Integrated Supply Chain Management for Perishable Products: Dynamics and Oligopolistic Competition Perspectives with Application to Pharmaceuticals

Sung Hoon Chung* Changhyun Kwon†

Abstract

We propose an integrated supply chain management framework that allows us to explicitly consider the impact of product perishability on a broad scale that includes manufacturers, distribution centers, wholesalers, and demand markets. The framework proposed herein also makes it possible to consider the oligopolistic competition across wholesalers that drives price and demand fluctuations. Furthermore, the supply chain decision rules are derived from necessary conditions in the framework. The inclusion of such salient features allows the framework to generate outcomes that suggest realistic managerial insights. We provide a numerical example in which two multi-national pharmaceutical firms producing a homogeneous medicinal drug and four oligopolistic wholesalers are considered.

Key words: pharmaceutical supply chain, perishable inventory dynamics, oligopolistic competition, variational inequality, interior point methods

1 Introduction

Pharmaceutical supply chains comprise complex processes across players including vendors, manufacturers, distributors, wholesalers, and healthcare providers. While topics discussed in other supply chain research such as facility location, capacity planning, production planning, inventory

*Department of Systems Science and Industrial Engineering, Binghamton University, SUNY, Binghamton, NY 13902, USA, Corresponding Author. +1-607-777-5933, schung@binghamton.edu

†Department of Industrial and Management Systems Engineering, University of South Florida, USA

management, and scheduling still play crucial roles in the management of pharmaceutical supply chains, we must also consider several critical factors pertaining to the pharmaceutical industry such as inventory management of perishable pharmaceuticals, its role in broad supply chain perspectives, and oligopolistic price competition, which necessitate the urgent need for integrated and sophisticated supply chain optimization techniques (Shah, 2004; Papageorgiou et al., 2001; Papageorgiou, 2009). Although extensive research has been done on perishable inventory management, multi-stage supply chain modeling, and price competition, there are very few, if any, works that study the intersection of all three areas. In this paper, we propose an integrated pharmaceutical supply chain management framework and analyze the impact of perishability on supply chain equilibrium performances for the oligopolistic competition model.

Drug perishability is one of the major concerns in pharmaceutical supply chains as drug quality and safety greatly rely on time (Masoumi et al., 2012; Vila-Parrish and Ivy, 2013). Pharmaceutical companies are required to stamp an expiration date on their products, until which the full potency and safety of the drugs are guaranteed if the drugs have been properly treated and stored. After expiration, products must be discarded or returned to the manufacturer, which may happen at various supply chain stages. Indeed, a substantial amount of pharmaceutical products are being discarded because they are outdated. For example, drugs, vaccines, and other medical supplies worth more than one million U.S. dollars were found to be spoiled and expired in the warehouse of the Health Department of Chicago in 2007 (Mihalopoulos, 2009). The challenge for managing pharmaceutical products in its supply chain lies in the difficulty and complexity of handling diminishing stocks at various stages of the supply chain and addressing the dynamic implication of such on a broad supply chain scale.

It is worth noting that while a substantial amount of unused/unsold drugs until their expiration dates exist, the vast majority of U.S. hospitals are suffering from drug shortages, according to the Food and Drug Administration (FDA). In particular, between July 1 and December 31 of 2010, more than 240 drugs and more than 400 generic varieties were backordered or even completely unavailable, and, unfortunately, it is expected that drug shortages will continue to increase (Cherici et al., 2011). While the reasons for such drug shortages come from multiple sources, it is suggested that the major culprit is the high degree of market concentration[1] in conjunction with mismanagement of

[1]It is surprising that there are only three firms (Sanofi Pasteur, Novartis, and GlaxoSmithKline) supplying influenza

supply chains, which forces pharmaceutical companies' decisions to stop production due to their financial challenges, especially for low margin drugs and vaccines (Scherer, 2007; Deo and Corbett, 2009). The consequences of drug shortages can be extremely detrimental, examples of which include delay of treatments and surgeries, use of alternative drugs that could be more expensive and/or less effective, emergence of the gray market, and patients' denial of treatments. Although it is impossible to force manufacturers to keep producing such drugs, their financial challenges can perhaps be mitigated through supply chain coordination and optimization.

The rest of this paper is organized as follows. In Section 2, we provide a literature review. We propose an integrated pharmaceutical model that explicitly considers the dynamic inventory management and oligopolistic competition in Section 3. A computationally efficient interior-point algorithm is presented in Section 4 and we present an numerical example in Section 5. Section 6 concludes this paper.

2 Literature Review

There is extensive research on the inventory management of perishable products. Ghare and Schrader (1963) propose an inventory management model for exponentially decaying products and Philip (1974) extends this model to use a Weibull distribution. Padmanabhan and Vrat (1995) suggest EOQ models for perishable items whose selling rates are dependent on the size of stock. For a thorough review of the early works on perishable inventory management, see Nahmias (1982).

While the vast majority of perishability literature focuses only on the inventory management aspect, a small number of studies also consider wider supply chain issues. Blackburn and Scudder (2009) study fresh produce supply chain strategies by considering the marginal value of time. They suggest that a hybrid model of a responsive stage (harvest to cooling) and efficient stages (cooling to retailers via transporters) is appropriate to minimize lost values in such supply chains. Masoumi et al. (2012) suggest a generalized network oligopoly model for pharmaceutical supply chains, but passively consider the dynamic aspect of pharmaceutical supply chains by adding a link multiplier that is simply a coefficient that reflects the loss of drug quantity during shipments. To the best of our knowledge, no studies explicitly consider the dynamics of perishable inventory management in the

vaccines to the U.S. market as of 2009; there were more than a dozen firms in the 1970s.

context of broad, competitive supply chains encompassing manufacturers, distributors, wholesalers, and demand markets, which is the focus of this paper. Importantly, unlike Masoumi et al. (2012), we provide the supply chain decision rules derived from necessary conditions for the Cournot-Nash equilibrium, which provides ample managerial insights into the problem.

With respect to oligopolistic competition, part of our interest is in the analysis of the impact of perishability on supply chain equilibrium outcomes. In this paper, we employ the Cournot and Fisher (1897) model of oligopolistic competition. For a detailed review of the Cournot and Fisher (1897) model, see Vives (2001). Deo and Corbett (2009) consider Cournot competition for the case of the U.S. influenza vaccine market with a focus on yield uncertainty. Wiggins and Maness (2004) study price competition for the case of anti-infectives. Perakis and Sood (2006) and Gallego and Hu (2014) study dynamic or multi-period pricing of perishable products under competition. Magazzini et al. (2004) propose a model of dynamic competition in pharmaceuticals for the case of patent expiration in major developed countries such as the USA, France, Germany, and the UK. None of the above research considers competition on a whole supply chain scale. Masoumi et al. (2012) propose a generalized network model that takes into account drug perishability and oligopolistic competition but does not capture the dynamic aspect of equilibrium solutions.

In this paper, we propose an integrated supply chain management framework, encompassing manufacturers, distributors, wholesalers, and demand markets, in which drug perishability is explicitly considered in the form of dynamic inventory management on a broad supply chain scale; the model allows us to capture the dynamics of perishable inventory control at manufacturing sites, distribution centers, and wholesalers over a planning horizon. In addition, we employ the Cournot and Fisher (1897) model to consider the oligopolistic drug price competition across agents, which is well matched with the perishability issue because the reduction of drug quantity due to expiration may cause price fluctuations. In summary, this paper is the first to explicitly consider drug perishability and price competition in a broad pharmaceutical supply chain perspective, which allows us to generate managerial insights through dynamic equilibrium solutions.

3 The Dynamic Pharmaceutical Supply Chain Model

The pharmaceutical supply chain network is depicted in Figure 1 and the notation used is summarized in Table 1. Nodes represent supply chain entities, and links represent material flows between corresponding nodes. In our model, we consider a single, homogeneous pharmaceutical product, a medicinal drug or vaccine subject to perishability. There are multiple pharmaceutical firms, wholesalers, and demand markets; a typical pharmaceutical firm is denoted by $f \in \mathcal{F}$, a typical wholesaler by $r \in \mathcal{R}$, and a typical demand market by $m \in \mathcal{M}$ where $\mathcal{F}$, $\mathcal{R}$, and $\mathcal{M}$ are the set of pharmaceutical firms, wholesalers, and demand markets, respectively. A pharmaceutical firm f may operate multiple manufacturing sites and distribution centers in spatially dispersed locations; a firm f's typical manufacturing site is located in $j \in \mathcal{J}^f$ where $\mathcal{J}^f$ is firm f's set of manufacturing locations such that $j = 1, 2, ..., \left|\mathcal{J}^f\right|$. A typical distribution center is located in $k \in \mathcal{K}^f$ where $\mathcal{K}^f$ is firm f's set of distribution locations such that $k = 1, 2, ..., \left|\mathcal{K}^f\right|$. In the case where a pharmaceutical firm f has no distribution centers, $k \in \mathcal{K}^f$ can be specified as dummy nodes. Wholesaler r has its own warehouse(s) in a spatially dispersed location(s); a typical warehouse is in location $n \in \mathcal{N}^r$ where $\mathcal{N}^r$ is wholesaler r's set of warehouses and it supplies pharmaceuticals to multiple demand markets where healthcare providers/pharmacies are located. Let $\mathcal{M}^r$ represent the set of demand markets to which the wholesaler r supplies pharmaceuticals. Note that $n = 1, 2, ..., |\mathcal{N}^r|$.

We assume that each pharmaceutical firm controls production quantities at manufacturing sites and product output flows to distribution centers and to wholesalers, while fulfilling orders from wholesalers over a specified planning horizon. They manage inventory levels at manufacturing sites and distribution centers by controlling input and output flows over a planning horizon. We also assume that each wholesaler controls orders to pharmaceutical firms and output flows to spatially dispersed demand markets. In addition, wholesalers are assumed to be in oligopolistic competition against one another. Since the wholesalers are in oligopoly markets, demands from markets are assumed to be always satisfied and the wholesalers are the ones that control the supply to the market.

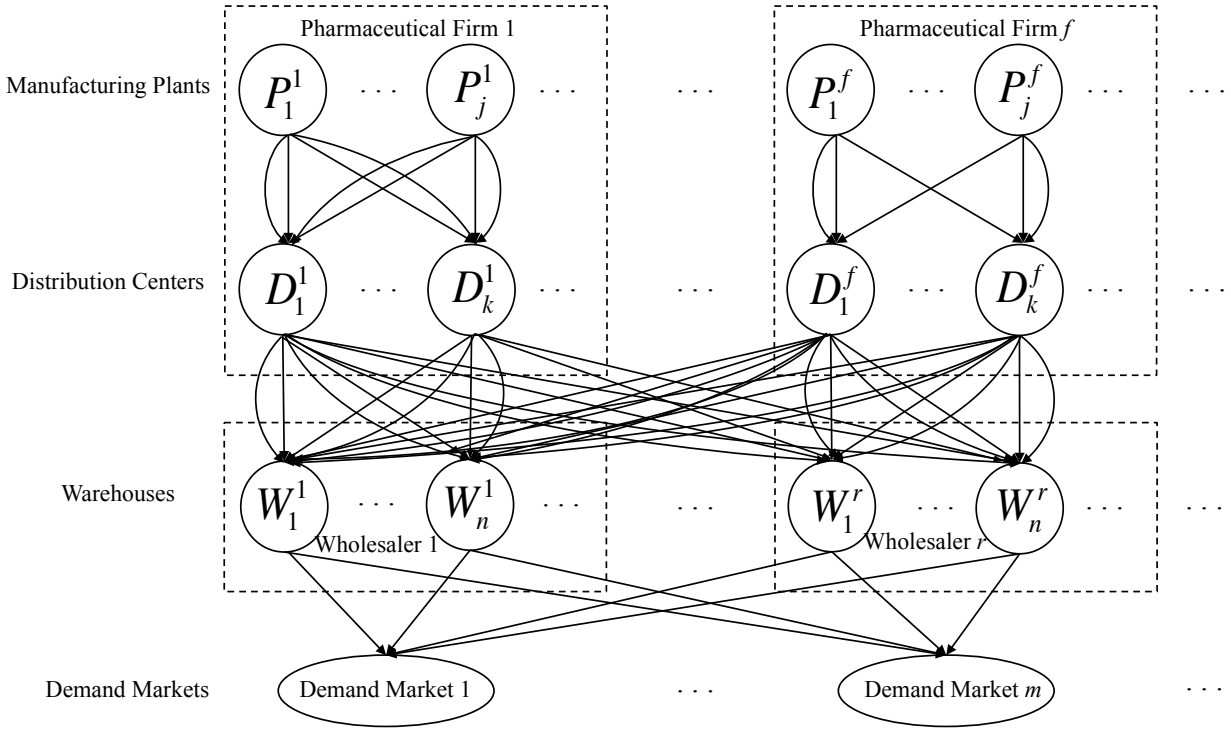

Figure 1: Pharmaceutical Supply Chain Network

Table 1: Notation

f	pharmaceutical firm	$\mathcal{F}$	set of pharmaceutical firms
r	wholesaler	$\mathcal{R}$	set of wholesalers
m	demand market	$\mathcal{M}^r$	wholesaler r's set of demand markets
j	index for manufacturing sites	$\mathcal{J}^f$	firm f's set of manufacturing sites
k	index for distribution centers	$\mathcal{K}^f$	firm f's set of distribution centers
n	index for warehouses	$\mathcal{N}^r$	wholesaler r's set of warehouses
$\mathcal{A}^f_{jk}$	firm f's set of links from j to k	$\mathcal{B}^{f,r}_{kn}$	set of links from firm f's k to wholesaler r's n

3.1 Pharmaceutical Product Deterioration

The deterioration of a pharmaceutical product can be expressed as the following exponential decay equation:

$$Q(t) = e^{-\delta t} Q_0 \tag{1}$$

where $Q(t)$ is the drug quantity at time t, Q_0 is the initial stock, and δ is a decay constant specific to a drug. Note that (1) is a unit-based exponential deterioration model that is well-suited for pharmaceuticals (see, e.g., Masoumi et al. (2012) for a paper employing this model) and is consistent with Ghare and Schrader (1963), implying that the drug quantity decreases as time passes due to expiration. For example, suppose a pharmaceutical company has 5,000 boxes of a certain drug at one of its distribution centers. The boxes have varied manufacturing dates and, therefore, expiration dates. In time, some of the 5,000 boxes will pass the expiration dates, meaning that there will be fewer than 5,000 boxes left to be distributed to wholesalers. The distribution center must discard less than, say, 5% of its inventory some days while it must discard more than 5% some other days. A convenient assumption is to use an average decay rate, say, 5% throughout the planning horizon, which can be captured by use of equation (1). Note that this decay model accommodates the expiration dates as well as a natural decay. Although exponential decay cannot accurately describe, on a daily basis, the inventory system of perishable pharmaceuticals having fixed lifetime, it is capable of describing the average decay over the planning horizon. Note that the use of exponential decay makes the computation very much tractable, which is a desired feature considering that our multi-level supply chain model is complex in nature. For the First-In-First-Out (FIFO) or Last-In-First-Out (LIFO) policies for products having fixed lifetime, see Nandakumar and Morton (1993) and Lian and Liu (2001). For the perishability model that uses a Weibull distribution, see Philip (1974), and for a value, instead of unit, deterioration model that is better suited for, e.g., food perishability, we refer readers to Blackburn and Scudder (2009).

3.2 Inventory Dynamics

It is imperative to consider the dynamic aspects of inventory management in pharmaceutical supply chains because the quantity of pharmaceuticals decreases over time due to expiration, which has the cascading impacts on a wider supply chain scale; the production rates, distribution flow rates, and

sales rates may need to be adjusted accordingly and even the drug price may fluctuate due to such changes and adjustments.

Let t_0 and t_f denote the initial time and terminal time, respectively, of a planning horizon. In our model, time t is discrete and $t \in [t_0, t_f]$. To introduce the inventory dynamics, we first illustrate pharmaceutical firms' controls in detail. A pharmaceutical firm f controls, at each instant of time t, 1) production rate $x_j^f(t)$ at manufacturing site j, 2) drug output flow rate $p_l^f(t), l \in \mathcal{A}^f$ from manufacturing site j to distribution center k, and 3) drug output flow rate $d_l^f(t), l \in \mathcal{B}^{f,r}$ from distribution center k to retailer r's warehouse in location n, where $\mathcal{A}^f$ and $\mathcal{B}^{f,r}$ are firm f's set of all links connecting manufacturing sites and distribution centers, and distribution centers and wholesaler r's warehouses, respectively. For notational convenience, we define $\mathcal{B}^f = \bigcup_{r\in\mathcal{R}} \mathcal{B}^{f,r}$. The total amount of order pharmaceutical firm f receives from wholesaler r at time t is denoted by $o^{f,r}(t)$. We assume that orders from a wholesaler are shipped out as soon as they are received. That is

$$\sum_l e^{-\delta t_l} d_l^f(t) = o^{f,r}(t) \tag{2}$$

where t_l represents discrete time required for delivery using link l. This implies that pharmaceutical firms is capable of considering the perishability when they ship drugs to fulfill orders, which may be useful when it comes to ones having a very short shelf life such as intravenous drugs. For drugs with a long shelf life, δ can be simply set to zero. We assume that there is supply-order coordination/contract between pharmaceutical firm f and wholesaler r, based on which pharmaceutical firm f serves as an order fulfilling firm given received orders from wholesalers. We introduce $o^f(t) = \sum_{r\in\mathcal{R}} o^{f,r}(t)$ to represent the total amount of orders pharmaceutical firm f receives from all wholesalers at time t.

Wholesaler r controls, at each instant of time t, order rates $\theta^{r,f}(t)$ to pharmaceutical firm f and we assume $\theta^{r,f}(t) = o^{f,r}(t)$, meaning that pharmaceutical firm f receives orders with no delay from wholesaler r as soon as they are placed. The notation of $\theta^r(t) = \sum_{f\in\mathcal{F}} \theta^{r,f}(t)$ represents the total amount of orders wholesaler r sends to all pharmaceutical firms at time t. Wholesaler r also controls sales rate $s_n^{r,m}(t)$ to healthcare providers/pharmacies in demand market m from its warehouse located in n. We group concatenations of variables into vectors where notational convenience is desired. For example, $x^f(t) = \left(x_j^f(t) : j \in \mathcal{J}^f\right)$, $x^f = \left(x^f(t) : t \in [t_0, t_f]\right)$, and $x = \left(x^f : f \in \mathcal{F}\right)$. We apply such notation rule for all other variables throughout this paper where no confusion arises.

Table 2: Control Vectors

$x^f(t)$	firm f's production rates at its manufacturing sites at time t
$p^f(t)$	firm f's output flow rates from manufacturing sites to distribution centers at time t
$d^f(t)$	firm f's output flow rates from distribution centers to wholesalers at time t
$\theta^r(t)$	wholesaler r's order rates to pharmaceutical firms at time t
$s^r(t)$	wholesaler r's sales rates to demand markets at time t

The control vectors are summarized in Table 2.

We consider inventories at 1) manufacturing sites, 2) distribution centers, and 3) wholesalers. Associated with each link $l \in \mathcal{L}$, where $\mathcal{L}$ is the set of all links, in the supply chain network illustrated in Figure 1 is a pre-specified time duration for material flows. It is possible for each pair of nodes to have multiple links depending on the speed of shipment. For example, a standard shipping between two nodes can be expressed as one link while an expedited shipping between the same two nodes can be expressed as another link. Let t_l denote the discrete time duration for link l. The firm f's inventory dynamics at manufacturing sites can be formulated as follows:

$$P_j^f(t) = e^{-\delta} P_j^f(t-1) + x_j^f(t) - \sum_{k \in \mathcal{K}^f} \sum_{l \in \mathcal{A}_{jk}^f} p_l^f(t) \qquad j \in \mathcal{J}^f, t \in [t_1, t_f] \tag{3}$$

$$P_j^f(0) = P_{j,0}^f \qquad j \in \mathcal{J}^f \tag{4}$$

$$P_j^f(t) \geq 0 \qquad j \in \mathcal{J}^f, t \in [t_0, t_f] \tag{5}$$

where $P_j^f(t)$ is the firm f's inventory level at manufacturing site j at time t, $t_1 = t_0 + 1$, $P_{j,0}^f \in \Re_+^1$ represents firm f's initial inventory at site j, and $\mathcal{A}_{jk}^f$ is firm f's set of all links connecting its manufacturing site j and distribution center k. Equation (3) represents a flow conservation showing that the inventory level at time t equals the summation of the inventory level at time $(t-1)$ multiplied by a deterioration factor $e^{-\delta}$ and the amount of production, subtracted by the amount of drugs sent to distribution centers[2]. The initial stock conditions are expressed in (4). If the stock at the terminal time is to be considered, constraints similar to (4) but with respect to the terminal time can be added.

[2]The deterioration factor according to equation (1) is $e^{-\delta t}$ for which $t = 1$ is used to represent the deterioration as one time unit elapses.

Likewise, firm f's inventory dynamics at distribution centers can be formulated as follows:

$$D_k^f(t) = e^{-\delta} D_k^f(t-1) + \sum_{j \in \mathcal{J}^f} \sum_{l \in \mathcal{A}_{jk}^f} e^{-\delta t_l} p_l^f(t - t_l) - \sum_{r \in \mathcal{R}} \sum_{n \in \mathcal{N}^r} \sum_{l \in \mathcal{B}_{kn}^{f,r}} d_l^f(t) \quad k \in \mathcal{K}^f, t \in [t_1, t_f] \quad (6)$$

$$\sum_{n \in \mathcal{N}^r} \sum_{k \in \mathcal{K}^f} \sum_{l \in \mathcal{B}_{kn}^{f,r}} e^{-\delta t_l} d_l^f(t) = o^{f,r}(t) \quad r \in \mathcal{R} \quad (7)$$

$$D_k^f(0) = D_{k,0}^f \qquad k \in \mathcal{K}^f \quad (8)$$

$$D_k^f(t) \geq 0 \qquad k \in \mathcal{K}^f, t \in [t_0, t_f] \quad (9)$$

where $D_k^f(t)$ is the firm f's inventory at distribution center k at time t, $D_{k,0}^f \in \Re_+^1$ represents firm f's initial inventory at distribution center k, and $\mathcal{B}_{kn}^{f,r}$ is firm f's set of all links connecting its distribution center k and wholesaler r's warehouse n. The second and the third term in the right-hand-side of equation (6) show the summation of drug input flows from manufacturing sites and the summation of drug output flows to wholesalers, respectively. Note that, in the second term, there is a deterioration factor $e^{-\delta t_l}$, where t_l is the shipping time for link $l \in \mathcal{A}^f$, implying that the flow from manufacturing sites is reduced by the factor of $e^{-\delta t_l}$ when it reaches the successor node due to perishability. The left side of (7) is the amount of shipment from pharmaceutical firm f's distribution centers to wholesaler r's warehouses and the right-hand-side of (7) is the amount of order wholesaler r places to pharmaceutical firm f at time t. Note that the firms do consider the amount of deterioration during the shipment when they send out pharmaceuticals as is apparent in the left side of (7) such that the wholesalers will receive the amount they order when the shipment arrives.

The wholesaler r's inventory dynamics can be formulated in a similar fashion:

$$W_n^r(t) = e^{-\delta} W_n^r(t-1) + \sum_{f \in \mathcal{F}} \sum_{k \in \mathcal{K}^f} \sum_{l \in \mathcal{B}_{kn}^{f,r}} e^{-\delta t_l} d_l^f(t - t_l) - \sum_{m \in \mathcal{M}^r} s_n^{r,m}(t) \qquad n \in \mathcal{N}^r, t \in [t_1, t_f] \quad (10)$$

$$W_n^r(0) = W_{n,0}^r \qquad n \in \mathcal{N}^r \quad (11)$$

$$W_n^r(t) \geq 0 \qquad n \in \mathcal{N}^r, t \in [t_0, t_f] \quad (12)$$

where $W_n^r(t)$ is the wholesaler r's inventory in its warehouse in location n at time t, $W_{n,0}^r \in \Re_+^1$ represents firm r's initial inventory in n, and $\mathcal{M}^r$ is the set of demand markets to which wholesaler

r's supply pharmaceuticals. Note that we do not allow backorders in the inventories as in (5), (9), and (12).

3.3 Mathematical Programming Formulation

Now we are ready to introduce objective functions of pharmaceutical firms and wholesalers. The net profit of pharmaceutical firm f can be expressed as follows:

$$F^f(x^f, p^f, d^f; o^f) = \sum_{t=t_0}^{t_f} e^{-\rho t} \left\{ \sum_{r\in\mathcal{R}} \sum_{l\in\mathcal{B}^{f,r}} \pi^{f,r} e^{-\delta t_l} d_l^f(t) - \sum_{j\in\mathcal{J}^f} c_j^f\left(x_j^f, t\right) - \sum_{l\in\mathcal{A}^f} z_{l,1}^f\left(p_l^f, t\right) \right.$$
$$\left. - \sum_{l\in\mathcal{B}^f} z_{l,2}^f\left(d_l^f, t\right) - \sum_{j\in\mathcal{J}^f} y_j^f\left(P_j^f, t\right) - \sum_{k\in\mathcal{K}^f} u_k^f\left(D_k^f, t\right) \right\} + \Psi^f(t_f) \qquad (13)$$

where ρ is the exogenous discount rate, $\pi^{f,r}$ represents the contracted unit price firm f charges wholesaler r, $c_j^f(\cdot)$ is the production cost function, $z_{l,1}^f(\cdot)$ and $z_{l,2}^f(\cdot)$ are the cost functions of material flows (e.g., shipping costs) between manufacturing sites and distribution centers, and between distribution centers and wholesalers, respectively. By use of the function $z_{l,2}^f(\cdot)$, the cost of material flow from the pharmaceutical firm f to wholesaler r can be set as desired. For example, if it's a constant function set as zero, then the firm f is not responsible for the material flow cost to wholesalers; the cost may be embedded in the drug price wholesaler r pays to firm f, denoted by $\pi^{f,r}$, agreed between firm f and wholesaler r. The cost function can also be defined in such a way that firm f is responsible for shipping to wholesalers. In addition, $y_j^f(\cdot)$ and $u_k^f(\cdot)$ are firm f's inventory cost functions at manufacturing sites and distribution centers, respectively. Note that the pharmaceutical firms make a profit based on the actual amount of pharmaceuticals the wholesalers receive, implying that pharmaceutical firms are responsible for perishability until the products reach the wholesalers. The wholesalers are only responsible for their own deteriorating inventory. The salvage value of inventories at terminal time is represented by $\Psi^f(t_f) = \Psi^f\left(P^f(t_f), D^f(t_f)\right)$. We assume that x^f, p^f, and d^f are subject to exogenous upper bounds due to, e.g., physical restrictions or contracts between pharmaceutical firms and wholesalers such that:

$$0 \le x_j^f(t) \le \bar{x}_j^f \quad j \in \mathcal{J}^f, t \in [t_0, t_f] \qquad (14)$$

$$0 \le p_l^f(t) \le \bar{p}_l^f \quad l \in \mathcal{A}^f, t \in [t_0, t_f] \qquad (15)$$

$$0 \leq d_l^f(t) \leq \bar{d}_l^f \quad l \in \mathcal{B}^f, t \in [t_0, t_f] \tag{16}$$

Note that $\bar{x}_j^f, \bar{p}_l^f, \bar{d}_l^f \in \Re_{++}^1$ are given constants. Now we are ready to define the set of firm f's feasible solutions as:

$$\Xi^f = \{(x^f, p^f, d^f) : (3)\text{–}(9) \text{ and } (14)\text{–}(16) \text{ hold.}\} \tag{17}$$

Note that the feasible set Ξ^f is compact and convex. The pharmaceutical firm f's problem is then:

$$\max\ F^f(x^f, p^f, d^f; o^f) \tag{18}$$

$$\text{s.t. } (x^f, p^f, d^f) \in \Xi^f \tag{19}$$

Turning our attention to wholesalers, the net profit of wholesaler r can be expressed as:

$$R^r(s^r, \theta^r; s^{-r}) = \sum_{t=t_0}^{t_f} e^{-\rho t} \left\{ \sum_{m \in \mathcal{M}^r} \sum_{n \in \mathcal{N}^R} \pi_m(s^{r,m}, t; s^{-r,m}) s_n^{r,m}(t) \right. \\ \left. - \sum_{f \in \mathcal{F}} \pi^{f,r} \theta^{r,f}(t) - \sum_{n \in \mathcal{N}^r} g_n^r\left(W_n^r, t\right) \right\} + \Phi^r(t_f) \tag{20}$$

where $\pi_m(s^{r,m}, t; s^{-r,m})$ is the unit price function of the pharmaceutical product at demand market m at time t that depends not only on wholesaler r's sales but also on all other wholesalers' sales at the same demand market m, and $g_n^r(\cdot)$ is the wholesaler r's inventory cost function at warehouse n. We define $s^{-r,m} = (s^{g,m} :\ g \in \mathcal{R} \setminus \{r\})$ where $\mathcal{R} \setminus \{r\}$ represents the set of all wholesalers but r. The first, second, and third term in (20) represent wholesaler r's revenue, the amount of money wholesaler r pays to pharmaceutical firms, and wholesaler r's inventory cost, respectively. The salvage value of inventories at terminal time is represented by $\Phi^r(t_f) = \Phi^r\left(W^r(t_f)\right)$. Like the pharmaceutical firm's case, we assume that wholesalers' controls, $s_n^{r,m}$, are subject to exogenous upper bounds such that

$$0 \leq s_n^{r,m}(t) \leq \bar{s}_n^{r,m} \quad \forall m \in \mathcal{M}^r, n \in \mathcal{N}^r, t \in [t_0, t_f] \tag{21}$$

where $\bar{s}_n^{r,m} \in \Re_{++}^1$, $\forall m \in \mathcal{M}^r, r \in \mathcal{R}$ are given constants. We define the set of wholesaler r's feasible

solutions as:

$$\Omega^r = \{(s^r, \theta^r) : (10)\text{–}(12) \text{ and } (21) \text{ hold.}\} \tag{22}$$

The feasible set Ω^r is also compact and convex. The wholesaler r's problem is then:

$$\max R^r(s^r, \theta^r; s^{-r}) \tag{23}$$

$$\text{s.t. } (s^r, \theta^r) \in \Omega^r \tag{24}$$

It is important to stress at this point that both the pharmaceutical firm's problem (18)–(19) and the wholesaler's problem (23)–(24) are in the form of convex programming if all cost functions are concave.

3.4 Nash Equilibria

The competition across players within the context of supply chain management has been considered in the literature; see, e.g., Chung et al. (2013), Chung et al. (2014), and Friesz et al. (2011). We assume that, in oligopolistic pharmaceutical supply chains, each wholesaler makes decisions in a noncooperative manner, implying that it seeks to maximize its own profit. At the state called an equilibrium, no firm can increase its profit unilaterally without other firms' further actions. We formally define such an equilibrium as follows.

Definition 1. [Wholesaler Nash Equilibrium] A vector of wholesaler r's decisions, $(s^{r*}, \theta^{r*}) \in \Omega^r$, is called a Cournot-Nash equilibrium if, for each firm $r \in \mathcal{R}$, the following condition is satisfied:

$$R^r(s^{r*}, \theta^{r*}; s^{-r*}) \geq R^r(s^r, \theta^r; s^{-r*}) \quad \forall (s^r, \theta^r) \in \Omega^r \tag{25}$$

where $s^{-r*} = (s^{g*} : \ g \in \mathcal{R} \setminus \{r\})$ and $s^{-r*} \in \Omega^{-r} = \prod_{g \in \mathcal{R} \setminus \{r\}} \Omega^g$.

4 Variational Inequality Formulation and Interior-Point Algorithm

In this section, we formulate the variational inequality (VI) that enables us to attain decision rules from which managerial insights may be derived and that provides computationally tractable algorithms such as interior-point methods. We now introduce $X = \left(X^f : f \in \mathcal{F}\right)$ and $Y = (Y^r : r \in \mathcal{R})$

where

$$X^f = \begin{bmatrix} x^f \\ p^f \\ d^f \end{bmatrix}, \qquad Y^r = \begin{bmatrix} s^r \\ \theta^r \end{bmatrix}$$

for notational convenience and present the following Variational Inequality (VI) formulation.

Theorem 1 (Variational Inequality Formulation)**.** Assuming that the profit functions $F^f(\cdot)$ and $R^r(\cdot)$ are concave, continuous, and twice continuously differentiable with respect to the corresponding arguments, then $X^* \in \Xi$ and $Y^* \in \Omega$, where $\Xi = \bigcup_{f\in\mathcal{F}} \Xi^f$ and $\Omega = \bigcup_{r\in\mathcal{R}} \Omega^r$, are the pharmaceutical supply chain's Cournot-Nash equilibrium if and only if the following variational inequality is satisfied:

$$\sum_{f\in\mathcal{F}} \left\langle \nabla_{X^f} F^f(X^*), X^f - X^{f*} \right\rangle + \sum_{r\in\mathcal{R}} \left\langle \nabla_{Y^r} R^r(Y^*), Y^r - Y^{r*} \right\rangle \geq 0 \quad \forall X^f \in \Xi^f, Y^r \in \Omega^r \tag{26}$$

where $< \cdot, \cdot >$ represents the inner product in the Euclidean space, $\nabla_{X^f} F^f(X^*)$ and $\nabla_{Y^r} R^r(Y^*)$ represent the gradients of $F^f(X^*)$ and $R^r(Y^*)$ with respect to X^f and Y^r, respectively.

Proof. see Friesz (2010) □

With the following vector function $H(\cdot)$ and vector Z defined as:

$$H(Z) = \begin{bmatrix} \nabla_{X^1} F^1(X^*) \\ \nabla_{X^2} F^2(X^*) \\ \vdots \\ \nabla_{Y^1} R^1(Y^*) \\ \nabla_{Y^2} R^2(Y^*) \\ \vdots \end{bmatrix}, \qquad Z = \begin{bmatrix} X \\ Y \end{bmatrix} \tag{27}$$

the VI formulation (26) can be re-written as follows:

$$\left\langle H(Z^*)^T, Z - Z^* \right\rangle \geq 0 \quad \forall Z \in \Lambda \tag{28}$$

where $\Lambda = \Xi \times \Omega$. We call the above problem $VI(H, \Lambda)$. From this re-formulation (28), we derive the Karush-Kuhn-Tucker (KKT) necessary conditions that will be a basis for our interior-point

algorithm.

4.1 Karush-Kuhn-Tucker Conditions

Theorem 2 (KKT necessary conditions for $VI(H, \Lambda)$)**.** Let us assume that $F(X)$ and $R(Y)$ are continuous on Ξ and Ω, respectively. Also, let $Z^* \in \Lambda$ be the solution of $VI(H, \Lambda)$. Let $g(Z)$ be constraints such that $g(Z) \geq 0$. If the gradients of the constraint satisfying $\nabla g(Z^*) = 0$ are linearly independent, then we introduce a so-called Lagrangian multiplier λ such that

$$H(Z^*) + [\nabla g(Z^*)]^T \lambda = 0 \tag{29}$$

$$\lambda^T g(Z^*) = 0 \tag{30}$$

$$\lambda \geq 0 \tag{31}$$

are satisfied. We call (29)–(31) the necessary conditions of $VI(H, \Lambda)$.

Proof. Note that Z^* is the solution of the following mathematical program:

$$\max \quad [H(Z^*)]^T Z \tag{32}$$

$$\text{s.t.} \quad Z \in \Lambda \tag{33}$$

The KKT necessary conditions for the above mathematical programming problem are:

$$H(Z^*) + [\nabla g(Z^*)]^T \lambda = 0 \tag{34}$$

$$\lambda^T g(Z^*) = 0 \tag{35}$$

$$\lambda \geq 0 \tag{36}$$

The above conditions are also sufficient because the assumed linear independency of binding constraint meets the constraint qualification. The equations and inequalities (34)–(36) are identical to equations (29)–(31). This completes the proof. □

Note that the necessary conditions of $VI(H, \Lambda)$, (29)–(31), are also sufficient because Λ is convex. The formal representation for this observation is ready in the next theorem.

Theorem 3 (Sufficient conditions for $VI(H, \Lambda)$)**.** If the gradients of the constraint satisfying $\nabla g_i(Z^*) = 0$ are linearly independent, Λ is convex, $Z^* \in \Lambda$, and (29)–(31) hold, then Z^* is also the solution to $VI(H, \Lambda)$.

Proof. Note that the mathematical programming problem (32)–(33) is in the form of convex programming. Also, (29)–(31) are sufficient conditions for the convex mathematical programming problem, (32)–(33). Thus,

$$[H(Z^*)]^T Z \leq [H(Z^*)]^T Z^* \quad \forall Z \in \Lambda \tag{37}$$

That is,

$$[H(Z^*)]^T (Z - Z^*) \leq 0 \quad \forall Z \in \Lambda \tag{38}$$

which implies that Z^* solves $VI(H, \Lambda)$. □

In summary, the key aspect that we would like to stress in this section is that a solution to (29)–(31) is also a solution to the integrated pharmaceutical supply chain problem expressed as $VI(H, \Lambda)$ and, subsequently, we will attempt to solve (29)–(31) using an interior point method.

4.2 Decision Rules from KKT Necessary Conditions

Decision rules with respect to supply chain control variables can be derived from the KKT conditions of the VI. This is of particular interest, as they may provide managerial insights into the pharmaceutical supply chain equilibrium performances. Note that the KKT conditions (29)–(31) can be rewritten with respect to each control vector as follows.

$$\nabla_{X^f} F^f(X^*) + [\nabla g_X(X^*)]^T \lambda_X = 0 \tag{39}$$

$$\nabla_{Y^r} R^r(Y^*) + [\nabla g_Y(Y^*)]^T \lambda_Y = 0 \tag{40}$$

$$[\lambda_X]^T g_X(X^*) = 0 \tag{41}$$

$$[\lambda_Y]^T g_Y(Y^*) = 0 \tag{42}$$

$$\lambda_X, \lambda_Y \geq 0 \tag{43}$$

where λ_X and λ_Y are Lagrangian multipliers for X and Y respectively and g_X and g_Y are constraints for X and Y respectively. By employing these conditions, the following theorem is derived.

Theorem 4 (Pharmaceutical firms' decision rules)**.** At equilibria, the firm f's decision rules with respect to each control variable $x_j^f,\ p_l^f$, and d_l^f are presented as follows.

$$x_j^f > 0 \rightarrow MC_x = e^{\rho t}\lambda_{g1},\ MC_x < e^{\rho t}\lambda_{g1} \rightarrow x_j^f = 0 \tag{44}$$

$$p_l^f > 0 \rightarrow MC_p = -e^{\rho t}\lambda_{g1} + e^{\rho t - \delta t_l}\lambda_{g2},\ MC_p < -e^{\rho t}\lambda_{g1} + e^{\rho t - \delta t_l}\lambda_{g2} \rightarrow p_l^f = 0 \tag{45}$$

$$d_l^f > 0 \rightarrow MC_d = e^{-\delta t_l}\pi^{f,r} - e^{\rho t}\lambda_{g2} - e^{\rho t - \delta t_l}\lambda_{g3},\ MC_d < e^{-\delta t_l}\pi^{f,r} - e^{\rho t}\lambda_{g2} - e^{\rho t - \delta t_l}\lambda_{g3} \rightarrow p_l^f = 0 \tag{46}$$

where $MC_x = \partial c_j^f(x_j^f, t)/\partial x_j^f$, $MC_p = \partial z_{l,1}^f(p_l^f, t)/\partial p_l^f$, and $MC_d = \partial z_{l,2}^f(d_l^f, t)/\partial d_l^f$, which imply the marginal cost arising at time t from the unit change of the production rate, x_j^f, output flow to distribution center, p_l^f, and outflow to wholesaler, d_l^f, respectively. In addition, λ_{g1}, λ_{g2}, and λ_{g3} are multipliers for constraints (3), (6), and (7), respectively.

Proof. In regard to the control vector x^f, we derive the following from (39).

$$\nabla_{x_j^f} F^{f*} + \left[\nabla_{x_j^f} g_X\right]^T \lambda_X = -e^{-\rho t} MC_x + \lambda_{g1} - \lambda_{b1} = 0 \tag{47}$$

where λ_X is a multiplier vector and λ_{b1} is a multiplier from (14). Also from (41), we derive:

$$x_j^f \lambda_{b1} = 0 \tag{48}$$

It follows that

$$x_j^f > 0 \rightarrow \lambda_{b1} = 0 \rightarrow e^{-\rho t} MC_x = \lambda_{g1} \tag{49}$$

$$e^{-\rho t} MC_x < \lambda_{g1} \rightarrow \lambda_{b1} > 0 \rightarrow x_j^f = 0 \tag{50}$$

which is identical to (44). The decision rules for p_l^f and d_l^f can be proven in a similar fashion. This completes proof. □

To interpret the decision rule (44), it is essential to note that the multiplier λ_{g1} represents the

shadow price of the inventory constraint (3) of firm f, and, therefore, $e^{\rho t}\lambda_{g1}$ is the future inventory cost increament as a result of increasing the production today. This follows that each firm f,by implementing the decision rule (44), equates its marginal production cost to a future inventory cost increment at its manufacturing site when the Cournot-Nash equilibrium is achieved. That is, at the equilibrium, $MC_x = e^{\rho t}\lambda_{g1}$ if $x_j^f > 0$. The decision rule also implies that if the future inventory cost increment is larger than the marginal cost of production, the firm should not produce ($x_j^f = 0$). Similar conclusions can be made for decision rules (45) and (46). Turning out attention to wholesalers, we present the following theorem.

Theorem 5 (Wholesalers' decision rules)**.** At equilibria, the wholesaler r's decision rules with respect to each control variable $s_n^{r,m}$ and $\theta^{r,f}$ are presented as follows.

$$s_n^{r,m} > 0 \rightarrow MP_s = e^{\rho t}\lambda_{g4},\ MP_s < e^{\rho t}\lambda_{g4} \rightarrow s_n^{r,m} = 0 \tag{51}$$

$$\theta^{r,f} > 0 \rightarrow MC_\theta = e^{\rho t}\lambda_{g4},\ MC_\theta < e^{\rho t}\lambda_{g4} \rightarrow \theta^{r,f} = 0 \tag{52}$$

where $MP_s = \pi_m$ and $MC_\theta = \pi^{f,r}$, which imply the marginal profit or cost arising at time t from the unit change of the sales rate, $s_n^{r,m}$, order rate, $\theta^{r,f}$, respectively. In addition, λ_{g4} is the multiplier for constraint (10).

This theorem can be proven in the same manner as for Theorem 4. The implication of the decision rules (51) and (52) is also identical as the pharmaceutical firm's case. That is, by implementing the decision rules, the wholesaler equates its marginal profit arising from increasing its sales by one unit to its marginal cost.

4.3 Interior Point Algorithm for Variational Inequalities

One of the significant advantages of employing the VI formalism is that it promotes a computationally tractable methods including fixed-point methods, complementarity problems, and interior-point methods. For theoretical details on how to use such methods from the VI formulation, we refer readers to Harker and Pang (1990), Facchinei and Pang (2007), and Friesz (2010). For the use of interior-point methods for the VI, see Nesterov et al. (1994), Wright (1997), and Ye (2011). For the VI application areas, see, for example, Chung et al. (2012), Chung et al. (2013), and Chung et al.

(2014).

A modified Newton step for (29)-(31) is as follows.

$$\begin{bmatrix} \nabla_Z H(Z^*) + \nabla_Z \left[\nabla g(Z^*)\right]^T \lambda & \left[\nabla g(Z^*)\right] \\ \nabla_Z g(Z)^T \lambda & g(Z) \end{bmatrix} \begin{bmatrix} \Delta Z \\ \Delta \lambda \end{bmatrix} = \begin{bmatrix} -H(Z^*) - \left[\nabla g(Z^*)\right]^T \lambda \\ -\lambda^T g(Z) + \sigma \mu e \end{bmatrix} \tag{53}$$

where μ is the duality measure, $\sigma \in [0, 1]$ is a step length adjustment coefficient, and $e = [\ 1 \quad 1 \quad 1 \quad ... \quad 1]^T$. Then, the interior-point barrier algorithm can be stated as follows.

Interior–Point Barrier Method— Given Z^0, λ^0 with $Z^0 \in \Omega$, $\lambda^0 \geq 0$.
for *k = 0 1, 2, ...* **do**
Solve (53) to obtain ΔZ and $\Delta \lambda$.
Find α_Z by solving

$$\begin{aligned} \max \quad & \alpha_Z \\ Z + \alpha_Z \Delta Z &\geq 0 \\ \alpha_Z &\leq 1. \end{aligned}$$

Find α_λ by solving

$$\begin{aligned} \max \quad & \alpha_\lambda \\ z + \alpha_\lambda \Delta z &\geq 0 \\ \alpha_\lambda &\leq 1. \end{aligned}$$

Determine the step length by $\alpha_k = \min(\alpha_Z, \alpha_\lambda)$.
Then, set
$(Z^{k+1}, \lambda^{k+1}) \leftarrow (Z^k, \lambda^k) + 0.99\alpha_k(\Delta Z, \Delta \lambda)$.
Check terminal criteria
end

Algorithm 1: Interior-Point Barrier Algorithm

It is worth pointing out that the leftmost matrix in (53) is sparse containing lots of zeros. In our numerical example presented subsequently, we use the matrix division operator using Gaussian elimination in Matlab to solve (53) while the sub-problems to find α_Z and α_λ are solved using CPLEX.

5 Numerical Example with Two Pharmaceutical Firms and Four Wholesalers

We consider a pharmaceutical supply chain network with two pharmaceutical firms and four wholesalers. The network is depicted in Figure 2. Each link is denoted by numbers in increasing order, and the numerical values in parentheses associated with each link mean corresponding shipping

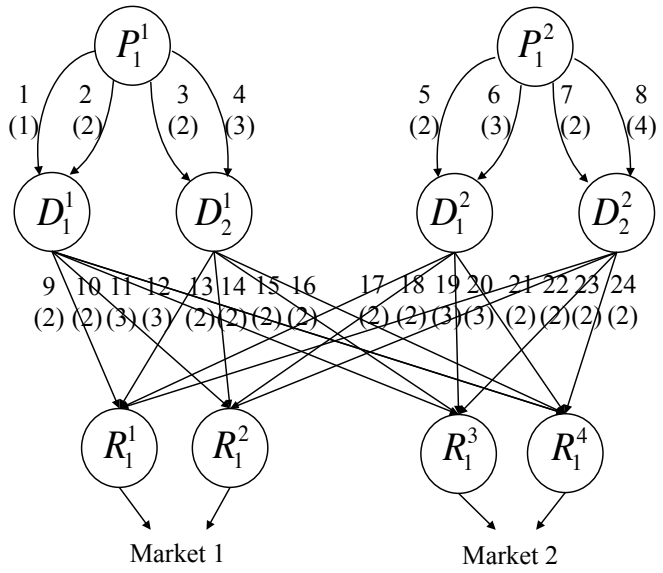

Figure 2: Supply Chain Network with 2 Pharmaceutical Firms and 4 Wholesalers

times. We use one week as a time unit in this example. Therefore, for example, it will take one, two, two, and three week(s) to ship materials using links 1, 2, 3, and 4, respectively.

5.1 Numerical Example Setup

We assume each pharmaceutical firm has one manufacturing site and two distribution centers, denoted by P_1^1, D_1^1, and D_2^1 for firm 1, and P_1^2, D_1^2, and D_2^2 for firm 2. Among the four wholesalers, the first two wholesalers supply pharmaceuticals to market 1 and the other two supply pharmaceuticals to market 2. We assume each wholesaler has one warehouse and warehouses are denoted by R_1^1, R_1^2, R_1^3, and R_1^4, for wholesaler 1, 2, 3, and 4, respectively. The set of links are $\mathcal{A}^1$ =(1, 2, 3, 4), $\mathcal{B}^{1,1}$ =(9, 13), $\mathcal{B}^{1,2}$ =(10, 14), $\mathcal{B}^{1,3}$ =(11, 15), $\mathcal{B}^{1,4}$ =(12, 16), $\mathcal{A}^2$ =(5, 6, 7, 8), $\mathcal{B}^{2,1}$ =(17,21), $\mathcal{B}^{2,2}$ =(18,22), $\mathcal{B}^{2,3}$ =(19,23), and $\mathcal{B}^{2,4}$ =(20,24). The pharmaceutical firm 1's control vector is $\big(x_1^1(t)$, $p_1^1(t)$, $p_2^1(t)$, $p_3^1(t)$, $p_4^1(t)$, $d_9^1(t)$, $d_{10}^1(t)$, $d_{11}^1(t)$, $d_{12}^1(t)$, $d_{13}^1(t)$, $d_{14}^1(t)$, $d_{15}^1(t)$, $d_{16}^1(t)\big)^T$, while pharmaceutical firm 2's control vector is $\big(x_1^2(t)$, $p_5^2(t)$, $p_6^2(t)$, $p_7^2(t)$, $p_8^2(t)$, $d_{17}^2(t)$, $d_{18}^2(t)$, $d_{19}^2(t)$, $d_{20}^2(t)$, $d_{21}^2(t)$, $d_{22}^2(t)$, $d_{23}^2(t)$, $d_{24}^2(t)\big)^T$. The wholesalers' control vectors are $\left(s_1^{1,1}(t), \theta^1(t)\right)^T$, $\left(s_1^{2,1}(t), \theta^2(t)\right)^T$, $\left(s_1^{3,2}(t), \theta^3(t)\right)^T$, and $\left(s_1^{4,2}(t), \theta^4(t)\right)^T$ for wholesaler 1, 2, 3, and 4, respectively.

Over a planning horizon, each firm adjusts its controls at each instant of time to maximize its overall profit in a non-cooperative fashion. We define the production cost function for pharmaceutical

firms as:

$$c_j^f(x^f, t) = c_{f,j,1}\left(x_j^f(t)\right)^2 + c_{f,j,2}x_j^f(t) \quad t \in [t_0, t_f],\ j \in \mathcal{J}^f,\ f \in \mathcal{F} \tag{54}$$

where $c_{f,j,1}$ and $c_{f,j,2}$ are exogenous constants, and define the flow cost functions as:

$$z_{l,1}^f(p_l^f, t) = z_{f,l,1}\left(p_l^f(t)\right)^2 + z_{f,l,2}p_l^f(t) \quad t \in [t_0, t_f],\ l \in \mathcal{A}^f,\ f \in \mathcal{F} \tag{55}$$

$$z_{l,2}^f(d_l^f, t) = w_{f,l,1}\left(d_l^f(t)\right)^2 + w_{f,l,2}d_l^f(t) \quad t \in [t_0, t_f],\ l \in \mathcal{B}^f,\ f \in \mathcal{F} \tag{56}$$

where $z_{f,l,1}$, $z_{f,l,2}$, $w_{f,l,1}$, and $w_{f,l,2}$ are exogenous and dependent on each link l. Inventory cost functions are defined as:

$$y_j^f(P_j^f, t) = y_{f,j}P_j^f(t) \quad t \in [t_0, t_f],\ j \in \mathcal{J}^f,\ f \in \mathcal{F} \tag{57}$$

$$u_k^f(D_k^f, t) = u_{f,k}D_k^f(t) \quad t \in [t_0, t_f],\ k \in \mathcal{K}^f,\ f \in \mathcal{F} \tag{58}$$

where $y_{f,j}$ and $u_{f,k}$ are exogenous and dependent on location j or k. Price functions are defined in such a way that the drug price decrease as the sales increases, and vice versa. In particular, the wholesaler r's price in market m at time t is specified as:

$$\pi_m^r(t) = \pi_{m,1}^r - \pi_{m,2}^r \sum_{r \in \mathcal{R}} \sum_{n \in \mathcal{N}^r} s_m^{r,n}(t) \quad m \in \mathcal{M}^r,\ r \in \mathcal{R} \tag{59}$$

where $\pi_{m,1}^r$ and $\pi_{m,2}^r$ are given constants. Finally, wholesalers' inventory functions are as follows:

$$g_n^r(W_n^r, t) = g_{r,n}W_n^r(t) \quad t \in [t_0, t_f],\ n \in \mathcal{N}^r,\ r \in \mathcal{R} \tag{60}$$

where $g_{r,n}$ are given constants.

5.2 Case Study

We assume that pharmaceutical firms 1 and 2 are large drug manufacturers producing a homogeneous, generic substitute of a brand drug (e.g., pharmacy-branded acetaminophen for Tylenol) for the U.S. market, and that pharmaceutical firm 1 is U.S. based, having all of its facilities in the U.S. while pharmaceutical firm 2 is U.S. based but having its manufacturing site and distribution centers

Parameter	Firm 1	Firm 2
$c_{f,j,1}, c_{f,j,2}$	0.001, 0.120	0.001, 0.084

Table 3: Coefficients of Production Cost Functions

outside the U.S. (e.g., Mexico). Accordingly, firm 2 has lower production costs and lower shipping costs between its manufacturing site and distribution centers but has higher shipping costs between its distribution centers and wholesalers located in the U.S. We set the planning horizon as 21 weeks in our case study. The time unit is in weeks, manufacturing and material flow units are in boxes[3] per week, and the price unit is in 1,000 U.S. dollars. We also assume that the salvage value of remaining inventories at the end of the planning horizon is zero, mainly for the sake of simplicity, but it is still a plausible scenario in case of, e.g., seasonal drugs.

The price function parameters are specified as $\pi^r_{m,1} = 2.7$ and $\pi^r_{m,2} = 0.01$ for wholesalers 1 and 2 in market 1, and $\pi^r_{m,1} = 3.0$ and $\pi^r_{m,2} = 0.01$ for wholesalers 3 and 4 in market 2, which implies that while the base price for market 2 (=3.0) is higher than that of market 1 (=2.7), the price sensitivity is the same for both markets. The price pharmaceutical firm 1 charges to all wholesalers is $\pi^{f,r} = 0.65$, and the price pharmaceutical firm 2 charges to all wholesalers is $\pi^{f,r} = 0.58$. All other parameter values are summarized in Tables 3–5.

We consider the following three cases to analyze the impact of perishability (Case 2) and discount rate (Case 3):

Case 1: Nominal case with decay constant $\delta = 0.01$ and discount rate $\rho = 0.03$.

Case 2: Same as Case 1 but decay constant is increased from 0.01 to 0.015 (50% increase)

Case 3: Same as Case 1 but discount rate is increased from 0.03 to 0.045 (50% increase)

The main routine of interior-point barrier algorithm is written in Matlab, and sub-algorithms were solved using CPLEX. Apple Macbook Pro with 2.8 GHz Intel Core i7, 16gb ram was used for implementation and the results are summarized in Figures 3–9.

Figure 3 shows pharmaceutical firms' production rates and drug output flows through links 1, 4, 5, and 8 over the planning horizon. We omit here flows through links 2, 3, 6, and 7 due to space limitation. Firm 1's results are on the left while firm 2's results are on the right in Figure 3. In all cases, both pharmaceutical firms decrease their production rates toward the end of the

[3]We assume that each box contains 1,000 acetaminophens.

Link	Parameter	Firm 1	Firm 2
1 / 5	$z_{f,l,1}, z_{f,l,2}$	0.001, 0.130	0.001, 0.1120
2 / 6		0.001, 0.104	0.001, 0.0896
3 / 7		0.001, 0.130	0.001, 0.1120
4 / 8		0.001, 0.104	0.001, 0.0896
9 / 17	$w_{f,l,1}, w_{f,l,2}$	0.001, 0.06	0.002, 0.06
10 / 18		0.001, 0.06	0.002, 0.06
11 / 19		0.001, 0.06	0.002, 0.06
12 / 20		0.001, 0.06	0.002, 0.06
13 / 21		0.001, 0.06	0.002, 0.06
14 / 22		0.001, 0.06	0.002, 0.06
15 / 23		0.001, 0.06	0.002, 0.06
16 / 24		0.001, 0.06	0.002, 0.06

Table 4: Coefficients of Flow Cost Functions for Each Link

Firm	Firm 1			Firm 2			W1	W2	W3	W4
Parameter	$y_{1,1}$	$u_{1,1}$	$u_{1,2}$	$y_{2,1}$	$u_{2,1}$	$u_{2,2}$	$g_{1,1}$	$g_{2,1}$	$g_{3,1}$	$g_{4,1}$
Value	.025	.015	.025	.025	.015	.025	.015	.015	.015	.015

Table 5: Inventory Cost Parameters

planning horizon. This is because it is optimal for wholesalers to deplete inventory at the end of the planning horizon, leading to a gradual decrease in production. Accordingly, drug output flow rates decrease as time passes. Compared to Case 1, production rates and material flows are lower in Cases 2 and 3, which implies that the higher decay constant and the higher discount rate make unfavorable conditions for the supply chain in our numerical example setup. In addition, both firms prefer relatively inexpensive links (i.e., links 4 and 8, compared to links 1 and 5, respectively) having longer transit times. Furthermore, firm 2's manufacturing rates and drug output rates are higher than firm 1's because firm 2 has lower manufacturing costs and shipping costs.

Figure 4 shows drug output flows from distribution centers to wholesalers over the planning horizon. Unlike the drug output flows from manufacturing sites, distribution flows increase over time. This is mainly because wholesalers increase their sales in later time periods to maximize profits while depleting their inventories as shown in Figure 8, which is the optimal strategy for wholesalers due to inventory cost, perishability, and competition. Unlike the wholesalers, pharmaceutical firms do not deplete their inventories as in Figure 7, which may seem somewhat unexpected. However, since there are shipping costs associated with material flows, the pharmaceutical firms do not pursue zero

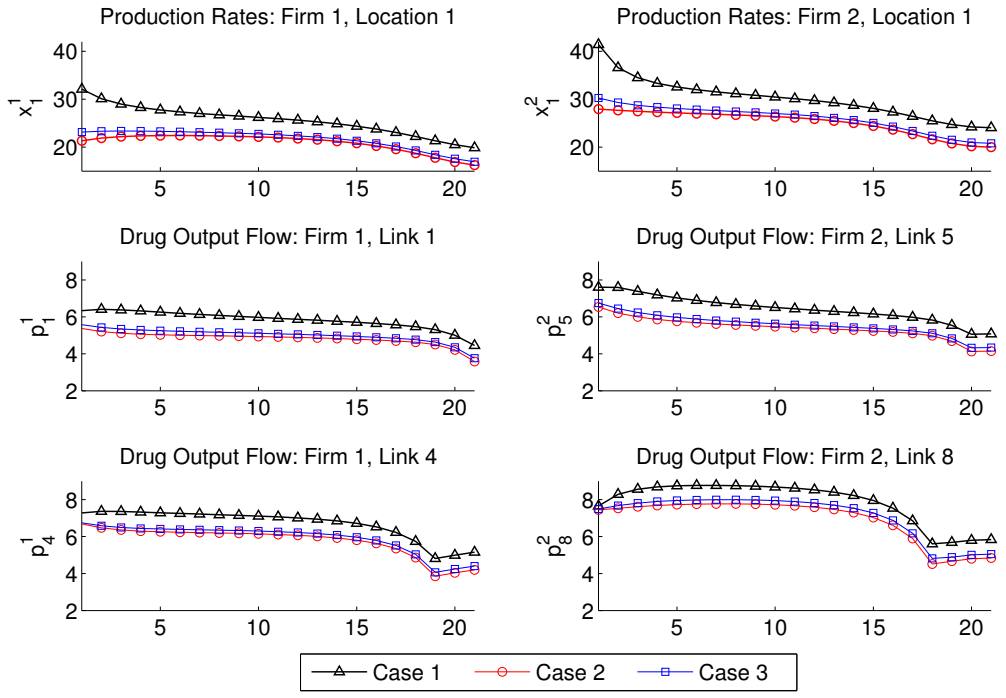

Figure 3: Pharmaceutical Firms' Production Rates

inventories at the end of the planning horizon and try to find the balance between the inventory cost and shipping cost. One important implication here is that pharmaceutical firms and wholesalers may have different inventory strategies depending on the phase of supply chains. In addition, note that the problem is solved in a noncooperative game setting, for which solutions may not be optimal but are equilibria. This implies that a manufacturing firm cannot lower its terminal inventory to maximize its own profit unless other players lower their inventories first.

Figure 5 shows wholesalers' sales rates. Of particular interest is to see how they adjust their sales rates over time. Sales rates are rather high in earlier time periods because wholesalers want to reduce their inventories quickly to avoid high inventory costs and, at the same time, to make a profit early. Then sales rates decrease to avoid low prices as a result of high competition in early time periods. As the wholesalers reduce sales after early periods, the prices increase. Finally, sales rates increase rather drastically near the end of the planning horizon to deplete inventories at the end of the horizon as can be seen in Figure 8 and, accordingly, prices drop rapidly. Note in particular that in case 2, sales rates are significantly different than in the other cases; they are highest in

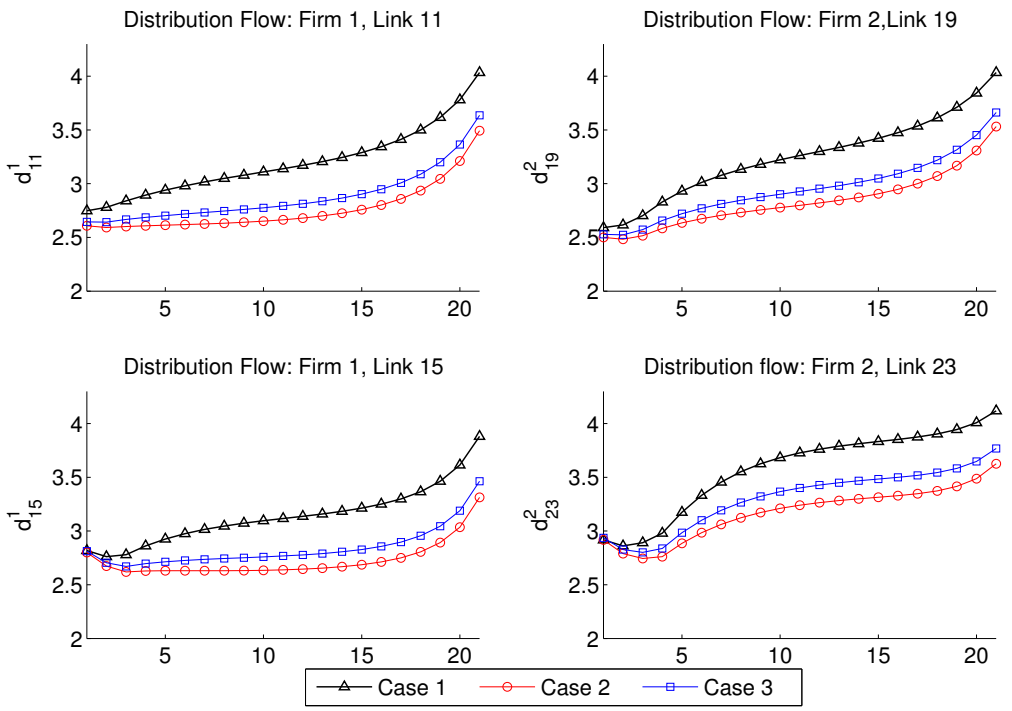

Figure 4: Pharmaceutical Firms' Distribution Flows

earlier periods, and wholesalers sell drugs quickly because of higher perishability, but due to price competition, the sales rates drop subsequently.

Price trajectories are shown in Figure 6. Note that in our case study the price function is defined (see (59)) in such a way that prices decrease as the total sales increase and vice versa. Therefore, prices drop near the end of planning horizon as firms increase sales to deplete their inventories.

Figures 7 and 8 show inventory levels at manufacturing sites, distribution centers, and demand markets. Note in particular that inventory levels are rather stable at manufacturing sites but change rather drastically at distribution centers especially in earlier periods because of flash sales in those periods. Wholesalers deplete their inventories at the end of the planning horizon. It is apparent in our specification that case 2 with a higher decay constant produces the lowest inventory levels for all supply chain stages due to perishability.

Figure 9 shows profits of pharmaceutical firms and wholesalers. The net profit decreases as perishability and discount rates increase because such makes the environment worse. Note that the most influential factor in terms of net profit is the decay constant, not the discount rate in our

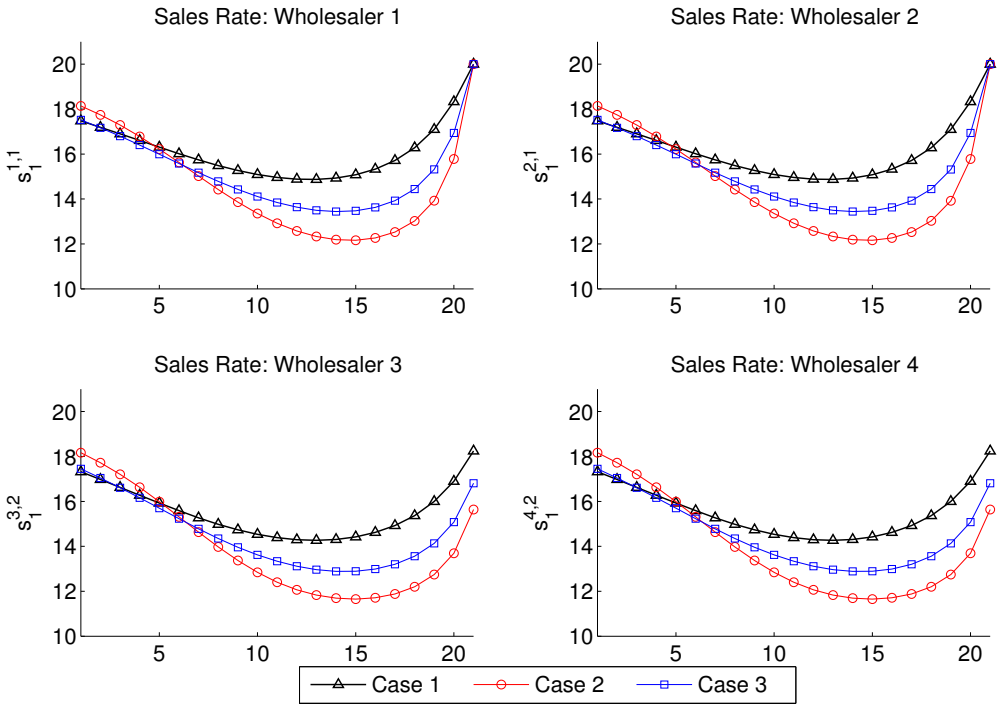

Figure 5: Wholesalers' Sales Rates

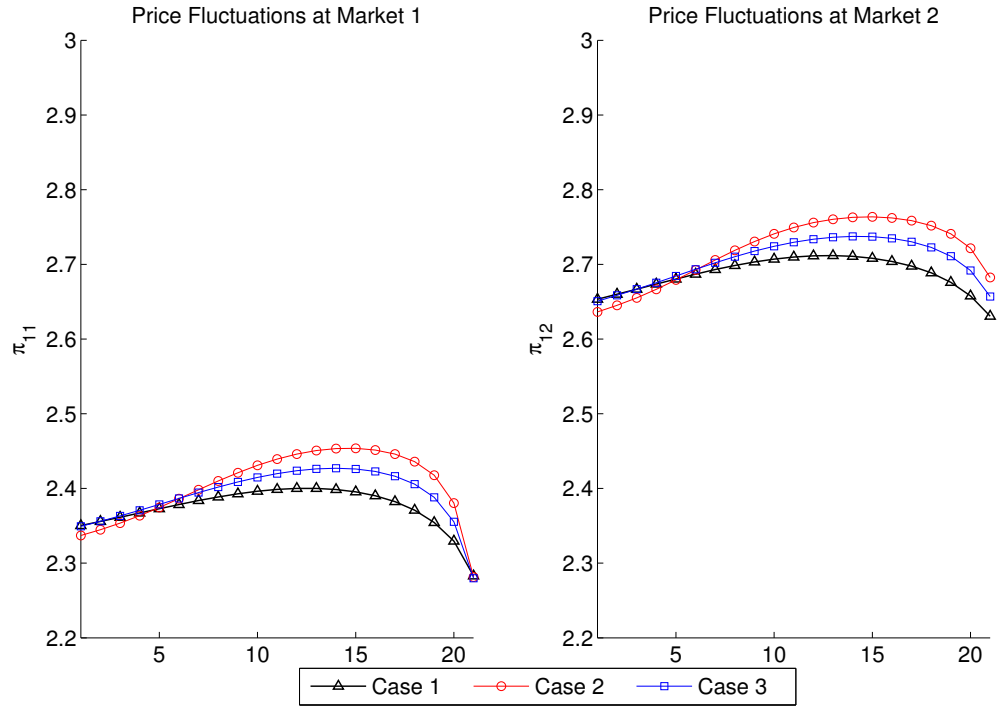

Figure 6: Price Trajectories in Each Market

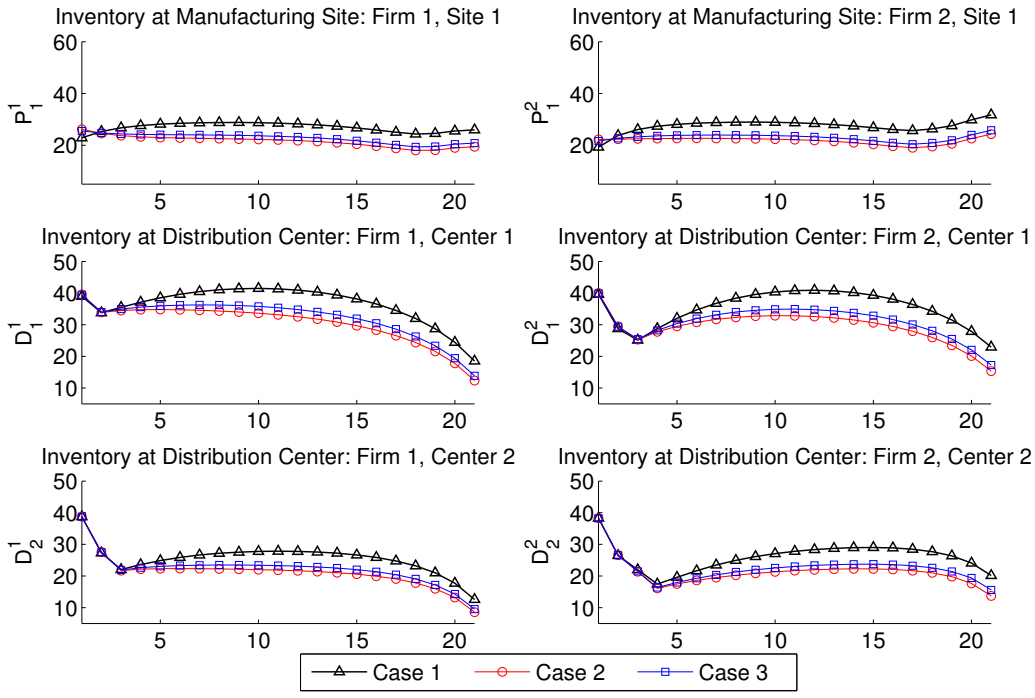

Figure 7: Pharmaceutical Firms' Inventories

parametrization.

6 Conclusions

In this paper, we have proposed a systematic, integrated pharmaceutical supply chain management framework that makes it possible to consider the impact of pharmaceuticals perishability on a wider supply chain scale via dynamic equilibrium solutions. In particular, we propose the formalism of dynamic optimization to tackle inventory management schemes at manufacturing sites, distribution centers, and wholesalers, explicitly considering deterioration of pharmaceutical products. In addition, our model enables us to capture price fluctuations as a result of wholesalers' oligopolistic competition and perishability of pharmaceutical products. Furthermore, we provide the supply chain decision rules derived from KKT necessary conditions, which presents ample managerial insights into the problem. In summary, our proposed model allows us to include key salient features such as oligopolistic competition, interdependence, drug deterioration, dynamic inventory control, and vertical integration to provide insights into complex pharmaceutical supply

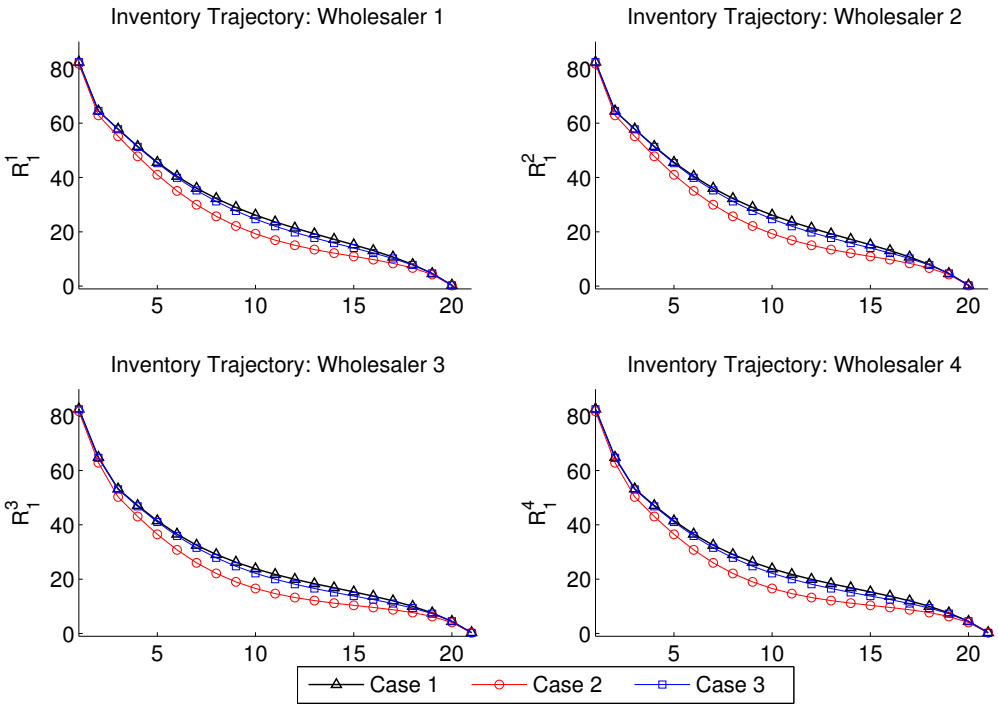

Figure 8: Wholesalers' Inventories

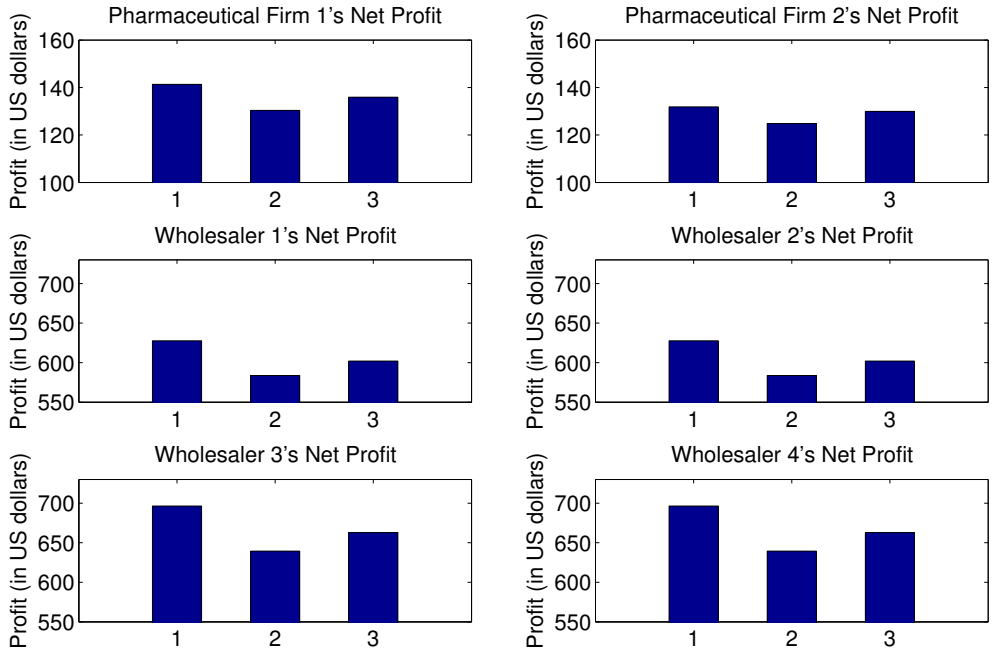

Figure 9: Each Firm's Net Profit

chain problems. The inclusion of above-mentioned salient features in our model gives rise to a computational challenge, which is resolved by use of the variational inequality formalism and the associated interior point method. In our numerical example, we show that, within the context of our specifications, perishability is indeed a factor that may dominate supply chain performances.

We note that our proposed framework is readily applicable beyond pharmaceutical supply chains to other perishable product supply chain problems with minor modifications. That is, this research lays a foundation for studying complex perishable product supply chain problems including food supply chains.

References

Blackburn, J. and G. Scudder (2009). Supply chain strategies for perishable products: the case of fresh produce. *Production and Operations Management 18*(2), 129–137.

Cherici, C., P. McGinnis, W. Russell, et al. (2011). Buyer beware: drug shortages and the gray market. *Premier Healthcare Alliance, August*.

Chung, S. H., T. L. Friesz, and R. D. Weaver (2014). Dynamic sustainability games for renewable resources–a computational approach. *Computers, IEEE Transactions on 63*(1), 155–166.

Chung, S. H., R. D. Weaver, and T. L. Friesz (2012). Oligopolies in pollution permit markets: A dynamic game approach. *International Journal of Production Economics 140*(1), 48–56.

Chung, S. H., R. D. Weaver, and T. L. Friesz (2013). Strategic response to pollution taxes in supply chain networks: Dynamic, spatial, and organizational dimensions. *European Journal of Operational Research 231*(2), 314–327.

Cournot, A. A. and I. Fisher (1897). *Researches into the Mathematical Principles of the Theory of Wealth*. Macmillan Co.

Deo, S. and C. J. Corbett (2009). Cournot competition under yield uncertainty: The case of the us influenza vaccine market. *Manufacturing & Service Operations Management 11*(4), 563–576.

Facchinei, F. and J.-S. Pang (2007). *Finite-dimensional variational inequalities and complementarity problems*. Springer Science & Business Media.

Friesz, T. L. (2010). *Dynamic optimization and differential games*, Volume 135. Springer.

Friesz, T. L., I. Lee, and C.-C. Lin (2011). Competition and disruption in a dynamic urban supply chain. *Transportation Research Part B: Methodological 45*(8), 1212–1231.

Gallego, G. and M. Hu (2014). Dynamic pricing of perishable assets under competition. *Management Science 60*(5), 1241–1259.

Ghare, P. and G. Schrader (1963). A model for exponentially decaying inventory. *Journal of Industrial Engineering 14*(5), 238–243.

Harker, P. T. and J.-S. Pang (1990). Finite-dimensional variational inequality and nonlinear complementarity problems: a survey of theory, algorithms and applications. *Mathematical programming 48*(1-3), 161–220.

Lian, Z. and L. Liu (2001). Continuous review perishable inventory systems: models and heuristics. *IIE Transactions 33*(9), 809–822.

Magazzini, L., F. Pammolli, and M. Riccaboni (2004). Dynamic competition in pharmaceuticals. *The European Journal of Health Economics, formerly: HEPAC 5*(2), 175–182.

Masoumi, A. H., M. Yu, and A. Nagurney (2012). A supply chain generalized network oligopoly model for pharmaceuticals under brand differentiation and perishability. *Transportation Research Part E: Logistics and Transportation Review 48*(4), 762–780.

Mihalopoulos, D. (2009). Expired or lost drugs costing city $1 million. *Chicago Tribune, February 3*.

Nahmias, S. (1982). Perishable inventory theory: A review. *Operations Research 30*(4), 680–708.

Nandakumar, P. and T. E. Morton (1993). Near myopic heuristics for the fixed-life perishability problem. *Management Science 39*(12), 1490–1498.

Nesterov, Y., A. Nemirovskii, and Y. Ye (1994). *Interior-point polynomial algorithms in convex programming*, Volume 13. SIAM.

Padmanabhan, G. and P. Vrat (1995). Eoq models for perishable items under stock dependent selling rate. *European Journal of Operational Research 86*(2), 281–292.

Papageorgiou, L. G. (2009). Supply chain optimisation for the process industries: Advances and opportunities. *Computers & Chemical Engineering 33*(12), 1931–1938.

Papageorgiou, L. G., G. E. Rotstein, and N. Shah (2001). Strategic supply chain optimization for the pharmaceutical industries. *Industrial & Engineering Chemistry Research 40*(1), 275–286.

Perakis, G. and A. Sood (2006). Competitive multi-period pricing for perishable products: A robust optimization approach. *Mathematical Programming 107*(1-2), 295–335.

Philip, G. C. (1974). A generalized eoq model for items with weibull distribution deterioration. *AIIE Transactions 6*(2), 159–162.

Scherer, F. M. (2007). An industrial organization perspective on the influenza vaccine shortage. *Managerial and Decision Economics 28*(4-5), 393–405.

Shah, N. (2004). Pharmaceutical supply chains: key issues and strategies for optimisation. *Computers & chemical engineering 28*(6), 929–941.

Vila-Parrish, A. R. and J. S. Ivy (2013). Managing supply critical to patient care: An introduction to hospital inventory management for pharmaceuticals. In *Handbook of Healthcare Operations Management*, pp. 447–463. Springer.

Vives, X. (2001). *Oligopoly pricing: old ideas and new tools*. MIT press.

Wiggins, S. N. and R. Maness (2004). Price competition in pharmaceuticals: The case of anti-infectives. *Economic Inquiry 42*(2), 247–263.

Wright, S. J. (1997). *Primal-dual interior-point methods*. Siam.

Ye, Y. (2011). *Interior point algorithms: theory and analysis*, Volume 44. John Wiley & Sons.