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Enhancing pharmaceutical supply chain resilience: A multi-objective study with disruption management

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ABSTRACT

In this study, we tackle the problem of pharmaceutical supply chain optimization using a multi-objective model that simultaneously considers cost minimization, environmental impact minimization, and maximizing of service level equity (minimum ratio). This represents the three alms of sustainability which are key in manufacturing. Furthermore, we developed a disruption model capable of effectively managing disruptions within the supply chain and compared the capabilities with the baseline model.

The result shows how the supply chain network behaves under different objectives. Minimizing costs led to maximizing capacity utilization, while environmental objectives result in reduced production levels to meet coverage requirements, and maximizing the minimum ratio expands more facilities. Using an epsilon constraint, the trade-off shows that the environmental budget limits the flexibility between the other total cost achievable and the minimum ratio. Comparing the baseline model and the disruption model underscores the importance of proactive disruption management in maintaining service levels and managing costs effectively. Ultimately, our study offers practical insights for optimizing pharmaceutical supply chains, balancing economic efficiency with social responsibility to navigate disruptions and challenges successfully.

1. Introduction and literature

The pharmaceutical industry occupies a crucial position in the global economy, experiencing a remarkable sixfold increase in the trade value of pharmaceutical goods from $113 billion in 2000 to $629 billion in 2019 (McKinsey, 2023; González Peña et al., 2021; PwC, 2021). In tandem with this growth, its supply chain—the Pharma SC—has become an extensive, global network characterized by numerous stages and participants (GEP Blogs, 2023; Moosivand et al., 2019). However, globalization has ushered in additional complexities - including inflations, geopolitical tensions, emergence of novel medicinal modalities, and evolving work practices- necessitating a proactive and adaptable management strategy for sustained success. Effectively navigating the complexities of managing the Pharma SC network is non-trivial, given the consequences of inefficiencies, which can manifest in significant delays, and compromised product quality, thereby posing pressing challenges for industry leaders (Doshi, 2022). The Pharma SC plays a critical role in ensuring drug availability and access, yet it remains susceptible to various risks, such as dependence on single-source inputs and inadequate awareness of supplier-related risks (GEP Blogs, 2023). Threats like natural calamities, cyber-attacks, trade disputes, and pandemics loom large, posing substantial hazards to the supply chain's integrity. To mitigate these risks, strategies such as digitalization, bolstered supply chain visibility, rigorous risk management protocols, and incorporation of cutting-edge technologies are imperative. Further, optimizing production schedules, managing inventory more effectively, and diversifying sourcing strategies are essential for enhancing resilience (Badejo and Ierapetritou, 2023a; Chopra and Sodhi, 2014; Ivanov, 2020). Pharmaceutical leaders must adopt a strategic, integrated approach, from focusing on continuous improvement to addressing broader, long-term challenges.

Given the pharmaceutical industry's pivotal role, it is crucial to adopt optimization techniques in its supply chain. Mathematical modeling is an effective method to streamline operations, improving economic and environmental efficiency and overall effectiveness (Shah, 2005, 2004). These models significantly enhance supply chain visibility, aid strategic planning, and promote stakeholder collaboration. This paper proposes developing mathematical model strategies to optimize the pharmaceutical supply chain. The proposed model considers feasible production schedules, inventory management, and interactions to

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optimize tactical decisions while focusing on long-term objectives.

Modeling the Pharma SC involves navigating challenges like service level expectations, market uncertainties, and complex manufacturing processes. Optimizing drug inventory amidst manufacturing constraints, demand volatility, and production variability is critical (Hansen et al., 2023; Sampat et al., 2021). Uthayakumar and Priyan (2013), Sampat et al. (2021), and Sabouhi et al. (2018) have proposed models that optimize inventory management, minimize backorders, and enhance operational efficiency by integrating production with distribution, addressing regulatory constraints, and preparing for disruptions through strategies like fortification and diversified sourcing. These models aim to improve supply chain efficiency by focusing on critical service levels, reducing reactive scheduling, and accommodating various disruptions, offering a comprehensive approach that considers multiple products, lead times, and spatial constraints. Subsequent research by Hasani and Khosrojerdi (2016), Goodarzian et al. (2021), Melançon et al. (2021), and Azadehranjbar (2021) further emphasizes efficiency and adaptability improvements in the pharmaceutical sector's supply chain. The strategic and tactical pharma SC design has placed efforts on balancing competing objectives (Amaro and Barbosa-Póvoa, 2008; Meijboom and Obel, 2007; Mousazadeh et al., 2015), I Duarte et al. (2022b; I 2022a) developed a tool for creating equitable and sustainable Pharma SC through a multi-objective mixed integer linear programming model that considers social, economic, and environmental sustainability. This tool, applied to the meningococcal meningitis vaccine supply chain, reveals tradeoffs and opportunities, highlighting the benefits of integrating sustainability into supply chain design. Similarly, Mousazadeh et al. (2015) and Rekabi et al. (2022) have explored decision-making under uncertainty and developed models that address congestion, job scheduling, and environmental impacts, offering solutions that balance multiple objectives. Collectively, these models contribute to advancing Pharma SC management by prioritizing efficiency, adaptability, and sustainability.

Supply chain resilience is fundamental to sustaining operations during disruptions or perturbations, focusing on both proactive and reactive capabilities to manage and mitigate potential impacts. This concept refers to a firm's ability to maintain, execute, and adapt its strategies to achieve planned performance outcomes despite challenges (Ivanov, 2018). Strategic design principles such as low vulnerability and high recoverability are critical, ensuring that supply chains can withstand and quickly recover from disruptive events at minimal cost. These events can severely affect operations and overall performance. Without adequate resilience, firms may experience financial losses, mismatches between demand and supply, and destabilization of operational policies in production, distribution, and inventory control, underscoring the necessity of resilient practices (Gupta et al., 2021; Ivanov et al., 2016; Pavlov et al., 2019; Yoon et al., 2020).

In addressing supply chain resilience, it is essential to balance design-for-efficiency with design-for-resilience (Ivanov and Dolgui, 2021). The former utilizes lean and agile principles to optimize the use of resources—material, time, capital, technology, and workforce—to reduce waste and enhance profitability. Meanwhile, design-for-resilience prepares supply chains to cope with severe disruptions, employing strategies like maintaining strategic redundancies such as inventory levels, capacity buffers, and backup suppliers. These measures help supply chains absorb shocks without degrading performance and, if necessary, reactive capabilities are employed to restore operations. The recovery process, however, can be costly and time-consuming. Thus, building resilience involves a continuous commitment to risk mitigation, preparedness for disruptions, stabilization of operations post-disruption, and effective recovery strategies to either return to or improve upon previous performance levels. The diagram presented in *Fig. 1* illustrates the comprehensive framework of supply chain resilience, encompassing both resistance and recovery strategies. Resistance strategies, employed pre-disruption, focus on minimizing the initial impact of disruptions and enhancing the supply chain's robustness. These include inventory

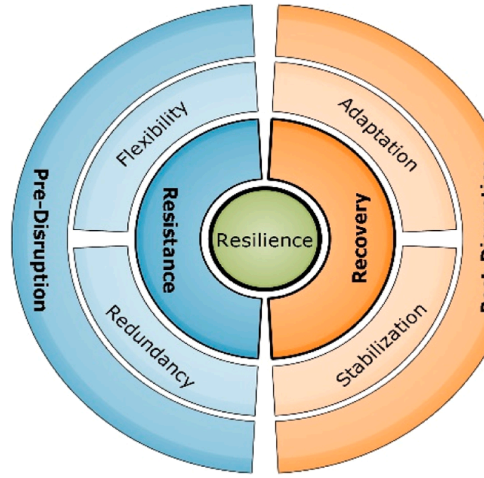

Fig. 1. Resiliency in Supply Chain Network.

optimization, capacity reservation, and node and arc fortification, which collectively ensure a buffer against unexpected supply interruptions. On the other hand, the recovery strategies, activated post-disruption, aim to restore and potentially enhance supply chain operations. Key recovery tactics involve process flexibility with multi-product facilities and capacity scalability, which allow for rapid adaptation and scaling of operations to meet changing demands and conditions. By integrating both resistance and recovery strategies, this paper provides a strategy to enhance the resiliency of a pharmaceutical supply chain network. Detailing how organizations can effectively prepare for disruptions and recover from them, ensuring operational continuity and competitive advantage. The complexity and interconnectivity of pharmaceutical supply chains significantly increase their vulnerability to disruptions, as highlighted by the COVID-19 pandemic's impact on global supply networks. This situation underscores the urgent need for resilience through optimization strategies and mathematical models (Badejo and Ierapetritou, 2023b; 2022a; 2022b; Montoya-Torres, 2021; Sawik, 2017; Xu and Song, 2020). Research, including studies by Jlassi, Halouani, and Mhamedi (2021)(Jlassi et al., 2021) and Ivanov et al.(Ivanov et al., 2019, 2017; Ivanov and Dolgui, 2021), emphasizes the importance of addressing regulatory, inventory, counterfeit, and financial risks, and the necessity for adaptability in managing disruptions. The role of flexibility, agility, and visibility in enhancing resilience is further supported by Shweta, Kumar, and Chandra(2022), aligning with initiatives for green supply chain practices as Kumar et al. (2018) advocated to promote sustainability. This body of work emphasizes resilience and sustainability, using a combination of technological innovation, strategic planning and environmental considerations.

While existing literature has extensively explored supply chain design and the management of product flow across various echelons in the pharmaceutical sector, our work introduces a novel model that optimizes the tactical aspects of the pharmaceutical supply chain. The proposed approach ensures feasible production schedules in multi-product settings. We further developed an enhanced model which efficiently addresses potential disruptions and demonstrates computational efficiency. Crucially, our research elucidates the interplay among three objectives within the pharmaceutical domain: economic viability, environmental sustainability, and social responsibility. This approach provides a holistic view of supply chain optimization that ensures sustainability.

2. Methodology

2.1. Model description

The Pharma SC under investigation is structured as a four-echelon network, from raw material sourcing at the supplier echelon, through transformation and inventory at the manufacturing sites and warehouses, to product delivery to the consumer echelon. The network initiates with the raw material suppliers ($s \in S$), tasked with providing raw materials ($r \in R \subset \mathscr{K}$). These suppliers are divided into two primary categories: suppliers of active pharmaceutical ingredients (APIs) and excipients (fillers), each critical for the production of pharmaceuticals. These raw materials are transferred to manufacturing facilities. ($f \in F$), at the manufacturing facilities, the raw materials are subjected to processing and formulation procedures to synthesize the intended pharmaceutical products. Within these facilities, it is possible to produce various products $p \in P \subset \mathscr{K}$, which depends on the composition of active ingredients. After the manufacturing phase, the finished products are packaged and routed to warehouses $w \in W \subset \mathscr{W}$. At the warehouse, customer demands, and inventory are managed. Notably, the warehouse echelon permits product sharing among warehouses, enhancing logistical flexibility. From the warehouse, products are sent to consumers regions $c \in C$, satisfy the demands, $\mathscr{d}_c$ for products. Products and raw materials can be shipped across nodes through m shipped by multiple $m \in M$ model of transportation

The proposed framework is based on the following important assumptions:

(1) ***Multi-period Demand Forecast***: A demand forecast for all products over several periods facilitates strategic planning and resource allocation to meet anticipated needs.
(2) ***Known Cost Structure***: The model assumes detailed knowledge of the cost structure, including:
   - Transportation Costs: Expenses for moving goods across the supply chain.
   - Product Allocation Costs: Costs related to distributing products to meet demand.
   - Unmet Demand Costs: Financial implications of not meeting demand.
   - Inventory Handling Costs: Expenses for storage and management of inventory.
   - Raw Material Costs: Prices of inputs needed for product manufacturing.
(3) ***Multi-Modal transportation options :*** This offers a range of $m \in M$ modes of transportation to guarantee the efficient transportation of raw materials and products. In the event of node disruptions, the transportation modes can be interchanged to ensure uninterrupted logistics. It should be noted that in this paper, we have addressed disruptions in nodes alone thus the multi-modal transportation modes are included to adapt to changes in node capacity and ensure distribution of raw materials and products.
(4) ***Fixed Facility Locations***: The geographical positions of suppliers, manufacturing sites, warehouses, and distribution centers are predetermined.
(5) ***Environmental Impact***: The environmental impact is available and obtained from the work of Duarte et al. (2022a; 2022b) and Mota et al. (2018). The ReCiPe LCIA methodology was used to quantify and evaluate the potential environmental impact associated with a product's life cycle. The method considers a range of impact categories (17 in this case) and using normalization factors, standardizes the different impact categories into a common unit enabling comparability (RIVM, 2022). Readers are directed to the supplementary information for further details of the categories.

2.2. Constraints

Supplier constraints: At the supplier echelon, Eq. (1a) ensures that raw material supply by each s does not exceed supplier capacity, and Eq. (1b) bounds the amount of raw material that flows through each transportation mode at every time period. The integer variable *sTrips* is the number of trips that are required to transport the required raw material r.

$$\sum_{f,m} Q^r_{s,f,m,t} \leq scap^r \; \forall \, (r,s,t) \tag{1a}$$

$$\sum_{r,s,f} Q^r_{s,f,m,t} \leq sTrips \times tcap_m \; \forall (m,t) \tag{1b}$$

Manufacturing facilities : At the manufacturing facilities, Eqs. (2a)-(2e) compute product quantities and resource utilization associated with event scheduling. Eqs. (2a)-(2c) ensure these events are properly scheduled, using binary variables $y_{f,t}$ and $X_{i,n,f,t}$, where $y_{f,t} = 1$ indicates an operating facility and $X_{i,n,f,t} = 1$ denotes task i occurring at event n in facility f at time t . In this context, events denote the initiation of a task. Eqs. (2d) limit the number of batches that can be processed in a facility during an event, and Eq. (2e) is the mass balance that tracks the concentration of each ingredient.

$$X_{i,n,f,t} \leq y_{f,t} \; \forall (i,n,f,t) \tag{2a}$$

$$\sum_i X_{i,n,f,t} \leq 1 \; \forall (n,f,t) \tag{2b}$$

$$\sum_{i,n} X_{i,n,f,t} \leq \; 1 \; \forall (f,t) \tag{2c}$$

$$B_{i,n,f,t} \leq B^{max} \times X_{i,n,f,t} \; \forall \; (i,n,f,t) \tag{2d}$$

$$\sum_{i,n} \rho C^k_i \times B_{i,n,f,t} \; = Q^k_{f,t} \; \forall (k,f,t) \tag{2e}$$

During production, the total number of batches produced is limited by the facility's capacity; this is shown in Eq. (2f). To hedge against sourcing uncertainty, raw materials are stored in the facility; the inventory of the raw material is tracked by Eq. (2g). Furthermore, the products are shipped to the warehouses, and the total amount of products shipped to the warehouse cannot exceed the number of products manufactured at the facility; this is captured by Eq. (2h). Eq. (2f) ensures that the products being shipped from facility to warehouse do not exceed the available quantity of products.

$$Q^p_{f,t} \leq fCap^p_f \; \forall (f,p,t) \tag{2f}$$

$$Inv^r_{f,t} = Inv^r_{f,t-1} - Q^r_{f,t} + \sum_{s,m} Q^r_{s,f,m,t} \; \forall (r,f,t) \tag{2g}$$

$$Q^p_{f,t} = \; \sum_{w,m} Q^p_{f,w,m,t} \; \forall (p,f,t) \tag{2h}$$

$$\sum_{p,f,w} Q^p_{f,w,m,t} \leq FWTrips_{mt} \times tCap_m \; \forall (m,t) \tag{2i}$$

Warehouse constraints : At the warehouses, Eq. (3a) tracks product inventory, while (3*b*) restricts the quantity of material stored to the capacity of the warehouse. Finally, Eq. (3c) ensures that the product flowing from warehouses to the consumer stays within the bounds of the capacity of the transportation modes.

$$InvW^p_{wt} = InvW^p_{w,t-1} + \sum_{f,m} Q^p_{fwmt} + \sum_{f,m} Q^p_{ww'mt} \; - \; \sum_{c,m} Q^p_{wcmt} \; \forall (w,t) \tag{3a}$$

$$InvW^p_{wt} \leq wCap^p_w \; \forall \; (p,w,t) \tag{3b}$$

$$\sum_{p,w,c} Q^{p}_{wcmt} \leq WCTrips_{mt} \times tCap_{m} \ \forall (m,t) \tag{3c}$$

Consumer Constraints: Eqs. (4a) shows the continuity equation for the products and captures the backorder from all consumers;Eq. (4b) represents the social constraints which ensures that each consumer's demand is satisfied to a level determined by the minimum coverage rate for each product θ^{p}, and Eq. (4c) computes the aggregated service level constraints at the given period t.

$$\sum_{w,m} Q^{p}_{wcmt} = \mathscr{d}^{p}_{c,t} - \mathscr{B}^{p}_{c,t} \ \forall (p,c,t) \tag{4a}$$

$$\mathscr{d}^{p}_{c,t} \times \theta^{p} \leq \sum_{w,m} Q^{p}_{wcmt} \ \forall (p,c,t) \tag{4b}$$

$$serviceLevel(t) = \frac{\sum_{w,m} Q^{p}_{wcmt}}{\sum_{p,t} \mathscr{d}^{p}_{c,t}} \ \forall \ (t) \tag{4c}$$

2.3. Objective functions

Economic Objective: This focuses on minimizing the overall operational costs within the supply chain, which includes various components such as raw material costs, production costs, inventory costs, transportation costs, and backorder penalties.

$$\max(TotalCost)$$

$$TotalCost = rm\mathscr{C}ost + pr\mathscr{C}ost + Inv\mathscr{C}ost + tranport\mathscr{C}ost + backorder\mathscr{C}ost \tag{5a}$$

The raw material cost $rm\mathscr{C}ost$ is calculated based on the unit cost of each material required for production. This is shown in Eq. (5b).

$$rm\mathscr{C}ost = \sum_{sfmt} Q^{r}_{sfmt} \times C^{r} \tag{5b}$$

The production cost ($pr\mathscr{C}ost$) has two components, which are the fixed and the variable cost. The fixed cost is constant regardless of the product produced. The binary variable X_{inft} determines if the equipment is used for a given task. The variable cost depends on the level of production output. Eq. (5c) shows the combination of these cost components.

$$pr\mathscr{C}ost = \sum_{i,n,f,t} fixed\mathscr{C}_{f} \times X_{inft} + \sum_{pft} var\mathscr{C}^{p}_{f} \times Q^{p}_{f,t} \tag{5c}$$

The inventory cost is computed by Eq. (6d) and involves the cost for raw materials and each product.

$$Inv\mathscr{C}ost = \sum_{r,f,t} h\mathscr{C}^{r}_{f} \times InvF^{r}_{ft} + \sum_{p,w,t} h\mathscr{C}^{p}_{w} \times InvW^{p}_{wt} \tag{5d}$$

The backorder cost is the penalty paid for unmet demand and computed with Eq. (5e).

$$backorder\mathscr{C}ost = \sum_{p,c,t} b\mathscr{C}^{p}_{ct} \times \mathscr{B}^{p}_{c,t} \tag{5e}$$

The transportation cost calculates the cost of moving commodities across arcs. There are two components: the fixed cost for using a particular transportation mode and the variable cost, which depends on the distance traveled. The expression in Eq. (6f) shows the calculations.

$$trport\mathscr{C}ost = \sum_{(m,t)} fixed\mathscr{C}_{m} \times \begin{bmatrix} sTrips_{mt} + \\ FWTrips_{mt} + \\ WCTrips_{mt} \end{bmatrix} + \sum_{(k,\mathscr{n},\mathscr{n}',m,t)} var\mathscr{C}_{m} \times \delta_{nn'} \times Q^{k}_{\mathscr{n},\mathscr{n}',m,t} \tag{5f}$$

Environmental objective: This seeks to minimize the ecological footprint of the entire supply chain network, focusing on minimizing emissions generated across all operations. The objectives are defined using the Life Cycle Analysis (LCA) methodology. This is shown in Eq. (6). Eqs. (6a) and (6b) show the total impact of emissions from facility operations and product transportation.

$$\min(envImp) \tag{6a}$$

$$envImp = facilityImpact + transportImpacts \tag{6b}$$

computes the emissions from facilities by multiplying the environmental impact characterization factor for producing one unit of product for each category ($s\mathscr{I}m^{p,\eta}$) by the quantity of products manufactured and the normalization factor for each category. It should be noted that the factor ensures that various environmental impact categories are comparable.

$$facilityImpact = \sum_{\eta,f} \kappa^{\eta} \times s\mathscr{I}m^{p,\eta} \times Q^{p}_{ft} \tag{6c}$$

$$transportImpact = \sum_{(\eta,\ k,\mathscr{n},\mathscr{n}',m,t)} \kappa^{\eta} \times d\mathscr{I}m^{\eta}_{m} \times \delta_{nn'} \times Q^{k}_{\mathscr{n},\mathscr{n}',m,t} \tag{6d}$$

Similarly, the emission from the transportation is computed by multiplying the environmental impact characterization factor of transporting a unit of product through a distance $d\mathscr{I}m^{\eta}_{m}$ by the distance traveled and the quantity of products that is transported. Eq. (6d) reflects this component of the environmental objective.

For both Eqs. (6c) and (6d), there are 17 environmental impact categories with varying units, this is different for each product as well as the transportation. The normalization term κ^{η} in these equations provides coefficients for each category (η), standardizing the assessment of diverse impacts onto a common scale (Duarte et al., 2022b; RIVM, 2022).

Effectiveness Objective: This objective maximizes the minimum of all service levels as detailed in Eq. (7).

$$\max_{c} \left\{ \min_{p,t} \left(ratioPharmD^{p}_{ct} \right) \right\} \tag{7a}$$

$$minRatio \leq ratioPharmD^{p}_{ct} \ \forall \ (p,\ c,\ t) \tag{7b}$$

$$ratioPharmD^{p}_{ct} = \frac{\left[\sum_{w,m} Q^{p}_{wcmt} \right]}{\mathscr{D}^{p}_{ct}} \ \forall \ (p,c,t) \tag{7c}$$

Eq. (7a) shows that the objective is a max-min objective, which is reformulated by Eqs. (7b) and (7c) (Floudas, 1995; Grossmann, 2012). To reformulate the Eq. (7a) , we introduced a new variable minRatio and ensures that the value of the minRatio is less than or equal to the values of the calculated ratio that is shown in Eq. (7b). Eq. (7c) calculates the delivery ratio for each of the products delivered to each consumer. By maximizing the minRatio, the lowest ratio is driven up. This objective strategically focuses on enhancing equity in product distribution within the supply chain, explicitly targeting maximizing the least satisfied consumer's service level. Doing so addresses disparities in demand fulfillment across different consumer segments. The essence of this approach lies in ensuring that product delivery is efficient and inclusively distributed among all consumers, regardless of the variability in their demand patterns.

2.4. Extension to consider disruptions

The equations governing the production capacities of facilities and warehouses have been revised to enhance the model's resilience against disruptions. Recognizing that disruptions may reduce or eliminate capacity, buffer mechanisms were introduced. These buffers enable capacity expansion at unaffected nodes within the network, effectively managing fluctuations in demand. Additionally, to strengthen the supply chain's robustness, the available transportation modes were diversified, thus contributing directly to the resilience of the network's arcs. It should be noted that in this paper, we have addressed disruptions in nodes alone thus the multi-modal transportation modes are included to adapt to changes in node capacity and ensure distribution of raw materials and products. Furthermore, we categorize node disruptions into two distinct modes: full disruption and partial disruption. Nodes experiencing full disruption completely lose their operational capacity, rendering them unavailable for use. Conversely, nodes subject to partial disruption exhibit reduced operational capacity. Regardless of the disruption level, expansion of disrupted nodes is not feasible. Furthermore, recovery from any form of disruption requires one week.

Mathematically, we introduced new integer variables $yE_{f,l,t}$. To modify Eqs. (2d) and (2f) incorporating additional integer constraints to address the adjustments in capacity level. In Eq. (8), the parameters $yDis_{f,t}$, indicates a facility's status, where 0means disrupted and 1 means operational. Eq. (8a) states that capacities can only be expanded if the facility is undisrupted, and Eq. (8b) ensures that the expansion levels for facilities follow a predefined order. The predefined order comprises three expansion levels, with expansion level *I* preceding expansion level *II*, and expansion level *II* preceding level *III*. Facilities in this case includes both manufacturing sites and warehouses.

$$yE_{f,l,t} \le yDis_{f,t} \ \forall \ (f,l,t) \mid ord(l) = 1 \tag{8a}$$

$$yE_{f,l,t} \le yE_{f,ll,t} \ \forall \ (f,l,ll,t| \ ord(l) < ord(ll) \ ) \tag{8b}$$

Following the determination of expansion decisions, Eq. (9) computes the potential capacity expansions at manufacturing sites and warehouses relative to their existing capacities. Eq. (9a) calculates the expansion at the facilities as the sum of the capacity associated with the expansion level selected. Similarly, Eq. (9b) calculates the expansion needed at the warehouse. Finally Eq. (9c) computes the increased batch size using the expansion in the facility divided by the number of event points.

$$fexpCap^k_{f,t} = \sum_l yE_{f,l,t} \times expCap_{l,k} \ \forall \ (k,f,t) \tag{9a}$$

$$wexpCap^k_{w,t} = \sum_l yE_{w,l,t} \times expCap_{l,k} \ \forall (k,w,t) \tag{9b}$$

$$Bexp_{f,t} = \frac{\sum_k fexpCap_{f,k,t}}{|k| \times |N|} \ \forall (f,t) \tag{9c}$$

The model incorporates expansions into the facility operating level and maximum batch size equations, capturing the nodes' enhanced capacity. Eq. (10a) and (10b) presents the updated capacity for manufacturing facilities and warehouses, respectively, while Eq. (10c) computes the new batch size so as to account for the extra capacity. In Eq. (10), the new capacity is derived by multiplying the old capacity with the disruption indicator, denoted as $\delta_{f,t} \in [0,1]$. These expressions substitute Eqs. (2f) and (3b) limiting the capacity level for the facilities and warehouses.

$$newFCap^k_{f,t} = fCap^k_f \times \delta_{f,t} + fexpCap^k_{f,t} \ \forall \ (f,k,t) \tag{10a}$$

$$newWCap^k_{f,t} = wCap^k_f \times \delta_{w,t} + wexpCap^k_{f,t} \ \forall (w,k,t) \tag{10b}$$

$$B_{f,t} \ = \ B^{max} + Bexp_{f,t} \ \forall (f,t) \tag{10c}$$

Once the updated capacities are computed, the quantity of products and inventory amount that can be stored are bounded by the new capacity. These are shown in Eqs. (11a) and (11b)

$$Q^k_{f,t} \le newFCap^k_{f,t} \ \forall (f,k,t) \tag{11a}$$

$$InvW^k_{w,t} \le newWCap^k_{w,t} \ \forall (w,k,t) \tag{11b}$$

It should be noted that the maximum batch size, $B_{f,t}$, also becomes variable computed in Eq. (10c). If directly employed, such as in the equation $(2d)$, a bilinear term - which is a product of continuous variable $B_{f,t}$ and binary variable $X_{i,n,f,t}$- arises as shown in Eq. (12a). This makes the model non-linear.

$$B_{i,n,f,t} \le B_{f,t} \times X_{i,n,f,t} \ \forall \ (i,n,f,t) \tag{12a}$$

To maintain linearity in the model, a linearization technique is employed, as illustrated in the Eqs $(12b) - (12d)$

$$B_{i,n,f,t} \le Bv^{max} \times X_{i,n,f,t} \ \forall \ (i,n,f,t) \tag{12b}$$

$$B_{i,n,f,t} \le B_{f,t} \ \forall \ (i,n,f,t) \tag{12c}$$

$$B_{i,n,f,t} \ge B_{f,t} - Bv^{max} \times \left(1 - \ X_{i,n,f,t}\right) \ \forall \ (i,n,f,t) \tag{12d}$$

The linearization is a bigM linearization for a Bilinear term (Floudas, 1995; Mohammadi and Harjunkoski, 2020), where Bv^{max} is the bigM value, chosen so that the Eq. $(12d)$ is satisfied. It should be noted that this approach is crucial in enabling us to explore a larger feasible solution space efficiently and to find near-optimal solutions within a practical computation time (Floudas, 1995; Grossmann et al., 2016).

The extra capacity increases the operational cost by adding a new term to Eq. $(6a)$; this is the cost of expansion and recovery of the disrupted facility. The new cost terms are shown in Eq. (14). Eqs. $(6b)$ and $(6c)$ are modified to $(13a)$ and $(13b)$:

$$pr\mathscr{C}ost = \sum_{i,n,f,t} fixed\mathscr{C}_f \times X_{inft} \ + \sum_{p,f,t} var\mathscr{C}^p_f \times Q^p_{f,t} \ + \sum_{(f,l,t)} f\mathscr{C}_{f,l} \times \ yE_{f,l,t} + \sum_h f\mathscr{R}_{f,t} \times yDis_{f,t} \tag{13a}$$

$$Inv\mathscr{C}ost = \sum_{r,f,t} h\mathscr{C}^r_f \times InvF^r_{ft} + \sum_{p,w,t} h\mathscr{C}^p_w \times InvW^p_{wt} + \sum_{p,d,t} h\mathscr{C}^p_d \times InvD^p_{dt} + \sum_{(w,l,t)} w\mathscr{C}_{w,l} \times \ yE_{w,l,t} \ + \sum_{(f,t)} w\mathscr{R}_{f,t} \times yDis_{w,t} \tag{13b}$$

As shown in the cost expression, the network's resilience depends on effectively managing consumer demands, achieved through the cost tradeoff between handling backorders and investing in expanding facilities, at manufacturing sites and warehouses. This balance is essential in assessing the network's ability to adapt and respond to demand volatility amid disruptions, ensuring its robustness, flexibility, and capacity to maintain operational efficiency in the face of demand variability. Such an approach positions the network for long-term sustainability.

The modified model corresponds to a Mixed Integer Linear Programming (MILP) problem with the continuous variables determining the flows, binary variables determining the operational status (task to be performed at the facilities and sequence), and the integer variables determining the transportation selections modes and the number of trips between arcs. In the following section, we elaborate on the solution procedure and the strategies employed to mitigate the computational complexity of the model.

2.5. Solution procedure

The section describes the approach taken towards handling integer variables and delineates the solution procedures utilized for addressing the multi-objective problem.

2.5.1. Dealing with the integer variables

Tightening constraints were used to enhance the model's computational efficiency. The constraint was used to improve the estimation for the integer variables(Floudas, 1995). Estimated upper bound is added as a ceiling of the total products divided by the available capacity as shown in Eqs. (14a) and (14b). This provides a good guess for the integer variables(Brunaud, 2019). Mathematically, it signifies that the number of trips between two nodes during a given time cannot exceed the maximum number of trips needed if there is just one transportation mode. For example, if a shipment of 10 pounds requires a truck with a 4-pound capacity, the constraint indicates a maximum of 3 trips to fulfill the transport.

$$nTrips_{m,t} \geq \frac{\sum_{k,n,n'} Q^k_{n,n',m,t}}{tcap_m} \ \forall (m,t) \tag{14a}$$

$$nTrips_{m,t} \leq 1 + \frac{\sum_{k,n,n'} Q^k_{n,n',m,t}}{tcap_m} \ \forall (m,t) \tag{14b}$$

2.5.2. Dealing with the multiple objectives

The multi-objective problem is addressed using the Pareto approach, which identifies the optimal tradeoff among the objectives. The procedure requires reformulating the problem as shown in Eq. (15a).

$$\min_{x \in \mathbb{F}} \{ f_1(x), \ f_2(x), \ -f_3(x) \} \tag{15a}$$

In Eq. (15a), x represents both integer and continuous decisions. Here, $f_1\ (x)$ represents the Total cost, $f_2(x)$ denotes the Environmental Impact (*envImp*), $f_3(x)$ is MinRatio, and $\mathbb{F}$ is the set of feasible boundaries defined by the constraints.

To address the multi-objective optimization problem, we employ a structured approach as outlined below(Badejo and Ierapetritou, 2022c):

- Step 1: Initially, we solve each objective independently to ascertain the optimal solution for that objective. This process is formalized in Eq. (15b) as follows:

$$\eta_i =: \ \min_{x \in \mathbb{F}} \{ f_i(x) \} \ \forall \ i \in \{1, 2, 3 \} \tag{15b}$$

this step establishes the baseline performance for each objective.
- Step 2: Based on the outcomes of Step 1, we determine the range of epsilon (ϵ) values, delineating the bounds for feasible solutions. This range is derived from the upper and lower limits identified in the solutions of $(15b)$ forming a vector of ϵ vectors.
- Step 3: The problem is then reformulated into a single objective framework by selecting one objective as the primary focus and applying epsilon constraints to the others. This method, known as epsilon constraint optimization, is depicted in the Eq. (15c).

$$\theta_j^* =: \min_{\substack{x \in F \\ f_i^m \leq \epsilon_j^m \ \forall \ m \in \{1, \ldots, M\}}} f_1(x) \ \forall \ j \in \mathscr{J} \tag{15c}$$

This step effectively transforms the multi-objective problem into a series of single-objective problems, each with its constraints defined by ϵ. It is important to note that m represents the discretization level, correlating to the desired number of Pareto points to be identified in the solution set.

- Step 4: Each epsilon-constrained optimization problem is solved, yielding solutions that illustrate the various tradeoffs between the primary and secondary objectives.

2.5.3. The rolling horizon framework

Rolling horizon framework are typically adopted to solve either operation problems affected by the uncertainty of the input data forecasts or large-scale optimization problems (Bhosekar et al., 2021; Kopanos and Pistikopoulos, 2014). In this case, we used the framework with the model for the optimal decisions. As depicted in Fig. 2, at each time step, the supply chain model is solved repeatedly, considered future time slots, and the initialization is determined by the current states of variables. Only the solutions for the current time step are implemented. In this way, the decisions of the optimal operations are updated with the current parameters and more accurate forecasts.

The subsequent section applies this framework to a case study, offering a detailed examination of the results and discussion.

3. Results and discussion

This section provides a comprehensive discussion of three case studies, each demonstrating different capabilities of the model. The first case study showcases the model's effectiveness in a more straightforward context involving two products and two raw materials. Subsequently, the second case study extends the complexity by introducing multiple products and raw materials, incorporating the dynamics of competing resources. These cases were approached with a focus on single and multi-objective optimization. The third case study underscores the importance of the extended model in addressing disruptive events within the supply chain. By incorporating disruption scenarios into the model, we showcase the model's resilience and its capacity to guide decision-making during unforeseen events. This case study shows the significance of the extended model in enhancing supply chain robustness and adaptability. In what follows, we describe the supply chain network in detail, followed by each case study.

3.1. Description of supply chain network

The network, as shown in Fig. 3, comprises four distinct echelons: suppliers represented by red nodes, manufacturing sites denoted by green nodes, and warehouses indicated by blue nodes, all interconnected to fulfill the demands emanating from ten consumers, illustrated as orange nodes. Within this network, the suppliers provide the essential raw materials for pharmaceutical production. The manufacturing sites, operating on weekly production cycles, undertake the conversion of these raw materials into final products. Each manufacturing facility possesses the capacity to produce a specified number of batches per week, with each batch adhering to a predefined Bill of Materials (BOM) to ensure the accurate composition of products during the manufacturing process. Notably, only one product can be manufactured in each batch. Warehouses within the network serve as

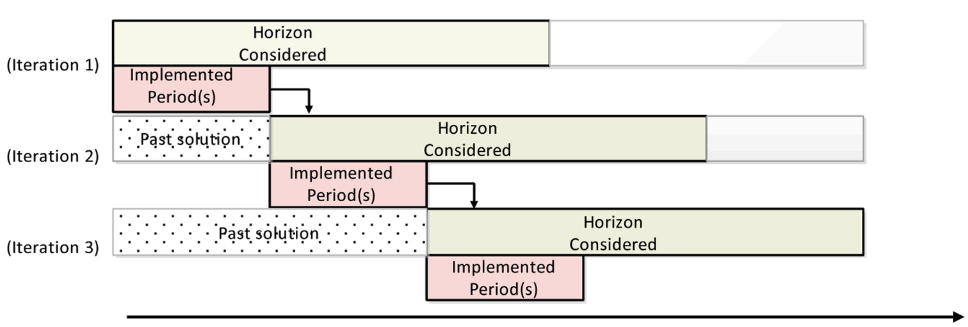

Fig. 2. Rolling Horizon Framework.

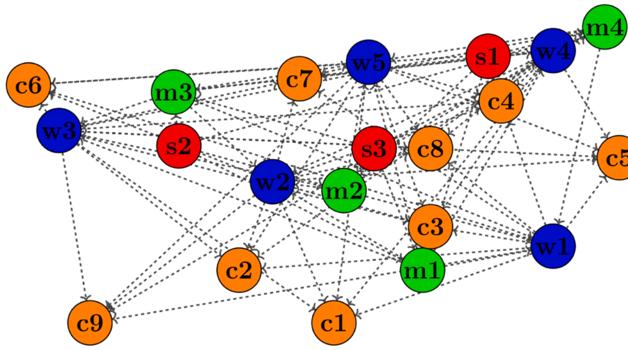

Fig. 3. Supply Chain Architecture.

storage hubs where products are stored, and their quality is maintained before being dispatched to consumer locations. Within each warehouse, inventory levels of products are optimized to mitigate the impact of production and demand volatility. Finally, at the consumer locations, product demands are realized and transmitted to the warehouses at the onset of each week.

The problem under consideration involves a multi-period optimization scenario spanning 10 discrete time periods, each representing a week. The primary objective is optimizing production processes to address spatial and temporal product demand fluctuations effectively. Demand from consumer nodes is observed at the beginning of each week, while product deliveries to these consumer nodes are scheduled for the end of the week. Within each week, supply chain operations must strategize production levels and inventory management to align with demand fluctuations and guarantee future demand fulfillment. This optimization task is guided by three overarching objectives that must be concurrently met.

3.2. Case study I: Multi-objective two products two raw materials

For the supply chain network described above, we examine a scenario involving two products derived from two distinct raw materials.

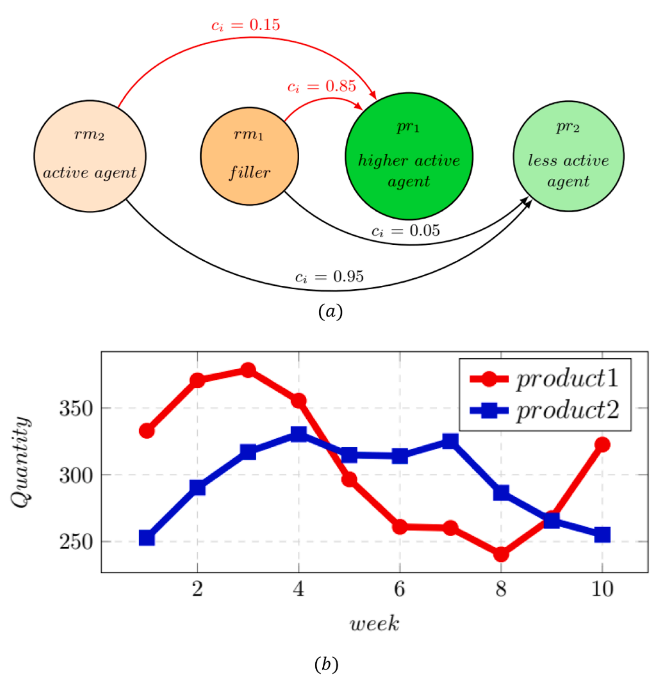

Fig. 4. Case I description; (a) Production recipe; (b) demands profile of products 1 and 2.

The production recipe for these products and their periodic demand from consumers is shown in Fig. 4a and Fig. 4b respectively. The primary goal of this supply chain network is to fulfill consumer demands while balancing the economic, environmental, and social objectives. To solve the problem, each objective is solved independently, and subsequently, we apply the multi-objective optimization approach to holistically address the problem, balancing the competing objectives of the network.

3.2.1. Individual objectives

Following the solution procedures outlined in Section 2.5, the model was formulated and solved using GAMS/CPLEX (version 38.2.1) on a PC equipped with an Intel Core i7–10,510 U processor, running at 2.30 GHz and 16 GB of RAM. The complexity of the resulting model features a total of 4911 variables, of which 560 are discrete, and 2450 constraints bind it. The results are presented in Table 1.

Addressing each objective individually reveals a tradeoff, as outlined in Table 1. When the total cost was minimized, the environmental impact was 70,502.6, and the minRatio was 78.6 %. Minimizing the environmental impact increases the total cost by 33 %, to 94,506.5, while this minRatio decreased to 75 %. And maximizing the minRatio increases the total cost to 91,001.2 (28 % increase) and the environmental impact to 73,336.4, a 41 % shift from the optimal value. These results highlight a tradeoff between the three objectives, as optimizing one without affecting the other objectives is impossible.

Analyzing strategies across different objectives, Fig. 5 shows the aggregated production profiles over all periods. For a detailed scheduling profile, we direct the reader to the supporting document. The figure indicates that minimizing total cost and maximizing the MinRatio increases the facility activity level compared to minimizing environmental impact. This is because increased production level increases the environmental impact; thus, for the environmental impact, the strategy is to achieve a minimum delivery level of 75 %. Examining the strategies for the other two objectives more closely, we see that cost minimization schedules, Fig. 5a, which represents the cost objective, dedicated facilities for a given products. This way, it can leverage the economy of scale due to the fixed cost of producing a particular product. Conversely, maximizing the minimum ratio, Fig. 5c uses facilities to produce enough to satisfy demands.

3.2.2. Multi-Objective solution

following the procedure in section 2, the multi-objective problem was solved. The results are depicted as the Pareto frontier in Fig. 6. In Fig. 6(a), the vertical axis represents the total cost, serving as the primary objective, while the horizontal axis denotes environmental impact, with color codes indicating the minimum ratio value. Fig. 6(b) employs the same axes, with color codes representing aggregated service levels.

The result shows that the environmental impact value significantly influences the interactions between the cost and minRatio objectives. For instance, as illustrated in Fig. 6(a), when the environmental impact value is lower (e.g., restricted to 51,000), the achievable minRatio is 75 % (minimum coverage level). However, relaxing the environmental constraint increases the flexibility to explore combinations of total cost and minimum ratios within the limits of the environmental bounds. This flexibility emphasizes the opportunity cost between total cost and minimum ratio: with a fixed environmental budget, increasing the minimum ratio results in an increased total cost. However, while the minRatio ensures that products are distributed to all consumers, it reduces the overall service level achievable, as shown in Fig. 6(b).

Observing the interactions between the minRatio and the total cost, it is noticed that satisfying all consumers reduces the overall service level and increases the total cost. This observation underscores that, within the constraints of satisfying all consumers to a certain degree (social constraint of ensuring equity), there is a higher penalty, such as reducing satisfaction for other consumers who are more profitable. In managerial terms, social constraints are crucial in ensuring fair

Table 1
Tradeoff table for the best and worst solutions for each objective.

Objectives	Total cost ($)	Environmental Impact	minRatio
Min (Cost)	71201.1	70502.6	78.6%
Min (EnvImp)	94506.5	51979.3	75.0%
Max(minRatio)	91001.2	73336.4	100%

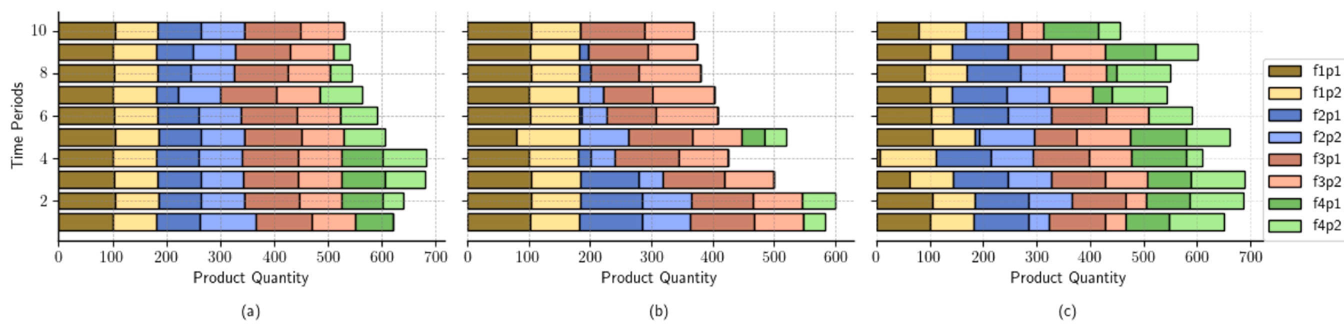

Fig. 5. Aggregated scheduling profile for objectives (a) Cost; (b) Env. Impact; (c) Max Ratio.

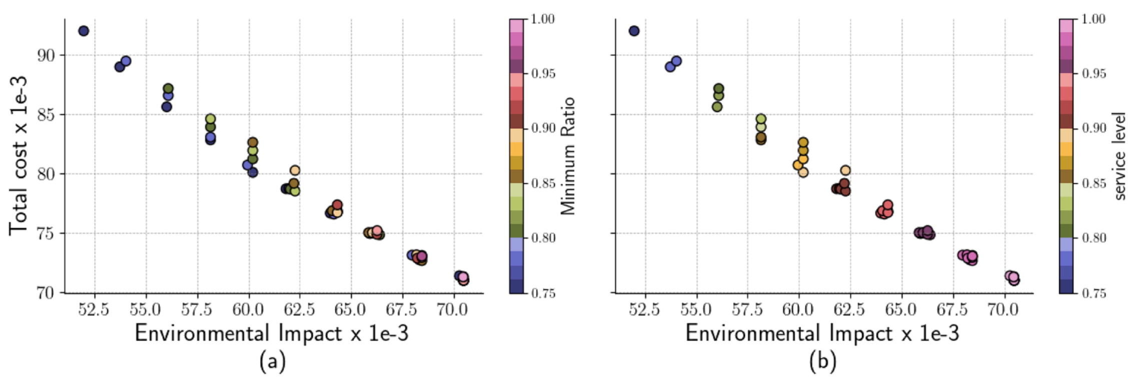

Fig. 6. Pareto Frontier for Case I: (a) Total cost vs Environmental Impact with minimum ratio; (b) Total cost vs Environmental Impact with service level.

treatment for all consumers and guaranteeing an equitable distribution of products, but they come at a higher cost. The environmental budget determines the limit of achievable outcomes, prompting a strategic tradeoff between cost and fairness.

3.3. Case study II: multi-objective, multiproduct interacting raw materials

In the second case study, we expand the scope of the problem to capture the manufacturing of ten products utilizing four raw materials. The recipe table for the product formulations is provided supporting document for reference. These products are categorized into five distinct types, each featuring two dosage variants. The broader product range shows the formulated model's capacity to handle problems of higher dimensions (scalability). While retaining its fundamental structure, the supply chain network is now tasked with managing the interactions between the product portfolios. Product demand for all products is available for 10 periods, and the minimum demand coverage is 40 %. The goal is similar to that of the first case study: determining the solution for each objective and analyzing the tradeoff from the multi-objective problem.

3.3.1. Individual objectives

Following a goal similar to the small case study, we explore the solutions obtained from the different objectives and the interplay between these objectives when a multi-objective problem is solved. The model was formulated and solved in GAMS/CPLEX (v 38.2.1) on a PC with intel corei7–10,510 U, 2.30 GHz, and 16 GB of RAM. The model (MILP) includes 21,951 variables (2160 discrete) and 10,390 constraints, considering a 5 % optimality gap and a maximum computation time of 1000 s., and the computational time required to solve for the minimum cost, minimum environment impact, and maximum minRatio were 400, 320, and 800 s, respectively. The resulting tradeoff table is shown in the Table 2:

The nature of the results obtained for the total cost and minimum ratio columns is similar to that observed in Case I. Specifically, minimizing cost, we noticed that the minRatio obtained in this case was 40 %, which means the environmental impact level was 128,415.0. Furthermore, minimizing environmental impact increases the cost by about 100 % while the minRatio stays the same at 40 %. Finally, when the minRatio is minimized, the cost increases to 141,894 and the environmental impact to 105,093. It is important to highlight that although the minimum ratio for total cost was 40 %, the overall service level was 97.5 %. This suggests periods when only 40 % of a product's demand was met. However, increasing the minRatio to 79.4 % reduces the service level to 81.2 % while increasing cost and environmental impact.

3.3.2. Multi-objective solution

The multi-objective problem was solved following the solution steps

Table 2
Tradeoff table for the best and worst solutions for each objective's case II.

Objectives	Total cost ($)	Environmental Impact	MinRatio
Min (Cost)	83739.5	128415.0	40%
Min (EnvImp)	190578	51567.4	40%
Max(minRatio)	141894	105093.0	79.4%

outlined in Section 2.5. The computational time required to solve the problem was 4516 s. The resulting Pareto Frontier is presented in Fig. 7. The solution reveals that the environmental budget determines the flexibility between the achievable total cost and minimum ratio. Unlike the first case study, in this case, it is established that if we minimize the cost, the minimum coverage value we can achieve is 40 %.

Thus, at lower environmental limits, there is a higher cost penalty to pay to achieve a higher minimum coverage. For instance, in Fig. 7, two achievable minimum ratios are observed when the environmental impact is confined to 70,000. In Fig. 7a, point one attains a 40 % minimum ratio with a cost of 147,000, and the corresponding point in Fig. 7b has a service level of 60.85 %. Conversely, point two achieves a 50 % minimum ratio with a higher cost of 153,000 and a lower service level of 57.4 %. Increasing the minimum environmental budget from 70,000 to 90,000 increases the number of feasible points along the isoenvironmental impact line, and points with a higher minimum ratio have a lower service level. Also, the marginal penalty for increasing the minimum cost is lower. This case study establishes that a higher number of products increases the complexity of the problem since they compete for resources (raw materials and production times); it is more challenging to balance the three objectives, particularly ensuring that the products are equitably distributed.

3.4. Case study III: model study under disruption

This case study compares the performance of the nominal model with the disruption model for situations under disruption. Case study I of two products and two raw materials examples were used for comparison. Furthermore, to ascertain the computational efficiency of the disruption model, we solved the large case study problem using the rolling horizon approach and see how well the model adapts to the demands and disruption variation. In what follows, we show the results for the model comparison case and the rolling horizon case.

3.4.1. Comparison with base model

For this problem, we investigated a scenario involving disruptions in manufacturing facility and warehouse nodes. The disruption scenario here is temporal; any facilities (manufacturing facility and warehouse) can shut down or partially produce. Fig. 8 shows the disruption profile of the facility and the warehouse in terms of capacity. As indicated, there are periods when the available capacity plus expansion cannot meet the actual facility level due to the level of disruption (weeks 5 and 6). If a facility is disrupted, it can operate at a partial level (partial disruption), or it cannot operate for the week (total disruption), and a disrupted facility cannot be expanded.

Fig. 8 presents the expansion profiles of manufacturing facilities and warehouses comparing the optimal expansion levels attained across all models (illustrated in Fig. 8c and d). The results reveal the supply chain network's adaptive capacity in response to disruptions. For the baseline model, there is no room for expansion at both the facility and the warehouse, which limits the production level, reducing the raw material consumed as well as the product demands satisfied. Conversely, when the disruption model is solved, the economic objective is constrained by the MinRatio of 75 %, this will make the expansion more evenly distributed between facilities available for expansion, increasing the total cost. The dynamics of the result here is such that there was an anticipatory capacity increase in weeks 3 and 4, where the capacity increased in preparation for the expected disruptions of weeks 5 and 6. This is a proactive strategy. Finally, when the disruption model is relaxed, a similar trend of result is noticed with that of the disruption model, the approach transitions to an economically driven strategy, which is less conservative with capacity usage. This shift is demonstrated by a slight increase in utilized capacity, suggesting a lean towards centralization and larger facility operations to attain economies of scale. The presence of unused capacity under both models points to a complex balancing act between maintaining operational readiness for disruptions and avoiding the inefficiencies of underutilized resources.

Further results for this case study are presented in Table 3 and Fig. 8 where four models are solved. The baseline model is the developed model, the baseline-relaxed model is the developed model relaxing the social constraint or setting the minimum coverage to zero. The disruption model is the one developed for disruption with active social constraint while the disruption-relaxed model is the disruption model with relaxed social constraints. Since we solve the same problem, the complexity of the baseline model is similar to case one (MILP with 4911 variables with 560 being discrete variables and 2450 constraints), while for the disruption model, the number of variables was 5431 (800 are discrete variables, and 4631 continuous variables) and there are 3550

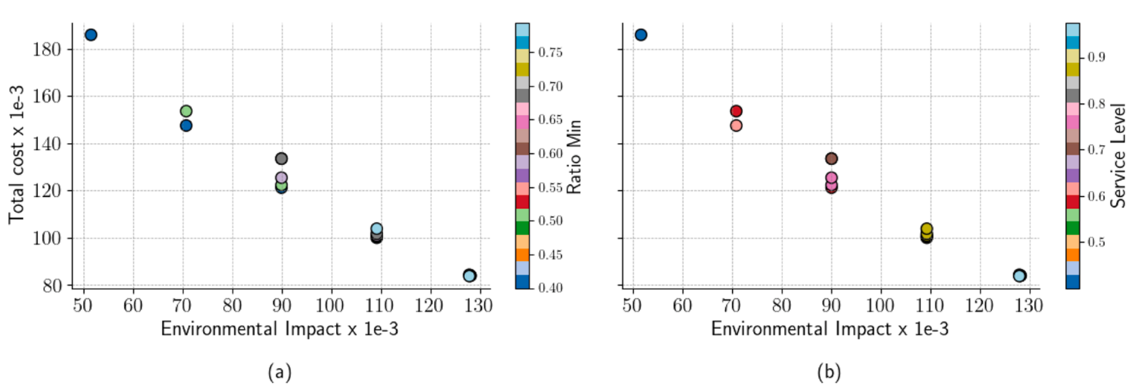

Fig. 7. Pareto Frontier for Case II: (a) Total cost vs Environmental Impact with minimum ratio; (b) Total cost vs Environmental Impact with service level.

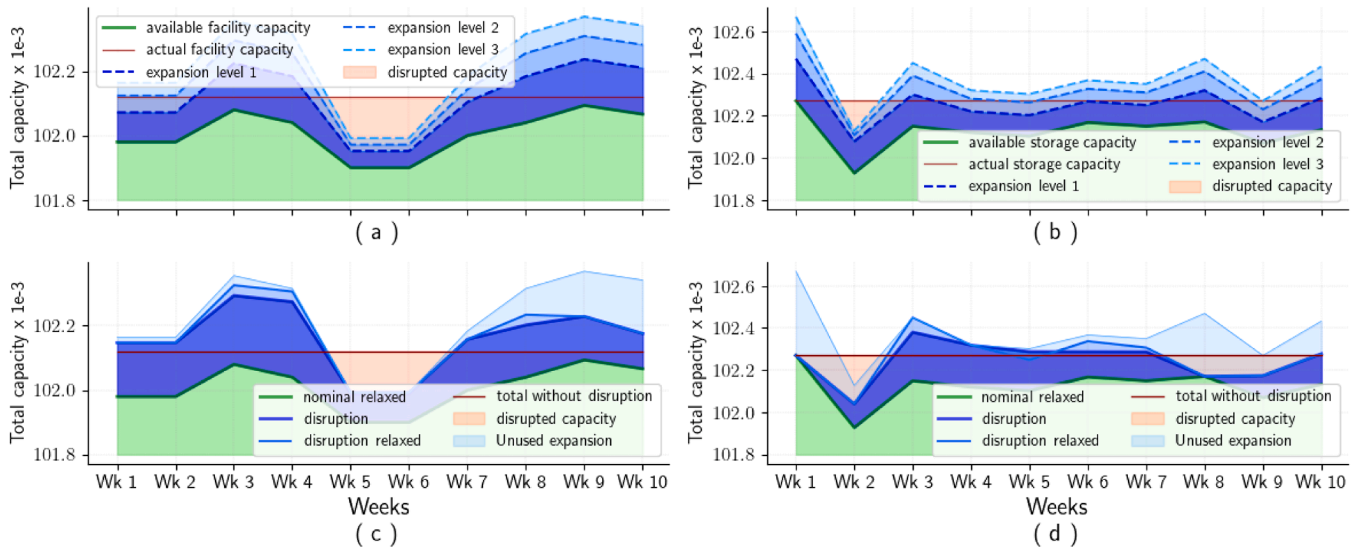

Fig. 8. Capacity profile for manufacturing facility and warehouses. (a)available capacity and the expansion levels at manufacturing facility; (b)available capacity and the expansion levels at warehouses; (c) comparison of capacity levels used by the models for manufacturing sites; (d) comparison of capacity levels used by the models for warehouses.

Table 3
Comparing results for nominal and disruption model.

Models	Total cost ($)	Env. Impact	Min. Ratio	Service Level	Solution time
Baseline	*Infeasible model*				*NA*
Baseline-social Relaxed	90,369.3	67,511.9	0 %	76 %	5 s
Disruption	87,963.3	73,652.1	75 %	86 %	12 s
Disruption-social Relaxed	81,426.2	77,041.3	31 %	93 %	8 s

constraints.

The economic objective was solved for each of the models, and Fig. 9 shows the distributions of the economic and environmental budgets. For the baseline model, there was no feasible solution. This is because of the social constraints on the minimum coverage. Relaxing the social constraints and solving the baseline model (*baseline-social relaxed*) results in a solution with 0 % minRatio and 76 % aggregated service level. Invariably, there is at least one period where the service level for a particular product for a particular consumer was 0 %. The increased in total cost because of the penalty incurred by backorder (24 % of the total demands are not met) as shown in Fig. 9. Table 3. When the disruption model was solved with active social constraint, the optimal solution ensures that a minRatio of 75 %. Solution guarantees all consumers at least 75 % of every product requested. However, the service level is 86 %. There were expansions as indicated by the increased level of raw material consumption Fig. 9a as well as environmental footprint due to production level in Fig. 9b. Finally, when the disruption-social relaxed model was solved the service level increases (indicated by the lower backorder in Fig. 9a), and solution guarantees 31 % delivery of all products to all consumers. Also, relative to the disruption without relaxation model there was a higher production level as more raw materials were consumed, which lowers the backorder.

There are two insights from these results: (i) The supply chain network exhibits a dynamic response to anticipated disruptions, which is a proactive resource allocation strategy, (ii) relaxing the disrupted model reflects a tradeoff between maintaining economic efficiency in operations and achieving social constraint during disruptions. When facility capacity is expanded, the transportation arcs are adjusted to accommodate the increased flow of products. This expansion involves scaling up the capacity of transportation modes to handle the additional volume. However, this adjustment comes with an extra cost due to the fixed cost associated with deploying additional trucks of the same mode.

3.4.2. *Rolling horizon approach for large scale problem*

This case study demonstrates the computational tractability of disruption model applied to the big case study. First, we conducted a sensitivity analysis by perturbing the minRatio from 0 % until the model becomes infeasible followed by a temporal analysis using the rolling horizon framework to assess the model's adaptability to the topological

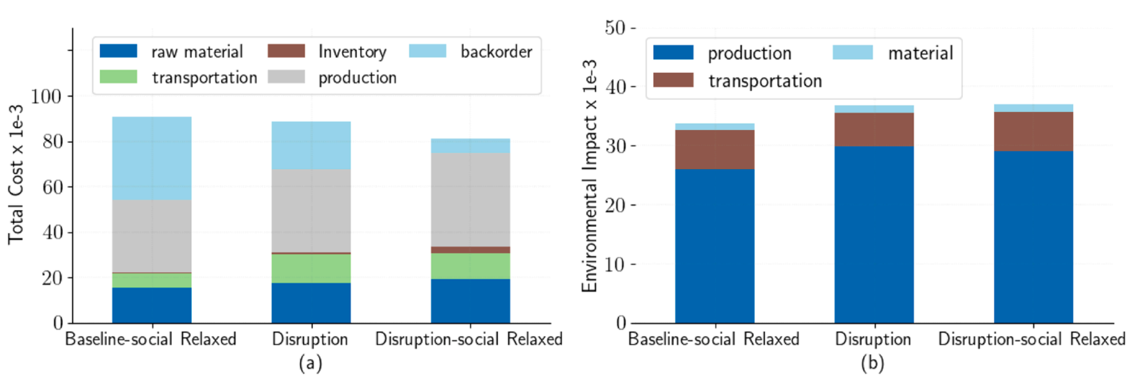

Fig. 9. Objective distribution for all models; (a) Cost Distribution; (b) Environmental Distribution.

disruption for a selected minimum ratio. The model (MILP) includes 23,351 variables (2480 discrete) and 16,350 constraints, considering a 5 % optimality gap and a maximum computation time of 1500 s.

The sensitivity analysis reveals that the problem becomes infeasible at minRatio of 0.6. This outcome suggests that even with the existing flexibility level, it may be impossible to meet the minRatio requirements if products are competing for the same resources. To mitigate such challenges, two approaches can be considered: outsourcing or grouping similar products together. For instance, if product 1 and product 2 are similar— for example different dosage forms—they can be grouped to aggregate their minRatio rather than calculating it individually. For cases within this feasible minRatio threshold, the model required a computational time of 1000 s. The computational time increases with the minRatio level. Fig. 10 shows the result of the sensitivity analysis, showing the relationship between the total cost (y-axis), minRatio (x-axis), environmental impact (indicated by the size of the markers) and the service level (indicated by the color gradients of the marker). The plot reveals a direct relationship between the minRatio and the total cost, as the minRatio increases, there is also an increase in the total costs. The environmental impact also increases with the minRatio and as the color gradation suggests that higher service level is associated with lower minRatio.

The slope of the curve in Fig. 10 illustrates the rate of change in total costs relative to changes in the minimum ratio (minRatio). A steeper slope indicates a more significant cost change, primarily driven by facility expansion. Notably, the steepest slopes between minRatio values of 0.2–0.3 and 0.4–0.5 suggest substantial cost increases, potentially pointing to significant facility expansions during these intervals. Conversely, less steep slopes observed in other segments imply that the focus shifts towards optimizing production levels and managing inventory rather than expanding facilities.

The observed general trend is that Increasing the minRatio results in higher total costs and environmental impacts, alongside a decline in service level, illustrating the trade-offs between social constraints, environmental impact, and cost implications. The observation that higher service levels are associated with lower minRatio suggests improved service efficiency at reduced ratios. This trend highlights the significant operational benefits of maintaining lower minRatio. Relaxing these constraints allows the supply chain greater flexibility and efficiency, enabling better resource allocation and cost-effective distribution. Consequently, the system can prioritize more profitable consumer segments, enhancing overall profitability. A reduced minRatio alleviates the burden of uniformly high service levels, which may not be economically viable across all segments.Fig. 11 represents the outcomes of solving the supply chain problem across different minimum ratios (minRatio) of 0 %, 30 %, and 50 %. This analysis was conducted over five iterations, each spanning 10 horizons and two time periods were implemented at each iteration, effectively covering a 10-week time horizon. The solution times recorded for these minRatio were 4200 s, 5050 s, and 6000 s, respectively, indicating that higher minRatio

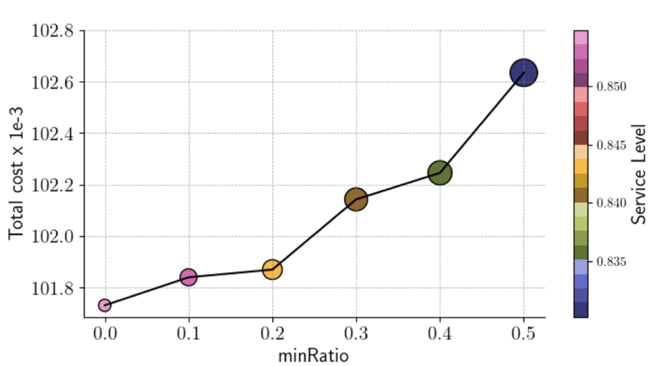

Fig. 10. Cost against minimum ratio.

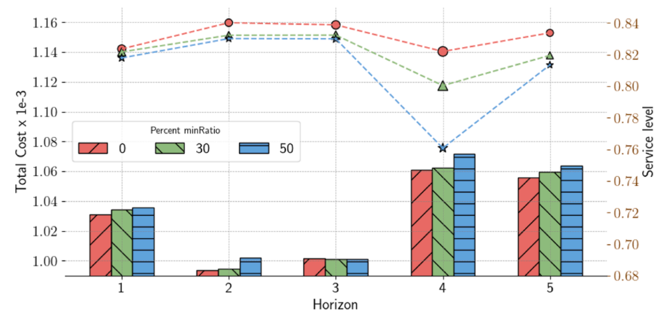

Fig. 11. Rolling horizon results for comparing minimum ratio values.

requires longer solution times. In the graph, the horizontal axis labels the horizon from 1 to 5, representing each set of two time periods over the 10-week span. The left y-axis quantifies the total cost, depicted by the bars, which are color-coded and patterned to correspond with different minRatio—solid red for 0 %, striped, green for 30 %, and blue hatch for 50 %. This visual differentiation allows for an immediate grasp of cost variations across different minRatio settings and horizons. The right y-axis measures the service level, shown through line plots with different symbols indicating the respective minRatio values—circles for 0 %, triangles for 30 %, and stars for 50 %. These lines show a trend of decreasing service level as the minRatio increases, which is typical in scenarios where higher minimum thresholds may limit flexibility in response to demand fluctuations.

Focusing on the 0 % minRatio in Fig. 11, we observe specific dynamics that illustrate how supply chain costs and service levels are influenced under minimal constraints. At zero minRatio, the cost increases result from capacity expansions undertaken to hedge against potential disruptions. Interestingly, horizons that show lower costs correlate with periods of reduced disruption levels, which are also associated with higher service levels. This pattern indicates that when disruptions are minimal, less capacity expansion is necessary, leading to reduced operational costs and improved service delivery.

Furthermore, the general trend in Fig. 11shows that increasing the minRatio leads to higher total costs and reduced service levels. This relationship stems from two main factors: the need to expand production capacity and the costs from backorders due to unmet demands. Expanding capacity requires significant investment, especially at higher minRatio, where more facilities must operate at higher utilization levels. Managing backorders involves addressing demand shortfalls, which are more pronounced under higher disruption levels.

In low disruption scenarios (horizon 2 and 3), it is feasible to expand production capacity, but the extent and allocation depend on the minRatio. A higher minRatio necessitates capacity increases across more facilities, leading to widespread but shallow enhancements. Conversely, at a lower minRatio capacity expansion happens at fewer facilities, allowing for more significant upgrades at each site. This strategic decision balances cost and operational flexibility. Under high disruption levels (horizon 1, 4, and 5), even increased capacity might not meet demand, resulting in substantial backorder costs. This highlights the complex balance between maintaining sufficient production capacity and managing service levels effectively.

4. Conclusion and recommendations

In this study, we explore the complexities of optimizing pharmaceutical supply chains, focusing on tactical network strategies. Our approach integrates a multi-objective model formulation, considering cost, environmental impact, and the minimum ratio objective. Furthermore, we developed an enhanced model capable of effectively managing disruptions within the supply chain.

Our analysis reveals insights into the behavior of the supply chain network under different optimization objectives. When minimizing costs, the network tends to maximize capacity utilization, leveraging economies of scale. Prioritizing environmental objectives leads to reduced production levels to comply with lower minimum coverage requirements. Maximizing the minimum ratio prompts a decentralized operational approach, enhancing distributed demand satisfaction. Using the ϵ-constraint approach, we examine the trade-offs between minimizing environmental considerations, maximizing minimum ratio, and minimizing total cost. Minimizing total cost yields higher service levels but often results in lower minimum coverage, potentially limiting demand fulfillment in less profitable regions. Maximizing the minimum ratio sacrifices overall service levels but increases minimum coverage, ensuring broader consumer reach and the environmental budget limits the flexibility between the other two objectives.

Comparing the baseline and enhanced disruption models highlights the importance of disruption management and mitigation strategies. During disruptions, the baseline model struggles to meet minimum coverage targets, leading to reduced service levels and increased total costs. In contrast, the enhanced disruption model demonstrates improved resilience, effectively responding to disruptions by optimizing capacity utilization. Furthermore, examining cases with and without relaxed social constraints shows the significance of social considerations in supply chain management. The social constraint acts as a lower bound for minimum coverage, guiding facility expansions strategies to meet demand requirements while maintaining social objectives. Overall, our study provides insights into the dynamic response of supply chain networks to disruptions. Balancing economic efficiency with social considerations offers valuable guidance for optimizing pharmaceutical supply chains.

One limitation of our study lies in its primary focus on the tactical level of supply chain management, potentially overlooking broader strategic or operational intricacies. Future research should explore the interplay between regions with varying standards of living to better capture equity considerations, particularly regarding minimum coverage requirements. Additionally, while our analysis considers the expansion of all facilities during disruptions, further investigation is needed, after supply chain design, to identify facilities that should be prioritized for fortification against disruptions, enhancing the resilience of the supply chain network.

CRediT authorship contribution statement

Oluwadare Badejo: Writing – original draft, Visualization, Software, Methodology, Conceptualization. **Marianthi Ierapetritou:** Writing – review & editing, Validation, Supervision, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.compchemeng.2024.108769.

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