**An optimisation-based framework for the conceptual design of reaction-separation processes**

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# Abstract

Prior to detailed process design, it is vital to first generate a good flowsheet that meets particular objective. This is particularly the case in bio-based materials and products, where, given a range of chemistries, the synthesis problem is not about the best way to make a particular product but rather the best way to convert a specific feedstock. In order to do so, an optimisation-based framework can be used to identify the optimal configuration of a process network that consists of both reactions and separation systems to achieve maximum economic potential is presented in this paper. A process superstructure, which includes the concept of master reaction stages and subsidiary separation stages, is introduced to facilitate the theory. The problem is formulated as a generalised mixed integer linear programming (MILP) model which accounts for the simultaneous selection of products and identification of the process configuration. The solution of the optimisation problem includes the best possible economic performance, identification of active reactions, reaction ordering and separation sequences along with the corresponding flowsheet of the optimal process. The economic criterion takes account of raw materials costs, product values and separation related costs. Two bio-based chemical case studies are presented to illustrate the applicability of the proposed methodology.

*Keywords:* Optimisation-based framework; Process superstructure; MILP; Reaction network; Distillation sequences

# Introduction

Polymers have been one of the most important bulk chemicals across the world since World War II. Global demand for polymers in 2013 was 250 million tonnes, of which the UK’s plastic demand accounts for approximately 1.5 percent (PlasticsEurope 2014). Polymers are consumed by various sectors which are dominated by packaging, construction and transport. As the largest polymer consumer in the UK, the plastic packaging sector was forecasted to have a 14.2 percent market growth between 2014 and 2018 (BP&R 2014). The UK is not only a large polymer consumer, but also an innovative and experienced plastic producer. The UK plastics industry processes 4.8 million tonnes of raw materials to produce 2.5 million tonnes of polymers annually, with an annual turnover of £19 billion in 2012. In general, the plastic sector accounts for about 7.5 percent of the chemicals industry in the UK and provides approximately 180,000 job opportunities (UKT&I 2012).

However, widely used polymers such as polycarbonate (Fiege et al. 2000), polyethylene and polyvinyl chloride are still produced from oil/gas-based feedstocks. Although developments in the technology of unconventional production of oil/gas, improvements in energy efficiency of vehicles all around the world and other demand/supply factors have contributed to the drop of the oil price for the last two years (Krauss 2015), petrochemical derived polymers are still facing the issues of increasing greenhouse gas emissions and waste accumulation (Gandini 2008). Currently, global companies such as P&G are devoted to exploring consumer driven processes and products with lower environmental impacts. Therefore, sustainability issues associated with the conventional polymer industry may lead to its diminished commercial competitiveness. One potential solution to mitigate these negative effects induced by the conventional polymer industry is through the development of sustainable bio-polymer production routes which can be more environmentally friendly (Abegg 2011). Recently, extensive research has been carried out on the synthesis of bio-renewable polymers. It was reported that various types of polymers, including polyethylene (Yoshida et al. 2008), polyesters (Singhvi and Gokhale 2013), polycarbonates (Hauenstein et al. 2015), polyamides and polyurethanes, can be prepared from biomass feedstocks via different polymerisation routes (Bart et al. 2012). These processes are normally identified by bio- or chemo-catalysis research, which typically focuses on the development of a single or few related reaction steps in laboratory experiments. However, the concept of quickly and methodically determining the most desirable product and generating a preliminary optimum reaction-separation network, provided with the large number of candidate reactions, is largely neglected. This is why computer-aided process synthesis optimisation is considered a very important tool which can be used to set the stage for detailed process design.

Process synthesis contains two strongly related stages: i) a higher-level decision-making process including the construction of process superstructure, definition of objectives for evaluating the system and systematic optimisation to determine the technologies that attain the objectives; ii) a lower-level decision-making process consists of decomposition of the optimal superstructure and detailed design of those subsystems (Nishida et al. 1981). Although process synthesis as a research area is only about a few decades old, it has experienced significant evolution with respect to research issues as well as to the application domains. It started with the design of chemical reaction networks (Siirola and Rudd 1971), separation systems (Naka et al. 1982), heat exchanger networks (Linnhoff and Flower 1978) and whole process flowsheets (Douglas 1988) from 1960s to 1980s. Then in the late 1990s and early 2000s, new research topics such as environmental impact minimisation (Stefanis et al. 2001) and supply chain design (Beamon 1998) were covered. Lately, process intensification using advanced technologies (Phan and Harvey 2012), system design at molecular scale and product design also have become more and more popular among both academia and industries (Li and Kraslawski 2004).

Recently, a large number of studies have considered process synthesis methods for integrated biorefinery processes. For instance, a mixed integer nonlinear program (MINLP) was developed to find the optimal processing routes for the production of ethanol, butanol, succinic acid and their blends with fossil based gasoline to achieve different objectives (i.e. maximum yield, minimum waste and minimum cost) (Zondervan et al. 2011). Later, Kelloway and Daoutidis (2014) proposed another MINLP method to identify the optimal products and process technologies in a biorefinery superstructure which results in the highest economic potential or carbon efficiency. A sensitivity analysis was also implemented to show the impact of changes in product prices and feedstock costs on the profitability of different biorefinery configurations. Tang et al. (2013) presented a robust MINLP model which handles the predefined uncertainties in energy economics, feedstock availability and biofuel market demands to determine the optimal biorefinery network structure with the maximum economic performance (Douglas 1988).

Aside from nonlinear programming, linear programming (LP) algorithms have been shown to be well-suited for the purpose of systematic synthesis of an optimal integrated biorefinery which simultaneously considers economic performance, environmental impact and energy requirement (Andiappan et al. 2014). Unlike nonlinear systems, the local optimum obtained in the linear system is also a guaranteed global optimum. Ponce-Ortega et al. (2012) introduced a disjunctive mixed integer linear program (MILP) for the identification of optimal biorefinery configurations for a given criterion (e.g., the economics, environmental, or safety, etc.). The feedstock and product were predetermined in the previous case whereas Murillo-Alvarado et al. (2013) further extended the method to include feedstock and product selection. Note that in his work, not only were the reaction technologies considered, but separation treatment technologies such as extraction were also taken into account as those decisions can have significant impacts on the economic performance, utility costs and sustainability of the system. Meanwhile, Kim et al. (2013) proposed a MILP-based assessment framework which also incorporated separation technology to identify the best strategy for the production of a specific fuel such as ethanol. Bao et al. (2011) presented a systematic approach which uses an MILP model to screen and determine the optimum reaction process networks with respect to economic performance given the starting feedstocks and the desired product. Later in his dissertation (Bao 2012), the practicability and accuracy of the method were improved as a simultaneous separation analysis was implemented. Last but not least, Voll and Marquardt (2012) adapted the reaction network flux analysis (RNFA) method from Hechinger et al. (2010), which also briefly mentioned the possibility of accommodating non-sharp separations into the system, to systematically rank a large number of alternative reaction pathways for a biorefinery.

Nevertheless, the aforementioned works have yet to provide automatic screening of various separation technologies and thus produce the optimum separation superstructure. Jaksland et al. (1995) developed a methodology, based on physicochemical properties of given substances and their relationships to separation techniques, to identify the most suitable separation technique, the sequencing of the separation tasks and the conditions of operation. In the case of designing the separation systems for multicomponent liquid mixtures, a qualitative and task-oriented approach was used by Barnicki and Fair (1990) to select the most appropriate technique from eight industrially significant separation methods. Among those techniques, distillation is by far the most widely used and most important technique for separating fluid mixtures in industrial settings and approximately 95% of all liquid separations involves distillation (Pohorecki et al. 2010). The design and analysis of distillation columns has been the interest of chemical engineers for decades. Equilibrium based methods were developed to obtain important design variables such as the number of required stages (Fenske 1932, Gilliland 1940, Underwood 1949), feed stage location (McCabe and Thiele 1925) and composition of the feed and outflows (Thiele and Geddes 1933) for the characterisation of multicomponent distillation columns. However, for complex multicomponent systems, these iterative methods can have difficulties in calculating the required results. Julka and Doherty (1990) proposed a simple non-iterative design procedure for multicomponent distillation columns, which was based on the geometry of the composition profiles in the state space, to determine the number of theoretical trays in the column the optimum, feed-plate location, and the exact product distribution (Julka and Doherty 1993). Non-equilibrium stage model, on the other hand, removes the requirement for increasingly complex modifications to the equilibrium stage model and was shown to be more effective and accurate (Krishnamurthy and Taylor 1985). Doherty and Perkins presented a dynamic model for multicomponent simple distillation using residue curve maps (Doherty and Perkins 1978), which was capable of characterising the distillation of ideal and non-ideal solutions as well as azeotropic ternary mixtures (Doherty and Perkins 1978, Doherty and Perkins 1979). However, residue curve maps enable one to gain insight into infinite-reflux column behaviour only (Tapp et al. 2004), whereas column profile maps (CPMs) obtained by using the difference point equation represent the finite-reflux case. This allows creative designs for the synthesis of more complex non-ideal distillation (Holland et al. 2004, Holland et al. 2010, Beneke et al. 2011).

Synthesis of the distillation sequence is also a vital procedure when designing a process (Nishida et al. 1981) as one cannot perform detailed design for a process before preliminary analysis is conducted. Generally, large fractionating columns are considered as a sequence of simple columns with two key components between which the separation takes place (Hengstebeck 1961). There are two main sequences that are used when designing distillation systems: direct and indirect distillation. Conventional crude distillation is normally an indirect sequence due to its energy saving edge over a direct sequence (Ji and Bagajewicz 2002). However, progressive distillation, which is a modified version of direct sequence, utilises a series of columns with non-sharp splits followed by a direct distillation sequence to reduce the energy requirement for crude feed stream preheating and intra-column heating (Devos et al. 1987). Most analyses on distillation sequences consider sharp separations only as a basic model (Wehe and Westerberg 1987, Wahl and Lien 1990, Harwardt et al. 2008). However, non-sharp distillation sequencing (which has the downside of significantly increasing the number of possible flowsheet), is the main research interest of several research groups (Bamopoulos et al. 1988, Aggarwal and Floudas 1990, Zhang and Linninger 2006, Ivakpour and Kasiri 2009) since it can be beneficial for the generation of multiple products and is more applicable to the real world. In addition, thermally coupled distillation columns are more effective in saving both operating and capital cost (Dünnebier and Pantelides 1999) and numerous work have been conducted on distillation sequencing of heat integrated systems (Andrecovich and Westerberg 1985, Floudas and Paules 1988, Wang et al. 1998, Caballero and Grossmann 2004). Distillation systems of azeotropic mixtures, although difficult, can also be automatically sequenced (Knapp and Doherty 1990, Bauer and Stichlmair 1996, Thong et al. 2004). On the other hand, complex distillation, i.e. distillation units with more than one feed stream or multiple product streams in addition to a single bottoms and a single distillate leaving conventional columns, was shown to be more efficient in terms of total energy consumptions, greenhouse gas emission, product purity and capital cost (Doherty and Malone 2001, Engelien and Skogestad 2005, Grossmann et al. 2005). Kim et al. (2010) proposed a novel method, which utilises inverse design procedures, column profile equations (Tapp et al. 2004) and the temperature collocation methodology (Zhang and Linninger 2004), to rigorously design the entire separation flowsheets using heat-integrated prefractionating columns to quantify usage of utilities and capital cost (Kim and Linninger 2010).

Despite the large number of process synthesis methods for reaction network optimisation of biorefineries and design of distillation sequences in the literature, there is limited research (Smith and Pantelides 1995, Ismail et al. 2001) reported for a more generic approach for the optimisation of an overall process that consists of both reaction and distillation systems. One may argue that the design of a process cannot be uncoupled from the problem of determining the optimum process configuration and flowrates (Douglas et al. 1985). Therefore, this paper presents such a method based on a mathematical programming model which can be easily modified to accommodate different aims (e.g. economic, energy, GHG, etc.) and study various chemical process systems. To develop this framework, we first generate a process superstructure, which includes master reaction stages and sub separation stages (Figure 1). Second, we develop an optimisation (MILP) model for the synthesis of reaction-separation pathways for the underlying superstructure (Section 3). Finally, in Section 4, two case studies are used to demonstrate the functionality of our framework.

# Problem statement

The problem can be described as follows: given a set of chemical feedstocks with finite amounts and a set of reactions starting from those chemical feedstocks with distillation as the main separation technique of the network, it is desired to develop a systematic methodology that can be used to determine the optimal configuration of a conceptual process that meets certain objectives (e.g. maximum profit). The conversion and selectivity of each reaction, as well as the boiling point and market value of each component are either known or estimated. Though the conceptual approach is preliminary, it should be accurate to some extent in making horizontal comparisons between numerous possible reaction networks and distillation sequences to set the stage for a more detailed process design. The model is formulated under the following primary assumptions:

* The process operates at steady stage, i.e. dynamics of reactions are neglected
* The major cost of the process is the raw material cost
* The reactor capital cost is assumed to be negligible in the model developed so far due to limited information on reactor availability for various reactions
* A simple overall cost model based on the difficulty of separation is used
* Sharp split assumption is used for the distillation system
* No recycle in the distillation system (i.e. top/bottom product from distillation column is not recycled to that column)

A detailed description of the developed model is presented in the following sections.

Figure : Conceptual diagram of the process superstructure

# Mathematical formulation

The process superstructure is shown in Figure 1. Here the concepts of master process stages and their subsidiary separation stages are introduced. Within each master stage, a mixer () is connected with a reactor (), which is subsequently connected to a purification unit () which consists of secondary separation stages (). As illustrated, the basic flow mechanism is that: i) inlet streams such as fresh feed and recycle streams () or product from other reactions () are firstly mixed in the mixer of each master stage to produce the reactor inlet stream (); ii) reactor outlet (), is subject to a bypass system allowing pure component, if any, to be removed directly () or be used as the reactant for other reactions (); iii) represents the flow that requires further purification and is equal to the flow that enters first separation column of the subsidiary separation system (); iv) coming out of each separation column are the distillate () and the bottom product () and each of them is subject to a split; v) it is a three-way split including the removal of pure product ( and ), mixtures that require further separation ( and ) and mixtures or pure components that are the reactants of the next master reaction ( and ). Note that in each separation unit, sufficient columns are provided and the optimisation would determine how many of them are to be used. Master stage is coupled with only if there are inter-stage streams, otherwise those two stages can be treated as two individual operational units.

The model aims to identify the optimal sequence of reaction & separation tasks and material flows, including recycle. The foregoing concepts are included in the detailed optimisation formulation in the following sections.

## Master stage mass balance

Different components are mixed at the mixing point before entering the reactor at master stage and the mass balance is simply written as:

|  |  |
| --- | --- |
|  | (1) |

followed by the reactor mass balance:

|  |  |
| --- | --- |
|  | (2) |

where is the stoichiometric coefficient of component in reaction . Taking the conversion into consideration, which is provide by the process chemistry data, the inlet of reactant at each reaction stage must be greater than the amount of that reactant required by the reaction, i.e.

|  |  |
| --- | --- |
|  | (3) |

The extent of reaction,, is a non-negative variable and is bounded by a maximum value , which is an arbitrary large number determined by either the user or the reaction maximum capacity:

|  |  |
| --- | --- |
|  | (4) |

In each reactor of master stage, up to one reaction can occur unless competitive reactions exist, which can be modelled using the binary variable as follows:

|  |  |
| --- | --- |
|  | (5) |
|  | (6) |

To simplify the model, all reactions are set to be active at most times in the whole process (i.e. in all active master stages):

|  |  |
| --- | --- |
|  | (7) |

where is a user defined parameter and can be adjusted for different scenarios but with a default value of 1 to reduce the complexity of the system.

In the case where there are simultaneous reactions, the extents of those reactions must be related to the inlet flowrate of the limiting reactant (), conversion and selectivity of that reaction. The resulting equation is bi-linear (given as Equation 1 in the Supplementary Documentation) and the linearised equations are as follows:

|  |  |
| --- | --- |
|  | (8) |
|  | (9) |
|  | (10) |
|  | (11) |

where is the selectivity of reaction set to be 1 for reactions that have no corresponding competing reactions and lie between 0-1 otherwise and is a dummy variable for linearisation.

The outlet from the reactor at master stage can bypass the separation unit at that stage if the flow is pure (i.e. the flow contains only one component) and either is removed directly or enters the next reaction stage depending on whether the component is the reactant of the active reaction in the next stage, which is to be decided by the optimisation. The mass balance at the bypass is as follows:

|  |  |
| --- | --- |
|  | (12) |

To simplify the problem, the bypass option for the reaction outlet stream is assumed to be unique, i.e. all of the flow is directed to whichever stream is determined to be active by the optimisation. Thus, the flowrate of each stream at the bypass split is constrained by the following conditions:

|  |  |
| --- | --- |
|  | (13) |
|  | (14) |
|  | (15) |
|  | (16) |

which allow a maximum one stream at the bypass to be active and the inactive streams will have flowrates of 0, where is an arbitrary number defined as the upper limit for all flowrates.

However, without any constraints on the price differences between a pure component and a mixture, the reaction outlet stream is bound to be removed directly at the bypass to avoid separation even if it is a mixture. Hence, in order to avoid multi-component mixtures from being removed into product streams directly, the economic value of the removal outlet is set to be 0 if it is an impure mixture, i.e.

|  |  |
| --- | --- |
|  | (17) |
|  | (18) |

where is the market price of component and the exclusiveness binary variable, , is set to be 0 if the direct removal is a mixture given as follows:

|  |  |
| --- | --- |
|  | (19) |
|  | (20) |

The binary variable indicating the existence of component in the direct removal stream of master stage, is determined by the flowrate of that component in the removal, i.e.

|  |  |
| --- | --- |
|  | (21) |
|  | (22) |

where is an appropriately large number. The constraints above allow the system to freely remove any pure components as products, but mixtures, which can be further separated to produce pure components with higher economic value accounting for corresponding separation cost, is incentivised to go through separation. In the case when all of the components in the reactor outlet are the reactant of another reaction in the network, it would enter that reactor directly without any separation. The conditions for this scenario are embedded in the objective function since with less separation, the economic potential is higher.

## Separation stage mass balance

As shown in Figure 1, each master separation unit is comprised of a number of sub separation stages denoted as. The mass balance at the inlet of each separation unit is written as follows:

|  |  |
| --- | --- |
|  | (23) |

In this work, distillation is selected to be the default separation technology. In a simple distillation column, the feed () is separated to form the top () and bottom () product, therefore the material balance around each distillation column can be stated as follows:

|  |  |
| --- | --- |
|  | (24) |

Since there is no recycle for the distillation columns, either the top or the bottom flow from a distillation column has three end destinations: the inlet of the subsequent separation stage (/), the direct removal stream (/) or the stream that enters the next master stage (/). Therefore, the split mass balances of component at both top and bottom of separation stage in master stage are modelled as follows:

|  |  |
| --- | --- |
|  | (25) |
|  | (26) |

However, instead of using binary variables as the split fraction, a new bi-linear system is introduced. This would allow the split fraction to vary from 0 to 1 depending on the accuracy required instead of being just 0 or 1. This adjustment is necessary because the method can now deal with cases such as: (i) a small part of non-pure mixture is removed directly if separating that part is not necessary and it is economically more efficient to directly remove the mixture as waste; (ii) part of the pure component can be removed directly if the amount of the rest entering the next master stage is sufficient for the reaction. To formulate the modification, 11 discretised split fractions (from 0 to 1) are firstly assigned to 11 points of, as shown in Table 1. Note that the number of points can be increased to improve the accuracy of the optimum results. In this work, 11 points are enough to test the functionality of the method while maintaining the CPU time of solving the model within acceptable range, and the detailed design that would follow can refine the results.

Table : Discretised split fraction

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|  | 0 | 0.1 | 0.2 | 0.3 | 0.4 | 0.5 | 0.6 | 0.7 | 0.8 | 0.9 | 1.0 |

Second, sets of binary variables are established for each point in each split stream at both top and bottom outflows of the distillation column indicating whether the corresponding value of split fraction at the assigned point is selected or not. For each stream, the number of active fraction points is not limited. However, having multiple active points brings only degeneracy in optimisation. Therefore, the default setting allows only one fraction point to be effective for each stream (/ and/) to simplify the model, i.e.

|  |  |
| --- | --- |
|  | (27) |
|  | (28) |
|  | (29) |
|  | (30) |

On the other hand, if either the top or bottom flow from separation stage is a mixture and requires further purification, the stream can be directed to subsequent stage, but the pathway selection from to must be unique, i.e.

|  |  |
| --- | --- |
|  | (31) |
|  | (32) |

The split fraction binary variables for streams going from stage to are thus formulated as follows:

|  |  |
| --- | --- |
|  | (33) |
|  | (34) |

Third, the sum of those split fractions at both top and bottom streams must be equal to 1 following the rule of mass conservation, i.e.

|  |  |
| --- | --- |
|  | (35) |
|  | (36) |

Finally, the mass balances at the split points of top/bottom outflows are simply as follows:

|  |  |
| --- | --- |
|  | (37) |
|  | (38) |
|  | (39) |
|  | (40) |
|  | (41) |
|  | (42) |

Equations (37) to (40) are bi-linear. They are linearised (details of the linearisation are given by Equations 2 to 17 of the Supplementary Documentation). On the other hand, the constraints on the flowrates of the streams which go from stage to are relaxed and become linear due to the previous mass balance and the fraction summation Equations ((25) - (26) & (35) - (36)).

The material balance at the inlet () of each separation stage () can be formulated as the sum of inter-stage flows originating from all stages of and having as the destination, i.e.

|  |  |
| --- | --- |
|  | (43) |

Normally the number of available separation stages is greater than the number of actual utilised stages. Therefore, the inlet flowrates of the inactive columns are set to 0, given by:

|  |  |
| --- | --- |
|  | (44) |

where is a binary variable indicating the separation column existence and the column sequencing degeneracy is avoided by imposing the following restrictions (i.e. it is not possible for column to be active while column is inactive):

|  |  |
| --- | --- |
|  | (45) |

The total amount of component that is directly removed () from the separation unit at stage and leaves that separation unit for the next master stage () is related to the sum of respective split streams at both top and bottom of each separation column. Hence:

|  |  |
| --- | --- |
|  | (46) |
|  | (47) |

Here, another point to note is that the removal of a mixture in the separation stage must be avoided unless the values of the respective pure component are not worth the effort of separating the mixture. Therefore similar constraints that are implemented for the economic value of the direct removal stream in the reactor outlet bypass split are also employed on the separation removal (given by Equations 19 to 31 of the Supplementary Documentation).

The post-separation mass balance of total removal at stage () and flowrate of component leaving stage for stage () can be written as follows:

|  |  |
| --- | --- |
|  | (48) |
|  | (49) |

## Separation mechanism

The separation mechanism in this conceptual design method is solely based distillation. The light key binary variable is introduced and is equal to 1 if component is the light key in separation stage of master reaction stage. Additionally, each component can only be treated as the light key once under the perfect separation assumption, i.e.

|  |  |
| --- | --- |
|  | (50) |

In each active separation stage, separation must take place and one and only one of the components is determined by the system to be the light key:

|  |  |
| --- | --- |
|  | (51) |

Furthermore, the light key can only be chosen from the components that are present in the inlet stream of that separation stage, which results in the following equation:

|  |  |
| --- | --- |
|  | (52) |

where is the binary variable indicating the presence of component in the inlet stream of separation stage and is defined as follows:

|  |  |
| --- | --- |
|  | (53) |
|  | (54) |

Accordingly, all components with lower boiling points than that of the light key will leave from the top of each stage (distillate) and the rest from the bottom stream (bottoms). This is expressed by the following equations:

|  |  |
| --- | --- |
|  | (55) |
|  | (56) |

Similarly to the light key constraints, in each stage, only one component can be treated as the heavy key and that component must be present in the inlet stream of that separation stage as well. This is modelled through the heavy key selection binary variable as follows:

|  |  |
| --- | --- |
|  | (57) |
|  | (58) |

The heavy key must be the component with the next highest boiling point than that of the light key which can be interpreted as: if component is determined by the system to be the light key in separation stage of master stage and component is present in that stage, then component must be the heavy key, i.e.

|  |  |
| --- | --- |
|  | (59) |

Note here that the components are ordered by increasing boiling points.

However, if component is not present and even component is not part of the inlet, the following equation is capable of determining the correct heavy key:

|  |  |
| --- | --- |
|  | (60) |

This condition essentially ensures that if component is the light key; all components from to are not the heavy key and component exists in the stage then component must be the heavy key.

## Other constraints

Apart from the abovementioned reaction/separation relevant conditions, a few other key constraints are required to allow the algorithm to be effectively functional. The first one is that to avoid reactor contamination, in each reaction stage, if all reactions with component as their reactant are not active, the inlet of that reaction stage must not contain unless it is defined to be inert, i.e.

|  |  |
| --- | --- |
|  | (61) |

where is the binary variable for the existence of in the inlet stream of the reactor at master stage and defined as:

|  |  |
| --- | --- |
|  | (62) |
|  | (63) |

The total addition of non-feedstock component must not be greater than the total removal of that component throughout the process which also allows recycle to be active:

|  |  |
| --- | --- |
|  | (64) |

The total amount of feedstock chemicals that are consumed in the system may also be limited to set the boundary for the system, i.e.

|  |  |
| --- | --- |
|  | (65) |

where is the maximum supply allowance of feedstock over a certain time period.

Note here, equation sets (21)-(22), (53)-(54) and (62)-(63) are only applicable for flowrates that are greater than 1. Therefore the unit of the flowrate is adjusted to avoid low flowrate values. The results generated by the model should also be checked to ensure that no flowrates are within the range of 0-1.

## Objective function

In this work, the main objective is to rank different process networks by their economic performance. Therefore, raw materials costs are included as it was reported to almost always be the largest contributor (typically 80 to 90%) to the total cost of production (Sari 2014). Meanwhile, distillation cost (capital and utility) is also estimated for the formulation to rank different column sequences. However, capital and operational costs related to reactors, labour and other costs are not considered in the current model. Thus, the objective function (total economic potential of the process) is given as follows:

|  |  |
| --- | --- |
|  | (66) |
|  | (67) |

where is the annual operational hour of the plant, is the product value of component in master stage , is the cost of adding component into mixing stage (the significance of this parameter is that it avoids overflow of reactant into reactors thus the value of AC is set to be very small but still effective in the model), is the flowrate of component entering the first mixing stage and is the annualised cost of the separation unit at stage , given as follows:

|  |  |
| --- | --- |
|  | (68) |

As Douglas mentioned in his book, the distillation capital cost is proportional to the column height, which can be found to be inversely proportional to the relative volatility of the key components and the operational (utility) cost is proportional to the vapour flowrate inside the column which is in a way proportional to the column feed flowrate (Douglas 1988). Therefore, the separation cost of each stage, is assumed to be proportional to the inlet flowrate of that stage and inversely proportional to the boiling point difference between the light and heavy key, i.e.

|  |  |
| --- | --- |
|  | (69) |

where is the separation cost coefficient, the estimation of which is based on overall distillation annual cost for well-known chemical separations such as benzene/toluene and methanol/ethanol systems (detailed analysis of separation cost coefficient is given in Section S3 of the Supplementary Documentation). Here, the boiling point of component is denoted as and the equation linearisation is performed as follows:

|  |  |
| --- | --- |
|  | (70) |
|  | (71) |
|  | (72) |
|  | (73) |
|  | (74) |
|  | (75) |
|  | (76) |
|  | (77) |

where is an arbitrary number used for the maximum flowrate in separation stage and , and are positive dummy variables.

Overall, the objective function (67) and those inequality/equality constraints from Equations (1) to (77) form a mixed integer linear program (MILP) which can be solved globally to determine the optimum reaction network along with the best corresponding separation sequencing strategy. To illustrate the applicability of the proposed approach, two case studies are presented, both of which are solved using the optimisation software GAMS (version 24.2.3). The initialisation procedure for GAMS is shown in Figure 2. Once a solution is obtained, the optimal reaction network and the associated process diagram are presented based on the results.

# Case Studies

This paper is a part of a 5-year collaborative project funded by the Engineering and Physical Sciences Research Council (EPSRC), the objective of which is to identify bio-polymer production processes that can be commercially competitive with low environmental impacts. Therefore, bio-derived chemicals and reaction networks starting from those chemicals that are common interest to the project team are the main focus. As a result, two components, d-limonene and itaconic acid, which can both be synthesised or extracted from biomass feedstocks are considered as the starting materials for the two case studies due to their potential to form innovative monomers and their large supply capacities. The bio-production routes for those two chemicals are not included in the optimisation model since they would not affect the overall ranking of the process network (i.e. both limonene and itaconic acid are being produced via industrialised technologies and it is assumed that a unique process is assigned to the production of each chemical).

Formulate constraints and the objective equation in GAMS

Input parameters required in the model, e.g. reaction conversion, selectivity and material cost

Compute all flowrates, binary variables and extents of reactions

Set initial guess of the inlet flowrate to the first master stage mixer

Calculate the economic potential of the process (the objective in this case)

Is the objective maximised, i.e. can the model generate higher value that is within all the boundaries?

Remover all unnecessary reactors and distillation columns and construct the optimum process flowsheet as well as the active reaction network

**Stage 1**

**Stage 2**

The objective is fed back to the program to generate the next best solution

**No**

**Stage 3**

**Yes**

Figure : Initialisation procedure for the solver. Stage 1 sets up the model. In stage 2, calculations are made to solve the model. Stages 3 involves the optimisation procedure to produce the optimum solution.

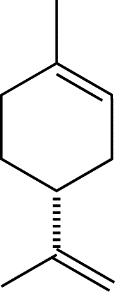
## Case I: D-limonene and its potential derivatives

The worldwide capacity of d-limonene production was estimated to be greater than 70,000 t in 2013 (Ciriminna et al. 2014) and is assumed to reach approximately 100,000 t in 2016. In this case study, the hypothetical limonene plant is designed to be capable of processing 15,000~20,000 t of limonene per annum with an annual operational time of 8500 hours.

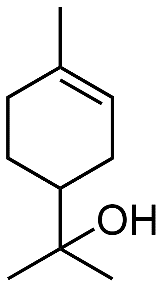
The proposed reaction network superstructure using d-limonene as the starting material is developed as shown in Figure 3. Small molecules such as are neglected in the network. The conversion, selectivity and reaction conditions of each reaction are listed in Table 2. The boiling point of each component is obtained from various databases and can be found in Table S4-1 of the supplementary Documentation. On the other hand, market prices of some of the uncommon chemicals are not easy to acquire (e.g. limonene dicarbonate and 5,6-epoxycarvone) and therefore a scientific estimation method – group contribution method (Jankowski et al. 2008) was implemented to provide approximate bulk prices for those compounds (details of the method can be found in the Appendix). Note here, this method acts as an approximation pricing tool to obtain rough estimations instead of speculative values. Though accuracy may not be satisfying, it is sufficient to prove the functionality of the method. In the future, the method can be avoided if proper data is provided.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Reaction No.** | **Conversion (mol %)** | **Selectivity (mol %)** | **Reaction conditions** | **References** |
| **R1** | 93 | - | 25 °C and 1 atm | (Adams et al. 2003) |
| **R2** | 100 | - | 170 °C and 1 atm | (Martín-Luengo et al. 2008) |
| **R3** | 100 | 59.5 | 75 °C and 1 atm | (Li et al. 2015) |
| **R4** | 100 | 40.5 | 75 °C and 1 atm |
| **R5** | 98 | 74.5 | 40 °C and 1 atm | (Wiemann Lars et al. 2012) |
| **R6** | 98 | 25.5 | 40 °C and 1 atm |
| **R7** | 100 | - | 140 °C and 30 bar | (Bahr et al. 2012) |
| **R8** | 32 | - | 50 °C and 1 atm | (Uguina et al. 2009) |
| **R9** | 90 | 62.6 | 100 °C | (Demidova et al. 2015) |
| **R10** | 90 | 37.4 | 100 °C |
| **R11** | 80 | - | - | (Kjonaas and Mattingly 2005) |

Table 2: Conversion/selectivity of each reaction

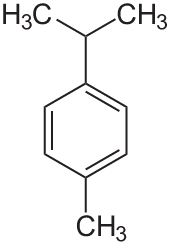


D-limonene (A)

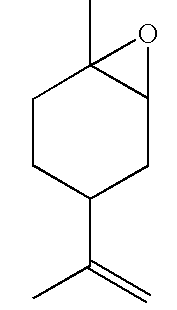


α-terpineol (B)

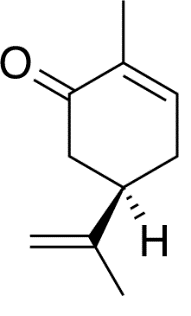
R1



R2

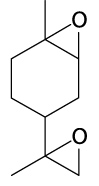


R3



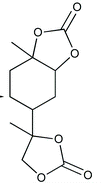
R4

R5

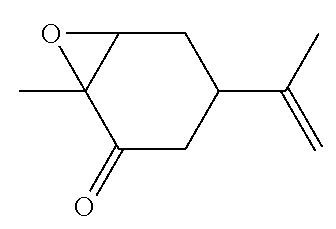


R6

R7



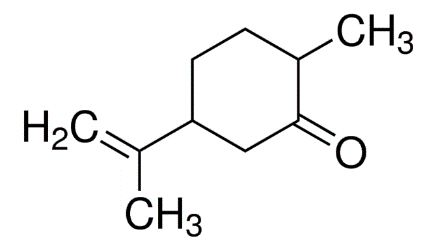
Carvone (E)



R8

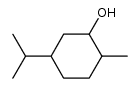
5,6-epoxycarvone (I)

R9



Dihydrocarvone (J)

R10



Carvomenthol (K)

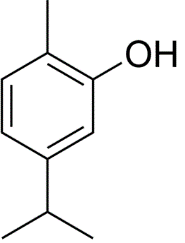
Limonene oxide (D)

Limonene dioxide (F)

Limonene dicarbonate (G)

P-cymene (C)

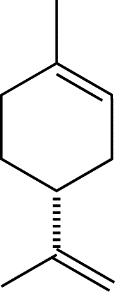
R11



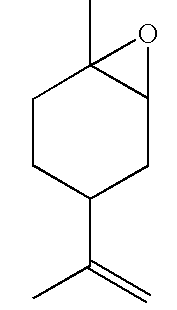
Carvacrol (H)

Figure : Proposed reaction network superstructure for the d-limonene case

As mentioned in the introduction, the selection of final product(s) is part of the optimisation procedure. The optimal reaction network generated by the model is shown in Figure 4. Starting from d-limonene, the competitive reactions 3 and 4 are preferred over the others. The produced limonene oxide is an end product which is sold at a market price, whereas carvone from R4 as an intermediate, is determined to further undergo reaction 11 which produces carvacrol at a conversion of 80%. The corresponding optimal process diagram is shown in Figure 5. As can be seen, fresh d-limonene is added to the first reactor to allow reactions 3 and 4 to take places. The product stream, which is composed of a mixture of limonene oxide and carvone, enters the associated distillation unit. Pure limonene oxide as the column light key leaves the top of the distillation column to be sold directly. From the bottom of that distillation stage, carvone is removed and enters the next master stage to be reacted to form the carvacrol, which is determined by the optimisation to be the optimal product of the process.



D-limonene (A)



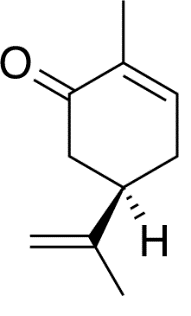
R3

R4

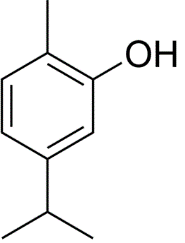
Limonene oxide (D)

R11

Figure : Optimal reaction network of the d-limonene case



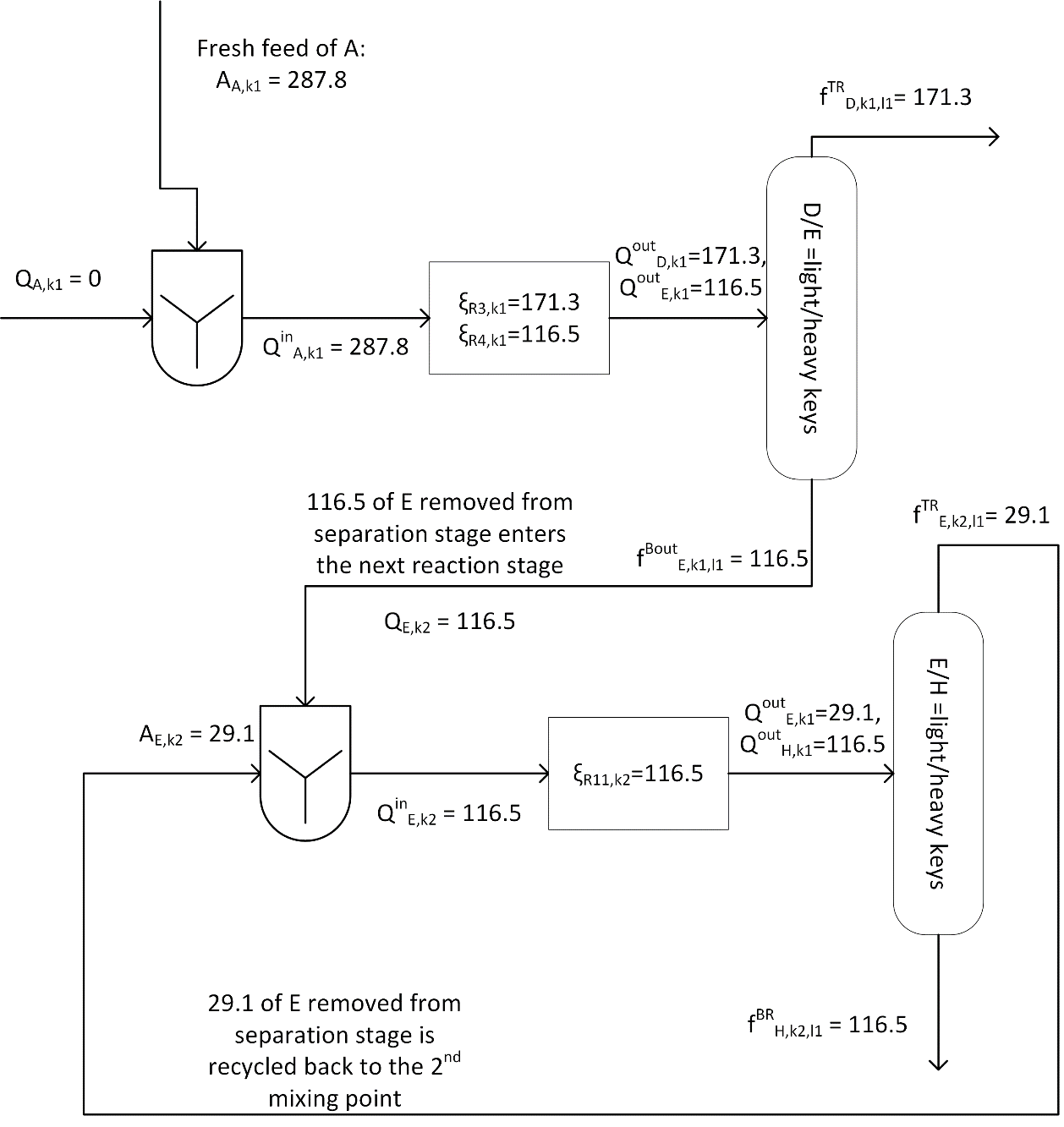
Carvone (E)



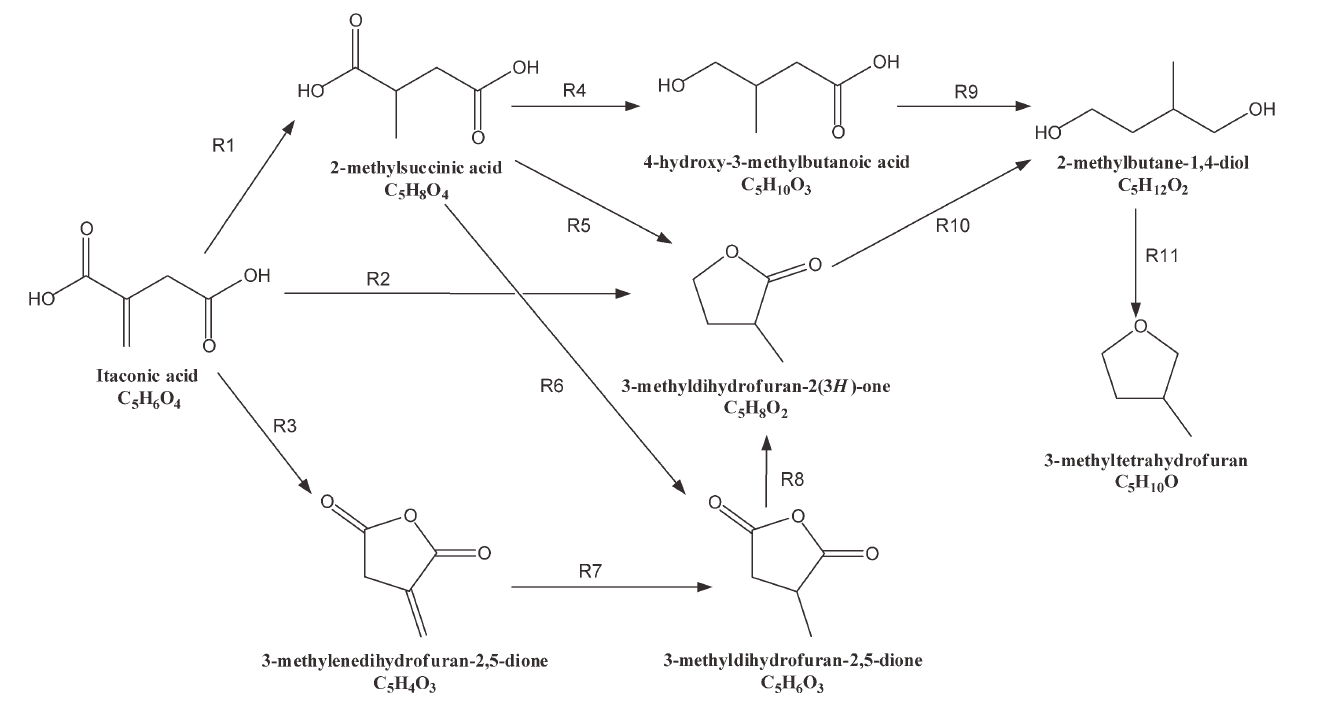
Carvacrol (H)

The outlet of the 2nd reactor is a two-component mixture due to the conversion of reaction 11, which is purified through the 2nd separation unit. Pure carvone as the distillate is recycled back to the 2nd master stage and mixed with fresh feed. Purified carvacrol is removed from the bottom of that stage and can be stored to be sold directly. The optimum annual economic potential of the process is million per annum with an estimated annual separation related cost of million. The production rates of limonene oxide and carvacrol are 171.3 and 116.5 mol/min respectively with the consumption rate of d-limonene at 287.8 mol/min. Hence a conceptual flowsheet has been determined directly using reaction chemistry and thermodynamic and economic data, which is the overall goal of this methodology.

Figure : Optimal process flowsheet of the d-limonene case, all numbers are in mol/min



## Case II: itaconic acid and its potential derivatives



**(A)**

**(B)**

**(C)**

**(D)**

**(E)**

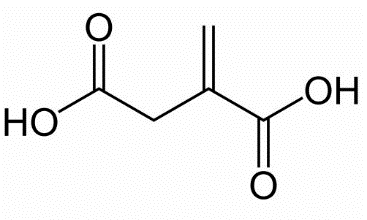
**(F)**

**(G)**

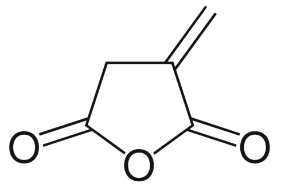
**(H)**

Figure : Proposed reaction network superstructure for the itaconic acid case

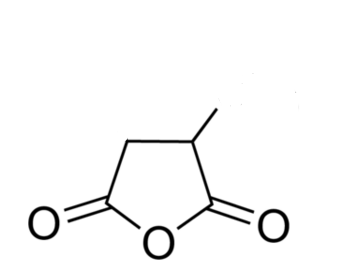
Itaconic acid is commercially produced from the fermentation of glucose mainly by the fungi *Aspergillus terreus* via submerged fungal fermentations (Okabe et al. 2009). The production of itaconic acid remained small at 40,000 t/yr in 2013 due to low demand as a result of few applications and the economic downturn. However, the total manufacturing capacity can be up to 80,000 t/yr and the market was predicted to grow ten times by 2020 (Weastra 2013). Therefore, it is reasonable to assume the production capacity can reach 100,000 t/yr in 2016. The same assumptions for the process plant in the previous case are also applicable here and the proposed reaction network superstructure is a sub-network taken from the work conducted by Voll and Marquardt (2012) as shown in Figure 6. Similar to the d-limonene case, boiling points of relevant chemicals are gathered from online databanks and market prices of those uncommon components were estimated by a group contribution method (Table S4-2 of the Supplementary Documentation). However, due to the lack of literature data for the conversion and selectivity of each reaction mentioned in the network, a constant conversion was used for all reactions and it is assumed that no competitive reactions are present. A sensitivity analysis is thus required to determine the effect of changing conversion to the optimal solution.



R3



R7



**Itaconic acid (A)**

**Itaconic anhydride (F)**

**Methyl succinic anhydride (G)**

Figure : Optimal reaction network of the itaconic acid case

The optimal reaction network at a reaction conversion of 90% was generated as shown by Figure 7. It can be seen that among reactions 1-3, the third one is favoured. It produces itaconic anhydride which is then converted to methyl succinic anhydride via reaction 7. Reaction 8 and subsequent reactions starting from 3-methyldihydrofuran-2(3*H*)-one are determined to be adverse to the overall economic potential of the process and hence inactive. The resulting process flowsheet is shown by Figure 8. As can be seen, itaconic acid is added to the first reactor and is processed at a conversion of 90% to form itaconic anhydride and the product enters the associated distillation unit with unreacted reactant. In the separation unit, the itaconic anhydride stream leaves the top of the distillation stage and is pumped to the next master stage mixing point. Purified itaconic acid is recycled back to the first master stage and mixed with fresh feed. Reaction 7 occurs in the 2nd reactor and the product stream contains both the optimal product-methyl succinic anhydride and unreacted itaconic anhydride which is purified in the 2nd separation unit and recycled to the 2nd reactor.



Figure : Optimal process flowsheet of the itaconic acid case, all numbers are in mol/min

The sensitivity analysis conducted has shown that changing the reaction conversions does not alter the basic structure of the optimal reaction network and its corresponding process flowsheet. However, the reduction in the conversion does lead to an increase in the flowrates of recycle streams, which results in an increase in the separation cost as shown in Figure 9. On the other hand, the annual consumption rate of itaconic acid and production rate of methyl succinic anhydride both remain constant due to the existence of recycles thus leaving the variation in separation cost as the main contributor to the change in overall process economic potential.



Figure : Sensitivity Analysis of the effect of changing conversions on the EP and Separation Cost

# Conclusions and future work

In this paper, we presented an MILP optimisation model along with a conceptual superstructure for the preliminary process synthesis of optimal chemical reaction networks integrated with distillation sequencing. The model allows us to quickly scan all the reaction pathways as well as different distillation sequences. Recycles of unreacted chemicals and direct removal of pure products or wastes are also implemented for the method to be more realistic. Another unique aspect of this model is that the innovative formulation of the separation mechanism, which not only allows the detection of components entering each distillation stage but also provides constraints for the system to logically select both light and heavy keys. The use of bi-linear conditions for the bypass mass balance within each separation unit also increases the flexibility and robustness of the algorithm. Two case studies have been solved to demonstrate the effectiveness and applicability of the developed approach. The case studies covered two popular bio-derived chemicals with the objective of maximising the plant economic potential. The solutions of the case studies illustrate the ability of the proposed method to generate both the optimal reaction network and process flowsheet.

Future work is still necessary to extend the approach described here to scenarios with biomass pretreatment and other reaction/separation technologies. This will allow the system to deal with more general biorefinery processes rather than just chemical reactions. In addition, energy balances and heat integration should be included in the model to estimate the energy/heat consumption of different process alternatives thereby providing the essential information to conduct Life Cycle Analysis (LCA). Meanwhile, the reactor cost can be estimated based on the enthalpy change of the reaction (Voll and Marquardt 2012) and multi-objective optimisation can thus be used to evaluate different superstructures based on all objectives simultaneously. Furthermore, integer cuts can also be applied to generate process alternatives for future study. Finally, a more sophisticated and well-calibrated case study is required to further test the functionality of the modified model.

|  |  |
| --- | --- |
| **Nomenclature** | |
|  | |
| **Indices** | **Descriptions** |
|  | Components |
|  | Reactions |
|  | Master Stages |
|  | Separation Stages |
|  | Discretised split fraction points |
|  |  |
| **Binary Variables** |  |
|  | if all the flow from reaction stage goes directly to the next stage; 0 otherwise |
|  | if all the flow from reaction stage goes to direct removal; 0 otherwise |
|  | if all the flow from reaction stage goes to the separation; 0 otherwise |
|  | if top removal of separation stage of master stage contains only pure component ; 0 otherwise |
|  | if bottom removal of separation stage of master stage contains only pure component ; 0 otherwise |
|  | if stream contains only pure component ; 0 otherwise |
|  | if separation stage in master stage is active; 0 otherwise |
|  | if component is the light key at separation stage of master stage ; 0 otherwise |
|  | if the stream from stage to stage is active at the top of stage in master stage ; 0 otherwise |
|  | if the stream from stage to stage is active at the bottom of stage in master stage ; 0 otherwise |
|  | if reaction occurs in master reaction stage ; 0 otherwise |
|  | if component is chosen as the heavy key at separation stage and in master stage ; 0 otherwise |
|  | if value of point p is chosen for top removal split fraction at separation stage of master stage ; 0 otherwise |
|  | if value of point p is chosen for top out split fraction at separation stage of master stage ; 0 otherwise |
|  | if value of point p is chosen for top split fraction for stream goes from separation stage to at master stage ; 0 otherwise |
|  | if value of point p is chosen for bottom removal split fraction at separation stage of master stage ; 0 otherwise |
|  | if value of point p is chosen for bottom out split fraction at separation stage of master stage ; 0 otherwise |
|  | if value of point p is chosen for bottom split fraction for stream goes from separation stage to at master stage ; 0 otherwise |
|  |  |
|  | if component exists in flow ; 0 otherwise |
|  | if component exists at the inlet of separation stage of master stage ; 0 otherwise |
|  | if component exists at the top stream of separation stage of master stage ; 0 otherwise |
|  | if component existsat the bottom stream of separation stage of master stage ; 0 otherwise |
|  | if component exists at the inlet stream of reaction stage ; 0 otherwise |
|  |  |
| **Continuous Variables** |  |
|  | Flowrate of component added to the master mixing stage |
|  | Separation cost of each stage of master stage |
|  | Total separation cost of master stage |
|  | Dummy Variable for linearisation of separation cost equation |
|  | Economic potential of the process |
|  | Flowrate of component ­ entering separation stage |
|  | Flowrate of component leaving the top of separation stage |
|  | Flowrate of component leaving the top of separation stage and going to stage , where |
|  | Flowrate of component leaving the top of separation stage and going straight to the next reaction stage |
|  | Flowrate of component leaving the top of separation stage and going straight to removal as product |
|  | Flowrate of component leaving the bottom of separation stage |
|  | Flowrate of component leaving the bottom of separation stage and going to stage , where |
|  | Flowrate of component leaving the bottom of separation stage and going straight to the next reaction stage |
|  | Flowrate of component leaving the bottom of separation stage and going straight to removal as product |
|  | Flowrate of component entering master reaction stage |
|  | Flowrate of component leaving master reaction stage |
|  | Flowrate of component entering separation at stage |
|  | Flowrate of component leaving separation stages of and goes directly to the mixing point at stage |
|  | Flowrate of component goes to direct removal at stage |
|  | Flowrate of component goes directly to the mixing point at stage |
|  | Flowrate of component entering mixing point at stage |
|  | Flowrate of component removed from the master separation stage |
|  | Total amount of out from separation going straight to the removal |
|  | Dummy Variable for linearisation of separation cost equation |
|  | Economic value of component in flow |
|  | Value of top removal of component at separation stage of master stage |
|  | Value of bottom removal of component at separation stage of master stage |
|  | Total value of component removed at master stage |
|  | Objective Function |
|  | Extent of reaction in master reaction stage |

# Acknowledgements

The support of the EPSRC under grant EP/L017393/1, “Sustainable Polymers” is gratefully acknowledged.

# Appendix: group contribution method

It is assumed that the cost of a molecule is well approximated by the sum of the costs of its constituent groups. Group contribution method can be defined as another optimisation problem: given a set of common compoundsincluding alkanes, alkenes, alcohols, organic acids and aromatic compounds, the actual costs of them, can be acquired from different online sources and thus an estimation on the costs of different groups can also be made via the least square method shown in equation 78.

|  |  |
| --- | --- |
|  | 78 |

To estimate the market value of each chemical involved in the two case studies, the well-known chemicals selected are components C1 to C17 listed in Table 3. All the market prices are bulk prices taken from Alibaba (Alibaba 2015). Molecular groups are classified based on the theory developed by Jankowski et al. (2008). The number of those groups in components C1 to C17 and the estimated cost of different groups are shown in Table 4. Table 5 shows the number of various groups that are present in different chemicals involved in both the d-limonene and itaconic acid cases. The estimated market values have been presented in Section S4 of the Supplementary Documentation.

Table : Market prices of well-known chemicals

|  |  |  |
| --- | --- | --- |
| **Component** | **Identification** | **Market Price ($/mol)** |
| **C1** | Cyclohexane | 0.126 |
| **C2** | Methylcyclohexane | 0.245 |
| **C3** | Methanol | 0.0256 |
| **C4** | Cyclohexanol | 0.250 |
| **C5** | Cyclohexene | 0.131 |
| **C6** | D-limonene | 0.409 |
| **C7** | p-cymene | 0.537 |
| **C8** | cyclohexene oxide | 0.147 |
| **C9** | alpha-pinene oxide | 0.457 |
| **C10** | Alpha-terpineol | 0.540 |
| **C11** | Carvone | 0.451 |
| **C12** | Benzene | 0.109 |
| **C13** | Succinic anhydride | 0.150 |
| **C14** | cyclohexanone | 0.118 |
| **C15** | propane | 0.0529 |
| **C16** | n-butane | 0.0697 |
| **C17** | itaconic acid | 0.208 |

Table : Number of groups in each known chemical and the estimated price of each group

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Compound /Groups** | | **C1** | **C2** | **C3** | **C4** | **C5** | **C6** | **C7** | **C8** | **C9** | **C10** | **C11** | **C12** | **C13** | **C14** | **C15** | **C16** | **C17** | **Estimated Price**  **($/mol)** |
|  | **G1** | 0 | 1 | 1 | 0 | 0 | 2 | 3 | 0 | 3 | 3 | 2 | 0 | 0 | 0 | 2 | 2 | 0 | 0.013 |
|  | **G2** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 | 1 | 0.023 |
| in a ring | **G3** | 6 | 5 | 0 | 5 | 4 | 3 | 0 | 4 | 2 | 3 | 2 | 0 | 2 | 5 | 0 | 0 | 0 | 0.019 |
| in a ring | **G4** | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0.028 |
| in an aromatic ring | **G5** | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 0 | 0 | 0.018 |
| in a ring | **G6** | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0.085 |
| in an aromatic ring | **G7** | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.170 |
|  | **G8** | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.085 |
| in a ring | **G9** | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0.139 |
| in fused rings | **G10** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.015 |
|  | **G11** | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0.043 |
|  | **G12** | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0.043 |
|  | **G13** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.177 |
| in a ring | **G14** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.146 |
| in fused rings | **G15** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.146 |
| in a ring | **G16** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0.041 |
|  | **G17** | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0.014 |
|  | **G18** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0.036 |
| in a ring | **G19** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 2 | 1 | 0 | 0 | 0 | 0.036 |

Table : Number of groups in each chemical involved in both case studies

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Components /Groups** | **G1** | **G2** | **G3** | **G4** | **G5** | **G6** | **G7** | **G8** | **G9** | **G10** | **G11** | **G12** | **G13** | **G14** | **G15** | **G16** | **G17** | **G18** | **G19** |
| **Components in the d-limonene case** | | | | | | | | | | | | | | | | | | | |
| D-Limonene | 2 | 0 | 3 | 1 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Limonene oxide | 2 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| Limonene dioxide | 2 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 2 | 0 | 0 | 0 |
| α-terpineol | 3 | 0 | 3 | 1 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| p-cymene | 3 | 0 | 0 | 0 | 4 | 0 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| carvone | 2 | 0 | 2 | 1 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Limonene dicarbonate | 2 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 4 | 0 | 0 | 2 |
| Carvacrol | 3 | 0 | 0 | 0 | 3 | 0 | 3 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| 5,6-epxoycarvone | 2 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 1 |
| Dihydrocarvone | 2 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Carvomenthol | 3 | 0 | 3 | 0 | 0 | 0 | 0 | 1 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| **Components in the itaconic acid case** | | | | | | | | | | | | | | | | | | | |
| itaconic acid | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 2 | 2 | 0 |
| 2-methylsuccinic acid | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 0 |
| 4-hydroxy-3-methylbutanoci acid | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 0 |
| 2-methylbutane-1,4-diol | 1 | 3 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 |
| 3-methyldihydrofuran-2(3H)-one | 1 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| 3-methylenedihydrofuran-2,5-dione | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 2 |
| 3-methyldihydrofuran-2,5-dione | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 2 |
| 3-methyltetrahydrofuran | 1 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |

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