



# Process engineering advances in pharmaceutical and chemical industries: digital process design, advanced rectification and continuous filtration

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1 **Process engineering advances in pharmaceutical and chemical industries: digital process**  
2 **design, advanced rectification and continuous filtration**

3

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17

18 **Highlights**

19 Systematic digital reaction route selection, catalytic distillation, reactive distillation,  
20 continuous manufacturing, continuous filtration

21

22 **Abstract**

23 This review paper presents some of the topics discussed at the 2018 “*Chemical process*  
24 *development trends*” seminar organized by the Swiss Process and Chemical Engineers Society  
25 in Basel, Switzerland. The first subject covers the use of computer aided tools for systematic  
26 reaction route selection, the second one addresses the recent development in the field of  
27 process intensification with a focus on reactive distillation and dividing wall column  
28 technology and the third topic highlights recent developments in the field of continuous  
29 filtration in the pharmaceutical industry.

30

31

## 1        **1. Introduction**

2        The “Chemical process development trends” seminar organized on 8<sup>th</sup> November 2018 by the  
3        Swiss Process and Chemical Engineers Society in Basel, Switzerland reviewed the recent  
4        advances in selected pharmaceutical and chemical process technology areas. The seminar was  
5        opened by Prof. R. Gani’s talk from PSE for SPEED Company Ltd. on digital pharmaceutical  
6        process design. This talk was followed by the contribution from D. Crettenand from RedElec  
7        SA on the use of electrochemistry as a “green” technology in the field of organic synthesis.  
8        Prof. A. Kiss from the University of Manchester presented an overview of recent advances in  
9        the field of reactive distillation and dividing-wall column rectification while Prof. A. Zogg  
10       gave a foresight of his future research portfolio at The University of Applied Sciences  
11       Northwestern Switzerland. Recent advances on the use of continuous filtration in the context  
12       of pharmaceutical manufacturing were highlighted by J. Cornevin from Novartis Pharma AG,  
13       while R. De Dier from The Janssen Pharmaceutical Companies of Johnson & Johnson  
14       presented the model based lyophilization process optimization.

15  
16       The aim of this review paper is to provide the broader chemical engineering community a  
17       deeper insight in some of the topics discussed at the seminar: the use of computer aided tools  
18       for systematic reaction route selection, recent reactive distillation and dividing wall column  
19       technology developments and continuous filtration implementation in the pharmaceutical  
20       industry.

## 21        **2. Digital process design methods for the pharmaceutical industry**

22        Methods and tools from process systems engineering (PSE), which are routinely used in the  
23        petrochemical and related industries, can also assist in the development, analysis, design,  
24        evaluation, and optimization of pharmaceutical processes. The scope and significance of these  
25

1 methods and tools depend on the available mathematical models and/or data. Even though the  
2 final verification is always made through experiment-based studies, model-based computer-  
3 aided systems can help to quickly evaluate and screen-out redundant processing options, to  
4 select and verify solvents, to plan and design experiments and to quickly reduce the search  
5 space related to reliable and efficient operation of the process operating in batch or continuous  
6 mode. Recently, there has been an increasing interest in the development and/or application of  
7 methods and tools from PSE for the pharmaceutical sector and among these, a model-based  
8 multi-functional computer-aided framework developed by Papadakis et al. [1] is worth  
9 mentioning.

10 The framework aims to assist in the development of pharmaceutical processes by providing  
11 detailed process understanding, selecting efficient reaction pathways through analysis of  
12 reactions, solid solubility analysis together with the need and use of solvents, and, identifying  
13 opportunities where continuous manufacturing might be an option. Systematic model-based  
14 methods and tools are applied in each step of the framework in order to create a data-rich  
15 environment that is a requirement for enhanced process understanding and to assist in the  
16 decision-making process in each case. To achieve these objectives, the framework integrates  
17 models and data, different model-based methods (defined by their specific work-flows and the  
18 associated data-flows for specific problems) and tools (that is, the tools that perform the  
19 needed work at each step of the work-flow). The integrated framework consists of four  
20 sections with their corresponding models, methods and computer-aided tools: reaction  
21 pathway selection; reaction analysis; downstream separation analysis; and, process  
22 simulation, evaluation, optimization and operation. An overview of the framework is  
23 illustrated in Fig. 1 (from Papadakis et al. [1]).

24

25

## 2.1 Reaction database

Almost all pharmaceutical processes are based on some form of organic synthesis that defines the reaction pathway, where organic chemistry has an important role to play in the development of synthetic routes for new drugs during early stage process development. To pursue synthesis at a high level, the needed access to chemical information is provided through a specially developed reaction database and integrated within the framework. An overview and extension of this database is presented below.

The reaction database [2] contains collected data for single and multiphase reactions involved in small molecule pharmaceutical processes. The collected data are represented through a specially developed ontology for knowledge representation. It has a search engine to retrieve necessary data when required for problem solution-analysis. The goal is to provide a data rich environment with process information available to assist during the early stage synthesis of pharmaceutical products. The reactions in the database are categorized according to the reaction type (for example, alkylation, epoxidation), the target product (active pharmaceutical ingredients like Ibuprofen, Ciproflexacin) to be produced (when single-step or multistep reactions are considered), the reaction product and the effect of the solvent used on the reacting system. Reaction conditions (temperature, pressure etc.), reaction components (reagents, catalysts etc.), reaction data (conversion, selectivity, etc.), scaling information and finally batch or continuous processing is included in the developed database. For each reaction type, it is possible to,

- Identify reactions that are used to produce different types of products (API, Intermediates).
- Identify reactions to be utilized, for a given compound availability.
- Investigate the function of different type of solvents in single/multiphase reactive systems.

- 1 • Facilitate the choice of the reaction conditions.
- 2 • Evaluate the reaction pathway in terms of yield, cost and sustainability metrics.
- 3 • Facilitate the reactor design from available experimental data and kinetic models.

4

5 The individual reaction data are supplemented with information on scalability, cost, expected  
6 yield, number of reaction steps, ease of separation and safety. The current version of the  
7 database covers 44 reaction types consisting of 350 reactions where 88 represent multiphase  
8 reaction systems and out of which 246 reactions involve the use of solvents (where the  
9 objective is to dissolve, phase creation, substrate/catalyst carrier, compound extraction). The  
10 total synthesis pathway data for 29 APIs and 25 building block chemicals are available. The  
11 data collection covers 307 reactions with measured data on conversion, selectivity, reaction  
12 yield, reaction conditions; 39 reaction systems with dynamic reaction data; 17 reaction  
13 systems with details of published kinetic models; 112 reaction systems with in-flow data; for  
14 227 reactions systems with data for batch operations. The special physical properties data  
15 cover 14 chemicals, 18 fine chemicals and 255 pharmaceuticals.

16

17 Each reaction is an individual record set in the database.

- 18 • Molecular structural information (Target product, by-products and substrates)
- 19 • Reaction centers (The collection of atoms and bonds that are changed during the reaction).
- 20 • Reaction system chemicals (Information of chemicals involved in the reaction such as  
21 reagents, catalysts, solvents etc.)
- 22 • Multistep reactions (Products that require multiple reaction steps, that is, reaction  
23 pathways)
- 24 • Reaction conditions (Conditions such as pH, temperature, pressure etc., at which the  
25 reaction takes place)

- 1 • Reaction classification (Type of reaction, i.e., esterification, amination, etc.)
- 2 • Post-processing of the database contents (Export option to other tools)

3

4 With the above information available and together with organic synthesis-design tools, an  
5 opportunity for an integrated approach to the synthesis route selection and productivity  
6 improvement taking into account process considerations (development time to establish the  
7 synthesis route, product quality, cost of manufacture linked to “green” chemistry metrics and  
8 the final approval of regulatory agencies) is now possible. One starting point on the use of the  
9 reaction database is the molecular structure of the API. The search engine of the database will  
10 check if reaction data for this API are available. If yes, the related data are retrieved through  
11 the search engine interface for further analysis as outlined in the work-flow of the framework  
12 [1]. If the data are not available, the properties of the API are predicted through associated  
13 property prediction tools available in the framework [1]. For the generation of the synthesis  
14 routes, Papadakis et al [2] give a detailed list of databases and systematic methods and tools  
15 based on artificial intelligence that may be employed. Other starting points are classes of  
16 reactions or specific reactants. With the synthesis routes established, the reaction database  
17 will determine the equilibrium constants for each reaction step and then suggest the minimum  
18 reaction data that would be needed to identify an appropriate kinetic model together with a list  
19 of corresponding experiments. Once all the necessary data are made available, the reaction  
20 and process evaluation are performed as outlined in the work-flow of the framework. It should  
21 be noted that the database contains collected data of known reacting systems, therefore, for  
22 new systems, data either need to be generated or collected. The search engine of the database  
23 points to the minimum data that are needed for any analysis and how the data could be  
24 obtained.

1 The application of the database is illustrated through the synthesis of ibuprofen, for which,  
2 data for three different reaction pathways are retrieved from the database and the production  
3 processes compared using the “green” chemistry metrics [2].  
4

## 5 **2.2 Solvent Selection and Database**

6 Solvent selection is part of the framework section dealing with downstream separation  
7 analysis. The complexity of product recovery and purification is related to the compounds  
8 present in the final reaction mixture. The selection of appropriate downstream separation tasks  
9 in terms of total number of operations needed, solvent requirements, operational costs, and  
10 sustainability, effect process performance and therefore, feasibility. In addition, due to the  
11 complexity of the main product, operational limitations are taken into account in order to  
12 define the design space of the separation operations. Methods and computer-aided tools for  
13 improvement of process efficiency through the use of solvents in multiphase and single-phase  
14 reactions [3] as well as solvents for crystallization [4], solvent based extractions [5] are  
15 studied through the solvent selection and design toolbox [6] available as an in-house tool  
16 within the framework [1]. The methods and tools available in the framework allows options  
17 for process intensification in terms of integration of reaction-separation tasks, minimization of  
18 reaction steps and solvent swapping options.  
19

## 20 **2.3 Simulation, evaluation, optimization and operation**

21 The objective here is to evaluate process flowsheets (or state task network) with respect to  
22 predefined performance criteria and identified targets for further process optimization and  
23 improvement. Available methods and tools allow the design and evaluation of PAT systems,  
24 study of crystallization operations, and study of process operations, including feasibility of  
25 converting batch operations to continuous modes. Note that different kinds of models and



1 model- and/or data-based analyses are needed for study of different aspects of pharmaceutical  
2 processes. Continuous or batch pharmaceutical process evaluation requires conventional  
3 single scale models based on mass and energy balance that are usually available in process  
4 simulators and also available in the framework [1]. However, since the pharmaceutical  
5 product also needs to satisfy product quality requirements, higher resolution models and/or  
6 online data are needed for product quality monitoring through an appropriate PAT system  
7 [19]. Here, multiscale models for crystal size distribution, crystal shape, effect of operational  
8 parameters, etc., need to be considered. This model-data based analysis is needed in addition  
9 to analysis of simulation results based on mass and energy balance for a complete evaluation  
10 of pharmaceutical processes. Papadakis et al. [7] provides an interesting illustration of model-  
11 based methods and tools for design and analysis of an industrial glucose isomerization  
12 process operation.

13

### 14 **3. Process intensification technologies**

15 Process Intensification (PI) is defined as a set of novel innovative principles applied in  
16 process and equipment design, which can bring significant benefits in terms of process and  
17 chain efficiency, lower capital and operating expenses, higher quality of products, less wastes  
18 and improved process safety. In other words it helps chemical engineers to achieve more (e.g.  
19 higher performance and efficiency) with less equipment and energy. Novel methods have  
20 been proposed recently for the and systematic process design and intensification, based on  
21 new representation of process units, flowsheets and superstructures using fundamental  
22 building blocks [8]. Such a general block-based superstructure allows the systematic  
23 identification of process intensification pathways.

24 Among PI technologies proposed, the most promising ones are in the functional (synergy)  
25 domain, as they integrate functions and steps into a single unit, thus taking advantage of

1 synergistic effects to overcome equilibrium limitations, leading to compact equipment and  
2 increase of overall efficiency. The PI area is expanding rapidly with tremendous support from  
3 industry, having a strong impact and significance for the development of more eco-efficient  
4 processes (see the RAPID institute in US). The scope of PI covers many technologies [9], but  
5 here we focus only on the most promising ones: reactive distillation and dividing-wall  
6 column, Figure 2. These PI techniques are able to simplify complex configurations, and thus  
7 reduce the numbers of steps required for reaction and separation stages.

8

### 9 **3.1. Reactive distillation technology**

10 Reactive distillation (RD) allows the reaction and distillation to take place at the same time in  
11 the single piece of equipment; the reactants being converted with the simultaneous separation  
12 of the products. By overcoming equilibrium limitations, RD brings ample process economic  
13 benefits, as it enhances the productivity and selectivity, reduces the energy use, eliminates the  
14 need for solvents, and intensifies the mass and heat transfer [10]. Moreover, RD simplifies  
15 complex process configurations and reduces the overall costs by half or more. For example, in  
16 case of methyl acetate synthesis a RD column replaced a conventional process consisting of  
17 10 key units (1 reactor, 8 distillation columns and 1 extraction column), allowing 80% savings  
18 in energy and capital costs.

19 Although RD has been implemented as high-efficiency systems in the large scale petro-  
20 chemical industry, more recently the RD technology found novel applications in the batch-to-  
21 continuous transition and synthesis of many products from the specialty chemicals, fine  
22 chemicals and pharma sectors: e.g. esters, ethers, monomers and polymers [11]. Remarkable,  
23 reactive distillation could be further enhanced by combining it with other intensified  
24 technologies – such as dividing-wall column, cyclic distillation, high-gravity distillation, heat-  
25 integrated distillation column, as well as membrane-, microwave- or ultrasound-assisted

1 distillation – to lead to the development of new processes and applications, particularly  
2 aiming at smaller scale of 10 ktpy or less [12].

3

### 4 **3.2. Dividing-wall column technology**

5 Dividing-wall column (DWC) found great appeal in the chemical industry as it offers major  
6 benefits: 25-40% lower energy requirements, high purity for all product streams, reduced  
7 maintenance costs, 40% smaller small footprint and up to 30% lower investment costs due to  
8 the reduced number of equipment units. Thermodynamically equivalent to Petlyuk distillation  
9 or fully thermally coupled distillation, DWC can replace a direct or indirect sequence of  
10 distillation columns by a more energetically-favorable configuration that avoids the remixing  
11 of internal streams. Details about the specific internals of DWC are available at equipment  
12 suppliers ([www.montz.de](http://www.montz.de)) and in recent review papers [13], [14]. Although DWC is mainly  
13 applied to ternary separations, more recent applications and research directions include the  
14 use of DWC technology in azeotropic, extractive, and reactive distillation [15]\*\*, [16], for  
15 example in the production of bio-alcohols, ethers, or furfural. By using an adaptable and  
16 flexible modular approach, the DWC can be applied in multi-purpose production scale and  
17 downstream processing of fine chemicals and pharmaceuticals. For example, Lonza has  
18 recently implemented in Visp, Switzerland, a flexible DWC that meets the demands of a  
19 changing production characterized by several production campaigns, processes and products  
20 produced in the same plant throughout a year [17].

21

### 22 **4. Filtration technologies in the context of continuous manufacturing**

23 Manufacturing in the pharmaceutical industry is presently almost entirely dictated by batch  
24 processes. This is the result of decades of strongly regulated historical batch processing.  
25 Nevertheless, there is a strong incentive to shift from batch to continuous manufacturing of

1 active pharmaceutical ingredients (APIs) and to leverage the advantages of steady-state  
2 operation [18]. Although pharma is a highly regulated and largely batch-oriented industry, the  
3 use of novel continuous manufacturing can lead to innovative products and help pharma  
4 companies resolve some long-standing issues related to cost, quality inspection, and supply  
5 chain. With an increased interest both from the industry, academia and regulatory bodies over  
6 the last 10 years [19], companies have adopted different approaches to integrate the process  
7 analytical technology [20] based continuous manufacturing technology in their  
8 manufacturing lines. While a lot of R&D has been focusing on continuous reaction and  
9 crystallization design, operation and control [20], little has been dealing with the interface  
10 between these two manufacturing clusters namely continuous isolation. This is because  
11 continuous isolation for APIs, e.g. continuous filtration, is a major technical challenge and  
12 involves the use of less established technologies. Nevertheless, recently, the versatility,  
13 flexibility and efficiency of continuous filtration has raised the interest of companies.

14 The current approaches to continuous filtration taken by R&D organizations can be clustered  
15 into two main strategies: automated batch filtration [21] and continuous flow filtration [22]\*\* ,  
16 Figure 3a and 3b. While the former is based on the well-established Nutsche filtration and is  
17 mainly an automation exercise, the latter requires integrating a less common technology to  
18 pharmaceutical development that is the cross flow filtration (CFF), which is a standard  
19 technology for the biotechnology industry. In both cases though, the main challenge lies in the  
20 fact that little to no continuous filtration equipment is designed to the standards of the  
21 pharmaceutical industry e.g. Good Manufacturing Practices (GMP), which triggers significant  
22 and cost intensive technology development and qualification efforts.

23 To best compare these two processes one has to consider in which context these will be  
24 implemented. A Nutsche continuous filtration will produce a cake with ca. 20-30% of residual  
25 moisture content, which is subsequently dried and analyzed. In comparison a CFF process

1 will produce a well flowing concentrated suspension (wet paste) which is suited for further  
2 processing [23]. While the cake filtration rate is dependent on the API crystal shape, which  
3 can vary from product to product, the CFF is less dependent on it, thus makes it a more  
4 versatile process. One should note that washing in CFF is consuming much more solvent than  
5 the Nutsche filtration. This disadvantage increases when equipment is scaled-up. Furthermore,  
6 CFF filtration can be easily integrated within continuous manufacturing and will leverage its  
7 advantages when coupled with other continuous processes. However, it can be also be a  
8 versatile filtration process coupled to classical batch manufacturing steps.

9

## 10 **5. Outlook**

11 The main challenge for methods and tools from PSE for applications in the pharmaceutical  
12 industry is how to provide reliable process understanding through the available data and  
13 models that are employed? With new chemicals being continuously synthesized, clearly,  
14 reliable predictive models and data analysis tools are needed together with a data collection  
15 system that is continuously extended with availability of new data. The objective here is not  
16 to provide the final optimal solution through these model-data based methods-tools, but to  
17 quickly reduce the search space so that the product development time and cost can be  
18 significantly and reliably reduced.

19 The main challenges of applying PI technologies such as reactive distillation and dividing-  
20 wall column to the production of fine chemicals and pharmaceuticals relate to ensuring  
21 sufficient modularity and flexibility in a low production scale multi-product environment, as a  
22 higher degree of process integration comes at reduced flexibility in operation. Such PI  
23 techniques can aid the batch-to-continuous transition by properly adapting them to multi-  
24 purpose production scale and downstream processing of fine chemicals and pharmaceuticals.

1 Regarding the routine use of continuous filtration in the pharmaceutical industry future  
2 challenges are related to equipment standardization of equipment and adequate process  
3 control.

4

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8

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10

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17

## 18 **Figures**

19 **Figure 1. Integrated systematic framework to assist the pharmaceutical process**  
20 **development.**

21 **Figure 2. Configurations for reactive distillation (top) and dividing-wall column**  
22 **(bottom)**

23 **Figure 3 Two continuous filtration strategies, a CFF from Bokela (a) and an automated**  
24 **Nutsche filtration (b) from Alconbury Weston Ltd.**

## General framework to enhance process understanding during the early stage chemical/bio/pharma process development

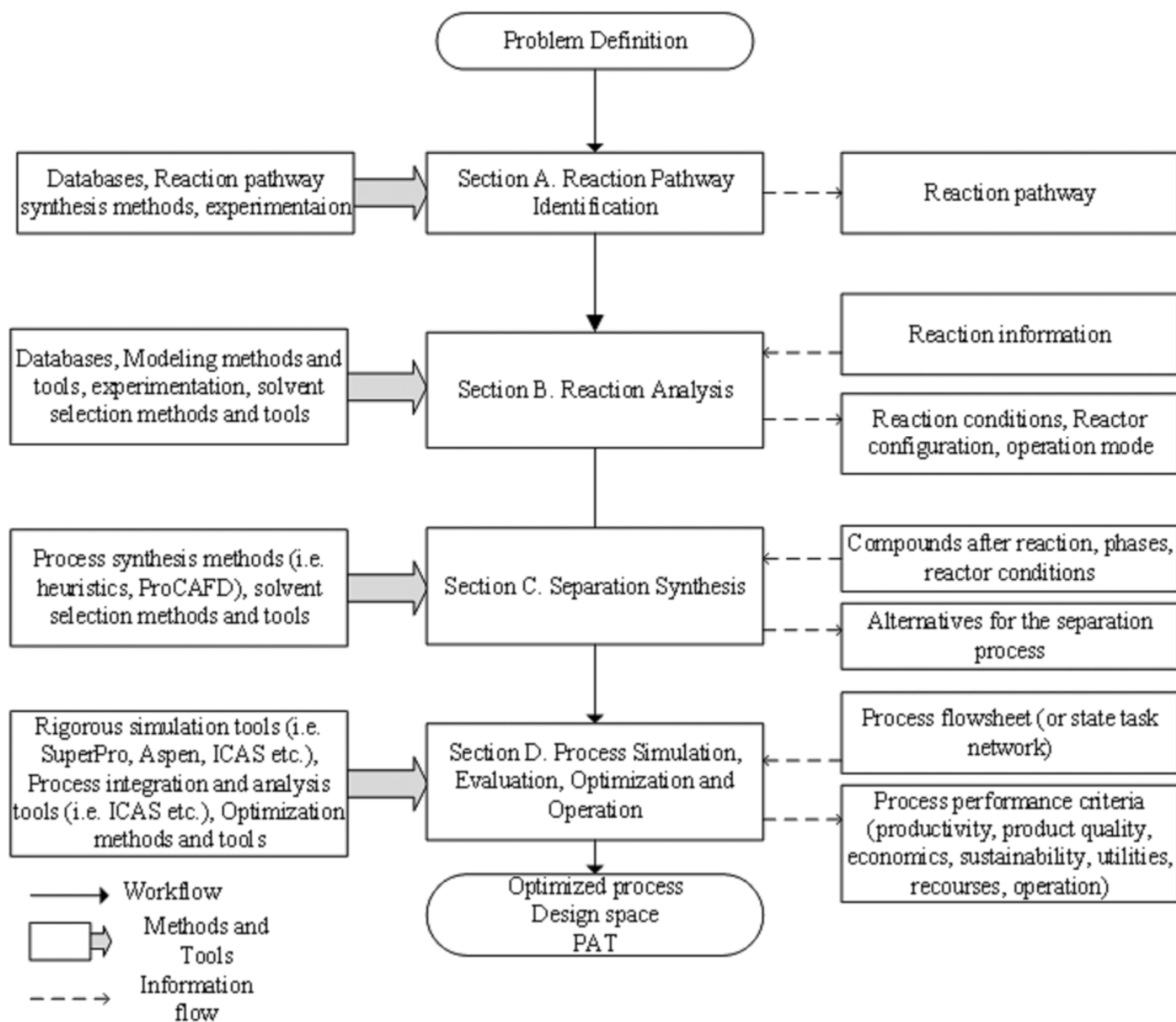
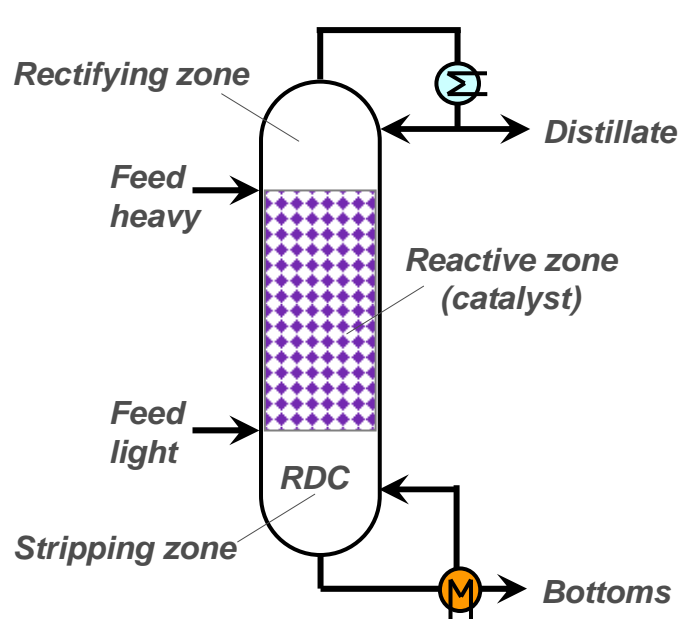
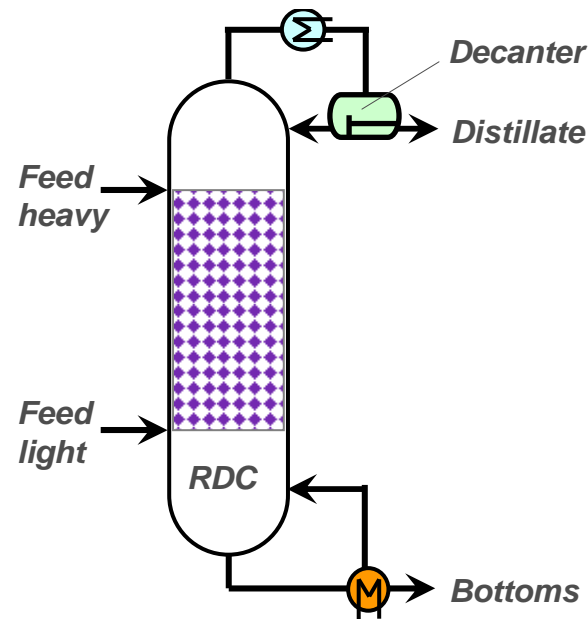


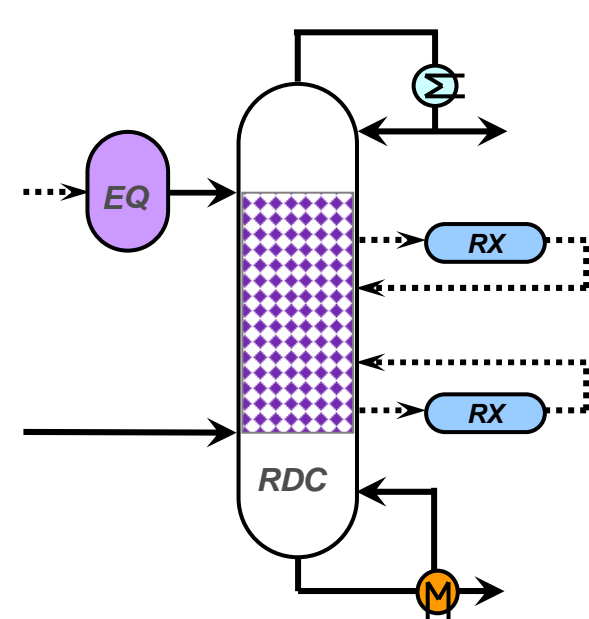
Figure 1



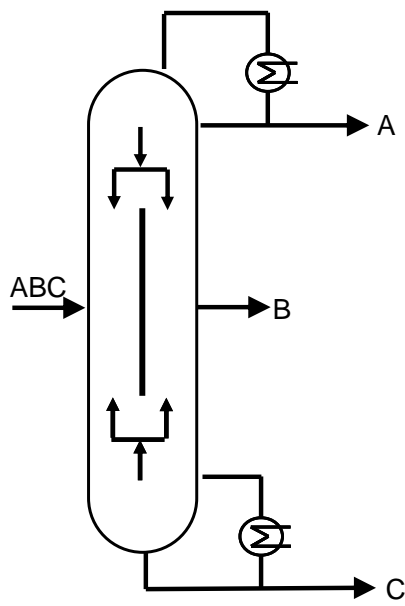
Reactive distillation column



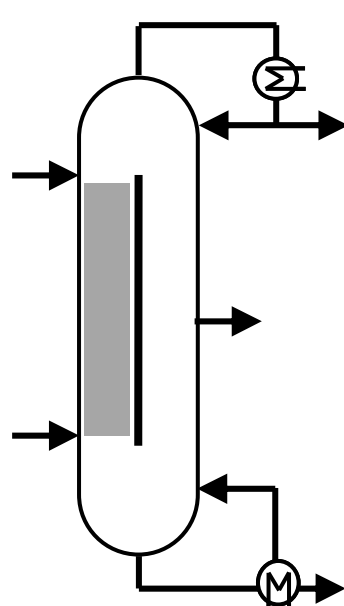
Heterogeneous azeotropic RD



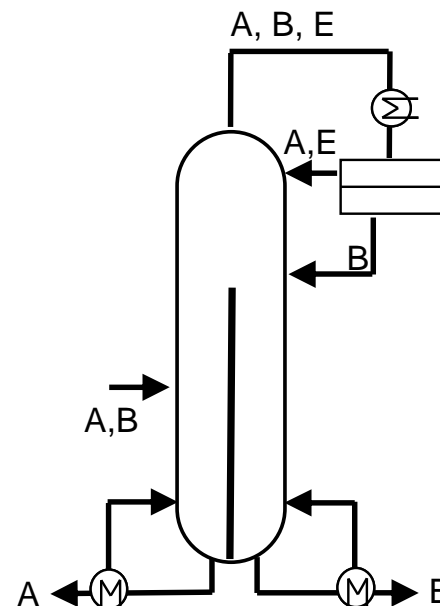
RD with pre-reactor & side reactors



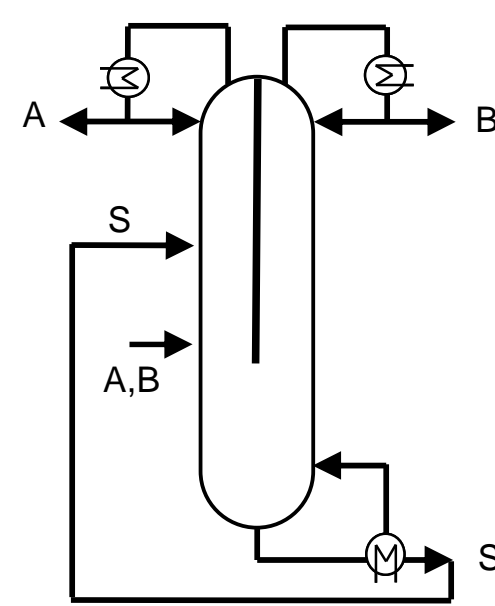
Dividing-wall column



Reactive DWC



Azeotropic DWC



Extractive DWC



Membrane

Rotor



Figure 3