Advanced Modeling and Optimization Strategies for Process Synthesis

Efstratios N. Pistikopoulos[1,2] and Yuhe Tian[3]

[1]Texas A&M Energy Institute, Texas A&M University, College Station, TX 77843; email: stratos@tamu.edu

[2]Artie McFerrin Department of Chemical Engineering, Texas A&M University, College Station, TX 77843

[3]Department of Chemical and Biomedical Engineering, West Virginia University, Morgantown, WV 26506; email: yuhe.tian@mail.wvu.edu

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Abstract

This article provides a systematic review on recent progress in optimization-based process synthesis. We first discuss the multi-scale modeling frameworks featuring targeting approaches, phenomena-based modeling, unit operation-based modeling, and hybrid modeling. Next, we present the expanded scope of process synthesis objectives highlighting the considerations of sustainability and operability to assure cost-competitive production in the current increasingly dynamic market with growing environmental awareness. Advances in optimization algorithms and tools are then reviewed, including the emerging machine learning and quantum computing-assisted approaches. The article concludes by summarizing the advances and perspectives for process synthesis strategies.

Contents

1. INTRODUCTION

Conceptual process design plays a critical role toward creating innovative chemical plants from an early stage. As shown in **Figure 1**, the typical conceptual process design procedure consists of defining the general chemical production problem, synthesizing process design solutions, analyzing and evaluating the designs (1). The step of process design synthesis is of particular importance which aims to select the optimal unit operations with optimal operating conditions and stream interconnections at the systems level (2). This is a challenging task considering the plethora of plausible unit operations and flowsheets which have been investigated in process systems and chemical engineering.

Process synthesis approaches can be generally categorized into knowledge-based methods, optimization-based methods, and hybrid knowledge/optimization methods. The hierarchical decision procedure introduced by Douglas (3) is one of the most classic knowledge-based methods and widely adapted in process design teaching and training. Guided by a

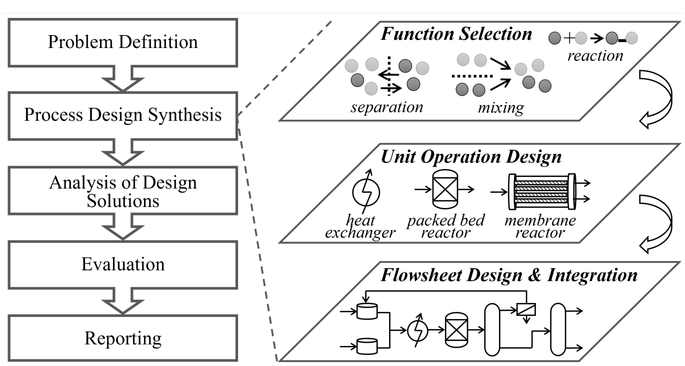

Figure 1

Procedure of conceptual process design with bottom-up synthesis.

series of heuristic rules, it offers a top-down approach to successively select the overall process input-output structure, recovery streams, and reactor and separator designs. Process synthesis can also be performed in a bottom-up manner (4), i.e. the basic physicochemical functions can be first determined followed by defining unit operations and flowsheets to carry out the functions (**Figure 1**). Process intensification will be achieved if multiple functions are integrated into a single unit operation (5). An example of knowledge-based function-oriented process synthesis and intensification approach is the means-ends analysis developed by Siirola (6). However, as process systems become larger with increasing complexity and interactions, heuristic-driven process design more often arrives at sub-optimal solutions without exploiting the full potential of process improvements.

Optimization-based methods employ mathematical programming to synthesize process designs based on a superstructure containing all the plausible unit operations and flowsheet structural alternatives of interest (7). These methods can provide a quantitative, systematic, and comprehensive outlook at the process systems level. Their potential and efficacy have been demonstrated in many chemical and energy systems leading to notable cost and energy savings (8), while challenges remain in the algorithmic, modeling, and tool developments before realizing widespread applications in industrial settings. For examples, the request for users to develop an all-inclusive superstructure specific to each design problem, the limited capability for systematic process intensification and innovation, the complexity to solve the resulting large-scale optimization models, and the lack of a well-accepted commercial software to automate process synthesis.

The last several years, however, have witnessed exciting progress in optimization-based process synthesis approaches (9, 10) which is also stimulated by the burgeoning scientific computing capabilities such as machine learning and quantum computing (11, 12). This article aims to review the recent advances in this area from the following aspects: Section 2 presents the multi-scale modeling frameworks for process synthesis, comprising targeting approaches, phenomena-based modeling, unit operation-based modeling, and, more recently, hybrid modeling. Section 3 briefs the expanded process synthesis objectives for sustainable and operable production. Section 4 reviews optimization algorithms and tools including the new developments aided by machine learning and quantum computing. Section 5 summarizes the challenges and opportunities.

2. PROCESS SYNTHESIS MODELING FRAMEWORKS

In this section, we present various types of modeling frameworks to represent chemical processes. We also highlight their methodological interactions and synergies toward a multi-scale process synthesis strategy.

2.1. Targeting Approaches

Given a chemical production problem with available raw materials, kinetic routes (and desired products), a first question is how good the process can be even before establishing any specific design configurations. To this purpose, generic thermodynamic and/or kinetic laws are normally utilized to identify the best possible performance targets against productivity, economics, energy use, carbon emissions, etc.

Attainable region (AR) theory is a representative class of targeting approaches, originated from reaction engineering by Horn (15). As illustrated in **Figure 2a**, AR for steady-

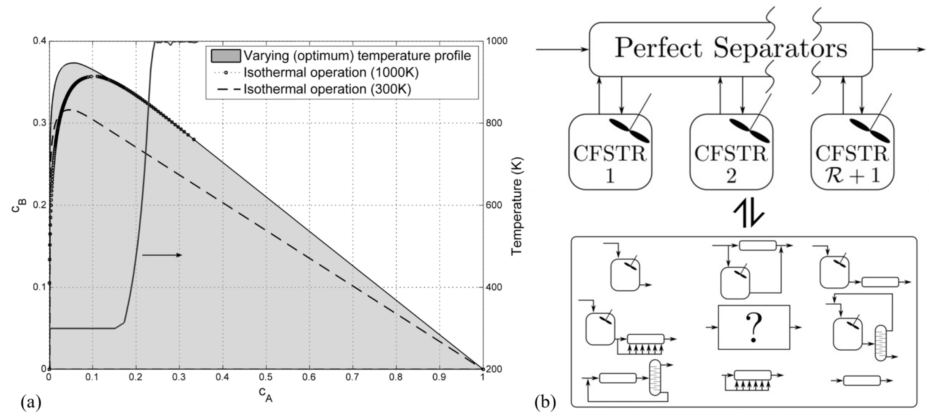

Figure 2

Attainable region for process synthesis: (a) AR, (b) CFSTR.
Reproduced from (13, 14) with permission

state reaction systems was defined as the region of all possible products in the concentration space under various reaction kinetics and feed regimes. It leveraged a generalized reactor network representation using ideal continuous stirred tank reactors, plug flow reactors, and differential side stream reactors to capture all plausible reactor designs. Key information provided by AR included the boundary of attainable region, the best possible performance targets (e.g., max productivity), and the structure of ideal reactors to achieve the targets. AR was also extended for thermodynamic attainable region based on heat and work balance (16). Feinberg and Ellison (17) proposed an AR representation for reactor-separator systems using continuous flow stirred tank reactors (CFSTRs). The CFSTR Equivalence Principle was proven that, given reaction kinetics and raw materials, any arbitrary steady-state reactor-mixer-separator system with total reaction volume greater than zero could be decomposed into a new CFSTR system as depicted in **Figure 2b**. A nonlinear programming formulation was developed for the CFSTR Equivalence Principle by Frumkin and Doherty (14). An extensive review on AR historical developments, theory, and applications can be found in Charis et al. (18).

Heat and mass exchange networks (HEN, MEN) are also frequently used as targeting approaches to determine minimum utility consumption, economic cost, etc. Klemeš and Kravanja (19) reviewed the HEN developments in the past decades via pinch analysis and mathematical programming. Using a mass exchange network state-space representation, Wilson and Manousiouthakis (20) introduced the Infinite DimEnsionAl State Space (IDEAS) approach to minimize utility cost. As shown in **Figure 3a**, IDEAS representation comprised a set of process operators (e.g., mass or heat pinch operators) which were connected through a distribution network (e.g., mixing and splitting operations). Successive works extended IDEAS for attainable region approximation to synthesize reactor networks via a sequence of linear programs of ever increasing size (21). **Figure 3b** presents the carbon, hydrogen, and oxygen Symbiosis Networks (CHOSYN) framework by Noureldin and El-Halwagi (22), which aimed to achieve maximal mass integration and utilization via atomic targeting based on a source-interception-sink representation.

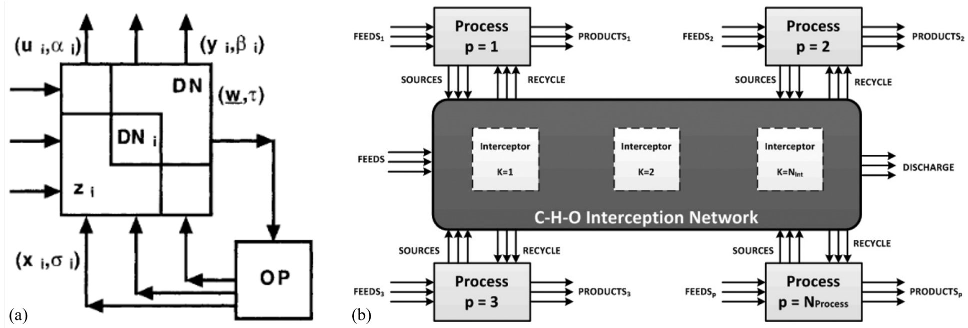

Figure 3

MEN-based targeting approaches: (a) IDEAS approach, (b) CHOSYN framework. Reproduced from (20, 22) with permission

2.2. Phenomena-based Modeling

Phenomena-based modeling uses a set of fundamental physicochemical building blocks that are shared in common by different chemical systems (e.g., reaction, separation, mixing/heating). It represents process designs from a lower aggregated level compared to unit operation-based modeling. Therefore, phenomena-based synthesis systematically addresses function selection and integration from which the optimal unit operation and flowsheet designs can be identified (as shown in **Figure 1**). This class of approaches has gained much interest in computer-aided process intensification. As illustrated in **Figure 4**, it opens up the opportunities to generate innovative or non-intuitive process designs with step-change performance improvements, e.g. by leveraging the flexibility to integrate multiple phenomena into a single unit to exploit multi-functional synergy. The suggested phenomenological designs can then be rigorously simulated and designed via unit operation-based modeling

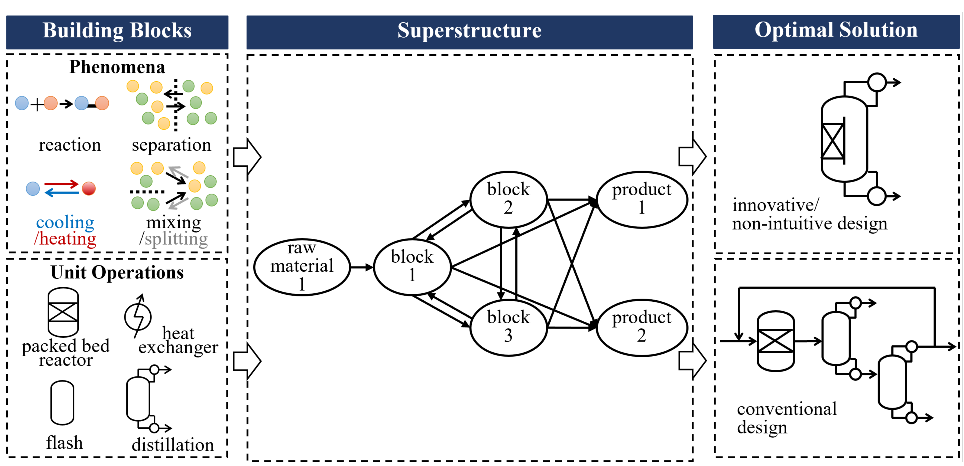

Figure 4

Phenomena-based and unit operation-based chemical process representation.

(Section 2.3). In what follows, we present a brief overview to elucidate the major features of such approaches. For more detailed discussions, readers are referred to the recent reviews by Tian et al. (23), Skiborowski (24), Tula et al. (25), etc.

Sundmacher et al. (26) proposed a function module-based process representation as given in **Figure 5a**. Function modules were defined for pre-processing, contacting, activating, reaction, heat supply/removal, separating, and product formation. Using reaction as example, the optimal design was obtained by optimizing the dynamic mass fluxes using elementary process functions. The Generalized Modular Representation Framework (GMF) developed by Pistikopoulos, Tian, et al. (27, 28) is shown in **Figure 5b**. Leveraging Gibbs free energy-based driving force constraints, GMF systematically identified the optimal conventional or intensified tasks (e.g., reaction, reactive separation, membrane-assisted reaction) from mass and heat exchange building blocks. The synergy between GMF and CFSTR Principle was explored to drive superstructure optimization-based process synthesis toward the best-possible performances at AR boundaries. The Sustainable Process Synthesis-Intensification Framework developed by Gani et al. (29) featured a stage-wise procedure to decompose the process synthesis-intensification design space. As shown in **Figure 5c**, phenomena building blocks were used to generate intensified and sustainable

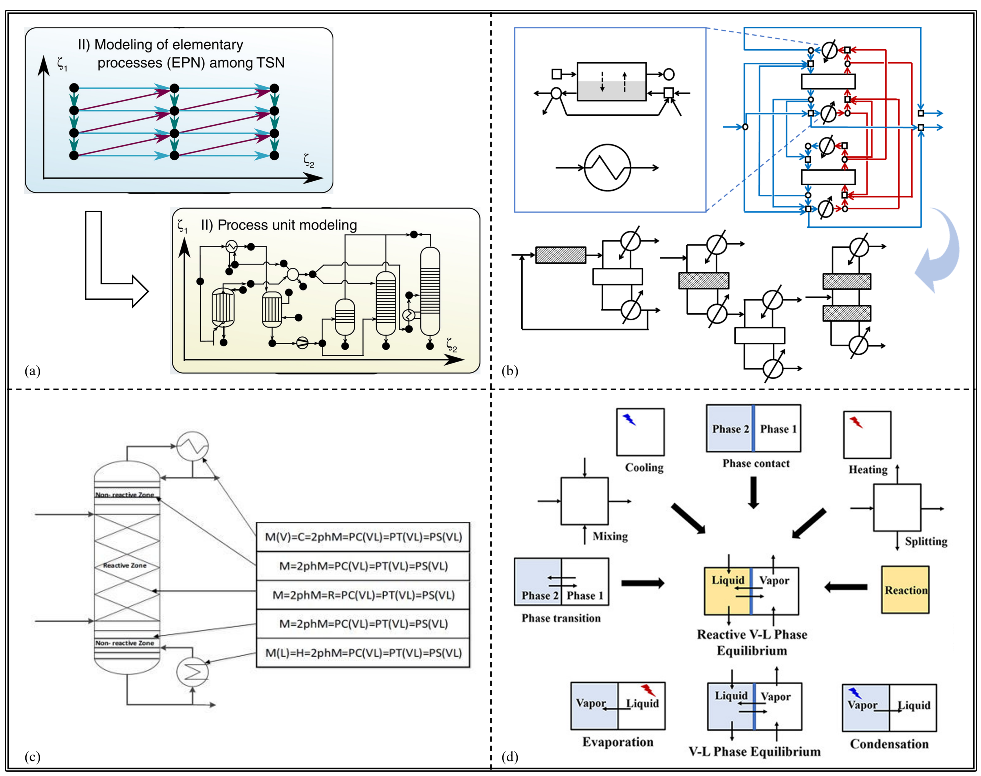

Figure 5

Phenomena-based modeling approaches – An indicative list. (a) Elementary process functions, (b) Generalized Modular Representation Framework, (c) Sustainable Process Synthesis-Intensification Framework, (d) Abstract building block. Adapted from (26, 29, 30) with permission processes (e.g., advanced distillation, reactive distillation, membrane separation). Some PBB examples included Mixing (M), 2-phase mixing (2phM), phase transition (PT), phase contact (PC), phase separation (PS), Reaction (R), and heating (H). The Abstract Building Block (ABB) approach (**Figure 5d**) was introduced by Hasan et al. (30), which formulated a 2-D grid structure to represent chemical processes using the building blocks such as mixing/splitting, heating/cooling, phase contact, phase transition, etc. The building blocks could also be assigned with different types of boundaries to allow free, partial, or no mass transfer for applications in, e.g. distillation, extraction, and membrane-assisted process systems.

2.3. Unit Operation-based Modeling

Immense efforts have been made on process synthesis using unit operations as the superstructure building blocks. Excellent reviews were presented by Chen and Grossmann (7) and Mencarelli et al. (31) on recent developments and challenges. Therein, the proper selection of unit operation-based representation approaches was emphasized to ensure tractable computational formulation with sufficient modeling accuracy and flexibility to extract the desired design information. **Figure 6** gives a few examples of such approaches which have been widely applied for process synthesis. **Figure 6a** shows the State-Task-Network (STN) by Yeomans and Grossmann (32). States referred to the physicochemical properties which defined the process streams and tasks were transformations connecting adjacent streams.

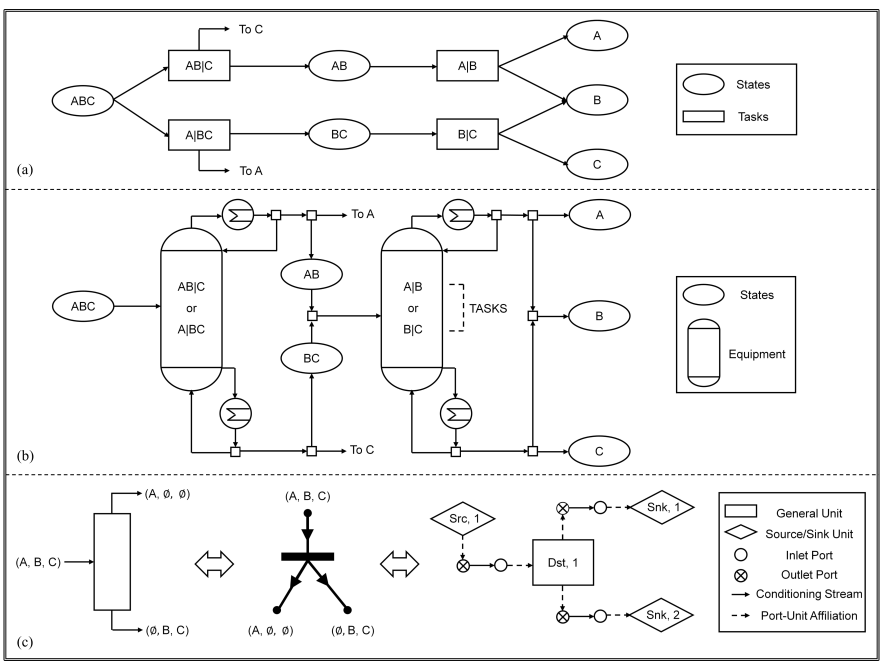

Figure 6

Unit operation-based modeling approaches: Ternary distillation sequence representation using (a) STN, (b) SEN (32), Distillation representation using (c) P-graph (33) and UPCS (34).

STN could be employed for continuous and/or discrete time network formulations, which were originated from production scheduling problems but also necessitated by many reviving design objectives such as resiliency (to be detailed in Section 3). The State-Equipment-Network (SEN) is shown in **Figure 6b**. SEN explicitly considered the equipment to carry out the task while the task assigned to each piece of equipment was determined via mathematically modeling. This was in reverse with STN. More recently, Ryu et al. (35) proposed a generalized process synthesis framework represented with simultaneous reactor, separation, and heat exchanger networks. To include all plausible unit connections in the superstructure, many works explored automatic superstructure generation (despite the types of units are required to be pre-postulated). Friedler et al. (33) introduced the P-graph (**Figure 6c**) which used a polynomial algorithm to generate the maximal superstructure based on a representation of material, operation nodes, and interconnecting arcs. Wu et al. (34) developed a UPCS superstructure representation using Units (i.e., unit operations, raw material sources, product sinks), Ports (i.e., stream inlet and outlet points), and Conditioning Streams (i.e., connections between ports). Via connectivity rules, fully connected minimal superstructure could be generated with all feasible routes.

It is also worth noting the rapidly increasing capability of large-scale process synthesis with temporal and/or spatial considerations for chemical plant design, supply chain optimization, etc. **Figure 7** gives a such example for multi-product plant synthesis using intermittent renewable energy sources (36). In this context, a verifiable multi-scale process synthesis framework is in essential need.

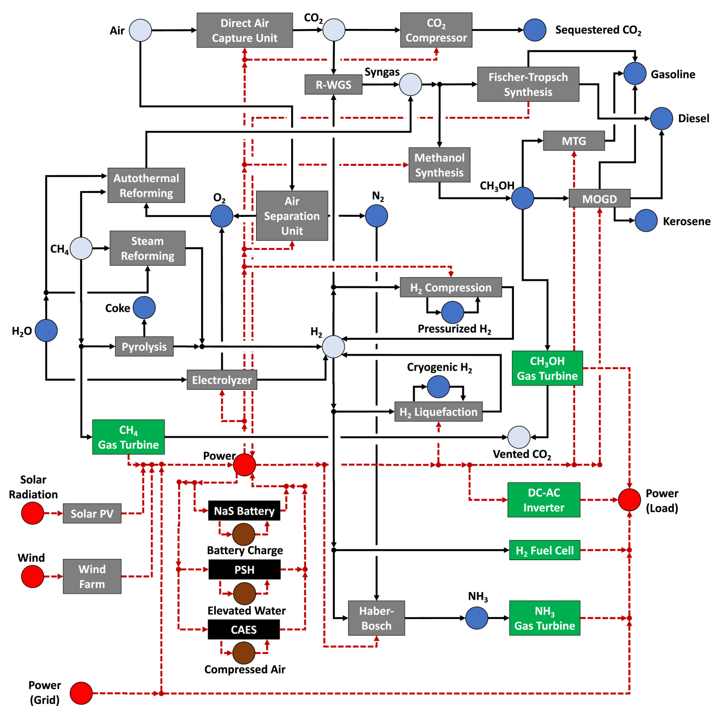

Figure 7

Plant-scale synthesis of multi-product energy system. Reproduced from (36) with permission

2.4. Hybrid Modeling

Data-driven/Surrogate modeling has been a powerful tool to reformulate rigorous first-principle models with reduced numerical complexity, thus resulting in computationally tractable and efficient (large-scale) process synthesis problems to attain better (or globally) optimal design solutions. Recent extensions to hybrid modeling open up even more exciting potential to more accurately describe process systems with imperfect mechanistic models (e.g., unknown modeling equations, simplified assumptions) by augmenting first principles and process data. In what follows, we briefly review these advances.

An early data-driven/surrogate modeling framework was proposed by Henao and Maravelias (37) which was designed to collect data from process simulators (e.g., Aspen, Matlab), train artificial neural network-based surrogates via a variable analysis approach, and formulate mixed-integer nonlinear models to be used in superstructure optimization. Wilson and Sahinidis (38) introduced ALAMO (Automatic Learning of Algebraic MOdels) to generate algebraic surrogate models of black-box systems. ALAMO allowed for a super set of potential basis functions, from which optimization and statistic methods were used to select the optimal subset of basis functions. The surrogate was iteratively refined by adding new data points obtained from error maximization sampling via derivative-free optimization. More data-driven modeling approaches include: MINOAn by Kim and Boukouvala (39) for mixed-integer optimization using approximations, PARIN (Parameter as Input Variable) by Mohammadi and Cremaschi (40) to build surrogate models of stochastic simulations accounting for parameter uncertainty as training inputs, OMLT by Ceccon et al. (41) to incorporate neural network and gradient-boosted tree surrogate models into larger optimization problems, etc.

An excellent review has been offered by Bradley et al. (42) on the methods integrating first-principle and data-driven modeling, which also included a chemical reactor case study to showcase hybrid modeling, physics-informed neural network (PINN), and model calibration. **Figure 8a-b** illustrate hybrid modeling via mechanism estimation (in which mass/energy balances can be strictly imposed) and mechanism correction (to compensate low quality mechanistic model) (43). An example of PINN, proposed by Raissi et al. (44), is depicted in **Figure 8c**. PINN utilized physical laws as prior knowledge to train neural net-

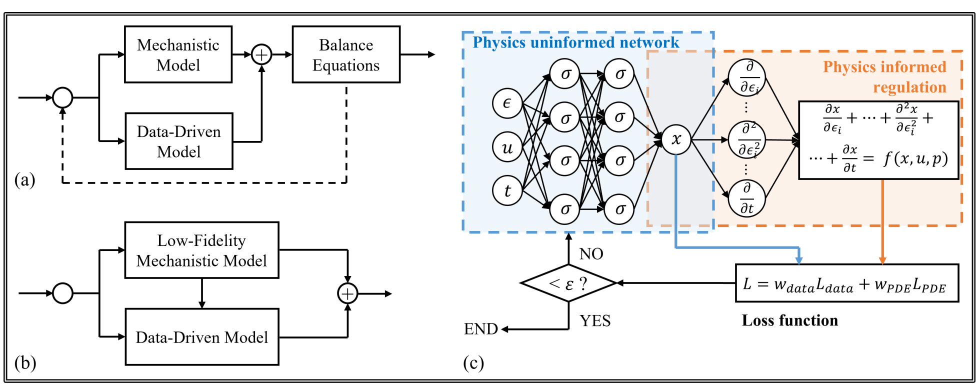

Figure 8

First-principle/data-driven modeling: (a) Mechanism estimation, (b) Mechanism correction (42) (c) Physics-informed neural network (44) work architectures. Namely, the model was iteratively trained to minimize the sum of loss functions by incorporating the physics informed regulations through the partial differential operators used in species and energy balances, etc. Process constraints (e.g., conversion laws) and temporal dynamics could be imposed by introducing biases.

ML-assisted modeling is also indispensable for chemical and manufacturing processes without well-accepted first principles models. One special case is process systems at incipient development stage where only experimental data are available in limited amount. Several works have investigated the use of neural networks to model such systems like carbon fiber synthesis, carbon nanorod manufacturing, silicon wafer planarization, etc. based on 30-40 experimental data (45, 46). Liu et al. (46) also integrated the Synthetic Minority Oversampling Technique (SMOTE) to generate larger amount of synthetic data in compensation of limited experimental data availability. These approaches show promises to quantitatively evaluate many new (lab-scale) process technologies and benchmark them with conventional counterparts at systems-level via process synthesis and optimization.

3. PROCESS SYNTHESIS OBJECTIVES

Economics has been the dominant driver for chemical process design which can be quantified via total annualized cost, profitability, return on investment, etc. In addition, sustainability and operability have become key process synthesis objectives to ensure economic promises in the current dynamic and volatile market environment with burgeoning environmental awareness. In this section, we review the process synthesis approaches to design sustainable and operable processes. A fundamental understanding is instrumental, yet currently lacking, to unravel the interactions between economics, sustainability, and operability which will elucidate the synergistic ways to enhance chemical process designs in all facets.

3.1. Sustainability

We first present a statistics survey which can well illustrate the growing significance of sustainability research in chemical engineering. The number of articles on process design with sustainability considerations is shown in **Fig. 9**. To ensure that the publications

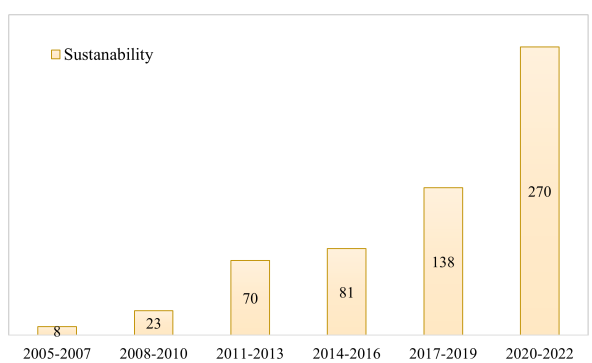

Figure 9

Statistics of articles on process design with sustainability considerations.
(Citation database: Web of Science Core Collection, Update: July 15, 2023)

have a focused research development on sustainability, the search was restricted to articles and review articles with "process design" topic and "sustainabl*" in title under Web of Science "Engineering Chemical" category. Specifically on process systems engineering methods for sustainable chemical engineering, Bakshi (47) provided a comprehensive review on the definition of hierarchical environmental-societal-economic sustainability metrics and the incorporation in process design. It also stressed the importance to expand the boundary of systems analysis, thus holistically evaluating sustainability across space, time, disciplines, and flows. Martin et al. (48) reviewed model-based sustainable process synthesis with application to carbon capture and utilization, biorefineries, and water desalination. More generally, the synthesis and design of sustainable systems have investigated: (i) explicit incorporation of process constraints or objectives on environmental impacts, life cycle analysis, waste minimization, etc. (49), (ii) process integration to recycle the use of chemicals, waste, and energy (50), (iii) consideration of more sustainable process technologies in place of their conventional counterparts such as intensified units (51), and (iv) use of alternative raw materials (e.g., solid waste, biomass) and energy sources (e.g., solar, wind) (52, 53). Readers are also referred to the reviews on synergistic concepts such as circular economy (9, 54), decarbonization (55), food-energy-water nexus (56, 57), electrification (58), net-zero emission energy transition (59), etc.

3.2. Process Operability

We adapt a general operability definition as the capability of process to perform satisfactorily under conditions different from the nominal design conditions (60). Specifically, we discuss operability objectives from the aspects of flexibility (i.e., capability to have feasible operation under changing conditions), safety (i.e., prevention of major hazards given possible failures), and resiliency (i.e., capability to tolerate and recover from undesirable changes and upsets). The statistics survey on process design with these operability considerations can be found in **Figure 10**, which indicates a notable growth in the last five years.

Flexibility – The earliest flexibility consideration was oriented to maintain desired output process/product specifications under input feed/utility disturbances during steady-state

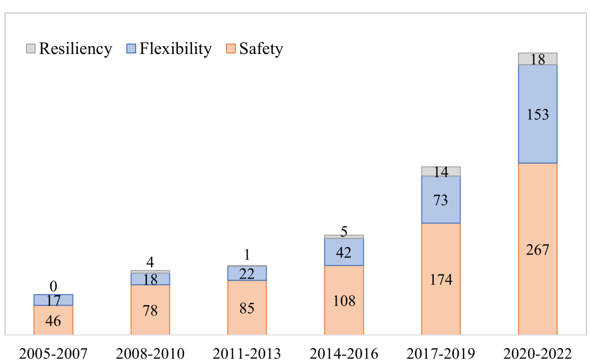

Figure 10

Statistics of articles on process design with operability considerations.
(Citation database: Web of Science Core Collection, Update: July 15, 2023)

process design. This led to the classical tri-level optimization formulation for process flexibility quantification by Swaney and Grossmann (61). On this basis, extensive efforts were made to develop dynamic flexibility and stochastic flexibility analyses (62) with application to chemical and, of much interest, pharmaceutical processes (63). The ongoing sustainable energy transition has significantly expanded process flexibility needs from all supply, demand, and network perspectives such as to accommodate varying bio-based feedstock compositions, intermittent renewable energy resources, and dynamic demand responses (64). Riese et al. (65) discussed the requirement of product flexibility, expansion flexibility, relocation flexibility, etc. in emerging modular plants and multi-product plants.

Safety – The integration of process safety with conceptual process design typically follows the principles of inherently safer design (66). The central idea is to achieve a safer chemical process by designing it to minimize hazardous inventories, substitute hazardous materials, moderate hazardous conditions, and simplify process complexity (67). More than twenty-five indices were developed to quantify inherent process safety, an extensive review of which can be found in Roy et al. (68). Model-based approaches have also been developed to characterize safe operating window under uncertainty (69), incorporate simultaneous material selection (70), and integrate inherent safety metrics with (phenomena-based) process synthesis (71). Process safety also motivates the consideration of modular process intensification, major principles of which are to create substantially smaller processes and integrate multiple process steps into a single unit (72).

Resiliency – The past several years suffered from ever more frequent major regional, national, and global disruptions including natural disasters, COVID-19 pandemic, geopolitical conflict, etc. with striking impacts on chemical and energy supply networks. As highlighted in Chrisandina et al. (73), the enhancement of system resiliency rerquires a multi-scale integration of chemical process systems ranging from molecular, unit, process, to supply chain. At the process level, Grossmann and Morari (60) quantified static resiliency as flexibility and assessed dynamic resiliency against the impact of feasible operating window, time delay, model uncertainty, etc. Ribeiro and Barbosa-Povoa (74) reviewed the definition and modeling approaches for supply chain resilience. The use of modular manufacturing facilities provides another promising solution at the supply chain level due to their dynamic mobility (75, 76).

To solve the operability problems (and more general, the optimization under uncertainty problems), large-scale multi-period or multi-stage optimization models are typically necessitated in which integer variables are used to model logical and other discrete decisions (121, 122). Major approaches for optimization under uncertainty include stochastic programming, which models uncertainty via probability distributions, and robust optimization, which employs an uncertainty set. Zakaria et al. (123) reviewed the uncertainty modeling approaches for stochastic optimization (e.g., Monte Carlo Simulation, Generative Adversarial Networks) with particular focus on renewable energy systems. Grossmann et al. (124) presented algorithmic advances in robust optimization with recourse and two-stage/multi-stage stochastic programming. Case studies were also provided on demand side management and supply chain risk management. More discussions on stochastic programming and state-of-the-art software tools can be found in Li and Grossmann (125) and Torres et al. (126). An overview was provided by Parnianifard et al. (127) to bridge robust optimization with hybrid modeling. Ning and You (128) reviewed machine learning-assisted approaches for optimization under uncertainty, such as data-driven (distributionally) robust optimization, data-driven stochastic programming, data-driven scenario-based optimization, etc.

4. OPTIMIZATION ALGORITHMS AND TOOLS

In this section, we present the optimization algorithms and tools to solve process synthesis problems. Brief discussions are provided on classic (mixed-integer) linear/nonlinear optimization and machine learning (ML)/quantum computing (QC)-assisted optimization.

4.1. (Mixed-Integer) Linear/Nonlinear Optimization

(Mixed-integer) Linear/Nonlinear optimization are well-established for process synthesis. Herein, we summarize an indicative list of algorithms, reviews/books, solvers in **Table 1**.

4.2. ML/QC Assisted Optimization

The impetus of machine learning and quantum computing offers potential to speed up the discovery and development of chemical process designs (11, 12). In what follows, we introduce the latest developments on data-driven optimization algorithms, reinforcement learning-driven process synthesis, and quantum computing-assisted optimization.

Data-Driven Optimization Algorithms – ML have been employed to investigate many challenging optimization problems, among which global optimization is a representative example (106). Several works applied clustering methods (114) to identify global optimum by learning the shape of different basins of local optima attractions. The synergy of data-driven modeling and global optimization can also be leveraged. Boukouvala et al. (115) proposed the ARGONAUT approach as algorithms for global optimization of constrained grey-box computational problems. The approach incorporated variable selection, bounds tightening and constrained sampling techniques to develop accurate and globally optimized surrogate representations of unknown equations. The DOMINO approach presented by Beykal et al. (116) aimed to solve bi-level mixed-integer nonlinear problems using data-driven optimization. Therein, a single-level optimization reformulation was achieved by collecting samples from the upper-level objective and solving the lower-level problem to global optimality at the sampling points.

Reinforcement Learning-Driven Process Synthesis – Reinforcement learning (RL) were recently used to drive process synthesis, instead of mathematical programming, by Stops et al. (117) and Wang et al. (118). These approaches started with a maximum pool of unit operations without requesting superstructure postulation. The intelligent RL agent (e.g., using Deep Q Network) would select among the available unit operations and generate arbitrary process design configurations represented via graphical neural network (117), input-output stream connection matrix (118), etc. The RL agent was repetitively trained and rewarded toward the generation of better process designs. The approaches offer promises toward automated process design, while challenges exist on the optimality of resulting design solutions and the algorithmic scalability as the number of available unit operations increases.

Table 1 (Mixed-integer) Linear/Nonlinear optimization algorithms, reviews, books, and solvers – An indicative list.

Optimization	Major algorithm	Review/Book	Solver	Solver review
Linear programming	Simplex, Ellipsoid algorithms	Winston (77)	Gurobi (79), IBM CPLEX (80)	(83, 84)
	Interior Point algorithms	Bazaraa (78)	GLPK (81), LP_Solve (82)	
Nonlinear programming	Successive quadratic programming	Bazaraa et al. (85)	CONOPT (88), IPOPT (89)	(93)
	Reduced-gradient algorithms	Biegler (86)	MINOS (90), KNITRO (91)	
	Interior point algorithms	Biegler (87)	SNOPT (92)	
Mixed-integer linear programming	Branch and Bound	Conforti et al. (94)	LINDO (96), SCIP (97)	(99)
	Cutting plane techniques	Marchand et al. (95)	Mosek (98), Gurobi	
			CPLEX, GLPK, LP_Solve	
Convex mixed-integer nonlinear programming	Branch and Bound	Grossmann (100)	DICOPT (102), SHOT (103)	(105)
	Outer Approximation	Floudas (101)	αECP (104)	
	Generalized Benders Decomposition			
	Generalized Disjunctive Programming			
Global optimization	Tight convex underestimators	Boukouvala et al. (106)	ANTIGONE (110)	(113)
	Domain branching	Ruiz and Grossmann (107)	BARON (111), LINGO (112)	
	Feasibility/Optimality-based bounds tightening	Tawarmalani and Sahinidis (108)		
		Floudas (109)		

Quantum Computing-Assisted Optimization – QC is defined as computing that follows the logic of quantum mechanics. In contrast with the "bit" used in classic computers which has a deterministic value represented by basic states 0 and 1, infinite number of states are possible for a QC "qubit" until measurement. The distinct computing fundamentals render QC the capability to reduce the number of calculation steps compared with classic algorithms and to speed up computation for linear algebra, linear and quadratic programming, machine learning and other problems in e.g. quadratic or exponential manner (119). Bernal et al. (12) presented a latest review on quantum computing fundamentals, QC-assisted mathematical programming and machine learning algorithms, the potential impacts and applications in chemical engineering. Ajagekar and You (120) highlighted QC applications for energy process systems, in which different quantum hardware were showcased to solve a facility location-allocation problem. Limitations of current quantum hardware architecture and algorithms were also identified in terms of precision and error mitigation, large-scale complex process application, etc.

4.3. Software Tools

There has been a surge of tool developments for process synthesis, design, and operability analysis as well as for applications in energy systems, process intensification, etc. An indicative list of commercial and academic developments is summarized in **Table 2**. The list of algorithm solvers can be found in **Table 1** and indicative surrogate modeling tools (e.g., ALAMO, MINOAN, PARIN, OMLT) are discussed in Section 2.4. Readers are also referred to Pistikopoulos et al. (9) for a comprehensive review of software tools used by the process systems engineering community.

5. CONCLUDING REMARKS

Substantial advances have been made on process synthesis modeling, optimization algorithms, and software tools. As can be noted, sustainability has become a key driver for process development which necessitates a holistic multi-layer systems-based strategy to assess the integral role of resources, processes, environment, and society (9, 47). Multi-scale modeling, as detailed in Section 2, is essential to enable such quantitative and verifiable analyses in both temporal and spatial domains. Integrated process and material design has also received increasing attention leveraging e.g. process-structure-property modeling (146, 147, 148). The scope of process synthesis applications is also expanded to address integrated energy systems, food-energy-water nexus, circular economy, electrification, energy transition, etc. (56, 58, 59) These processes invoke the commercial deployment of many novel chemical and energy technologies (e.g., electrolyzer, waste pyrolysis, microwave heating), which necessitates the establishment of (new) first principles/hybrid models as well as systems-level optimization for the incorporation to existing process practice.

On the other hand, an open question remains on how to drive systematic innovation using computer-aided strategies in addition to assessing available techniques. This is the central idea motivating phenomena-based process synthesis for process intensification, and much promise has been shown in generating non-intuitive unit/flowsheet designs with step-change improvements (23, 25). The potential of such approaches is worthwhile to be further exploited. Besides the current focus on distillation and membrane-based systems, the majority of PI methods remain unexplored e.g. rotating, micro-, and periodic processes (149).

Table 2 Software tools for process synthesis, design, and analysis – An indicative list.

Purpose	Tool	Reference	Notes
Process simulation & Optimization	Aspen	www.aspentech.com	Suite of tools, SQP optimization, RD, Petlyuk Column
	CHEMCAD	www.chemstations.com/	Steady-state simulation, Membrane simulation
	AVEVA (PRO/II, etc.)	www.aveva.com/en/	Suite of tools, Hydrogen& renewable processes, GHG calculation
	gPROMS	www.psenterprise.com/	Suite of tools, Dynamic optimization, Surrogate modeling
	ProMax	www.bre.com/	Up/Mid/Downstream modeling
	UniSim	www.honeywellforge.ai/	Plant monitoring, CCS/GHG/Green H_2 processes
	DWSIM	dwsim.org/	Open source, Python script compatible
	ChemSep	chemsep.org/	Column simulator, RD, DWC
Process synthesis (Superstructure-based)	Pyosyn	Chen et al. (129)	GDP, Graph representation, Superstructure generation
	MIPSYN-Global	Bogataj et al. (130)	Graphical modeling, Equation-oriented synthesis
	Super-O	Bertran et al. (131)	Sustainable synthesis-design, Database & Software interface
	ProCAPD	Kalakul et al. (132)	Integrated chemical product design, Library of product design templates
Design & Operability	Flexibility	Bynum et al. (133)	Vertex enumeration, Active constraint method, ML-based decision rules
	FlexJuMP.jl	Pulsipher et al. (134)	Flexibity analysis & quantification of complex systems
	Operability App	Gazzaneo et al. (135)	Operability-based design, Nonlinear process systems
	PAROC	Pistikopoulos et al. (136)	Multi-parametric optimization, Design & Control
	ProCACD	Tula et al. (137)	Process design-control, Open/Closed-loop analysis
Energy systems	IDAES	Lee et al. (138)	Algebraic modeling languages, Superstructure-based design, Model libraries
	Energiapy	Kakodkar et al. (139)	Multi-scale modeling, Circular economy metrics
	Comando	Langiu et al. (140)	Energy systems design & operation; Hybrid modeling
Process intensification	SYNOPSIS	Vedant et al. (141)	Phenomena-based synthesis, Design & operability, PI model library
	ProCAFD	Tula et al. (142)	Sustainability & Safety, Intensified/Hybrid designs
	SPICE	Monjur et al. (143)	Phenomena-based synthesis, Property-performance mapping
	toPSAil	Kim & Scott (144)	Pressure swing adsorption
Biomass process	BUS	Ng et al. (145)	Biomass utilization superstructure, Optimization-based web application

* SQP – Successive Quadratic Programming, RD – Reactive distillation, GHG – Green house gas, CCS – Carbon capture and storage
DWC – Dividing wall column, GDP – Generalized Disjunctive Programming

More constructive insights will be gained by elucidating the multi-functional synergies, dynamic driving forces, and scaling up/down mechanisms based on physicochemical fundamentals, thus to discover the truly out-of-the-box process design solutions. The synergistic integration of physicochemical principles, machine learning, and quantum computing may also provide a promising way to accelerate process design innovation.

There is also an increasing need toward the unification of process design, operability, and operations (150). As discussed in Section 3, a fundamental theory is still lacking to unravel the interactions between economics, sustainability, and operability from which a process design can be improved in all aspects (122). Additionally, the supply network is growing more and more dynamic due to uncertainties in resource availability, energy prices, market demands, regional/global disruptions, etc. The penetration of renewable energy sources renders process design an intrinsically dynamic problem. The emerging trend of distributed modular manufacturing, such as for stranded gas utilization, also emphasizes the importance of geographical mobility. The scale of the resulting optimization continues increasing which calls for efficient/tailored mixed-integer linear/nonlinear optimization algorithms (64, 75).

On top of methodological advances, software development and dissemination play a vital role for the adoption of optimization-based process synthesis in industrial settings. Chen and Grossmann (7) commented in 2017 that "there lacks a general-purpose mathematical programming synthesis tool akin to Aspen for flowsheet simulation", which still holds true to date. However, impressive progress has been made on this front as reviewed in Section 4, which are also benefited from the advances of Python-based open-source tools. Moreover, such efforts have been made for the dissemination of academic-oriented software tools to the broader academic and industrial community such as the hands-on training workshops organized by IDAES, PSE for SPEED, RAPID (SYNOPSIS, Reaction Software Ecosystems), etc. The cooperative engagement of industrial professionals and commercial software vendors with academic developers is certainly instrumental to further advance and promote the methodologies and tools.

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