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Multi-Objective Mathematical Model for Pharmaceutical Location-Routing Problem with Potential Demand Approach

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Facility location and routing problems have attracted significant research attention since the 1960s due to their practical relevance and complexity. Efficiently establishing production facilities, optimizing vehicle routes, and implementing effective inventory systems are essential for improving organizational performance. In this study, we propose an integrated location-routing model for the pharmaceutical supply chain, designed to satisfy all retailer demands through an appropriate inventory policy, ensuring no demand is unmet. The proposed mixed-integer mathematical model considers a four-tier supply chain, including manufacturers, distributors, wholesalers, and retailers, with the objective of establishing cost-effective warehouses while fulfilling all demand requirements. Demand uncertainty is addressed using a scenario-based probabilistic approach. The model is solved using GAMS for a small-scale case study. For larger-scale instances, where exact solutions are computationally challenging, a meta-heuristic approach—specifically, a genetic algorithm—is employed to efficiently obtain near-optimal solutions.

Keywords: *Demand uncertainty, Location routing problem, inventory system, Meta-heuristic algorithm, pharmaceutical supply chain*

1. Introduction

One of the main goals in shaping a supply chain (SC) is ensuring it responds to consumer demands effectively. Responding on time helps businesses to remain competitive in the market, and maximizes profits. To achieve these, all parts of the supply chain must be optimized to lower costs, enhance customer satisfaction, and rise up overall profits [21]. In essence, every supply chain consists of various interconnected components and stages, all working towards a common goal. Today, the problems in the pharmaceutical supply chain are of global concern due to its importance in providing essential products for human health and patient care. What was once a simple process with production in a single location has evolved into a complex network involving multiple centers, companies, and facilities [8]. These activities are not limited to a specific region but are carried out on a large scale. The main challenges in drug production involve making decisions about expanding facilities and planning drug production [46]. Two factors, namely meeting consumer expectations and increasing costs throughout the chain, compel the chain to seek ways to enhance its efficiency. Access to important and necessary medications, a fundamental aspect of healthcare systems, has led to the consideration of political criteria primarily focused on reducing cost growth within the pharmaceutical industry. Supply chain management involves overseeing all stages of the chain, starting from the creation of products to their delivery to customers [38]. This encompasses the entire flow of activities within the network, from sourcing raw materials to adding value to the final products. One important topic in supply chain analysis is facility location within the network. Facility location issues involve placing a set of facilities (resources) to minimize fulfillment costs of a set of customer demands while considering a set of constraints. Supply chain management emphasizes the integration of chain members, as decisions cannot be considered separately and optimization efforts are needed for efficiency improvement [34]. Decision integration is a crucial factor that significantly

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reduces supply chain expenditures and enhances customer satisfaction. Given the essential role of the two elements of facility location and routing in the continuity of a SC, the integration of these two elements results in a resilient and efficient SC [56]. In a supply chain, the most crucial factor after selecting optimal facility locations is proper routing, which significantly reduces transportation costs. In the present times, the presence of pandemic such as COVID-19 can bring about disruptions in the pharmaceutical production and distribution system. Therefore, providing a suitable solution for integrated decision-making and effective management of the pharmaceutical SC is important. Given the uncertainties surrounding the demand for essential commodities such as medicines, which follows a highly probabilistic trend, the presentation of a systematic approach for integrating location-routing decisions for pharmaceutical items is of utmost significance [50]. In today's competitive world, supply chain issues are particularly prominent, with the pharmaceutical sector being especially affected. An effective supply chain should ensure rapid delivery, increase profitability, and reduce operational costs at all levels [43]. Managing the supply chain within manufacturing companies involves making ideal decisions about production levels, storage quantities, transportation methods, and the selection of suppliers. Therefore, this improves a corporate's competitive advantage and leads to increased profitability. In developed countries, healthcare expenditures represent a large share of the gross national product, while the pharmaceutical industry contributes comparatively less. On the other hand, selecting suitable locations for establishing and operating production sites is crucial, as it falls under strategic and long-term decisions. Furthermore, optimal routing is crucial for efficiently delivering consumer products, ensuring the shortest and best routes are taken among multiple choices. Thus, considering the above-mentioned points, presenting a model for location-routing in a pharmaceutical SC is essential due to the challenges present in drug production and distribution. This research introduces a mathematical model for distribution centers' (DCs) location within a multi-level SC. Pharmaceuticals commodities are sent to DCs and wholesalers after production, then forwarded to retail stores, commonly known as pharmacies, before reaching customers. The focus of this research is on the routing between these two stages. Among this, the demand for each pharmacy is considered uncertain and probabilistic. Supply chain management is among the most crucial topics in industries and organizations. Various elements exist within the supply chain, and by examining and managing them, organizations reduce their operational cost which is a important goal. Supply chain planning is divided into three stages: (I) strategic, (II) operational, and (III) tactical planning [58]. Location-based issues are of great significance for industries that directly face end customers and operate at primary activity levels, such as consumer goods industries. In such sectors, market competition, customer loyalty, product pricing, timely product accessibility, and product quality are directly linked [61]. Therefore, a crucial element for profitability is delivering a timely and high-quality response to customer demands at the lowest possible cost. Lately, extensive studies have been conducted in the location-routing problems' field, yet many challenges remain unaddressed, particularly in the context of pharmaceutical SC management and the consumption of pharmaceutical items. The absence or scarcity of medications can pose significant threats to human lives. Thus, the formulation of a mathematical model for SC management in the realm of location and routing is of extreme importance. Moreover, multi-level location-routing within a supply chain, considering uncertain demands and potential transportation disruptions, remains an area where researchers have yet to fully investigate. Today, researchers believe that simultaneously addressing location-routing issues in a SC plays a significant role in cost reduction related to these aspects.

The research objectives can be succinctly stated as follows,

- To present a mathematical model for pharmaceutical SC management under crisis conditions.
- We considered demand uncertainy in this paper.
- To provide suitable solutions for solving the model (considering the model's NP-hard nature and choosing an appropriate solving method for large instances).
- To present an integrated location-routing model within the pharmaceutical SC context.

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The studied SC is a 4-tier chain composing of the manufacturer (factories), DCs, wholesalers, and retailers (customers). The supply chain operates over multiple periods and handles multiple products. The location of production centers, DCs, and wholesalers are not fixed and needs to be selected from several potential sites. Moreover, the transportation fleet is heterogeneous, with a probabilistic chance of vehicle breakdown and the number and capacity of vehicles are limited. Additionally, the demand is considered uncertain. By addressing these objectives, this study aims to contribute to the optimization and efficiency enhancement of pharmaceutical SCs, which are of importance for ensuring the essential medications availability and the well-being of human populations.

The study is arranged as follows: Section 2 reviews the literature. Section 3 describes the notations and assumptions and the formulation of the model. The solution approach is presented in section 4. Section 5 provides a numerical analysis of the presented model's parameters and results and also serves as a source of managerial insights. We have a conclusion in section 6.

2. Literature Review

A pharmaceutical SC is a complex network of interconnected stages, both direct and indirect, dedicated to meeting customer demands [5]. In this complex process, raw materials begin their journey from suppliers to factories [51]. Following transformation, the finished products embark on a journey through intermediate and distributor warehouses, finishing in their arrival at retailers and, eventually, in the hands of enthusiastic consumers. This journey highlights the multifaceted nature of the supply chain, where products alternate between storage and transportation activities [27]. At the core of this intricate system lie the foundational components of a conventional supply chain: suppliers, raw materials, production facilities, distributors, retailers, and the customer [35]. However, the scope of the SC extends beyond physical processes, encompassing the intricate flow of financial management, information system [42], and the exchange of vital knowledge [36]. Therefore, integrated planning is needed to deal with complex supply chain [17]. In today's highly competitive global markets, businesses face a critical need to not only meet but exceed customer expectations while delivering unique products [23]. This pressure has prompted companies to shift their investments towards the enhancement of their SCs. In a typical SC systems, the process begins with the procurement of raw materials, followed by their transformation into finished products within one or more manufacturing facilities. These finished products are then temporarily stored in intermediate warehouses before sending to retailers or customers [45]. Therefore, successful supply chain strategies must effectively oversee interactions across multiple levels of this supply chain, ensuring a delicate balance between cost efficiency and the delivery of exceptional services. Pharmaceutical SC unifies suppliers, manufacturers, and pharmacies into an efficient system, enhancing performance by reducing lead times [47], ensuring product safety, and meeting regulatory standards [41]. This integration goes beyond manufacturing; it ensures that products are not only produced but also distributed in the right quantities, to the correct locations, and at precisely the exact times. All of this is accomplished while minimizing the overall system costs and meeting rigorous service level requirements. Effective SC management is essential for reducing extra costs, maximizing profits, and meeting the ever-increasing expectations of consumers [19]. This requires a three-tiered decision-making process: operational, tactical, and strategic. At the strategic level, decisions involve factors like facility location, production capacity, transportation methods, and information systems, spanning several years into the future [52]. In the medium-term planning stage, the focus shifts to decisions related to inventory levels [43], pricing strategies, and supplier selection [39] for specific markets. Finally, at the short-term planning stage, on-the-ground decisions such as product allocation, order completion dates, and truck scheduling come into play. The relative importance of each planning

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horizon may vary depending on the organization's policy and scale, but adherence to these operational, tactical, and strategic decisions is crucial for SC success. The strategic placement of facilities is a critical factor in an organization's profitability and its broader impact on economic, social, cultural, environmental, and regional conditions. This long-term decision is less flexible and incurs high costs, but significantly influences service system performance and customer satisfaction [10]. Transportation is a cornerstone of economic and societal activities, playing a vital role in goods distribution and procurement [11]. Distribution costs can inflate product prices significantly, to highlight its significance. Moreover, vehicles can handle a substantial percentage of goods transportation, emphasizing the need for efficient routing and scheduling. Vehicle routing problems focus on finding optimal routes while considering capacity constraints, have gained prominence in service and procurement systems. These problems have evolved since their theoretical inception in 1959 with the truck dispatch problem, demonstrating their growing importance in supply chains. Despite their complexity, as they are categorized as NP-hard problems, they remain a vital research focus [28]. Efficient transportation, grounded in data-driven models and spatial relationships, supports integrated approaches to address transportation challenges, particularly in modern urban planning, fostering harmonious cities [31]. Overall, the intricate interplay between supply chain dynamics, facility location decisions, and the optimization of transportation networks is indispensable for modern businesses, offering the potential for cost reduction, improved service quality, and competitive success. The pharmaceutical supply chain holds plays a vital role in healthcare industry, ensuring the uninterrupted availability of life-saving medications and critical healthcare commodities arrives on time to patients and healthcare providers [7]. Timely and reliable access to medications is vital for the effective treatment of diseases, management of chronic conditions, and rapid response to healthcare emergencies. Therefore, the pharmaceutical supply chain's resilience and efficiency are paramount, making it an indispensable component of global healthcare infrastructure [25].

2.1. Pharmaceutical Supply Chain (PSC)

PSC plays a pivotal role in safeguarding public health by adhering to stringent quality control standards and regulatory practices, thereby ensuring the efficacy and safety of pharmaceutical products. [55] investigated a collaborative approach to ensure that drugs with unexpired usage dates could be reused. They considered a reverse SC including a manufacturer, end consumers, and third-party companies. The model was also multi-product and focused on entities like pharmacies and hospitals as customers. Moreover, they employed a Mulvey approach based on discrete scenarios to explore inherent uncertainty regarding low-demand items, linked to imprecise demand in the pharmaceutical market. [12] proposed a location-allocation-inventory model for PSC network design. This model is multi-objective, addressing cost minimization, reduced delivery times, and improved transportation system reliability. Moreover, they account for uncertainty in various parameters, such as costs and capacity, using a robust fuzzy optimization approach. Furthermore, the study introduces an efficient modification of the red deer algorithm for solving the multi-objective problem. [64] proposed a bi-objective MILP model for developing a perishable PSC network under demand uncertainty. Their model simultaneously minimizes the lost demand amount and the total network cost. It is a multi-period, multi-product model encompassing facility location, inventory management, and vehicle routing making it an strategic-operational model. Moreover, they consider various factors, including procurement discounts, product lifetimes, time windows, lost demand, and storing products for future periods. To solve this model, a novel hybrid approach combining goal programming, chance constrained programming, and fuzzy theory is introduced. [22] introduced an innovative cost-sharing agreement for the environmentally responsible disposal of antibiotics in a two-tier sustainable reverse supply chain for pharmaceuticals. This contract maximizes supply chain profitability, improves the social image of companies, increases sustainability, and reduces governmental penalties associated with pharmaceutical waste disposal. [14]

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developed a PSC model with three objective functions aimed at minimizing unfulfilled demands, total costs, and reducing waiting times at the firm entrance. It proposes a nonlinear programming model and employs multi-objective decision-making methodology to address conflicting targets. [1] propose a decentralized blockchain framework for selling pharmaceutical products online, eliminating intermediaries such as hospitals. Ethereum smart contracts are used to oversee interactions and record events, ensuring participants stay updated on transactions. Furthermore, smart contracts manage seller-consumer interactions by monitoring IoT container statuses and notifying consumers. Two mathematical programming models are developed by [7] for routing mobile pharmacies to minimize the mean absolute deviation of the stock-out severity index. They also find that focusing exclusively on equity results in high operational costs, and show methods to achieve equity with controlled cost increases. Moreover, [7] present a two-stage framework to minimize costs, with "pre-disaster" decisions made before demand is known and "post-disaster" decisions made after. They address demand uncertainty using robust optimization and stochastic programming. [18] present a multi-objective optimization method for PSC design to minimize costs and delivery times to hospitals and pharmacies, while maximizing transportation reliability. They developed a new MINLP model for production, allocation, inventory, distribution, ordering, and routing. [44] introduces an order-up-to replenishment policy combined with inventory routing optimization within a three-echelon SC framework. It includes a real-world case study from the pharmaceutical company Hovione Farmaciência.

2.2. Location Routing Problem for Pharmaceutical Products

Location routing problems assume a critical role in time management of delivery, especially perishable pharmaceutical products. A location-routing model is essential for pharmaceutical logistics because it uniquely addresses the industry's critical need for temperature control, product security, and urgent delivery, ensuring medication efficacy and patient safety. It strategically optimizes the placement of facilities and the routing of vehicles to meet these strict requirements while also improving efficiency and reducing costs. [16] focus on designing a green supply chain and developing a location-routing-inventory model. The study examines a two-objective mixed-integer model which involves the of DCs location and vehicle routing under fuzzy demand. The research addresses the facility location, using a limited capacity vehicle routing problem formulation. Moreover, the demand is considered as uncertain and a fuzzy solution approach is employed. [59] investigated the blood supply chain in China. They use robust optimization based on distribution which was the key point of their study. Also, they were a pioneer in the context of blood SCs. [54] develop an integrated pharmacy inventory and government decision model for a closed-loop SC in the pharmaceutical industry. This model addresses environmental, social, and economic sustainability by focusing on the reusing of drugs to reduce waste, alleviate the financial burden on patients, and examine the influence of government subsidies and incentives. The study highlights the feasibility of drug recycling plans and their potential benefits, taking into account the patients' receptiveness to utilizing recycled drugs and the role of non-profit pharmacies in obtaining sustainability goals within the circular economy framework. [65] developed a comprehensive multi-objective, probabilistic MILP model for a sustainable reverse and forward logistics network. This model considers various dimensions, including environmental impacts, processing time, and social responsibility, to address both original and return product flows within an uncertain demand context. Additionally, it utilizes probabilistic planning to handle uncertain parameters and employs a NSGA-II to obtain Pareto front solutions. [3] addressed the complexities of the drug SC,

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characterized by high turnover and product corruption. It focuses on integrated vehicle routing, and inventory management, aiming to analyze inventory and routing problems in the drug SC, considering travel time and perishable products dependencies. The Box-Jenkins predicting method is applied to deal with uncertain demand effectively. [60] presented a hybrid particle swarm intelligence heuristic method for solving the complex problem of multi-type vehicle assignment and MIP route optimization in pharmaceutical logistics. [48] studied a supply network configuration problem which integrates warehouse selection for inventory policy, vendor-managed inventory, and delivery routing optimization. The paper presents both deterministic and robust optimization models, including a special model to account for the COVID-19 pandemic's impact on delivery times and demand. [15] developed a bi-objective mathematical model for shaping a resilient pharmaceutical-health relief SC network under disruption, with a focus on minimizing delivery time and total costs. The study uses a scenario-based robust optimization method and compares the results with and without lateral transshipment, showing that lateral transshipment can enhance supply chain performance and reduce shortages during disruptions. [9] developed a hybrid heuristic algorithm for solving the VRP with Cross-Docking and Three-Dimensional Loading Constraints (3L-VRPCD). This algorithm outperforms the traditional MILP-based method in terms of computational efficiency and solution quality, particularly for medium to large-scale instances. Their paper also introduces a storage-pool-based strategy to enhance the heuristic's search process and reduce computational burden. Additionally, it analyzes and discusses the influences of various properties, such as loading conditions, on the 3L-VRPCD solutions. [4] addressed the capacitated VRP with urgency, considering factors like infectiousness rates and travel times as critical issues. It employs multi-objective optimization algorithms, including NSGAII, SPEA2-SDE, GrEA, HypE, and reference points-based evolutionary algorithm, to optimize two objectives: minimizing travel time and reducing infectiousness rates for vehicles serving medical facilities with urgency levels. [6] introduced a bi-objective capacitated VRP that considers two types of consumers based on priority, aiming to reduce total distance traveled by customers' and vehicles' average latency. It explores three scenarios for average latency calculation, including priority and non-priority customers. [24] addressed the integrated location-transportation problem with uncertain demand, specifically in the context of a pharmaceutical logistics network in Brazil. The paper introduces a mathematical model with multi-time scales, accounting for practical aspects like fleet sizing, safety constraints, and tax considerations. To tackle uncertainty, a robust counterpart and Fix-and-Optimize heuristics are presented. Using real data, the heuristics demonstrate a significant reduction (40%) in logistics costs and taxes compared to the MIP model. [2] introduce a multi-objective MILP model that integrates the two-echelon VRP with the vaccine SC, aiming to reduce the number of undelivered doses. They propose solving this complex model using a heuristic approach based on greedy random search. Moreover, [37] propose a model for nitrous oxide SC decisions, introducing a single-product multi-line production routing problem with time-dependent setups. The model investigates direct and indirect emissions, considering a heterogeneous fleet to minimize greenhouse gas emissions and costs. Furthermore, [49] present a bi-level optimization model to reduce transportation risks time-window penalties, transportation costs, and site selection costs in the face of uncertainties. The paper also uses the lognormal distribution to model the uncertainty in medical waste production. [20] introduce a MILP model for creating a robust infectious waste management reverse network amid the COVID-19 pandemic. The results illustrate the model's effectiveness in shaping a resilient waste management system during health crises. Moreover, [20] combines the lexicographic optimization method with the

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TH method to create an effective multi-objective solution for the bi-objective MILP model. Furthermore, it employs an information-sharing system to manage waste generation uncertainties.

In this research, the significant problem of pharmaceutical distribution, which is among practical issues closely related to the real world, is studied within a four-level supply chain. The focus is on a pharmaceutical manufacturing company, which proposes to distribute its products from multiple production centers to distribution centers, then to warehouses, followed by wholesalers, and ultimately to retailers. The company aims to make decisions regarding the establishment of production centers and transportation systems in a way that minimizes costs. A summary of this study in comparison with previous studies are shown in Table 1.

Table 1. Literature review

Author	Objective	Type of product	Approach
Stellingwerf et al. [53]	Minimizing total emissions	Drugs	Fico Xpress Mosel
Yang et al. [61]	Minimizing costs	Vaccines	Disaggregation-and-merging algorithm
Li et al. [29]	Minimizing costs	Commodities	Multi-objective algorithms
Moadab et al. [32]	Minimizing costs, negative societal impact caused by shortages, and environmental impact	COVID Test	Multiple Choice Goal Programming
Fallahi et al. [13]	Minimizing the total cost and total carbon emission	Blood plasma	ε-Constraint
Machiani et al. [30]	Minimizing total SCN costs, environmental effects, social impacts, and maximizing the reliability of demand delivery	Medical protective equipment	Augmented ε-Constraint, Multi-objective algorithms
This paper	Minimizing costs and delivery time	Pharmaceutical commodities	Genetic algorithm

3. Problem Definition

Location-routing problem includes the placement of factories, distribution centers, transportation issues, and routing, which affects to the routing of product transfers from factories to distribution centers, from DCs to wholesalers, and from there to retailers (customers). The location-allocation problem, when integrated with the discussed topic, addresses the distribution of products from wholesalers to retailers (customers). As a result, the investigation involves a mixed-integer problem that combines elements of location, routing, and allocation. In the proposed mathematical model, retailer (customer) demand is uncertain. However, based on historical data, customer demand can be estimated through multiple scenarios. At the beginning of the planning horizon, experts estimate potential demand. Based on the projected demand and factors such as warehouse storage capacity, available transportation options, and more, the optimization of supply and demand for each time

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period must be determined. Products manufactured in factories are transported to distribution centers, and from there, they are dispatched to designated warehouses for further distribution. Upon arrival at the warehouses, products are stored to prevent potential demand loss. They are then transported from the warehouses to wholesalers and, ultimately, to retailers. This study examines a mixed-integer model within a four-level supply chain scenario.

The proposed mathematical model tries to simultaneously determine the optimal locations and transportation flows across the entire system, while minimizing overall costs.

3.1. Assumptions

The assumptions employed in modeling the problem are outlined as follows:

1. The SC is a four-tiered chain, consisting of manufacturers (factories), distribution centers, wholesalers, and retailers (customers).
2. The SC is multi-period and multi-product.
3. The locations of manufacturing centers are not specified; they need to be selected from several potential active/initiated centers.
4. The locations of distribution centers are not specified; they need to be selected from several potential active/initiated centers.
5. The locations of wholesalers are not specified; they need to be selected from several potential active/initiated centers.
6. The locations of retailers are specified.
7. The transportation fleet is heterogeneous, and there is a probability of vehicle breakdown.
8. The capacity vehicles are limited.
9. Production capacity is limited.
10. Each DC is assigned to a maximum of one manufacturing center.
11. Each wholesaler is assigned to a maximum of one DC.
12. Time available is limited.
13. The number of available vehicles is specified.
14. Three levels of routing are considered: from manufacturing centers to DCs, from distribution centers to wholesalers, and from wholesalers to retailers.
15. Demand is considered uncertain.

The parameters and notations are used in mathematical model are as follows:

3.2. Sets and Indices

F : Index for factories
S : Index for distribution centers
D : Index for wholesale centers
W : Index for retail centers
V : Index for vehicles
T : Index for time period

3.3. Parameters

$Cost_f$: Cost of establishing/launching factory F.
$CCost_s$: Setup costs of distribution centers.
$ACost_d$: Setup costs of wholesale centers.
$BCost_{st}$: Holding Cost per Product Unit at DC s in Period t.
$HCost_{dt}$: Holding Cost per Product Unit at Center d in Period t.

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$CCap_{dt}$: Capacity of Wholesale Center d in Period t.
$ACap_{st}$: Capacity of DC s in Period t.
$TCost_{fst}$: Cost of transporting each unit of product from production centers *f* to DC s in period t.
$ICost_{sdt}$: Cost of transporting each unit of product from DC s to wholesale centers d in period t.
$WCost_{dwt}$: Cost of transporting each unit of product from wholesale centers d to retail centers w for sales in period t.
$Vcost_v^{veh}$: Cost of vehicle breakdown *v.*
$d1_{fsvt}$: The duration of vehicle breakdown *v* from production center *f* to DC s in period t.
$d2_{sdvt}$: The duration of vehicle breakdown *v* from DC s to wholesale center d in period t.
$d3_{dwvt}$: The duration of vehicle breakdown *v* from wholesale center *d* to retail *w* in period t.
$Hcap_v^{veh}$: Capacity of vehicle *v.*
big_M : A very large number
p_v : The probability of vehicle *v* breaking down.
$N1max^f$: The maximum number of potential production centers *f* that can be established in potential locations.
$N2max^s$: The maximum number of potential DC s that can be established in potential locations.
$N3max^d$: The maximum number of potential sales centers *d* that can be established in potential locations.
$time1_{fsvt}$: The time for vehicle *v* transportation from factory *f* to DC s in period t.
$time2_{sdvt}$: The time for vehicle *v* transportation from DC s to wholesale center d in period t.
$time3_{dwvt}$: The time for vehicle *v* transportation from the wholesale center *d* to the retail center w (customer) in period t.

3.4. Decision Variables

Q_{ft} : The quantity of products manufactured in factory f in period t.
QQ_{st} : The quantity of products stored at DC s in period t.
QA_{dt} : The quantity of products stored at wholesale center d in period t.
QB_{fst} : The quantity of goods going from factory *f* to DC s in period t.
QC_{sdt} : The quantity of goods going from DC *s* to wholesale center d in period t.
QD_{dwt} : The quantity of goods going from wholesale center *d* to retail center *w* in period t.
$Q1_{fsvt}$: The quantity of goods transported from factory f to DC s by vehicle *v* in period t.
$Q2_{sdvt}$: The quantity of goods transported from DC *s* to wholesale center *d* by vehicle *v* in period t.
$Q3_{dwvt}$: The quantity of goods transported from wholesale center *d* to retail center *w* by vehicle *v* in period t.
$y1_f$: If the production center f is established, it equals 1; otherwise, it is 0.
yA_s : If the DC s is established, it equals 1; otherwise, it is 0.
yB_d : If the wholesale center d is established, it equals 1; otherwise, it is 0.
$y2_w$: If the retail center w is established, it equals 1; otherwise, it is 0.

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xx_{fsvt} : If vehicle v moves from production center f to DC s in period t, it is 1; otherwise, it is 0.

xo_{sdvt} : If vehicle v moves from DC s to wholesale center d in period t, it is 1; otherwise, it is 0.

xu_{dwvt} : If vehicle v moves from wholesale center d to retail center w (customer) in period t, it is 1; otherwise, it is 0.

yt_{fsvt} : If vehicle v is allocated from production center f to DC s in period t, it is 1; otherwise, it is 0.

ye_{sdvt} : If vehicle v is allocated from DC s to wholesale center d in period t, it is 1; otherwise, it is 0.

yf_{dwvt} : If vehicle v is assigned from wholesale center d to retail center w in period t, it is 1; otherwise, it is 0.

3.5. Model

$$Minimize\ cost: = Location\ cost\ +\ Hold\ cost$$

$$Location\ cost\ (f1_1)\ = \sum_{d} ACost_d\, yB_d + \sum_{f} Cost_f y1_f + \sum_{s} CCost_s\, yA_s \tag{1}$$

$$Hold\ cost\ f(1_2)\ = \sum_{dt} QA_{dt} HCost_{dt} + \sum_{st} QQ_{st} BCost_{st} \tag{2}$$

Now, let's combine (1) and (2), resulting in the total cost being equal to:

$$\begin{aligned} Min\ F1 = \ & (f1_1) + f(1_2) \\ & = \sum_{d} ACost_d\, yB_d + \sum_{f} Cost_f yA_s + \sum_{s} CCost_s\, y1_f \\ & + \sum_{dt} QA_{dt} HCost_{dt} + \sum_{st} QQ_{st} Cost_{st} \end{aligned} \tag{3}$$

$$Min\ F2 = \left(\sum_{fsvt} xx_{fsvt} time_{fsvt} + \sum_{sdvt} xo_{sdvt} time_{sdvt} + \sum_{dwvt} xu_{dwvt} time_{dwvt} \right) \tag{4}$$

$Subject\ to$:

$$QB_{fst} \le big_M xx_{fsvt} \qquad \forall s, f, v, t \tag{5}$$

$$QC_{sdt} \le big_M xo_{sdvt} \qquad \forall s, d, v, t \tag{6}$$

$$QD_{dwt} \le big_M xu_{dwzt} \qquad \forall\ w, d, v, t \tag{7}$$

$$\sum_{fs} QB_{fst} \le big_M yA_s \qquad \forall t \tag{8}$$

$$\sum_{sd} QC_{sdt} \le big_M yB_d \qquad \forall t \tag{9}$$

$$\sum_{dw} QD_{dwt} \le big_M y_w \qquad \forall t \tag{10}$$

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$$yt_{fsvt} \leq yA_s \qquad \forall\, s‘f‘v‘t \qquad (11)$$

$$ye_{sdvt} \leq yB_d \qquad \forall\, s‘f‘v‘t \qquad (12)$$

$$yf_{dwvt} \leq y2_w \qquad \forall w‘d‘v‘t \qquad (13)$$

$$\sum_f Q1_{fsvt} xx_{fsvt} \leq Hcap_v^{veh} \qquad \forall s‘v‘t \qquad (14)$$

$$\sum_s Q2_{sdvt} xo_{sdvt} \leq Hcap_v^{veh} \qquad \forall\, d‘v‘t \qquad (15)$$

$$\sum_d Q3_{dwvt} xu_{dwvt} \leq Hcap_v^{veh} \qquad \forall\, w‘v‘t \qquad (16)$$

$$QQ_{st} + QB_{fst} \leq ACap_{st} \qquad \forall\, f‘s‘t \qquad (17)$$

$$QA_{dt} + QC_{sdt} \leq CCap_{dt} \qquad \forall\, d‘s‘t \qquad (18)$$

$$\sum_d yB_d \leq N3max^d \qquad (19)$$

$$\sum_s yA_s \leq N2max^s \qquad (20)$$

$$\sum_f y_f \leq N1max^f \qquad (21)$$

$$yB_d, yA_s, y_f, xx_{fsvt}, xo_{sdvt}, xu_{dwvt}, yt_{fsvt}, ye_{sdvt}, yf_{dwvt} \in \{0‘1\} \qquad (22)$$

$$QQ_{st}, Q1_{fsvt}, Q2_{sdvt}, Q3_{dwvt}, Q_{ft}, QA_{dt}, QB_{fst}, QC_{sdt}, QD_{dw} \geq 0$$

Equation (1) defines the location costs for three sections of the supply chain, which are part of long-term decision-making. Once a section is established and operational, it incurs specific costs. These costs are represented by multiplying a fixed value by a binary variable, indicating whether the section is active (1) or not (0). Equation (2) optimizes the holding cost per unit of product, which is influenced by the volume of stored materials. Equation (4) minimizes the maximum delivery time for products. Equations (5) to (7) ensure that at least one vehicle is required for product transfer. If no vehicle is deployed, the transfer of products between routes becomes impossible. Equations (8) to (10) specify that the corresponding center must be established and operational to facilitate product transfer. Equations (11) to (13) define the allocation of products to each center. Equations (14) to (16) represent vehicle capacity constraints for product transportation, ensuring that each vehicle operates within its designated capacity. Equation (17) defines the storage capacity of distribution centers, ensuring that the transferred product volume does not exceed the center's capacity. Equation (18) outlines the capacity of major sales centers. Equations (19) to (21) define the constraints for the maximum number of centers that can be selected. Equation (22) specifies the decision variables.

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4. Solving Procedure

The presented model is solved using GAMS software on a small scale. Since the model is an NP-hard problem, a genetic algorithm is used for larger instances.

4.1. Genetic Algorithm

One of the evolutionary algorithms is the genetic algorithm, which is a non-algebraic optimization algorithm and is suitable for functions that are difficult to optimize with algebraic methods. In the last decade, the genetic algorithm has been widely used as a simulation algorithm and search for answers in different fields (Katoch et al., 2021). The main reason for the increasing use of this algorithm is its high applicability in symptoms and the simplicity of its application and general approach. Features of genetic algorithm are as follows,

- The genetic algorithm starts searching from a population of answers and instead of finding a point, it identifies a suitable range in the space of variables and by choosing suitable parents, it follows an effective search in all the space of variables.
- In this algorithm, only the calculations related to the objective function are performed, and every time the algorithm is repeated and the solution space is searched, only the objective function is calculated, and there is no need for other calculations.
- This algorithm uses probabilistic rules instead of deterministic rules. Unlike many optimization methods that start from one point according to a certain rule and move to other points in the search space, this algorithm starts with a set of points and calculations will be performed on all of them at the same time. Therefore, the probability of being in the wrong place and getting stuck at a local point is reduced.
- The generality and independence of the algorithm's components make it possible to search for the answer regardless of the characteristics of the problem and can be used in any problem with any type of objective function.
- In this algorithm, calculations are done accurately and approximations are not used. This algorithm does not use any approximate calculations, such as linearization of the objective function, rounding of results, conversion of discrete to continuous variables, etc.

4.1.1. General Structure of Genetic Algorithm

The genetic algorithm was the first model developed based on the simulation of genetic systems (Katoch et al., 2021). Genetic algorithms belong to the class of random search methods. Despite their randomness, they have a goal-oriented structure, classifying them as evolved random algorithms. Unlike traditional algorithms, genetic algorithms begin with an initial set of random solutions, referred to as a population. Each individual of this population is called a chromosome, which represents a solution to the problem. The chromosome is a series of signs that evolve through successive repetitions, which are called generations. In each generation, chromosomes are evaluated by measuring fitness. In order to produce the next generation, new chromosomes, which are called offspring, are produced in two ways.

1) Integration of two chromosomes from the current generation using the crossover operator

2) Changing a chromosome through the mutation operator

The top chromosomes have a higher chance of selection and after repeating several generations, the algorithm converges towards the top chromosomes, which may indicate the optimal or suboptimal solution. Genetic operators follow the process of inheriting genes in order to produce offspring in each generation, and the evolution operator imitates Darwin's evolutionary process in order to produce a population from one generation to another.

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4.1.2. Crossover

The crossover is considered the main operator in genetic algorithms, which is performed on two chromosomes at any time. The simplest method of crossover is to choose a random crossover point so that the left side of the crossover point of one parent is connected to the right side of the crossover point of the other parent. The efficiency of this method is high by displaying the binary string. The efficiency of genetic algorithms is highly dependent on the efficiency of the crossover operator used in them. The crossover works as follows,

First, a crossover point is randomly selected and the right part of the crossover point in the first parent is replaced with the right point in the second parent. Suppose, the two chromosomes are as figure 1 and consider the crossover point as the border between the light and dark point.

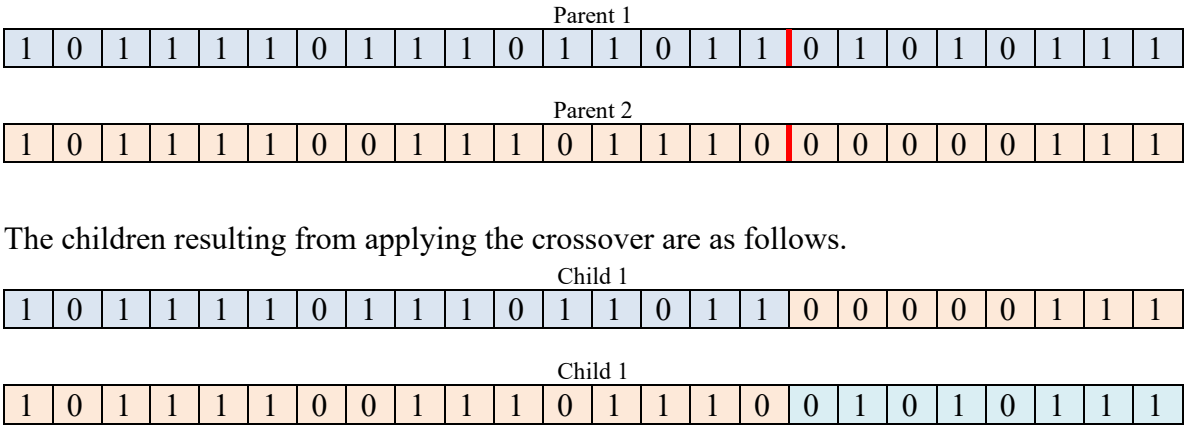

Figure 1. Example process of the crossover

4.1.3. Mutation

The mutation is the secondary operator responsible for injecting new information into the population at a low rate and producing random changes in different chromosomes. The main role of the jump operator is to identify points in the space that are less likely to be searched and reduce the probability of the algorithm getting trapped in the local optimal solution. In genetic algorithms, the mutation plays a decisive role. These roles are like replacing missing genes in the population by means of the selection operator or producing genes not present in the primary population. The mutation modifies one or more genes based on the mutation rate. Suppose the tenth gene of the following chromosome is selected for the mutation. Because the tenth gene of this chromosome is equal to zero, it changes to the value of one and the result of the operation will be as figure 2.

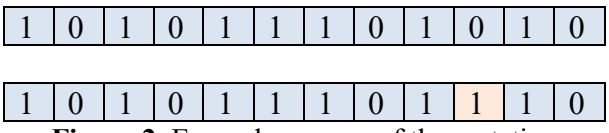

Figure 2. Example process of the mutation

The mutation rate is also considered as one of the parameters affecting the population. If this ratio is too low, many genes that may be useful will never be produced, and if it is too high, there will be a lot of chaos in the population, and the offspring will have little resemblance to their parents, and the algorithm loses the ability to learn from the past search.

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4.1.4. The Suggested Genetic Algorithm

As mentioned earlier, the genetic algorithm solved the problem in large dimensions. The reason for using this algorithm is that the genetic algorithm has been used in most of the articles on positioning-routing models and secondly, this algorithm has been used in a consolidated manner, which covers the shortcomings of non-consolidated algorithms. As the model is bi-objective model, we employ NSGA-II algorithm. Figure 3 is the flowchart of the proposed algorithm.

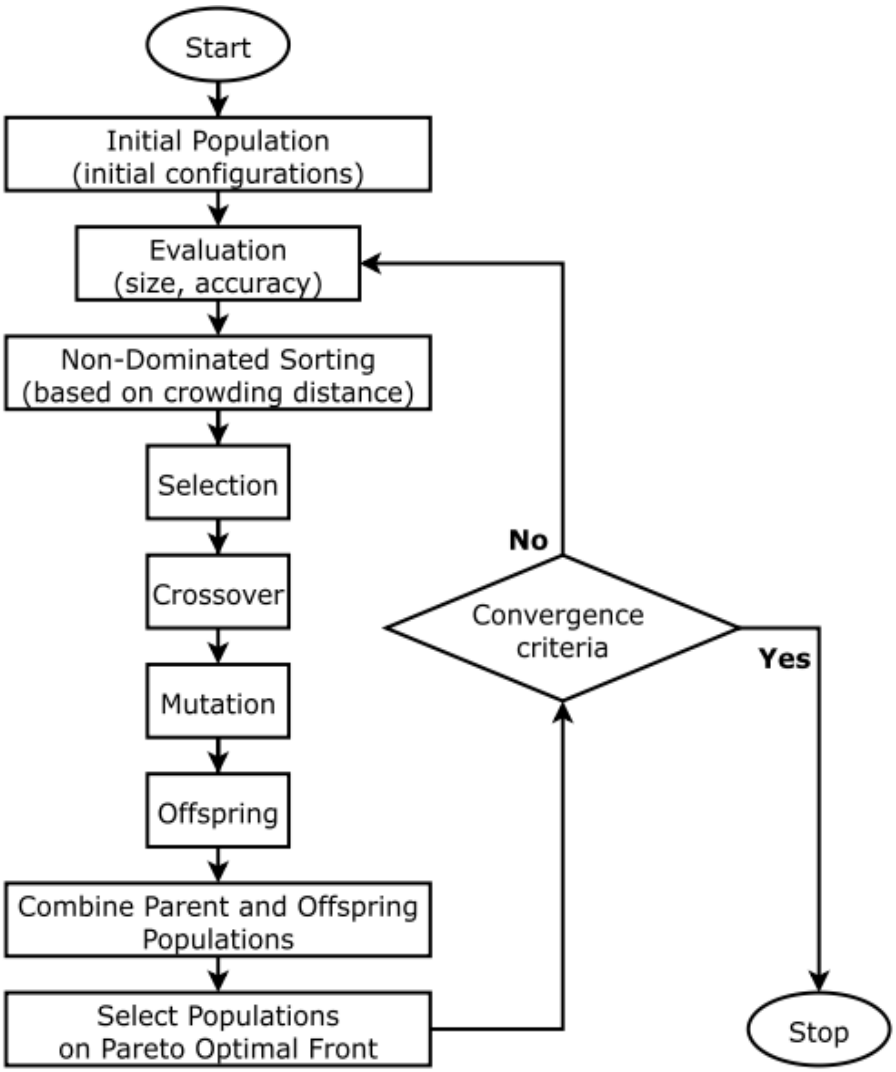

Figure 3. Flowchart of NSGA-II (Thonglek et al. [57])

5. Validation and Numerical Examples

Given that the model presented in the previous section constitutes an NP-hard problem, obtaining exact solutions for large-scale instances within a reasonable computational time is impractical. Consequently, a small-scale version of the problem was formulated and solved using exact optimization techniques to establish a benchmark. The exact solutions were generated via GAMS software, while the genetic algorithm was implemented in MATLAB. A comparative analysis

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revealed that the solutions obtained from the genetic algorithm closely approximate the exact solutions. This observation suggests that the proposed metaheuristic is a promising approach for addressing medium- and large-scale instances, as it demonstrates the capability to produce near-optimal solutions in small-scale test cases.

5.1. Model Analysis with Genetic Algorithm

Defining an appropriate solution representation is a key factor in enhancing the efficiency of the proposed algorithm. In this study, the adopted solution structure incorporates xz_{dwt}, where each chromosome corresponds to a specific retailer or customer. Each chromosome is represented as a vector whose length equals the number of wholesale levels plus one. Each position in the vector corresponds to a level, and the value stored in that position denotes the wholesale distribution center selected at that level. To illustrate this more clearly, an example is provided: consider a case with six wholesale centers, i.e., $r = 6$

Table 2. Example parameters for the algorithm

	0r	**1r**	**2r**	**3r**	**4r**	**5r**
d	3	1	5	2	4	d

The first cell in Table 2 (from the left) indicates that the retailer is initially allocated to wholesale center number 3 at the zero level. In the event of a disruption at this center, the customer is reassigned to wholesale center number 1. If this center is also disrupted, the retailer is then allocated to the next available wholesale center. This process continues sequentially up to the fourth level. The final cell, representing the fifth level, must be assigned to the wholesale center designated as the last in the allocation sequence.

Initialization:

A trial-and-error procedure was employed to identify the near-optimal values of the genetic algorithm parameters n, p_c and p_m. Various combinations of these parameters, selected from their respective predefined ranges, were systematically evaluated. For each combination, the genetic algorithm was executed on the problem instance, and the performance was assessed to determine the most effective parameter configuration. This approach facilitates the identification of parameter settings that achieve a favorable balance between solution quality and computational efficiency. The parameter values examined are summarized in Table 3.

Table 3. Parameter settings considered in the trial-and-error analysis.

Parameters	**Values Tested**		
$\boldsymbol{n}$	40	50	60
$\boldsymbol{p_c}$	0.5	0.6	0.7
$\boldsymbol{p_m}$	0.01	0.02	0.03

Fitness function: In this section, parents are selected according to the relevant selection strategy, and crossover and mutation are performed on them, in such a way that pairs that have a lower cost are selected.

Crossover Operation: In alignment with the principles of natural evolution, chromosomes are selected as parents and recombined to produce offspring. Within the proposed genetic algorithm, a

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single-point crossover operator is applied in each iteration to generate new solutions. Specifically, a crossover point is randomly chosen within the range $(1\ to\ r)$, and the offspring is constructed by combining the gene segments of both parents according to this point of division. This mechanism ensures the exchange of genetic material, thereby enhancing population diversity and promoting convergence toward high-quality solutions.

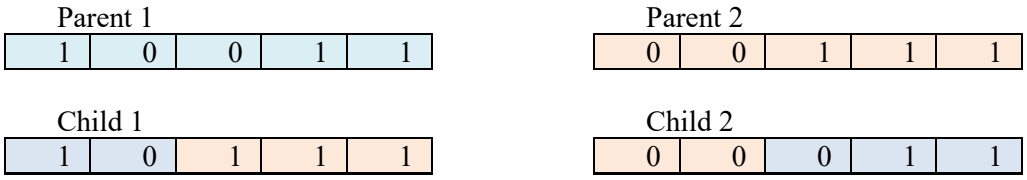

Figure 4. Crossover performance

Mutation: In this study, the applied mutation operator is the transfer mutation operator, which enhances solution diversity and prevents premature convergence. This operator randomly selects two genes within a chromosome and exchanges their positions, introducing variability without disrupting the overall structure of the solution. Such an approach helps maintain genetic diversity in the population, which is crucial for exploring the search space effectively.

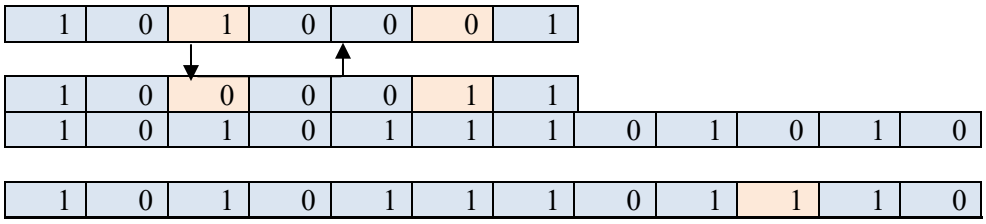

Figure 5. Mutation performance

To address the proposed optimization problem, a genetic-based solution framework was developed to systematically incorporate all scenarios examined in this study. The solution process begins with the **model initialization phase**, during which key structural parameters—such as mutation intervals and the number of decision elements—are defined. The framework is designed with a high degree of flexibility, enabling dynamic adjustments to the number of factories and distribution centers, as well as real-time evaluation and refinement of operational constraints.

Following initialization, the algorithm progresses to the **optimization phase**, which integrates multiple computational techniques to achieve cost-effective solutions. Specifically, three complementary methods were employed:

1. **Traveling Salesman Problem (TSP)**: to minimize total routing distance and improve distribution efficiency.
2. **K-Nearest Neighbors (KNN)**: to determine the optimal locations for distribution centers based on demand clusters.
3. **Simulated Annealing (SA)**: to enforce production capacity and payment constraints while preventing premature convergence.

The solution process is initiated by specifying the predetermined locations of wholesalers and consumers. Subsequently, optimal distribution routes are generated using the TSP algorithm. Based on retailer demand density, candidate distribution center locations are selected using KNN, ensuring proximity to high-demand areas. Finally, the SA method is applied to refine production and payment

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allocations under operational constraints. The program architecture allows dynamic modifications during execution, ensuring adaptability to changes in network structure and constraints. The validity and effectiveness of the proposed approach are demonstrated through graphical representations of the algorithm's execution, as shown in the subsequent figures.

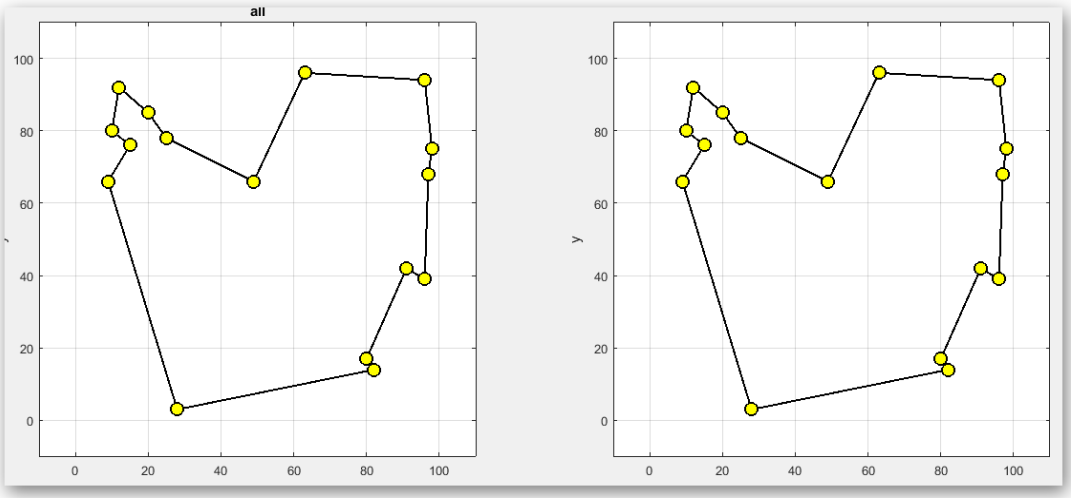

Figure 6. Locations of wholesalers (customers) and optimal routing

In the subsequent phase, the algorithm initiates the optimization process by employing a neighborhood search procedure to identify the optimal locations for factories and distribution centers, as well as the most efficient distribution routes.

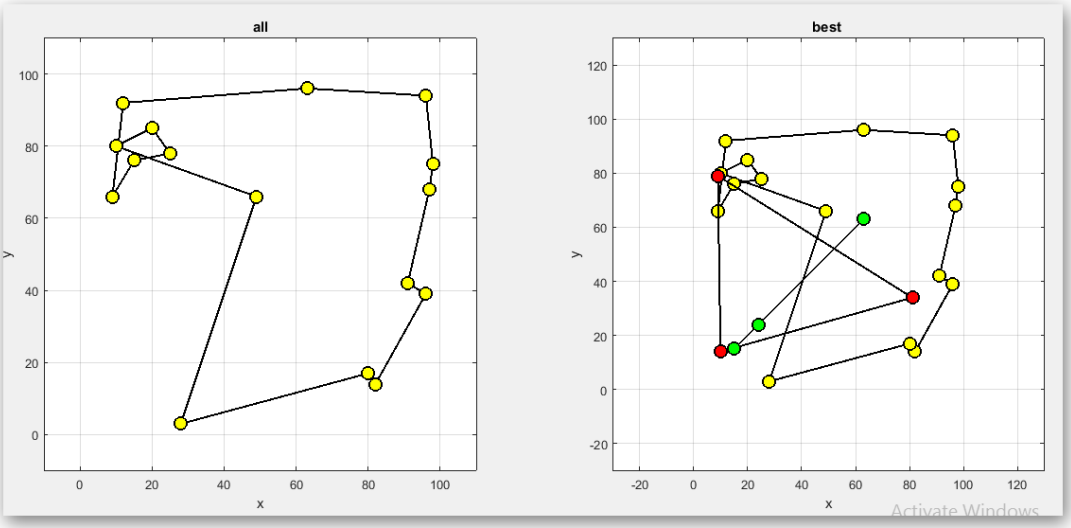

Figure 7. Optimum places of firms, distribution centers, and the best route

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Figure 8 illustrates the final stage of the optimization process, where the software determines the optimal facility locations and distribution routes.

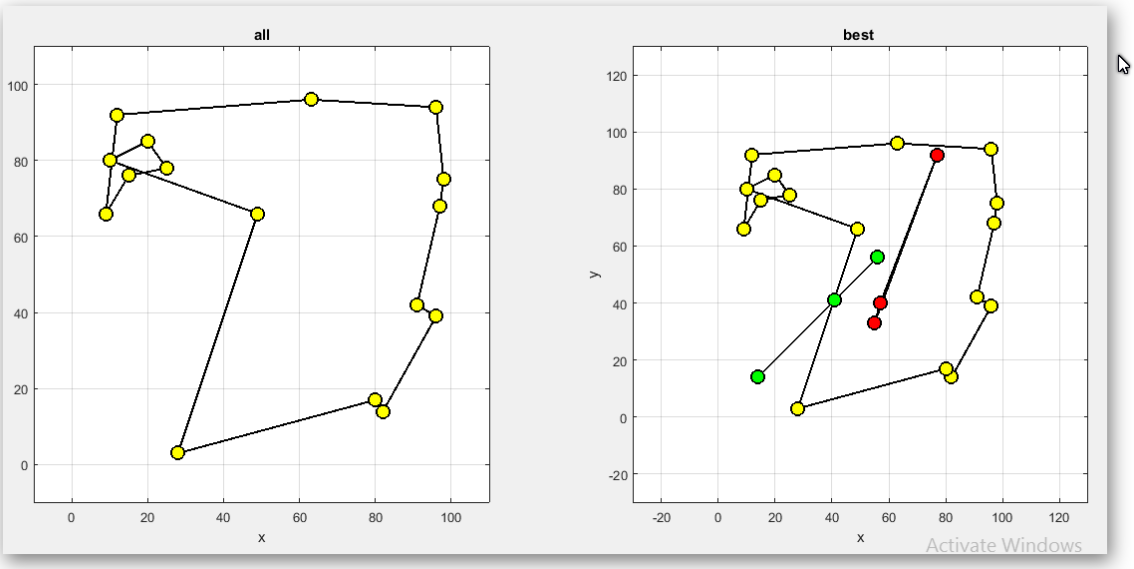

Figure 8. Optimal locations and final optimal route

5.3. Program Execution and Dynamic Optimization

During its execution loop, the program continuously evaluates potential locations and routing options to minimize the overall cost of the distribution network. It provides recommendations regarding both the optimal navigation routes and the location coordinates of distribution centers (DCs) and factories. These suggested coordinates are systematically recorded, as exemplified in Table 4. The iterative process continues until convergence to an optimal solution is achieved.

The final output, illustrated in the corresponding figure, represents the system's **fitness level**, which accounts for evaluated scenarios, including center locations and optimal timing, while minimizing total distribution costs. Notably, the methodology is fully dynamic, allowing all parameters to be adjusted, retested, and reassessed under new data conditions. The resulting optimized values for routes and locations are summarized in Table 4.

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Table 4. Optimal amount of centers and cost

Decision variable	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6	Sample 7	Sample 8	Sample 9	Sample 10
Location F	49	67	74	67	24	12	10	82	40	30
Location D	10	76	61	37	20	67	20	73	30	54
Location S	80	82	54	54	36	49	48	52	78	92
Cost of Transportation	34.2 M	23.1 M	45.3 M	45.5 M	17.5 M	55.0 M	33.2 M	35.3 M	49.9 M	21.4 M
Factory cost	868.4 Tr	861.7 Tr	492.2 Tr	250.7 Tr	87.8 Tr	569.1 Tr	822.0 Tr	11.4 Tr	815.2 Tr	733.2 Tr
Production	48387	460422	764934	753676	106099	77705	333487	193808	312157	624334

M: Million, Tr: Trillion

Table 5. Summary of objective function results

RUN	1	2	3	4	5	6	7	8	9
Z1	6432569	6335659	5996336	6012332	5889632	5666532	5789965	5998635	5888932
Z2	42	32	30	28	30	26	27	20	18

6. Sensitivity Analysis of The Parameters

In this section, we demonstrate that how variations in the inputs of the model affect the objective function. Given the complexity, scale, and numerous parameters of the model, this paper focus on analyzing a subset of parameters. This paper used GAMS software for solving and employing a loop to examine parameter values in a small-scale model with 5 repetitions. First, the parameter $cost_f^{fac}$ is reduced by 35% for two values of f. These values are then analyzed to evaluate the sensitivity of the model to these changes.

Table 6. Objective function results with changes in facility location costs

$F1$	$F2$	Objective Function
500	550	51068
325	357	49819
211	232	49562
137	151	49407
89	98	49306
58	63	49240

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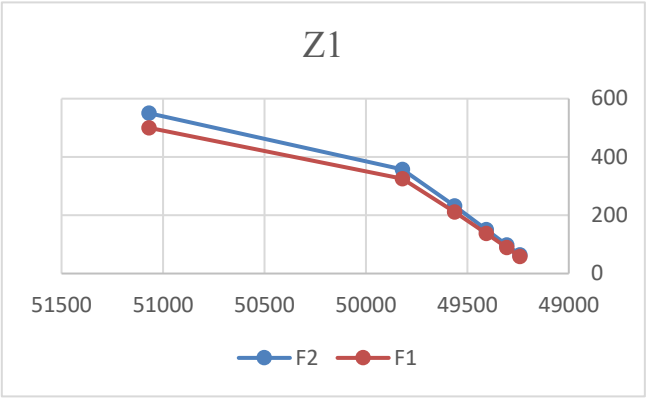

Figure 9. Sensitivity analysis of facility location costs

Figure 9 illustrates the sensitivity analysis of the first objective function, focusing on costs. We adjust the cost-related parameter to a constant value to observe changes in the first objective function, which encompasses location, maintenance, and transportation costs. The first objective function relates to costs, thereby the total cost should decrease as individual costs are reduced. With the reduction in costs, the first objective function, i.e., the total costs, also decreases. Furthermore, we analyze other parameters in 5 repetitions according to the previous method. For distribution centers, we increase D1 and D3 by 20% while decreasing D2 and D4 by 10% in each iteration.

Table 7. Objective function results with changes in location costs of distribution centers

$D1$	$D2$	$D3$	$D4$	Objective Function
120	185	175	125	50168
144	166	210	112	50161
172	149	252	101	50149
270	134	302	91	50139
248	121	362	82	50130
298	109	435	73	50122

We reduce the location costs for the distribution centers to a fixed ratio, similar to the previous method. As we can conclude form the Figure 10, changes in location costs significantly impact the main objective function. Moreover, this analysis focuses on costs, showing that as the location costs of the distribution centers decrease or increase, objective function 1 will correspondingly decrease or increase with the change in the input parameter. The input parameter for location costs is directly correlated with objective function 1.

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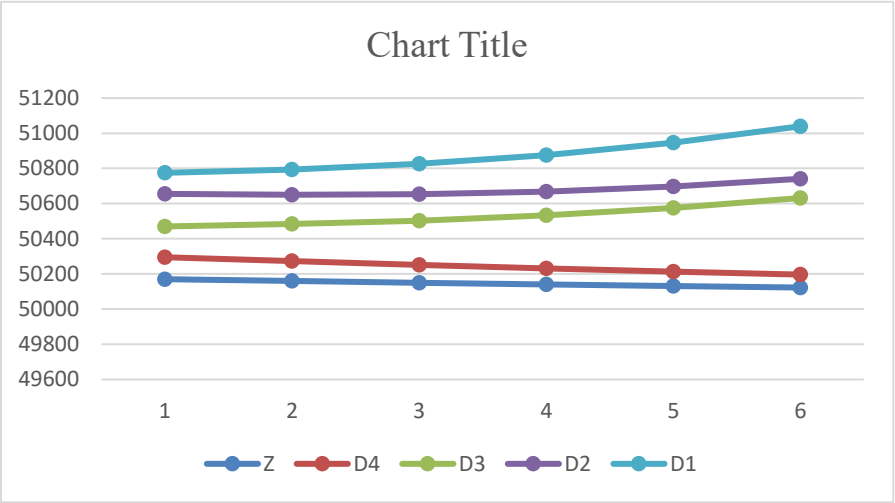

Figure 10. Distribution center location sensitive analysis chart

Table 8. Objective function results with changes in vehicle capacity

$V1$	$V2$	$V3$	**Objective Function**
1500	2000	1750	50168
900	1200	1050	50168
540	720	630	50168
324	432	378	50168
194	259	226	50168
116	155	136	50168

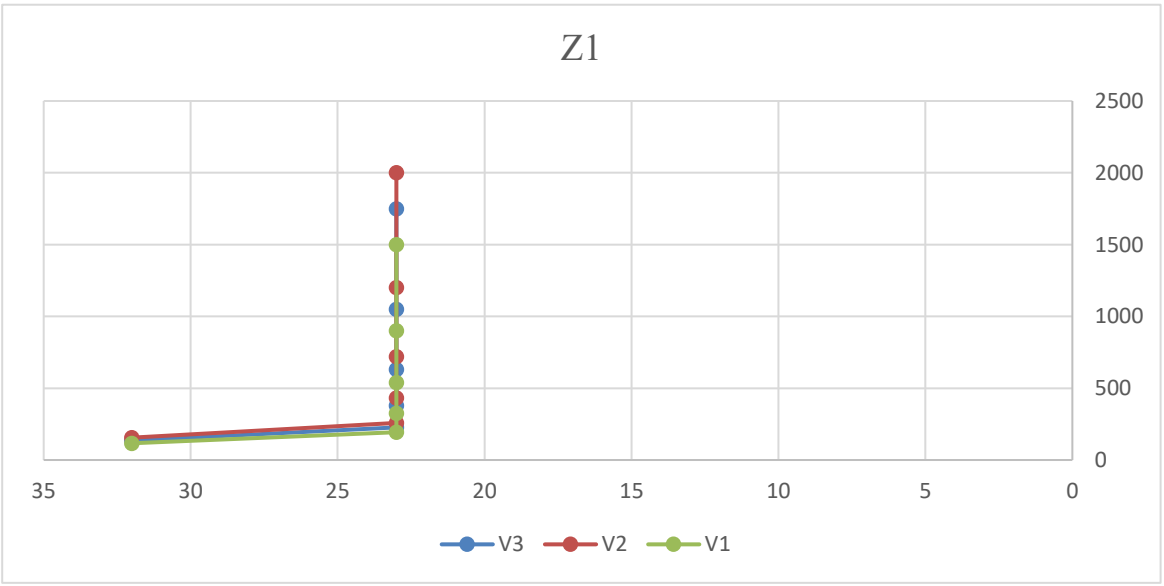

Figure 11. Objective function results with changes in vehicle capacity

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Figure 11 demonstrates that changes in vehicle capacity do not significantly impact the main objective function. This means that whether we increase the vehicle's capacity from 500 units to 1000 units or reduce it, the costs in objective function 1 are not significantly affected.
Table 9 demonstrate the production cost parameters for factories 1 and 2 for three products, increased by 20% in each iteration. These changes are reflected in the objective function 1.

Table 9. Objective function results with changes in production cost

F_{11}	F_{12}	F_{13}	F_{21}	F_{22}	F_{23}	**Objective Function 1**
10	15	25	15	30	20	50168
12	18	30	18	36	24	59931
14	21	36	21	43	28	71646
17	6	43	42	52	35	93528
21	31	52	50	62	41	111954

As we anticipated, the production costs for established factories 1 and 2 are positively correlated with the input parameter. The increase or decrease in these costs causes objective function 1, which is related to costs and is cost-natured. In contrast, objective function 2, which relates to time, remains unaffected by changes in cost-related inputs.

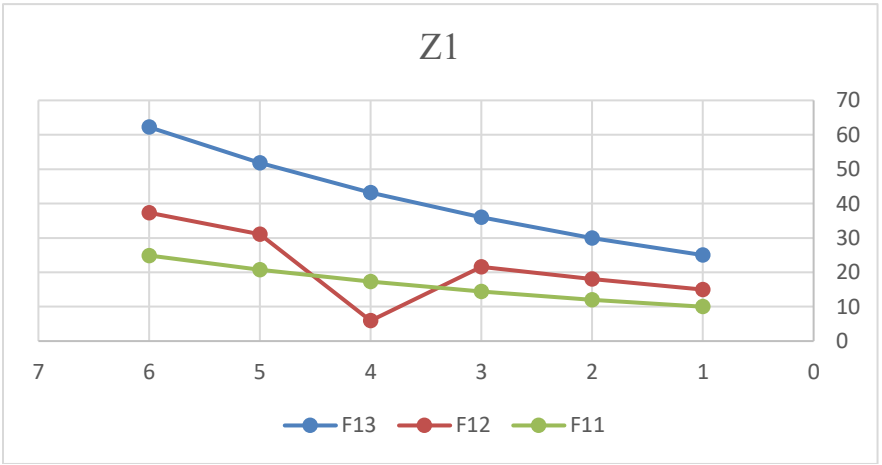

Figure 12. Objective function results with changes in factory 1 production costs

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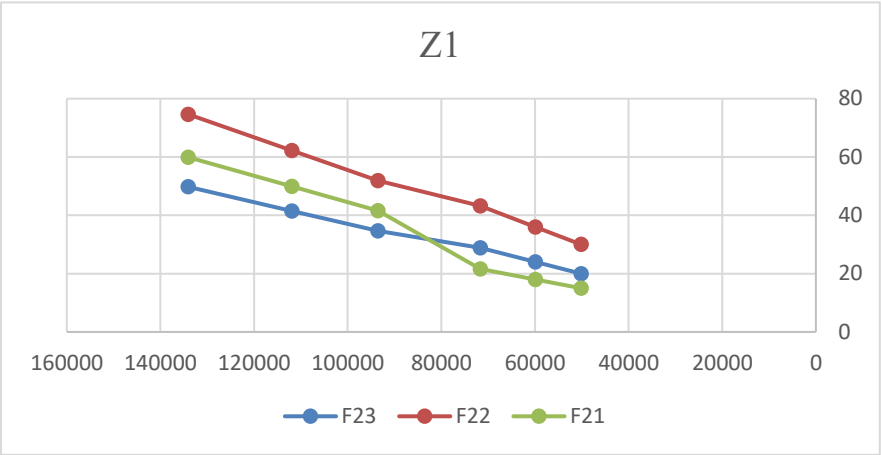

Figure 13. Objective function results with changes in factor 2 production costs

7. Conclusion

Providing an effective framework for determining production facility locations, vehicle routing, and inventory management significantly enhances organizational efficiency. In modern operations, supply chain optimization is a critical factor in reducing costs and increasing productivity. Among supply chain challenges, the location-routing problem (LRP) is particularly important, as selecting optimal routes and facility locations directly influences operational efficiency and organizational competitiveness.

In this study, a location-routing model is proposed for a four-level supply chain encompassing manufacturers, distributors, wholesalers, and retailers (customers). To reflect real-world conditions, demand is treated as uncertain and scenario-based, highlighting the stochastic nature of customer requirements. The primary objective of the model is to minimize total economic costs, including transportation, inventory, and facility establishment expenses.

Due to the NP-hard nature of the problem, GAMS software is employed for small-scale instances, while a meta-heuristic genetic algorithm is used for larger-scale problems. The model optimizes the location of three key components and determines the best routes across three distribution stages. The genetic algorithm simultaneously identifies optimal distribution paths and facility placements. Based on the results illustrated in previous chapters' charts and tables, the model provides optimal values for decision variables, including warehouse inventory levels, quantities transported per period, disposal amounts, and the optimal routing and facility location configurations.

7.1. Suggestions for Further Research

Based on this research, several directions for future studies can be suggested. First, developing new heuristic or meta-heuristic algorithms could improve the efficiency of solving the model. Additionally, future work could explore supplier selection using different approaches, such as fuzzy logic methods. Incorporating quality control measures would help minimize the costs associated with returned goods. Furthermore, the model could be enhanced by including delivery time considerations

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and applied to real-world scenarios with more concrete parameters. Examining alternative transportation routes, such as air and rail, and including the locations of retailers (customers) would also provide valuable insights.

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