Proceedings of the 2023 Winter Simulation Conference
C. G. Corlu, S. R. Hunter, H. Lam, B. S. Onggo, J. Shortle, and B. Biller, eds.

EFFECTS OF TIMING OF AGENTS' REACTIONS IN PHARMACEUTICAL SUPPLY CHAINS UNDER DISRUPTION

Rozhin Doroudi
Ozlem Ergun
Jacqueline Griffin

Department of Mechanical
and Industrial Engineering
Northeastern University
360 Huntington Ave
Boston, MA 02115, USA

Stacy Marsella

Khoury College of Computer Sciences
Northeastern University
360 Huntington Ave
Boston, MA 02115, USA

ABSTRACT

Disruptions in the supply chain network can have significant and far-reaching consequences, especially in pharmaceutical supply chains that affect health and financial outcomes and raise equity concerns. To inform strategies that can address this critical global problem, we study disruptions in pharmaceutical supply chains using multiagent simulations. These simulations include decision-theoretic agents with a theory of mind reasoning that allows them to reason about the other agents in the supply chain, including their trustworthiness. The simulations reveal how supplier-buyer interactions have non-local effects which can exacerbate and extend disruption impacts. In addition, a distributor's focus on its own short-term profit can lower its long-term profit and damage equity in health centers. We also demonstrate how agents adapt to changes in the environment and changes in other agents' behavior and how in the absence of explicit communication and coordination, the timing of these adaptations inhibits disruption mitigation efforts from transpiring.

1 INTRODUCTION

With globalization, supply chains have become critical to the health of the national and world economies. Supply chain disruptions are ubiquitous and pose severe challenges by reverberating throughout the supply chain, causing hardship for extended periods of time. This is especially true in pharmaceutical supply chains since these disruptions result in drug shortages which can have significant consequences in terms of their impact on patients' health outcomes and their financial impact on pharmaceutical supply chain stakeholders. The impact of drug shortages has been reported across the globe, including in the United States, Canada, Australia, and across Europe ((Hantel et al. 2019); (Lynas 2013); (Tan et al. 2016); (Pauwels et al. 2015)). While drug shortages have been going on for decades in the United States, shortages of medicines and healthcare supplies during the COVID-19 pandemic have further highlighted the criticality of supply chains which are robust to disruptions, demonstrating the importance of studying disruptions in pharmaceutical supply chains (McCarthy 2020). Reports from the American Society of Health-System Pharmacists (ASHP 2023) show that the drug shortage in the United States continues. A recent survey of oncology pharmacists (McBride, Hudson-DiSalle, Pilz, Hamm, Boring, Buie, and DeRemer 2022) reported that about sixty-four percent of these sixty-eight US organizations that participated in the survey encountered a minimum of one drug shortage each month. The implications of these shortages are the complication of care for cancer patients, delay in treatment, increased risk of a medication error, and impeding research and clinical trials. The authors emphasize the need for a more robust supply chain to resolve these issues. Similar recent surveys of the impact of sterile injectable drugs (ASHP 2022) and Amoxicillin (Cohen, Pettoello-Mantovani, Giardino, Carrasco-Sanz, Somekh, and Levy 2023) indicate that drug shortages continue to be a severe issue endangering public health and financially burdening the healthcare system.

In this work, we study disruptions in pharmaceutical supply chains using multiagent simulations with boundedly-rational decision-theoretic agents playing the roles of manufacturers, distributors, and health centers (Figure 1). Since manufacturing disruptions are frequent drivers of pharmaceutical shortages according to (ASHP 2023), we examine a supply chain that faces a manufacturing disruption for a limited time. This disruption results in shortages of products at the distributor level. The distributor that faces this shortage, in turn, must make rationing decisions to maximize its profit, while the health centers which receive products from this distributor adapt to these changes by dynamically updating a trustworthiness measure they attribute to their distributors. Trustworthiness is defined differently according to the context in which trust-building interactions occur. Here we define trustworthiness as the ability of the supplier to provide the promised amount of product at the promised time. This definition is consistent with standard performance-based supplier selection metrics (Choi and Hartley 1996).

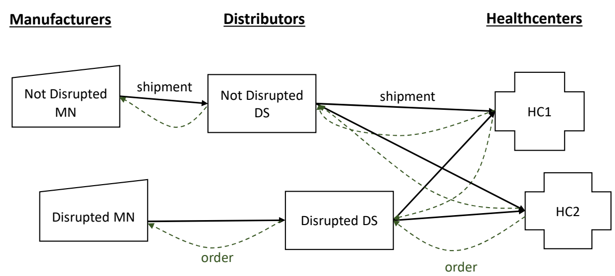


Figure 1: Graph showing the network structure of supply chain.

A key element of the simulation is that the agents can have beliefs about the beliefs and goals of the other agents in the network, a capacity for Theory of Mind reasoning (Pynadath and Marsella 2005), using a recursive modeling approach (Gmytrasiewicz and Durfee 1995) that informs their decisions. Since the supply chain of focus is a pharmaceutical supply chain and, therefore, part of a more extensive healthcare system, we consider, in addition to profitability, equity among health centers, i.e., equitable distribution of pharmaceutical drugs among health centers. Equity affects access to care for the patients that these health centers are serving (Dawes 2016).

Using this simulation, we specifically explore how the timing of agents' adaptations in behaviors can affect the effectiveness of disruption mitigation efforts by each supply chain agent. Health centers use a trustworthiness measure to decide how much to order from each distributor. They adapt to changes in the amount of products delivered to them by updating this trustworthiness measure. On the other hand, the distributor, which faces a shortage in product due to manufacturing disruption, switches back and forth between preferring each of the health centers to maximize its projected profit over its planning horizon. This results in disparities between health centers which hurts the system's equity. In addition, due to lead times and temporal aspects of disruptions, these shortsighted adaptations by health centers and the distributor can exacerbate the disruption's impact.

We exhibit that the supply chain benefits from this coordination under scenarios where health centers' timing of increasing and decreasing their order amount is better coordinated with the distributor's readiness to satisfy their demands on time. While this implicit coordination through reacting to a shortage of product can help mitigate disruption impacts, without explicit communication, this coordination may not transpire. In some cases, these shortsighted adaptions can exacerbate the situation. In addition, we study how disruption characteristics, including temporal characteristics of the disruption, interact with the timing of mitigation efforts by supply chain agents, which is critical for informing impactful response policies.

Authors in (Sen 2013) identified that the four main components of a comprehensive trust management scheme are evaluating, establishing, engaging, and using trust. Our study considers evaluating and using trust in the supply chain context. We define trust similarly to (Kim 2009) and (Jalbut and Sichman 2019). The authors in (Kim 2009) and (Jalbut and Sichman 2019) use a Beer Game framework (Forrester 1997) to study trust dynamics in a supply chain. While (Kim 2009) investigates the emergence of collaboration due to the existence of trust, (Jalbut and Sichman 2019) study trust-based supplier-buyer relationships compared to price-based interactions and conclude that communication and honesty help in developing trust-based relationships in the supply chain. An important differentiation of our work with the above-mentioned trust studies is that supply chain agents are provided with a Theory of Mind (ToM) reasoning capability. These agents have a model of other agents' behaviors in addition to a model of the environment. Thus, an agent can reason about how the other agents would react to its decisions and how the whole supply chain environment evolves due to all agents' decisions. Researchers in (Doroudi et al. 2020) also considered trust dynamics when supply chain agents are endowed with ToM reasoning capabilities. However, they considered a simpler trustworthiness update mechanism and looked at the supply chain performance from a profitability perspective, but we look at the supply chain performance from an equity perspective too.

The remainder of the paper is as follows, first we describe our simulation modeling framework including the network structure and the agent modeling, this is followed by experiment design and description of different scenarios studied. We discuss the experiments' results and conclude the paper with some recommendations and suggested future research.

2 SIMULATION MODELING FRAMEWORK

In this paper, we consider a pharmaceutical supply chain network that consists of three different echelons, manufacturers, distributors, and health centers, as shown in Figure 1. We use the multiagent simulation framework developed by (Doroudi et al. 2018) to model this supply chain network. In our work, decision-makers are PsychSim agents (Pynadath and Marsella 2005), or artificial decision-makers who possess a mental model of the supply chain environment and recursive modeling of other decision-makers, something in line with 'what I think you think.' This recursion can extend to include two levels of recursion, such as 'what I think you think that I think.' However, empirical studies showed that human subjects use one or at most two levels of reasoning (Doshi et al. 2010). (Hedden and Zhang 2002) showed that humans usually use first-level recursive models in more complex settings. Second-level recursive models provide no significant benefit while increasing the computational complexity of the problem significantly (Ficici and Pfeffer 2007). Since a supply chain setting is a complex environment, in our models, when an agent performs Theory of Mind (ToM) Reasoning, it uses one recursion level.

2.1 Actions Available to Agents

Supply chain agents perform some actions simultaneously and without explicit communication at each simulation iteration, as shown below:

1. Receive shipment from upstream agents (receive produced products)
2. Update inventory level and outstanding order level (in-production level if manufacturer)
3. Allocate product to downstream agents, backlog the demand if inventory at hand is not enough
4. Update inventory level and backlog level
5. Receive demand from downstream agents (from patients if health center)
6. Calculate order amount (production amount if manufacturer)
7. Order from upstream agents (start producing the product if manufacturer)

For some of these steps, allocation (step 3), production and order amount calculation (step 6), and ordering to upstream agents (step 7), PsychSim agents use decision rules which are commonly used in supply chain literature (Simchi-Levi et al. 2008).

Manufacturer agents have one rule for determining the production amount. They use a base-stock rule, defined in Eq. 1, for this action. P_t is the amount of product that needs to be produced at each period. D_t is the order amount of the downstream agents at time t. B_t is the backlog level of the agent at time t. I_t is the manufacturer's inventory level at time t, and Q_t is the product in-production at time t.

$$P_t = D_t + B_t - I_t - Q_t \tag{1}$$

Distributors need two decision rules, one for calculating the order amount from the upstream manufacturer and the other for allocating products to downstream health centers. They use a base-stock rule, provided in Eq. 2, to determine their order amount. In this equation, O_t is the quantity of product they should order at each time period t. S_t is the amount that has been ordered from upstream agents but has not been received yet. For allocation, two decision rules are available, either to allocate proportionally to the demand of the health centers (proportional rule) or to prefer one health center over the other (preferential rule). In the preferential rule, the distributor first satisfies the demand of the preferred health center and then satisfies the demand of the other health center from the remaining inventory.

$$O_t = D_t + B_t - I_t - S_t \tag{2}$$

Health centers need two decision rules, an order amount decision rule, similar to distributors, they follow a base-stock decision rule (Eq. 2), and an order splitting rule, which determines how much of this calculated order amount is assigned to each of the upstream agents. Health centers split their order amount proportional to the distributors' trustworthiness measure (explained in the next subsection).

At each simulation iteration, health center agents must treat a certain number of patients. These patients can be backlogged; other supply chain echelons can also backlog their demand. Backlogging demand results in a large cost stemming from endangering patients' health by delaying their care at the health center echelon and losing trust or credibility at the distributor and manufacturer echelons. The inventory cost is assumed to be smaller than the backlog cost. Allocating product to downstream agents or patients has an associated revenue. The manufacturer agents in this simulation may experience a disruption resulting from machine breakdowns, supplier uncertainty from supplier bankruptcy, or natural disasters. The disruption reduces the manufacturer's production capacity for a limited duration of time.

2.2 Trustworthiness Measure

At each time period, depending on the amount of product they actually receive from their distributors and the amount of product they expect to receive from that distributor, health centers update a trustworthiness measure attributed to the distributors according to Eq. 3.

$$T_{h,d,t} = \begin{cases} (1-\delta_g)T_{h,d,t-1} + \delta_g D_{h,d,t}, & \text{if } D_{h,d,t} \geq T_{h,d,t-1} \\ (1-\delta_l)T_{h,d,t-1} + \delta_l D_{h,d,t}, & \text{if } D_{h,d,t} < T_{h,d,t-1} \end{cases} \tag{3}$$

In this equation, $T_{h,d,t}$ is the trustworthiness measure that health center h associates to distributor d at time t. $D_{h,d,t}$ is the delivery rate of distributor d to health center h at time t, which is the ratio of what health center received from distributor d and what health center expected to receive from this distributor. δ_g and δ_l are sensitivity factors that determine how quickly the health center reacts to any change in the distributor's delivery rate. δ_g is the rate at which health centers gain trust in a distributor, thereby increasing the trustworthiness metric. δ_l is the rate at which health centers lose trust, or decrease, the trustworthiness they attribute to the distributor. Researchers argue that these two factors can differ, see (McKnight and Chervany 1996) and (Ebrahim-Khanjari et al. 2012). As is shown in the experiments, this trustworthiness update governs the timing of switching orders between distributors when the health center perceives changes in the delivery rates of the distributors. The initial value for the trustworthiness measure is **1** at the beginning of the simulations and gets updated according to Eq. 3. When health centers use this trustworthiness measure to split their orders, the order amount of health center h to distributor d, $O_{d,t}$, is calculated according to Eq. 4, where D is the total number of distributors.

$$O_{d,t} = (T_{h,d,t} / \sum_{r=1}^{D} T_{h,r,t}) * O_t \tag{4}$$

2.3 Metrics

In order to measure the supply chain performance in different scenarios, we define two performance metrics. The first metric is the supply chain agent's profit which is calculated as revenue from allocating products to downstream agents minus inventory holding and backlog costs according to Eq. 5. This metric is defined similarly across all echelons.

$$\sum_{t=1}^{N} (r_a A_t - c_h I_t - c_b B_t) \tag{5}$$

In Eq. 5, r_a is the per unit product revenue. A_t is the amount of product allocated to the downstream agent at time t. c_t is the inventory holding cost per unit product. I_t is inventory level of the agent at time t, c_b is backlog cost per unit product. B_t is the backlog level of the agent at time t. N is the duration of the simulation. The second metric measures the equitable distribution of products among health centers. The *disparity* metric specifically measures the gap between the backlog levels of the health centers (Eq. 6).

$$(MaxBl - MinBl)/MinBl * 100 \tag{6}$$

where $MaxBl$ and $MinBl$ are the maximum and minimum of the total patients backlogged by health centers, respectively.

3 EXPERIMENT DESIGN AND RESULTS

3.1 Experiment Design

The structure of the supply chain network in all of the following scenarios is shown in Figure 1. Each simulation run in these scenarios has a duration of 250 periods. At time period 70, one of the manufacturers (*Disrupted MN*) faces an unexpected disruption that reduces its production capacity. The patient demand stays constant throughout all scenarios, 120 units per period. However, distributor and manufacturer demands are changing due to changes in trustworthiness measures. The cost structure across all echelons is assumed to be the same, with a cost of 10 for backlogging each unit of demand, a per-unit-period inventory cost of 1, and a per-unit product revenue of 5. We assume that both the information and replenishment lead times are one period. *Disrupted DS* is the only agent endowed with ToM reasoning capabilities. It has a perfect model of goals, states, and actions of other agents but no model of disruption. In addition, it has a planning horizon of 6 periods (planning horizon is defined as the number of rounds of simulation that the agent considers when it performs ToM reasoning). This is the minimum planning horizon needed for *Disrupted DS* to see the effect of its immediate action due to the three echelons and 1-period information and replenishment lead times. *Disrupted DS*, maximizes its finite-horizon discounted profit over this 6-period planning horizon when performing ToM reasoning. The decisions to consider constant demand and deterministic disruption profile and lead time were deliberate, aiming to isolate the behavioral changes resulting from a reduction in product supply within the supply chain.

In scenarios 1 and 2, similar to (Jalbut and Sichman 2019) and (Kim 2009), we consider a symmetric trustworthiness update mechanism where the rate at which health centers lose and gain trust is the same. In scenario three we consider a more realistic case with an asymmetric trustworthiness update mechanism, in which rates of losing and gaining trust differ. In the final scenario, we examine a setting with a disruption with different characteristics compared to the first three scenarios to examine how the disruption characteristics impact agents' interaction dynamics.

3.1.1 Scenario 1 - Low Sensitivity Factor

In this scenario, at time period 70, one of the manufacturers faces a disruption (*Disrupted MN*), and its per period production capacity will decrease to 83% of its original per period production capacity. This disruption lasts for 50 periods. Both health centers have a low *sensitivity factors* of $\delta_g = \delta_l = 0.025$. *Disrupted DS* has three actions available, i.e. prefer *HC1* to *HC2*, prefer *HC2* to *HC1* or allocate proportionally with respect to their demand. When the disruption happens, *Disrupted DS* has limited inventory and decides how to ration this limited inventory among the health centers. After a few periods from the start of the disruption, *Disrupted DS* projects that it is more profitable to prefer one of the health centers to the other (since both health centers are the same, it does not matter which one) compared to allocate proportionally among them. This preferential treatment of one of the health centers results in a disparity between the number of patients backlogged by the health centers. When we run 50 simulations, we observe that, as shown in Figure 2(a), this disparity can be as large as about 50% between the health centers.

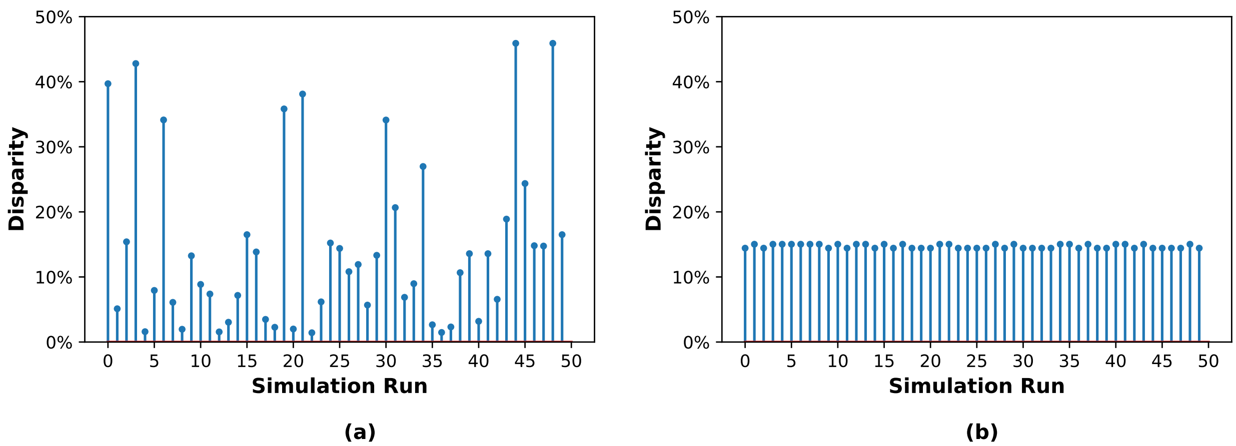


Figure 2: Disparity in number of patients backlogged among health centers, when sensitivity factor (a) $\delta_g = \delta_l = 0.025$ and (b) $\delta_g = \delta_l = 0.5$.

Suppose we enforce *Disrupted DS* agent to always allocate proportionally among the health centers and repeat the 50 simulation runs. In that case, we observe that this can close the disparity gap and increase profit of *Disrupted DS* and the health centers, see Table 1.

Table 1: Percentage of change in agents' profit when *Disrupted DS* is always allocating proportionally compared to when it selects an action which maximizes its profit.

Agent	Percentage of Profit Change
Both health centers	7.57
Not-Disrupted DS	0.19
Disrupted DS	17.17
Not-Disrupted MN	0.37
Disrupted MN	13.07
Supply Chain	7.05

Under the conditions of this scenario, the *Disrupted DS* selects actions that maximize its projected profit over its planning horizon, but this results in lower long-term profit over the simulation. Therefore, if *Disrupted DS* has this information about how allocating proportionally can result in higher long-term profit, it is incentivized to stick to this action, and the system becomes more equitable. Does this mean that when *Disrupted DS* faces disruption, it is always beneficial for *Disrupted DS* to allocate proportionally among the health centers? In order to answer this question in the following scenario, we study more reactive health centers to see how these dynamics play out under a different kind of behavior from health centers.

3.1.2 Scenario 2 - High Sensitivity Factor

This scenario's setting is very similar to scenario 1's, except that in this scenario health centers are more reactive to changes in the on-time delivery rate of the distributors. This is reflected in both health centers having higher sensitivity factors of $\delta_g = \delta_l = 0.5$. Similar to the previous scenario, after a few periods of disruption, the *Disrupted DS* projects preferring one health center to the other is more profitable than allocating proportionally among them. This change in the allocation scheme of the *Disrupted DS* leads to a disparity between the health centers. As shown in Figure 2(b), this disparity is not as significant as the previous scenario, but there still exists a disparity of about 15% between the health centers. First, let us clarify why the disparity is lower in this scenario, and then we try to close this disparity gap by requiring *Disrupted DS* to always allocate proportionally among health centers.

In this scenario, health centers are more reactive to *Disrupted DS* preferences. Since they react faster to these selections, this reflects in *Disrupted DS*'s projected profit over its ToM planning horizon. In other words, *Disrupted DS* can see that it cannot overwhelmingly prefer one health center to the other without damaging its projected profit. The reason behind this is that the health center which did not receive preferential treatment will immediately switch to the other distributor, and in the next period *Disrupted DS* needs to give it preferential treatment not to lose its demand. Thus *Disrupted DS* will be more equitable toward the health centers by switching between preferring one to the other and never overwhelmingly preferring one of the health centers, in other words, this reactivity of the health centers drives a more equitable behavior from the *Disrupted DS*.

Similar to scenario 1, if we limit available actions of *Disrupted DS* only to allocate proportionally, we can see that the disparity gap closes. However, this results in a considerable decrease in *Disrupted DS*'s profit and even a decrease in health centers' profit as seen in Table 2. When we have health centers with higher reactivity, limiting *disrupted DS* to allocate proportionally is unreasonable since we limit its ability to respond and adapt to these reactive health centers. Therefore, when the health centers are reactive, there seems to be a trade-off between profitability and equity. Based on results from scenario 1 and 2, we observe that the sensitivity factor of health centers plays an essential role in driving equitable behavior from the *Disrupted DS* and also the profitability of the overall supply chain. In the following scenario, we study a more realistic trustworthiness update for the health centers and take a deeper look at how sensitivity factors govern the timing of health centers' reactions and how this timing impacts equity and profitability.

Table 2: Percentage of change in agents' profit when *Disrupted DS* is always allocating proportionally compared to when it selects an action which maximizes its profit.

Agent	Percentage of Profit Change
Both health centers	-4.32
Not-Disrupted DS	-1.48
Disrupted DS	-23.31
Not-Disrupted MN	-0.66
Disrupted MN	-40.41
Supply Chain	-5.04

3.1.3 Scenario 3 - Asymmetric Trustworthiness Update

In this scenario, we consider different sensitivity factors for when the health center agents are losing their trust and gaining trust, i.e. $\delta_g \neq \delta_l$. It is reasonable to assume that negative interaction between suppliers and buyers affects a decline in trustworthiness at a higher rate compared to the rate trustworthiness recovers after a positive experience. Therefore, we consider a sensitivity factor $\delta_l = 0.5$ for losing trust and a sensitivity factor $\delta_g = 0.025$ for gaining trust. Table 3 shows that this asymmetric trustworthiness update mechanism results in a more profitable system for all supply chain agents than when health centers had a symmetric trustworthiness update, i.e. $\delta_l = \delta_g = 0.5$ (scenario 2). In addition, We observed that the health centers disparity gap closes to about 5%. In this scenario, *Disrupted DS* treats the health centers more equitably because it knows that its trustworthiness can go down fast and would not recover quickly.

Table 3: Percentage of change in supply chain agents' profit compared to symmetric trustworthiness update with $\delta = 0.5$.

Agent	Percentage of Profit Change
Both health centers	45.51
Not-Disrupted DS	11.40
Disrupted DS	236.38
Not-Disrupted MN	6.54
Disrupted MN	419.73
Supply Chain	51.04

Health centers' asymmetric sensitivity factors to update trustworthiness impact the amount of order they place to the distributors, as shown in Figure 3. This timing directly affects the inventory and backlog levels of the *Disrupted DS*, see Figure 4. As shown in these figures in the asymmetric case, after the disruption, health centers move away from the *Disrupted DS* and only come back to ordering normally to this distributor when *Disrupted DS* has recovered from the disruption and have the product in inventory to allocate to them. However, in the asymmetric case, they return to *Disrupted DS* when this distributor is still amid the disruption and is not ready to fully accept their normal ordering level. This results in a more significant backlog level compared to the asymmetric case. In addition, healthcentes would move away from *Disrupted DS* again, and it takes some time for them to get back to the normal ordering level for the second time, which in turn results in a higher inventory level for *Disrupted DS* right after the disruption.

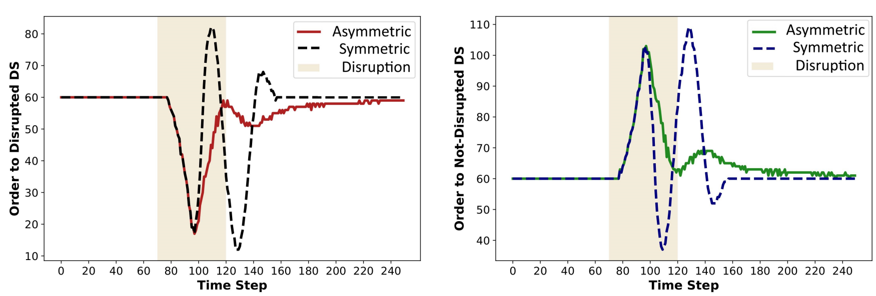


Figure 3: Order amount of health center when it uses asymmetric trustworthiness update with $\delta_l = 0.5$ and $\delta_g = 0.025$ versus when health center uses symmetric with $\delta = 0.5$.

Let us look at the profitability of the *Disrupted DS* throughout the simulation time in one simulation run as shown in Figure 5. We can see that in some periods, *Disrupted DS*'s profit is very low in scenario 2 (labeled as symmetric) compared to scenario 3 (labeled as asymmetric). The problem with periods with such low profitability is that the distributor might not be able to recover from these periods and be out of business. Similar results were observed for other simulation runs.

3.1.4 Scenario 4 - Disruption Characteristics

In this final scenario, we examine whether the characteristics of the disruption (i.e. its length and severity) affect the timing of health centers' reactions. Therefore, in this scenario, starting from time period 70

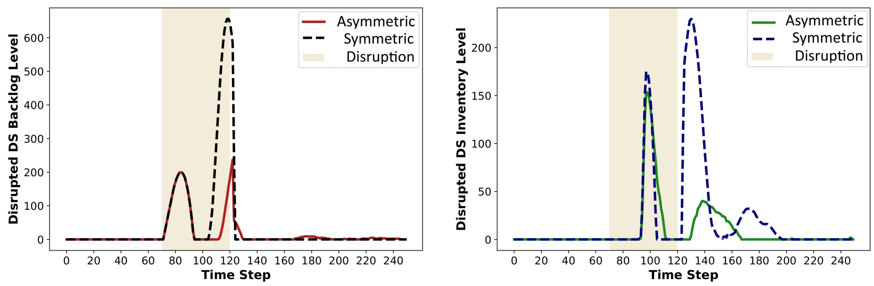


Figure 4: Backlog and inventory level of *Disrupted DS* when health centers use asymmetric trustworthiness update with $\delta_l = 0.5$ and $\delta_g = 0.025$ versus when health center uses symmetric with $\delta_l = \delta_g = 0.5$.

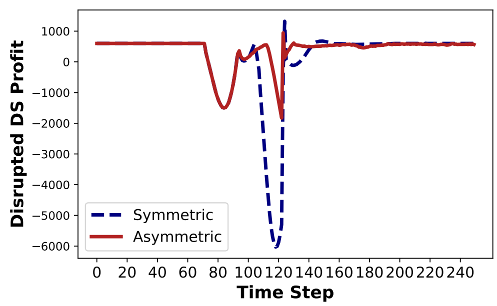


Figure 5: *Disrupted DS* profit throughout simulation in scenario 2 (labeled as symmetric) compared to scenario 3 (labeled as asymmetric).

Disrupted MN faces disruption, and its per period production capacity decreases to 17% of its original per period production capacity. This disruption continues for 50 periods. Note that the overall reduction in production capacity of the manufacturer throughout the simulation is the same as that of the previous scenarios; however, the reduction in capacity in this scenario spreads throughout a shorter period of time with more severity. Other settings of the scenario are the same as the previous ones.

Similar to previous scenarios, we run simulations with varying values for sensitivity factors to study how the timing of changes in the ordering behaviors of health centers change under a disruption with different characteristics. As shown in Figure 6, different combinations of sensitivity factors have different impacts on *Disrupted DS's* profitability. Under the short and severe disruption, the differences between profits for *Disrupted DS* for varying sensitivity factors are much smaller than the difference in the profits under the prolonged and mild disruption. Figure 7 presents a comparison between the simulations with the worst profit ($\delta_l = 0.5$ and $\delta_g = 0.025$) and the best profit ($\delta_l = \delta_g = 0.025$). While the backlog levels are very similar, the difference in profit is a result of the difference in the inventory and backlog costs.

4 CONCLUSION AND FUTURE RESEARCH

We use a multiagent simulation to simulate a pharmaceutical supply chain that consists of three echelons of manufacturers, distributors, and health centers. A disruption affects the manufacturing capacity of one of the manufacturers, and we observed how this disruption ripples across the supply chain and affects all agents in different scenarios. Since we are dealing with a pharmaceutical supply chain, which is part of the healthcare system, in addition to the profitability of the agents, we measured equity among the health centers.

We specifically study the dynamics of relationships between a distributor which is directly impacted by the disruption and its health centers. We observe that these dynamics have non-local effects which impact

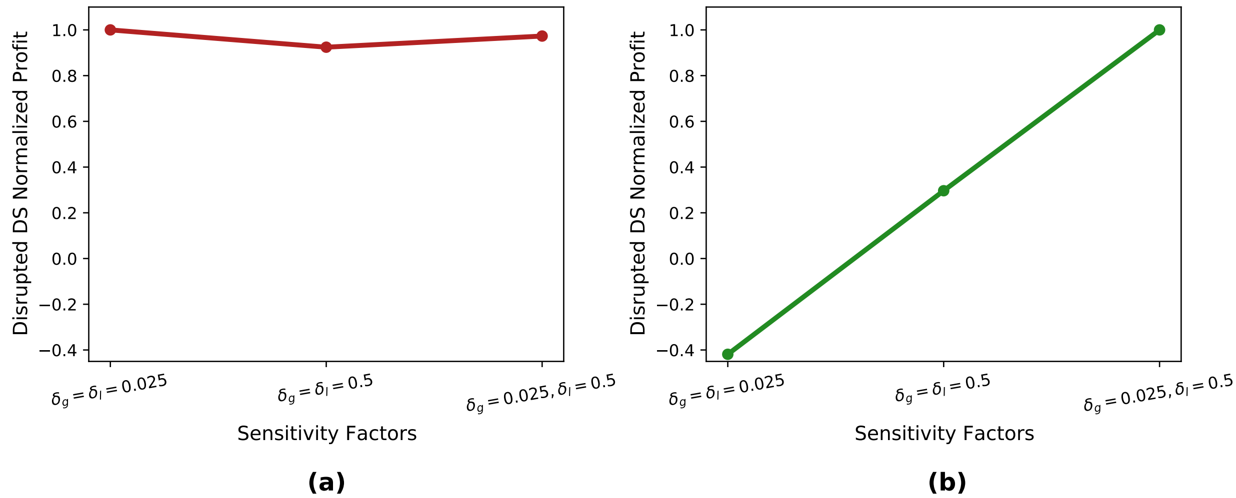


Figure 6: *Disrupted DS* normalized profit for different sensitivity factor values under (a) short and severe and (b) prolonged and mild disruptions.

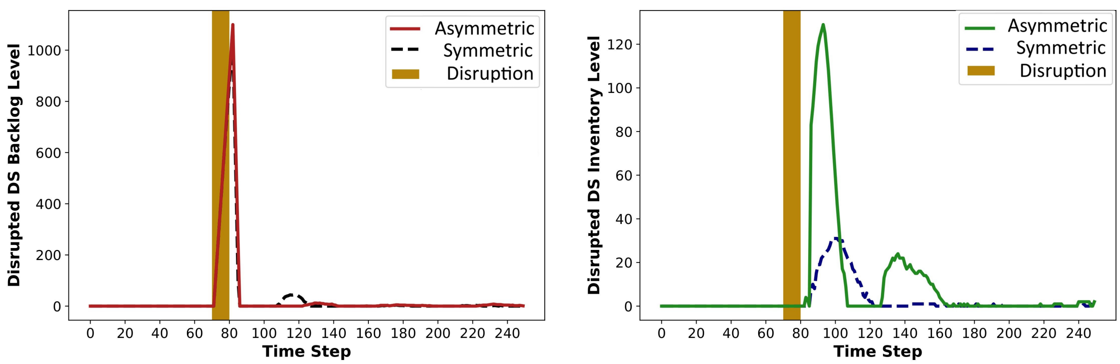
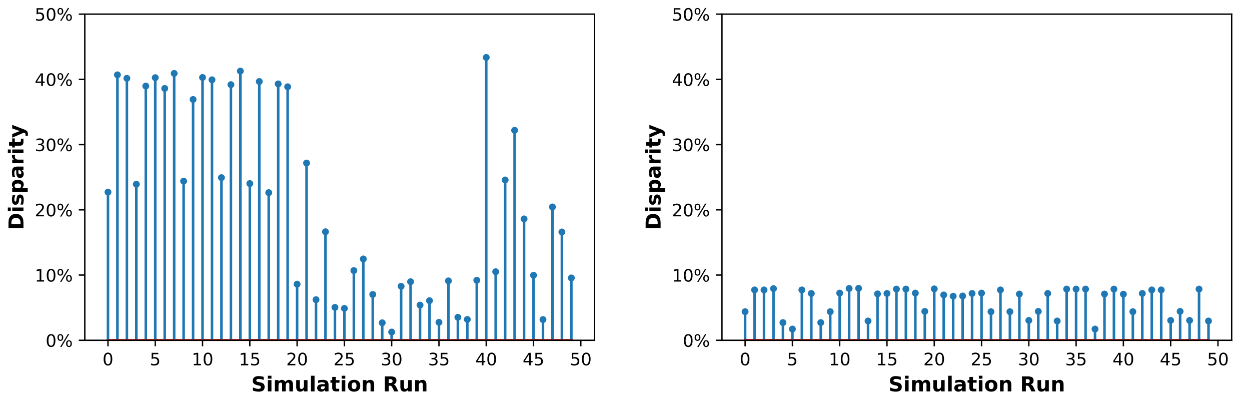


Figure 7: Backlog and inventory level of *Disrupted DS* when health centers use asymmetric trustworthiness update with $\delta_l = 0.5$ and $\delta_g = 0.025$ versus when health center uses symmetric updates with $\delta_l = \delta_g = 0.025$.

all supply chain agents. In addition, the timing of agents' reactions has a vital role in the effectiveness of mitigation efforts by the agents. When this timing is better aligned between the distributor and its health centers, the impact of the disruption is minimized. When it is not aligned, though, it exacerbates the disruption impacts. For this alignment of actions to transpire more robustly, explicit communication between the health centers and the distributor is required to coordinate their actions.

In these coordination efforts, one complicating factor can be the characteristics of the disruption. As shown above, the disruption characteristics have an essential role in determining the optimal timing for changes in health centers' ordering behavior. This, of course, requires data collection and a better understanding of disruption characteristics from the distributor side. As a result of better characterization of the disruption, potential disruption characteristics (how long the disruption will be and how the severity will change) can be identified, and a contingency plan for these potential disruptions can be prepared. One exciting avenue of future research is studying multiple disruptions with different frequencies and durations and severities to study how these features will impact supply chain profitability and coordination plans for mitigating disruption impacts. Again, this also suggests the criticality of more open communication between organizations in the supply chain, which nevertheless can be challenging to achieve in competitive



(a) (b)

Figure 8: Disparity in number of patients backlogged among health centers, when sensitivity factor (a) $\delta_g = \delta_l = 0.025$ and (b) $\delta_l = 0.5$ and $\delta_g = 0.025$.

supply chain networks. While challenging, policy strategies that further these communications will prove valuable. Two important factors held constant during this study are information and shipment lead times and the number of echelons in the supply chain, which determine how fast the disruption and changes in agents' behaviors will trickle down the supply chain and reach each agent. Future research is needed to study the impact of these temporal factors to examine how they would interact with the reactivity of health centers and disruption characteristics.

ACKNOWLEDGMENTS

This paper is part of a larger project which is supported in part by the National Science Foundation under grant CMMI 1638302. We would like to thank Pedro Sequeira, David Kaeli, Yifan Sun and Rana Azghandi for collaborating in building the infrastructure explained in (Doroudi et al. 2018) that was used in this work. We would also like to thank David Pynadath for his help with PsychSim, and Omid Mohaddesi and Casper Harteveld for their comments and feedback.

REFERENCES

ASHP 2022. "Severity and Impact of Sterile Injectable Drug Shortages". Technical report, American Society of Health-System Pharmacists.

ASHP 2023. "American Society of Health-System Pharmacists". Accessed 17th April 2023.

Choi, T. Y., and J. L. Hartley. 1996. "An Exploration of Supplier Selection Practices Across The Supply Chain". *Journal of Operations Management* 14(4):333–343.

Cohen, R., M. Pettoello-Mantovani, I. Giardino, A. Carrasco-Sanz, E. Somekh, and C. Levy. 2023. "The Shortage of Amoxicillin: An Escalating Public Health Crisis in Pediatrics Faced by Several Western Countries". *The Journal of Pediatrics* 257.

Dawes, D. 2016. "Why Health Equity Matters in an Era of Health Care Transformation". *Association of American Medical Colleges*.

Doroudi, R., R. Azghandi, Z. Feric, O. Mohaddesi, Y. Sun, J. Griffin, O. Ergun, D. Kaeli, P. Sequeira, and S. Marsella. 2018. "An Integrated Simulation Framework for Examining Resiliency in Pharmaceutical Supply Chains Considering Human Behaviors". In *Proceedings of the 2018 Winter Simulation Conference*, edited by M. Rabe, A. A. Juan, N. Mustafee, A. Skoogh, S. Jain, and B. Johansson, 88–99. Piscataway, New Jersey: Institute of Electrical and Electronics Engineers, Inc.

Doroudi, R., P. Sequeira, S. Marsella, O. Ergun, R. Azghandi, D. Kaeli, Y. Sun, and J. Griffin. 2020. "Effects of Trust-based Decision Making in Disrupted Supply Chains". *PloS One* 15(2):e0224761.

Doshi, P., X. Qu, A. Goodie, and D. L. Young. 2010. "Modeling Recursive Reasoning by Humans Using Empirically Informed Interactive POMDPs". In *Proceedings of the 9th International Conference on Autonomous Agents and Multiagent Systems*, Volume 1, 1223–1230.

Ebrahim-Khanjari, N., W. Hopp, and S. M. Iravani. 2012. "Trust and Information Sharing in Supply Chains". *Production and Operations Management* 21(3):444–464.

Ficici, S. G., and A. Pfeffer. 2007. "Modeling How Humans Reason About Others with Partial Information". *Harvard Computer Science Group Technical Report TR-01-07*.

Forrester, J. W. 1997. "Industrial Dynamics". *Journal of the Operational Research Society* 48(10):1037–1041.

Gmytrasiewicz, P. J., and E. H. Durfee. 1995. "A Rigorous, Operational Formalization of Recursive Modeling". In *ICMAS*, 125–132.

Hantel, A., M. Siegler, F. Hlubocky, K. Colgan, and C. K. Daugherty. 2019. "Prevalence and Severity of Rationing During Drug Shortages: A National Survey of Health System Pharmacists". *JAMA Internal Medicine* 179(5):710–711.

Hedden, T., and J. Zhang. 2002. "What Do You Think I Think You Think?: Strategic Reasoning in Matrix Games". *Cognition* 85(1):1–36.

Jalbut, A., and J. S. Sichman. 2019. "Impact of Trust on Agent-Based Simulation for Supply Chains". In *Proceedings of Multi-Agent-Based Simulation XIX: 19th International Workshop*, 45–58. Stockholm, Sweden: Springer.

Kim, W.-S. 2009. "Effects of a Trust Mechanism on Complex Adaptive Supply Networks: An Agent-based Social Simulation Study". *Journal of Artificial Societies and Social Simulation* 12(3):4.

Lynas, K. 2013. "Patient Care and Health Compromised by Drug Shortages in Canada: Survey of Physicians and Pharmacists". *Canadian Pharmacists Journal* 146(2):67.

McBride, A., S. Hudson-DiSalle, J. Pilz, M. Hamm, B. Boring, L. Buie, and D. DeRemer. 2022. "National Survey on the Effect of Oncology Drug Shortages in Clinical Practice: A Hematology Oncology Pharmacy Association Survey". *JCO Oncology Practice* 18(8):e1289–e1296.

McCarthy, S. 2020. "Coronavirus Could Cause Global Medicine Shortages as China's Factory Closures Hit Supply Chains". *South China Morning Post*. March 4. https://www.scmp.com/news/china/society/article/3064989/coronavirus-could-cause-global-medicine-shortages-chinas-factory (accessed March 9, 2023).

McKnight, D. H., and N. L. Chervany. 1996. "The Meanings of Trust". *Ethics* 78(2):156–159.

Pauwels, K., S. Simoens, M. Casteels, and I. Huys. 2015. "Insights into European Drug Shortages: A Survey of Hospital Pharmacists". *PloS One* 10(3):e0119322.

Pynadath, D. V., and S. C. Marsella. 2005. "PsychSim: Modeling Theory of Mind with Decision-theoretic Agents". In *IJCAI*, Volume 5, 1181–1186.

Sen, S. 2013. "A Comprehensive Approach to Trust Management". In *Proceedings of the 2013 International Conference on Autonomous Agents and Multi-agent Systems*, 797–800: International Foundation for Autonomous Agents and Multiagent Systems.

Simchi-Levi, D., P. Kaminsky, E. Simchi-Levi, and R. Shankar. 2008. *Designing and Managing the Supply Chain: Concepts, Strategies and Case Studies*. Tata McGraw-Hill Education.

Tan, Y. X., R. J. Moles, and B. B. Chaar. 2016. "Medicine Shortages in Australia: Causes, Impact and Management Strategies in the Community Setting". *International Journal of Clinical Pharmacy* 38(5):1133–1141.

AUTHOR BIOGRAPHIES

ROZHIN DOROUDI has a PhD of Industrial Engineering from Northeastern University. Her research focuses on leveraging Artificial Intelligence to study human behavior in critical supply chains. Her email address is doroudi.r@northeastern.edu

OZLEM ERGUN is a Professor of Industrial Engineering at Northeastern University. Her research focuses on the design and management of large-scale networks. Recently, Dr. Erguns work has been focused on the use of systems thinking and mathematical modeling in applications with societal impact. She has worked with organizations that respond to humanitarian crisis around the world. Her email address is o.ergun@northeastern.edu.

JACQUELINE GRIFFIN is an Associate Professor of Industrial Engineering at Northeastern University. Her research focuses on the development of new models and operations research methods to address the complexities of decision making in health and humanitarian systems. In particular, she examines decision making in the presence of multiple competing objectives in real-world applications. Her email address is ja.griffin@northeastern.edu.

STACY MARSELLA is a Professor in the Khoury College of Computer Sciences with a joint appointment in Psychology. His multidisciplinary research is grounded in the computational modeling of human cognition, emotion and social behavior as well as the evaluation of those models. His email address is marsella@ccs.neu.edu.