see Section 3.1, to identify the set of probability distributions of the retention times against which the fractionation must be protected. Continuous controls optimized in step 1 are given as input, i.e., they are fixed.
3. **Robust optimization** by solving (17) to determine fractionation times that guarantee product purity even under uncertainty.

¹ Here, we limit our discussion to the controls being present in the MIOCP formulation (7), i.e., the controls regarding the modifier (salt) concentration. Of course, additional controls can also be optimized. The key point is that the eluate collection control is fixed.

This iterative process continues until the fractionation times stabilize within a predefined tolerance $\epsilon > 0$.

We emphasize that the OCP (7) and the DROP (17), being two separate and independent problems, are solved on two, possibly different, grids: the control grid $\mathcal{G}^C$, see (10), and the measurement grid $\mathcal{G}^M$, see (14), respectively. We briefly discuss suitable choices for these grids.

On the one hand, we typically require that the measurement grid is sufficiently fine in order to evaluate the concentration profiles $c_{\text{out},i}(\cdot)$ with high accuracy, e.g., to compute the bounds used in the description of the ambiguity sets, see Step 3 in Section 3.1. Furthermore, solving the DROP (17) is not the computational bottleneck in our case, see Table 2 in Section 4.2, hence using a finer grid is also reasonable in that regard.

On the other hand, it is typically not possible in real-world applications to alter the process controls arbitrarily fast. Therefore, the control grid is chosen to be coarser, which is also justified in order to cope with the high computational complexity when solving the nominal OCP (7).

It is important to note that in principle we can choose the respective grids freely, e.g., with respect to their level of refinement and whether they are equidistant or not. However, based on the previous discussion and in favor of an easier exposition, we make the following assumptions:

Assumption 1 The measurement grid $\mathcal{G}^M$ and control grid $\mathcal{G}^C$ are equidistant, with grid sizes δ^M and δ^C , respectively. Furthermore, $\mathcal{G}^C \subseteq \mathcal{G}^M$, i.e., there exists some $k \in \mathbb{N}$ such that $k\delta^M = \delta^C$.

From solving the DROP (17), we obtain fractionation intervals $[\tilde{t}_-, \tilde{t}_+] \subseteq [0, t_f]$, with $\tilde{t}_-, \tilde{t}_+ \in \mathcal{G}^M$. These intervals are subsequently used as fixed values in the nominal control optimization, which, however, operates on the potentially different (coarser) grid $\mathcal{G}^C$. We therefore introduce a projection operator Π that maps intervals from the measurement grid onto the control grid. The projection Π yields the largest interval on the control grid fully contained in $[\tilde{t}_-, \tilde{t}_+]$. It is given by

$$\Pi([\tilde{t}_-, \tilde{t}_+]) := [\delta^C \cdot \lceil \frac{\tilde{t}_-}{\delta^C} \rceil, \delta^C \cdot \lfloor \frac{\tilde{t}_+}{\delta^C} \rfloor]. \quad (21)$$

We note that the projected fractionation interval does not necessarily maintain robustness, e.g., for multimodal peaks, i.e., peaks with multiple local maxima. In typical applications, as well as in our investigated case studies, see, e.g., Section 4.2, robustness is nonetheless always maintained. Should this not hold, one must use a more elaborate rounding scheme, which is a topic for future research. It is important to note, however, that robustness is always satisfied for the unrounded fractionation interval $[\tilde{t}_-, \tilde{t}_+]$, which is typically satisfactory from the application perspective.

Algorithm 1 illustrates the alternating optimization scheme that integrates the nominal OCP (7) with the DROP (17). The procedure starts with an initial guess for the fractionation times $[t_-^{(0)}, t_+^{(0)}]$. In each iteration, the OCP is first solved with fixed fractionation times, i.e., $\text{coll}(t) = 1$ if $t \in [t_-^{(j)}, t_+^{(j)}]$

and 0 elsewhere, to obtain the remaining controls and corresponding nominal concentration profiles $c_{\text{out},i}^{0,(j)}(\cdot)$ for each component i . Based on these profiles, the ambiguity sets $\mathcal{P}_i^{(j)}$ are constructed by specifying (13), see Section 3.1. Subsequently, the DROP (17) is solved to determine robust fractionation times $[\tilde{t}_-^{(j+1)}, \tilde{t}_+^{(j+1)}]$, which are then projected onto the coarser control grid via (21). The updated fractionation interval $[t_-^{(j+1)}, t_+^{(j+1)}]$ is then compared against the previous iterate, and the algorithm terminates once the changes fall below the chosen tolerance ϵ .

We point out that the initial values $[t_-^{(0)}, t_+^{(0)}]$ may be obtained by solving the MIOCP (7) once beforehand, with free fractionation times, i.e., with free eluate collection $\text{coll}(\cdot)$. However, solving (7) may lead to multiple fractionation intervals, particularly when choosing $\text{coll}_{\text{ref}} = 1$ for regularization, see (8), whereas a single fractionation interval is generally preferred. In contrast, the DROP (17) naturally ensures a single fractionation interval due to its formulation which is also desirable from a practical standpoint.

We emphasize that a theoretical convergence analysis of the alternating OCP-DROP framework, both regarding the convergence of the algorithm for fixed grids, as well as regarding the behavior for grid sizes going to zero, is beyond the scope of the present work and, given the complexity of the coupled optimization problems, not straightforward, see e.g., Example 2.3 in Dienstbier et al. (2023). Nevertheless, in all computational experiments considered in this work, as well as in further studies not shown here, we observed stable iterative behavior. In particular, the changes in the robust fractionation intervals obtained from the DROP, as well as the changes in the optimized salt controls obtained from the OCP, decrease over the iterations until the stopping criterion is satisfied.

Algorithm 1 Alternating OCP–DROP Framework

```

1: Input: Desired purity level  $R \in [0, 1]$ , tolerance  $\epsilon > 0$ , initial fractionation interval
    $[t_-^{(0)}, t_+^{(0)}]$  with  $t_-^{(0)}, t_+^{(0)} \in \mathcal{G}^C$ 
2: Output:  $c_{\text{in,salt}}^*(\cdot)$ ,  $c_{\text{salt,init}}^*$ ,  $t_-^*$ ,  $t_+^*$ 
3: procedure ROBUSTIFY CHROMATOGRAPHY PROCESS
4:   Initialize  $j \leftarrow 0$ 
5:   repeat
6:     Solve OCP (7) with fixed fractionation interval  $[t_-^{(j)}, t_+^{(j)}]$  to obtain  $c_{\text{salt,init}}^{(j)}$ ,
        $c_{\text{in,salt}}^{(j)}(\cdot)$ , and nominal concentration profiles  $\{c_{\text{out},i}^{0,(j)}(\cdot)\}_{i \in \{1, \dots, n_{\text{comp}}\}}$ .
7:     Construct ambiguity sets  $\mathcal{P}_i^{(j)}$ , see Section 3.1.
8:     Solve DROP (17) with  $\{c_{\text{out},i}^{0,(j)}(\cdot)\}_{i \in \{1, \dots, n_{\text{comp}}\}}$  and  $\mathcal{P}_i^{(j)}$ . Obtain  $\tilde{t}_-^{(j+1)}, \tilde{t}_+^{(j+1)}$ .
9:     Project onto control grid:  $[t_-^{(j+1)}, t_+^{(j+1)}] \leftarrow \Pi([\tilde{t}_-^{(j+1)}, \tilde{t}_+^{(j+1)}])$ .
10:     $j \leftarrow j + 1$ 
11:  until  $|t_-^{(j)} - t_-^{(j-1)}| \leq \epsilon$  and  $|t_+^{(j)} - t_+^{(j-1)}| \leq \epsilon$ 
12:  return  $c_{\text{salt,init}}^* = c_{\text{salt,init}}^{(j-1)}$ ,  $c_{\text{in,salt}}^* = c_{\text{in,salt}}^{(j-1)}$ ,  $t_-^* = t_-^{(j)}$ ,  $t_+^* = t_+^{(j)}$ 
13: end procedure

```

3.3 Key Features and Benefits

The proposed alternating OCP–DROP approach combines the strengths of control optimization and robust optimization, balancing performance and robustness. A benefit is the reduced computational complexity that is obtained by problem decomposition. The MIOCP (7) involves both continuous and discrete decisions and is generally hard to solve, especially under uncertainty. In the integrated approach, the fractionation times, which correspond to the binary collection control in (7), are determined by the DROP (17) and remain fixed during control optimization. Hence, in the decoupling approach we solve two computationally tractable optimization problems compared to a single, but intractable optimization problem. The structured outer description of the ambiguity in DROP establishes a principled alternative to sampling-based strategies, which approximate robustness by evaluating multiple specific uncertain realizations (Cebulla et al. 2025). The sampling-based strategy approximates robustness whereas the integrated approach enforces it by design through systematic uncertainty quantification and distributionally robust optimization, see Section 3.1, providing guaranteed purity under uncertainty.

Our approach couples robust decisions with dynamic optimization. Specifically, while DROP (17) identifies robust fractionation times for a given control trajectory, it does not optimize the time-dependent controls itself. The integrated approach closes this gap by coupling robust decision-making with control optimization. This coordination enables dynamic adjustment of process trajectories to maximize performance while maintaining robustness.

Another feature of our integrated approach is the balanced trade-off between robustness and optimality. In contrast, a fully robust formulation of the MIOCP would, in principle, yield globally robust-optimal solutions, but is computationally intractable. Similarly, incorporating gradient decisions into DROP would result in a non-convex DROP, which is intractable as well. The proposed alternating decomposition provides a practical compromise: robustness is iteratively established through DRO, and yield is subsequently refined through the control optimization step.

4 Computational Results

We now want to put our algorithm into practice. To this end, we first describe the experimental and computational setup, followed by a detailed presentation of a case study, where we evaluate our approach with regard to the quality of the obtained solutions and the efficiency of the algorithm.

4.1 Experimental Setup

The experiment involves a system with three components, focusing on the fractionation of the middle component (product). We choose a setting that is

to large extent identical to the one described in Cebulla et al. (2025), particularly regarding the chosen model parameters. We consider a realistic but hypothetical experimental setup. Indeed, the experimental conditions and model parameters, see Table 1, are chosen to reflect a realistic scenario. In our case study, the purity requirement for the product is set to $R = 0.95$. For the control regularization, see (8), we choose $\zeta_{\text{in,salt}} = 10^{-2}$, as well as $c_{\text{in,salt,ref}} = 0.1 \text{ M}$.

We set $t_f = 6 \text{ min}$ and the sample injection time is $t_{\text{inj}} = 10 \text{ s}$. We use a measurement grid $\mathcal{G}^M$ with grid size $\delta^M = 0.1 \text{ s}$ in order to compute yield and purity with a sufficient accuracy. Moreover, we use a control grid $\mathcal{G}^C$ with grid size $\delta^C = 2 \text{ s}$, thus having 180 control intervals in total. All controls are chosen as piecewise constant. As the robustification strategy, see Section 2.3, determines fractionation times on the finer measurement grid, the fractionation times have to be rounded according to (21).

The PDE model (1) is spatially semi-discretized with a higher-order finite volume scheme using 75 equidistant cells. More precisely, we use a WENO35 scheme in the interior, see Bock et al. (2021), and replace the nonlinear weights by the respective linear ones.

The uncertainty set P^s is generated by drawing 200 additional samples by perturbing all model parameters, i.e., all quantities listed in Table 1, excluding v_{sup} and L_c , and the piecewise constant salt inlet control with normally distributed errors with 2% relative standard deviation. Based on the set P^s , the set C^s is formed according to (18), the latter being used to eventually identify the extreme-case realizations, see (19). In case of non-uniqueness in the extreme-case quantification, i.e., when multiple profiles reach (or fall below) the given threshold of $\phi = 10^{-8}$ on the same interval of the measurement grid $\mathcal{G}^M$, the first found concentration profile is chosen as an extreme-case realization and added to C^e .

Lastly, to examine how the worst-case quantities, yield and purity, manifest themselves within the simulated realizations, we construct an additional uncertainty set. To this end, we focus on an inner description of the uncertainty realizations rather than the outer description $\{\mathcal{P}_i\}_{i=1}^{n_{\text{comp}}}$ given by constraints (13). Specifically, based on the currently identified robust fractionation times, we evaluate yield and purity over component-wise combinations of extreme-case concentration profiles and determine the corresponding worst cases. Formally,

Table 1 Model parameters and further quantities used in the EDM (1) for the case study.

Quantity	Value	Unit	Quantity	Value	Unit
v_{sup}	$5.09 \cdot 10^0$	cm min^{-1}	$K_{0,1}$	$1.00 \cdot 10^2$	M^{-1}
L_c	$2.50 \cdot 10^0$	cm	$K_{0,2}$	$1.50 \cdot 10^2$	M^{-1}
$c_{\text{load},\{1,2,3\}}$	$1.00 \cdot 10^{-4}$	M	$K_{0,3}$	$2.00 \cdot 10^2$	M^{-1}
$\tilde{D}_{\text{app},\{1,2,3\}}$	$1.00 \cdot 10^{-2}$	$\text{cm}^2 \text{ min}^{-1}$	$q_{\text{max},\{1,2,3\}}$	$3.50 \cdot 10^{-1}$	M
$\tilde{D}_{\text{app,salt}}$	$1.00 \cdot 10^{-1}$	$\text{cm}^2 \text{ min}^{-1}$	$\gamma_{\text{salt},1}$	$-5.00 \cdot 10^0$	M^{-1}
ε_t	$8.00 \cdot 10^{-1}$	—	$\gamma_{\text{salt},2}$	$-4.00 \cdot 10^0$	M^{-1}
$k_{\text{kin},\{1,2,3\}}$	$5.00 \cdot 10^2$	min^{-1}	$\gamma_{\text{salt},3}$	$-3.00 \cdot 10^0$	M^{-1}

this uncertainty set is given by

$$\mathcal{U} := \prod_{i \in \{1, \dots, n_{\text{comp}}\}} \{c_{\text{out},i}^-, c_{\text{out},i}^0, c_{\text{out},i}^+\}. \quad (22)$$

Computational Setup The computational experiments for solving the nominal OCPs are performed on an Ubuntu 24.04 system powered by an Intel Core i7-10700 with 64 GB of main memory. All variants of optimal control problems are prototypically implemented in MATLAB (R2024b) using CasADi 3.7.0 (Andersson et al. 2019). We use CasADi’s interface to IDAS as an integrator and IPOPT as NLP solver. For the integrator IDAS we set the maximum order to four. For IPOPT, we use a limited-memory BFGS approximation for the Hessian and we set the option `acceptable_tol` to 10^{-4} , `acceptable_iter` to 5, and we employ the warm start option by setting `warm_start_init_point` to ‘yes’, as we expect that the solution between neighbored OCPs will not deviate from each other significantly.

Solving the DROP is performed on an Ubuntu 24.04.4 LTS system powered by an AMD Ryzen 7 PRO 8840U processor and 64 GB of main memory. The algorithm (originating from Dienstbier et al. (2023)) is implemented in Python 3.12.3. Gurobi 12.0.2 (see Gurobi Optimization, LLC (2024)) was used as MIP solver to compute the robust fractionation times. For Gurobi, we tighten the feasibility tolerances by setting `FeasibilityTol` to 10^{-9} (default 10^{-6}) and `IntFeasTol` to 10^{-9} . Furthermore, we activate automatic problem scaling by setting `ScaleFlag` to 1, and we increase the emphasis on numerical precision by choosing the highest level for `NumericFocus` (3). Additionally, the concentration profiles obtained from the OCP solution were post-processed by setting all negative values to zero to avoid numerical issues when solving the DROP.

4.2 Case Study

We start our alternating approach with an initial guess that has been manually preselected, see Figure 3. Here, the salt inlet concentration is simply chosen as constant with $c_{\text{in,salt}} \equiv 0.5$ M and the fractionation interval is chosen such that the purity requirement of the product is met with 95.7%, while the yield is 100%. However, when evaluating the worst possible yield and purity of the product based on the extreme-case concentration profiles from the uncertainty set $\mathcal{U}$ (22), the purity drops down to roughly 73%, whereas the yield remains high with almost 98% in the worst case. This means that the purity requirements are severely violated under uncertain experimental conditions and the final product would have to be discarded, eventually. This result again shows the necessity of uncertainty protection.

Yields and Purities. We now employ our algorithmic approach for robustification. It only takes eight iterations until the fractionation times do not change anymore. The worst yields and purities obtained in iteration j of Algorithm 1,

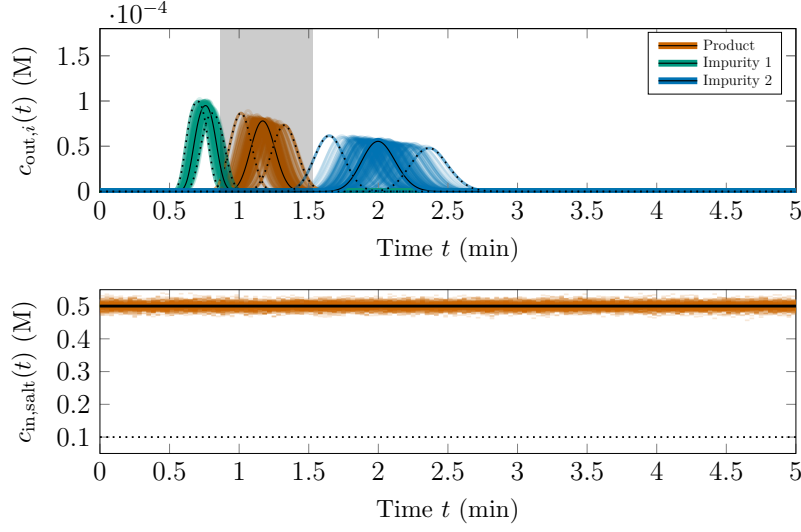


Fig. 3 Starting point for the alternating robustification approach. Top: The nominal profiles (solid black line) are well separated, the gray-shaded area signifies the fractionation interval, leading to more than the required 95% product purity. The leftmost and rightmost peaks (dotted black lines) lead to a worst-case purity of roughly 73%. Bottom: Chosen salt inlet control (solid black line) and applied (piecewise) perturbations.

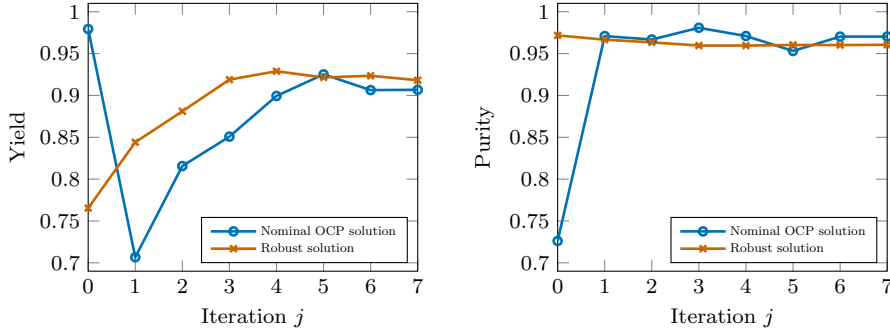


Fig. 4 Worst-case yields and purities along the iterations of the alternating approach (Algorithm 1), both after first solving the nominal OCP and then the DROP, i.e., Line 6 and Line 8 in Algorithm 1. The uncertainty set $\mathcal{U}$, see (22) is used to compute yields and purities. Worst-case yield and purity from solving the nominal OCP are based on the (projected) fractionation interval $[t_-^{(j)}, t_+^{(j)}]$, whereas the robust results are based on $[\tilde{t}_-^{(j+1)}, \tilde{t}_+^{(j+1)}]$.

both after first solving the nominal OCP (7) with fixed fractionation times and after computation of robust fractionation times, are shown in Figure 4.

In Figure 4 we observe that the obtained yield after robustification increases in the first few iterations, which means that it is indeed beneficial to alternate between nominal and robust optimization several times instead of only performing a single robustification step. The major drop of yield in the

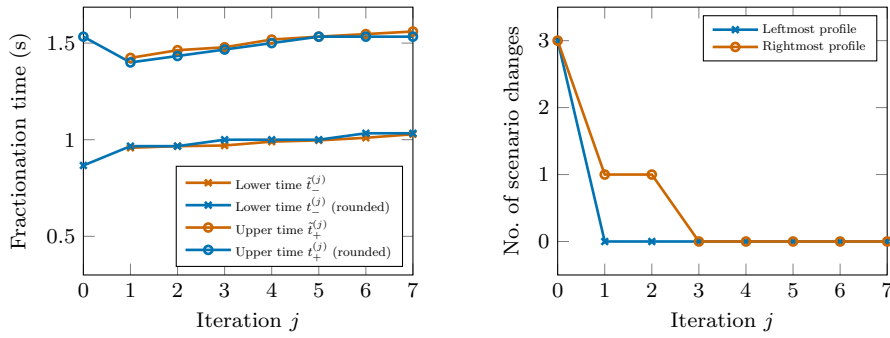


Fig. 5 Left: Unrounded and rounded fractionation times in iteration j , see (21). Iteration $j = 0$ refers to the user input for Algorithm 1. Right: Number of changes in the scenarios that correspond to the rightmost and leftmost concentration profiles for each component, see Section 3.1.2.

first iteration for the nominal OCP case can be explained by the fact that the fractionation interval becomes significantly smaller after one robustification step in iteration 0, see Figure 5. However, this is simply due to the fact that in the first iteration the purity constraint, i.e., our quality requirement, is violated. This is corrected in the first robustification step, leading to smaller fractionation times but now with satisfied purity requirement.

We observe that the purity level after robustification is slightly (0.5%–1.5%) higher than 95%, indicating that the ambiguity sets $\{\mathcal{P}_i\}_{i=1}^{n_{\text{comp}}}$ considered in DROP is only slightly more conservative than necessary. This however explains why the higher yield after solving the nominal OCP in iteration 5 has to be corrected again, as the obtained solution in this iteration is not feasible with respect to the outer description of ambiguities. However, if a particular solution along the iterations is sufficiently good for practical purposes, one could use that solution instead of using the solution obtained upon termination.

We note that the reason for the purity being higher after solving the nominal OCP is that in this case we compute the purity on the potentially smaller projected fractionation interval, whereas the robust results refer to using the larger unprojected interval.

Fractionation Times. In the left picture of Figure 5 we depict the fractionation times used when solving the nominal OCP (7). We observe that the initially chosen (guessed) times lead to a high worst-case yield but low worst-case purity for the product and are hence infeasible under robustness considerations. Therefore, the robustification makes the interval significantly narrower; in the subsequent iterations the fractionation intervals shift towards a higher time. In the end, the rounded fractionation times stay constant, hence convergence is achieved. We also remark that also the unrounded fractionation times, which are based on the finer measurement grid $\mathcal{G}^M$, would remain constant between

iteration 7 and 8 (not shown). Hence, convergence is actually also achieved on the finer grid.

In the right picture of Figure 5 we show the number of changes in the respective scenarios from the set P^s that correspond to the leftmost and rightmost peaks for all components. In iteration 0 a full sampling must be performed to identify leftmost and rightmost peaks, hence we set the number of changes to the number of components. However, from then on the scenarios for the leftmost peaks remain the same for all iterations and for the rightmost peaks only a single change occurs up to iteration 2. This means that from iteration 3 onward, it would not be necessary to perform a full, expensive sampling (with all 200 parameter and control samples from the set P^s), but we could simply use the previous scenarios to determine leftmost and rightmost peaks for the subsequent iterations. In fact, we believe that this behavior can be exploited more generally and is not only limited to this case study.

Final Result. In Figure 6 we depict the optimized concentration profiles and salt inlet control that we obtain after convergence of our alternating approach. There, both product purity and yield in the nominal case are approximately 100%. In the worst case, the purity is 97.0% and the yield is 90.7%, when considering the coarser control grid. If, in a real-world context, fractionation is also possible on the finer measurement grid, i.e., if we use the unrounded fractionation times depicted in Figure 5, we obtain a worst-case purity of 96.0% and yield of 92.3%.

Out of Sample Performance. So far, we evaluated the obtained solution on the sampling set $P^s =: P_0^s$ that has also been used during the optimization routine. To further check the quality of the solution we introduce ten further sampling sets $P_1^s, \dots, P_{10}^s$ containing further perturbed model parameters and controls with the same statistical setup, i.e., normally distributed errors with 2% relative standard deviation.

The evaluation of the worst-case realizations for each sampling set is depicted in Figure 7. We observe that only in a single (worst) case the purity requirement is not quite (but almost) met, whereas for the other sampling sets the purity requirement is always satisfied. Furthermore, the worst-case yields lie in most cases between 85% and 95%. To summarize, although it obviously cannot always be guaranteed that a solution remains robust feasible for different uncertainty sets, our robust solutions still lead to high-quality results here.

Computing Times. Lastly, we draw our attention to the runtimes taken by our alternating approach, see Table 2. The main contributions to the runtime are solving the nominal OCP, computing the robust fractionation times, and performing (200) simulations to compute the uncertainty set C^s . Accumulating over all iterations, the total time for solving the nominal OCPs is 567.29 s, the robustification time is 39.88 s, and the sampling time to compute the uncertainty set C^s is 3635.95 s. Hence, the sampling time clearly dominates and

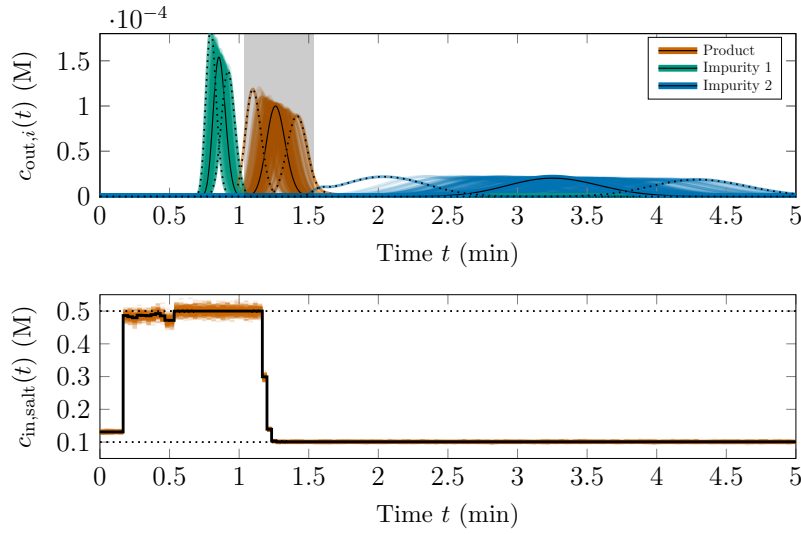


Fig. 6 Optimized chromatographic process upon convergence of the alternating approach. Top: The nominal profiles (solid black line) are well separated, leading to almost 100% yield and purity of the product when using the optimized fractionation interval (gray-shaded area). With respect to the leftmost and rightmost peaks (dotted black lines), we obtain a worst-case purity and yield of roughly 97% and 90.7%, respectively. Bottom: Optimized salt inlet control (solid black line) and applied perturbations.

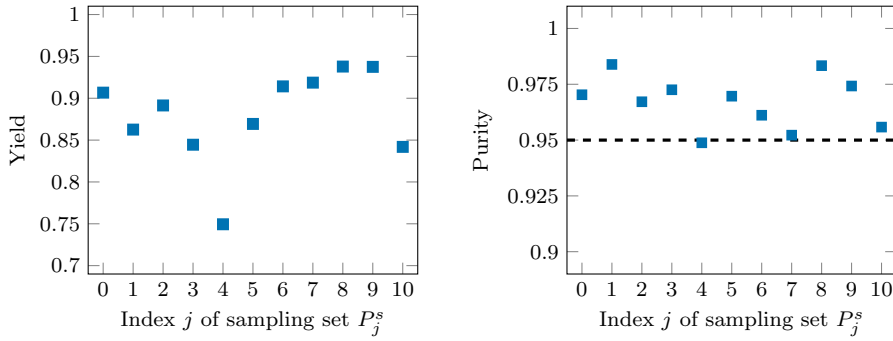


Fig. 7 Worst-case yields and purities evaluated for several additional sampling sets P_j^s . With the exception of the set P_4^s , the purity is always maintained.

makes up approximately 86% of the total time. To speed up computations it is hence crucial to improve on these times. One possibility, based on the observations shown in Figure 5, is to assume that the specific scenarios that lead to the leftmost and rightmost peaks do not change significantly in the course of iterations. Thus, instead of performing many simulations it may be sufficient to only perform simulations using these specific scenarios. As the current running times are still reasonable, we refrain from going into further detail here.

Table 2 Runtimes (in seconds) for solving the nominal OCP with IPOPT, for robustification, and for the sampling procedure to generate the set C^s . In iteration 0 no actual OCP is solved, but the chosen initial guess, see Figure 3, is used.

Iteration	OCP	DROP	Sampling
0	0.00	1.82	478.66
1	115.81	5.73	450.54
2	81.84	3.23	448.15
3	105.84	5.00	447.23
4	68.80	5.00	456.35
5	56.30	5.46	447.67
6	74.92	6.24	459.09
7	63.78	7.39	448.25

5 Conclusions and Outlook

In this work we presented a heuristic approach to robustly optimize chromatographic separation processes, alternately employing techniques from both (nominal) PDE-constrained optimization and robust optimization. We applied the proposed method to an experimental setup, where a product component is to be separated from two enclosing impurities. We observed that only few iterations were necessary for convergence and that the obtained solution was indeed robust with respect to the applied perturbations.

We now conclude with further remarks regarding our algorithmic approach. First of all, our approach can also be applied to chromatographic processes where further mixed-integer controls in the chromatography model are present, using the solution scheme outlined in Section 2.2.2. Of course, other constraints can also be added to the problem formulation if required. Moreover, we note that our approach is generally not limited to chromatographic processes, but can also be applied in other settings where a robust MIOCP can be decomposed into a robust finite-dimensional (mixed-integer) problem and an OCP.

Naturally, there is also room for improvements. For example, it is an open question how to generate ambiguity sets that are particularly suitable for real-world experiments. Therefore, we want to apply our algorithm to real-world scenarios to get further insights.

Furthermore, although it did not take much computational time to solve the OCP and the DROP, the time taken to compute the uncertainty set for the concentration profiles was rather high. Here we identify potential for improvements, e.g., by keeping the extreme-case realizations fixed for a certain amount of iterations.

Moreover, our algorithm requires that there actually exists a non-empty, robust fraction interval in each iteration. To ensure this property, it is eminent to start the procedure with a sufficiently good initial guess, i.e., initial controls and particularly fractionation times. In our case study, we selected a manually chosen and very simple initial guess, which was sufficient, but this will not always work. Solving an MIOCP with free eluate collection control may yield an initial guess suitable for the robustification procedure. Indeed, we observed

in other case studies (not shown here) that fewer iterations are needed in our proposed algorithm when the MIOCP formulation (7) is solved beforehand to obtain an initial guess. Generally, the initial guess plays an important role for the quality of the obtained solution and the algorithm may deliver different final robust fractionation times when using different initial guesses.

Lastly, it would certainly be beneficial to perform a thorough theoretical study of convergence properties of the proposed algorithm, both for fixed (measurement and control) grids, as well as for grid sizes going to zero.

Despite these open questions, we believe that the proposed approach gives a versatile method to robustly optimize chromatographic separation processes under various experimental conditions.

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Declarations

Author Contributions: Dominik H. Cebulla: Conceptualization, Methodology, Software, Writing - Original Draft, Visualization. Andrea Gilch: Conceptualization, Methodology, Software, Writing - Original Draft, Visualization. Jan Rolfes: Conceptualization, Validation, Writing - Review & Editing, Supervision. Christian Kirches: Conceptualization, Validation, Writing - Review & Editing, Supervision. Frauke Liers: Conceptualization, Validation, Writing - Review & Editing, Supervision.

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Abbreviations

DRO	distributionally robust optimization
DROP	distributionally robust optimization problem
EDM	equilibrium-dispersive model
MIOCP	mixed-integer optimal control problem
MIP	mixed-integer linear problem
NLP	nonlinear program
OCP	optimal control problem
ODE	ordinary differential equation
PDE	partial differential equation
RO	robust optimization
SIP	semi-infinite program
SUR	sum-up rounding
WENO	weighted essentially non-oscillatory

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