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Design and analysis of a satellite network with direct delivery in the pharmaceutical industry

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ABSTRACT

Creating and maintaining an efficient distribution network is essential for companies in the modern pharmaceutical industry. Medicine delivery usually takes place via depots and/or satellites, and the proposed model for assessing the issue determines the facility and routing decisions simultaneously. We develop a technique that iterates between an upper bound and a lower bound, based on a blended Lagrangian relaxation branch-and-cut approach where we exploit separability and linearity. We conducted computational experiments on real-life instances from the Dutch pharmaceutical industry distribution network. We show that the solution method can provide solutions for real-life cases within reasonable time windows.

1. Introduction

The efficient distribution of products to customers is one of the most important tasks of a manufacturing company. [Srivastava and Benton \(1990\)](#) state that the overall cost of transportation and warehousing is over 20% of the gross domestic product. Transportation costs are particularly important for the pharmaceutical industry. In the Netherlands, for example, this has been made much more crucial by the insurance companies when choosing whether to buy a particular brand, resulting in intense price competition among medicine suppliers. This competition has led to a significant decrease in the profit margins of medicine suppliers and distributors. The design of distribution networks has therefore become very useful to suppliers, since it provides an opportunity to both reduce logistics costs and improve customer service quality. Without efficient distribution networks, pharmaceutical companies cannot survive in this current competitive market.

There are two key factors relevant to designing an efficient distribution network: location and routing decisions. Traditionally, these two levels of decision-making have been handled independently of one another; it has been shown, however, that this strategy often leads to suboptimal solutions ([Salhi and Rand, 1989](#); [Li et al., 2016](#)). We are therefore tackling the distribution problem of the pharmaceutical industry by considering location and routing problems simultaneously. The distribution network needs to be designed in such a way that customer expectations with regard to short service times and tight supply deadlines are met. Although late-arrivals are unacceptable, it is possible to distribute the medicines earlier within a defined time window. Accordingly, we will develop a solution technique reflecting these challenges.

The distribution network of a pharmaceutical company consists of the design of depots, from which medicines are transported to customers. In practice, the fixed costs associated with opening an additional depot are very high. In light of this, opening satellites (distribution centers) may be a sound strategic choice, since they can extend service range and minimize routing costs. At satellites, vehicles can drop a portion of their holding capacity, and these unloaded medicines can then be transhipped to customers by another truck starting at the satellite. Accordingly, a satellite is considered as a facility that can supply customers if the satellite is open and

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Fig. 1. Sample solution to a medicine-distribution problem.

connected to a depot. The main advantage of a satellite in comparison to a depot is the former's significantly lower opening costs.

In summary, this study analyzes a real-world LRP (location routing problem) faced by pharmaceutical industry distributors. The attributes of the problem are as follows. There exists a set of depots, satellites, and customers. It is assumed that a fleet of vehicles is already available, hence no fixed costs are associated with the vehicles. Furthermore, the medicine packages are considered to be sufficiently small, allowing many customer demands to be satisfied by one vehicle. The travel time consists of the length of the route plus the service time needed at the satellites and customers. A feasible route starts and ends at the same node, and the travel time for the route cannot exceed a predetermined maximum route length. There are fixed costs associated with opening a depot or satellite. A satellite (distribution center) is an intermediary point for a customer and a distributor. The satellites can only supply customers if the satellite is located along a route that originates at a depot. Direct delivery from the depot is also possible within the medicine supplier situation. The facilities are capacitated in such a way that they can only handle a certain number of customer orders. In a feasible solution, every customer is visited within their designated time window. The challenge is to determine which depots and satellites to open and, simultaneously, to develop corresponding vehicle routes that visit the open satellites and customers. The objective is to minimize total costs, which may be divided into facility costs and routing costs.

Fig. 1 illustrates a possible feasible solution to the distribution problem the pharmaceutical industry is facing. The depots, satellites, and customers are depicted as rectangles, triangles, and circles, respectively. The dashed lines imply that the facility is not open in terms of the current solution, while the gray area is outside the service range of the activated depot. Therefore, the rightmost satellite is activated to be able to serve customers.

To solve this problem faced by medicine suppliers, we will design a mathematical model and develop a technique that iterates between lower bounds and upper bounds. For computing upper bounds, we will make use of the decomposed problem structure and develop heuristics based on node-based approaches, greedy techniques, enhanced Clarke and Wright routing techniques, and sub-network formations. For the lower bound, we will exploit the linearity as well as the separability and develop a blended branch-and-cut Lagrangian relaxation approach. We will test our solution technique for real life instances based on the Dutch pharmaceutical industry distribution network.

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Our contribution is twofold. First, we are extending the previous research on location-routing problems by considering a direct-shipment structure where links between depots and customers are allowed when this can lead to a better utilization of the network. Moreover, to the best of our knowledge, this is the first time that a Lagrangian relaxation with branch-and-cut on allocation constraints is applied to LRP within an iterative upper bound and lower bound heuristic.

The remainder of the paper is organized as follows. Section 2 reviews the literature most relevant to the problem under consideration. Section 3 provides the mathematical formulation. While in Section 4, the overall framework of the solution method is presented. Here, we will first elaborate on the upper bound heuristic created for the solution method. The procedure to find the lower bound at each iteration of the solution technique will then be explained. The computational results of the study are presented in Section 5, followed by conclusions.

2. Related literature

Distribution network design determines and manages the supplying of goods to the right location at the right time (Xu et al., 2001). In the classical facility location problem, it is assumed that each good is shipped directly from its origin to its destination by a single driver (Balinski, 1965). In such cases, the empty travel distances are relatively large, since the driver immediately returns to

home base after a drop-off (Üster and Kewcharoenwong, 2011). Some fifty years ago, the idea of determining location and routing decisions simultaneously was put forward (Von Boverter, 1961). This concept resulted in a body of research known as the location routing problem. Surveys on this topic are published by Min et al. (1998), Nagy and Salhi (2007), Balakrishnan et al. (1987), Prodhon and Prins (2014) and Drexel and Schneider (2015). In the five decades since the LRP was first introduced, numerous different variations have emerged which have been accompanied by the development of a variety of algorithms and heuristics (Laporte et al., 1988; Albareda-Sambola et al., 2005; Escobar et al., 2014; Koç et al., 2016; Menezes et al., 2016; Hof et al., 2017). Rodríguez-Martin et al. (2014) solved the hub location routing problem, and authors Karaoglan et al., 2011 solved the LRP with simultaneous pickup and delivery by means of a branch and cut algorithm. Prins et al. (2007) presented a cooperative metaheuristic involving the Lagrangian relaxation to solve the LRP with capacitated routes and depots. Duhamel et al. (2010) developed a population metaheuristic for homogenous fleet of vehicles. Prins et al. (2006) developed a metaheuristic and used path relinking for post-optimization. Hof et al. (2017) studied the battery swap station location-routing problem with capacitated electric vehicles. They developed a neighborhood search heuristic to determine the swap station locations and the vehicle routes.

One extension to the LRP is the inclusion of time windows. Customers in the modern industry often expect delivery within a time interval. The LRP therefore necessarily includes the presence of time windows (LRPTW). Ponboon et al. (2016) solved the LRPTW by using branch and price. Determining the exact travel time of a given route is difficult due to different factors, including traffic volume and time spent waiting at traffic lights (Laporte et al., 1989). Zarandi et al. (2011) considered the LRP with capacitated facilities, vehicles, and time window constraints. The travel times are uncertain and represented by triangular fuzzy variables. A simulation-embedded procedure is proposed in order to solve the problem. Koç et al. (2016) focused on heterogeneous fleets of vehicles with different vehicle related costs with known demands and time windows. They proposed a metaheuristic based on evolutionary search.

Another direction in the LRP literature is differentiating between different levels in the network (Santos et al., 2015). In the two-echelon vehicle routing problems (2E-VRP) and LRP (2E-LRP), the customers are not directly served from a central depot but via intermediate facilities (satellites). Here two different vehicle routes must be distinguished, namely the routes from depots to satellites, and the routes from satellites to customers.

The 2E-VRP has been studied by several authors (see, for example, Perboli et al. (2011), Jepsen et al. (2013), Baldacci et al. (2013), Santos et al. (2014)). A 2E-VRP, with a multi-depot, multi-product, heterogeneous fleets and time windows specifics is studied by Crainic et al. (2009). Soysal et al. (2015) considered environmental issues. Ahmadizar et al. (2015) introduced cross-docking facilities into the 2E-VRP. Recently, Grangier et al. (2016) analyzed a multi-trip 2E-VRP. As opposed to LRP, these do not include the location decisions in their process.

A relevant survey of two-echelon LRP has been published by Cuda et al. (2015). Jacobsen et al. (1980) and Madsen (1983) were among the first authors to focus on the 2E-LRP within the context of newspaper delivery. Lin and Lei (2009) followed these studies and used genetic algorithm to locate uncapacitated distribution centers. Nguyen et al. (2012b) tackled the 2E-LRP with a single central depot and a set of potential satellites with limited capacities. The depot location is already determined in their study. In Nguyen et al. (2012a), they then implemented a multi-start iterated local search strengthened by various heuristics. Boccia et al. (2010) studied the 2E-LRP with several plants and used tabu search handling the problem as two capacitated LRP at each echelon. Boccia et al. (2011) addressed the similar problem and introduced mixed-integer models with two-index and three index vehicle-flow formulations. Contardo et al. (2012) proposed a branch-and-cut algorithm for the same problem with multiple depots. Schwengerer et al. (2012) developed a variable neighborhood search (VNS) for the 2E-LRP with several plants. Where studies by Jacobsen et al. (1980), Nguyen et al. (2012b) dealt with a single depot, Contardo et al. (2012), Crainic et al. (2011a,b), Govindan et al. (2014), Laporte and Nobert (1988), Madsen (1983), Schwengerer et al. (2012) extended this with a multi-depot setting.

A similar problem to the 2E-LRP is the truck and trailer routing problem (TTRP). This problem arises where some customers have accessibility restrictions and cannot be reached with the trailer. In such routes the trailer needs to be decoupled from the truck where these parking locations are viewed as satellites. However, no capacity nor opening cost are linked to these satellites (Prodhon and Prins, 2014; Villegas et al., 2011). The TTRP has been focused by several authors (see for example Chao (2002), Scheuerer (2006), Gillett and Miller (1974), Tan et al. (2006), Lin et al. (2010), Lin et al. (2009), Lin et al. (2011), Caramia and Guerriero (2010), Derigs et al. (2013)).

The combination of the two echelon distribution structure with time windows has not yet been studied well. To the best of our knowledge, the most relevant work to our study is by Govindan et al. (2014). They introduced the two-echelon location routing problem with time windows (2E-LRPTW) differentiating between different levels in the network for sustainable supply chain network design. The aim of the 2E-LRPTW is to determine the number and location of facilities and to optimize the number of products delivered to lower stages and routes at each level. Intermediary facilities are used to facilitate the transportation among different echelons of the network. Govindan et al. (2014) used a metaheuristic to solve the 2E-LRPTW. The key difference between Govindan et al. (2014) and our work is twofold. First we generalize the model by considering direct delivery from depot to customer. We note that the complexity of the problem is increased with the direct delivery option as more decision variables and the constraints will be added to generalize the model. Second, to tackle this complexity, we develop a novel heuristic that builds on a problem specific upper bound heuristic and a blended branch-and-cut Lagrangian relaxation method. Numerical experiments show that our heuristic outperforms the metaheuristic developed by Govindan et al. (2014).

3. Problem formulation

In this section the formal definition of the problem will be given. Then a mathematical model will be proposed. Given a set D of potential depots, a set H of potential satellites and a set C of customers, the medicine suppliers' problem can be defined in directed

graph $G = (V, E)$, where $V = D \cup H \cup C$ is the set of nodes, and $E = \{(i, j) | i, j \in V\}$ is the set of all edges. Set H consists of two subsets H_C and H_D that respectively denote the set of all customer and distributor nodes of the satellites. Opening a depot or satellite is accompanied by a fixed opening cost: d_i and h_j for every $i \in D$ and $j \in H_D$, respectively. The maximum capacity of the depots and satellites is represented by ω_i and γ_j for every $i \in D$ and $j \in H_D$. Every edge $(i, j) \in E$ is associated with a positive routing cost c_{ij} and travel time t_{ij} . It is assumed that the travel time and distance are equivalent, and therefore these are used interchangeably. All open facilities and customers are connected via a set of routes given by R , and the maximum duration of a single route is given by Φ . A vehicle route is considered feasible if it starts and ends at the same facility and does not exceed the maximum route duration constraint. Each customer has a time window with a lower bound l_i and upper bound g_i for every $i \in C$. The service time associated with node $i \in V$ is given by s_i , where $s_i > 0$ for $i \in C \cup H_C$ and $s_i = 0$ for $i \in D$. Lastly, let u_i be the subtour elimination variable for every $i \in C \cup H_C$.

The following decision variables are used:

- $f_{ij} = 1$ if customer j is assigned to facility i , for every $j \in C \cup H_C$ and $i \in D \cup H_D$.
- $X_{ijr} = 1$ if edge (i, j) is traversed in route r , for every $(i, j) \in E$ and $r \in R$.
- $F_i = 1$ if facility i is open, for every $i \in D \cup H_D \cup H_C$.
- y_i , starting time of node i , for every $i \in V$.

The mixed integer linear program is as follows:

$$z = \min \sum_{i \in D} d_i F_i + \sum_{i \in H_D} h_i F_i + \sum_{i \in V} \sum_{j \in V} \sum_{r \in R} c_{ij} X_{ijr} \quad (1)$$

subject to

$$F_i = F_j \quad \forall i \in H_D, j = i + |H_D| \quad (2)$$

$$\sum_{i \in D} f_{ij} = F_j \quad \forall j \in H_C \quad (3)$$

$$\sum_{i \in D \cup H_D} f_{ij} = 1 \quad \forall j \in C \quad (4)$$

$$f_{ij} = 0 \quad \forall i \in H_D, j = i + |H_D| \quad (5)$$

$$\sum_{j \in C \cup H_C} f_{ij} \leq \omega_i F_i \quad \forall i \in D \quad (6)$$

$$\sum_{j \in C} f_{ij} \leq \gamma_i F_i \quad \forall i \in H_D \quad (7)$$

$$\sum_{r \in R} \sum_{i \in V} X_{ijr} = 1 \quad \forall j \in C \quad (8)$$

$$X_{ijr} = 0 \quad \forall i \in H_D, \forall j \in H_C, \forall r \in R \quad (9)$$

$$X_{ijr} = 0 \quad \forall i \in H_C, \forall j \in H_D, \forall r \in R \quad (10)$$

$$X_{ijr} = 0 \quad \forall i \in D \cup H_D, \forall j \in D \cup H_D, \forall r \in R \quad (11)$$

$$\sum_{j \in V} X_{ijr} - \sum_{j \in V} X_{jir} = 0 \quad \forall i \in V, \forall r \in R \quad (12)$$

$$\sum_{r \in R} \sum_{j \in C} X_{ijr} \geq F_i \quad \forall i \in H_D \quad (13)$$

$$\sum_{r \in R} \sum_{i \in V} X_{ikr} \leq M F_k \quad \forall k \in D \cup H_D \quad (14)$$

$$\sum_{r \in R} \sum_{j \in V} X_{ijr} = F_i \quad \forall i \in H_C \quad (15)$$

$$\sum_{i \in D} \sum_{j \in C \cup H_C} X_{ijr} + \sum_{k \in H_D} \sum_{m \in C} X_{kmr} \leq 1 \quad \forall r \in R \quad (16)$$

$$\sum_{r \in R} X_{ijr} \leq f_{ij} \quad \forall i \in D, \forall j \in C \cup H_C \quad (17)$$

$$\sum_{r \in R} X_{jir} \leq f_{ij} \quad \forall i \in D, \forall j \in C \cup H_C \quad (18)$$

$$\sum_{r \in R} X_{ijr} \leq f_{ij} \quad \forall i \in H_D, \forall j \in C \quad (19)$$

$$\sum_{r \in R} X_{jir} \leq f_{ij} \quad \forall i \in H_D, \forall j \in C \quad (20)$$

$$\sum_{r \in R} X_{ijr} + f_{ki} + \sum_{m \in D \cup H_D, m \neq k} f_{mj} \leq 2 \quad \forall k \in D \cup H_D, \forall i \in C \cup H_C, \forall j \in C \cup H_C \quad (21)$$

$$\sum_{j \in V} X_{ijr} + \sum_{j \in V} X_{jkr} \leq 1 \quad \forall i \in D, \forall k \in H_D, \forall r \in R \quad (22)$$

$$u_i - u_j + (n-1)X_{ijr} \leq n-2 \quad \forall i \in C \cup H_C, \forall j \in C \cup H_C, \forall r \in R \quad (23)$$

$$\sum_{i \in V} \sum_{j \in V} X_{ijr}(t_{ij} + s_i) \leq \Phi \quad \forall r \in R \quad (24)$$

$$y_{ir} = 0 \quad \forall i \in D \cup H_D, \forall r \in R \quad (25)$$

$$y_i - y_j + s_i + t_{ij} \leq M(1 - X_{ijr}) \quad \forall i \in V, \forall j \in C \cup H_C, \forall r \in R \quad (26)$$

$$l_i \leq y_i \leq g_i \quad \forall i \in C \quad (27)$$

$$F_i \in \{0, 1\} \quad \forall i \in D \cup H_D \cup H_C \quad (28)$$

$$f_{ij} \in \{0, 1\} \quad \forall i \in D \cup H_D, \forall j \in C \cup H_C \quad (29)$$

$$X_{ijr} \in \{0, 1\} \quad \forall i \in V, \forall j \in V, \forall r \in R \quad (30)$$

The objective function (1) minimizes the combination of the facility and routing costs. From the modelling perspective each satellite consists of two virtual nodes, namely a distributor and a customer node where distributor node receives delivery from a depot and the customer node delivers the goods to the customers. Constraints (2) guarantee that when the distributor node of a satellite is open, the customer node must be open as well. The customer node of a satellite can have outgoing edges to the customers, while the distributor node of a satellite must have exactly one incoming edge from a route with a depot at its origin. Constraints (3) guarantee that if a satellite is open it is linked to a depot. Constraints (4) state that every customer must be assigned to either a depot or a satellite. Constraints (5) guarantees that the customer node of a satellite must be allocated to a depot. Moreover, since every facility has a maximum number of orders it can handle, Constraints (6) and (7) impose limits on the number of customer orders allocated to each facility, while constraints (8) ensure that every customer is visited by precisely one route. The distributor node and customer node of a satellite can never be directly connected. Furthermore, a depot or distributor node of a satellite can never be directly connected to another depot or distributor node of another hub. Constraints (9), (10), and (11) express these routing restrictions. Constraints (12) guarantee the continuity of each route and that every route returns to its origin. When a satellite is open, the distributor node of the satellite must have at least one outgoing edge. Constraints (13) ensure this, while constraints (14) guarantee that a facility can only have one or more outgoing edges when they are open. Constraints (15) state that the customer node of an open satellite must be visited exactly once. Each route can only have a single depot or satellite as origin; this restriction is satisfied by constraints (16). Constraints (17)–(21) ensure that a route only consists of nodes that are allocated to the same depot or satellite. Constraints (22) forbid routes that do not start and end at the same open depot or satellite. Constraints (23) are the subtour elimination constraints. Constraints (24) guarantee that the travel time of each route does not exceed the maximum route length. Constraints (25) ensure that the starting time at a facility is set to zero. The arrival time at a customer or customer node of a satellite must be at least the aggregated arrival time at the previous node, the time needed to travel, and service time needed at the previous node. This arrival time restriction is satisfied by constraints (26). Every customer needs to be visited within its time window, a restriction which is satisfied by constraints (27). Finally, constraints (28)–(30) state the binary nature of the decision variables.

The problem studied is obviously NP-Hard as it can be reduced to the well-known VRP. The complexity is further increased as on top of the routing decisions, the LRP also involves the selection of depots, satellites and the assignment of routes to the facilities. We therefore develop a new heuristic for this NP-Hard problem.

4. Solution framework overview

The solution method uses a subgradient optimization technique that incorporates a lower bound technique with Lagrangian relaxation used in conjunction with the branch-and-cut algorithm, along with an upper bound technique. The general structure and pseudo code of the solution method is given in Fig. 2 and Algorithm 1, respectively.

Fig. 2. Solution framework overview for the direct shipment 2E-LRPTW.

The solution method leads to subgradient optimization that iterates between upper and lower bounds until the convergence criteria are met. The step size is an important factor in the speed of convergence, and the step size depends on the gap between the lower bound and the upper bound, along with other factors. Hence, it is desirable to provide the subgradient solution method with an initial upper bound. The upper bound heuristic leads to a feasible solution and has been designed based on the problem specific features consisting of the location phase, the allocation phase, the routing phase, the single-visit route phase, and the subnetwork phase. A clear representation of all phases in the upper bound heuristic is depicted in Fig. 3. After the first iteration, the location phase begins by activating the facilities that are open in the lower bound solution last found. The additional facilities required to create a solution are then selected using a node-based heuristic, where we estimate facility scores. When there are enough facilities active to create a solution, the allocation phase of the upper-bound heuristic will assign every customer an open facility based on a greedy heuristic. Thereafter, the routing phase forms an initial routing solution by means of an insertion-based C&W heuristic (Clarke & Wright). From this routing solution, the initial upper bound solution is derived.

We then work further towards improving these initial solutions by means of a single-visit route and a subnetwork formation phase. The single-visit routes phase determines whether this initial routing solution can be improved by examining single-visit routes. In a single-visit route, the vehicle visits a single customer before returning to its home base. The phase determines whether logistics costs can be reduced by inserting nodes from the single-visit routes into other routes. The advantage of the single-visit routes in comparison to the C&W heuristic is that the nodes from the routes do not need to have the same allocated facility. The resulting improved upper bound solution can then be compared to the best upper bound solution found so far. When the upper bound solution is an improvement on the best pre-existing upper bound solution found, the best upper bound is updated accordingly.

The subnetwork phase creates a subnetwork by deleting the direct edges connected to a depot or distributor side of a satellite. The resulting partial routes are called subroutes. From the ensuing network, an alternative upper-bound solution is derived by connecting the subroutes to their closest facility. This phase focuses on minimizing routing costs. When the alternative upper bound solution is better than the best existing upper bound solution, the alternative upper bound solution becomes the new best upper bound solution found. When no facilities are open in the previously found lower bound solution, the upper bound heuristic will naturally result in the same solutions found at the first iteration. This is based on the knowledge that the upper bound procedure remains the same for every iteration. However, when one or more facilities are open in the previous lower bound solution, the heuristic may find a tighter best upper bound found. To improve the solution method, the set of open facilities similar to previously examined sets of open facilities can be eliminated. The best upper bound solution found accelerates the lower bound phase, since it reduces the solution region considered by the branch and cut algorithm.

As stated, the subgradient method iterates between an upper bound and a lower bound. To compute this lower bound, a relaxed model is attained by the Lagrangian relaxation. The dual values of the constraints that force every customer to be visited (4) and allocated to a facility (8) give us a solution. Lagrange multipliers are used to dualize the relaxed constraints into the objective function. Each subproblem is then solved using a branch and cut algorithm. The resulting solution is the new best lower bound

Fig. 3. Upperbound heuristic phases demonstration.

solution that can be found for the original model. When the solution is not feasible with regard to the original model, the Lagrange multipliers are updated with the subgradient optimization. After this Lagrange multipliers optimization phase, a new iteration begins.

Let g denote the objective value for the relaxed model. The best upper bound (ub_{best}) and lower bound found are inserted into the formulation at every iteration by adding the following constraints.

$$ub_{best} - g \geq 0 \quad (31)$$

$$g - lb_{best} \geq 0 \quad (32)$$

The objective value can never exceed the upper bound, and thus the left side of constraint (31) must always be non-negative. Constraint (32) must be satisfied at every iteration, since the Lagrange multipliers are updated in such a way that the new objective value must shrink the interval in which the exact solution is located. Constraints (31) and (32) are added to the model after the upper bound phase and lower bound phase, respectively. Both constraints reduce the solution region considered by the branch-and-cut algorithm.

The solution method proceeds until the convergence criterion is met or until the maximum number of iterations is reached. After a predetermined number of iterations has taken place, the solution method terminates and returns to the interval in which the exact solution is located in the interval between lb_{best} and ub_{best} .

Algorithm 1: Solution procedure

```

// initialization ;
q = 1 // number of iterations ;
 $\lambda_i = \min_{j \in D \cup H_D} (c_{ij})$  // initial Lagrange multipliers ;
 $ub_{best} = \infty$  // initial best found upper bound ;
// main loop ;
repeat
    Create  $ub^q$  with -Upper bound phase- ;
    if  $ub^q < ub_{best}$  then
        |  $ub_{best} = ub^q$  ;
    end
    Add constraint  $(ub_{best} - g \geq 0)$  to the relaxed model ;
    Create  $lb_{best}$  with -Lower bound phase- ;
    if  $lb_{best} = ub_{best}$  then
        | return  $lb_{best}$  // optimal solution of the original model ;
    end
    Add constraint  $(g - lb_{best} \geq 0)$  to the relaxed model ;
    Update  $\lambda_i$  with -Lagrange multiplier optimization phase- ;
    q = q + 1
until q =  $q_{max}$ ;
return  $[lb_{best}, ub_{best}]$  // interval for the optimal solution ;

```

4.1. Upper bound

The speed of convergence is dependent on the quality of the bounds. The upper bound heuristic is designed such that the compact model is decomposed into sub problems, where we can make use of the nature of these specific partitions. The feasibility of the problem is checked in the first iteration. When no solution exists, the heuristic terminates. Fig. 3 displays the phases of the upper bound heuristic applied to a scenario. Each box illustrates the state of the network after each phase. The location phase determines the initial facilities to be opened, after which the allocation phase assigns every customer and customer side of an opened satellite to an open facility. When every customer has been allocated, the routing phase creates routes based on an insertion-based Clarke and Wright (C&W) heuristic. This feasible routing solution is improved, if possible, in the single-visit routes phase. The final phase of the upper bound heuristic is the subnetwork phase, which deletes all edges in direct connection with a depot or distributor side of a satellite. The subroutes in the resulting subnetwork are connected to their closest facility. Overall, the subnetwork phase focuses on minimizing the routing costs. The following subsections will detail each of these phases.

4.1.1. Location phase

The facilities that are active in the previous lower bound solution are opened at the start of the location phase. The last lower bound solution found follows from the lower bound phase of the solution method in the previous iteration. Additional facilities required to find a feasible solution are selected using a node-based heuristic where facility scores are computed.

The problem can be seen as a set covering location problem, the objective of which is to visit all customers at the lowest possible cost. These costs are comprised of direct routing costs and fixed facility opening costs. The facility score at node i (FS_i) is the sum of the fixed opening cost and the aggregated costs of every feasible edge in direct connection to that facility. Facilities with relatively high fixed opening costs and relatively many long edges directly connected to them will have a high facility score. By selecting the facilities with the lowest facility scores, the possibility of selecting a centralized facility with relatively low facility costs is higher than that of randomly selecting a facility. Eqs. (33) and (34) are applied to find the facility scores of depots and satellites, respectively.

$$FS_i = d_i + \sum_{j \in C} (c_{ij} + c_{ji}) \quad \forall i \in D \quad (33)$$

$$FS_i = h_i + \sum_{j \in C} (c_{ij} + c_{ji}) \quad \forall i \in H_C \cup H_D \quad (34)$$

The first active facility must be a depot, since every open satellite needs to be connected to a depot. There are two possible scenarios in which a depot is not already active: in the first iteration of the solution method, or when, in the last lower bound solution found, all facilities are closed. In both cases, the depot with the lowest facility score is opened. Once an open depot is in place, the additional facilities that are necessary can take the form of either depots or satellites.

When at least one depot is open, it becomes possible to determine whether every customer is within the service range of an open facility. A customer not covered will necessitate the opening of the facility with the lowest facility score within service range of this customer. Once all customers are covered, the capacity check can take place. The aggregated capacity of all facilities should be no less than the combined volume of customers and open satellites. When the maximum capacity is reached, the facility with the lowest facility score will be opened to ensure that sufficient capacity is available.

The principal focus of the node-based facility scores procedure is to minimize facility costs. However, the procedure may not always find the optimal facility location solution. Centralized facilities especially can have relatively high facility scores, since many

edges are directly connected to them. In this scenario, decentralized facilities, which could potentially have larger fixed opening costs, may be preferable to centralized facilities. Moreover, when the facility opening costs are relatively small in comparison to the routing costs, it may be wise to open more facilities than might at first appear strictly necessary. After the improved upper bound is attained, a subnetwork procedure will be run to account for these weaknesses.

4.1.2. Allocation phase

In the allocation phase, the customers are assigned to open facilities based on a greedy heuristic. First, the active satellites are allocated to their closest open depot. Thereafter, all customers are assigned to their closest open facility. A list is created containing details of the closest and second closest open facility for every customer. Customers, who can only be covered by a single depot or satellite, are automatically allocated to their closest active facility. The remaining customers are sorted based on the distance to their closest open facility, starting with the customer with the smallest distance. The remaining customers are allocated to the open facilities beginning with the first customer on the original sorting list. When a facility is at maximum capacity, the customers normally allocated to the facility will be allocated to their second closest facility. In this manner, all customers will be allocated to their closest feasible open facility using a greedy approach.

4.1.3. Routing phase

Once all customers have been successfully allocated to an open facility, routes need to be formed. Subsequently, the single customer routes phase may potentially improve the initial routing solution by examining the possibility of single-visit routes – journeys that visit a single customer and then return to their port of origin.

The routing problem may be viewed as a multidepot vehicle routing problem with time windows that can be tackled based on an insertion of a C&W savings algorithm developed in 1964 specifically to handle capacitated vehicle routing problems. The technique injects the edges into a route with the biggest potential savings based on the C&W savings calculation. Liu and Shen (1999) demonstrated that this algorithm was successful and easy to implement for the vehicle routing problem with time windows.

In the C&W algorithm, every customer is initially directly connected to their allocated facility. The insertion-based C&W Savings heuristic computes all the potential savings when creating a route in which a pair of customers is connected. Let S_{ij} denote the potential saving for connecting customers i and j for every $i, j \in C \cup H_C$. When both i and j are allocated to the same facility k , Eq. (35) calculates the savings by resulting from combining points i and j into a single tour.

$$S_{ij} = c_{ik} + c_{kj} - c_{ij} \quad \forall i, j \in C \cup H_C \quad (35)$$

The next step is to insert pairs of customers into a route. The order in which these pairs are inserted is based on the potential savings, starting with the pair with the largest value. When no further pairs can be inserted into a route, an additional route will be created to accommodate the remainder. The procedure is complete when all customers are located to a route.

We define two techniques for the formation of the routes: the sequential (type 1) version and the parallel (type 2) version. These versions differ in terms of the number of routes that are created at the same time. The sequential algorithm inserts customer pairs into *one* route at the same time, while the parallel algorithm inserts customer pairs into *two* routes at the same time. The second type is expected to result in more savings. Larger savings may be ignored by the sequential algorithm, since they cannot be inserted into the single route.

4.1.4. Single-visit route phase

A novel improvement procedure is proposed for the medicine suppliers' problem. The following phase concerns the single-visit routes in the initial upper bound solution. The procedure identifies single-visit routes and subsequently examines whether the node in these routes can be implemented in a different route. The main advantage of this technique is that the routes do not need to have the same facility as their origin, unlike in the C&W heuristic. The node can be inserted in another route if – and only if – the time windows, facility capacity, and maximum route-length duration constraints are still satisfied. For each single-visit route, the insertion alternative that reduces costs by the greatest amount is selected. Let k be the directly connected facility to the single visit node l , and let (i, j) be the edge in which l can be inserted. The cost reduction (RC_{ij}) can then be calculated using Eq. (36), where the savings of inserting node l into the route i to j is determined.

$$RC_{ij} = 2c_{kl} + c_{ij} - c_{il} - c_{jl} \quad \forall k \in D \cup H_D, i, j, l \in V \quad (36)$$

After costs can be diminished no further by deleting single-visit routes, the improved upper bound will be calculated. If the improved upper bound is better than the best upper bound found so far, then the best upper bound found is updated accordingly.

4.1.5. Subnetwork phase

The subnetwork phase has been designed specifically to account for possible defects in the facility scores procedure, which are discussed in Section 4.1.1. The subnetwork procedure designed for the medicine suppliers' problem is a unique approach where the key focus is to reduce the routing costs of the improved upper bound solution. The solution found in the subnetwork phase may well be accompanied by more facility costs, and thus the solution may be inferior when compared to the improved upper bound. To account for this negative outcome, the best upper bound found will only be updated if the approach does not terminate and finds a solution value better than the best upper bound found.

The first step of the subnetwork phase involves creating a subnetwork (Subnetwork phase (1) in Fig. 3). For every route used, the edges directly connected with a depot or distributor node of a satellite are deleted. The resulting partial routes are referred to as

subroutes. From this point on, every facility is closed, excluding those satellites that are open in the improved upper bound solution. Let set H_D^{open} denote all distributor ends of satellites that are open, and let S denote the set of subroutes, consisting of two subsets S_h and S_r . Subset S_h contains all subroutes that have a customer node of a satellite node included, while S_r contains all subroutes that include only regular customer nodes. Furthermore, let f^s and l^s be respectively the starting and ending node of subroute s for every $s \in S \subseteq R$. Finally, let c_i^s be the associated routing costs of connecting subroute s to facility i , for every $s \in S$ and $i \in D \cup H_D^{open}$.

The second step of the subset procedure links the subroutes to their closest facility (subnetwork phase (2) in Fig. 3). Subset S_h needs to be linked to a depot, while subset S_r can be linked to either a depot or a satellite that has already been opened. Eqs. (37) and (38) show the calculation of the connection costs:

$$c_i^s = c_{if^s} + c_{l^s i} \quad \forall i \in D, \forall s \in S_h \quad (37)$$

$$c_i^s = c_{if^s} + c_{l^s i} \quad \forall i \in D \cup H_D^{open}, \forall s \in S_r \quad (38)$$

Based on Eqs. (37) and (38), every subroute $s \in S$ is allocated to the facility that has the lowest associated connection costs. Following this allocation, the subroutes are connected to their respective facilities. However, the subroute can only be connected to a facility if the resulting volume of orders handled by the facility does not exceed its capacity. After this step, if a subroute is not connected to its allocated facility, the procedure is brought to a halt and no alternative upper bound is calculated. Since every subroute $s \in S$ is allocated to its closest facility, it is to be expected that the number of open facilities will be no less than the number of facilities open in the improved lower bound solution. The capacity constraints are therefore considered to hold.

The time window constraint for each customer is checked after the completion of the procedure. If the solution is feasible with regard to the capacity constraints and the time window constraints, the alternative upper bound value is calculated. The alternative upper bound value becomes the new best found upper bound, if the alternative upper bound is an improvement on the best upper bound found so far. It is anticipated that the subnetwork phase will lead to a different solution than the solution found at the improved upper bound, since the primary focus is on reducing the routing costs.

4.2. Lower bound

This section explains the procedure to find the lower bound at each iteration of the solution method. To calculate the lower bound, the branch-and-cut algorithm is applied in combination with the Lagrangian relaxation. The Lagrangian relaxation technique relaxes some of the main linear constraints of the model which are dualized in the objective function with convenient Lagrange multipliers to discourage violations. From this point on, each subproblem is then solved by the branch-and-cut algorithm.

4.2.1. Dualization

The constraints that every customer must be visited (4) and allocated to a facility (8) are dualized. In the resulting problem, the penalty cost is based on the Lagrange multiplier associated with the customers not visited. Let λ_i denote the Lagrange multiplier for each $i \in C$. The relaxed model has the following objective function given the Lagrange multipliers:

$$g = \min \sum_{i \in D} d_i F_i + \sum_{i \in H_D} h_i F_i + \sum_{i \in V} \sum_{j \in V} \sum_{r \in R} c_{ij} X_{ijr} + \sum_{j \in C} \lambda_j \left(2 - \sum_{i \in V} \sum_{r \in R} X_{ijr} - \sum_{i \in D \cup H_D} f_{ij} \right) \quad (39)$$

The relaxed model is subject to constraints (1)–(3), (5)–(7), (9)–(30). This model has less stringent constraints where we rely on the dual values of the relaxed constraints to lead to a solution. The optimal value of the relaxed model provides a lower bound to the original problem. For a strong Lagrangian relaxation, the Lagrangian multipliers must be selected such that the solution to the relaxed model is close to the optimal solution to the original problem.

4.2.2. Branch and cut

The branch-and-cut algorithm extends the branch and bound algorithm by adding cuts to strengthen the relaxation. The added cuts reduce the feasible region at the current LP relaxation. This reduction can lead to a reduction in the computation time. The initial standard set of valid inequalities (40) ensure that no customers can be assigned to a closed facility:

$$f_{ij} \leq F_i \quad \forall i \in D \cup H_D, \forall j \in C \cup H_C \quad (40)$$

Furthermore, inequality (41) concerns the least aggregated amount of capacity needed for a feasible solution.

$$|C| + \sum_{j \in H_C} F_j \leq \sum_{i \in D} \omega_i F_i + \sum_{j \in H_D} \gamma_j F_j \quad (41)$$

In a feasible solution, the open facilities should at least be able to handle the combined number of orders of all customers and open satellites. When the number of orders exceeds the aggregated capacity of the open facilities, it follows that an extra facility must be opened.

Let t_i^F denote the travel time of customer i to its closest facility for every $i \in C$. Moreover, let t_i^D denote the travel time of satellite i to its closest depot with $i \in H_C \cup H_D$. The following equations formally define the two variables:

$$t_i^F = \min_{j \in D \cup H_D} (t_{ij}) \quad \forall i \in C$$

$$t_i^D = \min_{j \in D} (t_{ij}) \quad \forall i \in H_C \cup H_D$$

With the new variables, three additional sets of valid inequalities can be proposed; the first two sets are:

$$t_i^F \leq y_i \quad \forall i \in C \quad (42)$$

$$y_i \leq \Phi - t_i^F \quad \forall i \in C \quad (43)$$

When a customer is allocated to their closest facility, and a route exists going directly to this customer from the facility, the arrival time at this customer would equal the time needed to travel from the facility to the customer. In all other scenarios, the arrival time at the customer will be no less than this travel time. Valid inequalities (42) represent this condition, while the same line of reasoning can be applied to the upper bound of the arrival time, denoted by inequalities (43).

The last set of proposed valid inequalities is as follows:

$$(0.5\Phi - t_i^D)F_i \geq 0 \quad \forall i \in H_C \cup H_D \quad (44)$$

The motivation in this set of inequalities is that a satellite can only be opened if the satellite is within service range of at least one depot. Since every route needs to have the same starting and ending node, the maximum service range of a depot is half the maximum travel time. Valid inequalities (44) can strengthen the LP relaxation, since satellites that cannot be covered will be disregarded.

4.2.3. Lagrange multipliers optimization

The strength of the lower bound in turn depends heavily on the Lagrange multiplier values selected. A poor choice of Lagrange multipliers will result in a weak Lagrangian relaxation. When the multiplier values are relatively low, the computation time of the branch-and-cut algorithm is correspondingly low, but the resulting lower bound value may only consist of relaxed costs and may therefore be weak. For multiplier values that are relatively high the computation time for the algorithm is relatively long, while in such cases the lower bound would be tighter.

The relaxed model provides a lower bound for the solution to the original problem. It follows $g \leq z$, where g and z denote the objective value of the original and relaxed models, respectively. Let λ denote the set of Lagrangian multiplier values. The best choice of Lagrangian multipliers is the optimal solution to the dual problem. To find the best Lagrangian multiplier values, the problem should be differentiated at the optimal solution. The initialization of the Lagrange multipliers is as follows:

$$\lambda_i^1 = \min_{j \in D \cup H_D} (\phi c_{ij}) \quad \forall i \in C \quad (45)$$

The value for ϕ is initially set to $\phi = 1$. In Section 5, experiments are performed in order to find the ϕ value, which makes the solution method perform better.

To ensure that a stronger lower bound is derived at every iteration, the Lagrange multipliers are adjusted using a subgradient optimization technique where we follow an iterative procedure that, from an initial set of multipliers, involves generating further Lagrange multipliers in a systematic fashion. Let δ^q be the step length at iteration q . The following equations are used to update the Lagrange multipliers:

$$\lambda_j^q = \lambda_j^{q-1} + \psi \delta^q \left(1 - \sum_{r \in R} \sum_{i \in V} X_{ijr} \right) \quad \forall j \in C, q > 1 \quad (46)$$

$$\delta^q = \frac{ub_{best} - lb_{best}}{\sum_{j \in C} \left(\left(\sum_{r \in R} \sum_{i \in V} X_{ijr} - 1 \right)^2 \right)} \quad (47)$$

The value of ψ is initially set to $\psi = 1$. Section 5 tests the impact of selecting different ψ values. The multiplier optimization proceeds until the solution method is terminated.

5. Computational results

We first validate our model and analyze the performance of our approach by using the Solomon instances. Thereafter we conduct a case study on a Dutch pharmaceutical distribution network. Finally we compare our solution technique performance with the previous work of Govindan et al. (2014) and we demonstrate the additional gains by direct delivery.

5.1. Validation

The generation of the instances required for the computational study is based on Solomon instances (Solomon, 1987). In total, the data-set contains 72 cases, split into two random data-sets R1 and R2, two clustered data-set C1 and C2, and two randomly clustered data-set RC1 and RC2. The sets R1, C1, and RC1 have a short scheduling horizon, while the sets R2, C2, and RC2 have a longer scheduling horizon (Solomon, 1987). The instances generated contain 10–25-customers (small-size) and 50–75 customers (medium-large-size). Three instances are created (R, C, or RC) for every size (10, 25, 50, 75). Each case is replicated 30 times and the average

Table 1

Cost intervals for depots and satellites.

Data set type:	R1	R2	C1	C2	RC1	RC2
Depots:	[17k, 25k]	[85k, 100k]	[38k, 50k]	[90k, 120k]	[17k, 26k]	[85k, 100k]
Satellites:	[8.5k, 13k]	[42.5k, 50k]	[19k, 25k]	[45k, 60k]	[8.5k, 13k]	[42.5k, 50k]

Table 2

Capacity intervals for depots and satellites.

Data set size $ J $:	10	25	50	75
Cap:	[8, 9]	[20, 24]	[40, 49]	[60, 74]

results are reported. The depot characteristics were generated using discrete uniform distributions. The operating costs for the depots and satellites can be found in Table 1. Costs for operating satellites are half the costs for operating depots. The intervals for depot and satellite capacity for each data-set and its instances are presented in Table 2.

The mathematical model formulated in Section 3 is Np-Hard as it can be reduced to the well-known VRP when decisions as to the selection of depots, satellites and the assignment of routes to the facilities are ignored. Nevertheless, we conduct experiments to compare our solution technique with the CPLEX-optimizer to assess the accuracy. Generally only instances up to 25 customers can be solved to optimality with CPLEX.

In Table 3 we report a comparative analysis for 10, 25, 50 and 75 customers together with its variants. CPLEX was not able to load problem sizes with 100 customers. We set the maximum allowed computation time to 2 h for this set of experiments.

In Table 3 the first four columns describe the instance sets. The next columns entail the solution time for the CPLEX solver, the gap between the LP relaxation value and the CPLEX solver, the solution time for the proposed technique, and the deviation between the CPLEX total cost and our method's total cost. Note that reported cost values are best found solutions within the time limits. The LP relaxation of an instance is obtained by only relaxing the x_{ijr} binary constraints. Such a partial relaxation provides better quality lower bounds compared to a full relaxation.

Results show that the proposed technique can find solutions to the instances in a significantly shorter amount of time than CPLEX. The method requires 0.03%, 0.09%, 0.55%, 1.58% of the CPLEX solution times for the 10, 25, 50, and 75 customer instances, respectively. Also, the objective values of the proposed technique do not differ much from the CPLEX objective values. We note that in a lot of instances no solution can be attained with CPLEX. For some of the 50 and 75 customer instances the computer ran out of memory while computing the solutions.

The two formulations for the routing phase, the sequential and parallel route formations are also examined. Table 4 presents the average results of the comparative experiments. Results indicate that type 2, using the insertion-based parallel C&W Savings algorithm to construct the routing, is the best option of the two. The average computation times are very similar, but the deviation from the solutions of the CPLEX solver are smaller for type 2. Analysis shows that this is due to the sequential routing missing potential larger savings. We therefore continue our experiments with parallel routing.

5.2. Dutch pharmaceutical distribution network

We conduct our experiments on a pharmaceutical distributor which wholesales, distributes, and retails pharmaceutical, surgical, medical, and healthcare products throughout Europe. The company supplies more than 110,000 pharmacies, doctors, health centres, and hospitals from over 288 distribution centres in 11 countries. We focus on the distribution planning problem of the company in the Northern Netherlands. The company faces distribution problems in the Northern Netherlands with different attributes with regard to the number of depots, satellites, facility capacities and geographical locations. Analysis of this case data allows us to group the different cases in categories. The cost of opening facilities, that is, depots and satellites, differs considerably according to the region. Accordingly, we can group the cases in terms of these costs into three classes. We refer to these cases as residing in Region 1, Region 2 and Region 3 with the costs increasing as the region id increases. The company further groups the distribution planning problem in the regions with regard to the density of the customers served. Based on practice, we group the cases into low, base, and high indicating the density of the customers within the region. The low set includes customers till 25, the base set 25–50 and the high group ranges from 50–75. Fig. 4 shows an example of an instance where dots denote the customers and their geographical positions. A further distinction could be made on the cases based on the distribution of the customers within the region.

5.2.1. Impact of single-visit routes and sub-network formation

We examine the improvement procedures in the upper bound phase. It is interesting to observe how these procedures function in different set of cases. The first improvement phase concerns single visit routes, while the second phase constructs a subnetwork to induce an upper bound additional to the one previously calculated at the routing phase. Readers are referred to review Fig. 3 for a clear overview of all upper bound heuristic phases applied to two different instances.

To evaluate the performance of the improvement procedures the cases are run and the average percentage of improvement in

Table 3
Validation.

Case	C	D	H	CPLEX		Proposed method	
				Time (s)	Gap	Time (s)	dev _{TC}
R101	10	2	2	3.23	0.25	0.08	0.01
R105	10	2	2	2.73	0.22	0.11	0.07
R108	10	2	2	1263.91	0.15	0.09	0.05
R201	10	2	2	5.46	0.09	0.06	0.02
R205	10	2	2	11.59	0.06	0.15	0.02
R208	10	2	2	390.13	0.04	0.10	0.00
C101	10	2	2	6.79	0.06	0.16	0.00
C105	10	2	2	7.32	0.04	0.17	0.00
C108	10	2	2	82.65	0.05	0.21	0.00
C201	10	2	2	1.12	0.04	0.15	0.02
C205	10	2	2	2.49	0.04	0.21	0.01
C208	10	2	2	4.51	0.04	0.10	0.03
RC101	10	2	2	2.82	0.28	0.15	0.08
RC105	10	2	2	443.01	0.26	0.13	0.04
RC108	10	2	2	1486.2	0.22	0.14	0.05
RC201	10	2	2	13.19	0.09	0.12	0.01
RC205	10	2	2	1331.01	0.07	0.20	0.02
RC208	10	2	2	7200	0.06	0.12	0.03
R101	25	2	3	40.8	0.36	2.01	0.02
R105	25	2	3	7200	0.32	2.00	0.02
R108	25	2	3	7200	0.25	10.25	0.02
R201	25	2	3	687.11	0.10	4.50	0.03
R205	25	2	3	7200	0.07	2.71	0.02
R208	25	2	3	7200	0.07	3.69	−0.01
C101	25	2	3	77.98	0.11	2.75	0.07
C105	25	2	3	23.91	0.12	2.76	0.08
C108	25	2	3	7200	0.11	6.70	0.07
C201	25	2	3	7.99	0.08	3.88	0.03
C205	25	2	3	1362.98	0.06	4.72	0.07
C208	25	2	3	7200	0.07	3.90	0.05
RC101	25	2	3	7200	0.43	4.70	0.07
RC105	25	2	3	7200	0.44	5.89	0.07
RC108	25	2	3	7200	0.45	4.15	−0.17
RC201	25	2	3	753	0.12	3.35	0.08
RC205	25	2	3	7200	0.10	3.35	0.03
RC208	25	2	3	7200	0.13	4.24	−0.04
R101	50	3	4	1610.12	0.48	1.81	0.04
R105	50	3	4	7200	0.48	19.10	−0.10
R108	50	3	4	–	–	80.87	–
R201	50	3	4	7200	−0.01	21.40	0.00
R205	50	3	4	7200	0.41	32.81	−0.28
R208	50	3	4	2867.34	0.11	52.89	−0.04
C101	50	3	4	7200	0.27	18.52	0.06
C105	50	3	4	7200	0.30	19.19	0.04
C108	50	3	4	7200	0.58	51.42	−0.36
C201	50	3	4	7200	0.18	50.14	−0.04
C205	50	3	4	7200	0.27	44.81	−0.12
C208	50	3	4	7200	0.22	59.76	−0.12
RC101	50	3	4	7200	0.68	26.00	−0.24
RC105	50	3	4	–	–	14.60	–
RC108	50	3	4	7200	0.59	31.68	−0.30
RC201	50	3	4	7200	0.25	31.48	0.11
RC205	50	3	4	–	–	45.89	–
RC208	50	3	4	–	–	39.65	–
R101	75	4	5	7200	0.55	18.67	0.04
R105	75	4	5	–	–	203.88	–
R108	75	4	5	–	–	19.67	–
R201	75	4	5	–	–	36.12	–
R205	75	4	5	–	–	92.32	–
R208	75	4	5	–	–	138.98	–
C101	75	4	5	7200	0.60	193.13	−0.24
C105	75	4	5	–	–	291.13	–
C108	75	4	5	–	–	136.74	–
C201	75	4	5	7200	0.18	194.52	0.05
C205	75	4	5	–	–	39.45	–
C208	75	4	5	–	–	68.48	–

(continued on next page)

Table 3 (continued)

Case	C	D	H	CPLEX		Proposed method	
				Time (s)	Gap	Time (s)	dev_{TC}
RC101	75	4	5	–	–	40.87	–
RC105	75	4	5	–	–	67.32	–
RC108	75	4	5	–	–	172.01	–
RC201	75	4	5	–	–	93.98	–
RC205	75	4	5	–	–	109.01	–
RC208	75	4	5	–	–	124.54	–

Table 4

Average results of different routing type formations.

Case	C	D	H	Sequential routing		Parallel routing	
				Time (s)	Deviation (%)	Time (s)	Deviation (%)
R1	10	2	2	0.102	5.18	0.091	3.84
R2	10	2	2	0.129	1.99	0.102	1.37
C1	10	2	2	0.126	0.48	0.184	0.11
C2	10	2	2	0.157	2.45	0.151	2.39
RC1	10	2	2	0.136	9.67	0.141	6.94
RC2	10	2	2	0.131	2.46	0.139	1.55
Avg				0.130	3.71	0.135	2.70
R1	25	2	3	3.568	3.72	4.771	2.36
R2	25	2	3	4.103	2.85	3.641	1.13
C1	25	2	3	4.664	6.41	4.077	6.80
C2	25	2	3	6.421	5.72	4.173	5.64
RC1	25	2	3	6.088	6.61	4.907	–1.79
RC2	25	2	3	4.515	5.86	3.643	3.16
Avg				4.893	5.20	4.202	2.88

Fig. 4. Northern Netherlands example customer distribution.

comparison of the initial feasible solution are recorded. Table 5 reports the results for the three regions with regard to the customer densities. Each specific case group has approximately 30 different instances varying with parameters within the attributes of the group it belongs to. Single visit column reports the results for the comparison of the upper bound from single-visit with the initial upper bound. Subnetwork column compares the upper bound from subnetwork with the single-visit. From the results, it is evident that the single visit routes phase is efficient, especially for instances concerning base or high number of customers. This outcome is consistent with the notion that instances with more customers have more routes, and are therefore expected to contain single visit routes which can be inserted into another route to reduce routing costs. Fig. 5 illustrates the case with two simple cases where the latter has more customers than the former. It can be observed that the single routes can subsequently be eliminated following the single routes procedure by augmenting the single route into the second tour depicted in the figure.

Table 5
Results of the improvement procedures.

Case	C	Single visit (%)	Subnetwork (%)
Region 1	Low	4.47	3.67
Region 2	Low	5.88	4.2
Region 3	Low	6.19	1.23
Region 1	Base	8.12	12.89
Region 2	Base	13.41	8.65
Region 3	Base	10.76	2.22
Region 1	High	10.78	15.01
Region 2	High	14.12	10.65
Region 3	High	8.89	1.87

Fig. 5. The single-visit routes phase applied to two examples.

Moreover, it may be inferred from the results that the subnetwork phase is most efficient for instances with relatively many customers, and relatively low fixed facility costs. In these instances, the subnetwork phase is clearly productive, since the routing costs are relatively high in comparison with the facility costs. The subnetwork phase rarely terminates, an outcome consistent with the reasoning set out in Section 5.6.

5.2.2. Evaluating valid inequalities

Valid inequalities are introduced to improve the strength of the branch and cut algorithm. To determine their effectiveness, experiments are performed on the Dutch pharmaceutical distribution network. We test all the combinations of inequalities (41) to (45) and we find that two combinations can reduce the computational time. We define inequalities (41) and (42) as combination V_1 . Combination V_2 includes all the proposed inequalities, where V_0 is the reference formulation with no inequalities included. The results of the experiments are presented in Table 6. Column V_0 gives the total computational time whereas V_1 and V_2 present the reduction percentage compared with the base case. As can be seen from the table, as the number of customers increase the time savings with the inequalities become significant and could lead to 20% percent reductions.

5.2.3. Evaluating Lagrange multipliers optimization scheme

To further improve the solution method, experiments have been conducted to find suitable values for the Lagrange multipliers optimization scheme. The instances within region 2 and relatively many customers, are the best representation of the real-world problem faced by a town. We now focus on region 2 with base and high settings. In Table 7, the first two columns denote the

Table 6
Impact of the valid inequalities.

Instance	C	Time (s) V_0	Reduction (%) V_1	Reduction (%) V_2
Region1	Low	27.12	2.12	2.43
Region2	Low	32.33	4.30	4.55
Region3	Low	29.88	3.34	3.52
Region1	Base	222.34	4.99	5.12
Region2	Base	301.89	5.01	5.32
Region3	Base	287.59	4.25	4.57
Region1	High	389.12	10.09	10.43
Region2	High	452.57	15.63	17.66
Region3	High	500.12	18.23	20.11

Table 7
Impact of Lagrange multiplier optimization schemes.

C	H	ϕ	ψ	lb_{best}
Base	2	1	1	46140
Base	2	1	1.5	45805
Base	2	1.5		52710
Base	2	2		50794
Base	2	0.5	1	25579
Base	2	0.5	1.5	25157
Base	2	1.5		28289
Base	2	2		28372
Base	2	3		28243
Base	3	1	1.5	42550
Base	3	1.5		46083
Base	3	2		48555
Base	3	3		47714
High	2	0.5	0.5	46269
High	2	0.5	1	48906
High	2	0.5	1.5	49458
High	2	1		48297
High	2	0.5	0.5	41344
High	2	0.5	1	43022
High	2	0.5	1.5	44414
High	2	1		42069
High	3	0.4	0.5	38437
High	3	0.4	1	38520
High	3	0.4	1.5	40488
High	3	0.5		33552
High	3	1		36291

characteristics of the instance. The following two columns show the ϕ and ψ values that were used. The last final two columns give the time until the solution method was stopped, and the current best found lower bound after the termination. In cases where the first iteration was not completed within the timeframe, the column denoting the ψ value is left blank.

It follows that the ϕ value can best be set to $\phi = 0.5$ for instances with a high number of customers and two satellites. With a high number of customers and three satellites the best found ϕ value is $\phi = 0.4$. Based on the results, the ψ value will be set to $\psi = 1.5$. For the chosen values, the Lagrange multipliers converge to the optimal value. We further conduct experiments on Region 1 and Region 3 where similar results are obtained.

5.3. Comparison

We now present the results for the experiments where we compare our solution techniques with that of Govindan et al. (2014). The authors made use of metaheuristics and genetic algorithms. They tested 12 problem instances and reported the performance. Table 8 provides the comparison of our performance and their results. In the second column the performance from Govindan et al., 2014 is reported. The next column shows the improvement with our techniques. On average our techniques outperform the previous work. In several cases this improvement could be around 10%. We note that the complexity of the problem is increased with the direct delivery option as more decision variables and the related constraints will be added to generalize the model. Moreover, the

Table 8
Performance comparison.

	Govidan et al.	Improvement (%)
Prob. 1	28619	5.12
Prob. 2	43864	4.89
Prob. 3	20730	6.12
Prob. 4	13771	5.53
Prob. 5	44514	7.18
Prob. 6	28619	10.02
Prob. 7	42034	4.37
Prob. 8	12197	8.99
Prob. 9	20703	9.54
Prob. 10	28853	5.84
Prob. 11	42457	8.87
Prob. 12	38476	10.26

Table 9
Comparative analysis of direct delivery.

Instance	C	Improvement(%)
Region 1	Low	5.88
Region 2	Low	7.01
Region 3	Low	6.56
Region 1	Base	10.97
Region 2	Base	12.11
Region 3	Base	12.89
Region 1	High	19.33
Region 2	High	20.09
Region 3	High	17.12

methodology used in this study is based on Lagrangian relaxation and branch and cut techniques rather than metaheuristics.

We further continue with comparative analysis by evaluating the cost structure with/without direct delivery cases. Table 9 presents these results. We observe that the results show a significant cost reduction in some case around 20%. We suggest the use of this delivery structure for better utilization of the network.

6. Conclusions

The competitive pharmaceutical market forces medicine suppliers to design efficient distribution networks. This paper started by presenting a model which reflected as closely as possible the distributional challenges faced by real-world medicine suppliers. We extend the previous literature on LRP by considering a direct delivery structure with time windows where linkages among layers are allowed if the resulting vehicle routing costs and facility opening costs diminish. The mathematical representation is NP-Hard which led us to search for efficient heuristics. Accordingly, a solution method involving the Lagrangian relaxation, branch and cut algorithm and upper bound heuristic is developed. Sets of valid inequalities have been proposed in order to strengthen the branch and cut phase of the solution method. Two valid inequalities proved particularly efficient: the valid inequality set that ensures no customers can be assigned to a closed facility, and the valid inequality concerning the least aggregated amount of capacity needed for a feasible solution.

The upper bound phase consists of a location phase, allocation phase, a routing phase, a single-visit routes phase and a sub-network phase. The single visit routes phase and subnetwork phase are specifically designed to address the medicine suppliers' problem. We specifically work on the problem in the Netherlands. Tests on the Dutch medicine suppliers problem instances demonstrated that both phases are efficient. The lower bound phase of the solution method derives a lower bound with a Lagrangian based branch and cut approach. The key constraints that every customer needs to be visited and allocated to an open facility are dualized. The subsequent dual problem was solved by means of the branch and cut algorithm. At the end of every iteration, the Lagrange multipliers are updated in the Lagrangian multiplier optimization phase. Computational results clearly indicate that the initialization and updating scheme of the Lagrange multipliers have a significant influence on the solving time of the solution method.

The solution method developed in this study was capable of finding strong solutions for the real-life instances in the medicine supplier network within reasonable time window. In conclusion, the solution method is observed as a efficient tool to support decision makers for the medicine suppliers' planning problem.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tre.2018.06.005>.

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