Optimization of Dynamic Networks

by

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This is to certify that I have examined this copy of a master's thesis by

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ABSTRACT

Many systems in engineering, sciences and management can be represented as networks. The network structures can be encountered in many real world applications. Although networks are generally considered as a stationary snapshot of a system, most of the networks exhibit dynamic behavior. In this thesis, the main objective is the development of mathematical models for dynamic networks and the development of solution algorithms to optimize the corresponding dynamic networks. Two different dynamic networks are considered in this thesis: Supply chain networks and metabolic networks. In the supply chain networks part, the concept of price elasticity of demand is superimposed into the dynamic supply chain network. The resulting nonlinear programming problem is solved using two approaches. In the first approach, the problem is formulized as a convex quadratic optimization problem and solved as an NLP problem. In the second approach, piecewise linear approximation is used to solve the system. In addition, dynamics of the wine fermentation is modeled using the metabolic network of the Saccharomyces Cerevesiae. The feedback relation between cell interior and exterior is integrated that gives rise to an optimization problem with Differential and Algebraic constraints. The integrated model is solved by hybrid system approach to estimate the parameters in the fermentation dynamics of wine.

ÖZET

Mühendislik, temel bilimler ve yönetim bilimlerindeki birçok sistem, ağlar kullanılarak temsil edilebilir. Ağ yapısına günlük yaşamdaki uygulamalarda da rastlanabilir. Ağlar genelde sistemlerin statik temsili olarak kabul edilse de, birçok ağ dinamik davranışlar gösterir. Bu tezdeki temel amaç, bu dinamik davranış gösteren ağların modellenmesi ve bu sistemlerin çözümü için matematiksel algoritmaların geliştirilmesidir. Bu tezde iki farklı dinamik network işlenmiştir: Tedarik zinciri ağları ve metabolik ağlar. Tedarik zinciri ağları kısmında, talebin fiyat hassasiyeti, çok katmanlı tedarik zinciri ağı modeliyle birlikte ele alındı. Bu birlikteliğin sonucunda oluşan doğrusal olmayan sistem iki farklı yaklaşım kullanılarak çözüldü. Birinci yaklaşımda, modelleme sonucunda oluşan içbükey karesel sistem doğrusal olmayan biçimde çözüldü. İkinci yaklaşım da ise parçalı doğrusal yakınlaştırma kullanılarak sistem çözüldü. Ayrıca Saccharomyces Cerevesiae adlı maya hücresinin metabolik ağ modeli kullanılarak, şarap fermantasyonunun dinamiği modellendi. Hücre içi ve dışı arasındaki geri besleme ilişkisi birleştirilerek, diferansiyel ve cebirsel denklem sistemi elde edildi. Oluşan birleşik model, hibrit sistem yaklaşımı kullanılarak fermantasyon dinamiğindeki parametrelerin bulunmasında kullanıldı.

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NOMENCLATURE

Indices:

a	production line a in production facility
k	node k in the SCN
k'	upstream node of node k in the SCN
k''	downstream node of node k in the SCN
n	product n
t	time t

Sets:

A	set of assembly lines
N_{cs}	subset of nodes k that represent customers
N_{dc}	subset of nodes k that represent distribution center
N_{pr}	subset of nodes k that represent manufacturing plants
N_{pw}	subset of nodes k that represent warehouses at plants
N_{rt}	subset of nodes k that represent retailers
N	set of product n
T	set of time intervals t

Decision Variables:

I_{nkt}	inventory level of product n in node k at time t
O_{nkt}	order accumulation level of product n in node k at time t
Prc_{nt}	price of product n at time t
PR_{nkat}	production level of product n in manufacturing plant k on assembly line a at time t
pr_{nkat}	boolean variable that shows whether production of product n in manufacturing plant k on assembly line a at time t takes place
$up_{nkk''t}$	amount of demand of product n come to plant warehouse k from downstream node k'' at time t

$ud_{nkk''t}$ amount of demand of product n come to distribution center k from downstream node k'' at time t

$ur_{nkk''t}$ amount of demand of product n come to retailer k from downstream node k'' at time t

$yp_{nkk''t}$ amount of flow of product n from plant warehouse k to downstream node k'' at time t

$yd_{nkk''t}$ amount of flow of product n from distribution center k to downstream k'' at time t

$yr_{nkk''t}$ amount of flow of product n from retailer k to downstream k'' at time t

h the price of product that makes the demand for that product 1.

Parameters:

C_{RE} revenue generated by the sales of the products

C_{HO} cost of holding inventory in the SCN

C_{TR} cost of transportation in the SCN

C_{RM} cost of purchasing raw materials

C_{PF} fixed cost of production in the production facilities

C_{PV} variable cost of production in the production facilities

C_{CS} cost of customer satisfaction

$\mathrm{E_x}$ price elasticity value

E_{xn} price elasticity of product n

$FC_{n,k}$ fixed cost of production of product n at manufacturing plant k

HC_{nkt} holding cost of product n in node k at time t

l_n production time of product n

m price of end product that makes the demand one

Prc_{nt}^{old} price of product n at time t

PR^{U}_{ncat} maximum amount of production of product n at manufacturing plant k on assembly line a at time t.

RC_n raw material cost of product n

$TC_{nkk''t}$ transfer cost of product n from node k to node k'' at time t

VC_{nk} variable cost of production of product n at manufacturing plant k

ur^{U}_{nk} maximum amount of product n that can be send from retailers

$ur^{old}_{nkk''t}$ amount of demand of product n come to retailer k from downstream node k'' at time t in the previous planning period

$\delta_{kk''}$ transportation delay between k and k''

R_a approximated revenue function

R_r real revenue function

ur_{max} the demand value that makes the difference between values of R_a and R_r maximum

Z the total profit generated by the SCN

Chapter 1

INTRODUCTION

This MS thesis addresses modeling and optimization of complex, dynamics networks. In this chapter, a brief overview of networks in general is provided. An introduction to supply chain and metabolic networks that are mainly addressed in this thesis are also examined. This chapter contains a brief introduction to Hybrid Systems since the networks studied in this thesis are modeled and optimized using hybrid system approach.

1.1.) Networks

Networks are important structural elements of modern daily life; electricity transmission lines, transportation highways, social relations, gene interactions, and metabolic reactions in a cell are examples of networks that we encounter during our daily lives. Besides, production and manufacturing systems are also perfect examples of networks in industrial or business settings. Networks represent either symmetric or asymmetric relations between discrete objects that are contained within. For the metabolic networks, the metabolites correspond to discrete objects that are called metabolites including chemical and biochemical entities within a cell and the reactions among these metabolites correspond to relations among these metabolites. The same idea is valid for production systems or supply chain systems; the echelons or the facilities within the echelons correspond to discrete objects (nodes) in the network representation of the system and the transfer of information and material among these nodes correspond to relations among them.

Although, a network can be considered as a static snapshot of a system, it is naturally a dynamic system that exhibit varying response in time and with respect to the changes in the environment. The main characteristic of a dynamic system is the existence of systematic behavior represented by simple or detailed mathematical models (sometimes called as fixed rule) that represents the position of the system in the time domain. In other words, in a given time under certain conditions, the characteristics of the system can be determined. A dynamic system can be represented by rate and state variables: rate variables show the scale of the change in the system for the given time interval and state variables show the current status of the system. This property is the direct result of the existence of fixed rule in the time domain by considering the state and rate variables simultaneously with the fixed rule describing the system behavior in the time domain. Therefore, a dynamic system can be represented with differential and difference equation. Consequently, if a system can be represented by difference or differential equations, it is classified as a dynamic system. The future states of a dynamic system can be analyzed with an iterative procedure. This procedure is called solution or integration of the system. If the integration procedure is applied until the end point of the system, the trajectory of the system is determined.

The characterization of a dynamic network can be analyzed by using the definitions of the dynamic systems. The relationship between the nodes can be described by a fixed rule in the time domain for a dynamic network. If the initial state of the system (or state of the node) is known for a given fixed rule, This rule can be integrated in the time domain and the trajectory of the system can be found. For that reason, for instance, in a Supply Chain Network, if the initial inventory of the system is known, by integrating the system (or by solving the system) the inventory levels in the future time periods can be calculated.

All future values of the inventory are called as a trajectory of inventory profile. Similarly, the trajectory of the concentration of the metabolites can be calculated in the same manner.

1.2.) Supply Chain Networks

A supply chain system is the combination of production and distribution entities that are responsible for procurement of the raw material, production of end and intermediate products from these raw materials and distribution of these products to the corresponding customers. Characteristics of these systems have shown significant change due to globalization that has caused disappearance of the boundaries of geographical regions. With this change, the conventional idea of geographical unification of facilities became invalid. All of the production and distribution facilities of the companies can be located in the different parts of the world with this new business rule. Therefore, the supply chain system responsible for the production and distribution of end products becomes a network, Supply Chain Network (SCN).

A typical SCN includes suppliers, plants, warehouses, distribution centers and retailers. Some of the semi-finished products are produced by the plants included in the system, but some of them are outsourced. The physical connections between these facilities are provided different transportation modes. Therefore, the network representation of a Supply Chain System (SCS) includes many parameters with distinct characteristics. The abundance of the parameters makes the network representation of SCS highly complex.

The main aim of the SCN is the satisfaction of the customer demand on time. However, every SCN should need a source of capital to continue its operations. Otherwise, the operations to produce end products cannot be accomplished. Every operation in the

SCN from raw material procurement to delivery of product to customers incurs a cost to the system. The revenue is created during selling of end products in retailer to the end customers.

An important consideration in SCNs is the presence of many production facilities that are capable to produce the same product around the globe. This existence causes competition between the service providers or producers. Therefore, companies should provide high quality service on time with lower costs for the survival.

In addition, changing patterns of customer demand have changed the characteristics of the SCN. Today, customers require smaller batches of more customized products with lower prices and the life cycles of the products have been shortened. Therefore, conventional assembly line manufacturing for mass production becomes undesirable, even economically infeasible. Therefore, satisfaction of customers on time becomes one of the most important aims of the companies.

Companies seek to establish and operate complex SCNs to achieve the goal of provision of high quality service with lower cost. In this complex SCN, facilities can be located in the different parts of the world. Advanced IT infrastructure is used to connect the information flow between these facilities.

For the survival of the SCN, all operations from procurement to end product delivery should be optimized with respect to forecasted demand, cost and revenue parameters and the existed network topology. The result of the optimization should include procurement, production and transportation schedule, optimal inventory level in the facilities of the each echelon and the level of satisfaction of customer demand on the each echelon.

A variety of approaches can be used to model supply chain systems. The most frequently used approaches are the continuous and discrete time modeling. If all processes that take place in a generic SCS are investigated, it is seen that the decisions in planning and operation of SCS include both continuous and discrete decisions. While, starting of production can be considered as a discrete decision that takes place in the SCS, the amount of the inventory in the system or the amount of the demand accumulated is considered as continuous decisions that are taken during the execution of the supply chain processes. This is because of the fact that any certain time cannot be determined for the amount of inventory or demand accumulated. Instead of this, the trajectory of the inventory or demand accumulation can be determined in the system. Therefore, these two variables show continuous characteristics.

Since the model that is used for the representation of SCS includes both continuous and discrete variables simultaneously, the SCS can be classifies as hybrid systems that exhibit discrete-continuous behavior in continuous time. The gap in representing real system and the mathematical model of the system can be decreased by using a hybrid systems approach. Due to this decrease, the power in the estimation of behavior of the system in real life increases.

1.3.) Metabolic Networks

Metabolic networks are defined as the collection of all chemical and biochemical entities and their interactions within a cell that define the functions of that cell. Due to growing need to understand the functions of biological organisms for industrial and medical purposes, modeling and simulation of metabolic networks has attracted a lot of attention recently. Traditionally, metabolic networks are modeled using Flux Balance Analysis (FBA) that considers steady-state (or stationary) nature of the cell. But it is important to consider the dynamic behavior of a cell since the environmental conditions continuously change. Sometimes due to the critical changes in the environment some of the reactions exhibit completely different behavior leading to discrete changes in the metabolic network. Therefore, a cell exhibits discrete-continuous behavior in continuous time. The concentration of the certain metabolites can be considered as a continuous variable for the metabolic network of a living organism because instead of values of concentration in a given time, the trajectory of concentration change is important. Also, living organisms show different behavior on their regulatory system with respect to level of value of a metabolite in the system. This behavior change can be resembled to a behavior of multi-level switch which is classified as discrete. Therefore, the metabolism of a living organism shows hybrid characteristics. Since hybrid systems exhibit the same characteristics, modeling a cell as a hybrid system gives an accurate representation.

To make the modeling actions successful, all bioinformatics applications need large amount of data. All metabolites and the reactions that take place in the cell and the some kinetic parameters of these reactions are required in modeling metabolic networks. Large amount of accurate data became available to the research community in life sciences, computational biology, systems biology and bioinformatics after the sequencing of human genome. A growing need in life sciences is to be able to elucidate the metabolic networks of complex biological organisms. So far, only metabolic networks or simple single-celled organisms such as Escherichia coli [1], Saccharomyces cerevisiae (baker's yeast) [2], Helicobacter pylori [3] were available. Recently, the focus has been on the modeling of mammalian cells such as human red blood cell [4] and Human cardiac mitochondria [5]

Each reaction in the metabolic network establishes an interaction among a number metabolites. The models for the reactions include stoichiometric equations that give relevant information on the metabolites that enters reaction and the new metabolites that is created during the reaction. In metabolic network analysis, the reaction sets is used to construct the model for the network. Therefore, mathematical representation of the metabolic network is used to analyze living organisms and their metabolism.

1.4.) Hybrid Systems

If the characteristics of the most of the process operations are investigated, it is observed that, they do not only include continuous events. Besides continous processes involves many discrete decisions that should be taken during the execution of the system. The process dynamics that includes this kind of nature is classified as a hybrid. Therefore, as a definition, hybrid systems are the systems that include both discrete and continuous decisions simultaneously and exhibit discrete characteristics in continuous time.

The discrete decisions in hybrid systems are not required to be integer or discrete, the significant feature of the system is the discontinuity of the dynamics that is included. Solution of the standalone continious system is one of the most difficult problems due to interaction of continuous system and the discrete components contained within. Therefore, obtaining optimal solutions to hybrid systems is an open research topic. Also the formulation of the system plays very important role on the difficulty of the problem.

Most of the hybrid systems are represented with a set of Ordinary Differential Equations (ODE), algebraic constraints and discrete decisions. Therefore, a set of Differential Algebraic Equations with discrete decisions can be classified as hybrid system. The non-continuous part can be represented using two approaches: Jumps and Switches

(Barton, Park). In the jumps, the differential variables change discontinuously and in the switch state variables change.

A hybrid system can be represented with finite automata. In finite automata, each state represents the continuous systems which are changed when the logical condition that determines the states is satisfied. Therefore, it can be said that the main characteristics of the hybrid systems is the transition between continuous subsystems. During the execution of the whole process, system passes from one continuous system to other.

The state of a point is determined by the continuous systems, but the decision of the choice of the continuous system is given by logical constraint that is satisfied. In a hybrid system, only one state can be active in one time. This means, out of all continuous systems, only one of them can be active at a time. Therefore, the set of satisfied logical constraints can map only one of the continuous systems.

In this thesis, two types of hybrid systems are represented. During the representation of the dynamic SCN, both continuous and discrete decisions are taken. In the SCN, level of inventory or level of demand accumulation show continuous behavior. The decision that determines the start of production in the plant show discrete behavior. In the model discrete part is represented by a binary variable. The hybrid system used during the modeling of the metabolic network is different from that of SCN. In the metabolic network part, a DAE is used to represent one state of the fermentation dynamic. During the fermentation if some given logical constraints are satisfied by the system variables, the DAE model changes. The meaning of this mathematical change can be defined as a transition from one continuous state to other one. In this model, the DAEs executed are the continuous subsystems and the logical conditions which are the concentration levels of some metabolites are the discontinuous states.

1.5.) Contributions

The main aim of this thesis is the optimization of the dynamic networks. Although networks are generally considered as a single snapshot of a system, the state of the each node can be represented by state and rate variables in dynamic networks. In other words, the state of a node can be investigated in the continuous time domain.

Besides, most of the real world dynamic networks show discrete behavior in addition to continuous behavior. The networks that reflects this kind of discontinuities in their dynamic structure is called as a hybrid systems. In the hybrid systems, the transitions of continuous dynamic system are occurred with respect to a rule.

The networks that we study in this thesis show dynamic behavior. Besides, the modeled networks include some discontinuities in addition their dynamic behavior. Therefore, these networks can be classified as a hybrid networks. Two main applications of these networks are studied: Supply Chain Networks and Metabolic Networks.

In the supply chain network part, multi-echelon, multi-product supply chain network is modeled. The modeled network shows the properties of the hybrid systems. The main contribution of this thesis to corresponding hybrid system is the consideration of the price elasticity of demand. The relationship between price and demand is established by applying principles of price elasticity of demand. The price elasticity concept gives a relationship between price of a product and demand to that product. Both demand and price are variable and both of them can be written in terms of each other in a system with price elasticity. In market dynamics, price elasticity causes decrease of demand as price increases and increase of demand as price decreases for the most of the product categories.

Price elasticity alone has been studied before in economics, but the inclusion of price elasticity concept in multi-echelon, multi-product supply chain network is investigated first time in this thesis to our knowledge. In this thesis, the effect of price elasticity on the operational efficiency and operational decisions of a supply chain network are considered. Although, economically, the effects of price elasticity studied, relationship between price elasticity and operational details of multi-echelon, multi-product supply chain networks is the main contribution of thesis on the dynamic supply chain networks. Besides, this is the first time that optimization approach is used during the determination of effects of price elasticity on the supply chain decisions.

In the metabolic network part, the fermentation dynamics of the Saccharomyces Cerevesiae is modeled by considering the reactions that take place in the yeast. The dynamic network modeled in this part of the thesis is the network of the reactions that take place in the living organism. The metabolites are represented by nodes of the network and the arches of the network represent the reactions. The model of the fermentation dynamic also shows hybrid behavior.

The dynamics of the fermentation processes is studied by decomposing the cell interior and exterior into two separate compartments. Therefore, instead of an integrative approach, a decomposed feedback relation is established in these studies. However, the fermentation processes takes place instantaneously in the cell. Therefore, instead of using separate feedback relation, an integrative approach should be used. In other words, a single set of equation should be used to model both cell interior and cell exterior. This is the main contribution of thesis on metabolic network. Besides, the model is classified as a Differential and Algebraic Equation system. Solution of this class of systems is very difficult and generally to solve the system with commercial solvers requires reformulation of system. The DAE system used in this thesis is classified as a very difficult to solve. In addition, solution strategy of the resulting large scale DAE system with a commercial solver is another contribution.

1.6.) Outline

This thesis includes five chapters. Literature review is provided in Chapter 2 summarizing similar studies on supply chain networks, metabolic networks and hybrid systems. In chapter 3, a multi-echelon, multi-product supply chain network with price elasticity is studied. In Chapter 4, the fermentation dynamics of the wine is studied. A model that integrates separate feedback relation between cell interior and cell exterior is developed. The corresponding model is solved. Comparisons between experimental results and result of simulation are made. The thesis is concluded with Chapter 5.

Chapter 2

LITERATURE REVIEW

2.1 Overview

Use of the networks on the representation of the supply chain systems and metabolic networks attracted a lot of attention recently because of the high accuracy in the representation. In SCN models, each entity or the facility of the system is represented by a node and the relation between these nodes or the flows (both information flow and material flow) is represented by the arcs and their limits. Similarly in the metabolic network models, each metabolite is represented by a node and the relation between these nodes which are the reactions take place in the living organism is represented by arcs.

The main benefit of the representation of real life entities such as SCS and metabolic reactions of the living organism by a network is ability of use of mathematical relations during the determination of the real life behaviors of these systems. By using the concrete realities of the mathematics, the invariants of the real life entities are solved.

2.2 Supply Chain Networks

The structure of the business has shown excessive change recently. The importance of single companies in the production network decreases because in this new business structure optimal behavior of the single company does not increase the efficiency of the production system as a whole.

With the globalization companies established the replicates of their plants or production system in the different parts of the world. In this manner, companies want to take the benefit of the economical advantages of the different countries on the cost of service they provided such as duties or work force cost. However, this trend started to show change in the last years. Now instead of establishing the replicates of the entities of the production system in the different parts of the world, companies divide the production processes into the different independent parts. Each part of the production processes are done in the most advantageous part of the world and finally assembled in the center production facility.

The above production system shows complex network properties, because the production of the end item is divided into different production stages. Each stage has its own production capacity and production time and cost. Also each stage is finished in different geographical regions. The end products of each production stage should be transferred to the other stages and this requires heavy logistic loads. The logistics of the partial end products are generally done with multi-modal transportation. Each mode has its own capacity, price and delivery time. This complex production system can be reduced into a complex dynamic network.

In the conventional supply chain system, each echelon of the system is represented with a single node. However, in the complex business environment, to increase the resemblance between real production system and its representative, more than one node is required for each echelon. Therefore, usually one node just represents the one entity or facility in a echelon. With the constraints of the links between each node, the new production system is called as supply chain network instead of supply chain system.

Different definitions of complex supply chain network and the reasons of complexities are investigated by different researchers. Kim and Rogers point the dynamic and unstable structure of the business environment [6]. In this, the period of mass production finished. The mass customization becomes the main idea of the new business strategy. In this new environment, the cycle time of the products and batch sizes of the demand decreases giving rise to highly complex supply chain systems. They point out that, on this uncertain and complex environment, the flexibility on the modeling becomes the most important factor on the sustainability of the system. This paper considers a supply chain as an integrated model of several business views. The main reason of this consideration is the object oriented approach of the writers. Because in the object oriented design, the main aim is the division of the responsibility of the each entities by the help of the classes. In this paper, a supply chain network is considered as an integration of the Goal, Input, Output, and Supply and Controlling objects. The representation of the corresponding system is implemented by using the foregoing objects.

Riddals et al. defines the SCS as a system of connected business enterprises established to satisfy the customer demand [7]. In this study, a SCS is considered as incorporation of the distinct generic procedure of the production and distribution processes. These processes are called as an echelon. Echelons of the SCS do not have to be in the diverse geographical regions. Therefore, different echelons of the SCS can be locates even in the same facility. They defined two different flows in the SCN, flow of information and flow of material. Flow of material is from supplier to demand owner and the flow of information goes from demand owner to supplier.

Biswas and Nahari connects the complexity of the supply chain to the followings: large scale nature of the network, hierarchical structure of decisions, randomness of inputs and operations, dynamic interaction between supply chain entities [8].

Perea et al. point the change in the structure of the business and the customer demand [9]. In this paper, it is concluded that, instead of using the heuristic decision making process companies should adopt systematic procedures for making decisions. Systematic procedures are required because of the changes in the market and customer behavior that make the system more complex. With these changes, the lowly dense and highly independent structure of the market is converted into highly integrated structure. In this integrated structure, centralized decision process making becomes very important for getting better result because of the integrated characteristics of the process.

Besides the definitions, different modeling and solution techniques are applied to the supply chain systems. Some researchers consider the echelons of the SCS separately instead of integrated consideration. Melachrinoudis and Min only focuses on the redesign of the warehouse network of a SCS [10]. In this paper, it is pointed out that consolidation of existing redundant warehouse with the non-redundant ones decreases the cost of the whole SCN. The problem represented in this paper is named as a Warehouse Consolidation Problem. The objective of the problem is the maximization of the potential cost savings. A MIP model is written to find the optimal decision. As result, the followings are found by the solution of the problem: Newly established warehouses, closed warehouse, and customer-warehouse assignment.

Perea et al models the multi-echelon, multi-product SCS [11]. The dynamics of the system is considered in the model and satisfaction of the past demand is also included. This is succeeded by holding the demand accumulated from each demand source. Later, if there is enough production capacity, this unsatisfied demand will be met. In the model, the inventory balance and order balance is established by differential equations. Incorporation of these differential equations into supply chain optimization model makes the model intractable. Therefore, both inventory balance and order balance equations are discretized in the time domain. The main assumption used during the modeling is the presence of two types of flows: Flow of information and flow of the material. Information flows from customers to suppliers and material flows from supplier to customers. In the system, to prevent the over dissatisfaction of the demand, satisfaction cost is added into system and for every dissatisfied demand an extra cost is incurred. In summary, this paper compares the result of the centralized and decentralized approach for the corresponding SCN. A Model Predictive Control (MPC) approach is used in the decentralized case. Overall SCN is modeled with a MILP and an illustrative example is solved to show the performance of the model and to make required comparisons.

Seferlis and Giannelos extends the model in [11] by adding the selection of transportation modes [12]. The SCN is also modeled with MILP and the unknown demand pattern is tried to be estimated by MPC. The SCN modeled is also classified as multi-echelon, multi-product, multi-period SCN. In the MPC part specific two layered optimization-based control approach is applied. This approach is applied to both deterministic and stochastic demand variations. The effects of the transportation delay, the length of the control horizons and models for demand forecast are investigated and compared at the end of the study.

Biswas and Narahari use object oriented approach to model a SCS [8]. Different from conventional analytical approaches, the main concerns in the object oriented modeling technique is the determination common building blocks of each SCS. By determining these commonalties, building a generic SCN model becomes easier and less time consuming. In this paper, two classes of objects are determined for a SCS: Structural objects and policy objects. Structural objects include customer, order, plant, warehouse, vehicle, supplier, retailer and distributor. There are two kinds of customers, internal and external. Any node of SCN that requires any end and intermediate product of the system is classified as internal customer. External customers are the non-member customer nodes those require any end and intermediate product of the SCS. In the class libraries, the order is considered with 5 different objects: External customer order, warehouse order, manufacturing order, late-customization order, and supplier order. Three different plants are considered in the model: Manufacturing plant, assembly plant, late customization center. Policy objects are the protocols used in the procurement, manufacturing transportation, and distribution of materials in the SCS. Mainly policy objects determine the behavior of the supply chain entities during execution of their tasks. Composition of a structural object with policy object makes the corresponding structural object different from its other replicas. The following policy objects are determined: Inventory policy, manufacturing policy, order management policy, demand planning policy, supply planning policy, distribution policy and demand planning policy. Each of these policy classes has their own subclasses. By combining these objects most of the SCNs with different topologies can be modeled.

The main difference of these object oriented approach from conventional modeling approaches is the requirement of the knowledge of the model developer. With the traditional modeling techniques, the modeler should write whole model from scratch and he should know mathematical modeling techniques. However, in the object oriented (OO) approach, the modeler does not have to write the model from scratch because in OO design, the commonalities in a generic SCNs are found and they are represented with software classes. Therefore, during the modeling, one can write model by just creating the software objects, and the remaining mathematical modeling part is handled by the objects themselves.

Besides modeling techniques, the way of finding solution for the deterministic multi-echelon supply chain management show difference. One way of solving the system is the use of optimization techniques. Mestan et al uses exact analytical optimization [13]. In this kind of optimization, the whole mathematical representation of the SCN is written formal way and the model is solved with an exact algorithm such as simplex or branch and bound. The advantage of use exact analytical optimization is the existence of the awareness of the distance between optimal solution and current solution. In addition in this type of optimization algorithms, if solution time of the problem is extended to infinity, the exact optimal solution will be found. However, modeling the system suitable for exact analytical optimization requires high degree of knowledge and experience. Also, time required to model the system becomes prohibitively long and the solution time required even to reach a feasible solution can be excessively long. In addition, representation of some real world supply chain phenomena can be very difficult to make the model suitable for solving in an exact analytical optimization techniques.

For that reason, simulation and simulation based optimization techniques are used in the supply chain analysis. Mele et al apply a simulation based optimization techniques to the multi-echelon SCN [14]. In their study, they model the SCN in the simulation format; therefore they do not have any obligation to make the model with set of equation that is suitable for an algebraic system solver. Instead, they model the system with a blackbox simulation model. To improve the objective function which is the maximization of the profit, a genetic algorithm routine is used. With respect to this algorithm, system tries to find the value of the optimal parameters that maximize the objective function. Benefit of this approach is the easiness of the modeling of system. Besides, all of the details of the system can be represented in the simulation easily compared to algebraic modeling.

In this thesis, on the Supply Chain Management part, our contribution is the consideration of the price elasticity of the demand for the multi-echelon, multi-product SCN. This is the first time that both price elasticity and such a complex SCN is considered together on the optimization domain. However, price elasticity is analyzed by itself and it is used in the SCS. In these studies, instead of use of optimization, some other algebraic methods are used and it is applied for at most two echelon SCSs. Price elasticity is used in supply chain context in [15]. In this study, the elasticity is not represented like price elasticity of demand. Instead, price is written as a function of the other parameters such as travel time and travel cost. Therefore, unlike our study, in system of equations is solved to find the best solution and VIs is used [15].

2.3 Metabolic Networks

The metabolic networks play very important role on the determination of the behavior of biological organisms in silico. Today, use of the biological organism for medical and commercial purposes is one of the hottest research topics. The key idea is the determination of the phenotype of the organism by looking at its genotype.

Until last decade, lack of the dependable data was one of the most important obstacles in the determination of the phenotype. With the sequencing of the whole genome of the living organisms, excessive amount of dependable data exists. After this step, the main requirement is development of systematic methods to learn the relationship between this data. Systems biology fills this gap to solve relationship between bulks of unsystematic data. Henry makes the definition and branches of the Systems Biology [16]. This paper claims that most approaches that study biology uses reductionist approach. Researchers just focus on the one component of an organism or biological system and try to uncover all the information about it. However, information for one component is not enough to see the behavior of the each component in the biological system. This unseen behavior is called as emergent properties of the components. It is called emergent because the properties discovered during the processes of the reductionist approaches do not become valid inside the system. During the interaction with other components, each individual shows these new emergent properties.

One of the most important methods that discover the emergent properties is Metabolic Flux Analysis (MFA). In MFA, determination of the flux distribution of the biological system is the main concern [17]. By determining this distribution, many important characteristic of the organism can be understood. First of all, upper bound for each flux can be determined. Therefore, the organism's capacity for the production of each product can be find out in this analysis. To determine this theoretical upper bound for the production of each metabolite, a system of equation is solved in MFA. To build the model, it is required to have all reactions take place in the system. Sequencing of the whole genome of the organisms makes the determination of all these reactions takes place in the organism possible [18].

There are many ways of modeling the cellular processes. Constraint based approach is one of them used in the MFA to measure the optimal flux distribution. The phenotypic functions of living organisms can be determined by using the constraint based approaches on the metabolic network of the corresponding organism [19]. The most important step of the constraint based model is the determination of the constraints for the model of the living organism. These constraints can be related with enzyme capacity, reaction stoichiometry, thermodynamics and biochemical loops. The main function of these constraints is determination of the feasible solution space. In the feasible solution space, all the possible flux distributions can be seen. Therefore, all the solutions in the solution space can be realized in the organism.

There two main ways of representation of this feasible space: Elementary nodes and extreme pathways [20]. These two concepts are used pathway definition of whole network of the living organism. Both of these methods use convex analysis which uses system of linear equalities. Both of the methods show the steady-state solution space of the cell stoichiometry. With respect to convex analysis, every valid flux distribution of a metabolic network can be represented as a nonnegative combination of the convex basis vectors. Both extreme pathways and elementary nodes have common properties. First of all for a given network, there is a unique set of extreme pathways and elementary nodes. Also each elementary node and extreme pathway consists of minimum number of reactions that it needs to exist as a functional unit. However, extreme pathways are the systematically independent subset of elementary nodes. Therefore, it can be said that no extreme pathway can be represented as a nonnegative linear combination of any other extreme pathways. During the calculation, the main difference for both methods is the consideration of the reversible reactions. Extreme pathways decompose each reversible reaction into two irreversible reactions and try to find pathways later. However, elementary nodes apply its specific algorithm to the reversible reactions with out any preprocessing. These two methods are used on the determination of the many important properties of the metabolic networks. Some of these properties are the calculation of the product yields, evaluation of pathway redundancy, determination of correlated decision sets, and calculation of minimal reaction sets.

With these methods, a new perspective is gained for the analysis of the metabolic network [18]. Therefore by this way, instead of individual reaction consideration, pathway oriented approach is applied. Specific characterizations of the metabolic networks are obtained by these methods. In mathematical terms, extreme pathways determine the cone of all feasible fluxes. In other words, all of the flux distributions that can take place in the living organism can be represented by convex combination of the extreme pathways. After this step, the main issue that should be determined is the selection which specific flux set from the flux cone or solution space by the organism.

Flux-Balance Analysis (FBA) is a tool used on the determination of the answer of the previous question. Therefore, it can be said that, MFA that is used to explorer the optimal cell performance is classified as FBA [17]. FBA requires two kinds of information: The stoichiometry of the biochemical pathways and the cellular composition information to determine the bounds of the specific fluxes [21]. FBA models play very crucial role on the determination of the upper bounds of the flux distributions takes place in the cell interior. In the FBA, the main aim is the determination of the most promising flux distribution from the solution space or the convex cone limited by extreme pathways. In the FBA the promising solution is found by adding an objective to the flux cone and solving an optimization problem. The optimization model solved is classified as a linear optimization (LP) model.

The FBA itself is used the model cell interior. However to model the living organisms' metabolic reactions, the environment should be considered too. Besides, with the FBA, only static view of the flow distribution is considered. However, there is a dynamic relation between cell interior and exterior. This dynamic structure is studied by Sainz et al. for batch wine fermentation [22]. In this study, the cell interior is modeled with a FBA model. The objective function of the FBA is chosen as a maximization of the biomass accumulation. The extracellular representation is provided by set of Ordinary Differential Equations (ODE). In their system, they divide the metabolites into two sets, extracellular and intracellular metabolites. The rate of change of concentration of intracellular metabolites is determined by FBA and rate of change of concentration of extracellular metabolites is determined by set of ODE. In the model, the feedback relation between cell exterior and interior is established by an iterative procedure. In this procedure, first the FBA is solved and optimal flux distributions are found. With respect to this distribution, the concentration profile of the cell exterior is updated. This updated new cell environment changes the bounds of interior fluxes. Therefore on the next iteration, the FBA founds new optimal interior fluxes. In the model, this iteration continues till one of the extracellular metabolites is run out of.

Raghunatan extends the work in [22] by adding parameter estimation routine to this paper [17]. In this work, a formal methodology for data reconciliation and parameter estimation with underdetermined stoichiometric models is developed and assessed. They model the system by a nonlinear programming.

Raghunatan use Variational Inequalities (VI) to model the fermentation process [23]. In this paper, cell interior is modeled by an LP and cell exterior is modeled by set of ODE. However they use VI for representing the piecewise functions coupling the environment and cell metabolism. In this model, ODEs represents the change of concentration of the environmental metabolites and VIs creates Differential Variational Inequalities (DVI). The objective of their model is the maximization of the biomass accumulation. During the solution of the model, the DVIs are discretized in the time domain and solved by IPOPT-C [24].

2.4 Hybrid Systems

Most of the processes exhibit discrete aspects in addition to more familiar continuous behavior. This type of systems are classified as a hybrid system. Barton and Park represents the main characteristics of hybrid systems [25]. When a discrete phenomenon is superimposed into a continuous system, the overall behavior of the continuous system shows big changes. In the hybrid system both discrete and continuous decisions take place. However, this existence does not make the system hybrid. The simultaneous consideration of these two decisions is the most important part on the classification of the system. Transition of the continuous subsystems with respect to satisfaction of the logical constraints is the main characteristics of the hybrid systems. Some times the transition time is known a priori but generally it is defined implicitly in the model. In this paper, the main problems exist on the formulation of the hybrid systems are stated also. The continuous state of the most hybrid systems is represented by a DAE. Therefore solution of a hybrid system is the iterative execution or solution of these DAEs. However there is not any stable and efficient way of solving DAEs. One of the most important indicators of the difficulty of the DAE system is the differential index.

Barton and Park defines the differential index as a number of times that one has to differentiate the system in order to make the system ODE [25]. Index 0 DAE system is classified as an ODE. From the higher index DAEs, only index-1 can be solved. The methods that solve index-1 DAEs are the Backward Differentiation Formulas and implicit Runge-Kutta methods. None of the standard numerical methods work on the higher index DAEs. Because of this index problem, solution of hybrid systems becomes very difficult. On the execution of the hybrid systems, continuous subsystems are solved sequentially and the model of each subsystem is determined during the state changes. In one or more of these changes, the derived DAE system can have higher index value which causes stop of execution.

Chapter 3

MODELING OF SCN WITH PRICE ELASTICITY

3.1 Problem Definition

The supply chain networks are complex systems that a number of products are produced and transferred from one node to another with the objective of satisfying the customer demand. The supply chain systems are traditionally decomposed into different cycles such as procurement, manufacturing, replenishment and customer order cycles due to modeling and computational challenges [27]. The nodes of the supply chain network are considered individually in such decomposition approaches. As a result of this decomposition, the accuracy of the model in representing interactions among the multi-echelon supply chains becomes weak due to preference of an individual benefit instead of system wide benefit. The inefficiencies in the modeling of interactions among the nodes of supply chain network can be eliminated by using an integrative modeling.

Besides decomposition properties, there exist many operational properties of supply chain networks. In a multi-echelon SCN, the production begins with arrival of raw materials from a supplier to production plant. Once a production of a specific product begins, an inventory of the corresponding product starts to accumulate in different stages of the SCN. The transportation of the end product is required to distribute this inventory in different stages of a SCN other than production plant. An important consideration in optimization of SCNs is the distribution of inventory and scheduling of production with transportation. In addition, integrative modeling should take into account that the information that is created by customer is transmitted in the opposite direction of material flow as shown in Fig. 3.1. The decisions in the optimization of operations in a SCN should achieve desired objectives. In some networks, the main objective is the minimization of cost, but in some others, it is the maximization of revenue. The decisions that are taken by an individual node are determined by other nodes in some SCNs; but in some other SCN this dependence is not observed.

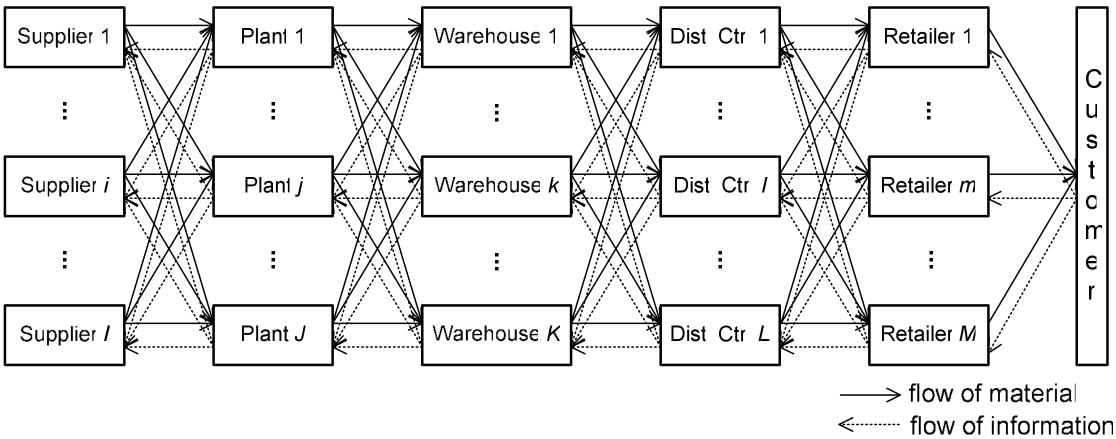

Fig. 3.1.: Multi-echelon, multi-product supply chain system.

In this thesis, we consider that all nodes show independent behavior; so there is no specific rule that determines decisions taken by a specific node. The holding cost of each product at each node is calculated separately. Besides transportation delay exists for the transfer of the product from one node to other node. However, transfer of a product from plant to plant warehouse is instantaneous, since plant and plant warehouse are located in the same geographical region. During the production phase, the plant can take unlimited amount of raw material from any supplier and the additional cost occurred because of this transfer is transportation and raw material cost.

Although the demand to retailer is satisfied immediately, the supply chain system does not have to immediately satisfy the demand of the previous node for the remaining nodes. Therefore, unsatisfied order is accumulated at each node to be satisfied in the future. Once material is sent from an upstream node, it reaches to corresponding downstream node after some transportation delay. Inventory and order accumulation balance is updated with respect to the amount of sent and received material.

Each product has a different production time and the production facility can produce one of these products at each time interval. Production schedule is non-preemptive: once the production of one product begins, none of the other products can be produced till production of that product is completed. Besides, switching from one product to another requires a setup time.

Orders and inventory shows dynamic behavior in the SCN. The dynamic behavior of the SCN is formulated as multi-period system of equations. In addition, the price elasticity equations that establish the relationship between price and demand are used in the model formulation. The price elasticity equation is represented in 2 different ways. In the first representation it is represented with differential equations; these differential equations are converted to difference equations in order to incorporate them into multi-period optimization problem. In the second representation price is written as a function of demand and the elasticity value. Also binary variables are used to model the production nodes since these nodes show discrete behavior by switching from one product to another in time.

3.1.1 Inventory Balance

The inventory is the material that is held in the nodes of the supply chain system, after periodic material transfer ends. All supply chain systems should hold inventory to make their operations to increase the customer satisfaction. Without inventory, the desired levels of customer satisfaction cannot be reached. The reasons of this are the uncertainty in the demand, existence of complex production systems, and delay in the transportation. The inventory balance of our system exhibits continuous behavior on the time domain and rate of change of inventory can be represented by differential equations. However, existence of differential equations could make the system computationally intractable. Therefore, the rate of change of inventory is discretized in the time domain and differential equations are written with difference equations. The inventory balances for different nodes of the supply chain network are modeled with the following equations.

Final Product inventory at plant warehouse:

$$I_{nkt} - I_{nk(t-1)} = \sum_{a} PR_{nkat} - \sum_{k''} yp_{nkk''t} \qquad \forall n \in N, \forall a \in A, \forall t \in T, \forall k \in N_{pr}, \forall k'' \in N_{ds} \quad (3.1)$$

Final Product at Distribution Center:

$$I_{nkt} - I_{nk(t-1)} = \sum_{k'} yp_{nk'k(t-\delta_{k'k})} - \sum_{k''} yd_{nkk''t} \qquad \forall n \in N, \forall t \in T, \forall k \in N_{ds}, \forall k'' \in N_{rt} \quad (3.2)$$

Final Product at Retailer:

$$I_{nkt} - I_{nk(t-1)} = \sum_{k'} yd_{nk'k(t-\delta_{k'k})} - \sum_{k''} yr_{nkk''t} \qquad \forall n \in N, \forall t \in T, \forall k \in N_{rt}, \forall k'' \in N_{cs} \quad (3.3)$$

3.1.2 Order Balance

Our SCN is triggered once demand is realized. However, in some cases demand cannot be satisfied immediately. In that case, past demand is accumulated in the corresponding node of the supply chain system and once the enough material is obtained, the accumulated demand may be satisfied. The satisfaction of accumulated demand is determined with respect to given cost and production parameters to optimize overall supply chain profit. The order balance equations are originally differential equations and to make the system computationally tractable, the differential equations are re-written with difference equations similar to the inventory balance equation (Eq. 3.1 to 3.3). The equations of order balance are the following:

Order Balance at Plant Warehouse:

$$O_{nkt} - O_{nk(t-1)} = \sum_{k''} up_{nkk''t} - \sum_{k''} yp_{nkk''t} \qquad \forall n \in N, \forall t \in T, \forall k \in N_{pw}, \forall k'' \in N_{dc} \tag{3.4}$$

Order Balance at Distribution Center:

$$O_{nkt} - O_{nk(t-1)} = \sum_{k''} ud_{nkk''t} - \sum_{k''} yd_{nkk''t} \qquad \forall n \in N, \forall t \in T, \forall k \in N_{dc}, \forall k'' \in N_{rt} \tag{3.5}$$

Order Balance at Retailer:

$$O_{nkt} - O_{nk(t-1)} = \sum_{k''} ur_{nkk''t} - \sum_{k''} yr_{nkk''t} \qquad \forall n \in N, \forall t \in T, \forall k \in N_{rt}, \forall k'' \in N_{cs} \tag{3.6}$$

3.1.3 Production

The production facility in our SCN is a single stage, multi-product facility that has multiple production lines. Therefore, only single product can be produced in one line of the facility at each time interval. Also preemption is not allowed in the plant; once a production of a product is started, the facility cannot produce any other product on the corresponding assembly line during the production time of selected product. In addition plant is designed to produce constant amount of product during each time interval once a produce order is received. In this production system, the switches between operational and non-operational phase of the manufacturing plant as well as the transition from one product to another are modeled by propositional logic. The production policies the production stage of SCN is modeled with the following equations:[13]

$$PR_{nkat} \leq pr_{nkat} PR^{U}_{nkat} \qquad \forall n \in N, \forall t \in T, \forall k \in N_{pr}, \forall a \in A \tag{3.7}$$

$$\sum_{n} pr_{nkat} \leq 1 \qquad \forall n \in N, \forall t \in T, \forall k \in N_{pr}, \forall a \in A \tag{3.8}$$

$$\sum_{t'=t}^{t+l_n-1} pr_{nkat'} + \sum_{m \neq n} \sum_{t'=t}^{t+l_n-1} pr_{mkat'} \leq 1 \qquad \forall n \in N, \forall t \in T, \forall k \in N_{pr}, \forall a \in A \tag{3.9}$$

Production of all products in an assembly line should be less than maximum production amount, PR^{U}_{nkat} in each time interval as given in Eq. (3.7). However, the batch production strategy cannot be applied since the production quantities should be equal to predefined batch size with this constraint. Therefore, if production node operates as a batch system, then the inequality in the Eq. (3.7) should be converted to equality. Production of single product in each time interval on every assembly line is guaranteed in Eq. (3.8). Production of only single product between t (production start time) and $t+l_n-1$ (production finish time) is assured with Eq. (3.9) for each production line.

3.1.4 Upper Bound on Demand Satisfied by the Retailer

In the modeled SCN, retailer does not have a capability of satisfying demand as much as it can by using its inventory. In the system, an upper bound exists for retailers that regulate the amount of flow of each product in each time interval that are referred to as the maximum flow (MF) constraints. Because of this regulation, system-wide average inventory increases. The details of this observation will be discussed in detail with an illustrative example and analysis part.

3.1.5 Objective Function

The objective of considered supply chain is the maximization of the profit which is formulated as revenue minus cost of operations. In the system, revenue is only created by the interaction between the retailers and customers. Once the customer buys a product, revenue is created in the system. Although, there exist only one source of revenue, there are many cost items in the system including holding cost of inventory in each node of system, transfer cost of materials between nodes, raw material cost that comes from supplier, fixed and variable cost of the production.

One of the most important goals in supply chains is the satisfaction of the demand generated by the customer. It is a well-known fact that the customer demand is highly sensitive to the price of the products [28]. In this paper, the relationship between the demand and price are modeled using the price elasticity concepts. Detailed analyses of the price elasticity of the demand as well as the formulation of objective function with required modifications are provided in the following section.

3.1.6 Price Elasticity

Price elasticity of demand (PEOD) is the response of demand to any change in the price of the material. According to market dynamics, the amount of demand for a product is inversely proportional with its price for the most of product categories. The PEOD is calculated by:

$$E_x = -\frac{\text{\% change in the demand}}{\text{\% change in the price}} \tag{3.10}$$

3.1.6.1 Use of Difference Equation for the Representation of Price Elasticity

The relationship between the quantity demanded by the customers for a product and the price of the product can be expressed with the following differential equation:

$$\frac{d\left(ur_{nkk''t}\right)}{ur_{nkk''t}} = -E_x \frac{d\left(Prc_{nt}\right)}{Prc_{nt}} \qquad \forall n \in N, \forall t \in T, \forall k \in N_{rt}, \forall k'' \in N_{cs} \tag{3.11}$$

where $ur_{nkk''t}$ is value of variable demand of product n that comes from downstream node k'' to node k at time t and Prc_{nt} is the price of product n at time t.
However, adding Eq. (3.11) into our constraint set makes our system nonlinear. To prevent nonlinearity, differential equation in Eq. (3.11) is converted to the following difference equations.

$$\frac{ur_{nkk''t} - ur_{nkk''t}^{old}}{ur_{nkk''t}^{old}} = -E_x \frac{Prc_{nt} - Prc_{nt}^{old}}{Prc_{nt}^{old}} \tag{3.12}$$

where $ur_{nkk''t}^{old}$ is the demand of product n from node k'' to node k at time t in the previous period and Prc_{nt}^{old} is the price of product n at time t in the previous period. In Eq. (3.12) both $ur_{nkk''t}^{old}$ and Prc_{nt}^{old} are the constants whose values were determined during the previous planning period. Therefore, we can express demand in terms of price and price in terms of demand (Eq. (3.13)).

$$ur_{nkk''t} = ur_{nkk''t}^{old} - E_x ur_{nkk''t}^{old} \frac{Prc_{nt} - Prc_{nt}^{old}}{Prc_{nt}^{old}} \qquad \forall n \in N, \forall t \in T, \forall k \in N_{rt}, \forall k'' \in N_{cs} \tag{3.13}$$

3.1.6.2 Use of Piecewise Linear Functions for the Representation of the Price Elasticity

Eq. (10) leads to $p(ur) = h/(ur^{(-1/E_x)})$ where h is the price that makes the demand to corresponding product one, *ur* is the demand and E_x is the elasticity value of the corresponding product [29]. The *h* value is calculated by using the price, demand and elasticity data of previous planning period. Also to use the elasticity data of previous planning period, it should be assumed that the price elasticity values of a product remain stable during its life time. According to one of the assumptions, retailers have to satisfy all of the demand that is submitted to them immediately. Therefore, at any time interval, demand of a product to retailer has to be responded with the same amount of flow of corresponding product. Because of this assumption, the revenue function will be the following:

$$R_r = \frac{h}{ur^{(-\frac{1}{E_x})}} ur = h\ ur^{(1-\frac{1}{-E_x})} \tag{3.14}$$

3.1.6.2.1 Piecewise Linear Approximation

Because Eq. (3.14) is nonlinear, using this term as a revenue function in the objective leads to a mixed-integer nonlinear programming problem (MINLP). One way of dealing with nonlinearity is the use of piecewise linear approximation. The possible approximation schemes can be seen in Fig. 3.2.

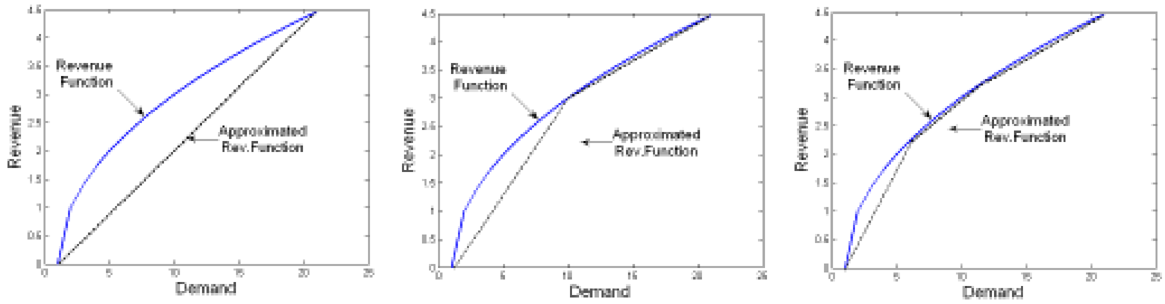

Fig. 3.2.: Possible approximation schemes

As seen in Fig. 3.2, the nonlinear revenue function can be approximated with piecewise linear functions that may have different number of segments. As the number of segments in the piecewise linear functions increase, the approximation error decreases. However, increase of number of segments causes increase in the computational complexity of problem. Therefore, the linearization methods must be both accurate and computationally efficient.

One way of linearization is using IP techniques to approximate revenue function [30]. In this method, a binary variable is defined for each segment of the piecewise linear function. This variable takes the value of 1, if the segment of piecewise linear equation corresponding to this variable is active. Although, the real revenue function can be approximated easily in this manner, because an additional binary variable is created for each segment of piecewise linear function for each time interval, the combinatorial complexity of the problem increases dramatically.

Because of the computational complexity issues with this approximation technique, we use a more efficient method to approximate nonlinear revenue function. We take advantage of the concave nature of the revenue function with this efficient approximation. By using this approximation, for maximization problems, a concave function can be approximated by using linear terms only [31]. The approximation of the revenue function with a piecewise linear functions consisting of 3 segments is illustrated in Fig. 3.3. To approximate the revenue function, the following equations are added into the system:

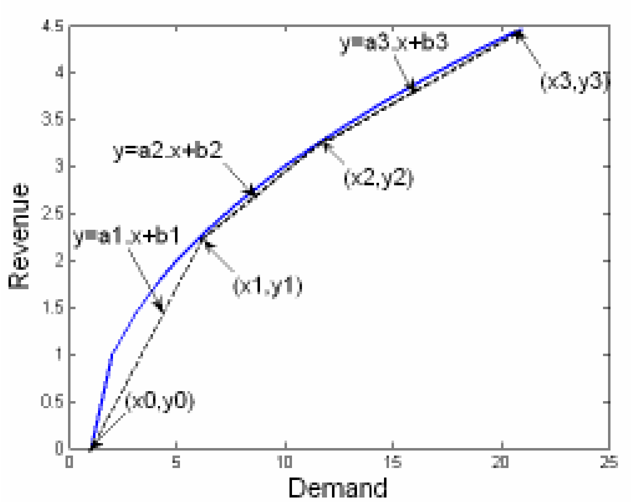

Figure 3.3: Sample approximation with 3 piece-wise functions.

$$
\begin{aligned}
&R_a = y_0 + \sum_j a_j r_j \\
&ur = x_0 + \sum_j r_j \\
&0 \le r_j \le x_{j+1} - x_j
\end{aligned}
\tag{3.15}
$$

where R_a is the approximated revenue function, ur is the current demand value which is equal to yr because of the assumption immediate satisfaction of the demand in the retailer node. By using the approximation technique in Eq. (3.15), the nonlinear revenue function can be represented without adding new binary variables.

The important point in the approximation in Eq. (3.15) is the choice of the number of segments in the piecewise linear equation and the selection of the upper and lower bounds for each segment j, x_j and x_{j+1}. The number of segments depends on the characteristics of the revenue function. For highly nonlinear revenue functions, the number of segments in the piecewise linear function should be increased. However, if system shows near linear behavior, small number of segments for satisfactory approximation is sufficient. Also, as seen from Fig. 3.4, the higher the price elasticity, the more linear the revenue function. Therefore, for highly elastic products, the revenue function can be approximated with a small number of segments in the piecewise linear functions.

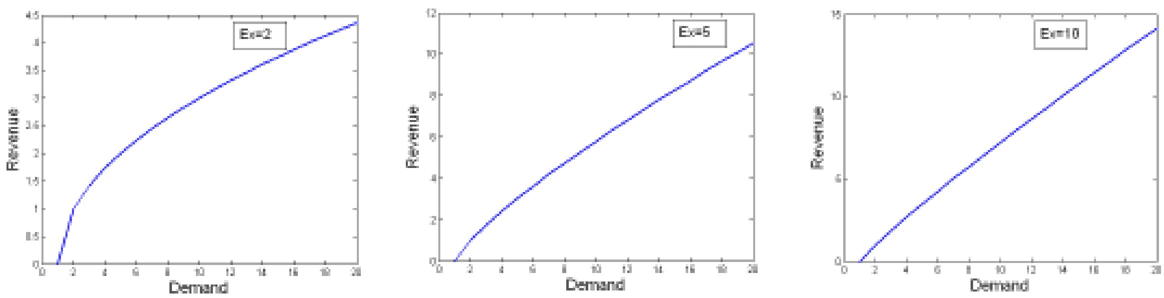

Fig. 3.4: Revenue function with respect different E_x values.

For this reason, the number of segments in the piecewise linear functions should be inversely proportional with the elasticity value for satisfactory approximation. In this thesis, to quantify the effect of number of segments in the piecewise linear functions during approximation, we determine the rate of convergence of approximated objective function to the real objective function. To determine exact number of piecewise linear segments, the number of discretization points are increased until the rate of change of the value of objective decreases to 10^{-4}.

Another important characteristic of Eq. (3.15) on the efficiency of the approximation is the increase in the rate of number of constraints with respect to increase in the number of discretization points. If the number of segments increases, first and second constraints of Eq. (3.15) do not make any contribution to the number of constraints of the whole system. However, because of the third constraint of Eq. (3.15), one additional constraint is added for each segment. We can avoid this increase by using the change of variables in Eq. (3.16).

$$r'_j = r_j - (x_{j+1} - x_j) \tag{3.16}$$

By using the Eq. (3.15) and Eq. (3.16), the number of constraints in the system does not increase in response to increase in the number of segments. However, the number of variables increases in response to each point and use of each change of variable in Eq. (3.16). The number of constraint in the system has more effect than number of variables on the performance of the system for linear programming problems. Therefore, without increasing the computational cost excessively, the nonlinear revenue function can be approximated accurately. The numerical details of approximation will be examined in the illustrative example section.

Another issue is the width of each discretization range or the value of x_{j+1}-x_j for each j. In this paper, because we quantify the success of approximation and because addition of one extra discretization point does not cause a significant computational cost, we make the trivial selection of equally spaced discretization points.

3.1.7 Price Elasticity and Revenue Relation

Supply chain systems give different responses to products with different elasticity values. Therefore, the main behavior of system with respect to elasticity value can be considered in 3 cases: [32]

Case a.) E_x<1:

If the elasticity value of a product is less than 1, then increase in the price causes increase in the revenue that the product creates. For supply chain systems, these products are the most profitable ones because increase in their price causes decrease in the production, inventory and transportation cost besides revenue increase.

Case b.) E_x=1:

If the elasticity value of a product is equal to 1, then system creates the same revenue from any price, demand combination of corresponding product. For supply chain systems, the price should be increased to its maximum value that creates the smallest demand to increase the profit by selling this product. The cost of supply chain will be minimized while revenue remains constant with this change.

Case c.) E_x>1:

If the elasticity value of a product greater than 1, then system can increase its revenue by decreasing price of corresponding product. However, decreasing the price increases the demand and this causes increase in the amount of production, inventory and transportation. This increase directly reflects to cost of production, inventory and transportation. It should be noted that increase in the revenue will be logarithmic; however, increase in the cost becomes linear. Therefore, producing and selling as much as possible is not always the optimal decision for the products whose elasticity is greater than 1.

Proof of claims:

If price elasticity concepts are valid, and then demand can be written in terms of price and price can be written in terms of demand [32].

$$\begin{aligned} Prc &= f(ur) \\ ur &= f(Prc) \end{aligned} \tag{3.17}$$

Then, the revenue is:

$$R = ur\, f(ur) \tag{3.18}$$

The rate of change of revenue with respect to demand is:

$$\frac{d(R)}{d(ur)} = \frac{d\left[ur\, f(ur)\right]}{d(ur)} = \frac{d(ur)}{d(ur)} f(ur) + ur\frac{d\left(f(ur)\right)}{d(ur)} \tag{3.19-a}$$

$$= f(ur) + ur\frac{d\left(f(ur)\right)}{d(ur)} \tag{3.19-b}$$

$$= Prc + ur\frac{d(Prc)}{d(ur)} \tag{3.19-c}$$

$$= Prc + ur\frac{Prc}{Prc}\frac{d(Prc)}{d(ur)} \tag{3.19-d}$$

$$\frac{d(R)}{d(ur)} = Prc - \frac{Prc}{E_x} \tag{3.19-e}$$

Because of Eq. (3.19-e), it can be said that if $E_x>1$, then increase in demand causes increase in revenue, if $E_x<1$, then increase in demand causes decrease in revenue and if $E_x=1$, revenue will be constant in any case.

Also increase in *ur* causes logarithmic increase in revenue for $E_x>1$ case, because:

If Prc_1 and ur_1 is given, one unit increase in ur_1 causes $Prc_1 - \frac{Prc_1}{E_x}$ increase in the revenue.

Because of the $\frac{ur_{nkk''t} - ur_{nkk''t}^{old}}{ur_{nkk''t}^{old}} = -E_x \frac{Prc_{nt} - Prc_{nt}^{old}}{Prc_{nt}^{old}}$ relation, the new price Prc_2 will be:

$$Prc_2 = -\frac{(ur_2 - ur_1)Prc_1}{ur_1}\frac{1}{E_x} + Prc_1 \quad (3.20)$$

With this new price, one unit increase in ur value will cause $-\frac{(ur_2 - ur_1)Prc_1}{ur_1}\frac{1}{E_x} + Prc_1 + \frac{(ur_2 - ur_1)Prc_1}{ur_1}\frac{1}{E^2{}_x} - Prc_1$ unit increase in the revenue which is less than $Prc_1 - \frac{Prc_1}{E_x}$.

3.1.8 Reformulation of the Objective Function

The objective of the supply chain system is the maximization of the profit. The total profit is given as,

$$Z = C_{RE} - C_{HO} - C_{TR} - C_{RM} - C_{PF} - C_{PV} \quad (3.21)$$

The total profit is calculated by subtracting all of the cost items including the cost of holding inventory (C_{HO}), transportation cost (C_{TR}), raw material purchasing cost (C_{RM}), fixed and variable production costs (C_{PF}, C_{PV} respectively) from the revenue generated by the sales of the products (C_{RE}). In this thesis, revenue function is written in two different ways. In the first way, it is modeled by using the price elasticity that is represented by using difference equation. In the second way, it is modeled by using price elasticity that is represented by piecewise linear functions.

3.1.8.1 Revenue Function by Using Difference Equation for Price Elasticity

The revenue is calculated from the following equation:

$$C_{RE} = \sum_{t \in T} \sum_{n \in P} \sum_{k \in N_{rt}} \sum_{k'' \in N_{cs}} Prc_{nt}\, yr_{nkk''t} \tag{3.22}$$

Because one of the assumptions is the immediate satisfaction of demand in the retailer node, value of $yr_{nkk''t}$ equals value of $ur_{nkk''t}$. Also due to validity of price elasticity concepts for our supply chain system, we may apply the change in Eq. (3.13) to the Eq. (3.22). The resulting revenue equation is the following:

$$C_{RE} = \sum_{t \in T} \sum_{n \in P} \sum_{k \in N_{rt}} \sum_{k'' \in N_{cs}} Prc_{nt} \left(ur^{old}_{nkk''t} - E_x\, ur^{old}_{nkk''t} \frac{Prc_{nt} - Prc^{old}_{nt}}{Prc^{old}_{nt}} \right) \tag{3.23}$$

The objective function of problem becomes convex quadratic after Eq. (3.22) is converted to Eq. (3.23). Therefore, the above mixed-integer linear programming problem can be solved to find optimal solution.

3.1.8.2 Revenue Function by Using Piecewise Linear Approximation for Price Elasticity

The real revenue function is represented by Eq (3.14). If the Eq (3.14) is used as a revenue function, the objective function becomes nonlinear. Therefore, as a revenue function the piecewise approximation in the Eq (3.15) is used to make the system linear.

3.1.8.3 Cost Functions

The costs are calculated with the following equations:

$$C_{HO} = \sum_{t \in T} \sum_{n \in P} \sum_{k \in N_{pw}} I_{npkt} HC_{pk} + \sum_{t \in T} \sum_{n \in P} \sum_{k \in N_{dc}} I_{npkt} HC_{pk} + \sum_{t \in T} \sum_{n \in P} \sum_{k \in N_{rt}} I_{npkt} HC_{pk} \tag{3.24}$$

$$C_{TR} = \sum_{t \in T} \sum_{n \in P} \left(\sum_{k \in N_{pw}} \sum_{k'' \in N_{dc}} yp_{nkk''t} TC_{kk''} + \sum_{k \in N_{dc}} \sum_{k'' \in N_{rt}} yd_{nkk''t} TC_{kk''} + \sum_{k \in N_{rt}} \sum_{k'' \in N_{cs}} yr_{nkk''t} TC_{kk''} \right) \tag{3.25}$$

$$C_{RM} = \sum_{t \in T} \sum_{n \in P} \sum_{k \in N_{pr}} \sum_{s \in N_{sp}} \sum_{a \in A} PR_{nkat} Req_{ns} RC_{ks} \tag{3.26}$$

$$C_{PF} = \sum_{t \in T} \sum_{n \in P} \sum_{k \in N_{pr}} \sum_{a \in A} pr_{nkat} FC_{nk} \tag{3.27}$$

$$C_{PV} = \sum_{t \in T} \sum_{n \in P} \sum_{k \in N_{pr}} \sum_{a \in A} PR_{nkat} VC_{nk} \tag{3.28}$$

3.2 Illustrative Example

The optimization approach presented in previous sections is illustrated on two different SCN topologies. In the first topology, SCN includes a production facility capable of producing two different product, warehouse, distribution center and retailer. Number of plants is increased from 1 to 2 in the second topology. All of the nodes except for the production facility in the SCN can handle two products simultaneously. Since the production facility has a single production line, it can produce only one of the two products at any time period. The data on the example SCN is given in Table 3.1. The supply chain system is modeled and solved by C#, ILOG Concert Technology platform [33]. Optimization is performed during 20 time interval in one planning period. The analysis of the SCN at the optimal solution and the affect of different parameters are presented in this section.

The price elasticity of a product is not independent from its environment; for that reason, the price elasticity value can show dynamic behavior. In this thesis, it is assumed that the price elasticity value of a product can change with respect to time or with respect to season of the year. The real life applications of this assumption can be observed in [34]. The response of demand for a product to the change in its price varies in different time intervals because first of all the substitution effect of other products changes the behavior of the customer. Also, the perception of the value of a product for a customer shows difference in different time intervals or seasons. This difference of perception of value causes different demand patterns and this different demand patterns can be represented with seasonally changing price elasticity of demand values. The solution statistics for the difference equation representation of the price elasticity are shown in the Table 3.2 and the solution statistics for the piecewise linear approximation of the price elasticity is shown in the Table 3.3.

Parameter	Value
PR^{U}_{nkat}	40
l_n	2
HC_{nkt}	2
$TC_{nkk''t}$	1
RC_n	1
FC_{nk}	1
VC_{nk}	1
$SC_{nkk''}$	1
ur^{U}_{nk}	10

$\delta_{Pr\text{-}Dc}$	3
$\delta_{Dc\text{-}Rt}$	2
Prc_{nt}^{old}	50
$ur_{nkk''t}^{old}$	2

Table 3.1: Case study parameters for the example problem.

Item	**Value**
# of variables	1,140
# of 0-1 variables	60
# of iterations	22,969
# of B&B nodes	1,765
CPU time (sec)	2.1

Table 3.2.: Model statistics for the example problem (time discretization is used).

Item	Value
# of variables	960
# of 0-1 variables	60
# of B&B nodes	0
# of iterations	3
# of constraints	2954
CPU time	0.00

Table 3.3.: Model statistics for the example problem (piece-wise linear functions are used).

3.3 Result and Analysis

3.3.1 Result and Analysis for the Difference Equation Representation of Price Elasticity

The flow from retailer to customers is limited with an upper bound (this upper limit is referred to as the maximum flow (MF) quantity). This upper bound has important effect on the inventory of the products held in different nodes. As seen in Fig. 3.5, if the maximum flow (MF) constraint is removed from system, for each value of the elasticity of product 2, the average inventory of product 2 hold in the system (sum of inventories of product 2 held at plant warehouse, distribution center and retailer) decreases. The reasons for the system to hold inventory include the fix cost of production, transportation delay, and the MF constraint. Therefore, in the absence of MF constraint, i.e., the system has unlimited transportation capacity between the retailer and the customers and the customers have infinite demand, makes system hold fewer inventories. The main reason of inventory decrease is the decrease in the order accumulated in the system.

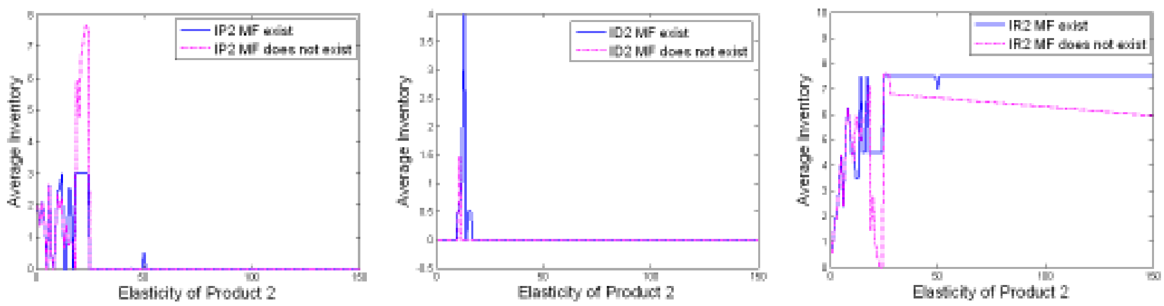

Fig. 3.5.: Average inventory of product 2 at plant warehouse (IP2), at distribution center (ID2) and at retailer (IR2) on the existence and absence of maximum flow (MF) constraint for 1 plant case.

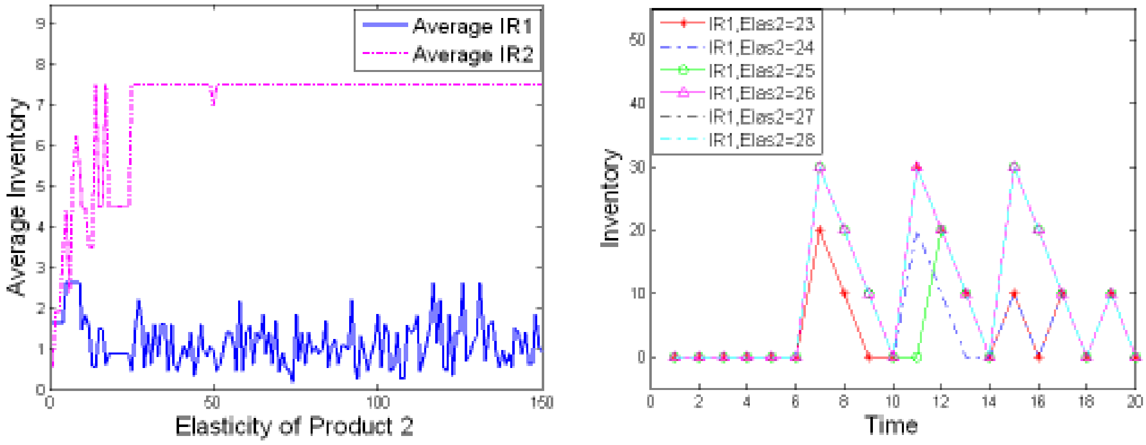

Fig. 3.6.: Amount of average inventory of product 2 (IR2) with the different values of Elasticity 2 for 1 plant case. a.) Amount of average inventory of product 1 and product 2 with different E_{x2} values. b.) Amount of inventory of product 2 during 1 planning period with different E_{x2} values.

Fig. 3.3 shows the relationship between the elasticity of product 2 and the amount of inventory held in the retailer. As seen from Fig. 3.6-a, as the elasticity of product 2 increases, the average inventory of product 2 increases and it is stabilized when E_{x2} is equal to 25. The same behavior is observed in Fig. 3.6-b. The inventory patterns of product 2 at retailer while Elasticity 2 is equal to 26, 27, and 28, overlap. For that reason, the average $IR2$ values do not change beyond E_{x2} is equal to 25. The main reason for the stability of average inventory is the MF constraint; the maximum amount of demand that can be satisfied by the system is bounded. As seen from Fig 3.7-a, because of MF, the price of product 2 stabilizes when E_{x2} reaches 25. The profiles presented in Fig. 6 are generated by keeping every parameter of the system constant while changing the E_{x2} values to create different price and demand relationship on the each run. However, as seen from Fig 3.7-a, this difference disappears when E_{x2} is equal to 25. Therefore, the inventory holding scheme of system for each elasticity value will be same for each planning period after this step and this result is represented in Fig 3.6-b.

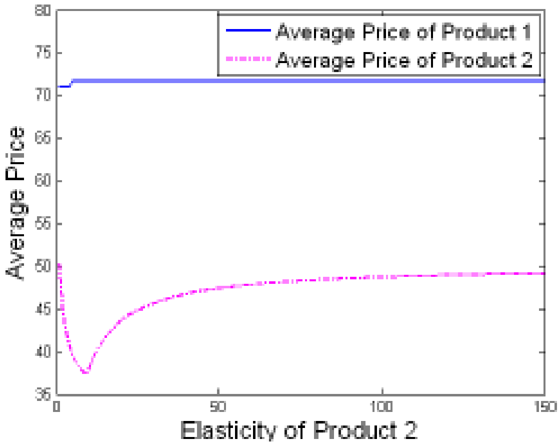

Figure 3.7-a. Average price of product 1 and 2. MF exists in the system, amount maximum production equals 40 for each period and Elasticity 1 is equal to 1.

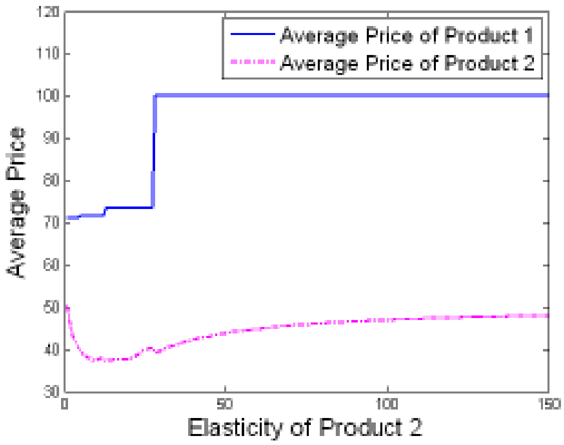

Figure 3.7-b. Average price of product 1 and 2. MF does not exist in the system, amount maximum production equals 40 for each period and Elasticity 1 is equal to 1.

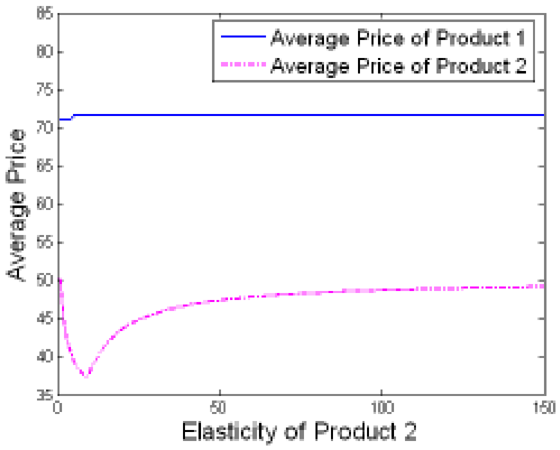

Figure 3.7-c. Average price of product 1 and 2. MF exists in the system, amount maximum production equals 60 for each period and Elasticity 1 is equal to 1.

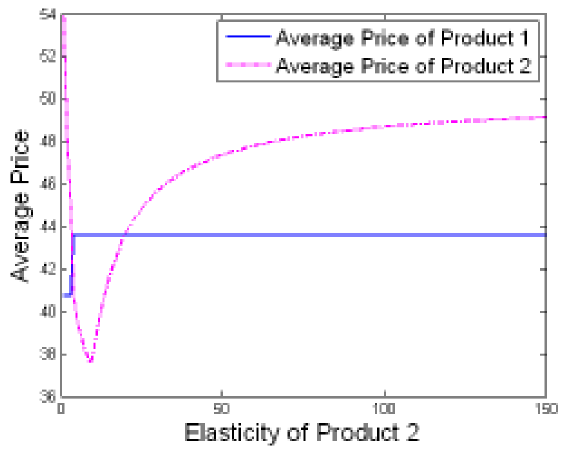

Figure 3.7-d. Average price of product 1 and 2. MF exists in the system, amount maximum production equals 40 for each period and Elasticity 1 is equal to 5.

Fig. 3.7.: The average price values of product 1 and 2 with respect to Elasticity 2 for 1 plant case.

Fig. 3.7 shows the average price of the product 1 and 2 with different values of key parameters that determine price behavior of the system. In the Fig. 3.7-a, the average price behavior of the system on default parameters (MF exists, max production equals 40, and E_{x1} is equal to 1) is presented. As can be seen from Fig.3.7-a, the average price of the product 1 is constant for each value of the Elasticity 2. Because the initial price of product 1 is 50, system still produces product 1 with the price displayed in Fig. 3.7-a. In addition, since E_{x1} is equal to 1, the revenue does not change for any price-demand combination. However, for each combination, the total cost changes. A legitimate approach to maximize the profit is to increase the price of product 1 as much as possible that will decrease the demand to the smallest non-zero value. This price is determined as 70 for the example problem. Another important characteristic of the system is the average price of product 2. First the price of product 2 decreases as the E_{x2} value increases as shown in Fig. 3.7-a. The average price of the product 2 increases when E_{x2} reaches 10. The reason of this change is the MF constraint. The upper limit on the maximum demand that can be satisfied by system is reached once the E_{x2} becomes 10. After this elasticity value, the total revenue of the system can be increased by decreasing the price increasing demand of product 2. However, supply chain system cannot satisfy demand if we continue to decrease price. Therefore, the optimal policy to increase the profit, is the increase of the price as soon as upper bound value of the demand that can be satisfied by system is reached with higher E_{x2} value and constant demand satisfaction value.

The results without the MF constraint are represented in Fig. 3.7-b. The most important observation in this figure is the price behavior of the product 1. After a certain elasticity value, the price of the product 1 becomes 100 as seen in Fig. 3.7-b. Because the initial price of the product 1 is 50 and its elasticity is 1, increase of its price to 100 causes the demand to decrease to 0. If elasticity of a product is very high, system will dedicate all its production capacity to that product to increase the profit without the MF constraint. For that reason production of product 1 is not an optimal choice if MF does not exist.

In the Fig. 3.7-c, the results are represented when the maximum production limit is increases to 60. The behavior of the system in Fig. 3.7-a and in Fig. 3.7-c are the same. This result shows that, in the presented system if MF limit exists, the max production constraint is not a binding constraint and shadow price of an extra unit of production limit is equal to zero.

In order to analyze the effect of price elasticity, E_{x1} is changed to 5 while keeping E_{x2} constant and the behavior shown in Fig. 3.7-d is obtained. At first, the average price of product 1 first decreases from its initial value which is 50. Then, it remains constant and after a while it increases with a small value and remains constant again. The main reason of this behavior is the fact that Elasticity 1 is greater than 1. Any decrease in the price results in an increase in the revenue. For that reason, different from Fig. 3.7-a, the system decreases its price as much as it can. For our case this lower average price limit is the 37. If the system decreases the price of product 1, the revenue of the system increases while the cost of the system also increases. Nevertheless, the increase in the revenue shows logarithmic behavior, but the increase in the cost is linear. Therefore, the price of the system cannot be decreased until reaching to smallest positive price value that maximizes demand. Also, as revealed in the Fig. 3.7-d, the price of product 1 increases after a while. The main reason of this is the dedication of production limit to the product 2 until reaching the MF limit. The system increases the price of product 1 to maximize the revenue, since the maximum amount of demand of product 1 is very limited and it is equal to the difference between maximum production capacity and MF limit.

Some of the arguments for Fig. 3.7 are also valid for Fig. 3.8. As seen from Fig. 3.8-a, the average demand of product 2 that is satisfied, increases until E_{x2} is equal to 10. During these steps some demand to product 1 exists and it is still satisfied. The main reason of this result is the MF constraint. If the MF constraint is removed, as seen in Fig. 3.8-b, the demand of product 1 is not satisfied and system dedicates itself to the product 2. Also as seen from Fig. 3.8-c increase of maximum production limit from 40 to 60 does not cause any change in the amounts of demand satisfied.

The result for increasing E_{x1} is shown in Fig. 3.8-d. Increase of E_{x1} does not change the behavior of product 2. However, its effect on the product-1 can be seen when Fig. 3.8-a and Fig. 3.8-d are compared. The average amount of demand of product 1 satisfied increases first. The reason of this increase is the decrease of price of product 1 during that interval and this is because system cannot reach MF limit for product 2. However after a while, the value decreases in Fig. 3.8-d and remain constant. The reason of this decrease is the dedication of supply chain system to the product 2 until reaching MF limit. During this interval, the system produces more product-2 with lower price and less product-1 with higher price to maximize the profit.

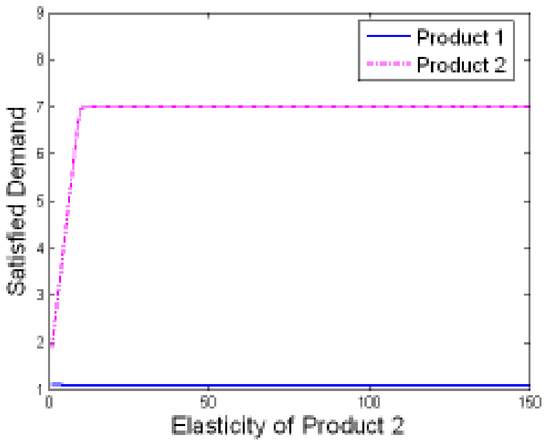

Figure 3.8-a. Average satisfied demand of product 1 and 2. MF exists in the system, amount maximum production equals 40 for each period and Elasticity 1 is equal to 1.

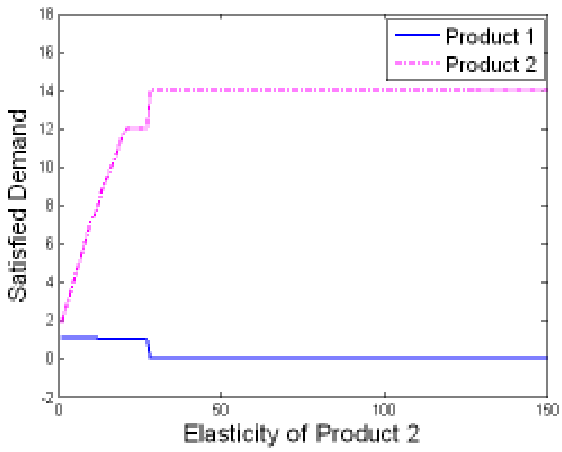

Figure 3.8-b. Average satisfied demand of product 1 and 2. MF does not exist in the system, amount maximum production equals 40 for each period and Elasticity 1 is equal to 1.

Figure 3.8-c. Average satisfied demand of product 1 and 2. MF exists in the system, amount maximum production equals 60 for each period and Elasticity 1 is equal to 1.

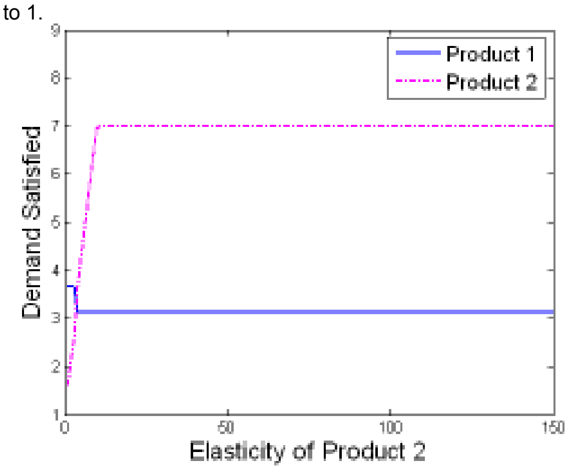

Figure 3.8-d. Average price of product 1 and 2. MF exists in the system, amount maximum production equals 40 for each period and Elasticity 1 is equal to 5.

Fig. 3.8.: The average satisfied demand values of product 1 and 2 with respect to Elasticity of Product 2 for 1 plant case.

To see the affects of the number of the plants in the system, the number of the plants is increased from one to two. These two plants exhibit same characteristics. The topology of this new SCN is shown in Fig. 3.9.

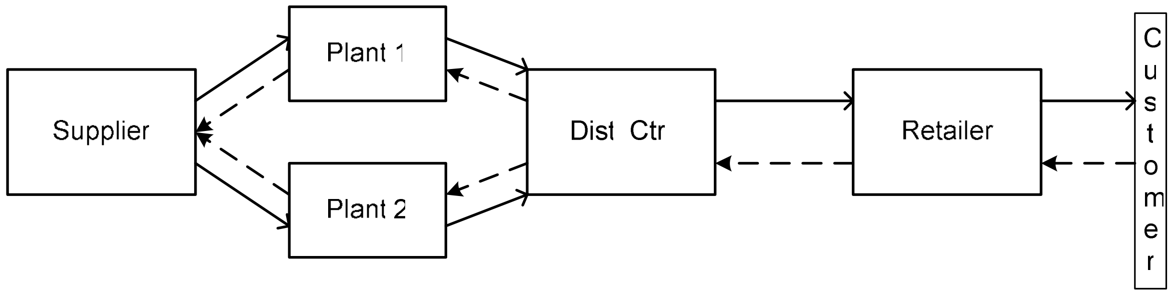

Fig. 3.9.: The new topology of SCN.

In SCN represented in Fig. 3.9, each plant is identical and they have only one production line. With respect to topology in Fig. 3.9, the new inventory profile of the product 2 is shown in Fig. 3.10. As seen in Fig. 3.10, the logical relationship between the existence of MF constraint and total inventory is still valid. Existence of MF constraint causes an increase in the total inventory held in the system.

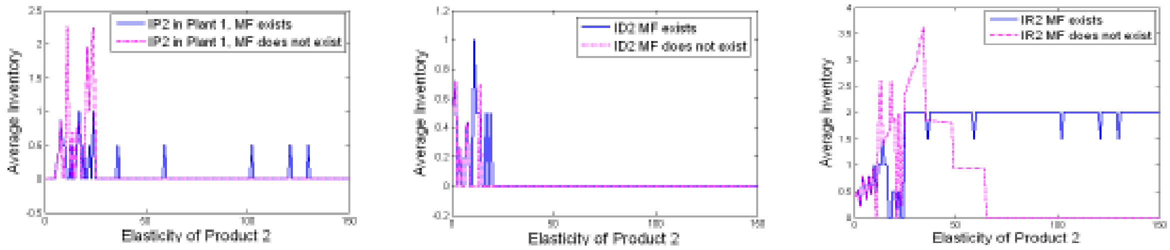

Fig. 3.10.: Average inventory of product 2 at plant warehouse, at distribution center, and at retailer on the existence and absence of maximum flow constraint for the SCN in Fig. 3.9

The relationship between existence of MF constraint and satisfied demand of product 2 for the 1 plant and 2 plants cases are shown in Fig. 11. As seen in Fig. 3.11-a, while the elasticity of product 2 increases, if the MF constraint exists, the satisfied demand of product 2 exhibits the same behavior for both 1 plant and 2 plants cases. However, as seen in Fig. 3.11-b, if MF constraint does not exist, the behavior in 1 plant and 2 plants cases show difference. In the first case, behaviors are same because of the MF constraint. The production capacity of the system cannot be used because of the this constraint and therefore the upper limit of the amount of the average satisfied demand remains same for both 1 plant and 2 plants cases. However, if MF does not exist, system will have an ability to use all its production capacity. This behavior can be seen in Fig. 3.11-b. In Fig. 3.11-b, in 1 plant case, on the average, system satisfies 14 units of demand, and in 2 plants case, 28 units of demand is satisfied. This shows that usage of one plant in full capacity, with the same network topology and arc capacities, on the average handles the satisfaction of 14 units of demand and usage of two plants handles satisfaction of 24 units of demand.

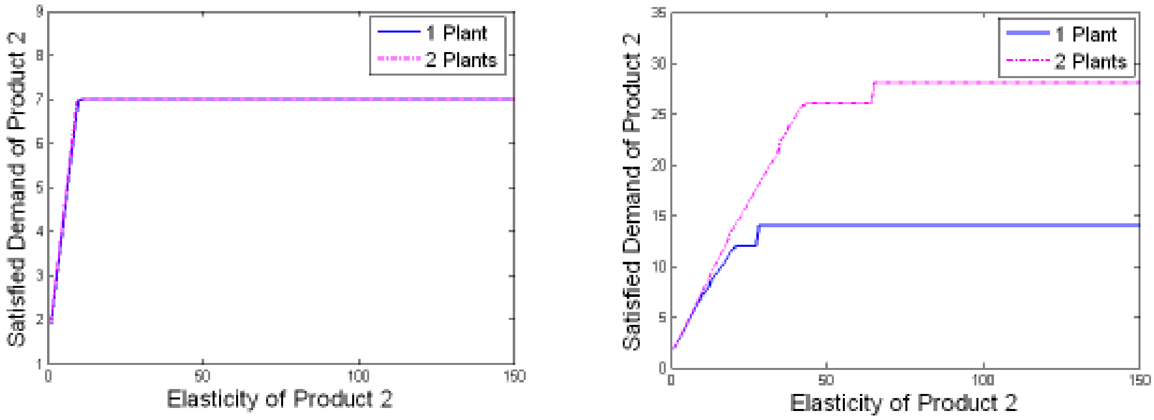

Fig. 3.11.: Amount of Satisfied Demand of Product 2 for 1 plant and 2 plants cases. a.) MF constraint exist. b.) MF constraint does not exist.

The relationship between the number of plants and the total average inventory in the system is shown in Fig. 3.12. If the number of plants is increased from one to two, the average inventory held in the system for both Product 1 and Product 2 decreases. The main reason of this decrease is the elasticity gained from one extra plant. Because of an additional plant, instead of holding inventory, system can make a dedicated production for any product and this causes a decrease in the total amount of inventory held in the system.

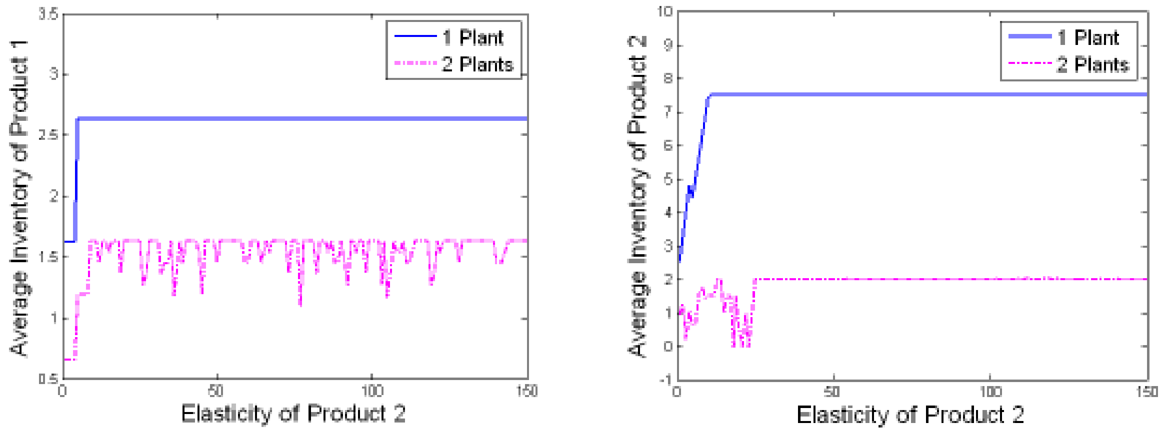

Fig. 3.12.: Amount of average inventory in whole SCS for 1 plant and 2 plants case a.) Average inventory of Product 1 in the whole system. b.) Average inventory of Product 2 in whole system.

The relationship between the profit and elasticity value is shown in the Fig. 13.3. While the elasticity of product 2 increases, the profit of the system increases too. This is because, as the elasticity value of a product increases, the increase of the demand becomes larger than price decreases. Besides, the system cannot meet demand more than a threshold value. The increase rate of the profit function shows remarkable decrease as soon as the threshold value is reached. However, the profit of the system increases continuously as seen from Fig. 3.13. The reason of this increase is shown in Fig. 3.8-a. Although the system cannot sell more than a certain amount of product, the system can increase the price of product without any decrease in the demand after certain elasticity value. This results in continuous increase in the profit of the system.

Also as seen in Fig. 3.13, the profit obtained in 2 plants case is higher than, profit obtained in 1 plant case. The main reason of this increase is the additional production capacity gained by an additional plant. Besides production capacity, the additional plant makes the production schedule of the system more elastic and this elasticity reduces the cost of handling.

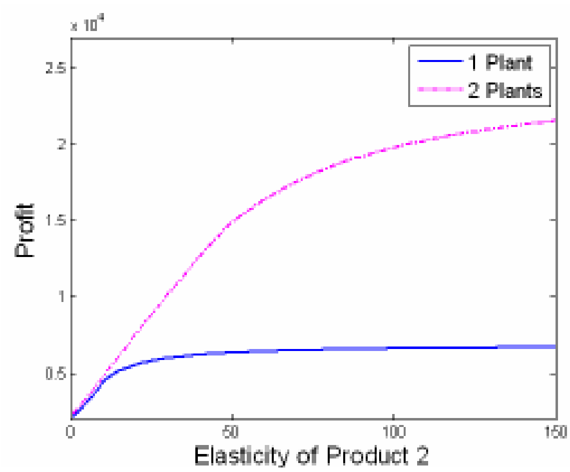

Fig. 3.13.: Profit with respect to increasing elasticity of value of product 2 for 1 plant and 2 plants cases.

3.3.2 Result and Analysis for the Piecewise Linear Approximation of the Price Elasticity

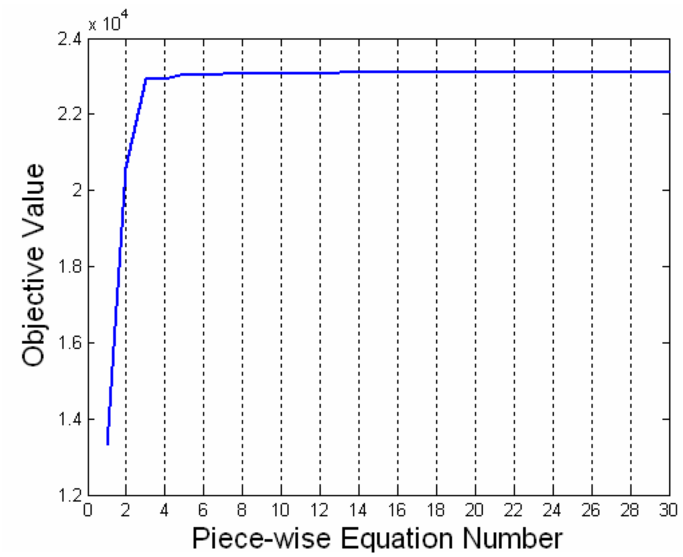

Fig. 3.14: Objective value change with-respect to piece-wise equation number. Ex1 and Ex2 are equal to 1.5.

As seen from Fig. 3.14, while the number of segments in the piecewise linear functions increases, the rate of change of the objective function value decreases. However, increase in the number of segments adds more variables. Therefore, the number of segments should be determined with respect to a quantitative measure. In our case, this measure is the percentage change of objective value between consecutive numbers of segments in piecewise linear functions. The runs to determine this number are made with products whose elasticity is equal to 1.5. We choose this number because, as the elasticity value decreases, the objective function exhibits more nonlinear behavior as shown in Fig. 4. In other words, the number of piecewise linear segments is determined considering the worst case. This approach is flexible to define different segments for different products or different characteristics in different seasons for a product.

In the case which is represented in Fig. 3.14, it is decided to use 18 segments in the piecewise linear functions because between 18 and 19 segments the percentage change in objective function value is equal to 5.6 10^{-4} which is acceptable.

Fig. 3.15 shows the relationship between average price and average demand satisfied with respect to E_{x2} for the constant price elasticity values for all seasons of a planning period. During the calculation of average price, the first 5 periods are not added into calculation because in the first 5 periods, it is impossible to sell product or to satisfy demand, due to delays. As seen in part b of Fig. 3.15, while value of E_{x2} is between 2 and 18, the amount of satisfied demand for product 1 and 2 take a constant value. However, because in this interval, the E_{x2} value increases, the average price of product 2 will increase. Because of increase of elasticity value, to satisfy the same amount demand with the previous time period, system does not need to keep price low, instead the price should be increased to keep amount of demand satisfied constant. In contrast, the price of product 1 remains constant in this interval. This is because, in this interval, the elasticity of product 1 does not change; therefore, the demand price relationship does not change. When E_{x2} is equal to 18, the average satisfied demand of product 2 increases but that of product 1 decreases and then remains constant. As seen from part a of Fig. 3.15, the foregoing change causes increases in the average price of product 1 but it causes decrease in the average price of product 2. However, after this point the average price of product 1 remains constant because of the unchanged value of E_{x1}. But the average price of product 2 continues to increase because of the increasing value of E_{x2}.

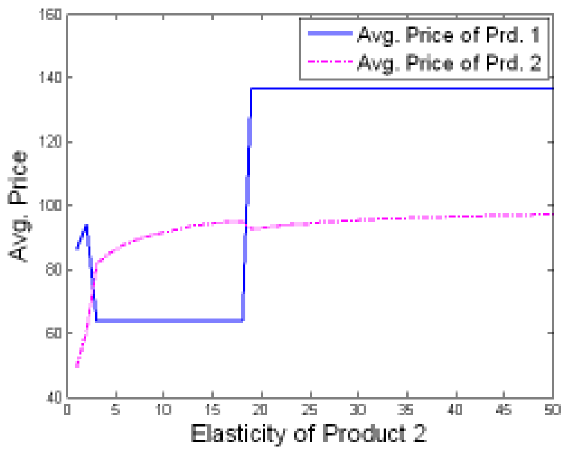

Fig. 3.15-a: Average price of Product 1 and Product 2 for non-seasonal price elasticity while MF exists and MaxProduction is equal to 40

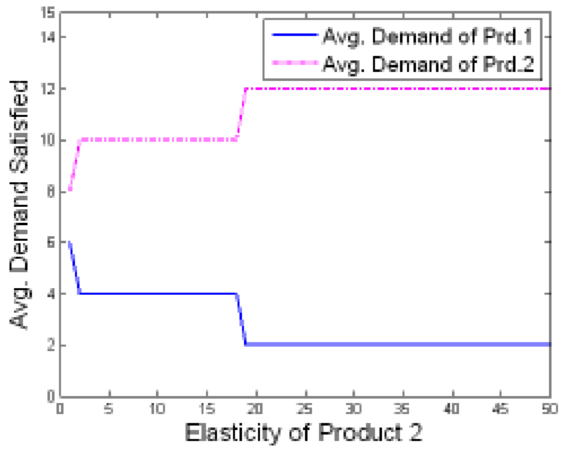

Fig. 3.15-b: Average satisfied demand of Product 1 and Product 2 for non-seasonal price elasticity while MF exists and MaxProduction is equal to 40

Figure 3.15: Average price and satisfied demand of product 1 and 2.

As seen in part a of Fig. 3.15, although the total amount of satisfied demand of product 1 is less than that of product 2, the average price of product 2 is higher than that of product 1 in the interval of E_{x2} is equal to 2 and 18. The reason of this behavior is the production schedule of products and elasticity values. As part a of Fig. 3.16 shows that, product 1 is the first product produced in the system at time period 1 and because of the delay, the first satisfaction of demand takes place at time period 6. But production of product 2 does not take place and because the initial inventory of product does not exist, system cannot satisfy the demand of product 2. Therefore, the price of product 2 is increased to 114.2 which is the price that makes demand 0. After period 8, the product 2 produced at period 2 reaches retailer and the first satisfaction of demand of product 2 takes place. The satisfaction of demand is the result of price decrease at time period 8. After period 8, although system sells more product 2, the price of product 2 becomes higher than that of product 1. This behavior is seen because the E_{x2} is higher than E_{x1}, so by keeping its price high, system can sell more product 2.

However, as Fig. 15 shows, after E_{x2} is equal to 20, the average price of product 1 exceeds that of product 2. Again, this is because, after that value, product 2 becomes the first product produced in the system. Therefore, at time period 6 and 7 price of product 1 becomes 300 which is the price that makes demand to that product 0. Also because, the elasticity of product 2 is higher than that of product 1, system dedicates nearly all its capacity to production 2. Therefore, at the last 2 periods, because all inventory of product 1 diminishes, no demand can be satisfied and its price reaches to 300. Therefore, average price of product 1 becomes higher than that of product 2.

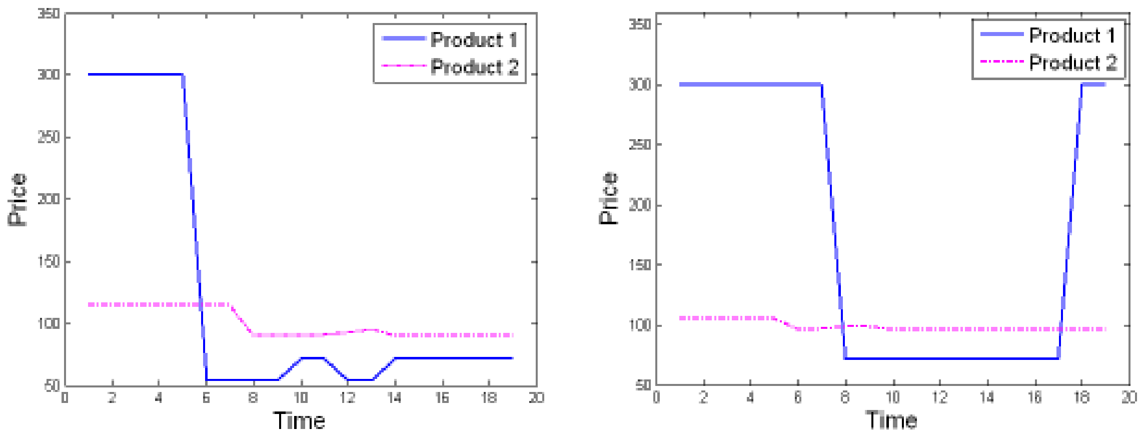

Figure 3.16-a: Price of product 1 and 2 in a planning period for non-seasonal price elasticity. MF exists, elasticity of product 2 is equal to 15, MaxProduction is equal to 40.

Figure 3.16-b: Price of product 1 and 2 in a planning period for non-seasonal price elasticity. MF exists, elasticity of product 2 is equal to 40, MaxProduction is equal to 40.

Figure 3.16: Price of product 1 and 2 while E_{x2} is equal to 15 and 40.

Although in Fig. 3.15, the average price of product 2 increases continuously as E_{x2} increases, it should be expected that the average price should first decrease and then it should increase. This is because of the limits of the SCS. These are production and transfer limits. The price of a product should be decreased until reaching this system limit. After that, because system cannot satisfy any more demand, with increasing elasticity value, the average price should increase. The reason for this behavior is the fact that for highly elastic products, small decrease in the price causes a large increase in the demand of that product.

The reason of nonexistence of expected behavior of average price is the satisfaction schedule of product 2. As seen in part b of Fig. 3.17, the demand of product 2 is not satisfied continuously. In other words, the satisfaction takes place in specific time periods and in the remaining time periods; system does not satisfy any demand. At this time periods, the price of the product increases to its highest finite value that makes demand to that product 0. If we consider these highest prices, the effect of elasticity can be shadowed. Therefore, if we only consider the prices that demand is satisfied, the expected behavior of the average price is captured (part a of Fig. 3.17).

Another important characteristic of the system is observed once a product, whose elasticity value is equal to 1, is added. In that case, the price of corresponding product increases to infinity. System behaves in this manner because of the fact that, for products whose elasticity is equal to 1, any price-demand combination creates same revenue. However, the same rule is not valid for the cost. The operational cost of a system depends on the total production level. Therefore, by increasing the price to the infinity, system maximizes its profit because by this manner the cost is minimized while the revenue remains constant.

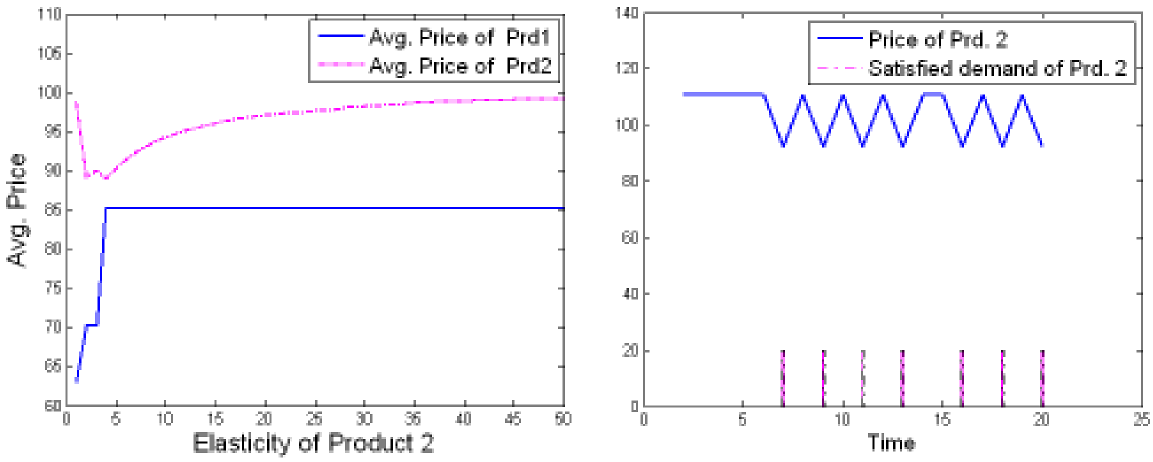

Figure 3.17-a: Average price of product 1 and 2 Calculations are made by taking the production schedule in account

Figure 3.17-b: Price and satisfied demand of product 2 while elasticity of product 2 is equal to 20

Figure 3.17: Relation of price, demand and E_{x2} with production schedule.

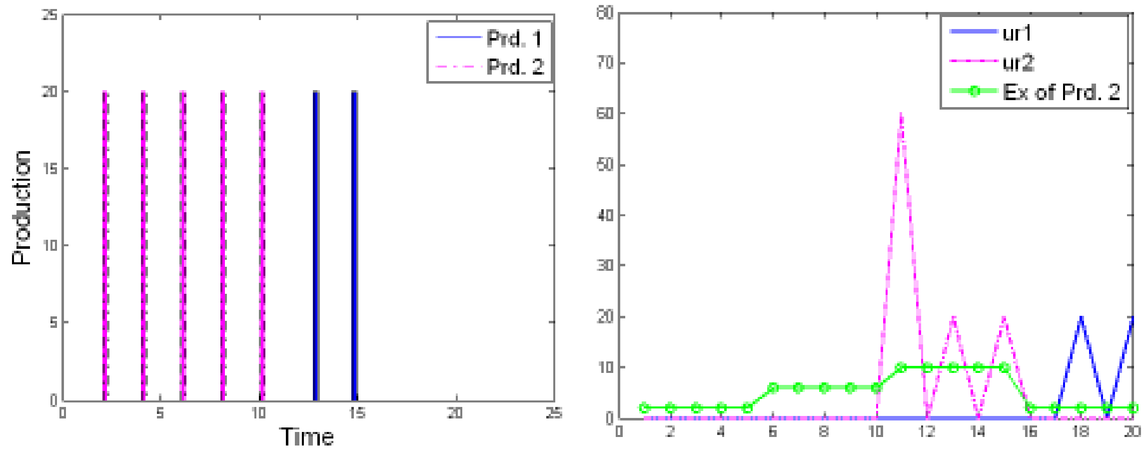

Figure 3.18-a: Production schedule of product 1 and 2 MF does not exist MaxProduction is equal to 20 and elasticity of product 1 is equal to 4

Figure 3.18-b: Satisfied order of product 1 and 2 with seasonal elasticity value of product 2 MF does not exist MaxProduction is equal to 20 and elasticity of product 1 is equal to 4

Figure 3.18: Relation between seasonal price elasticity, production and demand satisfaction schedule.

Fig. 3.18 shows the relationship between production schedule, satisfied demand and seasonality in the elasticity. As seen in part b of Fig. 3.18, E_{x2} value changes with respect to season of the year. There are 4 seasons in one planning period and there are 5 time periods in each season. During this planning period, the E_{x1} value remains in its initial value which is 4 in each time period. However E_{x2} becomes 2, 6, 10 and 2 during remaining 4 seasons respectively. In this case, the system satisfies the demand of product 2 only during the 3rd season. E_{x2} takes its maximum value during this season; therefore, a sale of products on that season is the most profitable. However, the system cannot produce enough products immediately. Therefore, as seen in part a of Fig. 3.18, in the first 2 seasons, the system produce product 2 in its maximum capacity and put them on the inventory. At the beginning of season 3, the satisfaction of customer demand starts. Because of the transportation delay and the low value of E_{x2} on the last season, the system does not make the production of product 2 in the 3rd season. Instead in the season 3, only product 1 is produced and it is sold on the season 4.

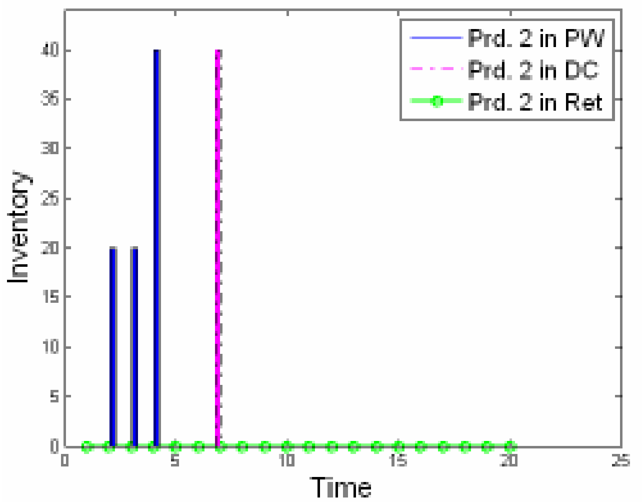

Figure 3.19: Inventory of product 2 in plant warehouse (PW), distribution center (DC) and retailer (Ret) on while price elasticity shows seasonal behavior. MaxProduction is equal to 20, E_{x2} and E_{x1} take same value as in Fig. 18

The relationship between the seasonal elasticity and inventory is shown in Fig. 3.10. If seasonal elasticity is considered, the system starts holding inventory. If we keep all but seasonality conditions on Fig. 3.10 constant and use non-seasonal elasticity value, the system does not hold any inventory in all of the nodes. The reason of inventory on the seasonal elasticity case, is the existence of season in which selling product is more profitable than the other seasons. Therefore, the system makes decisions to hold inventory in the seasons which is not profitable and decides to sell the inventory in profitable seasons whose elasticity is higher than the other periods. However, seasonality by itself is not the only reason of inventory. Delay also causes to hold inventory in this case, because the transportation delay prevents to immediate satisfaction of demand as soon as production takes place.

Chapter 4

MODELING OF FERMENTATION DYNAMICS

4.1 Problem Definition

The complete genomes of cellular organisms can be sequenced in a short time with currently available experimental methods [35]. However, the real challenge begins after sequencing. Because abundance of biological data requires a new and revolutionary understanding of biology focusing on how chemical and biological functions of organism are realized, a new and interdisciplinary field appeared, systems biology [23], [36]. In systems biology, the main concern is the determination of emergent properties of interconnected nodes of the data rather than determination of properties of a single object or node of data. In this paper, the emergent property that we are looking for is the fermentation dynamics of the yeast during wine formation [37].

The wine fermentation process takes place in the cell interior and exterior. Therefore a modeling technique should be developed to represent the changes occurs both in the cell interior and exterior. In the section 4.1.1 the theoretical background of the modeling of cell interior is explained in detail. In the section 4.1.2, the formulation of the cell exterior is explained. In section 4.2, the wine fermentation case is investigated. The fermentation takes place in both cell interior and cell exterior, but these two processes takes place instantaneously and simultaneously in the cell. Therefore separate formulation for cell interior and exterior is not a suitable approach to model the fermentation dynamic. In section 4.2.4, the developed technique to integrate the cell interior and exterior is described.

After the development of this integrative formula, the simultaneous changes occurred in the cell interior and exterior is modeled by single set of equations. Due to use of single set of equations, the changes occurred in the model also takes place simultaneously. By this the way, the representation gap, between behavior of the model and behavior of the living organism decreases.

4.1.1 Intercellular Representation

The fermentation process, takes place both in cell exterior and cell interior. In this part, the interior representation of the cell is explained in detail. All the reactions that takes place in the cell can be determined with current technology. However, this information by it self is not enough to model the cell with mathematical formulations. Some conversions are required to use the biological informations in mathematical models. The required conversions and the developed mathematical models is described in this part.

With today's technology the metabolic network and the set of reactions that take place in the cell can be determined easily [38]. We can acquire knowledge of components that comprise cells and how they interact using metabolic networks. A sample metabolic network is illustrated in Fig. 4.1. In Fig. 4.1 only the reactants and products of each reaction are shown without explicitly showing the stoichiometry of network. In this simple metabolic network, there are 5 reactions ($v1$ to $v5$) and 4 metabolites (A, B, C, D). In the reaction set, the network converts 2 mole of A to 1 mole of B and the remaining reactions makes similar effect in the network. The stoichiometry of the network in the Fig. 4.1 is represented in the Table 4.1. In this representation, each row corresponds to a metabolite and columns correspond to reactions that the metabolites participate. If the matrix element for a particular reaction and metabolite is negative, then the metabolite is consumed by the reaction. When the matrix element is 0, then the metabolite is not involved in the reaction.

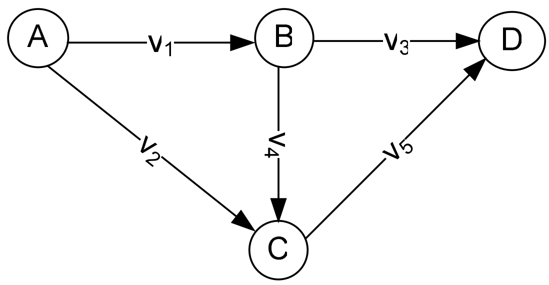

Figure 4.1: Sample Metabolic Network.

S_{ij}	v_1	v_2	v_3	v_4	v_5
A	-2	-2	0	0	0
B	1	0	-1	-1	0
C	0	1	0	1	-1
D	0	0	2	0	-2

Table 4.1: Stoichiometric Matrix representation of Metabolic Network in Fig. 1

The matrix in the Table 4.1 is called a stoichiometric matrix. According to the matrix in Table 4.1, for instance, reaction 3 takes 1 unit of metabolite B and produces 2 units of metabolite D. We can model internal flux of a cell by looking at this matrix. If we represent the rate of change of concentration metabolites with the differential equations, the corresponding set of reactions for the network in the example will be as follows:

$$\begin{aligned}\frac{dx_A}{dt} &= -2v_1 - 2v_2 \\ \frac{dx_B}{dt} &= v_1 - v_3 - v_4 \\ \frac{dx_C}{dt} &= v_2 + v_4 - v_5 \\ \frac{dx_D}{dt} &= 2v_3 - 2v_5\end{aligned} \tag{4.1}$$

Comparing the stoichiometric matrix in Table 4.1 and the set of ODE in Eq. (4.1), the ODEs can be written as:

$$\frac{dx}{dt} = Sv \tag{4.2}$$

where S is the stoichiometric matrix, $v=(v_1, v_2, v_3, v_4, v_5)^{\mathrm{T}}$ is the flux vector, and $x = (x_A, x_B, x_C, x_D)^T$ is the concentration of metabolites. Within the cell at steady state Eq. (4.2) can be converted to set of homogenous linear equations:
Eq. (4.2) is converted to a set of homogeneous linear equations in the following way:

$$0 = Sv \tag{4.3}$$

To determine the dynamic behavior in an organism, Eq. (4.3) does not give enough information. From Eq. (4.3) we can only model the flux cone that includes all possible fluxes of a cell. However, the main problem here is which flux set will be carried out by the cellular organism under different conditions. One of the main tools to answer to this question is the constraint based approach [19]. In this approach an LP is solved to predict the future behavior of organisms. First, the constraints based on stoichiometry and thermodynamics' of system are determined and an objective function is included in the system to find the most promising flux distribution. Different objective functions are then applied to mimic the behavior of the organisms; these include maximization of biomass or ATP production. The suitability of these objectives is tested with experiments. However, despite existence of many objective functions, the most promising one with respect to the experimental results is the maximization of the biomass. Also it was determined that with the objective of optimal biomass formation the prediction of internal flux distributions matches the experimental results better that any other objective [19]. Nevertheless it should be noted that in the cellular organism, there is no metabolite called biomass. To add it to our metabolic network, we have to add an artificial reaction that takes some of the existing metabolites from the system and produce biomass as illustrated in Fig. 4.2. For the wine fermentation process, the biomass for yeast includes Carbohydrate, DNA, RNA, Lipids, and Protein. The compositional coefficient of these metabolites in the artificial biomass metabolites is determined by solving a parameter estimation problem that minimizes the difference between experimental result and the result of the model.

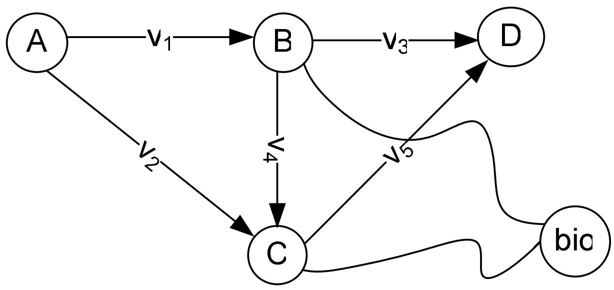

Figure 4.2: Sample Metabolic Network with Biomass

The LP model developed to predict the internal dynamics of the system is the following:

$$\begin{aligned} \max \quad & \textit{biomass} \\ \text{st} \quad & Sv = 0 \\ & v \geq 0 \end{aligned} \tag{4.4}$$

In the LP problem (Eq. (4.4)) all fluxes are greater than or equal zero. The main reason for this is the irreversibility of all reactions. If a reversible reaction exists in the system, we can still put the non-negativity constraint for each flux by decomposing it into two irreversible reactions.

4.1.2 Extracellular Representation

The fermentation process effects not only the cell interior but also cell exterior. In the previous section it is shown that FBA model can be used to represent the interior of the cell by using the steady state assumption. However, the steady state of the cell interior continuously change the characteristic of the cell exterior. In this section, it is shown that how cell interior effects the cell exterior. The relationship between the interior and exterior is described in detail.

In the LP represented in Eq. (4.4), the main assumption is the steady-state of the system. At steady state, the concentration of metabolites remains constant. However, here *constant* concentrations do not imply that all reactions stop. Instead, all reactions continue to be active, but there exists a balance between each reaction. Therefore, consumption and production of each metabolite are equal to each other, and that is the main reason for the steady state. However, this particular steady-state does not stay constant, because of the environmental stress changes. Although in the Fig. 4.1 and Fig. 4.2 the reactions are represented independent from cell exterior, there is a close relationship between cell interior and exterior. A more complete representation of the cell can be seen in Fig. 4.3.

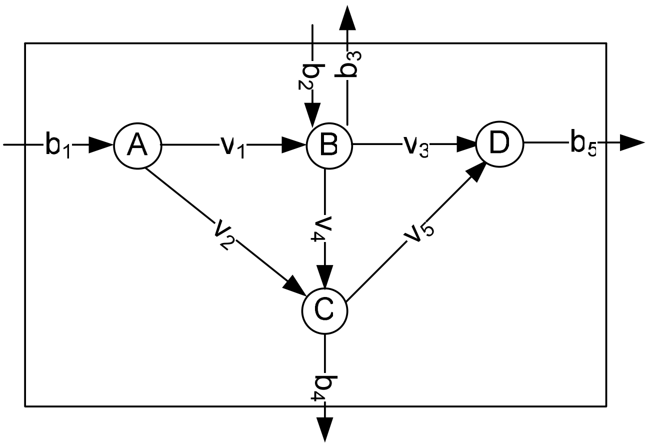

Figure 4.3: Sample Metabolic Network with Biomass and Cell Exterior.

As seen in the Fig. 4.3, the metabolite A cannot be produced in the cell, therefore it should be supplied by the environment. In the case of nonexistence of A, most probably all of the metabolic reactions will stop. The metabolite B can be both taken from and emitted to the environment. Therefore nonexistence of B will not terminate the system, but may decrease the performance of the system. If the system has to produce more B, then this may affect performance of v_3 and v_4 which effects biomass creation. In this study, metabolite accumulation in the extracellular medium is modeled with ODEs. For the network in Fig. 4.3, the ODE system is the following:

$$
\begin{aligned}
\frac{dX_A}{dt} &= b_1 C_{bio} \\
\frac{dX_B}{dt} &= (b_3 - b_2) C_{bio} \\
\frac{dX_C}{dt} &= -b_4 C_{bio} \\
\frac{dX_D}{dt} &= -b_5 C_{bio}
\end{aligned}
\tag{4.5}
$$

where, b_i is external flux value of the corresponding reaction, C_{bio} is the biomass concentration. Another important point is, as the reactions in the cell continue, certain metabolite concentrations in the environment can be depleted. For instance, after a while the concentration of the metabolite A may drop to zero if it is not supplied for the cell. For the case of the fermentation of the wine, the glucose level will drop to zero, as fermentation continues. Therefore, extracellular concentration changes and stresses occur due to these changes. This behavior of the organism is a response of the cell to the environmental stresses. This response is mainly given by changing the flux values of some reactions that take place in the organism. In the model, this behavior is represented by making changes in the upper and lower bounds of fluxes. Therefore, for different environmental conditions different flux cones are formed for the reactions that take place inside a cell. For instance, in Fig. 4.3, increase of metabolite *C* may affect the upper bounds of v_2 and v_4.

4.2 Problem

The developed models that represent the cell interior and exterior is used to model the fermentation of the wine. In this part, basic model and the required conversions on the model to represent the wine fermentation is described in detail. Besides, because changes in cell exterior and interior takes place simultaneously, to represent this characteristics of the fermentation, an integrated model is developed. In addition, many modifications are made to make the system solvable.

The yeast metabolism that we model includes 42 metabolites and 48 reactions (see Appendix). In the model, there are 6 external metabolites, (glucose, fructose, glycerol, ethanol, biomass, and ammonium). The LP model for intracellular fluxes is the following:

$$\begin{aligned} \max \quad & biomass \\ \text{st} \quad & Sv = 0 \\ & v^l \le v \le v^r \end{aligned} \tag{4.6}$$

where

$$\theta_{\Pr o}\left[\Pr otein\right] + \theta_{carb}\left[carbonhydrate\right] + \theta_{DNA}\left[DNA\right] + \theta_{lipgds}\left[lipids\right] + \theta_{RNA}\left[RNA\right] \rightarrow 1g\ biomass$$

where θ values are the parameters that should be estimated in the biomass composition.

From the result of the LP problem in Eq. 4.6, the optimal flux values that maximize the biomass are obtained under the assumption of steady-state. However, this steady-state characteristic of the system is not constant. In other words, as the concentration of extracellular medium changes, a new steady-state is formed. The concentration changes of the external metabolites are represented by system of ODEs:

$$\frac{dC_i}{dt} = v_i C_{bio} \tag{4.7}$$

where i Є *EXMET*(*glucose, fructose, glycerol, biomass, ammonium*) and C_i is the concentration of the corresponding metabolite.

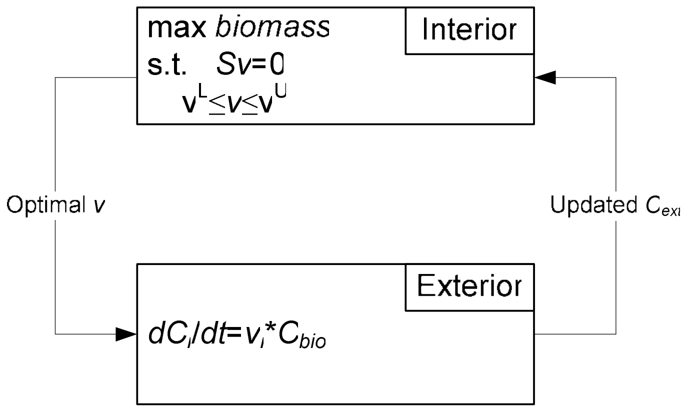

Figure 4.4: Feedback relation between interior and exterior.

The reaction sets Eq. (4.6) and (4.7) affect each other as the fermentation process continues. In the yeast cell, as a steady-state condition is formed, a new flux of intracellular reactions changes the concentration level of the environment. The environmental changes create a stress on the cellular organism, to change its previous steady-state. As the previous steady-state of cell changes, a new flux distribution appears which changes the environment. This feedback relation continues until cell death or inhibitation of metabolism is reached (Fig. 4.4). The missing piece in Fig. 4.4 is the lack of connection between exterior and interior of the cell. Specifically, to determine the new flux cone of the metabolic network, we have to know the kinetic relationship between cell exterior and interior. This can be done by finding kinetic parameters that determines the flow bounds in certain environmental conditions. This information is given by look-up tables [39 , 40], (Chapter *Heat Stress Response*, [41]) that specify bounds on reaction rates for given extracellular metabolite concentrations. The bounded reactions by these parameters are the following:

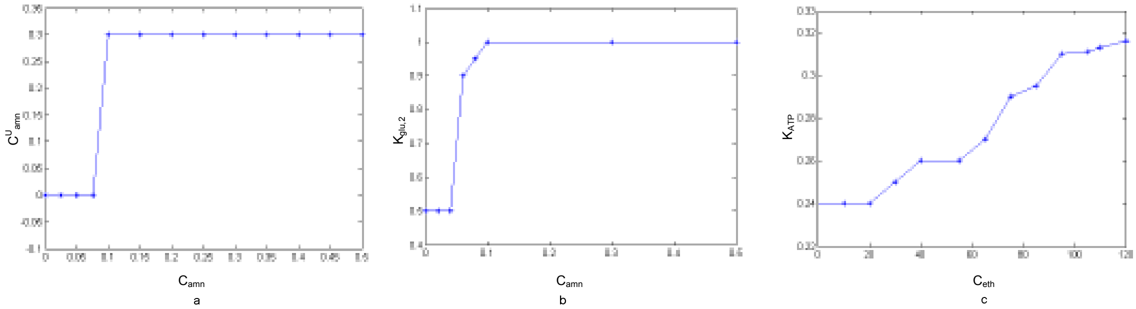

Figure 4.5: Glucose update rates.

4.2.1 Bounding the ammonium (NH4) uptake rate

The upper bound of the ammonium uptake rate depends on the ammonium concentration in the extracellular medium. The corresponding value can be seen in the Figure 4.5-a.

4.2.2 Glucose uptake rate

The uptake rate of the glucose is determined experimentally by the following equality:

$$v_{glu} = K_{glu,1}(C_{ammon})K_{glu,2}(C_{ammon})v_{glu,3}(C_{glu}, C_{eth}) \qquad (4.8)$$

where C_{glu} and C_{eth} are the concentrations of glucose and ethanol, respectively, in g/l. As seen from Fig. 5, $K_{glu,1}$ and $K_{glu,2}$ depends on the ammonium concentration and $v_{glu,3}$ depends on the C_{glu} and C_{eth} values. The value of $K_{glu,2}$ can be determined from Figure 4.5-b. The remaining coefficients are determined from the following equalities:

$$K_{glu,1}(C_{ammon}) = \begin{cases} K^{hi}_{glu,1}, C_{ammon} > \varepsilon \\ K^{lo}_{glu,1}, C_{ammon} < \varepsilon \end{cases} \qquad (4.9)$$

$$v_{glu,3}(C_{glu}, C_{eth}) = \begin{cases} v^{1}_{glu,3}(C_{glu}, C_{eth}), 0 < C_{glu} \le 5 \\ v^{2}_{glu,3}(C_{glu}, C_{eth}), 5 < C_{glu} \le 20 \\ v^{3}_{glu,3}(C_{glu}, C_{eth}), 20 < C_{glu} \end{cases} \tag{4.10}$$

The calculation of $v_{glu,3}$ is done by the following way:

$$\begin{aligned} v^{1}_{glu,3}(C_{glu}, C_{eth}) &= \sum_{j=\{3,4,7,8\}} \frac{v^{\max,j}_{glu,3} C_{glu}}{k^{j}_{glu} + C_{glu}(1 + \frac{C_{eth}}{k^{1}_{eth}})} \\ v^{2}_{glu,3}(C_{glu}, C_{eth}) &= \sum_{j=\{2,5,6\}} \frac{v^{\max,j}_{glu,3} C_{glu}}{k^{j}_{glu} + C_{glu}(1 + \frac{C_{eth}}{k^{2}_{eth}})} \\ v^{3}_{glu,3}(C_{glu}, C_{eth}) &= \sum_{j=\{1,5\}} \frac{v^{\max,j}_{glu,3} C_{glu}}{k^{j}_{glu} + C_{glu}(1 + \frac{C_{eth}}{k^{3}_{eth}})} \end{aligned} \tag{4.11}$$

where the values of the parameters in these equations can be found in Table 4.2.

i	$v^{\max,i}_{glu,3}$	k^{i}_{glu}	k^{i}_{eth}		i	$v^{\max,i}_{glu,3}$	k^{i}_{glu}	k^{i}_{eth}
1	7.45	1.8	17.24		5	2.7	10.8	17.24
2	1.9	1.8	46.03		6	1.08	1.67	17.24
3	1.05	0.27	46.03		7	1.31	0.18	17.24
4	4.86	10.8	46.03		8	1.31	0.36	17.24

Table 4.2: Values of Glucose update constants.

4.2.3 Bounding ATP consumption

The minimal ATP update rate is determined by the following equation:

$$\begin{aligned} &v^{L}_{ATP}(C_{ammon}, C_{eth}, C_{glu}) \leq v_{ATP} \\ &v^{L}_{ATP}(C_{ammon}, C_{eth}, C_{glu}) = K_{ATP}(C_{eth}).K_{glu,1}(C_{ammon}).K_{glu,2}(C_{ammon}).v_{glu,3}(C_{glu}, C_{eth}) \end{aligned} \quad (4.12)$$

where the dependence between K_{ATP} and ethanol concentration in the medium found in the Fig. 4.5

As indicated before, the corresponding flux bounds of the internal reactions are determined with respect to external metabolite concentrations, in Eq. (4.8)-(4.12). After a while these reactions and the resultant concentrations reach steady-state. As this new steady-state is formed, the external metabolite concentration is updated. To mimic this behavior, as shown in the Fig. 4.4, the Eq. (4.6) and Eq. (4.7) is solved iteratively and the connections between these two equations are formed by using the look-up tables and Eq. (4.8-4.12).

4.2.4 Formulation of integration of intra and extra-cellular reactions

Instead of decomposing the intra and extra-cellular reactions, an integrated approach is used to simulate the fermentation process. The main reason of this integration is the characteristics of the fermentation process. The fermentation process cannot be divided into compartments such as cell interior and exterior because the changes in interior and exterior takes place simultaneously. To decrease the representation gap between the model of fermentation and real fermentation process an integrated model is developed. To carry this out, we write the Karush-Kuhn-Tucker (KKT) conditions for Eq. (4.6) in Eq. (4.13).

$$
\begin{aligned}
& d + S^T \lambda + \mu^u - \mu^l = 0 \\
& S.v = 0 \\
& \mu^{uT}(v^u - v) = 0 \\
& \mu^{lT}(v - v^l) = 0 \\
& \mu^u, \mu^l, v^u - v, v^l - v \geq 0
\end{aligned}
\tag{4.13}
$$

where μ^u, μ^l, λ are the Lagrange multipliers.

The last two equalities correspond to complementarity conditions in Eq. (4.13) include nonlinearities and the following changes in these constraints are made for simplification:

$$
\begin{aligned}
& \mu^{uT}(v^u - v), \mu^u, (v^u - v) \geq 0 \Leftrightarrow \mu_i^u - \max(0, \mu_i^u - (v_i^u - v_i)) = 0 \quad i \in MET \\
& \mu^{lt}(v - v^l) = 0, \mu^l, (v - v^l) \geq 0 \Leftrightarrow \mu_i^l - \max(0, \mu_i^l - (vi - v_i^l)) = 0 \quad i \in MET
\end{aligned}
\tag{4.14}
$$

With the modification in Eq. (4.14) and addition of the differential equations that illustrate extracellular concentration change, the final DAE formulation is the following:

$$
\begin{aligned}
& \frac{dC_i}{dt} = v_i C_{bio} \\
& d + S^T \lambda + \mu^u - \mu^l = 0 \\
& S.v = 0 \\
& \mu_j^l - \max(0, \mu_j^l - (v_j - v_j^l)) = 0 \quad j \in MET \\
& \mu_j^u - \max(0, \mu_j^u - (v_j^u - v_j)) = 0 \quad j \in MET
\end{aligned}
\tag{4.15}
$$

where $i \in EXMET$. The set MET includes all of the metabolites in the network and $EXMET$ is the set of external metabolites that make up the biomass.

The system in Eq. (4.15) is classified as a DAE system. A DAE system solved for a given time-span. If one instance of the Eq. (4.15) is solved for a given time-span value, a steady-state for the given extracellular conditions will be observed. However, during the whole fermentation process, there are dynamic changes in the extracellular conditions and intracellular steady-state. Therefore, to model, this dynamic characteristic of the intra and extracellular conditions, the whole fermentation process is divided into discrete time steps, whose length is equal to time-span. To model the intracellular and extracellular relation, the look up tables in Eq. (4.8-4.12) is used. After one instance of the Eq. (4.15) is solved, a new intracellular steady-state and extracellular metabolite concentration is observed. By using the lookup tables in Eq. (4.8-4.12) and extracellular concentration on the determination of new v_u and v_l values, new steady-state by for the following time step whose length is equal to time-span is established. This computational process is executed till the end of fermentation process.

4.2.5 Parameter Estimation

During the formulation of the cell interior and exterior, the metabolite *biomass* is frequently used. However, there is not metabolite biomass in the cell. Biomass is actually an artifical metabolite that includes some of the real metabolites that represent the growth of the cell. Use of biomass makes the use of mathematical models suitable. Therefore, biomass is used as an indicator of the cell growth in this thesis.

The biomass is actually a collection of different substances. Therefore, to quantitatively represent the growth in the cell, biomass is created artificially from sum of the metabolites which are expected to be the main ingredients of growth. However, determination of the molecular composition and its coefficients is the main difficulty of this procedure. In this paper, the biomass is represented by composition of protein, carbohydrate, DNA, RNA and lipid. Therefore Eq. (4.16) is added to represent the biomass accumulation:

$$\theta_{\mathrm{Pro}}\left[\mathrm{Pr}\,otein\right]+\theta_{carb}\left[carbonhydrate\right]+\theta_{DNA}\left[DNA\right]+\theta_{lipgds}\left[lipids\right]+\theta_{RNA}\left[RNA\right]\rightarrow 1g\ biomass \quad (4.16)$$

Besides determination of composition of the biomass, the coefficients of these metabolites are another important issue that should be determined. In this paper, a parameter estimation scheme is applied to estimate the θ values in the Eq. (4.16) and value of $K_{glu,1}^{hi}$ in (4.9). During the estimation of these parameters, the Eq. (4.17) should be minimized.

$$\sum_{j}\sum_{t}(C_j(t)-C_j^{meas}(t))^2 \quad (4.17)$$

where $C_j(t)$ is the concentration level found by the model, $C_j^{meas}(t)$ is the concentration of measured coefficients by the experiments, $\forall j \in MEAS$ and $\forall t \in T$. In Eq. (4.17) *MEAS* represents the set of the measured metabolites in the experimental setup and *t* represents the time interval of the simulation takes place.

4.3 Solution and Analysis

The DAE system in the Eq. (4.15) is solved with MATLAB Version 7.2. However without any preprocessing, above system cannot be solved by most commercial solvers. The system in Eq. (4.15) has a DAE index greater than 1 therefore; with this form, MATLAB cannot solve the system. The main reason of above situation is the singularity of the algebraic part. To deal with that singularity we approximate the max operator in the last 2 equality of the system [42]. The function $f(x)$ = max(0*;* $g(x)$) behaves like in Fig. 4.6.

As seen from Fig. 4.6, there is a nondifferentiability at 0 point. We can smooth this nondifferentiability by using the approximation given in Eq. (4.18).

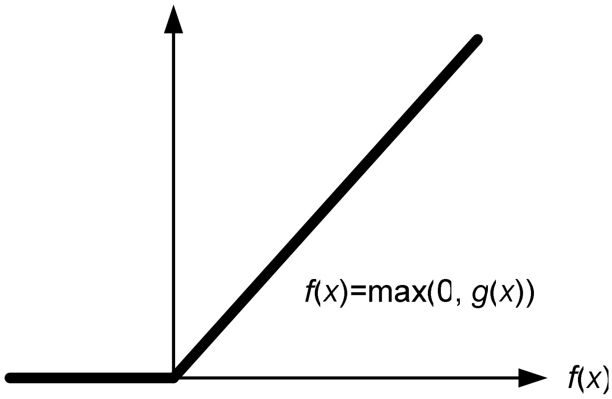

Figure 4.6: Graphical representation of the f(x)=max(0,g(x)).

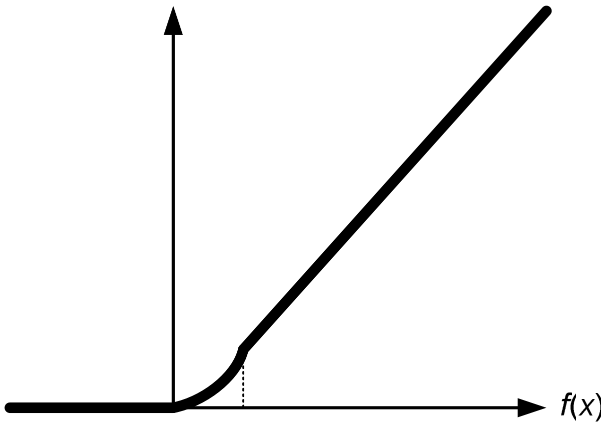

Figure 4.7: Smooth approximation of the f(x)=max(0,g(x)).

$$\bar{f}(x) = 0.5\left[g(x)^2 + \varepsilon^2\right]^{\frac{1}{2}} + \frac{1}{2}g(x) \tag{4.18}$$

where ε is a sufficiently small number. After the implementation of smoothing in Eq.(18), the resulting approximated function behaves as shown in Fig. 4.7.

After the foregoing change the updated Eq. (4.15) will be the following:

$$
\begin{aligned}
&\frac{dC_i}{dt} = v_i C_{bio} \\
&d + S^T \lambda + \mu^u - \mu^l = 0 \\
&S.v = 0 \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad (4.19)\\
&0.5\left[(\mu_j^u - (v_j^u - v_j))^2 + \varepsilon^2\right]^{\frac{1}{2}} + \frac{1}{2}(\mu_j^u - (v_j^u - v_j)) = 0 \quad j \in MET \\
&0.5\left[(\mu_j^l - (v_j - v_j^l))^2 + \varepsilon^2\right]^{\frac{1}{2}} + \frac{1}{2}(\mu_j^l - (v_j - v_j^l)) = 0 \quad j \in MET
\end{aligned}
$$

To solve DAE system in Eq. (4.19), the θ parameters in the Eq. (4.16) and value of $K_{glu,1}^{hi}$ in the Eq.(4.9) should be estimated. To estimate these parameters, we have used *fminsearch* solver of the MATLAB during the minimization of Eq. (4.17). This solver is DFO (Derivative Free Optimization) solver which implements a Nelder-Mead (NM) method. The solution of the parameter estimation is schematically represented in Fig. 4.6. At the end of the solution of the parameter estimation problem, the resulting parameter values are shown in Table 4.3. The DAE system in Eq. (4.19) can be solved by MATLAB's DAE solver, ode15s. The program simulated with the initial conditions in Table 4.4.

Parameter	**Value**
θ_{Carb}	0.0134
θ_{DNA}	0.00014
θ_{RNA}	0.000469

θ_{Pro}	0.0164
θ_{Lip}	0.000169
$K_{glu,1}^{hi}$	0.35

Table 4.3: Result of parameter estimation problem

Metabolite	Concentration
Biomass	0.1
Glucose	225
Fructose	115
Ethanol	1.25
Ammonium	1.24
Glycerol	0

Table 4.4: Initial metabolite concentration.

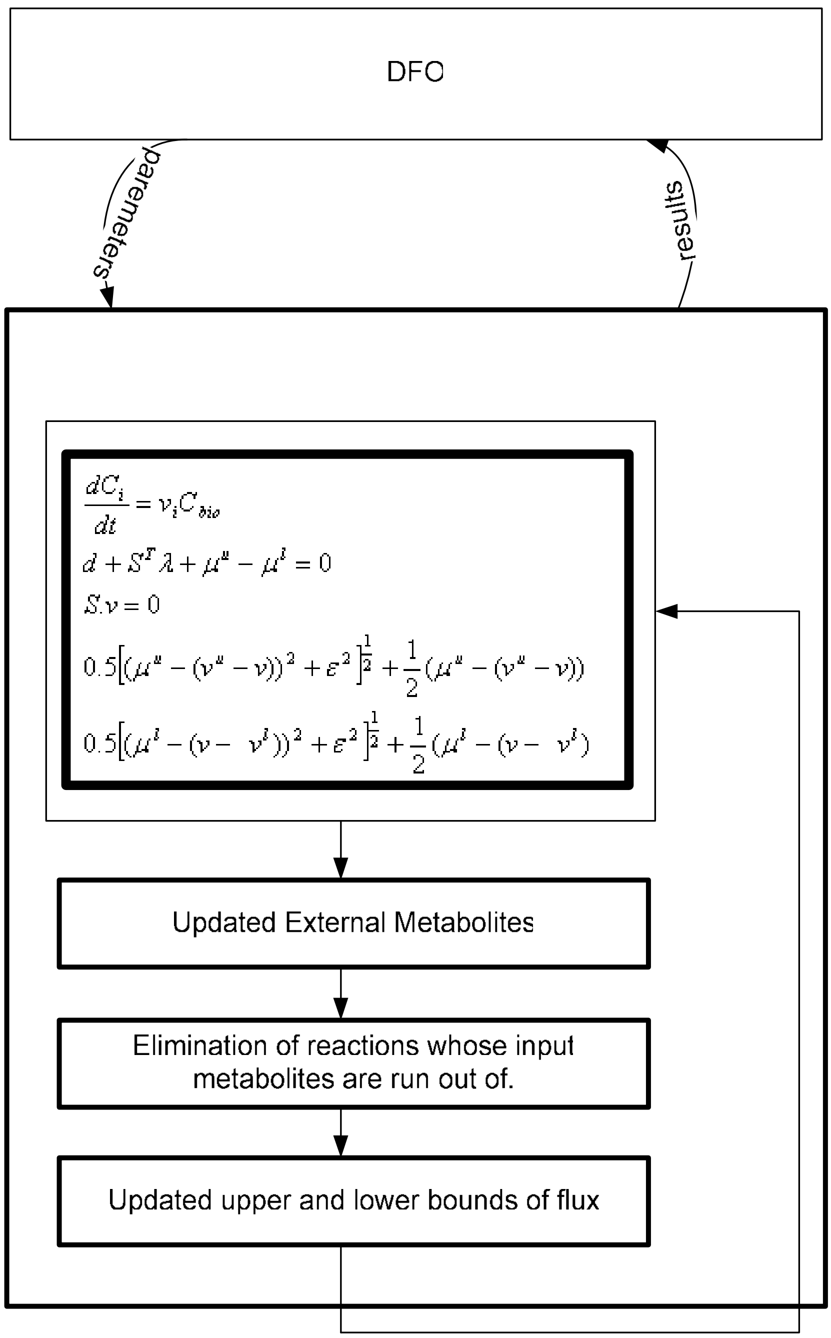

Figure 4.8: Parameter estimation problem.

Fig. 4.9 and 4.10 compares the experimental data and result of the model for *biomass* and *glucose* respectively. As shown, although there is not one to one correspondence between model and experimental data, the trends are same. The result of the simulation follows the experimental model very closely.

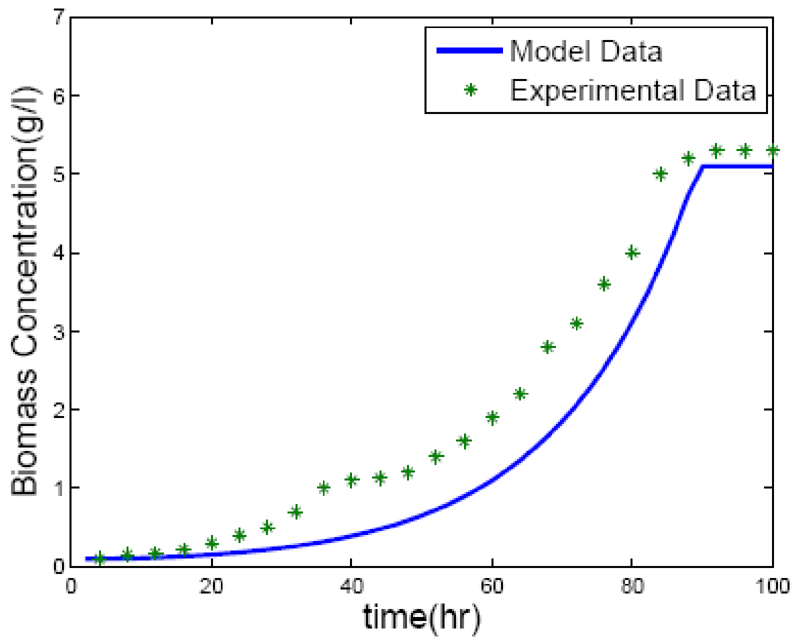

Figure 4.9: Comparison of biomass profile.

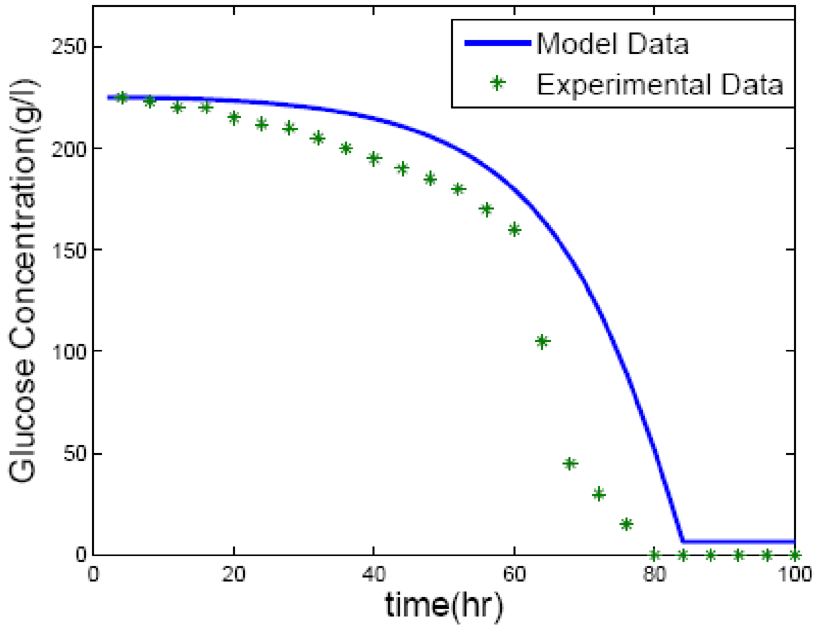

Figure 4.10: Comparison of glucose profile.

Chapter 5

CONCLUSION

The objective of this thesis is the development of dynamic network optimization methods and application of dynamic networks. Since the dynamic networks considered in this thesis also include some discrete decisions, hybrid system approach is used during the modeling. Two important network structures are examined in detail in this thesis. The first network structure is the SCN. The modeled SCN shows dynamic network properties as well as discrete behavior. The start or end of the production process is an example of discrete behavior during the execution. The second network structure is the metabolic network of Saccharomycse Cerevesiae also known as yeast that is used in fermentation of wine. A system of DAE is used to model the single state of the fermentation process. As the environmental concentration reaches to some predefined threshold values, the system changes the state by updating the DAE system. This system also shows hybrid system behavior because when satisfying some logical constrains on the concentration profile of the environment, transition among different continuous DAE systems occur.

A multi-echelon, multi-product supply chain system is modeled in the supply chain part including the price elasticity of demand. Due to using price elasticity in the model, the demand to the current product is determined with respect to its price. Because, demand depends on the price and the profit function which is the objective in our case becomes nonlinear. In this thesis, the nonlinearity is handled in two approaches. In the first approach, the objective is approximated with a convex quadratic function. In the second approach, the nonlinear objective function is approximated by using piecewise linear functions.

In the first approach, the revenue function becomes a differential equation and the set of constraints include both differential and algebraic equations. The differential equations are obtained by superimposition of the price elasticity into the system. The relation between price and demand is represented with a differential equation. At the end, the resulting differential and algebraic system is fully discretized in time. Characteristics of this supply chain system is illustrated on 2 product supply chain system that includes supplier, plant, plant warehouse, distribution center and retailer with different price and demand relationship measure. The effect of elasticity on the revenue function is investigated in detail. It is shown that as the price elasticity increases, the revenue function shows a linear behavior. The linear underestimator of revenue function and the error occurred because of this approximation is studied. The worst case performance of the approximation is derived.

The optimal price changes and inventory holding schemes are compared on different elasticity values and different network characteristics. It is proven that existence of maximum flow constraint (MF) in the system causes an increase in the total inventory. Also, because maximum flow constraint creates an upper bound on the value of demand satisfied, the price change will occur with respect to current demand and elasticity value.

The combined effects of the changing price elasticity and maximum flow constraint in the network is also investigated. It is shown that for the products that have larger elasticity value, decrease of the price is not always the optimal decision. It is also shown that, for the products with large price elasticity, decrease in the price causes logarithmic in the revenue but linear increase in the cost, so selling as much as possible is not always the optimal decision to maximize the profit.

An optimization model for integrated multi-product and multi-echelon SCS including seasonal price elasticity is also presented. The specification of corresponding SCS that includes suppliers, plants, plant warehouses, distribution centers and retailers, is illustrated on the 2 product case. The effects of increase in the number of plants on the optimal operational decisions are also investigated. It is shown that the effect of MF constraints in the system is still valid for different network topologies. In addition behavior of price and satisfied demand do not change its characteristics with changing topology. However, it is shown that, increase in the number of plants causes decrease in the average total inventory of system.

In the second approach, instead of representing the relationship between price and demand with differential equations and discretizing the whole system in the time domain, the price is written in terms of demand. In that case, the profit function which is the objective function becomes concave. The concave function is approximated with piecewise linear functions. The characteristics of the nonlinear revenue function with the consideration of seasonal price elasticity are investigated in detail. During the linear approximation the number of segments in the approximation scheme is determined by considering the convergence rate of approximated objective function to real one.

Effects of changing price elasticity on the optimal price changes and optimal amount of satisfied demand is presented. It is proven that increase in the price elasticity causes increase in the demand satisfied. Also it is shown that, the order of production in the system affects the average price of the product. However, if this order constraint is removed from the system, the average price behavior of the product exhibits the expected behavior.

It is also shown that the seasonal behavior of price elasticity causes the system to hold inventory by changing the production order of products. System produces the product while the E_x has small value, and holds inventory, to immediately satisfy the demand on time intervals in which the E_x value is high. Also, the effect of the transportation delay on the example problem is explained. In addition, affects of the seasonal price elasticity on the different node of SCS is illustrated.

In the second part of the thesis, the dynamics of the wine fermentation is modeled. The reactions and fermentation dynamics that take place inside the cell is modeled by using the FBA. The relationship between cell interior and the cell exterior is modeled with a set of differential equations. This relationship is established by using a feedback relation between exterior and interior. The concentration of the exterior determines the lower and upper bounds of the flow distribution. In mathematical terms, the cell exterior determines the flux cone of the distribution of fluxes. As the fermentation continues, in other words as the reaction that takes place inside cell is executed, the concentration of the exterior is changed.

In this thesis, instead of using two separate set of equation (one for interior and one for exterior), an integrated approach is used that considers all system equations simultaneously. The cell exterior and interior is modeled by using single set of equation and the relation is established without a separate feedback relation. However, because this single set of equation is used to model the single snapshot of fermentation, to model whole fermentation an iterative approach is used.

The whole fermentation process is discretized in the time domain. In each time step, the single integrated formulation of the fermentation process that considers both cell interior and cell exterior is solved. During transition time between the integration processes, the update of the concentration and reaction activation is made. Transition among different states of the continuous system takes place; therefore, the model of the whole fermentation process is classified as a hybrid system. In this hybrid representation, the single snapshot of the fermentation process is a continuous system. The transition between these continuous systems is occurred deterministically. In other words, the transition time of the corresponding hybrid system is known priori and these times are the time discretization points.

The integrated system is solved by using a DAE solver and the best biomass coefficients are found that minimizes the difference between result of the simulation and the result of experimental studies. The comparisons are made between the experimental and simulation fermentation dynamics by using the biomass parameters that parameter estimation routine. It is shown that the result of the hybrid system model and the experimental results are similar. This result proves the correctness and completeness of the model.

As a future work, because the formulation of fermentation dynamic is a DAE system, the sensitivity analysis of the solution approach used needs to be made. The main reason of this comes from the nature of DAE systems. In addition, the event location points should be added to improve the hybrid properties of the model. Besides, the hybrid system approach used in this study can be applied to the regulatory networks in the living organism. In the supply chain network part, the assumption of the system should be relaxed. The assumption of the immediate satisfaction of the customer demand is enforced in this study. Otherwise, the objective function becomes bilinear without this assumption. As future work in this subject, a new technique to solve the optimization problems with bilinear objective functions should be addressed to make the model more realistic without simplifying assumptions.

Appendix A: Metabolic Reactions

1. Glucose+1/6 ATP→glucose6P
2. glucose6P→fructose6P
3. 1/6 ATP+fructose6P→1/2 glyceraldehyde3P+1/2 dihydroxyacetoneP
4. dihydroxyacetoneP→glyceraldehyde3P
5. glyceraldehyde3P→1/3 ATP + _3Pglycerate + 1/3 NADH_cyt
6. _3Pglycerate→pep
7. pep→1/3 ATP+pyruvate
8. pyruvate→ 2/3 acetaldehyde + 1/3 CO_2
9. acetaldehyde + ½ NADH_cyt→ ethanol
10. acetaldehyde → ½ NADPH_cyt + acetate
11. dihydroxyacetoneP + 1/3 NADH_cyt→ glycerol3P
12. glycerol3P→ glycerol
13. glucose6P→1/6 CO_2 + 1/3 NADPH_cyt + 5/6 ribose5P
14. ribose5P→3/5 fructose6P + 2/5 erytrose4P
15. 5/9 ribose5P + 4/9 erytrose4P →2/3 fructose6P+1/3 glyceraldehyde3P
16. 3/7 pyruvate + 4/7 oxaloacetate_mit → 1/7 CO_2 + 6/7 isocitrate + 1/7 NADH_mit
17. isocitrate + 5/5 A_ketoglutarate →1/6 CO_2 + 1/6 NADH_mit
18. A_ketoglutarate →1/5 ATP + 1/5 CO_2 + 4/5 succinate + 1/5 NADH_mit
19. succinate → malate
20. malate →oxaloacetate_mit + ¼ NADH_mit
21. ATP + acetate→Acetil_CoA
22. isocitrate →1/6 CO_2 + 5/6 A_ketoglutarate + 1/6 NADPH_mit
23. ¼ ATP + ¾ pyruvate + ¼ CO_2 →oxaloacetate_cyt
24. 1/6 ATP+glucose6P→carbohidrate

25. 1/5 NADPH_cyt + A_ketoglutarate + 1/5 NH4_int→ glutamate
26. 1/5 ATP + glutamate + 1/5 NH4_int → glutamine
27. 5/9 glutamate + 4/9 oxaloacetate_cyt→5/9 A_ketoglutarate + 4/9 aspartate
28. 3/8 _3Pglycerate + 5/8 glutamate → 1/8 NADH_cyt + 5/8 A_ketoglutarate + 3/8 serine
29. ATP→ 1.5 NH4_int
30. 26087/100000 ATP + 1087/25000 CO_2 + 21739/100000 ribose5P + 21789/50000 glutamine + 17391/100000 aspartate + 13043/100000 serine→ 1087/25000 NADPH_cyt + 17391/100000 malate + 21739/50000 glutamate + 3913/10000 _5_Aicar
31. 0.4625 ATP + 509/10000 NADPH_cyt + 159/625 ribose5P + 4371/10000 glutamine + 3313/10000 aspartate + 4579/10000 _5_Aicar →77/500 NADH_cyt + 639/5000 malate + 4371/10000 glutamate + DNA
32. 489/1000 ATP + 6/25 ribose5P + 5271/10000 glutamine + 2993/10000 aspartate + 639/1250 _5_Aicar→337/2500 NADH_cyt + 71/1250 NADPH_cyt + 1073 /10000 malate + 5271/10000 glutamate + RNA
33. 2599/2500 ATP + 187/2000 pep + 169/500 pyruvate + 271/2500 NADPH_cyt + 101/2500 ribose5P + 623/10000 erytrose4P + 99/2000 NADPH_mit + 609/1000 glutamate + 1039/5000 glutamine + 2153/10000 aspartate + 591/5000 serine + 53/10000 SO_4→117/10000 glyceraldehyde3P + 527/5000 CO_2 + 4927/100000 A_ketoglutarate + 413/10000 malate + 47/2500 _5_Aicar + 371/5000 NADH_mit + Protein + 1/100 NH4_int
34. 2/5 ATP + 711/1000 NADPH_cyt + 331/5000 glycerol3P + 4163/5000 Acetil_CoA + 253/2500 serine→ Lipids
35. ATP→
36. ¼ ATP + oxaloacetate_cyt→oxaloacetate_mit

37. acetaldehyde + ½ NADH_mit→ ethanol
38. acetate→
39. CO_2→
40. ethanol→
41. glycerol→
42. → Glucose
43. pyruvate→
44. → SO_4
45. succinate →
46. biomass→ biomass
47. → Fructose
48. 1/6 ATP + Fructose→fructose6P

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