AN INTEGRATED SIMULATION FRAMEWORK FOR EXAMINING RESILIENCY IN PHARMACEUTICAL SUPPLY CHAINS CONSIDERING HUMAN BEHAVIORS

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ABSTRACT

The growing epidemic of drug shortages in the United States causes challenges for providers all across the critical health care infrastructure and demonstrates the lack of resiliency within drug delivery supply chains. With many drugs having no acceptable substitute, drug shortages directly translate to a public health and safety risk. One of the understudied elements driving this crisis is the role of human behavior and human decision making across the supply chain echelons. We propose an integrated simulation framework which allows for instantiating, testing, and improving supply chains when accounting for human components of the system. We demonstrate the potential insights that can be obtained with our method through several experiments in which supply chain decision makers account for how others might react to their decisions.

1 INTRODUCTION

Over the last decade there has been an epidemic of drug shortages affecting the United States. Between 2008 and 2014, there was a 393% increase in shortages for direct lifesaving emergency medicines (Hawley et al. 2016). More recently in 2017 and 2018, there have been multiple drug shortages for sterile injectable products that are endangering the lives of patients across the country., leading directly to cancelled heart surgeries (Thomas 2017). The underlying causes of the most recent shortages, for saline and other products, include manufacturing suspensions due to production challenges and the physical impact of Hurricane Maria in Puerto Rico, a critical manufacturing site (Food and Drug Administration). While the recent shortages have been linked to large events, this is not the case for all shortages. During the 2015 saline shortages, the lack of anticipation of the scale of shortages and failure to react quickly, were due to the shortages being

driven by the combination of many small distributed recall events. Further exasperating the crisis, each newly reported drug shortage can stretch on and continue to be in effect for subsequent years demonstrating the lack of resiliency within drug delivery supply chains.

Resiliency is one of the most pressing concerns for all supply chains operating in today's global market and pharmaceutical supply chains are not an exception. The ever-increasing complexity of global supply chains makes them even more vulnerable to disruption. Figure 1 was developed using data from IQVIA providing information on the monthly shipments of all antibiotic/anti-infective and oncology drugs between distributors and health centers across the United States over a six-year time period. In each state the top distributors (represented by four colors) differ such that a disruption in one manufacturer may cause states to be affected very differently. As a result of this increase in complexity of supply chains and a global concern for resiliency, there has been an increased interest by academics and practitioners in supply chain resiliency (Snyder et al. 2016). A key, and often understudied, element in resiliency of supply chains is the role of human behavior and human decision making across the supply chain echelons. The common assumption in studying supply chain resiliency is that decision makers are perfect optimizers (Su 2008). However, this is not the case in reality. Sterman and Dogan showed how human behavior in scarcity can aggravate the situation (Sterman and Dogan 2015). Rong et al. in a beer game experiment with disruptions, demonstrate that human behavior adds another layer of complexity to analyzing disruptions in supply chains (Rong et al. 2008).
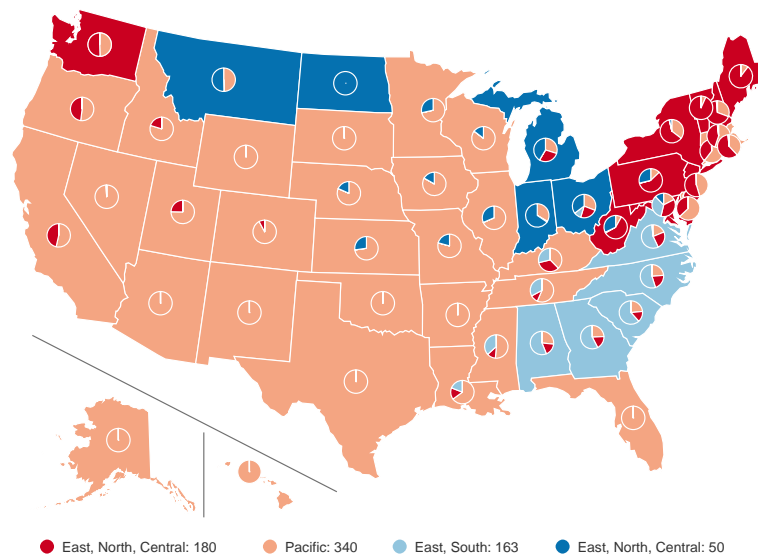

Figure 1: Total transactions for the top 4 distributors (represented by the colors) of antibiotic/anti-infective and oncology drugs in the United States from 2010 to 2016.

There exists a stream of research, known as behavioral operations research, which studies non-hyperrational actors in operational contexts. Although, this body of literature has grown to constitute a separate field (Croson et al. 2013), there is still a lack of a methodology for instantiating, testing, and improving supply chains when accounting for human components of the system.

In order to address this gap, we developed an integrated simulation framework comprised of three main components: Information and Physical Flow Simulation, PsychSim simulation, and a simulated game environment (gamettes). The value of utilizing this framework is that it integrates sophisticated supply chain models with realistic, yet computationally tractable, models of human decision making. The Information and Physical Flow Simulation models the flow of products and information, such as orders, in the supply chain network. Each entity in this Information and Physical Flow Simulation is equipped with a decision

maker, that can be a PsychSim decision maker, a simulated boundedly rational agent, or a human player interacting with the simulation via a game environment, i.e. a gamette.

To the best of our knowledge, there has been no study of resiliency of complex supply chains with multiple echelons and multiple agents in each echelon accounting for human behavior. While this framework can be used to study supply chain resiliency of different products our research focuses on resiliency of pharmaceutical supply chains.

The rest of the paper is organized as follows. In section 2 the overall simulation framework is explained and the following 3 sections elaborate on the three main components of the simulation framework. Section 6 presents the computational experiment settings and results from the different scenarios studied in this paper. Section 7 provides a discussion of future research directions.

2 HIGH-LEVEL SIMULATION FRAMEWORK

We designed an integrated simulation framework consisting of the (i) the Flow Simulator, (ii) the PsychSim simulation, and (iii) the simulated game environment, referred to as gamettes. The Flow Simulator serves as the central hub of the entire project architecture and simulates the information and physical flow in the drug supply chain. These information and physical flows are driven by the decisions and actions taken by the key stakeholders in the system, such as manufacturers, distributors, etc. These decisions and actions can be determined by the PsychSim simulation or the gamettes through a system by which they fetch data describing the current state from the Flow Simulator and then send operational decisions back to the simulator to advance the supply chain simulation.

Figure 2 shows the interaction of the aforementioned components. The Flow Simulator can run in a standalone mode to simulate the evolution of the supply chain system when some predefined policies inform decision making. In order to introduce simulated human behaviors in the supply chain, we employ the PsychSim simulation to provide a more sophisticated model of human decision making. Finally, the Flow Simulator can also work in collaboration with the gamette server to provide a simulated game environment to a set of human players to capture decision making. Further, the human decisions collected with the gamettes will be used to validate and improve Psychsim's model of human decision makers.
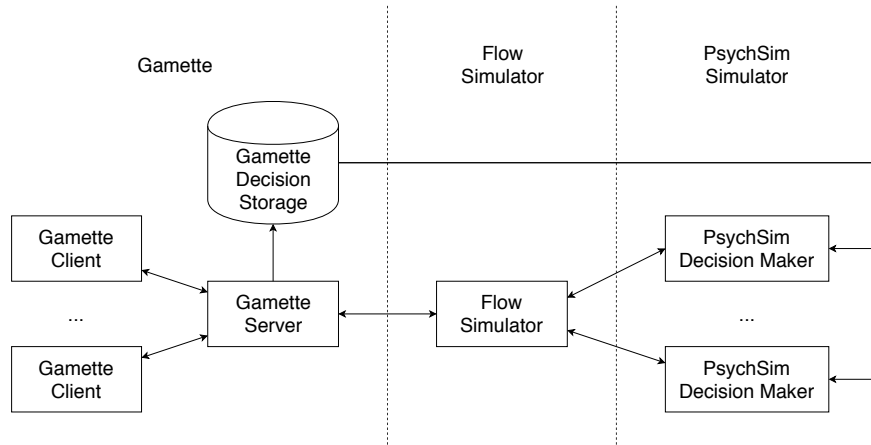

Figure 2: The Simulation Framework.

The Flow Simulator models the entire system and its evolution over time. At every point in time the status of all decisions makers, or agents, at all echelons of the supply chain, information about outstanding product orders and shipments, and unmet or backlogged demand is tracked and recorded. Correspondingly, based on the state of the system in each time period all system agents make decisions that effect the transition of the system in future periods. Within the Flow Simulator one option for modeling these decisions is the use of a static policy, such as a base stock policy for ordering products.

Alternatively to the static policies, more realistic models of decision makers can be employed by utilizing the PsychSim simulator, which models decision makers as boundedly rational agents who can reason about other decision makers in the system and account for estimates about future outcomes with forward projections (Marsella et al. 2004). The best decision, as a function of an agent's goals and estimates of the system via a forward planning approach, can be identified for every decision maker and these decisions can be enacted in the Flow Simulator.

In order to further inform the behavior of agents in the Flow Simulator, we developed gamettes, which are simulated game environments. The term "gamette" is a contraction of "game" and "vignette". Similar to a vignette, a gamette aims to provide a brief description of a situation as well as to portray someone. These gamettes are specifically designed to mimic any echelon of the supply chain found in the Flow Simulator. By having players, or gamette clients, interact with the Flow Simulator and collecting and recording their behavior we can validate the PsychSim model's ability to accurately model human behavior and decision making. As our work progresses, we plan, through experiments with the gamettes, to compare the actions of human players with PsychSim agent models. Additionally, when there is a discrepancy between the gamette and PsychSim predictions, the computational infrastructure will allow for the analysis of the features driving the incongruity, in turn, allowing for the improvement of future human behavior models.

3 INFORMATION AND PHYSICAL FLOW SIMULATOR

The Flow Simulator, which is at the core of the architecture, is implemented in Python. It models the entire supply chain system and its evolution over time. This includes a model of the structure of the supply chain system including the decision making agents at each echelon of the supply chain and the connections between agents. This allows for a variety of structures to be studied including asymmetric partially connected networks. Additionally, the Flow Simulator mimics the evolution of the system driven by the flow of information (e.g., orders) and physical flows (e.g., shipments) which are informed by the decisions of supply chain agents.

A summary of the types of decisions that are made by agents at each supply chain echelon that result in information and physical flows are summarized in Table 1. Each decision made corresponds to choosing a policy and its parameters. Examples of the policy options for each type of decision are provided in Table 1.

Table 1: Types of decisions made by each agent in different supply chain echelons and available policies for each decision type.

Echelon	Decision	Available Policies
Manufacturer	Production	Base-stock; constant level;
	Allocation of limited inventory	Proportional to orders; equally;
Distributor	Total amount ordered	Base-stock;
	Division of orders among manufacturers	Equally; proportional to service level;
	Allocation of limited inventory	Proportional to orders; equal amounts;
Health Center	Total amount ordered	Base-stock;
	Division of orders among distributors	Equally; Proportional to service level
	Allocation of limited inventory	Prioritize urgent patients; First-come, first-served;

3.1 Simulation Flow

The evolution of the system, resulting from implementation of the agents' choices of policies and exogenous factors (e.g., manufacturing suspensions, patient demand at health centers) is described as follows. First, at each time period, in each health center the patient demand is generated with a static probability distribution, such as a Normal or Uniform distribution. Next, the system state, including production capacity, inventory levels, and outstanding orders, is updated as a result of information and physical flows in the previous period and any supply chain disruptions (e.g., product recalls, manufacturing suspension). After the supply network state is updated, decision makers, or agents, choose policies to define production, ordering, and product fulfillment levels for all stakeholders it is connected to in the Flow Simulator network. Measures of the system performance driven by these decisions, including inventory costs, backlogged orders and unmet patient demand, are then calculated and updated.

4 PSYCHSIM

Distinct from the current state-of-the-art in supply chain modeling, we used a partially observable Markov game (POMG) model (Emery-Montemerlo et al. 2004) of the interdependent decision makers in the supply chain network to integrate realistic models of human decision-making and information processing by agents, thus incorporating dynamic and adaptive behaviors. Key to this approach is the adoption of the PsychSim modeling framework (Marsella et al. 2004), where distinct decision makers are simulated as boundedly rational agents trying to achieve their goals using deliberative approaches or calculations that can take into account future outcomes, including how other agents may react to any decision. A key contribution of this work is approximating traditional inventory ordering and allocation strategies, such as proportional inventory allocation and base-stock inventory ordering (Snyder and Shen 2011), in a computationally-efficient piecewise-linear abstraction that could be integrated with PyschSim.

4.1 World Modeling

PsychSim is built on the assumption of agents maintaining beliefs about other agents and those beliefs influencing an agents decision-making and communication with other agents (Marsella et al. 2004). To model a population of agents in a supply chain network we used PsychSim to model a POMG where agents continually interact with a world modeling the state of the supply chain network. Specifically, a POMG evolves as follows: at each discrete time-step the game is in some state. In our simulations, a time-step corresponds to a certain unit of time such as a day or a week. The system state corresponds to a combination of the states of all elements in the supply chain, including order and demand amounts, inventories, production levels, etc. Each agent has access to a partial view of the state referred to as an observation. Based on its observations, each agent maintains a probability, referred to as a belief, of being in some system state. At each time-step, every agent selects, simultaneously and without explicit communication, an action from a set of possible actions. In our supply chain domain this corresponds to the ordering, allocation or production policies that are available for each agent according to the echelon in which it operates. The state of the world changes at each discrete time-step as a consequence of all agents' actions. After executing some action, each agent is awarded a reward according to a reward or cost function that the agent wants to maximize or minimize, respectively. Such a function encodes the agents goals, i.e., it returns a value denoting how important some state is in regard to its goals.

4.2 Agent Modeling

The autonomous agents in our supply chains are faced with solving a complex task that mirrors the challenges of real-world decision-making; they must anticipate and react to the contingencies and disruptions that arise. They must not only maintain models of a dynamic supply and demand environment but also model other agents' behaviors (whether competitor, supplier or customer) relying on partial information about the

situations those agents are facing to make inferences about their unknown mental states and decision-making processes (Littman 2001; Hu and Wellman 2003; Claus and Boutilier 1998). As an agent changes its beliefs about others based on their behavior, the agent is also changing its own behavior, which in turn changes the beliefs and decision-making of the other agents. In other words, agents are *co-adapting*, whether we are talking about artificial agents in simulations or human agents in the real world.

In PsychSim, the world is composed of all the agents in the supply chain network. Each agent is modeled as an individual decision-maker, meaning that each agent makes its own decisions based on local observations and according to the models it has of the other agents. Regarding decision-making, each agent has available different actions, which are combinations of the various ordering amounts, order division and allocation policies that were designed based on human behavior modeling within supply chains, as listed in Table 1. As for modeling others, each agent has a theory-of-mind (a model) of all other agents. Each model contains the agents beliefs about the actions available to other agents and models of their goals. Taking into account the models of other agents and their own goals, each agent makes a decision, i.e., selects from one of its actions, by performing forward planning. Namely, the goal of each agent is to maximize the *expected* reward they will receive in the near-future if they select some action. A discount term factors the value of states in the near future against those farther ahead. A planning horizon determines how much into the future the agents plan their actions.

During planning, agents perform theory-of-mind reasoning by simulating in their minds how they and all other agents would choose their actions in each of the hypothetical future states. Specifically, for other agents they select actions that they believe the other agents would choose so as to maximize their goals, informed by their current models. Therefore, each selected action for another agent is the best response to the agent's own action at any hypothetical time-step. As a result, agents try to maximize their own gain while taking into account how other agents are also seeking to maximize their expected gains.

5 GAMETTES

Gamettes are short game-based scenarios where an individual player is immersed into a specific situation and has to make decisions by responding to a dialog or taking an action. To ensure that decision making is authentic, each gamette is constructed with scenes and characters. A scene is a setting where a scenario unfolds (e.g., hospital, office) and includes objects that the player can interact with (e.g., computer, phone). We refer to such object interactions as actions. Players, and the corresponding player-characters, can interact with non-player characters (NPCs) through dialog. Dialog may involve the player-character thinking (through thought bubbles) and expressing beliefs about others. At the start of each gamette, a tutorial is provided that denotes the player's reward function, designating the player's objectives and performance evaluation criteria. As players take actions and talk to NPCs, they are presented with choices. Player responses to these choices form the input for the agent models.

Gamettes are designed on a platform called StudyCrafter. StudyCrafter is a playful platform where users can create, play and share gamified projects on behavioral and social science research. According to the simulation framework, we create three types of gamettes for each agent type: manufacturer gamette, distributor gamette and health center gamette. In each gamette, the player is assigned to the role of an agent who is responsible for making 2 types of decisions. First, the players decide how to allocate drugs to its downstream nodes (or how to allocate drugs to the patients for the health center gamette). Second, they decide on the drug order amounts to be placed with their upstream suppliers (or production levels for manufacturer gamette).

A unique feature of our study is the tight coupling of the simulator and behavior models with the gamette. Thus, the input for the gamette instantiation is the state of the supply chain network. Each gamette communicates closely with the Flow Simulator using API calls to receive supply chain parameters and to send back players' decisions. The supply chain parameters (current inventory, received orders, on-order amounts, etc.) are received by the gamette at the beginning of each period. Then the player makes decisions and these decisions are communicated to the Flow Simulator at the end of each period. The simulator

then moves to the next time period and updates system network data for each player. In addition, when a disruption happens, the gamette receives disruption parameters from the simulator. The player is notified at the beginning of each period through a dialog or a news flash about the type and size of disruptions.

6   COMPUTATIONAL EXPERIMENTS

We demonstrate the value of the developed framework that integrates sophisticated supply chain models with realistic, yet computationally tractable models of human decision making by performing a set of initial experiments. In particular, we test the effect of distributor agents that are capable of performing forward planning in their ordering decisions. In this study, when a PsychSim agent is forward planning we assume that it has a perfect model of other agents in the supply chain. We used the aforementioned Flow Simulator and PsychSim to model a pharmaceutical supply chain with 2 manufacturers, 2 distributors and 2 health centers. The health centers are serving two types of urgent and non-urgent patients. At each time period if a health center is not able to fulfill any of its patients' demand, regardless of their type, it is assumed that the patients will seek help somewhere else and the unsatisfied demand of the health center in that time period will disappear. However, when in a certain time period a manufacturer or a distributor is not able to fulfill its demand, this demand will be backlogged. When there are no disruptions the manufacturers' production capacities are enough to fulfill all of their demands. In order to isolate the effect of agents' forward planning, patient demand is assumed to be constant. This means that all of the supply chain agents face constant demand and they do not need to keep safety stock.

There are two types of decisions each agent must make at each time period: manufacturers decide on production amount and the allocation of inventory to distributors; distributors decide on how much to order from manufacturers and the allocation of inventory to health centers; and health centers decide on how much to order from distributors and the allocation of inventory to urgent and non-urgent patients. In addition, approximating a classic static inventory policy, we assume that all agents adhere to a base-stock policy, placing orders or producing enough to bring their inventory position to a predefined level (up-to level). Distributors have two additional ordering policies available that are order the up-to level plus or minus a certain offset. When agents want to split their order between their upstream suppliers, we assume that they split it equally. For allocating inventory to customers in their downstream echelon, and to urgent and non-urgent patients in case of the health centers, they allocate proportionally to the orders received. As for the agents' goals, we created different reward functions at each echelon to model typical cost functions. Namely, we modelled the following goals: health centers try to minimize the loss of unsatisfied patients and inventory cost, and distributors and manufactures balance backlog and inventory costs. When there are no disruptions in the system, after the warm-up period, the simulation stabilizes and reaches a steady state. In the steady state, distributor and health center agents' order amounts and manufacturer agents' production amounts are equal to their up-to level. All agents have an inventory equal to their up-to level at the beginning of each time period and allocate all of it to their downstream echelon, so that at the end of each time period they have zero inventory. In the experiments discussed in this paper, a disruption decreases the production capacity of the manufacturers. Another factor that we study in our experiments is the network structure of the supply chain. We test different supply chain network topologies to explore how different connections between the agents influence their behaviors.

6.1 Scenarios and Results

In this section we discuss different scenarios that are studied. We start with a base network structure as illustrated in Figure 3 and then change the structure by deleting different links. Other instance parameter settings are shown in Table 2. A summary of results of all three scenarios can be found in Table 3. In all of the following scenarios a disruption at a manufacturer is assumed to reduce its capacity by 20% . In preliminary experiments, we tested the same network structures with different disruption severity levels

with greater reductions in capacity, but observed that the overall dynamics and results are similar across different levels of disruptions.
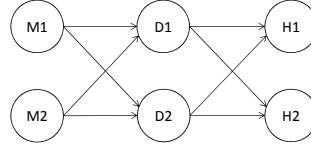

Figure 3: Network structure including M1,M2: manufacturers 1 and 2, D1,D2: distributors 1 and 2, H1, H2: health centers 1 and 2.

Table 2: Problem setting.

Urgent Demand	100 units per period
Non-urgent Demand	20 units per period
Lead Time (Information, Transportation, Production)	1 period
Distributors' up-to level offset	20%

Table 3: Summary of results of different scenarios reported in terms of changes in the total cost compared to the base case, i.e. in which none of the distributors are using forward planning.

		D1 Planning	**D2 Planning**	**Both Planning**
	Change in D1 Cost	-42%	29%	-13%
Scenario 1	*Change in D2 Cost*	30%	-41%	-13%
	Change in total lost patients	-6%	-6%	-11%
	Change in D1 Cost	-15%	0%	-12%
Scenario 2	*Change in D2 Cost*	15%	-17%	-14%
	Change in total lost patients	-12%	0%	-12%
	Change in D1 Cost	-78%	47%	-44%
Scenario 3	*Change in D2 Cost*	15%	-13%	5%
	Change in total lost patients	-3%	-1%	-4%

6.1.1 Scenario 1

In this scenario we used a supply chain network topology shown in Figure 3. The disruption happens in one of the manufacturers. We first analyze the base case in which none of the distributors is performing forward planning. Then we start altering the system by allowing one of the distributors to use forward planning feature to approximate how other agents will respond in the next 3 periods. We choose a 3-period look-ahead so that the agent is able to predict the effect of its ordering decision on its inventory given the lead time assumptions. The results in Table 3 are reported in terms of changes in the distributors' total costs compared to the base case. As we can see, the agent with the 3-period look-ahead "games" the system by adjusting its ordering policy in the aftermath of the temporary manufacturing disruption. This results in lower inventory and backlog levels compared with when it was not using forward planning. In this case the other distributor is disadvantaged since the distributor with look-ahead orders more and receives more of the limited capacity of disrupted manufacturer (see Figure 4 for changes in behaviour dynamics of distributors). We also tested the case where both distributors choose order policies using a 3-period look-ahead. In this case, both exhibit adaptive behavior and share the benefit of forward planning

(Figure 4). In addition, the system as a whole benefits from joint forward planning, which can be observed by the reduction in the number of lost patients.
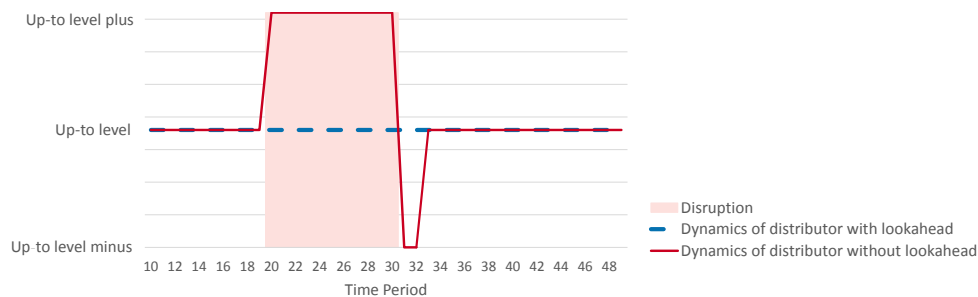

Figure 4: Scenario 1, dynamics of distributors when both use planning.

6.1.2 Scenario 2

In the second scenario, we delete the link between manufacturer 1 and distributor 2 in the network in Figure 3. Since the network is no longer symmetric, the effect of a disruption in manufacturer 1 can be different from the effect of a disruption in manufacturer 2. In this scenario we consider the reduction of production capacity of manufacturer 1. When distributor 1 is using forward planning, in the aftermath of the disruption, it will change its policy to "up-to level plus" so that it receives more products from manufacturer 1 and 2, reduces its backlog in future periods, and reduces its costs. On the other hand, distributor 2 does not use forward planning and keeps ordering with the"up-to level" policy. Furthermore, manufacturer 2, has enough inventory to fulfill both distributors' up-to level order amounts, but now that distributor 1 is ordering more it cannot fulfill both distributors' orders and allocates its available inventory proportionally among the two. As a result, in upcoming periods the backlog of distributor 2 increases. Additionally, when there is a disruption in one of the manufacturers the effect of the disruption may propagate through the whole supply chain reducing the number of patients the health centers serve. In turn, this reduces the health center orders to the distributors, since health centers' orders are backlogged to be received in the future but unserved demand disappears. We observe the impact of this as a change in distributor 1's ordering policy to "up-to level minus" at the end of the disruption interval (see Figure 5).

Distributor 2 is not connected to the disrupted manufacturer. Thus, when it is the only agent with a 3-period look-ahead, the only change that it observes in its forward planning is the reduction in health centers' demand. It can adapt its behavior with health centers' demand and switch to "up-to level minus", so costs will decrease. Distributor 2's forward planning has no negative effect on distributor 1, since it is ordering less from their shared manufacturer (see Figure 5).

When both of the distributors are forward planning both benefit from being proactive. Distributor 1's policy dynamics are similar to when it was the sole agent with forward planning. However, distributor 2 will first switch to an "up-to level plus" policy to adapt its behavior with distributor 1's change to an "up-to level plus" policy. After several time periods it switches to an "up-to level minus" policy to adapt to the change in health centers' demand (see Figure 6). In terms of the effect of distributors using forward planning on the number of lost patients, since distributor 1 is connected to the disrupted manufacturer, its forward planning and increasing of its orders benefits the health centers too. Whenever this distributor is forward planning, the number of lost patients decreases.

6.1.3 Scenario 3

In the third scenario we again assume that the link between manufacturer 1 and distributor 2 from Figure 3 network is deleted. However, in this scenario the disruption happens at the shared manufacturer. As demonstrated by the results in Table 3 when distributor 1 is using forward planning, either when it is the

only agent using forward planning or when both are planning, it will benefit while distributor 2 will be at a disadvantage. Because distributor 2 has only one manufacturer which is disrupted, whenever distributor 1 is behaving proactively it will directly negatively affect distributor 2.
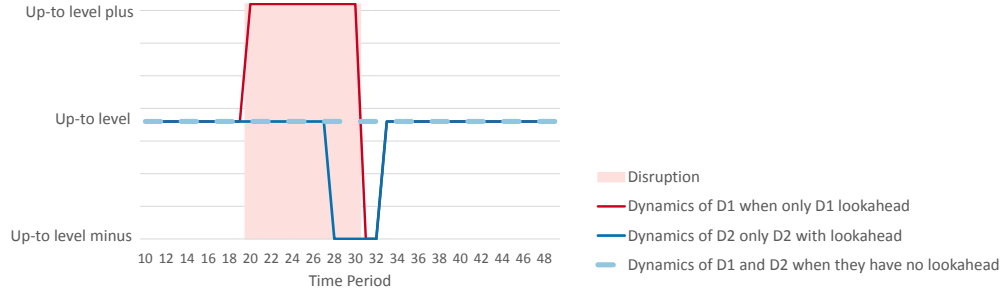

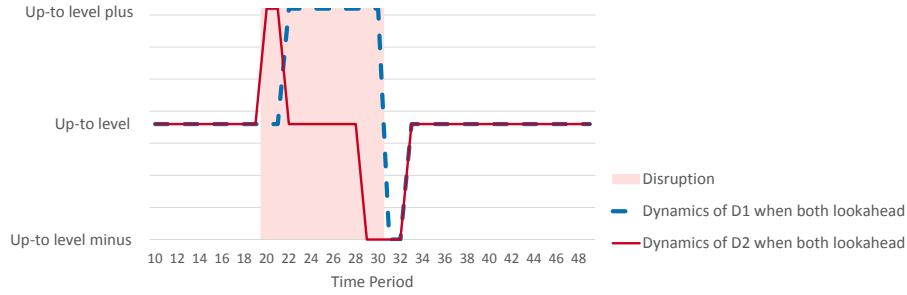Figure 5: Scenario 2, Dynamics of distributors when one of them uses planning.

Figure 6: Scenario 2, Dynamics of distributors when both use planning.

7 CONCLUSION AND FUTURE DIRECTION

The agents in our supply chain simulation are faced with solving a complex task that mirrors the challenges of real-world decision making; they must anticipate and react to the contingencies and disruptions that arise. They must not only maintain models of a dynamic supply and demand environment but also model the other agents (whether competitor, supplier or customer) relying on partial information about the situations those agents are facing and make inferences about others' unknown mental states and decision-making processes. In this paper we provide an integrated framework to model and study this situation. In our current experiments the agents with a perfect model of other agents benefit from anticipating how other agents might react to their decisions. We also observe that different network structures combined with different production, ordering and allocation policies can add to the complications that decision makers are faced with in the real world. One of the future directions of this research is building models of other agents for each agent, relying on partial information about the situations those agents are facing to make inferences about their unknown mental states and decision-making processes. Additionally, we plan to use this model to study the relationships between supply structures, characteristics of supply chain disruptions, and ultimately the resiliency of these systems.

Another important future direction is the study of information extracted on state-dependent human decision making with gamettes as well as tuning the reward and observation/belief functions used in the framework. Gamettes will have two major roles in building and validating the world modeling of the PsychSim framework. First, gamettes allow for comparing actions of human players with actions of

PsychSim agents. Second, they will provide an opportunity to study to what extent human players deviate from actual policies, allowing for improvement of future human behavior models.

We also propose to explore incorporating the achievement and maintenance of trust between an agents suppliers and customers as a meta-goal driving an agents behavior. To allow an agent to alter its behavior to achieve this meta-goal, we plan to explore alternative ways to operationalize the impact of trust on the supply chain decision making such as ordering from alternative suppliers and altering communications between customer and supplier agents.

To the best of our knowledge, no other researchers have created such a tightly integrated research infrastructure of systems models, human behavior models, and game methods.

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