Exploring new operational research opportunities within the Home Care context: the chemotherapy at home

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Abstract

Home Care (HC) services provide complex and coordinated medical and paramedical care to patients at their homes. As health care services move into the home setting, the need for developing innovative approaches that improve the efficiency of home care organizations increases. We first conduct a literature review of investigations dealing with operation planning within the area of home care management. We then address a particular issue dealing with the planning of operations related to chemotherapy at home as it is an emergent problem in the French context. Our interest is focused on issues specific to the anti-cancer drug supply chain. We identify various models that can be developed and analyze one of them.

Keywords: Health service, home care, operations planning, anti-cancer drug supply chain, scheduling

1 Introduction

Home Care (HC) services are a growing sector in the health care domain. Their development is accelerated by several factors such as the ageing of the population, the increase in chronic pathologies, the introduction of innovative technologies and the continuous pressure of governments to contain health care costs. Home Care organizations provide complex and coordinated medical and paramedical care for a limited period of time which, however, can be extended depending on patients' needs. An HC organization can be seen as either an alternative to or an extension of traditional hospitalization since patients' hospital stays can be shortened and treatments can be completed within the patients' homes. The inter-organizational coordination of care is crucial to promote the continuity of care essentially between the patient's discharge from the hospital and her/his admission to an HC organization.

As health care services move into the home setting, the need for developing innovative approaches that improve the efficiency of HC organizations increases. The particularity of HC organizations stems from the fact that they consider patients' homes as components of the health care supply chain and therefore, additional constraints have to be taken into account such as: (i) the necessity to provide care to one patient at a fixed time: since patients are not hospitalized inside the same unit, they need to be treated individually (ii) the necessity to synchronize all resources (i.e. humans and materials) involved in the care delivery process (iii) the necessity to customize care programs: the patient's health status and social situation make specific each delivery of care. Several investigations which take into account the specificities of home care operations planning have been undertaken in the operations management literature, focusing mostly on the efficient planning, scheduling and control of care activities.

Among HC problems which can be tackled with operations research based approaches, the chemotherapy at home practice is an emergent problem especially in the French context. Previously, anti-cancer drugs were prepared at patients' homes although there is a risk of error and toxicity. But now, due to a recent French health regulation, the preparation of anti-cancer drugs must be performed within a specific unit with an insulator or flow hood. This condition implies the centralized production and transportation under specific conditions and the respect of drugs' shelf life.

In Section 2, we propose a review of the existing literature pertaining to HC operations planning within the operations management literature. In Section 3, we present an overview of the anti-cancer drugs' supply chain before discussing a number of related models as examples. In Section 4, we tackle an artificial case dealing with a coupled production-delivery problem specific to anti-cancer drugs.

2 Literature review

This section surveys various operations research models and solution techniques that are available in the HC literature and identifies unexplored research opportunities for the operations research community. Basically, there are two classes of issues according to the planning horizon: long/medium term and short/very short term.

2.1 Long/Medium term planning

We identify several works dealing with: (i) districting problems and (ii) funding problems (e.g. single organization vs. government). As a districting problem, Blais *et al* [1] describe a districting study undertaken for the Côte-des-Neiges local community health clinic in Montréal. The territory which is the area in which the particular clinic is responsible for the logistics of home-care visits, must be partitioned into six districts by suitably grouping territorial basic units. Five districting criteria must be satisfied: indivisibility of basic units, respect for borough boundaries, connectivity, visiting personnel mobility, and workload balance. The problem is solved by means of a Tabu search technique. The optimality of this model is reviewed by Lahrichi *et al* [2], who argue that the demand cannot be forecasted in each district, and imply that a nurse assigned to one district does not need to be concerned with the increased workload for her colleagues in another district. The objective of their paper is to analyze the territorial approach to the delivery of home care services based on historical data (1998-99 and 2002-03). The analyzed data gather the total number of visits and the distribution of these visits among districts. The authors suggest two approaches. The first one consists in a dynamic assignment approach while the second one deals with the split of nurses into two groups: nurses assigned to a specified district and nurses working on all the territory or in a fixed subset of districts. To address the problems of workload inequities between nurses and inequities on the level of service depending on districts, Hertz and Lahrichi [3] present two models for assigning patients to nurses taking into account geographical location of patients and nurses' workload. The first model deals with linear constraints and a quadratic objective function while the second model deals with non linear constraints optimized by using a Tabu search algorithm. The nurse’s workload consists of: the visit load (i.e. the heaviness of each visit compared to a witness visit), the case load (i.e. for each category of patients, the number of patients assigned to a nurse) and the travel load (i.e. the distance between patients and the number of visits required by these patients). Boldy and Howell [4] present a case study of methods of allocating a given amount of home help resources to a number of geographical areas within a County Social Services Department. The approach adopted involves three steps: the assessment process (i.e. estimation of the clients’ needs), the allocation procedure (i.e. profile of clients, their number and the average level of provision required by each type of client) and the survey information (i.e. information about the type of client, the amount of home help actually received and the ideal amount of help judged necessary). This approach is based on the integration of data on clients, population and the provision of related services.

Dealing with a funding problem, Busby and Carter [5] describe a decision tool created for the Simcoe County Community Care Access Center (SCCCAC) (i.e. administrator of public home care for Simcoe County) in Ontario. The tool allows the SCCCAC to quantitatively assess the trade-offs between cost, quality (defined by the number of patient visits) and waiting time of their home care patients. This information can then be used to negotiate reasonable funding levels with the Ontario government and to appropriately allocate this funding among the various patient groups at the SCCCAC. Queuing theory is used to calculate the expected waiting time, the length of the queue, and the probability of waiting longer than some specified time. De Angelis [6] indicates that the main difficulty in allocating resources between services derives from the uncertainty concerning the number of patients who need services and the level of care each entitled patient requires. The author develops a model that produces an optimal schedule for admitting new patients to the home-health care system, subject to constraints on available resources, and taking into account minimum service standards, uncertainties and fixed budget. This model is linked to an epidemiological model based on an accurate forecast model of HIV/AIDS epidemics. It solves the problem for a single organization, which provides assistance within a given budget, and for public-health authorities, which have to evaluate the results of tentative budgets assigned to home care. The model developed is a stochastic linear programming model.

2.2 Short/Very short term planning

Investigations related to short term operations planning mainly concentrate on two hierarchical problems: allocation problems and scheduling-routing problems. Borsani *et al* [7] are interested in two planning levels, i.e. the assignment of the patients entering the system to a reference operator or team, and the scheduling model whose output is the weekly plan for each operator. They develop mathematical models by using integer linear programming techniques. The weekly plans generated by the proposed models are compared with the real ones according to a set of performance indicators: care continuity (i.e. reference operator), outsourced visits (i.e. patient family), preferential days and geographic coherence. The majority of works related to the short term planning concerns nurse job assignment. The problem presented by Steeg and Schröder [8] consists in assigning each job to a nurse while the number of nurses that visit a patient in a schedule is minimized. As a solution approach, the authors propose a hybrid constraint programming – large neighborhood search approach. The spatial decision support system described in [9] integrates a geographic-information-systems technology. This system encompasses data-management, scheduling, geocoding and visual interactive rerouting. The scheduling module represents the core module of this tool. It develops for each nurse a list of patients to be visited ordered in a way that maximizes nurses’ productivity. For this purpose, a heuristic approach is adopted integrating a set of procedures to build and improve daily nurses’ routes. Another optimization and planning tool is presented in [10]. The objective is to find an optimal job sequence for each nurse subject to a number of hard and soft constraints (e.g. qualification requirements, workload) and preferences related to patients or nurses (e.g. visits’ time windows, days off). One idea of this system is to present several possible solutions allowing thereby the dispatcher to select one plan or to re-calculate parts of the solution. The approach consists in finding a partition of jobs to nurses, and optimizing the sequencing within such partition, using a combination of linear programming, constraint programming and (meta-)heuristics. A third decision support system is described in [11]. The system consists of information databases, maps, optimization routines, and report facilities. The objective of the optimization module is to develop staff routes with respect to some restrictions and soft objectives. The problem is formulated using a set partitioning model and, for a solution method, the authors make use of a repeated matching algorithm. The visit plan proposed is evaluated according to two performance criteria: the efficiency of the plan (i.e. amount of travel time and number of allocated visits) and its quality (i.e. continuity of care). Cheng and Rich [12] are interested in finding an optimal schedule for nurses that minimizes the amount of overtime and past-time worked. The authors refer to the nurses as salaried and non salaried workers. The global problem is formulated as a vehicle routing problem with time window, many depots and compatibility information. The problem is formulated as a mixed integer linear programming problem and two formulation approaches are described: one using double-indexed variables and the other using triple-indexed variables. The implemented heuristic is a two-phase algorithm: the first stage builds several routes simultaneously and the second stage attempts to make improvements on these tours.

The amount of existing operations research works is quite modest because of the recent development of HC organizations. The papers we surveyed, the districting problem and the human resources planning problem or more precisely the nurse planning problem, were the main issues. Geographical constraints are common to all problems and seem to be the most important characteristic in the home care context. Home care delivery involves multidisciplinary care which integrates various human and material resources and has a strong need for resource synchronization and (therapeutic and organizational) activity coordination at the tactical and operational levels. At the tactical level, there is a need for coordination among the various resources, e.g. coordination between planning of nurses and planning of doctors, coordination between resource management and patient management, or coordination between admission-discharge planning and planning of doctors. These issues arise from the difficulty to forecast patient demand in home care organizations. At the operational level, time constraints, i.e. precedence/synchronization/exclusion constraints, have to be considered in a different way, since some patients require simultaneous or sequential interventions involving multiple resources. However, according to the literature review, there are no studies dealing with such issues. Another unexplored issue concerns material resource planning problems, i.e. consumable and non consumable resource planning problems; nevertheless, at first, there is a need to discuss and to clarify the particularities of these problems in the home care environment versus the industry.

The next section focuses on a problem dealing with the organization of the production and distribution processes of anti-cancer drugs.

3 Focus on the chemotherapy at home problem

Among HC problems for which operations research based approaches could be applied, the chemotherapy at home practice is an emergent problem especially in the French context. The problem was at first defined by the anti-cancer drug unit of the European Hospital George Pompidou. Previously, anti-cancer drugs (having shelf life time constraints) were prepared at the patient’s home although there is a risk of error and toxicity for the nurse, the patient and his/her family. Actually, due to a recent French health regulation, the preparation of anti-cancer drugs must be performed inside a specific unit with an insulator or flow hood. This condition implies the centralized production and transportation under specific conditions and the respect of drugs’ shelf life, and motivated us to study the anti-cancer drug supply chain. The sterile, personal, perishable and dangerous aspects of anti-cancer drugs make the problem particularly challenging. Drugs are sterile because of the hygiene and quality standard imposed on their production and transportation. They are personal since the necessary doses to their production depend on the *creatinine*, weight and height of the patient [13]. Thus, a drug produced for one particular patient can not be administered to another one. Each drug has a specific shelf life time beyond which it becomes obsolete, and therefore, it cannot be used. The shelf life time varies from 2 hours to a few days. Drugs are dangerous to people handling them without particular precautions [14]. These drugs can be presented in varied forms (syringe, diffuser and pocket) and can differ by their volumes, their stabilities, their costs and their administration durations. In addition, due to their personal character, these drugs have a very strong diversity.

Within this context, three stages of the anti-cancer drug supply chain have to be considered (*Figure 1*): the production of anti-cancer drugs, their distribution and their administration to patients at home.

[Include Figure 1 here]

3.1 Problem description

Production Phase

For each new patient that requires chemotherapy, a doctor determines a protocol of care. This consists in specifying the different steps of the treatment including the days of administration of the drugs. This protocol must be validated by the pharmacist responsible for the production unit of anti-cancer drugs. We classify the patient demands into two classes:

- Elective demands, i.e. patient demands are known in advance or at least the day before starting the production. We can distinguish two subclasses: demands relative to the drugs to be delivered the same day of their production, and demands relative to the drugs to be delivered the days following their production;
- Emergency demands, i.e. patient demands that must be satisfied within short timeframes.

A list of the elective demands is prepared the day before starting production; however, the order in which the related drugs have to be produced remains unknown. In fact, certain elective demands must be validated by the doctor before beginning their production process. Nevertheless, the demand validation (time) is uncertain. The main causes that lead to a delay in treatment are the worsening of the patient status, its weight loss and the variation in creatinine. The drug administration can even be cancelled due to the death of the patient, the change in or the end of the treatment.

Storage Process

The production dates of anti-cancer drugs depend on their validation dates and their emergency priority. Once produced, some drugs are stored whereas others are immediately delivered to their respective patients. The stored drugs are those of long enough shelf life time and non urgent use, for instance, when there is no nurse available for drug administration or when it is possible to produce the drug in advance to satisfy demand surge. For all these drugs, the countdown to expiry date starts at their production completion date. The risk of obsolescence incurred by these products is essentially related to the time criteria:

- Waiting time before being delivered (i.e. storage time) and before being administered (i.e. time window between the delivery date and the administration date);
- Delivery time, i.e. time window between the route's starting date and the drug's delivery date (the route may include a number of stops for the delivery of the drugs).

Distribution Phase

The delivery of the anti-cancer drugs can be performed by the nurses who have to administer them to patients or by a delivery person (a HC worker or an external service provider). We can distinguish three cases of delivery:

- Delivery of only one drug at a time, e.g. drugs with short shelf life time (and a long transportation path);
- Delivery of all the drugs in a single tour: this case is possible when the administration date as well as the shelf life time are long enough to allow the delivery of all the drugs without any risk of obsolescence;
- Delivery batches: after the production step, it is possible to constitute a list of drugs ready for delivery. This list progressively extends as the produced drugs arrive, and shortens as drug deliveries are performed. It is a dynamic list. Based on this list, it is necessary to decide which batches to form. Each batch will be delivered separately at a single tour. Therefore multiple routes have to be taken. The composition of the various batches depends on the drugs' production dates and shelf life times. At this level, some questions arise: *once a number of drugs are ready for delivery, is it worth to immediately deliver them? Or is it better to wait for additional drugs whose productions are not yet finished? Or rather to deliver only a part of the already available drugs (e.g. because of the geographical distribution of patients)?*

Administration Process

The service performed by a nurse at a patient's home comprises three stages (*Figure 2*): pre-administration, administration and post-administration of the anti-cancer drug. During the first stage, some measures can be necessary to check the patient's status before administering the prescribed drug. During this phase, drug availability is not compulsory but it has to be ready at the end of this stage. The drug has to be steady until the end of the service. The third stage consists in the assessment of the drug side effects. In addition, the nurse has to perform administrative activities such as updating the patient record. The durations of these three stages vary according to the patient status and the type of drug prescribed.

[Include Figure 2 here]

According to the service starting dates (i.e. earliest and latest dates) and the related service durations, we can deduce the earliest and latest dates to start drug administration (cf. *Figure 2*). The latest date to start drug administration represents the latest drug delivery date. The latest date to end drug administration constitutes the earliest drug expiry date (i.e. the drug has to be steady at least until that date).

This problem can be defined by these following questions: *which drugs to produce? When to produce them? Which drugs to deliver? When to deliver them (i.e. the route starting date and the delivery sequence of the drugs)? Who delivers them? When to administer them? Who administers them?* The penultimate question is not valid in the case of imperative care i.e. care with a fixed date. To address to this problem, we have to consider certain criteria such as the risk of obsolescence due to the drug shelf life time, the transportation time and the costs of production and delivery.

3.2 Modeling of the problem

The development of various models dealing with anti-cancer drug supply chain is based on parameters related to the home chemotherapy process:

- Parameters of the production process: Number of resources involved in the production of anti-cancer drugs; Setup time; Deterministic/stochastic demand;
- Parameters of the distribution process: Type and number of resources being involved in the delivery process; Time windows (i.e. patient's preference/availability, delivery person's work time); Deterministic/stochastic demand (i.e. number and location of HC patients);
- Parameters of the administration process: Type and number of resources involved in the administration of anti-cancer drugs; Number of depots (i.e. beginning and end points of nurse routes); Time windows (e.g. patient's availability, nurse's vacation);
- Objective functions:
  - Production: minimization of the setup total costs (sterilization), maximization of satisfied demand (i.e. number of drugs produced, satisfaction of emergency demands), …
  - Distribution/administration: minimization of travel distance, minimization of costs related to the drug obsolescence, maximization of profits collected by the visits of selected patients, maximization of total slack (i.e. time interval defined by the drug delivery date and the end date of patient availability) in order to extend the solution domain related to the nurses' routes, …

If we consider the case where the nurse is responsible for the delivery of anti-cancer drugs to her/his patients, two problems can be identified, namely the production scheduling problem and the nurse routing problem. In *Figure 3*, six possible models are shown in a matrix combining three criteria: time window, number of routes and objective function.

[Include Figure 3 here]

- *Model 1*: the objective of this model is to minimize production and delivery costs. The delivery of drugs must be carried out by the nurse in one route only, i.e. the nurse has to take along all the drugs required that day by his/her patients at the same time. However because of the drug shelf life time, the determination of its production date depends on its delivery date, and vice versa. The problem to be presented in Section 4 deals with a coupled production – delivery problem;
- *Model 2*: this model is an extension of *model 1* since multiple routes are authorized. The switch from *model 1* to *model 2* stems from the consideration of drugs with short shelf life times (i.e. this time period varies from 2 hours to a few days). This constraint can prevent us from finding a feasible solution in the case of a single route, which explains the transition to multiple routes. One or multiple resources can carry out all these deliveries;
- *Model 3:* time windows related to patients' availability and/or imperative care are considered in this model. Contrary to *model 1*, the integration of these additional constraints leads to separate production and distribution problems. Indeed, the drug production release date can be determined based on the patient's availability time windows and the drug shelf life time (i.e. the production problem). Independently, the distribution problem can be resolved based on the patient's availability time windows;
- *Model 4:* this HC problem is a vehicle routing problem with time windows. Performing all the visits in a single trip and within defined time windows increases the difficulty of the problem. Therefore as in *model 2*, the multiplicity of routes is allowed;
- *Model 5:* the objective of this model is to maximize the profit collected by the visits of selected patients. In practice, this model can be explained by the existence of additional time constraints, namely the total work time and the authorized workload of nurses. Within these conditions, it can be difficult to visit all patients in a single tour, thus a choice is to be made concerning which patients to visit. This choice depends on the profit made at a patient visit. The profit depends either on the cost of drug obsolescence or on the urgency of the care;
- *Model 6:* the objective of this model is identical to that of the *model 5* (i.e. maximization of the number of patients visited within nurse work time windows), except that we can consider multiple routes. We can assign weights to patients to affect their priority.

As discussed previously, when the delivery resource is different from the one who administers the medicines to patients (nurse ≠ delivery person), two categories of routes related respectively to the nurses and the delivery persons, have to be planned and coordinated. Thus, it is a question of optimizing both the nurses and the delivery persons' routes. Two approaches can then be considered:

- Two hierarchical stages: optimization of the production/delivery problem and thereafter optimization of the administration problem or vice-versa. The first optimization introduces inevitably a new constraint for the second optimization.
  - *Production/Delivery* ⇒ *Administration*: the determination of the delivery date impacts the determination of the nurse visit date (i.e. constraint of precedence), i.e. the earliest date to start drug

  administration corresponds to the drug delivery date, and the latest date to end drug administration is the drug expiry date. The latter is defined according to the production end date, the shelf life time and the administration time of the drug. Moreover, the patient’s availability time, the drug shelf life time and its delivery date, reduce the time window dedicated to the nurse visit. Thus, in this case, we deal with a synchronization constraint which makes the problem more delicate to solve, i.e. the drug delivery date and the nurse visit date have to be synchronized.
  - *Administration* ⇒ *Production*/*Delivery*: by taking into account the time windows relative to the patient’s availability, we have at first to optimize the nurses’ routes. Once the visit dates are identified, it is then possible to determine the earliest drug expiry dates, the earliest drug production dates (by considering the drug production time and the drug shelf life time) and consequently, the sequence of drugs’ production. The optimization of the drug delivery problem depends on the definition of the nurses’ visit dates and the time windows relative to the patients’ availability: the delivery person arriving earlier at the patient home is likely to wait before being able to deliver the drug.
- Global optimization: it consists in the coordination and the optimization of all three problems (i.e. the production scheduling problem, the delivery person routing problem and the nurse routing problem) at the same time.

The first approach is a sequential approach. It is possible to consider loops in order to adjust the solutions determined for each of the three problems: the production scheduling problem, the delivery person routing problem and the nurse routing problem. Even in the case where the delivery resource is different from the one who administers the drugs to patients, modeling the production and delivery problems yields the models stated previously (*models 1 - 6*) except for (*Administration* ⇒ *Production*/*delivery*) where additional constraints are to be considered (i.e. the dates of nurses’ visits).

4 Modeling of the coupled production-delivery problem

In order to look further into the chemotherapy at home problems, we start with the study of a simple problem specific to the anti-cancer drug supply chain, namely *model 1*. This model consists of a single machine scheduling problem (production problem) coupled with a traveling salesman problem (delivery problem). An extension of this model towards the other models described (*models 2 - 6*) can be developed in the future by integrating additional constraints.

4.1 Assumptions

The problem we consider is restricted to the analysis of the stages of production and delivery of anti-cancer drugs. The following assumptions are taken into account in our analysis:

- The treatment of each patient requires only one drug;
- The number of drugs to be produced each day, and thus, the number of patients to be visited each day, are known (deterministic demand case);
- The production and administration durations are also known precisely;
- Only one production resource is considered: jobs are to be sequenced on one machine;
- The setup time is sequence-independent and is included in the production duration;
- Activities can not overlap in their executions and once an activity is started it must be executed for its entire duration;
- Only one delivery resource is considered (i.e. only one nurse delivers the drugs);
- The nurse has to perform only one trip to deliver the drugs and to administer them to his/her patients. All the patients must be visited;
- Time windows are not taken into account;
- The production and delivery dates are interdependent. The delivery and the administration of the drug have to be carried out within the drug shelf life time period (i.e. coupling constraint).

Our problem is a traveling salesman problem coupled to a problem of production scheduling. The objective of this model is to minimize the total travel time.

4.2 Parameters and notations

The traveling salesman problem can be defined on a directed and complete graph $G = (V, A)$ in which V is a set of vertices and A is a set of arcs. $V = \{0, 1..., n\}$ where $\{0\}$ denotes the depot (the production unit) and $V/\{0\}$ is the set of n patients. $A = \{(i, j);\ i, j \in V;\ i \neq j\}$ represents connection between patients or between production unit and patients.

The geographical position of each patient is defined in an Euclidean coordinate system. The travel durations d_{ij} between two patients (vertices) i and j are calculated based on their respective coordinates (x_i, y_i) and (x_j, y_j).

These durations obey to the triangle inequality. Thereby, it is possible to determine a matrix of the shortest paths between the vertices of *V*. The considered traveling salesman problem is known as Euclidean.

For a given day, the production unit produces *n* different drugs corresponding respectively to *n* patients. Each drug *i* has a production duration p_i and requires a duration of administration s_i (the service time is limited to the administration time, cf. *Figure 2*). s_0 can be considered as the loading duration of all the drugs at the production unit. For each drug *i*, there is also an associated shelf life time, denoted by DLC_i.

Let d_i be the due date of the drug *i*, i.e. the end of production latest date. In the case we study, all due dates d_i are identical: $d_1 = d_2 = \ldots = d_n = u_0$ (u_0 is the hour of the beginning of the nurse route), in other words, the end of production latest dates related to the required drugs must coincide with the beginning date of the nurse round-trip.

The coupling between the production and the transportation problems involves variables t_i and u_i, respectively representing the starting of the production and of the administration for drug *i*. The shelf life time condition is determined according to these variables, p_i, the production duration of drug *i*, DLC_i, its shelf life time, and s_i, the service time relative to the patient *i*, as shown in Equation (1):

$$u_i + s_i \le t_i + p_i + DLC_i \quad \forall i \in \{1 \ldots n\} \tag{1}$$

Indeed, the gap between the end of the administration and the end of the production cannot exceed the shelf life time.

Note that when u_i is known, Equation (1) exactly amounts to introducing a release date $r_i = u_i + s_i - p_i - DLC_i$ for drug *i*, i.e. imposing an earliest date for the beginning of the production. The studied production scheduling problem can be then noted **1|*r***$\mathbf{1|r_i, d_i|\_}$ (or $\mathbf{1|r_i, u_0|\_}$) according to the notation for theoretic scheduling problems [15]. This problem is well-known to be polynomial and can be solved exactly with a simple earliest-release-date first policy. This property will be used in our solution method as explained subsequently.

The characteristics of *model 1* are represented in *Figure 4*.

[Include Figure 4 here]

4.3 Mathematical formulation

Besides the parameters presented previously, we use four variables relative to sequencing and to time-stamping for both the problem of production scheduling and the problem of nurse routing. u_i ($i \in V/\{0\}$) indicates the visit time to the patient *i*. t_i ($i \in V/\{0\}$) is the production starting time of drug *i* (t_0 is the production starting time). Let x_{ij} ($i \neq j$; $i, j \in V$) be a binary variable equal to 1 if the arc (*i*, *j*) is covered by the nurse and 0 otherwise. Define binary variables y_{ij} ($i \neq j$; $i, j \in V$), equal to 1 if the production of the drug *i* precedes the production of the drug *j* and 0 otherwise.

The problem can be formulated as follows:

$$Min \sum_j \sum_i x_{ij} \, d_{ij} \tag{2}$$

Subject to:

$$t_i + p_i - M\left(1 - y_{ij}\right) \le t_j \quad \forall i, j \in \{1 \ldots n\} \tag{3}$$

$$t_j + p_j - M \, y_{ij} \le t_i \quad \forall i, j \in \{1 \ldots n\} \tag{4}$$

$$\sum_i x_{ij} = 1 \quad \forall j \in \{0...n\} \tag{5}$$

$$\sum_j x_{ij} = 1 \quad \forall i \in \{0...n\} \tag{6}$$

$$u_i + s_i + d_{ij} - T(1 - x_{ij}) \leq u_j \quad \forall i \in \{0...n\}; \forall j \in \{1...n\} \tag{7}$$

$$u_i + s_i \leq t_i + p_i + DLC_i \quad \forall i \in \{1...n\} \tag{8}$$

$$t_0 \leq t_i \leq u_0 \quad \forall i \in \{1...n\} \tag{9}$$

$$u_i \geq u_0 \quad \forall i \in \{1...n\} \tag{10}$$

$$y_{ij} \in \{0,1\} \quad \forall i, j \in \{0...n\}; i \neq j \tag{11}$$

$$x_{ij} \in \{0,1\} \quad \forall i, j \in \{0...n\}; i \neq j \tag{12}$$

$$t_i \geq 0 \quad \forall i \in \{1...n\} \tag{13}$$

$$u_i \geq 0 \quad \forall i \in \{1...n\} \tag{14}$$

The objective function minimizes the total travel time for the nurse. The production costs are not considered. Constraints (3) and provide the relationship between the production starting times of any two drugs. Two drugs *i* and *j* ($i \neq j$) can not be performed simultaneously at the same machine, i.e. the precedence relationship between them in the scheduling sequence has to be defined ("drug *i* has to be produced before drug *j*" or "drug *j* before drug *i*"). Thus, we can note $t_i + p_i \leq t_j$ if "drug *i* has to be produced before drug *j*" or $t_j + p_j \leq t_i$ if "drug *j* has to be produced before drug *i*". The linearization of these inequalities is based on a binary variable y_{ij} and a very large number which is the constant *M*. Constraints and imply that each patient is visited only once and if the nurse visits one patient, she/he necessarily leaves him/her. Constraint indicates the relationship between the visit time at the patient *i* and the visit time at the patient *j*, the constant *T* is a very large number. Constraint is the coupling constraint: it evokes that the visit time at the patient *i* is closely linked to the production starting time of the drug *i*. Constraint defines lower and upper bounds on the production starting time of the drugs. Constraint ensures that no visit can be carried out before a given hour (i.e. the nurse's route beginning time). Constraints and denote that x_{ij} and y_{ij} are binary variables. Constraints and indicate that t_i and u_i are non-negative variables. Constraints (3), , , and are related to the anticancer drug production scheduling problem. Constraints – , , and are related to the nurse routing problem.

4.4 Solution method

In this subsection, we propose a very simple exact method to solve the problem. The objectives are twofold. First, it permits to perform some experiments that will be detailed in the next subsection. It provides a better understanding of the structure of the solutions. Secondly, it underlines how the polynomial complexity of the scheduling problem once the visit times are fixed, can be exploited in a solution approach. Furthermore, though simple, this approach is able to solve real instances in our context, seeing that a nurse is not going to visit more than 10 patients the same day. Note that a standard Integer Programming solver as Cplex 11.0 could be used instead for problems of that size, but we also aim here at opening the door to more efficient exact or heuristic approaches, by showing how the simplicity of the production problem once a route is fixed can be exploited in the solution process. Perspectives in this direction are numerous and will be an important part of our future researches on this subject.

Basically, the solution approach is a branch and bound (B&B) algorithm enumerating the routes from the production unit. The root node of the search tree corresponds to the nurse positioned at the production unit. When separating a node (the "branch" part of the algorithm), a descendant node is created for every possible next visit. Hence, the root node has *n* descendant nodes, which themselves have *n*-1 descendants and so on.

The evaluation of a node (the "bound" part of the algorithm) is composed of two steps. First, the feasibility of the production is evaluated. The release date of the drugs whose visit is not yet proceeded is fixed to t_0 while it is computed as explained above for the other drugs (seeing that u_i is known for the latter). If the solution is not feasible, i.e. the production of the last drug scheduled ends after u_0, the node is discarded, otherwise a bound is computed. At this stage, any existing bounding scheme for the TSP can be applied, the focus being limited to the transportation problem, independently of the production. For sake of simplicity we use a naïve standard scheme that can be described as follows: for every vertex, the minimum value of the outgoing arcs is computed; these values are summed, providing a first lower bound; these value are also (temporarily) subtracted from these outgoing arcs and the calculation is repeated for the incoming arcs; the lower bound used to prune nodes is the sum of the two sums respectively computed on outgoing and incoming arcs. If the lower bound exceeds the best solution known, the node is pruned, otherwise the separation rule is applied.

Actually, in order to detect more quickly the feasibility of the production once the visit time is fixed for a subset of patients, we apply a so-called reversed earliest due date policy (reversed EDD). Compared to the one described above, we begin to schedule the last drugs. Reversing the time axis, the schedule horizon starts at time u_0 and infeasibility is detected as soon as a product finishes after its release date (which becomes a due date with the non-reversed time axis). This rule is illustrated in *Figure 5*.

[Include Figure 5 here]

To solve the problem, we make use of the branch and bound algorithm with a best first search strategy, i.e. the next node to be processed is that with the lowest bound (smallest evaluation). This algorithm can be summarized as follows:

- Step 1: the search tree consists initially of only the root node.
- Step 2: according to the chosen search strategy, a node is selected from the pool of nodes corresponding to unexplored sub problems. For this sub problem P_l, we can define an ordered nurse visits sequence $\pi_l = (i_1, i_2, \dots i_k)$. Then, six stages are to be followed:
  - (a) Deduce the visit time u_{i_m} of patient i_m by using the travel times d_{rs} ($r, s = 1, 2, \dots k$);
  - (b) Calculate the production release date r_{i_m} ($m = 1, 2, \dots k$) by using equation (1);
  - (c) Determine the production starting time t_{i_m} ($m = 1, 2, \dots k$) by using the reversed EDD rule ;
  - (d) Evaluate the ordered production sequence (test if the constraint is respected);
  - (e) if the production sequence is infeasible discard the subproblem and go to step 2;
  - (f) Apply the lower bounding scheme; if the lower bound is greater than the best solution found so far, discard the node and go to Step 2.
- Step 3: if the solution associated with this node is complete, the best solution is updated, otherwise the children of this node are constructed through the addition of constraints (namely the next arc of the route).

The algorithm stops when no more node is in wait at Step 2. The development of the algorithm was in C++.

4.5 Analysis of results

Based on an artificial case, we intend to study the impact of variation of parameters specific to the anti-cancer drugs on the sequences of production and distribution of those drugs and on the solution domain related to the coupled production-distribution problem. The key parameters are the anti-cancer drug's shelf life time, its production time and its service time.

We have generated a set of tests. The tested problem is of small size with 8 drugs to be produced (8 patients to be visited in one round trip), one machine and one production unit from which the trip starts and ends. The positions of the patients and the production unit are indicated in *Figure 6*:

[Include Figure 6 here]

At first, we try to provide insight into how the variation of anti-cancer drug's shelf life time (*DLC*) can impact the solution domain. For this purpose, a series of tests was generated with $p = 0$ and $s = 0$. The drugs have an identical *DLC*. While varying the shelf life time (*DLC*), we notice according to *Table 1* that three fields of solutions arise:

- 1st field (D1): there is no solution for the production and delivery problem. This is due to the difficulty to deliver all the drugs in the same round trip (i.e. very constraining *DLC*). In this case, the drugs must be delivered in batches within several routes;
- 2nd field (D2): there is an optimal solution for the integrated routing and scheduling problem, which is different from the optimal solution to the routing problem. This is due to the coupling constraint . Indeed, when the optimal solution obtained for the nurse routing problem treated separately, does not respect this constraint, the search for a new solution satisfying all the constraints by the algorithm continues;
- 3rd field (D3): there is an optimal solution which coincides with the optimal solution of the routing problem. In this case, the DLC are not constraining any more. Obviously, the total traveling time is improved.

[Include Table 1 here]

Table 1 shows that for identical p, s and DLC, the sequence of production is the same as the sequence of distribution. For example, if p=0, s=0 and DLC=22 for all the drugs, the drugs have to be distributed with respect to the following order (0→1→2→4→3→5→6→8→7→0) which is the same as their order of production. That sequence of distribution generates the best total traveling time.

These test problems have been solved with identical p, s and DLC. For the remainder, we decided to vary one of these three parameters in order to visualize their impact on the sequences of production and distribution of the anti-cancer drugs. For the second series of tests, we divided the patients into two groups $G1$ and $G2$ with $G1 = \{1, 3, 5, 7\}$ and $G2 = \{2, 4, 6, 8\}$, and assigned to each group a different p (i.e. respectively p_1 and p_2) that varies while keeping the same DLC and s for all the drugs.

[Include Table 2 here]

Table 2 shows that the variation of p impacts on the sequences of production and distribution. More precisely, the sequence of production differs from the sequence of distribution as the gap between p_1 and p_2 increases. We also observe that if p_2 increases while keeping p_1 constant, the priority of production of drugs associated to $G2$ increases. These observations can be explained based on the following equation $r_i = u_i + s_i - p_i - DLC_i$ (for drug i), introduced in section 4.2. Actually, for identical s and DLC, $u_1 \leq u_2$ and $p_1 \neq p_2$, we distinguish three cases, i.e. ($p_2 - p_1 < 0$), ($0 < p_2 - p_1 < u_2 - u_1$) and ($p_2 - p_1 > u_2 - u_1$). The sequence of production is the same as the sequence of distribution in the two former cases except when these two cases are combined as shown in *Figure 7*.

[Include Figure 7 here]

The same arguments can be used to illustrate the cases when the service time s and the shelf life time DLC impact the sequences of production and distribution. For more details, see [16].

5 Conclusion

Home care service is a growing sector not only in France but also in several other European and North American countries. In this paper, we classified the existing OR papers in the home care area and tried to identify the issues that have not been explored yet within this field. We noted that the amount of existing OR investigations in the home care domain is limited and that the districting problem and human resource planning problem are among the most frequently treated issues. Our contribution focuses on an emergent issue, namely the analysis of the anti-cancer drugs' supply chain. We first identified a variety of models that can be considered by combining several criteria such as the number and the nature of resources being involved in the care process or time window specific to patient's availability. To our knowledge, this is the first study dealing with the planning of operations in an anti-cancer drugs' supply chain within the home care context. The simplified model we treated represents a starting point enabling, in the future, the study of more complex models that can be obtained by integrating additional constraints. Therefore, the model we analyzed can be extended towards other models we identified (*models 2 - 6*), for example, by modifying the objective function or adding time constraints. Another research perspective can be the analysis of cases where the drug delivery resources are different from those of their administration. Consequently, the constraints of coordination between the various resources involved in the patient treatment have to be integrated into the analysis.

In the case studied, we analyzed the impact of the variation of the anti-cancer drug key parameters on the solution domain related to the coupled production-distribution problem and on their production and delivery sequences. Three fields of solutions were distinguished. In the first field, there is no solution for the production and delivery problem. In the second one, there is an optimal solution which is different from the optimal solution to the routing problem treated separately. In the third one, the optimal solution coincides with the optimal solution of the routing problem treated separately. For this study, we used an artificial case; however, this analysis can be validated later with real data.

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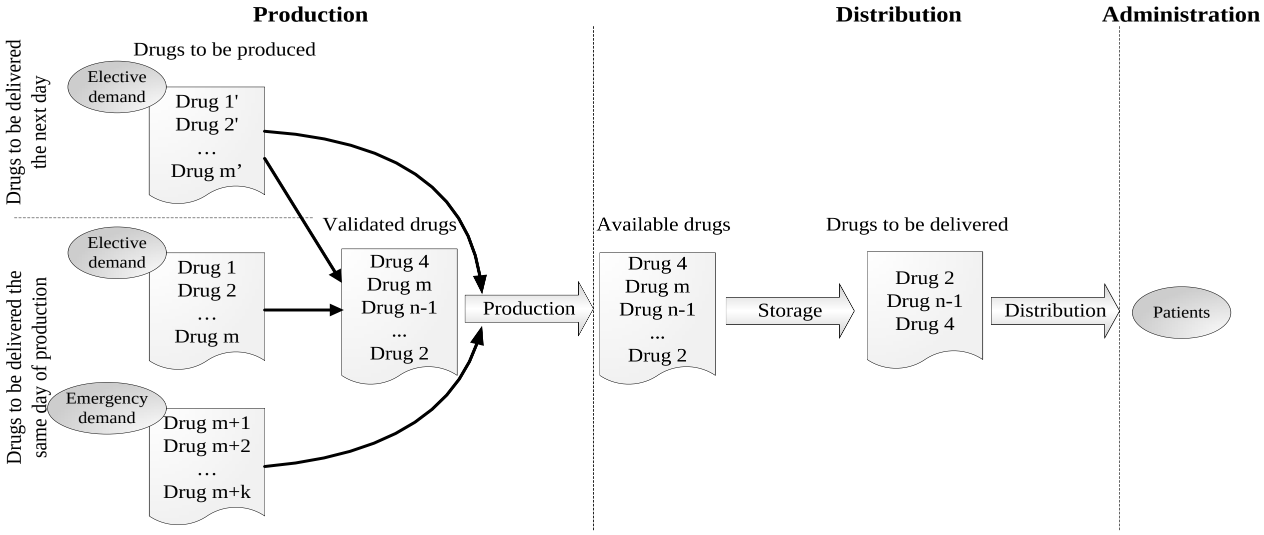


Figure 1. Anti-cancer drug supply chain

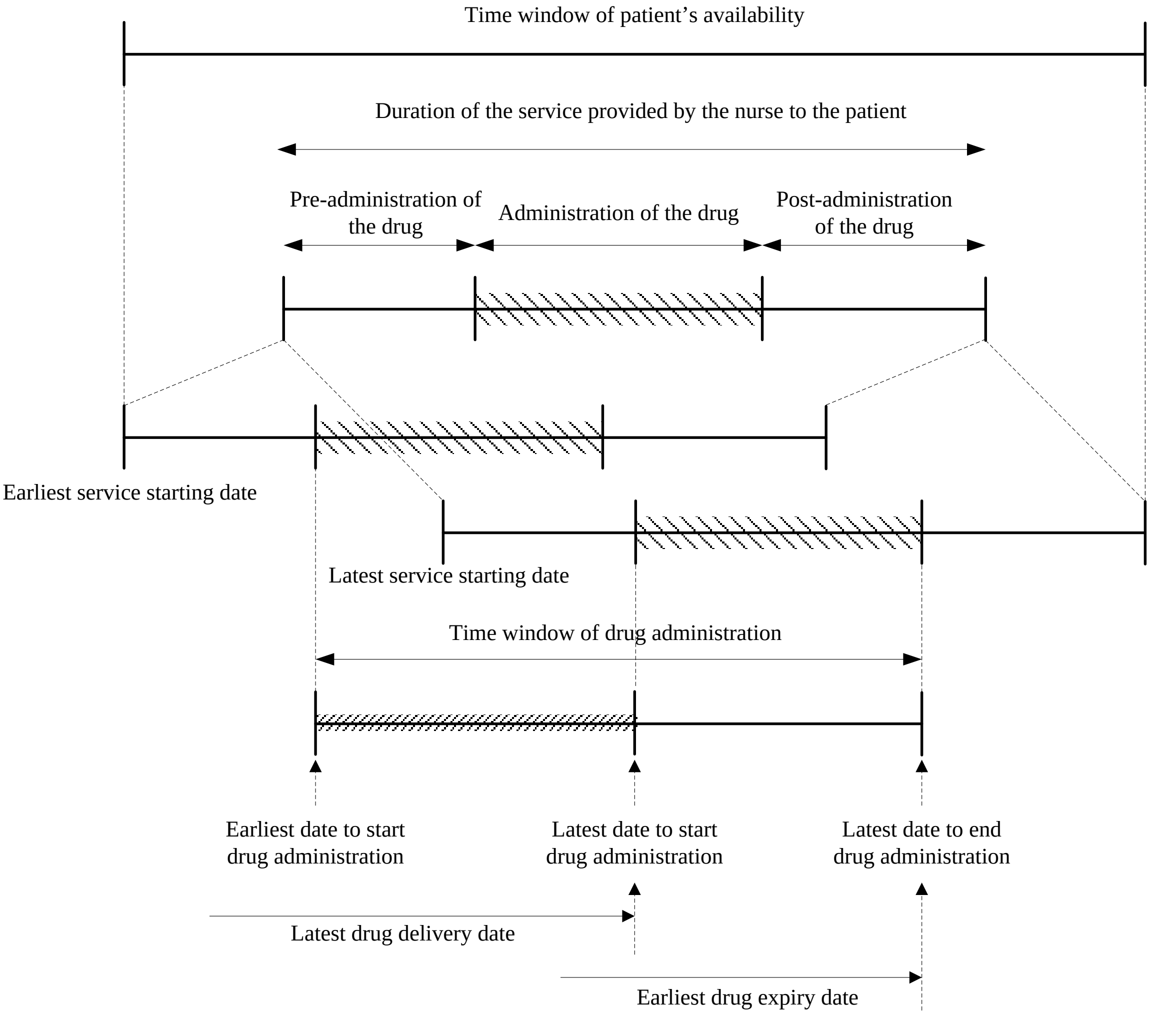


Figure 2. The availability of drugs, nurses, patients and their relationships

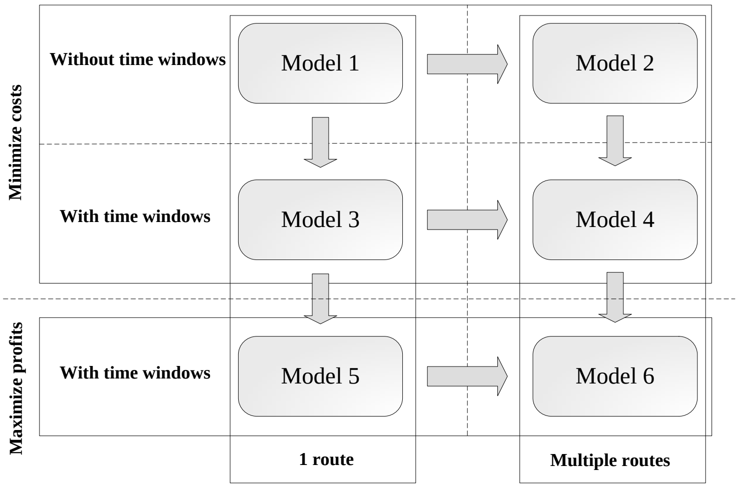


Figure 3. Classification of models related to the case where *nurse = delivery person*

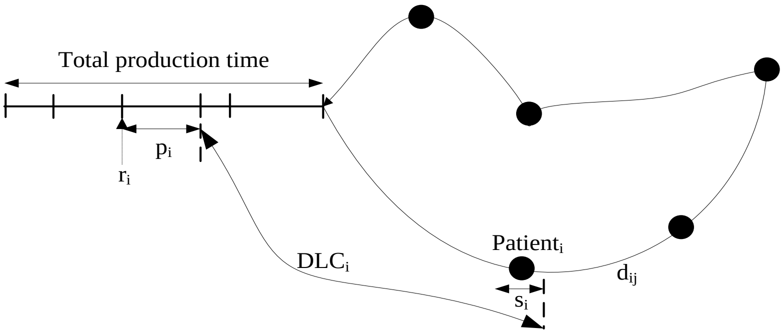
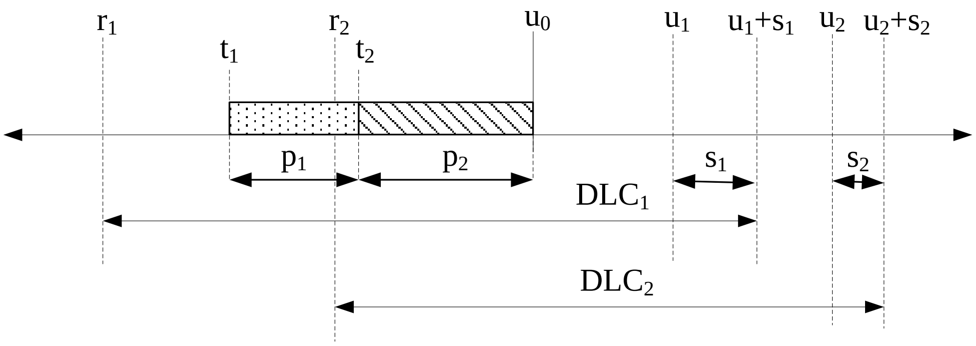
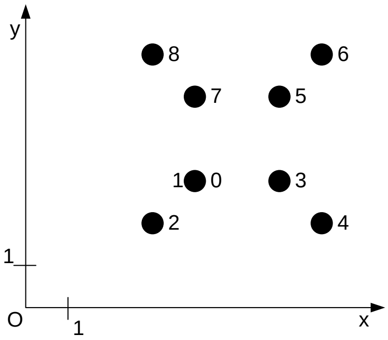


Figure 4. Representation of *model 1*



Delivery sequence: (1 -> 2)
Production sequence: (1 -> 2)

Figure 5. Example of the use of the reversed EDD rule



	0	1	2	3	4	5	6	7	8
0	∞	0	1,41	2	3,16	2,83	4,24	2	3,16
1	0	∞	1,41	2	3,16	2,83	4,24	2	3,16
2	1,41	1,41	∞	3,16	4	4,24	5,66	3,16	4
3	2	2	3,16	∞	1,41	2	3,16	2,83	4,24
4	3,16	3,16	4	1,41	∞	3,16	4	4,24	5,66
5	2,83	2,83	4,24	2	3,16	∞	1,41	2	3,16
6	4,24	4,24	5,66	3,16	4	1,41	∞	3,16	4
7	2	2	3,16	2,83	4,24	2	3,16	∞	1,41
8	3,16	3,16	4	4,24	5,66	3,16	4	1,41	∞

Figure 6. Travel times and positions of the patients and the production unit

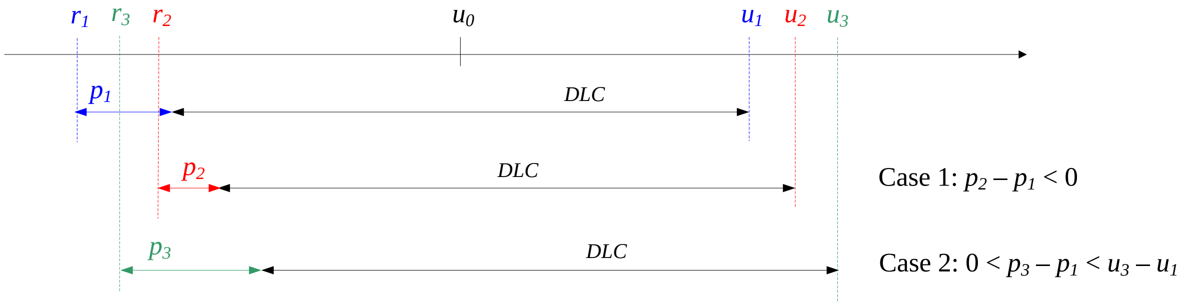


Figure 7. Counterexample related to the variation of the production time p (s=0)

Table 1. Effect of the *DLC* variation on the total travel time and on the ordered nurse visits sequence (p=0; s=0)

	DLC	Costs	Delivery sequence	Production sequence
D 1	13	∞	0 -> 0	0 -> 0
	14	∞	0 -> 0	0 -> 0
	14.5	∞	0 -> 0	0 -> 0
D 2	15	17.98	0 -> 1 -> 2 -> 4 -> 3 -> 5 -> 6 -> 7 -> 8 -> 0	0 -> 1 -> 2 -> 4 -> 3 -> 5 -> 6 -> 7 -> 8 -> 0
	15.5	17.98	0 -> 1 -> 2 -> 8 -> 7 -> 6 -> 5 -> 3 -> 4 -> 0	0 -> 1 -> 2 -> 8 -> 7 -> 6 -> 5 -> 3 -> 4 -> 0
D 3	16	17.66	0 -> 1 -> 2 -> 4 -> 3 -> 5 -> 6 -> 8 -> 7 -> 0	0 -> 1 -> 2 -> 4 -> 3 -> 5 -> 6 -> 8 -> 7 -> 0
	16.5	17.66	0 -> 1 -> 2 -> 4 -> 3 -> 5 -> 6 -> 8 -> 7 -> 0	0 -> 1 -> 2 -> 4 -> 3 -> 5 -> 6 -> 8 -> 7 -> 0
	17	17.66	0 -> 1 -> 2 -> 4 -> 3 -> 5 -> 6 -> 8 -> 7 -> 0	0 -> 1 -> 2 -> 4 -> 3 -> 5 -> 6 -> 8 -> 7 -> 0
	18	17.66	0 -> 1 -> 2 -> 4 -> 3 -> 5 -> 6 -> 8 -> 7 -> 0	0 -> 1 -> 2 -> 4 -> 3 -> 5 -> 6 -> 8 -> 7 -> 0
	19	17.66	0 -> 1 -> 2 -> 4 -> 3 -> 5 -> 6 -> 8 -> 7 -> 0	0 -> 1 -> 2 -> 4 -> 3 -> 5 -> 6 -> 8 -> 7 -> 0
	22	17.66	0 -> 1 -> 2 -> 4 -> 3 -> 5 -> 6 -> 8 -> 7 -> 0	0 -> 1 -> 2 -> 4 -> 3 -> 5 -> 6 -> 8 -> 7 -> 0

Table 2. Effect of the *p* variation on the ordered nurse visits sequence (*DLC*=50; *s*=0)

p_1	p_2	Costs	Delivery sequence	Production sequence
0	0	17.66	0 -> 1 -> 2 -> 4 -> 3 -> 5 -> 6 -> 8 -> 7 -> 0	0 ->①-> 2 -> 4 ->③->⑤-> 6 -> 8 ->⑦-> 0
0	1	17.66	0 -> 1 -> 2 -> 4 -> 3 -> 5 -> 6 -> 8 -> 7 -> 0	0 ->①-> 2 -> 4 ->③->⑤-> 6 -> 8 ->⑦-> 0
0	2	17.66	0 -> 1 -> 2 -> 4 -> 3 -> 5 -> 6 -> 8 -> 7 -> 0	0 -> 2 ->①-> 4 ->③-> 6 ->⑤-> 8 ->⑦-> 0
0	3	17.66	0 -> 1 -> 2 -> 4 -> 3 -> 5 -> 6 -> 8 -> 7 -> 0	0 -> 2 ->①-> 4 ->③-> 6 ->⑤-> 8 ->⑦-> 0
0	5	17.66	0 -> 1 -> 2 -> 4 -> 3 -> 5 -> 6 -> 8 -> 7 -> 0	0 -> 2 ->①-> 4 -> 6 ->③->⑤-> 8 ->⑦-> 0
0	7	17.66	0 -> 1 -> 2 -> 4 -> 3 -> 5 -> 6 -> 8 -> 7 -> 0	0 -> 2 -> 4 ->①-> 6 ->③-> 8 ->⑤->⑦-> 0
0	8	17.66	0 -> 1 -> 2 -> 4 -> 3 -> 5 -> 6 -> 8 -> 7 -> 0	0 -> 2 -> 4 ->①-> 6 -> 8 ->③->⑤->⑦-> 0