

## **ASSESSING RESILIENCE OF MEDICINE SUPPLY CHAIN NETWORKS TO DISRUPTIONS: A PROPOSED HYBRID SIMULATION MODELING FRAMEWORK**

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### **ABSTRACT**

The objective of the proposed hybrid simulation modeling framework is to improve the understanding and operation of medicine supply chains, to strengthen their resilience to ensure the availability of medicines. The framework draws upon hybrid simulation, supply chain resilience and medicine supply chain literature. The utility of the proposed framework is presented through the development of a case model of a generic (off-patent) case medicine in the Norwegian system to perform scenario-based experiments on disruption events and interventions. Two disruption scenarios are evaluated a demand shock e.g., hoarding, and a supply shock, e.g., a major disruption at a key supplier. The effect of these disruptions on the system without interventions is compared with proactive and reactive interventions, namely prepositioned stock, and flexible ordering. Future directions for framework development have been identified.

### **1 INTRODUCTION**

The medicine supply chain is vital (Ferner et al. 2019). Inadequate, missed or delayed treatment can lead to poorer patient outcomes and result in more costly outcomes for the wider society (Fox et al. 2014) yet medicine shortages globally are increasing (WHO World Health Organization 2018). Medicine supply chains are complex systems, as they are long fragmented, interconnected global systems, involving many actors, which can result in medicine shortages, due to a number of reasons including manufacturing issues, commercial withdrawal, medicine recalls and quality issues, availability of raw ingredients, increased demand, distribution problems (Pharmaceutical Services Negotiating Committee (PSNC) 2020).

In this paper we present a simulation study of interventions to ensure a stable supply of a generic medicine in Norway. A hybrid simulation modeling framework is proposed to evaluate the effect of alternative supply chain shortage interventions in response to various disruptions to support national decision making with respect to preparedness planning and emergency response. Section 2 summarizes selected medicine supply chain literature. In Section 3 we present a prototype model based on our proposed framework in accordance with the STRESS guidelines (Monks et al. 2018) and summarize the verification and validation process. Illustrative results are presented in section 4. In section 5 we discuss the contribution

and limitations of the modeling framework. Finally, section 6 concludes the paper and suggests how the modeling framework can be developed.

## 2 BACKGROUND

### 2.1 Medicine Supply Chains

Generic (off-patent) medicine shortages have been increasing in Europe in recent years and their causes are complex (Scholz 2020; DiPiro et al. 2021). They range from manufacturing problems, trade restrictions to unexpected peaks in demand. A potential reason for the increased shortages is that medicine supply chains (SC) are complex adaptive systems (CAS) (Choi et al. 2001) consisting of multiple interconnected decision makers interacting with each other and the external environment (Settanni et al. 2017; Azghandi et al. 2018; Papalexí et al. 2020). As CAS, they are subject to the bullwhip and ripple effects, which can lead to shortages. The bullwhip effect relates to production and inventory shortages due to demand and lead time fluctuations (Ivanov et al. 2014; Rasnick and Chatfield 2017) from which one can recover in the short term through coordination efforts (Sokolov et al. 2016). The ripple effect occurs when an initial disturbance to the system propagates outwards to disturb an increasingly larger proportion of the system (Ivanov et al. 2014) e.g., a major manufacturing error at a pharmaceutical production facility. Recovery from the ripple effect can take longer and require greater coordination and investment (Sokolov et al. 2016).

### 2.2 Supply Chain Resilience and Supply Chain Resilience Metrics

Robustness and resilience are important system states that help mitigate the effects of disruptions and uncertainty (Mackay et al. 2019). In this paper we adopt Behzadi et al. (2020) definition of SC resilience as the “ability to recover quickly and effectively from a disruption”. Robustness is the ability to absorb a shock, maintain the supply chain despite disruptions. Two key factors in resilient systems are 1) redundancy e.g. stock prepositioning which are only realized in the event of a disruption and 2) flexibility is building capabilities in the SC, that can identify threats and respond to them quickly improving performance in times of disruption and in general (Sheffi and Rice Jr 2005; Mackay et al. 2019). Mackay et al. (2019) proposed a typology of proactive and reactive redundancy and flexibility interventions, see Table 1.

Table 1: Proactive and reactive redundancy and flexibility interventions (Mackay et al. 2019).

Strategy	Type	Impact	Example
Insurance	Proactive redundancy	Increases robustness	Pre-positioning inventory
Expediting	Reactive redundancy	Increases resilience	Emergency orders
Strategic adaptive capability	Proactive flexibility	Increases both	Stress testing
Reconfiguration	Reactive flexibility	Increases resilience	Organizational flexibility

### 2.3 Medicine Supply Chain and Production Modeling

Settanni et al. (2017) review of medicine SC models from an operations research perspective highlighted that medicine SC modeling literature primarily focused on specific units within the SC. By focusing on a small number of supply chain echelons, rarely incorporating feedback between the echelons, and treating many aspects as deterministic, lacked a whole systems view.

Selected medicine SC models that examine drug shortage and resilience include Azghandi et al. (2018) who modeled the effects of saline product recalls considering different disruption patterns, with unlimited manufacturing capacity in the system and identical inventory policies at each echelon. Lücker and Seifert (2017) developed a mathematical model to evaluate the relationships between risk mitigation inventory, dual sourcing, and agility capacity, based on deterministic demand, at a single site in a single SC echelon.

A key paper by Tucker et al. (2020) developed two stochastic programs to examine incentive alignment in medicine SCs to reduce shortages, to configure the SC and determine the safety stock level. The model assumed, constant demand over the time horizon, drugs were produced by a single manufacturer, and each echelon component had identical disruption profiles and capacities.

## **2.4 Hybrid Simulation Modeling**

Hybrid simulation (HS) has been defined as the combination of at least two of the following methods discrete event simulation (DES), system dynamics (SD) and agent-based simulation (ABS) (Brailsford et al. 2019). Two key sectors identified in a review of HS are healthcare and SC as key sectors (Brailsford et al. 2019), as both sectors tend to exhibit a high level of complexity due to many interconnected aspects that a single model rarely manages to capture. The HS models reviewed typically used SD for population level aspects and DES or ABM for operational aspects such as service delivery, as illustrated in Umeda and Zhang (2008) SC HS model, which used DES to represent the operational processes, e.g. cross-docking, and SD to represent the strategic level issues, the management environment outside of a SC. HS is part of the wider field of hybrid modeling which utilizes the strengths of each of the modeling approaches to improve the modeling of CAS (Mustafee and Powell 2018).

This paper proposes a HS modeling framework to develop models to simulate medicine supply chains, from reusable model components, to understand the impact of different disruption events and interventions at different points in the system with respect to multiple metrics including resilience. We focus on resilience, the time it takes the system to recover, as it is key in a health critical SC when the system is no longer robust to a disruption(s). The proposed framework aims to capture the complexity of the system including feedback between the SC echelons, by modeling the individual components at the required level of detail as an integrated network. In section 3, we discuss the proposed framework and present an example case model.

## **3 METHOD**

### **3.1 Objectives**

The objective of the HS modeling framework is to produce models that can evaluate medicine SCs' resilience to disruptions. The models can evaluate existing interventions (prepositioned stock, export bans) and proposed interventions (flexible contracts e.g., prepositioned stock at suppliers) to mitigate the effect of disruptions, in terms of their severity and durations, at different supply chain echelons. The models help inform decision making by medicine SC actors on when and what types of interventions should be made to avoid or mitigate effects of shortages, hence improving both SC robustness and resilience.

#### **3.1.1 Model Outputs**

The framework currently captures a variety of parameters for agents, including, inventory levels, backlogs (outstanding orders), costs (holding, ordering, production, shortage, and manufacturing), and waiting times. Please note not all these parameters are captured in all agents, see 3.2.1 and 3.2.4 for more details.

#### **3.1.2 Experimentation Aims**

The experimentation aims are to evaluate the resilience of the medicine SC network for a case medicine to a variety of different disruption events. The example model based on a case medicine evaluates different disruption events. In this paper, scenario-based analysis is used to demonstrate the utility of this prototype model, the scenarios are presented and described in section 3.2.2.

### 3.2 Logic

#### 3.2.1 Base Model Logic

The key components of the HS modeling framework and the interaction between them is summarized in Figure 1. The input data for all the agents is discussed in section 3.3.

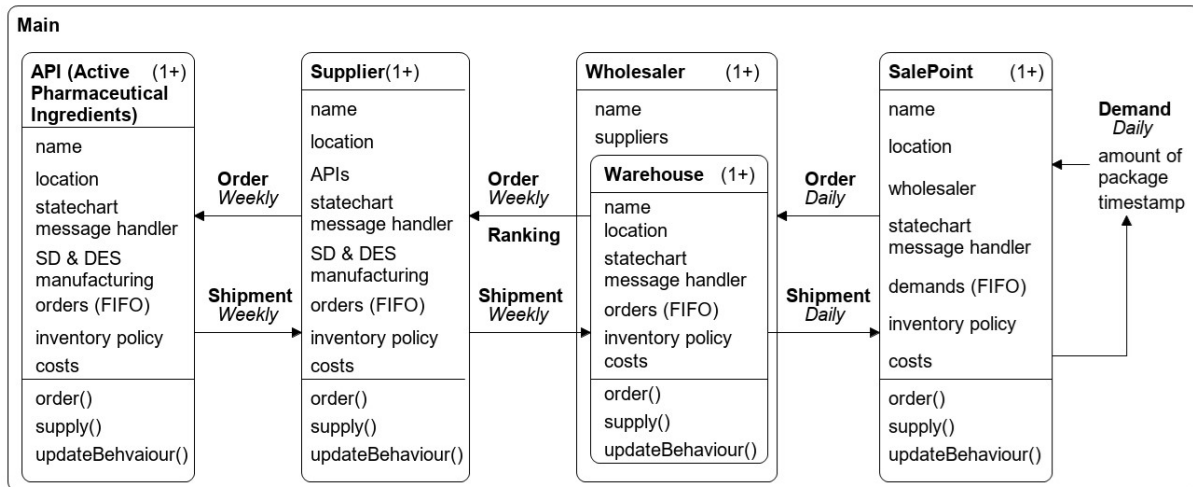


Figure 1: An overview of the HS modeling framework. Bold elements denote AnyLogic agents. High level variables and functions are stated. Queuing aspects of the model are signified by the First in First Out (FIFO) abbreviation. SD = System Dynamics. DES = Discrete Event Simulation.

The case model consists of five main agents i) SalePoint (Community and Hospital Pharmacies), ii) Wholesaler, iii) Warehouse, iv) Supplier and v) and Active Pharmaceutical Ingredients (API) producer, see Figure 2. The model contains 965 sale points, where demand for the packages of medicine is received and satisfied if sufficient inventory is available. Demand is generated stochastically daily, and all sale points are always open. If the demand cannot be satisfied the demand is added to the backlog and will be met when inventory is replenished. Sale points place orders to and receive shipments daily from their wholesaler’s warehouse with the shortest queue. Sale points operate a simple inventory policy consisting of a reorder point (ROP) and a quantity (Q) to order. Sale points record their inventory level, demand backlog, warehouse orders backlog, costs, demand history and warehouse order history.

The model contains three wholesalers which serve a cross-docking function ensuring that their sale points have sufficient stock to meet demand. Each wholesaler contains a variable to indicate the suppliers it can order from to replenish its warehouses, and a variable to indicate the warehouses it operates. The wholesaler is driven by the warehouses, each wholesaler has two, which operate in a similar way as sale points. The prepositioned stock is held at the wholesalers’ warehouses in this model and inventory management policy for the prepositioned stock mirrors the non-prepositioned stock inventory policy e.g. (ROP, Q). Prepositioned stock is only used if authorized to do so at an environment (Main) level, the highest level of the model where all agents are located, see Figure 1. Warehouses deliver to their sale points daily and place weekly orders at suppliers. The warehouses can split orders between multiple suppliers defined by a simple algorithm discussed in 3.2.3 and receives shipments from suppliers weekly. Warehouses record their inventory level (including prepositioned stock), sale point orders backlog, supplier orders backlog, costs, sale point order history and supplier order history.

The model contains three suppliers, who produce the case medicine, process orders received by and deliver weekly to warehouses. If the supplier has enough finished goods inventory on hand to satisfy the order the order can be satisfied and inventory shipped, otherwise the supplier transforms API, “raw

ingredients” into finished goods (inventory). This is represented as a hybrid SD-DES model, which will be described in section 3.2.4. Suppliers have a desired level of finished goods and raw ingredients they would like to maintain; they place orders from and receive shipments from the single API producer. Suppliers record their inventory level (raw ingredients and finished goods), production rates, warehouse orders backlog, API orders backlog, costs, warehouse order history and API order history.

The API producers are represented by a single agent as there is limited information about this part of the SC. The process of creating the API is represented in the model using a hybrid SD-DES model. The inventory levels and production rates (capacity) of the API agent is assumed large enough to meet the demand generated by the suppliers. The API producer receives orders from, and delivers shipments to, suppliers weekly. API producers record their inventory level (finished goods), production rates, supplier orders backlog, costs, and supplier order history.

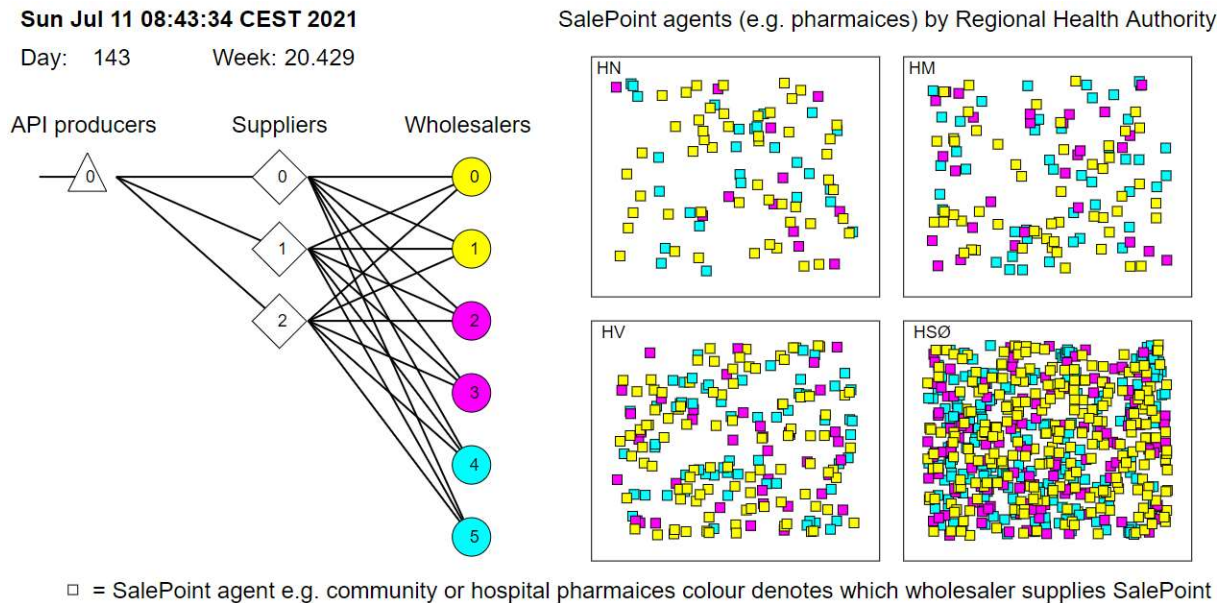


Figure 2: An overview of the prototype model. API producer = triangle. Supplier = diamond. Warehouse = circle. SalePoint = square. Colors denote which wholesaler the warehouse and sale point agents belong to.

### 3.2.2 Scenario Logic

The main agent in as show in Figure 1, is the environment in which the other agents (sale point, warehouse etc.) operate. Many of the events, ordering, shipping, etc. are initiated at the main agent and propagate through the model, the disruption events and interventions are controlled in the same way. Events are used to indicate the beginning and end of a disruption event and the changes to associated parameters to represent the disruption and the response. The illustrative hypothetical scenarios evaluated in this paper are provided in Table 2, based on the redundancy interventions summarized in Table 1.

Table 2: Illustrative scenarios disruption scenarios and proactive and reactive interventions.

Disruption	Base	Proactive redundancy	Reactive redundancy
<b>Demand increase</b> 80% increase (weeks 50-58)	<b>Demand 0</b> No interventions	<b>Demand 1</b> Prepositioned stock	<b>Demand 2</b> Flexible ordering
<b>Supply decrease</b> 90% decrease (weeks 50-58)	<b>Supply 0</b> No interventions	<b>Supply 1</b> Prepositioned stock	<b>Supply 2</b> Flexible ordering

The demand increase scenarios (Demand 0, Demand 1, Demand 2) the demand increases 80% for 8 weeks (56 days) before returning to its original level. This equates to an increase in sales from 26 to 46.8 sales/sale point/day, due to the demand arrival rate increasing from 20 to 36/day with an expected demand of 1.3 packages. The supply decrease scenarios (Supply 0, Supply 1, Supply 2) the production capacity of the primary supplier's SD production model reduces to 10% of its base value for 8 weeks (56 days), to simulate the effect of a major disruption e.g., a fire.

The interventions evaluated prepositioned stock (proactive redundancy) and flexible ordering (reactive redundancy) are implemented in the model using events. A Boolean variable authorizing the use of prepositioned stock is flipped from not authorized (false) to authorized (true) to indicate it can be used, and, at the end of the period the variable is set to false. The flexible ordering intervention enables wholesalers to place orders from two additional suppliers with undisrupted production capacities. The wholesalers split their order equally between the two undisrupted and the disrupted suppliers. The disruption scenarios and interventions begin on week 50 (day 350) and end on week 58 (day 406).

### **3.2.3 Algorithms**

Sale points and warehouses can see the internal operations of the agent they order from the warehouses and suppliers respectively. Each sale point examines the number of outstanding orders at each of the wholesaler's warehouses and places its order at the warehouse with the shortest queue of outstanding orders. The warehouse ranks all the available suppliers by the sum of the amounts of the outstanding orders plus the current order it would like to place divided by the supplier's capacity (production rate), the order can be split across a specified number of suppliers ranked in ascending delivery time.

### **3.2.4 Components and interaction**

The framework consists of 10 different agents, six: Main, SalePoint, Wholesaler, Warehouse, Supplier and API producer were introduced in section 3.2.1. The remaining four "Agents" Demand, Order, Ranking (of orders) and Shipment are passive entities that are passed between the other active agents, to facilitate interaction between the model components.

Demands are generated stochastically 24 hours a day (with an exponential interarrival rate of  $1/20 = 0.05$  days) at each of the model sale point agents. Demands contain the number of packages required (70% 1 package, 30% 2 packages), and a time stamp to record the time to satisfy the demand. Orders are passed from downstream echelons to upstream and contain information including origin, amount, recipient, a time stamp, and a flag to indicate if prepositioned stock can satisfy the order. Warehouses use a simple algorithm to rank suppliers prior to splitting an order between a defined number of suppliers, see section 3.2.3. Shipments record the amount of inventory (API or packages of medicine), shipped between upstream to downstream agents in the model and a flag to indicate if the shipment is from prepositioned stock.

The API producer and the suppliers use SD-DES to represent the production processes, of APIs and transformation of API to finished products, and order processing respectively. Figure 3 illustrates the mechanics of the supplier agent. Suppliers receive orders via the ABM state chart mechanism, which are added to the DES model toProcess queue. The DES model captures the queuing nature of order processing. The order progresses to the processing activity where it will remain until sufficient packages are available in the SD production model (finishedGoods stock). In the SD model, when there are enough packages to satisfy the order packages are removed from the finishedGoods stock and added to the Processed stock, and in the DES model the processing activity is complete and the order progresses to the toShip queue. In the DES, the orders that can be shipped (toShip queue) are sent to the agent that placed the order as a shipment weekly, the order is then moved to the shipped queue and, in the SD model the Processed stock is reduced by the amount shipped. An AnyLogic event monitors the finishedGoods stock level hourly, in the SD model and ends the delay for orders in the DES processing activity accordingly. Supplier also place orders to, and receive API from, the API producer through the sending of messages (orders and shipments) via state charts.

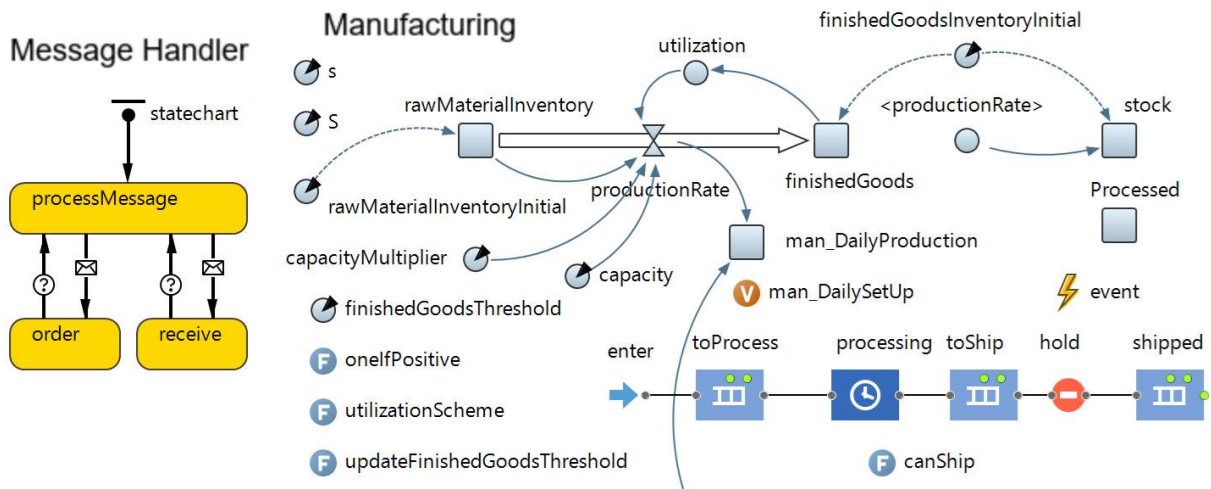


Figure 3: Supplier agent. ABM state charts are used to receive orders and goods and to place orders. SD used to represent continuous production process. DES used to represent order processing.

### 3.3 Data

#### 3.3.1 Data Sources

The data is primarily based on interviews with key Norwegian medicine SC stakeholders and publicly available sources. We are in the process of obtaining quantitative sales data to validate the model. Data relating to the structure of the system and hypothetical data relating to parameter values are used to illustrate the proposed use of the framework to a case medicine.

#### 3.3.2 Input Parameters

The model is driven by the sale point, warehouse, supplier, and API producer agents. The model contains 995 sale points distributed as follows wholesaler 1 = 426, wholesaler 2 = 183, wholesaler 3 = 310 and 76 independent sale points. The inventory policy parameters for all agents are presented in Table 3. The number of sale points per wholesaler were used to estimate the inventory policy parameters for the wholesalers' warehouses. Each wholesaler has two warehouses, and the demand is split equally between the two. The number of weeks inventory and prepositioned stock held at the warehouses are 3 and 6 weeks.

Table 3: Agent inventory parameters. p = packages. w = per warehouse each wholesaler has two.

	Sale Point	Wholesaler 1	Wholesaler 2	Wholesaler 3	Suppliers	API producer
Demand/Day <sup>p</sup>	26	11,076	4,758	8,060	14,435	7,217
Inventory Period (days)	7	21	21	21	30	60
Wholesaler Demand <sup>p, w</sup>		232,596 (116,298)	99,918 (49,959)	169,260 (84,630)		
Lead time (days)	1	7	7	7	7	7
Reorder point (ROP) <sup>p</sup>	26	38,766	16,653	28,210	101,042	50,521
Order quantity (Q) <sup>p</sup>	182	116,298	49,959	84,630	433,038	433,038
Prepositioned Stock <sup>p, w</sup>		232,596	99,918	169,260		

### **3.3.3 Assumptions**

Only key assumptions for the driving agents, sale point, warehouse, supplier, and API producer are mentioned here due to space constraints. Sale points are assumed to always be open; they have the same inventory parameter settings; they can see the queue size at the warehouses to select where to send their order to. Warehouses can see the outstanding orders and the capacity (production rate) of each supplier when deciding how to rank the suppliers. Warehouses can order from different suppliers each time they order, and they supply sale points on a FIFO basis. Suppliers can produce continuously if necessary, there are no disruptions to the production process other than the lack of raw ingredients to transform into finished goods, and they only provide goods to the wholesalers in the model. The API producer has an exogenous source of all the consumables and materials needed to produce the API, there are no disruptions to the production process, and it has enough capacity to satisfy the demand received from the suppliers.

## **3.4 Experimentation**

### **3.4.1 Initialization**

The initial parameters for the four main agents, sale point, warehouse, supplier, and API are initialized on startup, see section 3.3.2. The model is a terminating system with no warmup period. The disruption events assessed in the model occur in week 50 (day 350), the model exhibits some initial fluctuations in the initial ~60 days but settles into an equilibrium, thereafter, suggesting that it is sensitive to initial conditions. The model runs for 5 years, in days, and the time step for the SD components is 0.01 days.

## **3.5 Implementation**

The model was constructed in AnyLogic 8 Personal Learning Edition 8.7.3, Build: 8.7.3.202103181427 x64. Random sampling in AnyLogic utilized `java.util.Random`. Pre and post hoc analysis of input data and model data was undertaken in RStudio (Version 1.4.1106). R version 4.0.4 (2021-02-15) -- "Lost Library Book", Platform: x86\_64-w64-mingw32/x64 (64-bit). An experiment consisting of 50 replications takes ~1700-1900 seconds to run on a Windows 10, 64-bit, Intel® Core™ i5-8265U CPU @ 1.60GHz 1.80 GHz, 8.00 GB RAM. AnyLogic utilizes parallel processing.

## **3.6 Code Access**

The data and the model that support the findings of this study are available from the corresponding author, [JV], upon reasonable request. Please note that this is a proof-of-concept model and is under development.

## **3.7 Verification and Validation**

Extreme value tests, structured walk throughs, utilizing the visualization aspects of the model, and traces were used to validate the model, but given that the model is based on hypothetical data derived from qualitative interviews and publicly available reports, it is a challenging model to verify and validate. The hybrid nature of the model requires that the interfaces between paradigms needs to be validated.

## **4 ILLUSTRATIVE RESULTS**

Two disruption scenarios have been investigated, see Table 2 and section 3.2.2. The aggregate inventory levels for the suppliers, wholesalers' warehouses and sale points agents are provided in Figure 4 for the demand increase scenario (hoarding) and Figure 5 for the supply decrease scenario (major disruption at main supplier). The grey vertical lines in Figure 4 and Figure 5, represent the disruption and intervention period.



In the demand increase scenario Figure 4, if no intervention is activated (left column) the aggregate sale points inventory dropped to zero and took considerable time to recover to pre disruption levels (Demand 0 – Sale Points) due to production capacity constraints at the single supplier. The increased demand was satisfied by the prepositioned stock intervention (middle column, Demand 1 – Prepositioned stock), avoiding shortage at the sale points. The prepositioned stock took considerable time to return to the pre disruption level, due to the aforementioned supplier constraint. The flexible ordering intervention (right column), enabled wholesalers to split their orders equally across three suppliers, resulting in an increase of aggregate suppliers’ inventory as two redundant suppliers started production (Demand 2 - Suppliers) in response to the increased demand, which takes time to produce. The use of redundant suppliers reduced the time that aggregate sale points inventory was zero and the recovery time to pre disruption levels (Demand 2 – Sale Points).

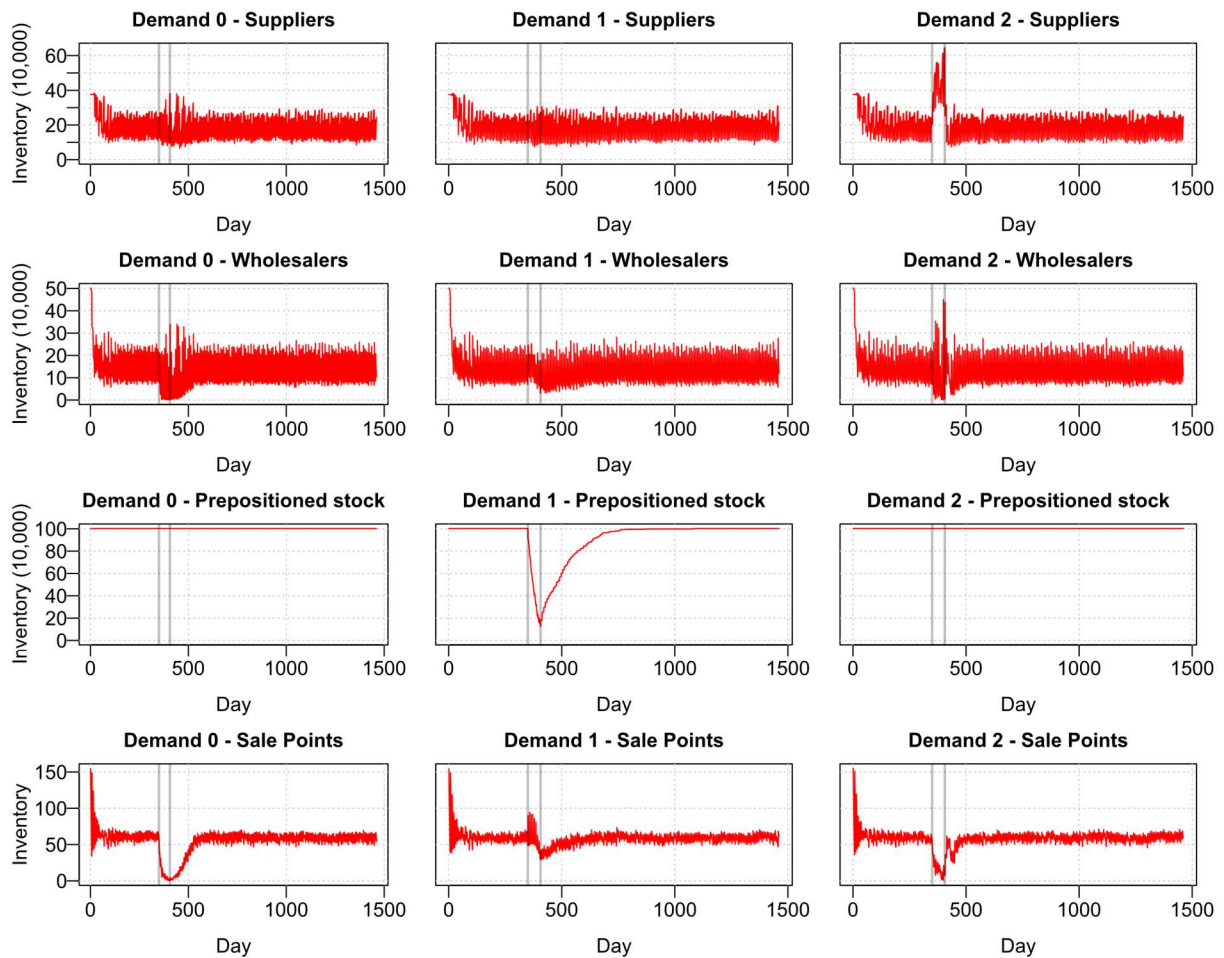


Figure 4: Demand increase results. Mean aggregate daily inventory level (50 model runs) by agent. Columns: Left = base. Middle = prepositioned stock intervention. Right = flexible ordering intervention.

In the supply decrease scenario Figure 5, if no intervention is activated (left column) all levels of the system are affected apart from the preposition stock. The aggregate sale points inventory drops to zero and the aggregate wholesale inventory drops substantially, as the main single supplier is running at reduced capacity and this ripples through the system. The prepositioned stock intervention (middle column) shields the sale points from the disruption (Supply 1 – Sale Points). The flexible ordering intervention (right

column) is effective at mitigating the disruption, by covering the supply lost from the main supplier via the additional two non-disrupted suppliers (Supply 2 – Suppliers) and the inventory in at the wholesalers (Supply 2 – Wholesalers).

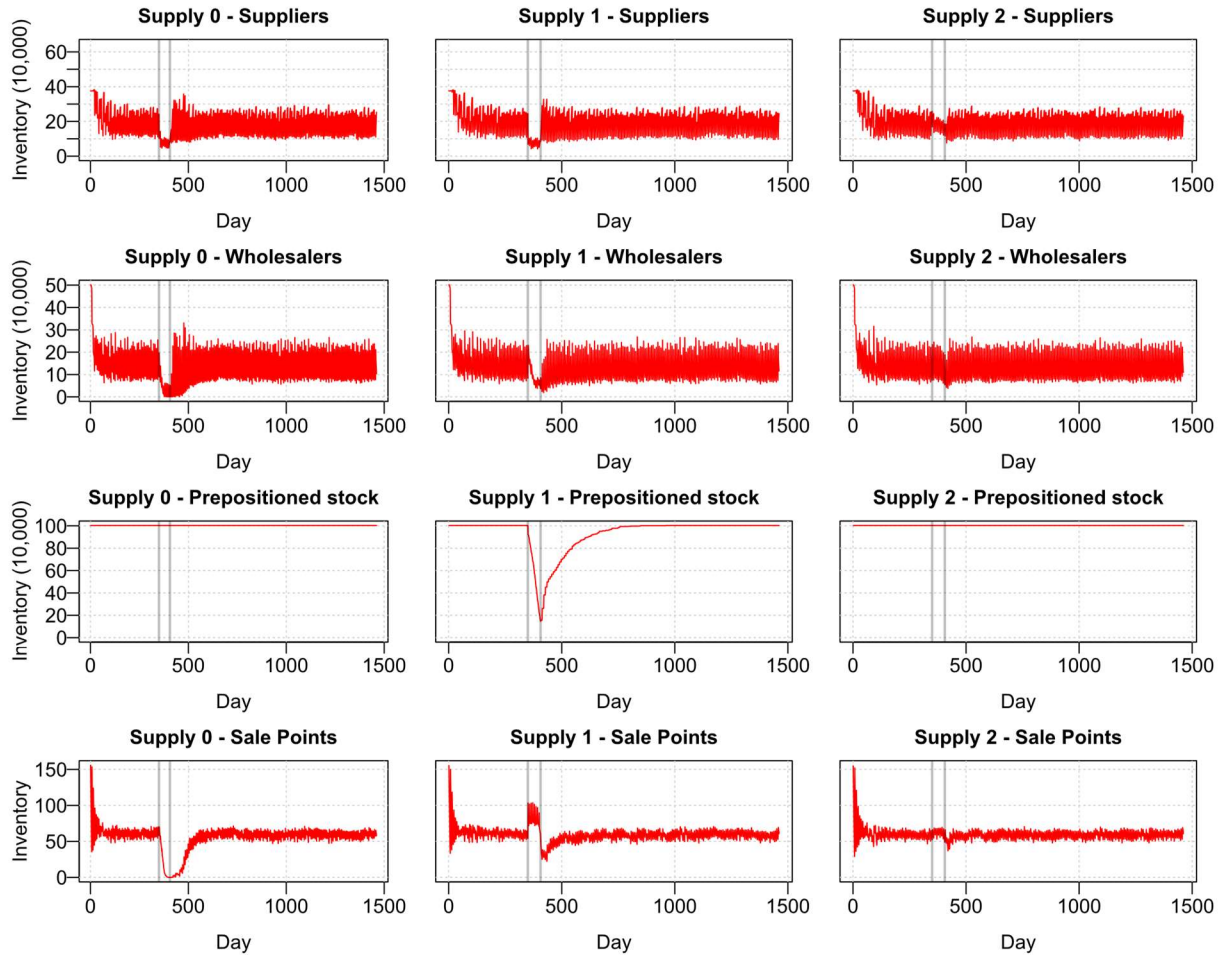


Figure 5: Supply decrease results. Mean aggregate daily inventory level (50 model runs) by agent. Columns: Left = base. Middle = prepositioned stock intervention. Right = flexible ordering intervention.

The model results suggest that the modeled SC is capable of absorbing and recovering from the examined disruptions, when interventions are implemented. Prepositioned stock is effective, but expensive given the associated costs, e.g., storage and wastage. The model suggests that it would take considerable time to replenish prepositioned stock following both disruptions, leaving the system vulnerable to subsequent disruptions.

## 5 DISCUSSION

The proposed HS modeling framework enables the evaluation of several SC disruption events and proactive and reactive interventions deployed to manage them. Through the proposed approach, different medicine SC network HS models can be constructed quickly, through the reuse of model components representing different SC actors which can be parameterized as needed, based available data.

Simple example scenarios were presented due to the uncertainty associated with the model parameters and the early stage of the framework development. The framework is designed so that any number of disruption events and interventions could happen concurrently, but care needs to be taken, when designing experiments, and these need to be discussed and agreed with model stakeholders, this is the subject of ongoing research.

The simple resilience measure illustrated through the inventory plots is the time it takes the system to return to its prior non-disruption state. Numerous SC resilience definitions and frameworks exist, the developed model can examine alternative resilience and robustness measures. We need to carefully consolidate the existing literature and select the most appropriate measure(s) for our needs.

The case model presented has several limitations. It is based primarily on hypothetical data and would benefit greatly from the identification and inclusion of historical quantitative data. HS models can be difficult to validate due to the interaction of multiple simulation paradigms across multiple agents, and the model needs to be verified and validated with many stakeholders, including Norwegian medicine SC stakeholders and the members of the research team. The model makes several simplifying assumptions, section 3.3.3, which need to be carefully considered as the framework develops. Finally, the model run time is too long and the code needs to be made more efficient to enable more effective experimentation.

## 6 CONCLUSIONS AND FUTURE WORK

The goal of the proposed HS modeling framework is to improve the understanding and operation of medicine SCs, with the capacity to incorporate adaptive behavior at specific supply chain actors or system wide. Model components, described in this proposed HS modeling framework, can be reused to represent alternative medicine SCs demonstrating the flexibility of the framework. There are several areas for future work that would improve the case model including, obtaining historical quantitative data to validate the model with stakeholders and to verify the model's design. Extensive sensitivity analysis is planned to validate the case model and identify the key parametric and structural parameters in the model. Many of the HS modeling framework agents can adapt their inventory policy in response to the dynamics of the system, this capability needs to be fully tested and implemented. The case model contains cost parameters for each of the agents, relating to inventory, ordering and where appropriate manufacturing, but these are not populated due to lack of data. The costs of potential interventions must be considered, the cost of prepositioned stock is straightforward to calculate as it is primarily, the ordering and holding costs, but the costs of substitution, rationing, and other interventions are less clear. These factors are vital for cost-effective analysis of SC network configurations. Costs are key in agents' decisions from sale points through to API producers to remain in the market. It may be possible to incorporate game theoretic and econometric methods to represent this dynamic, but we need to consider what it adds to the HS modeling framework. Finally, we plan to use design of experiments and simulation optimization approaches, to explore solution spaces more efficiently.

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