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Multiobjective strategies for New Product Development in the pharmaceutical industry

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ABSTRACT

New Product Development (NPD) constitutes a challenging problem in the pharmaceutical industry, due to the characteristics of the development pipeline. Formally, the NPD problem can be stated as follows: select a set of R&D projects from a pool of candidate projects in order to satisfy several criteria (economic profitability, time to market) while coping with the uncertain nature of the projects. More precisely, the recurrent key issues are to determine the projects to develop once target molecules have been identified, their order and the level of resources to assign. In this context, the proposed approach combines discrete event stochastic simulation (Monte Carlo approach) with multiobjective genetic algorithms (NSGAII type, Non-Sorted Genetic Algorithm II) to optimize the highly combinatorial portfolio management problem. In that context, Genetic Algorithms (GAs) are particularly attractive for treating this kind of problem, due to their ability to directly lead to the so-called Pareto front and to account for the combinatorial aspect. This work is illustrated with a study case involving nine interdependent new product candidates targeting three diseases. An analysis is performed for this test bench on the different pairs of criteria both for the bi- and tricriteria optimization: large portfolios cause resource queues and delays time to launch and are eliminated by the bi- and tricriteria optimization strategy. The optimization strategy is thus interesting to detect the sequence candidates. Time is an important criterion to consider simultaneously with NPV and risk criteria. The order in which drugs are released in the pipeline is of great importance as with scheduling problems.

1. Introduction

Traditionally, Process Systems Engineering (PSE) is concerned with the understanding and development of systematic procedures for the design and operation of chemical process systems, ranging from microsystems to industrial scale continuous and batch processes. This traditional definition of PSE has been broadened by the concept of the "chemical supply chain". Process Systems Engineering is now concerned with the improvement of decision making processes for the design and operation of the chemical supply chain. More precisely, it deals with the discovery, design, manufacture and distribution of chemical products in the context of many conflicting goals. The area of R&D and Process Operations has emerged among the major challenges in the PSE area: this topics, which has a shorter history than process design and control, expands upstream to R&D and downstream to logistics and product distribution activities.

In that context, optimal planning and scheduling for New Product Development (NPD) need increased attention to coordinate better product discovery, process development and plant design in the agrochemical and pharmaceutical industries. For downstream applications, areas that receive increased attention at the business level include planning of process networks, supply chain optimization, real time scheduling, and inventory control. Due to the pressure for reducing costs and inventories, in order to remain competitive, enterprise-wide optimization (EWO) that might be considered as an equivalent term for describing the chemical supply chain (Shapiro, 2001) has thus become a cornerstone in process industries.

Enterprise-wide optimization is an area that lies at the interface of Process Systems Engineering and Operations Research. As outlined in Grossmann (2005), a new generation of methods and tools that allow the full integration and large-scale solution of the optimization models, as well as the incorporation of accurate models for the manufacturing facilities is needed. Given the strong tradition that chemical engineers have in process systems engineering and in the optimization area (see Biegler & Grossmann, 2004 for a review), they are ideally positioned to make significant contributions in EWO.

The development of decision support strategies and systems for managing new product portfolios must be able to provide insights to managers on how to minimize risk while optimizing an objective or a set of objectives (e.g. maximization of expected net present

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value, minimization of time to market, etc.) in the presence of constraints. Moreover, the simultaneous consideration of all candidate projects is the key aspect in managing a NPD pipeline. This complexity has led to the common use of decomposition based in either strategic or operational strategies. Each of the two branches can be further subdivided according to the characteristics of the model used to support the decision making process.

An interesting contribution (Zapata, Varma, & Reklaitis, 2007) proposes a recent state-of-the art of the concerned problem. The main guidelines of their analysis are briefly recalled to position our work. First, a project can be analyzed in isolation (e.g. the net present value (NPV) of the project), or as performance assessment at the portfolio level (e.g. NPV of the portfolio), including all the interactions between projects. The time dimension distinguishes dynamic and static approaches. A dynamic model provides the specific state of the systems along each point of the time horizon (e.g. number of projects waiting for a given resource at a given time), while a static one uses average values to represent the system (e.g. average number of projects waiting for a given resource at any time). It is then possible to choose between deterministic and stochastic models. However, dynamic stochastic models can be viewed as either open loop or closed loop oriented. Open loop models only capture the response of the system to inputs from decision makers, while closed loop models also capture the response of the decision makers to the outcomes from the system.

Among the investigations dedicated to strategic decision support systems, the different techniques available depend on the type of data used, namely, qualitative and quantitative. On the one hand, the methodologies relative to static strategies are numerous in this area: it must be emphasized that a major drawback of such approaches is that they do not take into account project interactions. They include scoring methods (Coldrick, Longhurst, Ivey, & Hannis, 2005; Cooper, Edgett, & Kleinschmidt, 1999), analytical hierarchy approaches (Calantone, Benedetto, & Schmidt, 1999; Poh, Ang, & Bai, 2001) and fuzzy logic based approaches (Buyukozkan & Feyzioglu, 2004; Lin & Hsieh, 2004; Lin, Tan, & Hsieh, 2005). On the other hand, the methodologies that are based on quantitative information strive to provide a realistic simulation of the behaviour of each individual project along the time horizon considered, in order to determine what the possible outcomes are in terms of rewards and risk. This group includes dynamic deterministic strategies such as classical financial models (e.g. NPV, internal rate of return, etc.) (Cooper et al., 1999), as well as dynamic stochastic strategies, both closed loop such as real options (Copeland & Antikarov, 2001; Jacob & Kwak, 2003; Loch & Bode-Greuel, 2001; Newton, Paxson, & Widdicks, 2004; Santiago & Bifano, 2005), and open loop such as discrete event simulation (Chapman & Ward, 2002), and neural networks (Thieme, Song, & Calantone, 2000).

Most of the approaches that capture project interactions can be classified as dynamic stochastic open loop methodologies. An important contribution is the work of Blau, Pekny, Varma, and Bunch (2004) which proposes the use of stochastic optimization: the portfolio is modelled using a discrete event simulation and the optimization is implemented by a genetic algorithm; Rogers, Gupta, and Maranas (2002) formulate a real options decision tree that captures technical and market uncertainty as a stochastic MILP (Mixed Integer Linear Programming) that relates projects through a budget constraint. Rajapakse, Titchener-Hooker, and Farid (2005) present a decision support tool that uses sensitivity and scenario analysis on a discrete event model of the development pipeline. Finally, Ding and Eliashberg (2002) approach the problem of determining how many projects, that are assigned to develop the same product, have to be included in the pipeline to maximize the total expected profit. All of the techniques in this group are mainly focused on time independent decisions (excluding the work reported in Rogers et al., 2002) and therefore do not require closed loop models. Some work has been done to accommodate the higher level of complexity required by time dependent strategic decisions such as capacity expansion/contraction (Wan, Pekny, & Reklaitis, 2006). It must be yet pointed out that the non-Markovian nature of the associated decision problem has yet limited the size of the treated problem as expressed in project number.

At the operational level, decisions are time dependent and mostly Markovian in nature. This has motivated the development of operational decision support systems exclusively based on quantitative information and with a dynamic character (Honkomp, 1998; Jain & Grossmann, 1999; Subramanian, Pekny, Reklaitis, & Blau, 2001; Varma, 2005).

This literature review reveals that it is difficult to embed all the peculiarities of the problem in a generic formulation and to reconcile all levels at the involved scales. The complexity of the problem is attributed to several combined issues such as the stochastic behaviour of the system, the combinatorial aspect and consequently the size of industrial problems as well as the induced multilevel approach. Some recent works (Colvin & Maravelias, 2008, 2009) are trying to reconcile both strategic and operational levels, namely, the scheduling of clinical trials and the planning of the resources necessary to carry these trials out. A stochastic programming framework that addresses the two problems simultaneously is proposed in Colvin and Maravelias (2009). The underlying philosophy implies three levels: first, the structure of the problem is studied in order to reduce the number of pairs of scenarios; second, a finite-horizon approximation is developed so that problems can be formulated using fewer stages without compromising the quality of the solution; third, the sequential nature of the testing process is considered and modelled with a mixed-integer programming (MIP) formulation; a relaxation of this formulation is then used to obtain feasible and most often optimal solutions over the stages of interest. Finally, a rolling-horizon-based approach is implemented, where the decisions of the relaxed problem are used over few early periods and a new problem is formulated and solved as time evolves. This framework was recently improved including: (i) the selection and scheduling of R&D tasks with general precedence constraints under pass/fail uncertainty, and (ii) resource planning decisions (expansion/contraction and outsourcing). Furthermore, interdependencies between tasks in terms of probability of success, resource usage and market impact are considered with risk management approaches, taking into account conditional value at risk (Colvin & Maravelias, 2011), that was never considered in previous works. It must be also emphasized that all the reported approaches are based on a monoobjective optimization formulation even if the problem is multiobjective by nature.

This work is devoted to the development of a dynamic stochastic open loop methodology and involves a bi-and tricriteria optimization formulation of the NPD problem. It involves multi-stage decisions under uncertainty. The recurrent key issues are can be stated as follows: what are the projects to develop once target molecules have been identified? In what order? Which is the level of resources to assign? The proposed modelling approach is based on a discrete event simulator which is particularly useful for decision criteria evaluation, such as economic and risk metrics. This work can be viewed as an extension of the investigations previously dedicated to batch plant design and scheduling which are of major importance for such industries and which can be considered as part and parcel of the more general topics of NPD management. This kind of involves several criteria, the Net Present Value of a sequence, its associated risk (measured by an attractiveness ratio or by the so-called positivity probability) and the makespan that must be optimized simultaneously. Section 2 is first devoted to the key issues involved in New Product Development. Section 3 presents the principles of the discrete event simulation model developed and implemented for describing the pipeline behaviour.