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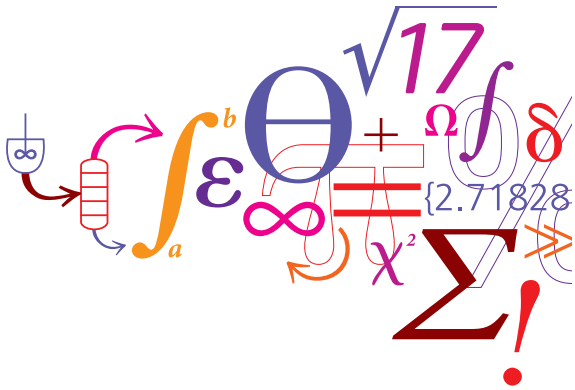

Philip Lutze
Ph.D. Thesis
December 2011

DTU Chemical Engineering
Department of Chemical and Biochemical Engineering

An Innovative Synthesis Methodology for Process Intensification

Ph. D. Thesis

Philip Lutze

31 December 2011

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Preface

This thesis is submitted as partial fulfilment of the requirements for the Doctor of Philosophy (Ph.D.) degree at the Technical University of Denmark (DTU).

The PhD-project has been carried out at the Center for Process Engineering and Technology (PROCESS) at the Department of Chemical and Biochemical Engineering from November 2008 till December 2011 under the supervision of Professor John M. Woodley and Professor Rafiqul Gani from the Computer Aided Process-Product Engineering Center (CAPEC). The project was partly funded by a scholarship from the Technical University of Denmark.

First, I would like to thank my supervisors John M. Woodley and Rafiqul Gani for giving me the opportunity to work on a very interesting and challenging project and for their valuable support, inspiring ideas and discussions, and for their constant enthusiasm throughout my whole project.

I also would like to thank Emmanuel A. Dada from ChemProcess Technologies Inc. and the collaborators from Argonne National Laboratory, USA for interesting project discussions and their support.

Many thanks, to all my co-workers/friends from the big “CAPEC-PROCESS-family” for providing this wonderful atmosphere in which it is easy to work and for all the shared social events inside and outside DTU.

Also many thanks to all my friends “outside” for their support and for the distracting discussions (mostly about football) whenever I had the chance to meet them.

I also wish to thank my mother Gabriele, my brother Robert, and my sister Miriam for all their encouraging words as well as for their understanding; especially in stressful times. A special thanks to my brother Robert for giving me the idea to become a chemical engineer.

Last but for sure not least, my special thanks goes to my girlfriend Martina for the wonderful time we share, for making me laugh, for her patience; simply for her love and her presence in my life!

Dortmund, December 2011

Philip Lutze

Abstract

Process intensification (PI) has the potential to improve existing processes or create new process options, which are needed in order to produce products using more sustainable methods.

A variety of intensified equipment has been developed which potentially creates a large number of options to improve a process. However, to date only a limited number have achieved implementation in industry, such as reactive distillation, dividing wall columns and reverse flow reactors. A reason for this is that the identification of the best PI option is neither simple nor systematic. That is to decide where and how the process should be intensified for the biggest improvement. Until now, most PI has been selected based on case-based trial-and-error procedures, not comparing different PI options on a quantitative basis.

Therefore, the objective of this PhD project is to develop a systematic synthesis/design methodology to achieve PI. It allows the quick identification of the best PI option on a quantitative basis and will push the implementation and acceptance of PI in industry. Such a methodology should be able to handle a large number of options. The method of solution should be efficient, robust and reliable using a well-defined screening procedure. It should be able to use already existing PI equipment as well as to generate novel PI equipment.

This PhD-project succeeded in developing such a synthesis/design methodology. In order to manage the complexities involved, the methodology employs a decomposition-based solution approach. Starting from an analysis of existing processes, the methodology generates a set of PI process options. Subsequently, the initial search space is reduced through an ordered sequence of steps. As the search space decreases, more process details are added, increasing the complexity of the mathematical problem but decreasing its size. The best PI options are ordered in terms of a performance index and a related set are verified through detailed process simulation. Two building blocks can be used for the synthesis/design which is PI unit-operations as well as phenomena. The use of PI unit-operations as building block aims to allow a quicker implementation/retrofit of processes while phenomena as building blocks enable the ability to develop novel process solutions beyond those currently in existence. Implementation of this methodology requires the use of a number of methods/algorithms, models, databases, *etc*., in the different steps which have been developed. PI unit-operations are stored and retrieved from a knowledge-base tool. Phenomena are stored and retrieved from a phenomena library.

The PI synthesis/design methodology has been tested for both building blocks on a number of case studies from different areas such as conventional and bio-based bulk chemicals as well as pharmaceuticals.

Resume på Dansk

Proces intensifikation har potentialet at forbedre eksisterende processer eller at generere nye proces optioner, som er nødvendige til at producere produkter med hjælp af vedvarende metoder. En vifte af intensiferet udstyr blev udviklet som potentielt skaber et stort antal af optioner at forbedre en proces.

Det er dog til dato kun en begrænset antal af implementeringer i industrien, som eksempelvis reaktiv destillation, skillevæg kolonner og omvendt flow reaktorer. En årsag til det er at identifikationen af den bedste PI option er ikke simple eller systematisk. Det er at beslutte, hvor og hvordan processen skal blive intensiveret for at opnå den største forbedring. Indtil i dag de fleste PI blev udvalgt baseret på case-baseret ”trial and error” procedurer hvilke ikke sammenligner forskellige PI optioner på et kvantitativt grundlag. Målsætning af dette PhD projekt er derfor at udvikle en systematisk syntese/design metodologi til at opnå PI. Det gør det muligt at hurtig identificere den bedste PI option på et kvantitativt grundlag og vil dermed understøtte en implementering og accept af PI i industrien. En sådan metode børe være i stand til at håndtere et stort antal af optioner. Den valgte løsning børe være effektiv, robust og pålidelig og benytte en veldefineret screening procedure. Det bør være i stand til at benytte eksisterende PI udstyr såvel som at generere ny PI udstyr.

Det lykkedes i dette PhD projekt at udvikle en sådan syntese/design metodologi. For at styre af kompleksiteten metodologien benytter en nedbrydende tilgang. Startende fra en analyse af eksisterende processer metoden generer et sæt af PI proces optioner. Efterfølgende det første søgnings rum bliver reduceret med hjælp af en kontrolleret sekvens af trin. Med faldende størrelsen af søgnings rum mere proces detaljer bliver tilføjet, hvilke øger kompleksiteten med henblik af den matematiske formulering men med reducering af den reelle størrelse. De bedste PI optioner bliver arrangeret i form af præstations indeks og en relateret sæt bliver verificeret med hjælp af detaljerede proces simulationer.

To ”byggeklodser” kan blive benyttet til syntese/design hvilke er PI enhedsoperationer såvel som fænomen baserede. Brugen af PI enhedsoperationer som ”byggeklodser” har som formål til at tillade en hurtigere implementering/retrofit af processer mens fænomen baserede ”byggeklodser” giver muligheden til at udvikle nye proces løsninger udover de nuværende eksisterende. Implementeringen af denne metodologi kræver anvendelsen af et antal af metoder/algoritmer, modeller, databaser osv. i de forskellige trin, hvilke blev udviklet. PI enhedsoperationer bliver gemt og hentet fra en videns baseret værktøj. For at benytte fænomener til at syntetisere processer ”forbindelses” regler blev udviklet til at

samle fænomener til enhedsoperationer og enhedsoperationer til processer. Fænomener bliver gemt og hentet fra et fænomen bibliotek.

Den Pi syntese/design metode blev testet for ”byggeklodser” på et antal af casestudier fra forskellige områder som konventionelle og bio-baseret bulk kemikalier såvel som lægemidler.

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Chapter 1.

Introduction

The chemical, pharmaceutical and bio-based industries produce products that are essential for modern society. Nevertheless, these industries face considerable challenges (see Fig.1.1). That is the need to develop sustainable processes for the future (Stankiewicz & Moulijn, 2000). Shifting to more sustainable productions means not only that existing processes need to increase the efficiency of the raw materials, solvents and energy in the system. It also means that new raw materials and new catalysts (e.g. biocatalysts) are introduced which drives the necessity to totally new production routes and processes. All of this has to happen under the uncertainty of profit margins due to quicker changing markets, stronger global competition as well as the lower expected lifetime of a product.

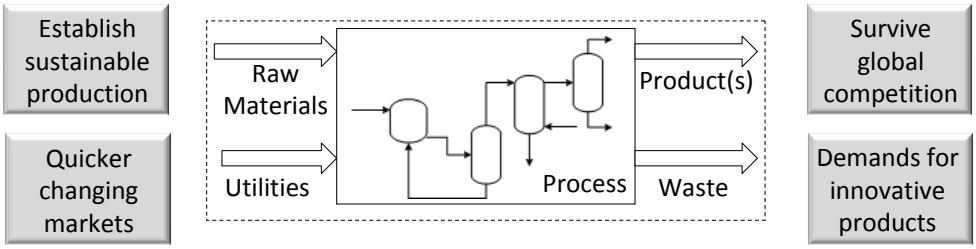


Figure 1.1. Challenges of the chemical and bio-chemical industry.

Hence, there is no other way then that the processes which exist and the processes which will be developed to match/face the future challenges need improved designs going beyond those achieved by using the toolbox of conventional process units (Moulijn *et al.*, 2008). Consequently the arguments for retrofit processes as well as design of new processes are several (Table 1), dependent on the industrial sector. One important and even necessarry tool, to match the future challenges in the process industry is process intensification (Moulijn *et al.*, 2008). This statement is supported by the declared motivations of the developers of process intensification (PI) equipment (see Figure 1.2), which is based on an analysis of 110 developed PI equipment obtained through a literature survey done within this project (details given in appendix A.1). Mostly, it has been stated that the motivation for PI was the improvement of the energy consumption (63% of the analyzed PI equipment), the improvement of the efficiency (57%), which are both related to operational costs, and operational costs itself (23%). But also the volume (37%), which could be also linked to efficiency, and the capital costs (16%) are important criteria.

Table 1.1. Industrial motivation for retrofitting processes (Rong *et al.*, 2000;Simon *et al.*, 2008).

Motivation
• Increased productivity
• Increased capacity
• Increased flexibility
• Increased safety
• Decreased energy usage
• Decreased waste
• Decreased operational costs
• Simplified process

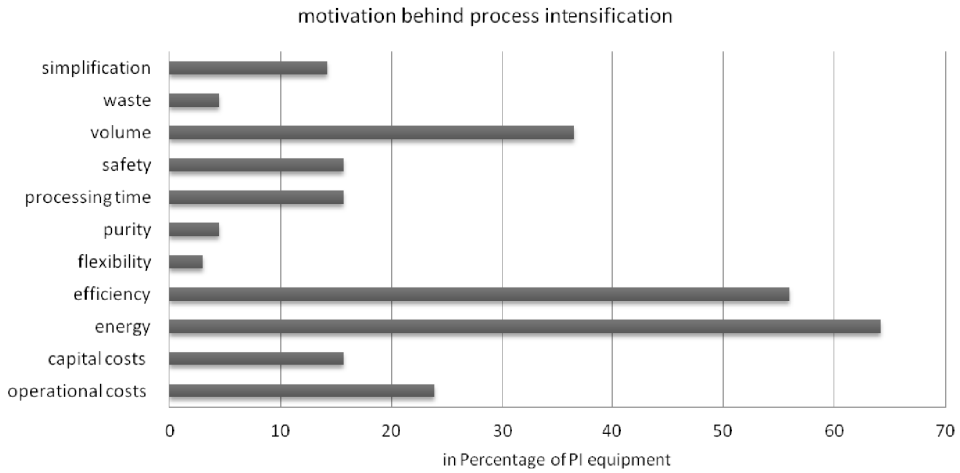


Figure 1.2. Reported motivations in terms of performance criteria for the development of 110 reported PI equipment (Appendix A.1) from the literature survey.

This has led to an increasing number of developments of new PI equipment and suggestions for new processes using PI (Freund & Sundmacher, 2008). This is proven, for example, by the increasing number of patents for heterogeneous catalytic reactive distillation (Fig. 1.3) which has been more than doubled when comparing the year 2000 and the year 2009. The patents claim not only the application of heterogeneous catalytic reactive distillation systems for different reaction systems but also using different column configurations (Lutze *et al.*, 2010).

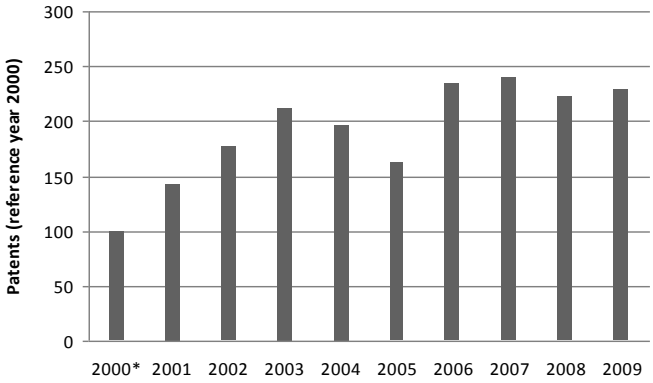
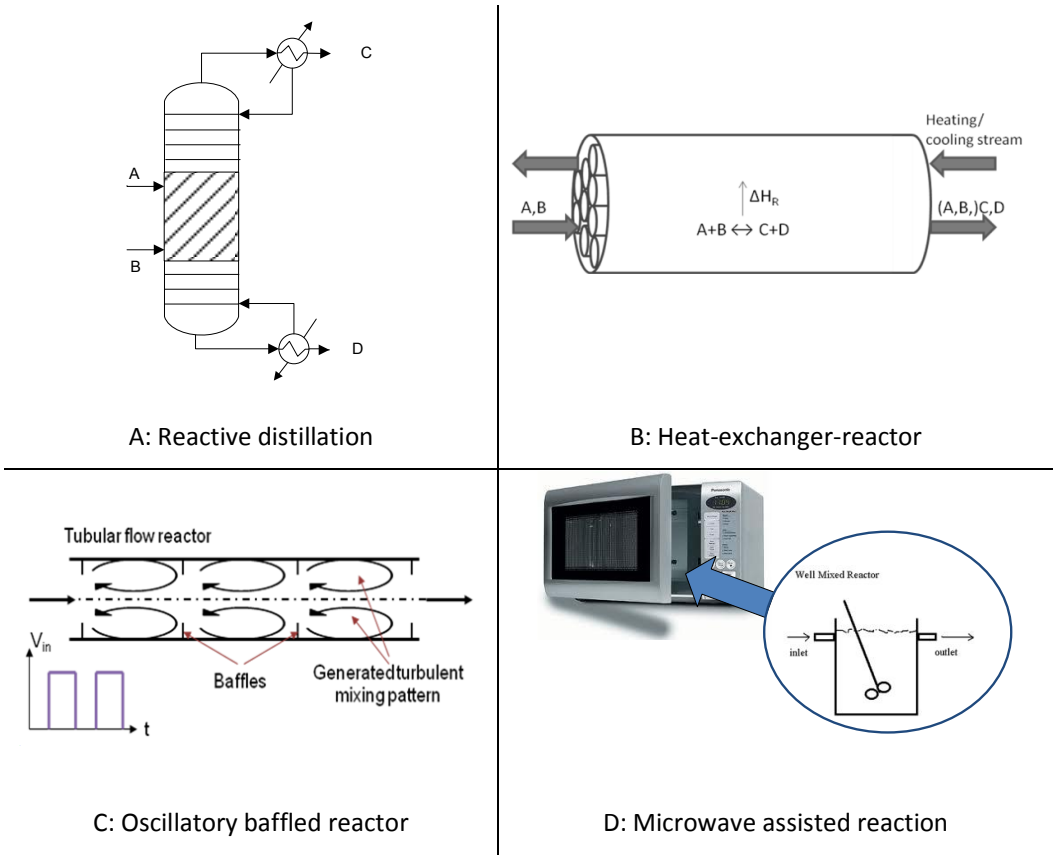


Figure 1.3. Number of claimed patents in heterogeneous catalytic distillation columns each year since 2000 (Patents in reference year = 100) taken from Lutze *et al.*, 2010.

Different options to intensify processes to reach a certain target exist. For example, looking at intensified reactor designs, there is: the reactive distillation which has replaced a complete process containing reactors, distillation and extraction columns in case of the methyl-acetate process (see Fig. 1.4A, e.g. in Sundmacher & Kienle, 2003); the heat-exchanger-reactor for improved reaction by enhanced provision of the necessary heat for the reaction (Fig. 1.4B, e.g. in Anxionnaz *et al*., 2008); the oscillatory baffled reactor (Fig. 1.4C, e.g. in Reay, Ramshaw & Harvey, 2008) for improved mixing; and microwave-assisted reaction (see Fig. 1.4D, e.g. in Reay, Ramshaw & Harvey, 2008). The diversity in how PI has been achieved in all these equipment, as well as the diversity in scope and goal could be one reason that there is still not a common agreement about a definition of PI.



A: Reactive distillation

B: Heat-exchanger-reactor

C: Oscillatory baffled reactor

D: Microwave assisted reaction

Figure 1.4. Four examples of developed PI reactors.

1.1. Background: Process intensification

1.1.1. What is Process Intensification?

The understanding about what PI is has changed since the term was defined in the early 80's (see Table 1.2). One of the first definitions for PI has been given by Ramshaw *et al.* (1983, 2000) pointing out that the keypoint of PI is the reduction of capital costs and volumes. In 2003, Tsouris and Porcelli enlarged that definition to "The term PI refers to technologies that replace large, expensive, energy-intensive equipment or processes with ones that are smaller, less costly, more efficient or that combine multiple operations into fewer devices (or a single apparatus)". Moulijn, Stankiewicz, Grievink and Gorak (2006) moved away from the essential decrease of volumes and stated "PI tries to achieve drastic improvements in the efficiency of chemical and biochemical processes by developing innovative, often radically new types of equipment and/or processes and their operations" while Becht, Franke, Geißelmann and Hahn (2008) broadened the definition even more

claiming that "PI stands for an integrated approach for process and product innovation in chemical research and development, and chemical engineering in order to sustain profitability even in the presence of increasing uncertainties".

Table 1.2. Selected Definitions of PI in the literature (extended from Van Gerven, 2009).

Process intensification	Reference (year)
"[is the] devising exceedingly compact plant which reduces both the 'main plant item' and the installations costs."	Ramshaw (1983)
"[is the] strategy of reducing the size of chemical plant needed to achieve a given production objective."	Cross & Ramshaw (2000)
"[is the] development of innovative apparatuses and techniques that offer drastic improvements in chemical manufacturing and processing, substantially decreasing equipment volume, energy consumption, or waste formation, and ultimately leading to cheaper, safer, sustainable technologies."	Stankiewicz & Moulijn (2000)
"refers to technologies that replace large, expensive, energy-intensive equipment or process with ones that are smaller, less costly, more efficient or that combine multiple operations into fewer devices (or a single apparatus)."	Tsouris & Porcelli (2003)
"tries to achieve drastic improvements in the efficiency of chemical and biochemical processes by developing innovative, often radically new types of equipment processes and their operation."	Moulijn *et al.* (2006)
"stands for an integrated approach for process and product innovation in chemical research and development, and chemical engineering in order to sustain profitability even in the presence of increasing uncertainties."	Becht *et al.* (2008)
"is a process development/design option which focuses on improvements of a whole process by adding/enhancing of phenomena through integration of unit operations, integration of functions, integration of phenomena and/or targeted enhancement of a phenomenon within an operation."	Lutze, Gani & Woodley (2010)

Recently, Van Gerven and Stankiewicz (2009) stated that a more fundamental definition is necessary but instead of queuing into the list of definitions they have defined four explicit goals of process intensification (PI): (1) maximize the effectiveness of intra- and intermolecular events; (2) optimize the driving forces at every scale and maximize the specific surface area to which these forces apply; (3) maximize synergistic effects, and, (4) give each molecule the same processing experience. According to Van Gerven and Stankiewicz, these goals can be achieved through four domains: structure, energy, synergy and time. However, since the desired behavior of a process or a unit operation is evaluated by its performance and attained by the interaction of the involved phenomena, the goals of PI are actually achieved by enhancements of the involved phenomena inside those four domains. Therefore, one definition of PI, not targeting specific improvements, developed and used in this PhD-project, is to define PI as the improvement of a whole process through enhancements of the involved phenomena in terms of the following PI-principles: (a) integration of unit operations, (b) integration of functions, (c) integration of phenomena, (d)

targeted enhancements of phenomena in a given operation (Lutze, Gani & Woodley, 2010). The advantage of this definition is that it is fundamental and it links the performance (process) improvement to the enhanced phenomena and to the principles (and phenomena) responsible for it. PI equipment illustrating this definition are presented in Figure 1.4. Consider the operation of a fast and highly exothermic reaction run in a flow reactor, which is limited by mass and heat transfer phenomena to remove the heat of reaction. The operating window of this reaction is limited to a certain temperature region and therefore, the process is not able to achieve the goal of complete conversion. Employing the first PI principle (a), the reaction can be enhanced through integration with the downstream process for separation of the product (*in-situ* product removal to drive the reaction to completion). In addition, the heat of reaction may be used to drive the separation. Suitable PI equipment for this case would be a reactive distillation (Fig. 1.4A). By applying principle (b), similar goals could be achieved through the integration of improved heating functions in the reactor, for example a HEX Reactor (Fig. 1.4B). The improvement could also be realized through PI principle (c), by, for example, the integration of a turbulent mixing phenomenon with the existing flow, reaction and heating phenomena in the reactor. Insertion of baffles inside the tube together with the oscillating (instead of continuous) pumping of the liquid through the flow reactor would enable turbulent mixing to be created without increasing the flow velocity. This technique is actually realized in an oscillatory baffled reactor (Fig.1.4C). Finally, PI could be achieved via principle (d) through the application of novel forms of energy, such as microwaves, to enhance the heat transfer or to change the reactor operation from meso-scale to micro-scale leading to enhanced mass and heat transfer (Fig.1.4D).

1.1.2. Where and how is intensification achieved?

The focus of PI has been mostly on improvement in the reaction and the separation tasks. This trend is not surprising since the cores of process design are the selection of the reactor and the downstream processing (Douglas, 1985). By optimizing/improving the reactor performance, it is possible to achieve significantly enhanced throughput or better efficiency/use of the raw materials and also sometimes to reduce the quantity and quality of the downstream processing. But what are the drivers behind the intensification, namely the limitations that must be overcome through the intensification.

For the reaction task, six main limitations have been identified (Fig 1.5), namely: limitations due to physical boundaries (such as unfavorable equilibrium, low selectivity, limited heat transfer and high

contacting that has been in almost 40% of PI reactors); high energy consumption (38%); high capital costs (63%); large volumes (63%); large numbers of units (63%).

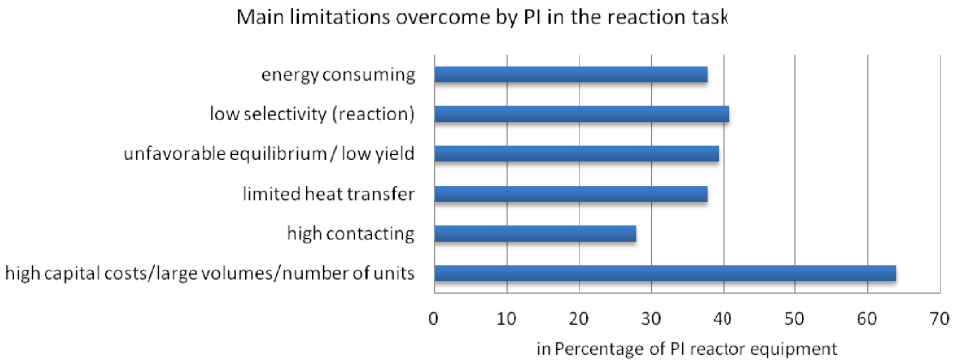


Figure 1.5. Identified main limitations overcome by PI in the reaction task for the development of 110 reported PI equipment (Appendix A.1) from the literature survey.

The reaction is mostly enhanced/intensified (see Fig. 1.6) by: improved mass transfer (32%; for example, through addition of mixing elements); by addition of phase transition phenomena (28%; for example, to shift an unfavorable equilibrium); by improved energy transfer (18%; for example, to use the energy from an exothermic reaction); by improved mass transfer (contacting) with the catalyst (14%).

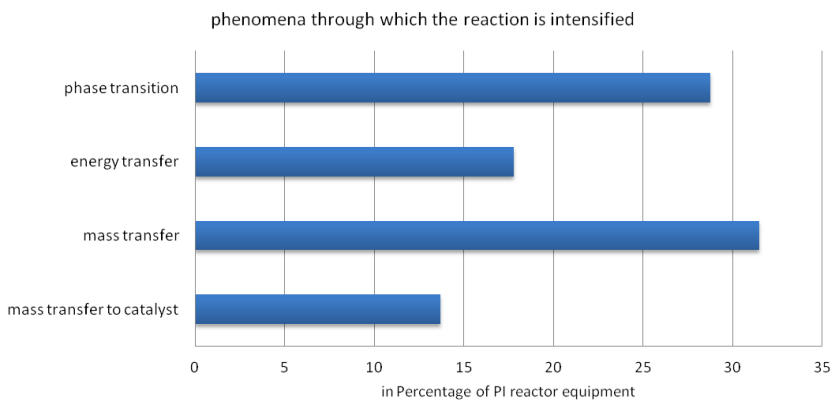


Figure 1.6. Identified main phenomena used to enhance the reaction phenomenon for the development of 110 reported PI equipment (Appendix A.1) from the literature survey.

For the separation task, five main limitations have been identified (Fig 1.7), namely: limitations due to physical boundaries (such as limiting equilibrium/azeotrope, difficult separation due to low driving forces as well as limited mass transfer creating phase contact for the phase transition in almost 50% of PI separators); the high energy consumption (73%); high capital costs (70%); large volumes (70%); large number of units (70%).

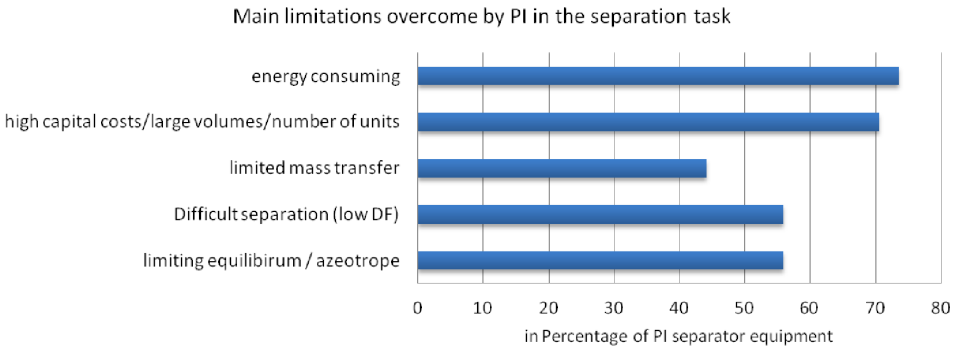


Figure 1.7. Identified main limitations overcome by PI in the separation task for the development of 110 reported PI equipment (Appendix A.1) from the literature survey (DF: Driving Force).

The separation is enhanced (see Fig 1.8) by: adding a second phase transition phenomenon (28%; for example to overcome an azeotrope); by adding a reaction (18%; for example to overcome an azeotrope); by enhanced of mass transfer (26%; for example the introduction of foams and microstructures for better contacting of two phases); and by enhanced energy transfer (16%; for example in microseparators).

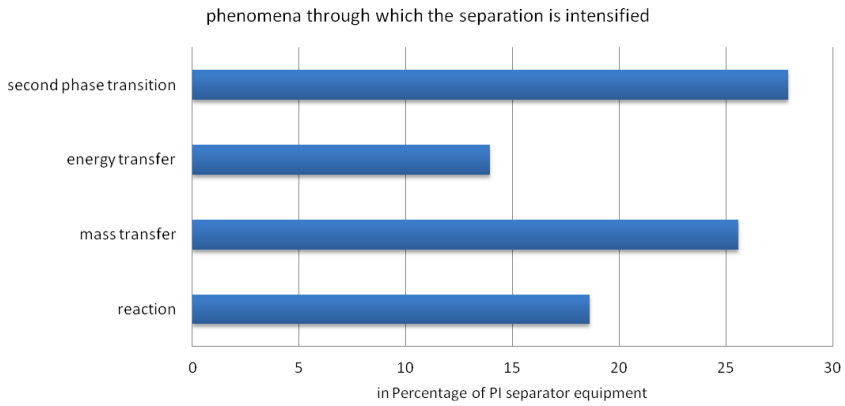


Figure 1.8. Identified main phenomena used to intensify the separation for the development of 110 reported PI equipment (Appendix A.1) from the literature survey.

1.1.3. Barriers for the implementation of PI

Despite the early promise, only a small number of successful implementations of PI equipment have been reported (Harmsen, 2010) and there are a number of challenges with respect to its application (see Table 1.3).

Table 1.3. Barriers for the implementation of a new technology (Rong et al., 2000; Moulijn et al., 2006; Stankiewicz, 2003; Becht et al., 2009; Charpentier, 2005; Harmsen, 2007).

Barriers for implementation of PI
i) Low maturity of the technology
ii) Knowledge to identify/decide when and where a process needs PI
iii) Knowledge which part of the process should be intensified for a desired improvement
iv) Knowledge about how and where to intensify
v) Missing criteria to evaluate PI
vi) Risk due to lack of precedent
vii) Expensive new pilot plant facilities
viii) Concerns about safety and control

Harmsen (2010) states that only three PI equipment have been implemented widely within the petrochemical industry: reactive distillation; dividing wall columns; and reverse flow reactors. This is partly in agreement with our own analysis in which the maturity of PI equipment is classified in terms of four categories: high, medium, low/medium and low. “Highly” mature PI equipment has been implemented for at least three different production processes. “Medium-mature” PI equipment have been run in pilot-plant facilities and have been implemented for at least two different industrial processes. The category “low/medium” includes PI equipment that have been successfully proven their potential within one process. The category “low” includes all remaining PI equipment. Based on this definition, only 22% of all PI equipment are classified as highly mature while around 60% of the PI equipment are classified as low or low/medium mature (see Fig. 1.9).

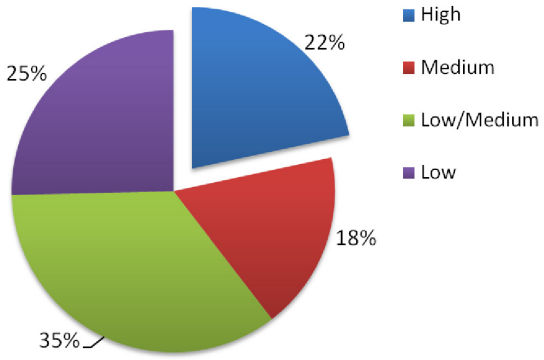


Figure 1.9. Proportion of maturity of the developed PI equipment based on the literature survey.

An example for highly mature PI equipment is reactive distillation, which has been implemented into several industrial processes such as methyl-acetate, MTBE and others (Lutze *et al.*, 2010). An example for a medium mature process is the hybrid configuration of reactive distillation with a pervaporation, which has been studied in research widely but implementation into the industry is still scarce. An example for a low/medium mature PI equipment is the HIGee Reactor (Ramshaw, 1983) while an example for low maturity is the application of microwaves for enhancements of reaction and separation.

Additionally, the application of "mature" technology has been limited with respect to diversity of the processes. One example is the application of heterogeneous catalytic distillation (HeCD) which has been analyzed based on patents concerning reaction systems and reaction characteristics (equilibrium, kinetics, heat of reaction) as well as configurations within the column and their integration with other units (Lutze *et al.*, 2010). HeCD has been mostly implemented within the petrochemical industry and for esterifications, etherification, alkylations and hydrogenation reactions. Current development shows the application of HeCD within those reactions to higher carbon numbers but these are probably not the only classes of reactions where HeCD might be advantageous or most advantageously applied (Lutze *et al.*, 2010). Furthermore, external or internal integration of HeCD with other unit operations such as pervaporation (Buchaly, Kreis & Gorak, 2007) or distillation (Arpornwichanop Koomsup & Assabumrungrat, 2008) or by using dividing wall column technology (Kaibel *et al.*, 2005) has not been reported for industrial application (Lutze *et al.*, 2010).

1.2. State-of-the-art: Process synthesis/design for PI

In general, the identification of a feasible (and optimal) process flowsheet to convert a raw material and necessary utilities (such as energy utilities, solvents, membranes, etc.) to the final product and waste (see Figure 1.10) is not an easy and intuitive part (Douglas, 1985). One of the reasons is that a large number of process options and a number of different utilities are potentially available as well as a number of decision criteria (operational constraints, performance constraints) need to be matched. Therefore, from the process systems engineering (PSE) toolbox, process synthesis tries to attack those issues and difficulties within the flowsheet synthesis/design. Process synthesis involves the identification of the optimal path to reach a desired product from a given starting point, of the desired quality and quantity, and subject to defined constraints on the process.

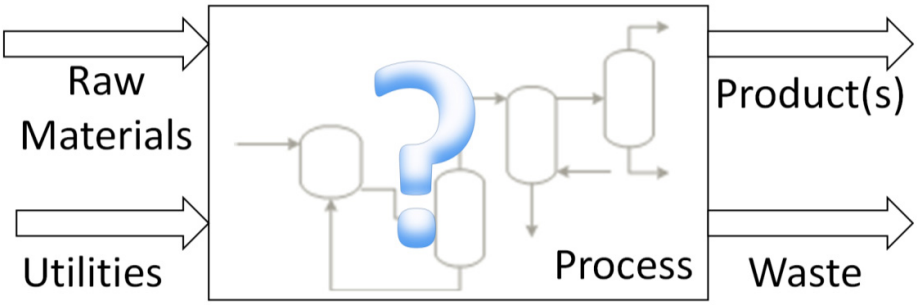


Figure 1.10. Simplified scheme of the general synthesis/design problem.

In general, existing methodologies for process synthesis can be classified either based on heuristics (Douglas, 1985; Siirola & Rudd, 1971; Barnicki & Fair, 1990), thermodynamic insights (Jaksland, Gani & Lien, 1995), mathematical programming such as superstructure optimization (Brüggemann *et al.*, 2004; Grossmann, Aguirre & Barttfeld, 2005) or combinations of these into hybrid methods (d'Anterroches & Gani, 2005).

Most of the process synthesis methodologies have been developed based on unit operations. However, also different scales and concepts have been used to synthesize processes. Examples of attempts and methodologies for synthesizing processes based on tasks (Siirola & Rudd, 1971); mass and heat building blocks (Papalexandri & Pistikopoulos, 1996), reactor/mass exchanger building blocks (Linke and Kokossis, 2003), as well as attempts based on phenomena (Rong, Kolehmainen & Turunen, 2008, Arizmendi-Sanchez & Sharratt, 2008) have been proposed.

A recent detailed overview of process synthesis methodologies is given by Li *et al.* (2009). In the following section 1.2.1, the main concept of the general process synthesis methodologies behind each class is explained and important contributions are highlighted.

In principle, the three main tasks of process synthesis methodologies are to generate options, evaluate these options and to give a method which effectively identifies the best option from those generated options (Li and Kraslawski, 2004). This is exactly what is needed to support the implementation of PI in industry and overcome some of the barriers PI is facing (Table 1.3; Moulijn *et al.*, 2006; Lutze *et al.*, 2010). Up to now, only a small number of synthesis/design methodologies incorporating PI have been developed. Those are highlighted in section 1.2.2.

1.2.1. General process synthesis/design methodologies

- Process synthesis based on heuristics:

Heuristics are a set of rules based on experience. Process synthesis based on heuristics apply heuristics for the selection of an equipment and for identification of the position of an equipment within the process flowsheet exploiting available process knowledge and process specifications.Two examples for heuristic rules (Douglas, 1985) are to decide which process scenario is necessary ("Use a continuous process for a large capacity process") or when a separation needs to be done ("Perform the easiest separation first").

Examples of this class are the heuristics for separation systems mostly for processes for the chemical industry (Siirola & Rudd, 1971; Barnicki & Fair, 1990) as well as recently for downstream processes for bioprocesses (Bauer & Schembecker, 2008).

One of the most important synthesis tools using heuristics within this class is the hierarchical decomposition by Douglas (1985). He decomposes the synthesis problems into 5 decision blocks:

1. Batch versus continuous.
2. Input–output structure of the flowsheet.
3. Recycle structure and reactor considerations.
4. Separation system synthesis.
5. Heat exchange network.

All of those decision blocks need to be filled with heuristic rules. Barnicki, Hoyme and Siirola (2006) give an exhaustive list of heuristics based on experience for selection of feasible separation process units (decision block 4.). The methodology enables the quick and stepwise evaluation of the synthesis problem. It has been shown to be successfully applied to the hydrodealkylation of toluene (Douglas, 1985).

However, the disadvantage of this approach is that all sub-problems are solved separately, especially reaction and separation not allowing synergy effects between those. Another disadvantage of pure heuristic approaches are that existing rules may be contradictory ("Perform easiest separation first" and "Remove component with the largest amount in the stream first") and that experience with this equipment has to be built before being able to describe it properly into heuristics. Also, heuristics identifying specific equipment may be contradictory.

- Process synthesis based on thermodynamic insights:

Knowledge about the thermodynamic behavior of all components within the process is exploited in process synthesis tools based on thermodynamic insights.

Jaksland, Gani and Lien (1996) developed a methodology for synthesis/design of separation systems based on this concept. They have linked physicochemical properties of pure components as well as mixtures to select suitable unit-operations in a database. An example is the necessary boiling point difference of two components to be separated in a distillation column. Input into their methodology is the specifications of all inlet and outlet streams of the desired system. The methodology consists of two communicating levels. The first one is unit-operation free and the second unit-operation dependent. In the first step, the system is analyzed by mixture properties (azeotropes, immiscibilities) as well as pure component properties of all components in the separation system which is retrieved from a database or generated using property prediction methods. For all binary pairs, the difference in binary ratio's of each pair is analyzed to identify a set of potentially suitable equipment. Using the mixture properties certain splits identified by separation factors based on pure component data are not possible such as separation of components based on the boiling point difference in case of occurring azeotropes. Additional, rules (based on the property ratio's) are used to select necessary mass separating agents (solvents, membranes) as well as to select the first separation. At the end, of level 1, a number of property differences exist to separate all components in the system. In level 2, pure component properties and mixture properties are used to select and screen the separation equipment for each task as well as for each generated process option. The methodology has been successfully applied to the production of MTBE and gas separation in an ammonia plant.

Other examples of the class of process synthesis methodologies are the method by Bek-Pedersen *et al.* (2004) in which the separation system as well as the position of the separation task is identified based on the driving force of each separation (see section 4). So far, this method has been exploited mostly to all types of distillation systems as well as other gas/vapor/liquid-liquid separation technologies (Bek-Pedersen & Gani, 2004; d'Anterroches & Gani, 2005).

To conclude, process synthesis based on thermodynamic insights enables a quick selection strategy suitable for separation equipment. The disadvantage of this methodology is the limitation to existing equipment within the database, the selection of one equipment for each task as well as no use of additional knowledge about the equipment and/or performance specifications based on costs, waste generation etc.

- <u>Process synthesis based on mathematical programming:</u>

The process synthesis problem can be defined mathematically (see also section 2) in which all process options are included into a fixed superstructure. Decision (binary) variables are enabling/disabling the occurrence of streams, unit-operations as well as structural parameters such

as stages within a column. Depending on the case, a mixed-integer linear problem (MILP) or a mixed-integer non-linear problem (MINLP) as well as steady state or dynamic problem need to be solved. An overview of solving a mathematical synthesis problem as well as examples is given by Grossmann and Daichendt (1996). In general, a large range of synthesis problems of whole processes (Li & Kraslawski, 2003; Li, Wozny & Suzuki, 2009) as well as unit-operations such as distillation columns (Grossmann, Aguirre & Barttfeld, 2005) have been solved using this approach. Also processes have been synthesized by means of evolutionary algorithms for sharp and non-sharp separations (Henrich *et al.*, 2008).

The advantage of these methods is that the identification of the best process flowsheet is based on a pure quantitative basis. However, disadvantages of these methods based on mathematical programming are the generation of the superstructure (not fully automated yet), the selection of suitable equipment for the superstructure as well as the computational expense (Li & Krasławski, 2004) which is a bottleneck limiting the use of those tools in industry (Klatt & Marquardt, 2009).

- <u>Process synthesis based on hybrid methods:</u>

Hybrid methods are synthesis methods integrating the concepts mentioned above to use the advantages of a quick screening based on thermodynamic insights or heuristics in an early step and mathematical programming strategies in later steps. Examples of hybrid methods are the combination of thermodynamic insights and mathematical programming through a group contribution approach by d'Anterroches & Gani (2005). The process groups (building blocks for synthesizing the flowsheet) are separation tasks identified by thermodynamic insights. Based on connectivity the identified process groups are connected to form process flowsheets which are quickly evaluated using the driving-force approach (Bek-Pedersen *et al.*, 2004). Another hybrid method is the simultaneous design/synthesis of separation processes incorporating heat integration (Li, Wozny & Suzuki, 2009).

An example of combining heuristics and mathematical programming is the methodology for the design of complex distillation sequences in which initial structures are identified first and rigorous simulation identifies the best option (Shah & Kokossis, 2002).

The advantage of these methods is that it potentially handles a large number of process options but is not losing the comparison of process options on a quantitative basis.

1.2.2. Process synthesis/design methodologies for PI

The challenge in the synthesis of PI flowsheets compared to conventional flowsheets is that the PI equipment is leass mature and full undersdtanding of all PI equipment is not yet established.

Although PI is potentially very useful, strategies to synthesize and handle the number and the complexity of highly integrated process options do not yet exist. Often the design of intensified processes reported in the scientific literature is case based in which improvements of the process by PI are made but only one pre-defined PI equipment is considered to improve the process and comparison with other intensified equipment were not made. Examples of case-based PI are: reactive distillation in esterification of acetic acid (Tang *et al.*, 2005); reactive stripping (distillation) in the desulfurization of diesel (Cardenas-Guerra *et al.*, 2010); oscillatory flow baffled reactors in the production of biodiesel; HiGee separator for stripping of hypochlorous acid; micro reactor for direct synthesis of hydrogen and oxygen (Reay, Ramshaw & Harvey, 2008); Marbond HEX reactor in the acrylics process (Anxionnaz *et al.*, 2008). Therefore, even though improvements to the base-case design have been made, there are no guarantees that better designs could not be found. However, for determination of the optimal or near optimal designs different PI options need to be considered. Hence, finding the best intensified PI option remains unsolved using this case-based approach.

- <u>Process synthesis for PI based on heuristics:</u>

A pure heuristic approach for process synthesis has not been developed within the area of PI. One of the reasons is that the expertise based on experience gained by using PI equipment is simply missing for most of the PI equipment. An exception is reactive distillation. Heuristics for the application of reactive distillation have been proposed by Barnicki, Hoyme and Siirola (2006).

- <u>Process synthesis for PI based on thermodynamic insights:</u>

Methods based on thermodynamic insights for the synthesis/design of intensified processes have not been reported in the literature yet.

- <u>Process synthesis for PI based on mathematical programming:</u>

Mathematical programming techniques such as superstructure optimization have been used for identification of the optimal structures within intensified unit-operations such as reactive distillation. In those approaches, the number of stages and the operating parameters are identified by creating an initial superstructure of stages, allowing reactive as well as non-reactive stages and using an MINLP solver to optimize the problem with respect to an objective function (Ciric & Gu, 1994). Also, evolutionary algorithms have been used to identify the best hybrid separation schemes of an initial search space (Koch *et al.*, 2010) or for the design of reactive distillation columns (Urselman *et al.*, 2011). However, to our knowledge, intensification of a whole process taking a large number of different PI equipment into the search space has not been proposed.

- Process synthesis for PI based on hybrid methods:

Currently, a few general hybrid PI synthesis/design methods are available which are covering specific parts or PI units of the process. That is, for the integration of superstructure optimization and heuristics, the process synthesis framework for reactive separations (Schembecker & Tlatlik, 2003); design and optimization of hybrid separation processes based on integration (Franke *et al.*, 2008). Examples of hybrid synthesis methodologies for PI based on the integration of superstructure optimization and thermodynamic insights are the design and optimization framework for hybrid separation processes (Marquardt, Kossack, & Kraemer, 2008); optimization of conceptual synthesis and design of reactive distillation (Sun, Huang, & Wang, 2009); and retrofit of multi-component distillation columns incorporating PI (Errico *et al.*, 2008).

Recently, a methodology for a general synthesis/ design incorporating PI has been proposed by PI Quick Scan process reviews in The Netherlands using heuristics (qualitative rules) for selection of a small set of options followed by quantitative calculations for identification of the most promising intensified process/equipment (van den Berg, 2001). However, details and systematic examples for this method have not been published.

The methodologies cited above have the bottleneck that their search spaces are based on a small selection of pre-defined PI unit operations which are, in some cases, covering only specific parts of the process. Questions on when this specific part of the process should be intensified as well as how to identify PI options are not addressed by those methods. Hence, finding a global optimum for the whole process cannot be guaranteed.

Hybrid synthesis/design methods going beyond unit-operations to achieve PI are the development of novel reactor networks based on elementary process functions (Peschel, Freund, & Sundmacher, 2010); the means-ends analysis (Siirola, 1996; Barnicki, Hoyme & Siirola, 2006; Siirola, 2011); the generalized modular representation framework (GMR) for process synthesis (Papalexandri & Pistikopoulos, 1996); the phenomena-based process synthesis based on manipulation and variation of process phenomena (Rong, Kolehmainen & Turunen, 2008); and the phenomena-based modularisation approach (Arizmendi-Sanchez & Sharratt, 2008).

The approach based on elementary process functions tracks a fluid element (Freund & Sundmacher, 2008) through a reactor with possibilities to integrate separation and heating/cooling (thermal). Starting from a definition of the objective of the investigation, the method decomposes the problem into three levels (Peschel, Freund, & Sundmacher, 2010; Peschel et al., 2011). The first level is the level of integration in which the optimal route in the state space is identified. In the second level operational constraints based on detailed mass and energy transport calculations are integrated

within the design of level 1. In the last level, the unit operation is identified to screen for technical constraints of the design. Reactor parameters such as interfacial areas, residence time and number of units, are not defined *a priori* but are investigated through a stepwise procedure. The method has been illustrated for a SO_2 oxidation reactor and a hydrofurmylation biphasic reactor. The knowledge-base or rules necessary to identify the unit-operations and the functions from the analysis has not been presented.

In the means-ends analysis approach by Siirola *et al.* (1996, 2006, 2011), the process inlet and outlet specifications are defined. Based on a set of rules, the tasks to satisfy the specifications are identified. By variations based on heuristics (expert knowledge) different process options are generated which are evaluated based on sets of performance criteria. The method has been illustrated by the generation of the reactive distillation unit for the production of methyl-acetate. The detailed step-by-step procedure for this case study is given in the appendix A.5. However, even though novel process/units may be identified, the application is not simple. Rules and/or algorithms for identification and variations of tasks as well as for identification of unit operations have not been published. Furthermore, it does not aim to generate all potentially feasible options and based on this cannot guarantee to find a (global) optimal solution.

Process synthesis by the GMR-approach is based on heat and mass building blocks instead of defined (conventional) equipment. Heat and mass building blocks may be or may not be connected using a set of connectivity rules. If a given connection of these blocks gives a feasible and promising solution, then in a subsequent step, unit operation(s) are identified for those. Until now, this approach has been successfully illustrated for column synthesis/design such as distillation, reactive distillation and absorption (Papalexandri & Pistikopoulos, 1996; Algusane *et al.*, 2003). The selection of the initial search space of building blocks is based on heuristics and thermodynamic insights. A complete set of rules how to identify unit operations has not been given yet. Even though it is a very promising approach, since then (2003), no additional papers have been published using this methodology.

The synthesis concept by Rong *et al.* (2004, 2008) is based on process phenomena. They classified process phenomena into “chemistry and chemical reaction phenomena, materials phases and transport phenomena, phases behavior and separation phenomena *etc.*”. Process phenomena are characterized by surface materials, operation modes, flow pattern, facility medium, geometry, energy sources, key variables as well as components and phases. Their methodology decomposes the synthesis problem into 10 hierarchical steps. The heart of their method consists of trial-and-error variations of the characteristics for the identified key process phenomena through seven different suggested PI principles. The method has been briefly illustrated by two conceptual examples which

are the production of peracetic acid (Rong, Kolehmainen & Turunen, 2008) and hydrogen peroxide (Rong *et al.*, 2004). Details about algorithms and the stepwise procedure are not given, including: a definition/description and systematic identification of phenomena; as well as strategies for variations of these phenomena; techniques how to find all currently available options; and a solution approach how to identify the best option. For each of their conceptual examples only the final design of the intensified process is presented.

Another concept, using phenomena to synthesize potentially novel process solutions is the modularisation approach by Arizmendi-Sanchez and Sharratt (2008). They have classified phenomena into phenomena in the structural level for the description of phases and interfaces; and phenomena in the behavioral level for the description of mass transfer, phase change, energy, change conditions and mechanical operations. Their concept is to aggregate phenomena to form phases. Phases can be aggregated to form tasks (such as stages or devices). Tasks can be aggregated to represent the whole process. Until now, only the library and classification of phenomena as well as the representation of one unit by phenomena have been presented. No details on algorithms, necessary tools and solution techniques to synthesize processes based on their modularisation approach have been published.

Hence, even though promising attempts in synthesis/design to achieve PI have been proposed, systematically finding the best intensified PI option for a whole process remains unsolved using the approaches above. This counts for the unit-operation based concepts as well as for the concepts going beyond unit-operations.

1.3. Motivation and objectives for this PhD-project

PI has lead to the development of a significant number of new equipment concepts and operating strategies to improve processes with respect to a range of different objectives (see section 1.1). Despite the potential, only a small number of successful implementations of PI equipment have been reported (Harmsen, 2010) and there are a number of challenges with respect to its application (Table 1.3). The application of process synthesis can overcome these issues (Moulijn *et al.*, 2006).

Currently available process synthesis/design methods incorporating PI are limited to specific parts or units of the process (see section 1.2). It is believed, however, that PI has the biggest impact on performance improvement when applied to the whole process (Moulijn *et al*., 2006). Therefore, even though improvements to the base-case design have been made, there are no guarantees that better designs could not be found. This has not been tackled in the current methodologies which are not focusing to intensify the whole process on a quantitative basis.

Another gap is how to design/synthesize PI going beyond PI equipment currently in existence which

may achieve potentially even higher improvements in the process (Freund & Sundmacher, 2008). Until now, some promising concepts to generate potentially novel PI designs have been proposed in literature but have not been developed in full detail giving algorithms for a systematic approach so far (see section 1.2).

Therefore, to push the implementation of process intensification, the following main objective of this PhD-project is the:

Development of a systematic synthesis/design methodology to achieve process intensification. This methodology should generate PI options improving a target specification, evaluate these PI options for feasibility and identifies the best options from the remaining options on a quantitative basis. Therefore, this methodology should be able to handle a large number of options. The method of solution should be efficient, robust and reliable. There should be workflows which guide the user through all decisions/actions to be made and integrates the methodology to all tools, databases, models which are necessary to take decisions. The methodology should be able to generate PI options using existing PI equipment for fast retrofit of an existing process. It should also be able to generate novel solutions going beyond PI equipment currently existing. For this the fundamental definition of PI (see section 1.1.1) should be exploited to enhance process phenomena using the PI principles (a-d). The methodology should contain a well-defined procedure for screening using a well-defined list of performance criteria from which the screening of PI options is based. The methodology should be generic, meaning that all tools, workflows and models are applicable for a wide range of different process industries.

1.4. Structure of the thesis

In **chapter 2**, the theoretical background for the developed methodology is explained in detail. That includes the decomposition-based solution approach used for handling the large number of process options as well as the developed concept to generate novel PI solutions by using a phenomena based approach for PI flowsheet design. In **chapter 3**, the developed workflow of the methodology is presented in detail including all algorithms and sub-algorithms. In **chapter 4**, the supporting tools and methods which have been developed and/or applied in order to follow the workflow are described. In **chapter 5**, the application of the unit-operation based synthesis/design methodology is highlighted by case studies. In **chapter 6**, case studies highlighting the application of the phenomena-based synthesis/design methodology are presented. The developed synthesis/design methodology and the results of their application to the case studies are discussed in **chapter 7**. That gives the basis for a summary of the main achievements of this PhD-project and for an outlook for future work in **chapter 8**.

Chapter 2.

Methodology – Overview & concepts

The developed synthesis/design methodology for process intensification is a hybrid method. It combines mathematical formulation with methods and tools based on thermodynamic insights as well as knowledge based on analyzing the existing PI equipment. Therefore, in this chapter the mathematical formulation of the PI synthesis problem is introduced in section 2.1.

Processes consist of a set of unit operations, which are connected to achieve the process target. The behavior of each unit-operation depends on the interaction of the involved phenomena within the operation (see Fig. 2.1). Typically, processes are synthesized through combinations of a set of known unit-operations as building-blocks. Known unit-operations are a fixed combination of phenomena within the operation *a priori*. The best flowsheet is identified from a set of feasible flowsheets.

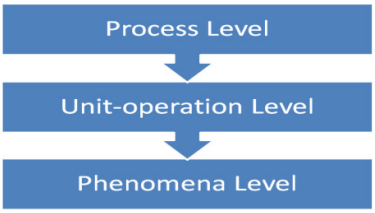


Figure 2.1. Dependency of the process levels.

In this PhD-project, the process synthesis problem is handled using two types of building blocks at different scales. One building block is PI unit-operations and the other one is phenomena (section 2.2). With the PI unit-operations as the building block, already developed PI equipment are used to generate intensified process options. Since the PI units in the initial search space are known *a priori*, shorter development times are expected in the final implementation of the process (unit-operation based method). On the other hand, in order to invent new unit operations, going beyond those currently in existence, to achieve potentially even higher improvements, the process should be investigated at a lower level of aggregation (Papalexandri & Pistikopoulos, 1996; Freund & Sundmacher, 2008). Hence, to extend the search space for process improvement, process synthesis/design incorporating PI needs to be investigated at the phenomenological level (Lutze, Gani & Woodley, 2011; see Fig. 2.2).

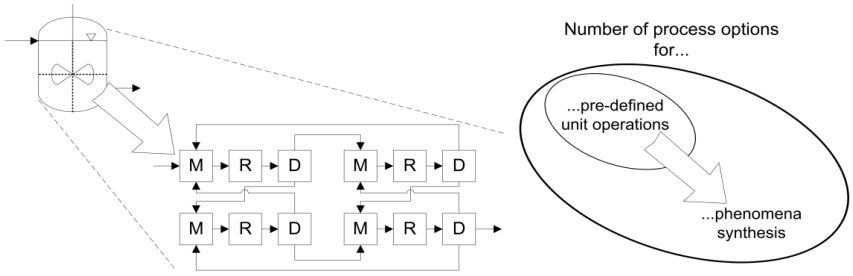


Figure 2.2. Representation of unit operations through phenomena (left; M: Ideal mixing phenomenon; R: Homogeneous reaction phenomenon; D: Dividing Phenomenon) and the extension of the search space through syntheses and design on the phenomena level.

Therefore, this chapter provides the concepts behind the use of phenomena as building blocks for synthesis of intensified processes (section 2.2). Independent of the selected building block for synthesis/design, a large number of process options may be generated to intensify a process. Therefore, an efficient solution procedure is necessary. Here, the decomposition-based solution approach (section 2.3) is used. Process intensification is evaluated using a set of performance metrics which is introduced in section 2.4.

2.1. Mathematical formulation of the PI synthesis problem

The mathematical formulation of the general PI-synthesis problem is given by Eqs. 2.1-2.5.

$$\min/\max F_{Obj} = \sum f_j\left(\underline{Y},\underline{X},\underline{d},\underline{\theta}\right) \tag{2.1}$$

Subject to $\underline{Y}$, $\underline{X}$, $\underline{d}$, $\underline{\theta}$ and,

Logical constraints:

$$g_{Logical,LB} \le g_{Logical}\left(\underline{Y}\right) \le g_{Logical,UB} \tag{2.2}$$

Structural constraints:

$$g_{Structural,LB} \le g_{Structural}\left(\underline{Y}\right) \le g_{Structural,UB} \tag{2.3}$$

Operational constraints:

$$g_{Operational,LB} \le g_{Operational}\left(\underline{Y},\underline{X},\underline{d},\underline{\theta}\right) \le g_{Operational,UB} \tag{2.4}$$

The complete process model:

$$\frac{\partial \underline{X}}{\partial t} = h_P\left(\underline{Y},\underline{X},\underline{d},\underline{\theta}\right) \tag{2.5}$$

Where $\underline{X}$ is a vector of design (optimization) variables such as, temperatures *T*, and/or compositions *x*; $\underline{Y}$ is a vector of binary decision variables for describing the existence of units $\underline{U}$ and streams $\underline{F}$; $\underline{d}$ is a vector of equipment parameters and $\underline{\theta}$ is a vector of product and process specifications. All feasible PI options must satisfy all the constraints. The logical constraints are related to

process/operation synthesis rules. For example, a continuous single phase reactor has at least one inlet and one outlet stream. The structural constraints define the connectivity between unit operations. For example, if the integration of two unit operations is not efficient or has higher energy consumption than the corresponding single unit operation, they cannot be combined. Process models h_p represent the set of model equations needed to describe the behavior of the process. These can be built through models of PI unit-operations as well as models of phenomena. Dependent on the scenario being studied, process models can be steady state, dynamic or distributed.

The objective function (Eq.2.1) in the above problem formulation could be replaced by performance criteria (Eq.2.6) while the process model (Eq.2.5) may be replaced by simpler versions (see Eq. 2.7).

$$\underline{\Psi}\left(\underline{Y}, X_{1..v}, \underline{\theta}\right) - \underline{\Psi}_{\text{Target}}\left(\underline{Y}, X_{1..v}, \underline{\theta}\right) \geq 0 \tag{2.6}$$

Short-cut process models:

$$\frac{\partial \underline{X}}{\partial t} = h_{P,simple}\left(\underline{Y}, X_{1..v}, \underline{d}, \underline{\theta}\right) \tag{2.7}$$

Performance criteria $\underline{\Psi}$ represent target values for the performance of the whole or part of a process that need to be matched through PI options. An example of a performance criterion is the yield in a desired reaction.

Short-cut models do not describe the full in-depth behavior of the process and therefore only cover a subset $\underline{v}$ of process variables $\underline{X}$, for example, fixed conversions in reactors or split factors in separators.

The starting point for the systematic computer aided methodology is to define the goal through the objective function F_{Obj}, which can either be a single function or a sum of weighted functions (Eq.2.1 and Eq.2.6).

2.2. Phenomena as building blocks for process synthesis

Here, the concept of phenomena as building blocks together with connection equations and principles to connect them (section 2.2.1-2.2.5) are presented.

2.2.1. Process levels for phenomena-based process synthesis/design

In this approach, the processes are aggregated at different levels (see figure 2.3). The lowest level is the phenomena level. Phenomena are connected in simultaneous phenomena building blocks (SPB's) by a set of general connectivity rules as well as a set of connectivity rules based on the operating windows of the involved phenomena (see section 2.2.3.). SPB's are one or more phenomena which take place at the same time and at the same position. The SPB's can be placed

within one or more stages of an operation to achieve a process task following another set of rules based on the connectivity of inlet and outlet streams of different SPB's which depends on the operating window of each SPB. One or several operations form a process flowsheet.

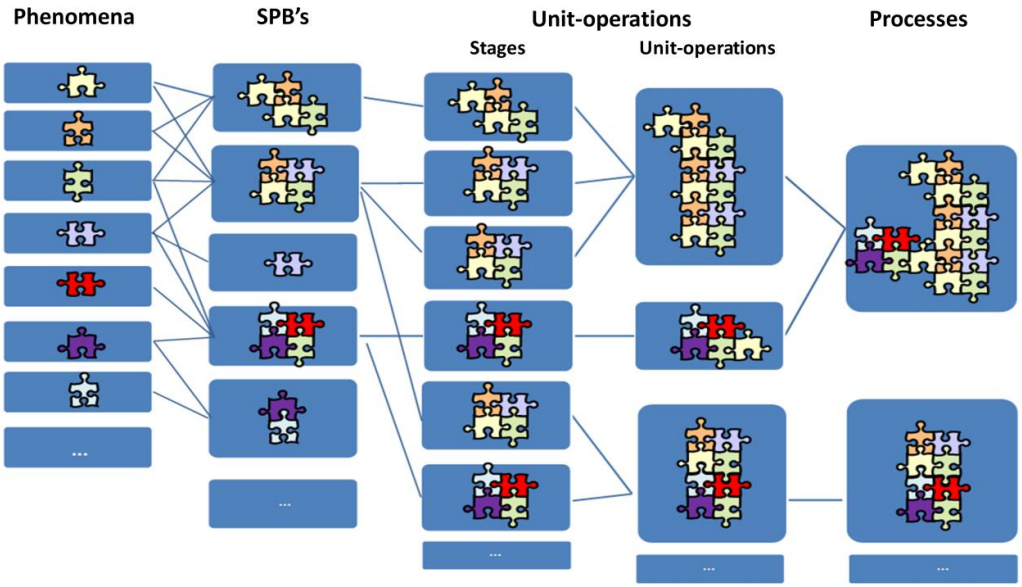


Figure 2.3. Process levels used for phenomena-based process synthesis/design (SPB: simultaneous phenomena building block).

2.2.2. Phenomena as building blocks

Phenomena as building blocks consist of mass, component, energy and momentum balances as well as constraint equations describing the phenomenon as well as the inlet and outlet stream conditions.

Overall mass balance (with c for coordinate axis):

$$\frac{\partial \rho}{\partial t} = \sum \left. \frac{\partial (\rho w_c)}{\partial c} \right|_{out}^{in} \tag{2.8}$$

Component balance for each component i:

$$\frac{\partial \rho_i}{\partial t} = \sum \left. \frac{\partial (\rho_i w_c)}{\partial c} \right|_{out}^{in} + r_i \tag{2.9}$$

Energy balance:

$$\frac{\partial (\rho u)}{\partial t} = \sum \left. \frac{\partial (\dot{e}_c)}{\partial c} \right|_{out}^{in} + q_{generated} \tag{2.10}$$

Momentum balance (with index f as the number of forces):

$$\frac{\partial(\rho w)}{\partial t} = \sum_f f_f \tag{2.11}$$

All equations in the building blocks have to be linked to additional constitutive equations such as equations representing thermodynamic properties or reaction kinetics.

In general, phenomena can be classified into 8 different classes:

- Mixing: Mixing phenomena describe the mixing within one phase or between several existing phases.
- Stream dividing: A stream dividing phenomenon divides a stream into two or more streams. Temperature, pressure and concentrations remain unchanged.
- Phase contact: Phase contact phenomena describe the contact (and the resistances) directly at the phase boundary of two (or more) phases.
- Phase transition: These phenomena describe the mass transfer of components between at least two phases. An example of a phase transition phenomenon is the vapor-liquid equilibrium relationship.
- Phase change: These phenomena describe the change of state of a complete stream. Concentrations within the phase do not change. An example is full evaporation of a liquid stream.
- Phase separation: Phase separation phenomena describe the degree of separation of the two phases. This may be ideal, meaning that the outlet streams are pure with respect to the occurring phases within each outlet stream or not.
- Reaction: Within a reaction phenomenon the mass of one (or more than one) component is changed between inlet and outlet streams.
- Energy transfer phenomena: Energy supply/removal between energy sources and sinks are described with energy transfer phenomena

Each class of phenomena (except of the stream dividing) can be further sub-classified. For example, for phase transition phenomena the subclasses are depending on the involved phases (e.g. V-L, L-L).

For each class of phenomena the number of inlet and outlet streams are defined which is important for connectivity between phenomena of different classes. Mixing phenomena have minimum one inlet stream and one outlet stream while dividing phenomena have one inlet and minimum two outlet streams. Reaction blocks are defined to have one inlet and one outlet stream. The inlet of phase transition phenomena is a mixture of two phases between which the mass transfer of components is realized. The outlet of a phase transition phenomenon is a mixture of two phases. Phase separation phenomena have one inlet and the number of outlets is given by the number of

phases separated from each other within this phenomenon. Energy transfer phenomena such as heating/ cooling and pressurizing/expanding are defined to have either one inlet and one outlet or two inlet and two outlet streams, where the streams are not in contact. An overview over the number of inlet and out streams for different phenomena is presented in Table 2.1. An overview of the states of these inlet/outlet streams of some phenomena is presented in Table 2.2.

Currently, 53 phenomena are available in the phenomena library and the list is given in appendix A.2.

Table 2.1. Number of inlet and outlet streams of some phenomena.

Number of Connectors	Phenomena Class												
	Mixing		Reaction		Dividing	Energy transfer		Phase transition			Phase separation		
	1-Phase Ideal mixing	2- Phase Perfectly mixed	Non-cat. one phase	heterog. solid catalyzed	dividing	simplified convective heating (without utility streams)	convective energy transfer between streams (co/ counter current)	V-L	S-L	L-L	V-L	S-L	L-L
Inlet stream													
1	x		x	x	x	x		x	x	x	x	x	x
2	x	x					x						
…	x	x											
N	x	x											
Outlet stream													
1	x	x	x	x	x	x		x	x	x			
2					x		x				x	x	x
…					x								
N					x								

Table 2.2. States of in- and outlet streams of phenomena.

Phases	**Phenomena Class**												
	Mixing		**Reaction**		**Dividing**	**Energy transfer**	**Phase change**	**Phase transition**			**Phase separation**		
	1-Phase Vapor	2- Phase V-L mixing	Non-cat. liquid phase	heterog. solid catalyzed	dividing	simplified convective heating (without utility streams)	Vapor to Liquid: Full Evaporation	V-L	S-L	L-L	V-L Ideal Split	S-L Ideal Split	L-L Ideal Split
Inlet stream: V	x	x			x	x	x						
V/L		x			x	x	x	x			x		
L		x	x		x	x							x
L1/L2										x			
L/S					x	x			x			x	
S				x	x								
Outlet stream V	x				x	x					x		
V/L		x			x	x		x					
L1			x		x	x	x			x	x	x	x
L2													x
L/S					x	x			x				
S				x	x							x	

2.2.3. Connection of phenomena

In general, phenomena can be connected in two ways. Phenomena can be connected into a simultaneous phenomena building block (SPB) in case the phenomena are occurring at the same time, at the same position and having a combined operating window (see Figure 2.4). This connection is called interconnection. All others can be connected sequentially when the necessary phenomena for the state change in the second SPB is provided to match input/output constraints of SPB's to be connected. It is defined that the dividing phenomenon is always a SPB itself. Throughout this document, the sign "-" is used for a sequential connection of phenomena while the sign "=" is used for an interconnection of phenomena.

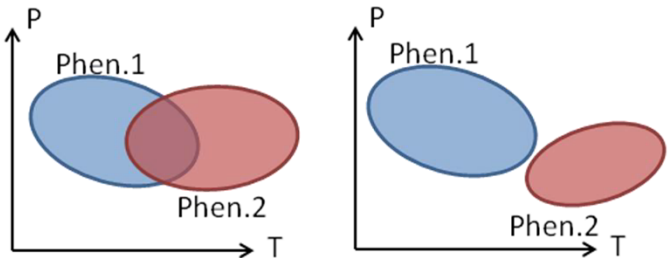


Figure 2.4. Two phenomena (Phen.1 & Phen.2) with matching operating window which can be interconnected (left) and with not matching operating window (right). Adapted from Schembecker & Tlatlik, 2003.

An interconnection of phenomena can be necessary, optional or unfeasible. A necessary connection means that a phenomenon cannot appear without a second (or more) phenomenon while an optional interconnection means that two or more phenomena can appear alone but also together in case of matching operating windows. Lists of necessary and optional interconnection rules for different phenomena classes are given in Table 2.3. Rules for necessary, optional and unfeasible interconnection between phenomena are given in Table 2.4.

Table 2.3. General table for the selection of interconnected phenomena from classes for the search space from the number of phenomena classes (N: Necessary, O: optional: dependent on what is desired in the task). Readable from the column to the row.

	Phenomena Class							
Presence of: / **Needs:**	Mixing	Phase contacting	Phase transition:	Phase separation	Energy transfer	Reaction	Dividing	…
Classes								
Mixing		N	N	N	N	N		
Phase contacting	O	N	N	N	O	O/N		
Phase transition:	O	N	O	N	O	O/N		
Phase separation	O	O	O	N	O	O		
Energy transfer	O	O	O	O	O	O		
Reaction	O	O	O	O	O	O		
Dividing								
…								

Table 2.4. Interconnectivity rules of a list of phenomena (N: Necessary; n; one of the selected ones are necessary; O: Optional, U: Unfeasible). Readable from the column to the row.

	Phenomena								
Presence of: / **Needs:**	Liquid-phase mixing	Vapor-phase mixing	2-phase (V-L) mixing	2-phase (V-L) contact	Phase transition: V-L by relative volatility	Phase transition: V-L by pervaporation	Phase separation: V/L	Heating	Cooling
Liquid-phase mixing	U		N					n	n
Vapor-phase mixing		U	N					n	n
2-phase (V-L) mixing			U	N				n	n
2-phase (V-L) contact			N	U	N	N		n	n
Phase transition: V-L by relative volatility				n	U				
Phase transition: V-L by pervaporation				n		U	N		
Phase separation: V/L					O	N	U		
Heating			O					U	U
Cooling			O					U	U
Dividing	U	U	U	U	U	U	U	U	U
	Allow splitting of streams to activate recycles, necessary for counter-current flow								

A phase transition phenomenon needs two phases between which components are transferred. Hence, a phase transition phenomenon has to be necessarily interconnected to a phase contact phenomenon describing the contact between the two phases which at the same time needs an interconnection to a two-phase mixing phenomenon describing how the phases are dissolved in each other (e.g. one phase bubbled in the second one). This necessary interconnection is illustrated in figure 2.5. An optional interconnection, for example, is a mixing phenomenon which may be or may not be connected to a heat phenomenon.

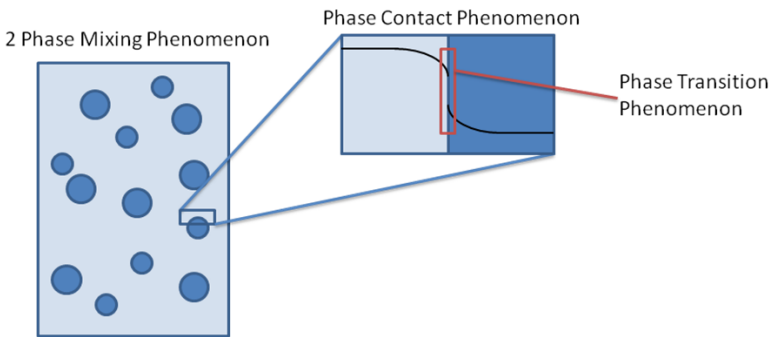


Figure 2.5. Relationship and difference between 2-Phase Mixing phenomena, Phase Contact Phenomena and Phase Transition Phenomena and their necessary interconnection.

The two phase mixing phenomenon needs to be interconnected to a description of the 1-phase mixing phenomena of each separate phase. Currently, the mixing phenomena in the phenomena library allow four different possibilities for the flow characteristics between two phases as illustrated in Figure 2.6.

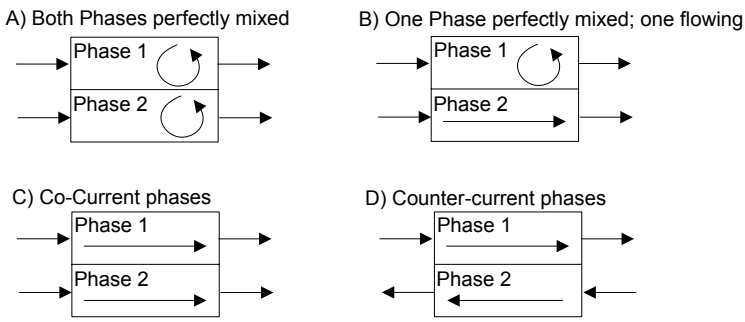


Figure 2.6. 2-phase mixing flow characteristics within a SPB.

2.2.4. Flow between SPB's

Three different flow patterns between SPB's with at least two phases are established which are co-current-flow, cross-flow as well as counter-current-flow (see Fig. 2.7).

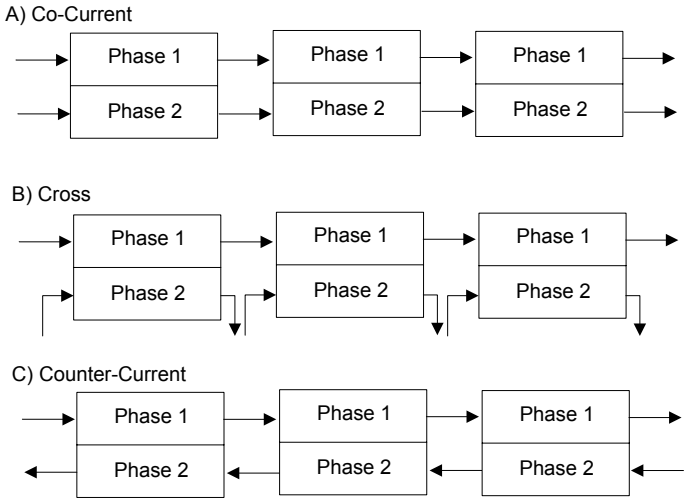


Figure 2.7. Connectivity options between 2-phase SPB's.

2.2.5. Illustration of the phenomena-based representation of unit operations

The concept of phenomena and the rules for their connection are illustrated through the representation of one unit operation in terms of phenomena. That is, a fermentor in aerobic operation, which involves a single stage where reactions, mixing and/or separation occur in multiple phases, is represented by phenomena (Figure 2.8-2.9).

In the fermentor substrate and oxygen are fed to achieve cell growth, which results in the formation of a product and side-products that are continuously removed. The fermentor is assumed to be operating in semibatch mode, perfectly mixed throughout the whole vessel.

The following phenomena are occurring simultaneously:

- 1-phase mixing: solid (S), liquid (L), gas (G);
- 2-phase mixing: solid-liquid (S-L);
- 2-phase mixing: gas-liquid (G-L);

- phase contact (G-L);
- phase transition (G-L) for oxygen absorption into the water as well as side-product (CO_2) stripping into the air;
- phase separation (G-L);
- phase contact (S-L) ;
- phase transition (S-L) for substrate supply from the liquid phase to the cell (solid) and product removal from the cell to the liquid
- Reaction in the cell;
- a divider for removal of a suspension of cell material, substrate and product(s).

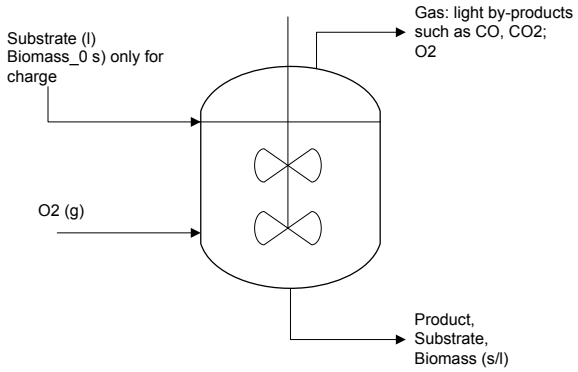


Figure 2.8. A fermentor in the unit-operation based representation.

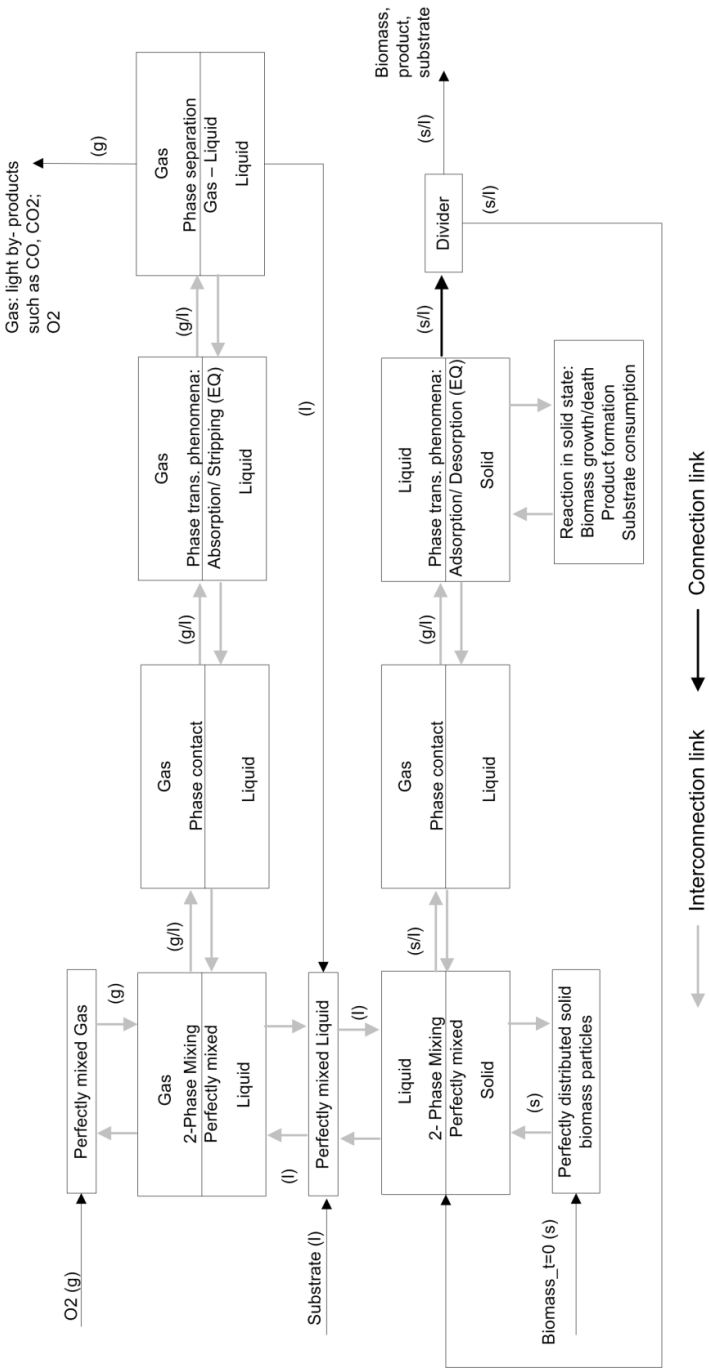


Figure 2.9. A fermentor in the phenomena based representation.

2.3. The decomposition-approach

Generating processes by combining units and/or combining phenomena is a complex problem due to the potentially large number of possible combinations. Therefore, an efficient and systematic solution approach is necessary. In the area of chemical engineering this type of combinatorial problems is not new. A similar problem is defined in computer-aided molecular design (CAMD) in which the objective is to identify a component or components with specific defined properties (Karunanithi, Achenie & Gani, 2004). The similarity of the structure of flowsheets and molecules has been reported before (d'Anterroches & Gani, 2005) comparing molecules to processes consisting of groups or unit operations respectively. This analogy can be extended to the case of unit-operations and phenomena since they are also building blocks in the same way as atoms in groups that represent a molecule (Lutze, Gani & Woodley, 2011; see Fig. 2.10).

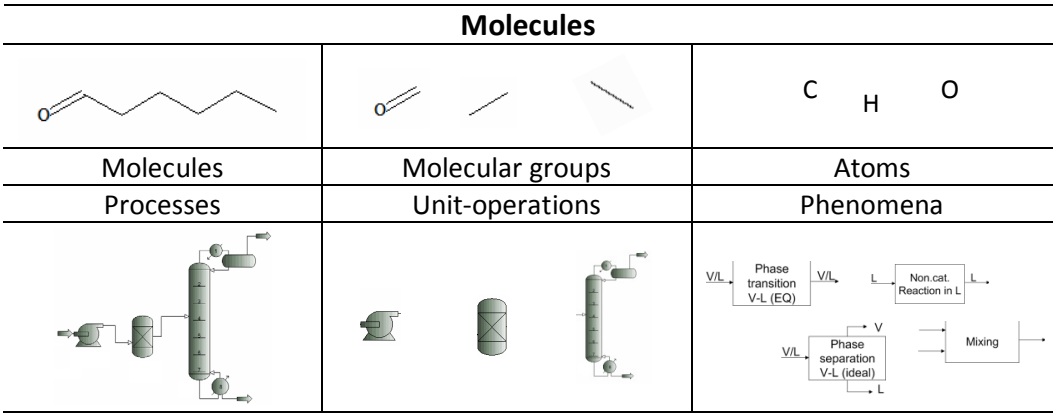


Figure 2.10. Similarity of molecules and processes.

Several solution procedures for the CAMD problem exist (Harper & Gani, 2000). One approach is proposed by Harper and Gani (2000) in which the problem solution procedure is decomposed into several steps. First, molecular groups are selected, then all feasible molecular structures are generated. Connectivity rules between these assure the feasibility of the molecule. All feasible molecules are subsequently screened by their performance. This method is very efficient because the performance calculation is decoupled from the combinatorial problem (Harper & Gani, 2000). Hence, this methodology is adapted in the PhD-project.

2.3.1. PI synthesis based on the decomposition-approach

As mentioned earlier (section 2.1), the PI synthesis problem as defined mathematically by Eqs. 2.1-2.5 could be complex and large depending on the number of decision variables needed to represent the existence of streams, unit operations and the corresponding process models as well as process variables. The decomposition scheme can be determined from an incidence matrix representation of the problem equations, where the columns represent variables, the rows represent the equation; and a cross-sign indicates the presence of a variable in the corresponding equation. If a tri-diagonal form is obtained, it means that the equations can be solved sequentially, while, any deviation from the tri-diagonal form means that a sub-set of equations must be solved simultaneously. The incidence matrix for the general synthesis problem (Eqs. 2.1-2.5), given in Table 2.5, does not show a tri-diagonal form, meaning that a mixed-integer non-linear (optimization) problem with likely very complex process models has to be solved simultaneously. Obtaining the global optimal solution of the process synthesis problem is not simple and may sometimes be impossible, dependent on the size and complexity of the mathematical problem as well as relying on good initial estimates.

Table 2.5. Incidence matrix for the PI process synthesis/design problem (taken from Lutze *et al.*, 2012).

Equation (Equation number, number of equations)	**Binary variables $\underline{Y}$**			**Process variables $\underline{X}$ (l+1..n)**		**Objective function**
	$\underline{Y}_{1+1..f}$	$\underline{Y}_{f+1..l}$	$\underline{Y}_{l+1..o}$	$\underline{X}_{v+1..w}$	$\underline{X}_{w+1..n}$	F_{obj}
Logical constraints (Eq.2.2, 1..f)	x					
Structural constraints (Eq.2.3, f+1..l)	x	x				
Operational constraints (Eq.2.4, l+1..h)	x	x	x			
Process/Phenomena models (Eq.2.5, h+1..m)	x	x	x	x	x	
Optimization residuals (m+1..n)	x	x	x	x	x	
F_{obj} (Eq.2.1)	x	x	x	x	x	x

Therefore, instead of solving the whole synthesis problem (Eqs. 2.1-2.5) simultaneously, the problem is decomposed (Karunanithi, Achenie & Gani, 2004) into a manageable set of sub-problems. This decomposition based solution procedure is highlighted through a conceptual example (see Table 2.6, where the additional equations of the decomposition scheme are given in italics). After solving logical and structural constraints (Eqs. 2.2-2.3) sequentially, the next set of equations is decomposed into

subsets of fixed binary variables. For each of them (meaning for each existing process option), operational constraints (Eq. 2.4) and a short-cut (simple) process/phenomena model (Eq. 2.7) are solved. The resulting feasible set is ranked according to performance criteria (Eq. 2.6). In case all process variables (if $v=n$) are fixed at this point, the objective function (Eq. 2.1) is calculated. If necessary, a small number of the top-ranked feasible alternatives could be further optimized (solving Eqs. 2.1, 2.4-2.5) to determine the optimal solution. Here, rigorous models are used (Eq. 2.5).

Table 2.6. Incidence matrix for the PI process synthesis/design problem. In Italic: Additional equations in the decomposition based solution strategy (taken from Lutze *et al.*, 2012).

Equation (Equation number, number of equations)	**Binary variables**			**Process variables (l..v)**		***Performance criteria***	**Process variables (v+1..n)**		**Objective function**
	$\underline{Y}_{1+1..f}$	$\underline{Y}_{f+1..l}$	$\underline{Y}_{l+1..o}$	$\underline{X}_{1..s}$	$\underline{X}_{s+1..v}$	$\underline{\Psi}$	$\underline{X}_{v+1..w}$	$\underline{X}_{w+1..n}$	F_{obj}
Logical constraints (Eq.2.2, 1..f)	x								
Structural constraints (Eq.2.3, f+1..l)	x	x							
For each subset of feasible flowsheet /set of fixed Y's solve Eqs.2.4, 2.6-2.7:									
Operational constraints (Eq.2.4, l+1..h)	x	x	x	x	x				
Simple process/phenomena models (Eq.2.7, h+1..v)	x	x	x	x	x				
Performance criteria (Eq.2.6)	x	x	x	x	x	x			
For most promising options solve Eq.2.5-2.1):									
Process/phenomena models (Eq.2.5, h+1..m)/*Additional equations through detailed process model (Eq.2.5, v+1..m)*	x	x	x	x	x		x	x	
Optimization residuals (m+1..n)	x	x	x	x	x		x	x	
F_{obj} (Eq.2.1)	x	x	x	x	x		x	x	x

2.4. A performance metric for PI

A performance metric is necessary to evaluate between certain process designs (see Table 1.3). But which ones are the most important criteria to be used to decide between PI designs? In the past, economic criteria primarily drove the decision for choosing and implementing a particular chemical process. However, during the last decade the use of sustainability metrics has been increasingly promoted to select between process options (Carvalho, Gani & Matos, 2008). These metrics are also relevant in terms of deciding between intensified process options. Besides metrics related to sustainability (here economic and environmental), safety and also an intrinsic intensified metric should ideally be incorporated in the decision making (Criscuoli & Drioli, 2007). For this reason, criteria metrics for PI have been developed, based on reported potential for improvements through PI. The classification is adapted from "The sustainability metrics" given by the Institution of Chemical Engineers (2002). Positive effects for each of the metrics are listed in table 2.7.

Table 2.7. Direction of improvement through PI for each metric (taken from Lutze, Gani & Woodley, 2010).

Environmental			Safety	Economic		Intrinsic intensified		
Waste	Efficiency	Energy	Safety	Capital costs	Operational costs	Residence time	Volume/ Equipment size	Simplification of the flowsheet
⇩	⇧	⇩	⇧	⇩	⇩	⇩	⇩	⇩

Information about the influence of intensified processes towards a metric is stored in the knowledge base. The use of metrics is important in several steps of the methodology. First, given a retrofit scenario the decision that the process needs certain improvements through PI are justified by the metrics. Second, the performance metrics are important for screening of the generated options in order to reduce the search space. Therefore, these metrics are also translated into logical and structural constraints. The translation is stored in a knowledge base and can be retrieved if necessary. The list of translated metrics is presented in the appendix A3.

To compare different processes (with different purposes) with each other, all metrics may also be calculated in the form of appropriate ratios, providing, thereby, a measure of impact independent of the scale of operation or, to weigh cost against benefit.

Chapter 3.

Methodology – Workflow

The workflow of the PI synthesis methodology decomposes (see section 2.3) the problem into six steps. In each step, the user needs to make certain decisions, use algorithms and/or tools to proceed to the next step. The necessary link between the steps and tools and algorithms is presented in Fig. 3.1.

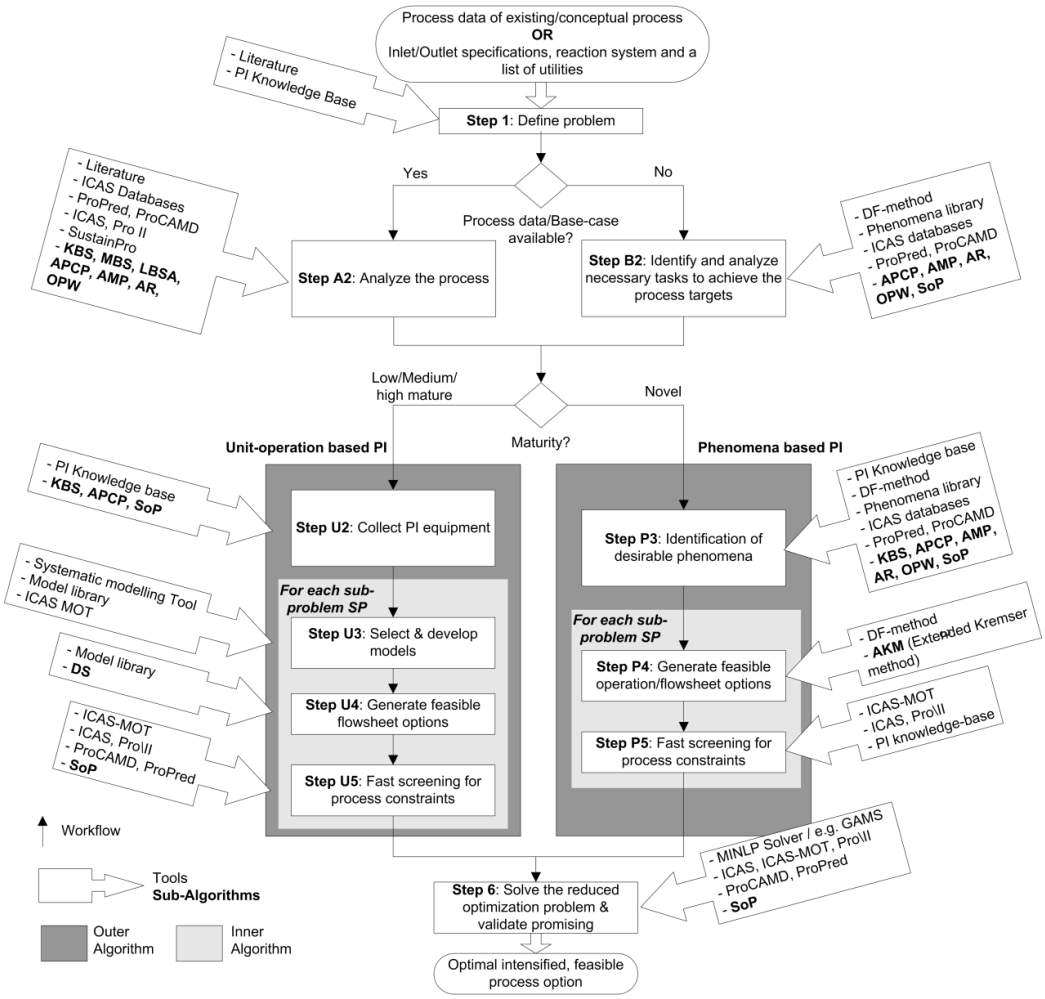


Figure 3.**1**. Workflow of the methodology (Abbreviations of the sub-algorithms: **MBS**: model-based search; **LBSA**: limitation/bottleneck analysis; **APCP**: analysis of pure component properties; **AMP**: analysis of mixture properties; **AR**: analysis of reactions; **OPW**: operating process window; **DS**: development of superstructure; **SoP**: selection of phenomena; **AKM**: apply the extended Kremser method; **KBS**: knowledge base search).

Steps of the unit-operation based synthesis workflow are marked with a “U” at the step number while the steps of the phenomena-based synthesis workflow are marked with a “P”. Furthermore, there is an outer algorithm (Steps 1-6) and an inner algorithm (Steps U3-U5 or P4-P5). The steps of the inner algorithm are indexed with “SP” after the step number. The decision regarding which workflow is to be followed depends on the maturity of the PI processes to be developed. For novel designs, the phenomena-based synthesis methodology is followed while for all others, the unit-operation based is followed.

The workflow containing all sub-steps is described in detail in sub-sections 3.1-3.2.

3.1. Workflow of the unit-operation based PI synthesis/design methodology

A brief overview of the unit operation based workflow is given in section 3.1.1 while the detailed algorithm for each step is presented in the sections 3.1.2-3.1.9.

3.1.1. Brief overview of the workflow

The starting point of the methodology is either a base case design of an existing or a conceptual process or input/output specification of the process.

In step 1, the synthesis/ design problem with respect to PI is defined, including the definition of the objective function (Eq. 2.1), the process/operation scenario and the constraints that the options need to match. Besides, the metrics for evaluation of generated options need to be selected from the available set of metrics as well as information about desired simplification of the flowsheet (complexity) and maturity of later considered equipment.

The objective of step 2 is to collect all data about the process, necessary to gain full understanding of the process which is needed to identify bottlenecks/ limitations for improvement in order to search for already existing PI strategies/equipment in a knowledge base. First, the process is translated into a task based flowsheet as well as phenomena based flowsheet in order to identify limitations/bottlenecks of involved phenomena in the design. In case of the selection for PI based on input/output specification, a base-case design is built using algorithms and rules based on identification of tasks and selection of the phenomena to fulfill the tasks. Available methods to identify bottlenecks/limitations are based on knowledge store in a PI knowledge-base tool as well as on model-based algorithms evaluating the performance of the process. If costs or sustainability are used as objective function, the method

described by Carvalho *et al.* (2007) is used. This method is based on mass and energy indicator calculation via decomposition of the flowsheet into a process graph and indicator sensitivity analysis. With knowledge about limitations/bottlenecks of the involved phenomena of the process, a PI knowledge base which stores/retrieves available information (described in detail in section 3), is consulted retrieving possible PI principles (predictive approach) and already developed PI equipment to overcome the obtained limitations/bottlenecks for process improvement. The obtained PI solutions are pre-screened already with respect to feasibility, e.g. process conditions, maturity and scale-up ability.

The objective of step 3 is to provide the process/operational mathematical models needed for the subsequent calculation/evaluation steps. The necessary models may be selected from a model library, or, if the model is not available, developed through a modeling tool using a systematic procedure proposed by Cameron and Gani (2011). Models are important, but for them to be reliable, validation is necessary and will require carefully collected and analyzed experimental data. All process options based on unreliable process models are removed from the search space. Models are saved for later retrieval into a model library.

In step 4, the objective is to generate all feasible intensified options through synthesis rules (logical constraints, Eq. 2.2) fixing sets of binary variables within a superstructure to give the set of feasible process options. Subsequently, structural constraints, again fixing sets of binary variables in a superstructure, are employed to get the set of structural promising process options. Redundant options are removed.

In step 5, all remaining PI options are fast screened using simple models (short-cut models, Eq. 2.7) or partly rigorous simulation for matching operation constraints (Eq. 2.4). The remaining process options are screened for additional process constraints based on performance metrics.

In step 6, the objective function (Eq. 2.1) for all remaining process options is calculated to identify the best option. The best among these can be found through optimization (that is, fine tuning the optimal solution). Depending on the size of the search space, the process options are optimized separately (NLP) or through applying complex superstructure optimization methods (MINLP; see Grossmann & Daichendt, 1996).

The reduction of the search space for the unit-operation based workflow is illustrated in figure 3.2. The initital search space is identified in step 2 and screened through stepwise applying constraints at different steps until the best option with respect to the objective function is identified. In general, the workflow is designed in a flexible way such that it is possible to go backwards in order to relax

constraints (if possible for enlargement of the search space of PI options if necessary) and then forward again to determine a new solution.

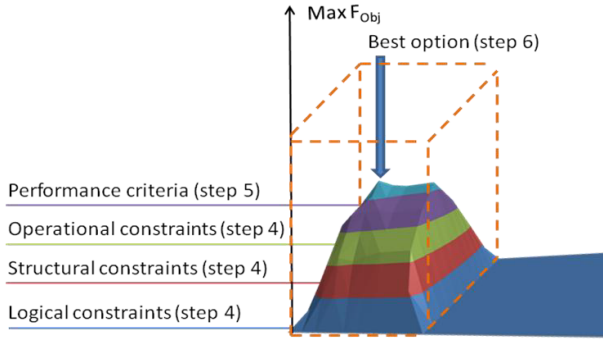


Figure 3.2. Search space reduction in the unit-operation based workflow.

3.1.2. Step 1: Define problem

The objective of step 1 is to define the investigated synthesis/ design problem incorporating PI in terms of objective, process/operation scenario, process boundaries, underlying assumptions and the performance metric for screening PI options. Step 1 is divided into 6 sub-steps.

Step 1.1: Define the objective function F_{obj} (Eq.2.1).

Step 1.2: Define the design and process scenario. The design scenario is either the improvement of the design of a whole process or specific parts of the process. The process scenario is defined as an input to be either a batch or a continuous process.

Step 1.3: Define the process and product specifications $\underline{\vartheta}$ which all new process options must match. This includes a list of raw materials, quality and quantity of the product, reactions in the process and also safety specifications.

Step 1.4: Define performance metric *PM*.

Note: The performance metric *PM* can be based on sustainability requirements such as operating and capital cost, safety, energy consumption, waste generation, efficiency, as well as intensification metrics (Lutze, Gani & Woodley, 2010), such as simplification of the flowsheet and volume reduction. Simplification is defined by the number of unit operations in the flowsheet. *PM* is used in steps U4/P4 and U5/P5.

Step 1.5: Define the maturity of the process.

Note: The maturity of PI equipment is classified in terms of three categories: high, medium and low. PI equipment applied in industry is defined as “highly” mature. “Medium-mature” PI

equipment have been run in pilot-plant facilities and have been implemented for at least two different processes. The category "low" labels all remaining PI equipment. The maturity is used for screening in step C2 and to decide between phenomena-based and unit-operation-based workflow.

Step 1.6: Translate $\underline{\vartheta}$ and $\underline{PM}$ into logical (Eq.2.2), structural (Eq.2.3), operational constraints (Eq.5) and performance criteria $\underline{\Psi}$ (Eq.2.6).

Step 1.6.1: Translate items of $\underline{\vartheta}$ and $\underline{PM}$ to logical constraints (Eq.2.2) by applying the rules 1.1-1.5.

Rule 1.1: "If the defined product is not in the list of raw materials, a reaction is present."

Rule 1.2: "If reactants enter pure the reaction has to be inside the first unit operation."

Rule 1.3: "If more than one reaction is present and the product of one reaction (R1) is the reactant of the second one (R2), R1 is before or at the same time as R2".

Rule 1.4: "If the purity of the product is defined, the product outlet has to be connected to a purification unit."

Rule 1.5: "If the maximum number of units/type of units is fixed (simplification), ensure that not more units are used."

Step 1.6.2: Retrieve structural constraints (Eq.3) for the items of $\underline{\vartheta}$ and $\underline{PM}$ from the knowledge-base using a forward search procedure (see section 2.3).

Step 1.6.3: Translate items of $\underline{\vartheta}$ and $\underline{PM}$ into operational constraints (Eq.2.4) or a performance metric (Eq.2.6) by applying the rules 1.6-1.8.

Rule 1.6: "Fixed values of a specification which the process must satisfy for operational feasibility are set to operational constraints (Eq.2.4)."

Rule 1.7: "Fixed values of a specification which the process or a part of the process must satisfy to potentially obtain a positive improvement in the objective function are set to operational constraints (Eq.2.4)."

Rule 1.8: "All untranslated items of $\underline{\vartheta}$ and $\underline{PM}$, after rules 1.1-1.7, are set to performance criteria (Eq.2.6)."

Note: Examples of operational constraints by rule 1.6 are specified product concentrations and product amount. An example of an operational constraint by rule 1.7 is a specified value for a yield or efficiency of a reaction.

Step 1.7: Decide if Step A2 or B2 have to be followed (Rule 1.9).

Rule 1.9: "If a base-case design exists then go to step A2. Else enter step B2."

3.1.3. Step A2: Analyze the process

The objective of step A2 is to identify the limitation of the process by analysis of the base-case design.

Step A2.1: Collect mass and energy data for the base-case design:

Step A2.1.1: Decide if the energy data of the base case design is required by using rule A2.1.

Rule A2.1: "If equations (2.1,2.4,2.6) are expressed only through mass-related design variables $\underline{X}$, energy data is not required."

Step A2.1.2: Collect the mass and/or energy data of the base-case design and the phase description of each stream. These data are provided as simulation data or directly as operational data from a plant. The simulation data can be provided from simulation-results of the base-case design (from process simulators like Pro\II (Pro\II, 2011) or ICASSIM in ICAS (Gani *et al.*, 1997).

Step A2.2: Transform the flowsheet into task-based and phenomena-based flowsheet. This involves three sub-steps.

Step A2.2.1: Identify for each unit operation of the base-case design the task of the process. For this a set of rules A2.2-A2.8 is used to identify the tasks: reaction, separation, heat supply/removal, pressure increase/decrease, phase change, mixing and dividing.

Rule A2.2: "If the component masses of input and output streams of a unit are different and the product of the reaction is the main product or a reactant of a subsequent reaction to form the main product, then the task is a reaction."

Rule A2.3: "If the component masses of input and output streams of a unit are different and the reactant of the reaction is a side-product of a previous reaction, then the task is a separation."

Rule A2.4: "If a unit has more than one outlet stream and the outlet streams have different compositions then a separation task is identified."

Rule A2.5: "If more than one stream enters a unit, only one stream leaves the unit and no reaction task has been identified, then the task of the unit is mixing."

Rule A2.6: "If more than one outlet stream exits a unit, all with the same composition, then the task of the unit is dividing the inlet stream."

Rule A2.7: "If one stream enters and leaves a unit with the same composition and the same phase but with a different temperature and/or pressure the task is heating/cooling in the case of changing T and/or pressure increase/decrease in the case of changing P."

Rule A2.8: "If one stream enters and leaves a unit with unchanged mass and composition but with different phases then the task is phase change."

Step A2.2.2: Identify the split of each separation task by analyzing the split factors ($\sigma_{sep,i}$) for each component involved in a separation (Eq.3.1) by applying rule A2.9 and afterwards rule A2.10.

$$\sigma_i^{sepu} = n_{i,out1} / n_{i,in} \tag{3.1}$$

Rule A2.9: "If the concentration of one of the components in one outlet stream is close to the desired purity of the product then the main task is the purification of this component. Else: If components with split factors close to 1 or 0 exist then the main task is identified to be a sharp separation of these components else (split factors between 0 and 1 exist) a non-sharp separation of the component is identified."

Rule A2.10: "If consecutive unit-operations fulfill the same task, combine them to one common task."

Step A2.2.3: Retrieve the list of phenomena involved in each unit operation from the PI knowledge-base (see Table 3.1).

Table 3.1. Link between unit operations and phenomena.

Unit operation	Important Phenomena
1-phase-Reactor	Mixing, heating/cooling, reaction
Separator	Mixing, heating/cooling, phase transition, phase separation
- Absorption	Mixing, heating/cooling, phase-transition G-L, phase separation
- Crystallization	Mixing, heating/cooling, phase-transition S-L, phase transition S-S, phase transition V-L, phase separation
- Distillation	Mixing, heating/cooling, phase-transition V-L, phase separation
- Evaporation	Mixing, heating/cooling, phase-transition V-L, phase separation
- Extraction	Mixing, heating/cooling, phase-transition L-L, phase separation
- Flash	Mixing, heating/cooling, pressurizing/expanding, phase transition, phase separation
Heat Exchanger	Mixing, heating/cooling, (phase transition V-L, phase transition G-L, phase separation)
Pump	Pressurizing/Expanding, (phase transition V-L, phase transition G-L, phase separation)
Mixer	Mixing phenomena, (phase transition L-L, phase separation, heating/cooling)

Step A2.3: Identify limitations/bottlenecks *LB* of the base-case. This objective is achieved by analyzing the collected data. Two methods are applied: A knowledge-based method (step A2.3.1) and a model-based method (step A2.3.2).

Step A2.3.1: Collect the limitations of the process by applying the algorithm **KBS**.

Step A2.3.1.1: Prepare a list of keywords *K* containing the following items: the process system, the reaction system, the tasks and the components.

Step A2.3.1.2: Apply the algorithm **KBS** to identify the limitations of the process. Save all retrieved limitations in a list *LB*. **KBS** is described in section 3.3.

Step A2.3.2: Apply the algorithm **MBS** for a model-based search of limitations in the base-case design.

Step A2.3.3: Identify most important limitations/bottlenecks by rule A2.11.

Rule A2.11: "If the number of items in *LB* is larger than 15, use the algorithm **LBSA** (see section sub-algorithms) to reduce the number of *LB* by identification of the most sensitive *LB*."

Step A2.4: Analyze the obtained limitations/ bottlenecks *LB* and their corresponding tasks in the base-case design. The objective is to identify the phenomena causing the limitation. This requires an analysis of pure component, mixture and reaction properties together with an analysis of the operational boundaries of the corresponding parts of the process.

Step A2.4.1: Analyze pure component properties by applying the algorithm **APCP** (see section 3.3).

Step A2.4.2: Analyze mixture properties by applying the algorithm **AMP** (see section 3.3).

Note: The following mixture properties *MP* are analyzed: formation of azeotropes, miscibility gaps and the formation of an explosive atmosphere.

Step A2.4.3: Analyze reactions which have been identified to be a limitation/bottleneck by applying the algorithm **AR** (see section 3.3).

Step A2.4.4: Determine the operating window of each task under investigation by applying algorithm **OPW** (see section 3.3).

Step A2.5: Link a limitation/bottleneck to a task and a corresponding phenomenon outside the unit-operation in which it occurs. This is achieved through sub-steps A2.5.1-A2.5.2.

Step A2.5.1: Identify potential tasks for additional analysis of a *LB* by the rules A2.12-A2.15:

Rule A2.12:"If the component is a substrate of a reaction, analyze the corresponding reaction."

Rule A2.13: "If the component is a solvent analyze the separation task in which it is initially added and add it to the list *LB* for potential replacement of the corresponding step by PI."

Rule A2.14: "If the component is a product of a side-reaction, add *occurring side-reaction* to *LB*."

Rule A2.15: "If the component is entering with a substrate then it is an impurity which is added to *LB* and may be removed before entering the system."

Step A2.5.2: Apply rule A2.16 to check if the limitation is in *LB*.

Rule A2.16:"If the task is already in the list *LB* then go to step A2.6 else add it to the list LB and go back to step A2.4."

Step A2.6: Select the workflow for each sub-problem SP by applying rule Workflow.

Rule Workflow: "If the maturity of the new design has been defined to be novel then enter step P3 for the phenomena-based workflow else enter the unit-operation based workflow (see Fig.3.1)."

3.1.4. Step B2: Identify and analyze necessary tasks to achieve the process targets

The objective of step B2 is to identify the necessary tasks to achieve the target of the process (given by the specifications and constraints in step 1) in case a base-case design is not given. Based on a subsequent analysis of these tasks, suitable phenomena to achieve the target of each task are identified and selected.

Step B2.1: List all components which are known to be present in the system

Step B2.2: Describe the assignment of each component by using rules B2.1-B2.3.

Rule B2.1: "If a component is in the list of outlet components but not present or in a smaller amount present in the inlet, the component is a product of a reaction".

Rule B2.2: "If a component is in the list of inlet components but not present or in a smaller amount present in the outlet, the component is a reactant of a reaction".

Rule B2.3: "Use the descriptions given in step 1 to label components as final product, solvent, impurity, catalyst or heating/cooling media."

B2.3: Define all reactions in the system:

Step B2.3.1: Check the presence of all reactions

Rule B2.4: "If a component has been identified to be a product/reactant then apply Rule B2.5 else enter step B2.4."

Rule B2.5: "Compare if all reactants/products are represented in the defined reactions. If yes go to step B2.3.3 else enter step B2.3.2."

Step B2.3.2: Search in the scientific literature for missing reactions and add missing components to the list of components.

Rule B2.6: "If not all reactions can be identified then stop."

Step B2.3.3: Identify the desirability of each reaction by applying rules B2.7-B2.9.

Rule B2.7: “If one component of a reaction is the desired product of the process or a reactant of a subsequent reaction to form the desired product then the reaction is desirable.”

Rule B2.8: “If one component is a reactant of a reaction which is not leading to the product of the process or not leading to a reactant of a subsequent reaction to form the desired product but it reacts with a side-product of one of these then the reaction is a desirable side-reaction.”

Rule B2.9: “All remaining reactions are undesirable.”

Step B2.3.4: Add all reaction tasks into a task-based flowsheet and connect all reaction tasks with their corresponding reactants (inlet)

Step B2.3.5: Apply the algorithm **AR** to analyze the reaction phenomena

Step B2.4: Identify necessary separation/mixing/heat supply/removal tasks for each outlet

Step B2.4.1: Identify necessary tasks to achieve the defined targets of the process:

Rule B2.10: “If a component has to leave the process in a composition not matching the outlet of the reaction tasks then add a separation task to achieve the desired product”.

Rule B2.11: “If components are leaving a task which is not connected to another task and the component is defined not to leave the process then ensure the recycle into the task in which the component is needed.”

Rule B2.12: “If a component has achieved a desired purity but the stream is in a the wrong state, pressure and/or temperature then add a phase change, a pressure changing and or temperature changing task into the task-based flowsheet”.

Step B2.4.2: Identify suitable phenomena by applying **APCP** and then **AMP.**

Step B2.4.3: Select potential best phenomena for each task by using the sub-algorithm **SoP**.

Step B2.4.4: Add all identified limitations due to the determination of the operating window in the algorithm **SoP** to the list *LB.* Add possible outlet components to each task.

Step B2.5: Identify additional necessary tasks based on the results of step B2.4.

Rule B2.14: ”If a new component is added through one of the tasks add this component to the list of components and go back to step B2.1.”

Rule B2.15: ”If the desired specification of a stream cannot be achieved by the identified phenomena behind the task then add a new task and go back to step B2.4.1.”

Step B2.6: Select the workflow for each sub-problem SP by applying rule Workflow.

Rule Workflow: "If the maturity of the new design has been defined to be novel then enter step P3 for the phenomena-based workflow else enter the unit-operation based workflow (see Fig.3.1)."

3.1.5. Step U2: Collect PI equipment

Step U2.1: Collect potential PI equipment: The available information is used to generate a list of candidate intensified equipment (step U2.1.1) through which the identified process limitations can be overcome (U2.1.2).

Step U2.1.1: Prepare a list of keywords $\underline{K}_{PI}$ for PI equipment search including all identified limitations/bottlenecks and the phenomena to be enhanced.

Step U2.1.2: Apply the algorithm **KBS** to identify the limitations of the process. Save retrieved equipment in a list Ω.

Step U2.2: Pre-screen candidate PI equipment for feasibility and maturity: The objective of this step is to remove all PI equipment which are not feasible for the process.

Step U2.2.1: Retrieve information about the necessary conditions for feasibility and maturity of each PI equipment from the PI knowledge-base by applying the algorithm **KBS.** The following matching criteria ω are used: involved phases, operating windows of integrated phenomena, reaction phase (if existent), binary ratio in pure component properties, heat of reaction (if existent). Additionally, retrieve the maturity of the PI equipment from the knowledge base.

Step U2.2.2: Collect and calculate necessary differences in pure component properties using the algorithm **APCP**.

Step U2.2.3: Screen candidate PI equipment for feasibility using rule U2.1.

Rule U2.1: "For each candidate PI equipment (from step U2.1.2), compare all matching criteria ω (see step U2.2.1) with the process conditions/boundaries (from step A2.4). If they are not matching or fulfilled then remove the PI equipment from the search space."

Step U2.2.4: Screen candidate PI equipment for maturity using rule U2.1-U2.3.

Rule U2.2: "If the maturity of the process is selected to be "high" then select external media (solvent, membrane) by entering the sub-algorithm SoP and apply only step SoP.4."

Rule U2.3: "If a solvent system is in the search space, the process is continuous and waste and/or operational costs have been selected as performance metric then apply APCP for known solvents (rule U2.2) to identify separation systems for solvent recycle using Jakslands method else add a blank task for solvent recycle into the flowsheet. Add for those, *a priori*,

distillation as the separation system because the solvent can be tuned to match the necessary pure component properties."

Step U2.3: Identify sub-problems.

Step U2.3.1: Identify sub-problems by rule U2.4.

Rule U2.4: "If for a task or a set of tasks fixed inlet and outlet streams have been defined and the identified PI equipment in the search space are not integrating one of these tasks with a task outside, a sub-problem *SP* is identified. Else, no sub-problem is identified."

Step U2.3.2: Prepare sub-list Ω^{SP} of candidate PI equipment to be solved in each identified sub-problem *SP*.

Step U2.3.3: Enter the inner algorithm for the sub-problem SP (step $U3^{SP}$).

3.1.6. Step $U3^{SP}$: Select & develop models

Because data are often incomplete, models are often used to supplement the missing data. Therefore, the objective of step $U3^{SP}$ is to provide the process and operational mathematical models (Eqs. 2.4 and 2.7) needed for all subsequent calculations and steps.

$U3^{SP}$.1: For each missing data item, define the problem/scenario that needs to be modeled.

$U3^{SP}$.2: Retrieve experimental data points $\underline{E_i}$ for the problem from scientific literature.

$U3^{SP}$.3: Retrieve models from a model library. If a model is available go to step U3.5. Otherwise, continue.

$U3^{SP}$.4: Develop the necessary models through a systematic modeling procedure. In this work, the procedure proposed by Cameron and Gani (2011) is used together with a systematic modeling tool ICAS-MoT (Heitzig *et al.*, 2011).

$U3^{SP}$.5: Validate the model by applying sub-steps $U3^{SP}$.5.1- $U3^{SP}$.5.3.

$U3^{SP}$.5.1: Perform a simulation with the model to check its performance against experimental data of $\underline{E_i}$ and calculate the residual (error) to be checked by rule U3.1.

Rule U3.1: "If the residual (error) is greater than 10% then increase the counting variable *cv* by 1 and go to step $U3^{SP}$.5.2 to improve the model, else set *cv* to 0 and go to step $U3^{SP}$.6."

$U3^{SP}$.5.2: Check status of the model for possible improvement by rule U3.2.

Rule U3.2: "If *cv=3* then go to step $U3^{SP}$.6, else go to step $U3^{SP}$.4 to improve the model by reformulation."

$U3^{SP}$.6: Save and/or remove models using rule U3.3.

Rule U3.3: "Remove non-validated models from the model library (*cv=3*) and remove all process options represented by or relying on the models from the search space of process options. All other models (*cv*=0) are saved in the model library."

3.1.7. Step U4^{SP}: Generate feasible flowsheet options

The objective of this step is to generate all process options and stepwise to screen all options by logical constraints (Eq.2.2) to identify the subset of feasible process options $\boldsymbol{NPO_L}$. This number is further reduced by stepwise screening (by structural constraints of Eq.2.3) to obtain the sub-set of structural promising options $\boldsymbol{NPO_S}$. This step is divided into a number of sub-steps.

U4^{SP}.1: Retrieve a suitable generic superstructure from the model library using rule U4.1.

Rule U4.1: "Use the information of consecutive equipment in the sub-problem (step U2.3) and the number of maximum inlet/outlet streams of the PI equipment in the search space (step U2.3), to search in the model library for a superstructure. If one superstructure matches these criteria then retrieve the superstructure from the model library and enter step U4^{SP}.3."

U4^{SP}.2: Develop a superstructure by using the algorithm **DS** (see section 3.3).

U4^{SP}.3: Determine the number of process options *NPO* represented by the superstructure.

U4^{SP}.4: Screen the generated process options *NPO* by stepwise applying logical constraints (Eq.2.2). Remaining process options are NPO_L.

U4^{SP}.5: Screen the process options NPO_L by stepwise applying structural constraints (Eq.2.3). Remaining process options are NPO_S.

U4^{SP}.6: Check if the search space is empty by applying rule U4.2- U4.3.

Rule U4.2: "If $NPO_L=0$ and $SP<SPmax$ then go to U3^{SP}.1 to solve the next sub-problem ($SP=SP+1$) else if $NPO_L=0$ and $SP=SPmax$ then stop. Else ($NPO_L>0$) check rule U4.3."

Rule U4.3: "If $NPO_S=0$ and $SP<SPmax$ then go to U3^{SP}.1 to solve the next sub-problem ($SP=SP+1$) else if $NPO_S=0$ and $SP=SPmax$ then go to step 1, change PI metric *PM* and start again. Else ($NPO_S>0$) continue."

3.1.8. Step U5^{SP}: Fast screening for process constraints

The objective of step U5 is to identify the set of PI process options that match the operational constraints by solving the short-cut model (Eq.2.7) and the operational constraints (Eq.2.4) simultaneously. From these the most promising PI options are identified by calculating the performance criteria (Eq.2.6) and subsequently ranked.

$U5^{SP}$.1: Solve operational constraints (Eq.2.4) and the short-cut process model (Eq.2.7) for each of the remaining process options to determine a feasible set of process variables $\underline{X}$. This step is divided into five sub-steps.

$U5^{SP}$.1.1: Determine the degree(s) of freedom *DoF* of the model (Eqs.2.4&2.7).

$U5^{SP}$.1.2: Specify initial process variables $\underline{X}$ to match *DoF* for each of the remaining process options.

Rule U5.1: "If a solvent or membrane need to be selected then enter the sub-algorithm **SoP** and apply steps SoP.4-SoP.7 to identify suitable solvents which match the operational constraints it is screened for."

$U5^{SP}$.1.3: Solve process model (Eq. 2.4) to identify a set of process variables satisfying the operational constraints (Eq.2.7).

$U5^{SP}$.1.4: Remove redundant process options by rule U5.2.

Rule U5.2: "If a feasible set of process variables does not exist, remove the process option from the number of remaining process options. Remaining process options are NPO_O."

$U5^{SP}$.1.5: Check for necessity of relaxation of constraints by rule U5.3".

Rule U5.3: "If $NPO_O=0$ and $SP<SPmax$ then go to $U3^{SP}$.1 to solve the next sub-problem ($SP=SP+1$) else if $NPO_O=0$ and $SP=SPmax$ then go to step 1, change PI metric *PM* and start again. Else ($NPO_O>0$) continue."

$U5^{SP}$.2: Identify the set of most promising options through performance screening NPO_P:

$U5^{SP}$.2.1: For each of the remaining process options in NPO_O, calculate the performance metric Ψ_p (Eq.2.6) from the set of process variables $\underline{X}$ determined in step $U5^{SP}$.1.3.

$U5^{SP}$.2.2: Rank all process options according to Ψ_p and select the most promising options.

The number of promising process options is NPO_P.

$U5^{SP}$.2.3: Check for necessity of screening by F_{obj} (Step $U5^{SP}$.3) by rule U5.4.

Rule U5.4: "If the objective function F_{obj} (Eq.2.1) is not selected for screening with short-cut process models (Eq.2.7), go to $U5^{SP}$.4."

$U5^{SP}$.3: Screen by F_{obj} (Eq.2.1).

$U5^{SP}$.3.1: Calculate the objective function F_{obj} (Eq.2.1).

$U5^{SP}$.3.2: Rank all process options according to F_{obj} and select the most promising options.

The number of promising options is NPO_P.

$U5^{SP}$.4: Check if all sub-problems *SP* have been solved (Rule U5.5- U5.6).

Rule U5.5: "If the number of remaining options is below 10 but higher than 2 then decide (user input) to repeat the screening through steps $U5^{SP}$.1- $U5^{SP}$.3 by complex models."

Rule U5.6: "If *SP=SPmax* and if *SP>1* then go to step $U5^{SP}$.5, else (*SP=SPmax* and *SP=1*) go to step 6. Else (*SP<SPmax*) return to step $U3^{SP}$.1 for the next sub-problem (*SP=SP+1*) to be solved."

$U5^{SP}$.5: Collect the obtained solutions of each sub-problem *SP* and go to step $U4^{SP}$.1.

3.1.9. Step 6: Solve the reduced optimization problem and validate promising

The objective of this step is to identify the best PI process option by optimization of the objective function F_{obj} with respect to logical, structural and operational constraints as well as the process model (Eqs.2.1-2.6) simultaneously.

Step 6.1: Identify the set of most promising process options by solving an MINLP problem (if necessary). The objective is to reduce the number of remaining options if this is necessary.

Step 6.1.1: Decide if this step is necessary by applying rule 6.1.

Rule 6.1: "If the search space NPO_P is smaller than 10 then do not solve an MINLP problem and go to step 6.2."

Step 6.1.2: Set-up and solve an MINLP problem (Eqs.2.1-2.4,2.7). For this, the MINLP solver tool GAMS (GAMS, 2011) is used.

Step 6.1.3: Select the best 5 process options (NPO_{MINLP}).

Step 6.2: For each process option, solve separately the reduced optimization problem (Eqs.2.1-2.5).

Rule 6.2: "If a solvent or membrane need to be selected then enter the sub-algorithm **SoP** and apply steps SoP.4-Sop.7 to identify suitable solvents which match the desired operational constraints for the solvent system."

Step 6.3: Rank all options by their objective function and select the best one.

Step 6.4: Validate the result from step 6.3 by rigorous simulation.

3.2. Workflow of the phenomena based PI synthesis/design methodology

In this section, first, a brief overview of the workflow is given in section 3.2.1 while the detailed algorithm for each step is given in the sections 3.2.2-3.2.8.

3.2.1. Brief overview of the workflow

Similar to the unit-operation based workflow (section 3.1), the starting point of the methodology is either a base case design of an existing or a conceptual process or input/output specifications of the process. Therefore, step 1 is the same as for the unit-operation based workflow (section 3.1.2).

The objective of step 2 is to collect all data about the process, necessary to gain full understanding of the process which is needed to identify bottlenecks/limitations and the responsible phenomena for improvement. This step is the same as for the unit-operation based workflow except for the search for existing PI equipment in a knowledge base (which is done in the unit-operation based method).

In step 3, the analysis of the process phenomena and the identified limitation/bottleneck are used for identification of desirable phenomena or desirable tasks to be integrated in order to overcome the limitation/bottleneck. For each PI possibility, the best phenomena fulfilling the desired PI are identified and selected. Output of this step is the initital search space of necessary and desirable phenomena within the process.

In step 4, all phenomena are interconnected to form SPB's and screened for best performance. Based on connectivity rules SPB's are inserted into stages to form operations. For this, the number of stages as well as their interconnection (co-current, counter-current, cross-current) to fulfill the necessary tasks needs to be determined. With this information, the SPB's are inserted into generic superstructures to form phenomena-based process options. The process options are screened by logical and structural constraints (Eq. 2.2-2.3).

In step 5, all remaining PI options are first screened for operation constraints (Eq. 2.4). The remaining process options are screened for additional process constraints based on performance metrics (Eq.2.6-2.7). The remaining phenomena based process options are transformed to units using a set of rules to be subsequently screened by additional operational constraints as well as performance metrics at the unit operational level.

In step 6, the best option among the remaining process options is identified using the step 6 as for the unit-operation based workflow.

The reduction of the search space for the phenomena-based workflow is illustrated in Figure 3.3. The initital search space is identified in step 3 and stepwise reduced through applying constraints at different steps until the best option with respect to the objective function is identified. In general, the unit-operation based search space is part of the phenomena based search space. The reason is that from the phenomena all different types of units can be potentially synthesized. Comparing, figure 3.2 and figure

3.3., the comparison of the search spaces for both building blocks (PI unit-operations, phenomena) are illustrated.

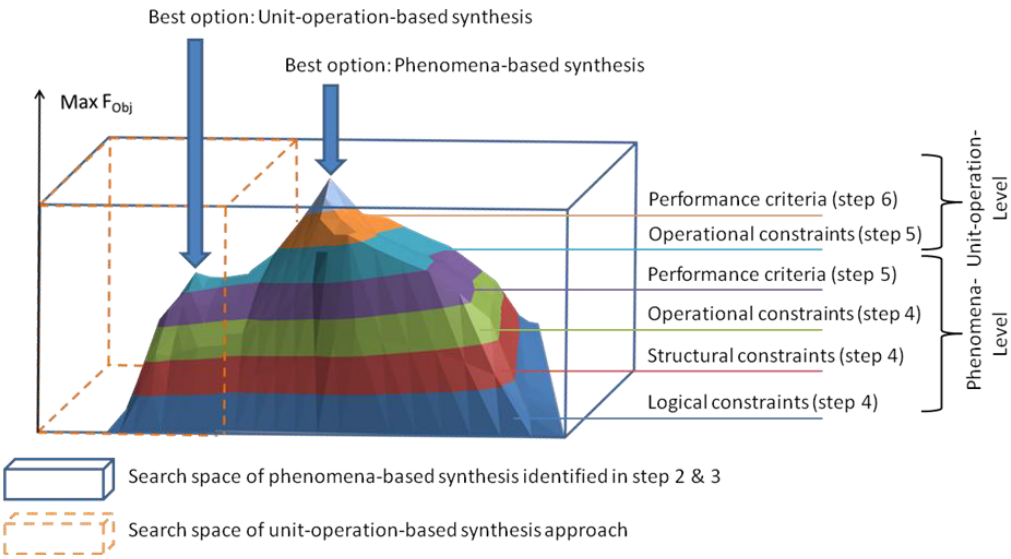


Figure 3.3. Search space reduction in the phenomena based workflow.

3.2.2. Step 1: Define problem

Step 1 is the same as for the unit-operation based workflow (see section 3.1.2).

3.2.3. Step A2: Analyze the process

Step A2 is the same as for the unit-operation based workflow (see section 3.1.3).

3.2.4. Step B2: Identify and analyze necessary tasks to achieve the process targets

Step B2 is the same as for the unit-operation based workflow (see section 3.1.4).

3.2.5. Step P3: Identification of desirable phenomena

The objective is to identify additional phenomena for synthesis of flowsheets which match the targets defined in step 1 and improve the necessary phenomena (identified in step 2). For the selection of the most promising phenomena, property analysis of single components and mixtures of components as well as reactions in the system are needed.

P3.1: Identify desirable tasks as well as phenomena $\underline{\Omega}_{PI}$ to enhance the existing necessary process phenomena using sub-steps P3.1.1-P3.1.3.

- P3.1.1: Prepare a list of keywords $\underline{K}_{PI}$ for identification of PI possibilities including all identified limitations/bottlenecks, tasks and the corresponding objective for PI ($\underline{F_{obj}}$, $\underline{PM}$).
- P3.1.2: Apply the algorithm **KBS** to identify the phenomena to be targeted for enhancment achieving the desired process improvement within a task.
- P3.1.3: Apply the algorithm **KBS** to identify additional desirable tasks of the process.

P3.2: Use algorithm **APCP** to identify potential phenomena for each item of $\underline{\Omega}_{PI}$ identified in step P3.1.

P3.3: Use algorithm **AMP** to identify potential phenomena for each item of $\underline{\Omega}_{PI}$ concerning mixture properties.

P3.4: Identify reaction phenomena if identified as additional desirable task

- P3.4.1: Check if a reaction task is identified (Rule P3.1)

  Rule P3.1: "If a reaction task is identified then enter step P3.4.2 else enter step P3.5."
- P3.4.2: Retrieve reaction data from databases/scientific literature by using the purpose of the task as the keyword.

  Note: If a reaction task is identified for separation of a component then search for reactions with this component as a reactant.
- P3.4.3: Enable phenomena applying rule P3.2.

  Rule P3.2: "If a reaction or reactions have been identified in step P3.4.2 then add phenomena for each of these reactions else go to step P3.5."
- P3.4.4: Use algorithm **AR** to analyze/compare/select potential reaction phenomena blocks for each task.

P3.5: Enter sub-algorithm **SoP** to select the best phenomena for each for each item of $\underline{\Omega}_{PI}$.

P3.6: Retrieve accompanying phenomena information from the knowledge base and select accompanying phenomena from the phenomena library for each identified phenomenon.

Note: Table 2.4 gives an overview of necessary connections to accompanying phenomena for each phenomenon.

P3.7: Apply the sub-algorithm **OPW** to determine the operating window for each phenomenon.

P3.8: Identify sub-problems.

P3.8.1: Identify sub-problems by rule P3.3.

Rule P3.3: "If all necessary tasks have been identified to be potentially integrated then one problem needs to be solved (*SP=1*). Else, the number of sub-problems (*SP*) to be solved is equally to the number of tasks which can be solved separately."

P3.8.2: Prepare list Ω^{SP} of integrated tasks and their corresponding phenomena to be solved in each identified sub-problem SP.

3.2.6. Step P4^{SP}: Generate feasible operation/flowsheet options

Inlet to this step is the initial search space of identified phenomena ($n_{P,tot}$). In step P4, phenomena are connected to simultaneous phenomena building blocks SPB's. SPB's are connected to form unit operations and unit operations are combined to form process flowsheets. Between each scale, screening steps are performed to identify the feasible sub-set. To connect SPB's to operations, the number of stages to achieve a process target is identified by the extended Kremser method (explained in detail in section 3.4). With the knowledge of the number of necessary stages, the SPB's are connected using generic superstructures (from a model library). This step is illustrated in Figure 3.4.

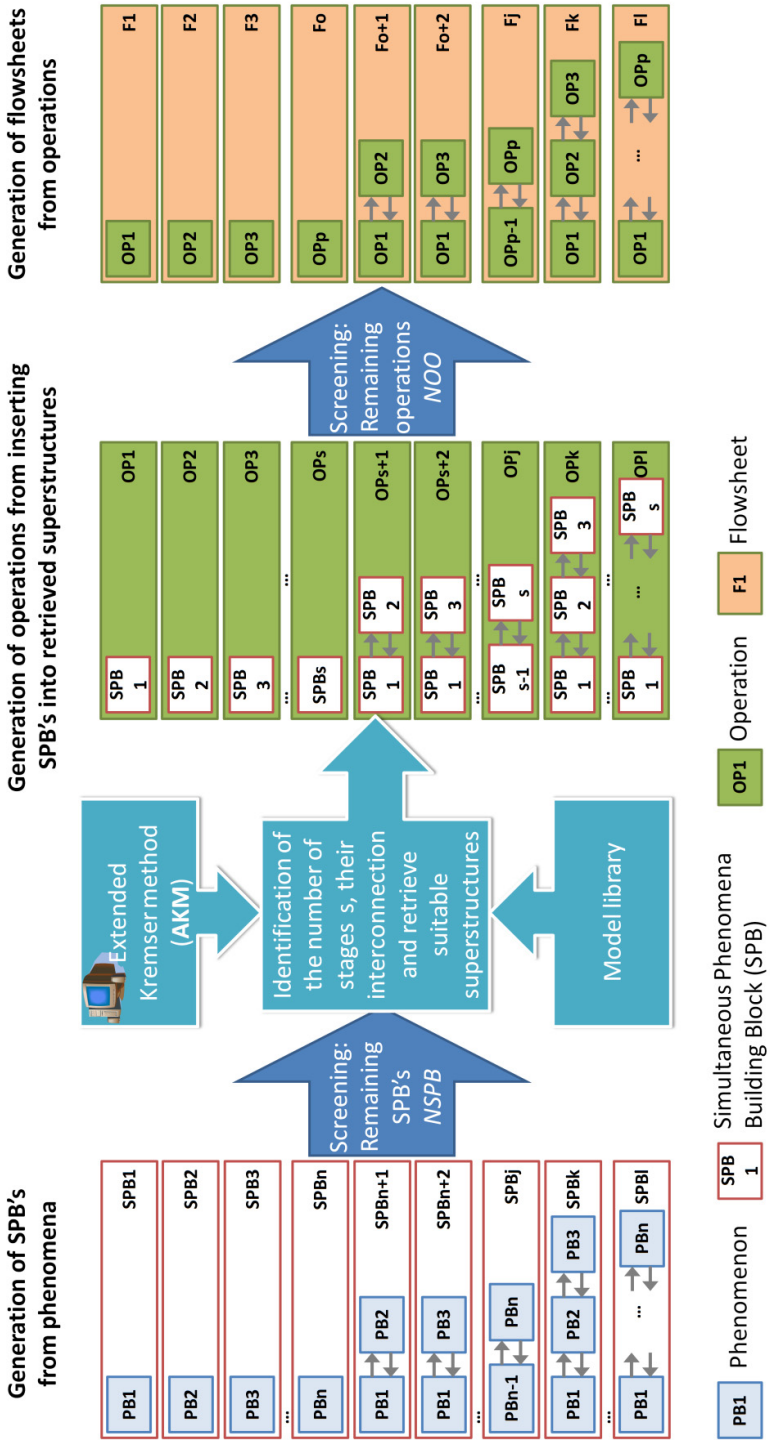


Figure 3.4. Graphical Illustration of the connection between phenomena, stages, operations and processes.

P4^{SP}.1: Generate all feasible simultaneous phenomena building blocks SPB from the phenomena in the search space:

P4^{SP}.1.1: Identify the maximum number of phenomena within an SPB $n_{P,max}$ by using table 2.6.

Note: Each phenomenon can only be present once in an SPB. Opposite energy transfer phenomena such as heating and cooling or pressurizing and expanding and different mixing phenomena such as perfectly mixed and flow mixing can only be present once within an SPB. A dividing phenomenon is defined to be one stage itself.

P4^{SP}.1.2: Interconnect all phenomena in the search space to SPB's by using the connectivity rules for each phenomenon (see table 2.6) stored in the knowledge base.

The theoretical maximum number of SPB 's can be calculated by giving the total number of phenomena in the search space $n_{P,tot}$ and the maximum number of phenomena within an SPB $n_{P,max}$ (from step P4.1.1) using the equation 3.2:

$$NSPB_{\max} = \sum_{k=1}^{n_{P,\max}} \left(\frac{(n_{P,tot}-1)!}{(n_{P,tot}-k-1)!k!} \right) + 1 \tag{3.2}$$

Note: The equation has been developed from the basis that a dividing phenomenon is always a single SPB and therefore one option is added. The use of the equation is illustrated through an example which is easy to follow. Assuming, the following phenomena in the search space ($n_{P,tot}$=4): Mixing (A), Heating (B), Pressurizing (C) and dividing (D), the maximum number of phenomena within an SPB is $n_{P,max}$=3 (dividing is an SPB on its own) and the total number of phenomena is $n_{P,tot}$=4. Hence, it gives 8 options (A=B=C, A=B, B=C, A=C, A, B, C, D) or with the equation:

$$NSPB_{\max} = \sum_{k=1}^{n_{P,\max}} \left(\frac{(n_{P,tot}-1)!}{(n_{P,tot,w/oD}-k-1)!k!} \right) + 1 = \underbrace{\frac{3\cdot2\cdot1}{(1)\cdot(3\cdot2\cdot1)}}_{k=n_{P,\max}=3} + \underbrace{\frac{3\cdot2\cdot1}{(1)\cdot(2\cdot1)}}_{k=2} + \underbrace{\frac{3\cdot2\cdot1}{(2\cdot1)\cdot(1)}}_{k=1} + 1 = 8$$

P4^{SP}.1.3: Screen the SPB by connectivity rules for matching operating windows of the involved phenomena (retrieved from the knowledge-base). The number of remaining feasible stage building blocks is *NSPB*.

P4^{SP}.2: Analyze the performance of each SPB to determine the potential connections of those within stages to fulfill a task.

This is achieved by applying the sub-steps P4.2.1-P4.2.7.

P4^{SP}.2.1: Select for each SPB the identification and application of the necessary tools for identification of the configuration by applying rules P4.1- P4.2.

Rule P4.1: "If the task under investigation is a separation then: for all SPB containing phase transition phenomena enter step $P4^{SP}$.2.2; and for all SPB containing a reaction and no phase transition specify the maximum conversion (determined in step P3.4.4) as outlet specification. Else the task is not fulfilled by the SPB."

Rule P4.2: "If the task under investigation is a reaction then: for all SPB containing a reaction phenomenon specify the maximum conversion (determined in step P3.4.4) as outlet specification; and for all SPB containing phase transition and reaction phenomena enter step $P4^{SP}$.2.2. Else the task is not fulfilled by the SPB."

$P4^{SP}$.2.2: Calculate the phase diagram for each SPB containing a phase-transition phenomenon.

Rule P4.3: "If no reaction is involved then select an appropriate thermodynamic model for the liquid and the vapor phase and calculate a phase diagram. Else use the element-based method given by Perez-Cisneros *et al.* (1997,2003; see also section 4.5) to calculate reactive phase diagrams."

$P4^{SP}$.2.3: Identify the key component for the SPB.

Rule P4.4: "The key component is defined to be the component which needs to be recovered/formed based on the specification as the purpose of the task under investigation."

$P4^{SP}$.2.4: Apply the DF method (Bek-Pedersen & Gani, 2004) to determine minimum reflux R_{min}.(see section 4.5).

$P4^{SP}$.2.5: For each SPB (including a phase transition phenomenon) apply the Kremser method using the sub-algorithm **AKM** to identify the number of stages for counter-flow, co-current-flow and cross-flow and the potential outlets.

$P4^{SP}$.2.6: Compare all SPB in their performance (outcome and number of stages) to select the flow connection (counter-flow, co-current-flow and cross-flow) by using rules P4.5-P4.8.

Rule P4.5: "Remove flow connections which are not fulfilling the tasks specifications."

Rule P4.6: "If the difference between the minimum number of stages between the first and the second lowest is larger than 10% then select only the first flow characteristic. Else apply rule P4.7."

Rule P4.7: "If the task is a reaction and can be achieved by one SPB within one stage then select crossflow-current. Else apply Rule P4.8."

Rule P4.8: "If the task is a separation and simplification and volume are selected as performance metric then select counter-current characteristics."

Rule P4.9: "If the PI target and/or the product/process specification are not matched then add the boundary of the best five stages to the list *LB* and go back to step P3.1 to identify more desirable tasks to be added/integrated."

$P4^{SP}$.2.7: Compare all SPB in their performance (outcome and number of stages) to identify the minimum number of stages necessary fulfilling the necessary outlet specification of the task.

Rule P4.10: "Calculate the maximum number of stages by multiplying the minimum number of stages with 1.5. If the maximum number of stages is below 3 then select 3 stages as maximum."

Rule P4.11: "If the change of composition in the inlet to outlet stream x1/x0 is < 0.5 and the configuration is co-current then add additional stages (Mulder, 2003)."

$P4^{SP}$.3: Generate the number of feasible operation/process options:

$P4^{SP}$.3.1: Retrieve the corresponding stage connection superstructure from the model library.

Rule P4.12: "If no superstructure for the case exists then apply sub-algorithm **DS**."

$P4^{SP}$.3.2: Generate all operation/process options by inserting the SPB's in the search space into the stages of the superstructure.

<u>*Note:*</u> The theoretical maximum number of operation options NOO_{max} depends on the number of SPB's, the number of (separate) tasks, the connection and the integration through recycles. For a crossflow arrangement, it can be calculated using equation 3.3. Input is the total number of stage building blocks *NSPB* fulfilling each separate task, the maximum number of stages within the operation $n_{S,max}$, the number of recycles n_R (depending on the number stages, stage arrangements and number of tasks n_T):

$$NOO_{\max,t} = n_T \sum_{k=1}^{n_{S,\max}} \left(NSPB_T^{\ k} + n_{R,k} NSPB_T^{\ k-1} \right). \tag{3.3}$$

$P4^{SP}$.3.3: Screen the operations/processes by connectivity rules for stages based on matching inlet/outlet specifications. The number of remaining feasible stage building blocks is NOO_t.

$P4^{SP}$.4. Screening through logical constraints. Remaining options are NOO_L or NPO_L respectively.

$P4^{SP}$.5. Screening through structural constraints. Remaining options are NOO_S or NPO_S respectively.

3.2.7. Step $P5^{SP}$: Fast screening for process constraints

The remaining phenomena based process options are screened by operational constraints and performance. Afterwards, the most promising options to a certain pre-defined metric are transformed

to unit operations using a set of rules. These options are additionally screened by operational constraints and performance on the unit-operation level.

$P5^{SP}$.1: Solve operational constraints (Eq.2.4) and the short-cut process model (Eq.2.7) for each of the remaining process options to determine a feasible set of variables $\underline{X}$. This step is divided into five sub-steps.

$P5^{SP}$.1.1: Determine the degrees of freedom *DoF* of the model (Eqs.2.4&2.7).

$P5^{SP}$.1.2: Specify process variables $\underline{X}$ not included in the operational constraints to match *DoF* for each of the remaining process options.

$P5^{SP}$.1.3: Solve process model (Eq. 2.4) to identify a set of process variables satisfying the operational constraints (Eq.2.7).

$P5^{SP}$.1.4: Remove redundant process options by rule P5.1.

Rule P5.1: "If the operational constraints are not satisfied then remove the option from the search space. Remaining options are NOO_O or NPO_O respectively."

$P5^{SP}$.2: Identify the set of most promising options through performance screening NOO_P or NPO_P respectively:

$P5^{SP}$.2.1: For each of the remaining options, calculate the performance metric Ψ_p from the set of process variables $\underline{X}$ determined in step $P5^{SP}$.1.3.

$P5^{SP}$.2.2: Rank all process options according to Ψ_p and select the most promising options. The number of promising process options is NOO_P.

$P5^{SP}$.2.3: Check for necessity of screening by F_{obj} by rule P5.2.

Rule P5.2: "If the objective function F_{obj} is not selected for screening at the phenomena level then go to step $P5^{SP}$.3."

$P5^{SP}$.2.4: Calculate the objective function F_{obj}.

$P5^{SP}$.2.5: Rank all process options according to F_{obj} and select the most promising options. The number of promising options is NOO_P or NPO_P respectively.

P5.3: Identify unit operations by using the knowledge base tool. It contains of five rules and of a list of already translated unit-operations:

Rule P5.3: "One or a series of perfectly mixed phenomena represent one or a series of continuous stirred tanks".

Rule P5.4: "A countercurrent series of perfectly mixed phenomena at the same pressure represent one tank with different compartments".

Rule P5.5: "One or a series of the same convective mixing phenomenon represent one or a series of channel flow units".

Rule P5.6: "A countercurrent series of the same convective mixing phenomenon at the same pressure represent one tank with different compartments".

Rule P5.7: "If rules P5.4 or P5.6 are valid and a series of the same phase transition phenomena also occur, the unit is a column."

Rule P5.8: "If a dividing phenomenon is splitting a stream into two parallel streams connected to the same type and the same sequence of SPB then it enables to split the volume of the unit into an arbitrary number of parallel units."

$P5^{SP}$.4: Calculate additional operational constraints, performance metric and/or objective function F_{obj} on the unit operation level (same steps than in step $P5^{SP}$.1- $P5^{SP}$.2, just at the unit operation level).

$P5^{SP}$.5: Check if all sub-problems SP have been solved (Rule P5.9).

Rule P5.9: "If SP = SPmax and if SP > 1 then go to step $P5^{SP}$.6, else (SP = SPmax and SP = 1) go to step 6. Else (SP < SPmax) return to step $P4^{SP}$.1 for the next sub-problem (SP = SP + 1) to be solved."

$P5^{SP}$.6: Generate the number of process flowsheet options:

$P5^{SP}$.6.1: Generate the theoretical maximum number of process flowsheet options:

The theoretical maximum number of operation options NPO_{max} with only possible connections per operation can be calculated by giving the total number of necessary tasks $n_{t,max}$, under investigation and the maximum operations for each task NOO_t using the following equation:

$$NPO_{\max} = \sum_{t=1}^{n_{t,\max}} \left(NOO_t^t \right) \tag{3.4}$$

$P5^{SP}$.6.2: Screen the operations by connectivity rules for operations (retrieved from the knowledge-base) and matching operating windows. The number of remaining process options is *NPO*.

$P5^{SP}$.6.3: Enter step $P4^{SP}$.5.

3.2.8. Step 6: Solve the reduced optimization problem and validate promising

Step 6 is the same as for the unit-operation based workflow (see section 3.1.9).

3.3. Sub-algorithms

3.3.1. ***MBS*** *(model-based search)*

The algorithm **MBS** has been developed to determine the limitations/bottlenecks through a model-based search. Four steps are needed.

MBS.1: Calculate the objective function F_{obj} (Eq.2.1), operational constraints (Eq.2.4) and performance criteria Ψ_i (Eq.2.6) for the whole process and for each task of the process of the base-case design.

MBS.2: Rank the tasks based on their contribution to the F_{obj} (Eq.2.1) and for each Ψ_i (Eq.2.6). Add those tasks to the list *LB* which contribute mostly to a negative performance of the base-case design.

MBS.3: Add all tasks to the potential list of limitations/bottlenecks *LB* in which an operational constraint is violated.

MBS.4: Check if operating costs or sustainability have been defined as performance criteria Ψ_i, operational constraints and/or objective function F_{obj} in step 1. If yes, calculate and analyze mass and energy indicators by applying the method and the tool "SustainPro" (see section 4.7) from the ICAS-toolbox developed by Carvalho *et al.* (2008). If not, leave **MBS**.

3.3.2. ***LBSA*** *(limitation/bottleneck sensitivity analysis)*

The algorithm **LBSA** has been developed for quick determination of the limitations/bottlenecks which have the potential to improve the process performance most when this task is enhanced.

LBSA.1: Replace all unit operations with their corresponding performance factors based on mass and/or energy. Table 3.2 gives the expression of the performance factors (Eqs.3.1,3.5-3.11) for each corresponding unit-operation.

Table 3.2. List of the performance factors (Eqs.8,21-27) to their corresponding unit operation.

Unit-operation	Performance factor for mass	Performance factor for energy
Reactor	$\lambda_r^0 = \frac{n_{i,out}}{n_{substrateA,in}}$ (3.5)	$\beta_{\mathrm{R}} = \frac{\dot{Q}}{n_{\mathrm{product},out} - n_{\mathrm{product},in}}$ (3.6)
Separator	$\sigma_{sep,i} = \frac{n_{i,out1}}{n_{i,in}}$ (3.1)	If $\dot{Q} > 0$ then $\beta_{\mathrm{sep}} = \dot{Q}\frac{n_{\mathrm{out,Thigh}}}{n_{\mathrm{in,Tlow}}}$ (3.7) If $\dot{Q} \leq 0$ then $\beta_{\mathrm{sep}} = \dot{Q}\frac{n_{\mathrm{out,Tlow}}}{n_{\mathrm{in,Thigh}}}$ (3.8)
Heat Exchanger	-	$\beta_{\mathrm{HX}} = \frac{\dot{Q}_{HX}}{n_{\mathrm{in}}}$ (3.9)
Pump/Expander	-	$\beta_{\mathrm{Pump}} = \frac{\dot{E}_{Pump}}{n_{\mathrm{in}}}$ (3.10)
Mixer	-	$\beta_{\mathrm{Mix}} = \frac{\dot{E}_{Mix}}{n_{\mathrm{in}}}$ (3.11)

LBSA.2: Perform a local sensitivity analysis for each task in which a limitation/bottleneck occurs by varying the corresponding performance factor for mass and/or energy by ±5%, 10%, 15%. For each item, the objective function F_{obj} (Eq.2.1) is calculated.

LBSA.3: Rank the limitations/bottlenecks corresponding to the most positive influence on the objective function, Based on this, select the 15 most sensitive limitation/bottlenecks and remove all others from the list *LB*.

*3.3.3. **APCP** (analysis of pure component properties)*

The algorithm **APCP** has been developed for the collection, generation and analysis of pure component properties. It is based on thermodynamic insights (Jaksland, Gani & Lien, 1995) by determining ratios of properties between binary pairs of components.

APCP.1 Generate/retrieve pure component properties *PCP.*

Note: An extensive list of important pure component properties *PCP* related to separation equipment can be found in Jaksland, Gani & Lien (1995). If the limitation is not related to a separation but to a mixing or a reaction task, the same list can be used to analyze mixing/contacting of components/reactants.

APCP.1.1: Retrieve pure component properties *PCP* from a database. Here, the ICAS-CAPEC database is used (Gani *et al.*, 1997).

APCP.1.2: Predict pure component properties if missing properties not available. Here, the property prediction tool "ProPred" from the ICAS toolbox (Gani *et al.*, 1997) is used.

APCP.2: Calculate the ratios of properties between binary pairs of components r_{kl} (Eq. 3.12).

$$r_{kl} = PCP_k / PCP_l \tag{3.12}$$

With $k \neq l$ and $k,l = 1...n$ with n: number of components.

APCP.3: Retrieve for each phenomenon within a limiting task the important pure component properties from the PI database (apply only for the identification of a limitation).

APCP.4: Analyze the ratios of properties between binary pairs involved in each phenomenon by applying the rules APCP.1- APCP.9 (apply this step only for the identification of a limitation).

Rule APCP.1: "If the binary ratio of a phase transition phenomenon in the corresponding *PCP* is close to unity the separation is difficult and responsible for a limitation."

Rule APCP.2: "If the binary ratio of the Octanol/Water partition coefficient Log(K_{ow}), the water solubility Log(Ws) and/or the solubility parameter is much larger than 1 in any 1-phase mixing phenomenon, then a phase split of the components may occur which is responsible for low contacting/mixing of the involved components and therefore responsible for a limitation caused by the mixing phenomenon."

Rule APCP.3: "If the components are highly viscous and the limitation has been identified to be a high energy consumption in this task, then the mixing phenomenon is identified to be one source for it."

Rule APCP.4: "If the components are highly viscous and the limitation has been identified to be a low contacting time, then the mixing phenomenon may not be ideal and is identified to be one source for it."

Rule APCP.5: "Heat transfer phenomena may be limited when heat capacities are large. Further studies are important in **AR** and **OPW**."

Rule APCP.6: "If $T_{in} \neq T_{out}$ in the task under investigation and the heat capacities are very small, temperature control may be difficult which means that the heat and mixing phenomena are limiting the process operation. Further studies are enabled in **AR** and **OPW**."

Rule APCP.7: "If a component has to be dissolved into another phase and the corresponding binary ratio of the phase transition phenomenon is large then the phase transition phenomenon is responsible for a limitation."

Rule APCP.8: ”If the ratio of the pure component properties of phase transition phenomenon which needs thermal energy (e.g. relative volatility) is large and the energy is used as one criteria then this is one reason for the limitation.”

Rule APCP.9: “If the binary ratio in a phase transition is large but the key components are very dilute then a large residence time/high contacting/large amount of solvent/high energy amount (depending on the phenomena under investigation) is needed limiting the process performance.”

APCP.5: Identify suitable phase transition phenomena using rule APCP.10-APCP.11 (apply this step only for the identification of phase transition phenomena).

Rule APCP.10: “If the binary ratio *PCP* is larger than 1.05 then the separation is potentially feasible.”

Rule APCP.11: Identify for each potentially feasible separation, the corresponding phase transition phenomenon using Table 3.3 and add it to the list of potential phase transition phenomena for the separation task.”

*3.3.4. **AMP** (analysis of mixture properties)*

The algorithm **AMP** has been developed for the collection, generation and analysis of mixture properties. This algorithm is divided into five steps.

AMP.1: Select mixture properties for analysis by the following four rules AMP.1-AMP.4:

Rule AMP.1: “If in the task vapor and liquid phases are involved then check for azeotropes.”

Rule AMP.2: “If in the task two liquid phases occur or one liquid phase but the analysis of binary ratios of the solubility parameter showed a large difference between two components then a detailed analysis of the miscibility is necessary.”

Rule AMP.3: “If safety has been selected as a performance metric in step 1 and a vapor/gas phase occurs then check the formation of an explosive atmosphere.”

Rule AMP.4: “If no mixture property is selected, leave **AMP** algorithm.”

AMP.2: Retrieve the selected mixture property MP_i from databases or the literature. Here, for azeotropes a database in ICAS (Gani *et al.*, 1997) is used.

AMP.3: Compute azeotropes and/or miscibility gaps using thermodynamic models describing the involved phases:

AMP.3.1 Check if step AMP.3 is necessary by applying rule AMP.5.

Rule AMP.5: ”If no detailed information about azeotropes and/or miscibility’s has been found then go to step AMP.3.2 else then go to step AMP.5.”

AMP.3.2: Select a thermodynamic model describing the phase relationship and retrieve parameters from a database. For this, the ICAS-CAPEC database manager is used (Gani *et al.*, 1997). The selection of the thermodynamic model depends on the availability of parameters in the database.

AMP.3.3 Check if the computation of the mixture properties is possible by rule AMP.6.

Rule AMP.6: "If no complete set of parameters exists then leave **AMP** algorithm."

AMP.4: Identify azeotropes and/or miscibility gaps (depending on the target) by usage of the selected thermodynamic model.

AMP.5: Identify a phenomenon responsible for a limitation by rule AMP.7 (apply this step only for the identification of a limitation).

Rule AMP.7: "If the process conditions are within the miscibility gap and/or close to an azeotrope then the phenomenon is responsible for a limitation."

AMP.6: Identify suitable phase transition phenomena using rule AMP.8 (apply this step only for the identification of phase transition phenomena).

Rule AMP.8: "If a miscibility gap is identified then phase transition by settling is put into the search space of phenomena."

*3.3.5 **AR** (analysis of reactions)*

The algorithm **AR** has been developed for the analysis of the involved reactions. Seven steps are needed to go through this algorithm.

AR.1: Check for application of the algorithm by rule AR.1.

Rule AR.1: "If no reaction *r* is in the list for limitations/bottlenecks LB then leave the **AR** algorithm."

AR.2: Collect data for reaction analysis:

AR.2.1: Collect experimental equilibrium data $\underline{E_{EQ}}$ and/or the equilibrium constant $\underline{K_{EQ}}$ and/or a model for determination of $\underline{K_{EQ}}$ by the change of the Gibbs-energy of the each reaction from the literature.

AR.2.2: In case batch reactions are investigated, collect information about residence time from the literature.

AR.2.3: Check if determination of the heat of reaction is required by rule AR.2.

Rule AR.2: "If energy data is not considered in Eqs.2.1-2.5 then go to step AR.3."

AR.2.4: Retrieve the heat of formation for each component from a database. Here the ICAS-database is used.

AR.2.5: Estimate the heat of reaction H_R [J/mol] through ideal heats of formation H_F for each component (Eq.3.13), namely

$$H_R = \sum H_{F,\text{Product}\,i} - \sum H_{F,\text{Reactant}\,j} \tag{3.13}$$

AR.3: Use the information of the equilibrium of the reaction to determine the theoretical equilibrium conversion $\lambda_{Reac,EQ}$ (Eq.3.5) of the reaction *r* at the operating conditions.

AR.4: Compare actual and theoretical conversion at the current operating point of the reaction in the base-case design (if existent) using (Eq.3.14):

$$\vartheta = \lambda_{R,Eq,i} - \lambda_{R,i} \tag{3.14}$$

AR.5: Analyze accompanying phenomena to explain performance of the reaction using a list of criteria (Table 3.3).

Table 3.3. Criteria indicating accompanying phenomena to be partly responsible for a low conversion in the reaction task.

Criteria No.	Criteria	Potential source
1	$\lambda_{Reac,EQ}$ small	Reaction phenomenon with an unfavorable equilibrium Inhibition by products possible
2	ϑ large $T_{in,reactor} \neq T_{out,reactor}$ H_R >>0 or H_R<<0	Heating/cooling and mixing phenomena insufficient. Inhibition by inert components possible.
3	ϑ large $T_{in,reactor} = T_{out,reactor}$ $H_R \approx 0$	Mixing phenomenon insufficient Inhibition by inert components possible
4	ϑ large Low miscibility of reactants (coming from 2nd phase)	Mixing phenomenon insufficient
5	ϑ large Mass balance not fully closed	Side-reaction phenomenon occurs
6	Performance criteria and/or F_{obj} time related τ large	Slow reaction phenomenon/ Mixing phenomenon insufficient
7	Side reaction slow Reactants fully used	Mixing/contacting insufficient
8	Side reaction slow Low miscibility of reactants (coming from 2nd phase)	Phase transition slow or slow due to insufficient mixing/contacting

AR.6: Check if inhibition potentially occurs by rule AR.3.

Rule AR.3: ”If criteria 1-3 are matching then go to step AR.7 else then leave **AR** algorithm.”

AR.7: Retrieve information of components responsible for inhibition from the literature.

*3.3.6. **OPW** (operating process window)*

The algorithm **OPW** has been developed for the determination of the operating window of each phenomenon and the unit operations.

OPW.1: Add the maximum and minimum temperatures and pressures for each phenomenon as operational constraints (Eq.2.4).

OPW.2: Add the miscibility boundaries and azeotropic boundaries as operational constraints (Eq.2.4) to all phenomena running in the corresponding phase.

OPW.3: Retrieve data about stability of components, membranes and catalysts/enzymes from the literature and add them to the operational constraints (Eq.2.4).

OPW.4: Combine the operational constraints for all phenomena involved in a unit to set the operating window of a unit (only necessary when at the unit operational level).

OPW.5: Check the position of the current process point and apply rule OPW.1 (only necessary when sub-algorithm is entered from step A2/B2).

Rule OPW.1: "If the operating point is on a boundary of the operating window for the temperature and the corresponding heat phenomena have not been analyzed for a limitation yet then go to step A2.4.1/B2.4.2 for analysis of the heat phenomena else then check rule OPW.2."

Rule OPW.2: "If the operating point is on a boundary of the operating window for the concentration and the corresponding mixing phenomena have not been analyzed for a limitation yet then go back to step A2.4.1/B2.4.2 else continue."

*3.3.7. **DS** (development of a superstructure)*

This algorithm has been developed to generate a superstructure based on the items in a search space Ω for a process or Ω^{SP} for a subproblem.

DS.1: Take the flowsheet of the base case design and add a binary variable *Y* to each stream.

DS.2: Take an item of Ω/Ω^{SP} together with the information for which task in the flowsheet it has been identified.

DS.3: Identify inlet and outlet streams of this item using the information of the task it is going to perform.

DS.4: Based on the information of the two previous steps, position the item into the flowsheet and add a binary variable *Y* to each stream connecting this unit.

DS.5: Delete item from Ω/Ω^{SP}

DS.6: Check if all items are in the superstructure by applying rule DS.1.

Rule DS.1: "If Ω/Ω^{SP} is not empty then go to step DS.2."

*3.3.8. **SoP** (selection of phenomena)*

This algorithm has been developed to select the potentially most promising phenomena for a specific task and to set up the intital search space of phenomena.

SoP.1: Identify the operating window of each phenomenon by **OPW**.

SoP.2 Predict the maximum possible (ideal solvent/membrane) number of outlets of each phase transition phenomenon using the information about their outlet constraints and the operating window.

SoP.3: Pre-screen phenomena by their potential performance within the operating window and check against the defined performance metric using the rules SoP.1-SoP.4.

Rule SoP.1: "If the necessary task to be fulfilled by a phenomenon is outside of the operating window of this phenomenon then remove the phenomenon from the search space."

Rule SoP.2: "If the desirable task to be fulfilled by a phenomenon is outside of the operating window of this phenomenon and the coupled task(s) then remove the phenomenon from the search space."

Rule SoP.3: "If efficiency, waste and/or operating costs are used as performance criteria or F_{obj} then screen out the phenomena of a desirable task in which the largest amount of substrate, product or solvent are potentially lost."

Rule SoP.4: "If the maximum possible outlet of a phenomenon shows that the desirable task specifications are not fulfilled without adding an additional task which is not in the list of tasks then remove the phenomenon when the simplification is used as criterion and another phenomenon fulfills this task without the necessity of an additional task."

SoP.4: Collect external media (solvent, membrane) data (if necessary) from the scientific literature and databases.

Rule SoP.5: "If no external medium has been found or the user input reveals to include a search for new external media, then enter step SoP.5 for solvent selection and/or for membrane selection. Else, discard phenomena and enter step SoP.7."

SoP.5: Apply the tool ProCAMD for solvent selection (Gani *et al.*, 2005).

Rule SoP.6: "In case of operating costs as one of the performance criteria or F_{obj}, add the costs to one of the indicators for selection of the solvent."

Note: ProCAMD is a software that helps to generate molecules matching a set of specified target properties and based on that to identify suitable potential solvents.

SoP.6: Additionally, add as solvents all components which are already present in the process

SoP.7: Set the membrane selectivity in each phase transition phenomenon to three different selectivities (S=2,10,100).

Note: This step can be replaced in case a targeted approach/tool for membrane selection based on PCP or mixture properties exists.

SoP.8: Generate driving forces of all selected phenomena

Rule SoP.7: "In case of unfixed pressures, select up to three different pressures covering a wide operating window for each selected phase transition phenomenon."

SoP.9: Analyze driving forces of selected phenomena to select the phenomena for the highest improvement by Rule SoP.8-SoP.9.

Rule SoP.8: "If the energy consumption is used as one performance criterion then remove options in parts of the compositions space having only 50% of the maximum driving force of all phase transition phenomena."

Rule SoP.9: "If the reduction by rule SoP.8 keeps less than 3 phase transition phenomena in the search space for a certain concentration region then add the best removed feasible phase transition phenomenon until 3 phenomena are reached again."

SoP.10: Analyze the search space:

Rule SoP.10: "If the search space is empty, recover the phenomena removed by rule SoP.3-SoP.4 and enter step SoP.4".

Rule SoP.11: "If for some phenomena additional tasks are necessary to achieve the specifications of the task under investigation then add the additional task and go to step P3.2 to identify phenomena to perform the new necessary task."

*3.3.9. **AKM** (apply the extended Kremser method)*

This algorithm has been developed to identify the configuration (co-, counter, cross-current) and the number of stages necessary to achieve a defined task in the process. Details about the extended Kremser method are presented in section 4.

AKM.1: Use the phase diagrams to calculate the *K*-values (Eq. 3.15):

$$K=y/x \tag{3.15}$$

with *y*: phase 1 and *x*: phase 2.

AKM.2: Identify the separation factor A or S respectively to be used from the table 3.4.

Table 3.4. Table of separation-factors used in the extended Kremser method.

Phenomena within a stage	Separation-factor
Phase-transition: G/L: Feed (liquid) enters in the first stage (Absorption)	$A = L/(V * K)$ K comes from: $Kx = y$
Phase-transition: G/L: Feed (gas) enters in the n-th stage (Stripping)	$S = V * K/(L)$
Phase-transition: L1 to L2 (Extraction)	$A = L1/(K * L2)$
Phase-transition: V/L: Feed enters in the n-th stage (gaseous): (Rectifying section)	$A = L/(V * K)$
Phase-transition: V/L: Feed enters in the first stage (liquid) (Stripping section)	$S = V * K/(L)$
Phase transition: V/L by pervaporation	$A = L/(V * P_1/P_2)$ With P as permeability

AKM.3: Calculate the separation factor at the feed and outlet stage.

AKM.4: Calculate the effective separation factors using the Edmister approach (Edmister, 1957):

$$A_E = \left(A_{N,i}(A_{1,i}+1)+0.25\right)^{0.5} - 0.5 \tag{3.16}$$

$$S_E = \left(S_{1,i}(S_{N,i}+1)+0.25\right)^{0.5} - 0.5 \tag{3.17}$$

AKM.5: Calculate the achievable recoveries or conversions (in case of reactive stages) and the necessary number of stages for co-current, cross-flow and counter-current stage (see figure 2.9) configurations.

*3.3.10. **KBS** (knowledge base search)*

At different steps of the methodology, existing knowledge about PI needs to be retrieved from a knowledge base tool. This is performed by applying this sub-algortihm. Data in the knowledge base can be searched through different keywords simultaneously in a forward or a reverse manner or integrating both. A 3-step algorithm is used. Input to the algorithm is a list of keywords, the class to be searched and the output-list in which the retrieved information will be saved.

KBS.1: Retrieve from the knowledge-base the information if a forward, reverse or a combined search is necessary.

<u>*Note:*</u> An example of a forward-search is the search for necessary conditions to implement an item of PI equipment. Entry is the “Equipment”-class following the selection of the PI equipment under investigation, for example reactive distillation (see Table A.4, appendix A.1). From here, the knowledge hub is reached by a downstream step in which the class “*Necessary conditions*” is

reached in which four sub-classes exist: "*General process properties*", "*Component properties*", "*Operational properties*" and "*Occurring phases*". Selecting "G*eneral process properties*" gives several items for application of reactive distillation (see Table appendix A.1) such as "Feed is liquid or vapour or both", "Reaction(s) is in liquid phase", etc.

KBS.2: Search for each keyword *K* in the knowledge-base.

Note: An example of a reverse-search is the search for PI equipment which have been already implemented for a certain reaction, for example esterification. Entry of the reverse search is the "*Reaction Class*" (see Fig.4.1) selecting the item "*esterification*" (see Table A.4, appendix A.1). Going one step reverse(back), the "*equipment class*" is reached (see Fig. 4.1). Examples for implemented PI equipment for esterification reactions are reactive distillation and reactive pervaporation (see Table A.4, appendix A.1).

KBS.3: Save retrieved items in the output-list.

Chapter 4.

Methodology – Supporting methods & tools

The developed methodology depends on a number of supporting methods and tools (see also Figure 3.1). These are presented in sufficient details in this section.

4.1. Knowledge-base tool

At different steps of the developed workflows (section 3.1 and 3.2) knowledge about existing PI unit operations (unit-operation based workflow) as well as PI principles (phenomena-based workflow, see section 1.1.1 for PI principles) needs to be provided. This includes, for example, knowledge about characteristics of existing PI equipment and their operating windows or knowledge about tasks and phenomena which can be used to overcome a limitation within an operation. Therefore, the purpose of the knowledge-base tool is to store and provide this necessary knowledge obtained from scientific literature in an efficient way.

In order to structure the information in a simple, efficient and flexible way, an ontology for PI knowledge representation has been developed (see section 4.1.1). Details on the design of ontology-based knowledge bases as well as an overview of knowledge bases in other research areas are given by Singh *et al.* (2010) and Venkatasubramanian *et al.* (2006). The following main items are stored in the knowledge-base tool:

- Existing PI equipment (section 4.1.2)
- Knowledge for identification of PI principles (section 4.1.3)
- Translated performance metric into logical, structural and operational constraints at different levels of abstraction: unit-operation, phenomena (appendix A.3)
- Rules for the transformation of phenomena into a unit-operation (see section 3.1.6; step $P5^{SP}$.3)

4.1.1. Architecture of the knowledge-base

The architecture of the knowledge base is briefly explained below. Each of the main items is represented by a knowledge hub, which branches out in several directions with stored information. The architecture is represented for the “existing PI equipment”-item in Figure 4.1. Starting from the principles of PI on

top, one goes downwards along the data specific paths. That is, for principle 1, a certain number of classes (e.g. Reaction-Separation) down to equipment (e.g. Reaction Distillation) which then connect a data/knowledge hub containing all collected data related to this process/unit.

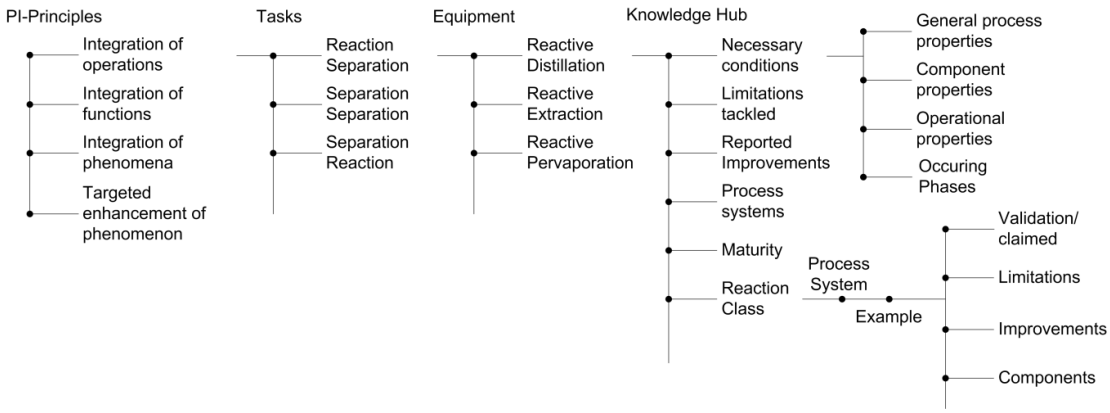


Figure 4.1. Ontology-based structure of the PI knowledge base.

4.1.2. Existing PI equipment.

Collected information about PI equipment in terms of the tasks they perform, the corresponding process conditions as well as component properties for application; examples of implementation of the PI equipment as well as its performance in different configurations are stored under different classes. A full list of classes is presented in Table 4.1. A detailed excerpt of the knowledge base is given in appendix A.1.

Table 4.**1.** List of the classes for existing PI equipment included in the knowledge base tool.

PI-principles, tasks comprising, equipment, knowledge hub, necessary conditions, phenomena enhanced, phenomena integrated, functions integrated, overcome limitations, shown improvements, process properties, component properties, operational costs, capital costs, waste, efficiency, energy, safety, residence time, flexibility, volume/equipment size, complexity, maturity of the technology, scale-up ability, reported development time, process properties, component properties, mixture properties, validation, process system, reaction class, availability of a design/synthesis methodology, application range of design/synthesis methodology, configuration, phases occurring, devices/ solvent used.

Each class may have several or only one item, for example the class “Equipment” for “Reaction-Separation tasks” currently comprises 24 items of equipment such as reactive distillation, reactive

extraction and reactive pervaporation. The knowledge-base is built up in columns and rows to achieve easy extension of the knowledge base to new PI equipment as well as new information classes.

This knowledge is necessary in step U2 (unit-operation based workflow; see section 3.1) for identification of PI equipment to overcome limitations/bottlenecks for a targeted process improvement, for checking of pre-feasibility and the maturity of the PI equipment in the search space as well as properties determining the operating window and therefore also the integration of a PI equipment into a flowsheet.

Currently, the knowledge base comprises around 12000 information items for 37 classes and 135 items of PI equipment and internals in around 200 different process configurations. The list of PI equipment and internals can be found in appendix A1.

4.1.3. Knowledge for identification of PI principles

An analysis of the characteristics and performance of the existing PI equipment stored in the knowledge base has led to the development of a decision table for identification of general PI principles independent from PI equipment to overcome a number of limitations/bottlenecks in the process. This is used by both workflows for identification of the phenomena to be enhanced for achieving a targeted process improvement. One of such a decision table to identify PI solutions for a number of limitations within a reaction and a separation task is presented in Table 4.2. As an illustration, an unfavorable equilibrium within a reaction task is considered which can be overcome by the integration of the necessary reaction task with a separation and/or a second reaction task removing one (or more than one) product.

Table 4.2. Decision Table regarding PI solutions to reported limitations in the process *(*A "○"means that this particular intensified option is reported to overcome this limitation, "●" means the activation of an option through a knowledge search*)*

Limitation/Bottleneck	**Integrated tasks:**							
Necessary task: Desirable task:	***Reactive*** ***Separation***	Reaction heat supply	Reaction mixing	***Reaction*** ***Reaction***	Separation Reaction	Separation mixing	Separation Separation	…
Separation is not sufficient								
limiting equilibrium	○				○		○	
azeotrope	○						○	
high energy demand					○	○	○	
limited mass transfer						○	○	
limited heat transfer						○	○	
driving forces too low	○				○		○	
…								
Reaction is not sufficient								
contact problems of educts; limited mass transfer			○					
product reacts further/is intermediate	○				○			
activation problems		○	○					
degradation by T	○	○						
degradation by pH					○			
difficulties to control conditions, reaction too exotherm/endotherm	○	○	○	○				
limiting equilibrium	●			●				
…								

4.2. Model library

The developed methodology is a method based on mathematical models to evaluate PI options on a quantitative basis. Therefore, different models, derived and validated with known data, in different modeling depths as well as superstructures for the unit-operation-based workflow and the phenomena-based workflow are necessary. Hence, a model library for storage as well as retrieval of models has been developed which contains:

- Superstructure library for units (see below and section 5)
- Models for PI equipment, reactions (see section 5)
- Superstructure library for phenomena (see section 6)
- Models for phenomena (Phenomena library; see section 6)

The superstructures in the model library contain a generic model to allow all kind of PI equipment to be inserted in the superstructure. One superstructure and the generic model are presented here which will be later used in the case studies in section 5. It is a generic model for the integration of up to four unit operations. The generic process model is integrated into a superstructure (see Fig.4.2) and consists of mass (Eq.4.1) and energy (Eq.4.10) balance equations, connection equations (Eq.4.2-4.9), connection rules of units (Eq.4.11) as well as constitutive equations describing the performance of the units (Eq.4.12). Each unit has a maximum of two inlet and two outlet streams. The inlet streams to a unit come from a mixer and the outlet streams go to a divider. The superstructure allows the direct introduction of identified intensified and conventional unit operations and focuses on PI through the integration of unit operations. This integration is realized either externally or internally, meaning that two tasks can be realized in a single unit, such as a reactive extraction, or a so called one-pot reactor (containing more than two reactions). Each unit (u_i) can be externally integrated with any other unit (u_j) by introducing a mixer unit, which connects an outlet stream of unit u_i with the inlet stream of unit u_j and an outlet stream of unit u_j with the inlet stream of unit u_i. the superstructure shown here is currently limited to a maximum of four units.

$$\frac{dn_i}{dt} = \sum_{u=1}^{u}\left(x_{i,in}^{u\alpha}F_{in}^{u\alpha} + x_{i,in}^{u\beta}F_{in}^{u\beta}\right) - \sum_{u=1}^{u}\left(x_{i,out}^{u\alpha}F_{out}^{u\alpha} + x_{i,out}^{u\beta}F_{out}^{u\beta}\right) - \sum_{u=1}^{u}\left(\lambda_i^{u\alpha} + \lambda_i^{u\beta}\right) \tag{4.1}$$

For each unit u, the connection equations for each inlet stream (Eq.4.2-4.3), the conversion in each unit (Eq.4.4-4.5), the outlet streams to the environment (Eq.4.6-4.9) and the connection streams to each unit k in the flowsheet (Eq.4.11) have to be solved.

$$Y^{u\alpha} \cdot F_{in}^{u\alpha} = \sum_{k=0}^{4} Y^{uk\alpha} \cdot F^{uk\alpha} \tag{4.2}$$

$$Y^{u\beta} \cdot F_{in}^{u\beta} = \sum_{k=0}^{4} Y^{uk\beta} \cdot F^{uk\beta} \tag{4.3}$$

$$x_{out}^{u\alpha} \cdot F_{out}^{u\alpha} = f\left(F_{in}^{u\alpha}, F_{in}^{u\beta}, x_{in,i}^{u\alpha}, x_{in,i}^{u\beta}, \sigma_i^{u\alpha}, \lambda_i^R\right) \tag{4.4}$$

$$x_{out}^{u\beta} \cdot F_{out}^{u\beta} = f\left(F_{in}^{u\alpha}, F_{in}^{u\beta}, x_{in,i}^{u\alpha}, x_{in,i}^{u\beta}, \sigma_i^{u\alpha}, \lambda_i^R\right) \tag{4.5}$$

$$Y_P^{u\alpha} \cdot F_P^{u\alpha} = Y_{out}^{u\alpha} \cdot F_{out}^{u\alpha} \cdot \varsigma_u^{u\alpha} \tag{4.6}$$

$$Y_P^{u\beta} \cdot F_P^{u\beta} = Y_{out}^{u\beta} \cdot F_{out}^{u\beta} \cdot \varsigma_u^{u\beta} \tag{4.7}$$

$$Y_{out}^{u\alpha} \cdot F_{out}^{u\alpha} = Y^{uk\alpha} \cdot F^{uk\alpha} \cdot \varsigma_k^{u\alpha} \tag{4.8}$$

$$Y_{out}^{u\beta} \cdot F_{out}^{u\beta} = Y^{uk\beta} \cdot F^{uk\beta} \cdot \varsigma_k^{u\beta} \tag{4.9}$$

$$\frac{\partial H}{\partial t} = \sum_{u=1}^{u}\left(\dot{H}_{in}^{u\alpha} + \dot{H}_{in}^{u\beta}\right) - \sum_{u=1}^{u}\left(\dot{H}_{out}^{u\alpha} + \dot{H}_{out}^{u\beta}\right) + \sum_{u=1}^{u}\left(\dot{Q}_{u,HX}\right) \tag{4.10}$$

$$Y_{in}^{u\alpha,\beta}, Y_{out}^{u\alpha,\beta} = f(\underline{Y}^u) \tag{4.11}$$

$$\underline{H}, \underline{\lambda}, \underline{\sigma} = f(\underline{X}, \underline{d}, \underline{\theta}) \tag{4.12}$$

The term $\dot{Q}_{u,HX}$ (Eq.4.10) describes the amount of energy exchanged with the environment in a unit.

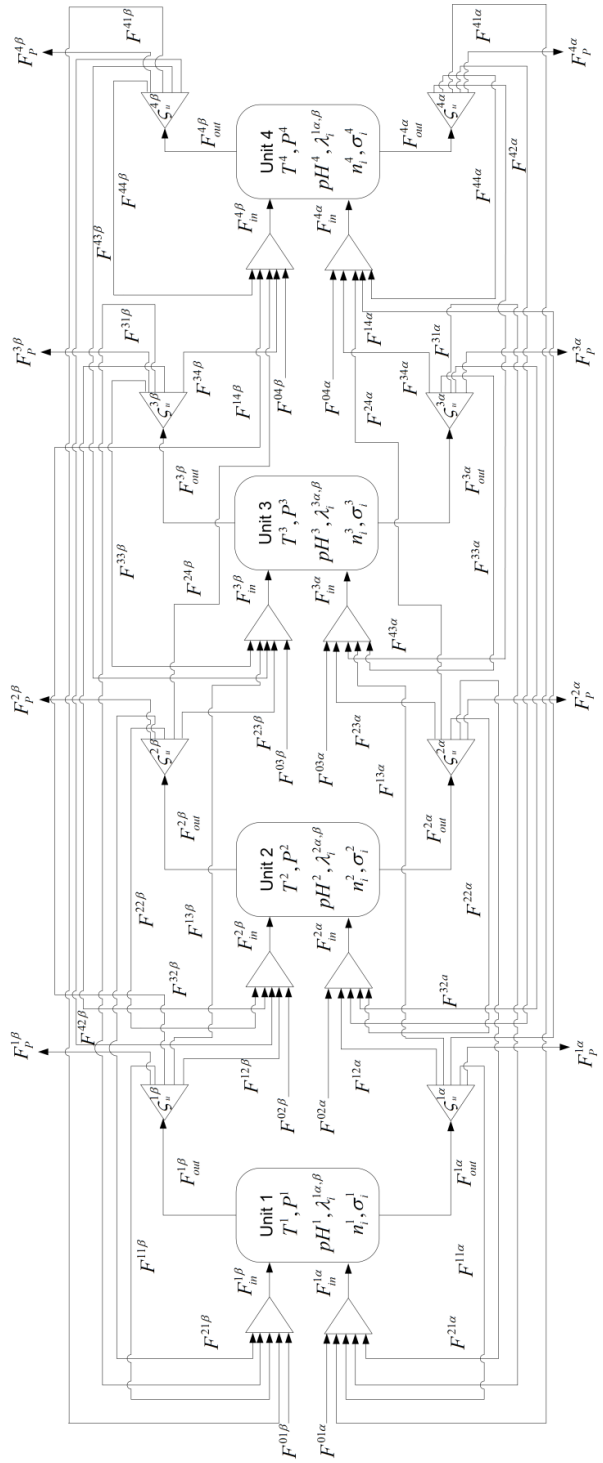


Figure 4.2. Superstructure for the integration of up to four units with a maximum of two inlet/outlet streams each. (Symbols: streams *F*, temperature *T*, pressure *P*, molar hold up's *n*, split factors *σ*, conversion rate λ, splitting factors *ς*; Subscripts: Component *i*, unit number *u* [1..4], bottom stream *α*, top stream *β*, inlet stream *in*, outlet stream *out*, leaving stream *P*; Binary variables Y are not shown.)

4.3. Method based on thermodynamic insights

In step U2 of the unit-operation based workflow and step P3 of the phenomena-based workflow, depending on the case, suitable PI separators or phase transition phenomena may need to be identified to improve the process. This needs a general and quick check if the underlying phenomena are potentially capable to separate the components. Since a large number of options may exist, the method should be quick and efficient using only as little data as possible.

The method developed by Jaksland, Gani and Lien (1995) is serving this purpose. It allows the identification of feasible and potentially most promising separation systems based on pure component properties. First, for all existing mixtures in the system, all binary ratio's of pure component properties are calculated (see Eq. 3.12). The difference of these binary ratio's determines the suitability of a separation based on a set of rules giving necessary minimum ratio's. For example, a large difference in the boiling point (binary ratio >> 1.05) of two components identifies a distillation as a potential easy separation of these two. In a second step, all the identified most promising systems are further screened taking additional information of important mixture properties into account. For a distillation, the occurrence of azeotropes will be taken into account.

In this PhD-project, this method based on thermodynamic insights has been further extended for analysis of known phenomena as well as for the identification of suitable phenomena for a given task (sub-algorithm **APCP** and **AMP**). For illustration, the link of some phenomena and their corresponding important pure component properties is presented in Table 4.3. For example, in the analysis of phenomena a large difference in the octanol-water partition coefficient implies that the liquid mixing phenomenon may not be perfect due to a high probability of a phase split limiting the mass transfer. On the other hand, when identifying phase transition phenomena, a large difference in the octanol-water partition coefficient implies a potential easy separation by a liquid-liquid extraction phenomenon.

Table 4.3. Illustration of the relationship between phenomena and pure component properties (T_M: Melting point; T_B: Boiling point; P_{LV}: Vapor pressure; R_g: Radius of gyration; V_M: Molar volume; Log(K_{ow}): Octanol/Water partition coefficient; VdW: Van der Waals volume; δ_{SP}: Solubility Parameter, c_p: heat capacity, ρ: density, ν: viscosity) adapted from Jaksland, Gani and Lien, 1995.

Phenomenon	Important pure component properties
Mixing (1-phase) phenomenon	Log(K_{ow}), δ_{SP}
Phase transition:	
- Solid-Liquid contact (crystallization)	T_M,
- Gas-liquid contact (stripping)	T_B
- Liquid-liquid contact (extraction)	Log(K_{ow})
- Pervaporation	R_g, V_M, VdW, δ_{SP}
- Liquid membrane	R_g, V_M, VdW
- Centrifugation	MW
- Vapor-liquid by relative volatility	T_B, P_{LV}
Heating/Cooling phenomenon	c_p, ρ, ν

4.4. Driving-Force (DF) method

In the phenomena based approach, potentially a large number of different phase transition phenomena may be used to fulfill a separation task. In order to reduce the complexity, a tool is desirable which quickly identifies the potentially most promising phenomena for a separation task.

The selected method is the Driving Force by Bek-Pedersen and Gani (2004) because it quickly allows the comparison of different phase transition phenomena or the same phase transition phenomenon at different process condition (pressures, temperatures) using thermodynamic properties of the mixtures.

The Driving Force between a binary pair to be separated D_{ij} is defined by Bek-Pedersen and Gani (2004):

$$D_{ij} = y_i - x_i \tag{4.13}$$

The driving force is a measure of the ability to separate components from each other. If the driving force is zero, for example, at the azeotrope point, a separation by this phase transition phenomenon is not possible. By plotting the driving force of different phase transition phenomena for one task, it is possible to identify the ease of a separation (larger driving force) by different techniques in different sections of the composition space. To illustrate this statement, four different phase transition phenomena are plotted into the Driving-Force diagram (Fig.4.3). Phase transition by PT_1 has the highest driving force. However, in the composition space in which the feed is introduced, PT_4 has the highest driving force.

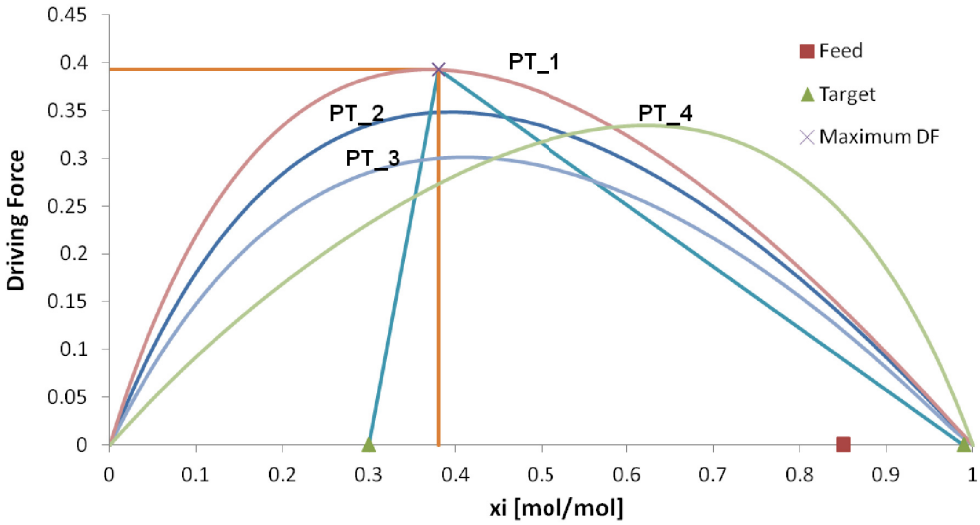


Figure 4.3. Driving Force-Diagram containing four different phase transition phenomena to separate two components.

This method is used in the sub-algorithm **SoP** for the identification and selection of suitable phase transition phenomena for a defined task.

4.5. Element based approach for reactive separations

For the integration of reaction and separation into one unit or into one SPB, the behaviour of this integration needs to be determined through reactive phase diagrams. However, for multi-component systems (more than two components) the calculation and the visualization is difficult (Perez-Cisneros, Gani & Michelsen, 1997). Therefore, a simple method is necessary to quickly determine the possible performance (outcome) and ease of a reactive separation. Therefore, for the design of reactive distillations systems, the element based approach developed by Perez-Cisneros, Gani and Michelsen (1997) is used.

In this approach, the phase separation and the reaction are solved simultaneously by transforming the problem into a phase separation problem for a mixture of elements and by minimizing the Gibbs Energy of the system. The elements are identified by a stepwise procedure (Perez-Cisneros, Gani &Michelsen, 1997). The number of elements (NE) is always less than the number of components in the system (NE=NC-NR, where NR is the number of reactions taking place).

For illustration, the reaction of isobutene and methanol to MTBE can be expressed by two elements A and B (isobutene (A) and methanol (B) react to MTBE (AB)). The advantage by the reduction from three components to two elements is obvious, since all graphical distillation design procedures such as McCabe-Thiele or the Driving-Force Method can be applied (see Sanchez Daza *et al.*, 2003). This method can be extended to any reactive separation system.

4.5.1. Calculation of the reactive bubble point

The following procedure for the calculation of the reactive bubble point (Perez-Cisneros, Gani & Michelsen, 1997) has been proposed. It assumes, that the thermodynamic data as well as reaction system is given and the elements have been identified by a systematic procedure.

Step 1: Give the liquid concentration W^l_j of the element *j* and the pressure P

Step 2: Guess a temperature T

Step 3: Solve the element mass balance and the chemical potential equation at steady state equation (Eqs.4.14-4.15) for all component moles n^l_j:

$$W_j^l \sum_{k=1}^{M} \sum_{i=1}^{NC} A_{ki} n_i^l - \sum_{i=1}^{NC} A_{ji} n_i^l = 0 \tag{4.14}$$

With *A* as the formula matrix representing the element-to-component transformation matrix (see Perez-Cisneros, Gani & Michelsen, 1997) *M* as the number of elements and *NC* as the number of components in the system.

$$\sum_{i=1}^{NC} \nu_{i,k} \mu_i^l = 0 \tag{4.15}$$

With *v* as the stoichiometric coefficient, μ as the chemical potential and *k* the index for the reaction *k*.

Step 4: Compute vapor mole fractions y_i from the isofugacity criterion of each component *i* at equilibrium (Eq.4.16)

$$f_i^l - f_i^v = 0 \tag{4.16}$$

Step 5: Calculate a correction from the temperature T through the closing condition that the sum of molar fractions of the components in the vapor is 1 (Eq.4.17).

$$\sum_{y=1}^{c} y_i - 1 = 0 \tag{4.17}$$

If nonconverged go back to step 3. Otherwise enter step 6.

Step 6: Compute element mole fractions for the vapor phase.

The driving force diagram (see section 4.5) for the MTBE system is presented in Figure 4.4.

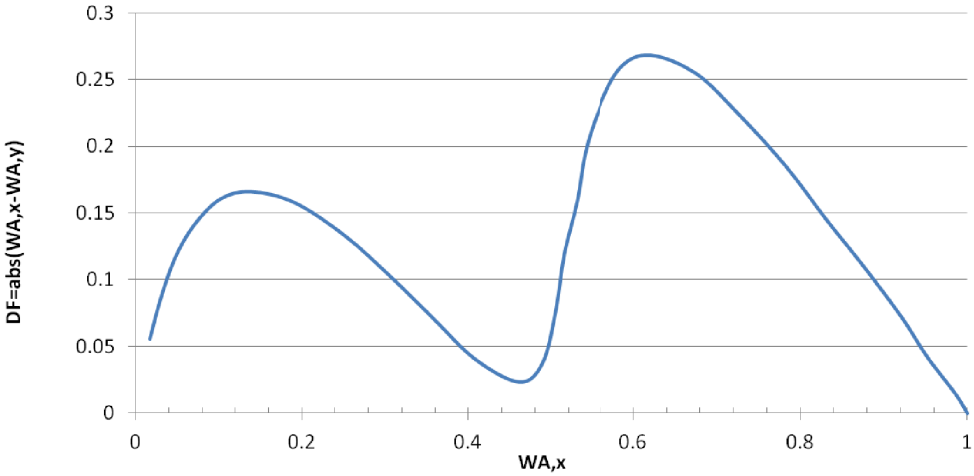


Figure 4.4. Driving Force-Diagram (see also section 4.5) of reactive VLE of the MTBE system at P=1 bar with WA,x as the concentration of element A in the liquid phase).

This method is employed in both workflows to identify the feasibility and the operating window of reactive-separation systems or reaction-phase transition phenomenon (step $P4^{SP}$.2.2), respectively, by identification of reactive azeotropes.

4.6. Extended Kremser Method

In step P3, it is necessary to identify the minimum number of stages for different flow arrangements (see section 2.2.4, Fig. 2.7) to synthesize feasible processes and to quickly identify the most promising options. For this, an equation linking the number of stages connected to the outlet-concentration/conversion achieved would be highly useful (see Fig 4.5).

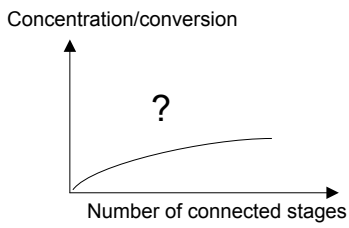


Figure 4.5. Relationship of the number of connected stages and the concentration/conversion within one or a number SPB put into stages of different flow arrangements.

For this the Kremser method, originally developed for absorption columns (see Seader & Henley, 1998) has been extended. The Kremser method has been selected because:

- it allows the comparison of three different configurations using the same method;
- it covers phase-transition with and without simultaneous reaction by extension;
- it is simple to use and needs only phase or reactive phase diagram calculations;
- it is a non graphical method (and therefore not restricted to 2D or 3D diagrams);
- it can be extended to multi-component systems.

The Kremser method is based on material balances around a column/flow arrangements (section 2.4.4) with feed inlet and outlet in top and bottom. A column is transformed into a series of countercurrent blocks between inlet and outlet streams. Columns with feeds or outlets within the column can also be handled since they can be transformed into two blocks of countercurrent flow arrangement as illustrated for a distillation column in Fig.4.6.

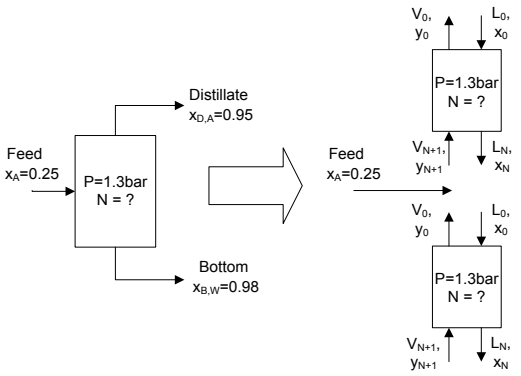


Figure 4.6. Transformation of a distillation column into two blocks of countercurrent flow arrangement.

Originally, the counter-current blocks have been defined for absorption and stripping processes (see Seader & Henley, 1998). In the absorption block the feed enters as a liquid and the desired component transits from the gas phase into the liquid phase. Similarly, in the stripping block, the feed enters as vapor (stripping agent) and the desired component transits from the liquid into the gas phase. The phase transition relationship is defined by equation (4.18).

$$K = y_i / x_i \tag{4.18}$$

Additional, absorption and stripping factors are defined (Eq.4.19-4.20).

$$A_E = L/(K \cdot V) \tag{4.19}$$

$$S_E = (K \cdot V)/L = 1/A_E \tag{4.20}$$

Absorption and stripping factors (Eqs. 4.19-4.20) have been adapted for different phase transition phenomena which have been listed in Table 3.5. In cases of simultaneous reaction and phase transition phenomena, the element-based approach in section 4.5 is used to generate reactive phase diagrams to calculate the necessary K-values.

The recovery of one countercurrent block (see Fig 4.6) is defined as:

$$\alpha = \frac{y_{n+1} - y_1}{y_{n+1} - y_0^*} \ . \tag{4.21}$$

With y_0^* as the vapor concentration in equilibrium to the entering liquid.

Through material balances in each stage from the top to the bottom, the stages are linked through inlet and outlets. The recovery can be derived for co-current, cross-current and counter-current flow arrangements by a simple equation using the absorption/stripping factor respectively (see equations 4.32-4.34). The complete derivation is given elsewhere (Seader & Henley, 1998).

Co-current:

$$\alpha = 1 - \frac{1}{1 + A_E} \tag{4.22}$$

Cross-current:

$$\alpha = 1 - \frac{1}{\left(1 + A_E/N\right)^n} \tag{4.23}$$

Counter-current:

$$n = \frac{Ln\left(\frac{1 - \alpha/A_E}{1 - \alpha}\right)}{Ln\, A_E} \tag{4.24}$$

The application of the extended Kremser method is illustrated in appendix A.4 comparing the method to the McCabe-Thiele method.

4.6.1. Derivation of the relationship between DF and Rmin to be used for the determination of the minimum ratio R=L/V

For the application of the extended Kremser method a reliable method giving a good estimate for the ratio of the two phase flows (L/V) is necessary. Here, the driving force method is used to find good initial estimates for a low energy consumption corresponding to *Rmin*. For simplification, it is shown

here for the phase transition phenomena by relative volatility. However, the results can be generalized for all types of phase transition phenomena or integrated reactive phase transition phenomena.

Two sections may exist in the arrangement. An absorption section in which the feed is vaporized and moves upwards and a stripping section on which the feed is liquefied and moves downwards (see Fig. 4.6).

Absorption section:

Feed is vaporized ($y_{in} = x_{Feed}$)

A mass balance around the absorption section gives:

$$y = L/V \cdot x + D/V \cdot x_D \tag{4.25}$$

Transformation of the distillate flowrate D:

$$y = L/V \cdot x + (V - L)/V \cdot x_D \tag{4.26}$$

Assuming that V and L are constant, V and F equal and defining a ratio of flows R with

$$R = L/V \tag{4.27}$$

gives for equation (4.26):

$$y = R(x - x_D) + x_D \tag{4.28}$$

Inserting this equation into the definition for the driving force (equation (4.13)) gives:

$$y = R(y - x_D)/(x - x_D) \tag{4.29}$$

In which the x is the equilibrium concentration to y.

Stripping section:

Feed is liquid ($x_{in} = x_{Feed}$)

A mass balance around the stripping section gives:

$$y = L/V \cdot x + B/V \cdot x_B \tag{4.30}$$

Transformation of the bottom flowrate B:

$$y = L/V \cdot x + (L - V)/V \cdot x_B \tag{4.31}$$

Assuming that V and L are constant, V and F equal and defining a ratio of flows R with

$$R = L/V \tag{4.32}$$

gives for equation (4.32):

$$y = R(x - x_B) + x_B \tag{4.33}$$

Inserting this equation into the definition for the driving force (equation (4.13) gives:

$$y = R(y - x_B)/(x - x_B) \tag{4.34}$$

In which the y is the equilibrium concentration to x.

Inserting the concentrations of the feed and the targets for the separation (distillate D and bottom B) into equations 4.29 and 4.34 determines a reflux ratio which corresponds to the minimum reflux ratio *Rmin*. A feed position not lying at the maximum driving force means a deviation from the minimum reflux ratio (see Fig.4.7).

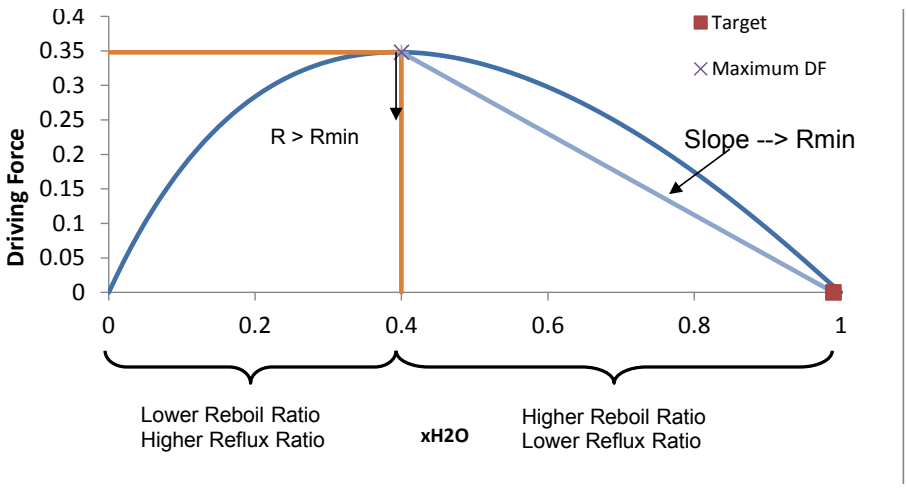


Figure 4.7. Relationship position of the feed and the position of the maximum driving force to Rmin.

4.7. Description of additional tools used

Several additional tools, not developed or extended within this PhD-project, are used following the unit-operation-based as well as the phenomena-based workflow. Tools are necessary for:

- providing pure component property data from a database (CAPEC-Database);
- providing mixture data based on thermodynamic models from a database (CAPEC-Database);
- prediction of pure compound properties in case a compound and/or a property is not found in the database (ProPred);
- selection of solvents (ProCAMD);
- analysis of the base-case design in order to identify the most sensitive limitation within an operation for achieving the highest improvement in the overall process (SustainPro);
- analysis of physical boundaries within non-reactive and reactive seperations (PDS);
- model derivation and analysis, parameter fitting (MOT);

- model simulation, optimization and validation (MOT, ICASSim, Pro\II);

Some of these tools are available in ICAS, an Integrated Computer Aided System, developed in CAPEC, a research center at the Technical University of Denmark, DTU such as: CAPEC-Database, ProPred, ProCAMD, SustainPro, PDS, MOT, ICASSim. Additionally, a commercial program is used which is Pro\II (Pro\II, 2011).

CAPEC-Database: This tool is managing the various databases within ICAS such as component and the reaction database. This tool is used in steps 2 and 3 for identification of pure component as well as mixture properties (based on the use of thermodynamic models).

ProPred: ProPred is for pure component property prediction. In this tool, properties of pure compounds are predicted from their molecular structure such as boiling point, melting point, octanol-water partition coefficient. Several methods for the prediction are used such as the Marrero-Gani approach (see Marrero & Gani, 2001). This tool is necessary in the sub-algorithm **APCP** to analyze the given process based on pure component properties whenever they are not found in the component database.

ProCAMD: In ProCAMD, the computer aided molecular design approach is implemented (see Harper & Gani, 2000) in which based on a set of given molecular groups a number of feasible components are synthesized to match a number of specified target properties. Within this PhD-project, this tool is used to identify solvents in the sub-algorithm **SoP** (if specified) in case of identified liquid-liquid phase transition phenomena.

SustainPro: In this tool, the method from Carvalho *et al.* (2008) is implemented. The process flowsheet of the base-case design is decomposed into a set of process graphs. For each of these process graphs, mass and energy indicators such as material-value-added or energy and waste costs are calculated needing information about costs/prices of input and output mass/energy. Based on these indicators limitations/bottlenecks are identified for improving the sustainability of the process. In this PhD-project, this tool is used in the sub-algorithm **MBS** for analysis of the base-case design.

PDS: PDS stands for process design studio. This tool is used for the analysis and the design of distillation columns as well as reactive distillation columns using the element approach (see section 4.5). In this project, this tool is used in the sub-algorithm **OPW** for identification of process boundaries (vapor-liquid phase diagrams, reactive and non-reactive azeotropes).

MOT: MOT stands for Modelling Testbed. In this tool, all necessary sub-tools for efficient and systematic model development, analysis, identification and application are integrated. In this project, it is used in steps U3-6 and P4-6 for model derivation and analysis, parameter fitting, simulation and optimization.

ICASSim: ICASSim is a steady-state rigorous simulation tool to perform mass and energy balances in a process. In ICASSim, steady state simulation models for a number of predefined unit-operations are available. Specific models, derived in MOT can also be integrated. In this project, ICASSim is used for validation of the results in step 6.4.

Pro\II: Pro\II is a commercial process engineering suite (Pro\II, 2011) from Invensys SIMSCI Esscor to perform mass and energy balance calculations for a specified process. In this PhD-project, it is used for validation of the obtained results by rigorous simulation in step 6.4.

Chapter 5.

Case studies – Application of the unit-operation based methodology

The application of the methodology using the unit-operation based workflow is highlighted through three case studies: the production of an intermediate (Neu5Ac) for the pharmaceutical industry taken into account a biocatalyst as well as chemical catalysts, the production of a bulk chemical hydrogen-peroxide, and the production of a biobased intermediate chemical hydroxy-methyl-furfural (HMF).

5.1. Production of N-acetyl-D-neuraminic acid (Neu5Ac)

The application of the methodology is highlighted through the production of N-Acetyl-D-neuraminic-acid (Neu5Ac) which is shown in detail in sections 5.1.3-5.1.10. Additional information as well as the results of the sub-algorithms are given in appendix A.6.

Neu5Ac has been attracting much interest as an intermediate for anti-viral, anti-cancer and anti-inflammatory compounds in the pharmaceutical industry as well as a building block for oligosaccharides (Schauer, 2000). Neu5Ac (D) is synthesized from pyruvic acid (C) and N-acetyl-D-mannosamine (B) in a reaction (R2, see also Fig.5.1). B is not recommended as a starting point because it is not available in the quantities necessary for a large-scale production (Tao *et al.*, 2010). Therefore, B is synthesized from N-acetyl-D-glucosamine (A) first (R1, see Fig.5.1).

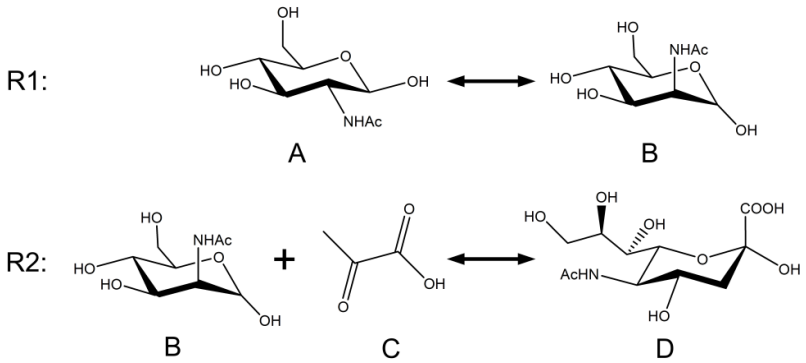


Figure 5.1. Enzymatic synthesis of Neu5Ac (D) from N-acetyl-D-glucosamine (A) in two steps (R1 and R2).

5.1.1. Base-Case Design

Mahmoudian *et al.* (1997) have described a chemo-enzymatic batch process in five steps (Fig. 5.2). In the first step, the first reaction (R1) takes place. The reaction is homogeneously catalyzed by sodium hydroxide (alk1) in which 20 mol.% of A are converted to B. Afterwards, B is enriched to a molar ratio of 1:4 (A:B) in two steps. The first enrichment is realized by precipitation of A with isopropanol followed by evaporation to dryness and the second by extraction of the B with methanol followed by evaporation of methanol. The enriched (in B) outlet stream, water and the substrate C (molar ratio 1:1.4 for B:C) enter the second reactor (fourth step) filled with an enzyme E2 (see abbreviation list) in which the second reaction (R2) takes place. Subsequently, D is purified (purity > 95 mol.%) by crystallization with glacial acetic acid in the fifth step. The selection of this process as the base case design is justified since similar batch processes are the main processes today in the industrial production of D (Zimmermann *et al.*, 2007).

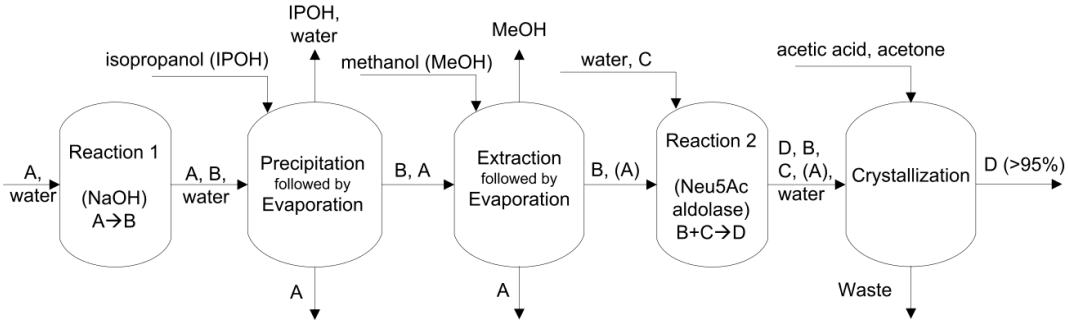


Figure 5.2. Simplified process scheme for a conventional chemo-enzymatic production route to D in batch mode (Mahmoudian *et al.*, 1997).

5.1.2. Non-intensified design options for the base-case design

Alternative operations for each step in the process are discussed in the scientific literature. Alternative catalysts/enzymes can be used for the first reaction: alk2 (Blayer *et al.*, 1999), E1 (Maru *et al.*, 2002) or E11 (Hu *et al.*, 2010). An alternative enzyme for the second reaction step R2 is E22 (Hu *et al.*, 2010). Both enzyme types E1 and E2 can also be integrated in whole cells WC (Lee, Chien & Hsu., 2007). For the downstream processing, precipitation, evaporation, crystallization, chromatography (Mahmoudian *et al.*, 1997), spray drying, extraction with methanol (Dawson, Noble & Mahmoudian, 2000) and liquid-

liquid extraction with a reactive solvent (Zimmermann *et al.*, 2008) can be used. All these non-intensified options will also be considered.

5.1.3. Step 1: Define problem

Step 1.1: The objective is to achieve PI (unit-operation) for the maximization of the ratio of the space-time-yield of the process η_P against the space-time-yield of base case design $\eta_{P,0}$ as F_{Obj}:

$$\max F_{Obj} = \eta_P / \eta_{P,0} = f_j\left(\underline{Y}, \underline{X}, \underline{d}, \underline{\theta}\right) \tag{5.1}$$

The space-time-yield is defined as the product produced per day and volume (Eq.5.2):

$$\eta_P = m_D / V_0 / t_R \tag{5.2}$$

Step 1.2: The design scenario is to develop a new design of the whole process. The process scenario is batch because even though the enzymes are expensive, they are stable enough to run in more than one batch operation (Blayer *et al.*, 1999). However, the long time stability of the enzymes is not satisfactory for a continuous operation yet (Hu *et al.*. 2010).

Step 1.3: The product D is produced from the raw materials A and C. All raw materials are pure and the purity of the product D is defined to be at least 95% (molar basis). Water is used as the solvent. The pressure is assumed to be 1 bar.

Step 1.4: Waste, efficiency, energy consumption, simplification, time yield of the reaction, the product yield of the whole process.

Step 1.5: The maturity of the process is defined to be “high”.

Step 1.6: Translate $\underline{\vartheta}$ and $\underline{PM}$ into logical (Eq.2.2), structural (Eq.2.3), operational constraints (Eq.2.5) and/or performance criteria $\underline{\Psi}$ (Eq.2.6):

Step 1.6.1: All rules have been applied to gather a set of logical constraints (Eq.2.2). The detailed results are listed in Table 5.1.

Step 1.6.2: Four PI metrics have been translated to six structural constraints (see Table 5.1).

Step 1.6.3: The result of the translation into operational constraints (Eq.2.5) and the PI screening criterion (Eq.2.6) is given in Table 5.1. The time-yield of the reaction ε_R is defined by equation (5.3) and the product-yield ε by equation (5.4).

$$\varepsilon_R = m_D / m_A / t_R\,. \tag{5.3}$$

$$\varepsilon = n_D / n_A \cdot 100\% \tag{5.4}$$

Step 1.7: A base case design exists, step A2 is entered (rule 1.9).

Table 5.1. Problem definition of the case study.

F_{obj}	Productivity $\eta_P / \eta_{P,0}$
Design scenario	Redesign of the whole process
Process scenario	Batch-Process
Logical constraints	L1: Reaction 1 necessary (Rule 1.1)
	L2: Reaction 2 necessary (Rule 1.1)
	L3: Reaction 1 has to be in the first unit (Rule 1.2)
	L4: Reaction 1 before or at the same time as Reaction 2 (Rule 1.3)
	L5: Product is component D which must be linked to a purification unit (Rule 1.4)
	L6: Use a maximum of 4 processing units and maximum two reactors (Rule 1.5).
Structural constraints by PI metric	Waste: Do not use two different solvents in one process.
	Efficiency: Do not integrate units which inhibit each others performance. Add units at the place in the flowsheet in which it has the highest efficiency.
	Energy: Do not connect units with alternating heat addition and heat removal.
	Simplification: Do not use repetitive units. Do not use enrichments before separations if not necessary. Do not use pre-reactors.
Operational constraints (Rule 1.6)	Product purity > 95% (molar basis)
	Raw materials are pure
	Water is used as solvent
Operational constraints (Rule. 1.7)	Time-yield of reaction step ε_R> 0.75 g (D) g^{-1} (A) day^{-1}
PI screening criterion for step C2.	Application of process technology of “high” maturity
PI screening criterion for step U5	Product-yield $\varepsilon > 40\%$

5.1.4. Step A2: Analyze the process

Step A2.1: Collect data of the process/ base-case design:

Step A2.1.1: Rule A2.1 identified that only mass data is required.

Step A2.1.2: Mass data of the base case design has been retrieved from the scientific literature (Mahmoudian *et al.*, 1997). The complete mass data is given in appendix A6 (Table A.10).

Step A2.2: Transform the flowsheet into task and phenomena-based flowsheets:

Step A2.2.1: Five tasks are identified from the unit operations in the base-case design. These are a conversion of A to B in the first step and a conversion of B and C to D in the fourth step (Rule A2.2), and three separations in the second, third and fifth steps (Rule A2.4).

Step A2.2.2: Using Rule A2.9 the following separations are identified: A separation of A/AB in the second step, a separation of A/AB in the third step and a separation of D/CAB in the fifth

step. Using rule A2.10, since tasks two and three are fulfilling the same objective, the number of tasks is reduced to four.

Step A2.2.3: The phenomena-based representation of the flowsheet is shown in Fig.5.3.

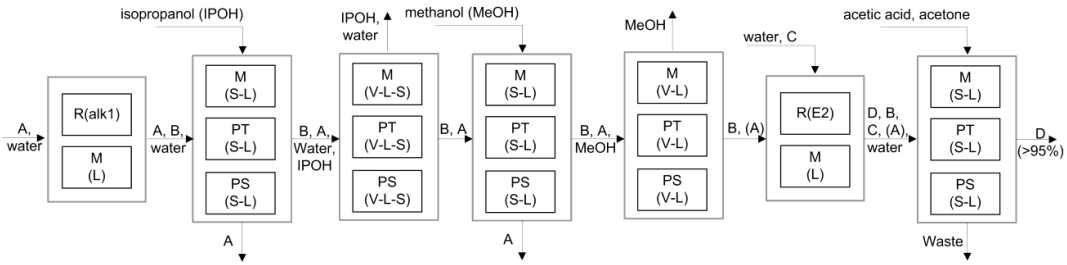


Figure 5.3. Transformation of the base-case design into a simplified mass related phenomena-based flowsheet (M: Mixing phenomena; R: Reaction phenomena; PT: Phase transition; PS: phase separation; V: Vapor; L: Liquid; S: Solid).

Step A2.3: Identify limitations and bottlenecks of the base-case design/process:

Step A2.3.1 Knowledge-based search for limitations of the process:

Step A2.3.1.1: The list of keywords <u>*K*</u> has been prepared: <u>*K*</u> ={"Production of D", "epimerase reaction", "aldolase reaction", "reaction A to B", "reaction C + B to D", "separation AB/B", "separation D/CAB", "A", "B", "C", "D"}.

Step A2.3.1.2: **KBS** is applied. No limitations have been found in the knowledge-base.

Step A2.3.2: **MBS** is applied. Output is the list of <u>*LB*</u>={LB_1:"Low conversion in reaction 1", LB_2:"Slow reaction 1", LB_3:"Low conversion in reaction 2", LB_4:"Slow reaction 2", LB_5:"Low productivity/efficiency in separating D/CAB", LB_6:"High waste generation for enrichment of B", LB_7:"High waste generation due to high dilution of substrates"}. The limitations LB_1–LB_5 are identified through the analysis of the contributors to the F_{obj} (Eqs.5.1-5.2) with a value of $\eta_{P,15,0} = 5.3\, gL^{-1}d^{-1}$. LB_6–LB_7 are identified by the analysis of the contributors to the generated waste of the base case design $m_{Waste,0}$= *465 kg (kg d)*$^{-1}$ (Eq., 5.5) which are the solvent (isopropanol) for precipitation (250 Liter) and the high dilution of the substrates in water (50 Liter).

$$m_{Waste} = \left(\sum m_{Waste,U}\right) / m_{D,out} \tag{5.5}$$

Step A2.3.3: A reduction of limitations/bottlenecks is not necessary (rule A2.11) since the number of limitations/bottlenecks is seven.

Step A2.4: Analyze <u>*LB*</u> and their corresponding tasks in the base-case design:

Step A2.4.1: The algorithm **APCP** is applied. Pure component properties are generated/retrieved (see Table 5.2) and analyzed (see Tables 5.3-5.4). The following limitations are explained: The LB_5 is explained by the low difference in the pKa-value of D and C (Table 5.3). The large difference in solubility in water as well as in the octanol-water partition coefficient Log(K_{OW}) (Table 5.3) between the components may be a hint for miscibility gaps responsible for poor mixing phenomena in the tasks which need further investigation in **AMP**.

Table 5.2. List of pure component properties of the system ("*": Retrieved from Zimmermann *et al.*, 2007 in step APCP.1.1); "**": Missing data predicted through the Marrero-Gani-Approach (Marrero & Gani, 2001) in APCP.1.2).

Component	T_M [K]	T_B [K]	Solubility in water Log (Ws) [log(mg/L]	Log(Kow)	Heat of fusion [kJ/mol]	pKa	Viscosity [cP]
A	426.5**	613.5**	7.57**	-2.67**	14.4**		772495.9**
B	570.4**	625.1**	5.55**	-4.97**	33.3**		264478.9**
C	286.8	438.2	5.66**	-0.83**	18	2.5*	3.38**
D	491.7**	704.6**	8.06**	-4.08**	45.16**	2.6*	9633621.5**
Water	273.15	373.15		-1.38			1

Table 5.3. List of binary ratio's of pure component properties of the system for the main components in the system.

Binary Pair	T_M [K]	T_B [K]	Solubility in water Log (Ws) [log(mg/L]	Log(Kow)	pKa	Viscosity [cP]
A/B	0.75	0.98	1.36	0.54		2.97
A/C	1.49	1.40	1.34	3.22		228549.08
A/D	0.87	0.87	0.94	0.65		0.08
A/Water	1.56	1.64		1.92		772495.9
B/C	1.99	1.43	0.98	5.99		78248.20
B/D	1.16	0.89	0.69	1.22		0.03
B/Water	2.09	1.68		3.58		264478.9
C/D	0.58	0.62	0.70	0.20	0.96	0.00
C/Water	1.05	1.17		0.59		3.38
D/Water	1.80	1.89		2.93		9633621.5

Table 5.4. List of binary ratio's necessary for analyzing occurring limitations/bottlenecks (LB) in corresponding phenomena.

Task	*LB*	Key Phenomena	Important pure component properties
Reaction 1	Low conversion, slow reaction	Mixing: Liquid phase	LogWs, Log(Kow), δ_{SP}
		Reaction 1	Heat of formation
Reaction 2	Low conversion, slow reaction	Mixing: Liquid phase	LogWs, Log(Kow), δ_{SP}
		Reaction 2	eat of formation
Separation D/CAB	Low productivity/efficiency in separating D/CAB	Mixing: S-L	LogWs, Log(Kow), δ_{SP}
		Phase transition: S-L	Melting point, heat of fusion at melting point, pKa-value
Inlet to the system	Waste generation due to high dilution of the substrates	Mixing: Liquid phase	LogWs, Log(Kow), δ_{SP}
Separation A/B	Waste generation due to high amount of solvent needed in extraction step	Mixing: S-L	LogWs, Log(Kow), δ_{SP}
		Phase transition: S-L	Melting point, heat of fusion at melting point, pKa-value

Step A2.4.2: For this step the algorithm **AMP** is used to analyze the system for azeotropes and miscibility gaps. No azeotropes have been found. The solubilites in water are 1.3 mol L^{-1} for A, 3.6 mol L^{-1} for C, 1 mol L^{-1} for D while the solubility for B depends on the concentration of C (Blayer *et al.*, 1999). The low water solubilities lead to the necessary high dilution which explains the large amount of solvents needed which are responsible for LB_6–LB_7.

Step A2.4.3: The algorithm **AR** is applied. It is identified that R1 and R2 are limited due to an unfavourable equilibrium and potentially inhibition (criteria 1, Table 3.3) as well as a slow reaction (criteria 6) and therefore responsible for LB_1-LB_4. Additional *LB*'s are identified (Zimmermann *et al.*, 2007): reaction R1 is inhibited by product D and substrate C (LB_8) while reaction R2 is inhibited by components B, C and A (LB_9).

Step A2.4.4: The algorithm **OPW** is applied. The operating window of all liquid phase phenomena is bounded by the solubilities of the components in water (see step A2.4.2).

Step A2.5: Identify limitations/bottlenecks to a phenomenon outside of the task

Step A2.5.1: Component C is a substrate. Hence, the sources of LB_6-LB_7 (see section A2.4.2) are identified to be in both reaction phenomena and the second reaction task is identified for additional investigation (Rule A2.12).

Step A2.5.2: No action needed.

Step A2.5.3: The reaction tasks have been already analyzed, step A2.6 is entered (Rule A2.16).

Step A2.6: The maturity is set to be "high" (see Table 5.1). Step U2 is entered.

5.1.5. Step U2: Collect PI equipment

Step U2.1 Collect potential PI equipment:

Step U2.1.1: The list of keywords contains $\underline{K}_{PI}$={(1):"Unfavourable equilibrium in reaction 1", (2): "Substrate and product inhibition in reaction 1", (3):"Slow reaction 1", (4):" Unfavourable equilibrium in reaction 2", (5): Substrate and product inhibition in reaction 2", (6):"Slow reaction 2", (7): "epimerase reaction", (8): "aldolase reaction"}.

Step U2.1.2: In total 24 PI equipment are retrieved from the knowledge-base (see Table A.11 in appendix A6). Also included in this table are the keywords responsible for the selection. *Note:* The reaction task can be single reactions or multiple reactions. For multiple reactions (R1 and R2 together), all combinations of catalysts/enzymes for each reaction R1 and R2 in a single unit are considered. Therefore, 15 different reactor combinations are potentially possible. Hence, a reactive-extraction can be run in 15 configurations. That gives in total 360 items of PI equipment and 13 items of non-intensified equipment (see section 5.1.2) in the search space.

Step U2.2: Pre-screen candidate PI equipment for feasibility and maturity:

Step U2.2.1-U2.2.3: The result of the pre-screening for feasibility is presented in Table A.11 in appendix A.6. In total, 91 intensified and 13 non-intensified options remain in the search space.

Step U2.2.4: After screening for maturity (Rule U2.4), the remaining equipment are a one-pot-reactor with 5 different catalysts/combinations (E1/E2, E11/E22, WC, alk1/E2, alk1/E22), 5 single reactors (alk1, E1, E11, E2, E22), reactive-extraction including all 10 remaining reactor configurations and 7 non-PI separations (precipitation, evaporation, crystallization, chromatography, spray-dryer, extraction with methanol, extraction with reactive solvent). A known solvent has been selected which is PBA/ TOMAC (Zimmermann *et al.*, 2008) (Rule U2.2). That gives in total 27 items of equipment.

Step U2.3: Identify sub-problems:

Step U2.3.1: The number of sub-problems is identified to be 1 (Rule U2.4).

Step U2.3.2: All equipment from step 2.2.4 are added to $\Omega^{SP=1}$.

Step U2.3.3: Step $U3^{SP=1}$ is entered for sub-problem 1.

5.1.6. Step U3$^{SP=1}$: Select & develop models

Note: The generic process model (described in section 2.3.3) is retrieved from the model library. Models to represent splitting and conversion factors (short-cut and detailed) need to be derived. This is shown in this section for the derivation of a detailed kinetic model of an OPR (E1/E2) using the algorithm U3$^{SP=1}$.1-U3$^{SP=1}$.6. The retrieval of one specific process option from the superstructure and the general model are explained in the Appendix A6.

U3$^{SP=1}$.1: A one-pot reactor containing enzymes E1 and E2 is modeled. It is assumed to be isothermal, isobaric and ideally mixed.

U3$^{SP=1}$.2: Here, experimental data for an OPR E_{OPR} which will be used for validation of the kinetic model are shown in Table 5.5.

Table 5.5. Experimental dataset E_{OPR}. for an OPR (E1/E2) taken from Zimmermann *et al.*, 2007.

Time [min]	c_A [mol/ L]	Time [min]	c_A [mol/ L]	Time [min]	c_D [mol/ L]
46	0.233	102	0.034	55	0.032
111	0.202	1134	0.032	111	0.063
994	0.119	1310	0.033	985	0.120
1143	0.147	1552	0.034	1134	0.141
1320	0.155	2389	0.040	1310	0.152
1561	0.165	2724	0.042	1561	0.168
2398	0.204	2882	0.042	2398	0.211
2724	0.214	3895	0.050	2724	0.226
2882	0.223	4081	0.054	2891	0.224
3895	0.268	4286	0.052	3904	0.239
4081	0.276	4416	0.053	4063	0.238
4295	0.274	4453	0.052	4286	0.251
4407	0.289			4388	0.243
4462	0.292			4453	0.242

U3$^{SP=1}$.3: A model is retrieved from the model library which has been developed by Zimmermann *et al.* (2007). Step U3$^{SP=1}$.5 is entered.

U3$^{SP=1}$.5. Validate the model by applying sub-steps U3$^{SP=1}$.5.1- U3$^{SP=1}$.5.3:

U3$^{SP=1}$.5.1- U3$^{SP=1}$.5.2: In the original model by Zimmermann *et al.*, 2007, two parameters are not given which are the dilution factors of the enzymes E_{EPI} and E_{ald}. Also, the units of the activities $\underline{A}$ and the reaction rates do not fit. Therefore, the model need to be improved (Rule U3.1). Step U3$^{SP=1}$.5.3 is entered.

U3$^{SP=1}$.5.3: The model has not been improved previously; hence step S3.4 is re-entered for model improvement (Rule U3.2).

U3$^{SP=1}$.4: The unknown dilution factors are replaced with the initial enzyme concentration *EA* in [U L^{-1}], see Eqs. (5.6-5.7).

$$v_{R1,E1} = \frac{EA_{E1}\left(A_V^A c_A / K_m^A - A_V^B c_B / K_{m,R1}^B\right)}{1 + c_A / K_m^A + c_B / K_{m,R1}^B + c_C / K_{i,R1}^C + c_D / K_{i,R1}^D} \tag{5.6}$$

$$v_{R2,E2} = \frac{EA_{E2}\left(A_V^f c_B c_C / K_{m,R2}^B / K_{i,R2}^C - A_V^r c_D / K_{m,R2}^D\right) / \left(1 + \left(c_A^0 + c_B^0 + c_C^0 + c_D^0\right) / K_V\right)}{1 + c_C / K_{i,R2}^C + K_m^C c_B / K_{m,R2}^B / K_{i,R2}^C + c_B c_C / K_{i,R2}^C / K_{m,R2}^B + c_D / K_{m,R2}^D + c_B c_D / K_{i,R2}^B / K_{m,R2}^D} \tag{5.7}$$

Five parameters, the four activities <u>*A*</u> as well as the Michaelis-Menten constant for component D, $K^D_{m,R2}$, have been fitted using an experimental data set of a semi batch reactor <u>*E*$_{OPR}$</u>. All other parameters are kept unchanged to the original model. The new parameter set is given in Table 5.6. The standard deviation from all data points is 97%. Afterwards, U3$^{SP=1}$.5 is entered.

Table 5.6. Parameter set for kinetic models. Fitted parameters are marked with "*".

Parameter	Value	Parameter	Value
A_V^A	5.440·10^{-7} mol U^{-1} min^{-1}*	$K_{m,R2}^B$	0.0131 mol L^{-1}
K_m^A	0.017 mol L^{-1}	$K_{i,R2}^C$	0.00849 mol L^{-1}
A_V^B	1.361·10^{-5}*	A_V^r	4.944·10^{-7} mol U^{-1} min^{-1}*
$K_{m,R1}^B$	0.0993 mol L^{-1}	$K_{m,R2}^D$	0.00277 mol L^{-1}*
$K_{i,R1}^C$	0.146 mol L^{-1}	K_V	0.035 mol L^{-1}
$K_{i,R1}^D$	0.687 mol L^{-1}	K_m^C	0.0941 mol L^{-1}
A_V^f	3.337·10^{-8} mol U^{-1} min^{-1}*	$K_{i,R2}^B$	0.0119 mol L^{-1}

U3$^{SP=1}$.5: Validate the model by applying sub-steps U3$^{SP=1}$.5.1- U3$^{SP=1}$.5.3.

U3$^{SP=1}$.5.1: The comparison of the model to the experimental data of a semi batch operation is shown in Fig.5.4. The standard deviation is acceptable (97%).

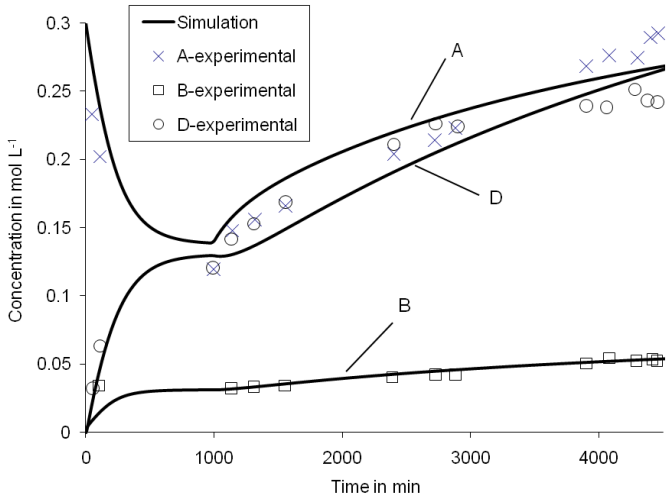


Figure 5.4. Comparison of the kinetic model (Eqs.5.6-5.7) with experimental data from Zimmermann *et al.*, 2007.

U3$^{SP=1}$.5.2: Model performance is satisfactory (rule U3.1), enter step U3$^{SP=1}$.6.

U3$^{SP=1}$.6: All missing data has been provided through models. Hence, all process options remain in the search space. *Note:* Since, no dynamic data of the recombinant enzymes E11 and E22 are found in the scientific literature, their kinetics are based on the kinetic rate expressions of the standard enzymes E1 and E2 (Eqs. 5.6-5.7) multiplied by an enhancement factor *E=3* (fitted to the input-output data of Hu *et al.*, 2010) to represent the faster conversion using these enzymes.

5.1.7. Step U4$^{SP=1}$: Generate feasible flowsheet options

U4$^{SP=1}$.1: The superstructure containing the generic model has been retrieved from the model library.

U4$^{SP=1}$.2: This step is not needed, since the superstructure from U4$^{SP=1}$.1 matches the maximum number of tasks, therefore step S4.3 is directly entered (Rule U4.1).

U4$^{SP=1}$.3: The number of generated process options of this superstructure without recycling both outlets into a single unit can be expressed by equation (5.8) in which *ps* is the number of processing steps and *NIU* the number of identified units.

$$NPO = \sum_{ps=2}^{4} \left(\underbrace{NIU^{ps}}_{\text{options by units}} \cdot \underbrace{2\sum_{2}^{ps}(ps-1)!}_{\text{options by recycle}} \right) \tag{5.8}$$

Based on the total of 27 intensified and non-intensified process equipment in the search space $NPO=9.7 \bullet 10^6$ process options are included. For comparison, the theoretical number of process options has been calculated for step U2.1-U2.2 as well (Table 5.7).

Table 5.7. Determination of the number of theoretical possible process options in step 2 (Eq.5.8).

Step	Number of identified units	Number of process options
Step U2.1.2	373	$3.5 \bullet 10^{11}$
Step U2.2.3	91	$1.2 \bullet 10^{9}$
Step U2.2.4	27	$9.7 \bullet 10^{6}$

$U4^{SP=1}$.4: All generated PI process options are checked stepwise against the logical constraints (Eq.2.2, Table A.12, appendix A.6). First, configurations with no reaction step are removed (L1-L2, Table 5.1). No pretreatment or enrichment of the substrate streams entering the system is necessary (L3). Hence, all configurations with a separation unit (S) as a first step are removed. Reactors cannot achieve a pure product stream, meaning that a separation step is needed as the last step (L5). This leads to the following remaining process configurations: R –S, R – S – S, R – R – S, R – S – R – S, R – R – S – S and R – S- S- S. Therefore, all other configurations are removed. Together with the last remaining logical constraint (L4), in total NPO_L=1914 feasible options are remaining in the search space (see Table A.12 in appendix A.6).

$U4^{SP=1}$.5: The stepwise screening for each selected structural constraint based on the PI metrics (step 1.4) is given in Table 5.8. The number of process options has been reduced from NPO_L=1914 to NPO_S=57. The remaining process options are given in Table 5.9.

Table 5.8. Results of the stepwise screening through a set of structural constraints.

PI Metric	Structural constraint:	Number of redundant options	Number of options remaining
Simplification	Do not use repetitive units. Do not use enrichments before separations if not necessary. Do not use pre-reactors.	1574	340
Efficiency	Do not integrate units which inhibit each others performance. Add units at the place in the flowsheet in which it has the highest efficiency.	246	94
Energy	Do not connect units with alternating heat addition and heat removal	26	68
Waste	Do not use two different solvents in one process	11	57

Table 5.9. Feasible process options (NPO_S) after screening with structural constraints.

Unit 1	Unit 2	Unit 3	Unit 4	NPO
OPRE (E1/E2; E11/E22; WC) OPR (E1/E2; E11/E22; WC)	$Cryst_{Purif}$ $Chrom_{purif}$	-	-	12
OPR (E1/E2; E11/E22; WC)	Evap LL	$Cryst_{Purif}$	-	6
OPR (E1/E2; E11/E22; WC)	Prec LL	$Chrom_{purif}$		6
R1(E1; E11)	R2(E2; E22)	$Cryst_{Purif}$ $Chrom_{purif}$		8
R1(E1, E11)	R2(E2; E22)	Evap LL	$Cryst_{Purif}$	8
R1(E1, E11)	R2(E2; E22)	Prec LL	$Chrom_{purif}$	8
OPR (E1/E2; E11/E22; WC)	Prec	Evap	$Cryst_{Purif}$	3
OPR (E1/E2; E11/E22; WC)	Evap	LL	$Chrom_{purif}$	3
OPR (E1/E2; E11/E22; WC)	Evap	LL	$Cryst_{Purif}$	3
			Total	**57**

$U4^{SP=1}$.6: The search space is not empty, continue to step S5.1 (Rule U4.2- U4.3).

5.1.8. Step $U5^{SP=1}$: Fast screening for process constraints

$U5^{SP=1}$.1: Solve operational constraints (Eqs.2.4&2.7):

$U5^{SP=1}$.1.1: *DoF=5* for processes without extraction and *DoF=7* for processes with extraction.

$U5^{SP=1}$.1.2: The following variables are specified: initial substrate concentrations $c_{C,0}$=1 mol L^{-1}, $c_{C,0}/c_{A,0}$=1.5, enzyme concentrations $EA_{E1,E11}$=1500 U L^{-1}, $EA_{E2,E22}$= 8000 U L^{-1}, Volume V_0=50 L and for the extraction processes $V_{solvent}/V_0$=0.5 and the starting time of the extraction $t_{LL\ start}=0.5t_R$.

$U5^{SP=1}$.1.3: The results of the simulation of the reactors are presented in Table 5.10.

Table 5.10. Results of process simulation for different reaction configurations at the same initial substrate amounts ($c_{C,0}$=1 mol L^{-1}, $c_{C,0}/c_{A,0}$=1.5) and same enzyme concentrations ($EA_{E1,E11}$ =1500 U L^{-1}, $EA_{E2,E22}$ = 8000 U L^{-1}, V_0=50 L; $V_{solvent}/V_0$=0.5; $t_{LL,\,start}$=0.5t_R).

Reaction configuration	Time-yield after reaction step [g g^{-1} day^{-1}]
OPRE (E1/E2)	0.09
OPRE (E11/E22)	0.87
OPRE (WC)	0.80
OPR (E1/E2)	0.12
OPR (E11/E22)	1.09
OPR (WC)	0.99
R1(E1) - R2(E2)	0.03
R1(E1) - R2(E22)	0.05
R1(E11) - R2(E2)	0.06
R1(E11) - R2(E22)	0.16

$U5^{SP=1}$.1.4: Rule U5.1 is applied: Feasible remaining reactor options are the integrated one-pot reactor with extraction (OPRE) and the one-pot reactor (OPR) catalyzed by either whole cells or E11/E22. This gives a total number of NPO_O =22 remaining process options.

$U5^{SP}$.1.5: Search space is not empty continue with step S5.2 (Rule U5.2).

$U5^{SP=1}$.2: Identify the set of most promising options through performance screening NPO_P.

$U5^{SP=1}$.2.1: The product yield (Eq.5.4) is calculated. The result is presented in Table 5.11.

Table 5.11. Results of the calculation of the product-yield (step S5.2) and the objective function (step S5.3) for all remaining process options. Process options marked with "*" remain in the search space for step 6.

Process Option	Process flowsheet	Product yield ε [%]	F_{obj} [-]
#1	OPRE (E11/E22) - $Cryst_{Purif}$	45.9	15.5
#2	OPRE (WC) - $Cryst_{Purif}$	12.1	
#3	OPRE (E11/E22) - $Chrom_{Purif}$	54.8	18.4
#4	OPRE (WC) - $Chrom_{Purif}$	24.8	
#5	OPR (E11/E22) - $Cryst_{Purif}$	62.0	20.9*
#6	OPR (WC) - $Cryst_{Purif}$	6.5	
#7	OPR (E11/E22) - $Chrom_{Purif}$	54.8	
#8	OPR (WC) - $Chrom_{Purif}$	14.8	
#9	OPR (E11/E22) – Evap - $Cryst_{Purif}$	65.7	20.9*
#10	OPR (WC) – Evap - $Cryst_{Purif}$	28.9	
#11	OPR (E11/E22) – LL - $Cryst_{Purif}$	57.8	19.5
#12	OPR (WC) – LL - $Cryst_{Purif}$	20.5	
#13	OPR (E11/E22) – Prec - $Chrom_{Purif}$	51.1	17.2
#14	OPR (WC) – Prec - $Chrom_{Purif}$	23.1	
#15	OPR (E11/E22) – LL - $Chrom_{Purif}$	43.4	14.6
#16	OPR (WC) – LL - $Chrom_{Purif}$	15.4	
#17	OPR (E11/E22) – Prec – Evap -$Cryst_{Purif}$	76.7	22.1*
#18	OPR (WC) – Prec – Evap - $Cryst_{Purif}$	22.9	
#19	OPR (E11/E22) – Evap – LL - $Chrom_{Purif}$	43.6	14.7
#20	OPR (WC) – Evap – LL - $Chrom_{Purif}$	15.8	
#21	OPR (E11/E22) – Evap – LL - $Cryst_{Purif}$	57.9	19.6
#22	OPR (WC) – Evap – LL - $Cryst_{Purif}$	20.8	

Note: The integrated one-pot reactor with extraction (OPRE) using a reactive solvent (PBA/ TOMAC, see Zimmermann *et al.*, 2008) does not improve the product-yield of a one-pot reactor (OPR) because also substrate is extracted (see Table 5.11).

$U5^{SP=1}$.2.2: All process options with a product-yield lower than 40% are removed leaving 11 PI options in the search space (see Table 5.11).

$U5^{SP=1}$.2.3: The objective function is used for screening, continue with step $U5^{SP=1}$.3 (Rule U5.3).

$U5^{SP=1}$.3: Screen by F_{obj} (Eq.5.1).

$U5^{SP=1}$.3.1: The objective function F_{obj} (Eq.5.1) is calculated (see Table 5.11).

$U5^{SP=1}$.3.2: The three most promising process options are selected (NPO_P=3). These are, the integration of both enzymatic steps in a one pot reactor OPR(E11/E22) and purify directly by crystallization (option #5) or purify it via an evaporation step (option #9) or via a precipitation/evaporation step removing substrate A (option #17) in the crystallization.

$U5^{SP=1}$.4: All sub-problems (SP=1) have been solved, step 6 is entered (Rule U5.4).

5.1.9. Step 6: Solve the reduced optimization problem and validate promising

Step 6.1: Solve a MINLP if necessary

Step 6.1.1: The search space NPO_P is smaller than 20, an MINLP solution is not necessary, step 6.2 is entered.

Step 6.2: The conversion reactors have been replaced by reactors with kinetic rate expressions (Eqs.5.6-5.7). The optimization of the remaining process options with respect to F_{obj} (Eq. 5.1) has been performed in ICAS-MoT. Optimization variables were the initial concentrations of the substrates A and C. All other variables such as enzyme concentrations have been kept fixed. The results are given in Table 5.12.

Table 5.12. Results of the optimization in step 6.

Process variable	Process Option #5	Process Option #9	Process Option #17
$c_{A.0}$ [mol / L]	0.932	0.932	1.3
$c_{C.0}$ [mol / L]	2.185	2.185	2.05
F_{Obj} [-]	31.2	31.2	32.3

Step 6.3: The process option with the highest objective function, mostly improving the space-time-yield of the process, has been identified to be process option #17 (see Fig. 5.5). The space-time-yield increases by a factor of 32.3 compared to the base case design.

Step 6.4: The most detailed model available for this case study has been used for the optimization. This step is not necessary.

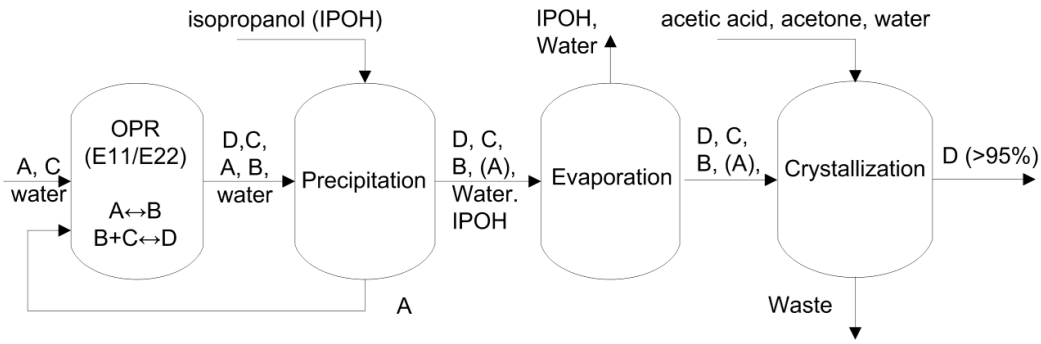


Figure 5.5. Simplified flowsheet of the PI process option #17.

5.1.10. Discussion of the results

The application of the PI synthesis methodology has managed to improve the base-case design. In total $3.5 \bullet 10^{11}$ PI process options have been generated from which through a stepwise reduction of the search space the best process option has been determined, all on a quantitative basis. Through PI, the base case design (Mahmoudian *et al.*, 1997) has been improved in the objective function by a factor of 32.3 by process option #17. The reasons are the use of better enzymes (E11 and E22) as well as the integration of both reaction tasks into one equipment, a one-pot-reactor. The advantage of the latter is that it drives the reaction beyond the unfavorable equilibrium from A to B by *in-situ* removal of B by the second biocatalytic reaction. In addition, the process is simplified since the number of equipment has decreased from 7 to 4. An analysis of the determined process values of the initial substrate concentrations in option #5 and option #9 shows that they are on the boundary for the operational constraint of the crystallization for both substrates (see appendix A6, Eqs.A.6.25-A.6.26) while process option #17 is bounded due to the solubility of compound A in water (step A2.4.2).
Other studies have shown that fed-batch reactors have the potential to further improve the yield (Hu *et al.*, 2010; Maru *et al.*, 2002). This option has not been considered in this work.

5.2. Production of hydrogen peroxide

The objective of this case study to find PI-options for the production of hydrogen peroxide, using the anthraquinone process route as the base-case design (Eul, Moeller & Steiner, 2001). Section 5.2.1 provides introduction to the process; section 5.2.2 describes the base-case design while sections 5.2.3-5.2.11 describe the step-by-step details of the application of the methodology (unit-operation based).

5.2.1 Introduction

Hydrogen peroxide (H_2O_2) is a bulk chemical with a market volume of around 3.000.000 metric tons per year (Zhou, Hammack & Sethi, 2008). Its main applications are in chemical synthesis as well as bleaching (Goor, Glenneberg & Jacobi, 2007). Reported plant capacities are up to 136.000 metric tons per year (Eul, Moeller & Steiner, 2001). Hydrogen peroxide is mainly produced by auto-oxidation via anthraquinones which is the major route used in industry as well as electrochemical synthesis and by oxidation of alcohols such as isopropanol and methylbenzolalcohol (Eul, Moeller & Steiner, 2001; Goor, Glenneberg & Jacobi, 2007). Recently, the production of hydrogen peroxide directly from the elements

hydrogen and oxygen received much attention (Eul, Moeller & Steiner, 2001; Goor, Glenneberg & Jacobi, 2007). However the direct synthesis is difficult because the reaction is very exothermic and the hydrogen peroxide forms an explosive atmosphere (see Fig. 5.6; Goor, Glenneberg & Jacobi, 2007).

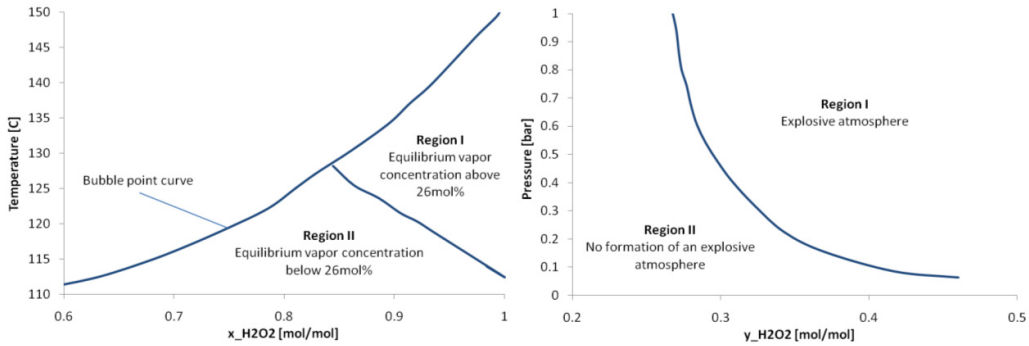


Figure 5.6. Dependence of the explosion range from the temperature and concentration of H2O2 in the liquid phase at P=1atm (left) and on the total pressure and the concentration of H2O2 in the vapor phase (right) from Goor, Glenneberg & Jacobi (2007).

The focus in this case study is on the identification of process intensification possibilities for the anthraquinone route because it is the major production route.

The simplified reaction scheme (see Fig. 5.7) is as follows:

Hydrogenation: $EAQ + H_2 \rightarrow EAQ.H_2$ (5.9)

Oxidation: $EAQ.H_2 + O_2 \rightarrow EAQ + H_2O_2$ (5.10)

Decomposition: $EAQ + H_2 \rightarrow [H_2EAQ]_{Waste}$ (5.11)

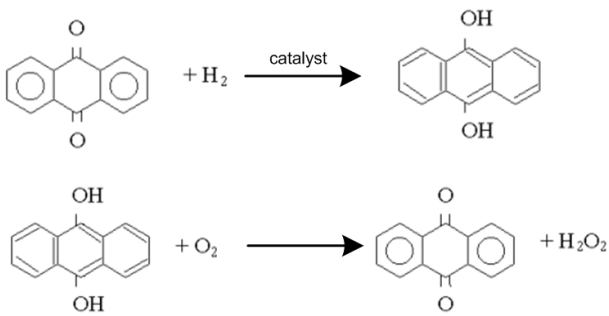


Figure 5.7. Main reactions (5.9-5.10) to produce hydrogen peroxide via the anthraquinone route. Top: Hydrogenation (Eq.5.9); Bottom: Oxidation (Eq.5.10).

5.2.2 Base case design

The flowsheet of the base-case design (Figure 5.8) is given by Eul, Moeller and Steiner (2001). It is assumed that the capacity of the process is capable for a production of 10000 kg/h product with 70 w.% H_2O_2 and 30 w.% H_2O.

The working solution contains around 15 w.% of 2-ethylantraquinone (EAQ) and 85 w.% of other heavy boiling solvents compared to hydrogen peroxide (Ranbom, 1982). EAQ is hydrogenated with hydrogen in a catalytic fixed bed reactor (Porter, 1961) and afterwards oxidized with air in a bubble column with perforated trays (Liebert, Delle & Kabisch, 1975). The hydrogen peroxide is recovered from the working solution in an extraction column using water which is immiscible with the working solution (WS). The product rich solution is purified at vacuum (P=0.1bar) in a distillation column (Goor, Glenneberg & Jacobi, 2007). The working solution is regenerated and recycled back to the hydrogenator.

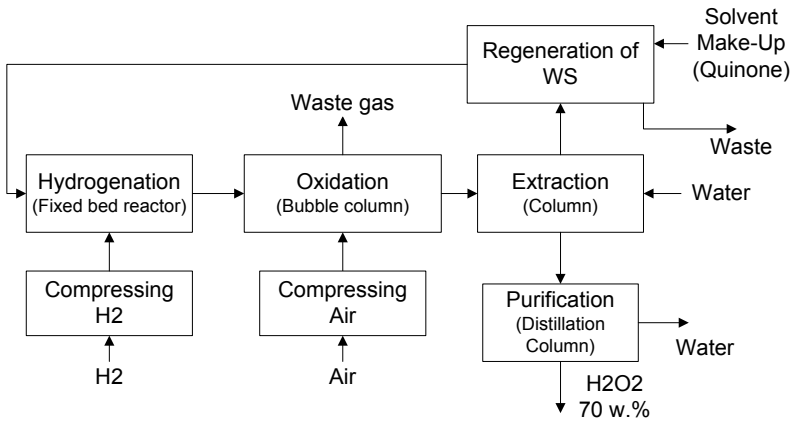


Figure 5.8. Simplified base-case design for the production of H_2O_2 by the anthraquinone-route.

5.2.3. Step 1: Define problem

Step 1.1: The objective is the identification of a PI option which increases the material and energy efficiency and minimizes the operational cost per kg product formed (Eq.5.12):

$$\min F_{Obj} = \left(\underbrace{\sum c_{RM,i} \dot{m}_{RM,i}}_{Raw\,Materials} + \underbrace{\sum c_{energy,i} \dot{E}_i}_{Energy} + \underbrace{\sum c_{solvent,i} \dot{m}_i}_{Make-Up} \right) / \dot{m}_{H2O2} \tag{5.12}$$

Step 1.2: The design scenario is to improve the whole process keeping the anthraquinone production route. The process scenario is continuous.

Step 1.3: The following operational constraints are set:

- The capacity is 10.000 kg/h of H_2O_2.
- The product purity is 70 w.% of H_2O_2 and 30 w.% & H_2O.
- The anthraquinone process is fixed.
- Due to safety reasons, the concentration of oxygen and hydrogen-peroxide in the hydrogenator should be zero.
- Raw materials: Pure hydrogen and air.
- Side-Reactions occur.
- Recovery of H_2O_2 in the last separation step = 0.99.
- Working solution (WS) and solvents are fixed.
- The operating pressure in the recycle system is fixed to 3.5 bar

Step 1.4: Define performance metric $\underline{PM}$.

The following performance metric $\underline{PM}$ is selected: Safety, efficiency, energy, simplification, waste.

Step 1.5: The maturity is selected to be “medium” using only existing PI technology.

Step 1.6: Translate $\underline{\vartheta}$ and $\underline{PM}$ into logical, structural, operational constraints and performance criteria $\underline{\Psi}$:

Step 1.6.1: All rules have been applied to gather a set of logical constraints (Eq.2.2). The detailed results are listed in Table 5.13.

Step 1.6.2: Four PI metrics have been translated to six structural constraints. The result is given in Table 5.13.

Step 1.6.3: The result of the translation into operational constraints and the PI screening criterion is given in Table 5.13.

Step 1.7: A base case design exists, step A2 is entered (Rule 1.9).

Table 5.13. Overview of the problem definition of the case study.

F_{obj}	Operational costs per product (Eq.5.12)
Design scenario	Redesign of the whole process
Process scenario	Continuous
Logical constraints	L1: Reaction 1 necessary (Rule 1.1)
	L2: Reaction 2 necessary (Rule 1.1)
	L3: Reaction 1 has to be in the first unit (Rule 1.2)
	L4: Reaction 1 before or at the same time as Reaction 2 (Rule 1.3)
	L5: Product is component D which must be linked to a purification unit (Rule 1.4)
	L6: Do not exceed the number of units of the base-case design (Rule 1.5).
Structural constraints by PI metric	Efficiency: Do not integrate units/tasks which inhibit each others performance.
	Energy: Do not connect units with alternating heat addition and heat removal.
	Simplification: Do not use repetitive units. Do not use enrichments before separations if not necessary. Do not use pre-reactors.
	Waste: Do not add two different solvents to the system.
Operational constraints (Rule 1.6)	The capacity is 10.000 kg/h of H_2O_2.
	The product purity is 70 w.% of H_2O_2 and 30 w.% & H_2O.
	The anthraquinone process is fixed.
	Due to safety reasons, the concentration of oxygen and hydrogen-peroxide in the hydrogenator should be zero.
	Raw materials: Pure hydrogen.
	Recovery of H_2O_2 in the last separation step = 0.99.
	Working solution and solvents are fixed.
	$P_{Recycle}$=3.5 bar
PI screening criterion in step U2.	Application of process technology of “medium” maturity
PI screening criterion in step U5	Check the performance of the reaction tasks. Keep only the two best options per reaction task if the performance of the second best is better than 95 %). Otherwise keep only the best option.

5.2.4. Step A2: Analyze the process

Step A2.1: Collect mass and energy data for the base-case design:

Step A2.1.1: Mass and energy data are required for the analysis (rule A2.1).

Step A2.1.2: Mass end energy data are collected using published information (Eul, Moeller & Steiner, 2001; Goor, Glenneberg & Jacobi, 2007; Ranbom, 1982; Liebert, Delle & Kabisch, 1975). Mass and energy data are summarized in the appendix A.7 (Table A.13).

Step A2.2: Identify the task-based flowsheet:

Step A2.2.1: Based on the rules A2.2-A2.8, eight tasks are identified for the base-case design. That are compressing of hydrogen and compressing of air (Rule A2.7), two reactions (a

hydrogenation and an oxidation) tasks (Rule A2.2), three separations (Rule A2.3), one combined with a mixing (Rule A2.5). The task based flowsheet is shown in Fig 5.9.

Step A2.2.2: The following separations are identified by Rule A2.9: Separation of water and hydrogen peroxide from the solvent, the separation of waste from the solvent.

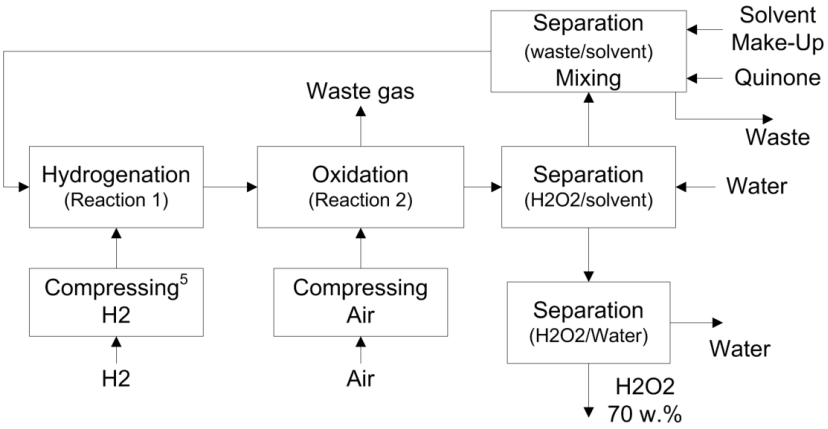


Figure 5.9. Task-based representation of the base-case design for the production of H2O2 by the anthraquinone-route.

Step A2.2.3: The list of phenomena involved in each unit operation is retrieved from the PI knowledge-base (see Table 5.14).

Table 5.14. Identified tasks, unit operations and phenomena in flowsheet.

Task	Unit-operation	Important phenomena
Hydrogenation	Fixed-Bed-Reactor	Mixing, heating/cooling, reaction
Oxidation	Packed-Bed-Reactor	Mixing, heating/cooling, reaction; phase transition G-L
Compressing H_2	Compressor	Pressurizing/Expanding, (phase transition V-L, phase transition G-L, phase separation)
Compressing Air	Compressor	Pressurizing/Expanding, (phase transition V-L, phase transition G-L, phase separation)
Separation (H_2O_2,Water/solvent)	Extraction-Column	Mixing, heating/cooling, phase-transition L-L, phase separation
Separation (H_2O_2/Water)	Distillation	Mixing, heating/cooling, phase-transition V-L, phase separation
Separation (Water/Solvent) Mixing (Solvent/Make-Up)	Separator Mixer	Mixing, heating/cooling, phase transition, phase separation

Step A2.3: Identify limitations/bottlenecks *LB* of the base-case.

Step A2.3.1: Collect the limitations of the process by applying the algorithm **KBS**.

Step A2.3.1.1: The list of keywords *K* is collected. It contains the following items: *K*={Production of H_2O_2; hydrogenation; oxidation; hydrogenation reaction task; oxidation reaction task; compressing (H_2) task; compressing (Air) task; separation (H_2O_2,Water/solvent); separation (H_2O_2/Water); separation (Water/solvent); Mixing (Solvent/Make-Up); Hydrogen-peroxide; Water; H_2, Air; Anthraquinone}.

Step A2.3.1.2: The algorithm **KBS** is applied. The details of the search are not given here. No limitations/bottlenecks are retrieved from the knowledge-base.

Step A2.3.2: The algorithm **MBS** for a model-based search of limitations in the base-case design is applied. The details of the algorithm are shown here.

Enter sub-algorithm MBS:

MBS.1: The objective function is calculated and with it the distribution of the factors within each task contributing to the objective function. Necessary cost indicators for utilities and raw materials are presented in Table 5.15-5.16.

Table 5.15. Cost indicators for utilities from Turton *et al.* (2009).

Utility	c_i
Heating(HP)($/GJ)	14.05
Cooling($/GJ)	0.40
Electricity($/kWh)	0.06

Table 5.16. Prices for the raw materials from ICIS, 2009 ("*": Assumed prices).

Raw material	c_i (US-$/kg)
Hydrogen	0.88
Hydrogen-peroxide	1.16
Water	0.0006
Solvent	2*

All operational constraints are calculated. None of them are violated. Additionally, the following performance criteria are calculated: Efficiency, energy and waste.

The efficiency of the reaction is calculated with equation (5.13) and of the separation with equation (5.14).

$$\varepsilon_r = \lambda_r^0 = \frac{n_{i,out}}{n_{substrate\,A,in}} \tag{5.13}$$

$$\varepsilon_{sep} = \sigma_{sep,i} = \frac{n_{i,out1}}{n_{i,in}} \tag{5.14}$$

For the calculation of the electrical energy, the theoretical work for pumping can be assumed through equation (5.15) and for compressing through equation (5.16) taken from Biegler, Grossmann and Westerberg (1997):

$$W_b = \mu(P_2 - P_1)/(\rho\eta_p\eta_m) \tag{5.15}$$

$$W_b = \mu(\gamma/(\gamma-1))RT[(P_2/P_1)^{(\gamma-1)/\gamma} - 1]/(\eta_p\eta_m) \tag{5.16}$$

With: η_p : pump efficiency, assumed to be 0.5

η_m : motor efficiency, assumed to be 0.9

The results of the calculation of the energy as well as the efficiency are presented in table 5.17, and the results of the waste calculation in table 5.18.

Table 5.17. Calculated efficiencies and energy consumption.

Task	Unit-operation	Efficiencies	Energy (GJ/h)
Hydrogenation	Fixed-Bed-Reactor	0.99 for hydrogen	22.6
Oxidation	Packed-Bed-Reactor	0.99 for hydrogen-peroxide 0.65 for oxygen	18.5
Compressing H_2	Compressor	-	4.1
Compressing Air	Compressor	-	9.6
Separation (H_2O_2,Water/solvent)	Extraction-Column	0.99	1.7
Separation (H_2O_2/Water)	Distillation	0.99	44.5
Separation (Water/Solvent) Mixing (Solvent/Make-Up)	Separator Mixer	-	-

Table 5.18. Waste generation in each task.

Task	Waste [kg/h]	What
Oxidation	41000	Purge (N_2)
Separation (Water/Solvent) Mixing (Solvent/Make-Up)	3000	Purge (mostly water, QC_9H_{12}, N_2, H_2O_2)
Separation (H_2O_2/Water)	11000	99.9% water

MBS.2: Based on their contribution to the F_{obj} (Fig 5.10) and on the energy (Fig 5.11), waste (Table 5.18) and efficiency (Table 5.17), the following limitations/bottlenecks are added $\underline{LB}$={LB_1: Low efficiency in the oxidation; LB_2: Large amount of waste in oxidation; LB_3: Large amount of waste in separation (H_2O_2/Water); LB_4: High energy/High costs for compressing air; LB_5: High energy/High costs for separation H_2O_2/water; LB_6: High energy for hydrogenation; LB_7: High energy for oxidation; LB_8: High costs for hydrogen; LB_9: High costs for make-up solvent; LB_{10}: High costs for waste stream}.

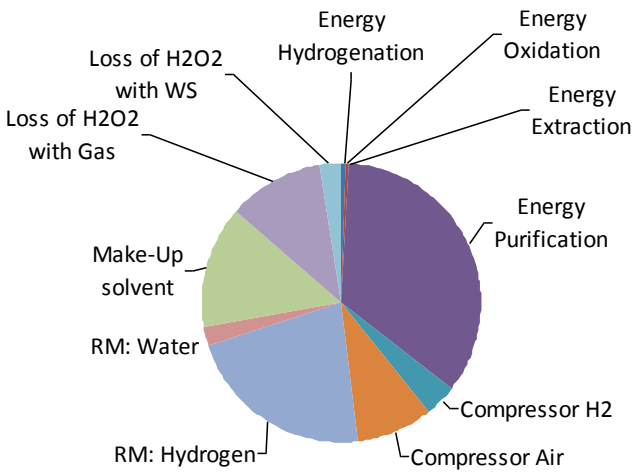


Figure 5.10. Contribution to the objective function.

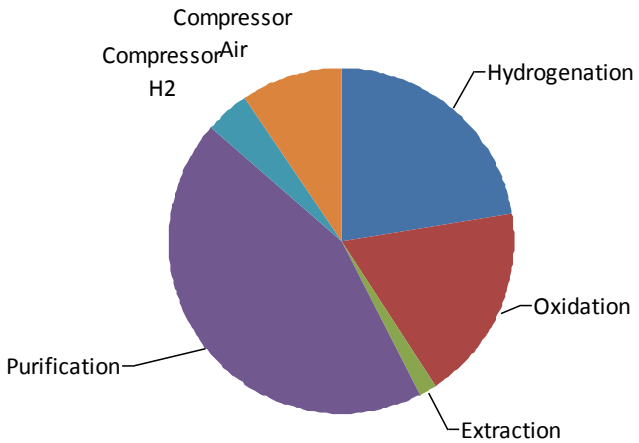


Figure 5.11. Contribution to the energy consumption.

MBS.3: No operational constraint is violated.

MBS.4: Because the operating costs are selected as objective function F_{obj}, "SustainPro" is used to calculate the task responsible for the most negative impact on two important mass and energy indicators (MVA and EWC). Based on the analysis of the indicators (Table 5.19-5.20), the following additional limitations/bottlenecks are: LB_{11}: Large amount of water necessary for extraction.

Table 5.19. Result of MVA (Material Value Added) analysis.

Indicator MVA (US-$/h)	Component	Open path
-4040.7	Water	Entrance: Extraction; Exit: Vapour in distillation column
-919.2	Water	Entrance: Extraction; Exit: Separation (water/solvent)

Table 5.20. Result of EWC (Energy and Waste Costs) analysis.

Indicator EWC (US-$/h)	Component	Open path
1406.3	Water	Entrance: Extraction; Exit: Vapour in distillation column
627.7	Hydrogen peroxide	Entrance: Product of reaction in Oxidizer; Exit: Product stream via Distillation
Indicator EWC (US-$/h)	**Component**	**Closed path**
1722.64	Anthraquinone	Recycle solvent make-up loop

Exit sub-algorithm MBS.

Step A2.3.3: *LB<15*, hence, this step is not necessary (Rule A2.11).

Step A2.4: The results of the analysis of the obtained limitations/bottlenecks *LB* and their corresponding tasks are given in Table 5.21. All details of the sub-steps including the application of the sub-algorithms (**APCP**, **AR** and **AMP**) are given in table A.15 in appendix A.7.

Step A2.5: By applying the rules given in this step, some limitations/botllenecks are linked/explained to other limitations/bottlenecks outside of the task in which they occur. The results are shown in table 5.21. Baed on the analysis, the base-case design needs improvement in four tasks which are: the hydrogenation; the separation of hydrogen-peroxide from the working solution; the oxidation task; and the task for compression of air.

Table 5.21. Overview of the identified limitations/bottlenecks (LB) and their source analysis.

LB	Responsible phenomenon	How (Step)
LB_1: Low efficiency in the oxidation	Phase transition by relative volatility and contacting	Step A2.4.1: APCP.4: solubility oxygen in working solution/water VP difference is large (Rule APCP.7):
LB_2: Large amount of waste in oxidation	Linked to raw material is unpure (see LB_{14})	Rule A2.15
LB_3: Large amount of waste in separation (H_2O_2/Water)	Linked to extraction (see LB_{11})	Rule A2.13
LB_4: High energy/High costs for compressing air	Linked to LB_{14}: Unpure raw material	Rule A2.15
LB_5: High energy/High costs for separation H_2O_2/water	Phase transition by relative volatility	Step A2.4.1: APCP.4: $r(T_B)$ large (Rule APCP.1)
	Linked to extraction (see LB_{11})	Why is water in the system (rule A2.13)
LB_6: High energy for hydrogenation;	Reaction (heat of reaction)	Step A2.4.3: AR
LB_7: High energy for oxidation	Reaction (heat of reaction)	Step A2.4.3: AR
LB_8: High costs for hydrogen	-	
LB_9: High costs for make-up solvent	side-reactions, linked to hydrogenation& oxidation	Rule A2.14 & rule A2.16 (new LB->LB_{12}& LB_{13})
LB_{10}: High costs for waste stream;	Linked to huge amount of N_2 (Linked to raw material is unpure (see LB_{14}))	Rule A.2.15 and rule A2.16
LB_{11}: Large amount of water necessary for extraction	Phase transition by extraction and mixing	Step A2.4.1: APCP.4: Dilution of the product in the solvent (Rule APCP.9)
LB_{12}: Side-reactions in hydrogenation	Mixing/contacting in hydrogenation limited by amount of catalyst	Step A2.4.3: AR.4 (criteria 7, Table 3.3)
LB_{13}: Side-reactions in oxidation	Mixing/contacting in oxidation limited by oxygen transfer	Step A2.4.3: AR.4 (criteria 8, Table 3.3)
LB_{14}: Unpure raw material		

Step A2.6: The maturity is selected to be ”medium” (step 1). Hence, step U2 is entered.

5.2.5. Step U2: Collect PI equipment

Step U2.1: Collect potential PI equipment:

Step U2.1.1: The list of keywords $\underline{K}_{PI}$ for PI equipment search includes all identified limitations/bottlenecks and the corresponding phenomena (see Table 5.21).

Step U2.1.2: The algorithm **KBS** is applied to retrieve potential equipment in a list Ω. The results are shown in the table A.16 in appendix A.7.

Step U2.2: Pre-screen candidate PI equipment for feasibility:

Step U2.2.1-U2.2.3: The sub-steps are performed. The result of the screening is shown in table 5.22.

Step U2.2.4: Pre-screen candidate PI equipment for maturity: The sub-steps are performed. The result of the screening is presented in table 5.22.

Note: For example, the integration of oxidation and purification in a reactive distillation is screened out due to the operating window analysis (OPW). The reason for removing this option from the search space is that the oxidation reaction has to take place at pressure above the atmospheric pressure in order to achieve the transport of oxygen into the liquid while due to the safety reasons the purification of hydrogen peroxide must take place at low pressures (see Fig. 5.6). Another example for the screening is a unit operation considering a solid product such as a reactive crystallizer which is removed due to not matching phases (see Table 5.22).

Table 5.22. Results of the pre-screening by feasibility and maturity in step U2.2. In Parenthesis is the reason for the removal.

Task	Retrieved potential PI equipments Ω
Separation: working solution/product	Remaining options: 10 Reaction- separation (~~Reactive distillation~~(OPW), reactive extraction, reactive membrane, ~~reactive crystallization~~(Phases), ~~reaction condensation~~(Phases), ~~reaction-absorption~~(Phases), Reaction Stripping, ~~reactive distillation with pervaporation~~(OPW); ~~heat-integrated distillation column~~(OPW),~~oscillatory baffled reactor-crystallizer~~ (Phases)), Separation-Reaction (~~Absorption-reaction~~(Phases), ~~reactive distillation~~(Doubled)~~, reactive extraction~~(Doubled)), Separation-separation (~~Adsorption distillation~~(Maturity)~~, extraction crystallization~~(Phases), extraction-distillation, ~~distillation-pervaporation~~(OPW), membrane extraction, d~~ividing wall column~~(OPW)); ~~HIGEE~~ (OPW), ~~spinning disc separator~~ (OPW); packed microchannel extractor; microchannel extractor; static mixer extractor; microchannel reactor-extractor, static mixer reactor-extractor
	~~Ionic liquid~~ (OPW)
Separation: water/product	Remaining options: 4 Separation-reaction (~~Absorption-reaction~~(OPW), ~~reactive distillation~~(OPW), ~~reactive extraction~~(OPW)), Separation-separation (~~Adsorption distillation~~(Maturity)~~, extraction crystallization~~(Phases), extraction distillation; distillation pervaporation, ~~membrane extraction~~(OPW), ~~dividing wall Column~~ (OPW), heat-integrated distillation column); heat transfer panels inside column; ~~HIGEE~~ (OPW), ~~spinning disc separator~~ (OPW);
	~~Ionic liquid~~ (OPW);
1. Reaction: hydrogenation	Options: 5 Reaction- separation (~~Reactive distillation~~(OPW), ~~reactive extraction~~(OPW), ~~reactive membrane~~(OPW), ~~reactive crystallization~~(Phases)~~, reaction condensation~~(Phases)~~, reaction-absorption~~(Phases), ~~reaction-stripping~~(OPW), ~~reactive distillation with pervaporation~~(OPW), ~~oscillatory baffled reactor-crystallizer~~ (Phases)); catalytic static mixer reactor; ~~microchannel reactor-extractor~~(OPW), microchannel reactor, millichannel reactor; monolithic reactor, foam reactor.
2. Reaction: oxidation	Remaining options: 9 Reaction- separation (~~Reactive distillation(OPW)~~, reactive extraction, reactive membrane, ~~reactive crystallization(Phases), reaction condensation~~(Phases)~~, reaction-absorption~~(Phases), reaction-stripping, ~~reactive distillation with pervaporation~~(OPW), ~~oscillatory baffled reactor-crystallizer~~(Phases)), Reaction- reaction (~~1-pot synthesis~~(OPW)); static mixer reactor; microchannel reactor-extractor; microchannel reactor; millichannel reactor; oscillatory baffled reactor; static mixer reactor-extractor
Compressing air	Use of Oxygen instead of air

Step U2.3: Identify sub-problem:

Step U2.3.1: The hydrogenation task is not integrated with another task and can therefore be solved separately (rule U2.4).

Step U2.3.2: Therefore, *SP=2* and $\Omega^{SP=1}$={catalytic static mixer reactor; microchannel reactor, millichannel reactor; monolithic reactor, foam reactor; fixed bed reactor (base-case design)} and $\Omega^{SP=2}$= Ω- $\Omega^{SP=1}$.

Step U2.3.3: The inner algorithm for the first sub-problem *SP=1* (step $US3^{SP=1}$) is entered.

5.2.6. Step $U3^{SP=1}$: Select and develop models

A generic process model is retrieved from the model library (see Fig. 4.2 and section 4.2). Specific models to represent splitting and conversion factors (short-cut and detailed) for each option have been derived using steps $U3^{SP=1}$.1-$U3^{SP=1}$.6. The details for each step are not given here.

The reaction model for the hydrogenation has been retrieved from Santacesaria *et al.* (1994, 1999).

$$\lambda_{\mathrm{EAQ.H2}}^{reactor\ j,L} = \frac{n_{EAQ,0} - m_{cat} r_{Hydrog}}{n_{EAQ,0}} \tag{5.17}$$

With:

$$\mathrm{r}_{\mathrm{Hydrog}} = k_{Hydrog}[EAQ.H2] \tag{5.18}$$

With the reaction constant is given by

$$\mathrm{k}_{\mathrm{Hydrog}} = 0.21 cm^3 / \left(g\ catalyst \cdot s \right). \tag{5.19}$$

And the mass of catalyst with

$$m_{cat} = V \cdot a / a_w \tag{5.20}$$

With *a* as the specific surface area of the catalyst particle and a_w as the metallic surface area of the catalyst (Eq. 5.21; Santacesaria *et al.*, 1994):

$$a_w = 149 m^2 / g \tag{5.21}$$

For the hydrogenation, the provision of catalysts is the important factor. Therefore, one important parameter is the provided specific catalytic surface areas *a* of different internals within conventional and PI reactors (taken from Eigenberger, 1992, Reitzmann, Bareiss & Kraushaar-Czarnetzki, 2006) which are given in table 5.23. The specific surface area of the catalyst particles in the base-case design is assumed to be $a=1000\ m^{-1}$ (Goor, Glenneberg & Jacobi, 2007).

Table 5.23. Specific surface area's a for different reactor internals (from Eigenberger, 1992, Reitzmann, Bareiss & Kraushaar-Czarnetzki, 2006) used in the catalytic hydrogenation ("*" from Goor, Glenneberg & Jacobi, 2007).

Catalytic Packing	Surface area/Volume a [m^{-1}]
Glass spheres dp=5mm	700
Glass spheres dp=10mm	300
Raschig rings - ceramic	400
Raschig rings - metal	500
Hollow ceramic cylinders	500
Full ceramic cylinders	500
Structured packing (wide- Sulzer Katapak)	450
Structured packing narrow channels)	1600
Monolith	2300
Foam	2550
Millichannel	2000
Microchannel	100000
Assumed Catalyst particles used in base-case design*	1000

For the energy balance, the heat of reaction in the hydrogenation is 55% of the total exothermic heat of formation from the elements while the last 45% is released in the oxidation (Eul, Moeller & Steiner, 2001).

No suitable model for the by-product formation has been found. Therefore, a simple model has been developed. The by-product formation is linked to the residence time in oxidation and hydrogenation reactors (Sethi *et al.*, 2007). Therefore, the amount of by-product formed is assumed to be:

$$m_{By-\mathrm{Pr}oduct} = m_{By-\mathrm{Pr}oduct}^{BaseCase} \cdot \left(t_{r,hydrogenation} + t_{r,oxidation}\right) / \left(t_{r,hydrogenation}^{BaseCase} + t_{r,oxidation}^{BaseCase}\right) \quad (5.22)$$

<u>*Note:*</u> The application of this step with all details are given for the derivation of a detailed kinetic model of a simple reaction-oxidation bubble-column reactor using the algorithm in the sub-problem SP=2 $U3^{SP=2}$.1-$U3^{SP=2}$.6). The retrieval of one specific process option from the superstructure and the general model is explained in appendix 6 for the case study on Neu5Ac (section 5.1).

5.2.7. Step $U4^{SP=1}$: Generate feasible flowsheet option

$U4^{SP=1}$.1: The superstructure containing a generic model has been retrieved from the model library (see Fig.4.2).

$U4^{SP=1}$.2: This step is not needed, since the superstructure from S4.1 matches the maximum number of tasks, therefore step $U4^{SP=1}$.3 is directly entered (Rule U4.1).

$U4^{SP=1}$.3: The number of generated hydrogenation options is: *NPO=6*.

U4$^{SP=1}$.4: The generated process options *NPO* are screened by applying logical constraints (see Table 5.13). All process options ($NPO_{SP=1}= NPO_{L,SP=1}=6$) remain in the search space.

U4$^{SP=1}$.5: The generated process options *NPO* are further screened by applying structural constraints (see Table 5.13). All process options ($NPO_{L,SP=1}= NPO_{S,SP=1}=6$) remain in the search space.

U4$^{SP=1}$.6: The search space is not empty (rule U4.2- U4.3). Step U5$^{SP=1}$ is entered.

5.2.8. Step U5$^{SP=1}$: Fast screening for process constraints

U5$^{SP=1}$.1: The substeps U5$^{SP=1}$.1.1- U5$^{SP=1}$.1.5 have been used to screen for violated operational constraints (see Table 5.1). This is not the case. All remaining processes for this sub-problem hydrogenation (*SP=1*) are feasible. All process options ($NPO_{S,SP=1}= NPO_{O,SP=1}=6$) remain in the search space. Step U5$^{SP=1}$.2 is entered (rule U5.2).

U5$^{SP=1}$.2: Identify the set of most promising options through performance screening $NPO_{P,\ SP=1}$:

U5$^{SP=1}$.2.1: For each of the remaining process options in $NPO_{O,\ SP=1}$, the performance metric Ψ_p (see table 5.13) has been calculated (Table 5.24).

Table 5.24. Results of the calculation of F_{obj} for different hydrogenation reactors.

Rank	PI Equipment	η [kg/m^3/h]	F_{obj} [US-$/h]	$F_{obj}/F_{obj,Base,case}$
1	microchannel reactor	6400	1473.3	0.94
2	foam reactor	163.2	1508.5	0.96
3	monolithic reactor	147.2	1512.4	0.97
4	millichannel reactor	128	1518.4	0.97
5	fixed bed reactor (base-case design)	64	1564.5	1
6	catalytic static mixer reactor	28.8	1677.1	1.07

U5$^{SP=1}$.2.2: The ranking is presented in table 5.24. Only the best two options, the micro channel reactor and the foam reactor are kept in the search space (see table 5.24). The number of promising process options is $NPO_{P,SP=1}=2$.

U5$^{SP=1}$.2.3: F_{obj} has been already used for screening, step U5$^{SP=1}$.4 is entered.

U5$^{SP=1}$.4: The sub-problem *SP=2* has to be solved (Rule U5.4). Step U3$^{SP=2}$ is entered.

5.2.9. Step U3$^{SP=2}$: Select and develop models

A generic process model is retrieved from the model library (see Fig. 4.2 and section 4.2). Models to represent splitting and conversion factors (short-cut and detailed) have been derived. This is shown in

this section for the derivation of a detailed kinetic model of a simple reaction-oxidation bubble-column reactor using the algorithm $U3^{SP=1}$.1- $U3^{SP=1}$.6.

$U3^{SP=2}$.1: A simple reaction-oxidation bubble-column reactor is modeled. It has two phases, one gas and one liquid. It is assumed to be isothermal, isobaric and ideally mixed.

$U3^{SP=2}$.2: For validation, the productivity of the base-case design (bubble column with perforated trays and air as oxidizer) is used (retrieved from Eickhoff & Schütte, 2002):

$$\eta_{O2}^{BaseCase} = 36\,kg\,H_2O_2 / m^3 / h \tag{5.23}$$

$U3^{SP=2}$.3: A model is retrieved from the model library which has been developed by Santacesaria *et al.* (1987, 1999). In the liquid phase the reaction is taking place and the oxygen is absorbed from the gas into the liquid until equilibrium is achieved. Here, only the component balance for oxygen is shown. For the one for nitrogen, the reaction rate is zero.

$$n_{O2}^{reactor\,j,L} = \left(Vr_{Ox} + k_L a_i \left(\frac{p_{O2}}{H} - \frac{n_{O2}}{V} \right) \right) \tag{5.24}$$

From the gas phase, the oxygen is removed into the liquid phase.

$$n_{O2}^{reactor\,j,G} / s = -k_L a_i \left(\frac{p_{O2}}{H} - \frac{n_{O2}}{V} \right) \tag{5.25}$$

The simplified reaction in the oxidizer (Eq. 5.10) is modeled with the following kinetic expression (Eq. 5.26).

$$EAQ.H2 + O2 \rightarrow EAQ + H2O2 \tag{5.10}$$

$$\mathrm{r}_{\mathrm{Ox}} = k_{Ox}[EAQ.H2][O2] \tag{5.26}$$

The Henry-coefficient of oxygen in the solution is given by (Eq. 5.27)

$$H = 109 \cdot 10^3\, atm \cdot cm^3 / mol \tag{5.27}$$

While the reaction rate constant is given by

$$\mathrm{k}_{\mathrm{Ox}} = 1.14 \cdot 10^{13} \exp((-14213/(RT))cm^3 / \left(mol \cdot s\right)). \tag{5.28}$$

The mass transfer coefficient for the bubble column reactor with perforated trays is given in Table 5.25.

Table 5.25. Mass transfer coefficients k_La in s^{-1} for different reactors for air-water (from Yue *et al.*, 2007, Voigt & Schügerl, 1979 and Reay, Ramshaw & Harvey, 2009) used in the oxidation.

Reactor equipment	k_La_min [$10^2 \cdot s^{-1}$]	k_La_max [$10^2 \cdot s^{-1}$]	k_La_avg [$10^2 \cdot s^{-1}$]
bubble column	0.5	24	12.25
bubble column with perforated trays	5	100	52.5
static mixer	10	250	130
packed column	0.04	102	51.02
millichannel	0.6	42	21.3
microchannel	30	2100	1065
oscillatory baffled reactor	2	12	7

Step $U3^{SP=2}$.5 is entered.

$U3^{SP=2}$.5: Validate the model by applying sub-steps $U3^{SP=1}$.5.1- $U3^{SP=1}$.5.3.

$U3^{SP=2}$.5.1: The model is applied ($\eta_{O2,calculated}^{BaseCase} = 39\, kg\, H_2O_2 / m^3 / h$) using the operation data from the base-case design and compared to the experimental data.

$U3^{SP=2}$.5.2: The relative failure is less than 10% and therefore acceptable (rule U3.1), enter step $U3^{SP=2}$.6.

$U3^{SP=2}$.6: The previous steps (for SP=2) have been successfully repeated for all PI equipment in the search space. The different mass transfer coefficients for different reactors have been retrieved from the knowledge-base (Table 5.25).

The extraction is strongly dependent on the working solution composition (Goor, Glenneberg & Jacobi, 2007). Water and the working solution are fully immiscible. The extraction is modelled using the equilibrium constant for hydrogen peroxide into water of $K_E=77.4$ from Lü *et al.* (2005). The efficiency in the sieve plate columns (base-case design) is low (around 20%, Lü *et al.*, 2004) while reported efficiencies in static mixers is around 50% while unpacked and packed microchannel-extractors may achieve 50% or 90% respectively (Su *et al.*, 2010). The pressure drop is calculated for the three latter ones using a modified Ergun equation (Su *et al.*, 2010).

The model parameters for the membrane for the separation of hydrogen peroxide (and water) from the working solution can be retrieved from Datta, Ranghava and Tsai (1997). The selectivity is larger than 100 and the flux through the membrane is 1 $kg/m^2/min$.

One membrane for the selective pervaporation of hydrogen peroxide against water has been patented (Parrish, 2006). The pervaporation membrane has a selectivity S=2.4 and is described through a short-cut model for the flux through the membrane J_i [m^3 /m^2 /h] using the experimental data available from Motupally, Becker and Weidner (2000) and Parrish (2006).

$J_i = Q_i * dP$ (5.29)

The permeability of the membrane for water Q_{H2O} and hydrogen peroxide Q_{H2O2} have been calculated at T=50C:

$Q_{H2O} = 0.0065\ m^3/m^2/h/Pa.$ (5.30)

$Q_{H2O2} = 0.0027\ m^3/m^2/h/Pa.$ (5.31)

5.2.10. Step U4$^{SP=2}$: Generate feasible flowsheet options

U4$^{SP=2}$.1: The superstructure presented in section 4.2 (Figure 4.2) has been retrieved from the model library.

U4$^{SP=2}$.2: This step is not needed, since the superstructure from step U4$^{SP=2}$.1 matches the maximum number of tasks. Step U4$^{SP=2}$.3 is directly entered (Rule U4.1).

U4$^{SP=2}$.3: The number of generated process options of this superstructure without recycling both outlets into a single unit can be expressed by equation (5.32) in which *ps* is the number of processing steps, $n_{RM,S}$ the number of different raw material/solvent combinations and *NIU* the number of identified units.

$$NPO = n_{RM,S} \cdot \sum_{ps=2}^{ps} \left(\underbrace{NIU^{ps}}_{\text{options by units}} \cdot \underbrace{2 \sum_{ps=2}^{ps} (ps-1)!}_{\text{options by recycle}} \right) \quad (5.32)$$

Based on the total of 24 intensified and 4 conventional (from the base-case-design) process equipment and two different raw material combinations in the search space $NPO = 2.1 \bullet 10^5$ process options are included. For comparison, the theoretical number of process options has been calculated for step C2.1.2 as well (Table 5.26).

Table 5.26. Determination of the number of theoretical possible process options in step C2 (Eq. 5.24).

Step	ps	NIU	$n_{RM,S}$	NPO
Step C2.1.2	4	74	6	$3.2 \bullet 10^9$
Step C2.2.4	3	26	2	$2.1 \bullet 10^5$

U4$^{SP=2}$.4: The generated process options *NPO* are screened by applying logical constraints (see Table 5.13). In total a number of $NPO_L = 1142$ process options remain in the search space. The remaining process options are presented in table 5.27.

Table 5.27. The number of process options remaining in the search space (BCD: Base case design; W: water; WS: working solution; PR: product rich; P: product).

Task 2 - Oxidation	Task 3 - Separation WS/PR	Task 4 - Separation W/P	Options
reaction stripping reactive extraction reactive membrane static mixer reactor static mixer reactor extractor microchannel reactor-extractor microchannel reactor millichannel reactor oscillatory baffled reactor fixed bed reactor (BCD)	reactive extraction reactive membrane reaction stripping extractive distillation membrane extraction packed microchannel extractor microchannel extractor static mixer extractor microchannel reactor-extractor static mixer reactor extractor bubble column (BCD)	extraction distillation distillation pervaporation heat-integrated distillation heat transfer panels inside column distillation (BCD)	1100
reaction stripping	None	extraction distillation	2
reactive extraction reactive membrane static mixer reactor extractor microchannel reactor-extractor	None	extraction distillation distillation pervaporation heat-integrated distillation heat transfer panels inside column distillation (BCD)	40

U4$^{SP=2}$.5: Screen the process options NPO_L by stepwise applying structural constraints (Table 5.28). Remaining process options are NPO_S=242.

Table 5.28. Results of the stepwise screening through a set of structural constraints.

PI Metric	Structural constraint:	Number of redundant options	Number of options remaining
Simplification	Do not use repetitive units.	68	1074
	Do not use pre-reactors.	450	624
	Do not use enrichments before separations if not necessary.	154	470
Energy	Do not connect units with alternating heat addition and heat removal	54	416
Efficiency	Do not integrate units/tasks which inhibit each others performance.	46	370
Waste	Do not add two different solvents	128	242

U4$^{SP=2}$.6: The search space is not empty (rule U4.2- U4.3). Step U5$^{SP=2}$ is entered.

5.2.11. Step U5$^{SP=2}$: Fast screening for process constraints

U5$^{SP=2}$.1: The substeps U5$^{SP=2}$.1.1- U5$^{SP=2}$.1.5 have been used. All remaining processes for *SP=2* are feasible. All process options ($NPO_{S,SP=2}$= $NPO_{O,SP=2}$=*242*) remain in the search space. Step U5$^{SP=2}$.2 is entered (rule U5.2).

U5$^{SP=2}$.2: Identify the set of most promising options through performance screening NPO_P:

U5$^{SP=2}$.2.1.: Using the performance criteria, the objective function of the oxidation task is calculated (Table 5.29). The oxygen price is assumed to be 0.07 US-$/kg calculated using the short-cut method from Wilcox (2009).

U5$^{SP=2}$.2.2: The ranking is presented in table 5.29. Only the best two options (see table 5.13), the microchannel reactor-extractor and the microchannel reactor are kept in the search space. The number of promising process options is reduced to $NPO_{P,SP=2}$=*25*.

Table 5.29. Calculation of the performance of the oxidation task (RM: raw material).

Rank	RM	PI Equipment	F_{obj} [US-$/h]
1	Air	microchannel reactor-extractor	1404
2	Air	microchannel reactor	1410
3	Air	static mixer reactor-extractor	1434
4	Air	static mixer reactor	1467
5	Air	reactive extraction	1482
6	Air	reactive membrane	1485
7	Air	bubble column (BCD)	1565
8	Oxygen	microchannel reactor-extractor	1568
9	Oxygen	static mixer reactor-extractor	1573
10	Oxygen	microchannel reactor	1575
11	Oxygen	static mixer reactor	1580
12	Oxygen	reactive extraction	1583
13	Oxygen	reactive membrane	1585
14	Oxygen	Bubble column (BCD)	1600
15	Oxygen	millichannel reactor	1650
16	Air	millichannel reactor	1804
17	Oxygen	oscillatory baffled reactor	1824
18	Air	oscillatory baffled reactor	2629

$U5^{SP=2}$.2.3: The objective function for the whole process (SP=2) has not been selected for checking the performance at this step, step S5.3 is entered (rule U5.3).

$U5^{SP=2}$.3: Screen by F_{obj} (Eq.5.12).

$U5^{SP=2}$.3.1: The objective function F_{obj} is calculated for each of the 25 options. The membrane cost is assumed to be 300 US-$/m^2 and needs replacement every 3 years (Nafion, 2011). The results are presented in table 5.30.

$U5^{SP=2}$.3.2: All processes are ranked according to their F_{obj}. The most promising which are the best four options are selected. All remaining options are removed. The number of promising options for SP=2 is $NPO_{P,SP=2}=4$.

Table 5.30. Calculation of the objective function for all remaining options in SP=2 (BCD: base case design).

Rank	Task 2 - Oxidation	Task 3 - Separation WS/PR	Task 4 - Separation W/P	F_{obj} [US-$/h]
1	microchannel reactor-extractor	None	heat-integrated distillation	846.9
2	microchannel reactor	packed microchannel extractor	heat-integrated distillation	851.5
3	microchannel reactor	microchannel extractor	heat-integrated distillation	872.8
3	microchannel reactor	static mixer extractor	heat-integrated distillation	872.8
5	microchannel reactor	extraction column (BCD)	heat-integrated distillation	908.9
6	microchannel reactor-extractor	None	distillation (BCD)	1117.3
6	microchannel reactor-extractor	None	heat transfer panels inside column	1117.3
8	microchannel reactor	packed micro-channel extractor	heat transfer panels inside column	1122.3
8	microchannel reactor	packed micro-channel extractor	distillation (BCD)	1122.3
10	microchannel reactor	microchannel extractor	heat transfer panels inside column	1229.1
10	microchannel reactor	microchannel extractor	distillation (BCD)	1229.1
10	microchannel reactor	static mixer extractor	heat transfer panels inside column	1229.1
10	microchannel reactor	static mixer extractor	distillation (BCD)	1229.1
14	microchannel reactor	extractive distillation	heat-integrated distillation	1294.3
15	microchannel reactor	extraction column (BCD)	heat transfer panels inside column	1409.4
16	microchannel reactor	extraction column (BCD)	distillation (BCD)	1409.4
17	microchannel reactor	membrane extraction	distillation-pervaporation	No improvement
...				No improvement
25	microchannel reactor	packed microchannel extractor	distillation-pervaporation	No improvement

$U5^{SP=2}$.4: All sub-problems *SP* have been solved, step U5.5 is entered (Rule U5.4).

$U5^{SP=2}$.5: All obtained solutions of each sub-problem *SP* are collected. The number of process options remaining are $NPO_P=8$. No additional logical and structural constraints as well as performance criteria are selected. Hence, step U4.1-U4.5 are not needed and step 6 is entered.

5.2.12. Step 6: Solve the reduced optimization problem and validate promising

Step 6.1: Identify the set of most promising process options by solving an MINLP problem (if necessary).

Step 6.1.1: The search space $NPO_P=4\cdot 2=8<15$. Hence, step 6.2 is entered.

Step 6.2: For each of the eight remaining process options, the mathematical model is optimized. Temperatures and pressures in the reactors have been fixed leaving the volume (reaction time) as the optimization variable. For the purification step, the pressure for purifying the product is fixed to P=0.1 atm while reflux ratio and the pressure for the heat integration are the optimization variables (Table 5.31). The reactors have been optimized separately using ICAS-MOT while the optimization of the purification step has been made in Pro\II.

Step 6.3: All options are ranked by their objective function values. The best option (see Table 5.31) is the hydrogenation in a microchannel reactor (catalyst on the wall) followed by a coupling of oxidation and extraction in a microchannel reactor-extractor. The purification is realized in a heat integrated distillation column (see Fig. 5.12).

<u>*Note:*</u> The key to the large process improvement is the energy savings in the purification as well as the lower residence times in the microchannel reactors allowing less degradation of the product and the solvents.

Step 6.4: The results have been obtained using the most detailed models. The distillation column has been successfully rigorously validated in Pro\II (see Figure 5.12).

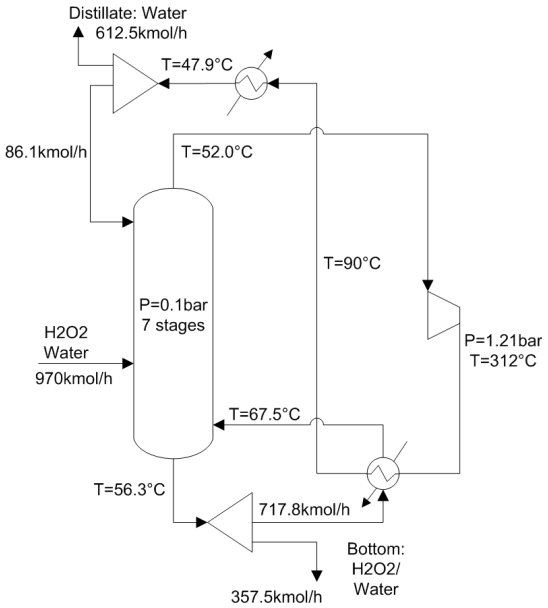


Figure 5.12. Heat integrated distillation column.

Table 5.31. Calculation of the objective function for all remaining options.

Rank	RM	Task 1 - Hydrogenation	Task 2 – Oxidation	Task 3 – Separation WS/PR	Task 4 – Separation W/P	F_{obj} [US-$/h]
1	Air	microchannel reactor	microchannel reactor-extractor	None	heat-integrated distillation	755.7
2	Air	microchannel reactor	microchannel reactor	packed microchannel extractor	heat-integrated distillation	760.3
3	Air	microchannel reactor	microchannel reactor	microchannel extractor	heat-integrated distillation	781.6
3	Air	micro channel reactor	microchannel reactor	static mixer extractor	heat-integrated distillation	781.6
5	Air	Foam reactor	microchannel reactor-extractor	None	heat-integrated distillation	790.9
6	Air	Foam reactor	microchannel reactor	packed microchannel extractor	heat-integrated distillation	795.5
7	Air	Foam reactor	microchannel reactor	microchannel extractor	heat-integrated distillation	816.8
7	Air	Foam reactor	microchannel reactor	static mixer extractor	heat-integrated distillation	816.8
	Air	Base Case Design				1564.5

5.3. Production of HMF

For a sustainable future, biomass is considered as a renewable feedstock to replace oil in the chemical industry. One example is the production of 5-hydroxymethylfurfural (HMF) from fructose. HMF is considered as a platform chemical for the production of a variety of high value chemicals as well as high value polymers (Bozell & Petersen, 2010). However, the production costs for HMF using this route and conventional equipment are too high (Boisen *et al.*, 2009). Therefore, it is checked if PI options can reduce the operational costs of this process route. Section 5.3.1 lists the state-of-the-art in the bio-based production of HMF from fructose; section 5.3.2 presents the base-case design while in steps 5.3.3-5.3.9 all details of the workflow (unit-operation) are presented.

5.3.1. State-of-the-art in the production of HMF

HMF can be produced from fructose by the following reaction scheme consisting of four reactions proposed by Kuster and Temmink (1977). The main reaction is to produce HMF and water from fructose (R1; Eq.5.33):

$$C_6H_{12}O_6 \leftrightarrow C_6H_6O_3 + 3H_2O\,. \tag{5.33}$$

HMF is degraded in water to levulinic acid and formic acid in a side-reaction (R2; Eq.5.34).

$$C_6H_6O_3 + 2H_2O \leftrightarrow C_5H_8O_3 + CH_2O_2 \tag{5.34}$$

Besides, two additional side-reactions are taking place to form humins which are the degradation of HMF (R3; Eq.5.35) and the degradation of fructose (R4; Eq.5.36). Humins are undetermined insoluble polymers (Rapp, 1977).

$$C_6H_6O_3 \leftrightarrow \left[C_6H_6O_3\right]_{\text{Humins.2}} \tag{5.35}$$

$$C_6H_{12}O_6 \leftrightarrow \left[C_6H_6O_3\right]_{\text{Humins.1}} + 3H_2O \tag{5.36}$$

Different process routes are discussed in academia and industry with respect to different catalysts, different solvents (water, DMSO, ionic liquids) or mixture of solvents (e.g. water-acetone), and different technologies for the reaction as well as the product recovery. An excellent review has been made by Boisen *et al.* (2009). A small overview is given in Table 5.32. That also includes intensified technologies such as reactive extraction to *in-situ* remove the product HMF (e.g. Román-Leshkov, Chheda & Dumesic, 2006) and circumvent the degradation of product and susbtrate; as well as ionic liquids replacing water as solvent and acting as catalysts at the same time (e.g. in Moreau, Finiels & Vanoie, 2006).

Table 5.32. Reported process routes (extended from Boisen *et al.*, 2009). Conversion and selectivity are molar based.

Reference	fructose concentration	Solvent	Catalyst	Reaction time & temperature	Reaction selectivity, conversion	Product recovery
Rapp, 1987	25w.%	Water	0.02 M oxalic acid (homog.)	2h , 140°C	55% selectivity, 60% conversion	Chromatography, evaporation and crystallization
Román-Leshkov *et al.*, 2006	10w.%	Water	0.1M HCL	3min, 180°C	51% selectivity, 50% conversion	
Tuercke *et al.*, 2009	10w.%	Water	0.1M HCL	1min, 185°C (Microreactor)	75% selectivity, 71% conversion	
Román-Leshkov *et al.*, 2006	10w.%	Water	0.25 M HCl (homog.)	3 min, 180°C	80% selectivity, 86% conversion	*In-situ* extraction with 2-butanol/ MIBK
Carlini *et al.*, 1999	20w.%	Water	Niobium phosphate (heterog.)	1h, 85°C	79.6% selectivity, 27% conversion	
Bicker *et al.*, 2005	1% w/V	90% Acetone in water	0.01M H_2SO_4 (homog.)	2 min, 180°C	77% selectivity, 98% conversion	Evaporation
Moreau *et al.*, 2006	27w.%	HMIM-Cl	Solvent (homog.)	1h, 90°C	92% selectivity, 100% conversion	Extraction

Environmentally, water seems to be the ideal solvent. However, it also pushes the decomposition of the product by the reverse reaction (Eq.5.33) as well as the production of the side-products (Eq. 5.34). It has been also reported that the production of humins preferably takes place in aqueous solutions (Román-Leshkov, Chheda & Dumesic, 2006).

Therefore, the water-route is studied to check if through PI a potential process to produce HMF, assuming a fructose price of around 0.5 US-$/kg (Sino Chemical Industry Co Ltd, 2010), for a price lower than 2 US-$/kg may exist. Only one catalyst is taken into the search space because the purpose is to highlight the methodology to systematically achieve PI and not a detailed catalyst screening. The catalyst in the search space is hydrogen chloride (homogeneous) because it has been proposed repeatedly for the water route and the kinetics are faster than the one from oxalic acid proposed by Rapp (1987, see Table 5.32). Even though, the side products levulinic acid and formic acid have a market value, they will not be considered as co-products in this study here.

5.3.2. Base case design

The largest scale reported in the literature (see Table 5.32) is the water route by Rapp (1987). A commercial production process is not known. Hence, this process has been selected as the base-case

design. This leads to the following process proposed by Rapp (1987) in which the fructose (25 w.% of fructose) is dissolved in water and fed to a reactor in which the reaction takes place for 2 hours at a temperature of 140 °C. Oxalic acid is used as catalyst (see table 5.31). The selectivity towards the main product is 55% and the conversion of fructose is 60%. The produced humins in the side reactions (Eqs. 5.35 & 5.36) are unsoluble and can therefore easily be separated using a filter. All acids are neutralized through the addition of a base (sodium hydroxide) following the reaction scheme given in equation (5.37).

Acid + Base -> Salt + Water (5.37)

The salt and afterwards the fructose are removed in a chromatography column through the addition of water. Subsequently, the water is evaporated and the HMF crystallized. The process flowsheet is given in figure 5.13.

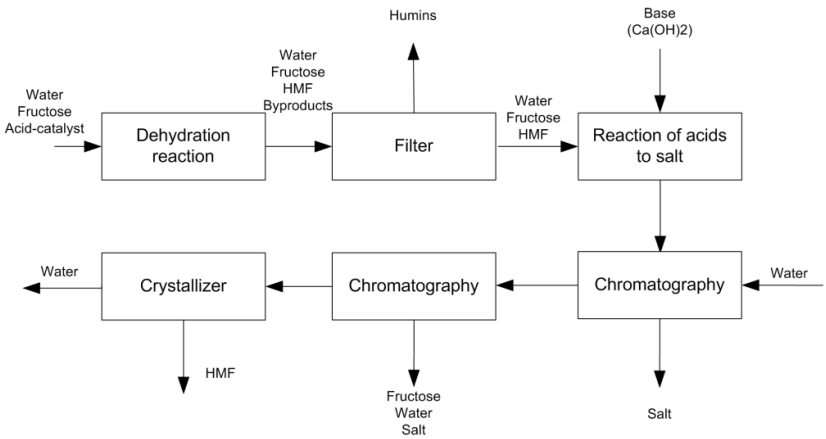


Figure 5.13. Simplified production route of HMF from fructose through a water route (Rapp, 1987).

5.3.3. Step 1: Define problem

Step 1.1: The objective is to achieve PI for process improvement and minimize the operational cost per kg product formed F_{Obj}:

$$\min F_{Obj} = \left(\underbrace{\sum c_{RM,i} \dot{m}_{RM,i}}_{Raw\,Materials} + \underbrace{\sum c_{energy,i} \dot{E}_i}_{Energy} + \underbrace{\sum c_{solvent,i} \dot{m}_i}_{Make-Up} \right) / \dot{m}_{HMF} \quad (5.38)$$

Step 1.2: The design scenario is to develop a new design of the whole process. The process scenario is continuous.

Step 1.3: The product HMF is produced from the raw material fructose. All raw materials are pure and the purity of the product is defined to be at least 95% (molar basis). The solvent of fructose is water. The filtration of the humins is 100%. One catalyst is considered which is hydrogen chloride.

Step 1.4: Waste, efficiency, energy consumption, simplification.

Step 1.5: The maturity of the process is defined to be “medium”.

Step 1.6: Translate $\underline{\vartheta}$ and $\underline{PM}$ into logical (Eq.2.2), structural (Eq.2.3), operational constraints (Eq.2.5) and/or performance criteria $\underline{\Psi}$ (Eq.2.6):

Step 1.6.1: All rules have been applied to gather a set of logical constraints (Eq.2.2). The detailed results are listed in Table 5.33.

Step 1.6.2: Four PI metrics have been translated to six structural constraints (see Table 5.12).

Step 1.6.3: The result of the translation into operational constraints (Eq.2.5) and the PI screening criterion (Eq.2.6) is given in Table 5.33. The yield for screening in step 5 is defined as

$$\varepsilon = \frac{n_{HMF}}{n_{Fructose,reactor,in}} \cdot 100\% \tag{5.39}$$

Step 1.7: A base case design exists, step A2 is entered (rule 1.9).

Table 5.33. Problem definition of the case study.

F_{obj}	Operational costs per product
Design scenario	Redesign of the whole process to produce HMF from fructose. No co-products are considered.
Process scenario	Continuous process
Logical constraints	L1: Reaction 1 necessary (Rule 1.1)
	L2: Reaction 1 has to be in the first unit (Rule 1.2)
	L3: Product is component D which must be linked to a purification unit (Rule 1.4).
Structural constraints by PI metric	Waste: Do not use two different solvents in one process. Recycle whenever possible
	Efficiency: Add units at the place in the flowsheet in which it has the highest efficiency. Recycle whenever possible.
	Energy: Do not connect units with alternating heat addition and heat removal. Use only the most energy efficient equipment when the principle behind the separation is the same, mass output is the same and capital costs are not considered.
	Simplification: Do not use repetitive units. Do easy separations first. Do not use pre-reactors. Do not use two different solvents in one process.
Operational constraints (Rule 1.6)	Product purity > 95% (molar basis)
	Raw materials are pure
	Water is used as solvent
PI screening criterion for step C2.	Application of process technology of “medium” maturity
PI screening criterion for step U5	Yield and selectivity of the reaction

5.3.4. Step A2: Analyze the process

Step A2.1: Collect mass and energy data for the base case design:

Step A2.1.1: Mass and energy data is necessary (Rule A2.1).

Step A2.1.2: The mass and energy data of the base case design have been retrieved from Rapp et al. (1987) and are presented in the appendix A.8.1.

Step A2.2: Transform the flowsheet into task-based and phenomena-based flowsheet.

Step A2.2.1: Six tasks are identified which are the dehydrogenation reaction (rule A2.2) and five separations (rule A2.4). The neutralization reaction is identified as a separation of by-products (rule A2.3).

Step A2.2.2: The separations are identified to separate acids from the solution, to remove salts from the solution, humins from the solution, to separate fructose from HMF and to separate water from HMF (rule A2.9).

Step A2.2.3: The following phenomena for each of the unit operations are retrieved from the PI knowledge-base (see Table 5.34).

Table 5.34. Link between unit operations and phenomena.

Unit operation	Important Phenomena
1-phase-Reactor	Mixing, heating/cooling, reaction
Separators	Mixing, heating/cooling, phase transition, phase separation
- Filtration	Mixing, heating/cooling, phase-transition G-L, phase separation
- Chromatography	Mixing
- Crystallization	Mixing, heating/cooling, phase-transition S-L, phase transition S-S, phase transition V-L, phase separation

Step A2.3: Identify limitations/bottlenecks *LB* of the base-case.

Step A2.3.1: Collect the limitations of the process by applying the algorithm **KBS**.

Step A2.3.1.1: The list of keywords *K* has been prepared: *K* ={“Production of HMF”, “dehydrogenation of fructose to HMF”, “separation of fructose from water”, “separation of acids”, “separation of salts”“separation of humins”, “separation of HMF from water”, “water”, “fructose”, “HMF”, “Levulinic acid”, “formic acid”}.

Step A2.3.1.2: The algorithm **KBS** is used to identify if limitations have been reported in the knowledge base. The following limitations are retrieved:

- LB_1: Occurring side reactions (see base case design)
- LB_2: Low selectivity and low conversion (Román-Leshkov *et al.*, 2006)

Step A2.3.2: Apply the algorithm **MBS** for a model-based search of limitations in the base-case design

Enter sub-algorithm MBS:

MBS.1: The objective function (Eq.5.37) has been calculated using the prices for utilities and raw materials given in Table 5.35 as well as the energy consumption and the waste generation.

For the calculation of the theoretical work for pumping equations 5.15-5.16 are used.

Table 5.35. Cost indicators for utilities from Turton *et al.* (2009) and prices for the raw materials from ICIS, 2009 ("*":Sino Chemical Industry Co Ltd, 2010; "**" estimated price from price for acetic acid to be 0.7 US-$/kg (ICIS, 2009)).

Utility	c_i (US-$/kg)	Raw material	c_i (US-$/kg)
Heating(HP)($/GJ)	14.05	Fructose*	0.5
Cooling($/GJ)	0.40	Water	0.0006
Electricity($/kWh)	0.06	HCL, Ca(OH)2	0.1
		Levulinic acid, oxalic acid**	1.0
		Formic acid**	0.5

The results of the calculations are presented in Table 5.36. The total operational costs per kilogram product are around 7.84 US-$. Additionally, the efficiency of the reaction (see Table 3.2) is calculated to be only 42%.

Note: The catalyst costs are not playing a big role (0.7% of the operational costs). Therefore, a recycle of catalyst is not necessary.

Table 5.36. Results of the calculation of the operating costs, the energy consumption and the waste generation in the base case design.

Task	Purpose/ source	Energy [MJ/kg HMF]	Waste [kg/ kg HMF]	Costs [US-$/kg HMF]	Cost distribution [%]
Dehydrogenation reaction	Energy – Preheating	42.6	-	0.60	7.63
	Energy – Pumping	5.7	-	0.34	4.33
	Energy – Reaction	7.6	-	0.11	1.36
	Raw material – Feed	-	-	2.74	34.98
	Catalyst - Feed			0.06	0.7
separation humins	Humins	-	0.8	-	-
Separation acids (reaction)	Raw material – Ca(OH)2			0.01	0.06
separation salt/ fructose	Energy - Cooling	11.8		0.005	0.06
	Preheating solvent	28.1	-	0.39	5.03
	Solvent - Water	-		0.08	1.06
	fructose	-	51.8	-	-
separation HMF/water	Energy - Evaporation	250.0	-	3.51	44.79
	water	-	107.3	-	-
	Total	613.6		7.84	

MBS.2: Based on the results, the following items are added to the list of limitations/bottlenecks for further analysis:

- LB_3: Large waste generation in the separation of fructose
- LB_4: High costs for raw materials

- LB_5: High costs and high energy consumption for the separation HMF/water
- LB_6: High costs and high energy consumption for the preheating of the solvent in the separation of fructose
- LB_7: Large amount of waste in the separation of HMF/water

MBS.3: No operational constraints are violated.

MBS.4: The tool SustainPro is used for additional identification of limitations/bottlenecks. The most negative indicators are presented in Table 5.37. Based on these indicators, no additional limitations/bottlenecks are detected. Exit sub-algorithm.

Table 5.37. Results of the Material Value Added (MVA) and Energy and Waste Costs (EWC) analysis.

Indicator MVA	Component	Open path
-1.86	Fructose	Fructose enters reactor and leaves chromatography
-0.23	Water	Water enters chromatography and leaves chromatography
-0.10	Water	Water enters chromatography and leaves crystallizer
Indicator EWC	**Component**	**Path**
0.34	Water	Water entering the reaction and leaves chromatography
0.22	Water	Water enters chromatography and leaves crystallizer

Exit sub-algorithm MBS.

Step A2.3.3: This step is not necessary because LB<15 (rule A2.11).

Step A2.4-A2.5: Both steps are applied. A list of pure component properties for the system is given in table 5.38. These have been collected from the databases of ICAS and Pro\II as well as predicted using the tool ProPred (see section 4.7).

Table 5.38. List of the pure component properties of the key components for the system HMF (The data with a star are predicted using the Marrero-Gani-approach (Marrero & Gani, 1997).

Component	MW [g/mol]	T_M [K] at P=1atm	T_B [K] at P=1atm	Dipole moment ω [Debye]	Radius of gyration R_g [Å]	Molar volume [m3/kmol]	Solubility parameter δ_{SP} [MPa^0.5]	HoV at T_B [kJ/mol]
HMF*	126.1	300.6	498.5				19.9	66.7
Levulinic acid	116.1	308.2	530.0	3.15	3.68	0.103	13.2	
Formic acid	46.0	281.7	373.7	1.42	1.85	0.038	10.5	41.21
Water	18.0	273.2	373.2	1.85	0.62	0.018	47.8	40.62
Fructose*	180.1	393.2	713.2	0.19		0.115	65.6	117.4
Humin		Very high						
Hydrogen chloride	36.5	158.9	188.2	1.08	0.21	0.03	22.0	16.18
Oxalic acid	90	462.6	569	2.62	3.22	0.06	36.9	

The results of the source analysis of the obtained limitations/ bottlenecks *LB* and their corresponding tasks are given in the table 5.39.

Table 5.39. Overview of the identified limitations/bottlenecks and their source analysis.

LB	Responsible phenomenon	How (Step)
LB_1: Occurring side reactions (see base case design)	Reaction	Step A2.4.3: AR (criteria 5, Table 3.3)
LB_2: Low selectivity and low conversion (Román-Leshkov, Chheda & Dumesic, 2006)	Linked to LB_1	Step A2.4.3: AR (criteria 5, Table 3.3)
LB_3: Large waste generation in the separation of fructose	Chromatography is a water-intensive separation (Rapp, 1987). No responsible phenomena found.	Step A2.4.4
LB_4: High costs for raw materials	Linked to LB_1 and LB_2	
LB_5: High costs and high energy consumption for the separation HMF/water	Phase transition by relative volatility and Linked to chromatography (see LB_3)	Step A2.4.1: APCP.4: r(T_B) large (Rule APCP.1) Why is water in the system (rule A2.13)
LB_6: High costs and high energy consumption for the preheating of the solvent in the separation of fructose	Linked to chromatography (see LB_3)	Why is water in the system (rule A2.13)
LB_7: Large amount of waste in the separation of HMF/water	Linked to chromatography (see LB_3)	Why is water in the system (rule A2.13)

Step A2.6: Step U2 is entered (rule workflow).

5.3.5. Step U2: Collect PI technology from Knowledge-Base

Step U2.1: Collect potential PI equipment:

Step U2.1.1: The list of keywords $\underline{K}_{PI}$ for PI equipment search includes all identified limitations/bottlenecks and the corresponding phenomena (see Table 5.39 and Table 5.34).

Step U2.1.2: The algorithm **KBS** is applied to search and retrieve potential equipment from the knowledge base into a list Ω. The results for each task under investigation are shown in the table 5.41.

Step U2.2: Pre-screen candidate PI equipment for feasibility:

Step U2.2.1-U2.2.4: The sub-steps are performed. The result of the screening is shown in table 5.40.

Note: For example, the reactive crystallization for separation of HMF from the reaction medium is removed by the not matching operating window (OPW) due to the necessary evaporation of the solvents (water) which would lead to dry out/precipitation of the substrate (see T_B in table 5.38). Because, humins are formed which will precipitate out, all units which cannot handle solids in their system are removed (membrane reactor, static mixer reactor, reactive adsorption, etc). Examples for not matching phases are unit operations considering a reaction in the vapor phase (reactive condensation) which is not the case here. Membrane distillation has been removed for the separation of fructose and water because the medium is too viscous while it also has been removed for the separation of solvent and HMF because of the low maturity.

Table 5.40. Pre-Screening of PI equipment by pure component properties.

System	Boiling point compared to HMF	Reactive Distillation with/without Pervaporation	All Reactor	Reactive extraction/ settler
Solvent	$T_{B,low}$	not feasible	feasible	feasible
	$T_{B,high}$	feasible	feasible	feasible
Catalyst	$T_{B,low}$	not feasible	feasible	feasible
	$T_{B,high}$	feasible	feasible	feasible
	Heterog.	feasible	feasible	feasible

The solvent in the working solution is water which is low boiling compared to HMF. Therefore, reactive distillation systems are removed from the search space (see Table 5.41).

Step U2.3: Identify sub-problems:

Step U2.3.1: No sub-problems (SP=1) are identified (rule U2.4).

Step U2.3.2: All candidate PI equipment (see table 5.41) is put into the list Ω.

Step U2.3.3: Enter the inner algorithm for the sub-problem SP=1 (step U3).

Table 5.41. Results of the pre-screening by feasibility and maturity in step U2.2. In Parenthesis is the reason for the removal.

Task	Retrieved potential PI equipments Ω	Conventional units
Dehydrogenation Reaction	Remaining options: 3 ~~Reactive distillation~~(OPW), reactive extraction, ~~reactive membrane~~ (OPW), ~~reactive pervaporation~~ (OPW), ~~reactive crystallization~~(OPW), ~~reaction adsorption~~ (OPW), ~~reaction condensation~~(Phases), ~~reaction-absorption~~(Phases), ~~reactive distillation with pervaporation~~(OPW), ~~oscillatory baffled reactor-crystallizer~~(OPW), ~~reactive chromatography~~ (too water demanding in the base case design), ~~1-pot synthesis~~(OPW); microchannel reactor-extractor; microchannel reactor; ~~microwave reactor~~ (maturity), ~~ultrasonic reactor~~ (maturity); ~~static mixer reactor~~(OPW), ~~foam reactor~~(OPW), ~~membrane reactor~~(OPW),	Remaining options: 1 Reactor
Filter humins		Remaining options: 1 Filter (precipitation)
Separation of acids/HMF		Remaining options: 1 Reactor
Separation salts/HMF		Remaining options: 1 Filter (precipitation)
Separation of fructose (to recycle)/HMF&H2O	Remaining options: 3 ~~extraction crystallization~~(Phases), extraction distillation; membrane extraction, heat-integrated distillation column; ~~HIGEE~~ (OPW), ~~spinning disc separator~~ (OPW); ~~membrane distillation~~ (OPW)	Remaining options: 2 Evaporation, distillation,
Separation (purification) of HMF/working solution (solvent)	Remaining options: 4 extraction crystallization, extraction distillation; membrane extraction, heat-integrated distillation column, ~~HIGEE~~ (OPW), ~~spinning disc separator~~ (OPW); ~~membrane distillation~~ (maturity)	Remaining options: 2 Evaporation, distillation,

5.3.6. Step U3: Select & develop models

Different depths of models describing the reaction and the separation equipment are required.
That are, simplified models to describe expected input and output of the reactors and the separators and more complex models to describe the performance of the units using kinetics and mass transfer coefficients. Simple models will be needed in step U5 while the more complex models are needed in the last sub-steps of step U5 and step 6.
All models have been developed using the developed algorithm (see section 3.1.6). However, only the results of this step are presented here.

- *Simple models:*

Simple models for the reactor are based on selectivity and conversion of the reactor (Table 5.42).
The selectivity towards the main product HMF is defined as (Eq.5.40).

$$S = \frac{n_{HMF}}{n_{Fructose,in} - n_{Fructose,out}} \cdot 100\% \tag{5.40}$$

The conversion is based on the substrate fructose (Eq.5.41):

$$\lambda = \frac{n_{Fructose,in} - n_{Fructose,out}}{n_{Fructose,in}} \cdot 100\% \tag{5.41}$$

Table 5.42. Simple models based on conversions and selectivities from the literature (1: Roman-Leshkov, Chheda, Dumesic, 2006; 2: Tuercke, Panic & Loebbecke, 2009; *: assumed to minimum as good as the reactor-extractor).

Reactor	Selectivity [%]	Conversion [%]
Reactor[1]	51	50
Microchannel reactor[2]	78	71
Reactor-extractor[1]	80	86
Microchannel reactor-extractor*	80	86

The necessary thermal energy for the distillations is approximated based on the heat of the vaporization. The heat of vaporization for each component in the system is given in Table 5.38. For the heat integrated distillation column, the thermal energy requirement is replaced by the mechanical energy necessary for the recompression of the vapor.

The separation of humins, acids and salts are assumed to be ideal, meaning that their separation efficiency from all other compounds is 1. The separation task of the precipitation of salt is not part of the investigation for PI here but the amount of base necessary for it will occur in the operational costs.

- *Complex models:*

For a more detailed evaluation in later steps (step 6), more detailed reactor models taking the kinetics into account are needed. For this, the simple conversion model is replaced by the reactor model given by Kuster and Temmink (1977). The initial parameters have been refitted to match reported values for all other reactor models. This was necessary because the reported model (Kuster & Temmink, 1977) does not distinguish between mass transfer rate and actual reaction rate which is important when comparing the performance of the microchannel reactor to a conventional reactor at the same conditions (see Table 5.32).

The stoichiometry of the reaction is given in section 5.3.1 (Eqs.5.33-5.36).

The reaction rate models are given by equations (5.42-5.46).

$$r1 = x_{cat} k1 \cdot n_F \tag{5.42}$$

$$r2 = x_{cat} k2 \cdot n_W \cdot n_{HMF} \tag{5.43}$$

$$r3 = x_W k3 \cdot n_{HMF} \tag{5.44}$$

$$r4 = x_W k4 \cdot n_{Fructose} \tag{5.45}$$

The kinetic expressions are given in equation (5.46). The kinetic constants ki_0 and activation energies *EAi* are given in Table 5.43:

$$ki = ki_0 \cdot \exp\left(-EAi / R / T\right) \tag{5.46}$$

Table 5.43. Reaction parameters.

	$k1_0$ 1/s	$k2_0$ 1/mol	$k3_0$ 1/s	$k4_0$ 1/s
Macro device	$9.0 \cdot 10^{19}$	$6.0 \cdot 10^{9}$	$3.05 \cdot 10^{11}$	$5.02 \cdot 10^{10}$
Micro device	$9.1 \cdot 10^{20}$	$3.0 \cdot 10^{9}$	$1.05 \cdot 10^{11}$	$1.35 \cdot 10^{10}$
	EA1 [J/mol]	*EA2* [J/mol]	*EA3* [J/mol]	*EA4* [J/mol]
	$160.6 \cdot 10^{3}$	$95.6 \cdot 10^{3}$	$114.8 \cdot 10^{3}$	$101.9 \cdot 10^{3}$

Besides the reaction, also the extraction needs to be modeled. The phase transition of HMF by extraction is modeled using equation 5.47.

$$n_{HMF,12} = k_L a \cdot n_{HMF,aq} \left(x_{HMF,aq} R - x_{HMF,org} \right) \tag{5.47}$$

It is assumed that through proper solvent selection, other components will not enter the solvent phase because of an existing difference in the solubility parameter between the compounds (Table 5.38).

The following parameters are needed to model the extraction units: the solvent dependent partition coefficient *R* (Eq.5.48); the equipment dependent contact area between the phases *a*; as well as the mass transfer coefficient K_L assumed to be independent of equipment and solvent (Eq.5.49).

The partition coefficient is:

$$R = x_{HMF,org} / x_{HMF,aq} \tag{5.48}$$

The mass transfer coefficient has been calculated using the kinetic and extraction model for the solvent 7:3 MIBK:2-butanol for the data given by Roman-Leshkov *et al.* (2006). The mass transfer coefficient is:

$$k_L = 4.85 \cdot 10^{-2} m/s \tag{5.49}$$

The value of k_La enhanced for different PI equipment is shown in Table 5.25. These factors have been used to distinguish between reactive-extraction in a column and in a micro device (enhancement factor E=18 for the micro device).

The partition coefficient is known for three different solvents (Roman-Leshkov & Dumesic, 2009). Based on these and the corresponding Hildebrandt's solubility parameters of the solvents and HMF, the behavior of unknown solvents with HMF is predicted. This is shown in the appendix A.8.3.

The loss of solvent to water is directly modeled using the predicted values for the water solubility for new solvent, retrieved from ProPred (see section 4).

5.3.7. Step U4: Generate feasible flowsheet options

U4.1: The superstructure containing a generic model has been retrieved from the model library (see Fig.4.2).

U4.2: This step is not needed, since the superstructure from S4.1 matches the maximum number of tasks, therefore step $U4^{SP=1}$.3 is directly entered (Rule U4.1).

U4.3: The number of options represented by this superstructure is calculated using (Eq.5.8).

The number of identified units is NIU=16. The number of processing steps is four, assuming that the removal of acids and humins is ideal and merged into one task. Therefore the total number of generated options assuming only one solvent/membrane is:

$$NPO = \sum_{ps=2}^{4} \left(\underbrace{NIU^{ps}}_{\text{options by units}} \cdot \underbrace{2\sum_{2}^{ps}(ps-1)!}_{\text{options by recycle}} \right) = 1.2 \cdot 10^{6} \tag{5.8}$$

U4.4: The generated process options are screened by applying logical constraints (see Table 5.44). The number of options is screened down by a factor of 10. In total NPO_L=1.1·10^5process options are remaining.

Table 5.44. Results of the stepwise screening through a set of logical constraints.

Logical constraint:	Number of redundant options	Number of options remaining
Generated options		1.2·10^6
Product formed	3.8·10^5	8.2·10^5
Reaction in the first step	5.2·10^5	3.0·10^5
Purification in the last step	1.9·10^5	1.1·10^5

U4.5: The generated process options NPO_L are further screened by applying structural constraints (see Table 5.33). In total NPO_S=12 process options are remaining. The details are given in Table 5.45. Note: The biggest reduction has been realized through fixing the recycle streams for each option by the first structural constraint (Table 5.45). Through this, for each option by equipment, only one option exists for the corresponding streams (see Eq.5.8).

Table 5.45. Results of the stepwise screening through a set of structural constraints.

PI Metric	Structural constraint:	Number of redundant options	Number of options remaining
NPO_L			1.1·10^5
Efficiency, waste	Recycle whenever possible	1.0·10^5	6.6·10^3
Simplification	Do not use pre-reactors	2.8·10^3	3.8·10^3
Simplification	Do not use repetitive units (2 units for the same task)	3.4·10^3	408
Simplification	Do the easy separation first	120	288
Waste, simplification	Do not use two different solvents	192	96
Energy	Use only the most energy efficient equipment when the principle behind the separation is the same, mass output is the same and capital costs are not considered.	84	12

The remaining options in the search space are shown in table 5.46.

Table 5.46. Process options (NPO_S) after structural constraints. Abbreviations: reactive extractor (RE), reactor (R), heat-integrated distillation column (HiDC),filter of acids and humins (Filter), Purification(Purif).

Unit 1	Unit 2	Unit 3	Unit 4	NPO_S
RE, Microchannel RE, Microchannel R, R	$HiDC_{Purif}$,			4
RE, Microchannel RE, Microchannel R, R	HiDC	$HiDC_{Purif}$,		4
RE, Microchannel RE, Microchannel R, R	Filter	HiDC,	$HiDC_{Purif}$,	4
			Total	12

U4.6: The search space is not empty (rule U4.2- U4.3). Step U5 is entered.

5.3.8. Step U5: Fast screening for process constraints

U5.1: The feasibility of the remaining process options is checked using the simple models (see step U3) to predict the outcomes for each process equipment in the system.

U5.1.1: The degrees of freedom of the simplified model is *DoF*=1.

U5.1.2: The initial concentrations are specified to be 50 w.% fructose in water.

U5.1.3-U5.1.4: The model has been solved for each process option in the search space. In total, 8 process options are removed because they do not have a feasible solution. For none of the reactors, a selectivity of 100% and a conversion of 100% is achieved which means that humin/acid separation are always necessary when fructose recycle is considered and *vice versa*. Hence, all options with 3 processing steps are removed (second row in Table 5.46).

U5.1.5: The search space is not empty. Step U5.2 is entered (rule U5.3).

U5.2: Identify the set of most promising options through performance screening NPO_P:

U5.2.1: For each of the remaining process options in NPO_O, the performance metrics yield and selectivity of the reaction are calculated.

U5.2.2: All process options are ranked according to their yield (Table 5.47). Based on the results only the best five options are kept in the search space (NPO_P=5). The flowsheet of these options together with the active streams for which the binary variables have been fixed to 1 (all others are zero) are shown in the appendix A.8.2.

Table 5.47. Process options (NPO_O) after performance screening using simple models. Abbreviations: reactive extractor (RE), reactor (R), heat-integrated distillation column (HiDC), Filter of acids and humins (Filter), Purification(Purif).; "*": kept in the search space.

Rank	Unit 1	Unit 2	Unit 3	Unit 4	Yield	Selectivity
#1	Microchannel RE	Filter	HiDC	$HiDC_{Purif}$	80.0*	80.0*
#1	RE	Filter	HiDC	$HiDC_{Purif}$	80.0*	80.0*
#3	Microchannel R	Filter	HiDC	$HiDC_{Purif}$	78.0*	78.0*
#4	Microchannel RE	$HiDC_{Purif}$			68.8*	80.0*
#4	RE	$HiDC_{Purif}$			68.8*	80.0*
#6	Microchannel R	$HiDC_{Purif}$			55.4	
#7	R	Filter	HiDC	$HiDC_{Purif}$	51.0	
#8	R	$HiDC_{Purif}$			25.5	

U5.2.3: The objective function is not selected for screening here (rule U5.4). Step U5.4 is entered.

U5.4: The number of remaining process options is below 10 and it is decided (user input) to check the remaining options with the complex models (rule U5.5).Step U5.1-U5.3 are repeated.

U5.1: The feasibility of the remaining process options is checked using the complex models (see step U3) to predict the outcomes for each process equipment in the system.

U5.1.1: The degree of freedom of the complex reaction model is *DoF*=3 and for the complex reactive extraction model is *DoF*=5. The initial concentrations of fructose and catalyst as well as the temperature need to be selected. Additionally, for reactive separations, solvents and the ratio V_{org}/V_{aq} need to be selected. The selection of the solvent through using the sub-algorithm **SoP**, steps SoP.4-SoP.7 is shown in appendix A.8.2. Three different solvents have been selected based on matching the Hildebrandt solubility parameter of HMF.

U5.1.2: The initial concentrations are specified to be 50 w.% fructose in water. The amount of catalyst is 0.1 mol/l. The temperature is selected to be 180°C. The ratio of V_{org}/V_{aq}=3 is specified. The solvents are THF, $C_7H_{11}BrCl_4$ and C_5H_9BrO.

U5.1.3-U5.1.4: The model has been solved for each process option in the search space.

A conversion of fructose of 100% is achieved. That means that options including a recycle of fructose are not necessary (Table 5.48) and removed. In total 3 process options are remaining (for which three different solvents can be used) .

U5.1.5: The search space is not empty. Step U5.2 is entered (rule U5.3).

U5.2: Identify the set of most promising options through performance screening NPO_P:

U5.2.1: For each of the remaining process options in NPO_O, the performance metric yield and selectivity of the reaction are calculated by complex models.

U5.2.2: Based on the results (Table 5.48) only one process option is kept in the search space (NPO_P=1) which is a microchannel reactor-extractor and a heat-integrated distillation column for the purification. The flowsheet of this option, together with the active streams for which the binary variables have been fixed to 1 (all others are zero), is presented in Figure 5.14. However, the process can be run with three different solvents.

Table 5.48. Process options (NPO_O) after performance screening using complex models. Abbreviations: reactive extractor (RE), reactor (R), heat-integrated distillation column (HiDC), Filter of acids and humins (Filter), Purification(Purif).; "*": kept in the search space

Rank	Unit 1	Unit 2	Unit 3	Unit 4	Solvent	Yield	g_{OP}	Selectivity
	Microchannel RE	Filter	HiDC	$HiDC_{Purif}$	THF	100	No	
					$C_7H_{11}BrCl_4$	100	No	
					C_5H_9BrO	100	No	
	RE	Filter	HiDC	$HiDC_{Purif}$	THF	100	No	
					$C_7H_{11}BrCl_4$	100	No	
					C_5H_9BrO	100	No	
3	Microchannel R	Filter	HiDC	$HiDC_{Purif}$		78	Yes	78,00
1b	Microchannel RE	$HiDC_{Purif}$	-	-	THF	100	Yes	83,03*
1a					$C_7H_{11}BrCl_4$	100	Yes	85,56*
1a					C_5H_9BrO	100	Yes	85,56*
2b	RE	$HiDC_{Purif}$	-	-	THF	100	Yes	82,67
2a					$C_7H_{11}BrCl_4$	100	Yes	83,03
2a					C_5H_9BrO	100	Yes	83,03

U5.2.3: The objective function is not selected for screening here (rule U5.4). Step U5.4 is entered.

U5.4: Only one main problem exists (no-side problem). Step 6 is entered (Rule U5.6).

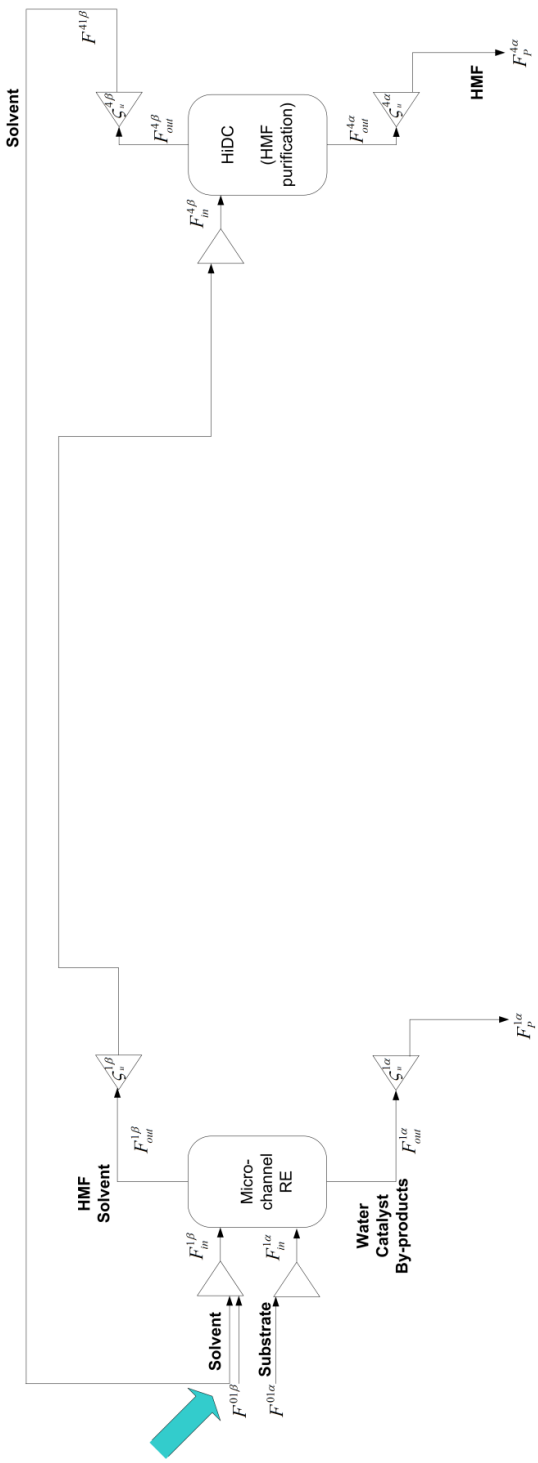


Figure 5.14. The remaining process option from the superstructure for the integration of up to four units with a maximum of two inlet/outlet streams each. (Symbols: streams *F*, splitting factors *ς*; Binary variables *Y* are not shown). The large arrow shows where the different solvents are considered through the superstructure.

5.3.9. Step 6: Solve the reduced optimization problem and validate promising

Step 6.1: Identify the set of most promising process options by solving an MINLP problem

Step 6.1.1: this step is not necessary because only 1 option is remaining in the search space (<15; rule 6.1). Step 6.2 is entered.

Step 6.2: For each process option, solve separately the reduced optimization problem. For this the selection of the best solvent is necessary (rule 6.2). The results are presented in Table 5.49.

Step 6.3: The last optimization of the remaining process option is solved three times for different solvents and subsequently ranked by their objective function (Table 5.49). The optimization variables are the solvent as well as the ratio of V_{org}/V_{aq} bounded between 1 and 5. The amount of catalyst is specified to be 0.1 mol/kg HMF in the aqueous phase.

Note: Using the ratio of solvent to water phase, the relation of phase transition and the reaction is influenced meaning that the selectivity and conversion can be optimized.

Table 5.49. Ranking of the remaining process options by their objective function ($T_{reaction}$=180°C; ncat=0.1 mol/kg HMF; 50 w.% fructose in the inlet; $T_{Inlet\ streams}$=40°C).

Rank	Unit 1	Unit 4	Solvent	V_{org}/V_{aq}	Selectivity	F_{obj} [US-$/kg HMF]
#1	Microchannel RE	$HiDC_{Purif}$	$C_7H_{11}BrCl_4$	5	97.47	1.21
#2	Microchannel RE	$HiDC_{Purif}$	THF	5	95.67	1.47
#3	Microchannel RE	$HiDC_{Purif}$	C_5H_9BrO	5	97.47	1.49
Base case design						7.84

The best option is the option of a microchannel reactive extractor with a purification of the HMF as the light boiling component in a Heat-integrated distillation column. The operational costs can be reduced by a factor of 6.5. The main contributor to the cost is still the substrate fructose followed by the costs for the running the reaction at a temperature of 180°C (see Figure 5.15).

Note: The main advantage of this option compared to the other two is that the solvent is the high boiling component compared to HMF and the components with the smaller flowrate (HMF) is evaporized.

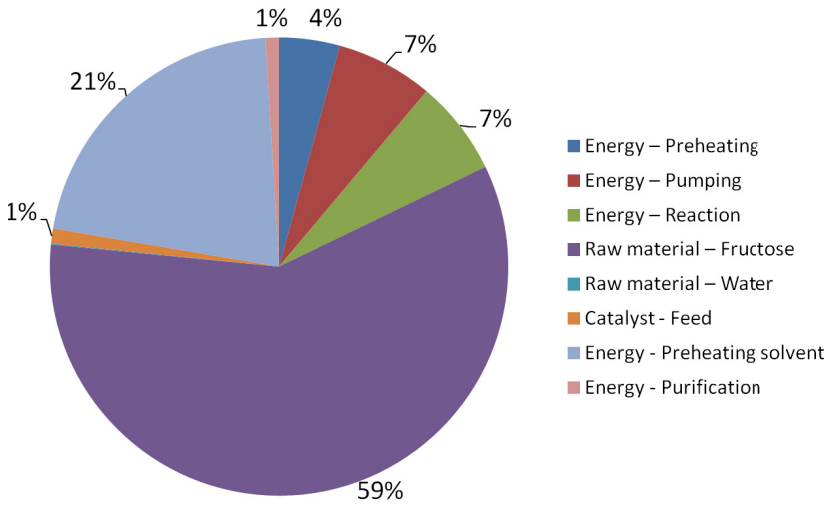


Figure 5.15. Distribution of the costs of the best option.

Step 6.4: The most detailed models have been used for obtaining the results in step 6.3. No additional validation has been made.

Chapter 6.

Case studies – Application of the phenomena based methodology

The application of the methodology using the phenomena based workflow is highlighted through three case studies: The first case study is the production of isopropyl-acetate from isopropanol and water. The second case study is the separation of a bulk chemical hydrogen-peroxide from water which takes place in the last step of the hydrogen-peroxide process via the anthraquinone route (see section 5.2). The third case study highlights the application of the phenomena based methodology for the production of cyclohexyl-acetate from cyclohexene and confirms that the existing PI solutions for this process can be systematically generated and are part of the generated search space here.

6.1. Production of isopropyl-acetate

The application of the methodology is highlighted through the production of isopropyl acetate (IPAc) which is shown in detail in sections 6.1.2.-6.1.7. Additional information is given in appendix A.9.
This case study has been selected for two reasons. First of all, isopropyl-acetate is an important bulk chemical product used widely as organic solvent and process improvement with respect to operational costs by PI is of high interest (Lai *et al.*, 2007). Secondly, PI for esterification reactions (and especially esterification of alcohol with acetic acid) have been widely studied before, mostly considering reactive distillation (Lutze *et al.*, 2010b). Comparisons to other PI equipment have not been found. Since reactive distillation has been widely considered to intensify the process (e.g. Tang *et al.*, 2005; Lai *et al.*, 2007), their design is checked against the performance of the outcome of the phenomena-based methodology at the end of this section (section 6.1.8). In this case study, only the reaction task is targeted by PI.

6.1.1. Base-Case Design

Isopropyl-acetate can be produced by a reaction of acetic acid (HOAc) and isopropanol (IPOH) to form isopropyl-acetate and as side-product water (H_2O). The stoichimetry of the reaction is given in equation (6.1) and takes place in the liquid phase. The reaction is catalyzed by a heterogeneous catalyst which is Amberlyst 15 (Tang *et al.*, 2005).

$$CH_3COOH + C_3H_7OH \leftrightarrow C_5H_{10}O_2 + H_2O\,. \tag{6.1}$$

The base-case design is a simple CSTR for a production of 50000 t/y of IPAc. The CSTR is assumed to run under isothermal conditions of T=330 K at P=1 bar. The feed is an equimolar mixture of HOAc and IPOH. The reaction is not complete. The inlet and outlet flows of the reactor are given in Table 6.1. The reaction is exothermic. Hence, the heat of reaction has to be removed which is in total 16.7 MJ/min (Table 6.1).

Table 6.1. Base-Case-Design of the reactor to produce isopropyl-acetate.

Process Variables	Inlet	Outlet
T [K]	330	330
Molar flows [mol/min]:		
IPOH	1430	499
HOAc	1430	499
IPAc	-	931
H2O	-	931
Q [MJ/min]	-1000	

6.1.2. Step 1: Define problem

Step 1.1: The objective is to identify one intensified apparatus for the reaction (with or without built-in-separation) which achieves a yield of 0.99 and with the lowest operational costs at lowest capital costs. The operational costs are represented by the yield, thermal energy and additional utility costs (membrane, solvents). The capital costs are represented by the volume to be constructed.

Note: The product purity is not defined since only the reaction task is under investigation.

Step 1.2: The design scenario is the development of a new reactor. The process scenario is continuous.

Step 1.3: The process and product specifications are defined.

- Raw materials (IPOH, HOAc) are pure.
- Production capacity is 50000 t IPAc/year.

Step 1.4: The following performance metrics *PM* are selected.

- Energy consumption per product formed
- Efficiency
- Simplification
- Volume
- Waste

Step 1.5: The maturity is selected to generate *novel* designs.

Step 1.6: All input ($\underline{\vartheta}$ and $\underline{PM}$) are translated into logical, structural, operational constraints and performance criteria $\underline{\Psi}$. The results are presented in Table 6.2.

Step 1.7: A base-case design is present, step A2 is entered (Rule 1.9).

Table 6.2. Problem definition of the case study: IPAc.

F_{obj}	Yield, volume and pieces of equipment
Design scenario	Design of PI equipment for the reaction task
Process scenario	Continuous
Logical constraints	L1: Reaction 1 necessary (Rule 1.1)
	L2: Reaction 1 has to be in the first stage (Rule 1.2)
Structural constraints by PI metric	Efficiency: S1: Do not integrate units which inhibit each others performance. S2: Add phenomena and stages to the position in the flowsheet in which they have the highest efficiency. S3: Always end the flowsheet with the phenomena giving the highest yield last.
	Energy: S4: Do not provide energy to streams without purpose S5: Do not connect units with alternating heat addition and heat removal.
	Simplification: S6: Do not use repetitive (sequential) units. S7: Do not use pre-reactors. S8: Do not use recycle streams if not necessary (when efficiency can be reached) S9: Remove options in which stages are redundant
Operational constraints (Rule 1.6)	Raw materials are pure
	Use raw materials according to the stoichiometry of the reaction(s) (Waste)
Operational constraints (Rule. 1.7)	Yield = 0.99 (phenomena level)
PI screening criterion for step C2.	Generate “novel” process options
PI screening criterion for step P5	Thermal energy consumption (phenomena level)

6.1.3. Step A2: Analyze the process

Step A2.1: Collect mass and energy data for the base-case design:

Step 2.1.1: Energy data is required (rule A2.1).

Step 2.1.2: Mass and energy data are collected (see table 6.1).

Step A2.2: Transform the flowsheet into a task-based and a phenomena-based flowsheet.

Step A2.2.1: Identify for each unit operation of the base-case design the task. Using rules A2.2-A2.8, a reaction task is identified (rule A2.2).

Step A2.2.2: Identify the split of each separation task. No separation is identified.

Step A2.2.3: The list of phenomena involved in the CSTR has been retrieved from the PI knowledge-base (see Table 3.1). The phenomena-based flowsheet is shown in the figure 6.1.

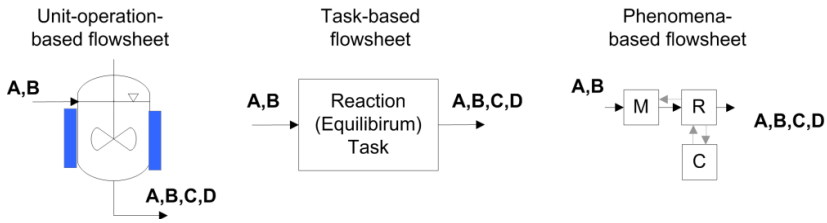


Figure 6.1. The base-case-design of a CSTR with a cooling jacket in the unit-operation-, task- and phenomena-based flowsheet (Phenomena: M: Ideal mixing (L-phase), R: pseudohomogenous reaction, C: Cooling; Components in bold: **A**: HOAc, **B**: IPOH, **C**: H_2O, **D**: IPAc).

Step A2.3: Identify limitations/bottlenecks *LB* of the base-case.

Step A2.3.1: Collect the limitations of the process by applying the algorithm **KBS**.

Step A2.3.1.1: The list of keywords *K* contains the following items: *K*={production of IPAc, esterification reaction, IPOH, HOAc, IPAc, H2O}.

Step A2.3.1.2: The algorithm **KBS** is applied for the knowledge-base search. The keyword "esterification reaction" has been found in the knowledge base. For this, the following information about limitations/bottlenecks is stored: unfavourable equilibrium in the reaction.

Step A2.3.2: The algorithm **MBS** is applied. It confirms that the LB is identified to be in the reaction.

Step A2.3.3: The number of limitations/bottlenecks (LB=1) is below 15, no reduction is required (rule A2.11).

Step A2.4: Analyze the obtained limitations/ bottlenecks *LB* and their corresponding tasks in the base-case design.

Step A2.4.1: The algorithm **APCP** is applied. The pure component properties are retrieved from the ICAS database. The analyzed pure component properties are shown in the table 6.3.

Table 6.3. List of pure component properties of the system at P=1 atm ("*":Missing data predicted through the Marrero-Gani-Approach (Marrero & Gani, 2001) in the tool ProPred in step APCP.1.2).

Component	T_B [K]	T_M [K]	Log (Ws) log(mg/L)	Log(Kow)	Radius of gyration R_g [Å]	Molar volume V_M [m³/kmol]	Van der Waals volume VdW [m³/kmol]	Solubility Parameter δ_{SP} [MPa^0.5]
HOAc	391.05	289.91	5.25*	-0.15*	2.61	0.1797	0.0333	19.0
IPOH	355.41	185.28	5.24*	0.53*	2.807	0.22	0.04216	23.4
IPAc	361.65	199.75	4.17*	1.32*	3.679	0.336	0.06299	17.2
H2O	373.15	273.15		-1.38	0.615	0.0559	0.01237	47.8

The binary ratio of the occurring components for each property is calculated (Table 6.4). The binary ratio's of the properties related to solubility (Log (Ws), Log(Kow)) hint that a potential phase split may occur between water and isopropyl-acetate, water and acetic-acid as well as between the two reactants. This has to be checked in more detail in Step A2.4.2 (rule APCP.2).

Table 6.4. List of the binary ratio of some pure components properties.

Binary mixture	T_B	T_M	R_g	V_M	Log (Ws)	Log(Kow)	δ_{SP}
W/HOAc	1.05	1.06	4.24	3.21	1.14	9.20	2.52
W/IPOH	1.05	1.47	4.56	3.94	1.15	2.49	0.73
W/IPAc	1.03	1.37	5.98	6.01	1.44	-1.05	2.79
HOAc/IPOH	1.10	1.56	1.08	1.22	1.00	-3.53	1.23
HOAc/IPAc	1.08	1.45	1.41	1.87	0.79	-0.11	1.11
IPOH/IPAc	1.02	1.08	1.31	1.53	0.80	0.40	1.36

Step A2.4.2: The algorithm **AMP** is applied to check for azeotropes as well as miscibility gaps between the components. Several low boiling azeotropes of ternary mixtures and binary pairs are formed. The molar compositions of the azeotropes and their boiling point at 1 atm are given in table 6.5.

Table 6.5. List of the identified azeotropes in the mixture at p=1 atm (Min.BP=Low boiling azeotrope). Compositions are given in mol.

Ternary/ Binary pair	T_B [K]	x_1	x_2	x_3	
IPOH/IPAc/W	347.37	0.2377	0.4092	0.3531	Min. BP
IPAc/W	349.72	0.5981	0.4019		Min. BP
IPOH/IPAc	351.69	0.5984	0.4016		Min. BP
IPOH/W	355.65	0.6875	0.3125		Min. BP
W/HOAc	371.97	0.8384	0.1616		Min. BP

Furthermore, a miscibility gap exists between water and the isopropyl acetate which has been computed using the NRTL model with parameters given by Lai *et al.* (2007). In a ternary mixture with isopropanol or acetic acid, the concentration of the third component has to be at least 0.38 mol/mol or 0.27 mol/mol respectively to potentially enter the 2-phase area (see figure 6.2). However, the water phase is always close to be pure in water. Hence, the effect on the reaction is not negative and is therefore not identified as a limitation.

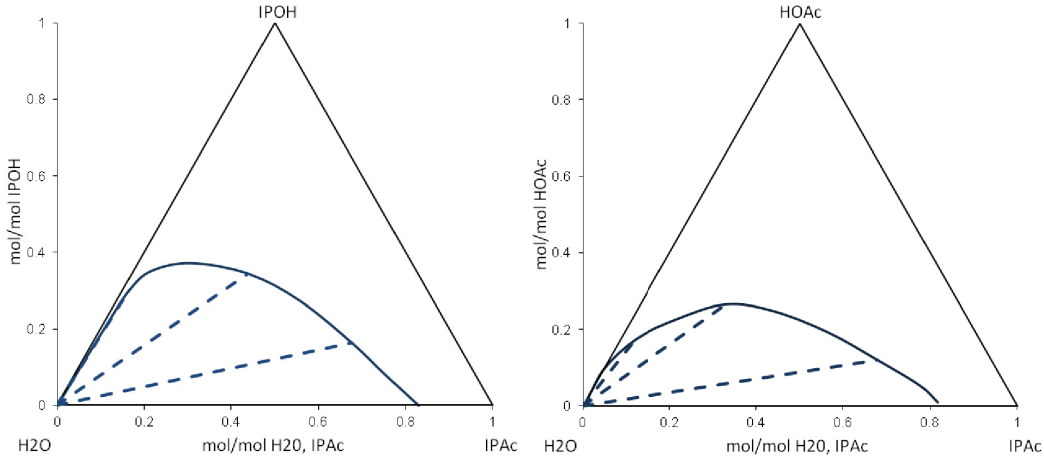


Figure 6.2. Ternary LLE diagrams of this system at P 1bar. (NRTL model with parameters from Lai et al., 2007).

Step A2.4.3: The reaction is analyzed using **AR**. The reaction model has been retrieved from Sanz and Gmehling (2006a,b) and is given in the appendix A.9. The reaction is slightly exothermic and only limited by the reaction phenomenon.

Step A2.4.4: The operating window of the reaction task is identified by using the sub-algorithm **OPW**. It is limited by the operating window of two phenomena: the reaction and the liquid phase mixing. The results are shown in the table 6.6.

Table 6.6. Operating window for the temperature of both phenomena responsible for the operating boundary of the 1-phase CSTR.

Phenomenon	Operating Window
Reaction (R)	T_{low}=185.3 K (Lowest Melting point) T_{high}=403 K (Catalyst degradation; Dow, 2011) Concentrations below dew point line.
Liquid mixing (M_{ld})	T_{low}=185.3 K (Lowest Melting point) T_{high}=391.2 K (Highest Boiling Point: Acetic Acid) Concentrations below dew point line.

Step A2.5: This step (linking of limitation to a source outside of the task) is not necessary because only one task is under investigation and the raw materials are pure.

Step A2.6: The phenomena-based workflow is selected because the maturity is selected to be novel (rule Workflow). Step P3 is entered.

6.1.4. Step P3: Identification of desirable phenomena

P3.1: Collect PI possibilities (see definition of PI):

P3.1.1: The list of keywords $\underline{K}_{PI}$ for identification of PI possibilities includes: Unfavorable equilibrium in the reaction.

P3.1.2: The algorithm **KBS** is applied. No potential for target enhancement has been identified through the knowledge base.

P3.1.3: The algorithm **KBS** is applied to identify additional tasks for enhancement of the necessary one. To overcome the limitation on the necessary task integration of reaction with a second reaction and/or a separation task is identified (see Table 6.7 and Figure 6.3).

Table 6.7. Decision Table regarding PI solutions to reported limitations in the process *(*A "○" in the second section means that this particular intensified option is reported to overcome this limitation, "●" means the activation of an option through a knowledge search*)*

Limitation in a phenomenon	Necessary task: Desirable task:	***Reactive Separation***	Reaction heat supply	Reaction mixing	***Reaction Reaction***
Separation is not sufficient					
limiting equilibrium		○			
azeotrope		○			
high energy demand					
limited mass transfer					
limited heat transfer					
driving forces too low		○			
Reaction is not sufficient					
contact problems of educts; limited mass transfer				○	
product reacts further/is intermediate		○			
activation problems			○	○	
degradation by T		○	○		
degradation by pH					
difficulties to control conditions, reaction too exotherm/endotherm		○	○	○	○
limiting equilibrium		●			●

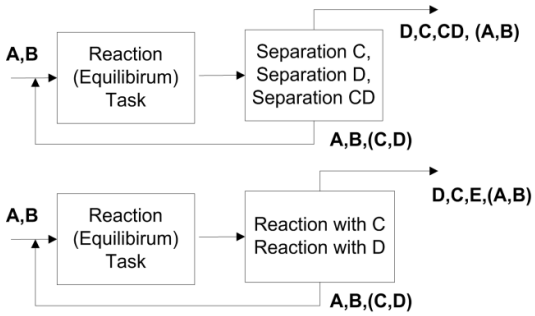


Figure 6.3. Identified tasks to overcome the limitation in the reaction.

P3.2: The algorithm **APCP** is used to identify potential phenomena blocks for each identified additional desirable task. The result is presented in table 6.8. The corresponding pure component properties are shown in Table 6.4.

P3.3: Using the algorithm **AMP**, a list of azeotropes has been found limiting the operating window of the phase transition phenomenon by relative volatility (see Table 6.5. in step A2.4.2).

P3.4: Use algorithm **AR** to identify potential reaction phenomena blocks for each task from the analysis of pure component properties.

P3.4.1: An additional reaction task is identified, step P3.4.2 is entered (rule P3.1).

P3.4.2: No reactions have been found in the literature/database.

P3.4.3: No additional reaction phenomenon is created (rule P3.2). Hence, P3.5 is entered.

P3.5: Select potential best phenomena for each identified additional desirable task: The result of the screening using the algorithm **SoP** is shown in the table 6.9. In total, two phenomena (highlighted in bold) are kept in the search space.

Table 6.8. Table Identified phenomena for each desirable task using the algorithm **APCP** and **AMP** (A: Acetic-Acid, B: Isopropanol, C: Water, D: Isopropyl-acetate) with pure component properties (T_M: Melting point; T_B: Boiling point; P_{LV}: Vapor pressure; R_g: Radius of gyration; V_M: Molar volume; Log(K_{ow}): Octanol/Water partition coefficient; VdW: Van der Waals volume; $\boldsymbol{\delta_{SP}}$: Solubility Parameter)

Task	Identified phenomena	How determined?	Note
Separation C/ABD	Phase transition by:		
	Solid-Liquid contact (crystallization)	T_M,	HOAc concentration low
	Gas-liquid contact (stripping)	T_B	Solvent necessary
	Liquid-liquid contact (extraction)	Log(K_{ow})	Solvent necessary
	Liquid-liquid settling	Immiscibility region	
	Pervaporation	R_g, V_M, VdW, $\boldsymbol{\delta_{SP}}$	Membrane necessary
	Liquid membrane	R_g, V_M, VdW	Membrane necessary
	Centrifugation	MW, Immiscibility region	
	Vapor-liquid by relative volatility	T_B, P_{LV}	HOAc concentration low
Separation D/ABC	Phase transition by:		
	Solid-Liquid contact (crystallization)	T_M,	IPOH concentration low
	Gas-liquid contact (stripping)	T_B	Solvent necessary
	Liquid-liquid contact (extraction)	Log(K_{ow})	Solvent necessary
	Liquid-liquid settling	Immiscibility region	
	Pervaporation	R_g, V_M, VdW, $\boldsymbol{\delta_{SP}}$	Membrane necessary
	Liquid membrane	R_g, V_M, VdW	Membrane necessary
	Vapor-liquid by relative volatility	T_B, P_{LV}	IPOH oncentration small
Separation CD/AB	Phase transition by:		
	Solid-Liquid contact (crystallization)	T_M,	IPOH or HOAc concentration low
	Gas-liquid contact (stripping)	T_B	Solvent necessary
	Liquid-liquid contact (extraction)	Log(K_{ow})	Solvent necessary
	Liquid-liquid settling	Immiscibility region	
	Vapor-liquid by relative volatility	T_B, P_{LV}	IPOH or HOAc concentration low
Reaction with C	Reaction phenomenon		Reaction

Table 6.9. Result of the screening of phenomena for each desirable task using the algorithm **SoP** (A: Acetic-Acid, B: Isopropanol, C: Water, D: Isopropyl-acetate). The remaining phenomena and tasks which are kept in the search space are written in bold.

Task	Identified phenomena	Screened Out
Separation C/ABD	Phase transition by:	
	Solid-Liquid contact (crystallization)	Not matching OPW with necessary task (Rule SoP.2)
	Gas-liquid contact (stripping)	Evaporation of reactants is not desirable (Rule SoP.3)
	Liquid-liquid contact (extraction)	Solvent need recycle, additional task (C/solvent) necessary (Rule SoP.3-4)
	Liquid-liquid split	Immiscibility region is not matching specifications (Rule SoP.1)
	Pervaporation	
	Liquid membrane	Suitable membrane not in database (Rule SoP.5)
	Centrifugation	Immiscibility region is between products (Rule SoP.1)
	Vapor-liquid by relative volatility	c_A not low, additional task (C/A) necessary (Rule SoP.3-4)
Separation D/ABC	Phase transition by:	
	Solid-Liquid contact (crystallization)	Not matching OPW with necessary task (Rule SoP.2)
	Gas-liquid contact (stripping)	Evaporation of reactants is not desirable (Rule SP.3)
	Liquid-liquid contact (extraction)	Solvent need recycle, additional task (D/solvent) necessary (Rule SoP.3-4)
	Liquid-liquid split	Immiscibility region is not matching specifications (Rule SoP.1)
	Pervaporation	Suitable membrane not in database (Rule SoP.5)
	Liquid membrane	Suitable membrane not in database (Rule SoP.5)
	Vapor-liquid by relative volatility	Only possible when C and B not in the system or c_A low which is all not the case (Rule SoP.7-8)
Separation CD/AB	Phase transition by:	
	Solid-Liquid contact (crystallization)	Not matching OPW with necessary task (Rule SoP.2)
	Gas-liquid contact (stripping)	Evaporation of reactants is not desirable (Rule SoP.3)
	Liquid-liquid contact (extraction)	Solvent need recycle, additional task (CD/solvent) necessary (Rule SoP.3-4)
	Liquid-liquid split	Immiscibility region is between products (Rule SoP.1)
	Vapor-liquid by relative volatility	*Note:* Possible until the ternary azeotrope
Reaction with C	Reaction phenomenon	No additional reaction found

Note: The phase transition by pervaporation is described using an existing membrane. The pervaporation membrane (Celfa CMC-VS-11V) is described by the flux in [g m^{-2} h^{-1}] (Eq. 6.1, see appendix A.9.2 for the fit and the experimental data used) and a separation factor of water from other components in the system to be 99.5 (Eq. 6.2) based on experimental data from Van Hoof, Dotremont & Buekenhoudt, 2005. It is assumed that the flux of water through the membrane only depends on the concentration of water on the feed side.

$$J_W = a \cdot x_W{}^2 + b \cdot x_W \tag{6.1}$$

With the parameters *a=12.331* and *b=185.85*.

$$\alpha_{i,w} = 99.5 \tag{6.2}$$

The phase transition by relative volatility is described using the NRTL model from Lai *et al.* (2007).

P3.6: All, accompanying phenomena by contacting the knowledge base for each identified phenomena are selected. In total a number of 13 phenomena (PB.1-PB.13) are identified. The details of the selection procedure as well as the list of phenomena can be found in appendix A.9.

Note: Two flow patterns for the liquid phase are used (see Figure 6.4) which are: perfectly mixed as well as flow mixing. From the knowledge base, the flow mixing can be currently realized in a tubular (PB.2) or in a rectangular flow (PB.3).

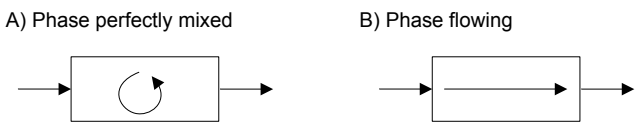


Figure 6.4. Different flow patterns for the liquid flow.

P3.7: The operating windows are determined applying the algorithm **OPW**. The result is presented in Table. 6.10

Note: Since, Amberlyst 15 is used as a catalyst the maximum allowable temperature to avoid catalyst degradation is 403 K (Dow, 2011) which is set to be the maximum limit of the operational window of the liquid phase reaction phenomena. In general, only a liquid phase occurs between the lowest boiling point, that is the temperature (347.34 K) of the ternary azeotrope of isopropanol, isopropyl-acetate and water at P=1 atm and the highest melting point, that is the melting point temperature (289.8 K) of acetic acid at P=1 atm.

Table 6.10. Operating windows for involved phenomena (Assumption: P=1 atm).

No.	Phenomena	Boundaries of the operating window
PB.1	M_{ld}	T_{low}=185.3 K (Lowest Melting point) T_{high}=391.2 K (Highest Boiling Point: Acetic Acid) Concentrations below dew point line.
PB.2	$M_{Fl,tub}$	T_{low}=185.3 K (Lowest Melting point) T_{high}=391.2 K (Highest Boiling Point: Acetic Acid) Concentrations below dew point line.
PB.3	$M_{Fl,rec}$	T_{low}=185.3 K (Lowest Melting point) T_{high}=391.2 K (Highest Boiling Point: Acetic Acid) Concentrations below dew point line.
PB.4	M_V	T_{low}=347.3 K (Lowest Boiling Azeotrope) Concentrations above boiling point line.
PB.5	2phM	T_{low}=347.3 K (Lowest Boiling Azeotrope) T_{high}=391.2 K (Highest Boiling Point: Acetic Acid) Concentrations in V-L regions between dew and boiling point lines.
PB.6	PT(VL)	T_{low}=347.3 K (Lowest Boiling Azeotrope) T_{high}=391.2 K (Highest Boiling Point: Acetic Acid) Concentrations in V-L regions between dew and boiling point lines.
PB.7	PT(PVL)	T_{low}=289.8 K (Melting Point of HOAc) T_{high}=347 K (Membrane stability)
PB.8	PS(VL)	Vapor- Liquid present
PB.9	D	
PB.10	H	
PB.11	C	
PB.12	R	T_{low}=185.3 K (Lowest Melting point) T_{high}=403 K (Catalyst degradation) Concentrations below dew point line.
PB.13	PC	Vapor- Liquid present

P3.8: Identify sub-problems:

P3.8.1: Only one sub-problem (SP=1) is identified in which all identified tasks and phenomena are included (rule P3.3).

P3.8.2: All tasks and corresponding phenomena are included into one list Ω^{SP}. Step P4 is entered.

6.1.5. Step P4: Generate feasible operation/flowsheet options

P4.1: Generate all feasible SPB's from the phenomena:

P4.1.1: The maximum number of phenomena within an SPB is $n_{P,max}$=13-1-2-1=9.

<u>*Note:*</u> The number of competing phenomena, meaning phenomena which cannot occur at the same place and time, is 1+2+1=4 (see above). These are: Heating vs. cooling (-1); liquid

mixing patterns flow and perfectly mixed cannot be connected within one SPB (-2); the dividing phenomenon is by definition a single phenomenon SPB itself (-1).

P4.1.2: Interconnect all phenomena in the search space to SPB's by using the connectivity rules for each phenomenon (see table 2.6):

The number of phenomena is $n_{P,tot,}=13$. Therefore, in total a number of 4019 SPB's is generated (Eq.6.3).

$$NSPB_{\max} = \sum_{k=1}^{n_{P,\max}} \left(\frac{\left(n_{P,tot} - 1\right)!}{\left(n_{P,tot} - k - 1\right)!k!} \right) + 1 = 4019 \tag{6.3}$$

P4.1.3: Screening of all SPB's for feasibility: Using connectivity rules and the information of the operating window of each phenomenon, a total number of 58 SPB's are feasible in terms of conditions of the operatings windows of the integrated phenomena. All 58 feasible SPB's are shown in Table 6.11.

<u>*Note:*</u> M=R=C=2phM only allows vapor-liquid inlet since heat of reaction is not enough for vaporization. Additional cooling would lead to a decrease in temperature and therefore would enable condensation of the vapor and not vaporization of the liquid.

Table 6.11. List of feasible SPB's. The flow mixing contains the tubular as well as the rectangular flow pattern.

SPB	Connected Phenomena	In	Out
SPB.1	M_{Id}	1..n(L)	1(L)
SPB.2	M_{Id}=R	1..n(L)	1(L)
SPB.3	M_{Id}=R	1..n(L)	1(L)
SPB.4	M_{Id}=C	1..n(L)	1(L)
SPB.5	M_{Id}=R=H	1..n(L)	1(L)
SPB.6	M_{Id}=R=C	1..n(L)	1(L)
SPB.7	M_{Id}=M_V=R=2phM=PC=PT(VL)	1..n(L,VL)	1(V/L)
SPB.8	M_{Id}=M_V=R=2phM=PC=PT(VL)=PS(VL)	1..n(L,VL)	2(V;L)
SPB.9	M_{Id}=M_V=R=2phM=PC=PT(PVL)=PS(VL)	1..n(L,VL)	2(V;L)
SPB.10	M_{Id}=M_V=H=2phM=PC=PT(VL)	1..n(L,VL)	1(VL)
SPB.11	M_{Id}=M_V=H=2phM=PC=PT(VL)=PS(VL)	1..n(L,VL)	2(V;L)
SPB.12	M_{Id}=M_V=H=2phM=PC=PT(PVL)=PS(VL)	1..n(L,VL)	2(V;L)
SPB.13	M_{Id}=M_V=C=2phM=PC=PT(VL)	1..n(VL)	1(VL)
SPB.14	M_{Id}=M_V=C=2phM=PC=PT(VL)=PS(VL)	1..n(VL)	2(V;L)
SPB.15	M_{Id}=M_V=R=H=2phM=PC=PT(VL)	1..n(L,VL)	1(V/L)
SPB.16	M_{Id}=M_V=R=H=2phM=PC=PT(VL)=PS(VL)	1..n(L,VL)	2(V;L)
SPB.17	M_{Id}=M_V=R=H=2phM=PC=PT(PVL)=PS(VL)	1..n(L,VL)	2(V;L)
SPB.18	M_{Id}=M_V=R=C=2phM=PC=PT(VL)	1..n(L,VL)	1(V/L)
SPB.19	M_{Id}=M_V=R=C=2phM=PC=PT(VL)=PS(VL)	1..n(L,VL)	2(V;L)
SPB.20, SPB.39	M_{Fl}	1..n(L)	1(L)
SPB.21, SPB.40	M_{Fl}=R	1..n(L)	1(L)
SPB.22, SPB.41	M_{Fl}=H	1..n(L)	1(L)
SPB.23, SPB.42	M_{Fl}=C	1..n(L)	1(L)
SPB.24, SPB.43	M_{Fl}=R=H	1..n(L)	1(L)
SPB.25, SPB.44	M_{Fl}=R=C	1..n(L)	1(L)
SPB.26, SPB.45	M_{Fl}=M_V=R=2phM=PC=PT(VL)	1..n(L,VL)	1(V/L)
SPB.27, SPB.46	M_{Fl}=M_V=R=2phM=PC=PT(VL)=PS(VL)	1..n(L,VL)	2(V;L)
SPB.28, SPB.47	M_{Fl}=M_V=R=2phM=PC=PT(PVL)=PS(VL)	1..n(L,VL)	2(V;L)
SPB.29, SPB.48	M_{Fl}=M_V=H=2phM=PC=PT(VL)	1..n(L,VL)	1(VL)
SPB.30, SPB.49	M_{Fl}=M_V=H=2phM=PC=PT(VL)=PS(VL)	1..n(L,VL)	2(V;L)
SPB.31, SPB.50	M_{Fl}=M_V=H=2phM=PC=PT(PVL)=PS(VL)	1..n(L,VL)	2(V;L)
SPB.32, SPB.51	M_{Fl}=M_V=C=2phM=PC=PT(VL)	1..n(VL)	1(VL)
SPB.33, SPB.52	M_{Fl}=M_V=C=2phM=PC=PT(VL)=PS(VL)	1..n(VL)	2(V;L)
SPB.34, SPB.53	M_{Fl}=M_V=R=H=2phM=PC=PT(VL)	1..n(L,VL)	1(V/L)
SPB.35, SPB.54	M_{Fl}=M_V=R=H=2phM=PC=PT(VL)=PS(VL)	1..n(L,VL)	2(V;L)
SPB.36, SPB.55	M_{Fl}=M_V=R=H=2phM=PC=PT(PVL)=PS(VL)	1..n(L,VL)	2(V;L)
SPB.37, SPB.56	M_{Fl}=M_V=R=C=2phM=PC=PT(VL)	1..n(L,VL)	1(V/L)
SPB.38, SPB.57	M_{Fl}=M_V=R=C=2phM=PC=PT(VL)=PS(VL)	1..n(L,VL)	2(V;L)
SPB.58	D	1(L;VL,V)	1..n(L;V; VL)

P4.2: Analyze and determine potential configurations:

P4.2.1-P4.2.5: For each SPB the steps have been performed to calculate the potential outcome of a stage at different connection possibilities using the conversion for purely reactive SPB's and

the Kremser method coupled with the element-based approach for reactive separations (co,crossflow and counter current flow connection).

P4.2.6: The results are presented in table 6.12. The minimum number of stages is 1. Crossflow is selected (Rule P4.7).

Table 6.12. Results of the performance calculation of connected stages for different flow configurations. First number is the conversion while the second number indicates the number of stages necessary to achieve that conversion.

SPB's	Co	Crossflow	Counter
	1,2 phases	2 phases	2 phases
SPB.1, SPB.3-4, SPB.10-14, SPB.20, SPB.22-23, SPB.29-33, SPB.39,SPB.41-42,SPB.48-52, SPB.58	No reaction	No reaction	No reaction
SPB.2, SPB.21, SPB.40	0.58/∞	1-phase	1-phase
SPB.5, SPB.24, SPB.43	0.55/∞	1-phase	1-phase
SPB.6, SPB.25, SPB.44	0.65/∞	1-phase	1-phase
SPB.7, SPB.10, SPB.13, SPB.15, SPB.18, SPB.26, SPB.29, SPB.32, SPB.34, SPB.37, SPB.45, SPB.48, SPB.51, SPB.53, SPB.56	0.57/∞	No separate phases	No separate phases
SPB.8, SPB.16, SPB.19, SPB.27, SPB.46, SPB.35, SPB.54, SPB.38, SPB.57	0. 67/∞	0. 69/∞	0.81/13(∞)
SPB.9, SPB.17, SPB.28, SPB.47, SPB.36, SPB.55	0.99/1	0.99/1	0.99/1

P4.2.7: The number of stages within one process is between 1 and 3 (Rule P4.10).

P4.3: Generate the number of feasible operation options for each separate task:

P4.3.1: A crossflow arrangement for 3 stages is retrieved from the model library with seven possible recycle streams of liquid depending on the position of the dividing phenomenon in the superstructure (see Figure 6.5).

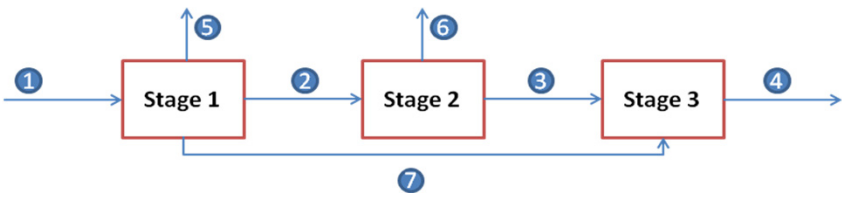


Figure 6.5. Existing forward connections enabled through the use of a dividing phenomenon within the 3-stage crossflow stage connection superstructure.

Note: Currently, the superstructure contains only the forward connections through the dividing phenomenon. Recycles are not considered yet (see also section 8: Open challenges).

P4.3.2: The number of generated process options is 218892 (Eq.6.4) which is calculated from the equation for the theoretical maximum number of operation options (Eq. 3.3).

The number of forward connections enabled by the dividing phenomenon are for processes containing 3 stages $n_{R,3}=6$ and for processes containing 2 stages $n_{R,2}=3$.

$$NOO_{\max} = 58^3 + 58^2 + 58^1 + 6 \cdot 58^2 + 3 \cdot 58^1 = 218892 \quad (6.4)$$

P4.3.3: The screening by feasible connections of SPB's, meaning that a two-phase outlet cannot enter a one-phase SPB and by checking the correctness of the potential additional forward connections through the dividing phenomenon (see appendix A.9.4), gives *NOO=121610* formally feasible options remaining in the search space.

P4.4: The result of the screening through logical constraints is presented in the table 6.13. Detailed examples for the screening are given in appendix A.9.4. Remaining options are NOO_L=24142.

Table 6.13. Overview of the search space reduction through screening by logical constraints.

Constraint	Number of remaining options
Formally feasible operations:	121610
Product is formed (L1)	102424
Reaction phenomenon before or simultaneously with phase transition phenomenon (L2)	64179
Process potentially acts within operating window	24142

P4.5: The result of the screening through structural constraints is presented in the Table 6.2. Remaining process options are NOO_S=506. Examples of all applied constraints can be found in the appendix A.9.6.

Table 6.14. Overview of the search space reduction through screening by structural constraints.

Constraint	Number of remaining options
NPO_L	24142
Energy redundant operations are removed ; e.g. –H–C– (S5)	12244
Remove all options with redundant phenomena not improving the yield after reaction phenomenon/phenomena (S1, S2, S4 & S9)	11153
Phenomena blocks with highest effect on improving the yield are last (S3)	7619
Process in 1 unit operation possible (S6 & S7)	518
No external recycle (S8)	506

6.1.6. Step P5: Fast screening for process constraints

P5.1: Solve operational constraints (Eq.2.4) and the short-cut process model (Eq.2.7). The yield is defined as operational constraint (see step 1, Table 6.1). The results are exemplary presented in Table 6.15. The number of remaining process options achieving a yield of 0.99 is reduced to NOO_O=118.

Table 6.15. Excerpt of the screening by operational constraints (yield).

Phenomena-based representation	Flow-Pattern	Yield
-M_{Id}=R-	Ideal	0.65
-$M_{Fl,tub}$=R-	Flow	0.65
-M_{Id}=M_V=R=H=2phM=PC=PT(PVL)=PS(VL)-	Ideal	>0.99
-$M_{Fl,tub}$=R=H-M_{Fl}=M_V=R=H=2phM=PC=PT(PVL)=PS(VL)-	Flow	>0.99
-M_{Id}=M_V=R=H=2phM=PC=PT(VL)=PS(VL)	Ideal	0.68
-$M_{F,tubl}$=M_V=R=H=2phM=PC=PT(PVL)=PS(VL)- $M_{Fl,tub}$=M_V=R=H=2phM=PC=PT(PVL)=PS(VL)- $M_{Fl,tub}$=M_V=R=H=2phM=PC=PT(PVL)=PS(VL)-	Flow	>0.99
-$M_{Fl,rec}$=M_V=R=H=2phM=PC=PT(VL)=PS(VL)- $M_{Fl,rec}$=M_V=R=2phM=PC=PT(PVL)=PS(VL)- $M_{Fl,rec}$=M_V=R=2phM=PC=PT(PVL)=PS(VL)-	Flow	0.8
….	…	…

P5.2: The thermal energy consumption is used as performance criterion for identification of the most promising options NOO_P: The results of the calculation are presented in Table 6.16.

Table 6.16. Excerpt of the performance screening by the thermal energy consumption.

Rank	Phenomena-based representation	Yield	Thermal energy [MW]
#1	-$M_{Fl,tub}$=M_V=R=H=2phM=PC=PT(PVL)=PS(VL)- $M_{Fl,tub}$=M_V=R=H=2phM=PC=PT(PVL)=PS(VL)- $M_{Fl,tub}$=M_V=R=H=2phM=PC=PT(PVL)=PS(VL)-	0.99	0.36
#1	-M_{Id}=M_V=R=H=2phM=PC=PT(PVL)=PS(VL)-	0.99	0.36
…	**…**	…	…
#23	-$M_{Id,tub}$=M_V=R=H=2phM=PC=PT(PVL)=PS(VL)-M=R=C-D	0.99	>0.36
…	…	…	…

In total 22 process options (NOO_P=22) remain in the search space having a yield higher than 0.99 at the lowest thermal energy consumption which is 0.36 MW, only used for the phase change. All remaining options in the search space are presented in table 6.17.

Table 6.17. Remaining process option after screening by process constraints in step P5.2.

Process Option	Stage 1	Stage 2	Stage 3
1		$M_{Fl,tub}$=R	$M_{Fl,tub}$=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)
2	$M_{Fl,tub}$=R	$M_{Fl,tub}$=H=2phM=Mv=PC=PT(PVL)=PS(VL)	$M_{Fl,tub}$=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)
3	$M_{Fl,tub}$=R=H	$M_{Fl,tub}$=H=2phM=Mv=PC=PT(PVL)=PS(VL)	$M_{Fl,tub}$=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)
4		$M_{Fl,tub}$=R=H	$M_{Fl,tub}$=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)
5	$M_{Fl,tub}$=R=H	$M_{Fl,tub}$=R=2phM=Mv=PC=PT(PVL)=PS(VL)	$M_{Fl,tub}$=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)
6	$M_{Fl,tub}$=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)	$M_{Fl,tub}$=R=2phM=Mv=PC=PT(PVL)=PS(VL)	$M_{Fl,tub}$=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)
7	$M_{Fl,tub}$=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)	$M_{Fl,tub}$=R=H	$M_{Fl,tub}$=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)
8	$M_{Fl,tub}$=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)	$M_{Fl,tub}$=H=2phM=Mv=PC=PT(PVL)=PS(VL)	$M_{Fl,tub}$=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)
9			$M_{Fl,tub}$=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)
10	D	$M_{Fl,tub}$=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)	$M_{Fl,tub}$=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)
11			M_{id}=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)
12	D	M_{id}=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)	M_{id}=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)
13		$M_{Fl,rec}$=R	$M_{Fl,rec}$=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)
14	$M_{Fl,rec}$=R	$M_{Fl,rec}$=H=2phM=Mv=PC=PT(PVL)=PS(VL)	$M_{Fl,rec}$=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)
15	$M_{Fl,rec}$=R=H	$M_{Fl,rec}$=H=2phM=Mv=PC=PT(PVL)=PS(VL)	$M_{Fl,rec}$=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)
16		$M_{Fl,rec}$=R=H	$M_{Fl,rec}$=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)
17	$M_{Fl,rec}$=R=H	$M_{Fl,rec}$=R=2phM=Mv=PC=PT(PVL)=PS(VL)	$M_{Fl,rec}$=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)
18	$M_{Fl,rec}$=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)	$M_{Fl,rec}$=R=2phM=Mv=PC=PT(PVL)=PS(VL)	$M_{Fl,rec}$=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)
19	$M_{Fl,rec}$=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)	$M_{Fl,rec}$=R=H	$M_{Fl,rec}$=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)
20	$M_{Fl,rec}$=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)	$M_{Fl,rec}$=H=2phM=Mv=PC=PT(PVL)=PS(VL)	$M_{Fl,rec}$=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)
21			$M_{Fl,rec}$=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)
22	D	$M_{Fl,rec}$=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)	$M_{Fl,rec}$=R=H=2phM=Mv=PC=PT(PVL)=PS(VL)

P5.3: Based on rules (P5.3-P5.8) and retrieved knowledge from the knowledge base, 22 different units are identified from the phenomena based process options which are presented in Figure 6.6.

Note: For example, the first option is identified as a flow reactor using rule P5.5 stating that a series of the same convective flow pattern are identified as a channel flow unit. Option 10 and 22 are identified using rule P5.8.

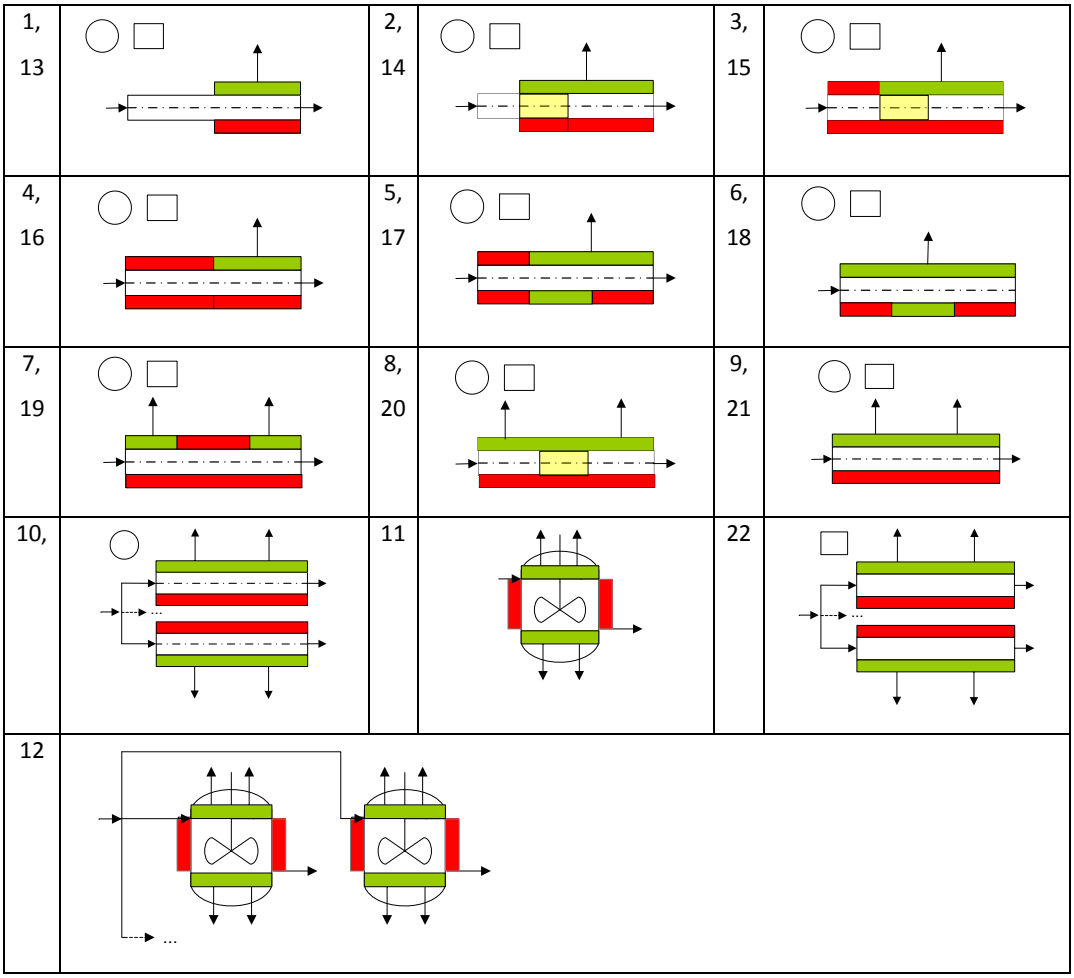


Figure 6.6. Identified unit operations (Red: Heat addition; Green: phase transition by pervaporation; Yellow: no reaction).

P5.4: All options are screened for operational constraints at the unit operation level. That is that the reactor volume of a single unit cannot exceed 50 m^3 and that the pressure drop using the membrane cannot exceed 1 bar. The following assumptions are made:

- Temperature of the reactants into the reactor is 330 K.
- Each stage runs until 90% of the maximum limit. The last reactive stage reaches the desired yield.
- CSTR: 10 wt.% catalyst, A/V=2/h with h/r_{max}=20.
- Flow reactor: 80 kg/m3 catalyst.
- Input flow for each reactant is 941 kmol/min.
- The channels of the rectangular flow are quadratic.

The pressure drop is calculated using equation (6.5).

$$\Delta p = \zeta / \mathrm{Re} \cdot \rho / 2 w^2 L / r \tag{6.5}$$

The Reynolds number is calculated with

$$\mathrm{Re} = wd / \nu \tag{6.6}$$

For the rectangular channel the corresponding radius is determined via the calculation of the hydraulic diameter (Eq.6.7):

$$d_h = 4 \frac{A}{P} \tag{6.7}$$

With *A*: cross sectional area of the channel and *P*: the perimeter of the cross-section.

The resistance factor ζ in the channel depends on the Reynolds number and on the shape of the channel. For example, for a laminar flow (Re<2300), the resistance factor is $\zeta = 64$ for a tube and $\zeta = 80$ for a rectangular channel (see Kast, 2002).

The results of the screening on operational constraints are presented in the table 6.18. In total 2 options, marked with an asteriks are kept in the search space. All other options are screened out because the necessary volume is violating he unit operational constraint (Volume of a single reactor below 50m^3) to reach the yield of 0.99 at a pressure drop below 1bar.

Table 6.18. Results for screening of operational constraints at the unit operational level. Process option 10,12 and 22 have been simulated for 100 parallel reactors. For these, in parenthesis, the volume of a single reactor is given. The rectangular channel is assumed to have a ratio of Width/Height=1

Process Option	V_{total} (V_{single}) in m^3
1-9, 13-21	no feasible solution (V too high)
10	141 (1.41)*
11,12	no feasible solution (V too high)
22	242 (2.42)*

P5.5: All sub-problems SP have been solved, step 6 is entered (Rule P5.3).

6.1.7. Step 6: Solve the reduced optimization problem and validate promising

Step 6.1: Identify the set of most promising process options by solving an MINLP problem (if necessary).

Step 6.1.1: Step 6.1 is not needed (Rule 6.1). Step 6.2 is entered.

Step 6.2-6.3: For each process option, the reduced optimization problem is solved separately.

<u>Additional design constraints besides operational constraints given in step P5.4:</u>

- Re > 20
- Maximum amount of catalyst : 80 kg/m3
- Height/width in the rectangular channel maximum 4 (with one width as the surface contact area to the membrane)

The pareto curve is plotted for the volume (representing the capital costs) against the necessary membrane area (representing the largest factor in the operational costs) at a yield=0.99 and a maximum of 100 parallel units (Figure 6.7).

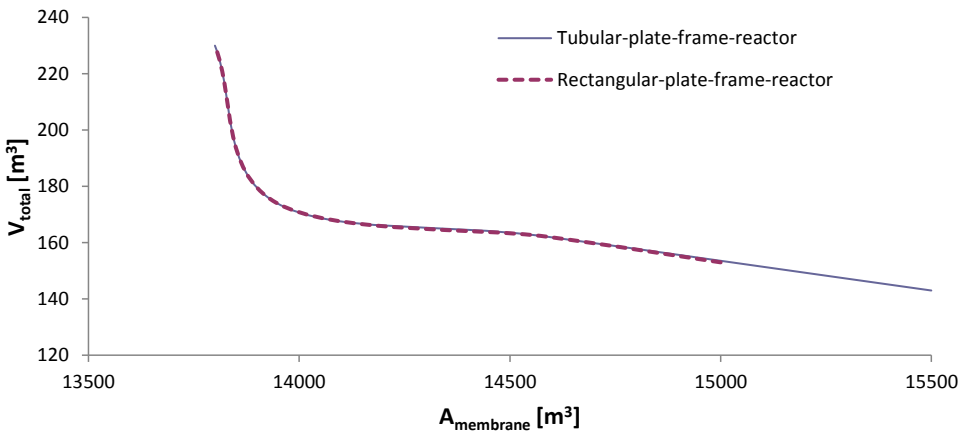


Figure 6.7. The Pareto-Curve of the 2 best options at a yield=0.99 and 100 parallel units. Both lines are overlapping.

The lines of the rectangular and the tubular plate-frame-reactor are constrained at the left because of the boundary of the volume of a single unit and to the right because of pressure drop constraints. Both options are performing similar in terms of yield, achieved concentration of IPAc in the outlet stream of 98 mol.% as well as total volume and necessary membrane area (Figure 6.7). However, the rectangular plate frame reactor always has a higher pressure drop (see Eq.6.5, Table 6.19) and a smaller operating window. Hence, the best identified option is a tubular plate

flow reactor with simultaneous separation of water by pervaporation and simultaneous addition of the necessary heat (Figure 6.8) by heat-exchanger tube.

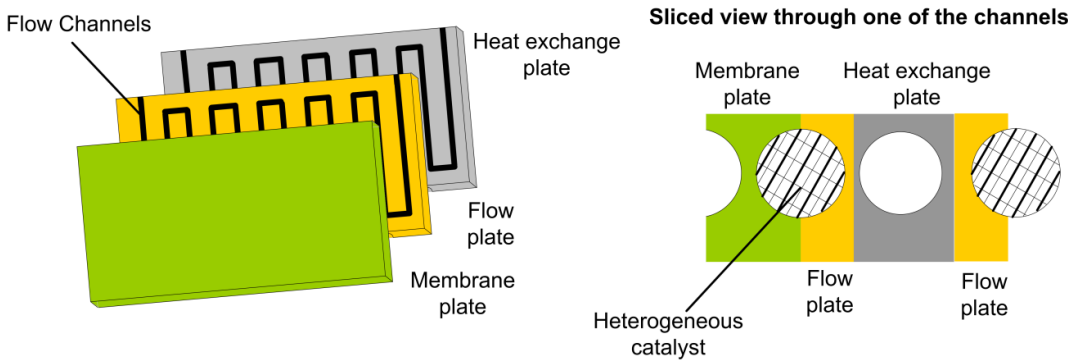


Figure 6.8. Detailed design of the tubular plate-frame-flow reactor-pervaporator.

However, the simpler construction is achieved for the rectangular flow reactor because a plate membrane module can be simply assembled which would lower the fabrication costs of this unit (Figure 6.9).

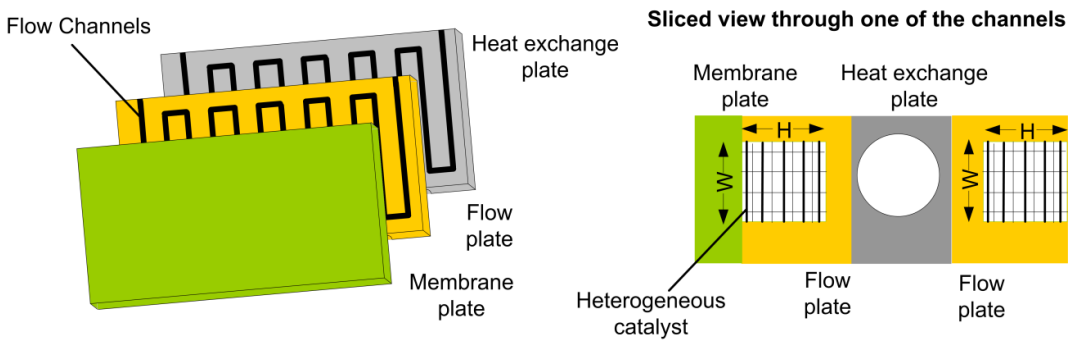


Figure 6.9. Detailed design of the rectangular plate-frame-flow reactor-pervaporator (Width/Height=W/H=1).

Table 6.19. Simulation results for two points for both remaining process option #10 and #22 for a number of 100 reactors in parallel.

Option	T [K]	Rectangular channel			$A_{membrane}/V$ [m^{-1}]	V_{single} [m^3]	r or r_h [m]	Δp [bar]
		W/H	H [m]	W [m]				
#10	373					1.51	0.01	0.43
#10	373					2.30	0.0167	0.03
#22	373	2	0.01	0.02	100	1.51	0.0067	4.23
#22	373	2	0.0167	0.033	60	2.30	0.011	0.3
#22	373	4	0.01	0.04	100	1.51	0.008	1.0
#22	373	4	0.0167	0.067	60	2.30	0.0133	0.07

Step 6.4: The results have been obtained with rigorous models. The best option is the tubular flow reactor from the performance point of view. If difficulties with respect to the manufacturing of round membrane "plates" cannot be solved the better option would be the rectangular channel reactor with a large width/height ratio (see table 6.19).

6.1.8. Comparison with reactive distillation

In the literature, as stated in the introduction to this chapter, for intensifying this reaction, only reactive distillation has been studied. Therefore, the new design (even though it is a result of targeting the intensification only in the reactor part) is benchmarked against the data obtained for a reactive distillation system (Lai *et al.*, 2007) as well as the data for the conventional base-case design by Corrigan and Stichweh (1968). The base-case consists of one reactor, six distillation systems, one extractor using water as a solvent and one decanter (Figure 6.10). Conversion and the amount of heat are known (Corrigan & Stichweh, 1968).

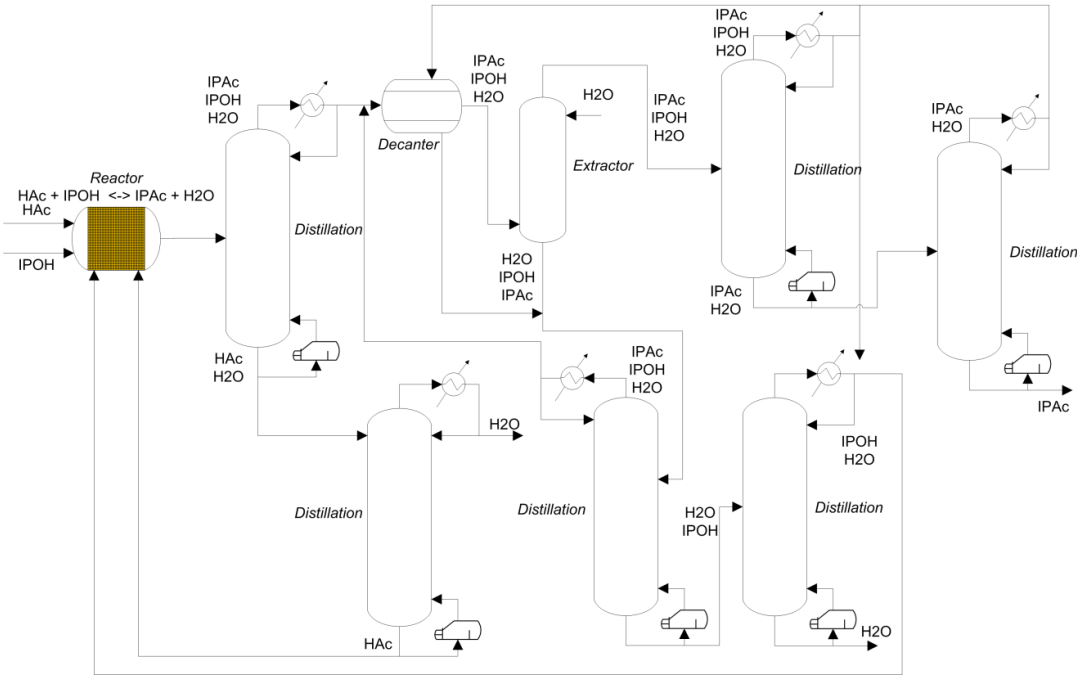


Figure 6.10. Base-case design for the production of IPAc (Corrigan and Stichweh, 1968).

The reactive distillation system proposed by Lai *et al.* (2005) consists of one reactive distillation column with a decanter at the top of the column and an external stripping column (Figure 6.11). The product is obtained as the bottom product from the stripping column. The mass and energy data for their process is given in table 6.20. Inlet to the process is raw materials at industrial grade.

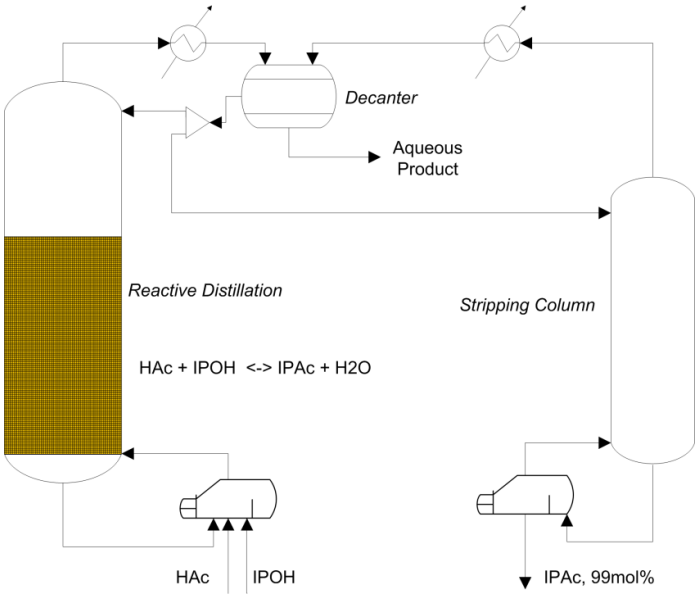


Figure 6.11. Reactive-distillation-stripper configuration for the production of IPAc (Lai et al, 2007). Colorized is the reactive zone containing Amberlyst-15.

Table 6.20. Mass and energy data of the reactive distillation configuration (Lai *et al.*, 2007)

	Inlet	Outlet	
		Aqueous	Bottom
Flowrates [kmol/h]			
HOAc	50.74	0.000087703	0.004697
IPOH	50.000173	2.3488458	0.4631242
IPAc		0.6657455	46.5003
H2O	26.029827	76.93945	0.0018788
total [kmol/h]	126.77	79.73	46.97
conversion (IPOH)	0.9300028		
conversion (HOAc)	0.9164426		
Heat [MW]	5.5711		
Catalyst			
cat density [kg/m3]	770		
cat costs [US-$]	74200		
Price [US-$/kg]	7.7162		
kg cat	9616.1323		

The rectangular flow reactor pervaporator has been selected and has been designed using the same input flows as for the reactive distillation system (Table 6.20). The temperatures of the inlet streams have been assumed to be T=300 K.

The specifications of the design of the rectangular flow reactor-pervaporator are given in Figure 6.12. With the phenomena based design retrieved from our methodology, a conversion of 99% based on IPOH is achieved compared to around 94% for conventional as well as 93% for the reactive distillation system (Figure 6.12). The thermal heat requirement of the novel design is only 1/10th of the thermal heat requirement of the conventional process and around 1/5th of the reactive distillation system. The amount of catalyst in the novel design can be reduced by 40% compared to the reactive distillation system.

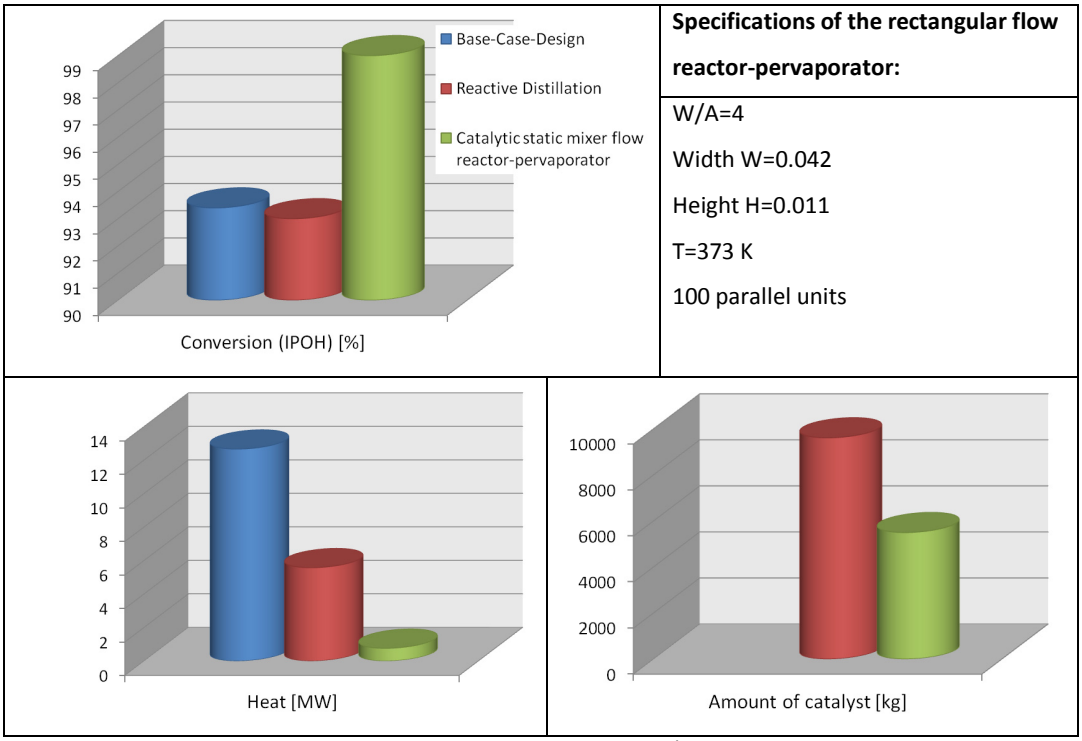


Figure 6.12. Comparison of the design for the production of 46.5kmol/h IPAC in the criteria conversion, heat and amount of catalyst.

6.2. Separation of hydrogen-peroxide and water

In this section, the methodology is tested to achieve PI in a separation task. The separation of hydrogen-peroxide from an aqueous solution is a very energy consuming step (see Table 5.17) in the anthraquinone route (see section 5.2.1). In a conventional process, this separation is done with a vacuum distillation in order to circumvent the formation of an explosive atmosphere. In the previous chapter of this thesis (section 5.2), this separation has been part of intensifying the anthraquinone process using the unit-operation based workflow. The realized PI was a heat integrated distillation column (see section 5.2). Here, it will be shown that the previous PI solution is also in the search space together with many more options which have not been in the PI knowledge-base.

6.2.1. Step 1: Define problem

Step 1.1: The objective is to generate a novel intensified PI separator matching the product

specifications in one unit and which minimizes the operational cost per kg product formed (Eq.6.8):

$$\min F_{Obj} = \left(\underbrace{\sum c_{RM,i} \dot{m}_{RM,i}}_{RawMaterials} + \underbrace{\sum c_{energy,i} \dot{E}_i}_{Energy} + \underbrace{\sum c_{solvent,i} \dot{m}_i}_{Make-Up} \right) / \dot{m}_{H2O2} \tag{6.8}$$

Step 1.2: The design scenario is the improvement of the separation process of H_2O_2 and water. The process scenario is batch.

Step 1.3: A mixture stream (1000 kmol/h) containing 15 mol.% of H_2O_2 and 85mol.% water at T=308.15 K and P=1 atm has to be purified to obtain a purity of H_2O_2 of 70 w.% of H_2O_2. The process is continuous. The recovery of H_2O_2 in the purification should not be lower than 99 mol.%.

Step 1.4: Additional performance metric is selected which are simplification, energy, capital costs, (raw material) efficiency as well as safety.

Step 1.5: The maturity is selected to a *novel* process.

Step 1.6.1-1.6.3: The performance metrics has been translated (Table 6.21).

All performance metric are translated into logical and structural constraints. The following operational constraints are set:

- Efficiency of product recovery (>99%),
- Product purity >70 w.%

For screening with respect to performance metric (in step P5) is the costs of the purification of H_2O_2.

Step 1.7: No base-case design exists. Therefore, step B2 is entered.

Table 6.21. Problem definition of the case study: separation of H_2O_2/ H_2O.

F_{obj}	Operational costs (Eq. 6.8)
Design scenario	Design of PI equipment for the separation task
Process scenario	Continuous
Logical constraints	Only stream connection and operating window constraints determined (in step A.2-P3).
Structural constraints by PI metric	Efficiency: S1: Do not integrate units which inhibit each others performance. S2: Add phenomena and stages to the position in the flowsheet in which it has the highest efficiency. S3: Always end the flowsheet with the phenomena giving the highest yield last.
	Energy: S4: Do not connect units/stages with alternating heat addition and heat removal. S5: Do not connect units/stages with alternating pressures. S6: Integrate heat by connecting hot and cold streams whenever possible.
	Simplification: S7: Do not use repetitive (sequential) units. S8: Remove redundant stages not improving the yield/separation S9: Use only up to two different pressures in the system
Operational constraints (Rule 1.6)	Purity of water (90 w.%) Purity of H_2O_2 (70 w.%) Boundaries of the explosive atmosphere (see Figure 5.6).
PI screening criterion for step C2.	Generate “novel” process options
PI screening criterion for step P5	Costs for the purification of H_2O_2 as the main product (phenomena level)
	Number of equipment representing the capital costs (unit-operational level)

6.2.2. Step B2: Identify and analyze necessary tasks to achieve the process targets

This step is applied assuming that no base case design exists in order to highlight the steps of this workflow.

Step B2.1: H_2O_2 and water are present in the system.

Step B2.2: H_2O_2 is the product (rule B2.3) and water is a solvent (rule B2.3).

Step B2.3: No reactions are identified. This step is not necessary (rule B2.4).

Step B2.4: Identify necessary separation/mixing/heat supply/removal tasks for each outlet

Step B2.4.1: Two separation tasks are identified (Figure 6.13): The purification of H_2O_2 and the purification of H_2O (rule B2.10).

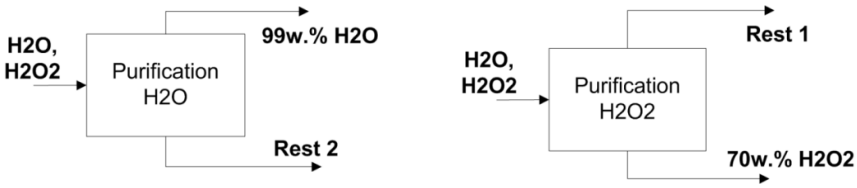


Figure 6.13. Identified tasks to achieve the process specifications.

Step B2.4.2: The algorithms **APCP** and **AMP** are applied. Table 6.22 shows the analyzed pure component properties.

Table 6.22. Normal property ratios of the components H_2O_2/H_2O involved in the separation task.

Boiling point	Van der Waals volume	Molecular Weight	Radius of gyration	Molar volume	Critical temperature
1.14	1.30	1.89	2.02	2.37	1.13
Refractive index	**critical pressure**	**Melting Point**	**Solubility Parameter**	**Triple point pressure**	**Triple point temperature**
1.06	1.02	1.002	1.04	17.63	1.002

The mixture has been analyzed by applying **AMP** with respect to azeotropes, miscibility gaps and the formation of an explosive atmosphere. No azeotropes or phase splits have been found for the binary mixture H_2O_2/ H_2O. Due to safety, concentrations above 70 w.% H_2O_2 have to be run below 397 K since this is the point in which an explosive atmosphere is formed (see Figure 5.6).

The identified necessary phenomena based on APCP and AMP are shown in Table 6.23.

Table 6.23. Identified phenomena for each desirable task using the algorithm **APCP** with pure component properties (T_M: Melting point; T_B: Boiling point; P_{LV}: Vapor pressure; R_g: Radius of gyration; V_M: Molar volume; Log(K_{ow}): Octanol/Water partition coefficient; VdW: Van der Waals volume; $\boldsymbol{\delta_{SP}}$: Solubility Parameter)

Task	Identified phenomena	How determined?
Purification H2O2/ Purification H2O	<u>Phase transition by:</u>	
	Gas-liquid contact (stripping)	T_B
	Liquid-liquid contact (extraction)	Log(K_{ow})
	Pervaporation	R_g, V_M, VdW, $\boldsymbol{\delta_{SP}}$
	Liquid membrane	R_g, V_M, VdW
	Vapor-liquid by relative volatility	T_B, P_{LV}

Step B2.4.3: The sub-algorithm **SoP** is applied and the results are presented in more detail here.

Enter sub-algorithm SoP:

SoP.1: For the phase transition phenomenon by pervaporation and liquid membranes information of the external medium is necessary. One membrane has been found in the literature (Parrish et al., 1999). The phase transition phenomena using a solvent are removed (rule SoP.1). The pervaporation phenomenon has a selectivity *S=2.4* and is described through a short-cut model for the flux through the membrane J_i [m^3 /m^2 /h] using the experimental data available from Motupally *et al.* (2000) and Parrish *et al.* (1999).

$$J_i=Q_i*dP \tag{6.9}$$

The permeability of the membrane for water Q_{H2O} and hydrogen peroxide Q_{H2O2} has been calculated at T=50°C:

$$Q_{H2O} =0.0065\ m^3 /m^2 /h /Pa. \tag{6.10}$$

$$Q_{H2O2} =0.0027\ m^3 /m^2 /h /Pa. \tag{6.11}$$

It is decided not to target for a new membrane (Rule SoP.1). The phase transition by relative volatility is used using the UNIQUAC model with the parameters taken from the Pro\II database version 8.1 (Pro\II, 2011). Step SoP.5 is directly entered.

SoP.5: **OPW** is applied. The operating windows are presented in the following table 6.24. The membrane is limited by the boiling point of the solution.

Table 6.24. Operating window of the phase transition phenomena with respect to temperatures.

Phenomena	**P=0.1 atm**		**P=1 atm**		**P=10 atm**	
	T_{Low} [K]	T_{high} [K]	T_{Low} [K]	T_{high} [K]	T_{Low} [K]	T_{high} [K]
Relative volatility	318.96	362.14	373.15	422.9	453.13	513.55
Pervaporation	-		273.15	$T_{b,mixture}$	-	

SoP.6: The driving force for the vapor-liquid phase transition phenomenon is plotted for three different pressures P=0.1 atm, P=1 atm and P=10 atm (rule SoP.3, see Figure 6.14). In that diagram also the process specifications for the separation of both components are inserted. These are the recovery of hydrogen-peroxide to be 99% and the purity of the product to be at 70 w.%.

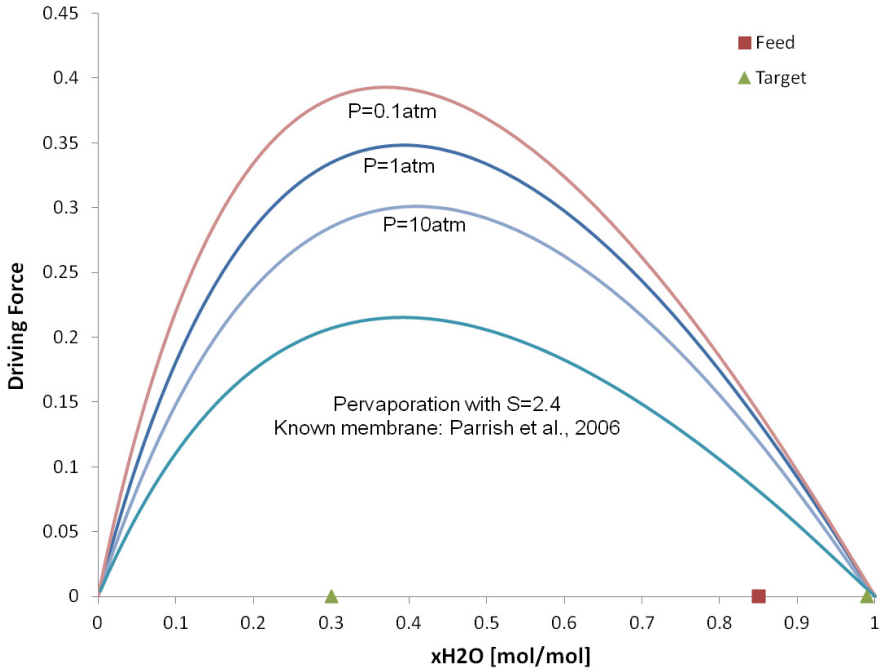


Figure 6.14. Identified Plot of driving force for the phase transition by relative volatility (UNIQUAC model with parameters from the Pro\II database version 8.1 (Pro\II, 2011)) at 3 pressures and by pervaporation at P=1 bar.

SoP.7: For the purification of H_2O_2, the phase transition phenomena at P=1 bar and P=10 bar are removed (rule SoP.4) because they are outside of the operating window due to the formation of an explosive atmosphere (see also figure in step B2.4.2). From the DF-diagram, it can be seen that the known membrane (S=2.4) has the lowest driving force. For the task to achieve the recovery specifications of H_2O the pervaporation phenomenon is neglected because of a very low driving force (rule SoP.4).

Note: An overview of the screening in the sub-algorithm is given in the Table 6.25.

Table 6.25. Overview of the screening of phase transition phenomena. Kept phase transition phenomena in the search space are written in bold letters.

Task	Identified phenomena	Removal/Selection criterion
Purification H_2O_2/ Purification H_2O	Phase transition by:	
	Gas-liquid contact (stripping)	Rule SoP.1
	Liquid-liquid contact (extraction)	Rule SoP.1
	Pervaporation	Only at high H_2O_2 (Rule SoP.5)
	Liquid membrane	SoP.1
	Vapor-liquid by relative volatility	P=1 bar&P=10 bar only at low H_2O_2 concentrations (Rule SoP.4)

SoP.8: All tasks can be fulfilled. No additional tasks are identified in this step. Step B2.4.4 is entered

Exit sub-algorithm SoP

Step B2.4.4: No physical limitation in the design is found.

Step B2.5: No additional necessary tasks are identified (Rules B2.14-B2.15).

Step B2.6: Step P3 is entered.

6.2.3. Step P3: Identification of desirable phenomena

Step P3.1: Identify additional desirable tasks for enhancement of the necessary ones

Step P3.1.1: The list of keywords $\underline{K}_{PI}$ for identification of PI possibilities includes the task and the objective function.

Step P3.1.2-P3.1.3: No additional tasks are identified.

Step P3.2-P3.5: The steps are not necessary since output of step P3.1.3 is zero.

Step P3.6: Identify accompanying phenomena by contacting the knowledge base for each identified phenomenon: In total 15 phenomena ($n_{P,tot}=15$.) are identified which are presented in the appendix A.11 (see Table A.28).

Step P3.7: The algorithm **OPW** is applied to determine the operating window of each phenomenon (see Table 6.26).

Table 6.26. Operating windows for involved phenomena.

No.	Phenomena	Boundaries of the operating window
PB.1	Mixing Vapour: Ideal M(V)	At P=0.1 bar: T_{low}=319.0 K (Lowest Boiling Point) At P=1 bar: T_{low}=373.2 K (Lowest Boiling Point) At P=10 bar: T_{low}=453.1 K (Lowest Boiling Point) Concentrations above boiling point line.
PB.2	Mixing Liquid: Ideal M(L)	At P=0.1 bar: T_{low}=273 K (Lowest Melting point), T_{high}=362.4 K (Highest Boiling Point) At P=1 bar: T_{low}=273 K (Lowest Melting point), T_{high}=422.9 K (Highest Boiling Point) At P=10 bar: T_{low}=273 K (Lowest Melting point), T_{high}=513.55 K (Highest Boiling Point) Concentrations below dew point line.
PB.3	2-phase mixing: M(V,L)	At P=0.1 bar: T_{low}=318.9 K (Lowest Boiling Point), T_{high}=362.1 K (Highest Boiling Point); At P=1 bar: T_{low}=373.2 K (Lowest Boiling Point), T_{high}=422.9 K (Highest Boiling Point); At P=10 bar: T_{low}=453.1 K (Lowest Boiling Point), T_{high}=513.6 K (Highest Boiling Point); Concentrations in V-L regions between dew and boiling point lines.
PB.4	Phase transition by relative volatility: PT(VL,0.1bar)	T_{low}=318.9 K (Lowest Boiling Point), T_{high}=362.1 K (Highest Boiling Point) Concentrations in V-L regions between dew and boiling point lines.
PB.5	Phase transition by relative volatility: PT(VL,1bar)	T_{low}=373.2 K (Lowest Boiling Point), T_{high}=422.9 K (Highest Boiling Point) Concentrations in V-L regions between dew and boiling point lines.
PB.6	Phase transition by relative volatility: PT(VL,10bar)	T_{low}=453.1 K (Lowest Boiling Point), T_{high}=513.6 K (Highest Boiling Point) Concentrations in V-L regions between dew and boiling point lines.
PB.7	Phase transition by pervaporation: PT(PVL,1bar)	T_{low}=273.2 K (Highest Melting Point), T_{high}=373.2 K (Lowest Boiling Point);
PB.8	Phase separation; Ideal: PS(VL)	Vapor- Liquid present
PB.9	Divider	
PB.10	Heating H	
PB.11	Cooling C	
PB.12	Phase change: ideal PCh	From V to L: inlet above dew point line, outlet below bubble point line From L to V: inlet below bubble point line, outlet above dew point line
PB.13	Pressure rise: Prise	
PB.14	Pressure decrease: Pdrop	
PB.15	Phase contact: ideal: PC	Vapor- Liquid present

Step P3.8: Identify sub-problems:

Step P3.8.1: Only one sub-problem (*SP=1*) is identified in which all identified tasks are included (rule P3.3).

Step P3.8.2: All tasks and corresponding phenomena are included into one list Ω^{SP}

6.2.4. Step P4: Generate feasible operation/flowsheet options

P4.1: Generate all feasible simultaneous phenomena building blocks SPB from the phenomena in the search space:

P4.1.1: Identify the maximum number of phenomena within an SPB $n_{P,max}$ (Eq.6.12):

The number of competing phenomena is 8 because: Heating and cooling (1), pressurizing and expanding (1), phase transition phenomena at different pressures (3) as well as phase change and two-phase phenomena (1) and stream dividing (1) cannot be connected within one SPB. Additionally, the dividing phenomenon is one SPB itself.

Hence, the maximum number of phenomena within a stage is $n_{P,max}$=15-7=8.

P4.1.2: All possible SPB are generated using the connectivity rules. In total a number of 14913 (see Eq.6.12) SPB's are generated.

$$NSPB_{\max} = \sum_{k=1}^{n_{P,\max}} \left(\frac{\left(n_{P,tot} - 1\right)!}{\left(n_{P,tot,w/oD} - k - 1\right)!k!} \right) + 1 = 12911 \tag{6.12}$$

P4.1.3: Screening of all SPB's for feasibility: Using connectivity rules and the information of the operating window of each phenomenon, a total number of 30 SPB's is feasible which are shown in Table 6.27.

Table 6.27. Feasible stages based on the phenomena in the search space.

SPB	Connected Phenomena	In	Out
SPB.1	M(L)	1..n(L)	1(L)
SPB.2	M(L)=H	1..n(L)	1(L)
SPB.3	M(L)=C	1..n(L)	1(L)
SPB.4	M(L)=H=PCh=M(V)	1..n(L)	1(V)
SPB.5	M(L)=Pdrop=PCh=M(V)	1..n(L)	1(V)
SPB.6	M(L)=Pdrop=H=PCh=M(V)	1..n(L)	1(V)
SPB.7	M(L)=Pdrop=C=PCh=M(V)	1..n(L)	1(V)
SPB.8	M(L)=Pdrop	1..n(L)	1(L)
SPB.9	M(L)=Prise	1..n(L)	1(L)
SPB.10	M(V)	1..n(V)	1(V)
SPB.11	M(V)=H	1..n(V)	1(V)
SPB.12	M(V)=C	1..n(V)	1(V)
SPB.13	M(V)=C=PCh=M(L)	1..n(V)	1(L)
SPB.14	M(V)=Prise=PCh=M(L)	1..n(V)	1(L)
SPB.15	M(V)=Prise=H=PCh=M(L)	1..n(V)	1(L)
SPB.16	M(V)=Prise=C=PCh=M(L)	1..n(V)	1(L)
SPB.17	M(V)=Pdrop	1..n(V)	1(V)
SPB.18	M(V)=Prise	1..n(V)	1(V)
SPB.19	M(V,L)=M(VL)=PC=PT(VL,0.1bar)=PS(VL)	1..n(L,V,VL)	2(V;L)
SPB.20	M(V,L)=M(VL)=PC=PT(VL,1bar)=PS(VL)	1..n(L,V,VL)	2(V;L)
SPB.21	M(V,L)=M(VL)=PC=PT(VL,10bar)=PS(VL)	1..n(L,V,VL)	2(V;L)
SPB.22	M(L)=PC=PT(PVL,1bar)=PS(VL)	1..n(L)	2(V;L)
SPB.23	M(V,L)=M(VL)=H=PC=PT(VL,0.1bar)=PS(VL)	1..n(L,V,VL)	2(V;L)
SPB.24	M(V,L)=M(VL)=H=PC=PT(VL,1bar)=PS(VL)	1..n(L,V,VL)	2(V;L)
SPB.25	M(V,L)=M(VL)=H=PC=PT(VL,10bar)=PS(VL)	1..n(L,V,VL)	2(V;L)
SPB.26	M(L)=H=PC=PT(PVL,1bar)=PS(VL)	1..n(L)	2(V;L)
SPB.27	M(V,L)=M(VL)=C=PC=PT(VL,0.1bar)=PS(VL)	1..n(L,V,VL)	2(V;L)
SPB.28	M(V,L)=M(VL)=C=PC=PT(VL,1bar)=PS(VL)	1..n(L,V,VL)	2(V;L)
SPB.29	M(V,L)=M(VL)=C=PC=PT(VL,10bar)=PS(VL)	1..n(L,V,VL)	2(V;L)
SPB.30	D	1(L;VL,V)	1..n(L;V;VL)

P4.2: Analyze and determine potential configurations:

P4.2.1-P4.2.5: For each SPB the steps have been performed to calculate the potential outcome and the necessary number of stages for different interconnections. This is done using the extended Kremser method (see section 4.6).

P4.2.6: The results of the SPB's achieving the desired separation (purity and recovery) are presented in Tables 6.28-6.29. Counter-current flow is selected by Rule P4.8.

Table 6.28. Number of stages to achieve the purity of H_2O_2 at $L/V_{min}/1.1$.

SPB's	Co	Crossflow	Counter	L/V_{max}
M(V,L)=M(VL)=PC=PT(VL,0.1bar)=PS(VL) M(V,L)=M(VL)=H=PC=PT(VL,0.1bar)=PS(VL) M(V,L)=M(VL)=C=PC=PT(VL,0.1bar)=PS(VL)	Not achieved	1.55	1.18	1.33
M(L)=PC=PT(PVL,1bar)=PS(VL) M(L)=H=PC=PT(PVL,1bar)=PS(VL)	Not achieved	Not achieved	1.92	1.21

Table 0.29. Number of stages to achieve the recovery (purity of H_2O) at $1.5*L/V_{min}$.

SPB's	Co	Crossflow	Counter	L/V_{min}
M(V,L)=M(VL)=PC=PT(VL,0.1bar)=PS(VL) M(V,L)=M(VL)=H=PC=PT(VL,0.1bar)=PS(VL) M(V,L)=M(VL)=C=PC=PT(VL,0.1bar)=PS(VL)	Not achieved	14.12	2.14	0.28
M(V,L)=M(VL)=PC=PT(VL,1bar)=PS(VL) M(V,L)=M(VL)=H=PC=PT(VL,1bar)=PS(VL) M(V,L)=M(VL)=C=PC=PT(VL,1bar)=PS(VL)	Not achieved	Not achieved	2.65	0.30
M(V,L)=M(VL)=PC=PT(VL,10bar)=PS(VL) M(V,L)=M(VL)=H=PC=PT(VL,10bar)=PS(VL) M(V,L)=M(VL)=C=PC=PT(VL,10bar)=PS(VL)	Not achieved	Not achieved	3.95	0.34

P4.2.7: For the task to achieve the recovery specifications 4 stages are selected while to achieve the purity of the product (H_2O_2) 2 stages are selected (Rule P.4.10).

P4.3: Generate the number of feasible operation options:

P4.3.1: A superstructure for two as well as four countercurrent flow stages are retrieved from the model library. The simplified scheme of the superstructure for four stages (heat integration possibilities are not shown) is presented in Figure 6.15. The optional boxes are accompanying boxes to assist the feasibility for a stage. For example, it can contain SPB's changing the pressure to allow pressure change between the stages but it cannot contain phase transition phenomena to serve the purpose of a separation. SPB's with included phase transition phenomena have to be inserted into stages 1-4.

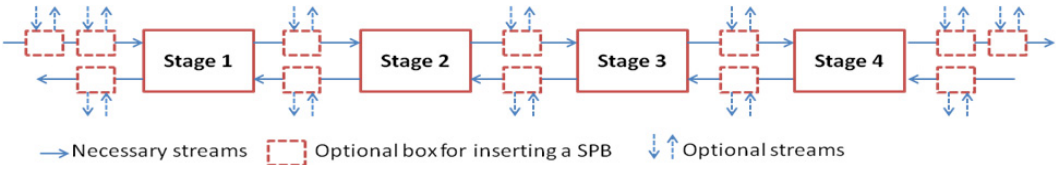


Figure 6.15. Simplified superstructure of a counter-current arrangement of four stages.

P4.3.2: The number of possible process options represented by this superstructure with the number of SPB´s is expressed by equation 6.13.

$$NOO_{\max} = n_{hi} \prod_{1}^{n_{tasks}} \left(NSPB^{n_{stages,task}} \right) \tag{6.13}$$

The number of heat integration possibilities n_{hi} between six stages is solved using a combinatorial expression (Eq.6.14):

$$n_{hi} = \sum_{k=2}^{n_{stages}} \left(\frac{n_{stages}!}{k!\left(n_{stages}-k\right)!} \right) \tag{6.14}$$

Therefore, using equations 6.13-6.14, a total number of $2.6 \cdot 10^{10}$ options are generated.

P4.3.3: No reduction is made.

P4.4: All generated options are screened by logical constraints to identify the number of feasible options which match the product and process specifications. For this, a number of NOO_L=$4.2 \cdot 10^7$ process options exists.

P4.5. The search space is screened by the structural constraints (seeTable 6.21), leaving 1736 most promising process options in the search space. The results of the screening for each structural constraint are presented in Table 6.30. Step P5 is entered.

Table 6.30. Reduction of the search space by structural screening.

Constraint	Number of options
NPO_L	$4.2 \cdot 10^7$
Energy: Do not heat top stages (rectifying), Do not cool bottom stages (stripping)	82944
Energy: Heat integration feasible	26100
Simplification: Use only up to 2 pressure changes	8352
Simplification: Remove options with redundant stages	2228
Efficiency: Only do a pressure change from the feed to the top for higher driving forces (lower energy consumption)	1736

6.2.5. Step P5: Fast screening for process constraints

P5.1: The algorithm P5.1.1-P5.1.4 has been applied. As initial values, the reflux ratio's determined in step P4.2 are used. All remaining options are feasible with respect to all specified operational constraints (see Table 6.21). Hence NOO_S= NOO_O=1736.

P5.2: Identify the set of most promising options through performance screening NPO_P:

P.5.2.1- P5.2.2: The cost for the stripping task is used for screening at this stage.

The prices for utilities are taken from Turton *et al.* (2009). The membrane price is based on the information for small membranes (Nafion, 2011).

Table 6.31. Cost indicators for utilities from Turton *et al.* (2009).

Utility	c_i
Heating(HP)($/GJ)	14.05
Cooling($/GJ)	0.40
Electricity($/kWh)	0.06
Membrane (US-$/m2)	300.00
Replacement of the membrane (in years)	3.00

The operation costs for the stripping section are calculated taking into account thermal energy, electricity and membrane costs (Eq. 6.15).

$$Cost_{Strip}=(\Sigma c_{Heat}\cdot Q_{heat}+c_{cool}\cdot Q_{cool}+c_{Elec}\cdot E+c_{Mem}\cdot A_{mem}/t_{replacement})/n_{Product} \quad (6.15)$$

In total only four different stripping configurations are in the search space. For each of them the stripping costs (Eq.6.15) are calculated and ranked according to their operational costs. The ranking is presented in the Table 6.32. Only the best two configurations are selected to be kept in the search space. Keeping only the first two stripping configurations in the search space reduced the number of process option to $NOO_O=746$.

Table 6.32. Cost Ranking of the stripping configurations by the $Cost_{Strip}$.

Rank	Stripping configuration		$Cost_{Strip}$ [US-$/kmol Product]
1	H=PT(VL,0.1bar)/ PT(VL,0.1bar)	H=PT(VL,0.1bar)/ PT(VL,0.1bar)	2.0
2	H=PT(VL,0.1bar)/ PT(VL,0.1bar)	H=PT(PVL,1bar)/ (PVL,1bar)	4.21
3	H=PT(PVL,1bar)/ (PVL,1bar)	H=PT(VL,0.1bar)/ PT(VL,0.1bar)	6.7
4	H=PT(PVL,1bar)/ (PVL,1bar)	H=PT(PVL,1bar)/ (PVL,1bar)	19

P5.2.3: The objective function F_{obj} is not used for screening (Rule P5.2) at the phenomena level. Step P5.3 is entered.

P5.3: Using the rules given in the knowledge-base: compressor/pump, heat-exchanger, column, reboiler, condenser, flash, membrane separator and dividing wall column with/without heat exchange between the separated zones are identified.

P5.4: The number of equipments in the process (NoE) is used as metric representing the capital costs for screening at the unit operational level. Only 7 flowsheets are remaining in the search space because they have the lowest number of unit operations in the fowsheet (less than 7 unit operations). The 7 remaining options are shown in table 6.33.

Note: Process options #2,3,6 and 7 are internal heat integrated distillation columns at two pressures in which the heat is transported from the rectifying to the stripping zone. Process options #1 and 4 are heat integrated divided distillation columns at two pressures in which the heat from the vapor leaving the rectifying section is used for the reboiler of the stripping zone. No heat is transported from the rectifying to the stripping section in the column itself. Options #5-7 are hybrid operations of a distillation column and a pervaporation.

P5.5: All sub-problems SP have been solved, step 6 is entered (Rule P5.3). $NOO_P=NPO_P$.

Table 6.33. Remaining process options in the search space after screening of the number of equipments at the unit operational level.

Option	Absorption				Stripping		NoE
	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	Stage 6	
1			C=PT(VL,0.1bar)	PT(VL,0.1bar)	PT(VL,0.1bar)	H=PT(VL,0.1bar)	6
2			C=PT(VL,1bar)	C=PT(VL,1bar)	H=PT(VL,0.1bar)	H=PT(VL,0.1bar)	4
3			C=PT(VL,1bar)	PT(VL,1bar)	PT(VL,0.1bar)	H=PT(VL,0.1bar)	6
4	C=PT(VL,10bar)	C=PT(VL,10bar)	C=PT(VL,10bar)	C=PT(VL,10bar)	H=PT(VL,0.1bar)	H=PT(VL,0.1bar)	4
5			C=PT(VL,0.1bar)	PT(VL,0.1bar)	PT(VL,0.1bar)	H=PT(PVL,1bar)	5
6		C=PT(VL,1bar)	C=PT(VL,1bar)	C=PT(VL,1bar)	H=PT(VL,0.1bar)	H=PT(PVL,1bar)	6
7	C=PT(VL,10bar)	C=PT(VL,10bar)	C=PT(VL,10bar)	C=PT(VL,10bar)	H=PT(VL,0.1bar)	H=PT(PVL,1bar)	6
…	…	…	…	…	…	…	>6

6.2.6. Step 6: Solve the reduced optimization problem and validate promising

Step 6.1: The remaining search space NPO_P is smaller than 10, steps 6.1.1-6.1.3 are not necessary (rule 6.1).

Step 6.2: For all remaining options, the objective function (Eq.6.8) is calculated (Table 6.34).

$$F_{obj}=(\Sigma c_{Heat}\cdot Q_{heat}+c_{cool}\cdot Q_{cool}+c_{Elec}\cdot E+c_{Mem}\cdot A_{mem}/t_{replacement})/n_{Product} \quad (6.8)$$

Table 6.34. Simulation results of each option.

Process Option	Heat (GJ/hr)	Cooling (GJ/hr)	Mechanical (kW)	$A_{membrane}$ [m^3]	Product [kmol/h]	cost/kmol product
#1	39.5	5.6	0.0853		255	2.18
#2		7.27	2440		254.26	0.58
#3		13.667	2440		256.13	0.59
#4		19	7004		247	1.73
#5	63	13		47000	253.7	5.82
#6	29		2800	65000	255	5.44
#7	249		107000	792000	255	77.72

Step 6.3: All process options are ranked according to their objective function. The results are presented in the table 6.35.

Table 6.35. Ranking of the remaining options by F_{obj}.

Rank	Process option	F_{obj} [US-$/kmol Product]
1	#2	0.58
2	#3	0.60
3	#4	1.73
4	#1	2.18
5	#6	5.44
6	#5	5.82
7	#7	77.72

The best one is option number #2 which is the internal integration of the rectifying section (at P=1 atm) and the stripping column (at P=0.1 atm) in one column (see Figure 6.16).

Step 6.4: The results in the previous step have been obtained using rigorous simulation in Pro\II.

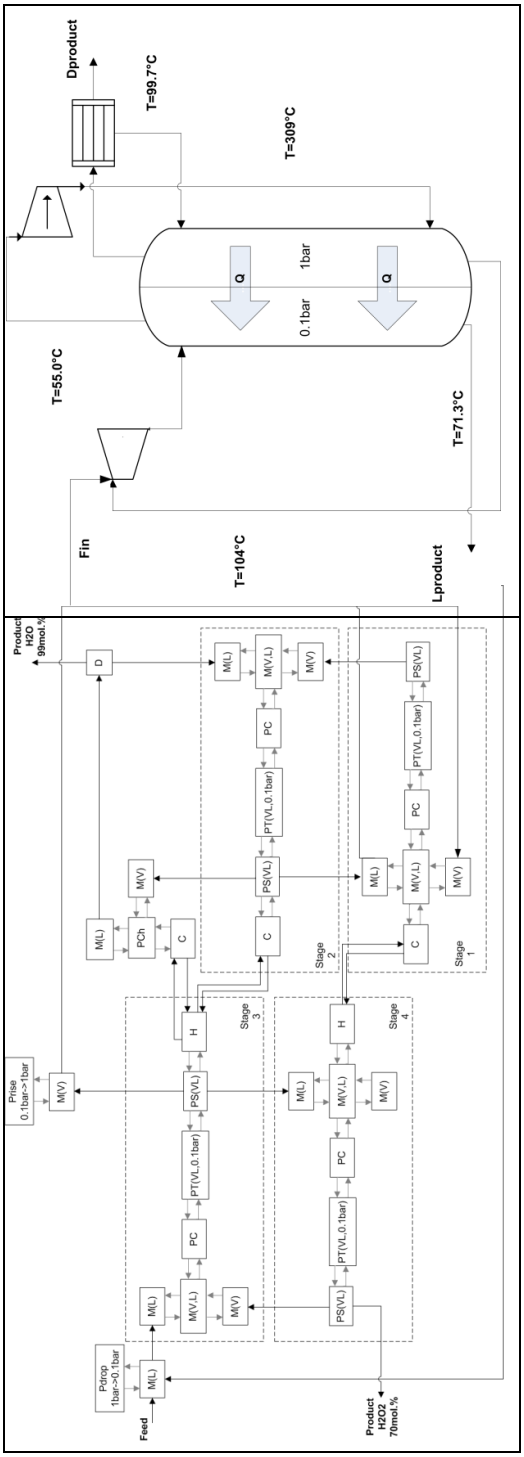


Figure 6.16. Process option #2 at the phenomena level (left) and at the unit operation level (right).

6.2.7. Discussion of the influence of the pre-selection of the membrane

In step B2.4.3 the sub-algorithm **SoP** is applied. In the first step (SoP.1) it has been decided to use only known membranes which limits the search space. Based on the results obtained in step 6.3, the properties of the membrane are targeted in a reverse approach to identify how the membrane should look like (in terms of selectivity and costs) in order to perform better than the best obtained result. With increasing selectivities of the membrane, the driving force for the separation of H_2O_2 and H_2O increases (see Fig. 6.17).

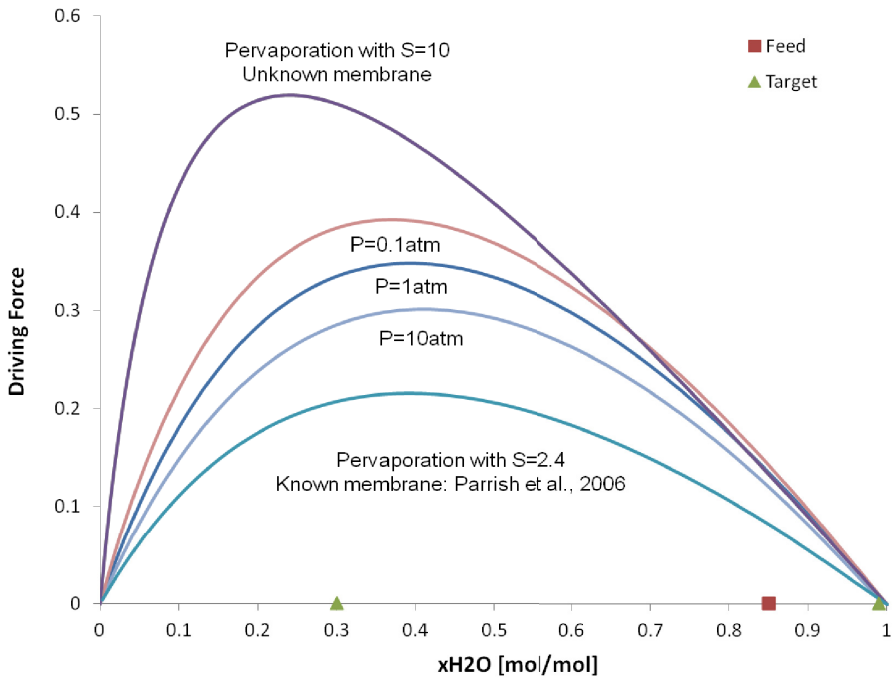


Figure 6.17. Driving Force of phase transition by relative volatility at different pressure and by pervaporation at different selectivities.

For that the second best option is used in which the phase transition phenomena by relative volatility at P=0.1 atm in the stripping section are replaced by phase transition phenomena by pervaporation. In the following table, a number of process options including membranes have been checked at different selectivities. It can be concluded that none of the systems with any membrane will lead to a better design than the one obtained before (see Table 6.36).

Table 6.36. Comparison of process options with membranes and the best option from step 6.3.

Process option	Cost per membrane	Remarks
Best option without a membrane	-	Costs are 0.59 US-$/kmol Product
PVL (S->∞)	C < 0	The cost for the evaporation (ΔHvap=30.58) of 1.7 US-$/kmol
C=PT(VL,1bar)- C=PT(VL,1bar)- C=PT(VL,1bar)- H= PVL (S=10)- H= PVL (S=10)	C < 0	The operating costs without taking the membrane costs into account are already higher (0.7 US-$/kmol) than the best design
C=PT(VL,1bar)- C=PT(VL,1bar)- C=PT(VL,1bar)- H= PVL (S=100)- H= PVL (S=100)	C < 0	The operating costs without taking the membrane costs into account are already higher (0.8 US-$/kmol) than the best design
C=PT(VL,1bar)- C=PT(VL,1bar)- C=PT(VL,1bar)- H=PT(VL,0.1bar)- H= PVL (S=10)	C < 0	The operating costs without taking the membrane costs into account are already higher (0.6 US-$/kmol) than the best design
C=PT(VL,1bar)- C=PT(VL,1bar)- C=PT(VL,1bar)- H=PT(VL,0.1bar)- H= PVL (S=100)	C < 0	The operating costs without taking the membrane costs into account are already higher (0.6 US-$/kmol) than the best design

6.3. Production of cyclohexanol

In the first two case studies, a reaction and a separation have been intensified using the phenomena-based methodology. The purpose of this case study is to show that whole prosesses and complex flowsheet options containing reactions and separations can be handled and complex schemes such as reactive distillations can be generated. As a case study, the production of cyclohexanol is used because in scientific literature different types of reactive distillation configurations have been proposed. Hence, it is considered to be a good verification of the developed methododology.

In section 6.3.1 a brief introduction to the production of cyclohexanol is given. In sections 6.3.2-6.3.4 the algorithm of the phenomena-based methodology is applied until it can be proven that reactive distillation schemes can be systematically generated.

6.3.1. Brief introduction to the production of cyclohexanol

Currently there are three commercial routes to produce cyclohexanol, the hydrogenation of benzene to cyclohexane and its subsequent oxidation by air to cyclohexanol (cyclohexanone), the hydrogenation from phenol and hydrogenation of benzene to cyclohexene and the further hydration to cyclohexanol (Steyer, Qi & Sundmacher, 2002) The first two process routes suffer through a large amount of by-product formation as well as safety issues through mixing with air and entering an explosive zone while the second process alternative suffers from the high price of the raw material (Steyer, Qi & Sundmacher, 2002). Hence, it is believed that the third process alternative has the highest market potential. One process alternative is patented from Asahi Chemical Co (Mitsui & Fukuoka, 1984). This process overcomes the drawbacks mentioned for the other processes. The process consists of a slurry reactor containing solid catalyst particles with a subsequent decanter and a distillation column, see Fig. 6.18.

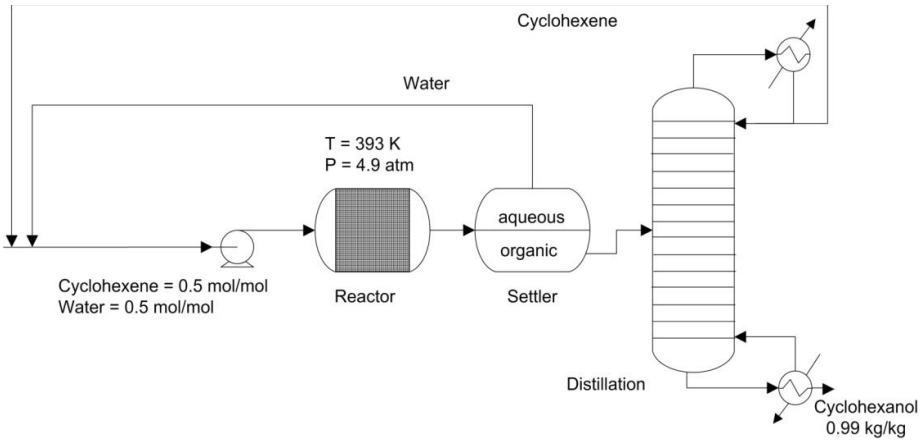


Figure 6.18. Asahi process for cyclohexanol production via direct hydration of cyclohexene (Mitsui & Fukuoka, 1984).

6.3.2. Step 1: Define problem

Step 1.1: The objective function is to identify a novel process solution using PI which minimizes the energy consumption in the production of cyclohexanol:

$$\min F_{obj} = \sum \dot{E} \tag{6.16}$$

Step 1.2: The design scenario is the improvement of the whole process and the process scenario is selected to be continuous production of cyclohexanol from cyclohexene.

Step 1.3: The specifications are:

- production capacity of 60000 t/ year of cyclohexanol from cyclohexene
- product quality is defined to be 99 wt.% of cyclohexanol.
- high yield (> 99% with respect to cyclohexene) of the process.
- The feed is a mixture of cyclohexene/ cyclohexane assuming a value up to 40 mol.% of cylcohexane in cyclohexene feed (Katariya, Steyer & Sundmacher, 2009).

Step 1.4-1.6: Since this is only a conceptual example to show that different reactive distillation options can be generated with this approach, no screening will be shown.

Step 1.7: A base-case design for non-pure feed of cyclohexene does not exist, step B2 is entered.

6.3.2. Step B2: Identify and analyze necessary tasks to achieve the process targets

Step B2.1-2.2: All components in the system are listed and assigned based on rules B2.1-B2.3 (see section 3.1.4). The identified function of each component in this system is given in Table 6.37.

Table 6.37. Assignment of function of components in the system.

Component	Function in the system
Cyclohexene	Reactant (Inlet)
Cyclohexane	Inert (Inlet)
Cyclohexanol	Product (Outlet)

B2.3: Define all reactions in the system:

Step B2.3.1: No reactions have been specified, step B2.3.2 is entered (rule B.2.5).

Step B2.3.2: In the scientific literature, two reaction routes are reported to produce cyclohexanol from cyclohexene. These are the direct hydration or in a 2-step route via indirect hydration via formic acid (Steyer & Sundmacher, 2007).

Direct hydration of cyclohexene to cyclohexanol (R.1):

$$C_6H_{10} + H_2O \leftrightarrow C_6H_{12}O \tag{6.17}$$

Indirect hydration via cyclohexyl formate from cyclohexene and formic acid (R.2; Eq.6.18) and subsequent hydration of cyclohexyl formate to cyclohexanol and formic acid R.3; Eq.6.19):

$$C_6H_{10} + CH_2O_2 \leftrightarrow C_7H_{12}O_2 \tag{6.18}$$

$$C_7H_{12}O_2 + H_2O \leftrightarrow C_6H_{12}O + CH_2O_2 \tag{6.19}$$

The missing components water, formic acid and cyclohexyl formate are added to the list of components (Table 6.38).

Table 6.38. Extended assignment of function of components in the system.

Component	Function in the system
Cyclohexene	Reactant (Inlet)
Cyclohexane	Inert (Inlet)
Cyclohexanol	Product (Outlet)
Water	Reactant(Inlet)
Formic Acid	Reactant (Inlet), only indirect hydration route
Cyclohexyl formate	Reactant, Product, only indirect hydration route

Step B2.3.3: At least one of the reaction schemes are necessary and therefore desirable reaction schemes forming the product (Rule B2.7).

Step B2.3.4: All reaction tasks are put into a task-based flowsheet and connected to their corresponding reactants (Figure 6.19).

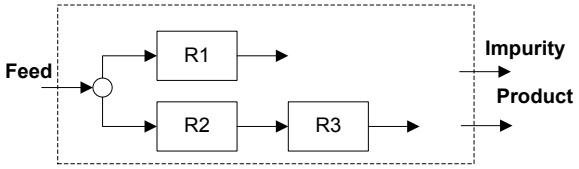


Figure 6.19. Task based flowsheet connecting inlets to the corresponding reactions.

Step B2.3.5: The algorithm **AR** to analyze the reaction phenomena is applied.

Enter sub-algorithm AR:

AR.1: Reactions are present in the system, enter AR.2 (Rule AR.1).

AR.2: Collect data for reaction analysis:

AR.2.1: Kinetic and equilibrium models are collected from the literature (see appendix A.11.1).

AR.2.2: No batch information is collected because the scenario is continuous.

AR.2.3: Information about heat of reaction is required (rule AR.2).

AR.2.4: The heat of formation for each component is collected from the ICAS database (see appendix A.11.1).

AR.2.5: The heat of reaction is estimated for each reaction using equation 6.20.

$$H_R = \sum H_{F,\text{Product}\,i} - \sum H_{F,\text{Reactant}\,j} \tag{6.20}$$

The first two reactions (R1 and R2) are exothermic while the third one is endothermic (Table 6.39).

Table 6.39. Calculated heat of reactions.

Reaction	Heat of reaction (kJ/kmol)
R.1	-39790
R.2	-65100
R.3	25310

AR.3: The conversions are calculated using the equilibrium constants of the reactions (Table 6.40).

Table 6.40. Equilibrium constants and conversion of the three reactions.

Reaction	Equilibrium constant K_{eq}	Conversions $\lambda_{Reac,EQ}$
R.1	1.42	21.7
R.2	1.43	21.8
R.3	1.38	54.0

AR.4: Base case does not exist.

AR.5: The limitation of all reactions is the unfavourable equilibrium (criterion 1) as well as the slow reaction rate for the hydration reaction R.1 (criterion 6,).The latter one can be seen when plotting the reaction rates of the reaction over the temperature (criteria 6, see figure 6.20).

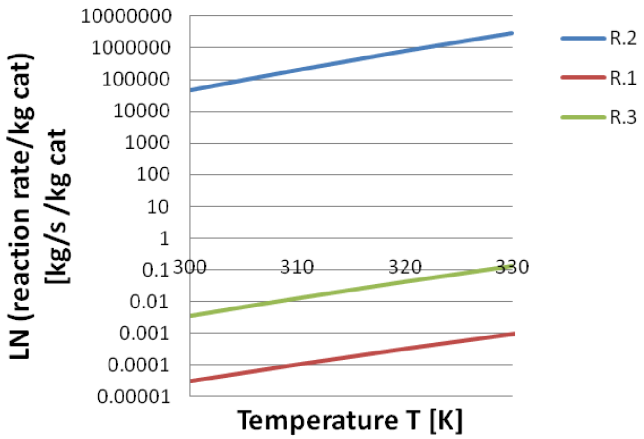


Figure 6.20. Relationship of the reaction rate per kg catalyst over the temperature for the three reactions.

AR.6: No inhibition is identified; leave AR (rule AR.3).

Exit sub-algorithm AR

Step B2.4: Identify necessary separation/mixing/heat supply/removal tasks for each outlet:

Step B2.4.1: From the outlet of the reactor, it is determined that two more separations are necessary:

- separation (purification) of Cyclohexanol (B2.10) and
- separation of the impurity cyclohexane (B2.10).

All other components are recycled (B2.11).

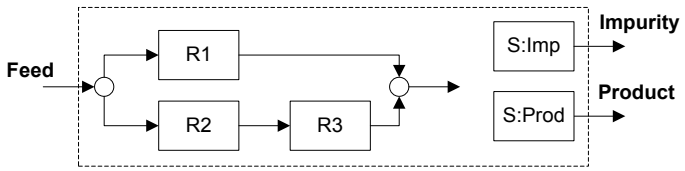


Figure 6.21. Task based flowsheet connecting inlets to the corresponding reactions and introducing outlet specifications.

Step B2.4.2: Identify suitable phenomena by applying **APCP** and then **AMP.**

Enter sub-algorithm APCP:

APCP.1 Generate/retrieve pure component properties *PCP.*

APCP.1.1: A list of pure component properties is retrieved from the ICAS-database (Table 6.41).

Table 6.41. List of pure component properties.

Components	T_B (p=1atm) K	T_M (p=1atm) K	Solubility parameter δ_{SP} Mpa^0.5	Dipole moment	Radius of gyration A	Van der Waals volume m³/kmol	MW g/mol
Cyclohexane	353,87	279,69	17	0,6085	3.242	0,0614	84.161
Cyclohexene	356,12	269,67	17	0,3297	3.157	0,05672	82.145
Cyclohexanol	434	296,6	24	2	3.601	0,06484	100.161
Water	373,15	273,15	48	2	0,615	0,01237	18.015
Formic acid	373,71	281,55	21	1	1.847	0,02274	46.026
Cyclohexyl formate	435,65	210	185.969	4	4.262	0,07654	128.171

APCP.1.2: Property prediction is not necessary.

APCP.2: For each task the binary ratios of the pure component properties have been calculated.

APCP.3-4: Steps are not necessary.

APCP.5: Suitable phase transition phenomena are presented in the table 6.42.

Exit sub-algorithm APCP

Table 6.42. Identified phenomena for each task using the algorithm **APCP**.

Task	Identified phenomena	How determined?	Note
Separation	Phase transition by:		
Cyclohexanol	Solid-Liquid contact (crystallization)	T_M,	HOAc concentration low
	Gas-liquid contact (stripping)	T_B	Critical if Cyclohexyl-formate present
	Liquid-liquid contact (extraction)	$Log(K_{ow})$	Solvent necessary
	Pervaporation	R_g, V_M, VdW, $\boldsymbol{\delta_{SP}}$	Membrane necessary
	Liquid membrane	R_g, V_M, VdW	Membrane necessary
	Vapor-liquid by relative volatility	T_B, P_{LV}	Critical if Cyclohexyl-formate present
Separation	Phase transition by:		
Cyclohexane	Solid-Liquid contact (crystallization)	T_M,	Critical if Cyclohexene present
	Gas-liquid contact (stripping)	T_B	Critical if Cyclohexene present
	Liquid-liquid contact (extraction)	$Log(K_{ow})$	Critical if Cyclohexene present
	Pervaporation	R_g, V_M, VdW, $\boldsymbol{\delta_{SP}}$	Critical if Cyclohexene present
	Liquid membrane	R_g, V_M, VdW	Critical if Cyclohexene present
	Vapor-liquid by relative volatility	T_B, P_{LV}	Critical if Cyclohexene present

Enter sub-algorithm AMP:

AMP.1: Occurrence of azeotropes and miscibility gaps are checked (AMP.1-AMP.2).

AMP.2-3: For the calculation of the activity coefficients, the NRTL model by Steyer & Sundmacher (2004) has been selected (see appendix A.11.2).

AMP.4: In total 11 binary azeotropes have been determined (Table 6.43).

Table 6.43. List of pure component boiling points T_B and binary azeotropes at p=1 atm.

Components	T_B in [K]	x_1 in [mol.-%]	Direct Hydration	Indirect Hydration
Cyclohexane/ Water	327.2	57.08	x	x
Cyclohexane/ FA	340	44.58		x
Cyclohexene/ FA	343.7	49.17		x
Cyclohexene/ Water	343.9	68.27	x	x
Cyclohexane/ Cyclohexene	353.3	68.9	x	x
Cyclohexane	353.8		x	x
Water/ Cyclohexyl formate	355.4	73.49		x
Cyclohexene	356.0		x	x
Cyclohexyl formate/ FA	361	14.79		x
Cyclohexanol/ FA	369.3	5.91		x
Water/ Cyclohexanol	369.6	89.7	x	x
Water	373.2		x	x
Formic-Acid	373.9			x
Water/ FA	376.5	70.64		x
Cyclohexyl formate/ Cyclohexanol	427.8	56.59		x
Cyclohexanol	434.1		x	x
Cyclohexyl-Formate	435.4			x

Additionally, the miscibility between the components has been determined. Four components show immiscibility's with each other. These are Water/ Cyclohexene, Water/ Cyclohexane, Water/ Cyclohexanol, Formic-Acid/ Cyclohexene and Formic Acid/ Cyclohexane. Exemplary, the ternary diagram of the system cyclohexene, cyclohexanol and water is presented in Figure 6.22, using

NRTL as thermodynamic model. Cyclohexene and water are highly immiscible while cyclohexanol is only partially miscible with water.

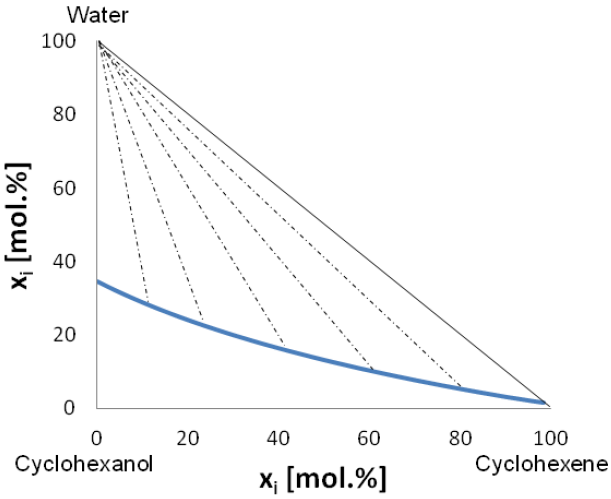


Figure 6.22. Task LLE for ternary system of cyclohexene – cyclohexanol – water simulated with NRTL model (from Steyer & Sundmacher, 2004) for T=323 K and p=1 atm.

AMP.5: Step is not necessary

AMP.6: Phase transition by settling is possible because an immiscibility region for the separation of cyclohexane exists but is critical because also cyclohexene splits.

Exit sub-algorithm AMP

Step B2.4.3: Since the target of this case study is to prove that a reactive distillation is generated only phase transition by relative volatitlty and LL split by settling are kept in the search space.

Step B2.4.4: The following bullet points are put into the list of limitations LB:

- LB_1: Reaction R1-R3 have an unfavorable equilibrium
- LB_2: Reaction R1 is slow
- LB_3: The reactants water and cyclohexene are only partly miscible
- LB_4: The separation of cylclohexane from the system is only possible by loss of water (lowest boiling point)
- LB_5: The separation of cyclohexyl-formate is critical in case cyclohexyl-formate is

present.

Step B2.5: No additional necessary tasks are identified.

Step B2.6: The phenomena-based workflow is entered (rule workflow).

6.3.3. Step P3: Identification of desirable phenomena

Step P3.1: Identify additional desirable tasks for enhancement of the necessary tasks.

Step P3.1.1: The list of keywords K_{PI} includes all identified limitations/bottlenecks LB (see step B2.4.4), process tasks (step B.2.4.1) and the corresponding objective (F_{obj}, *PM*).

Step P3.1.2: The algorithm **KBS** is used to identify desirable tasks of the process (Table 6.44). The reasoning behind the identification of the desired task is shown in the following table 6.45.

Table 6.44. List of necessary tasks and identified desirable tasks.

Necessary task	Identified desirable Task
Reaction 1	Reaction with cyclohexanol (not desirable), separation of cyclohexanol, Reaction heat supply
Reaction 2	Reaction with cyclohexyl-formate, separation of cyclohexyl-formate
Reaction 3	Reaction with formic-acid, reaction with cyclohexanol (not desirable), separation of formic acid, separation of cyclohexanol
Separation of the product: cyclohexanol	No limitation has been found here.
Separation of impurity: cyclohexane	Reaction with cyclohexane, Reaction with cyclohexene, Separation of cyclohexane

Note: One example for the enhancement of the reaction speed for reaction R1 is to check novel forms of energy identified through integration of reaction and heat supply (Table 6.45).

Table 6.45. Decision Table regarding PI solutions to reported limitations in the process *(*A "○" in the second section means that this particular intensified option is reported to overcome this limitation, "●" means the activation of an option through a knowledge search*)*.

Limitation/ Bottleneck	Necessary task: Desirable task:	Reaction Separation	Reaction heat supply	Reaction mixing	Reaction Reaction	Separation Reaction	Separation mixing	Separation Separation	…
	Separation is not sufficient								
	limiting equilibrium	○				○		○	
LB_4	azeotrope	○				●		●	
	high energy demand					○	○	○	
	limited mass transfer						○	○	
	limited heat transfer						○	○	
LB_5	driving forces too low	○				●		●	
	Reaction is not sufficient								
(LB_3)	contact problems of educts; limited mass transfer			●	●				
	product reacts further/is intermediate	○				○			
	activation problems		○	○					
	degradation by T	○	○						
	degradation by pH					○			
	difficulties to control conditions, reaction too exotherm/endotherm	○	○	○	○				
LB_2	Reaction is slow	●	●		●				
LB_1	limiting equilibrium	●			●				

Step P3.2-P3.3: The algorithms APCP and AMP are used to identify potential phenomena blocks for each identified additional desirable task: The results of this step are similar to step B2.3.

Step P3.4: The sub-algorithm AR is applied. From the database, the already existing reactions in the system R1-R3 are selected.

Step P3.5: The sub-algorithm SoP is used to select the potential best phenomena for each identified additional desirable task. In this sub-algorithm the operating windows are determined calling the sub-algortihm **OPW**.

Note: Since the target of this case study is to prove that a reactive distillation and extractive distillation can be generated using the phenomena based workflow, only phase transition by relative volatility (distillation) and phase transition by LL-settling (extraction) is kept in the search space (see Table 6.46). It has been identified that formic-acid degradas at temperatures above 330 K. Therefore when the reaction phenomena R2 and R3 are coupled with the phase transition phenomena, the pressure must be lowered to P=0.1 bar.

Table 6.46. Necessary tasks and examples of identified phenomena fulfilling them.

Necessary task	Examples of identified phenomena
Reaction 1/ Reaction with cyclohexene,	Reaction phenomenon R1
Reaction 2/ Reaction with formic-acid,	Reaction phenomenon R2
Reaction 3/ Reaction with cyclohexyl-formate	Reaction phenomenon R3
Separation of cyclohexanol	Relative volatility
Separation of cyclohexane	Relative volatility LL-settling
Separation of cyclohexyl-formate	Relative volatility
Separation of formic acid,	Relative volatility LL-settling

Step P3.6: Identify accompanying phenomena by contacting the knowledge base for each identified phenomenon: In total 22 phenomena ($n_{P,tot}=22$) are identified which are presented in the appendix A.11.3.

Step P3.7: The algorithm **OPW** is applied to determine the operating window of each phenomenon (see Table 6.47).

Table 6.47. Operating windows for involved phenomena (The description of phenomena behind the abbreviation can be seen in appendix A.11.4).

No.	Phenomena	Boundaries of the operating window at P=1bar
PB.1	M(V)	T_{low} (Lowest Boiling Point)< T Concentrations above boiling point line.
PB.2	M(L)	T_{low} (Lowest Melting point) < T < T_{high} (Highest Boiling Point) Concentrations below dew point line.
PB.3	M(VL)	T_{low}=318.9 K (Lowest Boiling Point) < T < T_{high} (Highest Boiling Point) Concentrations in V-L regions between dew and boiling point lines.
PB.4	M(LL)	T_{low} (Lowest Melting point) < T < T_{high} (Highest Boiling Point) Concentrations below dew point line and in immiscibility region.
PB.5	Mno(LL)	T_{low} (Lowest Melting point) < T < T_{high} (Highest Boiling Point) Concentrations below dew point line and in immiscibility region.
PB.6	PT(VL,1bar)	T_{low} (Lowest Boiling Point) < T < T_{high}(Highest Boiling Point) Concentrations in V-L regions between dew and boiling point lines.
PB.7	PT(VL,0.1bar)	T_{low} (Lowest Boiling Point) < T < T_{high}(Highest Boiling Point) Concentrations in V-L regions between dew and boiling point lines.
PB.8	PT(LL,1bar)	T_{low} (Lowest Melting point) < T < T_{high} (Highest Boiling Point) Concentrations below dew point line and in immiscibility region.
PB.9	PT(LL,0.1bar)	T_{low} (Lowest Melting point) < T < T_{high} (Highest Boiling Point) Concentrations below dew point line and in immiscibility region.
PB.10	PS(VL)	Vapor-Liquid present
PB.11	PS(LL)	Liquid-Liquid present
PB.12	D	
PB.13	H	
PB.14	C	
PB.15	PCh	From V to L: inlet above dew point line, outlet below bubble point line From L to V: inlet below bubble point line, outlet above dew point line
PB.16	PC(VL)	Vapor-Liquid present
PB.17	PC(LL)	Liquid-Liquid present
PB.18	Prise	
PB.19	Pdrop	
PB.20	R1	
PB.21	R2	
PB.22	R3	

Step P3.8: The whole system needs to be solved together (SP=1, rule P3.3).

6.3.4. Step P4: Generate feasible operation/flowsheet options

P4.1: Generate all feasible simultaneous phenomena building blocks SPB's from the phenomena in the search space:

P4.1.1: Identify the maximum number of phenomena within a SPB $n_{P,max}$:

The number of competing phenomena within a SPB is $n_{P,compete}=1+1+1+5+1=9$ because: Heating and cooling (1), pressurizing and expanding (1) cannot be connected and only one LL-mixing (1), only one phase transition phenomenon at different pressures or phase change (5), or stream divding can be present within one stage (1). Additionally, the dividing phenomenon is one stage itself. Hence, the maximum number of phenomena within a stage is calculated with equation 6.21:

$$n_{P,max}= n_{P,tot} - n_{P,compete} = 22-9=13 \quad (6.21)$$

P4.1.2: All possible SPB's are generated connecting of 1 up to $n_{P,max}$ phenomena within one SPB. That gives 1898712 SPB's (see equation below). The maximum number of SPB's can be calculated (see Eq.3.2=:

$$NSPB_{\max} = \sum_{k=1}^{n_{P,\max}} \left(\frac{\left(n_{P,tot}-1\right)!}{\left(n_{P,tot,w/oD}-k-1\right)!k!} \right) + 1 = 1898712 \quad (6.22)$$

P4.1.3: Screening of all SPB's for feasibility:

<u>*Note:*</u> This step has not been performed. However, some of the remaining SPB's in the search space are presented in Table 6.48.

Table 6.48. Example of feasible SPB's based on the phenomena in the search space.

SPB	Connected Phenomena
SPB.1	M(L)
SPB.2	M(V)=PCh=C=M(L)
SPB3	M(L1)=M(L2)=Mno(LL)=PC(LL)=PT(LL,1bar)=PS(LL)
SPB.4	M(L)=H=PCh=M(V)
SPB.5	M(V,L)=M(VL)=PC(VL)=PT(VL,1bar)=PS(VL)
SPB.6	M(V,L)=M(VL)=R1=PC(VL)=PT(VL,1bar)=PS(VL)
SPB.7	D
SPB.8	M(V,L)=M(VL)=R2=PC(VL)=PT(VL,0.1bar)=PS(VL)
SPB.9	M(V,L)=M(VL)=R3=PC(VL)=PT(VL,0.1bar)=PS(VL)
SPB.10	M(L)=Pdrop
…	…
SPB.?	…

P4.2: All SPB's can be analyzed to identify the number of stages based on their interconnection necessary to achieve a task target. Assuming, these are known and for each necessary task counter-current flow is selected because this configuration allows the best performance at high purifications to be achieved (Rule P4.5-P4-6 & RuleP.4.8).

P4.3: Generate the number of feasible operation options: Similar to step 4.1, the stages are now connected to form unit operations.

P4.3.1: A suitable superstructure is selected. Since we do have at least two separate tasks (operating window of reaction R2 and R3 are not matching, a superstructure containing of two generic column superstructures for handling two separate tasks in a countercurrent arrangement is retrieved from the knowledge base. A generic column superstructure is retrieved from the model library (see Figure 6.23).

P4.3.2-P4.3.3: The two separate tasks are connected by potentially integrating every outlet of the generic column into inlet of the other one and vice versa. Subsequently, all options are generated by inserting the SPB's into the stages of the superstructure.

Note: For example, a connection of stages SPB.1-SPB.7 to fulfill the tasks shown in figure 6.24 gives the reactive distillation set-up proposed by Steyer *et al.* (2002) while a connection of the stages SPB.1,SPB.2, SPB4., SPB.7-SPB.10 to fulfill the necessary process tasks, as shown in

figure 6.25, gives the reactive distillation configuration from Katariya *et al.* (2009). The phenomena-based flowsheet can be found in the appendix A.11.4.

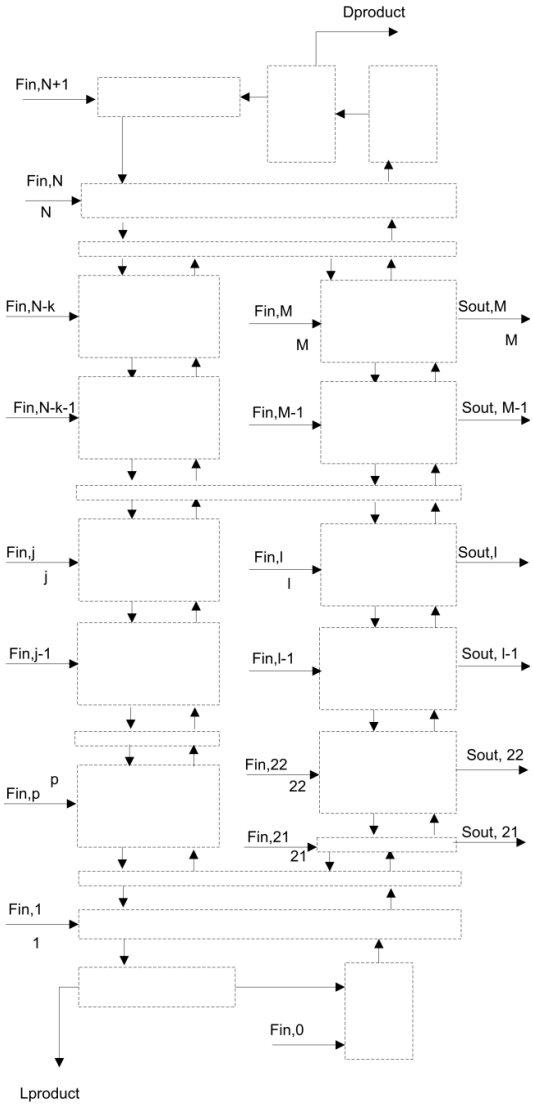


Figure 6.23. Generic column superstructure.

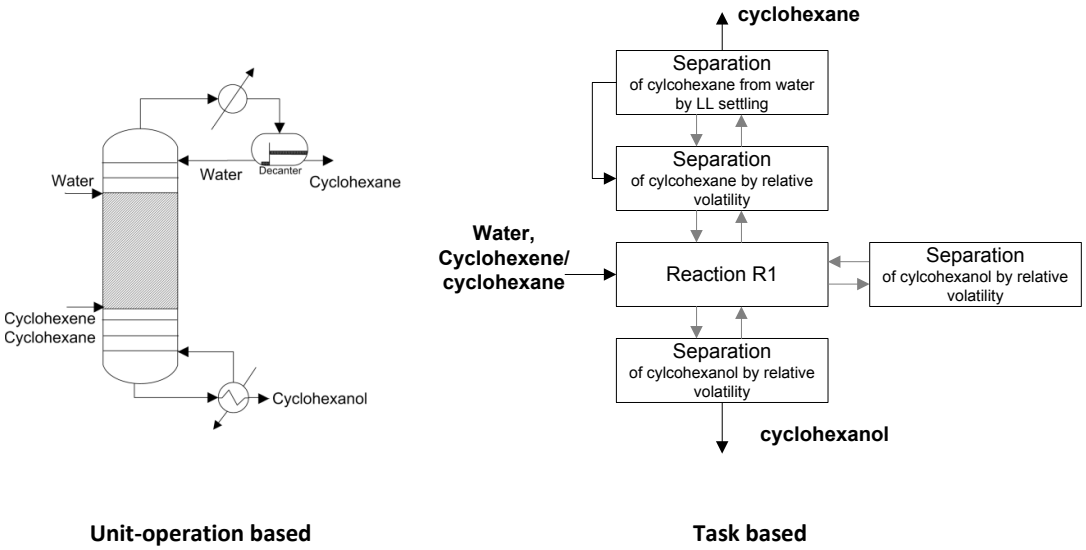
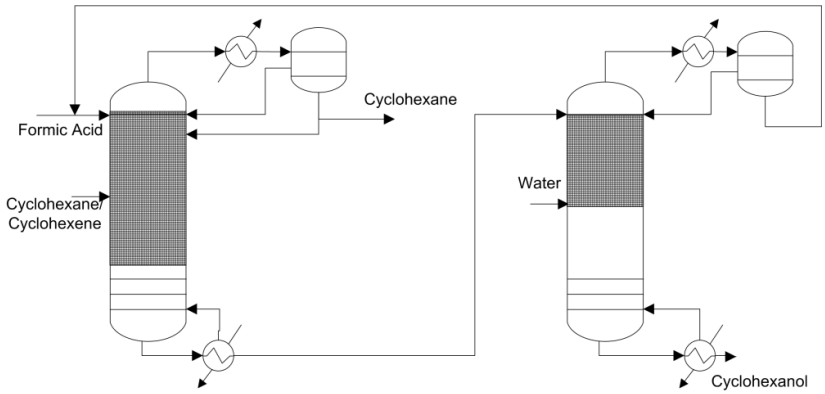
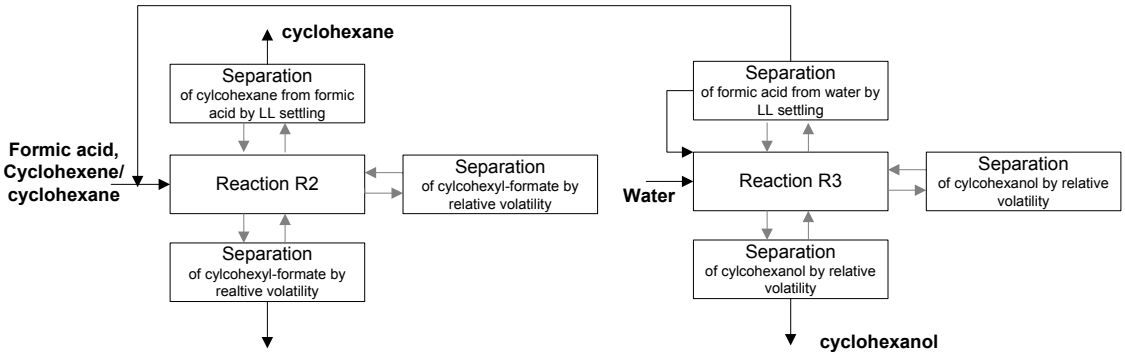


Figure 6.24. Flowsheet for direct hydration based on unit operations (left; Steyer, Qi & Sundmacher, 2002) and based on phenomena here represented by the tasks (right).



Unit operation based



Task based

Figure 6.25. Flowsheet for indirect hydration via formic acid ester based on unit operations (top; Katariya, Steyer & Sundmacher, 2007) and based on phenomena here represented by the tasks (below).

Chapter 7.

Discussion

In this PhD-project, a systematic synthesis/design methodology to achieve process intensification has been developed. Two building blocks, that is PI unit-operations and phenomena have been considered for solving the PI synthesis problem. The developed systematic PI synthesis/design methodology provides the means to identify, to generate and to evaluate PI options, from which the optimal intensified process option is obtained for the specified problem and the available data. The steps of the PI-methodology follow a rationale which may be common sense and also independently developed by others (PI Quick Scan process reviews in The Netherlands (van den Berg, 2001)). However, it has not been established as a hybrid synthesis method to achieve PI in a whole process:

- Using thermodynamic insights for the analysis of the process;
- Using knowledge for the identification of potential PI unit operations and/or phenomena;
- Using mathematical programming to identify the best feasible PI option from the set of potential PI unit operations;
- Generating PI solutions for a potentially quick implementation using the existing PI equipment;
- Generating novel (not predefined, not develeloped) PI equipment processes using the phenomena-based approach.

Hence, the scope of the developed methodology is beyond other PI synthesis methodologies (section 1, illustrated in Figure 7.1.) because it supports the user to answer all questions arising during a process synthesis problem (when; where; how/by which; why) on a quantitative basis, it includes a larger number of considered PI equipment and it can be applied to the whole process.

Comparing the developed phenomena based approach with PI synthesis methods beyond unit-operations, shows that the systematic way of identification of the PI solution covers other approaches at other levels of aggregation. As illustration, the reasoning of the case study for the production of cyclohexanol (case study 6.3) is compared with the reasoning by the application of the means-end analysis for the methyl-acteate process by Siirola (1971-2011). Reactive distillation systems have been proposed for both systems. Using, the phenomena based methodology, the unfavorable equilibrium in the reaction is identified as main limitation as well as the necessity to overcome this limitation in the reaction by coupling the reaction phenomenon with a suitable phase transition phenomenon. Since, all

components can be fully or partially (in case of azeotropes) be separated using the same phase transition phenomenon (relative volatility) the generated SPB's show overlapping operating windows. Whenever operating windows overlap for different phenomena, the phenomena can be connected or integrated. Identifying a suitable counter-current flow arrangement using the Kremser method and insertings SPB's into the stages of this flow arrangement, reactive distillation systems have been identified as a part of the solution search space. Now, the solution to the methyl-acetate production using the means-ends analysis by Siirola (1971-2011) is briefly highlighted. All details to that case are given in the appendix A.5. The identified equilibrium reaction task to form methyl-acetate does not run until 100% conversion. Therefore, a number of separation tasks is identified to separate (and recycle) the components in the system. All separation tasks can be separated using distillation-based separations. Since these tasks follow the same separation principle (distillation) and their input/outputs can be directly connected without temperature and/or pressure change, the tasks can be integrated into one column. Comparing the means-ends analysis solution path by Siirola (1971-2011) for the methyl-acetate example (see appendix A.5) with the phenomena based workflow solution path for the case study to produce cyclohexanol (section 6.3) shows that the reasoning for identification and integration are very similar. In fact, it can be concluded that the developed methodology in this PhD-thesis integrates the solution of the means-ends analysis because the phenomena level is lower than the tasks level (several different phenomena can fulfill one task in a process) and replaces the qualitative reasoning as well as the expert knowledge analysis needed in the means-ends analysis by a systematic generation and screening by quantitative measures (phenomena-based approach).

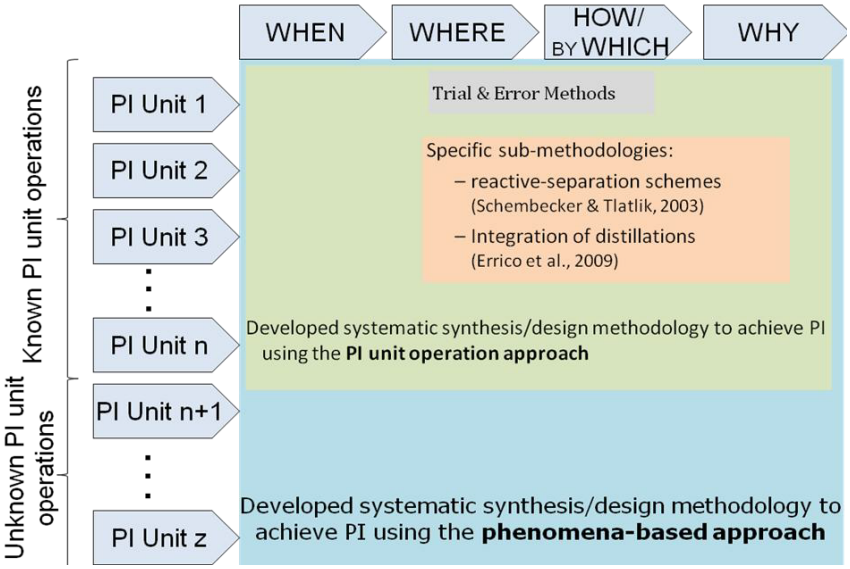


Figure 7.1. Context of the developed synthesis/design methodology (unit-operation based approach and phenomena-based approach) within other synthesis/design methodologies for PI.

The complexity of the mathematical synthesis problem introduced through the large number of generated options is successfully managed by the application of the decomposition approach. While the number of options decreases through each screening step the complexity of the calculations within the steps increases. This is underlined by looking exemplary for all case studies at the reduction of the number of process options for two case studies: Neu5Ac (unit-operation based approach); and IPAc (phenomena based approach). In both cases, a reduction from $3.5 \cdot 10^{11}$ or $6.5 \cdot 10^{10}$, respectively, to 1 option is made. The prescreening for feasibility as well as the screening by logical and structural constraints is based on a simple analysis of the necessary conditions as well as inlet/outlet constraints for a PI unit or a phenomenon while in the last step the most detailed models are used to identify the final solution. The reduction of the search space for both case studies is illustrated in Figure 7.2.

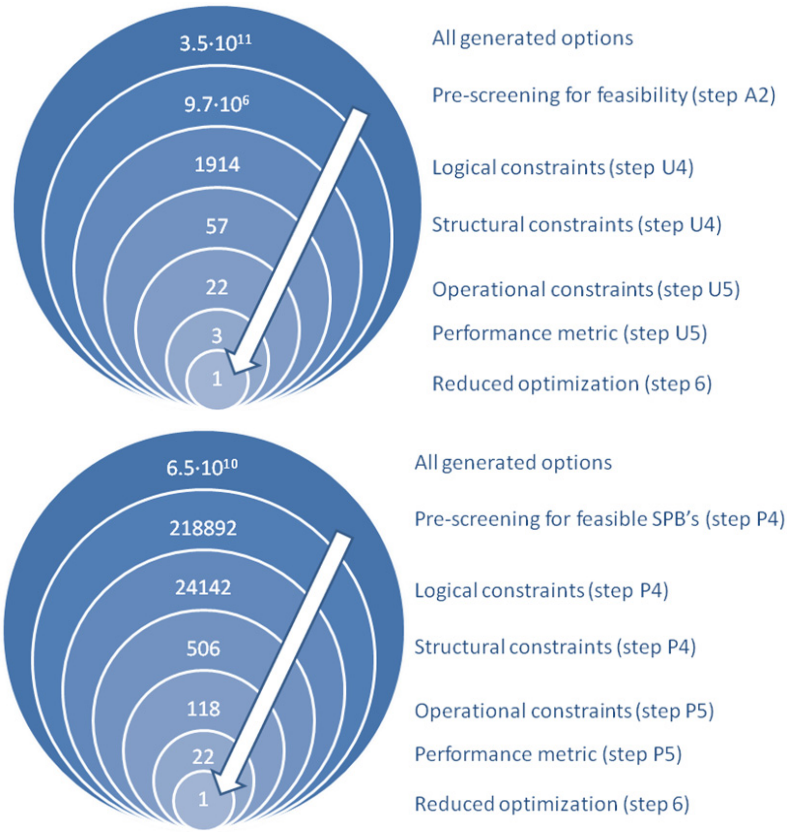


Figure 7.2. Search space reduction by the decomposition approach exemplary shown for the case studies Neu5Ac (top) and IPAc (bottom).

One important tool for the unit-operation based approach is the PI knowledge base. A knowledge base containing PI unit operations and examples of them has been also developed by the European Process Intensification Centre (Europic, 2009). However, their knowledge base is not open source. Besides PI equipment and examples of successful implementations as in the knowledge base of Europic (2009), since our PI knowledge base is tailored for the use within our synthesis/design methodology, it also contains logical and structural constraints; necessary conditions for a PI unit; knowledge about the task(s) a PI equipment may fulfill within a process; just to name some of the data (see Table 4.1).

In general, the developed methods and tools are generic and to show this, the methodology has been successfully applied to relevant case studies involving important products from the bulk chemical (H_2O_2, IPAc, cyclohexanol), bulk bio-based (HMF) and the pharmaceutical sector (Neu5Ac).

The PI unit-operation workflow aims to push the implementation of already exisiting PI equipment while the phenomena based approach aims to create novel PI process solutions beyond the ones currently existing which potentially gives even larger improvement as for the unit-operation based approach. This has been shown for the case study to purify H_2O_2 from an aqueous solution. However, the additional expense for the phenomena-based approach are the increased complexity due to the larger number of options as well as the increasing expected effort for the final implementation of the solution into a process.

However, currently, the developed methodology based on the unit-operation approach is limited to:

- PI equipment stored in the PI knowledge base:
- Availability and reliability of models for PI units (often not available; for example for application of microwaves);
- Fixed reaction paths as input;
- the manual handling of all the options.

The development of the phenomena-based approach has overcome the issues of the availability of models (because they are developed as the synthesis is made) and the restriction to unit operations. This also creates a new degree of complexity. However, it has been proven that the phenomena-based methodology is capable to generate complex systems (IPAc case study for a new reactor, H_2O_2 for a new separator) as well as to be applied to intensify whole processes (cyclohexanol). However, especially the last case study (cyclohexanol) shows that the large number of options cannot be handled manually anymore. An automation of the generation and screening in a software will be necessary.

The developed methodology based on the phenomena approach is limited to

- Phenomena in the phenomena library;
- Superstructures with fixed recycles (here, not all recycle possibilities have been enabled yet);
- Limited number of rules for the identification of units from the phenomena based flowsheet;
- The manual handling of all the options.

Chapter 8.

Conclusions

8.1. Achievements

The work done within this thesis has resulted in the **development of a systematic synthesis/design methodology to achieve process intensification**. This methodology allows the identification, generation and evaluation of PI options in a search space, from which the optimal intensified process option is obtained based on the specified synthesis problem and the available data. Process intensification using the developed methodology can be achieved by using two different building blocks: PI unit operations and phenomena. Within the methodology the following items have been achieved:

- Managing the complexity of the generation of a potentially large number of process options and based on this managing the complexity of solving the mathematical synthesis problem (section 2.1) **by using a decomposition based solution approach**. This approach has been successfully transferred from the CAMD area for the systematic design of components and mixtures (Karunanithi, Achenie & Gani, 2004). Through the decomposition approach, the mathematical PI synthesis/design problem is decomposed into manageable sub-problems for an efficient solution. That is simple calculations and simple analysis at early steps of the methodology for a quick and efficient search space reduction and more complex calculations in later steps for the identification of the best PI option.
- **Development of workflows** which guide the user to generate the necessary information necessary in each step to take decisions and to solve the specified PI synthesis/design problem systematically.
- **Development of sub-algorithms** for analysis of processes/phenomena based on pure component properties, mixture properties, reaction properties; for the development of superstructures; the selection of the best phenomena; the identification of operating windows of unit operations as well as phenomena; to apply the knowledge base search, to do a model-based search for process limitations of an existing process flowsheet for targeting PI.
- **Generation of PI processes using existing PI unit-operation for a potentially quick implementation of the identified best PI process solution.** For this a systematic classification of

purpose and characteristics of existing PI unit operations has been developed, Knowledge about PI unit operations are stored in a knowledge base tool.

- **Development of a PI knowledge base tool** for storage and retrieval of information of existing PI unit operations which enables the use of existing PI unit operations as building blocks for the methodology. The tool contains information such as: necessary conditions, tasks they fulfill in the process, a potential list of limitations/bottlenecks to be overcome, *etc.*, of around 110 PI unit operations. The PI knowledge base is developed in such a way that it can be easily extended through addition of additional columns (for new units) and rows (for new search classes). An ontology and an efficient search algorithm allow the simple and quick retrieval of information.
- **Generation of novel process solution beyond existing PI unit-operation through the development of a concept to synthesize processes by phenomena.** This includes the development and the definition of phenomena; a phenomena library for storage and retrieval of phenomena; connectivity rules to interconnect phenomena to simultaneous phenomena building blocks (SPB); connectivity rules to form unit operations from SPB's; and connectivity rules to form processes from unit-operations.
- **Development of superstructures to represent all process options in a search space.** Superstructures have been developed for the unit-operation based approach as well as the phenomena based approach which are stored in a model library.
- **Embedment of existing tools from the PSE community** into the methodology to calculate/generate the desired target of a step. Integrated tools are the method based on thermodynamic insights for analysis of the base-case design as well as identification of suitable PI equipment and/or process phenomena; the driving force method for the identification of suitable phenomena for a specific task; or the use of the element-based approach to generate reactive-phase transition equilibrium curves necessary for evaluation of integration possibilities of reaction and separation task
- **Development of a tool for quick and simple identification of the number of stages** to achieve a design specification of a process/task. This tool is based on the Kremser method which has been extended to all kinds of phase transition phenomena as well as to integrated reactive phase transition phenomena.
- **The development of a performance metric** to evaluate PI on a quantitative basis. This metric contains economic, safety, environmental as well as intrinsic intensified metrics.

The methodology together with the algorithms, tools and methods has been applied to six case studies. For all of them, PI has been identified to improve the process in the specified target. The following improvements have been achieved by PI using the unit-operation based approach:

- The space-time-yield in the production of Neu5Ac (section 5.1) has been improved by a factor of around 30. PI has been achieved by integrating of two reaction steps into a one-pot reactor using better enzymes. Additionally, the production is realized in four processing steps (compared to 7 in the base-case design).
- The operational costs in the hydrogen peroxide production (section 5.2) process via the anthraquinone route have been reduced by a factor of 2. PI has been achieved by replacing the hydrogenator column through a microchannel reactor and integrating oxidation reaction and extraction into a microchannel reactor-extractor. This allows a lower residence time of the product and the solvent in the reactors which decreased the degradation and loss of product and solvents. Additionally, the distillation column is replaced by a heat integrated distillation column giving large savings in the energy costs.
- In the production of HMF from fructose using water as solvent (section 5.3), the operational costs have been decreased from around 7 US-$ to around 1.2 US-$. This has been achieved by integrating reaction and subsequent extraction of the product into one microchannel device using a better solvent. In the microchannel reactor-extractor a selectivity and a conversion of the reaction of around 100% are potentially achieved. The costly downstream process for purification in the base case design has been replaced by a heat-integrated distillation of the product rather than distilling a large amount of water as in the base case design. This was enabled since the new identified solvent has been selected to be a high boiling solvent. Additionally, only two process steps are necessary for the production.

The following improvements have been identified by PI using the phenomena based approach:

- For the production of isopropyl acetate (section 6.1), a novel intensified reactor solution has been generated which is a tubular/rectangular millichannel reactor pervaporator (plate-and frame concept). Comparing, this with existing reactive distillation concepts and the conventional base case design, a decrease in the number of processing step, a decrease in the consumption of heat, a decrease in the amount of catalysts, while increasing the conversion to 100% has been realized.
- In the the purification step (separation of hydrogen peroxide from water within the production of hydrogen peroxide (section 6.2), the operational costs per kilogram product have been

reduced by a factor of 10. The best phenomena-based process solution is identified being a fully heat integrated distillation column at two pressures.

- In the production of cyclohexanol from cyclohexene and water (section 6.3), it has been shown that all existing PI unit operation solutions (reactive distillation integrated with an extractor; reactive distillation dividing wall columns) can be systematically generated. Besides a large number of additional process options have been generated for intensifying the process.

8.2. Open challenges & future recommendations

The developed methodology depends on the reliability and availability of the models. For the unit-operation based approach, these models are not always available and often not simple to develop since the physical effect responsible for the achieved enhancement of a phenomenon (for example in case of microwaves) is not always fully understood. This limits the current application of the unit operation based approach.

Thorugh the case studies, it has been confirmed that often a limitation is occurring in or caused by the reaction step. For example, hydrogen peroxide may also be produced from hydrogen and oxygen for which small (intensified) units are necessary due to safety issues. Therefore, it may be beneficial to couple the methodology with a tool which identifies all possible reaction routes. Currently, this tool does not exist. Another valuable extension of the phenomena based methodology would be to decide using a set of rules and the problem definition and/or indicators if a compartment, a series of units or a battery (parallel units) is going to be developed. This would allow, in case of reactors for example, to develop highly integrated unit concepts with locally (in all directions) different performances.

Up to now, the processes have been evaluated using the performance metric developed for PI and single criterion objective functions. However, important more complex methods to evaluate sustainability such as life cycle assessment (LCA) in which trade offs between different criteria are taken into account, have not been considered so far.

Mass integration has been considered establishing fixed recycle streams in the superstructures for both, the unit-operation based as well as the phenomena based approach. However, not all possible recycle streams have been considered yet. However, recycles may be beneficial for improving the process performance, for example of the overall conversion in a reaction process. However, how to evaluate and integrate recycles at early steps into the methodology remains unsolved.

Another important issue which PI faces and has not been tackled within this PhD-thesis is the integration of controllability of the developed PI process solution. It may be beneficial to ensure a controllability of the developed process simultaneously while generating the process options.

The developed methodology allows the generation of several billion process options which can be handled efficiently using the decomposition approach. However, the implementation of the developed methodology into a software (see Figure 8.1) to allow the automation of some of the steps will be highly beneficial to save even more resources and time and necessary to handle large and highly complex processes (which has been already seen for the cyclohexanol case study). In such a software the main workflow of the methodology is followed through a general interface. From there, all additional tools such as knowledge base tool and model library, databases are called. The sub-algorithms can be integrated as sub-programs (sub-functions) and called when necessary. The framework of such a software based on the developed methodology is illustrated in Figure 8.1.

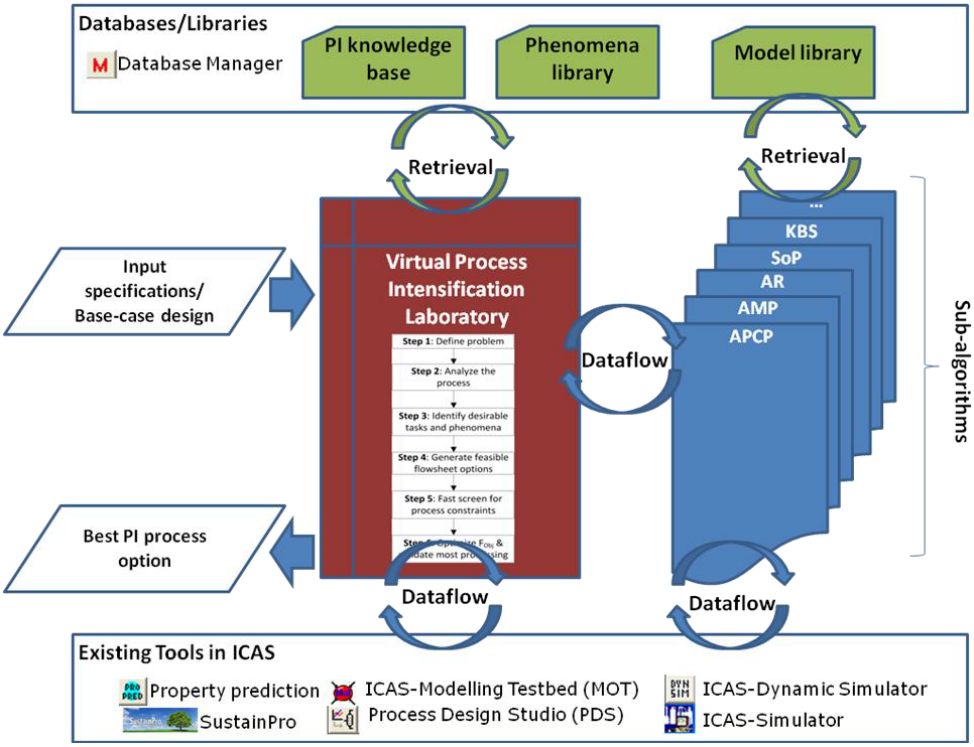


Figure 8.1. Proposed framework for implementation of the methodology into a software (here shown within the ICAS environment (Gani *et al.*, 1997)).

Abbreviation & Nomenclature

Abbreviation

A	N-acetyl-D-glucosamine
Alk1	Sodium hydroxide
Alk2	Calcium hydroxide
B	N-acetyl-D-manosamine
C	Pyruvic acid
Chrom	Chromatography
Cryst	Crystallization
D	N-acetyl-D-neuraminic acid (case study 5.1), Divider
DoF	Degree of freedom
E1	N-acylglucosamine-2-epimerase
E11	Immobilized recombinant of E1
E2	N-acetyl-D-neuraminic acid aldolase
E22	Immobilized recombinant of E2
EAQ	Ethyl-anthraquinone
Evap	Evaporator
EAQ.H2	Hydrogenated Ethylanthraquinone
H2O	Water
HMF	5-hydroxymethylfurfural
HOAc	Acetic acid
ICAS	Integrated Computer-Aided System
ICASSIM	Process simulation software in ICAS
IPAc	Isopropyl acetate
IPOH	Isopropanol
L	Liquid
LL	Liquid-Liquid-Extraction with reactive solvent
LLM	Liquid-Liquid-Extraction with methanol
MeAc	Methyl acteate
MeOH	Methanol
MINLP	Mixed integer non-linear programming
MoT	Modelling Testbed, see Heitzig *et al.*, 2011
NIU	Number of identified units
NOO	Number of operation options
NPO	Number of process options
NSPB	Number of simultaneous phenomena building blocks
OPR	One-pot reactor
OPRE	One-pot reactive extractor
PBA/TOMAC	Phenylboronic acid /Trioctylmethylammonium chloride
PB	Phenomena as building block
PI	Process intensification
Prec	Precipitation
ps	Processing steps
R1	Reaction 1
R2	Reaction 2
R3	Reaction 3

RM	Raw material
RV	Relative volatility
S	Separation
SP	Sub-Problem
SPB	Simultaneous phenomena building blocks
V	Vapor
WC	Whole cell

Nomenclature

a	Specific surface area (m^{-1})
A	Absorption-Factor (-)
A	Formula matrix (section 4.4)
A	Area (m^2)
c	Concentration (mol L^{-1})
c	Cost index (US-$/Unit)
C	Costs (US-$)
cv	Integer counting variable (-)
d	Equipment parameter
d	Diameter (m)
d_h	Hydraulic diameter (m)
e	Energy (J)
EA	Enzyme concentration (U L^{-1})
$f, h, k, l, m, n, o. s. v. w.$	Integer index variables
f	Force (N)
f	Fugacity (atm)
F	Molar flowrate (mol s^{-1})
h_P	Process model
H	Enthalpy (J)
H	Henry coefficient (atm m^3 mol^{-1})
H	Height of a channel (m)
H_F	Heat of formation (J)
H_R	Heat of reaction (J)
J	Flux (m^3 m^2 h^{-1})
kLa	Mass transfer coefficient (s^{-1})
K	Concentration ratio of one component between two phases
K_{eq}	Equilibrium constant (-)
K_{OW}	Octanol-water partition coefficient
L	Liquid flow (mol s^{-1})
L	Length (m)
m	Mass (g)
MW	Molecular weight (g mol^{-1})
n	Mole (mol)
P	Pressure (atm)
P	Permeability (m s^{-1})
P_{LV}	Vapor pressure (atm)
$\dot{Q}$	Heat Flow (J s^{-1})

Q	Pemeability (m^3 m^2 h^{-1} Pa^{-1})
r	Reaction rate (mol s^{-1})
r	Radius (m)
R	Reflux ratio (-)
R	Partition coefficient (-) in Eq. 5.48
R_g	Radius of gyration (Å)
Re	Reynolds number (-)
S	Stripping-Factor (-)
S	Selectivity (-)
t	Time (min)
T	Temperature (K)
v	Reaction rate (mol min^{-1} L^{-1})
V	Volume (m^3)
V	Vapor Flow (mol s^{-1})
V_M	Molar volume (m^3 $kmol^{-1}$)
VdW	Van der Waals volume (m^3 $kmol^{-1}$)
w	Velocity (m s^{-1})
W	Work (J)
W	Width of a channel (m)
x	Molar fraction (-)
X	Design variable
Y	Binary decision variable (-)

Greek letters

α	Recovery
δ_{SP}	Solubility parameter ($MPa^{0.5}$)
ε	Product-yield (mol mol^{-1} %)
ε_R	Time-yield of the reaction (g g^{-1} day^{-1})
η	Space-time-yield (g L^{-1} day^{-1})
Θ	Product parameter
ϑ	Deviation (-)
λ	Conversion (-)
ρ	Density (kg m^{-3})
ζ	Splitting factor (-)
ζ	Resistance factor in pipes/channels
σ	Separation factor (-)

Subscripts

0	Initial value at t=0
Abs	Absorption
avg	Average
B	Boiling point
eq	Equilibrium
HX	Heat exchange
hydrog	Hydrogenation
i	Component i
i	Inhibition
LB	Lower boundary

M	Melting point
Mix	Mixing, Mixer
ox	Oxidation
P	Product
P	Phenomenon
Purif	Purification of D
R	Reaction
Str	Stripping
UB	Upper boundary
tot	Total
α	Bottom outlet
β	Top outlet

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Appendix

This appendix includes all supplementary material to describe the information stored in the knowledge base such as list of PI equipment (A.1), a list of phenomena (A.2) and the database of constraints (A.3). Additionally, some important methods are highlighted by applying them in a conceptual example such as the Kremser method and the comparison to the McCabe-Thiele method (A.4) and the means-ends-analysis method applied to the methyl-acetate process (A.5). Finally, additional material for solving the case studies is included (A.6-A.11).

A.1. List of PI equipment in the knowledge base

In this section the list of 110 developed PI equipment (see Table A.1), 15 PI internals (Table A.2) as well as 13 general intensified PI beyond equipment/internals to intensify phenomena within existing operations (Table A.3) stored in the knowledge base tool are given. The information has been collected from the scientific literature and published information from industry. The different PI equipment are sorted by the task they fulfill within a process (conversion, separation, mixing and energy supply). In Table A.4, a detailed excerpt of the knowledge base is highlighted. Details about the knowledge stored for heterogeneous reactive distillation systems can be found in the published review paper: Lutze, Dada, Gani & Woodley (2011).

Table A.1. List of PI equipment in the knowledge base.

No.	Task 1	Task 2	Equipment	No.	Task 1	Task 2	Equipment
1	Conversion	Separation	Reactive Distillation / Catalytic Distillation	19	Conversion	Energy supply (Thermal)	Advanced Spiral-Type Heat Exchanger reactor
2	Conversion	Separation	Reaction Extraction (solvent-based)	20	Conversion	Energy supply (Thermal)	Printed circuit heat exchanger reactor
3	Conversion	Separation	Reaction Stripping in a Rotating packed-bed reactor	21	Conversion	Energy supply (Thermal)	Constant Power Reactor
4	Conversion	Separation	Reaction Crystallization	22	Conversion		non-catalytic static mixer reactor
5	Conversion	Separation	Reaction Condensation	23	Conversion		Catalytic Monolithic Reactor
6	Conversion	Separation	Reaction Membrane	24	Conversion		catalytic static mixer reactor
7	Conversion	Separation	Reactive Distillation with membrane/pervaporation	25	Conversion		Reaction Membrane with Catalyst
8	Conversion	Separation	Reactive Distillation with heat integration via dividing wall column	26	Conversion		Helix reactor
9	Conversion	Separation	Reactive Chromatography	27	Conversion	Separation	Helix-Reactor-Precipitation
10	Conversion	Separation	Oscillatory baffled reactor - Crystallization	28	Conversion	Mixing	Oscillatory baffled reactor (OBR)
11	Conversion	Separation	Reaction Absorption	29	Conversion	Separation	Spinning disc reactor
12	Conversion	Separation	Reaction Stripping	30	Conversion		non-selective membrane reactor
13	Conversion	Separation	Adsorption Reaction - Catalytic Reaction	31	Conversion	Mixing/ Energy supply (Thermal)	Microreactor - CSTR/STR (Batch)
14	Conversion	Separation	Reaction Adsorption	32	Conversion	Mixing	Microchannel reactor
15	Conversion	Separation	Simulated moving bed reactor	33	Conversion		Ultrasonic reactors
16	Conversion	Separation	Rotating annular chromatographic reactor	34	Conversion	Energy supply (Thermal)	Falling Film Microreactor
17	Conversion	Energy supply (Thermal)	Heat-Exchanger (HEX) Reactors	35	Conversion	Mixing/ Energy supply (Thermal)	Micro posted reactors
18	Conversion	Energy supply (Thermal)	Advanced Plate-Type Heat Exchanger reactor	36	Conversion	Energy supply (Thermal)	Microwave reactor

Cont'd. **Table A.1**. List of PI equipment in the knowledge base.

No.	Task 1	Task 2	Equipment	No.	Task 1	Task 2	Equipment
37	Conversion	Mixing	Multijet oscillating Disc Millireactor	56	Conversion		Pulsed Compression reactor
38	Conversion	Mixing	Slug Flow (Segmented) Reactor	57	Conversion	Energy supply (Thermal)	Photochemical reactor
39	Conversion	Separation	Slug Flow (Segmented) Reactor -Extractor	58	Conversion		Agitated Cell Reactor
40	Conversion	Mixing/ Energy supply (Thermal)	Millireactor	59	Conversion		static mixer reactor
41	Conversion	Energy supply (Thermal)	Sonochemical reactor	60	Conversion	Conversion	One-pot reactor
42	Conversion	Energy supply (Thermal)	Hydrodynamic cavitation reactor	61	Conversion	separation	One-pot reactor
43	Conversion	Energy supply (Thermal)	Millisecond reactor	62	Conversion	Conversion	One-Pot-Reactor-Extractor (non-solvent-based)
44	Conversion		Catalytic foam reactor	63	Conversion	Conversion/ separation	One-Pot-Reactor-Extractor (solvent-based)
45	Conversion		Monolithic reactor	64	Separation	Conversion	Chemical Absorption
46	Conversion		Structured catalyst-based reactor	65	Separation	Conversion	Membrane Reaction
47	Conversion	Energy supply (Thermal)	Catalytic Heat-Exchanger (HEX) Reactors	66	Separation		Reaction Crystallization
48	Conversion	Separation	Reaction LL-splitting	67	Separation	Conversion	Reactive Distillation
49	Conversion	Separation	Reaction Extraction (no solvent)	68	Separation	Conversion	Reaction Extraction
50	Conversion	Separation	Rotating Packed Bed Reactor/ HIGee Reactor	69	Separation	Separation	Adsorption Distillation
51	Conversion	Separation	Microchannel reactor-extractor	70	Separation		Extraction Crystallization
52	Conversion	Separation	Static mixer reactor-extractor	71	Separation	Separation	Extraction Distillation
53	Conversion		Rotor stator reactor	72	Separation	Separation	Distillation - Pervaporation
54	Conversion		Two Impinging stream reactor	73	Separation	Separation	Distillation - Pervaporation (Side)
55	Conversion		Jet Impingement Reactor	74	Separation	Separation	Dividing Wall columns

Cont'd. **Table A.1**. List of PI equipment in the knowledge base.

No.	Task 1	Des. Task	Equipment	No.	Task 1	Des. Task	Equipment
75	Separation	Energy supply (Thermal)	Heat-Integrated Distillation	93	Separation	Energy supply (Thermal)	Ultrasonic crystallization
76	Separation	Energy supply (Thermal)	Compact heat exchanger (CHE) inside column	94	Separation	Separation	Distillation - Batch distillation (side)
77	Separation		Membrane Crystallization	95	Separation		Electric flied enhanced stripping
78	Separation		Membrane Distillation	96	Separation		Electric-field enhanced extractors
79	Separation		Direct Contact Membrane Distillation	97	Separation		Agitated Cell Extractor
80	Separation		Air Gap Membrane Distillation	98	Energy supply (Thermal)	Mixing	static mixer heat exchanger
81	Separation		Sweep Gas membrane distillation /Membrane stripping	99	Energy supply (Thermal)		Advanced Shell and tube heat exchangers
82	Separation		Vacuum membrane distillation	100	Energy supply (Thermal)		Advanced Spiral heat exchangers
83	Separation		Membrane Absorption/Stripping	101	Energy supply (Thermal)		Advanced Plate-Type Heat Exchangers
84	Separation		Membrane Adsorption/Chromatography	102	Energy supply (Thermal)		Printed circuit heat exchanger
85	Separation		Rotating Packed Bed / HIGee	103	Energy supply (Thermal)		Micro heat exchanger
86	Separation		Spinning disc phase separator	104	Energy supply (Thermal)		Chart-flo heat exchanger
87	Separation		Centrifugal Extraction	105	Energy supply (Compressing)		Super-Sonic Shock Wave (CO2) Compressor
88	Separation		Centrifugal Adsorption	106	Energy supply (Thermal)		Vapor recompression by heat pump
89	Separation		Centrifugal Adsorption	107	Mixing		static mixer (S-L, S-G)
90	Separation	Separation	Membrane - Extraction	108	Mixing		static mixer (L,G, G-L)
91	Separation	Separation	Distillation - vapor permeation	109	Mixing		Micromixer
92	Separation	Separation	Distillation - vapor permeation (Side)	110	Mixing		Rotor stator mixers

Table A.2. List of intensified internals in the knowledge base.

No.	Task 1	Task 2	Intensified Internals	No.	Task 1	Task 2	Intensified Internals
111	catalyst provision	mixing (contacting)	Catalytic Monolith	119	Energy supply (Thermal)		Compact heat exchanger (CHE) inside column
112	catalyst provision	mixing (contacting)	Catalytic static mixing element	120	Energy supply (Thermal)		Heat transfer panels
113	catalyst provision	mixing (contacting)	catalytic foam	121	mixing (contacting)		foam
114	catalyst provision	mixing (contacting)	catalytic membrane	122	mixing (contacting)		membrane
115	catalyst provision		Catalytic surfaces	123	mixing (contacting)		Monolith
116	substrate supply/ catalytic provision	Separation	Integrated Resins	124	mixing (contacting)		Static mixing element
117	Separation		Dividing Wall (w heat transfer)	125	mixing (contacting)		Zoneflow elements / packings
118	Separation	Separation	Dividing Wall (w/o heat transfer)				

Table A.3. List of additional PI beyond equipment/internals in the knowledge base.

No.	Task 1	Task 2	Intensified concepts	No.	Task 1	Task 2	Intensified concepts
126	Energy supply (Thermal)		Inductive/Ohmic Heating	133	Mixing	Removal of hot spots, Circumvent clogging	Reverse flow
127	Energy supply (Thermal)		Microwave heating	134	Mixing		Oscillated pumping
128	Mixing/ Contacting/ Large Surface to Volume		geometrical change	135	Mixing/ Heat supply/ change of mixture properties		supercritical fluids
129	Mixing/ Contacting/ Large Surface to Volume		surface change	136	Mixing/ Heat supply/ change of mixture properties		hot/cold inert gas/steam
130	Mixing/ Contacting/ Large Surface to Volume		structured materials	137	separation		additional reaction as separator
131	Mixing/ Contacting/ Large Surface to Volume		size change	138	separation		Use of ionic liquids as solvent with no vapor pressure
132	Energy supply (Thermal)		Heat supply/removal through use of reaction energy				

Table A.4. Detailed example of the PI knowledge base ("***": not shown data).

Principle of intensified process	Integration of operations	Intensified process / unit	General process properties	Occurring Phases	Operational properties	Advantageous when…in conventional process	Reported improvements	Reaction class	***
Integration of operation	Reaction – Separation	Reactive Distillation	Feed is liquid or vapour or both	V/L	T higher than boiling point of vaporized component(s)/ mixture(s)	low yield and low conversion in reaction	Reduction of operational cost	Esterification	***
			No large amounts of solid inside feed		T, p lower than boiling points of reactants	- equilibrium limitations in reaction, (reaction far on the reactant side)	Reduction of capital cost	Etherification	
			Reaction(s) in liquid phase		Matching operating window of reaction and separation	- high amount of side-products or product is intermediate	Reduction of waste	Hydrogenation	
			***			- reaction highly exothermic	Increase in efficiency	Desulfurization	
			***			low selectivity in separation after reaction	Reduction in energy consumption	Hydration	
			***			***	***	***	
		Reactive Pervaporati on	***		***	low yield and low conversion in reaction	Increase in efficiency	Esterification	***
***	***	***	***		***	***	***	***	***

A.2. List of phenomena in the phenomena library of the knowledge base

The knowledge base contains currently a number of 49 phenomena usable for the phenomena based workflow for the generation/synthesis of novel process options. The 49 phenomena are presented in Table A.5 listed by their class (see section 2.2.2). Besides the description, also the information on whether or not a general mathematical model is stored on the library is given. Besides this information, also the important pure component properties for the identification of these phenomena to fulfill a task under investigation as well as information about the operating window of each phenomenon are stored in the knowledge base (but not shown here).

Table A.5. List of phenomena in the phenomena library.

Class	Subclass	Sub-Subclass	Phenomena	Full mathematical model available
Mixing	1-phase	Liquid	Perfectly mixed	x
			not mixed	x
			Convective tubular flow: no mixing in axial direction	x
			Convective rectangular flow: no mixing in axial direction	x
			Convective oscillating tubular flow	
		Vapor	not mixed	x
			Perfectly mixed	x
			Convective tubular flow: no mixing in axial direction	
		Solid	…	
	2-phase	V-L	Perfectly mixed	x
			not mixed	
			Bubble-flow (counter-current)	
			Bubble-flow (co-current)	
			Slug-Flow	
		L-L	Perfectly mixed	x
			not mixed	
			Bubble-flow (counter-current	
			Bubble-flow (co-current)	
			Slug-Flow	
		…		
	…			
Phase transition	V-L		by relative volatility	x
			by pervaporation	x
			by stripping	
			by absorption	
			by vapor permeation	
			…	

Cont'd. **Table A.5**. List of phenomena in the phenomena library.

Class	Subclass	Sub-Subclass	Phenomena	Full mathematical model available
Phase transition	L-L		by L-L contact (extraction)	x
			by L-L contact (splitting)	x
			by liquid membrane	
			by centrifugation	
			…	
	S-L		by crystallization	
			…	
	…			
Phase separation	V-L		Perfectly separated	x
			…	
	G-L		Perfectly separated	x
			…	
	S-L		Perfectly separated	x
			…	
	L1-L2		Perfectly separated	x
			…	
	G-S		Perfectly separated	x
			…	
	V-S		Perfectly separated	x
			…	
	L-S		Perfectly separated	x
			…	
	…			
Dividing	-			x

Cont'd. **Table A.5**. List of phenomena in the phenomena library.

Class	Subclass	Sub-Subclass	Phenomena	Full mathematical model available
Energy transfer	Thermal	source	Convective heating without contact	X
			Heat of reaction (exothermic)	
			Heat of condensation	x
		sink	Heat of vaporization	x
			Heat of reaction (endothermic)	x
			Convective cooling without contact	x
	Mechanical	source	Pumping	x
		sink	Expansion	x
	Microwave	source	Microwave heating	
	Radiation	source		
	Electrical	source		
	Ultrasound	source		
	...			
Reaction	L	catalytic	homogeneous/ pseudohomogeneous catalytic w/o inhibition	x
			homogeneous/ pseudohomogeneous catalytic w inhibition	x
			heterogeneous w/o inhibition	x
			heterogeneous w inhibition	x
		non-catalytic	without inhibition	x
			with inhibition	x
	V	catalytic	...	
		non-catalytic	...	
	...	...	...	
Phase contact	V-L		No resistance	x
			...	
	...			
Phase change	V-L	V to L	Full evaporation	x
		L to V	Full condensation	x
	S-V	S to V	Full sublimation	x
		V to S	Full deposition	x
	S-L	S to L	Full melting	x
		L to S	Full freezing	x

A.3. List of logical, structural, operational constraints and performance criteria translated from the performance metrics

The performance metrics for process intensification (see section 2.4) have been used for defining logical (Eq.2.2), structural (Eq.2.3) and operational constraints (Eq.2.4) as well as performance criteria for PI screening (Eq.2.6). This is used in the workflows for both building blocks (unit, phenomena). The constraints are retrieved in step 1 from the knowledge base when a certain performance metric has been selected by the user. All constraints stored in the knowledge base are listed in table A.6.

Table A.6. List of additional logical, structural and operational constraints as well as performance criteria for PI screening from the translation of the performance metrics.

Performance metric	Level	Type of Constraint	Constraint
Capital Costs	Unit	Logical	Fix a maximum number of units in the flowsheet
Capital Costs	Unit	Structural	Maximum number of units in the flowsheet
Capital Costs	Unit	operational	Use the volume as criterion
Efficiency	Unit	Structural	Do not integrate units which inhibit each others performance
Efficiency	Unit	Structural	Add units in the flowsheet in which it has the highest efficiency
Efficiency	Unit	Operational	Time-Yield
Efficiency	Unit	Operational	Efficiency of parts/steps of the flowsheet
Efficiency	Unit	PI screening	Time-Yield
Efficiency	Unit	PI screening	Product-yield
Efficiency	Unit	PI screening	Efficiency
Efficiency	Unit	PI screening	Productivity
Energy	Unit	Structural	Do not connect units with alternating heat addition and heat removal
Energy	Unit	Operational	Energy of the base-case design
Energy	Unit	Operational	Heat supply to the base-case design
Energy	Unit	PI screening	Energy of the base-case design
Energy	Unit	PI screening	Heat supply to the base-case design
Operational Costs	Unit	Structural	Make sure that in the flowsheet units are connected to ensure the high efficiency of the raw material usage and/or which allow the recycle of raw materials
Operational Costs	Unit	Operational	Efficiency
Operational Costs	Unit	Operational	Raw material consumption
Operational Costs	Unit	Operational	Utility costs of the base case design
Operational Costs	Unit	PI screening	Utility costs
Operational Costs	Unit	PI screening	Catalyst and membrane costs

Cont'd. **Table A.6.** List of additional logical, structural and operational constraints as well as performance criteria for PI screening from the translation of the performance metrics.

Performance metric	Level	Type of Constraint	Constraint
Safety	Unit	Logical	Only allow units not operating inside of an area of an explosive atmosphere
Simplification	Unit	Logical	Fix a number of maximum units in the flowsheet
Simplification	Unit	Structural	Number of maximum units in the flowsheet
Simplification	Unit	Structural	Do not use repetitive units
Simplification	Unit	Structural	Do not use enrichments before separations if not necessary
Simplification	Unit	Structural	Do not use pre-reactors
Waste	Unit	Structural	Do not use two different solvents in one process
Capital Costs	Phenomena	Structural	Identify possible units and allow only a number of units (defined in step 1 or by screening)
Capital Costs	Phenomena	operational	Use the volume as criterion
Efficiency	Phenomena	Structural	Do not integrate phenomena which inhibit each others performance
Efficiency	Phenomena	Structural	Add phenomena into the positions in which it has the highest efficiency
Efficiency	Phenomena	Structural	Do not connect phenomena in a series of co-current stages with descreasing efficiency/equilibrium
Efficiency	Phenomena	Structural	In counter-current connections, only do a pressure change from the feed to the top for higher driving forces if energy is selected as one performance criterion
Efficiency	Phenomena	Operational	Time-Yield
Efficiency	Phenomena	Operational	Efficiency of tasks of the flowsheet
Efficiency	Phenomena	PI screening	Time-Yield
Efficiency	Phenomena	PI screening	Product-yield
Efficiency	Phenomena	PI screening	Efficiency
Efficiency	Phenomena	PI screening	Productivity
Energy	Phenomena	Structural	Do not connect phenomena to a series with alternating heat addition and heat removal
Energy	Phenomena	Structural	Remove options in which phenomena are heated/cooled leading to a decrease of the efficiency
Energy	Phenomena	Structural	Remove options in which a SPB is heated/cooled not leading to target/opposite to the following step
Energy	Phenomena	Structural	In counter-current connections, do not heat top stages and do not cool bottom stages
Energy	Phenomena	Operational	Energy of the base-case design
Energy	Phenomena	Operational	Heat supply to the base-case design
Energy	Phenomena	PI screening	Energy of the base-case design
Energy	Phenomena	PI screening	Heat supply to the base-case design
Operational Costs	Phenomena	Structural	Make sure that in the flowsheet phenomena/ SPB's are connected to ensure the high efficiency of the raw material usage and/or which allow the recycle of raw materials
Operational Costs	Phenomena	Operational	Raw material consumption

Cont'd. **Table A.6.** List of additional logical, structural and operational constraints as well as performance criteria for PI screening from the translation of the performance metrics.

Performance metric	Level	Type of Constraint	Constraint
Operational Costs	Phenomena	Operational	Efficiency
Operational Costs	Phenomena	Operational	Utility costs
Operational Costs	Phenomena	PI screening	Utility costs
Operational Costs	Phenomena	PI screening	Catalyst and membrane costs
Safety	Phenomena	Logical	Only allow phenomena/SPB's not operating inside of an area of an explosive atmosphere
Simplification	Phenomena	Structural	Do not use enrichments before separations if not necessary
Simplification	Phenomena	Structural	Identify possible units and allow only a number of units (defined in step 1 or by screening)
Simplification	Phenomena	Structural	Use only up to a certain (define a number) number of pressure changes in the system
Simplification	Phenomena	Structural	Remove options with redundant stages
Waste	Phenomena	Structural	Do not use two different solvents in one process

A.4. Application of the extended Kremser method and comparison with other published methods

For the identification of the number of stages, in this work, the Kremser method (see section 4.6; Seader & Henley, 1998) has been used and extended to handle all types of phase transition phenomena as well as SPB's containing reaction and phase transition phenomena (see section 4.6). To highlight the application of the method, two examples are solved which are the separation of acetone-water by phase transition through relative volatility (section A.4.1) as well as the production of MTBE from methanol and isobutene by reaction and phase transition phenomena by relative volatility at the same time (section A.4.2). For comparison, the extended Kremser method has been tested against two other simple methods, that is Fenske-Underwood as well as McCabe-Thiele for the separation water-acetone and against the Ponchon-Savarit method for the production of MTBE (Sanchez Daza *et al.*, 2003). A description of the other methods (McCabe-Thiele, Fenske-Underwood, Ponchon-Savarit) can be found in Seader & Henley (1998).

A.4.1. System: Acetone-Water

The following assumptions/process specifications are made:

Feed: x_A=0.25 mol mol^{-1}; Distillate: x_A=0.95 mol mol^{-1}; Bottom-Product: x_W=0.98 mol mol^{-1}

Pressure: P= 1.3 bar

VLE data at P=1.3 bar have been generated using the Margules equation with parameters from the ICAS database (Table A.7). The K-values have been determined by using equation (4.18).

Table A.7. Data of VLE at P=1.3 bar using Margules and the determined K-values ($K_i=y_i/x_i$)

T [C]	y_A	x_A	K_A	y_W	x_W	K_W
107.1	0	0		1	1	1.000
95.1	0.447	0.02	22.350	0.553	0.98	0.564
84.9	0.652	0.05	13.040	0.348	0.95	0.366
76.8	0.754	0.1	7.540	0.246	0.9	0.273
73.1	0.784	0.15	5.227	0.216	0.85	0.254
71.2	0.793	0.2	3.965	0.207	0.8	0.259
70.2	0.793	0.25	3.172	0.207	0.75	0.276
69.6	0.79	0.3	2.633	0.21	0.7	0.300
69.2	0.787	0.35	2.249	0.213	0.65	0.328
68.9	0.784	0.4	1.960	0.216	0.6	0.360
68.6	0.784	0.45	1.742	0.216	0.55	0.393
68.3	0.787	0.5	1.574	0.213	0.5	0.426
67.9	0.793	0.55	1.442	0.207	0.45	0.460
67.5	0.804	0.6	1.340	0.196	0.4	0.490
67	0.818	0.65	1.258	0.182	0.35	0.520
66.5	0.836	0.7	1.194	0.164	0.3	0.547
66	0.859	0.75	1.145	0.141	0.25	0.564
65.5	0.885	0.8	1.106	0.115	0.2	0.575
65	0.912	0.85	1.073	0.088	0.15	0.587
64.5	0.942	0.9	1.047	0.058	0.1	0.580
64	0.972	0.95	1.023	0.028	0.05	0.560
63.6	1	1	22.350	0	0	

1. Method: Fenske-Equation:

1.1. The minimum number of stages can be determined by equation A.4.1 (Seader & Henley, 1998):

$$N_{\min} = \frac{Ln\left(\left(x_{D,A}/x_{D,W}\right)\cdot\left(x_{B,W}/x_{B,A}\right)\right)}{Ln\,\alpha_{A,W}} \qquad \text{(A.4.1)}$$

With $\alpha_{A,W} = \left(\left(K_A/K_W\right)_D \cdot \left(K_A/K_W\right)_B\right)^{0.5} = 8.51$ (A.4.2)

That gives using eq. A.4.1: $N_{\min} = \frac{Ln\left((0.95/0.05)\cdot(0.98/0.02)\right)}{Ln\left(8.51\right)} = 3.19$

1.2. Determination of the feed position:

$$N_{\min,R} / N_{\min,S} = \frac{Ln\left(\left(x_{D,A} / x_{D,W}\right)\cdot\left(x_{F,W} / x_{F,A}\right)\right)}{Ln\,\alpha_{A,W,DF}} / \frac{Ln\left(\left(x_{F,A} / x_{F,W}\right)\cdot\left(x_{B,W} / x_{B,A}\right)\right)}{Ln\,\alpha_{A,W,FB}} = 2.91$$

2. Method: McCabe-Thiele

The McCabe-Thiele diagram is drawn (see Fig.A.1). From the McCabe-Thiele Diagram, a minimum of five stages are determined starting from the top specification. The feed enters in the fourth stage.

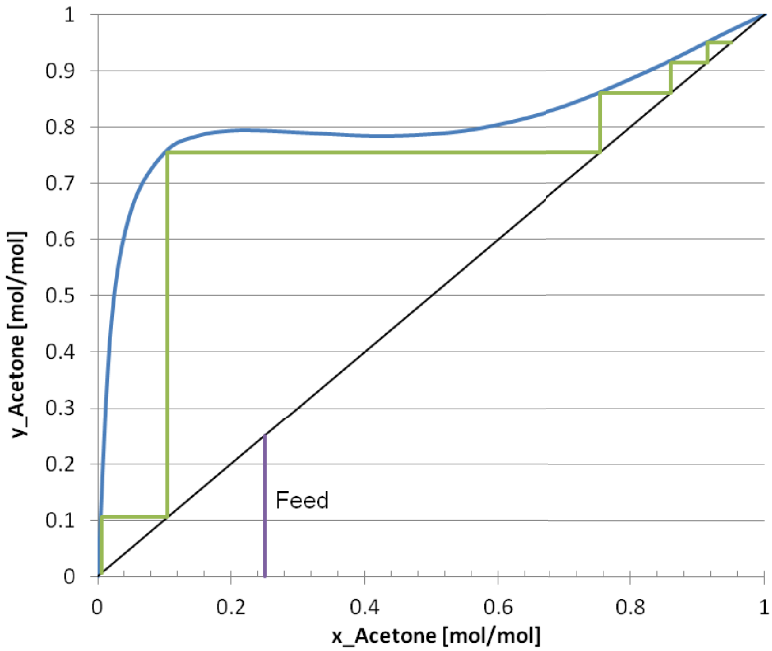


Figure A.1. Determination of Nmin by the McCabe-Thiele-Method starting from the distillate specification.

3. Method: Kremser

The given specifications are used to identify two sections, one above the feed which is an absorption section and one below which is a stripping section (see Fig. A.2).

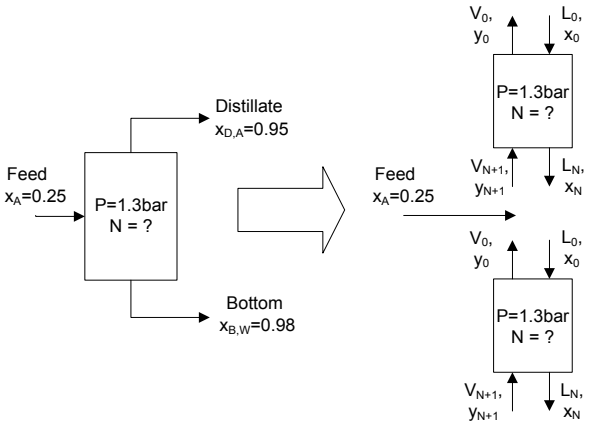


Figure A.2. Transformation of the distillation problem into two sections for the use of the Kremser-equations.

In order to determine the absorption as well as the stripping factors rather than just selecting a recommended value of 1.4 (Seader & Henley, 1998), the minimum reflux ratio is determined by the driving force method (see section 4.6.1). The driving force diagram is plotted, shown in Fig. A.3.

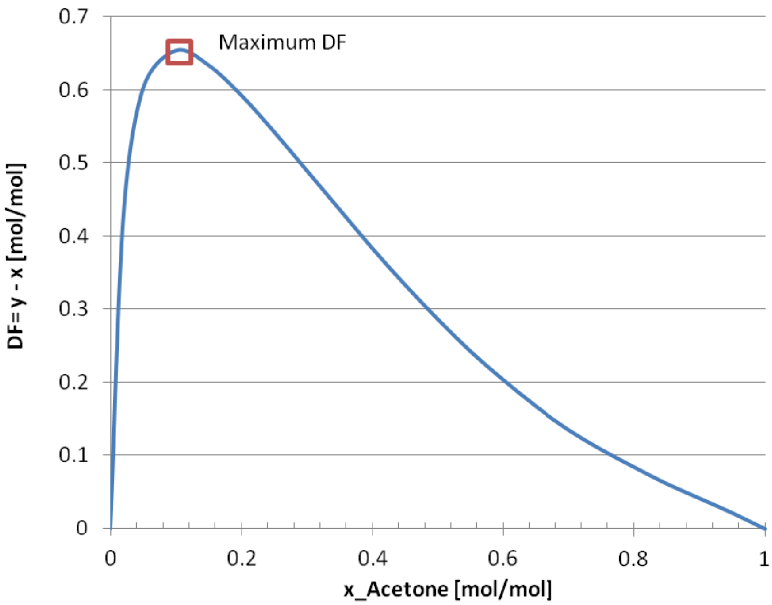


Figure A.3. Driving Force-Diagram of Acetone-Water at P=1.3 bar using the Margules equation with parameters from the ICAS database.

The minimum reflux for the absorption section is determined through the driving force approach (see section 4.6.1). It gives:

$$R_{\min} = (L/V)_{\min} = 0.746 \quad \text{(A.4.3)}$$

This value is used to calculate the separation factors at distillate and feed position (see Table 3.5).

It gives:

$$A_{1,W} = 1.332 \quad \text{(A.4.4)}$$

$$A_{N,W} = 2.704 \quad \text{(A.4.5)}$$

Analogous, the minimum reflux for the stripping section is calculated:

$$R_{\min} = (L/V)_{\min} = 3.36 \quad \text{(A.4.6)}$$

This value is needed to calculate the separation factors at feed and bottom position (see Table 3.5):

$$S_{1,A} = 0.944 \quad \text{(A.4.7)}$$

$$S_{N,A} = 6.650 \quad \text{(A.4.8)}$$

All separation factors (A.4.4-A.4.5 and A.4.7-A.4.8) are used to calculate the effective absorption and stripping factors respectively by using the Edmister approach (see Eqs. 3.16-3.17):

$$A_E = \left(A_{N,i}(A_{1,i}+1)+0.25\right)^{0.5} - 0.5 = 2.060 \quad \text{(A.4.9)}$$

$$S_E = \left(S_{1,i}(S_{N,i}+1)+0.25\right)^{0.5} - 0.5 = 2.233 \quad \text{(A.4.10)}$$

The concentration recoveries (see Eq. 4.21) are calculated assuming that the feed enters as a vapor for the absorption and as a liquid for the stripping section as well as as assuming that the component which changes the phase is not present in the inlet solvent feed. The concentration recoveries are:

$$\alpha_{Abs} = \frac{y_{n+1} - y_1}{y_{n+1} - y_0^*} = \frac{0.75 - 0.028}{0.75} = 0.963 \quad \text{(A.4.11)}$$

$$\alpha_{Str} = \frac{x_0 - x_n}{x_0 - x_{n+1}^*} = \frac{0.25 - 0.02}{0.25} = 0.92 \quad \text{(A.4.12)}$$

The concentration recoveries are inserted into the equation for countercurrent stages (Eq.4.24) to determine the number of stages for the absorption and stripping section:

$$N_{Abs} = \frac{Ln\left(\frac{1-\alpha/A_E}{1-\alpha}\right)}{Ln\, A_E} = 3.7 \quad \text{(A.4.13)}$$

$$N_{Str} = 2.5 \quad \text{(A4.14)}$$

Hence, the total number of stages is:

$$N_{total} = 6.2 \approx 7 \quad \text{(A.4.15)}$$

The entrance of the feed is in stage 4.

4. Conclusions

The result has been verified by rigorous simulation in Pro/II, giving a minimum of five stages to reach the specifications. This result is compared with the results of all three methods. Compared with the McCabe-Thiele method, the Kremser equation works equally fine, predicting a feasible number of stages. The Fenske-Underwood equation fails to predict a feasible solution.

A.4.2. Reactive system: Isobutene + Methanol = MTBE

The reaction is:

Isobutene + Methanol = MTBE (A.4.16)

First, the calculation of the reactive phase diagram is performed necessary to apply the methods. For this, the element-based approach is used (see section 4.5). The transformation of the components into elements gives two elements A and B with:

Isobutene = A

Methanol = B

MTBE = AB

The specifications of the design problem are given in Figure A.4.

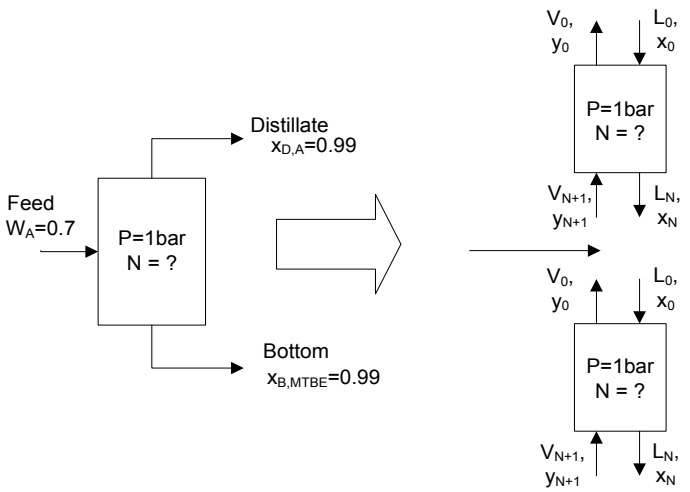


Figure A.4. System description and transformation of the distillation problem into two sections for the use of the Kremser-equations.

The reactive VLE data at P=1bar has been generated using the UNIFAC equation with parameters from the ICAS database. The K-values have been determined by using equation (4.18). The calculated data of the reactive VLE at P=1 bar using UNIFAC and the parameters from the ICAS database are presented in Table A.8.

Table A.8. Data of the reactive VLE at P=1bar using UNIFAC and the determined K-values ($K_i=y_i/x_i$)

WA,y	WA,x	K_A	WB_y	WB,x	K_B	DF (A)
0.0727	0.0171	4.252	0.9273	0.9829	0.943	0.0556
0.1144	0.0295	3.878	0.8856	0.9705	0.913	0.0849
0.1627	0.0469	3.469	0.8373	0.9531	0.879	0.1158
0.2103	0.0697	3.017	0.7897	0.9303	0.849	0.1406
0.2619	0.1015	2.580	0.7381	0.8985	0.821	0.1604
0.3047	0.1387	2.197	0.6953	0.8613	0.807	0.166
0.3491	0.1915	1.823	0.6509	0.8085	0.805	0.1576
0.3848	0.2523	1.525	0.6152	0.7477	0.823	0.1325
0.4083	0.3055	1.336	0.5917	0.6945	0.852	0.1028
0.4285	0.3574	1.199	0.5715	0.6426	0.889	0.0711
0.4485	0.4081	1.099	0.5515	0.5919	0.932	0.0404
0.4845	0.4611	1.051	0.5155	0.5389	0.957	0.0234
0.5272	0.4891	1.078	0.4728	0.5109	0.925	0.0381
0.5836	0.5051	1.155	0.4164	0.4949	0.841	0.0785
0.6338	0.5148	1.231	0.3662	0.4852	0.755	0.119
0.6902	0.5308	1.300	0.3098	0.4692	0.660	0.1594
0.7358	0.5405	1.361	0.2642	0.4595	0.575	0.1953
0.7867	0.558	1.410	0.2133	0.442	0.483	0.2287
0.8436	0.5845	1.443	0.1564	0.4155	0.376	0.2591
0.8885	0.6203	1.432	0.1115	0.3797	0.294	0.2682
0.9292	0.6745	1.378	0.0708	0.3255	0.218	0.2547
0.9497	0.7251	1.310	0.0503	0.2749	0.183	0.2246
0.9676	0.7823	1.237	0.0324	0.2177	0.149	0.1853
0.976	0.8305	1.175	0.024	0.1695	0.142	0.1455
0.9856	0.8748	1.127	0.0144	0.1252	0.115	0.1108
0.9932	0.9217	1.077	0.0068	0.0783	0.087	0.0715
0.9941	0.9518	1.044	0.0059	0.0482	0.122	0.0423
1.0002	0.9856	1.014	0	0.0144	0	0.0146
1	1	1	0	0	0	0

Based on this data, the driving force diagram is drawn (Figure A.5) with the moar fraction of element A on the x-axis. It can be seen that the DF diagram has two maxima, one at around WA,x=0.13 and the global one at WA,x=0.64. At WA,x=0.48 almost a reactive azeotrope occurs (DF->0). Thus, crossing this point will be difficult (large number of stages would be necessary).

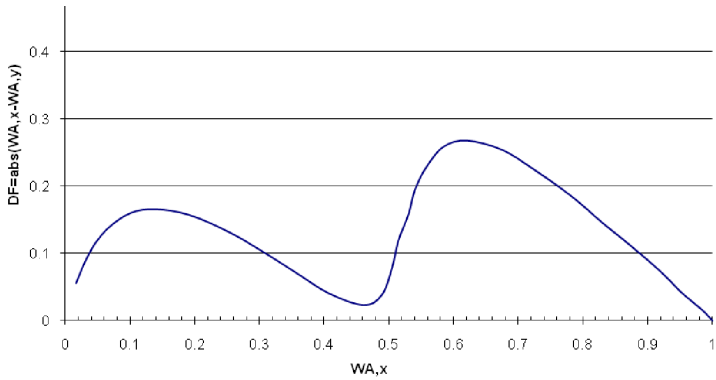


Figure A.5. Driving Force-Diagram of reactive VLE of the MTBE system at P=1bar.

The minimum reflux obtained using the driving force approach (see section 4.6.1) for the absorption section is:

$$R_{\min} = (L/V)_{\min} = 0.44$$

This value is needed to calculate the separation factors at distillate and feed position:

$$A_{1,B} = 3.56$$

$$A_{N,B} = 2.18$$

The minimum reflux for the stripping section is:

$$R_{\min} = (L/V)_{\min} = 1.39$$

This value is needed to calculate the separation factors at feed and bottom position:

$$S_{1,A} = 0.99$$

$$S_{N,A} = 3.06$$

The separation factors are used to calculate the effective absorption and stripping factors respectively by using the Edmister approach:

$$A_E = \left(A_{N,i}(A_{1,i}+1)+0.25\right)^{0.5} - 0.5 = 2.69$$

$$S_E = \left(S_{1,i}(S_{N,i}+1)+0.25\right)^{0.5} - 0.5 = 1.57 \qquad \text{(A.4.16)}$$

The concentration recoveries are determined assuming that the feed enters as a vapor for the absorption and as a liquid for the stripping and the component to change the phase is not present in the inlet solvent:

$$\alpha_{Abs} = \frac{y_{n+1} - y_1}{y_{n+1} - y_0^*} = \frac{0.3 - 0.01}{0.3} = 0.97 \quad \text{(A.4.17)}$$

$$\alpha_{Str} = \frac{x_0 - x_n}{x_0 - x_{n+1}^*} = \frac{0.3 - 0.01}{0.3} = 0.97 \quad \text{(A.4.18)}$$

With this, the number of stages for the absorption and stripping section is determined using the equation for countercurrent stages (see A.4.19):

$$N_{Abs} = \frac{Ln\left(\frac{1-\alpha/A_E}{1-\alpha}\right)}{Ln\, A_E} = 2.99 \quad \text{(A.4.19)}$$

$$N_{Str} = 5.42 \quad \text{(A.4.20)}$$

$$N_{total} = 8.41 \quad \text{(A.4.21)}$$

<u>*Comparison with other methods:*</u>

Using the Ponchon-Savarit method, Sanchez Daza *et al.* (2003) found six stages at a RR=0.75. The comparison with results in ASPEN retrieved from the paper confirms their results. The developed extended Kremser method has overestimated the number of stages necessary (N_{total}=*8.41*, Eq.A.4.21). Anyway, it has predicted a feasible number of stages and is much simpler and more flexible to be applied for other phase transition phenomena as well.

A.5. Means-Ends-Analysis

The means-ends analysis approach is developed by Siirola *et al.* (1971-2011) and is one alternative for process synthesis beyond the unit-operational approach (see also section 1). Within this PhD-project, it has been applied for one case study to show the applicability of this method for two reasons. One is to highlight that this method is very promising but sub-methods, tools and algorithms have not been developed yet to support a systematic guidance of the user to take the right decisions. Second, to show that, compared to the case study 3 using the developed phenomena based workflow (see section 6.3), a similar reasoning is followed but advantageously generates the solution in a broader way (taken more options into account) and in a systematic manner.

A.5.1 Problem description

The problem consists of producing methyl-acetate (MeAc) from methanol (MeOH) and acetic acid (HOAc) and water (H_2O) as the side product (Eq. A.5.1).

$$MeOH + HOAc \leftrightarrow MeAc + H_2O \quad \text{(A.5.1)}$$

The problem is that the reaction has an unfavorable equilibrium (Keq=16.7) and the system forms several binary azeotropes (computed using the UNIFAC model from Tang *et al.* (2005), see Table A.9) as well as an immiscibility region between the products (Tang *et al.*, 2005).

Table A.9. List of boiling points and azeotropes in the system (Tang *et al.*, 2005).

Component(s)	T_B, $T_{B,azeotrope}$ [C]	Concentrations [mol/mol]
MeOH/MeAC	53.7	(0.34/0.66)
MeAc/H_2O	56.4	(0.88/0.12)
MeAc	57.1	
MeOH	64.5	
H2O	100	
HOAc	118	

A conventional base case design of the process only using conventional process units needs nine distillations, extractive distillation and extraction columns (see Fig A.6) to match the desired purity specifications.

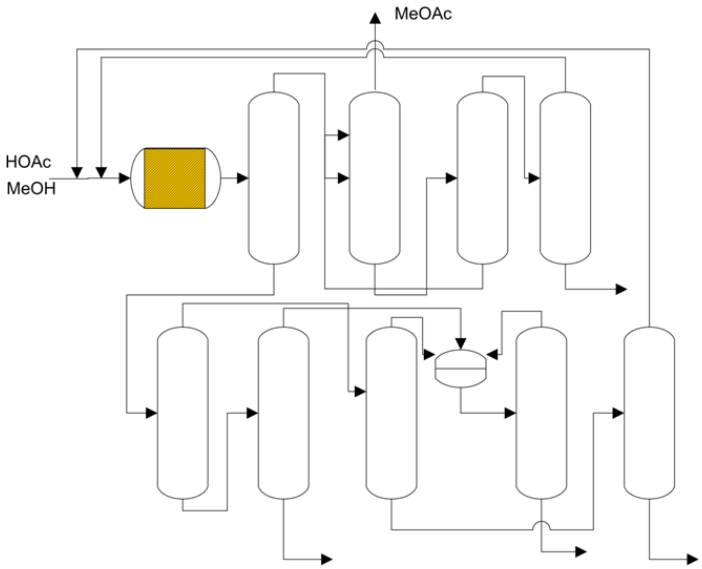


Figure A.6. Base Case Design for the production of methyl acetate (Sundmacher & Kienle, 2003).

A.5.2 Simplified solution procedure of the Means-Ends Analysis

A flowsheet can be expressed by several tasks which need to be addresses and sequenced in a specific order to come from the input to the output (products) of a certain state. A task fulfills a step towards going from the input to the output. If the property difference is not fully eliminated another tasks is introduced and followed. For process intensification, the tasks may be integrated within one unit operation. The means-ends analysis starts with giving the specifications (input and output) of the process as well as the reaction path and the species involved in the process. Subsequently from the first state, tasks are successively identified to reach the output(s). Afterwards, tasks are integrated at different levels to achieve PI.

A.5.3 Application of the method

First, the pure inlets of the reactants and the outlet (product) specifications are defined. Systematically, the task based flowsheet is generated using the stepwise identification of the outlet for each introduced task starting from the inlets into a reaction task. Step-by-step, the flowsheet is built (shown in Fig A.7). Here, only separations based on relative volatility (RV) and extraction are used. Whenever an azeotrope occurs, extraction is used.

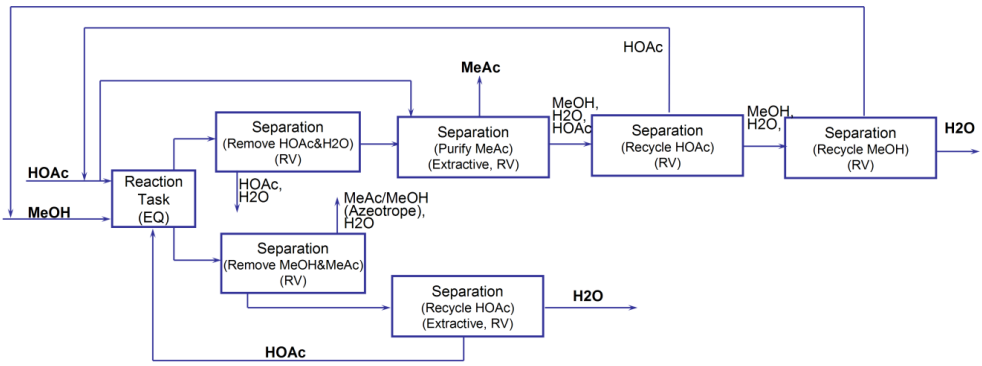


Figure A.7. Task based representation for the production of methyl acetate (RV: Relative volatility; in bold: allowed in and outlet streams of the system).

Now, merging the two separations ("Remove HOAc&H_2O" and "Remove MeOH&MeAc") into one distillation column which is possible since the separation is both based on relative volatility and the outlet of each separate task are matching, gives the flowsheet (see Fig. A.8) known to be the base-case design (see Fig. A.6).

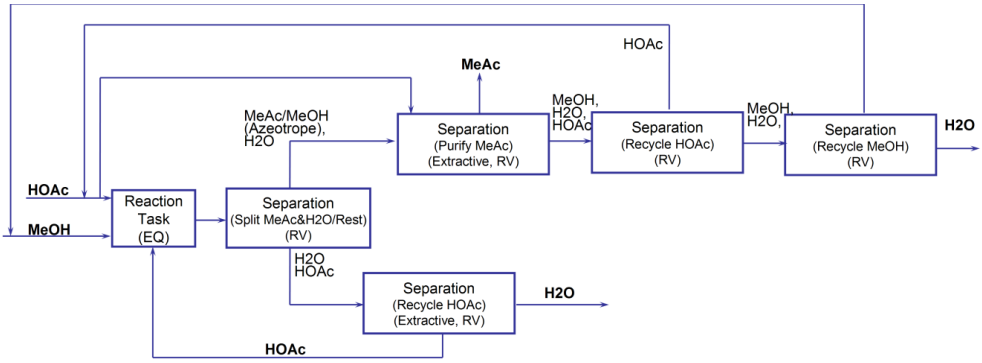


Figure A.8. Task based representation of the Base Case Design for the production of methyl acetate (in bold: allowed in and outlet streams of the system).

However, the question is, if the flowsheet can be further simplified. An analysis of the lower part of the flowsheet shows that an additional separation of HOAc (for recycle) exists only because it has not been fully converted in the reaction step. This separation task may also be achieved by a reaction fully converting HOAc by using an excess of MeOH. The analysis of the upper part of the flowsheet is that methanol is present which forms an azeotrope with the product. Methanol is only in the flowsheet because it has not been fully converted in the reaction. This separation task may also be achieved by a reaction fully converting MeOH by using an excess of HOAc. The task based flowsheet is updated (see Figure A.9).

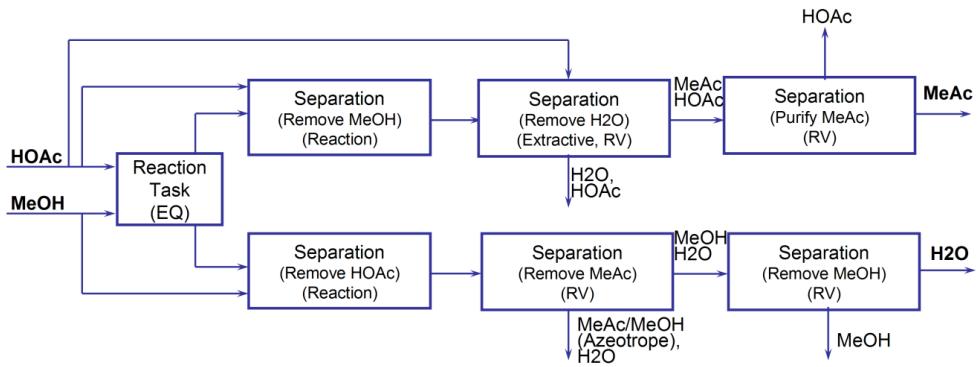


Figure A.9. Task based representation after alternative task identification for the production of methyl acetate (in bold: allowed in and outlet streams of the system).

In the next step, the tasks integration is performed which is trying to couple (integrate) as much tasks as possible. All separations are based on relative volatility, in some cases coupled with extraction. The

acetic acid from the last separation of the upper part (Purify MeAc) can be recycled to middle separation in the upper part (Remove H_2O). The output of this separation, H_2O and HOAc, can be recycled to the upper separation by reaction to provide excess of HOAc for removal of MeOH.

In the lower part of the task-based flowsheet, the outlet of the last separation (Remove MeOH), that is MeOH, can be recycled back to the middle separation (Remove MeAC) which has the positive effect in receiving more MeAc (since the lowest boiling point is the azeotrope of MeAc/MeOH). The MeOH/MeAc of the middle separation can be recycled back to the separation by reaction (remove HOAc) in which an excess of MeOH is needed. Also, the outcomes of both middle separations ("Remove H_2O") and "Remove MeAc") which are H_2O/HOAc and the azeotropic mixture of MeAc/MeOH/H_2O may be the inlet in the other one (not shown in Figure A.10). Therefore, these are coupled via the separations by reaction. Hence, the updated task based flowsheet is shown in Fig. A.10.

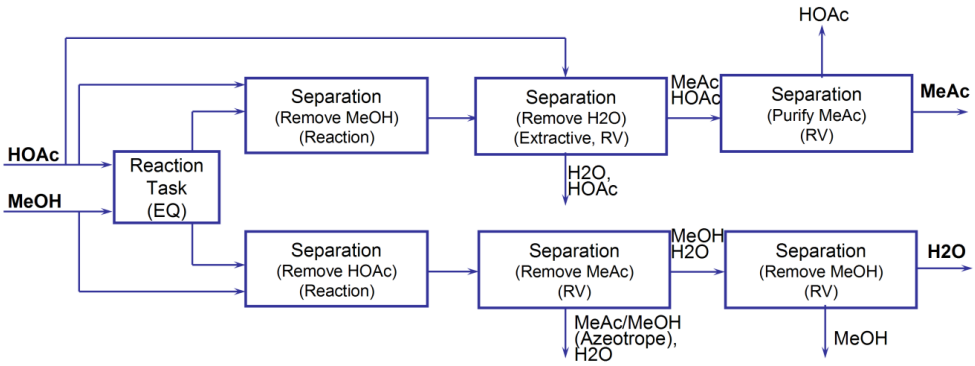


Figure A.10. Task based representation after task synergy identification for the production of methyl acetate (in bold: allowed in and outlet streams of the system).

Rearranging the blocks and identifying the temperatures and pressure at which these tasks can be performed, shows that the tasks can also be integrated within one column (see Fig A.11). The identified unit operation based on this is a reactive distillation column.

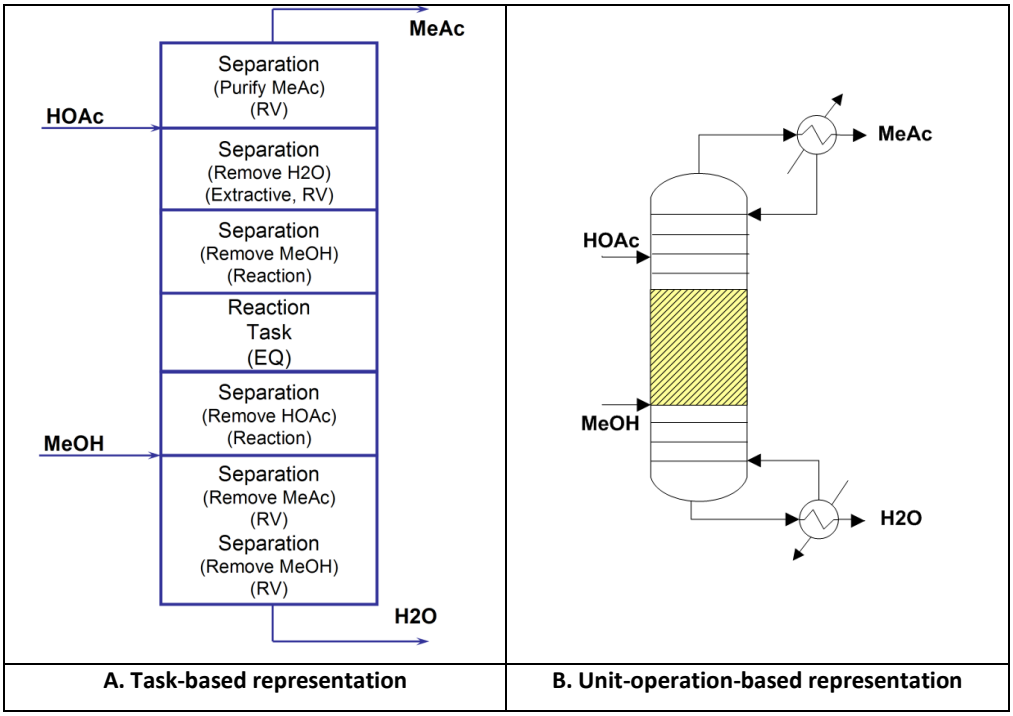


Figure A.11. Task-based and unit operation-based representation for the production of methyl acetate (in bold: allowed in and outlet streams of the system).

A.6. Additional material to the case study: Neu5Ac (section 5.1)

This section provides additional material for the solution of the case study to produce Neu5Ac (see section 5.1). In section A.6.1, the mass data of the base case design are given. An overview of retrieved PI equipment and the screening to the feasible process option is shown in A.6.2. In section A.6.3, the generation of specific process options from the superstructure is highlighted by explaining it for one example. In section A.6.4, the process model of the crystallization is presented. This is important to explain the position of the initial substrate concentrations for process options #3 and #15 on the process boundary after step 6.2 (see section 5.1.9 and Table 5.12).

A.6.1 Mass data of the base case design

Table A.10. Mass data of the base-case design ("*": Missing data calculated by mass balance).

	Reactor 1	Precipitation & Evaporation	Extraction & Evaporation	Reactor 2	Crystallization
Catalyst	NaOH			Neu5Ac aldolase	
Time	15-72h			46h	
Streams:					
In,1	Liquid	Liquid	Liquid	Liquid	Liquid
A [g]	4981*	4164		204*	
B [g]		817		795*	
Water (L)	50*	50*			
Methanol [L]			14		
Acetic Acid [L]					31.6*
Acetone [L]					28.6*
In,2		Liquid	Liquid	Liquid	Liquid
A [g]			1964	4.17	204
B [g]			817		151
Isopropanol [L]		250			
Water [L]					4.17
C [g]				534*	217.5
D [g]					961
Out,1	Liquid	Vapor	Vapor	Liquid	Liquid
A [g]	4164			204	204*
B [g]	817			151	139
Isopropanol [L]		250			
Water [L]		50		4.17	4.17
Methanol [L]			14		
C [g]				217.5	205.5*
D [g]				961	292
Acetic Acid [L]					31.6
Acetone [L]					28.6
Out,2		Solid	Solid		Solid
B [g]			22		
A [g]		2200	1760		12*
C [g]					12*
D [g]					669
Out,3		Solid	Liquid		
A [g]		1964	204		
B [g]		817	795		
Water [L]			4.17		

A.6.2. Overview over retrieved PI equipment and screening step for feasibility

Table A.11. Overview of retrieved PI equipment in step U2.1.2 and the results of the prescreening of PI equipment for feasibility (step U2.2.1-U2.2.3). List of keywords for step U2.1.2: $\underline{K}_{PI}$={(1):"Unfavourable equilibrium in reaction 1", (2): "Substrate and product inhibition in reaction 1", (3):"Slow reaction 1", (4):" Unfavourable equilibrium in reaction 2", (5): Substrate and product inhibition in reaction 2", (6):"Slow reaction 2", (7): "epimerase reaction", (8): "aldolase reaction"}. The abbreviation of catalysts/enzymes for the One-Pot-Reactor can be found in the list of abbreviations.

Step U2.1.2		Step U2.2.1-2.2.3
Retrieved PI equipment	Keyword $\underline{K}_{PI}$	Removed option because of:
Adsorption-Reaction	1,2,4,5	
Reactive Condensation	1,2,4,5	Reaction phase
Membrane Reactor	2,5	
Reactive Membrane	1,2,4,5	Operating window (catalyst mismatch)
Reactive Crystallization	1,2,4,5	Operating window (catalyst stability)
Reactive Precipitation	1,2,4,5	Operating window (catalyst stability)
Reactive Extraction	1,2,4,5	
Reactive Stripping	1,2,4,5	Phases
Reactive-Absorption	1,2,4,5	Reaction phase
Reactive Chromatography	1,2,4,5	
Reactive Comminution	1,2,4,5	Phases
Reactive Distillation	1-6	Phases
Reactive Distillation with internal heat-integration	1-6	Phases
Divided Reactive Distillation	1-6	Phases
Reactive Distillation with Membrane	1,2,4,5	Phases
Reactive Pervaporation	1,2,4,5	Phases
Reactive Distillation-Pervaporation	1,2,4,5	Phases
Reactive-Distillation-Vapor Permeation	1,2,4,5	Phases
Reactive-Flash	1,2,4,5	Phases
Simulated Moving Bed Reactor	1,2,4,5	
Spinning Disc Reactor	1,2,4,5	Operating window (reaction too slow)
Tubular Absorption-Extraction Reactor	1-4	Phases
Reactive- Extrusion	1-4	Phases
One-Pot-Reactor	1-6	Combinations with Alk2 (Operating window: inhibition)

Table A.12. Feasible process options (NPO_L) after logical constraints. Abbreviations: One-pot reactive extractor with ionic liquid (OPRE), one-pot reactor (OPR), reaction 1 (R1), reaction 2 (R2); alkaline catalyst (alk1), enzymatic reaction (E); whole cell catalyzed (WC); Enrichment: Precipitation (Prec), Evaporation (Evap), Liquid-liquid extractor with reactive solvent (LL), Extraction with methanol (LLM); Purification: Crystallization ($Cryst_{Purif}$), Chromatography($Chrom_{purif}$).

Unit 1	Unit 2	Unit 3	Unit 4	NPO
OPRE (E1/E2; E11/E22; WC) OPR (alk1/E2, E1/E2; E11/E22; WC)	$Cryst_{Purif}$ $Chrom_{purif}$	-	-	14
OPRE (E1/E2; E11/E22; WC) OPR (alk1/E2, E1/E2; E11/E22; WC)	LLM Prec Evap LL	$Cryst_{Purif}$ $Chrom_{purif}$	-	56
OPRE (E1/E2; E11/E22; WC) OPR (alk1/E2; E1/E2; E11/E22; WC) R1(alk1; E11; E1)	OPRE (E1/E2; E11/E22; WC) OPR (alk1/E2; E1/E2; E11/E22; WC); R2(E2; E22)	$Cryst_{Purif}$ $Chrom_{purif}$		180
OPRE (E1/E2; E11/E22; WC) OPR (alk1/E2; E1/E2; E11/E22; WC) R1(alk1; E11; E1)	Prec Evap LL LLM	OPRE (E1/E2; E11/E22; WC) OPR (alk1/E2; E1/E2; E11/E22; WC) R2(E2; E22)	$Cryst_{Purif}$ $Chrom_{purif}$	720
OPRE (E1/E2; E11/E22; WC) OPR (alk1/E2; E1/E2; E11/E22; WC) R1(alk1; E11; E1)	OPRE (E1/E2; E11/E22; WC) OPR (alk1/E2; E1/E2; E11/E22; WC); R2(E2; E22)	LLM Prec Evap LL	$Cryst_{Purif}$ $Chrom_{purif}$	720
OPRE (E1/E2; E11/E22; WC) OPR (alk1/E2; E1/E2; E11/E22; WC)	LLM Prec Evap LL	LLM Prec Evap LL	$Cryst_{Purif}$ $Chrom_{purif}$	224
			Total	1914

A.6.3. PI option generation: Process Option #17 (see Fig.5.12)

The PI option to be generated exemplary from the superstructure consists of a one pot reactor containing the enzymes E11 and E22 (E11/E22), a subsequent recovery of substrate A by precipitation with isopropanol, solvent recovery by an evaporator followed by a crystallization for purification of D (Process option #17, Fig.5.12). First, all binary variables related to feed streams and units are set (Eq.4.11). The one pot-reactor (OPR) has one inlet and one stream (Eq.A.6.1).

$$Y_{in}^{1\alpha} = Y_{out}^{1\alpha} = 1 \qquad \text{(A.6.1)}$$

The precipitation unit has one inlet and two outlet streams (Eq.A.6.2).

$$Y_{in}^{2\alpha} = Y_{out}^{2\alpha} = Y_{out}^{2\beta} = 1 \quad \text{(A.6.2)}$$

The evaporation has one inlet and two outlet streams (Eq.A.6.3).

$$Y_{in}^{3\alpha} = Y_{out}^{3\alpha} = Y_{out}^{3\beta} = 1 \quad \text{(A.6.3)}$$

The crystallization has one inlet and two outlet streams (Eq.A.6.4)

$$Y_{in}^{4\alpha} = Y_{out}^{4\alpha} = Y_{out}^{4\beta} = 1 \quad \text{(A.6.4)}$$

Substrate A and C and the solvent water are fed to the OPR (Eq.A.6.5).

$$Y^{01\alpha} = 1 \quad \text{(A.6.5)}$$

The outlet stream of the OPR is connected to the precipitation unit and the solid outlet (recovered substrate A) is recycled back to the OPR (Eq.A.6.6).

$$Y_{in}^{12\alpha} = Y_{out}^{2\alpha} = Y^{21\beta} = Y_{in}^{1\beta} = 1 \quad \text{(A.6.6)}$$

The precipitation needs liquid isopropanol as solvent and the liquid outlet is sent to the evaporation unit (Eq.A.6.7).

$$Y^{02\alpha} = Y^{23\alpha} = 1 \quad \text{(A.6.7)}$$

The vaporized outlet of the evaporation leaves the process while the solid outlet is fed to the crystallization unit (Eq.A.6.8).

$$Y_{P}^{3\beta} = Y^{34\alpha} = 1 \quad \text{(A.6.8)}$$

Both outlet streams of the crystallizer are leaving the process while acetic acid is added (Eq.A.6.9).

$$Y_{P}^{4\beta} = Y_{P}^{4\alpha} = Y^{04\alpha} = 1 \quad \text{(A.6.9)}$$

For simplification purposes, splitting of streams is not considered in this case study (Eq.A.6.10).

$$\varsigma_{u}^{1\alpha,12} = \varsigma_{u}^{2\alpha,23} = \varsigma_{u}^{2\beta,21} = \varsigma_{u}^{3\alpha,34} = \varsigma_{u}^{3\beta,P} = \varsigma_{u}^{4\alpha,P} = \varsigma_{u}^{4\beta,P} = 1 \quad \text{(A.6.10)}$$

All other binary variables are zero.

By introducing Eqs.A.6.1-A.6.10 into the general connection equations (Eqs.4.2-4.9), the following flow relations are derived: the feed stream to the OPR (Eq.A.6.11); the substrate recycle (Eq.A.12); the stream from the OPR to the precipitation (Eq.A.6.13) which is mixed with isopropanol (Eq.A.6.14); the liquid stream leaving the precipitation entering the evaporation (Eq.A.6.15); the vapour leaving from the evaporator (Eq.A.6.16); the liquid residual of the evaporator entering the crystallizer (Eq.A.6.17) which is mixed with acetic acid (Eq.A.6.18); the waste stream (Eq.A.6.19); and the final product stream leaving the system (Eq.A.6.20).

$$F^{01\alpha} = F_{in}^{1\alpha} \quad \text{(A.6.11)}$$

$$F_{out}^{2\beta} = F^{21\beta} = F_{in}^{1\beta} \quad \text{(A.6.12)}$$

$$F_{out}^{1\alpha} = F^{12\alpha} \quad \text{(A.6.13)}$$

$$F_{in}^{2\alpha} = F^{02\alpha} + F^{12\alpha} \quad \text{(A.6.14)}$$

$$F_{out}^{2\alpha} = F^{23\alpha} = F_{in}^{3\alpha} \quad \text{(A.6.15)}$$

$$F_{out}^{3\beta} = F_{P}^{3\beta} \quad \text{(A.6.16)}$$

$$F_{out}^{3\alpha} = F^{34\alpha} \quad \text{(A.6.17)}$$

$$F_{in}^{4\alpha} = F^{34\alpha} + F^{04\alpha} \quad \text{(A.6.18)}$$

$$F_{out}^{4\alpha} = F_{P}^{4\alpha} \quad \text{(A.6.19)}$$

$$F_{out}^{4\beta} = F_{P}^{4\beta} \quad \text{(A.6.20)}$$

The change of the concentrations between inlet and outlet streams of the reactor (Eq.A.6.21) and of each of the three separators (Eqs.A.6.22-A.6.23) is derived from Eqs.4.4-4.5. The defined process scenario is run in batch.

$$x_{i,in}^{1\alpha} F_{in}^{1\alpha} + x_{i,in}^{1\beta} F_{in}^{1\beta} = x_{i,out}^{1\alpha} F_{out}^{1\alpha} \left(\lambda_i^{R1} + \lambda_i^{R2} \right) \quad \text{(A.6.21)}$$

$$x_{i,out}^{u\alpha} F_{out}^{u\alpha} = \sigma_i^{u\alpha} \; x_{i,in}^{u\alpha} F^{u\alpha} \quad \text{(A.6.22)}$$

$$x_{i,out}^{u\beta} F_{out}^{u\beta} = (1 - \sigma_i^{\alpha}) x_{i,in}^{u\alpha} F^{u\alpha} \quad \text{(A.6.23)}$$

With Eqs.A.6.11-A.6.23 all flows are determined. The necessary constitutive equations for conversions and split factors are retrieved from the model library or derived in step U3.

A.6.4. Process model generation: Crystallization

The separation factor of the crystallization has been expressed as a function of the input concentration of component D (Eq.A.6.24) fitted to experimental data (Fig.A.12) from Mahmoudian *et al.* (1997).

$$\sigma^{\beta} = -0.0084 \left(x_D F_{in}^{2\alpha} MW_D / V_0 \right)^2 + 2.5041 \left(x_D F_{in}^{2\alpha} MW_D / V_0 \right) - 98.63 \quad \text{(A.6.24)}$$

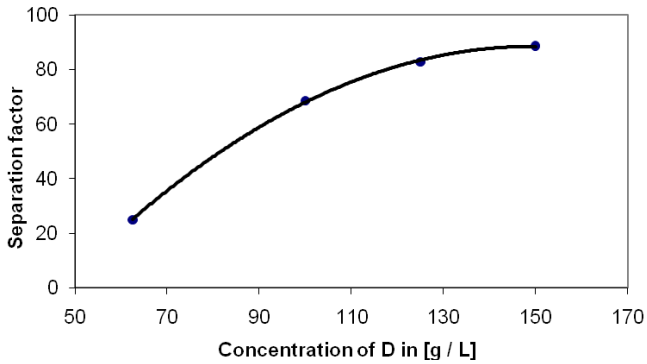


Figure A.12. Fitting curve of experimental values (•) obtained from Mahmoudian *et al.* (1997) for the crystallization separation factor of component D (on addition of five volumes of acetic acid to aqueous solutions) depending on the concentration of D in solution.

The application range of this equation is between 60 and 150 g L^{-1} of component D in solution. Concentrations of component D below and above this range have been given an efficiency of 20% or 90% respectively. Additionally, it is assumed that the obtained crystals are pure meaning that all other components are present in the second outlet stream α. Furthermore, since the crystallization is used as the final purification step, the ability for a separation in the crystallization is bound on ratios of concentration of the substrate through the product D in the input stream (Dawson *et al.*, 1997). Hence, the following operational constraints have been identified, that is the ratio of A over D (Mahmoudian *et al.*, 1997) and C over D (Yamaguchi *et al.*, 2006) on a molar basis (Eqs.A.6.25-A.6.26):

$$n_A / n_D \leq 0.3 \quad \text{(A.6.25)}$$

$$n_C / n_D \leq 2.2 \quad \text{(A.6.26)}$$

A.6.5.: Detailed results of the necessary sub-algorithms

- ***MBS** applied in step A2.3.2*

MBS.1: The space-time-yield of the base case design (F_{Obj}, Eq.5.1-5.2) is calculated for a reaction time of 15 hours in Reactor 1 (R1). It gives $\eta_{P,15,0} = 5.3 gL^{-1}d^{-1}$.

The product-yield (Eq.5.4) of the base case design is $\varepsilon_0 = 43.9 mol\, mol^{-1}\%$ and the time-yield of the reactions (Eq.5.3) of the base-case design, based on the input streams and the output after the second reaction step, is $\varepsilon_{R,0} = 0.16 kg\, kg^{-1} d^{-1}$.

The waste is calculated with Eq.5.5 and is $m_{Waste,0}$= *465 kg (kg Product)*$^{-1}$.

MBS.2: Main contributors to the objective function are identified to be both reaction steps (due to long residence times and low conversions: $\lambda_{R1}^{0} = 0.2$ and $\lambda_{R1}^{0} = 0.9$, see Eq.3.5, Table 3.2; section 3.3.2) as well as the last separation (low efficiency: σ_{Cryst}=0.7). The main contributors of waste are the solvent (isopropanol) for precipitation (250 L) and the high amount of water necessary to dilute the substrates (50 L). Therefore, they are added to the list of limitations/bottlenecks: *LB*={*LB*$_1$:"Low conversion in reaction 1", *LB*$_2$:"Slow reaction 1", *LB*$_3$:"Low conversion in reaction 2", *LB*$_4$:"Slow reaction 2", *LB*$_5$:"Low productivity/efficiency in separating D/CAB", *LB*$_6$:"High waste generation for enrichment of B", *LB*$_7$:"High waste generation due to high dilution of substrates"}.

MBS.3: The time-yield for each reaction (Eq.5.3) is calculated: $\varepsilon_{R1,0} = 0.26 kg\, kg^{-1} day^{-1}$ and $\varepsilon_{R2,0} = 0.36 kg\, kg^{-1} day^{-1}$. Both reaction tasks are violating the operational constraint ($\varepsilon_R > 0.75 kg\, kg^{-1} day^{-1}$, see Table 5.1). Hence, they are identified to be responsible for a limitation. However, there are already included in the list of *LB* (step MBS.2).

MBS.4: This step is not necessary.

- ***APCP*** *in step A2.4.1*

APCP.1: The workflow given by the sub-steps APCP.1.1-APCP.1.3 is used to generate/retrieve pure component properties *PCP*. All details are presented in Table 5.2.

APCP.2: The results are presented in Table 5.3.

APCP.3: The results are presented in Table 5.4.

APCP.4: By applying the rules, the following limitations/bottlenecks are explained: The limitation/bottleneck *LB*$_5$ is explained by the low difference in the pKa-value of D and C (Rule APCP.1). The difference in the solubility in water Log(Ws) and the octanol-water partition coefficient Log(Kow) between the components (important for mixing phenomena in the tasks responsible for *LB*$_1$-*LB*$_7$) needs further investigation for an occurrence of miscibility gaps (Rule APCP.2).

- ***AMP*** *in step A2.4.2*

AMP.1: Azeotropes (Rule AMP.1) and solubility (Rule AMP.2) are identified to be necessary mixture properties to be investigated in more detail.

AMP.2: No azeotrope is found. The solubilities of the components are retrieved from Blayer *et al.*, 1999. The solubilities in water are 1.3 mol L^{-1} for A, 3.6 mol L^{-1} for C, 1 mol L^{-1} for D while the solubility for B depends on the concentration of C.

AMP.3: Compute azeotropes and/or miscibility gaps using thermodynamic models describing the involved phases:

AMP.3.1: All information is available, therefore step AMP.5 is entered (Rule AMP.5).

AMP.5: The low solubilities of the components explain (Rule AMP.7) the large amount of solvents needed which are responsible for limitation/bottleneck LB_6-LB_7.

- ***AR*** *in step A2.4.3*

AR.1: Both reactions are responsible for limitations LB_1-LB_4 in the base-case design, the **AR** algorithm is applied (Rule AR.1).

AR.2 Collect data for reaction analysis:

AR.2.1: The equilibrium constants are retrieved from the literature and are $K_{EQ,R1}=0.24$ and $K_{EQ,R2}=28.7\ L\ mol^{-1}$ (Zimmermann *et al.*, 2007).

AR.2.2: The reaction times are given in Table A.9.

AR.2.3: The determination of the heat of reaction is not required (Rule AR.2), step AR.3 is entered.

AR.3 The theoretical equilibrium conversion of the reactions at the operating conditions with equimolar substrates are $\lambda^0_{R1,EQ} = 0.2$ and $\lambda^0_{R2,EQ} = 0.87$.

AR.4: The deviation of actual and theoretical calculated conversions is low: $\vartheta_{R1} = 0$ and $\vartheta_{R2} = 0.03$.

AR.5: Reaction 1 and reaction 2 are both limited due to an unfavourable equilibrium (criterion 1, Table 3.3) and a slow reaction (criterion 6, Table 3.3).

AR.6: Inhibition might be possible (criterion 1, Table 3.3), hence, step AR.7 is entered.

AR.7: The first reaction is inhibited (LB_8) by the product D and the substrate C while the second reaction is inhibited (LB_9) by the substrates B and C as well as A (Zimmermann *et al.*, 2007).

A.7. Additional material to the case study: H_2O_2 (section 5.2)

In this section, additional tables for the solution of case study to produce hydrogen peroxide via anthraquinone route (section 5.2) are given. It includes the mass and energy data of the base case design (Table A.13), the identified limitations/bottlenecks of this base case design (Table A.14) as well as the list of retrieved PI equipment to overcome these limitations for process improvement (Table A.15).

Table A.13. Mass and energy data of the base case design for the production of hydrogen peroxide.

	Stream							
Coming from	0	Compressor H2	Regeneration WS	Hydrogenation	0	Compressor Air	Oxidation	Oxidation
Going to	Compressor H2	Hydrogenation	Hydrogenation	Oxidation	Compressor Air	Oxidation	Extraction	0
Properties								
T [C]	20	40	30	55	20	40	50	20
P [bar]	1	3.5	3.5	3.5	1	3.5	3.5	3.5
Molar flows [kmol/h]								
H2	224	224						
N2					1270	1270	3	1267
O2					340	340	0.5	116.5
H2O			80	80			38	42
EAQ			450	224.2			445	
WS			2950	2950			2945	5
H2O2							223	
H2.EAQ				223				
Waste				1.8			5	

Cont.d **Table A.13.** Mass and energy data of the base case design for the production of hydrogen peroxide.

	Stream							
Description	Water				Product		Solvent Make-Up (Quinone)	Waste
Coming from	0	Extraction	Extraction	Distillation	Distillation	Oxidation	0	Regeneration WS
Going to	Extraction	WS Generation	Distillation	Top - 0	Bottom - 0	Extraction	Regeneration WS	0
Properties								
T [C]	35	49	49	49.7	65.0	50	30	30
P [bar]	3.5	3.5	4.5	0.1	0.1	3.5	3.5	3.5
Molar flows [kmol/h]								
H2								
N2		3				3		3
O2		0.5				0.5		0.5
H2O	930	208	760	609	151	38		128
EAQ		445				445	5	
WS		2945				2945	5	
H2O2		13	210	1	209	223		
H2.EAQ								
Waste		5				5		5

Table A.14. Overview of the identified limitations/bottlenecks (LB) and their analysis.

LB	Responsible phenomenon	Step	How
LB_1: Low efficiency in the oxidation	Phase transition by relative volatility	Step A2.4.1: APCP.4 (Rule APCP.7):	solubility oxygen in working solution/water VP difference is large
LB_2: Large amount of waste in oxidation	-		
LB_3: Large amount of waste in separation (H2O2/Water)	-		
LB_4: High energy/High costs for compressing air	-		
LB_5: High energy/High costs for separation H2O2/water	Phase transition by relative volatility	Step A2.4.1: APCP.4 (Rule APCP.1)	Tb is large why is water in the system
LB_6: High energy for hydrogenation;	heat of reaction	Step A2.4.3: AR.4 (criteria 2, Table 3.3)	Data from Eul, Moeller & Steiner, 2001
LB_7: High energy for oxidation	heat of reaction	Step A2.4.3: AR.4 (criteria 2, Table 3.3)	Data from Eul, Moeller & Steiner, 2001
LB_8: High costs for hydrogen	-		
LB_9: High costs for make-up solvent	-		
LB_{10}: High costs for waste stream;	-		
LB_{11}: Large amount of water necessary for extraction	Phase transition by extraction and mixing	Step A2.4.1: APCP.4 (Rule APCP.9)	Dilution of the product in the solvent

Table A.15. Retrieved potential PI equipments Ω to intensify the process.

Task	Keyword	Retrieved potential PI equipments Ω
Separation: working solution/product	LB_3, LB_{11}	Options: 26 Reaction-separation (Reactive distillation, reactive extraction, reactive membrane, reactive crystallization, reaction condensation, reaction-stripping, reaction-absorption, reactive distillation with pervaporation, heat-integrated distillation column, oscillatory baffled reactor-crystallizer), separation-reaction (absorption-reaction, reactive distillation, reactive extraction), Separation-separation (Adsorption distillation, extraction crystallization, extraction distillation, distillation pervaporation, membrane extraction, dividing wall column); HIGEE, spinning disc separator; packed microchannel extractor; microchannel extractor; static mixer extractor; microchannel reactor-extractor; static mixer reactor-extractor
		Ionic-liquid
Separation: water/product	LB_5	Options: 13 Separation-reaction (Absorption-reaction, reactive distillation, reactive extraction), Separation-separation (Adsorption distillation, extraction crystallization, extraction distillation, distillation pervaporation, membrane extraction, dividing wall column, heat-integrated distillation column); heat transfer panels inside column; HIGEE, spinning disc separator;
		Ionic liquid
1. Reaction: hydrogenation	LB_6, LB_1, LB_{12}	Options: 15 Reaction- separation (Reactive distillation, reactive extraction, reactive membrane, reactive crystallization, reaction condensation, reaction-stripping, reaction absorption, reactive distillation with pervaporation, oscillatory baffled reactor-crystallizer); catalytic static mixer reactor; microchannel reactor-extractor, microchannel reactor; millichannel reactor; monolithic reactor, foam reactor.
2. Reaction: oxidation	LB_1, LB_7, LB_9, LB_{13}	Options: 16 Reaction- separation (Reactive distillation, reactive extraction, reactive membrane, reactive crystallization, reaction condensation, reaction-stripping, reaction absorption, reactive distillation with pervaporation, oscillatory baffled reactor-crystallizer), Reaction-reaction (1-pot synthesis); static mixer reactor; micro reactor-extractor, microchannel reactor; millichannel reactor; oscillatory baffled reactor; static mixer reactor-extractor
Compressing air	LB_2, LB_4, LB_{10}, LB_{14}	Use of Oxygen instead of air

A.8. Additional material to the case study: HMF (section 5.3)

In this section, additional material to solve the case study to produce HMD (section 5.3) is given. It includes the mass and energy data of the base-case design of Rapp (1988) given in section A.8.1, the superstructure containing all options satisfying operational constraints and performance metrics using simple models (A.8.2) as well as the selection of solvents for the reactive extraction units by applying sub-algorithm **SoP** is shown in detail (A.8.3).

A.8.1 Mass and energy data of the base-case design

Table A.16. Mass and energy data for the base case design by Rapp (1988) for the production of HMF from fructose (0: outside; DR: Dehydration reaction; RoA: Reaction of acids; Cryst: Crystallizer; Chrom: Chromatography).

	S1	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**	**S9**	**S10**	**S11**
From	0	DR	0	Filter	Filter	Chrom1	Chrom2	Cryst	Cryst	0	Chrom2
To	DR	Filter	RoA	0	RoA	0	Cryst	0	0	Chrom1	0
T [C]	138	138	40	40	40	40	40	55	55	40	40
P [bar]	3.3	3.3	1	1	1	1	1	0.05	0.05	1	1
Mass flow rates (kg/h)											
Fructose	5.5	2.1	0.0	0,0	2.1	2.1	0.0	0.0	0.0	0.0	2.1
Water	16.4	17.4	0.0	0,0	17.4	144.7	109.1	109.1	0.0	139.0	5.6
Oxalic acid	0.05	0.1	0.0	0,0	0.1	0.1	0,0	0.0	0.0	0.0	0.1
Ca(OH)2	0,0	0.0	0.045	0,0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
HMF	0,0	1.3	0.0	0,0	1.3	0.3	1.0	0.0	**1.0**	0.0	0.3
Polymers	0,0	1.0	0.0	0,6	0.4	0.4	0.0	0.0	0.0	0.0	0.4

A.8.2. Superstructure of the remaining options after screening for operational constraints and performance metric using simple models

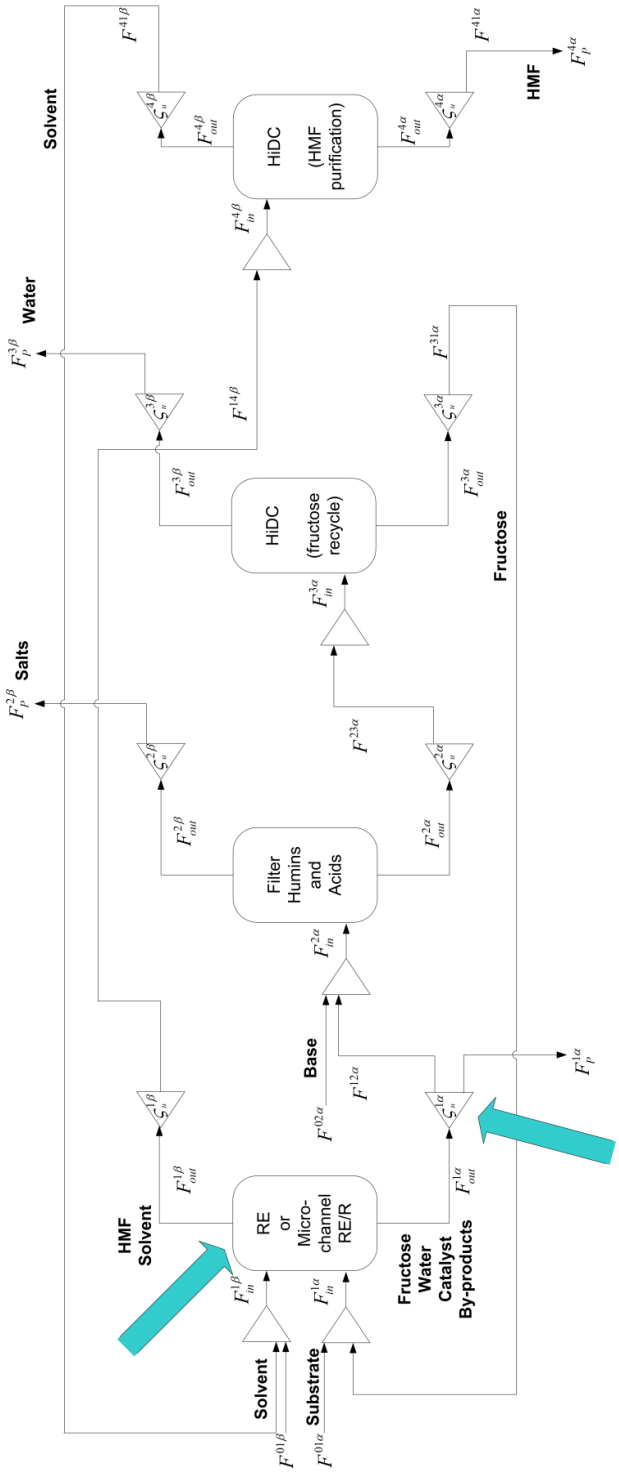


Figure A.13. The five remaining process options after screening by operational constraints and performance metrics using simple models from the superstructure for the integration of up to four units with a maximum of two inlet/outlet streams each. (Symbols: streams *F*, splitting factors ς; Binary variables Y are not shown). The large arrow shows where the four different superstructures are enabled (selection of unit in task 1 and the selection for a recycle of fructose or not. In case of the microchannel reactor the recycle is necessary).

A.8.3 Solvent selection in step 5

Here, the result of the solvent selection is shown using the steps of the sub-algorithm SoP.4-SoP.7.

SoP.4: Solvents for the system (water-route) suggested in literature (Roman-Leshkov & Dumesic, 2009) are retrieved. That is, pure solvents MIBK (Methyl-isobutyl-ketone), 2-butanone, THF (Tetrahydrofuran) as well as a mixture of 7:3 MIBK-2-butanol. Besides, also new solvents should be identified (Rule SoP.5). Step SoP.5 is entered.

SoP.5: The tool ProCAMD (see section 4.7) is used for identification of new solvents for the system. The target properties of the solvent are listed in Table A.17 together with the translation into pure component properties.

Table A.17. Target solvent properties and their related pure component properties (δ_{SP}: Hildebrandt solubility parameter; log (WS): Water solubility; T_B: Boiling point temperature).

Target solvent properties	Related pure component properties
High solubility for HMF	δ_{SP}
Immiscible in water	log (Ws)
Easy separation from HMF by relative volatility	T_B

The identified solvents are presented in Table A.18. The best identified solvents are the ones using ProCAMD matching exactly the solubility parameter of HMF. The best solvent from the literature is THF. Therefore, these three solvents are put into the search space.

Table A.18. Target solvent properties and their related pure component properties (δ_{SP}: Hildebrandt solubility parameter; log (WS): Water solubility; log (K_{OW}): Octanol-water partition coefficient; T_B: Boiling point temperature; T_M: Melting point temperature; Hvap: Heat of vaporization; R: Partition coefficient; "*": predicted from known data, see Fig.A.15).

	T_B [K]	T_M [K]	Log (K_{OW})	Log WS [mg/l]	δ_{SP} [$MPa^{0.5}$]	Hvap at T_B [kJ/mol]	R (Eq. 5.48)
HMF	498.49	300.64	0.02	5.57	19.93	66.68	
Solvents from literature:							
MIBK-2-butanol							1.65
MIBK	396.4	216	1.33	4.05	17.54	41.11	0.9
2-butanone	351	202.03	0.53	4.79	18.6	29.11	5.4
THF	338.15	164.85	0.45	4.51	18.97	29.29	7.1
Best Solvent from ProCAMD:							
$C_7H_{11}BrCl_4$	560.89	296.86	5.13	1.42	19.93	79.7	11.18*
C_5H_9BrO	453.3	252.23	2.42	3.0	19.92	49.7	11.18*

An important parameter for the solvent selection is the partition coefficient R (see Eq.5.48). This parameter is correlated to the solubility parameter of the solvent to the solute (HMF). For the untested solvents (see Fig.A.14), this value has been predicted from the reported values of the known solvents in the literature (see Fig. A.15).

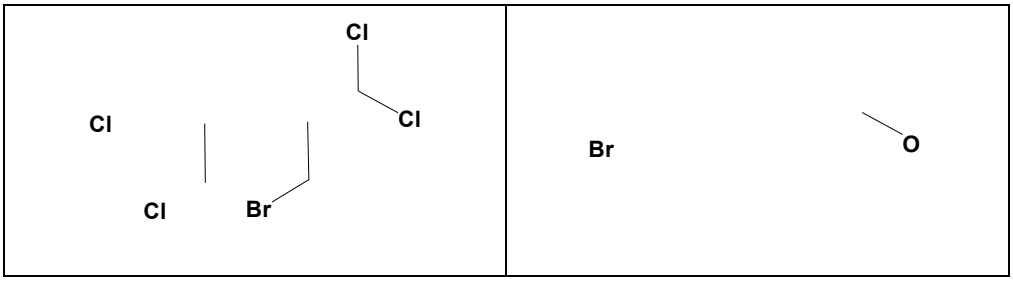


Figure A.14. High boiling solvent $C_7H_{11}BrCl_4$ (left) and low boiling solvent C_5H_9BrO (right) for the extraction of HMF from an aqueous phase.

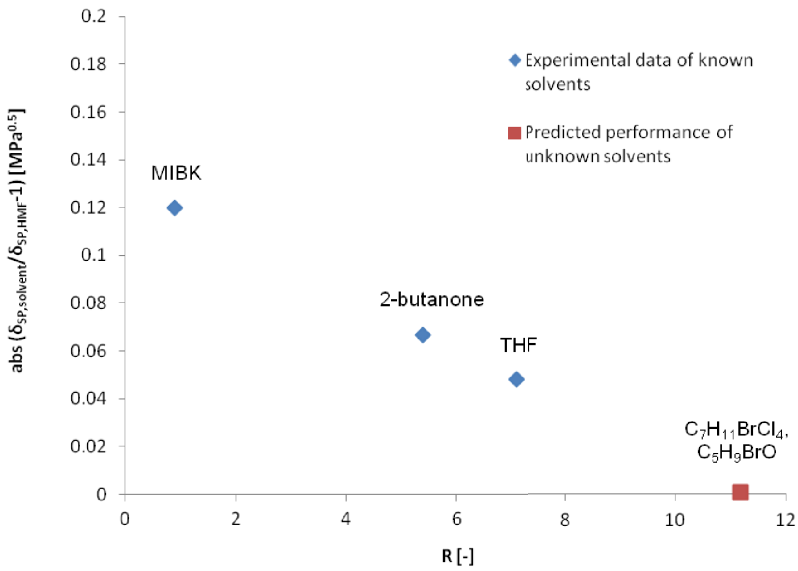


Figure A.15. Relationship of the deviation from the Hildebrandt solubility parameter of the solvents from the solute (HMF) and the partition coefficient R.

SoP.6: No, additional solvents from the known components in the system have been added to the search space.

SoP.7: No membrane needs to be selected. Step is not necessary.

A.9. Additional material to the case study: IPAc (section 6.1)

This section includes additional material to the case study for the production of isopropyl acetate using the the phenomena based workflow. First the reaction kinetics is given (A.9.1) and the selection of the phenomena in step P3.6 is explained in more detail (A.9.2). Additionally, the detailed model of the phase transition phenomenon by pervaporation is given (A.9.3). Subsequently, the list of logical constraints for the superstructure is presented in section A.9.4 followed by the detailed stepwise screening by logical and structural constraints in section A.9.5-A.9.6. Finally, in section A.9.7, the stepwise procedure of step B2 is followed, to highlight the algorithm for cases in which a base case design not exists.

A.9.1 Reaction kinetics

The reaction rate for the production of isopropyl-acetate from isopropanol and acetic acid (see Eq. 6.1) can be expressed through equation (A.2.1) with parameters taken from Sanz and Gmehling (2006a,b):

$$r = 1.02\times10^{7}\exp\left(\frac{-64.59}{RT}\right)a_{HOAc}a_{IPOH} - 1.90\times10^{7}\exp\left(\frac{-73.63}{RT}\right)a_{IPAC}a_{w}. \quad \text{(A.9.1)}$$

The activity of each component is:

$$a_i = x_i\gamma_i. \quad \text{(A.9.2)}$$

The molar fractions of the liquid can be determined through the change of moles of the component i over the overall moles in the batch reactor (Eq. A.9.3).

$$x_i = \frac{n_i}{\sum n_i}. \quad \text{(A.9.3)}$$

Activity coefficients obtained using UNIQUAC are expressed as function of binary parameters and molar fractions. The equations and parameters are not presented here as they can be found in literature (Sanz & Gmehling, 2010a,b).

A.9.2 Selection of phenomena in step P3.6

In this step, all accompanying phenomena by contacting the knowledge base for each identified phenomena are used. The additional identified phenomena are: phase transition by relative volatility and phase transition by pervaporation.

A general table of phenomena classes and the possible (inter)connection has been presented in Table 2.3 and 2.4.

The detailed selection procedure is presented in table A.19 and is here briefly explained for the first two phenomena. Since, this procedure is an iterative procedure; the first selection is abbreviated with S1, the second with S2, and so on.

S1: The first phenomenon in the search space is the reaction taking place in the liquid phase. Hence, liquid phase mixing phenomena need to be selected. Additional, a stream dividing phenomenon is by definition also always selected. The reaction is exothermic. Hence, cooling and heating phenomena are selected. This selection can be followed by looking at the reaction phenomenon in the first row and the second last column (Table A.19). Moving this column downwards, the abbreviation S1 is put for each phenomenon selected. Following this column downwards, all selected phenomena are marked.

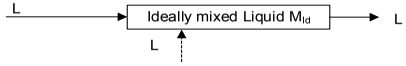
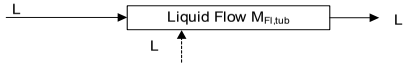
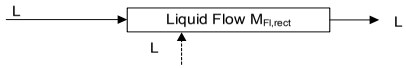
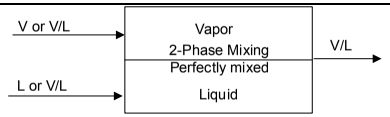
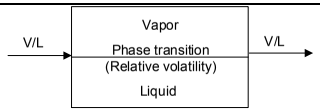
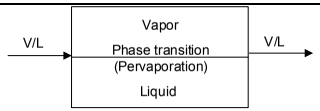
S2: The second phenomenon in the search space is the phase transition phenomenon by relative volatility. For occurrence, a phase contact and thermal heat/cooling are necessary as well as a suitable phase separation phenomenon (Table 2.4). Hence, for all of these suitable V-L phenomena are selected (Table A.19).

The procudre stops when all phenomena in the search spce have been the basis for a search. In total 12 repetitive steps (S1-S12) are necessary, giving in total a number of 12 phenomena (PB.1-PB.12). The selected phenomena are presented in Table A.20.

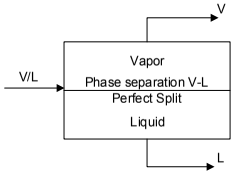
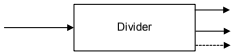
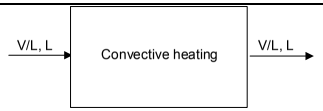
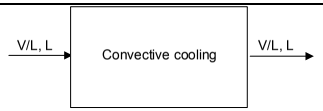
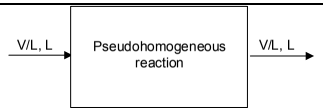
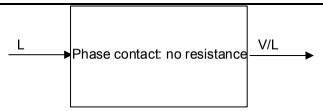
Table A.19: Detailed selection procedure of additional phenomena for the search space from the identified phenomena using the table before (I: Identified phenomena through the analysis, S1-S12: Sequential selection of phenomena, A: already selected in a previous sequence).

Class			Mixing					Phase transition		Phase separa-tion	Dividing	Energy Transfer		Reac-tion	Phase contact
	Subclass		1-phase				2-phase	V-L		V-L	-	Thermal		-	V-L
		Phenomena	M_{Id}	$M_{Fl,tub}$	$M_{Fl,rec}$	M_V	*2phM*	*PT(VL)*	*PT(PVL)*	*PS(VL)*	*D*	*H*	*C*	*R*	*PC*
Used as basis for search in:			S9	S10	S11	S12	S5	S2	S3	S6		S7	S8	S1	S4
Mixing	1-phase	M_{Id}	S1				A			A		A	A	S1	
		$M_{Fl,tubular}$		S1			A			A		A	A	S1	
		$M_{Fl,rectangular}$			S1					A		A	A	S1	
		M_V				S5	S5			A		A	A		
		...													
	2-phase	*2phM*					S4					A	A		S4
		...													
Phase transition	V-L	*PT(VL)*						I							A
		PT(PVL)							I						A
Phase separation	V-L	*PS(VL)*						S2	A	S2					
Dividing	-	*D*	A	A	A	A	A	A	A	A	S1	A	A	S1	A
Energy transfer	Thermal	*H*						A	A			S1		S1	
		C						A	A				S1	S1	
		...													
	....	...													
Reaction	-	*R*												I	
Phase contact	V-L	*PC*						S2	A						S2

Table A.20: Descriptions of the phenomena potentially involved in the process.

No.	Phenomena	Building Block	Description	Models:
PB.1	L-phase mixing: Perfectly mixed (M_{Id})		Convective mixing of one phases Inlet: minimum 1 stream, Outlet: 1 outlet stream, liquid stream	Mass, Energy and momentum balances Constraint equation on inlet and outlet streams
PB.2	L-phase mixing: Tubular Flow ($M_{Fl,tub}$)		Convective mixing of one phases Inlet: minimum 1 stream, Outlet: 1 outlet stream, liquid stream	Mass, Energy and momentum balances Constraint equation on inlet and outlet streams
PB.3	L-phase mixing: Rectangular Flow ($M_{Fl,rec}$)		Convective mixing of one phases Inlet: minimum 1 stream, Outlet: 1 outlet stream, liquid stream	Mass, Energy and momentum balances Constraint equation on inlet and outlet streams
PB.4	V-phase mixing: Perfectly mixed (M_V)		Convective mixing of one phases Inlet: minimum 1 stream, Outlet: 1 outlet stream, liquid stream	Mass, Energy and momentum balances Constraint equation on inlet and outlet streams
PB.5	2-Phase Mixing: perfectly mixed Vapor – Liquid (2phM)		Convective mixing of two phases Inlet: minimum 2 streams, Outlet: 1 outlet stream,	Mass, Energy and momentum balances Constraint equation on inlet streams Constraint equation giving interfacial area, degree of mixing: here Perfectly mixed
PB.6	Phase transition phenomena V-L: Relative volatility (PT(VL))		Inlet: 1, Outlet of a 2-phase-mixing phenomena block gas-liquid Outlet: 1 (V/L) Both phases are in outlet in equilibrium.	Mass, Energy and momentum balances Constraint equation on inlet streams Phase – Equilibrium equations for each component
PB.7	Phase transition phenomena V-L: Pervaporation (PT(PVL))		Inlet: 1, Outlet of a 2-phase-mixing phenomena block gas-liquid Outlet: 1 (V/L)	Mass, Energy and momentum balances Constraint equation on inlet streams Flux equation for pervaporation membrane

Cont'd **Table A.20:** Descriptions of the phenomena potentially involved in the process.

No.	Phenomena	Building Block	Description	Models:
PB.8	Phase separation V-L: Perfect split (PS(VL))		Inlet: 1, Outlet of a 2-phase-mixing phenomena block Solid-liquid Outlet: 2, one vapor, one liquid Both phases are in outlet in equilibrium.	Mass, Energy and momentum balances Constraint equation on inlet and outlet streams
PB.9	Divider (D)		Inlet: 1 Outlet: minimum 2 Outlet streams are equilibrium.	Mass, Energy and momentum balances Splitting factor(s)
PB.10	Simplified heat exchange phenomena: Heating (H)		Inlet: 1, Outlet: 1 Phases not in contact	Mass, Energy and momentum balances Constraint equation on inlet streams
PB.11	Simplified heat exchange phenomena: Cooling (C)		Inlet: 1, Outlet: 1 Phases not in contact	Mass, Energy and momentum balances Constraint equation on inlet streams
PB.12	Pseudo-homogeneous reaction (R)		Inlet: 1, Outlet: 1	Mass, Energy and momentum balances Constraint equation on inlet streams
PB.13	Phase contact V-L: No resistance (PC)		Inlet: 1, Outlet: 1	Mass, Energy and momentum balances Constraint equation on inlet and outlet streams

A.9.3 Fit of experimental data (Van Hoof et al., 2005) and the model of the phase transition by pervaporation

Here, the fit and the the experimental data for the developed empirical equation of the phase transition phenomenom by pervaporation (Eq.6.1) is presented (Figure A.16).

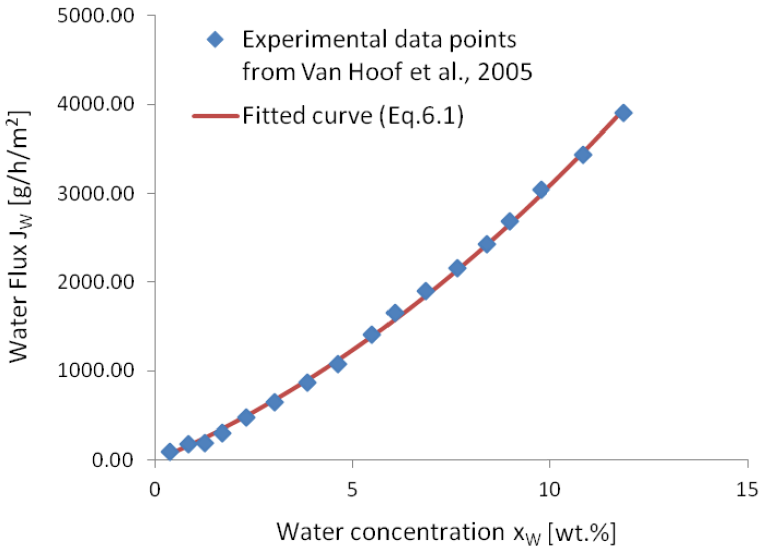


Figure A.16. Different flow patterns for the liquid flow.

A.9.4. Logical constraints for the dividing phenomenon within a 3 stage crossflow arrangement

Not all connections in the superstructure are feasible. It depends on the position of the dividing phenomena in the superstructure. The different positions of D within 2 or 3 stage superstructures and their corresponding active streams are shown in Table A.21. All streams for the liquid phase given in the superstructure for a crossflow connection enabled by the position of the stream dividing are presented in Figure 6.4. This information of possible stream connections are translated into mathematical constraints to be used for screening in step P4.3.3 for identification of feasible connections.

Table A.21: Logical constraints for feasible forward connections established by the use of a dividing phenomenon

Number of stages in the flowsheet	Position of D	Active streams
3	No divider	❶, ❷, ❸, ❹
2	No divider	❶, ❷, ❸
3	D in stage 1, D not in stage 2 and not in stage 3	❶, ❷, ❸, ❹, ❼
		❶, ❷, ❸, ❹, ❺, ❼
		❶, ❷, ❻, ❹, ❼
		❶, ❷, ❻, ❹, ❺, ❼
3	D in stage 2	❶, ❷, ❸, ❹, ❻
2	D in stage 1	❶, ❷, ❸, ❺,

A.9.5. Examples of the screening by logical constraints in step P4.4

The number of process option has been reduced in this step from 121610 to 24142 process options. For each logical constraint an example is given to highlight the procedure of the stepwise screening. The phenomenon describing the ideal mixing of the vapor flow is not inserted. In all visualized examples (Figures A.17-A.23), grey connectors mean interconnection (simultaneous occurrence) while black connectors mean sequential connection.

- **Formation of product**

  At least one reaction phenomena has to be included in the process. The left option (Figure A.17) stays in the search space because a reaction phenomenon is included in the process. The right option (Figure A.17) is removed from the search space since no reaction phenomenon is included in the process.

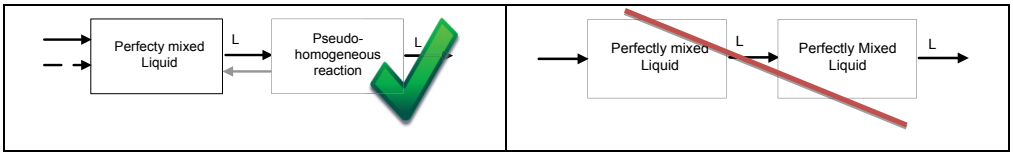


Figure A.17. Example for logical constraint: formation of product.

- **No separation in mixtures containing only reactants**

  Reaction phenomenon should occur at least before or simultaneously with a phase transition phenomenon. The upper example (in Figure A.18) is removed from the search space because a

separation takes place before the reaction which led to reactant loss. The lower example (in Figure A.18) stays in the search space because the reaction takes place in the first stage.

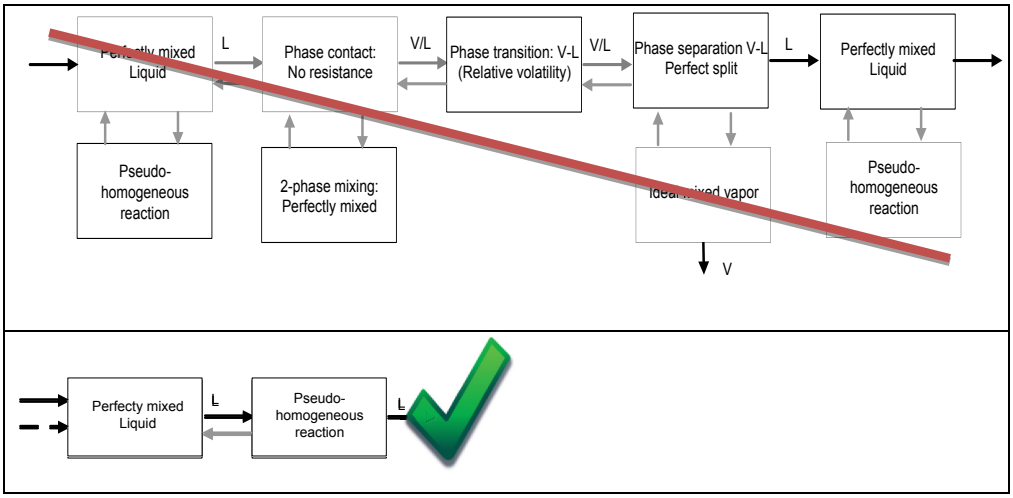


Figure A.18. Example for logical constraint: no separation of raw materials.

- **Feasibility of the process**

  The upper example (in Figure A.19) is removed because in the last stage a liquid stream leaving a phase separation phenomenon cannot be connected to a exothermic reaction phenomenon without simultaneous phase creation phenomenon since the liquid stream is at its boiling point which would lead to a creation of vapor. The lower example (in figure A.19) is possible because the introduction of a cold liquid stream from the outside into the stage leads to a cooling effect.

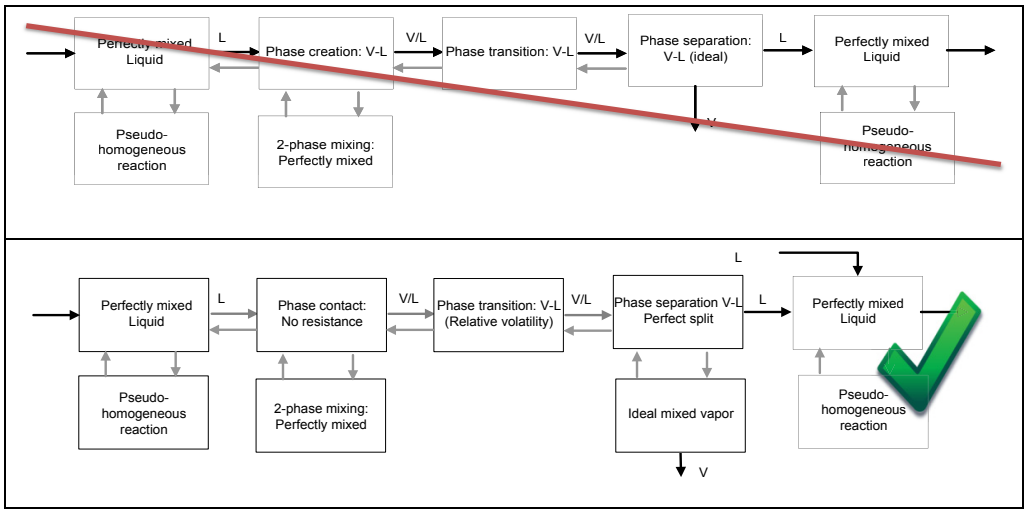


Figure A.19. Example for logical constraint: Feasibility of connected streams.

A.9.6. Examples of the screening by structural constraints in step P4.5

The number of process options has been reduced by applying structural constraints in this step from 24142 to 506 process options. Here, for each structural constraint, one example is given to highlight the procedure of the stepwise screening as well as the logical constraint itself.

- **Remove energy redundant options**

  Remove all options in which energy is wasted by sequential cooling, followed by heating, followed by cooling of the mixture. The upper example (in Figure A.20) is removed because the reactants are cooled first with subsequent heating in the next stage. In the lower example (in Figure A.20), the reactants are pre-heated before introduced into the next stage in which additionally the heat of reaction is used for the creation of a vapor-liquid-mixture.

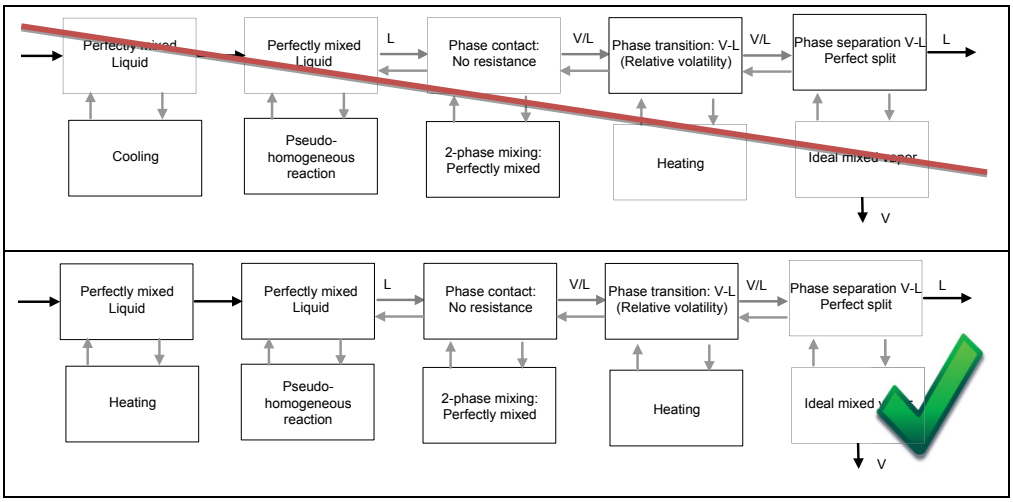


Figure A.20. Example for structural constraint: Remove energy redundant options.

- **Phenomena not linked to improve the yield**

  Remove all options in which all leaving streams get additional treatment which is not related to improve the yield. The upper example (Figure A.21) is removed from the search space because there is no improvement expected with additional mixing of the liquid after reaction.

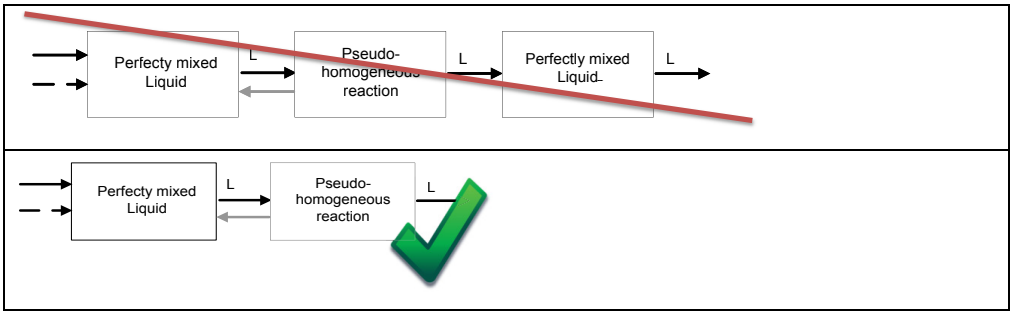


Figure A.21. Example for structural constraint: Phenomena not linked to improve the yield.

- **Remove options which potentially decrease the efficiency in last step**

  Apply structural rules, gained by the analysis of the driving force and the operational window to ensure that the phenomena leading to highest improvement of the objective function are last. The left example (Figure A.22) is kept in the search space and the right example (Figure A.22) is removed from the search space because the yield of the reaction increases with lower temperatures.

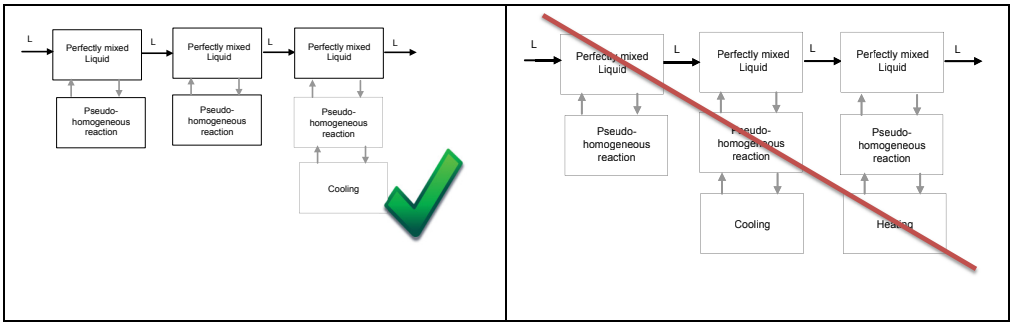


Figure A.22. Example for structural constraint: Remove options which potentially decrease the efficiency in the last step.

- **Process in 1 unit operation possible**

  Apply structural rules to identify the minimum number of units represented by the phenomena-based process option. The constraint is set to be 1 unit. The left option (Figure A.23) is kept in the search space since flow mixing patterns in a series represent one flow reactor with or without changing shell properties. The right option (Figure A.23) is removed because two ideal mixing phenomena in a series represent two CSTR in series which exceed the number of units allowed.

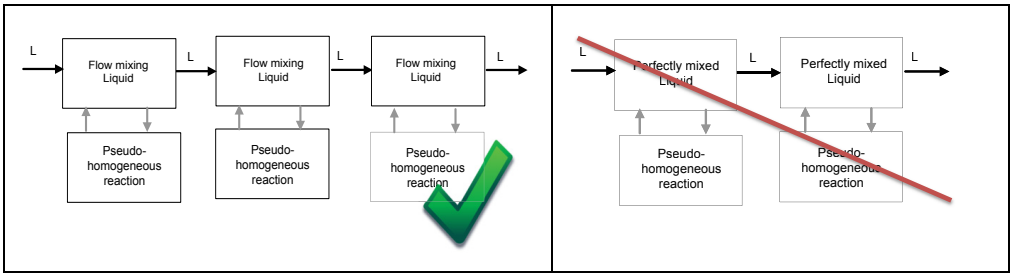


Figure A.23. Example for structural constraint: Realization in 1 unit operation possible.

- **No external recycle**

  Apply structural rules to remove external recycles or forward recycles. An example of a removed process options is the sequence of flow mixer reactors in stage 2 and 3 and a dividing phenomenon in stage 1, enabling the active streams ❶, ❷, ❸, ❹, ❺, ❼ (see Table A.20 and Figure 6.5).

A.9.7. Step B2: Step B2: Identify and analyze necessary tasks to achieve the process targets

Here, the workflow of step B2 is highlighted with a conceptual example using the IPAC case study described in section 6.1. Step B2 of the workflow is needed in case no base-case design is known (see section 3.1.5). The first step (Step 1) is the same as for the case with base case design (see section 6.1.2). Therefore, step B2 is directly entered here.

Step B2.1: The components present in the system are: IPOH, HOAc, IPAc, H2O and Amberlyst 15.

Step B2.2: The components IPOH and HOAc are identified as reactants (Rule B2.2) and the components IPAc and H2O are identified as products (Rule B2.1). Amberlyst 15 is identified as the catalyst (Rule B2.3).

B2.3: Define all reactions in the system:

Step B2.3.1: All reactions are identified (Rule B2.4). Step B.2.3.3 is entered (Rule B2.5).

Step B2.3.3: The identified reaction is desirable (Rule B2.7).

Step B2.3.4: One task is identified connected to the inlets, as presented in the figure A.24.

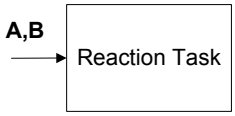


Figure A.24. Result of step B2.3.4 which is the identification of the desired reaction task and the corresponding reactants.

Step B2.3.5: The algorithm **AR** is applied. The reaction has an unfavorable equilibrium.

Step B2.3.6: The algorithm **OPW** is applied. The result is shown in Table A.22. The information about the unfavorable equilibrium is added to *LB*.

Table A.22: Identified operational window of the reaction.

Phenomenon	Operational Window
V/L, L → Pseudo-homogeneous reaction → V/L, L	T_{low}=289.8 K (Melting Point of HOAc) T_{high}=403 K (Catalyst degradation; DOW, 2011)

The predicted outputs are added to the task-based flowsheet (see Figure A.25).

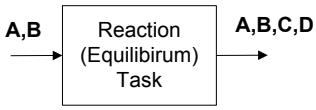


Figure A.25. Extended task-based flowsheet after step B2.3.6 giving the potential outlet of the system.

Step B2.4: Identify necessary separation/mixing/heat supply/removal tasks for each outlet:

Step B2.4.1-4: All necessary tasks are identified (no purity has been defined in step 1).

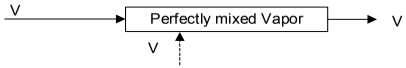
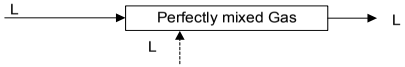
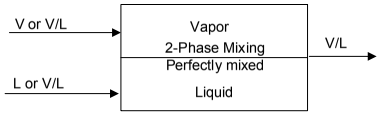
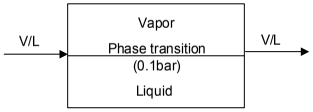
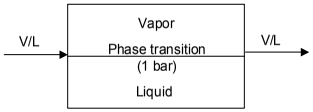
Step B2.5: No new components or boundaries have been identified (rule B2.14-B2.15).

Step B2.6: Step A2.1 is entered following the same result as given in section 5.1.

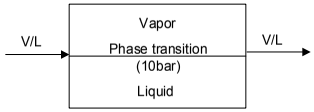
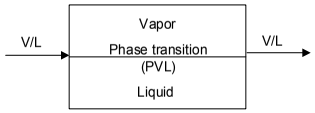
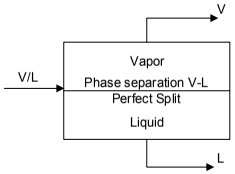
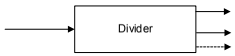
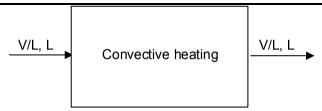
A.10. Additional material to the case study: Separation of H_2O_2/H_2O (section 6.2)

Here, additional material for the case study of the separation of H_2O_2 from aqueous solution (section 6.2) is given. It includes the list of identified phenomena (Table A.23) which, in total, contains 15 phenomena.

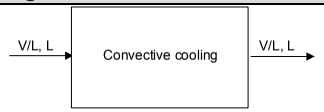
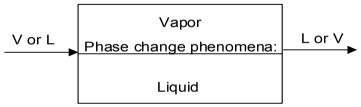
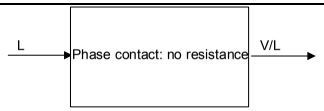
Table A.23: Descriptions of the phenomena potentially involved in the process.

No.	Phenomena	Building Block	Description	Models:
PB.1	1-phase mixing: Perfectly mixed Vapor		Convective mixing of one phases Inlet: minimum 1 stream, Outlet: 1 outlet stream, vapor stream	Mass, Energy and momentum balances Constraint equation on inlet and outlet streams
PB.2	1-phase mixing: Perfectly mixed Liquid		Convective mixing of one phases Inlet: minimum 1 stream, Outlet: 1 outlet stream, liquid stream	Mass, Energy and momentum balances Constraint equation on inlet and outlet streams
PB.3	2-Phase Mixing: perfectly mixed Vapor – Liquid (convective)		Convective mixing of two phases Inlet: minimum 2 streams, Outlet: 1 outlet stream, dispersed phase g/l	Mass, Energy and momentum balances Constraint equation on inlet streams Constraint equation giving interfacial area, degree of mixing: here Perfectly mixed
PB.4	Phase transition phenomena V-L: P=0.1 bar		Inlet: 1, Outlet of a 2-phase-mixing phenomena block gas-liquid Outlet: 1 (V/L) Both phases are in outlet in equilibrium.	Mass, Energy and momentum balances Constraint equation on inlet streams Phase – Equilibrium equations for each component
PB.5	Phase transition phenomena V-L: P=1 bar		See PB.4	See PB.4

Cont'd **Table A.23:** Descriptions of the phenomena potentially involved in the process.

No.	Phenomena	Building Block	Description	Models:
PB.6	Phase transition phenomena V-L: P=10 bar		See PB.4	See PB.4
PB.7	Phase transition phenomena Pervaporation: P=1 bar		Inlet: 1, Outlet of a 2-phase-mixing phenomena block gas-liquid Outlet: 1 (V/L)	Mass, Energy and momentum balances Constraint equation on inlet streams Flux equation for pervaporation membrane
PB.8	Phase separation: V-L Perfect split		Inlet: 1, Outlet of a 2-phase-mixing phenomena block Solid-liquid Outlet: 2, one vapor, one liquid Both phases are in outlet in equilibrium.	Mass, Energy and momentum balances Constraint equation on inlet and outlet streams
PB.9	Divider		Inlet: 1 Outlet: minimum 2 Outlet streams are equilibrium.	Mass, Energy and momentum balances Splitting factor(s)
PB.10	Simplified heat exchange phenomena: Heating (H)		Inlet: 1, Outlet: 1 Phases not in contact	Mass, Energy and momentum balances Constraint equation on inlet streams

Cont'd **Table A.23:** Descriptions of the phenomena potentially involved in the process.

No.	Phenomena	Building Block	Description	Models:
PB.11	Simplified heat exchange phenomena: Cooling (C)		Inlet: 1, Outlet: 1 Phases not in contact	Mass, Energy and momentum balances Constraint equation on inlet streams
PB.12	Phase change: Ideal from V to L or L to V		Inlet: 1, has to be coupled to a state change phenomena such as heating/ cooling or pressurizing/ expanding Outlet: 1	Mass, Energy and momentum balances Constraint equation on inlet and outlet streams
PB.13	Pressurizing		Inlet: 1, has to be coupled to a mixing phenomenon Outlet: 1	Mass, Energy and momentum balances Constraint equation on inlet and outlet streams
PB.14	Expanding		Inlet: 1, has to be coupled to a mixing phenomenon Outlet: 1	Mass, Energy and momentum balances Constraint equation on inlet and outlet streams
PB.15	Phase contact V-L: No resistance (PC)		Inlet: 1, Outlet: 1	Mass, Energy and momentum balances Constraint equation on inlet and outlet streams

A.11. Additional material to the case study: Production of cyclohexanol (section 6.3)

Here, additional material for the case stuy to produce cycloheaxol is given. This appendix contains the kinetic models for the direct and indirect hydration route of cyclohexene to cyclohaxanol (A.11.1), the NRTL model to describe the phase transition by relative volatility (A.11.2), the list of identified phenomena in the search space (A.11.3) and the phenomena-based flowsheets for the direct and indirect hydration route (A.11.4).

A.11.1. Kinetic models of the reaction involved in the process

The retrieved kinetic models of the reactions and their parameters from literature are given in Table A.24-A.25.

Table A.24. Kinetic and equilibrium constants for direct hydration route.

Reaction: Cyclohexene + water ⇔ cyclohexanol	**Reference**
Thermodynamic equilibrium constant: K(T) = 2.37*10^-5*exp(30.236kJ/mol/RT) T in Kelvin; R=8.314 J/ (mol K)	Qi & Sundmacher, 2002
Forward rate constant: kf(T)=kf,0*exp(-103.2 kJ/mol/RT) With kf,0= 2.77*10^8 (1/s) and T in Kelvin; R=8.314 J/ (mol K)	Qi & Sundmacher, 2002
Heterogeneous rate constant: kf(T)=kf,0,het*exp(-93.7 kJ/mol/RT) in mol/s / kg_catalyst With kf,0,het= 7.71*10^12 (mol/(kf_cat*s)) and T in Kelvin; R=8.314 J/ (mol K)	Steyer & Sundmacher, 2007

Table A.25. Kinetic and equilibrium constants for the indirect hydration route.

R.2 : Cyclohexene + formic acid ⇔ cyclohexyl formate	**Reference**
Heterogeneous rate constant: kf(T)=kf,0,het*exp(-114.4 kJ/mol/RT) in mol/s / kg_catalyst With kf,0,het= 4.57*10^25 (mol/(kf_cat*s)) and T in Kelvin; R=8.314 J/ (mol K)	Steyer & Sundmacher, 2007
R.3: Cyclohexyl formate + water ⇔ cyclohexanol + formic acid	**Reference**
Heterogeneous rate constant: kf(T)=kf,0,het*exp(-100.2 kJ/mol/RT) in mol/s / kg_catalyst With kf,0,het= 1.21*10^16 (mol/(kf_cat*s)) and T in Kelvin; R=8.314 J/ (mol K)	Steyer & Sundmacher, 2007

The calculation of the equilibrium constant is done via the Gibbs-enthalpy (Eq.A.11.1):

$$K = \exp\left(-\frac{\Delta G^R}{RT}\right) \tag{A.11.1}$$

With the reaction stoichiometry: $aA + bB \leftrightarrow cC + dD$

$$\Delta G^R = c\Delta G_c^0 + d\Delta G_d^0 - a\Delta G_a^0 - b\Delta G_b^0 \tag{A.11.2}$$

and

$$\Delta G^0 = \Delta H^0 - T\Delta S^0 \tag{A.11.3}$$

Necessary data has been published by Katariya, Steyer & Sundmacher (2009) and is shown in Table A.26.

Table A.26. Parameters for calculation of equilibrium constant (Katariya, Steyer & Sundmacher, 2009).

	ΔH^0 [J/mol]	S^0 [J/(mol K)]	c_p [J/(mol K)]	K_{ads}
Cyclohexene	-37820	216,33	148,83	0,056839
Cyclohexanol	-351831	203,87	213,59	0,77324
Water	-285830	69,95	75,38	19,989
FCE	-487129	275,5	219,5	3,677
Formic Acid	-425379	129	99,84	7,729E-07

A.11.2. NRTL model for the cyclohexanol system

The parameters for the NRTL model have been retrieved from Steyer & Sundmacher (2004) and are given in Table A.27.

Table A.27. NRTL Parameters determined by Steyer & Sundmacher, 2004.

Binary pair	g12 (J/mol)	g21 (J/mol)	alpha12
Cyclohexene (1) + cyclohexanol (2)	3300.09	157.301	0.79362
Cyclohexene (1) + water (2)	13522.7	21495.6	0.24319
Cyclohexene (1) + cyclohexane (2)	35.3067	36469.3	0.89828
Cyclohexanol (1) + water (2)	-569.408	12237.7	0.26904
Cyclohexanol (1) + cyclohexane (2)	958.747	6334.27	0.86274
Water (1) + cyclohexane (2)	26171.4	17556.3	0.25118

Their model has been checked against experimental datapoints from the same authours as well the UNIFAC model with parameters from ICAS database and a model in which the liquid phase is described as ideal. The analysis shows best agreement for using the parameter set for the NRTL model (exemplary shown for the mixture cyclohexene-cyclohexanol, Figure A.26).

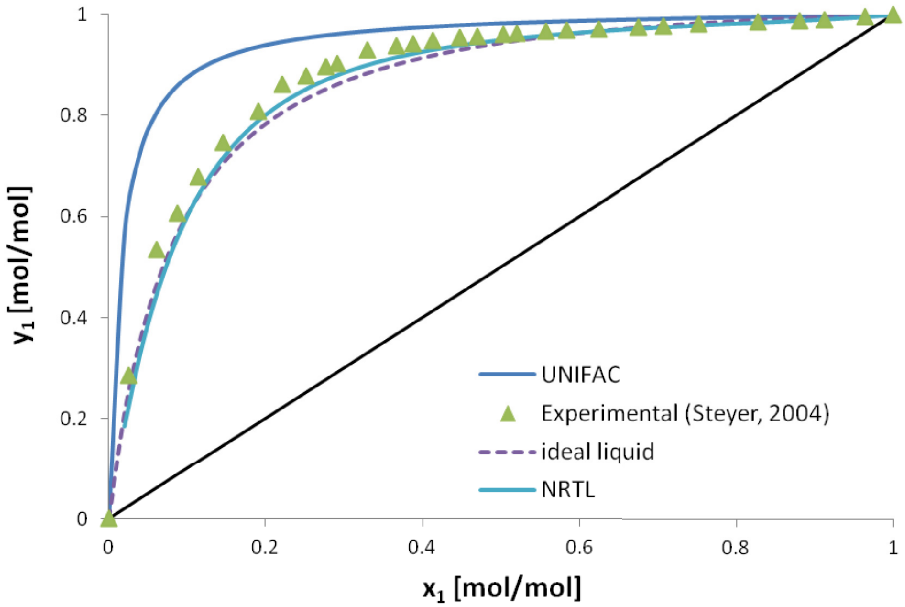


Figure A.26. Comparison of experimental (Steyer & Sundmacher, 2004) and simulated VLE data for the binary pair cyclohexene (1) - cyclohexanol (2) at p=1 atm.

A.11.3. List of identified phenomena

The list of identified phenomena contains in total 23 phenomena (Table A.28).

Table A.28. List of identified phenomena potentially involved in the process for the production of cyclohexanol.

No.	Phenomena	Description	Models:
PB.1	1-phase mixing: Perfectly mixed Vapor (M(V))	Convective mixing of one phases Inlet: minimum 1 stream, Outlet: 1 outlet stream, vapor stream	Mass, Energy and momentum balances Constraint equation on inlet and outlet streams
PB.2	1-phase mixing: Perfectly mixed Liquid (M(L))	Convective mixing of one phases Inlet: minimum 1 stream, Outlet: 1 outlet stream, liquid stream	Mass, Energy and momentum balances Constraint equation on inlet and outlet streams
PB.3	2-Phase Mixing: perfectly mixed Vapor – Liquid (M(VL))	Convective mixing of two phases Inlet: minimum 2 streams, Outlet: 1 outlet stream, dispersed phase g/l	Mass, Energy and momentum balances Constraint equation on inlet streams Constraint equation giving interfacial area, degree of mixing: here Perfectly mixed
PB.4	2-Phase Mixing: perfectly mixed: Liquid – Liquid (M(LL))	Convective mixing of two phases Inlet: minimum 2 streams, Outlet: 1 outlet stream, dispersed phase l/l	Mass, Energy and momentum balances Constraint equation on inlet streams Constraint equation giving interfacial area, degree of mixing: here Perfectly mixed
PB.5	2-Phase Mixing: Not mixed: Liquid – Liquid (Mno(LL))	Convective mixing of two phases Inlet: minimum 2 streams, Outlet: 1 outlet stream, dispersed phase l/l	Mass, Energy and momentum balances Constraint equation on inlet streams Constraint equation giving interfacial area, degree of mixing: here Perfectly mixed
PB.6	Phase transition phenomena V-L: PT(VL,1bar)	Inlet: 1, Outlet of a 2-phase-mixing phenomena block gas-liquid Outlet: 1 (V/L) Both phases are in outlet in equilibrium.	Mass, Energy and momentum balances Constraint equation on inlet streams Phase – Equilibrium equations for each component
PB.7	Phase transition phenomena V-L: PT(VL,0.1bar)	See PB.5	See PB.5

Cont'd **Table A.28**. List of identified phenomena potentially involved in the process for the production of cyclohexanol.

No.	Phenomena	Description	Models:
PB.8	Phase transition phenomena LL settling (PT(LL,1bar))	Inlet: 1, Outlet of a 2-phase-mixing phenomena block gas-liquid Outlet: 1 (L/L)	Mass, Energy and momentum balances Constraint equation on inlet streams Flux equation for pervaporation membrane
PB.9	Phase transition phenomena LL settling (PT(LL,0.1bar))	See PB.8	See PB.8
PB.10	Phase separation: V-L Perfect split (PS(VL))	Inlet: 1, Outlet of a 2-phase-mixing phenomena block Solid-liquid Outlet: 2, one vapor, one liquid Both phases are in outlet in equilibrium.	Mass, Energy and momentum balances Constraint equation on inlet and outlet streams
PB.11	Phase separation: L-L Perfect split (PS(LL))	Inlet: 1, Outlet of a 2-phase-mixing phenomena block Solid-liquid Outlet: 2, one vapor, one liquid Both phases are in outlet in equilibrium.	Mass, Energy and momentum balances Constraint equation on inlet and outlet streams
PB.12	Divider (D)	Inlet: 1 Outlet: minimum 2 Outlet streams are equilibrium.	Mass, Energy and momentum balances Splitting factor(s)
PB.13	Simplified heat exchange phenomena: Heating (H)	Inlet: 1, Outlet: 1 Phases not in contact	Mass, Energy and momentum balances Constraint equation on inlet streams
PB.14	Simplified heat exchange phenomena: Cooling (C)	Inlet: 1, Outlet: 1 Phases not in contact	Mass, Energy and momentum balances Constraint equation on inlet streams

Cont'd **Table A.28**. List of identified phenomena potentially involved in the process for the production of cyclohexanol.

No.	Phenomena	Description	Models:
PB.15	Phase change: Ideal from V to L or L to V (PCh)	Inlet: 1, has to be coupled to a state change phenomena such as heating/ cooling or pressurizing/ expanding Outlet: 1	Mass, Energy and momentum balances Constraint equation on inlet and outlet streams
PB.16	Phase contact V-L: No resistance (PC(VL))	Inlet: 1, Outlet: 1	Mass, Energy and momentum balances Constraint equation on inlet and outlet streams
PB.17	Phase contact L-L: No resistance (PC(LL))	Inlet: 1, Outlet: 1	Mass, Energy and momentum balances Constraint equation on inlet and outlet streams
PB.18	Pressurizing (Prise)	Inlet: 1, has to be coupled to a mixing phenomenon Outlet: 1	Mass, Energy and momentum balances Constraint equation on inlet and outlet streams
PB.19	Expanding (Pdrop)	Inlet: 1, has to be coupled to a mixing phenomenon Outlet: 1	Mass, Energy and momentum balances Constraint equation on inlet and outlet streams
PB.20	Pseudo-homogeneous reaction (R1)	Inlet: 1, Outlet: 1	Mass, Energy and momentum balances Constraint equation on inlet streams
PB.22	Pseudo-homogeneous reaction (R2)	Inlet: 1, Outlet: 1	Mass, Energy and momentum balances Constraint equation on inlet and outlet streams
PB.23	Pseudo-homogeneous reaction (R3)	Inlet: 1, Outlet: 1	Mass, Energy and momentum balances Constraint equation on inlet streams

A.11.4. Phenomena-based representation of two flowsheet for the direct and the indirect route to produce cyclohexanol

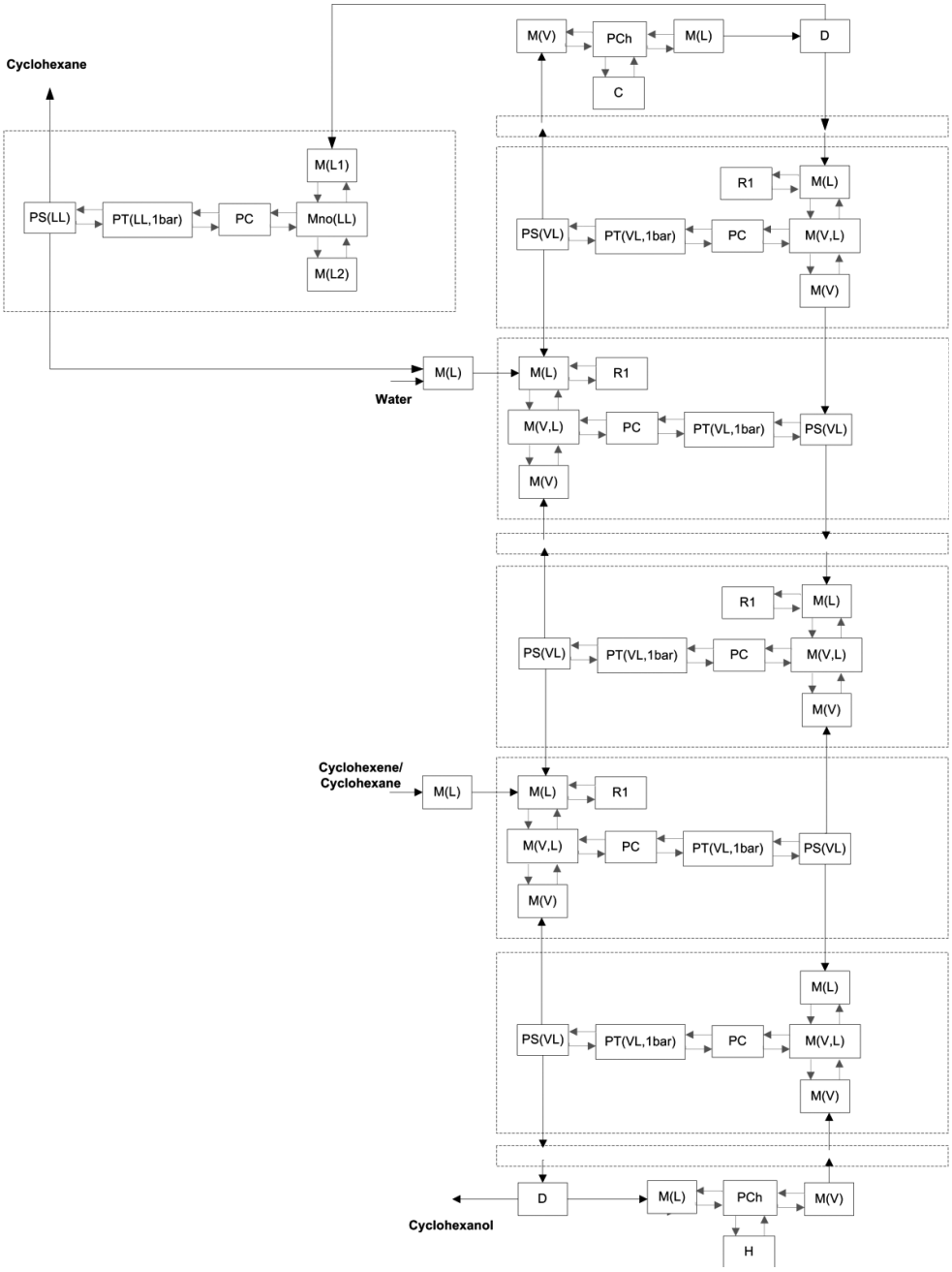


Figure A.27. Phenomena-based flowsheet for the direct hydration route via reactive distillation.

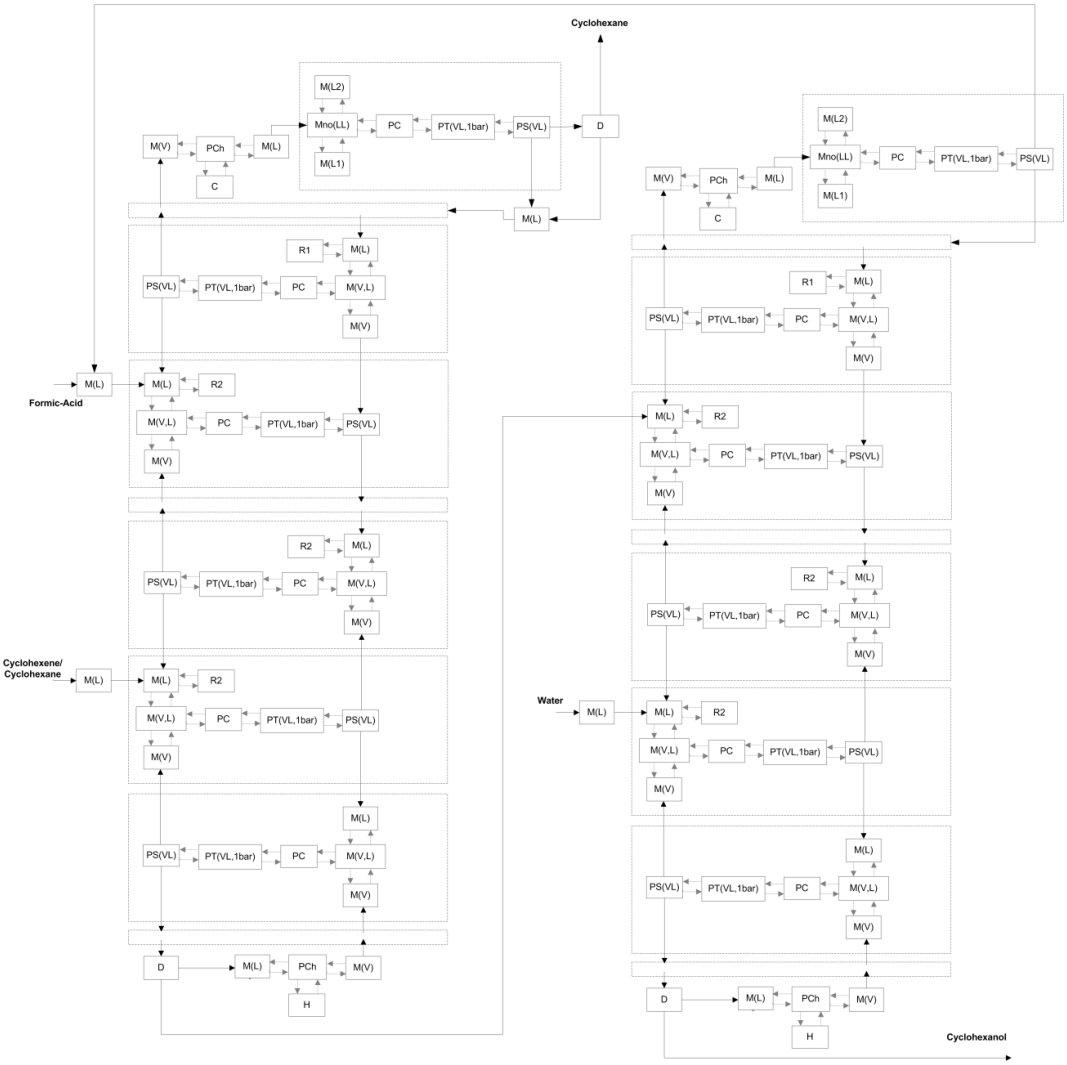


Figure A.28. Phenomena-based flowsheets for the indirect hydration route via two integrated reactive distillations.

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