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Hierarchical hybrid simulation optimization of the pharmaceutical supply chain

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ABSTRACT

In this paper, a global simulation optimization approach is developed to imitate and optimize the performance of the Pharmaceutical Supply Chain (PSC). Firstly, a hierarchical hybrid simulation model is developed in which aggregate and detailed data levels are addressed simultaneously. The model consists of two types of interdependent paradigms: the system dynamics paradigm, which depicts the echelons of pharmacies and wholesalers in the PSC, and the discrete event paradigm, which simulates the manufacturers with their detailed production operations, as well as the echelons of suppliers. Secondly, the "As is" scenario analysis and a screening process are performed to extract significant input parameters as well as sensitive outputs of the model. The final step optimizes the performance of PSC. The proposed approach validity is appraised by being applied to the PSC of a leading pharmaceutical company in Jordan. As a result, the opportunity loss cost has considerably decreased for both the manufacturer and wholesalers' echelons and the service level has improved throughout the PSC.

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1. Introduction

Pharmaceutical supply chain (PSC) is a very complicated supply chain due to heterogeneous stakeholders, internal and external environments, and distinct related characteristics of healthcare industry such as pharmaceuticals, medical equipment, and patients' flow. PSC is also very sensitive, as it must guarantee that the right drug reaches the right people at the right time and in the right condition. Typically, PSC network consists of multi echelons including pharmacies, drugs wholesalers, drugs manufacturers, and raw material (RM) suppliers. Yet, PSC networks are continuously evolving with increasing number of customers, different types of products, increasing number of suppliers and manufacturers. Over the past decades, PSC has faced tremendous challenges such as lack of coordination, shortage or excess of drugs, and high demand uncertainty [1, 2]. Shortage of drugs is not a simple incident that can be diagnosed by one or more explicit sources; rather, it is a dynamic crisis caused by multiple interrelated aspects.

Low manufacturing velocities, multi-procedures of quality assurance, and supply chain dynamics are the key players in PSC drug shortage [3].

Optimizing the PSC can be carried out analytically [4] or heuristically [5]. However, these approaches are generally applied under simplification assumptions such as sole stage or product and restricted variability [6]. In real situations, PSC is a complex system with multi-product and multi-echelon. It operates under a high level of stochasticity in which analytical optimization may fail. Additionally, similar to other SC, PSC includes manufacturing and non-manufacturing functions, encompasses different planning scopes at various management levels, and involves dissimilar data details [7]. In such turbulent circumstances, simulation would be the optimal approach that gives practitioners the ability to imitate such complex systems using different scenarios without altering processes on ground [8].

Mostly, single simulation methodology, including discrete-event (DE) [9, 10] or system dynamics (SD) [11, 12] is adopted in literature for PSC simulation modelling. However, considering the combination of discrete and continuous issues within the PSC, as well as the challenges related to different abstraction levels, relying solely on an individual simulation approach proves inadequate in accurately capturing the PSC system [13]. Lately, hybrid simulation, where two or more traditional simulation modelling paradigms are integrated into one model, has proved excellent capabilities in resolving complicated scenarios such as PSC [7, 13]. According to Eldabi *et al.* [14], interest in hybrid simulation has experienced remarkable growth in the last decade. With its evolving complications, Brailsford *et al.* [15] highlighted the need to explore the application of hybrid simulation in the modern operation management area.

Simulation optimization (SO) can be defined as the process of testing various variables' values in order to find the most desirable combination of values from simulation models [16]. The valuable advantage of SO is the ability to handle stochasticity and complex interactions at a level that can hardly be formulated by traditional optimization [17]. The early initiatives to embed optimization in simulation modelling were either non-generic and based on ad hoc approaches or were heavily dependent on users to implement "seat of the pants" analysis [17]. Later, intelligent search procedures have been implemented within SO to find optimal or near-optimal solutions by exploring a small portion of available alternatives [18]. For PSC literature, SO is rarely adopted, mostly, the PSC entities are considered as disjoint systems to be locally controlled and optimized. Chen *et al.* [19] proposed a DE-SO approach for the clinical SC that included patient demand, demand scenario forecast, and mathematical programming-based planning. Franco and Alfonso-Lizarazo (20) developed a SO approach based on the sample path method for optimizing tactical and operational decision levels in PSC. They considered uncertainty in demand, cost, and lead-time in the pharmacy-hospital echelon.

This study develops a global SO approach to optimize the PSC performance at different data levels using hierarchical hybrid (HH) simulation modelling. The developed HH simulation model can holistically imitate multi-echelon multi-product PSC. In this model, both aggregate, such as material and information flow between the PSC entities, and detailed data levels, including production process details are taken into consideration. Particularly, the proposed model allows for the integration of different sub-models with different data levels into an overall global SO model, hence, avoiding inconsistencies resulted from combining models with different data levels [21, 22]. Moreover, the proposed HH simulation model handles the dynamic nature of stochastic market demand on daily basis, at the same time, it can simulate the discrete detailed processes occurring in real PSC (e.g., replenishment and production processes).

2. The hierarchical hybrid simulation optimization (HH-SO) approach

The proposed SO approach consists of three main steps. First, a HH simulation model is developed to simultaneously address aggregate and detailed data levels in the PSC. Then, the "As is" scenario analysis is performed, and a screening process is applied via sensitivity analysis in order to extract major effective parameters as well as sensitive outputs. The performance of PSC concerning sensitive outputs is optimized in the third step. Fig. 1 depicts the major steps in the proposed approach while the next subsections further discuss them.

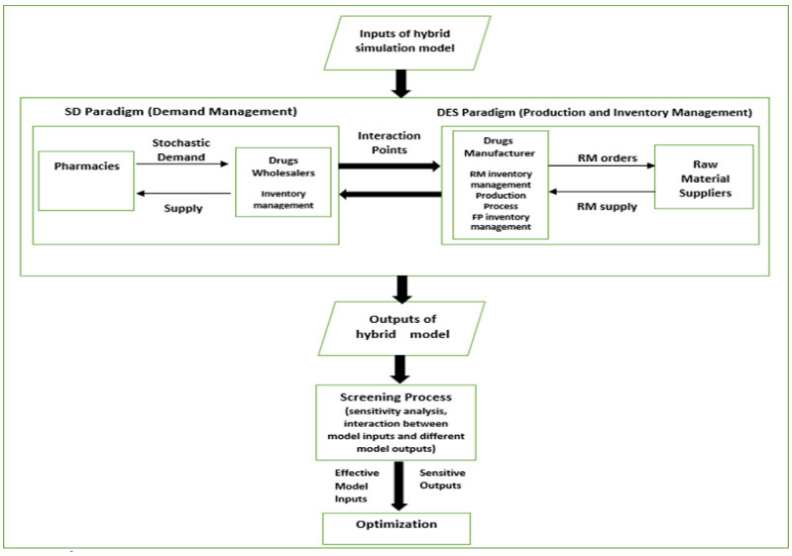

Fig. 1 The proposed approach flowchart

2.1 The hierarchical hybrid (HH) simulation modelling

Fig. 1 depicts the hybridity in the proposed simulation model while the hierarchy in the simulation model is described in Fig. 2. The HH simulation model consists of two types of interrelated paradigms: SD paradigm that depicts the pharmacies and wholesalers' echelons in the PSC, and DE paradigm that simulates the manufacturers with their detailed production operations, order receiving, order fulfilment, inventory management, replenishment, and storage processes, and the suppliers' echelons. SD is used to depict the dynamic and stochastic nature of market demand due to its capabilities in buffering and self-adaptation to turbulence in market demand, which is considered a frequent situation in PSCs. On the other hand, DE is adopted to emulate discrete physical and business processes such as production, order fulfilment, and inventory management. It is worthy to recap how critical inventory management is for effective PSC due to its enormous effect on both cost-related and service-related KPIs [23]. However, multi-echelon inventory management is strongly dependent on the performance of drugs suppliers and distribution centres [24]. Consequently, optimizing the PSC operations while considering inventory levels would be beneficial to achieve higher profit margins as well as higher service levels [25].

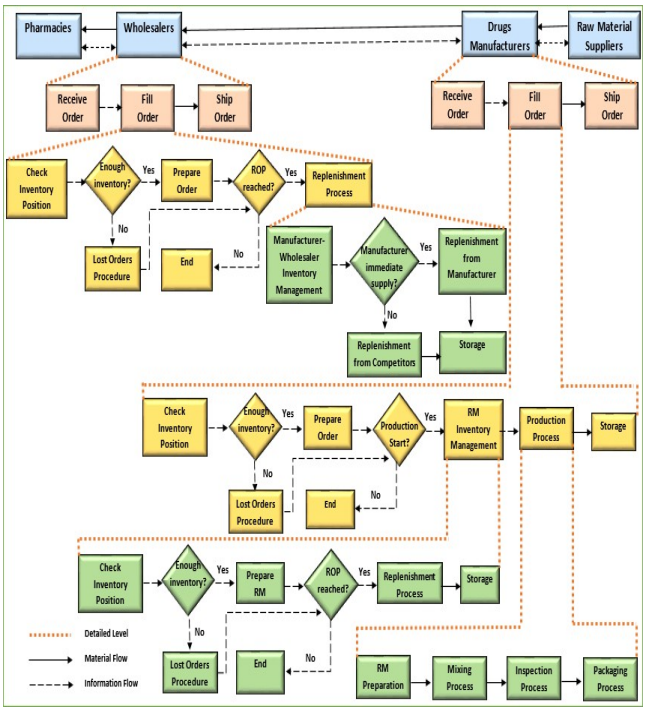

Fig. 2 The proposed hierarchical simulation model

Model building, verification, and validation

All PSC processes are simulated by either SD or DE sub models. Each sub model is verified and debugged separately. In addition, control variables are used to test and verify sub models' logic and outputs. Then, the sub models are combined and aggregated gradually until the global HH simulation model is completely developed and verified. Regarding model validation, the proposed model/approach is validated by being used to simulate the PSC performance of a leading pharmaceutical company in Jordan. Major model outputs are compared to actual values obtained from the model's implementation. The results are comparable with an acceptable level of accuracy. Hence, the model is considered to be validated. More details about this step are presented in Section 3.

Model inputs, outputs, and assessment

The model input parameters are classified into three categories, as illustrated in Table 1, input parameters for SD sub models, input parameters for DE sub models, and input parameters for both paradigms. The third type of inputs is called interaction points since they affect and connect the SD and DE paradigms concurrently. The inputs include the number of entities, number of materials (both raw and finished), market demand, variables related to the inventory management system at different echelons, and production process variables. Table 2 shows the model outputs, which include different cost items, service level, lost orders, and different profit measures for different echelons.

Two distinct types of KPIs for both the wholesalers and manufacturers' echelons assess the model: the cost-related KPIs is represented in the opportunity loss cost while the service-related KPIs is expressed in the service level. Both measures are essential not only because they are highly related to the drugs' shortage critical challenge in PSC, but also due to their direct influence on the market share and competencies of PSC entities. In the developed model, the annual opportunity loss cost is calculated based on stochastic daily demand. While the average service level is estimated as the proportion of the annual supply to the annual demand for each PSC entity in the wholesalers and manufacturers' echelons.

Table 1 Inputs for the HH simulation model

Parameter	Symbol	Sub model	
		SD	DE
Number of drugs	I	√	√
Number of drugs wholesalers	J	√	√
Number of drugs manufacturers	K	√	√
Number of RMs	L		√
Number of RM suppliers	M		√
Number of RMs needed to produce drug i	Ni		√
Pharmacies stochastic demand for drug i from wholesaler j	$DPij$	√	
Wholesaler j order quantity of drug i from drugs manufacturers k	$Wjik$	√	√
Other demand of drug i from drugs manufacturers k	$Diks$		√
Other demand selling price (per unit) of drug i from drugs manufacturer k	$SPik$		√
Wholesaler j reorder point of drug i	Rji	√	√
Wholesaler j initial inventory of drug i	Vji	√	√
Wholesaler j holding cost (per unit) of drug i	Hji	√	
Wholesaler j ordering cost (per order) of drug i	Oji	√	
Wholesaler j purchasing cost (per unit) of drug i from drug manufacturer k	$Pjik$	√	
Wholesaler j opportunity loss cost (per unit) of drug i	Cji	√	
Drugs manufacturer k lead time distribution for drug i	Tki	√	√
RM l order quantity for drugs manufacturer k form RM supplier m	$Alkm$		√
RM l reorder point for drugs manufacturer k	Blk		√
RM l initial inventory at drugs manufacturer k	Elk		√
RM l holding cost (per unit) at drugs manufacturer k	Flk		√
RM l ordering cost (per order) at drugs manufacturer k from RM supplier m	$Glkm$		√
RM l purchasing cost (per unit) at drugs manufacturer k from RM supplier m	$Qlkm$		√
Amount of RM l needed to produce 1 batch of drug i	Ul		√
RM supplier m lead time distribution for RM l	Vml		√
Drugs manufacturer k initial inventory of drug i	Wki	√	√

Table 1 (Continuation)

Drugs manufacturer *k* production start point of drug *i*	*Xki*	√
Drugs manufacturer *k* production batch size of drug *i*	*Yki*	√
Drugs manufacturer *k* number of mixing machines	*NMk*	√
Drugs manufacturer *k* number of packaging machines	*NPk*	√
Drugs manufacturer *k* mixing time to produce 1 batch of drug *i*	*MTki*	√
Drugs manufacturer *k* packaging time to produce 1 batch of drug *i*	*PTki*	√
Drugs manufacturer *k* setup and inspection time to produce 1 batch of drug *i*	*STki*	√
Drugs manufacturer *k* mixing cost to produce 1 batch of drug *i*	*MCki*	√
Drugs manufacturer *k* packaging cost to produce 1 batch of drug *i*	*PCki*	√
Drugs manufacturer *k* setup and inspection cost to produce 1 batch of drug *i*	*SCki*	√

Table 2 Outputs of the HH simulation model

Parameter	Symbol	Parameter	Symbol
Wholesaler *j* lost orders of drug *i*	*WLOji*	Drugs manufacturer *k* service level of drug *i*	*MSLki*
Wholesaler *j* service level of drug *i*	*WSLji*	Drugs manufacturer *k* opportunity loss cost of drug *i*	*MLCki*
Wholesaler *j* opportunity loss cost of drug *i*	*WLCji*	Drugs manufacturer *k* total lost orders	*MLOk*
Wholesaler *j* total lost orders	*WLOj*	Drugs manufacturer *k* total holding cost	*MHCk*
Wholesaler *j* total holding cost	*WHCj*	Drugs manufacturer *k* total ordering cost	*MOCk*
Wholesaler *j* total ordering cost	*WOCj*	Drugs manufacturer *k* total purchasing cost	*MPCk*
Wholesaler *j* total purchasing cost	*WPCj*	Drugs manufacturer *k* total opportunity loss cost	*MLCk*
Wholesaler *j* total opportunity loss cost	*WLCj*	Drugs manufacturer *k* total production cost	*MPrCk*
Wholesaler *j* service level	*WSLj*	Drugs manufacturer *k* service level	*MSLk*
Wholesaler *j* revenue	*WRj*	Drugs manufacturer *k* revenue	*MRk*
Wholesaler *j* profit	*WPj*	Drugs manufacturer *k* profit	*MPk*
Wholesaler *j* profit margin	*WPMj*	Drugs manufacturer *k* profit margin	*MPMk*
Drugs manufacturer *k* lost orders of drug *i*	*MLOki*		

Model structure

As can be seen in Fig. 2, four hierarchical levels are presented in the proposed model with different levels of details. The highest or aggregate level, shown in blue, controls the material and information flow between the PSC echelons. The next highest level, shown in pink, controls the order fulfillment processes in the echelons of wholesalers and manufacturers. It receives input data from the lower level regarding inventory details, processes it, and then provides the necessary outputs and actions to the next higher level in the HH simulation model. The third level, shown in yellow, simulates inventory management of produced drugs in wholesalers and manufacturers' echelons. Finally, the lowest level, shown in green, is simulating the replenishment process for wholesalers' echelon as well as RM inventory management and production process in manufacturers' echelon. The system checks the inventory level, if there is enough inventory, the order will be prepared to be shipped, and the new inventory level will be compared to the reorder point (ROP), if it is reached, a signal will be sent to the replenishment sub model in level four. If there is not enough inventory, a signal will be sent to the lost orders sub model.

A basic feature of this HH simulation model is its capability to handle aggregate data such as material and information flow between the PSC entities, at the same time; it handles detailed data related to the drugs production process. This is achieved by employing the hierarchy concept in parallel with simulation hybridity. As mentioned earlier, most scholar work concentrates on one part while ignoring the other due to modelling complexity and computation time constraints.

It is worth noting that most activities, represented as rectangular boxes in Fig. 2, are entire processes that are simulated separately by either SD or DE sub models. For example, as shown in Fig. 2, the replenishment process is composed of multi sub-activities in which information related to inventory position and immediate replenishment ability is exchanged between wholesalers and manufacturers' echelons. If the manufacturer with the lowest prices has enough inventory to fulfil the wholesaler order immediately, then the order is purchased from this source. Otherwise, the wholesaler will look for other manufacturers (competitors) with different prices and lead time distributions to fulfil the order.

2.2 Screening process of the model's inputs and outputs

In a global simulation model, like the one developed in this study, the number of input parameters is too large to be directly fed into an optimization step. Moreover, the targets of the optimization process are considerably diversified than to be gathered in one objective function and optimizing such objective function would not be attainable due to potential conflict between these targets and/or computation time constraints. For such a complicated scenario, a screening process is proposed, first, to select the influential model inputs and hence use them as decision variables in the optimization step. Second, to specify the sensitive outputs of the HH simulation model that are highly influenced by the variation in input parameters. One practical way to perform this screening process is to use sensitivity analysis or "What-if" scenarios. In sensitivity analysis, a large number of simulation trials are performed in which the model outputs are monitored while varying the model inputs in order to decide which outputs are more sensitive to these variations (sensitive outputs) and which inputs variation has significant effects on these outputs.

In theory, the screening process is a sensitivity analysis or "What-if" scenarios when all the HH simulation model inputs are varied to monitor the resultant change in all the HH simulation model outputs. In other words, the theoretical screening process would include the following steps: firstly, instead of using one value for each input of the simulation model, a range of values is used for each input (one value at a time), secondly, the simulation model is run at each value and the simulation model outputs are monitored. The outputs that significantly vary with the variation in the input parameters are considered as sensitive outputs, accordingly, they will be chosen to be the optimization targets or the objective function terms for the optimization step. However, in reality, not all input parameters can be changed because not all of them are under control. For instance, in a real existing PSC, the number of entities (e.g., wholesalers, manufacturers, suppliers) are fixed and not subjected to changes in normal situations. As a result, there is no use in varying the number of PSC entities and monitor the sensitive outputs since the number of entities is already fixed in a certain PSC. Another example is the inputs whose values are determined externally, hence cannot be practically varied by the decision makers such as market demand. Based on that, the prospect decision variables to be fed to the optimization step are defined as all the input parameters that can be controlled by decision makers in a certain PSC. These prospect decision variables (shaded in Table 1) are chosen based on the authors' experience with real-world PSC in parallel with experts' opinions. They include reorder point, initial inventory, and order quantity for different entities in the PSC plus the production start point for the drugs' manufacturers. It is worth mentioning that the algorithm is generic enough to choose different prospect decision variables based on studied cases.

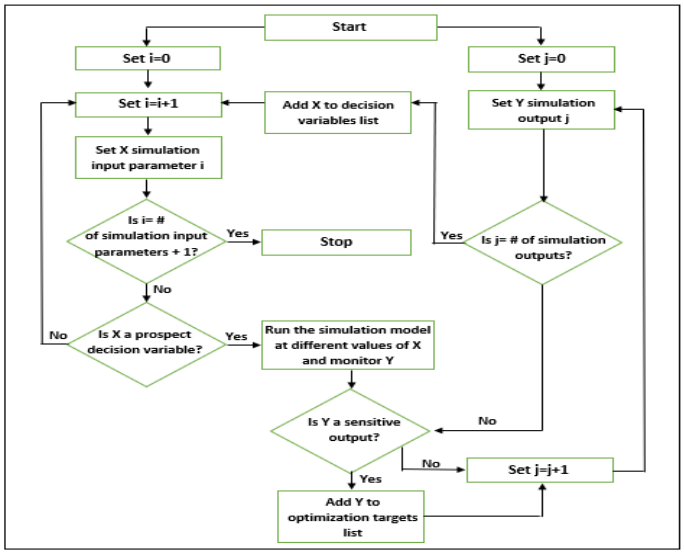

Fig. 3 The screening process flowchart

To perform the screening process a code is programmed within the used simulation toolkit, the algorithm behind this code is shown in Fig. 3. The user enters an array that consists of the prospect decision variables (variable X in Fig. 3) with the selected range of variation. The program will start scanning the input parameters, if the input parameter is in the prospect decision variables list, the simulation model will perform multi-simulation runs according to the pre-specified range of variation and monitor the simulation model outputs (variable Y in Fig. 3). Then, the model will check the variation range in all the simulation model outputs to decide if the output is sensitive or not. If it is, it will be added to the optimization targets. After the screening process is completed, two lists of variables are ready to be fed to the optimization step, the decision variables list, which contains the influential inputs of the HH simulation model, and the optimization targets list that includes the sensitive outputs of the HH simulation model.

2.3 Optimization of the model sensitive outputs

Due to the complexity and stochasticity nature of simulation systems, an analytical expression for the objective function does not exist in SO, instead, it is estimated as a function of the stochastic simulation outputs either if the decision variables are discrete or continuous. In case of continuous decision variables, gradient-based methods such as stochastic approximation are used. Yet, in discrete decision variables with finite feasible region, ranking and selection methods could be used. If the feasible region is finite but significantly large, metaheuristics such as Tabu search, genetic algorithm, simulated annealing, neural networks are used (18).

In this paper, OptQuest optimization package, which is included in AnyLogic simulation software, is used. This optimization package uses scatter search, Tabu search, and neural networks algorithms to search within, the simulation runs, for optimal or near-optimal solutions [26]. Essentially, OptQuest used adaptive memory of the search history to guide the solution searching process, preventing evaluating pre-investigated alternatives. In practice, the user should create an optimization experiment by determining the optimization targets (which are in our case the sensitive outputs obtained from the screening process), the decision variables (which are the influential inputs of our simulation model obtained from the screening process), the constraints, and the stopping criteria of the optimization process.

Fig. 4 illustrates the interaction between the simulation and optimization packages which can be summarized in the following points:

- The simulation software performs simulation runs based on decision variables, obtained from the optimization package, and exports simulation outputs to the optimization package.
- Based on the embedded search methods, the optimization package guides the subsequent simulation iterations to ensure that the new solution is closer to optimal than the previous one.

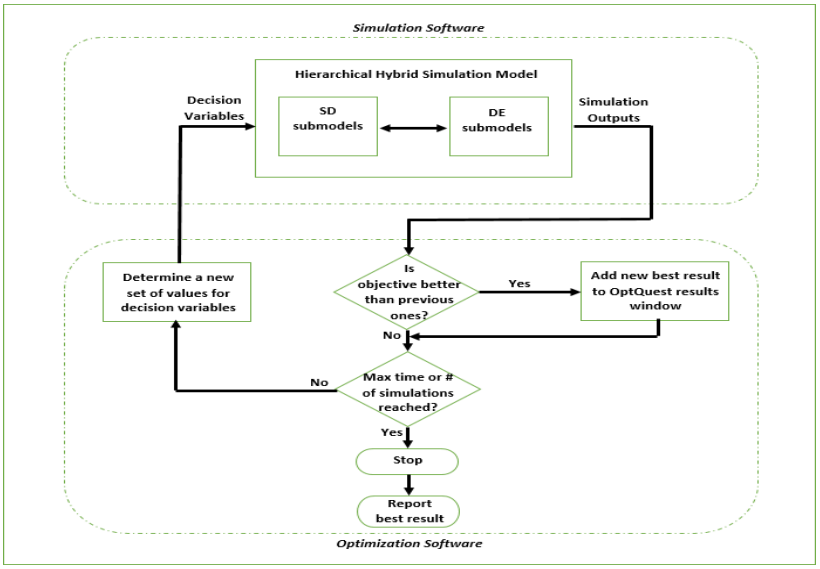

Fig. 4 The interaction between the simulation and optimization packages

- The process will end when the stopping criterion is reached which could be based on simulation time or number of simulation iterations.

3. Implementation, results, and discussion

To validate the proposed approach with its three steps shown in Fig. 1, it was applied to the PSC of a leading pharmaceutical company in Jordan. The considered PSC network is described in Subsection 3.1 while Subection 3.2 illustrates the analysis and results obtained by applying the proposed approach to this PSC.

3.1 The PSC network

Generally, Jordanian pharmaceutical companies concentrate on the secondary pharmaceutical production process, which is taken into account in the current study, in which the active ingredient of the drug is processed and mixed with excipients to produce the drug in its commercial form. Since the core of any PSC is the drugs' manufacturer, the authors contacted one of the largest pharmaceutical companies in Jordan. Multi structured and semi-structured interviews were conducted with employees at different levels in order to collect qualitative as well as quantitative data to be used in this study. The first route of interviews was dedicated to qualitative analysis in order to determine the major obstacles the company is facing regarding with the SC arena. The results of this step showed that for a certain type of drugs, which is injectable, the company's PSC suffers from a shortage problem, which leads to relatively high opportunity loss cost (8.5 % of the annual revenue). Based on the results obtained from the elementary qualitative analysis, the second route of interviews focused on gathering all the necessary data needed to simulate the PSC of injectable drugs.

The considered PSC network for injectable has two parallel material flows, the primary is a four-echelon and the other is a three-echelon. The first echelon is the RM suppliers' echelon that provides the drug's manufacturer with RMs including active pharmaceutical ingredients (APIs), excipients, vials, labels, and boxes. Five local suppliers are responsible for supplying the company with RMs at different prices and stochastic lead-time distributions. However, based on practical data given by the pharmaceutical company, RM supply is regular with no shortage occurrence. Consequently, RM feed is assumed to be unlimited in the HH simulation model. The second echelon is the manufacturer echelon. The considered pharmaceutical company produces three different types of injectable. The preparation stage includes receiving and storing RMs in the RM warehouse at the pharmaceutical company. The production process is composed of four main stages, which are RM preparation, mixing, inspection, and packaging. Since the production process is secondary, the main operation is the dilution of the APIs with the specified types and amounts of excipients to produce the commercial form of the three injectable. The dilution or mixing is a batch production process that produces different batch sizes for each injectable. After the mixing process, various quality control procedures are applied in order to collect and test samples from the products to check different measures such as the concentration of the API in the produced injectable. This inspection process is followed by the final step, which is the packaging process. The company has two identical production lines each with mixing and packaging machines. Also, each line can produce the three types of injectable interchangeably. Since the company has two different types of customers (the public health sector and the wholesaler), two slightly different packages are used for each injectable. Finally, the finished products (FPs) are stored in the FP warehouse at the company.

The third echelon comprises two entities, the wholesaler that is responsible for providing pharmacies with injectable, and the public health sector that provides hospitals with the injectable. The public health sector demand is deterministic, and it is replenished via periodic tender protocols. It is important to mention that if the company inventory is not enough to satisfy the wholesaler demand, the wholesaler replenishment would occur from other pharmaceutical companies (competitors) at different prices and stochastic lead time. Finally, the fourth echelon following the wholesaler represents the pharmacies with stochastic daily demand.

3.2 Results and analysis

Based on the qualitative and quantitative data collected from the company as well as the wholesaler entities, a HH simulation model, like the one shown in Fig. 2, was built to imitate the "As is" scenario for the injectable supply chain. The software package used to build the hybrid simulation model is AnyLogic, a multimethod simulation modelling tool that supports DE, SD, and agent based (AB) methodologies [27]. Moreover, it supports Java coding which enabled authors to develop customized and complex events and subprograms for this HH simulation model. AnyLogic optimization package, used in the third step of the proposed approach, is built on top of the OptQuest Optimization Engine, which is considered one of the most powerful optimization tools available [26, 27].

The HH simulation model, with its various sub models, was constructed gradually until it was totally developed. Throughout the developing process, each sub model was verified and debugged separately in parallel with numerical and graphical testing of some variables to check the logic as well as accuracy. A good example of the graphical testing and representation of the HH simulation model outputs is shown in Fig. 5. Fig. 5 is a screenshot of the graphical interface constructed to check the behavior of the HH simulation model through monitoring the plots of major variables and outputs versus simulation time. These include the wholesaler inventory status and lost orders, the drug's manufacturer FP inventory status (with its two components of wholesaler package and public health sector package for each injectable), and the drug's manufacturer lost orders and accumulative lost orders. Meanwhile, the tested sub models were continually aggregated into the HH simulation model until it was completed and totally verified. The major outputs of the "As is" scenario are illustrated in Table 3, based on a one-year run (in the model's time unit: 365 days).

Table 3 Comparison between the major outputs of the "As is" scenario and the "After optimization" scenario

Simulation model output	Unit	"As is" scenario	"After optimization" scenario	Change (%)
The wholesaler lost orders	box	887	346	-61.0
The wholesaler ordering cost	JD*	85,000	72,000	-15.3
The wholesaler opportunity loss cost	JD	483,380	190,101	-60.7
The wholesaler service level	%	98.8	99.5	0.7
The pharmaceutical company lost orders	box	9920	8480	-14.5
The pharmaceutical company RM holding cost	JD	1,819,799	1,767,452	-2.9
The pharmaceutical company opportunity loss cost	JD	3,478,500	3,147,000	-9.5
The pharmaceutical company service level	%	86.6	88.9	2.3

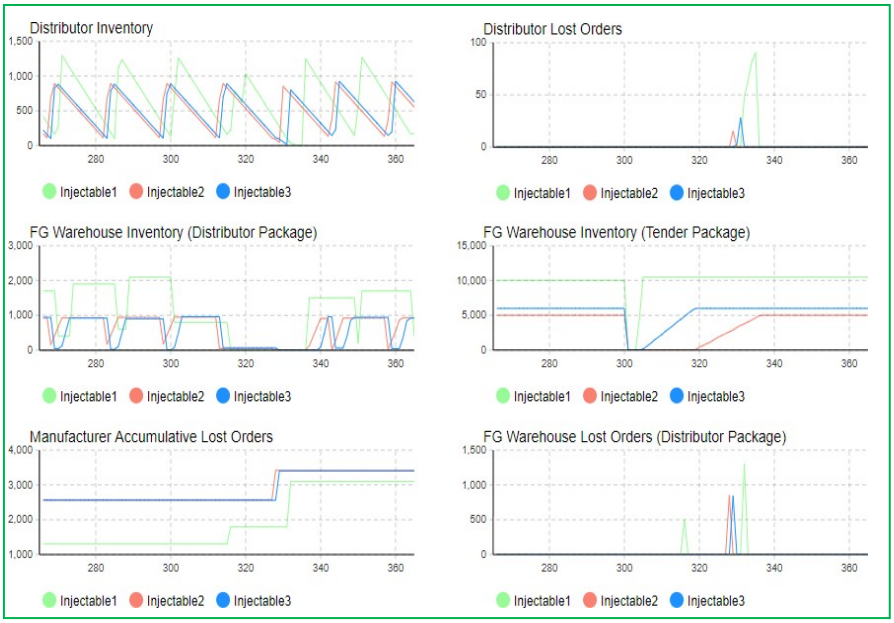

Fig. 5 The graphical interface used to monitor major variables and outputs of the simulation model

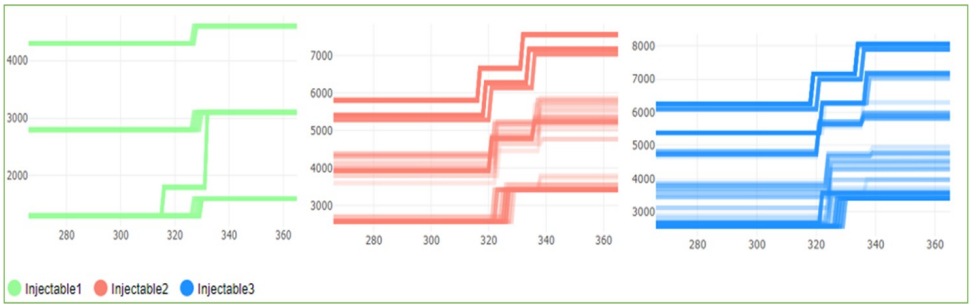

Fig. 6 The pharmaceutical company lost orders (boxes) versus simulation time (days) at different values of the wholesaler order quantities

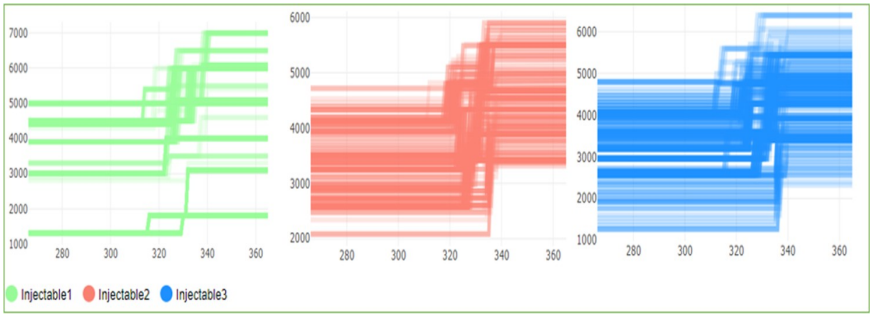

Fig. 7 The pharmaceutical company lost orders (boxes) versus simulation time (days) at different values of the wholesaler reorder points

To check the HH simulation model validity, the "As is" scenario major outputs were compared to their actual values obtained from the company and the wholesaler. For instance, the annual opportunity loss costs for both the company and the wholesaler were compared to those calculated by the HH simulation model. The difference was found to be less than 5 %, which is considered to be within the acceptable level of accuracy.

To perform the second step of the proposed approach which is the screening process, the "As is" scenario inputs and outputs were fed into the screening process algorithm described in Fig. 3. Figs. 7 and 8 are graphical representations of the screening process's significant outcomes. Each one of the six plots in the Figs. shows the sensitive simulation outputs (which are the pharmaceutical company lost orders) of multiple "What-if" scenarios for each injectable. For instance, the green plot in Fig. 6 is the pharmaceutical company lost orders versus simulation time (in days) at different values of the wholesaler order quantity from injectable 1. While the green plot in Fig. 7 is the pharmaceutical company lost orders versus simulation time (in days) at different values of the wholesaler reorder point of injectable 1. The same is true for injectable 2 (red plots) and injectable 3 (blue plots). It could be seen clearly in the Figs that the pharmaceutical company lost orders are sensitive and highly dependent on the replenishment process of the wholesaler, represented in the order quantities and reorder points of each one of the three considered injectable. As mentioned earlier in the case description, the pharmaceutical company suffers from high annual opportunity loss cost for the injectable products, actually, the "As is" scenario results have assured this issue. However. It could not give explanations or possible reasons for this problem. The screening process outcomes have revealed that this shortage problem is not related to the company's internal factors such as production scheduling or RM availability. Instead, it is closely related to the lack of information sharing between the pharmaceutical company and the wholesaler entities.

As described in Section 3, the screening process results in two key results: influential inputs and sensitive outputs. In the considered implementation, the screening process has revealed six influential simulation inputs, as shown in Figs. 7 and 8, which are the wholesaler order quantity and reorder point for each one of the three injectable products. On the other hand, there are three sensitive simulation outputs which are the pharmaceutical company's lost orders for each

injectable. For optimization purposes, the opportunity loss cost was used rather than the number of lost orders, since it is more meaningful and representative to decision makers.
In summary, the objective function of the optimization model was set to minimize the pharmaceutical company opportunity loss cost for each injectable and the decision variables are the wholesaler order quantity and reorder point for each injectable. It is worth noting that the decision variables lower and upper bounds are set based on the capabilities and available possibilities discussed with the wholesaler.

After the optimization model (the objective function and decision variables) is specified, the optimization experiment was performed, with 500 iterations, on OptQuest Optimization Engine of AnyLogic. The new values of the decision variables, obtained from the optimization step, were used to simulate the PSC performance. Table 4 compares the influential inputs of the "As is" scenario and the "After optimization" scenario. It could be seen in the table that the wholesaler order quantities have increased by 23.1 %, 11.1 %, and 44.4 % for injectable 1, 2 and 3, respectively. While the reorder point has increased by 500 % and 100 % for injectable 1 and 3, respectively.

Furthermore, Table 3 compares the major outputs of the "As is" scenario and the "After optimization" scenario. Obviously, the lost orders have considerably dropped by 14.5 % for the pharmaceutical company and 61 % for the wholesaler. As a result, the opportunity loss cost has lowered by 9.5 % for the pharmaceutical company and 60.7 % for the wholesaler. Moreover, the service level has improved for both the pharmaceutical company and the wholesaler, with a 2.3 % and 0.7 % increase in turn. Another plus point is that other costs such as RM holding cost and the wholesaler ordering cost have also declined after performing the optimization process.

Table 4 Comparison between the influential inputs of the "As is" scenario and the "After optimization" scenario

Simulation model output	Unit	"As is" scenario	"After optimization" scenario	%Change
The wholesaler order quantity from injectable1	box	1300	1600	23.1
The wholesaler order quantity from injectable2	box	900	1000	11.1
The wholesaler order quantity from injectable3	box	900	1300	44.4
The wholesaler reorder point of injectable1	box	100	600	500
The wholesaler reorder point of injectable2	box	100	100	0
The wholesaler reorder point of injectable3	box	100	200	100

4. Conclusion and future research

The current study has presented a HH-SO approach that simulates the aggregate as well as the detailed levels in PSC. A three-step procedure has been proposed that develops a HH-SO model to mimic the processes within a four-echelon PSC, including material and information flow, order receiving, order fulfillment, inventory management, replenishment, and storage processes. Also, the production process, which is frequently ignored or simplified when SCs are simulated in related literature, is minutely modeled. A screening process is then performed to filter influential inputs as well as sensitive outputs of the simulation model. Later, the outputs of the screening process are used to optimize the performance of the PSC.

Using a case study, the proposed approach has depicted validity in handling real PSC implications such as multi echelons and multi products, stochasticity in demand and lead times, and variation in data granularity levels. The results obtained have shown that although this approach is designed to optimize the sensitive outputs of the simulation model, such as opportunity loss cost and service level at different PCS echelons; the values of other outputs are indirectly improved after applying the proposed approach. It is important to note that the suggested approach can be used with supply chains other than those for pharmaceuticals. This would alter the "discrete event simulation" paradigm's modelling of the particulars of the other supply chain's production process. But the fundamental structure of the "system dynamics" paradigm would hold.

Regarding future work, the utilization of agent-based modeling (ABM) in a hybrid simulation environment would enhance the interaction among PSC entities, thereby increasing the responsiveness and autonomy of hybrid simulation models. The employment of ABM, with its intelligent characteristics such as reaction, evolution, and adaptation, would facilitate the study of

complex adaptive systems, wherein the intricate behavior of the entire system emerges from the interaction of a large number of components capable of adjusting their performance over time based on their own experiences.

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