



Feasibility/Flexibility-based optimization for process design and operations

Huayu Tian^a, Jnana Sai Jagana^b, Qi Zhang^{b,*}, Marianthi Ierapetritou^{a,*}^a Department of Chemical and Biomolecular Engineering, University of Delaware, Newark, DE 19716, United States^b Department of Chemical Engineering and Materials Science, University of Minnesota, Minneapolis, MN 55455, United States

ARTICLE INFO

Keywords:

Feasibility

Flexibility

Feasibility-based optimization

Robust optimization

ABSTRACT

This paper provides an overview of concepts and computational approaches for the evaluation of feasibility/flexibility and how they can be used for process design and process operations optimization. It emphasizes more recent topics in this area, in particular feasible region evaluation, feasibility-based optimization, and optimization with flexibility requirements. The description of process feasibility and the feasibility-based optimization problem are presented as a way to efficiently incorporate multiple constraints and avoid unnecessary exploration of the infeasible space in the black-box optimization context. The relationship between flexibility analysis and robust optimization is also highlighted, and opportunities in exploring synergies therein are outlined. Applications in pharmaceutical design and process scheduling are used to provide context in the utilization of the presented approaches.

1. Introduction

Operational flexibility is of critical importance to the process industry, which is more true than ever due to faster-changing markets, a growing demand for product customization, increased use of resources with high variability, and more stringent safety and environmental regulations. For example, the use of intermittent renewable energy sources such as solar and wind in sustainable processes requires highly dynamic operation, and the uncertainty in weather conditions further adds to the need of process flexibility in such systems. Here, properly quantifying flexibility is important as these operational considerations must be taken into account already at the process design stage. Another prominent example is pharmaceutical manufacturing, where the identification of the so-called design space has been a major focus since the launch of the Quality by Design (QbD) initiative by FDA (ICH, 2009). The design space is defined as “the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality” (ICH, 2009). Characterization of the design space offers the industry operational flexibility since working within the design space is not considered a change and would not initiate a regulatory post-approval change process (ICH, 2009). Additionally, it provides regulatory agencies with a convenient tool to monitor the compliance of the pharmaceutical production processes (García-Muñoz et al., 2015).

While *feasibility* generally refers to a solution satisfying a set of

constraints, the notion of *flexibility* (Grossmann et al., 2014) was specifically introduced for the case with uncertainty where there is possible recourse in the form of the control variables. The process systems engineering (PSE) community has contributed a large body of research on the quantification of feasibility and flexibility and their incorporation into the optimization of process design and operations. It is worth mentioning that a concept similar to feasibility and flexibility is the process operability which is most commonly adapted in the process control community. The similarities and differences between flexibility and operability are elaborated in Lima et al. (2009). Algorithms to quantify and analyze process operability are summarized in Gazzaneo et al. (2019). This paper provides an overview of the feasibility and flexibility work, emphasizing the more recent advances and topics in this area. Among other related works, approaches on surrogate-based feasibility analysis and feasibility-based optimization are reviewed. A perspective is also provided on the relationship between flexibility analysis and robust optimization and how the synergies therein can be exploited to more efficiently solve optimization problems with flexibility requirements.

The remainder of this paper is organized as follows. In Section 2, the major concepts and formulations in traditional feasibility and flexibility analysis are presented. Then, feasible region evaluation and feasibility-based optimization are reviewed in Sections 3 and 4, respectively. In Section 5, the optimization problem with flexibility requirements is discussed, highlighting the relationship between flexibility analysis and

* Corresponding authors.

E-mail addresses: qizh@umn.edu (Q. Zhang), mgi@udel.edu (M. Ierapetritou).

robust optimization. Finally, some concluding remarks are provided in Section 6.

2. Traditional feasibility and flexibility analysis

The concept of feasibility and flexibility analysis was initially introduced by (Halemane and Grossmann, 1983) and (Swaney and Grossmann, 1985a). Since then, much research has been done on the solution of the problems formulated in that pioneering work. That line of research is referred to here as “traditional” feasibility and flexibility analysis, which is briefly reviewed in the following.

2.1. Mathematical formulations

To describe the mathematical formulations of the feasibility and flexibility problems, the following notation is considered following what is most commonly used in the literature. First the process is assumed to be described by the following set of constraints:

$$h(d, z, y, \theta) = 0 \quad (1)$$

$$g(d, z, y, \theta) \leq 0 \quad (2)$$

where h is the vector of equations that describe the physical process (such as mass and energy balances); g is the vector of inequalities which must be satisfied if operation is to be feasible (such as process operating limits and product specifications); d is the vector of design variables; y is the vector of state variables; z is the vector of control variables; and θ is the vector of uncertain parameters. One common simplification in the literature is that based on equality constraints h , the state variables can be expressed as an implicit function of d , z , and θ as follows (Halemane and Grossmann, 1983):

$$y = y(d, z, \theta) \quad (3)$$

Substituting y into g yields the reduced set of inequalities:

$$g(d, z, y(d, z, \theta), \theta) = g(d, z, \theta) \leq 0 \quad (4)$$

A flexibility test problem for a design d is to determine whether by proper adjustment of the control variables z , the inequalities $g_j(d, z, \theta)$, $j \in J$, hold for all $\theta \in T = \{\theta : \theta^L \leq \theta \leq \theta^U\}$. The first step to answer this question is to consider for a fixed value of θ whether a design d can meet the constraints. This can be accomplished if we can select the control variables z so as to minimize the largest g_j :

$$\psi(d, \theta) = \min_z \max_{j \in J} g_j(d, z, \theta) \quad (5)$$

where $\psi(d, \theta)$ is called the feasibility function. If $\psi(d, \theta)$ is negative, we can have feasible operation; whereas if $\psi(d, \theta)$ is positive, the operation is infeasible even if we do our best in trying to adjust the control variables z . If $\psi(d, \theta) = 0$, it means that we are on the boundary of the feasible region of operation.

The flexibility test problem can then be formulated as follows:

$$\chi(d) = \max_{\theta \in T} \psi(d, \theta) \quad (6)$$

where $\chi(d)$ corresponds to the flexibility of design d over the range T . If $\chi(d)$ is negative, it means that feasible operation can be attained over the entire range of T ; whereas a positive $\chi(d)$ reveals that for some realizations of uncertain parameters in T , feasibility cannot be guaranteed.

Substituting Eq. (5) into Eq. (6) yields the general mathematical formulation of the flexibility test problem:

$$\chi(d) = \max_{\theta \in T} \min_z \max_{j \in J} g_j(d, z, \theta) \quad (7)$$

An extension to the flexibility test problem is to calculate the flexibility index (Swaney and Grossmann, 1985a), which is a metric that has been derived to quantify the degree of flexibility of a given design d . The

flexibility index, denoted by F , is defined as follows:

$$F(d) = \max_{\delta \in \mathbb{R}_+} \delta \quad (8)$$

$$\text{s.t. } \max_{\theta \in T} \min_z \max_{j \in J} g_j(d, z, \theta) \leq 0$$

where $T(\delta)$, which is a function of a nonnegative scalar δ , denotes the set of all allowed realizations of the uncertain parameters θ . Traditionally, $T(\delta)$ is assumed to be a hyperrectangle defined as

$$T(\delta) = \{ \theta : \theta^N - \delta \Delta \theta^- \leq \theta \leq \theta^N + \delta \Delta \theta^+ \} \quad (9)$$

where θ^N is a nominal point, and $\Delta \theta^-$ and $\Delta \theta^+$ are incremental negative and positive deviations from θ^N , respectively. The flexibility index problem is to find $F(d)$ which represents the largest δ such that the design d is feasible for all $\theta \in T(\delta)$. An example of the largest possible $T(\delta)$ is shown in Fig. 1 as the rectangle inscribed in the projection of the feasible region onto the θ -space; it illustrates how the flexibility index is representative of the degree of operational flexibility of the given design. Flexibility index is greater than or equal to zero.

2.2. Methods for feasibility and flexibility quantification

Several methods have been proposed to solve the feasibility and flexibility problems. To quantify the feasibility/flexibility using flexibility index, full or partial vertex enumeration (Halemane and Grossmann, 1983; Swaney and Grossmann, 1985b) has been proposed for the convex case, and active-set-based reformulation of the resulting bilevel problem (Grossmann and Floudas, 1987) for nonlinear systems, and parametric programming (Bansal et al., 2002) that unifies the solution of the linear, convex, and nonconvex, nonlinear systems. The readers are referred to (Biegler et al., 1997) for more details of the algorithms and examples.

Other methods have been proposed as alternative representation for feasible region to achieve a complete feasible region characterization and quantification. As pointed out by (Ierapetritou, 2001), convex hulls can approximate the feasible region more accurately (less conservative) than prespecified geometric shapes such as rectangles and ellipses, where a new metric was also proposed to evaluate process flexibility based on the volume of the convex hull. Goyal and Ierapetritou (2002) presented the idea of approximating the feasible region from inside using the simplicial approximation approach and from the outside using the tangent planes at specific boundary points. To further extend the geometric representation to nonconvex and disjoint feasible regions, Banerjee and Ierapetritou (2005) proposed a surface reconstruction approach. The feasible region can also be identified by properly sampling the boundary. (Zilinskas et al., 2006) used sample points which are uniformly distributed over a unit hypercube to identify the feasible

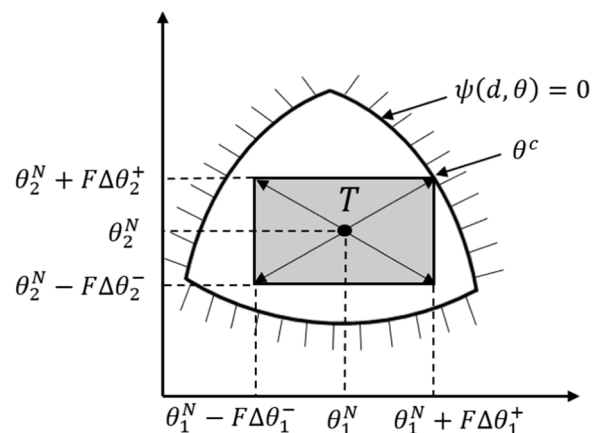


Fig. 1. Illustration for feasible region and flexibility index of an example problem in two-dimensional space.

region. (Bates et al., 2007) utilized search cones to identify the feasible region with uniform sampling points. Based on the use of auxiliary vectors to construct an approximation space, (Lai and Hui, 2008) proposed a novel method to estimate the size of the feasible space. (Adi et al., 2016) applied a random line search algorithm to identify feasible proximity points followed by the Delaunay triangulation technique to generate simplexes on the basis of the identified near-boundary points and finally determine the volumetric flexibility index. Instead of estimating the contour of the feasible region, (Zhao and Chen, 2018) used the cylindrical algebraic decomposition (CAD) method to decompose the feasible space into a finite number of valid cells arranged cylindrically which are described by analytical expressions, and then the combination of formulas were used to depict the complete region. Based on this idea, (Zheng et al., 2021) computed the integral of analytical expressions to deduce the theoretical value of the feasible hypervolume.

Extensions of the traditional flexibility analysis approach include stochastic flexibility (Pistikopoulos and Mazzuchi, 1990; Straub and Grossmann, 1990), flexibility measures using nonlinear confidence regions (Rooney and Biegler, 2001), and dynamic flexibility (Dimitriadis and Pistikopoulos, 1995). For a comprehensive review of the evolution of flexibility analysis, we refer the reader to the review paper by (Grossmann et al., 2014).

3. Feasible region evaluation and design space application

The launch of the Quality by Design initiative and the design space concept for pharmaceutical manufacturing have attracted a lot of attention over the past few decades. This has raised the issue of explicitly handling feasibility in process design and operations, leading to a large number of methods to evaluate and quantify feasibility. Experiment-based methods require a high number of experiments to determine the feasible region. To reduce the experimental load, one method is to use mathematical models of the underlying processes. The feasible region can be interpreted as the region of the input domain where the corresponding predicted model response satisfies all the required constraints. In the general deterministic case, the constraints are formulated as follows:

$$h'(d, x) = 0 \quad (10)$$

$$g'(d, x) \leq 0 \quad (11)$$

where d is the vector of design variables and x is the vector of input variables. Here, we make a distinction between the input variables x and the control variables z used in the flexibility analysis formulation (see Section 2) since x can encompass more than just operational decisions; it may also include other parameters such as feed input and material attributes. The goal of feasibility analysis is to determine the set of feasible x given a design d .

The feasibility function can then be defined as

$$\psi'(d, x) = \max_{j \in J} g_j'(d, x). \quad (12)$$

The purpose of feasibility analysis (design space evaluation) is to identify the region where $\psi'(d, x)$ is negative. Note that this general deterministic feasibility function can be extended to the stochastic case and dynamic case, where uncertain model parameters, time dependency, and control variables can be introduced.

In the following, we review the methods and applications for solving the feasibility analysis (design space evaluation) problem for different cases.

3.1. Surrogate-based feasibility analysis/design space evaluation

For the cases where process models are in closed form and easy to evaluate, straightforward sampling methods and geometry-based

methods mentioned in Section 2 can be applied. For computationally expensive models, they might not be suitable since a large number of function evaluations is often required. Surrogate-based methods have been developed to reduce computational cost, where a simple surrogate model is fitted to the feasibility function and then used to predict the feasible region. (Banerjee and Ierapetritou, 2004) used the high dimensional model representation (HDMR) as a surrogate for the original black-box model. Kriging model and adaptive sampling strategies have also been investigated for feasibility analysis (Boukouvala and Ierapetritou, 2012, 2014). Adaptive sampling strategies are designed to identify the samples that provide the most important information regarding the feasible region boundary, so that a small number of sample points is needed in total to accurately characterize the feasible region. To achieve this, a novel expected improvement function for feasibility has been proposed based on Kriging surrogate (Boukouvala and Ierapetritou, 2014). By maximizing this function, samples will be put along feasibility boundary while considering model prediction uncertainty (Wang and Ierapetritou, 2018b). Using this function, radial basis functions (RBF) (Bano et al., 2018; Wang and Ierapetritou, 2017) and artificial neural networks (ANN) (Metta et al., 2020) were investigated and displayed good performance. Partial least-squares (PLS) models were also studied as the surrogate model with the advantage of reducing the dimensionality of feasibility representation to latent variable space (Facco et al., 2015).

Surrogate-based flexibility analysis approach	Basic model	Sampling strategies	Reference
HDMR-based method	High Dimensional Model Representation (HDMR)	Distribution-dependent	(Banerjee and Ierapetritou, 2004)
GP-based method	Gaussian process	Initial and adaptive sampling	(Boukouvala and Ierapetritou, 2012, 2014; Wang and Ierapetritou, 2018b)
RBF-based method	Radial basis functions (RBF)	Initial and adaptive sampling	(Bano et al., 2018; Wang and Ierapetritou, 2017)
ANN-based method	Artificial Neural Networks (ANN)	Initial and adaptive sampling	(Metta et al., 2020)
PLS-based method	Partial least-squares (PLS) models	N/A	(Facco et al., 2015)

3.2. Design space under uncertainty

When model uncertainty is considered, for example, when the model parameters p are uncertain, the uncertainty will propagate to the model predictions and there will be a confidence interval or distribution of probability associated with the feasibility function $\psi'(d, x, p)$. In this case, a stochastic measure is needed to evaluate how likely the process is to be feasible. This is also aligned with the concept of “assurance of quality” as advocated by ICH. Peterson (2008) first proposed to use a Bayesian approach to account for model parameter uncertainty and the correlation structure of the data. The Bayesian design space, or a design space associated with a reliability level can be represented by the following model:

$$\Pr(Y \in A | x, data) \geq R, \quad (13)$$

where A is the acceptance region, Y is the model response, x is the input vector, $\Pr(\cdot)$ is the probability of Y belonging to A , R is a prespecified reliability level. The posterior predictive distribution is used to compute the probability that the response is feasible. This method has been further applied in (Bano et al., 2018; Kusumo et al., 2019; Lebrun et al., 2013, 2012; Peterson et al., 2009; Stockdale and Cheng, 2016).

An alternative approach to generate the probability of predictions is through various sampling methods such as Monte-Carlo simulation. These approaches have been applied in some studies and showed effectiveness (Figuerola et al., 2013; García-Muñoz et al., 2015; Kotidis et al., 2019; Kucherenko et al., 2020; Mortier et al., 2016; Van Bockstal et al., 2017). The main disadvantage is that it is computationally expensive since a large number of simulations are needed. (Laky et al., 2019) proposed an algorithm that apply flexibility index formulation to replace the Monte-Carlo sampling.

The stochastic prediction can also be modeled by stochastic simulation. Wang and Ierapetritou (2018b) used stochastic Kriging (Ankenman et al., 2010) as the surrogate for the stochastic feasibility function with heteroscedastic noise and investigated different adaptive sampling approaches to reduce computational cost.

3.3. Design space for dynamic systems

In the above sections, feasibility is considered in the static case. For dynamic systems, time-dependent design space has been discussed. This is closely related to the concept of dynamic flexibility briefly discussed in Section 2.2. According to (Dimitriadis and Pistikopoulos, 1995), the formulation for constraints include the path constraints and the points constraints, where the variables describing the operation of the process now depends on the time variable t :

$$g^{path}(d, y(t), z(t), \theta(t), t) \leq 0 \quad (14)$$

$$g_k^{point}(d, y(t^k), z(t^k), \theta(t^k), t^k) \leq 0, \quad k = 1, \dots, NP \quad (15)$$

The evolution of the design space along time provides required information for batch processes such as batch freeze-drying processes (Mortier et al., 2016; Van Bockstal et al., 2017) and cell cultivation processes (Hirono et al., 2022). It is also useful for adapting to process changes (e.g., due to fouling, clogging, environmental conditions) during operation (Bano et al., 2019). A recent review discussed the construction of dynamic design space as a direction forward for QbD in general (von Stosch et al., 2020).

Control strategies have been investigated recently to improve process robustness and efficiency for continuous pharmaceutical manufacturing (Su et al., 2019). The introduction of control systems will add recourse to the process, similar to traditional flexibility analysis formulation. As shown by (Boukouvala, 2013; García-Muñoz et al., 2010), a design space can be significantly enlarged if a correct control strategy is employed.

3.4. Applications of feasibility analysis

Feasibility analysis and design space characterization have been applied to various areas, including chemical reaction systems, pharmaceutical manufacturing, biopharmaceutical manufacturing, material design, and integrated planning and scheduling problems. Details are summarized in Table 1.

As an illustration, the design space of a direct compaction (DC) pharmaceutical manufacturing process is shown below (Wang et al., 2017). The DC line consists of feeders, co-mill, blender, and feed frame and tablet press unit operations to produce tablet products from powder materials, as shown in Fig. 2.

Semi-empirical models have been developed for each unit operation, and integrated as a process simulation in gPROMS. Details of process models are provided in (Wang et al., 2017). Six operating variables were selected as critical process parameters based on sensitivity analysis which are “flow rate of API (FR_{API})”, “flow rate of excipient (FR_{Exp})”, “comill rotation speed (RPM_{comill})”, “blender blade speed ($RPM_{blender}$)”, “tablet press fill depth ($FillDepth$)”, “tablet thickness set point ($Thickness$)”. The algorithm has a framework that is similar to the left half of Fig. 4. It starts with an initial sampling plan to build the surrogate

Table 1
Design space applications.

Application area	Problem type	References
Material design Pharmaceutical and biopharmaceutical processes	Deterministic Deterministic, stochastic/ probabilistic, dynamic	(Banerjee et al., 2010) (Bano et al., 2018, 2018; Boukouvala and Ierapetritou, 2012; Castagnoli et al., 2010; Chatzizacharia and Hatziaframidis, 2014; Ding and Ierapetritou, 2021; Hirono et al., 2022; Kotidis et al., 2019; Lebrun et al., 2013, 2012; Metta et al., 2020; Mortier et al., 2016; Rogers and Ierapetritou, 2015; Stockdale and Cheng, 2016; Tabora et al., 2019; Van Bockstal et al., 2017; Wang et al., 2017; Wang and Ierapetritou, 2017, 2018a)
Chemical reaction systems	Stochastic/ probabilistic	(Figuerola et al., 2013; García-Muñoz et al., 2015; Kucherenko et al., 2020; Kusumo et al., 2019; Laky et al., 2019)
Integrated planning and scheduling problems	Deterministic	(Badejo and Ierapetritou, 2022; Dias and Ierapetritou, 2019)

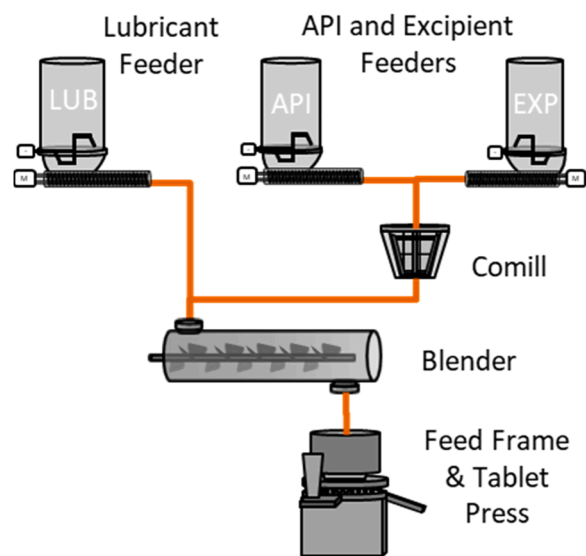


Fig. 2. Flowsheet of the DC manufacturing line.

model for feasibility function, then followed by an iterative procedure to add new samples and refine the surrogate model near feasibility boundary. One example of the infill criterion is the expected improvement function for feasibility (Boukouvala and Ierapetritou, 2014), which is able to balance exploration and exploitation when selecting new samples. The algorithm terminates when the sampling budget is used up.

The results of surrogate-based feasibility analysis are shown in Fig. 3. The feasible space bounded by the red dotted line denotes the region in operating space that meets all the required constraints on intermediate material and product specifications. Based on the results, we notice that input variables FR_{API} , FR_{Exp} , $RPM_{blender}$ are feasible almost over their entire ranges, while RPM_{comill} , $FillDepth$, $Thickness$ need to be carefully maintained to assure product quality. Thus, incorporated with proper control strategies, the process will be more robust and be able to meet the strict product quality requirements without economic losses.

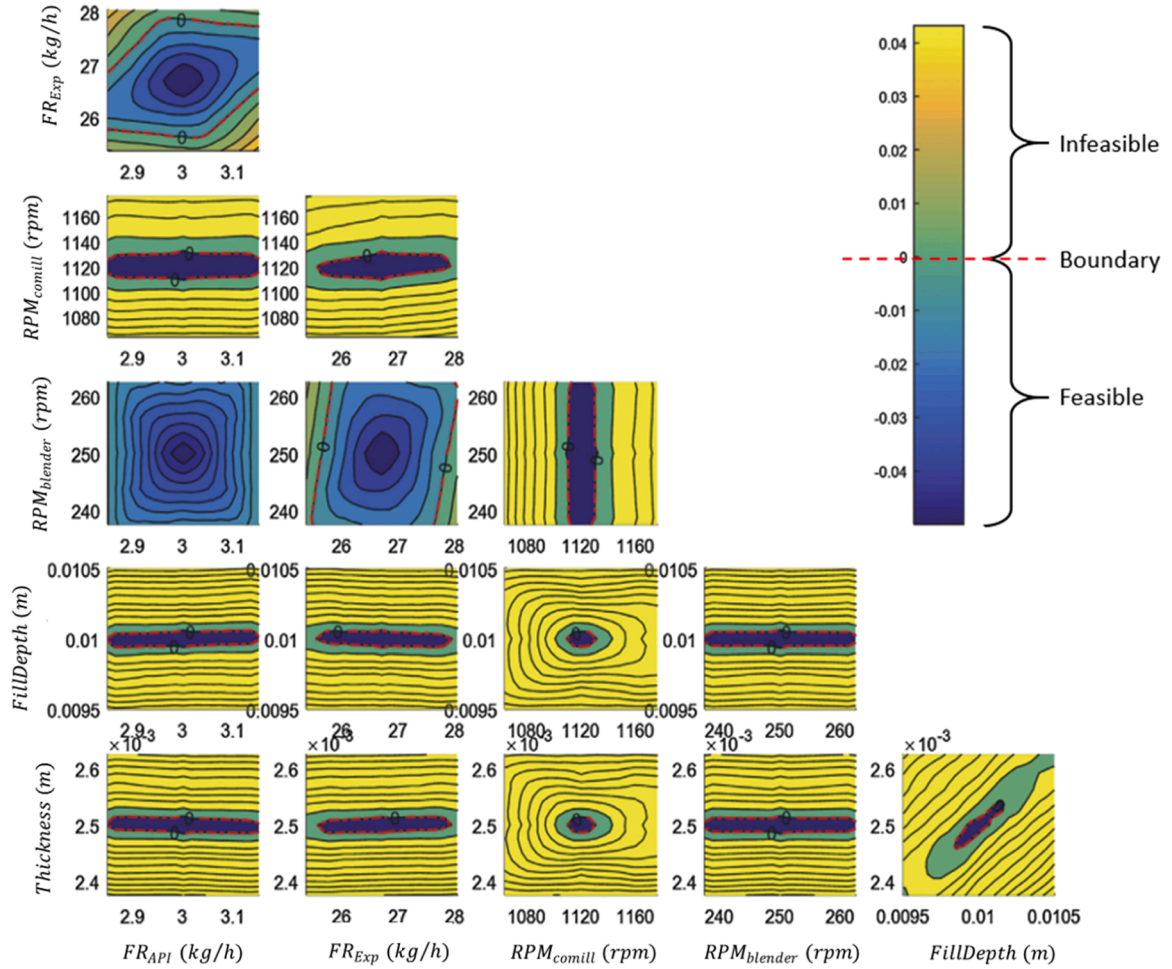


Fig. 3. Contour plots of the feasibility function of the DC manufacturing line (The red dotted line is the feasible region boundary. The area within the red dotted line is the feasible region with feasibility function values less than or equal to zero). Reproduced from (Wang et al., 2017).

4. Feasibility-based optimization

The feasibility-based optimization problem can be formulated as

$$\begin{aligned} \min & f(d, x) \\ \text{s.t. } & g(d, x) \leq 0 \\ & h(d, x) = 0 \end{aligned} \quad (16)$$

where $f(d, x)$ is the objective function. The aim is to identify the optimal set of input variables while satisfying the feasibility constraints.

As feasibility is essentially described by a set of constraints, feasibility-based optimization is to find the optimal solution of input parameters while satisfying all the constraints. This makes the feasibility-based optimization problem belong to the category of simulation-based optimization problems (Amaran et al., 2014) if, in general, the process model is considered as a simulation. So, it is possible to utilize plentiful approaches from the simulation-based optimization literature to solve feasibility-based optimization problems. The solution of simulation-based optimization has many challenges. First, mostly the simulation is only available as a black box for the evaluation of the objective function and constraints. Second, many simulations are computationally expensive to run, limiting the number of function evaluations that can be performed in search of the optimal solution. Third, the derivative information is usually unavailable or hard to estimate due to the computational burden and output noise. Thus, it becomes challenging to utilize the conventional optimization approaches such as derivative-based and random search methods. Surrogate models have been proposed to approximate the expensive function evaluations

and facilitate optimization (Bhosekar and Ierapetritou, 2018). One issue that needs to be considered is how to handle black-box feasibility and black-box objective function(s) in the surrogate-based optimization (SBO) framework, with a focus on balancing the sampling cost between feasibility characterization and objective improvement.

The first type of strategy is to consider both feasibility and optimization aspects together in one infill criterion. There have been both unconstrained and constrained formulations for the infill criteria to extend the efficient global optimization (EGO) framework (Jones et al., 1998). Bagheri et al. (2017) surveyed the existing constraint handling methods for EGO and modified the unconstrained method by introducing a newly defined probability of feasibility.

The second type of strategy is to design separate stages that focus on feasibility and optimization, respectively. For example, Basudhar et al. (2012) used the first stage to drive the optimization based on expected improvement (EI) function and probability of feasibility indicated by probabilistic SVM models, and the second stage to refine the constraint boundary approximation by selecting samples in sparse regions with a high probability of misclassification. Boukouvala and Ierapetritou (2014) proposed a novel expected improvement function for locating feasibility boundaries in the feasibility stage, followed by an optional global search stage and trust region-based local search stage.

The one-stage approach is expected to be more economical in terms of sampling cost as every sample is added with the consideration of both aspects. However, when the original function is complex, for example, when feasibility function is hard to approximate with a small number of samples, it will be beneficial to focus on feasibility refinement first and

then perform optimization within the feasible space. Therefore, there is a trade-off between sequential and simultaneous considerations of the two objectives depending on the nature of the problem.

Note that both approaches can be used to address the integration of uncertainty in the design and process operations problems and have found different applications. Wang and Ierapetritou (2018a) proposed a feasibility-enhanced EI function that considered objective and feasibility simultaneously for a stochastic direct compaction pharmaceutical manufacturing process. Wang et al. (2017) used penalized feasibility EI function and penalized EI function for the feasibility and optimization stage, respectively, for a deterministic pharmaceutical manufacturing process.

Again, as an illustration, Fig. 4 shows a flowchart of the two-stage feasibility-based optimization algorithm with the first stage to accurately characterize the feasible region and the second stage to identify the optimum within the feasible region.

The algorithm was applied to the DC manufacturing line (Wang et al., 2017). The input variables are “flow rate of API (FR_{API})” and “refill strategy of API (RS_{API})” because they are influential to the calculation of total costs as well as the generation of wasted products caused by temporal process variations. The objective function is the total operation cost, including material cost, utility cost and waste cost.

The termination condition is the total number of sampling points, which is 100 in the case study. After 20 initial sample points and 80 adaptive sampling points (40 for feasibility stage and 40 for optimization stage), the algorithm stops and returns an optimal solution listed in Table 2. The returned optimal solution suggests a low API flow rate and a less frequent refill strategy in order to reduce the overall total cost.

5. Optimization with flexibility requirements

Most existing works on flexibility analysis consider the flexibility test or flexibility index problem for a given design d . Yet often, optimizing the design while meeting certain flexibility requirements with respect to the uncertain parameters θ is of interest. This problem was formulated early on by Halemane and Grossmann (1983); however, surprisingly, it has not been widely applied in that form. In the following, the original approach proposed by Halemane and Grossmann (1983) is presented and its equivalence to robust optimization is shown. This equivalence can be exploited to develop alternative solution algorithms or extend the flexibility concept to new classes of problems.

Table 2

Optimization results for the DC. Reproduced from (Wang et al., 2017).

(lb ~ ub) [kg/h]	RS_{API} (lb ~ ub) [%]	$cost_{total}$ [\$ /day]
2.8774 (2.85 ~ 3.15)	27.09 (10 ~ 70)	98,175

5.1. Formulation with feasibility constraint

Halemane and Grossmann (1983) formulate the design under uncertainty problem as follows:

$$\min_d f_1(d) + \mathbb{E}_{\theta \in T} \left[\min_z \{f_2(d, z) : g(d, z, \theta) \leq 0\} \right] \quad (17a)$$

$$\text{s.t. } \max_{\theta \in T} \min_z \max_{j \in J} g_j(d, z, \theta) \leq 0 \quad (17b)$$

where f_1 and f_2 denote the (first-stage) design and (second-stage) operating costs, respectively. The objective is to minimize the total expected cost subject to the feasibility constraint given in (17b), i.e. it requires the solution to be feasible for all $\theta \in T$ given the flexibility in the control variables z that can be chosen after the realization of the uncertainty. Problem (17) is generally intractable due to the expectation term in the objective function; hence, Halemane and Grossmann (1983) approximate it using a set of discrete scenarios, which results in the following formulation:

$$\min_{d, \bar{z}} f_1(d) + \sum_{s \in S} p_s f_2(d, \bar{z}_s) \quad (18a)$$

$$\text{s.t. } g(d, \bar{z}_s, \bar{\theta}_s) \leq 0 \quad \forall s \in S \quad (18b)$$

$$\max_{\theta \in T} \min_z \max_{j \in J} g_j(d, z, \theta) \leq 0 \quad (18c)$$

where S denotes the set of scenarios. Each scenario $s \in S$ is defined by a specific realization of the uncertainty $\bar{\theta}_s$ and the corresponding probability p_s . The control decisions for scenario s are denoted by $\bar{z}_s$, which must be feasible given $\bar{\theta}_s$, which is enforced by constraints (18b).

To solve problem (18), Halemane and Grossmann (1983) developed an algorithm that first formulates a master problem which is (18) but with the feasibility constraint (18c) replaced by constraints over a finite set of critical points C (each point c being a possible realization of the uncertainty denoted by θ_c), i.e.

$$g(d, z_c, \theta_c) \leq 0 \quad \forall c \in C. \quad (19)$$

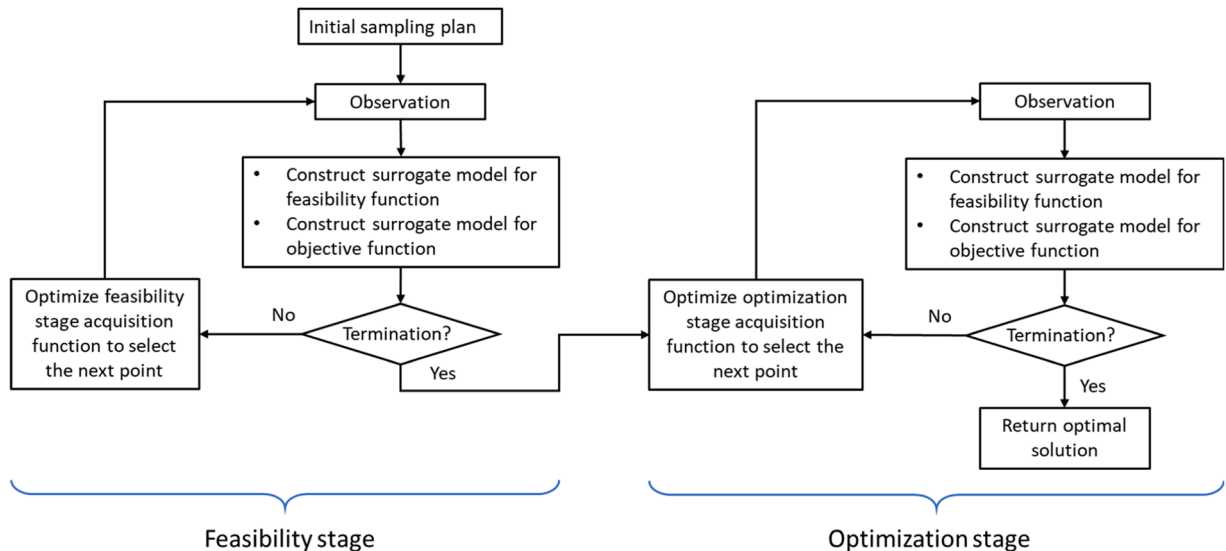


Fig. 4. Flowchart of the two-stage feasibility-based optimization algorithm. Reproduced from (Wang et al., 2017).

As shown in Fig. 5, the master problem is solved to obtain a design d . Then, the flexibility test problem is solved for the proposed design to check if the feasibility constraint is satisfied. If it is not yet feasible, the solution of the flexibility test problem provides a new critical point that can be added to C after which the master problem is re-solved. The algorithm iterates between the master and the flexibility test problem until the feasibility constraint is satisfied at which point the obtained design d is the optimal solution to problem (18).

Note that without the feasibility constraint (18c), problem (18) becomes a standard scenario-based two-stage stochastic program. In fact, this is the most common variant of (18) that is used in the literature for process design under uncertainty (Grossmann et al., 2016; Steimel and Engell, 2015; Zhou et al., 2013). However, while a two-stage stochastic program with a sufficiently large scenario set can provide a good approximation of problem (18), it can generally not guarantee that the solution is feasible for all $\theta \in T$. Further note that design problems of the form (18) can in theory also be solved using feasibility-based optimization (see Section 4), which focuses on the black-box setting.

5.2. Relationship to robust optimization

There is a close relationship between flexibility analysis and robust optimization (Ben-Tal et al., 2009), which was independently developed in the operations research community. This relationship was first formally established for linear optimization problems in (Zhang et al., 2016). It was shown that the flexibility index problem can be formulated as a two-stage robust optimization problem, where $T(\delta)$ represents the so-called uncertainty set. Recently, alternative definitions of the flexibility index based on uncertainty sets with shapes other than a hyperbox have been proposed (Pulsipher et al., 2019), many of which are drawn from the robust optimization literature.

Problem (18) is a robust optimization problem; however, the feasibility constraint (18c) is more commonly expressed in the robust optimization literature as follows:

$$g(d, z(\theta), \theta) \leq 0 \quad \forall \theta \in T \quad (20)$$

where the notation $z(\theta)$ indicates that the control variables z can be chosen after the realization of the uncertainty and hence are functions of

θ . Initial works in robust optimization, especially in PSE (Li et al., 2011; Li and Ierapetritou, 2008; Lin et al., 2004), only considered the static case in which z are constant, which is rather limiting compared to the flexibility analysis approach. This changed with the introduction of *adjustable* robust optimization (Ben-Tal et al., 2004), which incorporates recourse. Another possible reason for why problem (18) for a long time has not been recognized as a robust optimization problem is that robust optimization problems are typically formulated to optimize the worst case. In the design problem, it would lead to the following formulation:

$$\min_{d, z(\cdot)} f_1(d) + \max_{\theta \in T} f_2(d, z(\theta)) \quad (21a)$$

$$\text{s.t. } g(d, z(\theta), \theta) \leq 0 \quad \forall \theta \in T. \quad (21b)$$

The worst-case objective function avoids the use of a possibly large set of scenarios to approximate the expected cost and the associated potential computational challenges. However, conceptually, there is nothing that prevents us from using the same objective function as in problem (18) in a robust optimization formulation. In fact, in many settings, that may be the more appropriate choice.

The most popular approach to solving problem (21) is the column-and-constraint generation algorithm (Zeng and Zhao, 2013). Interestingly, this is essentially the same algorithm as the one proposed by Halemane and Grossmann (1983) three decades earlier.

It is also worth mentioning that flexibility analysis was developed for general nonlinear optimization problems whereas robust optimization has mainly been applied to linear and mixed-integer linear programs, where many of the solution approaches rely on linear programming duality. More recently, advances have been made in nonlinear robust optimization (Isenberg et al., 2021; Leyffer et al., 2020; Yuan et al., 2018), leading to further convergence between the flexibility analysis and robust optimization approaches.

5.3. The role of endogenous uncertainty

The robust optimization formulation of the flexibility index problem involves endogenous (i.e. decision-dependent) uncertainty since the uncertainty set $T(\delta)$ depends on the decision variable δ . While Zhang et al. (2016) show that one can obtain a tractable reformulation with a fixed uncertainty set if $T(\delta)$ is a hyperbox and the problem is convex, more involved solution methods are needed for more complex uncertainty sets. In recent years, there has been a growing interest in robust optimization with endogenous uncertainty (Lappas and Gounaris, 2018; Zhang and Feng, 2020), which could be leveraged to extend flexibility analysis to broader classes of problems. For example, the design problem (18) could be extended to incorporate an uncertainty set $T(\delta)$ with variable size δ ; this would allow us to determine a design that maximizes flexibility, i.e. maximize δ , or balances cost and flexibility.

5.4. Extension to multistage problems and discrete recourse

Design optimization with flexibility requirements gives rise to two-stage robust optimization problems where the control variables z are the second-stage decisions. When extending the flexibility concept to operational or planning problems, often multiple stages of decision making are involved, where uncertainty is realized and recourse decisions can be taken at multiple time points. Significant advances have been made in recent years in multistage robust optimization with applications in PSE (Lappas and Gounaris, 2016; Shang and You, 2019; Zhang et al., 2016). Here, the decision rule approach (Georghiou et al., 2018) has proven to be very effective, where the recourse variables are explicitly stated as functions of the uncertain parameters. For example, the following decision rule defines the recourse variables at time t , z_t , as an affine function of all uncertain parameters realized up to time t , i.e. θ_k where $k \leq t$:

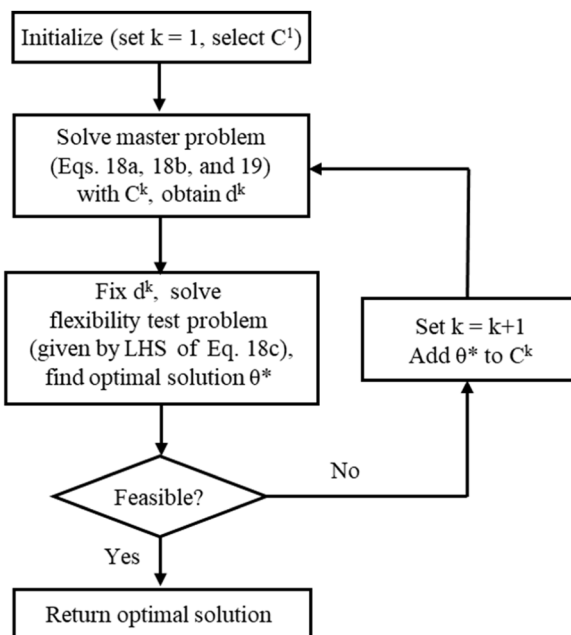


Fig. 5. Algorithm proposed by Halemane and Grossmann (1983) for solving the design under uncertainty problem with feasibility constraints.

$$z_t = p_t + \sum_{k=1}^t Q_{tk} \theta_k. \quad (22)$$

Such a decision rule inherently satisfies nonanticipativity and can be applied to problems with arbitrarily many stages. Importantly, the recourse decisions are now specified by the variables p and Q , which can be chosen before the actual realization of the uncertainty. As such, all methods for static robust optimization can be applied to solve decision-rule-based multistage robust optimization problems. Note that in general, decision rules only approximate the fully adjustable recourse decisions; however, they are highly effective as they typically lead to solutions that are very close to the true optimum while being much more tractable. As such, they can also be used to solve problem (21) approximately (Zhang et al., 2016).

Figs. 6 and 7 show some results from a multistage robust optimization problem that considers the scheduling of a cryogenic air separation plant over a one-week time horizon with an hourly time discretization (Zhang et al., 2016). The plant operates under time-sensitive electricity prices and also has the opportunity to sell interruptible load to the electricity reserve market. Interruptible load is operating reserve that electricity consumers can provide by reducing (interrupting) their load when power demand exceeds supply in the grid. In that case, the grid operator can request from the electricity consumer a load reduction up to the committed amount of interruptible load; however, it is uncertain when and how much load reduction will be requested by the grid operator. One must decide at the beginning of the scheduling horizon how much interruptible load the plant will provide. Then, in each time period, the plant operation can be adjusted depending on the realized load reduction request. Therefore, recourse can be taken in every time period, resulting in a problem with 169 stages.

Fig. 6 shows the liquid oxygen flows and inventory profile in the base case where no interruptible load is provided and, consequently, there is no uncertainty in the problem. Positive columns indicate accumulation of products, and negative columns (demand) indicate depletion of products. Fig. 7 shows the target liquid oxygen flows and inventory profile, where “target” refers to the case in which no load reduction is ever requested during the scheduling horizon. In addition, the green columns in Fig. 7 represent the cumulative recourse actions in terms of changes in production and purchase rates. Negative production recourse indicates time periods in which interruptible load is provided. One can see that most of the lost production is made up by increasing production after load reduction (positive production recourse). It was shown that significant financial benefits can be achieved by providing interruptible load, even when making rather conservative assumptions about the uncertainty in load reduction. Further, it can be noted that the target inventory levels are, in general, higher in Fig. 7 compared to Fig. 6, highlighting the utilization of flexibility in the plant when providing interruptible load.

Another important extension is the incorporation of mixed-integer recourse variables, which can similarly be achieved using decision rules albeit more complex ones (Feng et al., 2021; Nasab and Li, 2021).

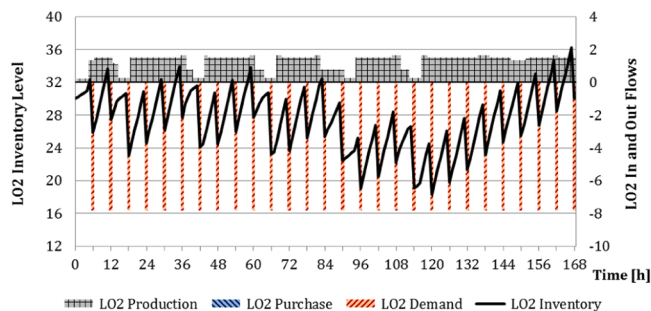


Fig. 6. Liquid oxygen flows and inventory profile when no interruptible load is provided. Reproduced from (Zhang et al., 2016).

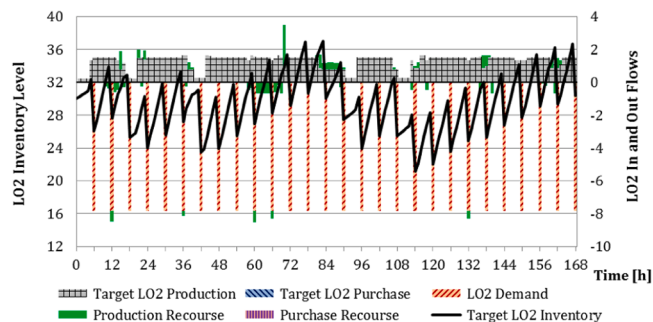


Fig. 7. Target and recourse liquid oxygen flows, and target inventory profile when interruptible load is provided. Reproduced from (Zhang et al., 2016).

Depending on the application, the flexibility of mixed-integer recourse can lead to significant performance improvements compared to only having continuous recourse (Jagana et al., 2023). Other approaches for considering discrete recourse in robust optimization include K -adaptability (Subramanyam et al., 2020) and (Postek and Hertog, 2016).

Conclusions

In this paper, the concepts of process feasibility and flexibility are highlighted, and ideas of evaluating and integrating those within process design optimization and process operations are described. Process feasibility describes the feasible space of process operation, which is determined by multiple process and product constraints. The characterization of the feasible space provides complete and accurate evaluation of process-critical parameters to ensure product quality. It also reveals a degree of flexibility of process operations since feasible operation can be achieved in the entire feasible region instead of only the nominal point. Feasibility is a very practical concept. It has been widely studied and applied in many industrial problems. An example is the design space evaluation for pharmaceutical manufacturing processes. Utilizing the ideas of surrogate-based feasibility analysis, feasibility-based optimization has been utilized to address simulation-based optimization problems. The constraints are integrated within the feasibility function and explicitly handled. A two-stage algorithm has been shown to perform effectively for a variety of different applications and reviewed in this perspective.

Given uncertainty in model parameters, it is often desired (or necessary) to perform process design optimization that satisfies certain flexibility requirements with respect to the uncertain parameters. This problem, initially introduced by the PSE community in the flexibility analysis literature, can be shown to be equivalent to a two-stage robust optimization problem, which has been extensively studied in the Operations Research community. This motivates the exchange of solution strategies from these two areas to solve complex problems of this kind. One such example is the efficient approximate modeling of recourse variables using decision rules, which can also be extended to the multistage case that is often more relevant in a process operations context. The effectiveness of this approach is demonstrated in a process scheduling problem involving a power-intensive chemical plant that operates under time-varying electricity prices and provides interruptible load to the power grid, where the load reduction requested by the grid operator in each time period is uncertain. More opportunities remain in the integration of flexibility analysis and robust optimization approaches, e.g. in the design of processes with maximum flexibility, which can be formulated as a problem with a decision-dependent uncertainty set.

CRediT authorship contribution statement

Huayu Tian: Conceptualization, Methodology, Software, Writing –

original draft, Writing – review & editing. **Jnana Sai Jagana**: Conceptualization, Methodology, Software, Writing – review & editing. **Qi Zhang**: Conceptualization, Supervision, Writing – review & editing. **Marianthi Ierapetritou**: Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no competing financial interests or personal relationships that could have influenced the work reported in this manuscript.

Data availability

No data was used for the research described in the article.

Acknowledgments

The authors would like to acknowledge financial support from the US Food and Drug Administration through Grant FDABAA-20-00123 and the US National Science Foundation through Grant #2215526.

References

- Adi, V.S.K., Laxmidewi, R., Chang, C.-T., 2016. An effective computation strategy for assessing operational flexibility of high-dimensional systems with complicated feasible regions. *Chem. Eng. Sci.* 147, 137–149.
- Amaran, S., Sahinidis, N.V., Sharda, B., Bury, S.J., 2014. Simulation optimization: a review of algorithms and applications. *4OR - Q. J. Oper. Res.* 12, 301–333.
- Ankenman, B., Nelson, B.L., Staum, J., 2010. Stochastic Kriging for simulation metamodeling. *Oper. Res.* 58, 371–382.
- Badejo, O., Ierapetritou, M., 2022. Integrating tactical planning, operational planning and scheduling using data-driven feasibility analysis. *Comput. Chem. Eng.* 161.
- Bagheri, S., Konen, W., Allmendinger, R., Branke, J., Deb, K., Fieldsend, J., Quagliarella, D., Sindhya, K., 2017. Constraint handling in efficient global optimization. In: *Proceedings of the Genetic and Evolutionary Computation Conference*, pp. 673–680.
- Banerjee, I., Ierapetritou, M., 2005. Feasibility evaluation of nonconvex systems using shape reconstruction techniques. *Ind. Eng. Chem. Res.* 44, 3638–3647.
- Banerjee, I., Ierapetritou, M.G., 2004. Model independent parametric decision making. *Ann Oper Res* 132, 135–155.
- Banerjee, I., Pal, S., Maiti, S., 2010. Computationally efficient black-box modeling for feasibility analysis. *Comput. Chem. Eng.* 34, 1515–1521.
- Bano, G., Facco, P., Bezze, F., Barolo, M., 2018a. Probabilistic Design space determination in pharmaceutical product development: a Bayesian/latent variable approach. *AIChE J.* 64, 2438–2449.
- Bano, G., Facco, P., Ierapetritou, M., Bezze, F., Barolo, M., 2019. Design space maintenance by online model adaptation in pharmaceutical manufacturing. *Comput. Chem. Eng.* 127, 254–271.
- Bano, G., Wang, Z., Facco, P., Bezze, F., Barolo, M., Ierapetritou, M., 2018b. A novel and systematic approach to identify the design space of pharmaceutical processes. *Comput. Chem. Eng.* 115, 309–322.
- Bansal, V., Perkins, J.D., & Pistikopoulos, E.N. (2002). Flexibility analysis and design using a parametric programming framework. *48*, 2851–2868.
- Basudhar, A., Dribusch, C., Lacaze, S., Missoum, S., 2012. Constrained efficient global optimization with support vector machines. *Struct. Multidiscip. Optim.* 46, 201–221.
- Bates, R.A., Wynn, H.P., Fraga, E.S., 2007. Feasible region approximation: a comparison of search cone and convex hull methods. *Eng. Optim.* 39, 513–527.
- Ben-Tal, A., El Ghaoui, L., Nemirovski, A., 2009. *Robust Optimization*, 28. Princeton University Press. Vol.
- Ben-Tal, A., Goryashko, A., Guslitzer, E., Nemirovski, A., 2004. Adjustable robust solutions of uncertain linear programs. *Math. Program.* 99, 351–376.
- Bhosekar, A., Ierapetritou, M., 2018. Advances in surrogate based modeling, feasibility analysis, and optimization: a review. *Comput. Chem. Eng.* 108, 250–267.
- Biegler, L.T., Grossmann, I.E., Westerberg, A.W., 1997. *Systematic Methods of Chemical Process Design*. Prentice Hall PTR.
- Boukouvala, F., 2013. *Integrated Simulation and Optimization of Continuous Pharmaceutical Manufacturing*. Rutgers. The State University of New Jersey, New Brunswick, New Jersey.
- Boukouvala, F., Ierapetritou, M.G., 2012. Feasibility analysis of black-box processes using an adaptive sampling Kriging-based method. *Comput. Chem. Eng.* 36, 358–368.
- Boukouvala, F., Ierapetritou, M.G., 2014. Derivative-free optimization for expensive constrained problems using a novel expected improvement objective function. *AIChE J.* 60, 2462–2474.
- Castagnoli, C., Yahyah, M., Cimarosti, Z., Peterson, J.J., 2010. Application of quality by design principles for the definition of a robust crystallization process for casopitant mesylate. *Org. Process Res. Dev.* 14, 1407–1419.
- Chatzizacharia, K.A., Hatziaavramidis, D.T., 2014. Design space approach for pharmaceutical tablet development. *Ind. Eng. Chem. Res.* 53, 12003–12009.
- Dias, L.S., Ierapetritou, M.G., 2019. Data-driven feasibility analysis for the integration of planning and scheduling problems. *Optim. Eng.* 20, 1029–1066.
- Dimitriadis, V.D., Pistikopoulos, E.N., 1995. Flexibility analysis of dynamic systems. *Ind. Eng. Chem. Res.* 34, 4451–4462.
- Ding, C., Ierapetritou, M., 2021. A novel framework of surrogate-based feasibility analysis for establishing design space of twin-column continuous chromatography. *Int. J. Pharm.* 609, 121161.
- Facco, P., Dal Pastro, F., Meneghetti, N., Bezze, F., Barolo, M., 2015. Bracketing the design space within the knowledge space in pharmaceutical product development. *Ind. Eng. Chem. Res.* 54, 5128–5138.
- Feng, W., Feng, Y., Zhang, Q., 2021. Multistage robust mixed-integer optimization under endogenous uncertainty. *Eur. J. Oper. Res.* 294, 460–475.
- Figueroa, I., Vaidyaraman, S., Viswanath, S., 2013. Model-based scale-up and design space determination for a batch reactive distillation with a dean-stark trap. *Org. Process Res. Dev.* 17, 1300–1310.
- García-Muñoz, S., Dolph, S., Ward, H.W., 2010. Handling uncertainty in the establishment of a design space for the manufacture of a pharmaceutical product. *Comput. Chem. Eng.* 34, 1098–1107.
- García-Muñoz, S., Luciani, C.V., Vaidyaraman, S., Seibert, K.D., 2015. Definition of design spaces using mechanistic models and geometric projections of probability maps. *Org. Process Res. Dev.* 19, 1012–1023.
- Gazzaneo, V., Carrasco, J.C., Vinson, D.R., Lima, F.V., 2019. Process operability algorithms: past, present, and future developments. *Ind. Eng. Chem. Res.* 59, 2457–2470.
- Georghiou, A., Kuhn, D., Wiesemann, W., 2018. The decision rule approach to optimization under uncertainty: methodology and applications. *Computat. Manag. Sci.* 16, 545–576.
- Goyal, V., Ierapetritou, M., 2002. Determination of operability limits using simplicial approximation. *AIChE J.* 48, 2902–2909.
- Grossmann, I.E., Apap, R.M., Calfa, B.A., García-Herreros, P., Zhang, Q., 2016. Recent advances in mathematical programming techniques for the optimization of process systems under uncertainty. *Comput. Chem. Eng.* 91, 3–14.
- Grossmann, I.E., Calfa, B.A., García-Herreros, P., 2014. Evolution of concepts and models for quantifying resiliency and flexibility of chemical processes. *Comput. Chem. Eng.* 70, 22–34.
- Grossmann, I.E., Floudas, C.A., 1987. Active constraint strategy for flexibility analysis in chemical processes. *Comput. Chem. Eng.* 11, 675–693.
- Halemane, K.P., Grossmann, I.E., 1983. Optimal process design under uncertainty. *AIChE J.* 29, 425–433.
- Hirono, K., A., Udagama, I., Hayashi, Y., Kino-oka, M., Sugiyama, H., 2022. A dynamic and probabilistic design space determination method for mesenchymal stem cell cultivation processes. *Ind. Eng. Chem. Res.* 61, 7009–7019.
- ICH. (2009). Q8(R2) Pharmaceutical Development. In.
- Ierapetritou, M.G., 2001. New approach for quantifying process feasibility: convex and 1-D quasi-convex regions. *AIChE J.* 47, 1407–1417.
- Isenberg, N.M., Akula, P., Eslick, J.C., Bhattacharyya, D., Miller, D.C., & Gounaris, C.E. (2021). A generalized cutting-set approach for nonlinear robust optimization in process systems engineering. *67*, e17175.
- Jagana, J.S., Amaran, S., Zhang, Q., 2023. Mixed-integer recourse in industrial demand response scheduling with interruptible load. In: *Proceedings of the 33rd European Symposium on Computer Aided Process Engineering*.
- Jones, D.R., Schonlau, M., Welch, W.J., 1998. Efficient global optimization of expensive black-box functions. *J. Global Optim.* 13, 455–492.
- Kotidis, P., Demis, P., Goey, C.H., Correa, E., McIntosh, C., Trepekli, S., Shah, N., Klymenko, O.V., Kontoravdi, C., 2019. Constrained global sensitivity analysis for bioprocess design space identification. *Comput. Chem. Eng.* 125, 558–568.
- Kucherenko, S., Giamalakakis, D., Shah, N., García-Muñoz, S., 2020. Computationally efficient identification of probabilistic design spaces through application of metamodeling and adaptive sampling. *Comput. Chem. Eng.* 132.
- Kusumo, K.P., Gomoescu, L., Paulen, R., García Muñoz, S., Pantelides, C.C., Shah, N., Chachuat, B., 2019. Bayesian approach to probabilistic design space characterization: a nested sampling strategy. *Ind. Eng. Chem. Res.* 59, 2396–2408.
- Lai, S.M., Hui, C.-W., 2008. Process flexibility for multivariable systems. *Ind. Eng. Chem. Res.* 47, 4170–4183.
- Laky, D., Xu, S., Rodriguez, J., Vaidyaraman, S., García Muñoz, S., Laird, C., 2019. An optimization-based framework to define the probabilistic design space of pharmaceutical processes with model uncertainty. *Processes* 7.
- Lappas, N.H., Gounaris, C.E., 2016. Multi-stage adjustable robust optimization for process scheduling under uncertainty. *AIChE J.* 62, 1646–1667.
- Lappas, N.H., Gounaris, C.E., 2018. Robust optimization for decision-making under endogenous uncertainty. *Comput. Chem. Eng.* 111, 252–266.
- Lebrun, P., Boulanger, B., Debrus, B., Lambert, P., Hubert, P., 2013. A Bayesian design space for analytical methods based on multivariate models and predictions. *J. Biopharm. Stat.* 23, 1330–1351.
- Lebrun, P., Krier, F., Mantanus, J., Grohgan, H., Yang, M., Rozet, E., Boulanger, B., Evrard, B., Rantanen, J., Hubert, P., 2012. Design space approach in the optimization of the spray-drying process. *Eur. J. Pharm. Biopharm.* 80, 226–234.
- Leyffer, S., Menickelly, M., Munson, T., Vanaret, C., Wild, S.M., 2020. A survey of nonlinear robust optimization. *INFOR: Inf. Syst. Oper. Res.* 58, 342–373.

- Li, Z., Ding, R., Floudas, C.A., 2011. A comparative theoretical and computational study on robust counterpart optimization: I. robust linear optimization and robust mixed integer linear optimization. *Ind. Eng. Chem. Res.* 50, 10567–10603.
- Li, Z., Ierapetritou, M.G., 2008. Robust optimization for process scheduling under uncertainty. *Ind. Eng. Chem. Res.* 47, 4148–4157.
- Lima, F.V., Jia, Z., Ierapetritou, M., Georgakis, C., 2009. Similarities and differences between the concepts of operability and flexibility: the steady-state case. *AIChE J. NA-NA*.
- Lin, X., Janak, S.L., Floudas, C.A., 2004. pdf A new robust optimization approach for scheduling under uncertainty. *Comput. Chem. Eng.* 28, 1069–1085.
- Metta, N., Ramachandran, R., Ierapetritou, M., 2020. A novel adaptive sampling based methodology for feasible region identification of compute intensive models using artificial neural network. *AIChE J.* 67.
- Mortier, S., Van Bockstal, P.J., Corver, J., Nopens, I., Gernaey, K.V., De Beer, T., 2016. Uncertainty analysis as essential step in the establishment of the dynamic Design Space of primary drying during freeze-drying. *Eur. J. Pharm. Biopharm.* 103, 71–83.
- Nasab, F.M., Li, Z., 2021. Multistage adaptive stochastic mixed integer optimization through piecewise decision rule approximation. *Comput. Chem. Eng.* 149, 107286.
- Peterson, J.J., 2008. A Bayesian approach to the ICH Q8 definition of design space. *J. Biopharm. Stat.* 18, 959–975.
- Peterson, J.J., Miró-Quesada, G., del Castillo, E., 2009. A Bayesian reliability approach to multiple response optimization with seemingly unrelated regression models. *Qual. Technol. Quant. Manag.* 6, 353–369.
- Pistikopoulos, E.N., Mazzuchi, T.A., 1990. A novel flexibility analysis approach for processes with stochastic parameters. *Comput. Chem. Eng.* 14, 991–1000.
- Postek, K., & Hertog, D.d. (2016). Multistage adjustable robust mixed-integer optimization via iterative splitting of the uncertainty set. 28, 553–574.
- Pulsipher, J.L., Rios, D., Zavala, V.M., 2019. A computational framework for quantifying and analyzing system flexibility. *Comput. Chem. Eng.* 126, 342–355.
- Rogers, A., Ierapetritou, M., 2015. Feasibility and flexibility analysis of black-box processes Part I: surrogate-based feasibility analysis. *Chem. Eng. Sci.* 137, 986–1004.
- Rooney, W.C., Biegler, L.T., 2001. Design for model parameter uncertainty using nonlinear confidence regions. *AIChE J.* 47, 1794–1804.
- Shang, C., You, F., 2019. A data-driven robust optimization approach to scenario-based stochastic model predictive control. *J. Process Control* 75, 24–39.
- Steimel, J., Engell, S., 2015. Conceptual design and optimization of chemical processes under uncertainty by two-stage programming. *Comput. Chem. Eng.* 81, 200–217.
- Stockdale, G.W., Cheng, A., 2016. Finding design space and a reliable operating region using a multivariate Bayesian approach with experimental design. *Qual. Technol. Quant. Manag.* 6, 391–408.
- Straub, D.A., Grossmann, I.E., 1990. Integrated stochastic metric of flexibility for systems with discrete state and continuous parameter uncertainties. *Comput. Chem. Eng.* 14, 967–985.
- Su, Q., Ganesh, S., Moreno, M., Bommireddy, Y., Gonzalez, M., Reklaitis, G.V., Nagy, Z. K., 2019. A perspective on Quality-by-Control (QbC) in pharmaceutical continuous manufacturing. *Comput. Chem. Eng.* 125, 216–231.
- Subramanyam, A., Gounaris, C.E., Wiesemann, W., 2020. K-adaptability in two-stage mixed-integer robust optimization. *Math. Program. Comput.* 12, 193–224.
- Swaney, R.E., Grossmann, I.E., 1985a. An index for operational flexibility in chemical process design. Part I: formulation and theory. *AIChE J.* 31, 621–630.
- Swaney, R.E., Grossmann, I.E., 1985b. An index for operational flexibility in chemical process design. Part II: computational algorithms. *AIChE J.* 31, 631–641.
- Tabora, J.E., Lora Gonzalez, F., Tom, J.W., 2019. Bayesian probabilistic modeling in pharmaceutical process development. *AIChE J.* 65.
- Van Bockstal, P.J., Mortier, S., Corver, J., Nopens, I., Gernaey, K.V., De Beer, T., 2017. Quantitative risk assessment via uncertainty analysis in combination with error propagation for the determination of the dynamic Design Space of the primary drying step during freeze-drying. *Eur. J. Pharm. Biopharm.* 121, 32–41.
- von Stosch, M., Schenkendorf, R., Geldhof, G., Varsakelis, C., Mariti, M., Dessoy, S., Vandercammen, A., Pysik, A., Sanders, M., 2020. Working within the design space: do our static process characterization methods suffice? *Pharmaceutics* 12.
- Wang, Z., Escotet-Espinoza, M.S., Ierapetritou, M., 2017a. Process analysis and optimization of continuous pharmaceutical manufacturing using flowsheet models. *Comput. Chem. Eng.* 107, 77–91.
- Wang, Z., Escotet-Espinoza, S., Singh, R., Ierapetritou, M., 2017b. Surrogate-based Optimization for Pharmaceutical Manufacturing Processes. In: 27th European Symposium on Computer Aided Process Engineering, pp. 2797–2802.
- Wang, Z., Ierapetritou, M., 2017. A novel feasibility analysis method for black-box processes using a radial basis function adaptive sampling approach. *AIChE J.* 63, 532–550.
- Wang, Z., Ierapetritou, M., 2018a. Constrained optimization of black-box stochastic systems using a novel feasibility enhanced Kriging-based method. *Comput. Chem. Eng.* 118, 210–223.
- Wang, Z., Ierapetritou, M., 2018b. Surrogate-based feasibility analysis for black-box stochastic simulations with heteroscedastic noise. *J. Global Optim.* 71, 957–985.
- Yuan, Y., Li, Z., & Huang, B. (2018). Nonlinear robust optimization for process design. 64, 481–494.
- Zeng, B., Zhao, L., 2013. Solving two-stage robust optimization problems using a column-and-constraint generation method. *Oper. Res. Lett.* 41, 457–461.
- Zhang, Q., Feng, W., 2020. A unified framework for adjustable robust optimization with endogenous uncertainty. *AIChE J.* 66.
- Zhang, Q., Grossmann, I.E., Lima, R.M., 2016a. On the relation between flexibility analysis and robust optimization for linear systems. *AIChE J.* 62, 3109–3123.
- Zhang, Q., Morari, M.F., Grossmann, I.E., Sundaramoorthy, A., Pinto, J.M., 2016b. An adjustable robust optimization approach to scheduling of continuous industrial processes providing interruptible load. *Comput. Chem. Eng.* 86, 106–119.
- Zhao, F., Chen, X., 2018. Analytical and triangular solutions to operational flexibility analysis using quantifier elimination. *AIChE J.* 64, 3894–3911.
- Zheng, C., Zhao, F., Zhu, L., Chen, X., 2021. Analytical solution of volumetric flexibility through symbolic computation. *Chem. Eng. Sci.* 239.
- Zhou, Z., Zhang, J., Liu, P., Li, Z., Georgiadis, M.C., Pistikopoulos, E.N., 2013. A two-stage stochastic programming model for the optimal design of distributed energy systems. *Appl. Energy* 103, 135–144.
- Žilinskas, A., Fraga, E.S., Mackutė, A., 2006. Data analysis and visualisation for robust multi-criteria process optimisation. *Comput. Chem. Eng.* 30, 1061–1071.