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New Product Development with Discrete Event Simulation: Application to Portfolio Management for the Pharmaceutical Industry

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ABSTRACT: New product development (NPD) constitutes a challenging problem in the pharmaceutical industry. Formally, the NPD problem can be stated as follows: Select a set of R&D projects from a pool of candidate projects to satisfy several criteria (e.g., 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 be developed, together with the order in which they enter the pipeline and the corresponding resource allocation. In this context, this work presents the development and implementation of a discrete event simulator for drug portfolio management based on object-oriented techniques and used as a tool for evaluating each drug or sequence of drugs. Evaluation methods based on bubble charts are used for selecting the best drugs according to the considered evaluation criteria. Imprecision modeling has been tackled in two ways: a classical probability approach and an interval-based one. Both approaches are illustrated by a numerical example, which shows that the tendencies obtained by the interval-based approach can be difficult to interpret for the decision maker, because of the growing uncertainty along the pipeline. In addition, the risk, which is taken into account through failure probability for some stages and which is strongly involved in the NPD process, must be an integral part of the modeling approach. The repetitive use of simulation with representative sampling turns out to be the most efficient strategy.

■ INTRODUCTION

A fundamental challenge in managing a pharmaceutical or biotechnology company is to determine the optimal allocation of finite resources across the huge number of available investment opportunities. In that context, the optimal management of the new product pipeline has emerged at the forefront of all strategic planning initiatives of a company. This issue is traditionally identified as a complex one because it integrates various areas such as product development, manufacturing, accounting, and marketing. The complexity of the problem is mainly attributed to the great variety of parameters and decision-making levels involved. A strategic investment plan should simultaneously address and evaluate in a proper manner the following four main issues: product management, clinical trial uncertainty, capacity management, and trading structure. It is also generally viewed as a multistage stochastic portfolio optimization problem. The main challenge is to configure a product portfolio to obtain the highest possible profit, including any capacity investments, in a rapid and reliable way. These decisions have to be made in the face of considerable uncertainties in factors such as demands, sales prices, and outcomes of clinical tests that might not turn out as expected.

This type of problem has recently received attention from the process systems engineering community utilizing previous works from the process planning and scheduling area. Various mixed-integer linear programming (MILP) optimization models have been proposed in Schmidt and Grossmann¹ for the scheduling of testing tasks with no resource constraints with a discretization scheme to induce linearity in the cost of testing. These models have been extended in Jain and Grossmann² to account for resource constraints. A simulation–optimization framework proposed by Subramanian et al.³ takes into account uncertainty

in duration, cost, and resource requirements. A literature review of optimization approaches by Shah⁴ presents works dedicated to the supply chain of pharmaceutical industries. A single-objective genetic algorithm presented by Blau et al.⁵ has been used to optimize product sequences evaluated by a commercial discrete event simulator.

This work lies in this perspective: The underlying idea is to use a multiobjective framework, as already initiated by Aguilar-Lasserre et al.,⁶ to model both the conflicting nature of the criteria (i.e., risk minimization and profitability maximization) and the imprecise nature of some parameters (demand, operating times, etc.). In that context, this work aims at the development of an architecture that combines an optimization procedure and a simulation model to represent the dynamic behavior of the pipeline with its inherent uncertainty and to help in decision making. The objective is thus to propose a general methodology framework to support decisions and management of pharmaceutical products involved in their life cycle, from early stages to mature sales. This article is focused on only the first part of the methodology, that is, the development of a discrete event simulator. The goal is to model the various paths and the precedence relations between the activities involved in new product development by discrete event simulation (DES) principles used in previous works for batch plant design.^{7,8} The problem of evaluating and selecting which new products to develop and then sequencing or scheduling them is not a trivial

task because of the dependencies between products both in the marketplace and in the development process itself. Discrete event simulation (DES) is a common tool used to understand how a system works and would work if changes were implemented, without undertaking expensive trials. This technique has thus been chosen, and it must be highlighted that experience in DES has been gained in our research group over several years (see, for instance, the work about batch plant modeling proposed by Bérard et al.⁹). Based on this experience, DES development appear to be well fitted in terms of its internal structure and its performance for the problem under consideration. This is why DES was considered as the basic tool for the present work, even if some modifications and adjustments are necessary to obtain an efficient tool to tackle the NPD pharmaceutical projects of this study.

Some investigations^{5,10–12} have used commercial simulation software tools based on discrete event simulation [e.g., CSIM (<http://www.mesquite.com>) Simulator Extended Industry Suite V5, GenSight software (<http://www.gensight.com/Project-Portfolio-Management/Overview/Home.htm>)] with specific advantages. However, limitations in the ability of graphically based simulators to interact with other applications forced us to develop our own simulator. This explains our main motivation to use and adapt the simulator previously developed in our group. The C++-implemented DES can easily be modified for modeling the NPD problem considered here. This constitutes the first step of a general framework for managing NPD projects that will consider the integration of this simulation tool into a more general-purpose simulation–optimization framework.

Uncertainty, imprecision, and multiple criteria are important factors to take into account in decision making. This applies particularly in the problem of portfolio selection, as it typically involves multiple objective functions (net present value, risk, and makespan) and includes uncertainties and imprecision in several parameters. For modeling the imprecision involved in the NPD problem, a first solution was to use interval bounds to model some imprecise parameters associated with a probability distribution within a Monte Carlo framework. The concept of degree of difficulty (DoD) was also used to reflect the relative difficulty in carrying out a process task. Another objective of this article is to study an alternative imprecision modeling method based on interval analysis, to select the best approach to embed at the optimization step.

This work involves five sections. The three stages of the life cycle of a pharmaceutical product, namely, discovery, development, and commercialization, are described first. The extension of the DES previously developed for batch plant scheduling to the NPD problem is then presented and illustrated with a nine-drug portfolio problem. The performances of each drug and of sequences of drugs are studied, as well as the limitation of resource capacities. Then, a literature review is carried out, followed by interval analysis applied to the nine-drug problem. Finally, a comparison between interval analysis and the probabilistic approach is made.

■ LIFE CYCLE OF A PHARMACEUTICAL PRODUCT

Basically, three stages are involved in the life cycle of a pharmaceutical product: discovery, development, and commercialization, as can be seen in Figure 1. In the discovery stage, thousands of molecules are applied to targets developed to simulate various disease groups. Once an active molecule is discovered, various

permutations of the structure of the molecule are tested to see if the activity can be enhanced. The most active molecule from these structure–activity relationships is tested for toxicological results on rats or mice. If no particular worrisome toxic end points are observed, the molecule is promoted to the status of “lead” molecule and becomes a candidate for development.

In the development stage, enormous sums of money and resources are committed to the lead molecule to observe its behavior, first, in healthy volunteers; second, in patients affected by the disease; and finally, in large-scale clinical studies conducted in concert with the Food and Drug Administration (FDA). Coincident with these studies, process research and formulations work is conducted to both supply the drug for testing purposes and design and construct a commercial plant if the product is launched. Other parallel studies involve extensive long-term (i.e., two-year) chronic studies in animals to identify any indication of oncogenicity at different dosage levels.

If the drug is effective in the clinical studies, has no unacceptable side effects, and is approved by the FDA, it moves to the commercial stage. Target markets are identified for a staged launch or “ramp-up” of the new compound. After a few years, a mature sales level is usually reached and maintained until patent coverage on the molecule expires and/or competition from generics is realized. Once generics are available, an attempt is usually made to gain approval of the drug for alternative markets and perhaps in different dosage forms. Regardless, sales diminish after expiration of the patent.

■ FROM BATCH PLANT SCHEDULING AND DESIGN TO NPD MANAGEMENT

In a DES, a process is described as it evolves with time, and changes take place only a finite number of times, that is, on event occurrence dates. The DES was developed using the C++ object-oriented language, according to the approach proposed by Bérard et al.⁹ The power of object-oriented techniques lies in the ability to produce “modular” code (known as classes) that can be “easily” modified and reused. The ability to contain software complexity into classes and to realistically represent entities from the real world in software makes object-oriented techniques ideally suited to simulations that are inherently complex.

A four-layer framework (see Figure 2) was proposed in Bérard et al.,⁹ based on the items engine, event, object, and supervisor, with the aim of developing a standard library for simulator classes that are general to any case, thus minimizing the task of treating different study cases or the variants of a given one (i.e., design or scheduling objectives). In this approach, at the lowest level, the common engine can be found. Initially, the events in the next level are generic events common to all batch plant simulations: In this case, the definition must be adapted because, in this work, we have to consider the whole life cycle of a project related to a product. In the same way, the objects taken into account present some similarities but differ in their appreciation. For instance, in batch plant scheduling (BPS) problems, material resources consist of equipment, whereas in NPD problems, resources can be viewed more globally. In fact, the main differences at this step occur from a terminology point of view, and this can be easily transposed in the NPD formulation (see Table 1).

Following the classical terminology used in object-oriented approaches, the so-called main objects of the DES are described in the next subsection. To treat a particular problem, specific objects should be derived from this basic structure.

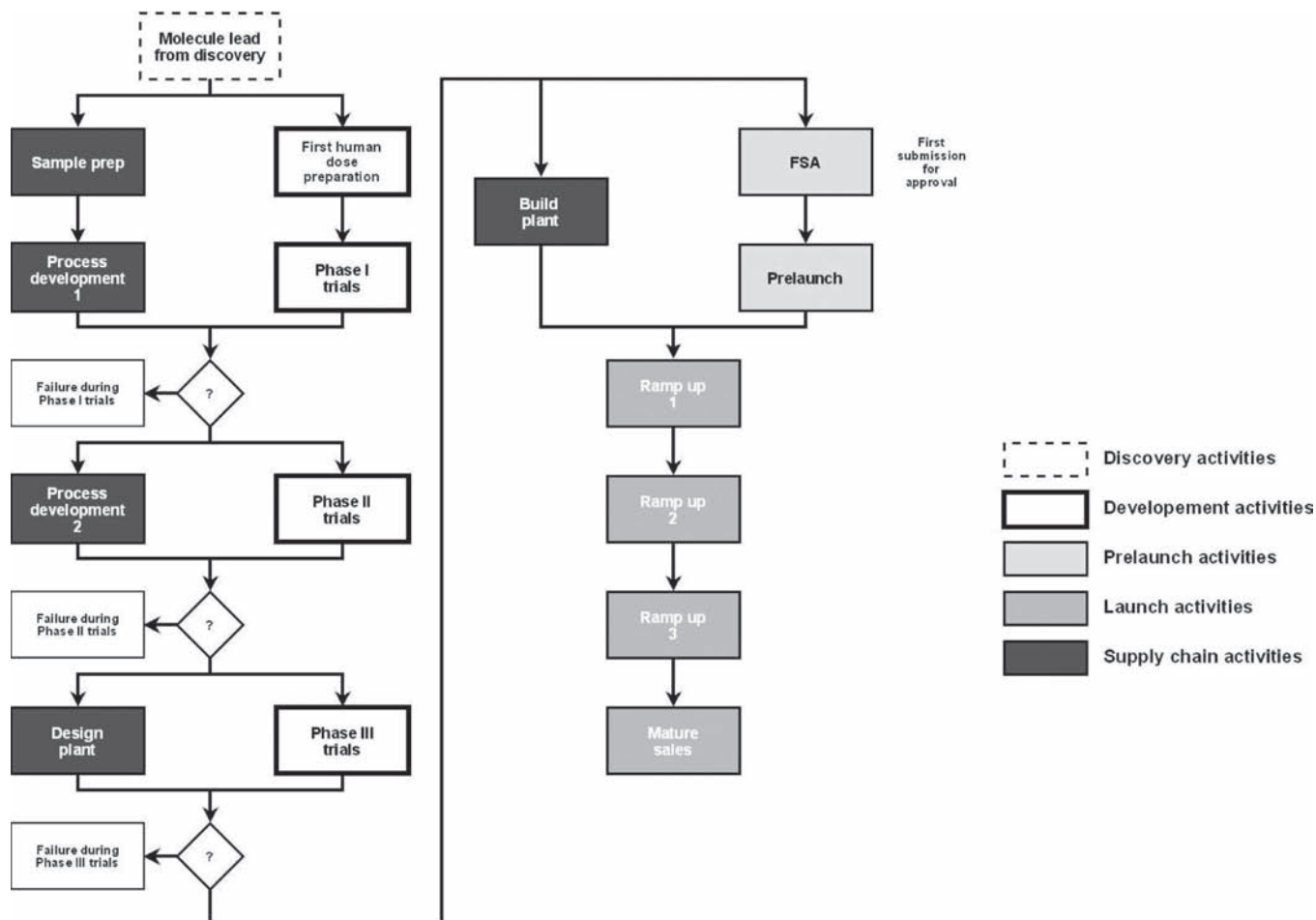


Figure 1. Typical pharmaceutical R&D pipeline.

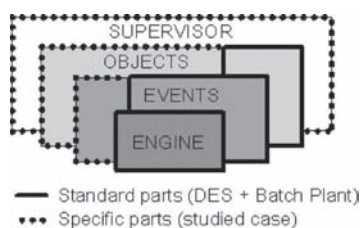


Figure 2. DES framework.

Model Classes. The core of the simulator is the engine, which has two functions: to order the events in its calendar by their occurrence date and to activate them if the necessary resources are available; if not, it reports the event to a later date.

As previously mentioned, an event represents a change of the real system at a given time. The class event is a basis class from which the different events must be defined. If resources for this activity are available, the event is activated; conversely, if resources are not available, the activity will be scheduled later.

An event is characterized by its occurrence date, its action on the system, and a type that enables to give priorities when two or more events have the same occurrence date. As a general rule, events that release resources have priority over the others, and when events have the same type, the classical FIFO rule (first in first out) is applied. This is useful when different projects compete for the

Table 1. Terminology in BPS and NPD Project Problems

batch plant scheduling (BPS)	NPD project
product i	project related to a product i (PRP i)
equipment item j	resource of a given step j
recipe k	succession of activities k (also called recipe)
unit operation of recipe l	activity l

same resources. The event class previously developed was generic enough to embed in the NPD formulation.

■ SIMULATOR VALIDATION: APPLICATION TO A NINE-DRUG PROBLEM

Simulation for Each Drug. Because of failure probabilities at phase I, II, and III trials, the problem is, by definition, a stochastic one. The problem data are listed in Table 2. Each simulation is repeated a large number of times (300), selecting random sampling values from a uniform random number generator for defining failure or success. If the generated number is less than a given probability value (see Table 4, below), the drug succeeds at the considered phase; otherwise, it fails and is stopped. Probability distributions for various economic and risk indicators, as well as statistical parameters, can be deduced from results gathering. For each drug launched in the process, the net present

Table 2. Data for the Nine-Drug Problem with Resource Limitations

activity	duration (days)			cost (\$MM)			total available resources (\$MM)
	min	ML	max	min	ML	max	
FHDP	300	400	500	72	80	88	275
sample prep	300	400	500	1.8	2	2.2	10
phase I	225	300	375	70	80	90	350
phase II	375	500	625	75	80	85	175
phase III	575	775	975	150	200	250	250
process development 1	600	800	1000	7	10	13	16
process development 2	600	800	1000	7	10	13	16
design plant	550	750	950	8	10	12	12
FSA	275	375	475	18	20	22	100
prelaunch	75	100	125	45	50	55	550
build plant	600	750	900	52	62	72	120
ramp-up 1	250	350	450	9	12	15	25
ramp-up 2	250	350	450	19	22	25	50
ramp-up 3	250	350	450	35	40	45	100
mature sales	250	350	450	46	53	60	150

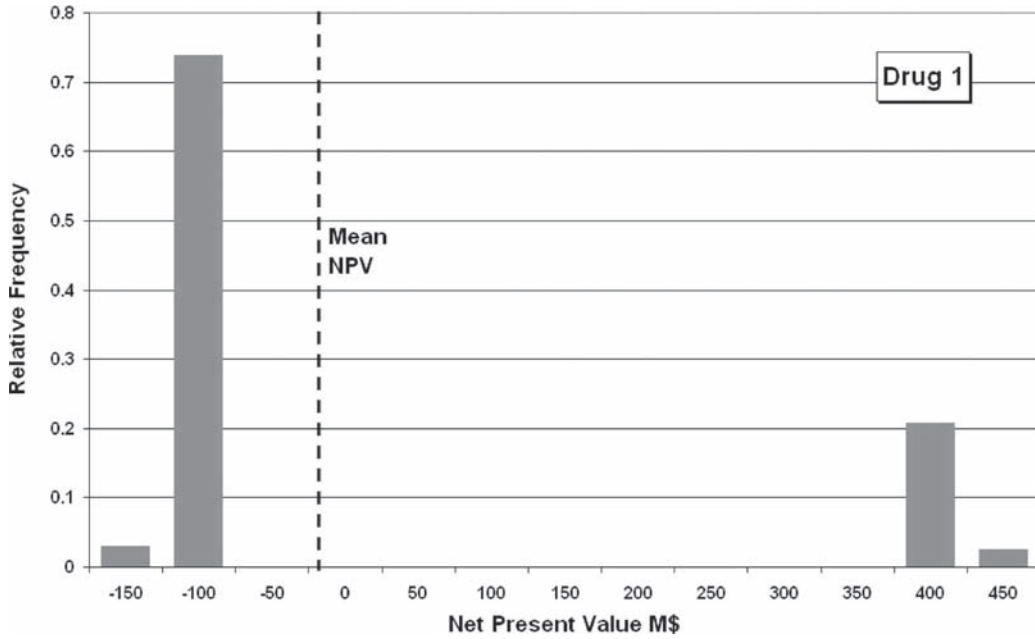


Figure 3. Relative frequencies for product/project 1.

value (NPV) is computed by cumulating each of its intermediate values. The computation of the net present value can be summarized as

$$NPV_{\text{drug}} = \sum_m \frac{-c_m + r_m}{(1+i)^{d_m}} \quad (1)$$

where c_m is the cost for a given drug m , r_m is the sales revenue for the same drug m , d_m is the makespan for a sequence, and i is the interest rate considered in this work.

A reward/loss ratio (A) is obtained by dividing the mean reward (mean of positive values of NPV) by the mean loss (mean of negative values of NPV). This ratio A gives the attractiveness of the project under consideration and can be used to refine the decision concerning drugs to be launched.

Figure 3 represents the relative frequency for NPV values for the first drug. In all cases, there is a higher frequency for negative values (losses) than for positive values (rewards). This is due to the values of the failure probabilities (mainly in phase II), which cause the drug to be stopped before it reaches the mature sales stage. In Figure 3, the mean NPV corresponds to the mean value of NPVs obtained from each of the 300 simulations. When a drug fails at one of the trial phase, its NPV has a negative value. The only occurrence of a positive NPV corresponds to a product that succeeds at all phases. Therefore, the NPV distribution presents two modes: one for negative NPVs and another for positive NPVs. Because this distribution is bimodal, there is no real solution corresponding to the global mean value. This is valid for all of the examples treated in the article. When considering the

global mean NPV, one must be aware that this represents only as a statistical parameter indicating whether real solutions tend toward negative or positive values. The same trends were observed by Blau et al.⁵

To represent the NPV trends more clearly, the maximum and mean values for the NPV related to each drug are used to compare the behaviors of the various drugs. As mentioned above, another item for choosing a strategy is the attractiveness A , defined as the ratio of mean positive NPV value (reward) to the mean negative NPV value (loss) reported in Table 3. The ranking is established by performing a tradeoff between max NPV, min NPV, and ratio A . The best solution is drug 7, followed by drugs 1, 3, and 5; drug 4 is the worst solution.

Bubble Chart Ranking. A bubble chart is a graphical technique used in the pharmaceutical field for ranking projects (see Figure 4). Each drug is plotted in a bubble format with capital (investment) cost as its diameter, according to its success probability (x axis) and attractiveness A (y axis). Obviously, the best solutions are located at the upper-right side of the bubble chart and must have diameters that are as small as possible.

The same example as in the previous section is treated here. The ratio A is reported in Table 3. Assuming independent success probabilities for phases I, II, and III, the overall success

probability is the product of the three individual probabilities (see Table 4). The average value of the capital cost is used to define the bubble size, as proposed by Blau et al.⁵ and reported in Table 4.

Clearly, the bubble chart shows two groups of solutions: the good ones consisting of drugs 3, 5, 7, and 9; the bad ones involving drugs 2, 4, 6, and 8; and an intermediate one, drug 1. Except for rank one, where it is difficult to conclude among drugs 7, 5, and 3 because they have practically the same success probabilities, drug 7 is better regarding ratio A , but drugs 5 and 3 are better in terms of capital cost. Finally, we chose to rank drug 7 in first position followed by drug 3. It can be highlighted that drug 7 is ranked first for the two types of rankings (simulation and bubble chart), with the pair of drugs 8 and 4 being the worst solutions. Therefore, the two types of ranking procedures give the same trends.

Weighted Attractiveness. In the two previous sections, attractiveness is used as a criterion for ranking solutions. However, this ratio does not take into account the frequencies of positive and negative values of NPV. That is why the weighted attractiveness (WA) can be used

$$WA = \frac{[(\text{frequency of values} > 0) \times (\text{mean NPV} > 0)]}{[(\text{frequency of values} < 0) \times (\text{mean NPV} < 0)]} \quad (2)$$

Table 3. Drug Ranking According to Attractiveness

drug	max NPV	mean NPV	pos	neg	A	rank
1	455	-20	404	102	3.96	2
2	393	-50	400	101	3.96	3
3	410	24	358	101	3.54	4
4	259	-20	217	100	2.17	9
5	403	20	314	100	3.14	6
6	355	-55	323	101	3.20	5
7	717	105	575	102	5.64	1
8	291	-55	254	101	2.51	8
9	267	-30	250	100	2.50	7

The ranking according to simulation (established by performing a tradeoff between max NPV, mean NPV, and WA) is reported in Table 5. The best solution is drug 7, followed by drugs 1, 2, and 3; drug 4 is the worst solution. The rankings with the ratios A and WA are similar.

The new bubble chart is presented in Figure 5 with the ratio WA instead of the ratio A . For the best solutions, namely, drugs 7, 3, 5, and 9, the two charts are globally the same. Figure 5 exhibits more concentrated worse solutions than in the previous case. The ranking reported in Table 4 is globally valid when the ratio WA is used.

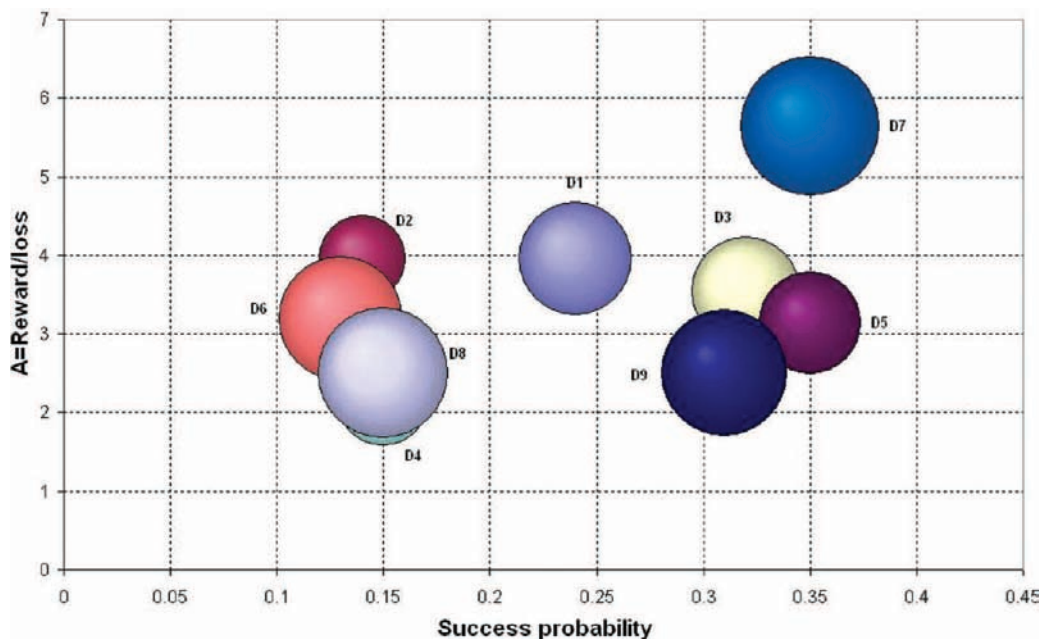


Figure 4. Bubble chart for all products/projects.

Table 4. Success Probability by Product

product	disease	phase 1	phase 2	phase 3	overall probability	capital cost (M\$)	DoD	BC ranking
1	III	0.9	0.3	0.9	0.24	50	5	5
2	I	0.85	0.2	0.85	0.14	30	2	6
3	I	0.95	0.35	0.95	0.32	45	8	2
4	II	0.87	0.22	0.8	0.15	34	9	8
5	II	0.97	0.36	0.99	0.35	40	3	3
6	I	0.83	0.18	0.86	0.13	60	7	7
7	I	0.94	0.4	0.94	0.35	75	1	1
8	II	0.86	0.2	0.88	0.15	65	4	9
9	II	0.98	0.34	0.92	0.31	62	10	4

Table 5. Drug Ranking According to Simulation and Weighted Attractiveness

drug	WA	rank	drug	WA	rank
1	1.24	3	6	0.48	6
2	0.59	5	7	2.79	1
3	1.52	2	8	0.48	8
4	0.41	9	9	1.07	7
5	1.48	4			

In conclusion, it can be emphasized that, even though the weighted attractiveness ratio gives more accurate information, the ratios *A* and *WA* lead to similar conclusions concerning the drug ranking of the considered example both by simulation and by bubble chart.

Sequence Simulation. Product development is generally influenced by the other products considered in the pipeline and by competitor products. Traditionally, four frequently occurring types of dependencies are taken into account, as discussed in the following subsections:

Financial Return Dependencies. Competition between similar products reduces the profit for each one because a smaller part of the market is gained; this is true for products coming from the same company or from other companies. This dependency gives a relation for sales taking into account the quantity of products that will arrive until the stage of mature sales (*MS*). For a given sequence of products for the same disease, if two drugs (or three or four) arrive before stage *MS*, sales for each drug will be 0.85 (or 0.75 or 0.60, respectively) of the values for sales for every drug.

Technical Dependency. This type of dependency modifies the success probability. On one hand, if the first drug in the sequence of drugs targeted for disease *I* fails, the probability of technical success for all succeeding drugs decreases by 50%. On the other hand, if the first in the sequence for testing disease *I* succeeds, the probability of technical success for all succeeding drugs for disease *I* increases by 10%. It must be emphasized that this technical dependency is not quite common in the pharmaceutical industry and is even a controversial issue, according to our fruitful discussions with French pharmaceutical managers. This explains why it was not taken into account in the modeling of this work.

Manufacturing Cost Dependency. Manufacturing cost dependencies occur when the combined cost of a development activity for two similar drug candidates is less than the sum of the cost of the individually considered projects. This is taken into account as follows: For any sequence of drugs for disease *I*, the first drug uses full capital, the second (or third or fourth) drug in the sequence uses one-half (or one-third or one-fourth, respectively) of its individual capital.

Resource Dependency. Learning effects frequently lead to resource dependencies. A common example occurs when the development times are reduced when taking into account the experience gained by developing two functionally similar drug types one after the other.

Ranking with Positivity Probability. A sequence is defined by a set of drugs launched in a given order into the pipeline. The definition of a sequence of drugs is a piece of required information by the discrete event simulation model. The 10 sequences of Table 6 were randomly defined. For each row of this table, the numbers represent the launching ranks; a zero means that the drug is not launched. Note that sequence 3 involves drug 7, the best prospect according to the previous studies, in the “pole position”. In sequence 4, the two best solutions, namely, drugs 7 and 3, as found with the bubble chart analysis are in positions 1 and 2. As in the two previous studies, each simulation was repeated 300 times, selecting random sampling values from a uniform random number generator to define successes and failures.

Frequencies for drugs of sequence 1 are displayed in terms of phases of the pipeline in Figure 6. The highest failure frequencies are obtained for stage 2. Stages 1 and 3 have frequencies located in the same range of values. This is because the success probability values are quite similar for phases *I* and *III*, whereas the success probability of phase *II* is much lower (see Table 4).

The mean NPV related to each sequence can be used to rank the sequences. Another measure of performance commonly used is the positivity probability, defined as the number of times the NPV was positive divided by the total number of runs; it is reported in Table 7. The ranking of sequences is established by performing a tradeoff between the mean NPV and the positivity probability. The best solutions are sequences 4, 7, and 10, and the worst are sequences 2 and 9.

The best solution (sequence 4) involves drugs 7 and 3 in the first and second positions, respectively. These solutions are now identified as the best ones, when the drugs were studied individually. On the other hand, sequence 7, where drug 8, one of the worst solutions identified in the previous studies, is in the pole position, is in second rank. Therefore, it seems difficult to correlate the performances of sequences with those of each drug.

Ranking with Weighted Attractiveness. In this case, the weighted attractiveness (*WA*) is used instead of the positivity probability (*PP*) for ranking sequences. The ranking of sequences is now established by performing a tradeoff between mean NPV and *WA* and remains the same as in the previous subsection.

Partial Conclusion. Concerning the release of only one drug into the pipeline, simulations with statistical indicators such as the mean

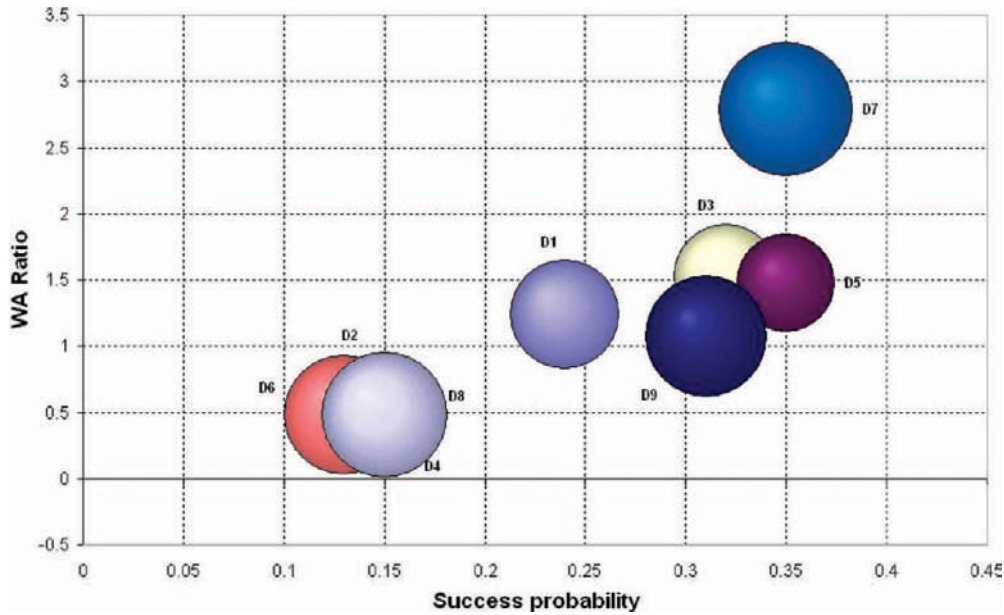


Figure 5. Bubble chart according to weighted attractiveness.

Table 6. Sequences Considered

sequence	P1	P2	P3	P4	P5	P6	P7	P8	P9
1	6	0	4	7	1	0	5	3	2
2	3	9	4	7	1	8	5	6	2
3	5	2	7	8	3	6	1	4	9
4	4	0	2	0	6	5	1	0	3
5	4	1	0	0	0	2	3	5	6
6	4	2	1	3	5	0	0	0	0
7	5	0	4	0	2	3	6	1	0
8	2	3	0	7	1	6	0	5	4
9	1	0	0	0	4	5	0	3	2
10	1	0	3	0	4	0	6	2	5

NPV and attractiveness give the same results as the bubble chart ranking method with either attractiveness or weighted attractiveness.

When sequences of drugs are launched into the process, the mean NPV can be considerably increased compared to that obtained for only one drug. However, the NPV can vary sharply from one sequence to another. Sequences are ranked according to two pairs of indicators, namely, mean NPV and PP or mean NPV and WA: the obtained results are identical. Sequences with all of the drugs launched give poor results, and the best results are obtained for sequences involving six and four drugs. Furthermore, when a sequence involves drugs with good (bad) individual performances, its ranking is good (bad).

In this example, a strict comparison with the solutions obtained by Blau et al.⁵ was not carried out because the technical dependency was not taken into account in this work.

RESOURCE CAPACITY MANAGEMENT

To analyze the impact of changing resource capacities at each stage of the system, two cases are now considered. First is a case with a limited capacity by stage (see Table 2): resource is reallocated only once a drug emerges from a stage. This study was carried out in the previous sections. In the new case, there is no limited

capacity for stages (unlimited capacity). First the sequence (1, 2, 3, 4, 5, 6, 7, 8, 9) is launched in that order into the pipeline. For the sake of illustration, a particular sequence was selected among the 300 sequences simulated. The results are reported in Figure 7. Only two drugs (1 and 9) completed all of the processes with positive NPVs. In the Gantt chart located at the top of the figure, some spaces between tasks represent waiting times for an available resource before proceeding to the next step. For drug 9, launched in the last position, the waiting time is greatest because some processing steps are occupied by drugs launched before it; as a result, its makespan is highest. The NPV of this solution is -333 M\$, with a mean makespan of 3733 days.

The same sequence was studied again without limitations on resource capacity (see Figure 8). In that case, drugs do not wait for a resource considering its capacity. As shown in the Gantt chart, four drugs (1, 5, 7, and 9) have now positive NPVs. Because of the unlimited resources, the makespan globally decreases. The new NPV of this solution is 114 M\$, with a mean makespan of 3100 days. Obviously, performances increase when constraints are relaxed.

COMBINING DISCRETE EVENT SIMULATION AND INTERVAL ANALYSIS

Imprecision Modeling. As extensively discussed in Klir and Wierman,¹³ uncertainty can be considered to be the result of some information deficiency: the information to form the basis of a certain model might be incomplete, imprecise, fragmentary, not fully reliable, or vague. As a result, these various information deficiencies are associated with different types of uncertainty, which can be modeled by different well-established theories, for instance, classical set theory, fuzzy set theory, probability theory, and possibility theory. Our analysis is restricted to imprecision modeling, which is prevalent in the problem definition and which occurs due to partial lack of information. Traditionally, two classes of methods of imprecision representation have become prominent: probability theory and nonprobabilistic uncertainty modeling. The former class attempts to model uncertain parameters as random variables. The latter class includes interval

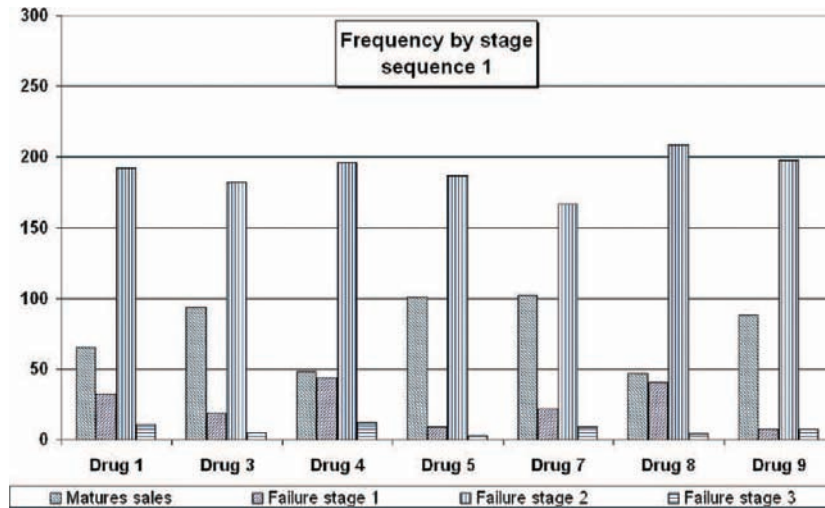


Figure 6. Relative frequencies for sequence 1.

Table 7. Ranking of the 10 Sequences

sequence	mean NPV	PP	rank	sequence	mean NPV	PP	rank
1	240	0.40	5	6	410	0.35	4
2	70	0.35	10	7	650	0.36	2
3	120	0.38	7	8	150	0.35	6
4	680	0.42	1	9	70	0.38	9
5	125	0.33	8	10	600	0.40	3

computation and fuzzy set theory. Fuzzy set theory has indeed been considered as a powerful alternative for several years, with many applications in various fields.^{14–16} Its idea is to quantify uncertain model parameters by using fuzzy numbers and to trace the propagation of the uncertainties through the system by using fuzzy arithmetic. The advantage of this approach over the method of interval computation is to express parametric imprecision by fuzzy numbers, representing the more or less possible values of some parameters.

Probability Methods. According to the theory of probability, uncertain model parameters are represented by random variables and quantified in terms of a probability density function. The computation of the probability density function of the model outputs is then performed in a numerically using Monte Carlo methods. This means that the models are evaluated for a large number of combinations of parameter values, generally generated randomly according to a predefined distribution. However, the application of probability theory assumes that historical data exist for each unknown parameter involved in the process. This might not be true in the case of new product development because this phase is, by definition, at a preliminary stage. Moreover, probability measures are not well-suited to express the intrinsic fuzziness of natural language that is used to verbally quantify imprecise information.

Interval Modeling and Fuzzy Methods. *Interval Modeling.* Interval modeling is a very popular and elementary nonprobabilistic uncertainty model. It is generally applied in the form

$$X = [x_l, x_r] = \{x \in \mathbb{R} \mid x_l \leq x \leq x_r\} \quad (3)$$

Intervals represent an appropriate model to mathematically describe uncertainty in those cases where only a possible value range between crisp bounds x_l and x_r is known for the uncertain quantity and no additional information concerning variations, fluctuations,

value frequencies, preferences, and so on, between interval bounds is available, nor are there any clues as how to specify such information.

A sound theoretical basis has been developed for the mathematical treatment of interval-valued quantities.^{17–20} This represents the fundamental means for extending engineering computations to dealing with intervals. Generally, interval analysis consists of the mapping of interval input quantities X_i to interval result quantities Z_j . The major beneficial feature of interval modeling concerns the enabling of best- and worst-case studies in absolute terms at a reasonable numerical cost as a result of the direct search for these cases.

A limitation of the interval model is, however, its binary treatment of information. An element either belongs to the interval, or it does not belong to the interval. A gradual assignment of elements to the interval or a weighting of elements within the interval cannot be taken into account. Consequently, the degree of confidence that a particular event occurs—as needed, for instance, in safety assessments—cannot be deduced using interval quantities alone.

Fuzzy Set Modeling. A direct generalization and enhancement of the interval model is a fuzzy set.^{21–25} This represents an extension of the interval by a component of gradual assignment; the interval internal values $x \in [x_l, x_r]$ are assessed or weighted with the aid of membership values, $\mu(x)$, from a continuous scale. The semantics of the membership values $\mu(x)$ can generally be categorized into three groups to express similarity, preference, or uncertainty. This semantics of $\mu(x)$ is relevant, for example, in the fields of fuzzy control and regression analysis.

An understanding of membership degrees as preferences utilizes a numerical expression of the intensity of being in favor of the associated elements x of the fuzzy set. The membership values $\mu(x)$ also serve as the basis for subsequent considerations. An association with possibility theory exists insofar as the membership values $\mu(x)$ can be understood as the degree of possibility with which the underlying uncertain quantity can take on the associated values x . The membership scale is usually normalized with the bounds of 0 for no membership and 1 for full membership. Specifically, a normalized fuzzy set is described by

$$\tilde{X} = \{(x, \mu(x)) \mid x \in \mathbb{R}, 0 \leq \mu(x) \leq 1\} \quad (4)$$

The concept of fuzzy sets in its present form was initially formulated by Zadeh²¹ almost 50 years ago, after which considerable

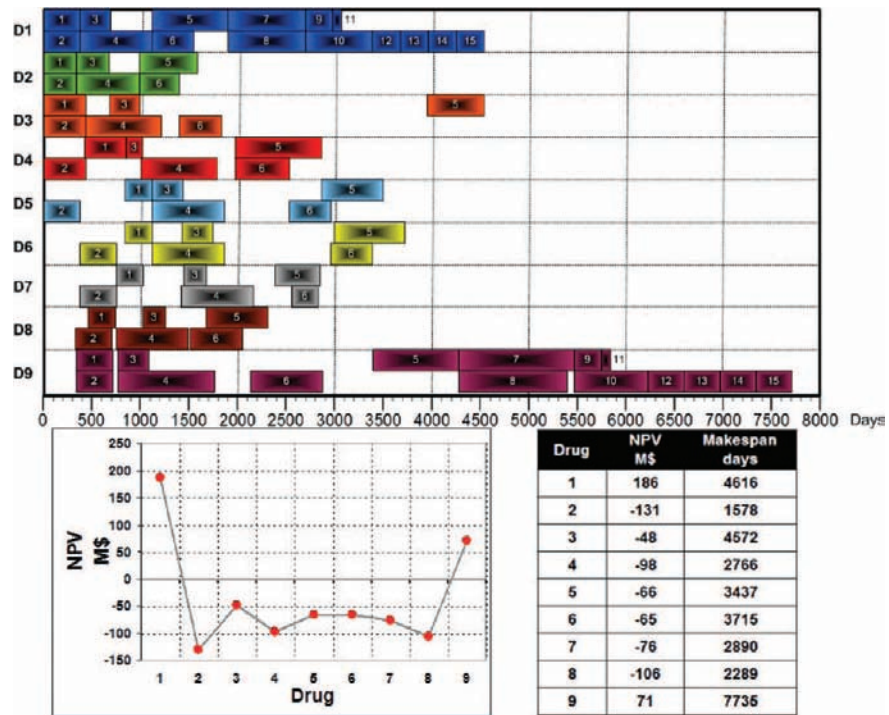


Figure 7. Simulation with capacity constraints.

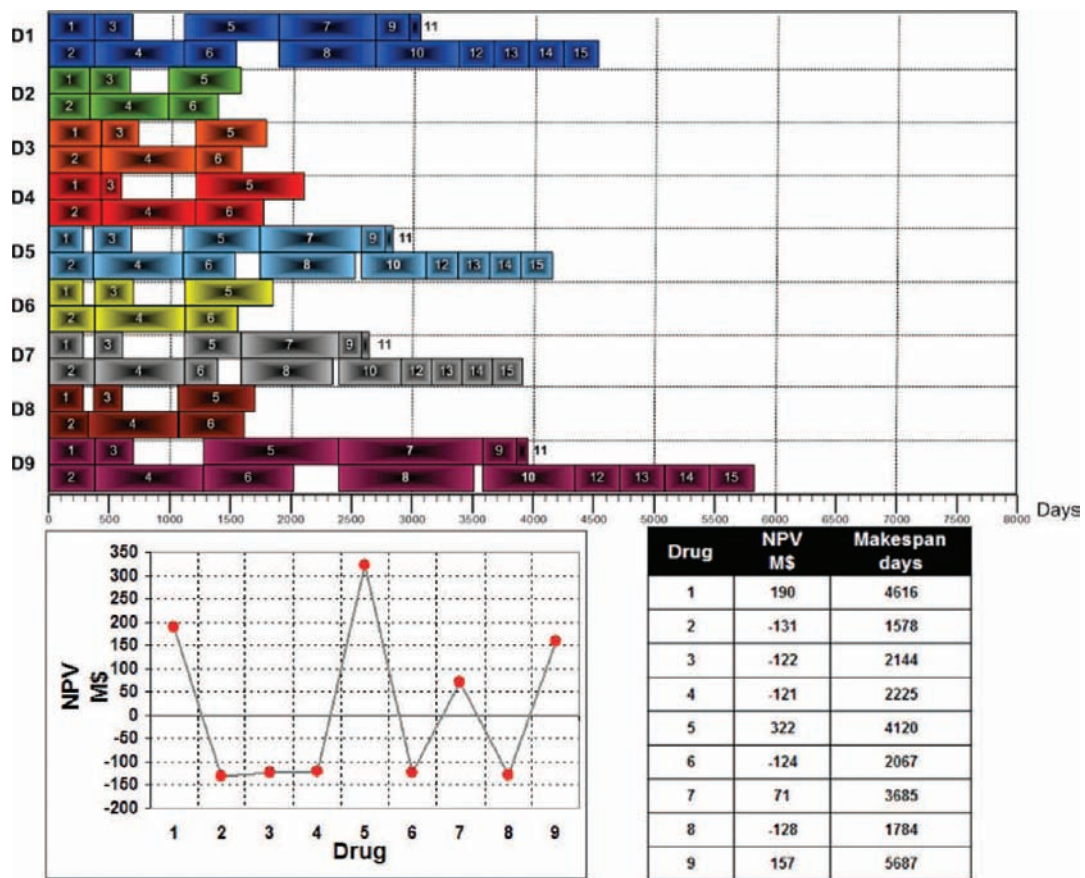


Figure 8. Simulation without capacity constraints.

developments have been reported and summarized in comprehensive books.^{22–25} In basic mathematics literature, the connection of fuzzy sets \tilde{X}_i to produce fuzzy results \tilde{Z}_{ij} , which is referred to as fuzzy analysis, is solved with the aid of the extension principle. This includes both the mapping model f for computing result values $z_i \in \tilde{Z}_j$ from input values $x_i \in \tilde{X}_j$ and a rule for specifying the membership values of the result values.

In the processing of fuzzy quantities through engineering computations, the original form of the extension principle has been revealed as being unsuitable for implementation in numerical algorithms. Thus, an alternative method of solution for fuzzy analysis has been developed based on α -discretization and the use of α -cuts.

Selection of the Imprecision Modeling Technique: Interval Modeling versus Fuzzy Set Concepts for NPD Problem. The integration of fuzzy set theory in discrete event system simulation to cope with the representation of qualitative uncertainty has already been studied.^{26–28} Fuzzy and temporal logics can be combined to establish a temporal-logic-based simulation system that is capable of handling possibilistic values of both system state variables and event occurrence times. The problem of processing fuzzy data within a discrete event simulation process was discussed by Grieco et al.,²⁶ and new methods that are able to avoid time paradox problems have been proposed.

A previous work²⁹ developed a discrete event simulation model of an industrial production system using fuzzy concepts to represent uncertainties in the performance of people (time and duration of their intervention). The work focused on semiconductor manufacturing, but its approach can be applied to other kinds of batch processes presenting similar features. A solution to the problems related with the management of fuzzy uncertainty in discrete event simulation is proposed. Recently, fuzzy uncertain durations³⁰ have been considered, in which a fuzzy ranking measure is merged with an activity scanning simulation algorithm for performing fuzzy simulation time advancement and event selection for simulation experimentation.

Although many types of fuzzy sets²¹ have been used to describe uncertainties, triangular and trapezoidal fuzzy sets are very often used in applications because the parameters defining them can be easily specified in linguistic terms.³¹

It must still be emphasized that data gathering (a four-tuple for each duration) is a hard task in a production environment. This is all the more true for NPD management problems, for which the degree of imprecision can be higher. Hence, subjectivities in selecting distributions and estimating related parameters are unavoidable. This explains why only an interval analysis was performed here and preferred to a fuzzy method. It must also be highlighted that the imprecision resulting from probability success parameters was not taken into account in this imprecision analysis.

Discrete Event Simulation and Interval Analysis. The combination of interval analysis with discrete event simulation to handle subjectivity, vagueness, or imprecision in estimating activity durations and capital costs in NPD problems is presented in this section. In particular, application to the control of interval-time advancement and event selection for the simulation experiment of discrete event simulation is described. Illustrations of interval analysis (IA) with discrete event simulation and an example that compares the IA discrete event simulation with a traditional Monte Carlo based simulation are also provided. The IA discrete event simulation focuses on considering time values as intervals instead of crisp numbers. In other words, the processing time and arrival time of entities are influenced by ill-defined uncertainty, and event occurrence is represented by

interval analysis. From a theoretical point of view, no difference exists between classical and interval analysis simulations because only the formalism used to represent variables (i.e., event occurrence times) changes. The following steps are performed:

- Initiation of a start event or activation of an activity, where the start time of an activity is determined: $T^S(i) = \max_{j=1, \dots, J} T^A(i, j)$, where J is the set of entities (i.e., resources and logical dependencies) required by activity i , T^S is the start time of activity i , and $T^A(i, j)$ is the available time of entity j at activity i .
- Determination of the due time of an end event, which should equal the start time of the current activity plus its activity duration: $T^{EE}(k) = T^S(i) + D(i)$, where $T^{EE}(k)$ is the due time of end event k , recorded in the end event list, and $D(i)$ is the duration of activity i .
- Simulation advancement and end event selection, that is, updating of the simulation from the current time to the time of next event or more end events that will happen, when the start and end events that are due at the updated simulation time are selected for initiation: $m_Now = \min_{k=1, \dots, K} T^{EE}(k)$, where m_Now is the simulation time and K is the number of end events recorded in the end event list.

When intervals are used to represent activity durations, all of the times in the above operations become intervals. Hence, the above operations can be expressed in interval arithmetic.

Interval Arithmetic. Interval theory has a well-developed specific arithmetic in which the main arithmetic operations are defined in terms of real arithmetic operations and applied to interval bounds. Given $a, b \in \mathbb{R}$, where $a < b$. Then, the subset $\{x \in \mathbb{R} \mid a \leq x \leq b\}$ is an interval of real values, or simply an interval, that is represented by $X = [a, b] = \{x \in \mathbb{R} \mid a \leq x \leq b\}$. Let $A = [a, b]$ and $B = [c, d]$ be two interval numbers. The basic arithmetic operations of addition, subtraction, multiplication, and division of these two interval numbers are defined as follows:

$$[A] + [B] = [a, b] + [c, d] = [a + c, b + d] \quad (5)$$

$$[A] - [B] = [a, b] - [c, d] = [a - d, b - c] \quad (6)$$

$$[A] \times [B] = [a, b] \times [c, d] = \quad (7)$$

$$[\min(a \times c, a \times d, b \times c, b \times d), \max(a \times c, a \times d, b \times c, b \times d)] \quad (8)$$

$$[A] \div [B] = [a, b] \times \left[\frac{1}{d}, \frac{1}{c} \right] \quad \text{if } 0 \notin [c, d] \quad (9)$$

$$\max(A, B) = \frac{a + b + |a - b|}{2} \quad (10)$$

$$\min(A, B) = \frac{a + b - |a - b|}{2} \quad (11)$$

■ EXTENSION OF THE DISCRETE EVENT SIMULATOR FOR NPD FORMULATION WITH INTERVAL ANALYSIS

Duration and Cost Modeled As Intervals. The imprecise data embedded in the NPD problem discussed in the previous sections involve the duration and operating cost for each stage, as

Table 8. Example of Interval Data Design for Drug 1

stage	interval value for duration (days)	interval value for cost (M\$)
first human dose preparation	[384, 416]	[77, 83]
sample preparation	[384, 416]	[1.9, 2.1]
phase I	[288, 312]	[76, 83]
process development 1	[768, 832]	[9.5, 10.5]
process development 2	[768, 832]	[9.5, 10.5]
phase II	[480, 520]	[77, 83]
phase III	[744, 806]	[190, 210]
design plant	[720, 780]	[9.5, 10.5]
FSA	[360, 390]	[19, 21]
build plant	[720, 780]	[60, 64]
prelaunch	[96, 104]	[48, 52]
launch I	[336, 364]	[11.4, 12.6]
launch II	[336, 364]	[21, 23]
launch III	[336, 364]	[39, 41]
mature sales	[336, 364]	[51, 55]

well as the mature sales and capital cost for each drug. All of these parameters have been represented by a triangular representation, based on the experience of pharmaceutical managers; for the second group of parameters related to each drug, the concept of degree of difficulty (DoD) introduced by Blau et al.⁵ was used to reflect the more or less difficult way to develop a drug. Recall that it takes on values ranging from 1 (low difficulty) to 10 (high difficulty) (see Table 4). The resources required for a drug candidate with a degree of difficulty of 5 represent an average value. The degree of difficulty is then used to scale the resource cost distributions in a linear fashion. The example that serves as an illustration here is the nine-drug portfolio presented and analyzed in detail in the previous section. The aforementioned parameters have been designed as intervals $A = [a, b]$ as follows:

- For the duration and operating cost for each stage, the bounds of interval A are taken as equal to the average value of the initial data $\pm 4\%$.
- For the mature sales and capital cost for each drug, the bounds of interval A are taken as equal to the value deduced from DoD $\pm 4\%$.

The value of $\pm 4\%$ was considered first to examine the effect of imprecision propagation along the pipeline process and to verify that it does not impede result interpretation and decision making.

For the considered example, this procedure leads to the interval parameters relative to drug 1 listed in Table 8.

Parallel Activities. Although the NPD problem is mainly linear, some parallel stages are involved for which the following stage can start only when all parallel stages have finished. Consider two parallel stages, P_1 and P'_1 , and their associated end dates $t_1 = [a_1, b_1]$ and $t'_1 = [a'_1, b'_1]$.

The earliest date t_2 at which the following stage P_2 can begin can be computed as

$$\begin{aligned} t_2 &= \max[(a_1, b_1), (a'_1, b'_1)] \\ &= [\max(a_1, a'_1), \max(b_1, b'_1)] \end{aligned} \quad (12)$$

The waiting time, WT, of one parallel item can thus be computed as either

$$WT = \max(t_1, t'_1) - t_1 = \max(0, t'_1 - t_1) \quad (13)$$

or

$$WT = \max(t_1, t'_1) - t'_1 = \max(t_1 - t'_1, 0) \quad (14)$$

$$t_1 - t'_1 = (a_1, b_1) - (a'_1, b'_1) = (a_1 - b'_1, b_1 - a'_1) \quad (15)$$

Finally

$$\begin{aligned} WT &= \max[(0, 0), (a_1 - b'_1, b_1 - a'_1)] \\ &= [\max(0, a_1 - b'_1), \max(0, b_1 - a'_1)] \end{aligned}$$

Net Present Value Computation. The computation of the net present value can be summarized as

$$NPV_{seq} = \sum_{\text{drugs}} \sum_m \frac{-[c_m^-, c_m^+] + [r_m^-, r_m^+]}{(1+i)^{d_m^-, d_m^+}} \quad (16)$$

where NPV_{seq} is the net present value of a given sequence, m represents a step of the NPD pipeline relative to a drug, $[c_m^-, c_m^+]$ represents the cost interval for a drug at step m , $[r_m^-, r_m^+]$ represents the sales interval for a drug at step m , $[d_m^-, d_m^+]$ represents the duration interval for a drug at step m , and i is the actualization rate.

In this expression

$$(1+i)^{d_m^-, d_m^+} = [(1+i)^{d_m^-}, (1+i)^{d_m^+}] \quad (17)$$

■ SIMULATION EXAMPLE

The simulation example that serves as a test bench is investigated here in an interval-based fashion. The objective is to compare the results obtained by the two analysis approaches: (a) using interval discrete event simulation and (b) using traditional simulation with stochastic parameters. The idea is to determine whether the interval approach is sound in the NPD problem, meaning that it does not induce too large uncertainties at the end of the simulation of the whole process, which is often considered as a major drawback for both fuzzy and interval-based approaches. Consequently, with such information, it is difficult for the decision maker to reach a conclusion.

Ideal Simulation for Each Drug (Success Probabilities Equal to 1). Some preliminary simulation runs were performed considering a success probability equal to unity at each critical step of the NPD pipeline (phases I, II, and III). The results are displayed in Table 9. It must be highlighted that the spread of uncertainty is highest for the step related to sales involved at the final stage of the process: this can be explained by the cumulated uncertainty influence of time and cost at the latest stage of the process.

The results are also compared with those obtained with the probability approach. It can be clearly observed that the NPV deduced from the probabilistic approach corresponds approximately to the average value of the interval bounds.

Ideal Simulation for 10 Sequences (Success Probabilities Equal to 1). In this section, the 10 sequences that were previously investigated have been considered for simulation with interval data. The results for the first sequence are displayed in Figure 9, with a special emphasis on phases I, II, and III and mature sales, where the respective contribution of each drug to the portfolio of the sequence is illustrated. Such diagrams allow for the detection

Table 9. NPV for Nine Drugs Obtained from Interval Analysis (Top Row) and Probabilistic Approach (Bottom Row)

drug	phase 1 NPV (M\$)	phase 2 NPV (M\$)	phase 3 NPV (M\$)	mature sales NPV (M\$)
1	[-111, -107] -109	[-125, -119] -122	[-168, -159] -163	[343, 428] 384
2	[-110, -105] -107	[-132, -126] -129	[-179, -169] -173	[328, 405] 364
3	[-111, -107] -109	[-119, -113] -116	[-157, -149] -153	[287, 380] 331
4	[-111, -107] -109	[-117, -111] -114	[-154, -146] -150	[157, 232] 193
5	[-110, -106] -108	[-130, -123] -126	[-175, -166] -170	[179, 404] 286
6	[-111, -107] -109	[-121, -115] -118	[-161, -152] -156	[249, 350] 297
7	[-109, -105] -107	[-134, -128] -131	[-182, -171] -176	[382, 737] 550
8	[-110, -106] -108	[-127, -121] -124	[-172, -162] -167	[181, 286] 231
9	[-111, -107] -109	[-114, -109] -112	[-150, -142] -146	[210, 251] 229

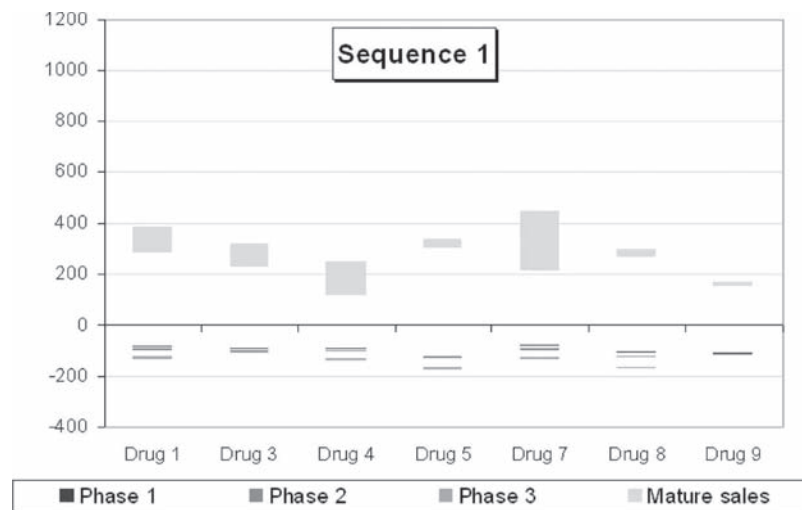


Figure 9. Evaluation of the first sequences with an interval-based approach.

of the major sources of uncertainty in a given sequence. With the help of similar diagrams associated with sequences 2–10 and involving drug 7, it can be seen that drug 7 contributes significantly to the uncertainty.

Simulation for 10 Sequences with Success Probabilities. In this section, the simulation of the 10 sequences has been carried out taking into account the success probability (see Table 4). Because this parameter was not modeled with an interval, a sampling set of simulations was performed. Of course, this hybrid method combining interval and probabilistic approaches is time-consuming, but the objective here is to determine whether the interval concepts need to be investigated in more detail. As previously, 300 simulations were run. The lower (upper) bound of the resulting interval was taken equal to the minimum (maximum) value of the lower (upper) bounds over the 300 simulation interval values. The results are presented in Figure 10

and Table 10. A distinction is made according to the positive and negative parts of the interval (P and N intervals, respectively), to mimic what happens with the bimodal distribution when considering a probabilistic approach. The same approach as described previously was used to build the two intervals corresponding to a sequence. Note that, when an interval overlapped negative and positive values, it was allocated to the negative section. A first comment can be made concerning the mean values obtained from the probabilistic approach. They are all located in the interval. Figure 10 also shows the average value obtained over all values, both positive and negative. For sequence 8, it can be seen that the average is slightly higher than the upper bound of the so-called positive interval. This situation is not paradoxical because the spread of imprecision was not considered equivalent for the two methods. A lower spread was considered for intervals to examine the consistency of this approach for NPD problems.

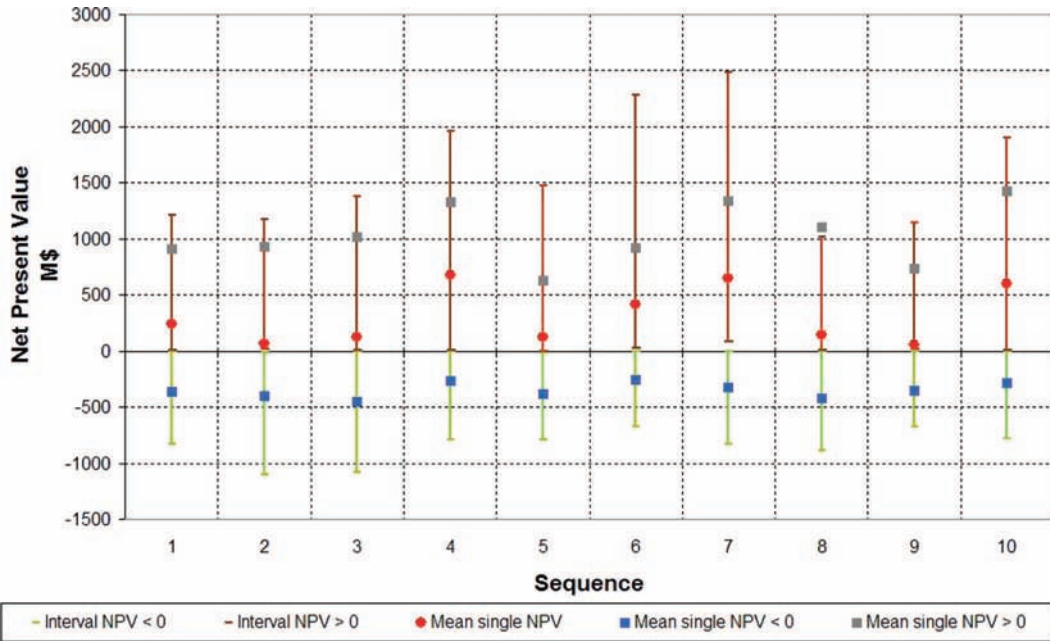


Figure 10. P and N intervals for each sequence relative to NPV.

Table 10. Comparison between Interval-Based and Probabilistic Approaches for 10 Sequences with Success Probabilities (M\$)

sequence	N interval for NPV		mean NPV < 0 (probability)		P interval for NPV		mean NPV > 0 (probability)	
1	-793	-3	-358	11	1111	911		
2	-996	-62	-406	8	1092	926		
3	-1009	-34	-447	28	711	1018		
4	-704	-4	-267	1	1583	1333		
5	-751	-2	-378	38	1619	626		
6	-638	-29	-257	126	1242	916		
7	-936	-1	-324	1	2870	1342		
8	-796	-14	-417	49	1051	1105		
9	-634	-4	-351	160	1076	732		
10	-900	-84	-282	4	2042	1422		

From all of these simulation results, it can clearly be seen that the propagation of uncertainty along the pipeline process is too great and disturbs decision making. The interest of the probabilistic approach is to clearly highlight the two-peaked distribution that is typical of new drug development. Such information is lacking for the interval-based approach. Moreover, the concept of risk might be difficult to appreciate. For all of these reasons, the examination of the interval-based approach was not pursued further. Even though this result might be considered negative, we found it to be important to report this study because both interval- and fuzzy-based approaches are attractive candidates to account for imprecision. Yet, it must be said that the typical nature of the problem considered here makes their application difficult.

CONCLUSIONS AND PERSPECTIVES

A discrete event simulator (DES) previously developed in C++ for batch plant scheduling (BPS) has been adapted to the new

product development (NPD) problem. C++ programming has the ability to produce, using the notion of class, modular code that can be easily modified. Among the four layers of the DES, the layers engine and events are the same for the two types of problems. However, some existing objects and classes had to be adapted to the NPD problem, and more specific classes had to be designed.

Then, the DES was evaluated on a recently published work concerning the portfolio management of nine drugs for treating three diseases, four drugs for disease I, four drugs for disease II, and only one for disease III. In all of the numerical studies, because the problem was, by definition, stochastic, each simulation was repeated a large number of times (300), selecting random sampling values from a uniform random number generator to define failure or success for drugs at trial phases. In this evaluation section, the simulations were carried out with limitations on resource capacities.

First, each of the nine drugs was launched alone into the pipeline to evaluate individual performances by means of three ranking methods. The first one was based on the mean net present value (NPV) and the attractiveness A , defined as the ratio of the mean positive NPV to the mean negative NPV. Then, the classical bubble chart ranking commonly used in the pharmaceutical field was implemented. Each drug was plotted in a bubble format, as attractiveness versus success probability, with the diameter of each bubble giving its investment cost. The two previous studies were performed again, using the weighted attractiveness, WA , instead of A . To compute WA , the numerator and denominator of A are weighted by the number of positive and negative NPV values, respectively. It was observed that, even though the weighted attractiveness ratio gives more accurate information, ratios A and WA led to the same conclusions concerning drug ranking for the considered example both by simulation and by bubble charts.

Ten different sequences of the drugs were then investigated. In that case, the mean NPVs were considerably increased compared to those obtained for individual drugs. However, the NPV can vary strongly from a sequence to another. Sequences were ranked

according to two pairs of indicators, namely, mean NPV and PP or mean NPV and WA, and the results were found to be identical. [Note that PP is the positivity probability, defined as the ratio of the number of positive NPVs to the total of runs per sequence (300).] Sequences with all nine drugs launched together gave bad results, whereas the best results were obtained for sequences involving six and four drugs. Furthermore, when a sequence involved drugs with good (bad) individual performances, its ranking was good (bad). Taking into account the highly combinatorial nature of the problem (about one million sequences), all of the sequences could not be exhaustively evaluated.

All of the studies of the present work were carried out under constraints on resource capacities. This constraint was relaxed, and an example with no limited capacity for stages (unlimited capacity) was studied for a particular sequence involving the nine drugs, 1–9, launched in that order. The Gantt charts displayed for the last sequence showed that some waiting times for an available resource disappeared for the unconstrained problem, leading to better performances concerning both the mean NPV and the makespan.

Finally, it must be emphasized that several criteria, namely, the net present value of a sequence, its associated risk (equivalently measured by an attractiveness ratio or by the so-called positivity probability), and the makespan, are important to evaluate a sequence quality and must be considered simultaneously for decision making.

The aim of modeling imprecision with interval analysis was to compare various approaches to model the uncertainty embedded in the NPD problem. Several levels of uncertainty can be identified: those associated with cost and activity durations and those related to the success probabilities involved at three steps of the NPD pipeline (the so-called phases I, II, and III). Two approaches were used: a classical probability approach and an interval-based one. Both approaches were illustrated with a numerical example, which showed that the tendencies obtained by the interval-based approach might be difficult to interpret for the decision maker, because of the growing uncertainty along the pipeline. In addition, the risk, which is taken into account through failure probability for some stages and which is strongly involved in the NPD process, must be an integral part of the modeling approach. At this level, it was difficult to model this parameter by an interval approach, and the repetitive use of simulations with representative sampling was the procedure employed to address this issue. All of these reasons explain why there is no need to develop a proper interval-based framework for NPD problems with uncertainty. Further work will now be focused on implementing an optimization strategy to try to find the optimal sequence, naturally incorporating the decision of which drugs to launch.

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■ ACRONYMS

BC = bubble chart
 DES = discrete event simulation
 DoD = degree of difficulty
 FDA = Food and Drug Administration
 FSA = first submission for approval
 IA = interval analysis
 NPD = new product development

NPV = net present value

WA = weighted attractiveness

WT = waiting time

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