Optimization Issues in Chemotherapy Delivery

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6

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6.1. Background presentation

Cancer chemotherapy involves a group of substances that prevent or even kill cancer cells. The manufacture of cancer chemotherapy agents involves the handling of toxic products and hence it is a complex and expensive process (Maraninchi *et al*. 2016).

Nevertheless, the efficacy of cancer chemotherapy is now established without controversy. It allows us to obtain interesting results in certain pathologies. The active products of chemotherapy treatments are so-called cytotoxic (toxic to the cell) drugs. These toxic products have side effects for the patient, and they also pose risks for the people handling them. These risks related to the preparation and handling of the toxic products are significant. On the other hand, there are many manufacturing constraints to consider: each preparation has a dosage adapted to each patient; the preparation must be ready in time to be administered to the patient and the sterility of the preparation must be guaranteed while protecting the personnel carrying out the preparation.

The *Centre hospitalier régional et universitaire (CHRU) de Tours* occupies a privileged place in the Centre-Val de Loire region in France. At the Bretonneau Hospital, where the *Centre régional de cancérologie Henry S.*

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Kaplan (oncology center) specializing in oncohematology is located, all types of cancer are treated. This center has a pharmaceutical unit called the *Unité de biopharmacie clinique oncologique* (UBCO, the oncology clinical biopharmacy unit), certified ISO 9001, which produces on average 25,000 preparations each year for oncohematology specialties (Datalogic success stories, Aubert *et al*. 2009).

DEFINITION.– ISO 9001 standard (International organization for standardization 9001): this is a standard established to take into account the quality management for a given product. It is based on a certain amount of information provided in a document by the manufacturer and approved by a recognized organization. This document determines the rules, guidelines and characteristics of a product that guarantee an optimum level of order and safety when using the product.

In order to improve the chemotherapy production process and the quality of patient care, several optimization issues have been identified. The following three issues are presented in this chapter (Billaut 2014): the problem of optimizing the production of preparations, the problem of optimizing the consideration of residues and, finally, the problem of optimizing distribution. For each of these, we present an example, a mathematical model of a case and a discussion on the general case.

6.2. Production planning issues

We begin by describing the production environment of a unit like UBCO.

A cancer chemotherapy preparation unit is a controlled atmosphere area. Each preparation device present within the unit is a completely enclosed system called an isolator.

Several types of isolators may exist; a UBCO isolator is shown in Figure 6.1 This device consists of a first part, called the sterilizer, which can contain up to 12 baskets placed on a central rail. Each basket corresponds to a preparation to be made, intended for a patient. All the baskets placed in the sterilizer at the same time are called a “batch”. This then connects with the sterile isolation chamber, where two preparers can work face to face at the same time (on some devices, they are side by side, and on others, more than two preparing stations are available). The preparations made are evacuated

by an airlock, and the waste is evacuated in containers provided for this purpose, placed under the isolation chamber (they are to be incinerated).

The preparation procedures are carried out in accordance with the prescriptions of oncologists.

The different manufacturing phases are described in Figure 6.1.

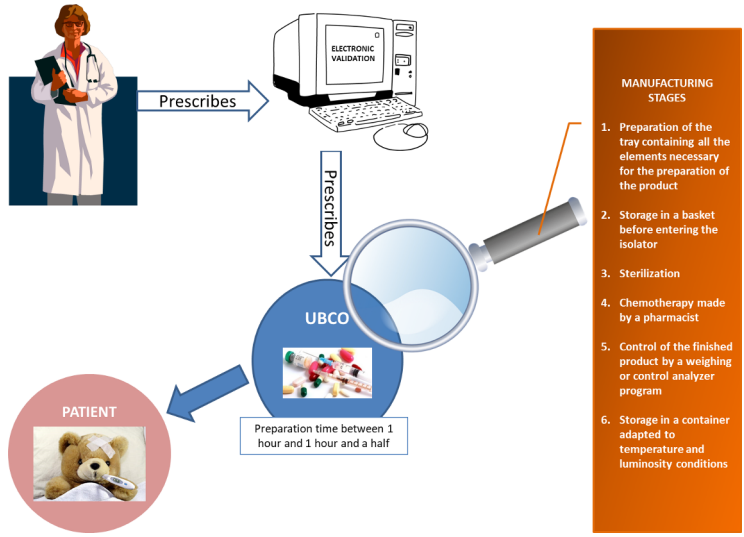

Figure 6.1. *Chemotherapy implementation steps*

The following photographs show an isolator and a sterilizer.

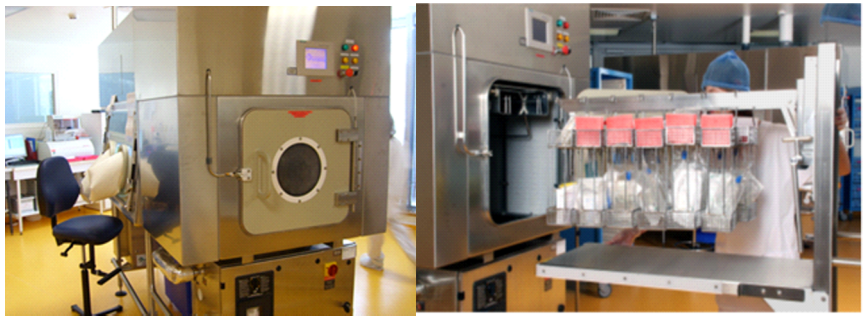

Figure 6.2. *Isolator (left) and part of the sterilizer carrying the baskets (right). For a color version of the figure, please see www.iste.co.uk/sarazin/health.zip*

This production line is covered by additional controls, arriving at different stages.

All these activities have been computerized, and two software programs have been implemented at UBCO to ensure complete traceability of manufacturing (from prescription to patient administration) and to plan activities on a daily basis [6.19]. A total of 10 steps are outlined for each chemotherapy preparation. These are mainly the steps related to the preparation and control of the tray (bags, cytotoxic product, etc.), the sterilization of the elements (equipment number or isolator and load cycle), the preparation (dosages in a controlled environment) and various controls (visual, weighing or analytical).

6.3. Modeling the scheduling problem

It is possible to propose a complete model of the chemotherapy preparation production system (Billaut *et al*. 2014). Such a model makes it possible to study the behavior of the system in the event of an increase in the workload or in the event of a hazard.

However, a complete model is not essential if the objective is to propose a tool to guide the daily production of the service. To provide an interactive decision support tool, a "reduced" model of the production system is sufficient (Mazier *et al*. 2007; Mazier *et al*. 2010) to the extent that some decisions are not made by the system but are deliberately left to a decision-maker.

6.3.1. *Complete model*

In this part, a more generic vocabulary is adopted, which departs from the field of application and approaches scheduling problems (operational research field). In particular, "job" is the making of a preparation; "desired delivery date" is the date by which the preparation must have reached the patient and "machine" is one of the two production lines associated with an isolator (that is, a dispensing pharmacist).

The problem is to schedule a set J of n jobs. Each job J_j is associated with a runtime denoted by p_j (which varies according to the preparations) as well as a desired delivery date (or due date) denoted by d_j. Each job $J_j$is also

associated with a start date at the earliest noted r_j, which corresponds to the approximate date on which validation of the doctor's prescription is expected (in Figure 6.3, the end date of the doctor's visit corresponds to this date r_j). The sterilization time is the same for all jobs, and the inspection time is also the same.

An isolator, that is, a sterilizer, and the two operators associated with it, can be considered as a small two-step production workshop with a "max-batch"-type machine with finished capacity on the first stage and two machines parallel to the second stage. Therefore, there are as many small workshops of this type as isolators. All the jobs have the same production range, which consists of passing through a workshop of this type, then finishing with a single, common machine, which is the one that carries out the control. A Gantt diagram representing the progress of some jobs is shown in Figure 6.3.

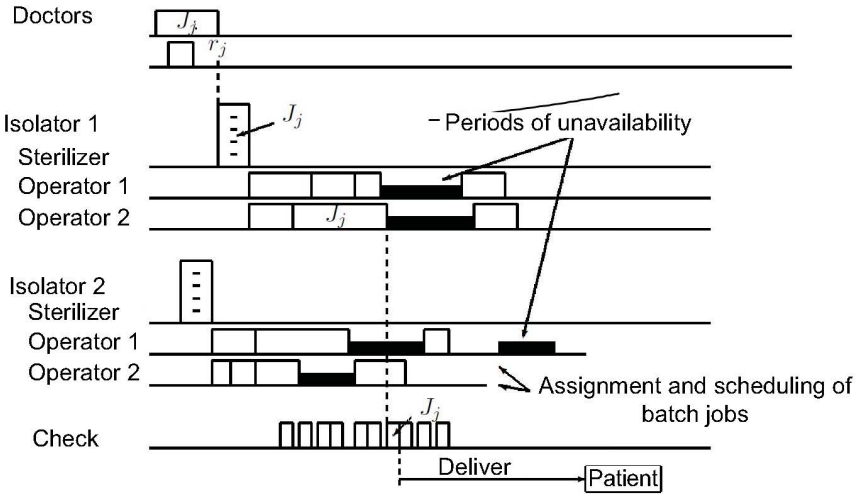

Figure 6.3. *Overall model of the preparation production workshop*

The problem consists of determining, for each job, which isolator is assigned to it and on which date sterilization starts (same date for all job batches); which isolator machine it is then assigned to and on which date it is performed and, finally, on which date the control on the last machine takes place.

Over a time frame of 1 day, UBCO makes about 150 preparations. Given the complexity of this type of production facility, the use of an exact (optimal) method to resolve the entire day's planning cannot be done in a timely manner. To solve this problem, it is thus necessary to have recourse to speed up methods, called "approximates" because they do not guarantee one will find the optimal solution (Tabu method, genetic algorithm, etc.).

6.3.2. *Scale model used*

To propose an interactive decision support method, the planning problem was broken down into the following three phases, naturally leading to a simplification of the workshop model:

1) at each decision moment (approximately every 2 minutes, requests are made to know the new validated prescriptions), an assignment to an isolator of each preparation to be made is proposed;

2) the decision-maker validates certain proposed assignments and sets up his/her own batches to initiate sterilization;

3) when the batches to be sterilized are validated by the decision-maker, assignment and scheduling of the preparations for each compounding pharmacist are proposed.

Assignment to isolators. At a given moment, we denote by J_1 all the jobs to be done, already assigned to an isolator. J_2 is the set of new jobs sent to the department and not assigned to an isolator. Each machine is associated with unavailability periods (allowing for staff arrival times and breaks). Note that two machines are associated with the same isolator.

The procedure involves sorting the jobs of $J_1 \cup J_2$ in the order of the increasing desired delivery dates. Then, the jobs are taken in that order and assigned to the isolator that contains the machine that allows the earliest completion of the job. However, J_1's job remains assigned to the same isolator.

These assignments are proposed to decision-makers in the form of a list (see Figure 6.4). Among all the jobs assigned to an isolator, a decision-maker selects the jobs he/she wants to produce and then starts the calculation that will insert them into the schedule.

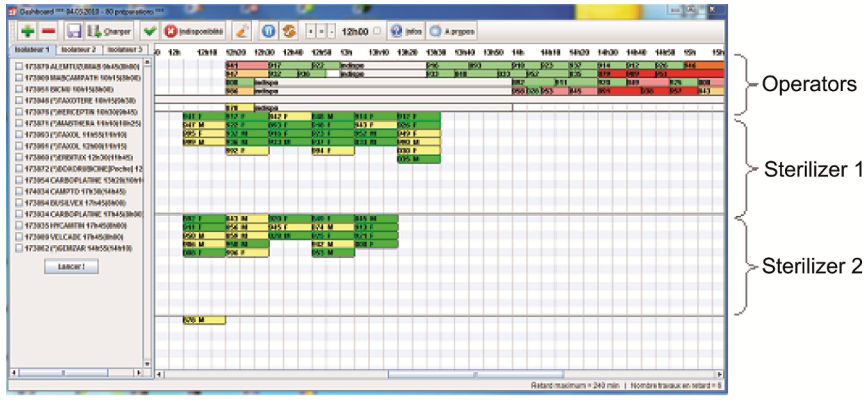

Figure 6.4. *Screenshot showing (left) the list of jobs assigned to isolator 1*

We note that the baskets corresponding to the unselected jobs are stored in a temporary zone, waiting to pass through the isolator (see Figure 6.5).

Figure 6.5. *Storage area for baskets ready for sterilization. For a color version of the figure, please see www.iste.co.uk/sarazin/health.zip*

Scheduling and assignment of tasks. The assignment and scheduling within an isolator is modeled by the following linear program using time-indexed variables [6.10]. We denote by n the number of jobs in the batch to be scheduled and $x_{j,t}$ a binary variable with value 1 if the job J_j is running on the date t and 0 otherwise ($1 \leq j \leq n$ and $0 \leq t \leq H$) with H the

duration of a working day broken into steps of 5 minutes (an amplitude of 10 working hours leads to a value of $H = 120$).

The objective function under consideration aims to reduce patient waiting times. If we denote by T_j late delivery of the preparation J_j, this is the maximum delay function denoted by $T_{max} \geq 0$, defined as $T_{max} \geq max_{1 \leq j \leq n} T_j$, which must be minimized.

The constraints are as follows.

Each job must be fully completed, that is, $\forall j, j \in \{1, \ldots, n\}$:

$$\sum_{t=r_j}^{H} x_{j,t} = p_j \quad [6.1]$$

At any given moment, there can be no more than m_t job in progress, that is, $\forall t, t \in \{0, \ldots, H\}$:

$$\sum_{j=1}^{n} x_{j,t} \leq m_t \quad [6.2]$$

with m_t the number of machines available at the moment t (this allows us to take into account the unavailability of the preparers, known in advance).

Finally, a job cannot be preempted, it must be done in one go. We have $\forall j, j \in \{1, \ldots, n\}$ et $\forall t, t \in \{0, \ldots, H\}$:

$$p_j\left(x_{j,t} - x_{j,t+1}\right) + \sum_{t'=t+2}^{H} x_{j,t'} \leq p_j \quad [6.3]$$

This constraint reflects the fact that as soon as $\left(x_{j,t} - x_{j,t+1}\right)$ becomes 1, in other words, as soon as the job J_j stops, jobs can no longer be performed at any date $t' \geq t + 2$ (the p_j are simplified on each side). In other words, jobs are stopped only once, which prohibits pre-emption.

The objective function takes its value thanks to the following constraints: $\forall j, j \in \{1, \ldots, n\}$ and $\forall t, t \in \{0, \ldots, H\}$:

$$T_{max} \geq t \times x_{j,t} - d_j \quad [6.4]$$

to the extent that the end date of the J_j is the highest value of $t \times x_{j,t}$, its delay is the highest value of $t \times x_{j,t} - d_j$.

The model is written as:

MIN T_{max}

s.c. (1), (2), (3), (4)

$T_{max} \geq 0$

$x_{j,t} \in \{0,1\}, \quad \forall j \in \{1, \dots, n\}, \quad \forall t \in \{0, \dots, H\}$

This model has nH binary variables and O(nH) constraints. With a relatively small value of n ($n \leq 12$) and $T = 120$, that is a maximum of 1,440 variables.

Once this linear program has been solved using a solver (that is, GLPK and Gurobi), the assignment of the job to the machines must be carried out (we know it exists, the constraints guarantee it, but the model does not provide the assignments). By considering each job as a fixed time interval, the definition of a job assignment to machines can be solved by a bicolor problem in an interval graph, which can be solved in polynomial time [6.21].

6.3.3. *Implementation and impact*

The thus obtained solution can very easily be implemented. The machine assignment indicates at the time of entry into the sterilizer on which side of the rail the basket corresponding to the job should be placed and the sequences on each machine indicate in which order the baskets should be placed.

The IT solution was implemented through PLANIF software, which enabled UBCO to switch from a manual management mode for sterilization launches to a tool-guided launch, with a good level of readability on the workload of the day (Tournamille *et al*. 2007).

The PLANIF tool allows the production of jobs to be smoothed over time according to needs, which has had the effect of significantly reducing waiting times for all departments, with sterilization schedules different from those used without the application. From the internal point of view of the operation of the UBCO, the planning made it possible to avoid filling the isolators with non-emergency preparations, to have a margin of safety in the

event of an emergency treatment and to find a significant space saving at the level of the working surface. The average sterilizer load is about seven baskets at a time (Aubert 2009, p. 30).

6.4. Problem linked to the consideration of residues

In this section, we study the circuit used by cytotoxic products necessary for chemotherapy.

6.4.1. *Presentation of the problem*

The bottles of cytotoxic active ingredients, referred to here as raw materials, are stored in specially designed refrigerators. As long as they are not opened or reconstituted, they are considered non-perishable and in infinite quantities. It is assumed that a stock management system is in place to prevent shortages.

Once a bottle is taken out of the refrigerator, it is placed in a basket to make a preparation. In the isolator, the bottle is opened by the dispensing pharmacist and possibly shared by all the preparations that require it. In other words, the same bottles can be used in several preparations, if they are sterilized at the same time.

Once the bottle is opened, the product is activated, and it acquires an expiry date, which depends on the nature of the contents. The product remaining in the bottle after the quantity necessary for preparation has been taken, which is called residue.

Once the batch is finished, if there is still material left in the bottle, it is put back in the refrigerator until it is next used or until it is disposed of because the expiry date has passed.

The raw materials used for cancer treatments have several characteristics:

– They are *very expensive*. Cancer drug prices are described as “exorbitant” and even “unfair” (Maraninchi 2016). For example, Keytruda, used for certain lung cancers and known to have removed Jimmy Carter's tumor, aged 91, is sold at a price of 100,000 euros per year in the United States (Delchaux 2016: about 9,000 US dollars for four bottles of 50 mg). In (Maraninchi 2016), it is stated that “American cancer specialists have

expressed their concerns about the prices of these innovations, moving to see them rise from 10,000 to more than 120,000 dollars per patient per year in fifteen years". These costs are too high for social security (Paillé 2016).

– They are *unstable*. Once reconstituted, a cytotoxic product has a very limited shelf life. In the same way as an antibiotic, once reconstituted, it must be stored in optimal conditions (refrigerator) and consumed relatively quickly, before losing its properties. Data on the physicochemical stability of injectable anti-cancer drugs are not readily available. Studies have been conducted on this stability (Respaud 2011) to avoid their waste. On the other hand, once the preparation has been made, it must be administered to the patient before a certain period of time has elapsed. There is therefore both an expiry period for the residue contained in the bottle and an expiry period for the preparation once it has been made. For example, Eloxatin (used against colon cancer) retains its physicochemical properties for 24 hours after reconstitution and the infusion solution should be used immediately. Oxaliplatin (used against cancer of the large intestine) retains its physicochemical properties for 48 hours after reconstitution and the infusion solution should be used immediately. Dacarbazine (used for the treatment of metastatic malignant melanoma) has a stability of 1 hour after reconstitution, and the stability of the diluted infusion solution is 30 minutes.

However, it should be noted that drug package inserts do not contain preservatives and hence are not intended for multiple use. In other words, the recommendations are to throw away any bottles that are not fully used, and therefore to not have any residues. In Respaud's study (Respaud 2011), it is indicated that a fine management of the residues allowed a saving of approximately 10% of the annual budget of injectable anti-cancer drugs, which represents for 1 year a sum of approximately 750,000 euros.

We place ourselves in this context and propose to optimize the use of the bottles, rather than systematically discarding their contents.

We start by showing the difficulty of the problem in a very simplified environment. We then present a model of the problem in the global environment.

6.4.2. *Special case: one machine and one product*

Let us consider a production workshop composed of a single machine. It is assumed that all the jobs to be performed (which are independent tasks) consume a certain quantity of the same product. Therefore, we only have one anti-cancer drug to use, the same for all the jobs. We need to schedule a set J of n jobs. Every job J_j is characterized by a noted execution time p_j, a desired end date noted d_j and a quantity b_j, the consumption of the product. We know the price of a noted bottle for the product W, the volume of a noted bottle V (it is considered that there is only one possible capacity) and the shelf life of the product in the bottle after reconstitution, denoted by T.

Without loss of generality, it is considered that $b_j \leq V$, $\forall j, j \in \{1, \ldots, n\}$. It is assumed that the time to deliver the preparation to the patient is much longer than the stability of the preparation, so this time is not of concern, but the stability of the product in the bottle after reconstitution is.

It is possible to define new objective functions associated with the consideration of residues (Billaut 2011):

– the first is linked to the economic aspect, in other words, to the costs of discarded products;

– the second is linked to the ecological aspect, in other words, to the quantity of products thrown away.

Since we place ourselves in a static context (the number of jobs is known and fixed), we know precisely the minimum quantity of products to use. This quantity is equal to $B = \sum_{j=1}^{n} b_j$. The minimum number of bottles to open is therefore equal to $F^{min} = \left\lceil \frac{B}{V} \right\rceil$. The mandatory minimum loss is $Q^{min} = F^{min} \times V - B$. If we consider a given scheduling σ, which requires the opening of $F(\sigma)$ bottles (on an $F(\sigma) \geq F^{min}$), then the quantity of product lost is therefore equal to

$$Q(\sigma) = \left(F(\sigma) - F^{min}\right) \times V + Q^{min}$$

The cost of the σ solution is equal to

$$K(\sigma) = W \times F(\sigma)$$

The quantities V, F^{min}, Q^{min} and W are constant (in our particular case, where there is only one type of bottle).

The problem of finding a solution σ that minimizes the quantity of product lost Q (σ) is therefore equivalent to the problem of finding a solution that minimizes the cost of open bottles K(σ) and amounts to minimizing the number of open bottles F(σ).

In order to take into account the desired end dates and not to degrade the solution too much, a tolerance threshold on the value of the greatest delay can be defined. For example, the value of the greatest delay must be less than or equal to a certain value ε. If we denote by C_j the end date of the jobs J_j, then we define the delay of J_j with the variable $T_j = \max(0, C_j - d_j)$ (as before) and the maximum delay per $T_{max} = max_{1 \leq j \leq n} T_j$. We have the following constraint:

$$T_{max} \leq \varepsilon$$

equivalent to

$$C_j \leq d_j + \varepsilon, \quad \forall j \in \{1, \ldots, n\}$$

EXAMPLE.– Let us consider a set with $n = 6$ jobs with $V = 10$, $T = 10$ and the following data:

j	1	2	3	4	5	6
p_j	8	7	5	2	3	5
b_j	2	4	5	8	6	5
d_j	15	17	20	22	25	30

The minimum number of bottles to open is $F^{min} = 3$ because $\sum b_j = 30$ and $V = 10$.

One solution to the problem can be represented by a Gantt chart where each job takes one dimension for time, the other for its resource consumption. Two jobs using the same bottle combine the two dimensions, time and volume, and are therefore represented by making the upper right corner of a job coincide with the lower left corner of the job that follows it.

The optimal solution for the T_{max} is the solution given by the EDD (earliest due date first or increasing d_j order), or the sequence $\sigma = (J_1, J_2, J_3, J_4, J_5, J_6)$ presented in Figure 6.6 (a symbol indicates the opening of a new bottle). The greatest delay is 0.

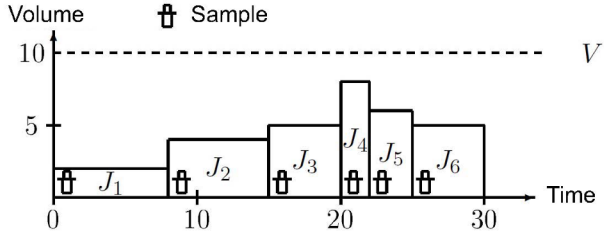

Figure 6.6. *Gantt diagram for the sequence σ = (J_1, J_2, J_3, J_4, J_5 〖, J〗_6)*

In this solution, jobs J_1 and J_2 cannot use the same bottle because $p_1 + p_2 > T$, just like jobs J_2 and J_3 (because $p_2 + p_3 > T$). Jobs J_3 and J_4 cannot use the same bottle because $b_3 + b_4 > V$, just like jobs J_4 and J_5 (because $b_4 + b_5 > V$). Finally, jobs J_5 and J_6 cannot use the same bottle because $b_5 + b_6 > V$. This solution, for which the greatest delay is equal to 0, requires the opening of $F(\sigma) = 6$ bottles, one per job.

Now, we consider the sequence $\sigma = (J_1, J_4, J_2, J_5, J_3, J_6)$ depicted in Figure 6.7.

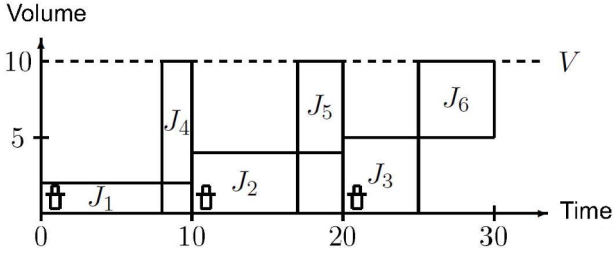

Figure 6.7. *Gantt diagram for the sequence σ = (J_1, J_4, J_2, J_5, J_3 〖, J〗_6)*

In this solution, jobs J_1 and J_4 can use the same bottle, the same for J_2 and J_5, and also for J_3 and J_6. In total, only $F(\sigma) = 3$ bottles are used. We note

that $F(\sigma) = F^{min}$, which means that the solution is optimal for this criterion (you cannot find a solution with fewer bottles). However, the value of T_{max} is no longer equal to 0 but equal to 5 (job J_3 ends on date 25 when it is due on date 20). The solution is therefore degraded in terms of maximum delay but improved in terms of the number of bottles used. This shows that the two criteria are in conflict. We refer to T'Kindt (2006) for a general presentation of multi-criteria scheduling problems.

COMMENT.– If it is assumed that a chemotherapy preparation can be made from several bottles, then the model should be adapted accordingly. In this case, for the example shown in Figure 6.6, the J_6 would not need a new bottle.

The *linear programming model* problem can be modeled as a linear integer program. We denote by u_k a binary variable equal to 1 if the bottle K is used (Billaut 2015). If all jobs have a due date equal to the sum of the durations (that is, ignoring the constraint on the largest delay), then the problem is exactly the problem called "two-constraint bin packing", also called the "vector packing problem" (see, for example, Alves 2014). the problem can be modeled as a linear integer model. We cal u_k a binary variable equal to 1 if the bottle k (we also say the *bin* k) is used, and 0 otherwise. We call $y_{j,k}$ a binary variable equal to 1 if job J_j is assigned to the bottle k, and 0 otherwise.

It is assumed that the jobs are numbered in EDD order.

We try to minimize the number of bottles used, let $\sum_{k=1}^{n} u_k$.

Each job must necessarily be assigned to a bottle, in other words, $\forall j \in \{1, \ldots, n\}$, we have:

$$\sum_{k=1}^{n} y_{j,k} = 1 \qquad [6.5]$$

The total duration of the job in a bottle may not exceed the time limit T, that is, $\forall k \in \{1, \ldots, n\}$:

$$\sum_{k=1}^{n} p_j y_{j,k} \leq T \times u_k \qquad [6.6]$$

The total consumption of the job in a bottle may not exceed volume V, that is, $\forall k \in \{1, \ldots, n\}$:

$$\sum_{j=1}^{n} b_j y_{j,k} \leq V \times u_k \qquad [6.7]$$

If we denote by ε the value that the greatest delay cannot exceed, we then have $\forall j \in \{1, \ldots, n\}$ and $\forall k \in \{1, \ldots, n\}$:

$$\sum_{h=1}^{k-1} \sum_{i=1}^{n} p_i y_{i,h} + \sum_{i=1}^{j} p_i y_{i,k} \leq d_j + \varepsilon + M\left(1 - y_{j,k}\right) \quad [6.8]$$

The expression $\sum_{h=1}^{k-1} \sum_{i=1}^{n} p_i y_{i,h}$ gives the sum of the duration of the job in the $k-1$ first bottles (bins). Furthermore, $\sum_{i=1}^{j} p_i y_{i,k}$; in other words, the sum of the duration of the job precedes J_j in the bin (the jobs are numbered according to EDD, so this order takes precedent within a bin) plus J_j. The obtained end date of the job is thus J_j, which must be less than or equal to $d_j + \varepsilon$. This constraint should only be satisfied if J_j is in the bin k, hence the presence of $M\left(1 - y_{j,k}\right)$.

To eliminate symmetries, the following constraints are added to ensure that the bottles are used in the order of their increasing numbering, $\forall k \in \{1, \ldots, n\}$:

$$u_{k+1} \leq u_k \quad [6.9]$$

The model is written as:

$$\text{MIN } \sum_{k=1}^{n} u_k$$

$$s.c. [6.5, 6.6, 6.7, 6.8, 6.9]$$

$$u_k \in \{0,1\}, \quad \forall k \in \{1, \ldots, n\}$$

$$y_{j,k} \in \{0,1\}, \ \forall j \in \{1, \ldots, n\}, \quad \forall k \in \{1, \ldots, n\}$$

This model includes $n(n+1)$ binary variables and $n^2 + 4n$ constraints.

6.4.3. *General case*

For a real implementation, the circuit of the cytotoxic products should be studied finely. A non-reconstituted bottle is taken out of stock, a refrigerator, and placed in the basket in which it is used. As long as it is not opened and reconstituted, the product is considered viable and can be kept for a

sufficiently long period of time. The bottle is opened in the isolator, reconstituted and possibly shared between all the preparations that require it. If a preparation requiring the bottle is expected within a short time, it may remain in the isolator for some time. Otherwise, it comes out and is placed back in the refrigerator. This time, its life is limited and it cannot exceed a certain time (see Figure 6.8).

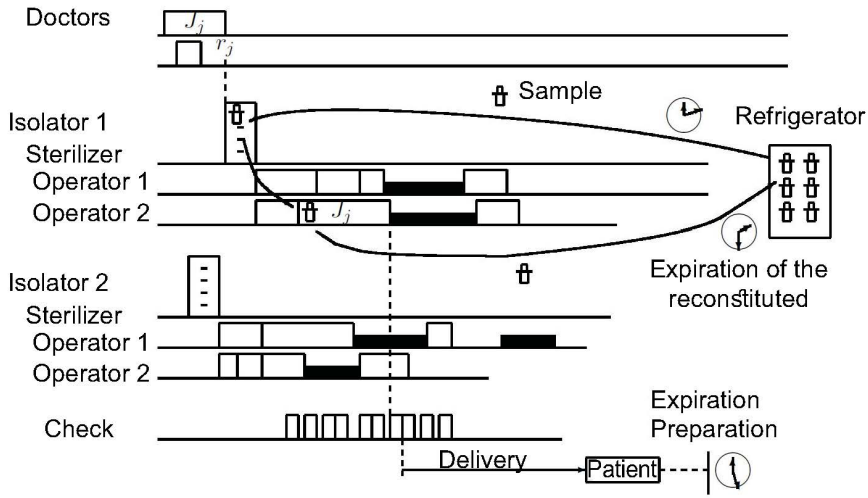

Figure 6.8. *Comprehensive model of the preparation production workshop with bottle circuit* (Billaut 2011)

For each product, we know the volume of the containers, specific to each product, the price per unit volume and the shelf life once reconstituted.

A linear programming model can be developed based on the mathematical model in section 2.1 and on the mathematical model of this section generalized to several types of bottles. Such a model requires a very large number of binary variables and a very large number of constraints, which makes the model unusable for practical use. On the other hand, the development of a metaheuristic method approach is justified.

An interesting way to better optimize the management of residues is to go through optimization at two levels. Indeed, the shelf life of products in open bottles often exceeds the day. It is therefore necessary to broaden the working time frame: a time frame of 30 days is undoubtedly sufficient for a relevant study. On such a time frame, given the complexity of the problem, it is then possible to develop planning software that will study the best distribution of preparations over a 30-day time frame, to reduce product losses as much as possible, given their stability. The implementation of such a production plan then comes down to coordinating appointments with patients – when protocols allow this, of course – and this is with the various oncology services. Then, at a second level, it is possible to schedule the preparations by the day, while optimizing the use of the residues. The implementation of such a procedure requires prior acceptance by all the services concerned.

6.5. Consideration of distribution

Due to the high volatility of the drugs prepared and in order to minimize patient waiting, the distribution of preparations is an important aspect of the problem. The problem has two specificities: transport times are not negligible compared to production times and it is not possible to indefinitely store the preparations made pending their distribution. It is therefore necessary to coordinate production and distribution. This aspect of the problem is discussed here and is referred to in the literature as "*integrated production and distribution*".

6.5.1. *Presentation of the problem*

At the CHRU in Tours, distribution takes place at three different hospital sites, including two remote from the production center and that require a vehicle.

Various articles considering this problem can be found in the literature (Bilgen 2004; Chen 2004). Much of the literature is devoted to problems that arise at a strategic level. We are here at an operational level and many fewer items address these problems (see for example Kergosien 2017; Viergutz *et al*. 2014; Ullrich 2013).

The resolution of this problem requires the resolution of three interrelated sub-problems:

PROBLEM 1	Production scheduling presented in the previous sections.
PROBLEM 2	Creation of "batch tours" (different from sterilization batches), which consist of determining which preparations will be delivered together in the same round, that is, assigned to the same batch/round. Once a batch is known, a departure date for the round is associated with each batch. This date corresponds to the end time of production (that is, control) of the last batch preparation of the round.
PROBLEM 3	Design of each round. This second problem consists in determining the order in which deliveries are made within each batch. This problem is also called the "vehicle routing problem" in the literature (Desrosiers 1995) and has been the subject of numerous studies because of its complexity as the number of deliverables increases.

The last two problems are usually solved together because the choice of preparations composing the batch has a direct impact on the duration of the round (delivery time and delivery date of each preparation). Distribution decisions are difficult to make and have a significant impact on delivery dates. Here are two examples:

– *Example 1:* if the decision-maker adopts a strategy that consists of only delivering a few preparations in the same round, so that the delivery person must return more often to the place of production, then they will be led to make many round trips that are probably useless and thus the number of chemotherapies ready to be delivered is likely to accumulate very quickly. This effect will cause a significant increase in delivery dates, especially for chemotherapies from the last rounds.

– *Example 2:* if the decision-maker adopts a strategy of delivering all chemotherapies ready to be delivered (produced and stored) without waiting, then the delivery person's rounds may become longer and longer and ultimately have the same effect as before. For example, if two preparations intended for two patients on the same ward, 15 minutes from the production site for example, are completed at 9:55 am for the first and 10:05 am for the second. Suppose the delivery person is back to start a new round at 10:00 am. Then they will take the first chemotherapy but not the second. They will have to come back to the same department on their next round, whereas if they had waited 5 minutes, then they could have delivered both chemotherapies at the same time and therefore saved time overall.

On the other hand, it is difficult to estimate the time the delivery person must wait for their next round. To wait too long would cause too many preparations to be accumulated and ready for delivery. Distribution decisions are therefore very strongly linked to production decisions. Indeed, producing preparations in a new order impacts the end dates of production and therefore requires a modification of batches and rounds. These production decisions must therefore also take into account the delivery locations of chemotherapies and delivery dates. Finally, an important problem constraint adds complexity to the problem. This is the stability of the preparations once they have been produced (expiry dates). Some preparations with a very limited shelf life should not be produced long before the start of the round and should be delivered first. Otherwise, the delivery person could be led to stop their round in progress in order to go back for the urgent delivery, which would be very detrimental for the overall solution.

6.5.2. *Special case: flow shop workshop and a single vehicle*

Consider that the production workshop is a flow shop-type workshop in m machines, that is, all jobs have the same range and must be carried out first on machine M_1, then on machine M_2 and finally on machine M_m. This is a good approximation of the process as the production of a chemotherapy preparation always follows the same path, first with the doctor's visit, then sterilization and preparation and finally control. We are freeing ourselves here from the allocation problems that complicate the problem.

The problem first consists of scheduling a set J of n jobs on the machines. With every job J_j are associated a noted execution time $p_{i,j}$ (duration of J_j on M_i, a desired delivery date noted d_j and a noted delivery site j). The production site is marked 0. We know $tt_{i,j}$, the time to go from the site i at site j ($0 \leq i, j \leq n$). Once the jobs are finished, the problem is to group them in batches to distribute them. Once the batches are defined, the problem is to determine a route to follow to distribute all the jobs in each batch. We note D_j the delivery date of J_j. The delay of J_j is now measured against the delivery date, so we have:

$$T_j = \max(0, D_j - d_j)$$

Several criteria can be defined, for example, the criterion T_{max}, already addressed in section 2.1.1, the sum of the delays denoted by $\sum T_j$ and the number of late deliveries denoted by $\sum U_j$, where $U_j = 1$ if $T_j > 0$, and 0 otherwise.

EXAMPLE.– Consider a problem where scheduling is done on a single machine, with the following six jobs. The distance matrix (7×7) is as follows (note that, in the general case, this matrix is not symmetrical). The locations of the sites are shown in Figure 6.9, and only one vehicle is available for delivery.

j	1	2	3	4	5	6
p_j	8	7	5	2	3	5
d_j	15	17	20	22	25	30

$$tt_{i,j} = \begin{pmatrix} 0 & 3 & 3 & 3 & 4 & 2 & 3 \\ 3 & 0 & 6 & 1 & 7 & 4 & 5 \\ 3 & 6 & 0 & 5 & 3 & 4 & 1 \\ 3 & 1 & 5 & 0 & 7 & 5 & 5 \\ 4 & 7 & 3 & 7 & 0 & 3 & 3 \\ 2 & 4 & 4 & 5 & 3 & 0 & 4 \\ 3 & 5 & 1 & 5 & 3 & 4 & 0 \end{pmatrix}$$

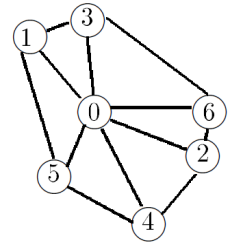

Figure 6.9. *Geographical distribution of sites*

We seek to minimize the sum of delays, $\sum T_j$.

We show in Figure 6.10 two solutions to the problem. In the first solution, the scheduling sequence is $(J_1, J_2, J_3, J_4, J_5, J_6)$; in other words, the jobs are sorted according to EDD (not optimal for the criterion $\sum T_j$ to a machine but optimal for the criterion T_{max}). Batches are $\{J_1\}$, $\{J_2\}$, $\{J_3\}$, $\{J_4, J_5\}$ and $\{J_6\}$. In the $\{J_4, J_5\}$ batch, the delivery sequence is J_5 then J_4. The delivery dates of the jobs are (11, 18, 24, 32, 29, 39), which gives a total delay equal to 28. In the second solution, which does not respect the intuitive order of EDD, the sequence is $(J_4, J_1, J_3, J_5, J_2, J_6)$. Each job forms a batch on

its own. Delivery dates are equal to (13, 29, 19, 6, 24, 35), which leads to a total delay of 17, which is much better.

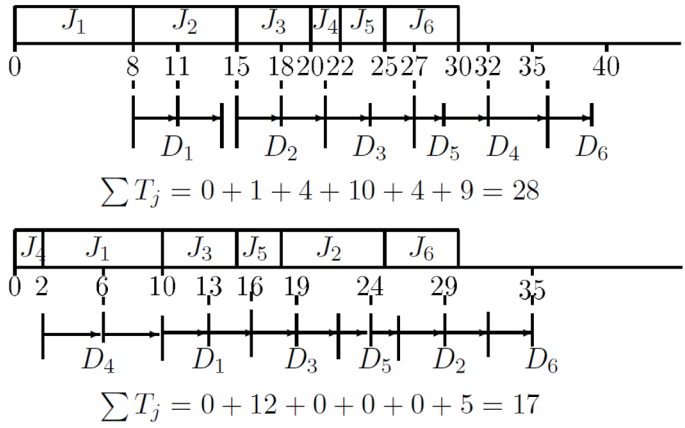

Figure 6.10. *Two examples of scheduling and routing*

Integer linear programming model. A linear integer programming model can be proposed. The first challenge is to link the two levels of planning. The second difficulty consists of finding an effective model for a good resolution by a solver.

Let us consider a flow shop scheduling problem and a single vehicle rounding problem. The following binary decision variables are defined: $z_{j,k}$, $j \in \{1, \ldots, n\}$, $k \in \{1, \ldots, n\}$ for sequencing the jobs in the workshop; $y_{j,r}$, $j \in \{1, \ldots, n\}$, $r \in \{1, \ldots, n\}$ for assigning jobs to batches and $x_{i,j,r}$, $i \in \{0, \ldots, n\}$, $j \in \{0, \ldots, n\}$, $r \in \{1, \ldots, n\}$ for job sequencing within batches:

$$z_{j,k} = \begin{cases} 1 \text{ if the work } J_j \text{ is in position } k \\ 0 \text{ otherwise} \end{cases}$$

$$y_{j,r} = \begin{cases} 1 \text{ if the work } J_j \text{ is in the batch/round } r \\ 0 \text{ otherwise} \end{cases}$$

$$x_{i,j,r} = \begin{cases} 1 \text{ if the curve } (i,j) \text{ is in the batch/round } r \\ 0 \text{ otherwise} \end{cases}$$

The following continuous variables are also required: $C_{k,i} \geq 0,\ k \in \{1, \ldots, n\},\ i \in \{1, \ldots, m\}$ to indicate the end date of the job in position k on the machine M_i, $t_r \geq 0,\ r \in \{1, \ldots, n\}$ the departure date of the round r, $A_j \geq 0, j \in \{0, \ldots, n\}$ the time required to deliver the job J_j on its round and $T_j \geq 0, j \in \{1, \ldots, n\}$ delay in job J_j.

The objective function is:

$$\text{MIN } \sum_{j=1}^{n} T_j$$

The delay of J_j is greater than or equal to its delivery date $t_r + A_j$ minus its due date d_j, if J_j is on round r. It is expressed by $\forall j \in \{1, \ldots, n\}$, $\forall r \in \{1, \ldots, n\}$:

$$T_j \geq t_r + A_j - d_j - M(1 - y_{j,r}) \quad [6.10]$$

Each job is only at one position, so $\forall j \in \{1, \ldots, n\}$:

$$\sum_{k=1}^{n} z_{j,k} = 1 \quad [6.11]$$

In each position, there is only one job, so $\forall k \in \{1, \ldots, n\}$:

$$\sum_{j=1}^{n} z_{j,k} = 1 \quad [6.12]$$

Each job is necessarily in a batch, so $\forall j \in \{1, \ldots, n\}$:

$$\sum_{r=1}^{n} y_{j,r} = 1 \quad [6.13]$$

The scheduling part is classic. It reflects the precedence constraints related to the range of jobs and disjunctive resources. The case of working in the first position and the case of the first machine are treated separately in the constraints. The set of constraints is as follows:

$$C_{1,1} = \sum_{j=1}^{n} p_{j,1} z_{j,1} \quad [6.14]$$

$$C_{k,1} = C_{k-1,1} + \sum_{j=1}^{n} p_{j,1} z_{j,k} \quad \forall k \in \{2, \ldots, n\} \quad [6.15]$$

$$C_{1,i} = C_{1,i-1} + \sum_{j=1}^{n} p_{j,i} z_{j,1} \quad \forall i \in \{2, \ldots, m\} \quad [6.16]$$

$$C_{k,i} \geq C_{k-1,1} + \sum_{j=1}^{n} p_{j,i} z_{j,k} \quad \forall k \in \{2, \ldots, n\}, \ \forall i \in \{2, \ldots, m\} \quad [6.17]$$

$$C_{k,i} \geq C_{k,i-1} + \sum_{j=1}^{n} p_{j,i} z_{j,k} \quad \forall k \in \{2, \ldots, n\}, \ \forall i \in \{2, \ldots, n\} \quad [6.18]$$

The part related to routing is as follows. The link between the $x_{i,j,r}$ and $y_{j,r}$ variables is as follows (among others, if J_j is not on round r, then all $x_{i,j,r}$ and $x_{j,i,r}$ variables are equal to 0):

$$\sum_{j=0}^{n} x_{i,j,r} = y_{i,r} \quad \forall i \in \{1, \ldots, n\}, \forall r \in \{1, \ldots, n\} \quad [6.19]$$

$$\sum_{i=0}^{n} x_{i,j,r} = y_{j,r} \quad \forall j \in \{1, \ldots, n\}, \forall r \in \{1, \ldots, n\} \quad [6.20]$$

The following constraints impose that a round cannot begin before the end of the round jobs, nor before the return of the vehicle from the previous round.

$$t_r \geq C_{k,m} - M\left(2 - z_{j,k} - y_{j,r}\right) \ \forall j \in \{1, \ldots, n\}, \ \forall k \in \{1, \ldots, n\}, \forall r \in \{1, \ldots, n\} \quad [6.21]$$

$$t_r \geq t_{r-1} + \sum_{i=0}^{n} \sum_{j=0}^{n} tt_{i,j} \times x_{i,j,r-1} \ \forall r \in \{2, \ldots, n\} \quad [6.22]$$

The delivery time of J_j in its round is given by $\forall j \in \{0, \ldots, n\}$, $\forall j \in \{1, \ldots, n\}$, $\forall r \in \{1, \ldots, n\}$, $i \neq j$ (with $A_0 = 0$):

$$A_j \geq A_i + tt_{i,j} - M\left(1 - x_{i,j,r}\right) \quad [6.23]$$

Each round starts from the depot, that is, $\forall r \in \{1, \ldots, n\}$:

$$\sum_{i=0}^{n} x_{0,i,r} \leq 1 \quad [6.24]$$

This model includes $n(n+1)^2 + 2n^2$ binary variables, $0(n^2)$ continuous variables and $O(n^3 + nm)$ constraints, including $2n^2(n+1)$ constraints with a very high constant M.

6.5.3. *General case*

In the general case, the preparations, once controlled, are taken out of the room through an airlock and placed in a refrigerator awaiting delivery. Many hospital sites have patients waiting for treatment. Several delivery people are

responsible for delivering the preparations, usually with one delivery person assigned to a particular site.

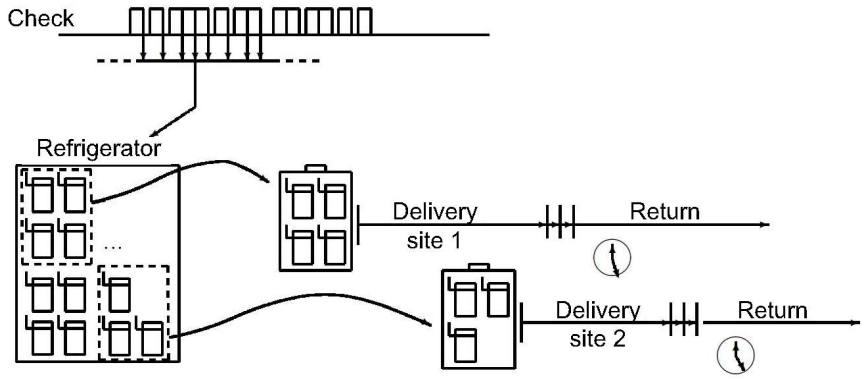

Figure 6.11. *Consideration of distribution*

The solution of the problem for instances of real size as a whole requires the implementation of approached methods. Once again, metaheuristics seem to be very promising methods (Ta *et al*. 2015; Billaut *et al*. 2017).

This problem was at the heart of the ANR ATHENA ANR-13-BS02-0006 project, which dealt more generally with the resolution of complex integrated problems.

6.6. Conclusion

After about 10 years of collaboration between the *Laboratoire d'informatique de l'université de Tours and le CHRU de Tours* (the computer science laboratory of the University of Tours and the CHRU of Tours), in this chapter we come to a synthesis on three problems related to the production of chemotherapy.

The first problem we addressed is the daily planning of chemotherapy production. Two software programs have been developed to solve this problem: one for the planning itself and the other for production traceability. The particularity of the problem lies in the structure of the workshop, where each machine is a mini-workshop composed of a max-batch-type machine on the first level (the sterilizer) and several parallel machines on the second

level (the dispensing pharmacists). The whole process ends with a single machine in charge of checking the preparations. The interactive method used to solve the problem was described.

The second problem we addressed concerns the consideration of residues. These are active products used in chemotherapy preparations, which are very expensive and volatile. This brings new complications to the problem: first, the fact that once a preparation is made it must be administered to the patient within a specific time window; second, the desire to reduce the loss of these products implies the introduction of new objective functions, not only linked to the end dates of the jobs, but also to their consumption and the life of the products. Treatment of this problem requires the prior implementation of a system to monitor chemotherapy product stocks. In the case where the production system is reduced to a single machine and for a single product, the problem is close to the two-constraint bin packing problem and we present a linear integer programming model that solves this problem.

The third problem concerns the consideration needed in distribution. Given transport times and production times, this problem is strongly connected to production. In the case where production is carried out in a flow shop, and with only one vehicle for distribution, we present a linear programming model.

Research perspectives on these issues are numerous. The problems are very complex, and the development of efficient methods is a real challenge. The realization of a software suite for an effective implementation of the associated algorithms is also a difficult task, which requires a solid partnership between the various participants of the project.

Another problem related to the production of chemotherapy concerns the scheduling of outpatient appointments to administer treatments. To improve the production process, backlog management and/or distribution planning, patients treated with chemotherapies requiring the same cytotoxic products and/or located in the same department could be scheduled for the same day. To our knowledge, no studies have looked at the coupling of appointment scheduling with chemotherapy production. However, the appointment scheduling problem can itself be very complex when all resource constraints must be taken into account (availability of nurses, doctors, compliance with care protocols, available beds, etc.) (Condotta *et al*. 2014; Hahn-Goldberg 2014).

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