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Global Supply Chain Network Optimisation for Pharmaceuticals

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Abstract

In the pharmaceutical industry, the historically high margins of profit are harder to come by so it has become vital to look at each enterprise as a whole and try to extract the maximum value from its supply chain. In this work we address an optimisation problem for the product allocation-distribution structure of a pharmaceutical company supply chain, from primary (active) ingredients production to final product distribution to markets. Given the multi-period demand profile of the company's portfolio, the model tries to allocate the products to sites and to address other issues that supply chain managers usually face. The objective is set as the maximization of the company's NPV. The full space model is not tractable in a reasonable time, so two decomposition algorithms have been developed: a heuristic method where frames of products are optimised sequentially and a Lagrangean decomposition method. The first algorithm reduces the CPU substantially while maintaining the quality of the final results.

Keywords: supply chain networks, large-scale optimisation, pharmaceuticals

1. Introduction

In the past, the large R&D in full based multinationals have always enjoyed a very important economic status. This comfortable position was possible due to: a) high productivity of the R&D activities, b) long effective patent lives of new compounds and ability of these to provide technological barriers to entry, c) limited number of substitution products that could compete with drugs in a given therapeutic area (leading to high demands of these compounds) and d) low price sensitivity due to separation between prescribing and paying responsibilities. The corporate strategy was to explore the price inelasticity ensuring high margins of profits and investing a significant proportion in R&D.

In the past 30 years, the operating context of this industry has evolved and become much more challenging. Nowadays, R&D productivity is declining and costs rising due to new regulatory requirements, increasing the time to market. This leads to effective

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patent lives shortening, which, in addition with product substitutes in many therapeutic areas (either alternative products or off-patent generics), has shortened the market exclusivity period of new drugs. Simultaneously, healthcare payers are exerting strong pressure on prices and prescription policies.

1.1 Previous works in supply chain in the pharmaceutical industry

Rotstein et al (1999) model the supply chain of a pharmaceutical industry, from the drug development stage until final manufacture. The demand forecasts are uncertain, dependent on the clinical outcomes. This paper is the first to approach the problem in a holistic perspective by considering production issues and capacity investment together. The expected NPV is estimated for a composition of scenarios. Papageorgiou et al (2001) take the same initial model, insert a higher degree of detail in the production process and take into account the trading structure of the company. However, this time the problem is formulated as a deterministic, multi-site, multi-product and multi-period problem. Levis and Papageorgiou (2004) introduce an uncertainty factor, where the demand forecasts are dependent on the results of the clinical trials for each product. Gatica et al. (2003) address the issue of product development and uncertainty in clinical tests outcomes, but from a different perspective of the previous works. They consider several pharmaceutical drugs in different stages of the development process. The multi-stage, multi-period, stochastic problem gives rise to a multi-scenario MILP model.

1.2 Solution methods for large MILP models

Gupta and Maranas (1999) formulate a problem, characterized by the production planning of multiple products, in multiple sites, with deterministic demands due at the end of a finite number of time periods. The authors develop a decomposition algorithm based on Lagrangean Relaxation in conjugation with a specific heuristic procedure. The main strategy is to decompose the original model into a collection of smaller, more tractable sub-models. Jayaraman and Pirkul (2001) address a supply chain design/ product allocation problem. In order to solve it, they relax three blocks of constraints that allows them to decompose the original problem in three different sets of sub-problems. The first two ones, after a minor heuristic procedure, are converted in sets of independent knapsack sub-problems. The third sub-problem is a trivial one that can be solved in linear time. Maravelias and Grossmann (2001) introduce a good example of a model composed of two (or more) independent sub-models with one linking constraint. Making use of this feature, the authors duplicate the linking constraint variables and build a Lagrangean decomposition scheme, resulting in two independent sub-models.
Iyer and Grossmann (1998) and Levis and Papageorgiou (2004) give two examples of hierarchical algorithms. In the first step, an aggregated version of the model, with a reduced variable space, is solved in order to make the “here-and-now” decisions. In the second step, a detailed model is solved subjected to the decision variables estimated in the previous step. Rotstein et al (1999) execute a similar procedure in a reduced scenario space in the first sep.

2. Problem Description

The participants in the enterprise’s supply chain are primary sites (active ingredient manufacturers) and respective storage facilities, secondary sites and respective warehouses and final product market areas. The distribution network within each market area is out of the scope of this work.

Each primary site may supply the active ingredient to any of the secondary sites and be located in any place around the world. There are five geographical areas for secondary sites and markets. Since the transportation costs are very significant at this end of the supply chain, material flows between two different areas are not allowed. Each secondary geographic area produces and consumes some product families, but not all, from the company's portfolio and a single sourcing policy is followed, i.e. each product (both primary and secondary) will be produced in one and only one site on each time period. The model assumes an initial allocation of products to sites. Due to several events, such as organic growth or merges/acquisitions, this configuration may not be optimal anymore, so the model allows the assignment of products to sites to change between different time periods ("allocation transfer"). For secondary products, this can only take place between sites in the same geographical area.

3. Mathematical Model

Indices and sets: i primary products, c primary sites, l primary sites resources, p secondary products, s secondary sites, r secondary sites resources, j geographical areas, m market locations and t time periods. P_j, S_j and M_j are the sets of secondary products (produced and consumed), sites and markets belonging to area j.

Parameters: D_{ptm} demand forecasts, MT_{rp}/MTP_{il} manufacturing requirements of secondary and primary products, A_{rts}/AP_{itc} availability of secondary and primary resources, CPS_{ps}/CPP_{ic} secondary and primary products production costs, CTS_{sm} transportation costs of secondary products between sites and markets, CTP_c average transportation costs between primary and secondary sites, PF_{ip} secondary product composition, $V2_{pm}$ selling price, $CTA_{ps}/CTAP_{ic}$ secondary and primary products allocation transfer costs, TF_p secondary product yield, $V1_i$ internal selling price of primary products, TRS_s/TRP_c secondary and primary sites location tax rates, CU_p indirect costs of unattended demand, K_{rp} equals 1 if product p uses resource r, CIV inventory costs, Max upper limit of production rates.

Continuous variables: Z NPV (objective function), PR_{pst}/PRP_{ict} production rates in secondary and primary sites, IV_{pst} inventory of secondary products in secondary sites, IVP_{it} inventory of primary products, TS_{psmt} secondary products flow from sites to markets, TP_{ist} primary products flow to secondary sites, SL_{pmt} secondary product sales, U_{pmt} unattended demand.

Binary Variables: X_{pst}/XP_{ict} allocation of secondary and primary products, XT_{pst}/XPT_{ict} secondary and primary products allocation transfers decisions.

The key constraints of this model are the ones concerning allocation of products. Constraint (1) accounts for the single sourcing option, constraints (2) and (3) state that the effect of allocation transfers will only occur θ periods after the decision has been taken and constraint (4) limits the number of transfers that can happen in each time period. In this paper, only the secondary products allocation constraints are shown, but the formulation is the same for the primary products.

$$\sum_{s \in S_j} X_{pst} = 1 \quad \forall t, p \in P_j, j = 1,2,3,4,5 \tag{1}$$

$$XT_{pst-\theta} \geq X_{pst} - \sum_{\alpha=1}^{\theta} X_{pst-\alpha} \quad \forall p,s,t > \theta \tag{2}$$

$$X_{pst-\alpha} \leq 1 - XT_{pst-\theta} \quad \forall p,s,\alpha = [1,\theta] \tag{3}$$

$$\sum_{p \in P_j} \sum_{s \in S_j} XT_{pst} \leq 3 \quad \forall j,t \tag{4}$$

The capacity constraint for secondary resources (5) states that the resources utilization needed to meet the desired production rates has to be lower than their availability. The Primary resources availability constraint has the same formulation without the changeover term.

$$\sum_{p} MT_{rp} PR_{pst} \leq A_{rts} - \left(\sum_{p} K_{rp} X_{pst} - 1 \right) COT \quad \forall r,s,t \tag{5}$$

Other constraints are production, (6) and (7), flow balances between echelons, (8) and (11), sales, (9), unfulfilled demand (10) and inventory, (12) and (13).

$$PR_{pst} \leq Max\, X_{pst} \quad \forall p,s,t \tag{6}$$

$$PRP_{ict} \leq Max\, XP_{ict} \quad \forall i,c,t \tag{7}$$

$$SL_{pmt} = \sum_{s \in S_j} TS_{psmt} \quad \forall j = 1,2,3,4,5, p \in P_j, m \in M_j, t \tag{8}$$

$$SL_{pmt} \leq D_{pmt} \quad \forall j = 1,2,3,4,5, p \in P_j, m \in M_j, t \tag{9}$$

$$U_{pmt} = D_{pmt} - SL_{pmt} \quad \forall j = 1,2,3,4,5, p \in P_j, m \in M_j, t \tag{10}$$

$$TP_{ist} = \sum_{p} \frac{PR_{pst} PF_{ip}}{TF_p} \quad \forall i,s,t \tag{11}$$

$$IV_{pst} = IV_{pst-1} + PR_{pst} - \sum_{m \in M_j} TS_{psmt} \quad \forall j = 1,2,3,4,5, p \in P_j, s \in S_j \tag{12}$$

$$IVP_{it} = IV_{i,t-1} + \sum_{c} PRP_{ict} - \sum_{s} TP_{ist} \quad \forall i,t \tag{13}$$

A special set of constraints is also included to account for forbidden flows between the secondary geographical areas as well as a set of non-negativity constraints. The objective function is the NPV, as mentioned before. The income is provided by sales of secondary products. The costs term includes secondary and primary production, inventory and transportation costs as well as tax costs in both locations.

Z = sales revenues - primary products/ sites costs - secondary products/ sites costs - (sales revenues - secondary products/ sites costs) TRS_s - (internal sales revenues of primary products - primary products/ sites costs) TRP_c (14)

4. Solution Methods

Two algorithms were developed to tackle the problem: Lagrangean decomposition and product frames algorithm (PFA). The first method makes use of the intrinsic structure of the model matrix. The problem can be described as two separated sub-problems (concerning primary and secondary sites and products) with one binding constraint, (11). Doubling one of the two variables in the binding constraint, PR_{pst}, a decomposition scheme based in Lagrangean relaxation is built, as described in Reeves (1993). The two sub-problems obtained are independent and easier to solve than the original problem. The sum of the optimum solutions will constitute an upper bond to the original problem while the set of values of binary variables will provide a lower bond, through a heuristic method. The values are used to update the Lagrangean multipliers. The iterative cycle is repeated until the convergence criterion is met.

In the PFA, the list of secondary products is separated in several groups (frames) that are allocated sequentially instead of simultaneously. During this process, all the variables concerning the products outside the frame being optimised (both binary and continuous ones) are not modified. In the modified version of this algorithm (PFA modified) the products demanding higher resources usage are optimised first, and all the binary allocation variables of the secondary products that are still to be allocated are relaxed. This provides a partial solution for each frame that will be closer to the full space solution, while keeping a reduced binary variable space.

An aggregated version of the model (AM) has also been developed, where dimension *m* is removed. The demand profiles, transportation costs of secondary products and final market prices are calculated as average quantities over the dimension *m*. The variable block TS_{pstm} is deleted, the sales block is modified to SL_{pst}, constraint (8) is substituted by constraint (15) and the objective function, constraints (9), (10) and (12) are modified. This reduces significantly the number of continuous variables (~30%).

$$\sum_{t}\sum_{s\in S_j} PR_{pst} \leq \sum_{t} DJ_{ptj} \quad \forall j = 1,2,3,4,5,\ p \in P_j \tag{15}$$

5. Illustrative Examples

Two examples motivated by an industrial situation were generated to test the model. The first set contains 6 primary sites, 6 primary products, 33 secondary sites, 30 secondary product families, 10 market areas and 12 time periods. This results in a model with 29,880 continuous and 12,480 binary variables. The second set has 10 primary sites, 10 primary products, 70 secondary sites, 100 secondary product families, 10 market areas and 12 time periods. This model contains 185,760 continuous variables and 84,096 binary ones. The algorithm performances are shown in Table 1.

The Lagrangean decomposition method did not provide good results because the secondary product allocation sub problem alone demands a high computation time to solve. This is aggravated by the weak dependence between the primary sub-problem and the PR_{pst} variable, which increases the number of iterations needed for convergence.

All the tests were performed on Unix based machines with 2 GB RAM and 1.8 GHz Pentium IV processor, running CPLEX 9.0 solver.

Table 1. Performance and results obtained with the different solution methods. [a] not solvable in 250,000 s CPU, [b] two cycles, [c] one cycle , AM – Aggregated version of the model.

	First Example			Second Example		
	Opt	Gap (%)	CPU(s)	Opt	Gap (%)	CPU(s)
LP	475,847	-	-	1,006,351	-	-
LP (AM)	486,130	-	-	1,057,058	-	-
Full Space 1	469,190	1.4	100,002	[a]	-	-
Full Space 2	467,190	1.9	7,111	-	-	-
Full Space (AM)	473,909	2.5	29,714	[a]	-	-
PFA (AM)	448,224	6.1	1,927[b]	909,546	16.2	6,973[b]
PFA modified (AM)	473,120	0.6	447[c]	1,035,799	2.1	75,911[c]
PFA modified	474,118	0.4	450[c]	[a]	-	-

6. Conclusions and Future Work

The full space model of the large problem is solvable neither for the detailed model nor for the aggregated version. The PFA on its simplest version is fast to solve but does not provide good quality results, especially with the large problem. Clearly, the modified version allows obtaining better results than with the first one. For the smaller first example, it is even faster since it only demands one complete cycle to find a good solution. With these methods only the aggregated model of the second example is solvable with reasonable result quality.

Future work on algorithm design is required to solve large problems. This may be attained trough decomposition/hierarchical procedures or via hybrid approaches of mathematical programming and heuristic methods.

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