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International Journal of Data and Network Science

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A new Bi– level production-routing-inventory model for a medicine supply chain under uncertainty

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C H R O N I C L E

Article history:
Received: January 1, 2018
Received in revised format: June 16, 2018
Accepted: June 20, 2018
Available online:
June 27, 2018

Keywords:
Production-Routing-Inventory Problem
Medicine Supply Chain
Uncertainty
Multi-objective

A B S T R A C T

This research presents a new bi-level bi-objective production-routing-inventory model for a medicine supply chain. In this case, the production is executed by multi-separated producers in a multi-production line for different kinds of medicines which will be saved in stores for delivering to customers. The capacitated vehicle routing problem is considered in designing a distribution system from stores to customers. The goal of this model is to make a suitable trade-off between the customer satisfaction and the budget cost. This problem has been formulated in a bi-level form where the first objective function is the minimization of the budget during the scheduled time and the second one is the minimization of the shortage amount associated with the lost sale of medicine demands delivering to drug stores. Uncertainty is considered as a nature of the main parameters of the problem. Then the robust approach was used to handle the associated uncertainty of related parameters and the resulted problem is solved by Benders decomposition algorithm. The results indicate that the model make an improvement in medicine supply chain.

1. Introduction

Decisions in supply chain field are divided into two categories including designing decisions and management decisions. The first group of decisions are nominated as designing supply chain problem that generally includes strategic decisions such as identifying the number of factories, stores or facilities (Govil & Proth, 2002). In fact they are the best combinations are the supply chain elements and the interaction among them which could lead to the maximum customer satisfaction, whereas supply chain management decisions mostly focus on product flow from raw materials to warehouses and products under production process which finally lead to delivering the products to customers. The major areas which should be determined in supply chain are planning, monitoring, and the management of different parts of the chain such as inventory, producers, transportation and etc. So the need for cooperation among factors is felt when the process has already prepared and implemented before taking basic facilities into account and also making profit becomes more difficult when engineers analyze products which have the potential of deteriorating or the time will affect their quality. So, neglecting these subjects impose great

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doi: 10.5267/j.ijdns.2018.6.002

disadvantages on each level of supply chains. For example: a large inventory in stock is one of the main consequences of unsuitable estimation of the production quantity and product's demand. Another part affected by this subject is transportation specially the long travel time for far destinations and the lack of maintenance equipment during the transportation process was lead to the shortage in products at the point of delivering to the customers. These problems affected all supply chain because of the butterfly effect (Jaipuria & Mahapatra, 2014).

On the contrary with previous studies in the supply chain of medicine as a perishable product which chiefly focus on two levels, this research considers three level. When a product is produced the expiry date is calculated according to the time of production. So, some levels which have great importance in the considered problem begin from production process as the first stage. Mathematical model is used as an optimization technique to design process for obtaining high-quality products and an integrated system functions. The following options are mentioned in article must be controlled. The main problem is production quantity and the allocation of medicine to pharmacies in order to prevent shortage occurrence or having excess inventory. Since the demand of drugs is uncertain in the country so the drug supply in each stage is very crucial. Another thing is determining which pharmacy should serve each customer in each time period. This work must be done in a network with the lowest price so customer satisfaction rises and the total cost will decrease consequently. This research continues to explain the beginning moment of medicine lifecycle till the time it will be delivered to customers in order to get full comprehension of details in the proposed supply chain.

1- The process starts after receiving raw materials from suppliers. At the end of this step, the amount of each medicine for production in each time period is determined according to the available time for production and the demand uncertainty. Demand in each period of time is acquired by using the simulation and probability function (Singh et al., 2016).

2- Another case is warehouses which are located in exact places. Storage of finished products in existing warehouses will form the required inventory for transition to delivery points. Replenishment policy is obtained according to maintainable life. Inventory discussion with perishable drugs will be more important. So, products will be planned in a way that meet the customer demand and prevent spoiling. Production process should be programmed in a way that minimize the shortage and, prevent the extra inventory of medicine and spoilage process (Singh et al., 2016).

3- At the end, inventory will be delivered to the customers by using the transportation network. The vehicle-routing problem is supposed to consider several types of vehicle, speed, different capacities, and warehouses. Also the paths in the network have different traffic volumes. Traffics along with failure probability of appliances are two factors of uncertainty in the transportation of drugs that will be specified according to their distribution function. These factors will change transportation costs in each mane of the transportation network (Singh et al., 2016).

This research presents a new bi-level bi-objective production-routing-inventory model for a medicine supply chain. In this case the production is done by multi-separated producers in a multi-production line for different kinds of medicines which will be saved in stores for delivering to customers. The capacitated vehicle routing problem is considered in designing a distribution system from stores to customers. The goal of this model is to make a suitable trade-off between the customer satisfaction and the budget cost. This problem has been formulated in a bi-level form which first objective function is involved with minimizing the budget during the scheduled time and the other is about minimizing the shortage amount which is related to the lost sale of medicine demands delivering to drug stores. Uncertainty is considered as a nature of the main parameters of the problem. Then the robust approach was used to deal the associated uncertainty of related parameters. The remainder of this paper is as follows. Literature review and relevant research in production-routing-inventory medicine problem and perishable products have been discussed in section 2. The problem is defined and relevant assumptions are presented in section 3 and the mathematical model under uncertainty is proposed after describing the notations and definition of decision variables. Problem testers are presented in section 4 in order to validate the model and the computational results of solving it. Finally section 5 includes conclusions and presentation of future research directions.

2. Literature review

The scope of our analysis is in the most well-known categories of supply chain issues mentioned as production-routing-inventory problem. This problem has been studied by many researchers. It seems logical to consider the lifecycle of products at the end of the production stage and tracking the process until delivering to customers, especially when the product is perishable like medicine(Bertolini et al., 2013). Decision making in PIRP has generally analyzed according to the manager's decision in different fields. The decisions could be the number of production centers, distribution and customer's level, supplier selection, product retrieval centers, and transportation network(Bertolini et al., 2013). Another production-distribution planning model has formulated in a multi-objective form for perishable products in comparison with the traditional model of production-distribution with two-divided model(Amorim et al., 2012). Singh et al. (2016) presented review article about medicine supply chain management. According to this review, medicine supply chain management has been more complicated because of regarding to interest savings in human life and the need for participation of different stockholders such as medicine producers, wholesalers, distributors, customers, the information of service providers, and the regulatory agencies. According to this study, there is a limited research available in medicine supply chain field. The object of presenting this paper is to detect the gaps in literature with reviewing research articles about various strategic issues of supply chain management in chemical sector. Jebbor et al. (2016) has perused previous studies in medicine supply chain scope which includes supply techniques, and medicine supply chain management in 2016. According to this paper, efficient factors have high costs on hospital service level and creation of an efficient logistics management. So, an effective and organized planning could lead to a noticeable improvement, in addition to random events.

Nematollahi et al. (2017) studied two-level of medicine supply chain with random demand. In this model, a medicine supplier has a meeting with drug retailer in a fixed time interval and the order is sent after offering in a certain time. Medicine retailer decides to affect medicine supplier profitability by using a periodic review inventory system. In this paper, each member has been studied under decentralized and centralized decision structures at the first stage of decision making then cooperation models in two different scenarios has presented. Results showed that decision making in drug delivery time and service level could be more profitable socially for each member. Despite the importance and the value of pharmaceutical market, the significant part of logistics cost is due to the medicine supply chain that poor management methods and reactive with national inevitable shortage of medicine generally lead to medicine shortage and has direct effects on suffering patients and their death. Nematollahi et al. (2017) presented a random model for discovering optimal policies of medicine inventory in a health care system in order to minimize the effect of medicine shortage in the presence of unknown disturbances. Postacchini et al. (2016) presented a model for designing a medicine supply chain by using simulation method. Transfer policy (side emergency transfer or the equivalence of the inventory in general), reordering policy in the inventory management system (economic order quantity or economic time of ordering) and also required service level are studied in the paper. Kalantari and Pishvaee (2016) presented a main programming model for medicine supply chain that included multi suppliers, a producer and some distribution centers. At first, a multi-objective possibilistic integer linear programming has been presented in order to reduce logistics cost and increase the l satisfaction level of selecting suppliers. Then a new model of robust possibilistic programming was developed to regulate the degree of stability in decisions because of the uncertain nature of input parameters in the proposed problem. Gholamian et al. (2013) considered a compound decision making method that included all criteria, factors, and transactions between the medicine supply chain. This study has tried to evaluate the medicine supply chain and the best tracking system (among traditional systems, barcode, and RFID tags) is selected by regarding to the importance of tracking medicine in it. So a heuristic method has been used by obtaining the combination of two known decision making methods that are Chokoet integral and analytic network process. Also Proms method is used to gain graphical results. Bagheri et al. (2011) used three stages of review, quality, and quantity through educational intervention with research check list which aimed to examine the influence of education on medicine supply chain management in the health homes of MASJEDSOLEYMAN city. The results of the study showed that the current state of country's health homes is far from the favorable state in terms of medicine chain management. Educational intervention indicated that education lead to improve medicine chain management in all three dimensions of supply, maintenance, and drug distribution. The most important discoveries of this research are an increase in contributors in medicine chain management process, modification, and improvement in relation with medicine maintenance process, arrangement of drugs on the pharmaceutical shelves, return drugs that are close to the expiration date, supply requirements of health home drugs by nurses and focusing on educating patients or their companions in order to use medicine properly and it's maintenance at home. Zarenejad and Eshkevari (2010) aimed to develop an agile supply chain model based on Oscor model. So, firstly we divided supply chain into three distinct parts of supply, production, and distribution. Moreover there are 9 main-index and 21 sub-index for supply part, 11 main-index and 30 sub-index for production part, 9 main-index and 26 sub-index for distribution part are detected as success factors in agile supply chain that has been given to academic experts and industries to be confirmed by them in the forms of separated questionnaire. Accordingly, a conceptual model is presented in order to make each process of supply chain agile such as supply, production and distribution. Also, prioritizing an indicators base on the importance of their impact on the supply chain's agility is acquired by two mathematical algorithms of FUZZY TOPSIS and FRIEDMAN STATISTICAL TEST. Then in the next step, indicators that have the most influence on supply chain have been used in designing the final model by determining the regression coefficients. Though, there are many issues in this subject that are investigated. As an example, the integrity among producers, storage, and transferring materials have not been considered in drug delivery system. On the other hand, the lack of uncertainty approach in this problem is evident, in order to the importance of pharmaceutical products. So, in this study by using new methods, we tried to eliminate the mentioned obstacles in previous works. By considering previous studies in this field is clear that this research has the following specified innovations:

- A research in the field of medical products which are in the groups of perishable goods and include production, distribution, and routing are not in a supply chain literature.
- Uncertainty is considered during process such as demand, production capacity and transportation costs in the network routs.
- From a different view point, customer satisfaction and budgetary consideration are considered simultaneously and the mathematical model of the problem is formulated in a bi-level multi-objective form.
- Optimization approaches are used in this research for dealing the uncertain data.
- Drug corruption is formulated from another view point that the expiration date is periodic and drugs can be delivered until they are usable.
- Benders decomposition algorithm is used in this problem for discovering exact solution.
- So, in this research, we considered the possible assumptions for modeling the medicine supply chain as far as possible. For these assumptions, we proposed a multi-objective mathematical model to optimize the production process, the quantity of inventory and production delivery trough network routs with vehicles and facilities allocation. On the other hand, the aim of this paper is to present a robust model with minimal changes in results. By analyzing the literature in this subject, it is obvious that a paper with three level of chain for medicine supply chain and three-state of uncertainty have never been examined before.

3. Problem definition

In this study, three levels of the drug supply chain have been considered. Components of supply chain include three centers namely drug producer, distribution centers and drug retail centers that are pharmacies. It is important to note that producers are out-of-the-way with retail centers, hence drugs are sent by heavy transportation vehicles such as railing and airfreight. Then, when these products are stored in several warehouses, they are delivered to retailers in smaller and similar geographic areas. Therefore the trucks are utilized. Restrictions and control elements in each level for modeling the problem are considered. Assumptions for modeling the problem are as follow:

- The problem in the first level is an allocation problem.(for allocating the producers to warehouses)
- In the second level, routing of the transportation vehicles is investigated and also is done in a weighted graph.
- The VRP problem in this study has capacity with several warehouses and without removal in the return way and the warehouses are in the beginning and terminal of the routes.
- Each customer at each period of time could be served up by maximum one transportation vehicle.
- Each transportation vehicle must begin its route from the warehouse which there it finishes its route.
- Products can be stored in the warehouses at the scheduling horizon, but the optimal decision is that the time keeping the drug should be minimized.
- Drugs degeneration occurs in the storing time.

In the following, sets, parameters and decision variables which are used for formulating the problem are expressed.

Sets

J set of all distributor points or warehouse, $j \in \{1, \dots, J\}$
I set of customers points, $i \in \{1, \dots, I\}$
V set of transportation vehicles from warehouse to customer, $v \in \{1, \dots, V\}$
P set of drug's types, $p \in \{1, \dots, P\}$
M set of potential producers, $m \in \{1, \dots, M\}$
S set of heavy transportation vehicles from producers to warehouse, $s \in \{1, \dots, S\}$
T set of time periods, $t \in \{1, \dots, T\}$

Parameters

tc_{ijvt} Transportation cost from node “i” to node “j” by vehicle “v” at time “t”
D_{pit} Demand of product “p” by customer “i” at time “t”
$Capv_v$ Capacity of vehicle “v”
fv_v Fixed cost of utilizing vehicle “v”
fd_j Cost of initiation warehouse “j”
pv_p Amount of product “p”
$capm_{mpt}$ Fixed production capacity in producer “m” in drug “p” at time “t”
$caps_s$ Capacity of heavy transportation vehicle “s”
vc_{mpt} Variable cost of drug “p” for production by producer “m” at time “t”
$Init_{pj}$ Incipient inventory of drug “p” in warehouse “j”
fh_{jp} Holding cost of drug “p” in warehouse “j”
fm_m Opening cost of corporation “m”
fs_s Fixed cost of heavy transportation vehicle “s” utilization between producers and warehouse
fl_{pit} Lost sale cost of drug “p” for customer “i” at time “t”
Ed_p Lifetime of drug “p” delineated based on time periods
sp_{mp} Material consumption coefficient for drug “p” by producer “m”
SS_{pj} Safety stock for drug “p” in warehouse “j”
C number of customers
bigM : a huge number

Variables

Q_{pmjst} quantity of drug “p” produced by producer “m” and transferred to warehouse “j” by transportation vehicle “s” at time “t”
X_{pit} quantity of drug “p” delivered to customer “i” at time “t”

I_{pjt} inventory level of drug "p" in warehouse "j" at time "t"
U_{iv} additional variables
W_{pmjst} binary variable equals to 1 if and only if vehicle "s" transfers drug "p" from producer "m" to warehouse "j" at time "t" and otherwise 0
Av_{ijt} binary variable equals to 1 if and only if customer "i" is assigned to warehouse "j" at time "t" and otherwise 0
Nc_{ijvt} binary variable equals to 1 if and only if vehicle "v" move from point "i" to point "j" at time "t" and otherwise 0
Y_j binary variable equals to 1 if and only if warehouse "j" is founded and otherwise 0
R_m binary variable equals to 1 if and only if producer "m" is initiated and otherwise 0

$$\min Z_1 = \sum m\epsilon M \sum p\,\epsilon P \sum t\epsilon T\, vc_{mpt} \sum s\epsilon S \sum j\epsilon J\, Q_{pmjst} + \sum m\epsilon M \sum p\epsilon P \sum t\epsilon T \sum s\epsilon S \sum j\epsilon J\, fs_s\, W_{pmjst} \quad (1)$$
$$\sum j\,\epsilon J \sum p\epsilon P \sum t\epsilon T\, fh_{jp} I_{pjt} +$$
$$\sum m\epsilon M\, fm_m\, R_m + \sum v\epsilon V \sum t\epsilon T\, fv_v \sum i\epsilon I \sum j\epsilon J\, Nc_{ijvt} + \sum i\epsilon I \sum j\epsilon J \sum v\epsilon V \sum t\epsilon T\, tc_{ijvt} Nc_{ijv}$$
$$\sum j\epsilon J\, fd_j Y_j$$

$$\min Z_2 = \sum p\epsilon P \sum i\epsilon I \sum t\epsilon T\, fl_{pit} max\{0, D_{pit} - X_{pit}\} \quad (2)$$

s.t

$$\sum s\epsilon S \sum j\epsilon J\, Q_{pmjst} sp_{mp} \leq Capm_{mpt} R_m \qquad \forall\, m \in M, p \in P, t \in T \quad (3)$$

$$\sum p\epsilon P\, Q_{pmjst} pv_p \leq Caps_s \sum p\epsilon P\, W_{pmjst} \qquad \forall\, m \in M, j \in J, s \in S, t \in T \quad (4)$$

$$I_{pj(t+1)} = I_{pjt} + \sum s\epsilon S \sum m\epsilon M\, Q_{pmjst} - \sum i\epsilon I\, X_{pit} Av_{ijt} \qquad \forall\, j \in J, p \in P, t \in T \quad (5)$$

$$I_{pj1} = Init_{pj} \qquad j \in J, p \in P \quad (6)$$

$$I_{pj1} \leq \sum_{t'\epsilon t}^{t'=t+Ed_p} \sum i\epsilon I\, X_{pit'} Av_{ijt'} \qquad j \in J, p \in P, t \in T, t' \leq T \quad (7)$$

$$I_{pjt} \geq SS_{pj} \qquad j\epsilon J, p \in P, t \in T \quad (8)$$

$$\sum j\epsilon J\, Av_{ijt} = 1 \qquad t \in T, I \in I \quad (9)$$

$$\sum i\epsilon I \sum j\epsilon J\, Nc_{ijvt} \leq 1 \qquad t\epsilon T, v \in V \quad (10)$$

$$\sum j\epsilon IUJ\, Nc_{jivt} = \sum j\epsilon IUJ\, Nc_{ijvt} \qquad i\epsilon I \cup J, t \in T, v \in V \quad (11)$$

$$\sum j\epsilon IUJ\, Nc_{jivt} + Nc_{jivt} - Av_{ijt} \leq 1 \qquad i\epsilon I, j \in J, v \in V, t \in T \quad (12)$$

$$X_{pit} \leq bigM \sum j\epsilon J\, Av_{ijt} \qquad i\epsilon I, p \in P, t \in T \quad (13)$$

$$\sum j\epsilon IUJ \sum v\epsilon V\, Nc_{ijvt} = 1 \qquad i\epsilon I, t \in T \quad (14)$$

$$U_{Iv} - U_{iv} + CNc_{Iivt} \leq c - 1 \qquad i\, c\epsilon C, p \in P, t \in T, v \in V \quad (15)$$

$$\sum i\epsilon I \sum p\epsilon P\, X_{pit} pv_p \leq Capv_v \sum i\epsilon I \sum j\epsilon J\, Av_{ijt} \qquad t\epsilon T, v \in V \quad (16)$$

Q,X,I,NP ≥ 0 (17)
W,Av,Nc,Y,R $\in$ {0,1} (18)

The first objective function is minimizing the total cost in time horizon in the supply chain planning. The four major components of costs include the total cost of production, total cost of inventory, total cost of opening facilities and total cost of transportation. Each of these costs include one or more case. Transportation costs include both fixed costs and costs proportional with time and length of the trip. Establishing or opening costs are related to the construction, manufacturing and distribution centers. The second objective function in this model minimizes amount of unsatisfied demand of customers. Lost demand of customers for different products have different value. Capacity of production lines are indicated at constraint (3). Constraint (4) indicates the capacity of transportation from suppliers to distribution centers in various states. Balance between inventories are satisfied by constraint (5). Constraint (6) indicates the initial inventory in the warehouse. To show products corruptibility constraint (7) offers a new way to avoid excessive replenishment. In fact, this limitation does not allow the amount of inventory in warehouse exceeds its consumption in the next period until they are totally corrupt. Constraint (8) controls the safety stock for each product in each centers and time period. Constraint (9) allocates each customer to only one distribution center. Constraint (10) Specifies that only one vehicle can move between any two trips of the network. Flow equilibrium between different tips is satisfied in constraint (11). In the Constraint (12) routes of each vehicle are made successively. Constraint (13) states that if a vehicle of a node's customer travels to other customers, it must be assigned to at least one distribution center. Constraint (14) ensures that if a vehicle ends its delivery process in one tip only travel to one point. In constraint (15) some restrictions for preventing the formation of the sub-tours is being offered. Constraint (16) represents the capacity of the vehicles. Constraint (17) shows the domain of continuous variables and constraint (18) is related to binary variables. The proposed mathematical model equations have some terms that are non-linear. To achieve faster approaches we have used linearization process step by step in terms of non-linear strip deals. First, to make the equation maximum between zero and $D_{pit} - X_{pit}$ linear, we should use ls_{pit} as the unmet demand of product p for customer i in the period t. Putting this variable higher than their difference convert objective function to:

$$Min\ Z_1 = \sum_{p\in P}\sum_{i\in I}\sum_{t\in T} fl_{pit}\, ls_{pit} \tag{19}$$

$$ls_{pit} \geq D_{pit} - X_{pit} \qquad \forall\, i \in I,\ p \in P, t \in T \tag{20}$$

The next constraint is a kind of limitation to avoid products from corruption. In this phase, we define a new variable which replaces the two variables multiplied in the constraint (7).

$$AvX_{pijt} bigM(1 - Av_{ijt}) \leq X_{pit} \qquad \forall\, j \in J, i \in I\ \ p \in P, t \in T \tag{21}$$

In this part of the model development, the uncertainty of Mulvey is base of the model we use for modeling. It involves scenarios to classify the objective function and constraints. For each scenario, a response is obtained and then by compiling the answers you can get a policy that is not predictable and can be implemented. As a result of the decision changes will be minimized since the objective function is minimized simultaneously. A response will be robust when the expected difference in set of scenarios between objective response and the optimal value of objective function is being minimized any scenario. Therefore, we define the variables scenario based on the decisions we make, depending on the parameters of each scenario. By this definition, we can establish new parameters and variables of robust method for each scenario as following table.

S_ω Limited set of scenarios for uncertain demands
γ Design factor for changes in the objective function
P^ω Probability of happening scenario w
D^ω_{pit} Customer (i) demand for the product type (p) at the time of the scenario (w)
θ^ω Additional variables for scenarios (w)
X^ω_{pit} The amount of product type (p) delivered to the customer (i) at the time of the scenario (w)
I^ω_{pjt} Inventory levels of the drug type (p) in the warehouse (j) at the time of the scenario (w)
Av^ω_{ijt} Binary variable equal to 1 if and only if the client (i) goes to the warehouse at the time of allocation (t) scenario (w) and otherwise 0
Nc^ω_{ijvt} Binary variable equal to 1 if and only if the car (v) goes from the point (i) to (j) in the time (t) under the scenario (w) and otherwise 0
U^ω_{iv} Additional variables
tc^ω_{ijvt} Shipping cost from node (i) to node (j) by the car (v) under the scenario (w)

$$\begin{aligned} Min\ Z_1 = \sum_{\omega\in S_\omega} P^\omega \Big(&\sum_{m\in M}\sum_{p\in P}\sum_{t\in T} vc_{mpt} \sum_{s\in S}\sum_{j\in J} Q_{pmjst} + \\ &\sum_{m\in M}\sum_{p\in P}\sum_{t\in T}\sum_{s\in S}\sum_{j\in J} fs_s W_{pmjst} + \sum_{j\in J}\sum_{p\in P}\sum_{t\in T} fh_{jp}\, I^\omega_{pjt} + \sum_{m\in M} fm_m R_m + \\ &\sum_{v\in V}\sum_{t\in T} fv_v \sum_{i\in I}\sum_{j\in J} Nc^\omega_{ijvt} + \sum_{i\in I}\sum_{j\in J}\sum_{v\in V}\sum_{t\in T} tc^\omega_{ijvt} Nc^\omega_{ijvt} + \sum_{j\in J} fd_j Y_j \Big) + \end{aligned} \tag{22}$$

$$\gamma \sum_{\omega \in S_\omega} P^\omega [(\sum_{m\in M}\sum_{p\in P}\sum_{t\in T} vc_{mpt} \sum_{s\in S}\sum_{j\in J} Q_{pmjst} + \sum_{m\in M}\sum_{p\in P}\sum_{t\in T}\sum_{s\in S}\sum_{j\in J} fs_s W_{pmjst} + \sum_{j\in J}\sum_{p\in P}\sum_{t\in T} fh_{jp}\, I^\omega_{pjt} + \sum_{m\in M} fm_m R_m + \sum_{v\in V}\sum_{t\in T} fv_v \sum_{i\in I}\sum_{j\in J} Nc^\omega_{ijvt} + \sum_{i\in I}\sum_{j\in J}\sum_{v\in V}\sum_{t\in T} tc^\omega_{ijvt} Nc^\omega_{ijvt} + \sum_{j\in J} fd_j Y_j) - \sum_{\omega \in S_\omega} P^\omega (\sum_{m\in M}\sum_{p\in P}\sum_{t\in T} vc_{mpt} \sum_{s\in S}\sum_{j\in J} Q_{pmjst} + \sum_{m\in M}\sum_{p\in P}\sum_{t\in T}\sum_{s\in S}\sum_{j\in J} fs_s W_{pmjst} + \sum_{j\in J}\sum_{p\in P}\sum_{t\in T} fh_{jp}\, I^\omega_{pjt} + \sum_{m\in M} fm_m R_m + \sum_{v\in V}\sum_{t\in T} fv_v \sum_{i\in I}\sum_{j\in J} Nc^\omega_{ijvt} + \sum_{i\in I}\sum_{j\in J}\sum_{v\in V}\sum_{t\in T} tc^\omega_{ijvt} Nc^\omega_{ijvt} + \sum_{j\in J} fd_j Y_j) + 2\theta^\omega]$$

$$Min\ Z_2 = \sum_{\omega \in S_\omega} P^\omega \left(\sum_{p\in P}\sum_{i\in I}\sum_{t\in T} fl_{pit}\, ls^\omega_{pit}\right) + \gamma \sum_{\omega \in S_\omega} P^\omega \left[\sum_{p\in P}\sum_{i\in I}\sum_{t\in T} fl_{pit}\, ls^\omega_{pit} - \sum_{\omega \in S_\omega} P^\omega \left(\sum_{p\in P}\sum_{i\in I}\sum_{t\in T} fl_{pit}\, ls^\omega_{pit}\right) + 2\theta^\omega\right] \quad (23)$$

subject to

$$(\sum_{m\in M}\sum_{p\in P}\sum_{t\in T} vc_{mpt} \sum_{s\in S}\sum_{j\in J} Q_{pmjst} + \sum_{m\in M}\sum_{p\in P}\sum_{t\in T}\sum_{s\in S}\sum_{j\in J} fs_s W_{pmjst} + \sum_{j\in J}\sum_{p\in P}\sum_{t\in T} fh_{jp}\, I^\omega_{pjt} + \sum_{m\in M} fm_m R_m + \sum_{v\in V}\sum_{t\in T} fv_v \sum_{i\in I}\sum_{j\in J} Nc^\omega_{ijvt} + \sum_{i\in I}\sum_{j\in J}\sum_{v\in V}\sum_{t\in T} tc^\omega_{ijvt} Nc^\omega_{ijvt} + \sum_{j\in J} fd_j Y_j) - \sum_{\omega \in S_\omega} P^\omega (\sum_{m\in M}\sum_{p\in P}\sum_{t\in T} vc_{mpt} \sum_{s\in S}\sum_{j\in J} Q_{pmjst} + \sum_{m\in M}\sum_{p\in P}\sum_{t\in T}\sum_{s\in S}\sum_{j\in J} fs_s W_{pmjst} + \sum_{j\in J}\sum_{p\in P}\sum_{t\in T} fh_{jp}\, I^\omega_{pjt} + \sum_{m\in M} fm_m R_m + \sum_{v\in V}\sum_{t\in T} fv_v \sum_{i\in I}\sum_{j\in J} Nc^\omega_{ijvt} + \sum_{i\in I}\sum_{j\in J}\sum_{v\in V}\sum_{t\in T} tc^\omega_{ijvt} Nc^\omega_{ijvt} + \sum_{j\in J} fd_j Y_j) + \theta^\omega \geq 0 \quad \forall\ \omega \in S_\omega \quad (24)$$

$$\sum_{p\in P}\sum_{i\in I}\sum_{t\in T} fl_{pit}\, ls^\omega_{pit} - \sum_{\omega \in S_\omega} P^\omega \left(\sum_{p\in P}\sum_{i\in I}\sum_{t\in T} fl_{pit}\, ls^\omega_{pit}\right) + \theta^\omega \geq 0 \quad \forall\ \omega \in S_\omega \quad (25)$$

$$ls^\omega_{pit} \geq D^\omega_{pit} - X^\omega_{pit} \quad \forall\, i \in I,\ p \in P, t \in T, \omega \in S_\omega \quad (26)$$

$$\sum_{s\in S}\sum_{j\in J} Q_{pmjst} sp_{mp} \leq Capm_{mpt} R_m \quad \forall\, m \in M, p \in P, t \in T \quad (27)$$

$$\sum_{p\in P} Q_{pmjst} pv_p \leq Caps_s \sum_{p\in P} W_{pmjst} \quad \forall\, m \in M, j \in J,\ s \in S, t \in T \quad (28)$$

$$I^\omega_{pj(t+1)} = I^\omega_{pjt} + \sum_{s\in S}\sum_{m\in M} Q_{pmjst} - \sum_{i\in I} X^\omega_{pit} Av^\omega_{ijt} \quad \forall\ j \in J,\ p \in P, t \in T, \omega \in S_\omega \quad (29)$$

$$I^\omega_{pj1} = Init^\omega_{pj} \quad \forall\ j \in J,\ p \in P, \omega \in S_\omega \quad (30)$$

$$AvX^\omega_{pijt} bigM(1 - Av^\omega_{ijt}) \leq X^\omega_{pit} \quad \forall\, j \in J, i \in I\ \ p \in P, t \in T, \omega \in S_\omega \quad (31)$$

$$I^\omega_{pjt} \geq SS_{pj} \quad \forall\ j \in J,\ p \in P, t \in T, \omega \in S_\omega \quad (32)$$

$$\sum_{j\in J} Av^\omega_{ijt} = 1 \quad \forall\, t \in T,\ i \in I, \omega \in S_\omega \quad (33)$$

$$\sum_{i\in I}\sum_{j\in J} Nc^\omega_{ijvt} \leq 1 \quad \forall\, t \in T,\ v \in V, \omega \in S_\omega \quad (34)$$

$$\sum_{j\in I\cup J} Nc^\omega_{jivt} = \sum_{j\in I\cup J} Nc^\omega_{ijvt} \quad \forall\, i \in I \cup J, t \in T,\ v \in V, \omega \in S_\omega \quad (35)$$

$$\sum_{u\in I\cup J} Nc^\omega_{iuvt} + Nc^\omega_{ujvt} - Av^\omega_{ijt} \leq 1 \quad \forall\, i \in I, j \in J, v \in V, t \in T, \omega \in S_\omega \quad (36)$$

$$X^\omega_{pit} \leq bigM \sum_{j\in J} Av^\omega_{ijt} \quad \forall\, i \in I, p \in P,\ t \in T, \omega \in S_\omega \quad (37)$$

$$\sum_{j\in I\cup J}\sum_{v\in V} Nc^\omega_{ijvt} = 1 \quad \forall\, i \in I, t \in T, \omega \in S_\omega \quad (38)$$

$$U^\omega_{Iv} - U^\omega_{iv} + CNc^\omega_{Iivt} \leq C - 1 \quad \forall\, i \in C, p \in P,\ t \in T, \omega \in S_\omega,\ v \in V \quad (39)$$

$$\sum_{i\in I}\sum_{p\in P} X^\omega_{pit} pv_p \leq Capv_v \sum_{i\in I}\sum_{j\in J} Av^\omega_{ijt} \quad \forall\, t \in T,\ v \in V, \omega \in S_\omega \quad (40)$$

$$Q, X, I, NP \geq 0 \quad (41)$$

$$W, Av, Nc, Y, r \in R \quad (42)$$

4. Solution Method

Some studies in the introduction have used accurate methods for solving their model. Sarin et al. (2010) have developed Benders decomposition algorithm for solving schedule problem of Courses University. Li and Womer (2009) focused on a problem project planning with limited resources and a combination Benders have been used to solve the problem. Redjem et al. (2012) and Rabeh et al. (2011) issued of nursing home care to study contralateral routing, scheduling and software to solve LINGO_11 the issue of their own. Bard and Purnomo (2007) developed an integer programming model and then by using the Lagrange method the problem was solved. Maenhout and Vanhoucke (2010) used an exact algorithm branch and price to solve the issue nursing planning. (Gamst & Jensen, 2012; Rasmussen et al., 2012) presented a model for long-term home care scheduling problem, then the branch and price algorithm was implemented to solve this problem. Price cutting approach by Trautsamwieser and Hirsch, (2014) was used to solve home care scheduling problem. One of the innovations of our research is presented as a bi-level model. The bi-level optimization, there are two levels of optimization, the optimized upper-level and lower-level optimization. Upper-level introduced as the leader and lower-level optimization introduced as the follower. The primary problem with the internal constraints is the solution space optimization of the upper-level. As a result, it is a non-convex problem and it is complicated to solve. In addition, this model can decide on continuous variables and integer ones. According to the proposed model the objective function leading to minimize transport costs and the cost of other entities. Furthermore, the purpose is to minimize the amount of unmet demand of customers. In the introduction section several researches studied the exact methods to solve different bi-level mixed integer linear programming (MIBLP). Most of bi-level linear programming problems (BLP) focused on the problems that don't have integer decision variables. Numerical techniques based on the ownership issue bi-level, the global optimal solution is in the answer that some part of space is determined by the limits of upper and lower levels. Moore and Bard (1990), Bard, (1983), Vicente et al. (1996), Chen and Florian (1992) and Tuy et al. (1993) have created different algorithms based on numerical optimization techniques. Altering techniques of bi-level structure use techniques such as Karush-Kuhn-Tucker optimality conditions (KKT) for lower-level issue with additional restrictions on the upper-level. Thus, the bi-level has convert to a single issue. Shi et al. (2006), Shi et al. (2005) and Bialas and Karwan, (1978) and Hansen et al., (1992) used optimality conditions of KKT to correct the problem with new restrictions on single level. They have various forms of Branch and Bound to solve the final model.

5. The numerical results

In this section, numerical examples show how the model works and verify the viability and applicability of the proposed model. For this purpose, numerical examples are provided for the bi-level performance evaluation of proposed objective and to demonstrate its usefulness.

Table 1
Results of numerical example

Problem	Number of producers	Number of distributors	Number of customers	Number of drugs	Number of vehicles	Number of vehicle S	Number of time periods
1	2	3	5	10	5	5	2
2	3	4	10	15	6	6	3
3	4	5	15	20	7	7	4
4	5	6	20	25	8	8	5
5	6	7	25	30	9	9	6

Table 1 shows denial optimal numerical examples. The size of the problem be determined based on characteristics such as manufacturers, distributors, customers, product type, vehicle distribution centers to customers and manufacturers to distribution centers and finally the horizon timing. As the paper has been developed for non-deterministic situations, three scenarios are intended to be defined as follows:

The first scenario considers lowest fuel price, the time horizon that led to the sending of the highest orders for products with lowest price. In the second scenario it can be seen that the price of fuel is most likely to occur and orders mainly based on this scenario. In the third scenario the price of fuel is at the highest level which leads to the highest prices of finished product. So your customers reduce their demands to lower levels for this scenario. In this study to get the answer of the uncertain model it is solved with GAMS software. Table 2 shows the computational results of numerical examples by using Benders algorithm and the execution time for the five numerical examples is also shown in
Table **3**. The results show the suitability of the model applied for the mixed integer bi-level bi-objective model provided under uncertainty. Based on Benders decomposition algorithm, in each iteration the cutting out duplication in Benders decomposition algorithm and adding to the main proposed models will accelerate the convergence of high and low the models. Between the three sections, the third cut plays

an important role in changing the limits and reducing the number of iterations. To illustrate this effect, for example, Fig. 1 shows the convergence allocation model of numerical example 4.

Table 2
Computational results of numerical example

case	Objective function	
	Z_1	Z_2
1	9280.199	12304.8
2	10572.001	22144.4
3	18493.786	35625
4	28994.036	47374.2
5	34578.913	54923.7

Table 3
Running time of numerical example

case	Running time
1	12.18
2	27.36
3	50.25
4	85.03
5	138.17

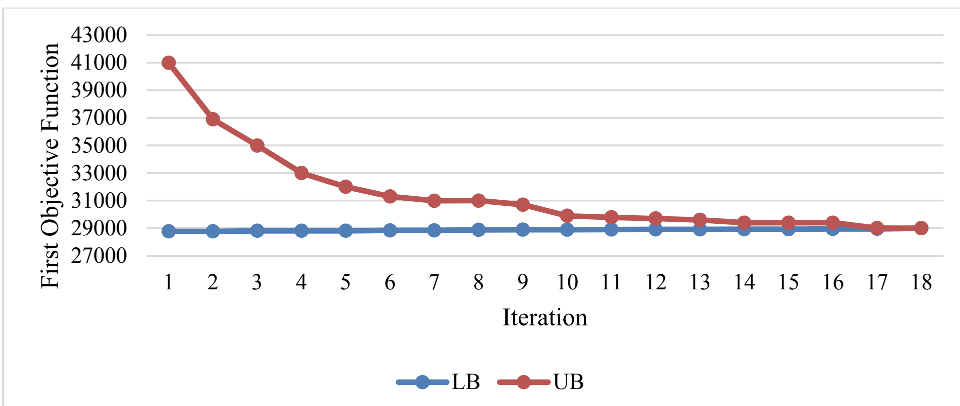

Fig. 1. Convergence diagram of allocation model for case No 4

Also, a system by running radio distribution was proposed to simulate the policy. Simulation model was programmed by MATLAB software to show the comparison between the model and the actual system. Based on data experimental center performance simulation model was evaluated in comparison to the real system. For this purpose, the variance analysis method (ANOVA) is used. So we use F-test and t-test for equality of variance test and average equity for model simulation and the real system was calculated. Table 4 shows ANOVA test results which represents that the performance of simulation model is similar to the real system and there is not a meaningful difference between the simulation model and real systems.

Table 4
ANOVA for comparing simulation model with real system

Factor	F-test (with equal variance)			T-test (with equal average)		
	F-value	*p*-value	$H_0 : \delta_1^2 = \delta_2^2$	*T*-value	*p*-value	$H_0 : \mu_1 = \mu_2$
Z_1	0.54	0.277	will not be rejected α=0.05	0.7	0.681	will not be rejected α=0.05
Z_2	0.77	0.436	will not be rejected α=0.05	1.15	0.682	will not be rejected α=0.05

Then, the performance of the bi-level model compared with simulation models for finding the difference between the results and the proposed national simulation results. With the implementation of model for

50 times, the proposed model and simulation model were compared to the average target functions. For this purpose (ANOVA) test was used by two examples. To test the average equity (H0: y1=y2), values of objective functions the proposed model was tested with simulation models. The results show that, at a significance level of 0.05 differences there is not a meaningful difference between the proposed model and simulation model which is presented in (**Error! Reference source not found.**).

Table 5
ANOVA for comparing simulation model with proposed model

Factor	average		t-test (with equal average)		
	Proposed model	Simulation model	T-value	p-value	$H_0 : \mu_1 = \mu_2$
Z_1	872	1758	1.45	0.015	will be rejected at α=0.05
Z_2	334	791	0.74	0.021	will be rejected at α=0.05

6. Conclusion

This paper presents a novel bi-level bi-objective model for a medicine supply chain (considering drug as a perishable product). The model encompasses the main features of this chain. The integrated process from producers to customers includes different distribution and routing modes that deal with uncertain parameters. The uncertainty has been considered in this paper for all the process time including demand, production capacity and transportation costs in the network routes. The two objective functions are namely about the lost demand and the supply chain's costs and the both involve with uncertain parameters. By using the Mulvey approach the model has been developed under uncertainty and then it has been solved by implementing a Bender's decomposition method based on game concepts. The numerical results show the accuracy and efficiency of the proposed model and prove that a noticeable saving has been made in the lost sale and the associated costs of the supply chain. For the further research the following options can be considered: first of all warehouses on the location of retailers can be added to the current model in order to compare it with the vendor managed inventory systems. Moreover different capacities and speeds can be considered for the vehicles and finally considering the risk of disruption may result in nice managerial insights in this field of study.

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