Chapter 2
Fundamentals of Process Intensification: A Process Systems Engineering View

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Abstract This chapter gives an overview of the fundamentals of process intensification from a process systems engineering point of view. The concept of process intensification, including process integration, is explained together with the drivers for applying process intensification, which can be achieved at different scales of size, that is, the unit operation scale, the task scale, and the phenomena scale. The roles of process intensification with respect to process improvements and the generation of more sustainable process designs are discussed and questions related to when to apply process intensification and how to apply process intensification are answered through illustrative examples. The main issues and needs for generation of more sustainable process alternatives through process intensification are discussed in terms of the need for a systematic computer-aided framework and the methods and tools that should be employed through it. The process for the production of methyl-acetate is used as an example to highlight the generation of more sustainable process alternatives through this framework. Perspectives, conclusions, and future work are proposed in order to further develop the field of process intensification using a systems approach.

2.1 Introduction

The objective of process synthesis is the selection of the best (optimal) process flowsheet from among numerous alternatives for converting specified raw materials into specific desired products, subject to predefined performance criteria [1]. More

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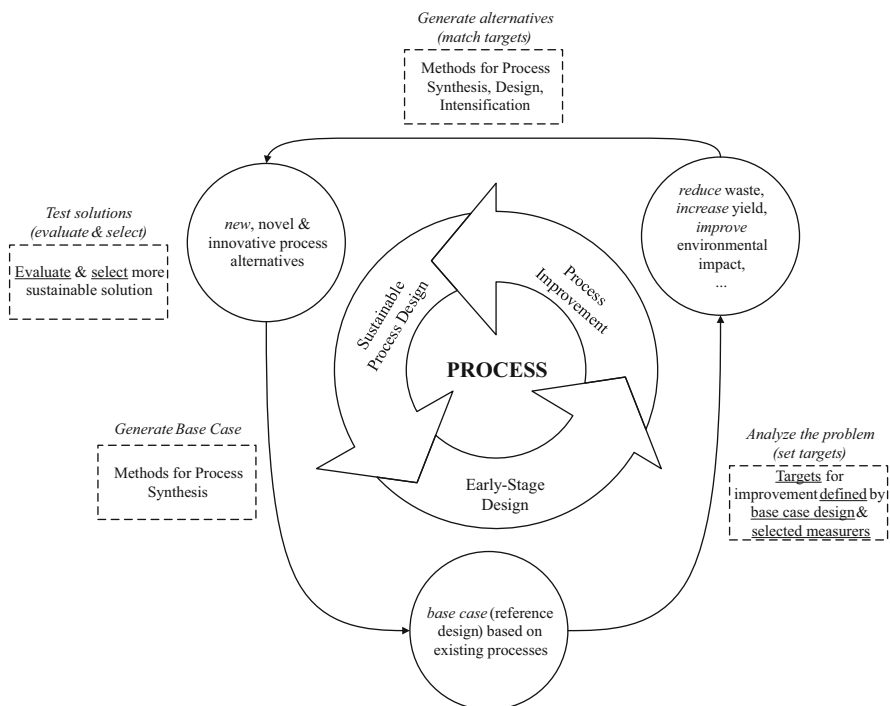
Fig. 2.1 Role of process intensification within sustainable process design

sustainable design is defined as the design of process flowsheets that correspond to lower values of a set of targeted performance criteria based on economical, operational, and environmental factors [2]. As shown in Fig. 2.1, the sustainable design is obtained through improvements with reference to the early stage design (also called reference design or base-case design). The role of process synthesis in finding the early stage design and/or the more sustainable design is to generate the feasible process alternatives. The generation of alternatives can be done in various ways, for example, trial and error, rule-based heuristics, process integration (mass and energy), process optimization, process intensification, and many more. In this chapter, process intensification, which also includes process integration, is presented. Through the improvements as shown in the middle layer of Fig. 2.1, the following improvements related to the physical system can be obtained through process intensification [3]:

- Catalysts—the screening and selection of novel catalysts for reactive systems
- Solvents—the generation, screening, and selection of environmentally friendly solvents for separation processes
- Materials—the design of new materials for the design of novel, innovative unit operations that combine reaction, separation, or reaction–separation systems

- Energy—the use of process integration concepts to generate more sustainable process alternatives with respect to reduced waste and environmental impact

Process intensification has been receiving increased attention and importance because of its potential to obtain innovative and more sustainable process design alternatives. But what is process intensification? Many definitions have been proposed for process intensification and a few are highlighted here. Stankiewicz and Moulijn [4] defined process intensification as the development of novel and sustainable equipment that compared to the existing state-of-the-art, produces dramatic process improvements related to equipment sizes, waste production, and other factors. Reay et al. [5] defined process intensification as process development that involves reduction in equipment (unit operation) sizes that lead to improvements in reaction kinetics, better energy efficiency, reduction in capital cost, and improvement in process safety. Ponce-Ortega et al. [6] defined process intensification as an activity characterized by five principles—reduced size of equipment, increased throughput of process, reduced equipment holdup or inventory, reduced usage of utilities and raw materials, and, increase efficiency of process equipment. The above definitions provide insights into the different scales at which process intensification can be employed.

With the exception of process integration, there are, however, not many published methods to determine the intensified solutions for processes, even though successful intensified solutions have been reported by many. Examples of process intensification methods have been proposed at unit operation scale by Bessling et al. [7], at task scale by Agreda et al. [8] and at phenomena/molecular scale by Freund and Sundmacher [9]. These methods however, mainly focus on the design of new/novel unit operations that enhances/integrates a particular set of tasks and/or phenomena within the process, but does not consider the interaction of the rest of the unit operations that constitute the final (total) process design. They are also specific to the characteristic of the unit operations studied.

With a systematic and generic method for find process intensification solutions, Lutze et al. [10] recently proposed a definition for process intensification that covers all three scales and consider the overall process. According to Lutze et al. [10], process intensification is defined as the targeted improvement of a process at the unit operations scale, the task scale, and/or the phenomena scale. With overall improvement as the objective, at the unit operations scale the individual equipment that constitute the final process design of any chemical or biochemical process is identified and/or designed; at the task scale, the functions (tasks) performed by each unit operation are identified and analyzed; and, at the phenomena scale, the phenomena that satisfies the tasks to be performed are identified and analyzed. In this way, links between the scales are established and allows the search in various scales to find the design of new, innovative, and sustainable processes. This method can be applied to the design of new processes as well as, the retrofitting of existing processes, in order to make them more sustainable. This concept of scales is illustrated through Fig. 2.2 where at the lower scales, a small set of tasks and phenomena are employed to represent various
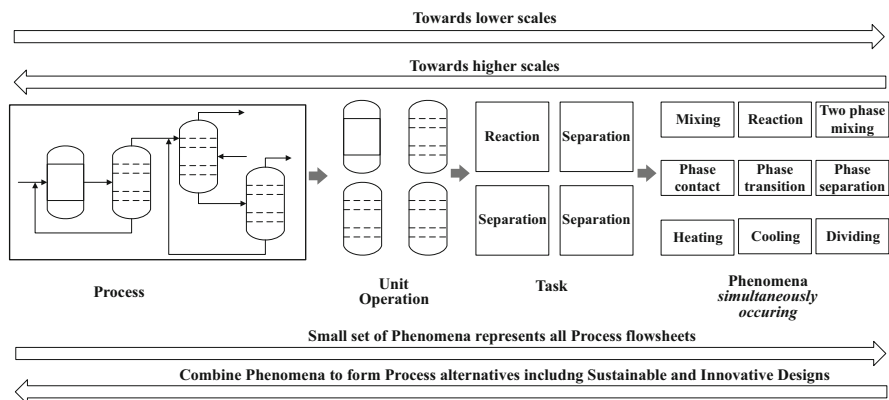
Fig. 2.2 Multiscale method for process intensification

process flowsheet alternatives. Moving from the higher to the lower scale increases the possibility for process innovation because of the following reasons:

- New alternatives that match the functions of unit operations can be generated through the combination of tasks, leading to new flowsheet alternatives.
- New ways to perform tasks can be generated by combining different phenomena, leading to the generation of novel and (more sustainable) flowsheet alternatives.

Therefore, if processes are designed at scales lower than the unit operation scale, there is an increased chance of finding a more sustainable overall process design. This is highlighted by the process intensification solutions reported by Agreda et al. [8] and Siirola [11] for the production of methyl-acetate from the reaction of methanol and acetic acid. Papalexandri and Pistikopoulos [12] proposed the idea of combination of phenomena to generate new unit operations. Peschel et al. [13], Lutze et al. [10, 14] and Babi et al. [2] illustrate the use of phenomena-based approaches to achieve process intensification.

Process integration can be considered as a special case of process intensification and is commonly defined as the design and analysis of the best (optimal) network for mass and energy utilization applied to the design (or retrofitting) and operation of new as well as existing processes [15]. Consequently, process integration is concerned with two integration concepts within a chemical (and biochemical) process—mass and/or energy integration [16, 17]. Mass integration is the efficient utilization of mass within the process (for example, minimization of fresh water use in a process) through the analysis and optimization of mass flows within the process. Analogously, energy integration is the efficient utilization of energy within the process (for example heat integration) through the analysis and optimization of energy needs within the process. As the use of water and energy are related to the performance criteria for more sustainable designs and are achieved through the integration of two or more operations, they are therefore also regarded as special cases of process intensification. Methods for performing process integration focus

on the selection and combination of existing as well as novel process technologies in the best (optimal) manner for the efficient use and utilization of mass and/or energy. Therefore, in this chapter, unless otherwise indicated, PI includes process intensification as well as process integration.

The objective of this chapter is to present and discuss the fundamentals of process intensification. First, the concept of PI is introduced, followed by a discussion on when and how to employ PI? This includes a discussion on the role of process intensification in sustainable process design as well as the connection between process integration and process intensification. Also, examples of successful application of process intensification are given. Next, the methods and tools needed to determine process intensification solutions are presented in terms of a general mathematical problem formulation, a brief overview of the different solution techniques, the need for a systematic computer-aided framework, and the associated methods and tools. The application of this framework is highlighted through a case study involving the production of methyl-acetate by reaction of methanol with acetic acid. The chapter ends with a discussion of perspectives, conclusions, and future work on the role of process intensification in relation to the design of more sustainable and innovative processes as well as pointing out some of the recent achievements. Note that even though process integration is regarded as a special case of process intensification, it is only briefly covered in this chapter. Also, recent developments on process integration can be found in the review of the state-of-the-art by Klemes et al. [18].

2.2   When and How to Apply PI?

In the chemical and biochemical process industry, improvements in economic as well as environmental factors are required for new as well as existing processes [3, 19]. PI plays a major role in achieving the desired improvements in processing options through the design of processes that constitute more sustainable alternatives, that is, hybrid/intensified unit operations (equipment). A hybrid/intensified unit operation, is an operation that enhances the function of one or more unit operations for performing a task or a set of tasks through a new design of the unit operation or the combination of more than one unit operations. For example, reactive distillation is a combination of reaction and separation (see Fig. 2.3a) and a membrane reactor is a combination of reaction and in situ removal of a reactant or product (see Fig. 2.3b).

Process Integration can be applied in the following forms for achieving process improvement:

- Heat integration (heat exchanger networks) where energy efficiency is increased through energy consumption minimization. This was the first type of process integration, first developed by Linnhoff et al. [20] and further extended and
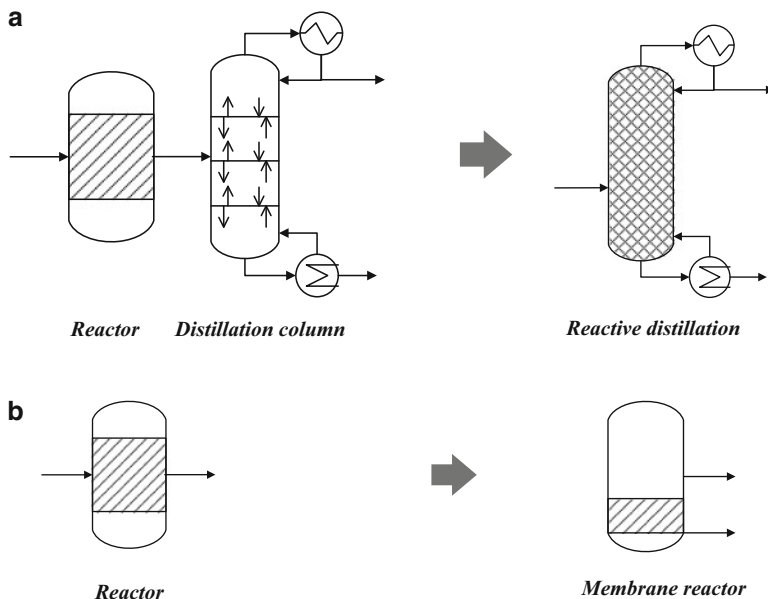
Fig. 2.3 Examples of hybrid/intensified unit operations: (**a**) reactive distillation (**b**) membrane reactor

solved using a mixed integer non-linear programming (MINLP) approach by Papoulias and Grossmann [21].
- Mass integration (mass exchanger networks) where the flow route of mass within the process is optimized, for example, through the use of concentration differences [16, 18].
- Supply-chain management where the total supply-chain cost (related to suppliers, storage, retailers, customers etc.), is minimized based on the concepts applied for heat and mass integration [18, 22].

The impact of process integration on cost reduction and environmental factors have been reported by numerous authors, see for example, Papoulias and Grossmann [21], Singhvi et al. [22] and Kazantzi and El-Halwagi [23] for overall capital cost and/or operating cost reduction through increased process integration. As the cost reduction due to more efficient use of energy and water resources is achieved, it also reduces the waste and has a positive impact on the environment, making the process thereby more sustainable.

Babi et al. [24] proposed a 3-stage sustainable process synthesis–design method (see Fig. 2.4) including the use of PI. According to this method, in the first stage, the optimal processing paths are synthesized to convert a set of raw materials into a desired set of products. In the second, the optimal processing path (flowsheet) is selected for further study that includes identification of the process bottlenecks or hot-spots. These hot-spots help to define targets for improvement, which when
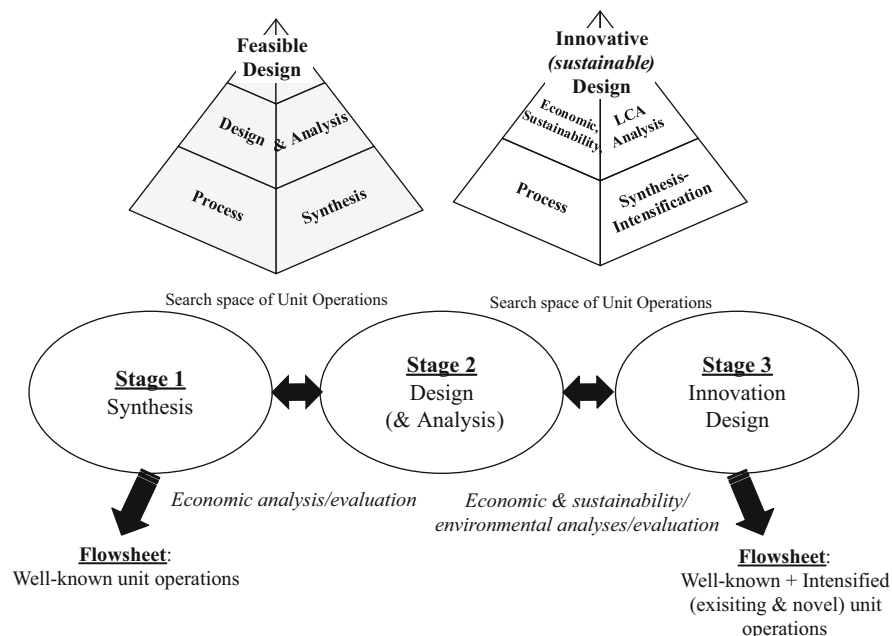
Fig. 2.4 Three-stage sustainable process design method that incorporates PI

matched would lead to more sustainable and innovative solutions. In the third-stage, methods with or without considering PI are applied to generate process alternatives that match the desired targets for process improvements. Here, applications of different PI methods are possible.

From Fig. 2.4, it can be noted that for existing processes with already identified hot-spots, entry to the 3-stage method is at stage 3. Alternatively, if the process exists but the hot-spots have not been identified, then the entry to the 3-stage method is at stage 2, while for a totally new process synthesis problem, the entry is at stage 1. Therefore, opportunities to apply PI exist whenever deficiencies (bottlenecks or hot-spots) in design and/or operation of a process are identified. A classic example is the flowsheet (see Fig. 2.5) for the production of methyl-acetate by reaction of methanol with acetic acid. Can the number of unit operations be decreased? Can the product yield and purity be increased? Can the process be made more sustainable? As Fig. 2.3b indicate, the answer is yes. Another classic example in the case of heat integration is the combination of a heat exchanger that needs to reduce the temperature of a stream with another that needs to increase the temperature of a stream. Integration in this case saves energy as well as cooling medium and thereby makes the process after integration more sustainable.

As the definition of PI implies, to apply PI, a combination of operations, tasks, and/or phenomena need to occur simultaneously subject to the specified objectives and constraints of the process. That is, which combination of operations, tasks,
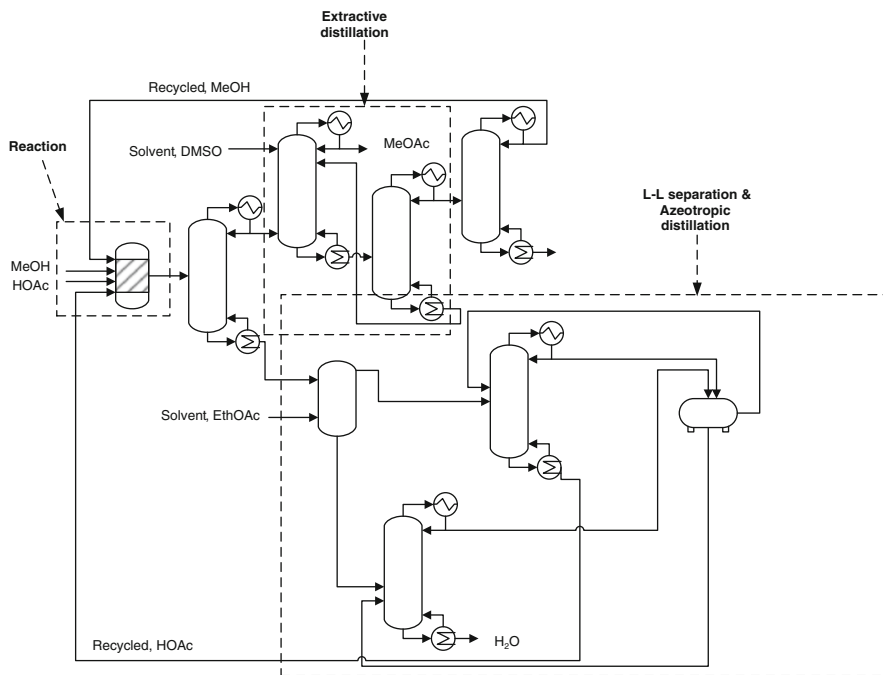
Fig. 2.5 When to apply PI—process flowsheet for the production of methyl-acetate

and/or phenomena would lead to an alternative that is better than the base-case design according to a set of performance criteria and subject to the principal requirements of PI? Siirola [11] proposed a combination of tasks that lead to the well-known intensified solution of a reactive distillation column for the production of methyl-acetate (see Fig. 2.5). Babi et al. [24] proposed a phenomena-based approach where combinations of a set of phenomena lead to a set of tasks, whose combinations lead to a set of new or existing unit operations that when combined give a final set of PI solutions. Babi et al. [24] also illustrated their method to the methyl-acetate production and reported same reactive distillation solution as well as other feasible PI solutions.

Through the use of intensification design concepts, novel hybrid/intensified unit operations (see Table 2.1) that exploit mechanisms (phenomena) related to, for example, heat and mass transfer are determined. Heat-transfer mechanisms are enhanced through the use of passive and active techniques, for example, rough surfaces (passive) and electrostatic fields (active). Mass transfer mechanisms are enhanced through the use and enhancement of three external physical characteristics, rotation (for example, use of a rotor), vibration (for example, high frequency ultrasound), and mixing (for example, inline mixers) [5]. In a reactive distillation, on the other hand, the phenomena of reaction and separation (for example, vapor–liquid equilibrium) take place simultaneously on every stage or transfer unit.

Table 2.1 List of reported hybrid/intensified unit operations

Unit operation (equipment)	Techniques for equipment intensification	Application	Reference
Compact heat exchanger	Channel size reduction	Power generation	[25]
Foam heat exchanger	Surface enhancement by metal-coated polymer foam	Micro-power generation	[26]
Micro-heat exchangers	Chemical etching	"Lab-on-a-chip"	[27]
Spinning disk reactor	Rotation and agitation of catalyzed disks	Pharmaceuticals-Darzen's reaction	[28]
Membrane reactors	Combination of reactor and membrane unit	Esterification reactions	[29]
Reactive distillation	Combination of catalyst (for reaction) and distillation	Esterification reactions	[11]
Divided-wall column	Thermal coupling of two adjacent columns into a single column	Extractive distillation	[30]
Deodorizer	Surface enhancement by metal-coated surface	Deodorization	[31]
HiGee (rotating disks)	Metal foam inside a rotating pack-bed	De-aeration	[32]
Inline mixers	Use of baffles	Polymer processing	[33]

Another similar example is a membrane reactor, which provides the opportunity for in situ product/by-product removal thereby simplifying the downstream processing steps [29, 34]. Table 2.1 lists various hybrid/intensified unit operations and their reported area of application.

The synthesis of heat exchanger networks using a pinch-based temperature interval method was first introduced by Linhoff and Flower [35] for energy (heat) integration. The method utilizes concepts based on thermodynamic and physical insights. The minimum utility requirements (heating and cooling) are identified first, followed by the design and analysis of an (heat) exchanger network. However, this method does not guarantee the best (optimal) solution to the energy integration problem, that is, the use of the minimum number of heat exchangers for the design of the integrated heat exchanger network. Therefore, the synthesis of heat exchanger networks was further developed using mathematical programming, see for example, Papoulias and Grossmann [21]. Here, the heat integration problem is defined as a MINLP problem that can be reduced to a mixed integer linear programming (MILP) problem for design and analysis of the optimal integrated heat exchanger network.

Similar concepts as proposed by Linhoff and Flower [35] have been extended to the design and analysis of mass exchanger networks; see for example, El-Halwagi and Manousiouthakis [36]. The minimum mass requirements, that is, the amount (mass) of a targeted species p that can be transferred into a lean process stream (above the mass pinch point) and the minimum amount (mass) of an external mass separating agent required for removal of the targeted species p (below the
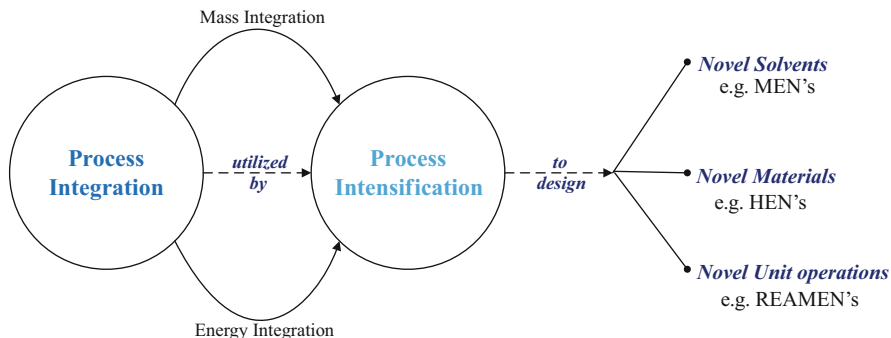
Fig. 2.6 The utilization of process integration in process intensification. Examples of process intensification that employ mass and energy integration are shown. *MEN* mass exchanger network, *HEN* heat exchanger networks, *REAMEN* reactive mass exchanger network

mass pinch point) are first identified followed by the design of the best (optimal) mass exchanger network.

Process intensification also utilizes the concepts from process integration in order to design hybrid/intensified unit operations that integrate mass and/or energy within a single-unit operation and/or reduce the number of unit operations, compared to a conventional process. This is shown in Fig. 2.6. As an example, consider a divided-wall column (single-unit operation) that integrates the separation of a ternary zeotropic mixture (mass) having a lower utility consumption (energy) compared to the conventional approach that uses a two-column sequence [24].

At whichever scale, process intensification is performed, the output is expected to be a better, more sustainable process compared to a selected reference (base-case) design. Stankiewicz and Moulijn [37] proposed that process intensification can be decomposed into two main classifications [9], intensified unit operations (hybrid/intensified equipment) and intensified methods. This is shown in Fig. 2.7. In each classification different subclassifications can be made with respect to intensified unit operations and available methods.

Since according to Fig. 2.7, multiple intensified unit operations exist, therefore, there is a need for the development of intensified methods that incorporate within their search space these unit operations for the design of (sustainable) chemical and biochemical processes. However, to go beyond the current search of these hybrid/intensified unit operations and to find truly predictive methods that also provide the opportunity to generate and design novel, innovative unit operations, these methods must operate at lower scales, for example, the phenomena/molecular scale [10, 38]. Table 2.2 provides examples of process intensification at the unit operations scale, task scale, and phenomena scale.
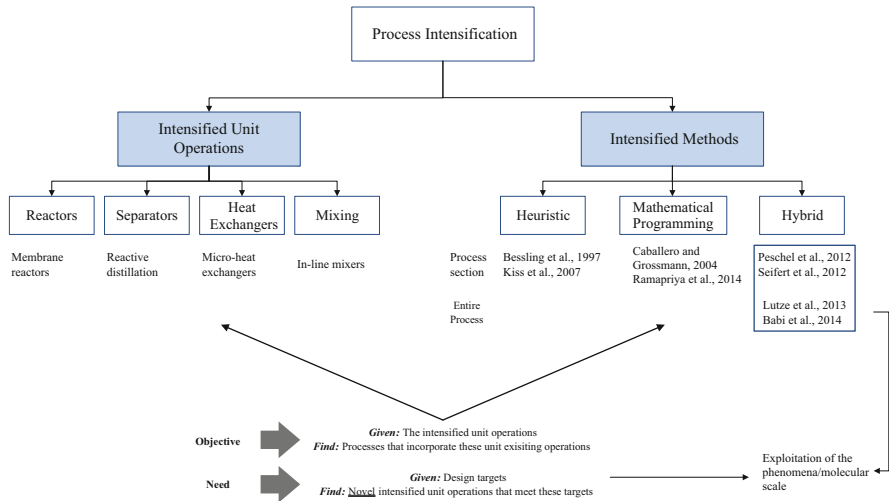
Fig. 2.7 Classification of PI operations

Table 2.2 List of PI solutions at different scales: unit operations, tasks, and phenomena

Process	Hybrid/ intensified unit operation	Remarks	Reference
	Unit operations		
Production of ethyl acetate	Pack-bed reactive distillation	Analysis of homogenous/heterogeneous catalysts and process operation conditions	[39]
Separation of acetone–butanol ethanol	PDMS/ceramic composite membrane	Analysis of molecular transport during pervaporation	[40]
Waste water treatment	Bioreactor	Kinetic study for the effect of oxidation processes	[41]
	Task (functional)		
Production of methyl-acetate	Reactive distillation	Integration of all reaction and process tasks	[8]
Crystallization	Crystallizer coupled with ultrasounds	Effect of paracetamol crystallization	[42]
Transesterification of DMC with ethanol	Microwave-assisted reactive distillation	Investigation of the impact of enhancing the reaction mechanism using micro-wave heating	[43]
	Phenomena/ Molecular		
Production of ethylene oxide	Membrane-based reactor	Analysis of a novel reactor design concept	[38]
Production of iso-propyl acetate	Plate-frame-flow reactor-pervaporator	Analysis of a novel reaction–separation reactor	[10]
Production of dimethyl-carbonate	Divided-wall column	Analysis of the effect on separation for dimethyl-carbonate and methanol	[24]

2.3   Methods and Tools for Achieving PI

The general sustainable process design problem highlighted in Fig. 2.3 can be formulated mathematically through (2.1)–(2.5)

$$\min/\max F_{\text{obj}} = F_{\text{obj}}(x, y, d, z, \Theta)$$
$$s.t. \tag{2.1}$$

$$h_1(x, y, d, z, \Theta) = 0 \tag{2.2}$$

$$b^u \leq B_1 x + B_2 y \leq b^u \tag{2.3}$$

$$h_3{}^l \leq h_3(x, y) \leq h_3{}^u \tag{2.4}$$

$$g^l \leq g(x, y) \leq g^u \tag{2.5}$$

where

$$y_j = 0/1, j = 1, 2, \dots n_y, x \geq 0 \tag{2.6}$$

The objective function to be minimized/maximized is defined by (2.1) and is subject to a set of design and optimization variables x; a set of binary decision integer variables y (0, 1); a set of equipment variables d; a set of thermodynamic variables z; and a set of process specifications Θ. Equation (2.2) represents a system of linear and/or non-linear process model equations. The process models are considered at steady state consisting of phenomena and, mass and energy balance equations. Note that in general, process models can be used for steady state, dynamic, or both. Equations (2.3) and (2.4) represent the process flowsheet physical constraints and equipment design specifications, for example, the process flowsheet structure and equipment design parameters. Equation (2.5) represents a set of intensification constraints, for example, intensified equipment design specifications and performance criteria (sustainability metrics and LCA factors) that the feasible (intensified) flowsheet alternatives must satisfy. Based on the mathematical formulation presented through (2.1)–(2.5), process synthesis-intensification is performed for the design of more sustainable processes that contain intensified/hybrid unit operations.

The process synthesis-intensification problem to be solved, (2.1)–(2.5), can be formulated as a MINLP problem when the objective function and/or constraints include both linear and non-linear equations and, binary integer variables (for the selection of phenomena, tasks, and/or unit operations). In order to manage the complexity for finding the best (optimal) solution to the synthesis-intensification problem, an efficient and systematic solution approach is required. One method is the decomposition-based solution strategy method where the problem is decomposed into a set of subproblems that are solved according to a predefined calculation order. Most of the subproblems require bounded solution of a subset of equations. The final subproblem is solved as a set of NLP or MILP.

Feasible, intensified flowsheet alternatives are identified as follows:

(a) First, the process model equations, (2.2), are solved subject to the constraints defined in (2.3) and (2.4) in order to generate a set of flowsheet alternatives.
(b) These alternatives are then evaluated using the intensification performance criteria, (2.5), in order to select a set of feasible (intensified) flowsheet alternatives.
(c) For the remaining flowsheet alternatives, the objective function value, (2.1), is calculated and ordered. The flowsheet alternative(s) that give the best (optimal) objective function value are selected as the more sustainable (innovative) designs.

Multiple performance criteria can be used in order to evaluate the opportunities for performing process intensification or process integration. A list of performance criteria [3, 10, 24] for the application of process intensification is given in Table 2.3 and are based on criteria defined at the unit operations scale, task scale, and phenomena scale.

2.3.1   Solution Approaches

Methods that have been developed for performing process intensification at the unit operations (process) scale, task scale, and phenomena scale, systematize the generation and selection of the best (more sustainable) intensified flowsheet design. In order to increase the efficiency of these methods, computer-aided tools have been developed in order to perform model-based analyses (for example, reactor analysis), environmental analyses (for example, LCA), etc.

The classification of methods for performing process synthesis can also be used for classifying the methods for process intensification. Process synthesis can be performed through the application of three types of methods, heuristic-based methods, mathematical programming and hybrid-based methods. In heuristic-based methods, knowledge-based methods that consist of sets of heuristic rules are applied [44–46]. In mathematical programming-based methods, an optimization problem is formulated and solved using a generated superstructure that contains a finite number of unit operations and their corresponding interconnections, commonly derived by making use of engineering judgement, heuristics, and/or thermodynamic considerations [21, 47, 48]. In hybrid-based methods the know-how of the previous two methods, heuristics and mathematical programming are utilized. These methods keep the simple structure of heuristic/knowledge-based methods, but replace the fixed rules with guidelines based on thermophysical insights, generated through the analysis of the behavior of the chemical system [49–51]. Hybrid methods move beyond the well-used unit operations scale and operate at different scales for performing process synthesis [11, 12].

For process intensification, unlike process synthesis, heuristic-based methods, and mathematical programming methods for the design of entire chemical and biochemical processes have not yet been proposed. However, methods for the

Table 2.3 Improvements and performance criteria for performing process intensification

Performance criteria	Improvements					
	Raw material utilization	Separation efficiency	Energy efficiency	Waste minimization	Process economics	Environment outlook
Effective use of resources (raw material)	*			*	*	*
New processing routes	*	*	*	*	*	*
Equipment capital investment		*	*		*	*
Utility consumption	*	*	*	*	*	
Sustainability metrics			*	*	*	
LCA factors			*	*	*	
Integration of unit operations (sustainable technologies)	*	*	*	*	*	*
Integration of tasks	*	*	*	*	*	*
Integration of phenomena	*	*	*	*	*	*

*Indicates the performance criteria that are used as a measure of improvements

intensification of specific parts (reaction and separation) of a process have been proposed. For heuristic-based methods, rule-based design decisions based on process know-how and thermophysical properties have been proposed for the use of reactive distillation [7] and reactive divided-wall columns [52]. For mathematical programming-based methods, methods for sequencing and selection of divided-wall columns [53, 54], for reactive distillation [55] and reactive distillation plus membrane separation [56], have been proposed.

Hybrid methods for process intensification have been proposed for intensification of an entire chemical and biochemical process and specific parts of a process. For intensification of specific parts of a process, Siirola [11] proposed the means–ends analysis that identifies tasks (based on expert knowledge) to satisfy a set of process specifications. Peschel et al. [13, 38] proposed a method for generating novel intensified reactor network designs based on elementary process functions and Seifert et al. [57] proposed a modular concept for process design where sections of a process are modularized in order to generate flexible process designs. For intensification of entire processes, Lutze et al. [10] and Babi et al. [2] proposed a phenomena-based method where the process phenomena are combined in order to fulfill tasks. Once these tasks are fulfilled, the combined phenomena are translated into unit operations. Such a method provides the opportunity to innovate because the generated unit operation from phenomena may either be novel (new, innovative) or existing.

2.3.2   Phenomena-Based Approach

A multi-level, multi-stage, computer-aided framework for process synthesis-intensification is highlighted. The framework offers process synthesis-intensification at the unit operations scale [58], at the task scale [11] and at the phenomena scales [10]. The framework is applied to the production of methyl-acetate (MeOAc) in order to generate intensified flowsheet alternatives inclusive of the well-known reactive distillation process proposed by Agreda et al. [8] using a phenomena-based synthesis method.

Concept of phenomena-based synthesis: This concept is similar to computer-aided molecular design methods [59] where molecules (similar in concept to unit operations) are designed subject to a set of target (desired) properties and using functional groups (different combinations of atoms, which are similar in concept to tasks) and/or atoms (similar in concept to phenomena) as the building blocks. Consider, for example, atoms that can be combined to form functional groups, in the same manner phenomena building blocks (PBBs) can be combined to form simultaneous phenomena building blocks (SPBs). These SPBs are combined to form operations in the same way that groups are joined together to form molecules. By combining building blocks at lower scales (molecules or PBBs), new molecules

and/or new process flowsheets are in principle obtained. Also, a small set of building blocks are used for representing multiple molecules and flowsheets.

Phenomena-based process flowsheet representation: The PBBs involved in a process need to be identified. This is done through the analysis of a knowledge-base of unit operations, the tasks that they perform and the phenomena that they employ. Based on a study of multiple chemical (and biochemical) processes, it was found that most processes can be represented by using the following eight PPBs: mixing (M) (including two-phase-mixing (2phM)), heating (H), cooling (C), reaction (R), phase contact (PC), phase transition (PT), phase separation (PS) and dividing (D).
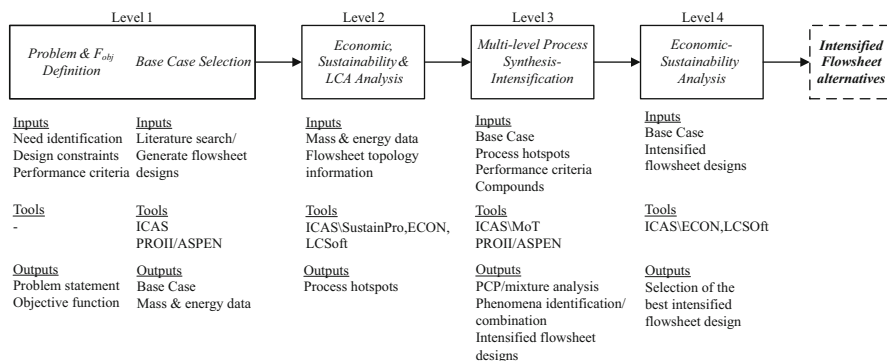
Combination of PBBs to represent tasks, unit operations and flowsheets: One or more PBBs are combined to form SPBs, subject to a set of combination rules that fulfill the objectives of any task. Two examples of these combination rules for combining PBBs are: (1) H and C PBBs cannot be combined to form SPBs because this combination is thermodynamically not feasible; (2) R and PT PBBs can be combined to form SPBs because the energy from an exothermic reaction can be used to drive simultaneous reaction–separation tasks. Note that other involved phenomena are then added to the SPB in order to complete the free connections. As an example of the final SPB for the R = PT combination, consider combining the following PBBs, M, 2phM, PC and PS, to fulfill the requirement of simultaneous reaction-reparation task, M = 2phM = R = PC(VL) = PT(VL) = PS(VL), where PT (VL) is a PBB representing a VL-separation task. A combination of SPBs forms operations that are translated to known or new (novel) unit operations that constitutes the final (more sustainable) flowsheet alternatives. An example of the representation of a reactive distillation (RD) column using SPBs having a reactive section is shown in Fig. 2.8.

The multi-level computer-aided synthesis-intensification framework: The multi-level framework is presented in Fig. 2.9. The input and output of each stage is highlighted together with the different computer-aided tools used at the different levels of the synthesis-intensification framework. The computer-aided tools are available in the updated version of ICAS version 17 [60], except for the commercial process simulators (PROII and ASPEN).
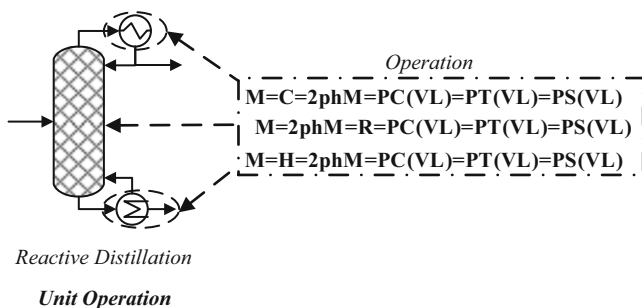
Fig. 2.8 Combination of SPBs to form an operation that fulfill a task (for example, a reaction-separation task)

Level 1		Level 2	Level 3	Level 4	
Problem & F_{obj} Definition	*Base Case Selection*	*Economic, Sustainability & LCA Analysis*	*Multi-level Process Synthesis-Intensification*	*Economic-Sustainability Analysis*	***Intensified Flowsheet alternatives***
Inputs Need identification Design constraints Performance criteria	Inputs Literature search/ Generate flowsheet designs	Inputs Mass & energy data Flowsheet topology information	Inputs Base Case Process hotspots Performance criteria Compounds	Inputs Base Case Intensified flowsheet designs	
Tools -	Tools ICAS PROII/ASPEN	Tools ICAS\SustainPro,ECON, LCSoft	Tools ICAS\MoT PROII/ASPEN	Tools ICAS\ECON,LCSOft	
Outputs Problem statement Objective function	Outputs Base Case Mass & energy data	Outputs Process hotspots	Outputs PCP/mixture analysis Phenomena identification/ combination Intensified flowsheet designs	Outputs Selection of the best intensified flowsheet design	

Fig. 2.9 Systematic process synthesis-intensification framework (adopted from Babi et al. [2])

The first level of the framework defines the problem, the objective function to be minimized (or maximized) and a selection/generation (if not available) of base-case design at the unit operations scale. The second level performs economic sustainability and LCA analyses to systematically and logically identify process hot-spots that are translated into intensification (design) targets/constraints for process improvements/design. The inputs to the analyses are detailed mass and energy balance data and the base-case process flowsheet information. The third level performs process synthesis-intensification at the three different scales (unit operations, tasks, phenomena) subject to the following condition: the new synthesized (intensified) flowsheets must have a reduction in the number of unit operations compared to the base-case design.

The base-case design at the unit operations scale is translated to the task-based flowsheet that is further translated to the phenomena-based flowsheet. All identified PBBs from the base-case design and additional (desirable) PBBs obtained from analysis of the chemical system, constitute the final PBB search space. All possible combination of the PBBs are calculated and screened using the combination rules for obtaining a feasible set of SPBs. Next, SPBs are combined to form operations that fulfill tasks that are translated to unit operations. Only those operations and their combination to flowsheets are retained if they satisfy all constraints and move the objective function in the desired direction.

2.3.3 Computer-Aided Tools

Different computer-aided tools can be employed for performing and evaluating process intensification at the three different scales and in the three different stages (see Fig. 2.4). Examples of these tools and their application are presented in Table 2.4.

Table 2.4 Tools for performing process intensification. Adopted from Babi et al. [2]

Method	Tool-name/ tool-type	Features	Intensification remarks
Property model-based	ICAS-utility[a] /Analysis	Group contribution-based property models used for VLE, LLE, SLE, distillation boundary, residue curve, etc., calculations	Use of phase diagrams for reaction, separation, and/or reaction–separation understanding
CAMD; Database search	ProCAMD[a]/ Selection	Search and selection of solvents for various types of solvent based separation processes	Selection of environmentally friendly solvents that affect the separation of compounds
Driving force-based; Equilibrium-based	PDS[a]/ Design, Analysis	Generation of phase and driving force diagrams for design of distillation columns	Use of driving force diagrams for the optimal design of hybrid/intensified unit operations
Model/Heuristic-based	ECON[a]/ Analysis	Economic calculation and evaluation based on the models from Peters et al. [61]	Economic evaluation of processes for identifying economic design targets for achieving process intensification
Model-based	SustainPro[a]/ Analysis	Indicator-based method [62]	Environmental evaluation of processes for identifying sustainability design targets for achieving process intensification
Model-based	LCSoft[a]	Indicator-based method using cradle to the gate concept for LCA analysis [63]	
Model-based	CAPSS[a]/ Analysis	Pure component property analysis [58]	Pure compound property evaluation for identifying feasible hybrid/intensified unit operations
Model-based	ProPred[a]	Group contribution-based property models [64]	Pure compound property prediction
Equation-oriented problem solution	MoT[a], Aspen Custom Modeller/ Analysis	Process and property models can be generated and solved for evaluation.	Model-based evaluation and design of intensified/hybrid unit operations
Model-based calculations	Aspen Plus, PROII/ Analysis	Models for well-known and hybrid/intensified unit operations	Model-based simulation and analysis of multiple intensified process alternatives

[a]Part of ICAS [60]

The tools listed in Table 2.4 are computer-aided and therefore, provide the opportunity for rapid investigation of alternatives at the different stages of process design. At the core of process simulation/investigation of the intensified flowsheet alternatives, are the property models that must accurately predict the properties of the pure compounds and mixtures present in the chemical (and biochemical) system. If the property models are accurate, then their coupling to the process models produce accurate and reliable process designs.

Many intensified solutions may need the use of an appropriate solvent or process fluid. For generation of alternative solvents and/or process fluids that are

environmentally acceptable as well as easy to operate and inexpensive, model-based tools such as ProCAMD are used. For the selection of intensification design targets, model-based economic and sustainability indicator-based environmental evaluations are performed.

2.4 Case Study: Production of Methyl-Acetate

Application of the systematic synthesis-intensification framework is illustrated through the well-known production process for methyl-acetate (MeOAc). The objective here is to highlight the fundamental concepts of PI as well as to illustrate how intensified flowsheet alternatives inclusive of the well-known reactive distillation process proposed by Agreda et al. [8] can be generated using the phenomena-based method. The key steps of the framework are highlighted through the production of methyl-acetate (MeOAc) from an equilibrium-limited reaction between methanol (MeOH) and acetic acid (HOAc) with water (H_2O) as a by-product. The reaction is a liquid phase reaction catalyzed by Amberlyst 15. A molar feed ratio of 2:1 for the base-case design for MeOH and HOAc are used respectively with a total production of 122×10^3 t/year [65].

2.4.1 Level 1

The synthesis-intensification problem is defined as follows [2]: Find intensified process design alternatives for the production of MeOAc having a conversion of HOAc ≥ 92 % by maximizing the profit (objective function) defined by (2.7).

$$F_{\text{obj}}(C_{\text{Prod}}, C_{\text{RM}}, C_{\text{Ut}}) = \text{Opt}\left\{ \left(\sum m_j C_{\text{Prod},j} - \sum m_j C_{\text{RM},j} - \sum E_j C_{\text{Ut},j} \right) \bigg/ \text{kg Prod} \right\}$$

(2.7)

In (2.7), C, m, and E represent the costs, mass, and energy flows, respectively. The following constraints are specified compared to the base-case design: the use of solvents is to be minimized; the number of unit operations in the intensified flowsheet alternatives must be less; sustainability metrics and LCA factors must be the same or better. From a literature survey a base-case design (see Fig. 2.5) is available [8]. The base-case design consists of ten unit operations (one reactor, five distillation columns, one liquid–liquid extractor and decanter). It should be noted that if a base-case design does not exist, the framework has the option to generate one. The base-case design is then simulated to obtain detailed mass and energy balance data.

2.4.2   Level 2

Economic, sustainability, and LCA analyses are performed. Two potential process hot-spots are identified. These are limited equilibrium (the reaction does not go to full completion), which means high flow of raw material in the reactor outlet, and high energy consumption for solvent recovery in the extractive distillation section (see, Fig. 2.5). These process hot-spots are then translated into intensification (design) targets that must be matched through the design of a more sustainable intensified process. Two criteria to be considered could be: reduce process energy demand and improve sustainability and LCA factors.

2.4.3   Level 3

Identification of desirable tasks and phenomena: Using the appropriate computer-aided tools (see Table 2.4), the chemical system pure compound and mixture properties are analyzed. The following minimum boiling binary azeotropes are found: HOAc/H_2O (slightly pressure-dependent), MeOH/MeOAc (pressure-dependent), and MeOAc/H_2O (slightly pressure-dependent). Next, the base-case design is represented in terms of tasks and then in terms of phenomena. The selected PBBs obtained from representation of the base-case design at the phenomena level are R, M (assuming four types of mixing: ideal, flow, rectangular, vapor), 2phM, PC(VL), PS(VL), PT(VL) H, C and dividing (D) PBBs. The additional (desirable/beneficial) PBBs that are added based on thermodynamic insights [58] are PS(VV), PT(PVL), PT(VV) (key PBBs for pervaporation and vapor permeation membranes, respectively). Considering all possible combinations of the identified PBBs, 16278 SPBs are obtained, out of which 64 are found to be feasible using the combination rules of PBBs to SPBs.

Generation of sustainable intensified alternatives: Starting with the first reaction task and using thermodynamic insights [58], HOAc is removed from the reactor effluent containing MeOH/MeOAc. Since H_2O is present in the reactor effluent and also forms an azeotrope with MeOAc, H_2O is also found in the top and bottom of the first separation task (see Fig. 2.10a). The first separation task is achieved by a VL-separation, that is, using a PT(VL) PBB. In order to reduce the number of azeotropes in the mixture of H_2O, MeOAc, and MeOH, H_2O is removed using an SPB that contains a PT(PVL) PBB, which translates into a pervaporation membrane. Two VL-separation tasks operating at different pressures are employed next to separate HOAc/H_2O and MeOAc/MeOH mixtures, thereby avoiding the use of solvents (see Fig. 2.10a). Flowsheet alternative 2 (see Fig. 2.10b) is generated by a priori removal of H_2O before the HOAc separation, thereby further reducing the size of flowsheet alternative 1.

   Flowsheet alternative 3 (see Fig. 2.10c) is generated by combining the first reaction and separation PBBs, thereby making it feasible to combine the first
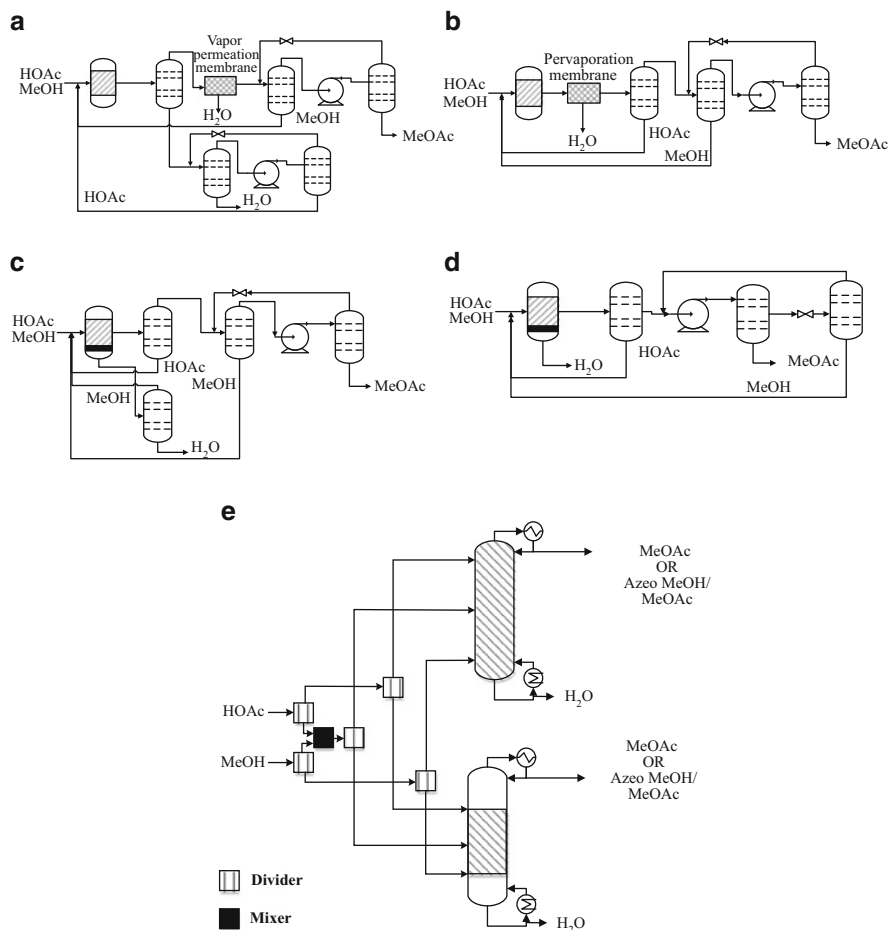
Fig. 2.10 The generated flowsheet alternatives for the production of MeOAc [2]. (**a**) Flowsheet alternative 1, (**b**) Flowsheet alternative 2, (**c**) Flowsheet alternative 3, (**d**) Flowsheet alternative 4 (**e**) Flowsheet alternatives 6–9

reaction and separation tasks for the in situ removal of water using a $R = PT(PVL)$ SPB. The reactor outlet contains some H_2O because of the raw material feed molar ratio that affects the membrane behavior. The rest of the flowsheet is similar to flowsheet alternative 1 (see Fig. 2.10a). Flowsheet alternative 4 (see Fig. 2.10d) is generated by changing the MeOH–HOAc feed ratio resulting in an easier and lesser separation tasks after the membrane reactor. Flowsheet alternative 5 is not shown in Fig. 2.10 for reasons of confidentiality.

Flowsheet alternative 6–9 are generated through the combination of the remaining reaction and separation tasks, thereby producing a reactive distillation superstructure [2] that consists of reactive stages only, reactive and separation stages, single- and double-feed configurations (see Fig. 2.10e). It should be noted

Table 2.5 Values of selected performance criteria for the base-case design and 4 intensified (and more sustainable) alternatives

Performance metrics	Base-case	Alternatives			
		3	4	5	9
Feed ratio	2:1	2:1	2:1	1:1	1:1
Energy usage (MJ/kg MeOAc)	21.9	20.6	19.1	3.6	2.2
Raw material (kg/kg MeOAc)	0.88	0.87	0.87	0.87	0.88
Utility cost ($/kg MeOAc)	0.1	0.09	0.08	0.01	0.01
Carbon footprint (eq. kg of CO_2)	0.92	0.56	0.52	0.09	0.05
Fobj, (2.6)	2.06	2.08	2.09	2.16	2.16

that among the different SPBs that can be generated, only those that have the potential to overcome the process hot-spots are considered in order to identify the more sustainable flowsheet alternatives.

2.4.4 Level 4

Selection of the best, intensified alternative is dependent on economic factors, sustainability metrics, and LCA factors in addition to the objective function value and constraints. Table 2.5 gives values of a selected set of performance criteria for the base-case design and four selected alternative (intensified) designs from the 9 generated alternatives. For each alternative, the conversion of HOAc ≥ 92 % has been achieved, no solvents have been used and the number of unit operations have been reduced from 10 (the base-case) to 1 (alternative 9).

The finding of non-trade-off-intensified designs that offer improvements in economic, sustainability/LCA factors is shown in Fig. 2.11 where the ratios of different performance criteria with respect to the base-case (multiplied by 100) have been plotted. Not that for profit, the inverse has been taken. The base-case design is at the boundary while the more sustainable alternatives are all within the boundary, indicating clearly that these alternatives are more sustainable than the base-case. Alternatives 5 and 9 give the best results.

2.5   Perspectives, Conclusions, and Future Work

The design of novel, innovative, more sustainable equipment (unit operations) and methods for the selection and design of the best (optimal) innovative process are required for successful achievement of PI. Research and development in intensified equipment design, overall PI solutions, and methods–tools to identify them will continue to remain an active area as,
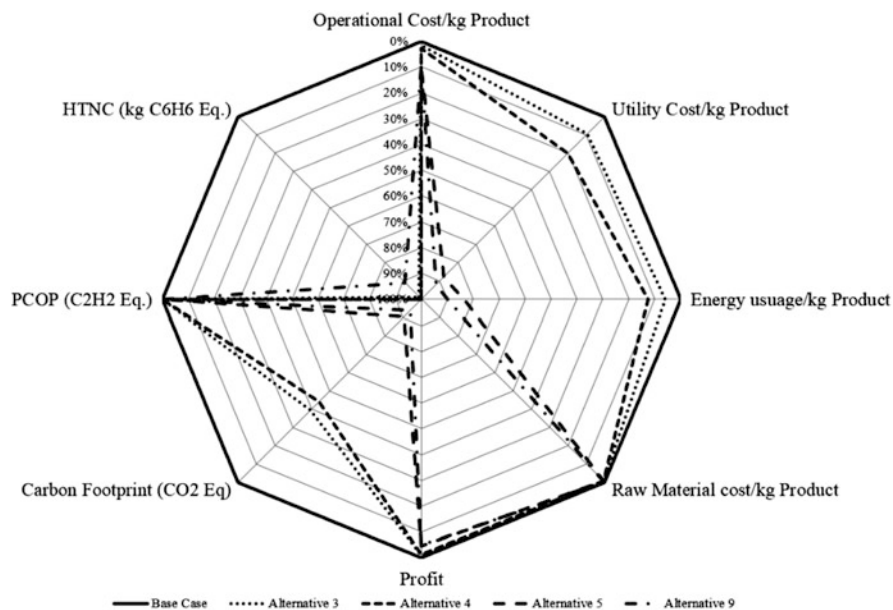
Fig. 2.11 Economic and LCA improvements relative to the base-case design. *PCOP* photochemical oxidation potential, *HTNC* human toxicity (non-carcinogenic impacts)

- New design concepts for unit operations for multiple applications in the chemical and biochemical industry will need to be developed
- Accurate models are needed for a better understanding of the complex behavior of reacting, separating and reacting–separating mixtures in hybrid/intensified unit operations
- Suitable (novel) materials need to be found for construction of these hybrid/intensified unit operations for pilot scale testing
- Methods for chemical (and biochemical) process design and optimization need to be further extended or developed for the selection of a wider range of hybrid/intensified unit operations that are more flexible and versatile from a sustainable point of view

Other challenges to application of PI also need to be addressed, for example, the controllability of hybrid/intensified unit operations, because it is well-known that the combination of phenomena, that lead to the combination of tasks and unit operations, also lead to a reduction in the degrees of freedom available for process control. Therefore, finding/developing the best, more sustainable control strategies need to be investigated. This can be addressed by integration of process design and process controller design and by making a priori design decisions that correspond to the best control strategy.

Process intensification can be performed at different scales (unit operations, task, and phenomena) and performing PI at each scale increases process innovation.

Process intensification improves the performance of an existing process as well as improves the design of a new process in terms of economic and environmental improvements. It is imperative that chemical and biochemical manufacturers remain competitive through the design of economically viable, innovative, more sustainable processes. Therefore, PI plays an important role in identifying the more sustainable and innovative process designs. In this respect the three-stage approach of process synthesis stage, process design (and analysis) stage, and innovation stage (process intensification) where new (or novel) hybrid/intensified unit operations could be generated, could become an important tool.

References

1. Gani R, Babi DK (2014) Systematic computer aided framework for process synthesis, design and intensification. In: Letcher T, Scott J, Darrell PA (eds) Chemical processes for a sustainable future. Royal Chemical Society, Cambridge, pp 698–752
2. Babi DK, Lutze P, Woodley JM, Gani R (2014) A process synthesis-intensification framework for the development of sustainable membrane-based operations. Chem Eng Process 86:173–195. doi:10.1016/j.cep.2014.07.001
3. Moulijn JA, Stankiewicz A, Grievink J, Górak A (2008) Process intensification and process systems engineering: a friendly symbiosis. Comput Chem Eng 32(1–2):3–11. doi:10.1016/j.compchemeng.2007.05.014
4. Stankiewicz A, Moulijn JA (2000) Process intensification: transforming chemical engineering. Chem Eng Prog 96(1):22–24
5. Reay D, Ramshaw C, Harvey A (2008). In: Reay D, Ramshaw C, Harvey A (eds) Process intensification. IChemE, Rugby.
6. Ponce-Ortega JM, Al-Thubaiti MM, El-Halwagi MM (2012) Process intensification: new understanding and systematic approach. Chem Eng Process 53:63–75. doi:10.1016/j.cep.2011.12.010
7. Bessling B, Schembecker G, Simmrock KH (1997) Design of processes with reactive distillation line diagrams. Ind Eng Chem Res 36(8):3032–3042. doi:10.1021/ie960727p
8. Agreda VH, Partin LR, Heise WH (1990) High-purity methyl acetate via reactive distillation. Chem Eng Prog 86(2):40–46
9. Freund H, Sundmacher K (2008) Towards a methodology for the systematic analysis and design of efficient chemical processes. Chem Eng Process 47(12):2051–2060. doi:10.1016/j.cep.2008.07.011
10. Lutze P, Babi DK, Woodley JM, Gani R (2013) Phenomena based methodology for process synthesis incorporating process intensification. Ind Eng Chem Res 52(22):7127–7144. doi:10.1021/ie302513y
11. Siirola JJ (1996) Strategic process synthesis: advances in the hierarchical approach. Comput Chem Eng 20:S1637–S1643. doi:10.1016/0098-1354(96)85982-5
12. Papalexandri KP, Pistikopoulos EN (1994) A multiperiod MINLP model for the synthesis of flexible heat and mass exchange networks. Comput Chem Eng 18(11–12):1125–1139. doi:10.1016/0098-1354(94)E0022-F
13. Peschel A, Jörke A, Freund H, Sundmacher K (2012) Model-based development of optimal reaction concepts for plant wide process intensification. Comput Aided Chem Eng 31:150–154. doi:10.1016/B978-0-444-59507-2.50022-6
14. Lutze P, Román-Martinez A, Woodley JM, Gani R (2012) A systematic synthesis and design methodology to achieve process intensification in (bio) chemical processes. Comput Chem Eng 36:189–207. doi:10.1016/j.compchemeng.2011.08.005

15. El-Halwagi MM (1997) Pollution prevention through process integration: systematic design tools. Academic, San Diego
16. El-Halwagi MM (2006) Process systems engineering- process integration. Elsevier
17. Smith R (2005) Chemical process: design and integration. WILEY-VCH Verlag GmbH, Weinheim
18. Klemeš JJ, Varbanov PS, Kravanja Z (2013) Recent developments in process integration. Chem Eng Res Des 91(10):2037–2053. doi:10.1016/j.cherd.2013.08.019
19. Harmsen J (2010) Process intensification in the petrochemicals industry: drivers and hurdles for commercial implementation. Chem Eng Process 49(1):70–73. doi:10.1016/j.cep.2009.11.009
20. Linnhoff B, Townsend DW, Boland D, Hewitt GF, Thomas BEA, Guy AR, Marsland RH (1982) A user guide on process integration for the efficient use of energy. IChemE, Rugby
21. Papoulias SA, Grossmann IE (1983) A structural optimization approach in process synthesis— II. Comput Chem Eng 7(6):707–721. doi:10.1016/0098-1354(83)85023-6
22. Singhvi A, Madhavan KP, Shenoy UV (2004) Pinch analysis for aggregate production planning in supply chains. Comput Chem Eng 28(6–7):993–999. doi:10.1016/j.compchemeng.2003.09.006
23. Kazantzi V, El-Halwagi MM (2005) Targeting material reuse via property integration. Chemical Engineering Progress 101(8), 28–37. http://www.scopus.com/inward/record.url?eid=2-s2.0-27844440901&partnerID=tZOtx3y1
24. Babi DK, Holtbruegge J, Lutze P, Gorak A, Woodley JM, Gani R (2015) Sustainable process synthesis–intensification. Comput Chem Eng 81:218–244. doi:10.1016/j.compchemeng.2015.04.030
25. Oxley P, Brechtelsbauer C, Ricard F, Lewis N, Ramshaw C (2000) Evaluation of spinning disk reactor technology for the manufacture of pharmaceuticals. Ind Eng Chem Res 39 (7):2175–2182. doi:10.1021/ie990869u
26. Lutze P, Gorak A (2013) Reactive and membrane-assisted distillation: recent developments and perspective. Chem Eng Res Des 91(10):1978–1997. doi:10.1016/j.cherd.2013.07.011
27. Asprion N, Kaibel G (2010) Dividing wall columns: fundamentals and recent advances. Chem Eng Process 49(2):139–146. doi:10.1016/j.cep.2010.01.013
28. Alfa Laval (2015) A new degree of deodorization control. http://local.alfalaval.com/de-de/wichtige-industrien/lebensmittel-molkerei-getraenke/oele/Documents/Desodorierung_Alfa%20Laval%20SoftFlex%E2%84%A2%20semi-continuous.pdf
29. Alfa L (2015) Gasketed plate-and-frame heat exchangers. Heat Exchangers. http://www.alfalaval.com/products/heat-transfer/plate-heat-exchangers/Gasketed-plate-and-frame-heat-exchangers/
30. Ramshaw C (1993) The opportunities for exploiting centrifugal fields. Heat Recovery Syst CHP 13(6):493–513. doi:10.1016/0890-4332(93)90003-E
31. Al Taweel AM, Yan J, Azizi F, Odedra D, Gomaa HG (2005) Using in-line static mixers to intensify gas–liquid mass transfer processes. Chem Eng Sci 60(22):6378–6390. doi:10.1016/j.ces.2005.03.011
32. Babi DK, Gani R (2014) Hybrid distillation schemes: design, analysis, and application. In: Gorak A, Sorensen E (eds) Distillation. Elsevier, London, pp 357–381. doi:10.1016/B978-0-12-386547-2.00009-0
33. Linnhoff B, Flower JR (1978) Synthesis of heat exchanger networks: I. Systematic generation of energy optimal networks. AIChE J 24(4):633–642. doi:10.1002/aic.690240411
34. Zhao CY, Lu W, Tassou SA (2006) Thermal analysis on metal-foam filled heat exchangers. Part II: tube heat exchangers. Int J Heat Mass Transf 49(15–16):2762–2770. doi:10.1016/j.ijheatmasstransfer.2005.12.014
35. Osakada K, Shiomi M (2006) Flexible manufacturing of metallic products by selective laser melting of powder. Int J Mach Tool Manuf 46(11):1188–1193. doi:10.1016/j.ijmachtools.2006.01.024

36. El-Halwagi MM, Manousiouthakis V (1989) Synthesis of mass exchange networks. AIChE J 35:1233–1244. doi:10.1002/aic.690350802

37. Stankiewicz A, Moulijn JA (2004) Re-engineering the chemical processing plant. Marcel-Dekker, New York

38. Peschel A, Karst F, Freund H, Sundmacher K (2011) Analysis and optimal design of an ethylene oxide reactor. Chem Eng Sci 66(24):6453–6469. doi:10.1016/j.ces.2011.08.054

39. Calvar N, González B, Dominguez A (2007) Esterification of acetic acid with ethanol: reaction kinetics and operation in a packed bed reactive distillation column. Chem Eng Process 46 (12):1317–1323. doi:10.1016/j.cep.2006.10.007

40. Liu G, Gan L, Liu S, Zhou H, Wei W, Jin W (2014) PDMS/ceramic composite membrane for pervaporation separation of acetone–butanol–ethanol (ABE) aqueous solutions and its application in intensification of ABE fermentation process. Chem Eng Process 86:162–172. doi:10.1016/j.cep.2014.06.013

41. Leyva-Díaz JC, López-López C, Martín-Pascual J, Muñío MM, Poyatos JM (2015) Kinetic study of the combined processes of a membrane bioreactor and a hybrid moving bed biofilm reactor-membrane bioreactor with advanced oxidation processes as a post-treatment stage for wastewater treatment. Chem Eng Process 91:57–66. doi:10.1016/j.cep.2015.03.017

42. Jordens J, Gielen B, Braeken L, Van Gerven T (2014) Determination of the effect of the ultrasonic frequency on the cooling crystallization of paracetamol. Chem Eng Process 84:38–44. doi:10.1016/j.cep.2014.01.006

43. Werth K, Lutze P, Kiss AA, Stankiewicz AI, Stefanidis GD, Górak A (2015) A systematic investigation of microwave-assisted reactive distillation: influence of microwaves on separation and reaction. Chem Eng Process 93:87–97. doi:10.1016/j.cep.2015.05.002

44. Douglas JM (1985) A hierarchical decision procedure for process synthesis. AIChE J 31 (3):353–362. doi:10.1002/aic.690310302

45. Bayer B, Schneider R, Marquardt W (2000) Integration of data models for process design—first steps and experiences. Comput Chem Eng 24(2–7):599–605. doi:10.1016/S0098-1354(00)80002-2

46. Gernaey KV, Gani R (2010) A model-based systems approach to pharmaceutical product-process design and analysis. Chem Eng Sci 65(21):5757–5769. doi:10.1016/j.ces.2010.05.003

47. Hostrup M, Gani R, Kravanja Z, Sorsak A, Grossmann I (2001) Integration of thermodynamic insights and MINLP optimization for the synthesis, design and analysis of process flowsheets. Comput Chem Eng 25(1):73–83. doi:10.1016/S0098-1354(00)00634-7

48. Grossmann IE (2012) Advances in mathematical programming models for enterprise-wide optimization. Comput Chem Eng 47:2–18. doi:10.1016/j.compchemeng.2012.06.038

49. Siirola JJ, Powers GJ, Rudd DF (1971) Synthesis of system designs: III. Toward a process concept generator. AIChE J 17(3):677–682. doi:10.1002/aic.690170334

50. Kobus A, Kuppinger F-F, Meier R, Düssel R, Tuchlenski A, Nordhoff S (2001) Improvement of conventional unit operations by hybrid separation technologies—a review of industrial applications. Chem Ing Tech 73(6):714. doi:10.1002/1522-2640(200106)73:6<714::AID-CITE7142222>3.0.CO;2-S

51. d'Anterroches L, Gani R (2005) Group contribution based process flowsheet synthesis, design and modelling. Fluid Phase Equilib 228–229:141–146. doi:10.1016/j.fluid.2004.08.018

52. Kiss A, Pragt H, van Strien C (2007) Computer aided chemical engineering. In: 17th European Symposium on Computer Aided Process Engineering, vol 24, Elsevier, Amsterdam, pp 467–472. doi:10.1016/S1570-7946(07)80101-5

53. Caballero JA, Grossmann IE (2004) Design of distillation sequences: from conventional to fully thermally coupled distillation systems. Comput Chem Eng 28(11):2307–2329. doi:10.1016/j.compchemeng.2004.04.010

54. Madenoor Ramapriya G, Tawarmalani M, Agrawal R (2014) Thermal coupling links to liquid-only transfer streams: a path for new dividing wall columns. AIChE J 60(8):2949–2961. doi:10.1002/aic.14468

55. Urselmann M, Barkmann S, Sand G, Engell S (2011) Optimization-based design of reactive distillation columns using a memetic algorithm. Comput Chem Eng 35(5):787–805. doi:10.1016/j.compchemeng.2011.01.038
56. Amte V (2011) Computer aided chemical engineering, vol 29. doi:10.1016/B978-0-444-53711-9.50144-9
57. Seifert T, Sievers S, Bramsiepe C, Schembecker G (2012) Small scale, modular and continuous: a new approach in plant design. Chem Eng Process 52:140–150. doi:10.1016/j.cep.2011.10.007
58. Jaksland C, Gani R, Lien K (1995) Separation process design and synthesis based on thermodynamic insights. Chem Eng Sci 50:511–530. doi:10.1016/0009-2509(94)00216-E
59. Harper PM, Gani R (2000) A multi-step and multi-level approach for computer aided molecular design. Comput Chem Eng 24(2–7):677–683. doi:10.1016/S0098-1354(00)00410-5
60. Gani R, Hytoft G, Jaksland C, Jensen AK (1997) An integrated computer aided system for integrated design of chemical processes. Comput Chem Eng 21(10):1135–1146. doi:10.1016/S0098-1354(96)00324-9
61. Peters MS, Timmerhaus KD, West RE (2003) Sign and economics for chemical engineers. In: Peters MS, Timmerhaus KD, West RE (eds) 5th edn. Mc Graw Hill, New York. http://catalogs.mhhe.com/mhhe/viewProductDetails.do?isbn=0072392665
62. Carvalho A, Matos HA, Gani R (2013) SustainPro—a tool for systematic process analysis, generation and evaluation of sustainable design alternatives. Comput Chem Eng 50:8–27. doi:10.1016/j.compchemeng.2012.11.007
63. Kalakul S, Malakul P, Siemanond K, Gani R (2014) Integrated of life cycle assessment software with tools for economic and sustainability analyses and process simulation for sustainable process design. J Clean Prod 71:98–109. doi:10.1016/j.jclepro.2014.01.022
64. Marrero J, Gani R (2001) Group contribution based estimation of pure component properties. Fluid Phase Equilib 183–184:183–208. doi:10.1016/S0378-3812(01)00431-9
65. Huss RS, Chen F, Malone MF, Doherty MF (2003) Reactive distillation for methyl acetate production. Comput Chem Eng 27(12):1855–1866. doi:10.1016/S0098-1354(03)00156-X