Global supply chain planning for pharmaceuticals

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\textbf{Abstract}

The shortening of patent life periods, generic competition and public health policies, among other factors, have changed the operating context of the pharmaceutical industry. In this work we address a dynamic allocation/planning problem that optimises the global supply chain planning of a pharmaceutical company, from production stages at primary and secondary sites to product distribution to markets. The model explores different production and distribution costs and tax rates at different locations in order to maximise the company’s net profit value (NPV).

Large instances of the model are not solvable in realistic time scales, so two decomposition algorithms were developed. In the first method, the supply chain is decomposed into independent primary and secondary subproblems, and each of them is optimised separately. The second algorithm is a temporal decomposition, where the main problem is separated into several independent subproblems, one per each time period. These algorithms enable the solution of large instances of the problem in reasonable time with good quality results.

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1. Introduction

In the past 30 years, the operating context of the pharmaceutical industry has evolved and become much more challenging. The establishment of regulatory authorities and market maturity have led to an increase in the costs and time to develop new drugs, decreasing the productivity of the research and development (R&D) stage and shortening the effective patent lives of new molecules. These two factors, in conjunction with the appearance of many substitute drugs in several therapeutic areas, have led to the reduction of the exclusivity period of new products. Another factor having an impact on the operation of this industry was the transition of the paying responsibilities from individuals to governmental agencies and insurance companies, which in association with high demands for pharmaceuticals, due to aging populations, put strong pressure on prices and prescription policies (Shah, 2004).

From the point of view of manufacturing, the global pharmaceutical industry can be divided into five sub-sectors: large R&D based multinationals, generic manufacturers operating in the international market, local companies based in only one country, contract manufacturers without their own portfolio and biotechnological companies mainly concerned with drug discovery. The first group, the intensive R&D based industries, is economically the most important and tends to have large and complex supply chains due to the global nature of its activity. In addition, these companies are the most vulnerable to the global financial, regulatory and social changes so this work will focus on their supply chains.

The industry’s preferred mechanism to overcome the productivity crises has been to increase investment in current business activities, primarily R&D and sales, the two extreme ends of the supply chain. This has been implemented by organic growth or by mergers and acquisitions (M&A) to exploit economies of scale. However, statistics show that productivity continues to decline after a decade of vigorous growth in investments on these areas (Coe, 2002). There are no significant economies of scale in sales activities. The revenues generated by a pharmaceutical company are directly proportional to its sales, general and administrative (SG&A) expenditure, suggesting that two merged companies will not
necessarily be more profitable than they would be separately, i.e. there is no improvement on the return rates. Further more, despite the theoretical higher probability of successful product development with greater scale in R&D, in reality it does not translate into improved pipeline value. Companies will only improve their profit margins if they change the relationship between volume and costs, which can be achieved through productivity gains in the supply chain.

Supply chain optimisation is an excellent way to increase profit margins and is becoming current practice, not only in pharmaceutical industries but also in other areas of business. Arntzen et al. (1995) described the restructuring of the supply chain at Digital Equipment Corporation with savings of over US$ 100 million. They developed a large mixed integer linear programming (MILP) model that incorporates a global, multi-product bill of materials for supply chains with arbitrary structure and a comprehensive model of integrated global manufacturing and distribution decisions. Camm et al. (1997) described a project related to P&G’s supply chain in North America. The main objective of the study was to streamline the work processes to eliminate non-value added costs and duplication. The study involved hundreds of suppliers, over 50 product lines, 60 plant locations, 10 distribution centres and hundreds of customer zones. It allowed the company to save $200 million before taxes. Kallrath (2000) reported on a project in BASF where a multi-site, multi-product, multi-period production/distribution network planning model was developed, aiming to determine the production schedule in order to meet a given demand. Neiro and Pinto (2004) described a petroleum supply chain planning problem of Petrobras in Brazil, which comprises 59 petroleum exploration sites, 11 refineries and five terminals, with 20 types of supplied petroleum and 32 products to local markets. Sousa et al. (2008) considered an industrial global supply chain of a multinational agrochemicals company, comprising two subsystems: US network and worldwide formulation network.

Supply chain management in the process industries has long been used as a tool to define production and distribution policies, as well as product allocation. This is the case of Cohen and Lee (1988) who described the modelling of a supply chain composed of raw material vendors, primary and secondary plants (each one with inventories of raw materials and finished products), distribution centres, warehouses and customer areas. Later, Cohen and Moon (1991) used supply chain optimisation to analyse the impact of scale, complexity (the operating costs are a function of the utilisation rates and number of products being processed in each facility) and weight of each cost factor (e.g. production, transportation and allocation costs) on the optimal design and utilisation patterns of the supply chain systems.

Timpe and Kallrath (2000) described an MILP model, which combined production, distribution and marketing and involved plants and sales points, to cover the relevant features required for the complete supply chain management of a multi-site production network. Jayaraman and Pirkul (2001) developed a Capacitated Plant Location Problem (CPLP) type model for planning and coordination of production and distribution facilities for multiple commodities, comprising raw materials suppliers, production sites, warehouses and customer areas. The authors followed a holistic approach to the supply chain, resulting in a deterministic, steady-state, multi-echelon problem. Park (2005) considered both integrated and decoupled production and distribution planning problem, consisting of multiple plants, retailers, items over multiple periods. The author proposed mixed integer optimisation models and a two-phase heuristic solution to maximise the total net profit. Oh and Karimi (2006) highlighted the importance of duty drawback regulations in the production-distribution planning problem, and incorporated three main regulatory factors: corporate taxes, import duties and duty drawbacks, in the proposed linear programming (LP) model.

Tsiaikis and Papageorgiou (2008) considered the optimal configuration and operation of multi-product, multi-echelon global production and distribution networks, integrating production, facility location and distribution with financial and business issues such as import duties, plant utilisation, exchange rates and plant maintenance. An MILP model was formulated and applied to a case study for the coatings business unit of a global specialty chemicals manufacturer. Verderame and Fouldas (2009) proposed a discrete-time multi-site planning with production disaggregation model to provide a tight upper bound on the true capacity of daily production and shipment profiles between production facilities and customer distribution centres. Salema et al. (2010) presented a general dynamic model for the simultaneous design and planning of multiproduct supply chains with reverse flows, where time is modelled along a management perspective to deal with the strategic design and the tactical planning simultaneously. The applicability of the model is proved in an example based on Portuguese glass industry. You et al. (2010) addressed a simultaneous capacity, production, and distribution planning problem for a multisite supply chain network including a number of production sites and markets and propose a multiperiod MILP model and two decomposition approaches for solution.

When performing long term process planning, uncertainty factors (e.g. in product demand) have to be taken into account in order to produce robust models whose output decisions will perform well in a variety of scenarios (Verderame et al., 2010). Tsiaikis et al. (2001) addressed a strategic problem of stochastic planning for multi-echelon (although with rigid structure) supply chains.

Iyer and Grossmann (1998) extended the work of Liu and Sahinidis (1996), a specific problem of long-range capacity expansion planning in the chemical industry. The inputs were a set of available chemical processes, an established production and distribution network and demand forecasts affected by uncertainty leading to an MILP, multi-period planning model with multiple scenarios for each time period. Ahmed and Sahinidis (2003) considered forecast uncertainty parameters by specifying a set of scenarios in a stochastic capacity expansion problem. A multistage stochastic mixed integer programming formulation with fixed-charge expansion costs was formulated.

Oh and Karimi (2004) developed a deterministic MILP model for the capacity-expansion planning and material sourcing in global chemical supply chains with the introduction of two important regulatory factors, corporate tax and import duty. Guilen et al. (2005) proposed a two-stage stochastic optimisation approach to address a multiobjective supply chain design problem. The Pareto-optimal solution was obtained by the ε-constrained method. Puigjaner and Lainez (2008) proposed a scenario-based MILP stochastic model considering both process operations and finance decisions with an objective of maximising the corporate value. A model predictive model strategy was integrated with the stochastic model for solution.

Several authors addressed the issue of supply chain optimisation and long term process planning in the pharmaceutical
industry. Rotstein et al. (1999) started a series of papers dedicated to the specific problem of supply chain optimisation in the pharmaceutical industry. Later, Papageorgiou et al. (2001) published a paper based on the previous one, where the production stage is formulated with high degree of detail and including the trading structure of the company. The proposed deterministic model considers up to 8 possible products in the company’s portfolio. Li and Papageorgiou (2004) extended this work to account for uncertain demand forecasts, dependent on the results of the clinical trials for each product. Gatica et al. (2003) proposed an MILP approach for the problem of capacity planning under clinical trials uncertainty, where four clinical trial outcomes for each product are considered as is typical in the pharmaceutical industry. Amaral and Barbosa-Póvoa (2008) considered the integration of planning and scheduling of generalised supply chains with the existence of reverse flows. The developed approach was applied to the solution of a real pharmaceutical supply chain case study.

So far, most of the problems referred in this review concern detailed or very detailed descriptions of supply chains of relatively small systems (i.e. 1 or 2 sites, and up to 8 products). The long term strategic planning of large pharmaceutical companies has not been addressed in any of the previous works. In this work we build a model of the global supply chain of a large pharmaceutical company, with a long list of products in its portfolio and an extensive network of manufacturing sites with locations all over the world. The allocation policy of products to sites also differs from previous works. In each time period, each product will be produced at a single location (single sourcing policy), however the product/site assignment may change along the time horizon reflecting actual practice. This feature increases significantly the binary variables space.

In order to keep the model size within reasonable limits, it cannot be too detailed in its description of the supply chain. Nevertheless, even with this approach, it is necessary to use decomposition algorithms. The development of decomposition approaches is a promising research direction in the area (Grossmann, 2005; Maravelias and Sung, 2009).

To solve a typical large MILP model, Iyer and Grossmann (1998) used a bi-level decomposition (hierarchical) algorithm to solve the original model. In the first step, the design stage, the capacity expansion variables were aggregated in a new variable set, time independent, and the processes to develop are chosen. In the second level model (operation model), only the processes chosen to be developed are subjected to investment. Bok et al. (2000) proposed a bi-level decomposition. The relaxed problem making the decisions for purchasing raw materials generates an upper bound to the profit, while the subproblem yields a lower bound by fixing the delivery from the relaxed problem. Levis and Papageorgiou (2004) solved an aggregated model, computationally less expensive, although detailed enough to make the “here-and-now” decisions. In the second step, the values of the corresponding variables were fixed and the detailed model is solved. Üster et al. (2007) used a Benders decomposition approach for a multi-product closed-loop supply chain network design problem. Three different approaches for adding multiple Benders cuts are proposed. Li and Ierapetritou (2009) formulated the integrated production planning and scheduling as bilevel optimisation problems with one planning problem and multiple scheduling problems. A decomposition approach based on convex polyhedral underestimation was proposed and successfully applied to the integrated planning and scheduling problem of multipurpose multiproduct batch plants.

Some authors solved the large models resulting from supply chain optimisation problems through Lagrangean decomposition. In their work, Gupta and Maranas (1999) formulated an extension of the “economic-lot-sizing” problem, characterised by determination of the production levels of multiple products, in multiple sites, with deterministic demands and multiple time periods. Jayaraman and Pirkul (2001) relaxed three blocks of constraints concerning assignment of customers to warehouses, raw materials availability and material flows balance. This allowed them to decompose the original problem in three different sets of subproblems. Maravelias and Grossmann (2001) introduced a good example of a model composed of two (or more) independent submodels with one linking constraint. Jackson and Grossmann (2003) built a multiperiod optimisation model for the planning and coordination of production, transportation and sales for a network of geographically distributed multiplant facilities supplying several markets. Two Lagrangean decomposition methods were adopted to tackle the problem, spatial and temporal decompositions. In both cases, the authors followed the regular algorithm of Lagrangean decomposition to reach the optimal solution of the original problem, as described in Reeves (1995). The numerical examples show the temporal decomposition to work significantly better than the spatial decomposition. Eskigun et al. (2005) developed a Lagrangean heuristic for the proposed large-scale integer linear programming model for supply chain network design problem of an automotive company with capacity restriction on vehicle distribution centres. Shen and Qi (2007) embedded Lagrangean relaxation in branch and bound to solve an integrated stochastic supply chain design problem which is formulated as a non-linear programming (NLP) model. The Lagrangean relaxation subproblems are then solved by a low-order polynomial algorithm.

Chen and Pinto (2008) proposed several various decomposition strategies for the continuous flexible process network model by Bok et al. (2000), including Lagrangean decomposition, Lagrangean relaxation, and Lagrangean/surrogate relaxation. Among the four decomposition strategies, it was proved that the solutions generated from Lagrangean relaxation are better, although its CPU time is lower. Hinojosa et al. (2008) proposed an MILP formulation for a dynamic two echelon multi-commodity capacitated plant location problem with inventory and outsourcing aspects. The authors solved the resulting, independent subproblems from a Lagrangean relaxation scheme and a dual ascent method to find a lower bound on the optimal objective value. Nishi et al. (2008) used an augmented Lagrangean decomposition and coordination approach for the proposed framework for distributed optimisation of supply chain planning for multiple companies. An augmented Lagrangean approach with a quadratic penalty function was used to decompose the original problem into several subproblems for each company to eliminate duality gap. Puigjaner et al. (2009) used the optimal conditional decomposition (OCD), a particular case of Lagrangean decomposition, for the supply chain design-planning model extended from the work by Puigjaner and Lainéz (2008). In the OCD, the difference from the classic Lagrangean decomposition is its automatic updating process of Lagrange multipliers. You and Grossmann (2010) proposed a spatial decomposition algorithm based on the integration of Lagrangean relaxation and piecewise linear approximation to solve mixed integer
nonlinear programming (MINLP) model for large-scale joint multi-echelon supply chain design and inventory management problems. From the literature discussed above, there is a gap in the research on supply chain planning taking both primary and secondary manufacturing in the pharmaceutical industry into account. This paper aims to fill this gap.

The rest of our paper is organised as follows. Section 2 introduces a brief description of the typical supply chain and its components in the pharmaceutical industry. Section 3 is concerned with the problem description. The mathematical formulation of the model is presented in section 4. In Section 5, two decomposition algorithms are conceived to solve the large model resulting from the problem formulation. In Section 6, the model as well as the performance of the developed algorithm is tested with two illustrative examples. Some concluding remarks are drawn in Section 7.

2. Supply chains in the pharmaceutical industry

A supply chain may be defined as an integrated process where several business entities work together to produce goods, services, etc. (Shah, 2005; Barbosa-Póvoa, 2009; Papageorgiou, 2006). This is a major issue in many industries, as organisations begin to appreciate the criticality of creating an integrated relationship with their suppliers and customers. Typically, in manufacturing industries, the stages are: raw materials acquisition, primary (and secondary) manufacture and distribution to retailers and customers. Each one may comprise one or more sub-stages and products may be kept in storage units (e.g., warehouses) between stages (Papageorgiou, 2006).

Many companies, especially multinationals, possess complex trading structures where, for tax purposes, the manufacturing plants, intellectual property and distribution centres are considered to be different entities. This brings more flexibility to supply chain optimisation as it allows the practising of several different pricing policies.

Supply chains in the pharmaceutical industry, one typical industry of products with a high added value per mass unit, comprise two manufacturing stages: primary manufacturing for active ingredient (AI) production and secondary manufacturing for formulation and packaging. As very high-value products, AIs are usually produced in low amounts and in few centralised locations worldwide (Sousa et al., 2007).

2.1. Primary manufacturing

The customer-facing end is driven by orders. These ones represent disturbances that propagate backwards in the supply chain (in the opposite sense of materials flow), being amplified as they get closer to the first stages (bullwhip or Forrester effect). Primary sites are responsible for active AI production and may face significant fluctuations in demand. They are characterised by long cycle times, which make it difficult to ensure end-to-end responsiveness.

The production volumes involved are usually low resulting in multipurpose plants to spread the capital cost between products. The changeover activities, that take place when the manufactured product changes, include thorough cleaning to avoid cross-contaminations. This usually takes a long time so it is desirable to keep the planning complexity (number of different products using the same resource) at a low level and long campaigns become the norm, otherwise equipment utilisation is too low.

Since the production volumes are low, transportation costs are not significant at this end of the supply chain, so primary sites may be located anywhere in the world, even distant from secondary manufacturers. The factors ruling the choice of location will be tax rates, existence of skilled working force, political and economic stability etc.

2.2. Secondary manufacturing

Secondary manufacturers prepare and formulate the products in a suitable form for final consumers. This involves adding the AI to some “excipient” inert materials along with further processing and packing.

As it was pointed out above, secondary sites are often geographically separate from AI producers. This is frequently the result of tax and transfer price optimisation within the enterprise. At this end of the supply chain, due to large amounts of inert products added to the AI plus the packing, the transportation costs become very significant, so usually there are many more secondary than primary locations, serving regional or local markets.

3. Problem description

As referred to before, the aim of this project is the supply chain optimisation of a large pharmaceutical company. The supply chain components are primary sites (AI manufacturers) and respective storage facilities, secondary sites and respective warehouses and final product market areas. The distribution networks within each market area are out of the scope of this work.

Each primary site may supply the AI to any of the secondary sites and be located in any place around the world. For secondary sites and markets, we consider several geographical areas. The structure of a supply chain example with five geographical areas (including Europe, Asia, Africa and Middle East, North America and South America) is shown in Fig. 1. Since transportation costs are very significant at this end of
the supply chain, material flows between two different geographical areas are not allowed.

We assume the following information is known:

- multi-period demand forecast profile of the company’s portfolio;
- production, transportation and allocation specific costs;
- tax rates;
- the company’s supply chain structure, with primary and secondary locations available.

The model aims to make the following supply chain decisions:

- where to allocate the manufacture of primary and secondary products and how to manage the available resources during the whole time horizon;
- what production amounts and inventory levels shall be set for each manufacturing site;
- how to establish the product flows between echelons, i.e. between primary and secondary sites and between secondary sites and markets.

Each geographic area produces and consumes some, but not all, product families from the company’s secondary (final) products portfolio. Within each geographic area, it was decided that a single sourcing policy would be followed, i.e. each product (both primary and secondary) will be produced in one and only one site on each time period. The product/site assignment may change between different time periods (“allocation transfer”), although the number of exchanges is limited. In line with the single sourcing policy, this transfer can only take place between sites in the same geographical area.

The model includes the occurrence of changeover activities as these significantly affect the equipment availability. However, due to the global scope of the project and the dimension of the problem, some production details as scale-up times and qualification runs are not considered.

The location of the several members in the SC is an extremely important issue to large multinational enterprises, as the profit after taxes may change significantly due to the different tax rates in different countries. So, the objective is set as the maximisation of the enterprise’s net profit value (NPV). The terms of the objective function are listed below. A cost for unfulfilled demand has also been considered. Revenues come as the maximisation of the enterprise’s net profit value (NPV).

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### 4. Mathematical formulation

#### 4.1. Notation

<table>
<thead>
<tr>
<th>Indices</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>m</td>
<td>market locations</td>
</tr>
<tr>
<td>p</td>
<td>secondary products</td>
</tr>
<tr>
<td>r</td>
<td>secondary sites resources (manufacturing equipments)</td>
</tr>
<tr>
<td>s</td>
<td>secondary sites</td>
</tr>
<tr>
<td>t, tt</td>
<td>time periods</td>
</tr>
<tr>
<td>Sets</td>
<td></td>
</tr>
<tr>
<td>Mj</td>
<td>markets in geographical area j</td>
</tr>
<tr>
<td>Pj</td>
<td>secondary products in geographical area j</td>
</tr>
<tr>
<td>Sj</td>
<td>secondary sites in geographical area j</td>
</tr>
<tr>
<td>Parameters</td>
<td></td>
</tr>
<tr>
<td>Aort</td>
<td>Availability of resource r in time period t in secondary site s (hour)</td>
</tr>
<tr>
<td>APri</td>
<td>Availability of resource l in time period t in primary site c (hour)</td>
</tr>
<tr>
<td>CIV</td>
<td>Inventory handling costs ($/kg)</td>
</tr>
<tr>
<td>COT</td>
<td>Changeover time in secondary sites resources (hour)</td>
</tr>
<tr>
<td>COTP</td>
<td>Changeover time in primary sites resources (hour)</td>
</tr>
<tr>
<td>CPPi,l</td>
<td>Production cost of primary product i in site c in site l ($/kg)</td>
</tr>
<tr>
<td>CPSp,s</td>
<td>Production cost of secondary production in site s ($/kg)</td>
</tr>
<tr>
<td>CTAp,s</td>
<td>Cost of transferring the allocation of secondary production p to site secondary site s ($)</td>
</tr>
<tr>
<td>CTAPl,i</td>
<td>Cost of transferring the allocation of primary product i to primary site c ($)</td>
</tr>
<tr>
<td>CTPc</td>
<td>Average transportation costs from primary site c to secondary sites ($/kg)</td>
</tr>
<tr>
<td>CTSam</td>
<td>Transportation cost of secondary products from secondary site s to market m ($/kg)</td>
</tr>
<tr>
<td>CUp</td>
<td>Cost of not satisfying the whole demand of secondary product p ($/kg)</td>
</tr>
<tr>
<td>Dpmt</td>
<td>Demand forecast of product p in market m in time period t (kg)</td>
</tr>
<tr>
<td>Kpr</td>
<td>Equals 1 if product p uses resource r and 0 otherwise</td>
</tr>
<tr>
<td>Kgl</td>
<td>Equals 1 if product i uses resource l and 0 otherwise</td>
</tr>
<tr>
<td>Max</td>
<td>Upper limit of the production amount in one time period (kg)</td>
</tr>
<tr>
<td>MTp,r</td>
<td>Manufacturing demand of secondary product p in resource r (hour/kg)</td>
</tr>
<tr>
<td>MTPil</td>
<td>Manufacturing demand of primary product i in resource l (hour/kg)</td>
</tr>
<tr>
<td>PFp</td>
<td>Product p formulation as a function of primary product i</td>
</tr>
<tr>
<td>T</td>
<td>Number of time periods</td>
</tr>
<tr>
<td>TFp</td>
<td>Transformation factor for final product p (yield)</td>
</tr>
<tr>
<td>TRPc</td>
<td>Tax rate on primary site location</td>
</tr>
<tr>
<td>TRS</td>
<td>Tax rate on secondary site location</td>
</tr>
<tr>
<td>VIl</td>
<td>Internal price of primary product i ($)</td>
</tr>
<tr>
<td>V2pm</td>
<td>Selling price of product p in market m ($)</td>
</tr>
<tr>
<td>XPTN</td>
<td>Allocation transfer limit of primary products in each time period</td>
</tr>
<tr>
<td>XTj</td>
<td>Allocation transfer limit of secondary products in geographical area j in each time period</td>
</tr>
</tbody>
</table>

### Binary variables

- **Xsp**: Equals 1 if secondary product p is produced at site s in time period t, 0 otherwise
- **XPcri**: Equals 1 if primary product i is produced at site c, 0 otherwise
- **XPTcij**: Allocation transfer decision variable (equals 1 if XPcri,t+1 = 1 and XPcri,t = 0)
- **XTsip**: Allocation transfer decision variable (equals 1 if Xsp,t+1 = 1 and Xsp,t = 0)
Continuous variables

- $IV_{opt}$: Inventory of secondary product $p$ in site $s$ at time period $t$ (kg)
- $IVP_{it}$: Inventory of primary product $i$ at time period $t$ (kg)
- $PRP_{cit}$: Production of primary product $i$ in site $s$ in time period $t$ (kg)
- $PRP_{cit}$: Production of primary product $i$ in site $c$ at time period $t$ (kg)
- $TP_{sit}$: Amount of primary product $i$ transported to site $s$ in time period $t$ (kg)
- $TS_{spmt}$: Amount of product $p$ transported from site $s$ to market $m$ in time period $t$ (kg)
- $SL_{pmt}$: Sales of product $p$ in market $m$ in time period $t$ (kg)
- $U_{pmt}$: Unsatisfied demand of product $p$ in market $m$ in time period $t$ (kg)

$Z$: NPV, objective function ($\$)

4.2. Secondary product allocation constraints

$$\sum_{s \in S_j} XP_{cit} = 1 \forall j, p \in P_j, t$$ (1)

$$XT_{sp,t-1} \geq XP_{cit} - XP_{cit-1} \forall s, p, t > 1$$ (2)

$$XP_{cit} \leq 1 - XT_{sp,t} \forall s, p, t$$ (3)

$$\sum_{s \in S_j} \sum_{p \in P_j} XT_{sp,t} \leq XTN_t \forall j, t$$ (4)

Eq. (1) guarantees that, within each geographical area, each product is allocated to one and only one secondary site in each time period. Eqs. (2) and (3) guarantee that each allocation transfer will only take place after the actual decision has been taken. Eq. (4) limits the number of allocation transfers occurring in each time period.

4.3. Primary product allocation constraints

$$\sum_{c} XP_{cit} = 1 \forall i, t$$ (5)

$$XPT_{cit,1-1} \geq XP_{cit} - XP_{cit-1} \forall c, i, t > 1$$ (6)

$$XP_{cit} \leq 1 - XPT_{cit} \forall c, i, t$$ (7)

$$\sum_{c} \sum_{i} XPT_{cit} \leq XPTN_t \forall t$$ (8)

Eqs. (5)–(8) play the same role in primary products allocation as Eqs. (1)–(4) respectively for secondary products.

4.4. Capacity constraints

$$\sum_{p} MT_{Pr} \cdot PRP_{opt} \leq A_{sit} - \left( \sum_{p} K_{Pr} \cdot XP_{opt} - 1 \right) \cdot COT \forall s, r, t$$ (9)

$$\sum_{i} MTP_{il} \cdot PRP_{cit} \leq AP_{cit} - \left( \sum_{i} K_{Pl} \cdot XP_{cit} - 1 \right) \cdot COTP \forall c, i, t$$ (10)

Eqs. (9) and (10) limit the production of secondary and primary products in accordance with resource availability, respectively. Note that although more general resources can be considered in the proposed model, the resources in the examples discussed later refer to the manufacturing equipments in the production sites.

4.5. Mass/flow balance constraints

$$PRP_{cit} \leq \max \cdot XP_{cit} \forall c, i, t$$ (11)

$$SL_{pmt} = \sum_{s \in S_j} TS_{spmt} \forall j, p \in P_j, m \in M_j, t$$ (12)

$$SL_{pmt} \leq D_{pmt} \forall j, p \in P_j, m \in M_j, t$$ (13)

$$U_{pmt} = D_{pmt} - SL_{pmt} \forall j, p \in P_j, m \in M_j, t$$ (14)

Each secondary product will only be produced in the secondary site where it was allocated, as shown in Eq. (11). Eq. (12) is the flow balance between storage facilities (in the secondary sites) and the markets; and the markets; Eq. (13) ensures that the sales of each product in each time period is less than or equal to the respective demand and Eq. (14) estimates the unmet demand in order to introduce a penalisation term in the objective function. The link between production and outgoing flows from secondary sites (Eqs. (11) and (12)) is provided by the inventory constraint, Eq. (17).

$$PRP_{cit} \leq \max \cdot XP_{cit} \forall c, i, t$$ (15)

$$TP_{sit} = \sum_{p} \frac{PRP_{cit} \cdot PF_{ip}}{TF_{ip}} \forall s, i, t$$ (16)

Eq. (15) gives the production relations in the primary sites. Eq. (16) establishes the primary products flow to secondary sites based on production amounts, product formulations and manufacturing losses of secondary products.

4.6. Inventory constraints

$$IV_{opt} = IV_{opt-1} + PRP_{opt} - \sum_{m \in M_j} TS_{spmt} \forall j, s \in S_j, p \in P_j, t$$ (17)

$$IVP_{it} = IVP_{it-1} + \sum_{c} PRP_{cit} - \sum_{s} TP_{sit} \forall i, t$$ (18)

Eqs. (17) and (18) are the inventory balances for secondary and primary sites, respectively.

4.7. Non-negativity constraints

$$IV_{opt}, IVP_{it}, PRP_{opt}, PRP_{cit}, SL_{pmt}, TP_{sit}, TS_{spmt}, U_{pmt} \geq 0$$ (19)

4.8. Objective function

The total NPV must include:

- Sales revenue:
  $$\Pi = \sum_{p} \sum_{m} \sum_{t} V_{2pm} \cdot SL_{pmt}$$ (20)

- Primary and secondary products production costs (per site):
  $$KP_{c} = \sum_{c} \sum_{t} CPP_{ci} \cdot PRP_{cit} \forall c$$ (21)
Primary and secondary products transportation costs (per site);

\[ K_{P_c} = \sum_{p \in P_j} \sum_{t} \text{CPS}_{sp} \cdot \text{PR}_{cpt} \forall j, s \in S_j \]  \hspace{1cm} (22)

\[ K_{T_c} = CTP_{c} \sum_{i} \sum_{t} \text{PRP}_{ct} \forall c \]  \hspace{1cm} (23)

\[ K_{T_s} = \sum_{p \in P_j} \sum_{t} \sum_{c} \text{CTS}_{sm} \cdot \text{TS}_{spt} \forall j, s \in S_j \]  \hspace{1cm} (24)

Primary and secondary sites inventory handling costs;

\[ K_{I_{prim}} = CIV \cdot \sum_{i} \sum_{t} \text{IVP}_{it} \]  \hspace{1cm} (25)

\[ K_{I_s} = CIV \cdot \sum_{p \in P_j} \sum_{t} \text{IVP}_{spt} \forall j, s \in S_j \]  \hspace{1cm} (26)

Primary and secondary products allocation costs (per site);

\[ K_{A_c} = \sum_{i} \sum_{t} \text{CAT}_{api} \cdot \text{XPT}_{cit} \forall c \]  \hspace{1cm} (27)

\[ K_{A_s} = \sum_{p \in P_j} \sum_{t} \sum_{c} \text{CTS}_{AP} \cdot \text{XT}_{spt} \forall j, s \in S_j \]  \hspace{1cm} (28)

For each site, the total costs before taxes will be as follows. Here, the average inventory costs are considered for primary sites (see below).

\[ K_c = K_{P_c} + K_{T_c} + \frac{K_{I_{prim}}}{\phi_c} + K_{A_c} \forall c \]  \hspace{1cm} (29)

\[ K_s = K_{P_c} + K_{T_s} + K_{I_s} + K_{A_s} \forall s \]  \hspace{1cm} (30)

Tax costs on primary and secondary site locations;

\[ \phi_c \geq \text{TRP}_{c} \cdot \left( \sum_{i} \sum_{t} V1_{i} \cdot \text{PRP}_{cit} \right) - K_c \]  \hspace{1cm} (31)

\[ \phi_s \geq \text{TRS}_{s} \cdot \left( \sum_{p \in P_j} \sum_{t} \sum_{m} V2_{pm} \cdot \text{SL}_{pm} \right) - K_s \]  \hspace{1cm} (32)

The NPV is given by Eq. (33):

\[ Z = N \sum_{c} \left( K_c + \phi_c \right) + \sum_{s} \left( K_s + \phi_s \right) - \sum_{p} \sum_{m} \sum_{t} \text{U}_{pm} \cdot \text{CU} \]  \hspace{1cm} (33)

As mentioned above, transportation costs at the primary end of the supply chain are not significant, so average costs for transportation of primary products between secondary and primary sites are used, depending on the primary site location and its distances to the secondary sites. This reduces the number of variables since it is possible to express the primary products flow variables, TP_{pm}, with one dimension less. One consequence of this procedure is that the primary product inventory costs cannot be assigned to a specific primary site (because the model formulation does not allow the inclusion of the site index in the variable IV_{Pit}), which prevents the accurate calculation of tax costs on these locations. Another consequence is that the product flow from one specific primary site to one specific secondary site is not unknown from the model. Thus, the primary product production amount is used to calculate the transportation cost in any specific primary site.

5. Solution methods

With the purpose of testing the model, two sets of data, with different sizes, were generated to simulate hypothetical problems. The smaller problem is solvable in an hour; however, the larger one does not terminate in a reasonable time (CPU < 50,000 s). This motivated us to develop heuristic procedures to solve the larger instances of this model, corresponding to real-world problems.

According to previous works by other authors, (see Section 1) the most suitable approaches for this kind of models are decomposition and/or aggregation methods and Lagrangean decomposition procedures. In this paper, we propose two decomposition methods. The first one consists of separating the SC in its two echelons, primary and secondary (spatial decomposition algorithm). In the second method the model is decomposed into several independent subproblems, one per each time period (temporal decomposition algorithm).

5.1. Spatial decomposition algorithm

During the last few years, computational hardware has experienced enormous improvement. Faster computer processors allow the solution of ever-larger problems within reasonable CPU times. Nevertheless, the state-of-the-art of optimisation tools always tends to lag the requirements of realistic problems.

The principle underpinning decomposition methods is problem size reduction, through decomposition into smaller subproblems, deletion of hard constraints, or, as often happens, a combination of both.

Our model’s structural matrix (Fig. 2) shows that it can be composed of two ready decomposable subproblems, corresponding to primary and secondary echelons connected by a linking constraint (Eq. (16)), the flow balance between the two areas of the supply chain.

![Fig. 2 – Structural matrix. Lines correspond to the model constraints and the columns correspond to the variables.](chart.png)
In the following description, "primary binary variables," refers to those variables concerned with primary products allocation while "secondary binary variables" are related to secondary products allocation. This is a three-step method, based on the structure of the supply chain model, as illustrated in Fig. 3.

- Step 1: the secondary binary variables are relaxed and an integer set of primary variables is generated. Simultaneously, this provides an estimate of the production amounts, sales and inventory for both primary and secondary products, as well as an upper bound to the problem.
- Step 2: the primary binary variables are fixed and the program optimises each of the secondary geographical areas, \( j \), separately, until a complete set of integer secondary binary variables is generated.
- Step 3: the secondary binary variables are fixed and the model reallocates the primary products and adjusts the production amounts.

The first step uses an aggregated version of the model, i.e. ALLOCATIONS1, (see Appendix) whose solution process is faster than the original model. Between the first and the second steps a set of operations is performed to convert the results obtained with the aggregated model into values that can be used in the detailed model. In the second step, each geographical area, \( j \), is optimised separately in the original model with primary binary variables and secondary variables in other areas fixed (model ALLOCATIONS2), until a complete set of secondary binary variables is generated. These variables, in turn, are fixed in the original model (MILP model ALLOCATIONS3) in the third step of the procedure, where primary products are reallocated optimally.

The second and third steps may be repeated iteratively until the objective function is no longer improved, or a specified number of iterations are reached. On the other hand, there is no guarantee that the optimum will be found, since both solutions, from the second and third steps, are lower bounds to the problem. On the other hand, in each step, it is possible to calculate an upper bound to the difference to the optimum integer solution, given by the difference between the result of step 1 and the actual value of \( Z \) (Fig. 4).

5.2. Temporal decomposition algorithm

This work is oriented towards long-term planning, where each time period has the duration of several months. Under these circumstances, the inventory relations (constraints) do not significantly influence the final allocation decisions. A possible approach is to decompose the problem into several independent subproblems, one per time period that can be optimised separately. Two kinds of constraints link the different periods: allocation transfer and inventory constraints (Eqs. (2), (3), (6), (7), (17) and (18)).

Setting the inventory variables to 0 at the end of each time period leads to Eq. (34) and (35). Each one of the new equations may now be written independently for each time period, i.e. without depending on variables referring to adjacent time periods.

\[
0 = PR_{pt} - \sum_{m \in M_j} TS_{pmi}\forall j, p \in P_j, s \in S_j, t
\]  
(34)

\[
0 = \sum_{c} PR_{ct} - \sum_{s} TP_{sit} \forall i, t
\]  
(35)

Eqs. (2), (3), (6) and (7) need to be reformulated more carefully; the allocation decisions information has to be passed between time periods. This is achieved through modification of the allocation constraints, as detailed below. In fact, each sub-model (corresponding to each time period) is not
fully independent; it uses some information (allocation decisions) from previous (or subsequent) time periods, as there is a limit on the product/site allocation transfers that can occur in each time period. According to this, the optimisation process has to be performed following either the direct or inverse chronological sequence of time periods. In order to reduce the relations between time periods, each allocation transfer decision is assumed to take place in the same time period as the transfer itself.

Using the variables substitution expressed in Eq. (36), Eqs. (2), (3), (6) and (7) are reformulated for each time period \( t = t_{T-1} \) (using inverse chronological sequence).

Variable substitution

\[
X_{sp, t+1} = XXS_{sp} \quad \text{and} \quad XP_{c, t+1} = XXP_{c} \forall s, p, c, l, t \tag{36}
\]

Secondary sites

\[
X_{opt} \leq 1 - XT_{opt} \forall s, p, t = t_{T} \quad \text{and} \quad t < T \tag{37}
\]

\[
XT_{opt} \geq XXS_{sp} - X_{opt} \forall s, p, t = t_{T} \quad \text{and} \quad t < T \tag{38}
\]

Primary sites

\[
XP_{cl} \leq 1 - XPT_{cl} \forall c, l, t = t_{T} \quad \text{and} \quad t < T \tag{39}
\]

\[
XPT_{cl} \geq XXP_{c} - XP_{cl} \forall c, l, t = t_{T} \quad \text{and} \quad t < T \tag{40}
\]

The inclusion of binary allocation variables in the capacity balance constraints (Eqs. (9) and (10)) to account for the changeover operations may result in the generation of infeasible capacity balance constraints in the following time period being optimised in the solution process (see relationship below).

\[
A_{sr, t-1} < \left( \sum_{p} K_{pr} X_{opt} - 1 \right) \cdot COT \forall s, r, t \tag{41}
\]

\[
AP_{cl, t-1} < \left( \sum_{i} K_{pl} XP_{cl} - 1 \right) \cdot COTP \forall c, l, t \tag{42}
\]

If the solution of these infeasibilities involves the reallocation of more products than the allocation transfer upper limit (Eqs. (4) and (8)), then the model will be infeasible. In order to prevent this, extra constraints are included:

\[
A_{sr, t-1} \geq \left( \sum_{p} K_{pr} X_{opt} - 1 \right) \cdot COT \forall s, r, t, r < t \tag{43}
\]

\[
AP_{cl, t-1} \geq \left( \sum_{i} K_{pl} XP_{cl} - 1 \right) \cdot COTP \forall c, l, t, r < t \tag{44}
\]

In the first step of the algorithm, each time period is optimised separately and sequentially. The information concerning product/site assignment is passed to the following time period and so on, until all time periods have been optimised and a complete set of binary variables is generated. In this step, the objective function is a function of \( t \). In the second step, the binary variables are fixed and the continuous variables are recalculated in order to improve the final NPV.

ALLOCATIONT1 is the MILP model used to calculate the binary variables in each time period. It comprises the production and sales constraints and modified allocation constraints, i.e. Eqs. (36)–(40).

ALLOCATIONT2 is the original model, where all the time periods are optimised simultaneously, with the binary variables fixed at the values calculated on step 1. So ALLOCATIONT2 is a LP model.

Fig. 5 shows the flowchart of the temporal decomposition algorithm, in which the optimisation process in the first step is performed following the inverse chronological sequence of time periods.

### 6. Illustrative examples

Two examples motivated by industrial processes were generated in order to test the model as well as the performance of the developed decomposition algorithms. The dimensions of each example are presented in Table 1.
Table 1 – Example problems.

<table>
<thead>
<tr>
<th>Problem 1</th>
<th>Problem 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 active ingredients</td>
<td>10 active ingredients</td>
</tr>
<tr>
<td>6 primary sites</td>
<td>10 primary sites</td>
</tr>
<tr>
<td>5 secondary geographical areas</td>
<td>5 secondary geographical areas</td>
</tr>
<tr>
<td>30 secondary product families</td>
<td>100 secondary product families</td>
</tr>
<tr>
<td>33 secondary sites</td>
<td>70 secondary sites</td>
</tr>
<tr>
<td>10 market areas</td>
<td>10 market areas</td>
</tr>
<tr>
<td>12 time periods (4 months each)</td>
<td>12 time periods (4 months each)</td>
</tr>
</tbody>
</table>

Table 2 – Comparison between the number of binary variables in the full variable space model and decomposition algorithms.

<table>
<thead>
<tr>
<th></th>
<th>Problem 1</th>
<th>Problem 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full space</td>
<td>12,480</td>
<td>84,096</td>
</tr>
<tr>
<td>Spatial dec. alg.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st Step</td>
<td>864</td>
<td>2400</td>
</tr>
<tr>
<td>2nd Step (min/max)</td>
<td>1080/3360</td>
<td>9840/24,626</td>
</tr>
<tr>
<td>3rd Step</td>
<td>864</td>
<td>2,400</td>
</tr>
<tr>
<td>Temporal dec. alg.</td>
<td>1040</td>
<td>7008</td>
</tr>
</tbody>
</table>

Fig. 6 – Influence of the problem’s size in the solving time. CPU time increases exponentially with the size of the problem (1) and (2) – faster processors allow moving the curve to the right.

All the tests were performed on a Windows XP based machine with 1 GB RAM and 3.4 GHz Pentium 4 processor, running the GAMS 22.8 (Brooke et al., 2008) with CPLEX 11.1 solver (ILOG, 2007).

Statistics concerning the number of integer (binary) variables in the full space models and in the different steps of the decomposition algorithm are shown in Table 2. Taking into account the relationship between size and CPU expressed in Fig. 6 and the values in Table 2, it is to be expected that the sum of the CPU times to solve the three steps of the decomposition algorithm will be lower than the time to solve the full model.

Tables 3 and 4 show the results of the decomposition algorithms. The performance of these methods is highly dependent on the set of data being optimised. The spatial decomposition method is particularly sensitive to the parameter excess capacity as defined in Eq. (45) that relates demand and available manufacturing capacity. This parameter is affected by the time taken on each changeover operation, as this affects the manufacturing equipment availabilities.

Table 3 – Decomposition algorithms’ performance for problem 1 (COT = 100).

<table>
<thead>
<tr>
<th></th>
<th>Z_{opt}</th>
<th>Gap$^a$ (%)</th>
<th>CPU (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LP</td>
<td>437,995</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Full space</td>
<td>426,178</td>
<td>2.7</td>
<td>1560</td>
</tr>
<tr>
<td>Spatial dec. alg.</td>
<td>420,172</td>
<td>4.1</td>
<td>289</td>
</tr>
<tr>
<td>Temporal dec. alg.</td>
<td>416,208</td>
<td>5.0</td>
<td>9</td>
</tr>
</tbody>
</table>

$^a$ With respect to the LP model solution.

Table 4 – Decomposition algorithm’s performance for problem 2 (COT = 100).

<table>
<thead>
<tr>
<th></th>
<th>Z_{opt}</th>
<th>Gap$^a$ (%)</th>
<th>CPU (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LP</td>
<td>1,008,746</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Full space</td>
<td>954,454$^b$</td>
<td>5.4</td>
<td>50,022</td>
</tr>
<tr>
<td>Spatial dec. alg.</td>
<td>959,531</td>
<td>4.9</td>
<td>3,165</td>
</tr>
<tr>
<td>Temporal dec. alg.</td>
<td>974,874</td>
<td>3.4</td>
<td>53</td>
</tr>
</tbody>
</table>

$^a$ With respect to the LP model solution.

$^b$ Terminated by the CPU time limit of 50,000 s.

Fig. 7 – CPU dependence on excess capacity of step 2, of the spatial decomposition algorithm, for each geographical region, j. CPU and EC values are an average over many runs with different values of COT.

Table 5 – Statistics for the spatial decomposition algorithm. The changeover time (COT = 300) represents up to 10% of the availability of each resource.

<table>
<thead>
<tr>
<th></th>
<th>CPU (s)</th>
<th>Optimum</th>
<th>Gap (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>923</td>
<td>1,002,529</td>
<td>3.1</td>
</tr>
<tr>
<td>Step 2$^a$</td>
<td>j = 1</td>
<td>414</td>
<td>994,831</td>
</tr>
<tr>
<td></td>
<td>j = 2</td>
<td>1,026</td>
<td>977,326</td>
</tr>
<tr>
<td></td>
<td>j = 3</td>
<td>12</td>
<td>976,087</td>
</tr>
<tr>
<td></td>
<td>j = 4</td>
<td>4,958</td>
<td>962,594</td>
</tr>
<tr>
<td></td>
<td>j = 5</td>
<td>16</td>
<td>956,641</td>
</tr>
<tr>
<td>Step 3</td>
<td>227</td>
<td>985,910</td>
<td>1.0</td>
</tr>
<tr>
<td>Final</td>
<td>7,576</td>
<td>985,910</td>
<td>1.0</td>
</tr>
</tbody>
</table>

$^a$ j refers to secondary geographical areas.

Table 6 – COT influence on the solution time of decomposition algorithms for problem 2.

<table>
<thead>
<tr>
<th>COT</th>
<th>Spatial dec. alg.</th>
<th>Temporal dec. alg.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CPU (s)</td>
<td>Optimum</td>
</tr>
<tr>
<td>100</td>
<td>3,165</td>
<td>959,531</td>
</tr>
<tr>
<td>133</td>
<td>3,438</td>
<td>956,851</td>
</tr>
<tr>
<td>300</td>
<td>7,576</td>
<td>995,910</td>
</tr>
<tr>
<td>500</td>
<td>10,800</td>
<td>967,861</td>
</tr>
</tbody>
</table>
Fig. 8 – Primary product allocations from temporal decomposition algorithm for problem 2 (COT = 100).

Fig. 9 – The primary products productions from the temporal decomposition algorithm for problem 2 (COT = 100).

Table 5 presents the CPU times for the three steps of this method, where the first and third steps represent about 15% of the total solution time when COT = 300. Table 6 shows how the changeover time (COT) affects the CPU time to solve problem 2 with the spatial decomposition algorithm, by changing the available capacity. Fig. 7 relates the average computational

Fig. 10 – Breakdown of the total cost from the temporal decomposition algorithm for problem 2 (COT = 100).
time to solve each of the secondary areas and their excess capacity, defined in Eq. (45).

The temporal decomposition algorithm has, by far, the best performance of both solution algorithms developed in this work; its sensitivity to the excess capacity parameter is much lower than that for the spatial decomposition algorithm. One downside of this algorithm is that the quality of its results is highly dependent on the demand profile, i.e. large changes in demand levels between consecutive time periods will reinforce the importance of the inventory relations and lead to poorer quality results, while Eqs. (43) and (44) will introduce many limitations on the possible product allocation.

Fig. 8 shows the allocation of the primary products (I1–I10) to primary sites (C1–C10) obtained by the temporal decomposition algorithm for problem 2, from which we can see not only the product allocations, but also the allocation transfer decisions. Primary products I1, I3, I8, I9 and I10 are all allocated to one primary site, while other primary products make allocation transfers, in which both I4 and I7 have the maximum number of allocation transfers (two transfers). Fig. 9 shows the production at each primary site in each time period. C5 and C8 are the most productive primary sites, while C6, C7 and C10 are the three ones with the lowest production amounts. Within each site, we can also see that the productions vary throughout all the time periods.

Fig. 10 gives the percentage of each cost term in the total cost given by the temporal decomposition algorithm. The tax cost on the secondary sites, the transportation cost (of primary and secondary products), the production costs (of primary and secondary products), the inventory handling costs (on primary and secondary sites) and allocation costs (of primary and secondary products), occupy a tiny portion of the total cost. Particularly, the tax cost on the primary sites are zero, as the cost on primary sites is higher than the revenue, but the tax cost on the secondary sites accounts for around 40%.

7. Concluding remarks

In this work, we have defined a problem important to the pharmaceutical industry, reviewed relevant related published works, developed a model to cover the global network allocations and allocation transfers and investigated two solution algorithms to tackle this particular large MILP problem.

In the spatial decomposition method, the sensitivity analysis to the changeover time shows that, for this particular set of data, the optimum value is not affected significantly, since the bottleneck of the supply chain is the capacity of primary sites. On the other hand, the CPU time increases significantly. This is particularly the case for the “critical” secondary geographical areas, where \( j = 2 \) and \( j = 4 \). These correspond to areas where the capacity used is close to the limit, mainly due to a lower excess capacity (Eq. (45)), which becomes more critical as the changeover time increases.

The temporal decomposition method performs well with these sets of data although the quality of the results may be poor in other cases. Nevertheless, it opens new possibilities to explore even larger instances of the problem, such as its stochastic version, where demand and other parameters may be uncertain.

Acknowledgements

The funding for R.T.S. from the Portuguese Science and Technology Foundation (FCT), and for S.L. from the Overseas Research Student Award Scheme (ORSAS) and the Centre for Process Systems Engineering (CPSE) is gratefully acknowledged.

Appendix A. Appendix: Aggregate Model

The variables space of the detailed model may become very large for realistic problems, mainly because of the tetradimensional transportation variables of secondary products from sites to markets, \( TS_{spmt} \). We develop an aggregate version of the model, without transportation variables that, in spite of being less detailed, is more tractable and suitable for the development of algorithms (the number of variables is reduced by \( \sim 30\% \))

A.1. Parameters

The aggregated model uses all the parameters of the detailed model except demands, secondary products’ transportation costs and secondary products’ selling price that are substituted by aggregated or average parameters.

\[
\begin{align*}
D_{jpt} & \quad \text{Total demand of secondary product } p \text{ in area } j \text{ in time period } t, \text{ Eq. (A1)}. \\
CTS_{jspj} & \quad \text{Average secondary product } p \text{ transportation cost from site } s \text{ to markets in area } j, \text{ Eq. (A2)}. \\
V_{2pj} & \quad \text{Average price of secondary product } p \text{ in markets in area } j, \text{ Eq. (A3)}. 
\end{align*}
\]

\[
\begin{align*}
D_{jpt} & = \sum_{m \in M_j} D_{pmt} \forall t, j, p \in P_j \\
CTS_{jspj} & = \frac{\sum_{m \in M_j} (CTS_{spm} \sum_{t} D_{pmt})}{0.1 + \sum_{t} \sum_{m \in M_j} D_{pmt}} \forall j, p \in P_j, s \in S_j \\
V_{2pj} & = \frac{\sum_{m \in M_j} (V_{2pm} \sum_{t} D_{pmt})}{0.1 + \sum_{t} \sum_{m \in M_j} D_{pmt}} \forall j, p \in P_j
\end{align*}
\]

A.2. Variables

Almost all the variables from the detailed model are kept in the aggregated model, but some of them have to be redefined in order to fit the dimensional changes in the parameters. Variable \( TS_{spmt} \) is simply removed.

\[
\begin{align*}
S_{spjt} & \quad \text{Sales of product } p \text{ from site } s \text{ in time period } t; \\
U_{pjt} & \quad \text{Unsatisfied demand of product } p \text{ in area } j \text{ in time period } t;
\end{align*}
\]
A.3. Constraints

Eq. (12) has to be substituted and Eqs. (13), (14) and (17) have to be modified to be according with the redefined set of variables.

\[ \sum_{\tau} \sum_{s \in S_t} PR_{opt} \leq \sum_{\tau} D_{\rho_{pt}} \cdot V_j, p \in P_j \]  

(A4)

\[ SL_{opt} \leq D_{\rho_{pt}} \cdot V_j, s \in S_t, p \in P_j, \tau \]  

(A5)

\[ U_{\rho_{pt}} = D_{\rho_{pt}} - \sum_{s \in S_t} SL_{opt} \cdot V_j, p \in P_j, \tau \]  

(A6)

\[ IV_{\rho_{pt}} = IV_{\rho_{pt-1}} + PR_{opt} - SL_{opt} \cdot V_j, p \in P_j, \tau \]  

(A7)

A.4. Objective function

- Sales revenues;  
  \[ \Pi = \sum_{j} \sum_{p \in P_j} \sum_{s \in S_t} V_{2 \rho_{pt}} \cdot SL_{opt} \]  
  \[ \text{(A8)} \]

- Primary and secondary products production costs (per site);  
  \[ K_{P} = \sum_{i} \sum_{t} CPP_{ci} \cdot PR_{opt} \cdot V_j, \forall c \]  
  \[ \text{(A9)} \]

- Tax costs on primary and secondary site locations;  
  \[ \phi_c \geq TRP_c \cdot \left( \sum_{i} \sum_{t} V_{1 \rho_{pt}} \cdot PR_{opt} \right) - K_c \]  
  \[ \forall c \text{ (A19)} \]

- Primary and secondary sites inventory handling costs;  
  \[ K_{I_{prim}} = CPI \cdot \sum_{i} \sum_{t} IVP_{pt} \]  
  \[ \text{(A13)} \]

- Primary and secondary products allocation costs (per site);  
  \[ K_{A_{c}} = \sum_{i} \sum_{t} CTAP_{ci} \cdot XPT_{opt} \cdot V_j, \forall c \]  
  \[ \text{(A15)} \]

- Primary and secondary sites inventory handling costs;  
  \[ K_{I_{s}} = CPI \cdot \sum_{i} \sum_{t} IVP_{pt} \cdot V_j, s \in S_t \]  
  \[ \text{(A14)} \]

- For each site, the total costs before taxes will be as follows:  
  \[ K_c = K_{P_c} + K_{T_{c}} + K_{I_{prim}} + K_{A_{c}} \cdot V_j, \forall c \]  
  \[ \text{(A17)} \]

- Tax costs on primary and secondary site locations;  
  \[ \phi_s \geq TRS_s \cdot \left( \sum_{p \in P_j} \sum_{t} V_{2 \rho_{pt}} \cdot SL_{opt} \right) - K_s \]  
  \[ \forall j, s \in S_j \text{ (A20)} \]

The NPV is given by Eq. (A21):

\[ Z = \Pi - \left( \sum_{j} (K_c + \phi_c) + \sum_{s} (K_s + \phi_s) \right) - \sum_{j} \sum_{P_{opt}} \sum_{p} \sum_{t} U_{\rho_{pt}} \cdot CU \]  

(A21)

References


