An optimization-based approach for delivering radio-pharmaceuticals to medical imaging centers

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Abstract It is widely recognized that early diagnosis of most types of cancers can increase the chances of full recovery or substantially prolong the life of patients. Positron Emission Tomography (PET) has become the standard way to diagnose many types of cancers by generating high quality images of the affected organs. In order to create an accurate image a small amount of a radio-active agent needs to be injected in the patient's body. These agents are produced in specially equipped pharmacies and then distributed to medical imaging centers which are located in metropolitan and rural areas. Due to the relatively fast decay process of the radio-activity levels it is very important that they arrive at the imaging centers well before the time that the patient enters the room where PET scanner is located. In this paper we discuss the distribution process of radio-pharmaceuticals and develop a flexible and efficient mathematical model. Our objective is to serve a number of customers within a pre-specified time interval at minimum transportation cost. At the same time the model ensures that all orders arrive at the imaging centers well before the patients enter the PET scanners. In addition the model takes into consideration the availability and capacity of the transportation vehicles. To demonstrate the effectiveness and efficiency of our optimization model we present preliminary computational results in a variety of test cases which show that it can achieve substantial savings in transportation costs.

1 Introduction

The transportation of products is a fundamental aspect in every efficient supply chain. With the fast development of economic globalization a variety of products routinely need to be transported to an ever increasing number of geographically dispersed customers. In recent years the distance among customers and production sites have increased dramatically, resulting in larger transportation costs. The most common transportation means are vehicles for ground transportation (e.g., pick up tracks and vans) which are mostly used for small quantities and/or light products. On the other hand, cargo planes are used for feaster long-distance deliveries and boats for larger quantities

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and heavier products. Each transportation means has a specific capacity and traveling speed. In most cases the products have to arrive at the customer locations within a pre-specified time interval which may make their transportation time-critical and complex.

A daily activity in today's pharmaceutical, medical, chemical and food industries involves the long-distance transportation of perishable products. The quality of such products may decay at rapid rates immediately after their production and during transportation. If a product does not meet certain quality criteria, the customer may discard it and refuse payment, in which case the manufacturing company may incur substantial loss of profit as well as customer dissatisfaction. In order to make sure their products arrive on time, in good quality and at minimum cost, companies have to carefully choose their transportation routes.

This paper develops an efficient and flexible optimization model that is able to find the most cost effective transportation routes of products manufactured in the radio-pharmaceutical industry. Nuclear medical imaging is routinely used for many diagnostic tests by physicians. In order to create an image for diagnostic purposes a small amount of a radio active agent is injected to the body of the patient and travels to the organ of interest. The emitted radiation is then detected and high accuracy images of the organ can be generated by Positron Emission Tomography (PET) scanners. Fludeoxyglucose (FDG) is the most commonly used radio-pharmaceutical PET. After FDG is injected into a patient's body, a PET scanner can form two or three dimensional images of the distribution of the FDG around the organ that needs to be examined. FDG has been used extensively for diagnosis, staging and monitoring treatment of cancers, particularly Hodgkin's disease, non-Hodgkin's lymphoma, colorectal cancer, breast cancer, melanoma and lung cancer. It has also been approved for use in diagnosis of Alzheimer's disease. When searching for tumors in the human body a dose of FDG is typically between 5 and 15 millicurie (denoted by mCi). The dose is injected rapidly into a saline drip running into a vein. The patient then waits for one hour for the sugar to distribute and be taken by organs that use glucose. To avoid consumption of the radioactive sugar by muscles (which use sugar) the patient must be in minimal physical activity. After one hour the patient is placed in a PET scanner for a series of scans, a process that may last from 20 minutes to one hour.

Sales of FDG have been growing since 2010 and are expected to exceed $880 million by 2017, while the market for PET radio-pharmaceuticals will increase to $3.5 billion by 2017 [3]. The production of FDG takes place in manufacturing facilities that contain special purpose equipments called cyclotrons [12]. Production is structured in batches and delivery takes place in doses. A dose contains the radio-active agent that will be injected to a patient before he/she enters the PET scanner. A fundamental activity in every manufacturing facility is the creation of a daily plan for the production of batches and distribution of doses to imaging centers and hospitals. An individual batch may provide sufficient product for up to forty or more individual doses.

A delivery schedule is a collection of doses that are assigned to transportation vehicles and routed to customer locations which are typically medical imaging centers or hospitals. Delivery schedules are site specific based on geography and local customer demand requirements. Typically, delivery schedules vary depending on the day of the week and/or seasonal ordering patterns. It is crucial that an order arrives at an imaging center at a certain time prior to the time that is going to be injected to the patient. If it arrives later, it may be discarded and the customer is not obliged to pay the cost of the doses. Other constraints associated with delivery schedules include the limited number of delivery vehicles available at the manufacturing site and the capacity of each vehicle.

Every day, it is necessary to create delivery schedules. Current practice is the delivery schedules to be generated manually by experienced personnel in the radio-pharmacies and as a result they are not optimized. This may result in two major issues: (a) the delivery of some orders may arrive at a customer location later than the actual injection time specified in the contract, resulting in extra cost for the pharmaceutical company as it needs to replace the order free of charge in a later time or day, and (b) since the delivery routes are not optimal they may cost more to the pharmaceutical company simply because the vehicles travel longer distances. Apart from the increased monetary cost, longer delivery routes result in the release of more greenhouse gas emissions which negatively affect the climate and human health. The main contribution of our work is to address the above limitations by defining an efficient mathematical optimization model that determines the routes that are the most cost effective and guarantee that all doses arrive at a customer location before their injection times. To the best of our knowledge this is the first paper that deals with the distribution of radiopharamceuticals.

The paper is structured as follows. In section 2 we present the work that has been done in the area of transporting short-lived products that is relevant to our problem. In section 3 we discuss the details of the problem and define the notation we will use in the rest of the paper. In section 4 we present the mathematical optimization model and we discuss its functionality and in particular the purpose that each constraint serves. In section 5 we present a number of numerical results obtained by our model and the savings in transportation costs achieved. Finally, in section 6 we conclude the paper and give directions of future work.

2 Literature review

The problem we study in this paper falls in the general category of the vehicle routing problem (VRP) which is well studied in the area of Operations Research [10]. There are many papers dealing with several variations/extensions of the VRP, mainly because of its wide applicability in real-world applications. However, there is very limited research in the distribution of radio-pharmaceuticals and for this reason we focus on the application of VRP in the distribution of short-lived products which must arrive at the customer site between a specified time window. Emphasis is given in applications in the medical field. The original VRP formulation was introduced by Dantzig and Ramser [4] back in 1959. A detailed review of the classical VRP has been written by Toth and Vigo [20] and Parragh et al [17]. Laporte [13] provides an overview of major VRP definitions as well as efficient exact and approximate algorithms for solving it. Savelbergh [18] focused on the complexity of the VRP and proved that it is an NP-hard problem.

In the classical VRP we are given a set of trucks with a limited capacity and a set of customers each having a known demand of a product that is manufactured in a specific location. The distance and traveling times from the manufacturing site to each customer location are known. The aim is to determine the minimum cost or distance routes such that (a) every customer is served by only one vehicle, (b) all routes start and end at the depot and (c) the transportation vehicles do not carry weight more than their capacity. A very popular extension of the VRP is the case where the customers request the delivery of their orders to arrive during a pre-specified time interval. This extension is known as the VRP with Time Windows (VRPTW) and it is often used in the transportation of perishable products. Many transportation problems in the radiopharmaceutical industry can be modeled as VRPTW.

In general, there two types of approaches used to solve VRPTWs: (i) exact (e.g., branch-and-cut, branch-and-price) and (ii) heuristics (e.g., tabu search, genetic algorithms). The literature is very large and we will only present a few papers that study the modeling and solution techniques for problems similar to ours. In [1] the authors describe an exact algorithm for solving the VRPTW where a single vehicle can participate in more than one routes. Their application area comes from the distribution of perishable goods where the routes are small and can be combined. In [2] an branch-and-cut algorithm is proposed in order to find the minimum number of vehicles required to visit a set of customers subject to time window constraints and capacity limitations. The authors introduce a wide variety of cuts and use then to tighten the relaxation of the MILP problem. Tarantilis and Kiranoudis [19] developed an efficient and robust meta-heuristic algorithm for solving the problem of distributing fresh milk using a heterogeneous fleet of vehicles. Hsu *et* al [11] proposed a model for the stochastic VRP with time windows and obtained optimal delivery routes, loads, fleet dispatching and departure times for delivering perishable products. Zanoni and Zavanella [21] developed an MILP model and a heuristic algorithm for solving the shipping of a set of perishable products from a single vendor to a common buyer with the objective of minimizing the sum of inventory and transportation costs. Osvald and Stirn [16] study the problem of distributing fresh produce and emphasize in the perishability of the transported products. They formulate the problem as VRP with time windows and time-dependent travel times. Their aim is to find transportation routes that minimize the distance and time traveled, the delay costs for servicing late a customer and the costs related with perishability. Doerner *et* al [6] developed a model and several heuristics for solving a novel type of a vehicle routing problem where time windows for the pickup of perishable goods depend on the dispatching policy used in the solution process. The application area is motivated by a project carried out with the Austrian Red Cross blood program to assist their logistics department. Dessouky *et* al [5] study the coordinated solution of the a facility location problem together with a VRP in order to ensure quick distribution of medical supplies in response to an emergency situation. Migahlaes and de Souza [15] present a model and an algorithm for solving VRP for the classical pharmaceutical industry, where the customer orders may change dynamically. More recently, Luo *et* al [14] propose a mathematical model for a VRP with stochastic demands and real-time vehicle control for distributing medical supplies in large-scale emergencies.

3 Problem description

It is common that pharmaceutical companies outsource the delivery of the doses to logistics companies, which are responsible for providing the transportation vehicles together with the drivers and the load and unload equipment. A driver may be allowed to work up to a certain number of hours, denoted by T (e.g., 8 hours), or drive a distance of a maximum number of miles per day (e.g., 250 miles). Also there is a maximum number of vehicles (denoted by N) that the logistics company makes available to the pharmaceutical company.

Mathematically the transportation of the doses to the medical imaging centers can be expressed as a general vehicle routing problem with time widows. Let $G = (V, E)$ be a complete undirected graph where $V = \{0, 1, 2, \dots, n\}$ represents the nodes of the graph and $E = \{(i, j) : i, j \in V\}$ is the set of edges connecting the nodes. The set of nodes consists of the radio-pharmacy, denoted by 0, and the imaging centers. For convenience we will denote the set of the imaging centers as $V_c = \{1, 2, \dots, n\}$. Also, throughout the paper we may refer to imaging centers as *customers*. Every imaging center places an order which consists of a number of doses. Let D_i represent the number of doses ordered by the i-th imaging center. In addition, the j-th dose ordered by the i-th imaging center has an injection time, T_{ij}^{INJ}, associated with it. All doses ordered by the a specific imaging center are delivered by the same vehicle. This means that the delivery vehicle must arrive at the imaging center before the earliest injection time, that is

$$T_i^{INJ} = \min\{T_{ij}^{INJ} : j = 1, \dots, D_i\}, \forall i \in V_c \tag{1}$$

Furthermore, every imaging center may require the delivery to arrive during a certain time window, $[e_i, \ell_i]$, where e_i represents the earliest and ℓ_i the latest arrival times. The latest arrival time may be a certain number of minutes, p_i, prior to T_i^{INJ} defined by (1). Therefore the vehicle must arrive at the i-th imaging center no later than

$$\ell_i = T_i^{INJ} - p_i. \tag{2}$$

It is also possible that some imaging centers do not allow deliveries prior to a certain time. For example, an imaging center may not accept doses to be dropped off before the center opens for business. In this case e_i will be set to the opening time of the imaging center. In the case where doses can be dropped off any time in the day (even when the imaging center is closed) we set $e_i = 0$.

The distance and the time it takes to drive between node i and node j are denoted by d_{ij} and t_{ij}, respectively. We obtain distances and drive times by using the *geo-coding* services offered by Google [9]. The service can provide the distance and duration matrices of a network of any number of nodes. The distance and duration measures are not symmetric. This means that in general we have $d_{ij} \neq d_{ji}$ and $t_{ij} \neq t_{ji}$. The cost, c_{ij}, of driving from a location i to a location j is defined as

$$c_{ij} = (m + f)d_{ij} + g \tag{3}$$

where the m is the cost of traveling one mile, f is the fuel surcharge that the logistics company asks for every mile traveled, and g is a flat amount charged by the drivers for every customer site they visit (typical value ranges of m, f and g are \$1.1-\$1.5, \$0.055-\$0.065, and \$10-\$15). Also there is a fixed cost, F, associated with every vehicle used.

The fleet of vehicles is homogeneous, meaning that all vehicles have the same weight capacity, denoted by W_{VEH}. During transportation to customer locations the doses are placed and sealed in lead or tungsten containers in order to minimize the radiation exposure. The weight of each container is denoted by W_{CON} (usually a container may weigh 32.5 lbs). Hence the total weight of the order of the i-th customer is defined by $W_i = D_i W_{CON}$. We assume that one vehicle will deliver all doses ordered by a customer, that is, we do not consider split orders. This means that all orders weigh less than the vehicles' capacity, i.e., $W_i \leq W_{VEH}$. If the order of the i-th customer weighs more than the vehicle's capacity, then this customer can be split into the appropriate number of *dummy* customers, $(i_1, \ldots, i_d)$ so that each of them is assigned orders whose total weight is less than the vehicle capacity.

Once a vehicle arrives at a customer location the drivers need to spend some time unloading the containers, signing certain documents and picking up empty boxes. This is called *service time* of customer i and is denoted by s_i. The service time may be fixed for all customers (e.g., 30 minutes) or may be a function of the number of doses ordered by the corresponding imaging center (e.g., $s_i = D_i s$, where s is the nominal time allocated for servicing one dose, typically 3 minutes).

Besides the parameters, described above, we need to introduce a number of variables whose optimal values will be determined by the solution of the mathematical model, described in the next section. More specifically, we use the binary variables y_{ij} to represent the order by which the network nodes are visited by the transportation vehicles, that is, $y_{ij} = 1$, if node i precedes node j, and $y_{ij} = 0$ otherwise.

Since every vehicle has a maximum weight capacity, we are also interested in the total weight carried by it during the complete route. Hence we define the variable w_i representing the total weight a vehicle has delivered until it has reached customer i. We also define the variable x_i representing the arrival time of a vehicle to customer site i (note that, in the implementation of the model, x_i is measured in minutes after midnight of the day of the delivery). Since the doses have to arrive at the customer before the dose with the earliest injection time we always have $x_i \leq \ell_i$, where ℓ_i is the latest time that a vehicle must arrive at a customer site and is defined in (2).

The objective of the pharmaceutical company is to determine delivery routes which will minimize the total transportation cost and guarantee that all orders reach the imaging centers before the specified injection time of each dose. In the remaining of this section we summarize the variables and parameters used in the mathematical description of the optimization model presented in the following section.

Parameters and sets

- n: number of medical imaging centers placing orders
- V: the set of all nodes in the network, $V = \{0, 1, \ldots, n\}$
- V_c: the set of all customer nodes in the network, $V_c = \{1, \ldots, n\}$
- E: the set of arcs in the network, $E = \{(i, j) : \forall i, j \in V\}$
- T: maximum time a driver is allowed to drive during a day
- N: maximum number of available vehicles
- D_i: the total number of doses ordered by imaging center i
- F: fixed cost for dispatching a vehicle
- c_{ij}: the cost of traveling from node i to node j
- d_{ij}: the distance of traveling from node i to node j
- t_{ij}: the time of traveling from node i to node j
- p_i: the time a vehicle must arrive at a customer prior to the injection time
- s_i: the service time needed by a driver to spend in an imaging center
- W_{VEH}: the vehicle weight capacity of each available vehicle
- W_{CON}: the weight of each container that seals a dose
- W_i: the weight of the total number of doses ordered by customer i
- $[e_i, \ell_i]$: the time window a dose must arrive in an imaging center

Variables

w_i: measures the weight a vehicle has delivered until it reaches customer i
x_i: the arrival time of a vehicle to customer site i
y_{ij}: 1, if node i is visited immediately before node j; 0 otherwise

4 Mathematical description of the optimization model

In this section we formally define the optimization model (equations (4) through (17)) and discuss in detail its major variables and constraints and the purpose they serve.

$$\min \sum_{i\in V}\sum_{j\in V} c_{ij}y_{ij} + F\sum_{j\in V_c} y_{0j} \tag{4}$$

$$\text{s.t.} \sum_{j=0,i\neq j}^{n} y_{ji} = 1,\ \ \forall i \in V_c \tag{5}$$

$$\sum_{j=0,i\neq j}^{n} y_{ij} = 1,\ \ \forall i \in V_c \tag{6}$$

$$\sum_{j\in V_c} y_{0j} \leq N \tag{7}$$

$$W_i \leq w_i \leq W_{VEH},\ \ \forall i \in V_c \tag{8}$$

$$w_i \leq W_{VEH} + y_{0i}(W_i - W_{VEH}),\ \ \forall i \in V_c \tag{9}$$

$$w_j \geq w_i + W_j - W_{VEH} + y_{ij}W_{VEH} + y_{ji}(W_{VEH} - W_j - W_i),\ \forall i,j \in V_c, i\neq j, \tag{10}$$

$$e_i \leq x_i \leq \ell_i,\ \ \forall i \in V_c \tag{11}$$

$$x_i \geq e_i + y_{0i}(t_{0i} - e_i),\ \ \forall i \in V_c, \tag{12}$$

$$x_i \leq y_{i0}(T - t_{i0} - s_i - \ell_i) + \ell_i,\ \ \forall i \in V_c \tag{13}$$

$$x_j \geq x_i - \ell_i + y_{ij}(\ell_i + t_{ij} + s_i),\ \ \forall i,j \in V_c \tag{14}$$

$$x_i \geq 0,\ \ \forall i \in V_c \tag{15}$$

$$w_i \geq 0,\ \ \forall i \in \{1,2,\ldots,N\} \tag{16}$$

$$y_{ij} \in \{0,1\},\ \forall i,j \in V \tag{17}$$

The objective function is defined in (4). In terms of the transportation costs we define it as the distance traveled by each vehicle multiplied by the cost per mile plus the fuel surcharge (see (3)). We have also added the fixed cost for using a vehicle.

To ensure the meaningfulness of our routes and avoid cycling, each customer should be visited once. After visiting that customer, we can only go for one customer next. Each truck can only deliver customers one by one and each customer can be only delivered once. These requirements are enforced by constraints (5) and (6). The maximum number of vehicles that are available every day in a radiopharmacy is enforced by constraint (7).

As stated by constraint (8) the total weight, w_i, delivered up to customer i should always be less than or equal to the capacity of the vehicle and greater than or equal to the weight of the order placed by customer i. Constraint (9) takes care of the case when the i-th imaging center is the first one to be visited by a vehicle. Indeed, when $y_{0i} = 1$ constraint (9) becomes $w_i \leq W_i$, which in conjunction with (8) gives us the stronger constraint $w_i = W_i$. When the i-th imaging center is not the first to be visited, then $y_{1i} = 0$ and constraint (9) becomes $w_i \leq W_{VEH}$ which is redundant. By combining the two constraints (8) and (9) we are able to strengthen the feasible region of our problem resulting in a faster location of the integer optimal solution.

The case where imaging center i is not the first one to be visited deserves special attention. This case is taken care of by constraint (10). In this case the value of the variable w_i is equal to the weight of the orders of all the imaging centers that were visited between the pharmacy and the i-the center itself. For example, if center j is immediately after center i, then $y_{ij} = 1$ and $y_{ji} = 0$. As a result, constraint (10) becomes $w_j \geq w_i + W_j$ which means that the weight delivered to center j is at least equal to that delivered in center i plus the weight of the order of center i. If, on the other hand, center j is visited immediately before center i then we have $y_{ij} = 0$ and $y_{ji} = 1$, and constraint (10) becomes $w_j \geq w_i - W_i$. This constraint states that the weight delivered between the pharmacy and the j-th imaging center is not less than the weight delivered between the pharmacy and the i-th imaging center. In addition if center j is visited immediately before center i, we can deduce that $w_i \geq w_j + W_i$. Combining the last two inequalities we obtain the equation $w_i = w_j + W_i$. If centers i and j are not visited successively, then constraint (10) becomes $w_j \geq w_i + W_j - W_{VEH}$. By noting that the right hand side of the above constraint is always less than zero and by using the fact that $W_i \geq 0$ and the constraint (8), we can deduce that (10) becomes redundant.

In addition, a very important requirement in the delivery of radio-pharmaceuticals is the time window that a dose must arrive at an imaging center. We use the variable x_i in order to measure the time when a vehicle arrives at customer i. Constraint (11) defines the time window that a vehicle is allowed to arrive at customer i. The lower bound e_i defines the time after which the vehicle must arrive at the customer. If the driver of the vehicle can drop the orders any time at the customer or imaging center then $e_i = 0$, otherwise a value must be specified. The upper bound ℓ_i defines the latest time that the vehicle must arrive at the customer. Usually the customers and imaging centers request a dose to arrive a certain number of minutes before its injection time to the patient. Therefore the upper bound ℓ_i is initialized according to equation 2.

Constraints (13) and (14) define tighter upper and lower bounds on the arrival time at a customer location taking into consideration the customer sites that precede or follow site i. We analyze first constraint (13), which sets an explicit upper bound on the arrival time at the last customer site visited in a route. That is, if the i-th imaging center is the last one visited in a route then $y_{i0} = 1$ and (13) becomes $x_i \leq T - t_{i0} - s_i$. On the other hand, constraint (14) connects the arrival time between two consecutive locations. For example, if customer i precedes customer j, then $y_{ij} = 1$ and (14) becomes $x_j \geq x_i + t_{ij} + s_i$. Otherwise (i.e., when $y_{ij} = 0$), constraint (14) becomes $x_j \geq x_i - \ell_i$ which is redundant due to the constraint (11).

Finally, all the variables are continuous except y_{ij} which are binary. These requirements are described by constraints (15) to (17) in the optimization model.

5 Computational results

To illustrate the efficiency and practicality of the proposed mathematical model we initially present a case study describing the distribution of orders during a typical day in a radio-pharmacy. Due to confidentiality of company and patient data we do not present the names or the locations of the medical imaging centers or hospitals that placed orders. We solve the model by using the FICO-Xpress optimization package, which includes a powerful modeling language (Mosel) [7] and efficient solvers [8] that can solve problems with integer and continuous variables as well as linear and nonlinear constraints.

The current practice in the radio-pharmacy of interest is to have employees (typically the pharmacists) to produce the distribution schedules and routes for the delivery vehicles. Although the pharmacists have great domain knowledge and experience, oftentimes they come up with sub-optimal delivery schedules, resulting in routes that cost more to the company and may not guarantee the on-time arrival at an imaging center. In addition, having pharmacists determining the delivery routes takes valuable time away from their main tasks and decreases their productive time by at least 30 minutes per day. We expect the optimization model we have developed to be a valuable decision support tool for every radio-pharmacist, since it will save them a lot of time and at the same time produce cost effective delivery routes saving a large amount of money to the pharmaceutical company.

The data for the model's parameters are obtained from two main sources. The first source is the pharmacy's Enterprise Resource Management (ERM) system, which stores information related to the doses ordered by the customers (e.g., the number of doses ordered by each imaging center, the injection times of the doses, the time windows when the orders must arrive at the customer, the addresses of the customers, etc). The second source is the Google Geocoding API [9] which can provide the distance and duration matrices of a set of customer locations provided that their addresses are available. Note that both matrices are not symmetric. We used the addresses of the radio-pharmacy and all the customers that have placed orders and created the corresponding distances, d_{ij}, and traveling times, t_{ij}.

For our case study, we selected a typical week day which consists of 16 imaging centers, denoted by C1 to C16. Those centers were requesting 67 doses in total. Table 1 presents more details about the orders placed by each imaging center. The doses were produced at the manufacturing site (radio-pharmacy) which is denoted by C0. The orders were ready for pickup by the drivers at 04:00 in the morning. All doses in an order have to arrive at the corresponding imaging center 30 minutes prior to the dose with the earliest injection time, described in the third column of Table 1. Orders can be delivered any time at all customer locations (even when they have not opened yet). This means that the early time is set to zero (i.e., e_i=00:00 or midnight). The service time at each customer location was set to 10 minutes. In the fourth column of Table 1 we have recorded the arrival time obtained by the optimal solution of our mathematical model. As can be seen all orders arrived well before the earliest injection time minus 30 minutes (the specified common early time).

The total transportation cost was $1,258.36 and the total distance traveled by all drivers was 950.96 miles. The optimal routes are shown in Figure 1.A. On the left side of every connecting arc there are two values. The values in parentheses denote the drive time from one location to the next, whereas the other values denote the distance. As can be seen a total of 6 vehicles (equivalently, six drivers) were used to deliver the orders to all imaging centers.

In contrast, the routes determined by the pharmacist (actual routes) cost $1,493.83 and the total number of miles covered was 1,154.83. Figure 1.B shows the graph of the actual routes and Table 2 compares the total cost and distance for the optimal and actual routes. In addition, it summarizes the improvements we get when the optimal

Customer ID	Doses ordered	Earliest dose injection time	Arrival time
C1	5	07:15	04:05
C2	4	08:00	04:32
C3	5	07:15	04:23
C4	3	08:45	06:39
C5	2	09:00	06:23
C6	6	08:45	06:33
C7	6	07:30	06:37
C8	2	09:00	07:15
C9	3	09:15	05:50
C10	4	09:30	06:27
C11	1	10:30	09:36
C12	3	08:45	04:37
C13	4	08:30	07:28
C14	13	12:30	04:38
C15	3	09:45	05:38
C16	3	08:00	04:02

Table 1 Details for the orders placed by imaging centers.

routes are used. As can be seen, there was a total of 15.76% reduction in transportation cost and 17.65% reduction in traveled distance. In addition the actual routes needed 8 vehicles, which represents an increase of two vehicles more than those needed by our model. This is quite important since it demonstrates better utilization of the vehicle capacity which is very useful when the logistics company does not have availability of the extra drivers or may charge more for offering additional vehicles.

	Delivery cost	Travel distance	Number of vehicles
Optimal routes	1,258.36	950.96	6
Actual routes	1,493.83	1,154.83	8
Improvements	15.76%	17.65%	33.33%

Table 2 Summary of the improvements in total cost, distance traveled and vehicles used between the optimal and actual routes.

Examining Figures 1.A and and 1.B closer we can see that our optimization model determined a much better way of delivering the orders to customers C10 and C11. More specifically, our model used one vehicle to travel to C10 and then to C11, whereas the pharmacist decided to use two vehicles to travel separately to C10 and C11. The total distance traveled by the vehicle of our model was 165+148=313 miles. On the other hand, the two vehicles sent by the pharmacist, traveled a total of 293+165=458 miles. It is these type of route consolidation that can provide substantial savings in traveling distance (in this case 458-313=145 miles), monetary cost and number of vehicles needed. An exactly similar situation arises with customers C9 and C13. Our model used one vehicle and traveled a total of 114+96=210 miles, whereas the pharmacist used two vehicles which traveled a total of 114+207=321 miles.

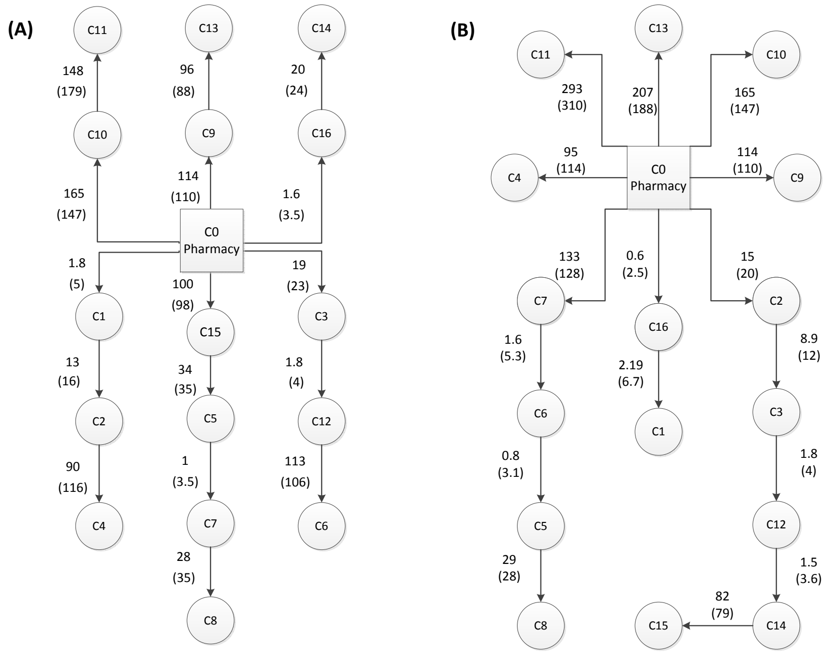

Fig. 1 The optimal routes are shown in graph (A) and the actual routes in graph (B). The distances are measured in miles and the drive times (in parentheses) are measured in minutes. The doses of all orders are available for pickup by drivers on 04:00. The actual routes are determined by experienced pharmacists or other personnel working in the radio-pharmacy.

We also used our model to compute optimal routes and compare them with those determined by pharmacists for a period of one week during the month of May 2014. That week contains some customers that are located far from the radio-pharmacy and some others that are located in close proximity. Also the total number of imaging centers that place orders in each day may vary. In Table 3 we include the number of customers (i.e., imaging centers) assigned to each batch for all the days. As can be seen the first batches in each day contain more customers. This is because the radiopharmacies try to satisfy as much demand as possible early in the day. The size of the MILP problems corresponding to batches assigned early in the day is larger and will therefore require more time to be solved than the later batches. Table 4 summarizes the improvements we get when we use the routes computed by our optimization model. It should be mentioned, however, that the size of all MILP problems is relatively small and the Xpress solver finds the optimal solution in few seconds. For this reason we do not report the CPU time needed to solve these problems. Our main focus is on the savings we obtain in the delivery cost and transportation distance compared to those obtained by pharmacists or other experiences personnel.

In all cases the optimization model produced routes that are more cost effective and need fewer vehicles than the actual ones. The highest improvements are obtained in batch 1 of day 1 where we have more than 20% improvements in both the cost and miles traveled. This is because the imaging centers fulfilled by that batch are far away

Day♯.Batch♯	Number of customers	Day♯.Batch♯	Number of customers
Day1.Batch1	16	Day3.Batch1	14
Day1.Batch2	13	Day4.Batch1	16
Day1.Batch3	10	Day4.Batch2	14
Day2.Batch1	14	Day5.Batch1	17
Day2.Batch2	13	Day5.Batch2	16
Day2.Batch3	11	Day5.Batch3	12

Table 3 Summary of the total number of imaging centers in each batch and day.

from each other and from the radio-pharmacy. Therefore, determining a cost effective set of routes for delivering the orders becomes difficult for human experts even when they have extensive experience in the subject.

On the other hand there are batches where the routes determined by the optimization model and the human expert do not differ much in terms of cost and distance traveled (see for example batch 3 in day 2 and batches 2 and 3 in day 1). This is also expected because most of the imaging centers in those batches are located close to each other and to the radio-pharmacy. As a result there is not much loss if a sub-optimal route is selected.

Table 5 summarizes the total improvements we obtain for all batches when we use our optimization model. We obtain savings in both the total delivery cost and traveling distance. The cost savings represent great news for the pharmaceutical company as they can invest them in other activities such as research and development of new drugs. The savings in the traveling distance has the important benefit of reducing the emissions released to the environment by the delivery vehicles and the positive impact to the quality of air and people's lives.

Finally we tested our optimization model on few days that contain a larger number of customers in order to see how computation time grows in terms of the size of the MILP problem. We could only obtained data for three days, which contained more than 25 customers placing orders. These represent large cases in the radiopharmaceutical industry. The details are shown in Table 6 and the results are summarized in Table 7. We can see that the optimization model is solved in relatively short time. We believe that the running time can be reduced further if valid inequalities and heuristics were introduced during the solution process. We plan to investigate this in a follow up paper. We should also mention that it was not possible to obtain the actual routes (i.e., the routes determined by the experienced personnel) and for this reason we do not report any improvements. We expect, however, the improvements to be larger than those reported in Table 2 as it is impossible for any human expert to determine the optimal routes as the number of customers becomes larger.

6 Conclusion

We have presented a new way of determining routes for delivering radio-pharmaceuticals to medical imaging centers that are geographically dispersed. The mixed integer optimization model we have developed can provide the most cost effective transportation routes and guarantees that all doses will reach the imaging centers before the time they

	DAY 1	Delivery cost	Distance traveled	Vehicles used
Batch 1	Optimal routes	1058.22	846.94	4
	Actual routes	1339.73	1090.67	6
	Improvements	21.01%	22.35%	
Batch 2	Optimal routes	517.19	343.89	5
	Actual routes	535.42	359.67	7
	Improvements	3.4%	4.39%	
Batch 3	Optimal routes	367.22	222.7	4
	Actual routes	380.03	233.79	5
	Improvements	3.37%	4.74%	
	DAY 2	Total cost	Total distance	Vehicles used
Batch 1	Optimal routes	1035.21	827.02	4
	Actual routes	1125.25	904.98	5
	Improvements	8.0%	8.61%	
Batch 2	Optimal routes	635.23	446.09	6
	Actual routes	693.93	496.92	7
	Improvements	8.46%	10.23%	
Batch 3	Optimal routes	238.41	154.47	3
	Actual routes	240.88	156.61	3
	Improvements	1.026%	1.366%	
	DAY 3	Total cost	Total distance	Vehicles used
Batch 1	Optimal routes	313.86	202.48	3
	Actual routes	337.84	223.26	4
	Improvements	7.11%	9.31%	
	DAY 4	Total cost	Total distance	Vehicles used
Batch 1	Optimal routes	1258.36	950.96	7
	Actual routes	1493.83	1154.83	8
	Improvements	15.76%	17.65%	
Batch 2	Optimal routes	539.94	380.9	3
	Actual routes	596.58	421.28	3
	Improvements	9.5%	9.58%	
	DAY 5	Total cost	Total distance	Vehicles used
Batch 1	Optimal routes	786.21	611.44	4
	Actual routes	807.65	630.0	5
	Improvements	2.65%	2.95%	
Batch 2	Optimal routes	398.52	267.11	5
	Actual routes	445.30	307.62	5
	Improvements	10.50%	13.17%	
Batch 3	Optimal routes	555.68	420.50	4
	Actual routes	582.17	443.44	5
	Improvements	4.55%	5.17%	

Table 4 Comparisons of optimal and actual routes and the improvements we obtain. The costs are in USD and the distances in miles.

	Total cost	Total distance	♯ of vehicles
Optimal routes	7,704.05	5674.50	52
Actual routes	8,578.61	6423.07	63
Actual − Optimal	874.56	748.57	11
Improvements	10.19%	11.65%	17.46%

Table 5 Summary of the total cost, distance and number of vehicles used for a week.

Day♯.Batch♯	Number of customers
Day6.Batch1	27
Day7.Batch1	32
Day8.Batch1	35

Table 6 Number of customers in larger batches.

	DAY 6	Delivery cost	Distance traveled	Vehicles used	CPU time (s)
Batch 1	Optimal routes	1876.32	1383.87	12	209
	DAY 7	Total cost	Total distance	Vehicles used	CPU time
Batch 1	Optimal routes	2338.51	1748.93	14	241
	DAY 8	Total cost	Total distance	Vehicles used	CPU time
Batch 1	Optimal routes	2524.89	1883.34	15	265

Table 7 Computational results for batches containing a larger number of customers. The CPU time is measured in seconds.

need to be injected to the patients. The optimization model has been applied on an illustrative example which demonstrates the monetary and mileage savings as well as the better utilization of the transportation vehicles. We have also tested the model on a typical week where each day has a different demand. From that computational study we were able to deduce that higher savings in delivery costs and distance are obtained when the number of the imaging centers increases and the distance between them and the production facility is large.

We plan to extend the model to cover the cases where (i) the fleet of transportation vehicles is not homogeneous, that is there are vehicles with different capacities and diving speed, (ii) determine which customers to serve first when there are not enough vehicles to fulfill all orders, and (iii) determine the best strategy by which a vehicle would collect empty containers (used in previous days) from the imaging centers it visits.

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