GALATASARAY UNIVERSITY
GRADUATE SCHOOL OF SCIENCE AND ENGINEERING

MEDICAL DECISION SUPPORT APPLICATIONS USING ARTIFICIAL INTELLIGENCE TECHNIQUES

Elif DOĞU

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MEDICAL DECISION SUPPORT APPLICATIONS USING ARTIFICIAL INTELLIGENCE TECHNIQUES

(YAPAY ZEKA TEKNİKLERİ İLE TIBBİ KARAR DESTEK UYGULAMALARI)

by

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Long, long ago, when there was still hope in hearts of young people, I started my PhD as a young woman, who wanted to make the world a better place. Soon I learned that not all the stories are fairy tales and life has much more unpleasant surprises than I can ever imagine. Anyway, life goes on.

Considering my thesis, I want to express my gratitude to my beloved advisor Prof. Dr. Y. Esra Albayrak for making me an academician and for her invaluable support. I also thank to Assoc. Dr. Esin Tuncay MD for saving my life and then accepting to be my co-advisor. I am grateful to Prof. Dr. Şule Önsel Ekici for sharing her knowledge with me.

And considering my life,
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Now, after all these years, I am completing my PhD as a grown-up, a wife and hopefully a mother soon. I gave up on the rest of the world and learned that nothing is actually a problem, if my loved ones are healthy. Happiness is in the clichés.

This thesis dedicated to our little family with Burç Doğu, who made me believe in fairytale love again.

April 2019
Elif DOĞU

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AIDS : Acquired Immune Deficiency Syndrome
ALB : Albumin
ALT : Alanine aminotransferase
ANN : Artificial Neural Network
AST : Aspartate aminotransferase
BCG : Bacille Calmette-Guérin
BiPAP : Bi-level positive airway pressure (machine)
BMI : Body-Mass Index
BPM : Breaths per minute
CCI : Charlson Comorbidity Index
CM : Cognitive map
CO2 : Carbondioxide
COPD : Chronic Obstructive Pulmonary Disease
CRP : C-reactive protein
DM : Diabetes Mellitus
Emb : Ethambutol
ESR : Erythrocyte sedimentation rate
FCM : Fuzzy cognitive map
FEV-1 : Forced expiratory volume in 1 second
FVC : Forced vital capacity
GOLD : Global Initiative for Chronic Obstructive Lung Disease
HCT : Hematocrit
HGB : Hemoglobin
HIV : Human Immunodeficiency Virus
IFCM : Intuitionistic fuzzy cognitive map
IFS : Intuitionistic fuzzy set
Inh : Isoniazid
LoS : Length of stay
MAPE : Mean absolute percentage error
MDR-TB : Multi-drug resistant tuberculosis
mMRC : modified Medical Research Council
N : Nominal (variable)
NIMV : Non-invasive mechanical ventilation (machine)
O : Ordinal (variable)
O2 : Oxygen
PH : The degree of acidity – pH.
PLT : Platelet
PPM : Pulses per minute
Pza : Pyrazinamide

Rif : Rifampicin
RMSE : Root mean square error
RR-TB : Rifampicin resistant tuberculosis
S : Scale (variable)
SBFCM : Statistical-Based Fuzzy Cognitive Map
SPO2 : Oxygen saturation
Stm : Streptomycin
TB : Tuberculosis
TOT PROT : Total protein
WHO : World Health Organization
XDR-TB : Extensively drug resistant tuberculosis

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ABSTRACT

Medical science is very receptive to the support and integration of technological developments, and artificial intelligence has a major role in technological advancements of this era. The purpose of this thesis is to build frameworks and establish mathematical models that will assist decision makers (physicians) in critical decision moments by using artificial intelligence techniques of engineering in medical decisions. Within the scope, three diseases are included: Diabetes, Tuberculosis and Chronic Obstructive Pulmonary Disease (COPD). All three of them are reported among top ten global causes of death by World Health Organization (WHO), recently in the global health statistics. In order to contribute to the management of these diseases by establishing medical support systems, four different artificial intelligence techniques are used. Fuzzy C-means algorithm is used for diagnosis of diabetes, intuitionistic fuzzy cognitive maps, which are found effective in social sciences as marketing, are used for detection of multi-drug resistant tuberculosis, the novel statistical-based fuzzy cognitive map is proposed for the management of COPD and, artificial neural networks are used to predict the length of hospital stay of COPD patients. Each section of this thesis is an independent application of different artificial intelligence techniques, constructing medical decision support frameworks. According to the numerical applications, the most successful results are obtained using the approaches that combine the powers of artificial intelligence and human knowledge.

RÉSUMÉ

La science médicale est très réceptive à l'intégration des développements technologiques, et l'intelligence artificielle y joue un rôle majeur dans les avancements de notre époque. Le but de cette thèse est de construire des modèles mathématiques qui aideront les décideurs (médecins) à prendre des décisions critiques en utilisant des techniques d'ingénierie en intelligence artificielle. Trois maladies sont incluses dans le champ d'application : le diabète, la tuberculose et la maladie pulmonaire obstructive chronique (MPOC). L'Organisation mondiale de la santé (OMS) a récemment déclaré ces maladies parmi les dix principales causes de décès dans le monde. Afin de contribuer à la gestion de ces maladies en construisant des systèmes de support médical, quatre techniques d'intelligence artificielle différentes sont utilisées. L'algorithme de C-moyenne floue est utilisé pour le diagnostic du diabète, des cartes cognitives floues intuitionnistes sont utilisées pour la détection de la tuberculose multi-résistante, la nouvelle carte cognitive floue à base statistique proposée pour la gestion de la MPOC et enfin, des réseaux de neurones artificiels sont utilisés pour prédire la durée du séjour à l'hôpital des patients de MPOC. Chaque section de cette thèse est une application indépendante de différentes techniques d'intelligence artificielle, construisant des systèmes d'aide à la décision médicale. Selon les applications numériques, les résultats les plus aboutis sont obtenus en utilisant des approches associant les pouvoirs de l'intelligence artificielle et du savoir humain.

ÖZET

Tıp bilimi, teknolojik gelişmelerle desteklenmeye ve bütünleşmeye son derece açıktır. Yapay zeka ise çağımızın en önemli teknolojik gelişmelerinden biridir. Bu tezin amacı, tıbbi kararlarda mühendisliğin yapay zeka tekniklerini kullanarak, karar vericilere (doktorlara) kritik karar anlarında yardımcı olacak matematiksel modeller oluşturmaktır. Tezin kapsamında üç hastalık yer almaktadır: Diyabet, Tüberküloz ve Kronik Obstrüktif Akciğer Hastalığı (KOAH). Bu üç hastalık da, yakın zamanda Dünya Sağlık Örgütü'nün (WHO) küresel sağlık istatistiklerinde ilk on küresel ölüm nedenleri arasında rapor edilmiştir. Tıbbi karar destek sistemleri kurarak bu hastalıklarla savaşılmasına katkıda bulunmak için tezde dört farklı yapay zeka tekniği kullanılmıştır. Diyabet tanısı için bulanık C-ortalama algoritması kullanılmış, çok ilaca dirençli tüberkülozun tespiti için daha önce sosyal bilimlerde, özellikle pazarlama alanında etkisi görülmüş olan sezgisel bulanık bilişsel haritalama uygulanmış, KOAH'nın değerlendirilmesi için yeni bir istatistik temelli bulanık bilişsel haritalama yöntemi önerilmiş ve KOAH hastalarının hastanede kalış sürelerini tahmin etmek için yapay sinir ağları kullanılmıştır. Bu tezin her bölümü, tıbbi karar destek sistemleri oluşturmayı hedefleyen farklı yapay zeka tekniklerinin bağımsız birer uygulamasıdır. Sayısal uygulamalara göre, en başarılı sonuçlar yapay zekanın ve insan bilgisinin güçlerini birleştiren yaklaşımlar kullanılarak elde edilmiştir.

1. INTRODUCTION

Decision analysis is one of the industrial engineering fields, however; critical decision moments occur anytime and anywhere in life. Even if senior managers, top executives, financial experts who deal with massive amounts, people working with major risk factors etc. make rather more stressful decisions, the most crucial decisions to be made are about someone's health. A manager's decision is a profit or loss issue for a company, however; a physician's decision is a matter of life or death for a person. In the decision-making process, physicians need previous in-depth researches, analyzed statistics, current information on the subject, test results and medical history of patient; which means a well-organized health-care information system is required. In Turkey, this information system is in installation process and it has not been completed yet. Therefore, physicians make these decisions alone or just get the opinion of their colleagues who are working at the same clinic. These important decisions bring great responsibility. Physician makes these decisions according to his/her own experience and research, also takes entire responsibility of possible results that bring stress and anxiety to the working environment. The decision, which may occur once in a patient's lifetime, is confronted by the physician every day. In Turkey, considering the working conditions of physicians where they could be assaulted by patient's relatives, physicians need all kinds of support while deciding on a patient.

At this point, the general purpose of this study is to build frameworks and establish mathematical models that will assist decision makers (physicians) in critical decision moments by using artificial intelligence techniques of engineering in medical decisions. Formerly, medical scientific studies were usually case-based, statistical or probabilistic

however, in the recent decades there have been many developments for the detection, diagnosis and treatment of diseases. Health care applications are improved with technological developments and the complexity of medical decisions is increased. Along with computer-aided systems, numerous opportunities emerged for the application of machine learning and artificial intelligence techniques to assist in medical decision-making.

Within the scope of this thesis, three diseases are included: Diabetes, Tuberculosis and COPD. All three of them are reported among top ten global causes of death by WHO, recently in the global health statistics. These diseases not only create global inequalities, but also ground immense economic burden for the countries. In order to contribute to the management of these diseases by establishing medical support systems, four different artificial intelligence techniques are used. All applications are conducted in Yedikule Chest Diseases Training & Research Hospital in Istanbul, Turkey with precious contributions of chest disease specialists Assoc. Prof. Esin Tuncay MD, Assoc. Prof. Gülfidan Aras MD, Zehra Dilek Kanmaz MD, Tuğba Mandal MD, and Özlem Yılmaz Ünlü MD. Each section of this study is an independent application of different artificial intelligence techniques, having the common purpose of constructing medical decision support frameworks.

In Section 2, Fuzzy C-Means technique is used for diagnosis of Diabetes Mellitus (DM) disease, which occurs when the pancreas cannot produce enough insulin or when insulin that it produces cannot be used effectively. High frequency of urination and hunger and thirst are general symptoms of high levels of blood glucose. Global estimates of 2016 claims that 415 million people are living with diabetes and 90% of them belongs to Type 2 DM.

DM has equal rates for men and woman, and a rate of 8.3% in total adults. Diagnosis of the disease is not challenging however, it requires blood glucose measurements in different times. In emergency cases where the patient is unconscious, the possibility to overlook the disease is high. Fuzzy c-means clustering algorithm, in which each variable can belong to more than one class, is used to classify the two groups of patients with and without diabetes through other blood test data and demographic factors. In the

first application with 100 patients of the hospital, the algorithm correctly classified 81% of patients.

In Section 3, Intuitionistic Fuzzy Cognitive Maps technique is used for the risk assessment of Multidrug-Resistant Tuberculosis (MDR-TB). This technique is chosen because its applicability and effectiveness is observed as a decision support system in a previous study in marketing field, which is also a social science as medicine (Dogu & Albayrak, 2018). First, Fuzzy Cognitive Maps (FCM) and Intuitionistic Fuzzy Cognitive Maps (IFCM) are explained in detail and their uses in social sciences are discussed. Second, to implicate the effectiveness of IFCM in social sciences, its use in strategic marketing management is given. Marketing decisions are challenging in profit-oriented companies because of their complex nature. Many factors influence the marketing strategy in the New Product Development process. IFCM method is advantageous for assessing the criteria that influence the pricing strategy of a company in earlier stages of the product's life cycle in the market. A framework is formed based on a profound analysis of literature and experts' opinions, in terms of criteria affecting pricing strategy and the causal relationships between them. Intuitionistic fuzzy sets and cognitive mapping are used together to capture the hesitation of the decision makers caused by lack of information and to define cause-and-effect relations between the criteria to represent the complexity of strategic marketing decisions. Third, IFCM is applied for the detection of MDR-TB with parallel steps of the marketing case. Tuberculosis (TB) bacteria may develop resistance to the drugs, which is used in TB treatment. MDR-TB is a type of TB that does not respond to at least rifampicin and isoniazid, the 2 most powerful anti-TB drugs. MDR-TB requires a more compelling treatment and it is more difficult to diagnose. The experience of physician is the key factor in the success of MDR-TB diagnose. The existence of TB bacteria in the body can be observed relatively faster with a standard sputum smear however, drug-susceptibility tests require nearly 45 days. To cope with this infectious disease, it is vital to estimate the resistance in a newly diagnosed TB patient to plan the initialization of the treatment in the testing period. Herein, the purpose of Section 3 is to build a framework and establish a mathematical model that will help decision makers (physicians) while estimating the risk of multi-drug resistance when a new tuberculosis

patient arrives, using intuitionistic fuzzy cognitive maps. Intuitionistic fuzzy sets are utilized to reflect the decision makers' hesitancy degrees in the model.

In Section 4, the novel Statistical-Based Fuzzy Cognitive Maps technique is proposed for COPD management. COPD is one of the most common chronic respiratory diseases. COPD is a global burden that induces many decision-making problems. Medical decisions are naturally originated from personal experience of the physician and statistical analysis of previous data. A decision made using only the statistics of the collected data would be incomplete and overly objective without the physician's interpretation, on the other hand, a decision made using only the physician's opinion would be overly subjective and incomplete. Thereupon, a proper medical decision must be a combination of expert judgment and data analysis for accurate detection, certain diagnosis and effective treatment. Because of its structural advantages in revealing the behavior of complex systems, and in capturing human judgment by means of fuzzy information, FCM and its extensions are widely used in medical decisions. In Section 4, a novel approach called Statistical-Based Fuzzy Cognitive Map (SBFCM) is proposed which aggregates the power of statistical analysis with dynamical nature FCMs. The SBFCM method is developed in order to evaluate the factors that affect the length of hospital stay (LoS) of COPD patients that apply to the hospital with an acute exacerbation. Fifty factors, including LoS, are adopted as system concepts and are observed under four groups. A real-case application is conducted and different scenarios are analyzed for a better understanding of the system behavior.

In Section 5, a prediction model of LoS of COPD patients, which is already deeply examined in Section 4, is constructed using artificial neural networks technique. Artificial neural networks are mathematical models that are able to capture the knowledge contained in the data by imitating human neurons. They are useful in detecting nonlinear and complex relationships between different kinds of variables where conventional statistical methods may fail to detect. They are able to acquire knowledge from experience, generalize the acquired knowledge and make predictions of further unknown factors.

Section 5 can be considered as the further research of Section 4 and a comparison of the novel SBFCM with conventional approach. In artificial neural networks, the performance of prediction varies with the architecture of model. Especially, input variable selection of the model is directly related to prediction performance of the output variable. In the conventional approach, which is widely used in the literature, inputs of the model are selected as the variables that are significantly correlated with the output variable ($p < 0.05$). In Section 5, two artificial neural network models are constructed. Model I represents the conventional approach and the inputs are the correlated variables with LoS. Model II is the proposed approach and the inputs are selected considering the results of SBFCM method, which is calculated in Section 4. In the numerical application, Model II outperformed Model I with 79.95% accuracy, revealing the power of expert opinion involvement in medical decision support systems.

2. DIAGNOSIS OF DIABETES MELLITUS DISEASE WITH FUZZY C-MEANS

Diabetes Mellitus is a serious public health problem with its increasing number of cases and prevalence over the past decades. In April 2016, WHO published the Global report on diabetes, which calls the world leaders for action to diminish exposure to the risk factors and to develop accessibility and quality of health care for people who have diabetes mellitus.

108 million adults were living with diabetes in 1980s and in 2014; this number is increased to 422 million adults, worldwide. Age-standardized global prevalence augmented from 4.7% to 8.5% in adults. In 2012, 1.5 million deaths are recorded as caused by DM. High levels of blood sugar, by augmenting other cardiovascular diseases' risk, triggered another 2.2 million deaths. Which totally means 3.7 million deaths that occurs before the age of 70. The percentage of deaths is higher in low- and middle-income countries (WHO, 2016a).

Diagnosis of diabetes is not difficult however; its process needs time and consciousness of the patient. When an unconscious patient is brought to emergency for a reason that is not related to DM, it is highly problematic to understand if he/she had DM as a comorbid disease. This information is vital because it might change the treatment given in an emergency.

The demographics, examination and blood test results are the fastest information gathered on a patient. In this study, fuzzy c-means clustering algorithm is performed to classify the patients' DM status using this information. Fuzzy c-means clustering is a machine-learning algorithm, which is widely used as a decision aid in medical

problems. In the last five years, Dutta et al. used weighted fuzzy c-means algorithm to identify the target class thresholds for the classification of diabetic retinopathy images (Dutta et al., 2018), Prakash et al. implemented multidimensional thresholding, region-growing, fuzzy c-means and neural network algorithms for automatic segmentation of brown adipose tissue which normalizes metabolic disorders in diabetes (Prakash et al., 2016), Oliveira et al. integrated deformable models with fuzzy c-means for retinal vessel segmentation that help to predict cardiovascular related diseases as diabetes and hypertension (Oliveira et al., 2016), Iliyasu et al. used possibilistic fuzzy c-means with evidence accumulation clustering for the diagnosis of hepatitis, breast cancer and diabetes (Iliyasu et al., 2016), Tasgaonkar and Khambete integrated Mahalanobis metric classification and fuzzy c-means for exudate detection in color fundus imaging for diabetic patients (Tasgaonkar & Khambete, 2015), Mahendran and Dhanasekaran used fuzzy c-means for detection and localization of retinal exudates for diabetic retinopathy (Mahendran & Dhanasekaran, 2015), Hassanien et al. used bee colony swarm optimization, pattern search and fuzzy c-means for retinal blood vessel localization (Hassanien et al., 2015) and Ozsen and Ceylan compared artificial immune system and fuzzy c-means on the classification of breast cancer and diabetes (Ozsen & Ceylan, 2014).

2.1 Fuzzy C-Means Clustering Method

Fuzzy c-means is an extension of conventional k-means clustering method that uses the fuzzy sets. To develop the method in clustering, a family of fuzzy sets is defined a fuzzy c-partition on a data points' universe. Since fuzzy sets accept for membership degrees, the crisp classification idea can be extended into a fuzzy classification concept. Then, membership degrees can be assigned to the several data points of each fuzzy set (fuzzy class, fuzzy cluster). Hence, a single point can have different membership degrees for many classes (Ross, 2010). Fuzzy c-means clustering was developed by J.C. Dunn in 1973 (Dunn, 1973), and improved by J.C. Bezdek in 1981 (Bezdek, 1981).

Fuzzy c-means is grounded on the objective function's minimization:

$$J_{\mathrm{m}} = \sum_{i=1}^{D} \sum_{j=1}^{N} \mu_{ij}^{m} \left\| x_i - c_j \right\|^2 \tag{2.1}$$

where D is the number of data points, N is the number of clusters, m is fuzzy partition matrix exponent for controlling the degree of fuzzy overlap (with m > 1, fuzzy overlap refers to how fuzzy the boundaries between clusters are, that is the number of data points that have significant membership in more than one cluster.), x_i is the i'th data point, c_j is the center of the j'th cluster and m_{ij} is the degree of membership of x_i in the j'th cluster. For a given data point, x_i, the sum of the membership values for all clusters is one.

Fuzzy c-means algorithm performs 5 steps during clustering:

1. The cluster membership values, m_{ij} are initialized randomly.
2. The cluster centers, c_j are calculated using Equation (2.2)

$$c_j = \frac{\sum_{i=1}^{D} \mu_{ij}^{m} x_i}{\sum_{i=1}^{D} \mu_{ij}^{m}} \tag{2.2}$$

3. Update m_{ij} according to Equation (2.3)

$$\mu_{ij} = \frac{1}{\sum_{k=1}^{N} \left(\frac{\left\| x_i - c_j \right\|}{\left\| x_i - c_k \right\|} \right)^{\frac{2}{m-1}}} \tag{2.3}$$

4. The objective function, J_{m} is calculated.
5. Steps 2-4 are repeated until J_{m} improves by less than a pre-defined minimum value or until after a number of iterations.

2.2 Numerical Application for a State Hospital in Istanbul

For the numerical application, patient data is gathered in a full-fledged state hospital in Istanbul. A sample of 100 patients admitted to hospital with diverse complaints is prepared. After an interview with the physicians, mostly demographic factors and blood test results are included in application for a faster diagnosis. 23 types of patient data are observed: Age, gender, height, weight, glucose, urea, creatinine, total protein, ALB, CRP, ESR, WBC, HGB, HCT,PLT, AST, ALT, PH, CO2, O2, SPO2, breaths per minute (BPM) and number of pulses per minute (PPM).

Numerical application is performed with MATLAB Software Fuzzy Logic Toolbox. First, the data matrix (100x23) is prepared as in Table 2.1.

Table 2.1 Sample Patient Data

Patient No	Age	Gender	Glucose	…	SPO2	BPM	PPM
1	73	1	91	…	89	20	105
2	65	1	215	…	85	25	90
…	…	…	…	…	…	…	…
99	75	1	201	…	76	18	100
100	70	0	425	…	91	15	110

Membership values are randomly initialized and for the first iteration, the value of the objective function is calculated as 899932896162.19. Stopping condition of the algorithm is set as 50 iterations. The objective function converged after 20 iterations as shown in Figure 2.1.

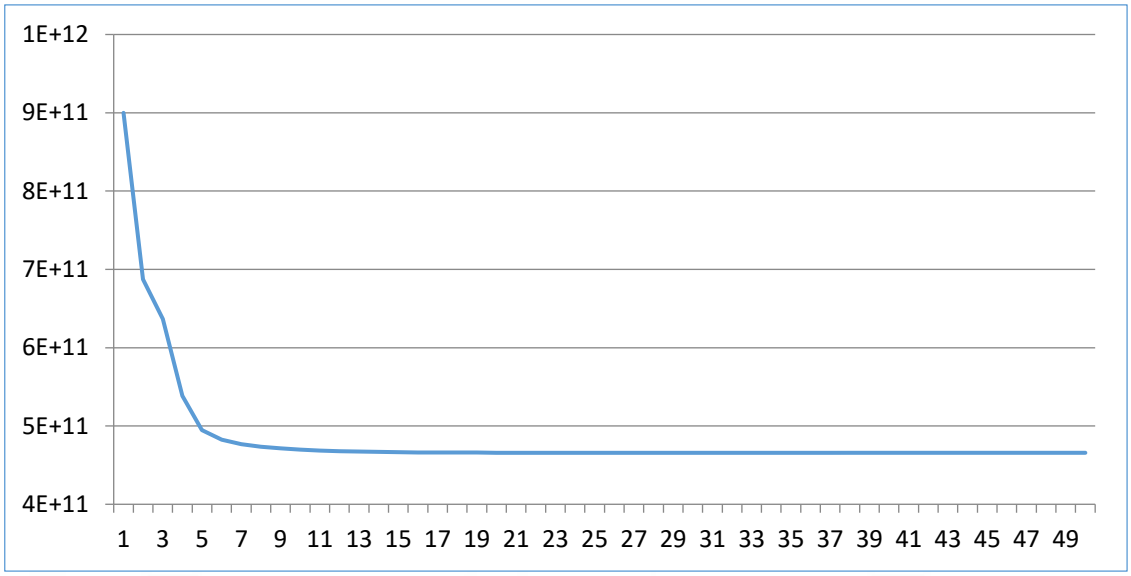

Figure 2.1 Convergence of the Objective Function

Membership degrees calculated by the algorithm for each patient and the patient's DM status are given in Table 2.2.

Many factors affect the performance and accuracy of a segmentation algorithm. This chapter is about proposing fuzzy c-means algorithm for faster diagnosis of diabetes via other patient information in an emergency. A sample of 100 patients from a state hospital in Istanbul is evaluated. The results of the numerical application are interpreted by the physicians. When the threshold value is chosen as 0.5 between the two classes, 19 out of 100 patients were incorrectly classified, which are marked as (*) in Table 2.2. Fuzzy c-means reached an accuracy of 81%. In order to obtain better results, the data set might be extended and additional information on the patients might be used in the model. As a medical decision support model, 81% accuracy is interpreted as useful by the physicians. The model can be integrated with preprocessing steps as data reduction or factor analysis. As further research directions, other clustering algorithms as logistic regression, neural networks etc. can be implemented to the same data for comparison and integrated models can be proposed for better accuracy.

Table 2.2 Fuzzy c-means results and DM status of the patients

Patient 1-25	DM Status	Patient 25-50	DM Status	Patient 51-75	DM Status	Patient 76-100	DM Status
0.007	0	0.992	1	0.000	0	0.062*	1
0.450*	1	0.005	0	0.003	0	0.603	1
0.028	0	0.010	0	0.533*	0	0.371*	1
0.908	1	0.175	0	0.022	0	0.529	1
0.044	0	0.717	1	0.298	0	0.168	0
0.215	0	0.013	0	0.283	0	0.774	1
0.800	1	0.211	0	0.028	0	0.688	1
0.050	0	0.583*	0	0.065	0	0.008	0
0.010	0	0.676*	0	0.402*	1	0.010*	1
0.716	1	0.424	0	0.443	0	0.004	0
0.740	1	0.492	0	0.381	0	0.003	0
0.908	1	0.015	0	0.837	1	0.842	1
0.604	1	0.357	0	0.075	0	0.020*	1
0.003	0	0.929	1	0.028*	1	0.098*	1
0.114*	1	0.001	0	0.905	1	0.003	0
0.012	0	0.000	0	0.014	0	0.625	1
0.765	1	0.388*	1	0.410*	1	0.617	1
0.710	1	0.260	0	0.040	0	0.058*	1
0.116*	1	0.015	0	0.703	1	0.044	0
0.035*	1	0.346	0	0.607	1	0.838	1
0.870	1	0.007*	1	0.023	0	0.015	0
0.071*	1	0.624	1	0.290	0	0.094	0
0.630	1	0.132	0	0.037	1	0.978	1
0.522	1	0.703	1	0.514	1	0.708	1
0.044	0	0.013	0	0.702	1	0.555	1

3. DETECTION IN SOCIAL SCIENCES WITH INTUITIONISTIC FUZZY COGNITIVE MAPS

Cognitive Maps (CM) were introduced by Tolman (Tolman, 1948) in his cognitive psychology research but as a modelling tool for decision making, first practical application was done by Axelrod (Axelrod, 1976) in politics.

CMs are a type of directed graph that offers a means to model interrelationships or causalities among concepts; there are various forms of CMs, such as signed digraphs, weighted graphs, and functional graphs. The differences amongst these various forms can be found in Kardaras and Karakostas (Kardaras & Karakostas, 1999).

Simple binary relationships (i.e., increase and decrease) are used in a conventional (crisp) CM. CMs have a clear way to visually represent causal relationships, they expand the range of complexity that can be managed, they allow users to rapidly compare their mental models with reality, they make evaluations easier, and they promote new ways of thinking about the issue being evaluated (Ross, 2010).

CMs graphically describe a system in terms of two basic types of elements: concept variables and causal relations. Nodes represent concept variables, Ci, where i = 1, . . .,N. A concept variable at the origin of an arrow is a cause variable, whereas a concept variable at the endpoint of an arrow is an effect variable. For example, for Cj → Ci , Cj is the cause variable that impacts Ci, which is the effect variable. Arrows represent the causal relations between concept variables (w), which can be positive or negative as shown in Figure 3.1.

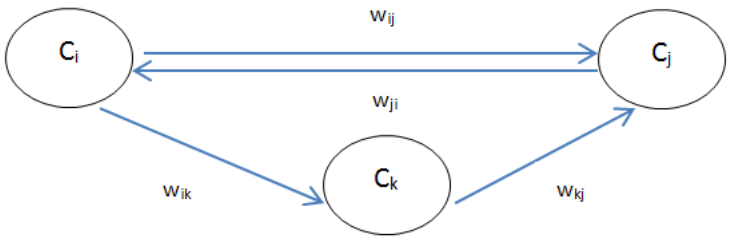

Figure 3.1 Concepts and Causal Relations

Although they are easy to use, CMs have trouble while quantifying causal relationships among variables. CMs have lack of capability to differentiate the strength of relationships, it just express the relation positively or negatively (w=1 or w=-1). Also every node just makes its decision according to the number of positive impacts and the number of negative impacts; thus, a CM is an oversimplified model for many applications. If one were to emphasize that the simple binary relationship of a CM needed to be extended to include various degrees of increase or decrease (small decrease, large increase, almost no increase, etc.), then using fuzzy numbers or intuitionistic fuzzy numbers is more appropriate.

Afterwards, FCM is proposed which is a causal knowledge-driven methodology for modeling complex decision systems, coming out from the combination of fuzzy logic and neural networks (Kosko, 1986). Extensions by Taber and Kosko (Kosko, 1992; Taber, 1994) allow fuzzy numbers or linguistic terms to be used to describe the degree of the relationship between concepts in the FCM. FCM has been used in modeling and preparing decision supportive systems tool in different scientific and managerial problems. More particularly in social sciences where data collection is demanding and the combination of these data is vague, confusing or tough to interpret, there exist numerous FCM applications.

In the last decade, major drawbacks of FCM are discussed and many extensions have been proposed using intuitionistic fuzzy sets. In 2011, IFCM has been introduced and applied in medical decision making field (Iakovidis & Papageorgiou, 2011). In 2013,

the method has been developed; IFCM-II has been proposed and discussed (Hadjistoykov, P. & Atanassov, 2013; Papageorgiou, E. I. & Iakovidis, 2013). In 2014, Temporal Intuitionistic Fuzzy Cognitive Map (TIFCM) has been introduced which extends the IFCM with temporal parameters (Hadjistoykov, P. P. & Atanassov, 2014).

3.1 FCM and IFCM Methods

FCM is proposed by Kosko (Kosko, 1986) as an expert-based and causal methodology aiming to structure complex decision systems. FCM is a directed graph with nodes as system concepts and edges as causal relations. Each concept represents a variable / a factor of the system and each arrow represents the cause-and-effect relationship between two concepts.

Let C_i and C_j be two different concepts of a system, then the arrow with a direction from C_j to C_i is called w_{ji} and it shows the degree of causality between C_j and C_i as shown in Figure 3.2. The presence of w_{ji} makes C_j and C_i the cause variable and the effect variable, respectively. In conventional CM, w_{ji} takes only the crisp values –1,0 and 1 which represents a decrease, no relation and an increase. In FCM, w_{ji} values can be linguistic terms, which are represented by fuzzy sets.

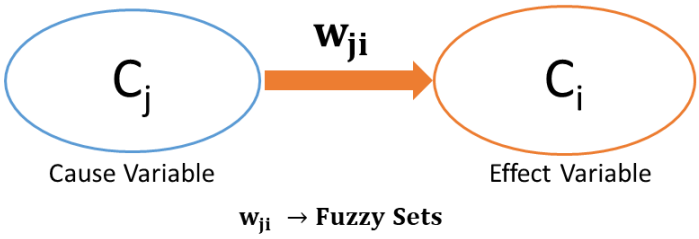

Figure 3.2 Concept nodes and relation edges of FCM

In FCM, the final value of each concept in other words, the strength of each variable in the system is calculated with an algorithm of iterative steps using Equation (3.1) where $s_i(k)$ is the value of concept i at iteration k, w_{ji} is the weight of connection from C_j to C_i, $s_i(k+1)$ is the value of concept i at iteration k+1, and f is the threshold function.

$$s_i^{k+1} = f\left(s_i^k + \sum_{\substack{i=1 \\ j \neq i}}^{N} s_j^k . w_{ji}\right) \tag{3.1}$$

IFCM (Iakovidis & Papageorgiou, 2011) is an extension of FCM with Atanassov's intuitionistic fuzzy sets (IFS) (Atanassov, 1986). IFS differ from fuzzy sets with their ability of representing hesitation degrees of decision makers in the mathematical model.

IFSs were first introduced by Krassimir T. Atanassov in 1986 and were developed in 1999 (Atanassov, 1986, 1999). The concept of IFS can be viewed as an alternative approach to define a fuzzy set in cases where available information is not sufficient for the definition of an imprecise concept by means of a conventional fuzzy set (Li, 2005).

Let $X = \{x_1, x_2, \dots, x_n\}$ be a finite universal set. An IF set A in X is defined as:

$A = \{\langle x_l, \mu_A(x_l), \upsilon_A(x_l)\rangle | x_l \in X\}$ with the functions;

$\mu_A : X \to [0,1]$,$x_l \in X \to \mu_A(x_l) \in [0,1]$ and

$\upsilon_A : X \to [0,1]$, $x_l \in X \to v_A(x_l) \in [0,1]$

defining the degree of membership ($\mu_A(x_l)$) and the degree of non-membership ($\upsilon_A(x_l)$) of the element $x_l \in X$ to the set $A \subseteq X$ and for every $x_l \in X$, $0 \leq \mu_A(x_l) + \upsilon_A(x_l) \leq 1$.

$\pi_A(x_l) = 1 - \mu_A(x_l) - \upsilon_A(x_l)$ is Atanassov's intuitionistic fuzzy index, the degree of indeterminacy membership, of the element x_l in the set A and for every $x_l \in X$, $0 \leq \pi_A(x_l) \leq 1$.

Atanassov's intuitionistic fuzzy index represents the hesitancy in the mathematical model and this is the originality of working under an intuitionistic environment. Conventional fuzzy numbers represent the ambiguity of the information however; they

do not consider the lack of information. Therefore, in the applications where decision makers claim that they are hesitant about the information they give, IFSs are more suitable to represent this information in the mathematical model.

In IFCM method, Equation (3.1) is updated using IFS hence, in Equation (3.2) of IFCM, instead of w_{ji}, there are two weight values namely the influence weight w_{ji}^{μ} and the hesitancy weight w_{ji}^{π} (Iakovidis & Papageorgiou, 2011).

$$s_i^{k+1} = f\left(s_i^k + \sum_{\substack{i=1 \\ j \neq i}}^{N} s_j^k . w_{ji}^{\mu} . \left(1 - w_{ji}^{\pi}\right)\right) \tag{3.2}$$

3.2 IFCM in Strategic Marketing Management

Marketing decisions are challenging in profit-oriented companies because of their complex nature. Many factors influence the marketing strategy in the New Product Development (NPD) process. With this aspect, strategic marketing decisions for launching a product to the market can be observed as multiple criteria decision-making (MCDM) problems. IFCM method is advantageous for assessing the criteria that influence the pricing strategy of a company in earlier stages of the product's life cycle in the market. A framework is formed based on a profound analysis of literature and experts' opinions, in terms of criteria affecting pricing strategy and the causal relationships between them. Intuitionistic fuzzy sets and cognitive mapping are used together to capture the hesitation of the decision makers caused by lack of information and to define cause-and-effect relations between the criteria to represent the complexity of strategic marketing decisions. Contrary to conventional MCDM methods that require complete data, IFCM method is able to deal with lack of information and hesitancy of the decision makers.

3.2.1 Definition of Marketing

Marketing is one of the most important activities in profit-oriented companies in this new era of global consummation. Creating a product or a service is just the starting point of a race where many of the runners cannot even see the finish line. Technological advances of the last 15 years bring out competitive markets in all industries around the world. Technology gives the consumer the chance of reaching every single product in the world via internet. A company's competitors are not only other domestic companies but also all the companies worldwide, producing a substitutable service or product.

By definition, marketing is managing profitable customer relationships (Kotler & Armstrong, 2012). In the industry, marketing is a process that starts from the concept of a product and lasts until the product is reached to the end-user. It is a long-term orientation, and an elongated progression that needs planning and management. Marketing systems have high levels of the dynamic complexity. For example, a firm would decrease prices to gain market share when capacity utilization is low if the managers believe competitors cannot respond by cutting their own prices. Therefore, marketing decisions are made at the strategic level of companies. Strategic marketing management is one of the major concerns of today's competitive societies. Marketing decisions are always influenced by many internal and external factors, and they must be made rapidly because of the competitive market structures. Due to their complexity caused by many influencing factors, marketing decisions are generally interpreted as multiple criteria decision-making (MCDM) problems in the literature.

3.2.2 Basic Concepts in Strategic Marketing Management

The essence of marketing is a transaction–an exchange–intended to satisfy human needs and wants (Stanton, 1981). Marketing is not just a department in the company, but a process that requires management. It focuses not only on the tasks of its own department but also is responsible to arrange and plan all the company's activities.

Marketing is neither static nor seasonal hence the compatibility and the efficiency of the marketing plan is significant.

When conceived as a process, the content of marketing includes strategic and tactical planning, research and analysis, the creation of goals and objectives, development of long-term relationships with customers, decisions for competitive advantage compared to other companies, implementation of marketing activities, control, social responsibility, and ethics. If these factors are put in order, it is noticed that marketing comprises five main steps; (1) research, (2) segmentation, market targeting, positioning, (3) marketing mix constitution, (4) implementation of the strategy and (5) control (Kotler, 1999).

The second and the third steps form the marketing strategy. Marketing strategy involves two key questions (Kotler & Armstrong, 2012): Which customers will the company serve? How can value be created for these customers? Thus, segmentation, targeting, and positioning are three of the pillars of modern and customer-driven marketing strategy approach.

Segmentation is to find customer groups homogeneous between them and heterogeneous compared to other groups (Freter & Baumgarth, 2004). It has a strong impact on marketing strategy formulation and on the success of the marketing efforts. In segmentation, it is crucial to find customers who respond similarly to the offered marketing efforts. Different segments with different needs entail different marketing mixes. Major segmentation variables for consumer markets are geographic (world region or country, country region, city or metro size, density, climate), demographic (age, gender, family size, family life cycle, income, occupation, education, education, religion, race, generation, nationality), psychographic (social class, lifestyle, personality) and behavioral variables (occasions, benefits, user status, user rates, loyalty status, readiness stage, attitude toward product) (Kotler & Armstrong, 2012). Segmentation aims to find the distinctive qualities of current markets, divide markets into segments according to these qualities, determine the size and the growth of these segments and observe the competitors.

After a company has defined its market segments, it can choose one or many of these segments. The target market is the segment served. Market targeting involves testing each market segment's attractiveness and selecting one or more segments to enter. A company should target segments in which it can profitably generate the greatest customer value and sustain it.

Once the target market is defined, the company must consider creating a value for the customers. This step is called positioning. A position is a complex set of perceptions, impressions, and feelings and it is important to note that customers position the company's value offering with or without its help (Bradley, 2003). Positioning is arranging for a product to occupy a clear, distinctive, and desirable place relative to competing products in the minds of target consumers, accordingly, marketers plan positions that distinguish their products from competing brands and give them the greatest advantage in their target markets (Kotler & Armstrong, 2012). Consumers make positioning of products according to their opinions of these products to speed up, simplify and optimize their shopping. In addition, positioning for a company can be interpreted as the differentiation of a product from its competitors. Hence proposing a value, a difference from other products is the major concern of positioning. A product with a favorable position in target customers' minds creates a competitive advantage for the company. Positioning step is more important for the new products because once a product is positioned in the customer's mind, it is nearly impossible to change.

Marketing mix elements, also known as 4P's, are product, price, promotion, and place (McCarthy, 1960). Each P represents different strategies for marketing and is vital to the success. It is a framework, which helps to structure the approach to each market. The mix is a bundle of variables that are offered to the customer. The company produces the product, sets a price, distributes and implements promotional activities on the market. For the implementation step, all departments of the company should perform effectively with collaboration: R&D, production, marketing/sales, human resources, logistics, finance, and accounting. Lastly, the company must follow market responses and customer feedbacks, evaluate the results and take corrective actions to improve the performance. If the business fails, the fault must be sought in the strategic steps. The

company should assess the validity of the marketing strategies constantly by monitoring the new data and change these strategies in the right direction if necessary.

Price is one of the 4P's which means it is only an element of the company's broader marketing strategy. If the company has selected its target market and positioning carefully, then its marketing mix strategy, including price, will be straightforward. The price also creates a position in customers' minds. Setting an initial price for a new product is vital to the success of this product. Therefore, the aim of the model is to evaluate the criteria that affect pricing strategy of a company in the new product development process.

3.2.3 Technological Device Manufacturer Company Application

In order to show its applicability in social sciences, an IFCM application model is executed in a technological device manufacturing company, which produces personal computers (PC's), laptops, tablet PC's, smartphones, portable media players and all accessories of these products with a wide range. The company is global and has an important market share around the world. In terms of financial resources, the company is able to spare an elevated budget for the R&D expenses. These conditions provide the high capability of new products and effective NPD processes for the company. Since its foundation, this company uses the Blue Ocean Strategy as its general marketing strategy and has a sufficient marketing communication with the customers. Blue Ocean Strategy suggests that an organization should create new demand in an uncontested market space, or a "Blue Ocean", rather than compete head-to-head with other suppliers in an existing industry (Kim, W. C. & Mauborgne, 2005). Blue Ocean Strategy has specific features:

- It restricts the size of the target market while creating a new demand.
- It builds a reliable brand image to provide customer loyalty.
- It eliminates competitors by creating its own market.

Since the company uses this strategy successfully, the demand of the current products considerably high. The company has the advantage of economies of scale because of the large production amounts to meet the global demand. Fixed production costs are minimized and logistics network is well supported.

Launching of a new laptop of this company is selected for the application. With a marketing insight, a laptop is a specialty product; which is unique, one-of-a-kind product that consumers will spend considerable time, effort, and money to acquire (Ferrell & Hartline, 2011). The company has already produced various laptops however the new model has a faster microprocessor than the other laptops that belong to the same product line. In this NPD process, the new laptop will be launched using a pricing strategy and the marketing managers of the company require to determine the most effective factors on pricing before making a decision.
Three decision makers chosen by the company from marketing department (one brand manager and two category managers) will give required information for the numerical application and discuss the results about the applicability of the proposed model.

The objective of the numerical application is to find the values and ranking order of the criteria, which are effective while launching a new laptop to the market. Therefore, the company will be able to determine the priorities in NPD process.

Step1: Strategic marketing criteria are the 17 concept nodes as shown in Table 3.1.

Step2: Causal relationships and their directions are determined by the experts thereby the IFCM is designed.

Step3: Experts are requested to assign IFSs to the weights of causal relationships. They set the degrees of membership (degree of influence) and the degrees of indeterminacy membership (degree of hesitation). Then the degrees of non-membership are calculated.

Table 3.1 Strategic marketing criteria

Criterion	*Definition*	*Ref.*
C_1: New Product Capability	The company's ability to develop innovative products	(Aaker & McLoughlin, 2010)
C_2: Research& Development	The company's technological advantage, patents, and technical capabilities	(Aaker & McLoughlin, 2010)
C_3: Cost Structure	The proportion of fixed costs in the total costs for any level of production for the company	(Kotler & Armstrong, 2012)
C_4: Economies of Scale	The cost advantages that an enterprise gets due to expansion	(Stigler, 1958)
C_5: Logistics	The company's strength of planning, implementing and controlling the physical flow of materials, final goods, and related information from points of origin to points of consumption to meet customer requirements at a profit	(Kotler & Armstrong, 2012)
C_6: Management Style	The suitability of the company's management method to Management by Values (MBV)	(Dolan & Garcia, 2002)
C_7: Marketing Communication	The promotions that the company uses to persuasively communicate customer value and build customer relationships	(Kotler & Armstrong, 2012)
C_8: Accessibility to Capital	The company's financial resources and the quickness to find the capital	(Aaker & McLoughlin, 2010)
C_9: Market Share	Market share is the percentage of a market (defined in terms of either units or revenue) accounted for by a specific entity	(Davies & Geroski, 1997)
C_{10}: Market / Segment Size	The number of consumers in the company's target market	(Ferrell & Hartline, 2011)
C_{11}: Number of Competitors	The number of sellers, their relative market shares, and the differentiation that exists between the competing companies and products for a market	(Wilson & Gilligan, 2005)
C_{12}: Consumer Fidelity	The loyalty of consumers to the products of a company in a long period of time	(Kotler & Armstrong, 2012)
C_{13}: Brand Image	The beliefs about products that the consumers develop regarding their various attributes	(Proctor, 2000)
C_{14}: Product Type Convenience	The convenience of the product type (mass or special) to the market structure (low or high differentiation) and to the company's financial resources (low or high)	(Kotler & Armstrong, 2012)
C_{15}: Breadth of the Product Line	Systems capability, the diversity of the product line of a company	(Aaker & McLoughlin, 2010)
C_{16}: Product Support	A part of the augmented product, support service for the use of the product, an important part of the consumers' overall brand experience	(Kotler & Armstrong, 2012)
C_{17}: Price Elasticity of Demand	The percentage change in quantity demanded in response to a one percent change in price	(Marshall, 1997)

Step4: w matrix is constructed according to data given by the experts. A part of the matrix is shown for the first five criteria.

$$w_{(5x5)} = \begin{bmatrix} 0 & \langle 0.45,0.55\rangle & \langle 0.4,0.6\rangle & 0 & 0 \\ \langle 0.85,0.15\rangle & 0 & \langle 0.8,0.2\rangle & 0 & 0 \\ \langle 0.45,0.55\rangle & \langle -0.85,-0.11\rangle & 0 & \langle -0.9,-0.1\rangle & 0 \\ 0 & \langle 0.45,0.5\rangle & \langle 0.9,0.1\rangle & 0 & \langle 0.5,0.48\rangle \\ 0 & 0 & \langle 0.55,0.45\rangle & \langle 0.8,0.2\rangle & 0 \end{bmatrix}$$

Negatively signed membership and non-membership values exist in the w matrix; they indicate a negative influence between concepts. The experts decide first the direction of the causal relationships and then define their degrees using IFSs; the element $\langle -0.9,-0.1\rangle$ of w matrix means a negative causal relationship with the degree $\langle 0.9,0.1\rangle$.

Step5: IFCM iterations are coded in MATLAB R2013a on an Intel(R) Core(TM) i7 PC and 8 GB RAM computer:

- $A_i^0 = 1$ for i=1,2,…,17 (Iterations begin with the greatest value for each criterion to observe the effect of subsequent iterations)
- The threshold function is chosen as the hyperbolic tangent (tanh) to have the final values between [-1,1].

Step6: Values converged in 18 iterations. For example, the fifth concept's (Logistics) final value 0.990646 is obtained:

- The fifth column of w matrix is calculated,

$\mu(w_{j5}) - 1.\pi(w_{j5})$ = (0,0,0,0.48,0,0,0,0.56,0,0.65,0,0,0,0,0,0,0)

- The row vector A_i^0(1x17) is multiplied with the fifth column of w matrix to find

$\sum_{j=1}^{N}{}_{j\neq 5} A_j^{(0)}\left[\mu(w_{j5}) - h_s.\pi(w_{j5})\right]$= 1.69

- $A_5^0 = 1$ is added to 1.69 to find $A_5^0 + \sum_{\substack{j=1 \\ j\neq 5}}^{N} A_j^{(0)}\left[\mu\left(w_{j5}\right) - h_s.\pi\left(w_{j5}\right)\right]$=2.69
- tanh(2.69) is calculated and A_5^1=0.990827 is obtained.
- Next iterations are A_5^2=0.990827, A_5^3=0.990573, A_5^4=0.990643, A_5^5=0.990645 and when all the values are converged, A_5^{18}=0.990646.

As another example with a negative final value, 17th concept - "Price Elasticity of the Demand":

- $\mu\left(w_{j17}\right) - 1.\pi\left(w_{j17}\right)$=(0,-0.9,0,0.6,-0.51,0,-0.56,0,0,0,0.72,-0.43,-0.78,-0.72,0,0,0)
- $\sum_{\substack{j=1 \\ j\neq 17}}^{N} A_j^{(0)}\left[\mu\left(w_{j17}\right) - h_s.\pi\left(w_{j17}\right)\right]$ =-2.58
- $A_{17}^0 + \sum_{\substack{j=1 \\ j\neq 17}}^{N} A_j^{(0)}\left[\mu\left(w_{j17}\right) - h_s.\pi\left(w_{j17}\right)\right]$=-1.58
- tanh(-1.58)=-0.918602=A_{17}^1
- A_{17}^2=-0.999894, A_{17}^3=-0.999911, A_{17}^4=-0.9999104,…, A_{17}^{18}=-0.999910.

While calculating the final values, some of them might converge in earlier iterations. Number of iterations depends on the epsilon ($\varepsilon = A_i^{k+1} - A_i^k$) value that is pre-defined in the MATLAB code. The final values of the system concepts are given in Table 3.2.

According to the results, Brand Image, Market Share, Consumer Fidelity, Market/Segment Size and New Product Capability criteria have the maximum positive influence on the pricing strategy of the company; they have the greatest value. Logistics and Product Type Convenience criteria have the minimum positive influence. Number of competitors and Price Elasticity of the Demand criteria, on the other hand, have the maximum negative influence on pricing decisions.

Table 3.2 Final values of the criteria and the ranking order

Final values of the Criteria		
C1	New Product Capability	1
C2	Research & Development	0.9998
C3	Cost Structure	0.9995
C4	Economies of Scale	0.9998
C5	Logistics	0.9906
C6	Management Style	0.9970
C7	Marketing Communication	0.9998
C8	Accessibility to Capital	0.9993
C9	Market Share	1
C10	Market / Segment Size	1
C11	Number of Competitors	-1
C12	Consumer Fidelity	1
C13	Brand Image	1
C14	Product Type Convenience	0.9880
C15	Breadth of the Product Line	0.9951
C16	Product Support	0.9995
C17	Price Elasticity of the Dem.	-0.9999

The ranking order of the Criteria		
C13	Brand Image	1
C9	Market Share	1
C12	Consumer Fidelity	1
C10	Market / Segment Size	1
C1	New Product Capability	1
C4	Economies of Scale	0.9998
C7	Marketing Communication	0.9998
C2	Research & Development	0.9997
C3	Cost Structure	0.9995
C16	Product Support	0.9995
C8	Accessibility to Capital	0.9993
C6	Management Style	0.9970
C15	Breadth of the Product Line	0.9951
C5	Logistics	0.9906
C14	Product Type Convenience	0.9880
C17	Price Elasticity of the Dem.	-0.9999
C11	Number of Competitors	-1

3.2.4 Discussions on the Results

Through an in-depth marketing literature survey, seventeen factors that influence the company's pricing decisions are determined and then defined by four marketing experts. New Product Capability, R&D, Cost Structure, Economies of Scale, Logistics, Management Style, Marketing Communication, Accessibility to Capital, Market Share, Market/Segment Size, Number of Competitors, Consumer Fidelity, Brand Image, Product Type Convenience, Product Support and Price Elasticity of the Demand criteria of the MCDM pricing problem are set as the concepts of the system. Three experts from the company determined the direction of causal relationships between concepts and

defined their degrees using IFS based on the information from the market surveys. The lack of information and the expert's hesitations are represented in the model using the indeterminacy membership degrees of IFS. Weight matrix is constructed and a conceptual map of the system is obtained. Considering the synergy level of the application field, the most powerful factors on pricing decisions are determined with iterative steps of IFCM method. Brand Image, Market Share, Consumer Fidelity, Market/Segment Size and New Product Capability criteria had the maximum positive influence in numerical application. Results are interpreted by three decision makers, in other words, three "marketers" of the company. Certain points of the data and the results draw attention:

1) While preparing the data, marketers give more self-confident answers to the questions about the criteria under the headings *Innovation, Manufacturing/Operations,* and *Management* because these criteria are related to the company itself. Therefore, the IFSs assigned to these criteria have relatively smaller hesitation (π) values. On the other hand, the IFSs assigned to *Market* and *Consumer* criteria have greater hesitation degrees caused by the lack of information and risk-averse attitude.

2) The technological device manufacturer company in this case study is one of the most successful companies around the world and has a well-organized marketing department, which leads the Blue Ocean marketing strategy carefully. The department has a large marketing communications network and sufficient financial resources to conduct wider market surveys. Their marketers' hesitation degrees might be less than other companies in the market.

3) Results provide a ranking order of the criteria, however; it is observed that all positive and negative values are notably close to 1 and -1, respectively, which means all the criteria have a great positive or negative influence of the pricing strategy decision. It indicates that the criteria of the decision framework are well chosen and defined. None of the criteria can be eliminated from the model. All the criteria have a certain and important effect.

4) The criteria that have maximum positive influence (Brand Image, Market Share, Consumer Fidelity, Market/Segment Size and New Product Capability) are significant for a technology company whose products differ from the competitors' in terms of functionality and who stays distant from the highly competitive area, positions its products in an uncontested market neutralized of the competition. Indeed, the company presents the products to a narrow target market and provides a competitive advantage with superior design features. An excellent example of customer demand's impact on pricing occurs. When a new model of a technological device is introduced, customers wait in line for hours and are willing to pay a premium price just to use the new model primarily.

5) Logistics and Product Type Convenience are the least important criteria according to the results. This is also meaningful for a company who adopts Blue Ocean strategy. The company only sells its products in its own stores and produces the exact targeted products for its pre-defined narrow target market, which renders the logistics network and the convenience of the product type less important amongst the other factors.

6) Two criteria have the most negative influence on pricing decisions: Price Elasticity of the Demand and Number of Competitors. This situation does not depend on the company chosen for the case study; it is originated from the nature of pricing decisions. These two criteria will always have negative effects of pricing decisions; the model observes their values' closeness to -1 and their ranking order for the company. In this case study, Number of Competitors has the most negative influence because the price elasticity is relatively controlled by the company through Blue Ocean strategy.

7) Three marketers indicated that the results are noteworthy for their company; the model is useful and applicable while making pricing decisions in NPD process.

The usefulness of the model is observed by its effect on the decision-making process by revealing beneficial results and the case study shows that the IFCM method is applicable as an evaluation technique in marketing strategy. The model offers the

decision maker some flexibility to incorporate his/her own opinion in the model. Managers could use such approaches while making their strategic decisions in case of incomplete information and vagueness.

3.3 IFCM in Multi-Drug Resistant Tuberculosis Detection

Tuberculosis is a global burden and one of the leading causes of morbidity and mortality (WHO, 2016b). It is one of the top 10 causes of death worldwide. TB is known for centuries, has a vaccine, also a standard treatment that takes six months. The medicine solved the problem of TB decades ago by finding the cure; it is not a problem of medicine anymore, it is a problem of management. TB is not just a disease, but also an issue of social inequality and poverty. Contagiousness and mismanagement of TB treatment are the most important reasons why MDR-TB is continuously emerging and spreading around the world. Utilization of incorrect or low quality medications, poor healthcare conditions, poor quality of life, and dropping the treatment prematurely may lead to drug resistance, which is transmitted especially in crowded areas as hospitals and prisons.

MDR-TB is a type of TB that does not respond to the two most powerful first-line anti-TB drugs: rifampicin and isoniazid. MDR-TB can be treated with second-line TB drugs with an extensive treatment up to two years. About 480.000 people worldwide developed MDR-TB in 2015 (WHO, 2016b). When a new TB case is diagnosed, it is vital to capture the drug resistance risk. This study is a risk assessment model for MDR-TB using IFCM which is an effective decision-making tool in medical problems considering the hesitation degrees of decision makers.

The aim of this chapter is to determine the factors that are important for the development of resistance in TB and establish a framework that will form the basis of subsequent statistical research in Turkey as recently driven in Ethiopia (Gobena et al., 2018) and India (Avashia et al., 2018). Today, the factors that play a role in the occurrence of MDR-TB are known as basic concepts,

however due to the lack of statistical data, the contribution of these factors to the development of resistance cannot be measured. After a patient is diagnosed with TB, a number of drug-susceptibility tests are performed to determine whether it is TB or MDR-TB and the test results are completed in approximately 45 days. Since the prevalence of TB is higher than the prevalence of MDR-TB, standard TB treatment is given to the patient during this process. If the patient is MDR-TB, it is a waste of time and, also an unnecessary load of chemicals to the patient's body, especially to the liver. The treatment of MDR-TB is longer, and requires more expensive (≥US$ 1000 per person), more toxic drugs and the latest data reported to WHO show a treatment success rate for MDR-TB of 55%, globally (WHO, 2018). Considering that liver health is essential to the effectiveness of the rest of the treatment, it is vital for the patient to predict resistance quickly in a TB patient. This application will be the first step in constructing a decision support system to forecast the resistance status of a TB patient before the drug-susceptibility tests.

3.3.1 Cognitive Mapping in Human Health

Cognitive mapping has been widely used in medical decision-making especially accompanied by fuzzy logic. Since medical decisions involve vagueness, ambiguity and fuzziness, FCM and its extensions as IFCM are used in detection, diagnosis and treatment planning.

First in 2003, FCM is proposed as the computational modeling method, which tackles the complexity and allows the analysis and simulation of the clinical radiation procedure and this approach is used to determine the success of radiation therapy process estimating the final dose delivered to the target volume (Papageorgiou, E. I. et al., 2003). In the same year, the method is used to constitute a qualitative and quantitative computer model comprised of the experience and knowledge of specialists

for differential diagnosis of specific language impairment (Georgopoulos, Voula C et al., 2003).

In 2005, Cognitive Map method is used for important communication skills that physicians need over the course of caring for a person with cancer (Back et al., 2005). In 2008, CM is applied for reshaping the diagnostic process and improving the management of digital imaging (Lettieri et al., 2008). Lastly in 2010, CM is used again for medical diagnosis support (Froelich & Wakulicz-Deja, 2010). Apart from these, CM has not been used in the last five years in medical decision-making.

In 2009, IFCM is introduced for medical decision making by adding a factor of hesitancy into the weights of a standard FCM and its applicability is discussed (Papageorgiou, E. I. & Iakovidis, 2009). In 2011, IFCM is used for pneumonia severity assessment and the results obtained revealed its comparative advantage over the respective FCM model by providing decisions that matched better with the ones made by the experts (Iakovidis & Papageorgiou, 2011). In 2013, IFCM-II is proposed which enabled an intuitionistic estimation of hesitancy at the output concepts, thus offered a natural mechanism to assess the quality of its output and used in the same pneumonia severity assessment problem.

Besides these methods, FCM is widely used with detection, diagnosis and treatment objectives in medical decision-making for various diseases. The complete literature survey is classified and given in Table 3.3 with chronological order.

Table 3.3 Publications with chronological order

Publication	**Field**	**Objective**	**Method**
(Papageorgiou, E. I. et al., 2003)	Radiation Therapy	Treatment	FCM
(Georgopoulos, Voula C et al., 2003)	Language Impairment	Diagnosis	FCM
(Back et al., 2005)	Oncology	Other	CM
(Georgopoulos, V. & Stylios, 2005)	Speech Pathology	Diagnosis	FCM
(Papageorgiou, E. I., Spyridonos, et al., 2006)	Tumor Grading	Diagnosis	FCM
(Papageorgiou, E., Stylios, et al., 2006)	Tumor Grading	Detection	FCM
(Papageorgiou, E., Stylios, et al., 2007a)	Knowledge Extraction	Detection	FCM
(Papageorgiou, E. I., Georgoulas, et al., 2007)	Tumor Characterization	Diagnosis	FCM
(Papageorgiou, E. I., Stylios, et al., 2007b)	Tumor Grading	Diagnosis	FCM
(Georgopoulos, V. C. & Stylios, 2008)	Language Impairment	Diagnosis	FCM
(Lettieri et al., 2008)	Healthcare Technology Management	Diagnosis	CM
(Papageorgiou, E. I., Papandrianos, et al., 2008)	Medical Informatics	Diagnosis	FCM
(Papageorgiou, E. I., Papandrianos, et al., 2008)	Thyroid	Diagnosis	FCM
(Papageorgiou, E. I., Spyridonos, et al., 2008)	Tumor Characterization	Diagnosis	FCM
(Stylios, C. D. & Georgopoulos, 2008)	Speech Pathology	Detection	FCM
(Stylios, C. D. & Georgopoulos, 2008)	Language Impairment	Diagnosis	FCM
(Stylios, C. D. et al., 2008)	Speech Pathology	Detection	FCM
(Papageorgiou, E. I., 2009)	Radiation Therapy	Treatment	FCM
(Papageorgiou, E. I. & Iakovidis, 2009)	Pneumonia	Detection	IFCM
(Papageorgiou, E. I., Papadimitriou, et al., 2009)	Urinary Tract Infections	Diagnosis	FCM
(Papageorgiou, E. I., Papandrianos, et al., 2009)	Infectious Diseases	Detection	FCM
(Froelich & Wakulicz-Deja, 2010)	Corneal Ulcer	Diagnosis	CM
(Papageorgiou, E. I., 2010)	Knowledge Extraction	Detection	FCM
(Papageorgiou, E. I. & Froelich, 2010)	Pulmonary Infection	Detection	FCM
(Stylios, C. S. & Georgopoulos, 2010)	Obstetrics	Detection	FCM
(Groumpos, 2011)	Tumor Grading	Detection	FCM
(Iakovidis & Papageorgiou, 2011)	Pneumonia	Detection	IFCM
(Papageorgiou, E. I., 2011)	Medical Informatics	Treatment	FCM
(Stylios, C. D. & Georgopoulos, 2011)	Obstetrics	Diagnosis	FCM
(Froelich et al., 2012)	Prostate Cancer	Detection	FCM
(Giabbanelli et al., 2012)	Obesity	Detection	FCM
(Groumpos, 2012)	Tumor Grading	Diagnosis	FCM
(Lee et al., 2012)	Pulmonary Infection	Diagnosis	FCM
(Lee et al., 2012)	Dental Implant Abutments	Diagnosis	FCM
(Lucchiari & Pravettoni, 2012)	Diagnostic Errors	Diagnosis	FCM
(Papageorgiou, E. I., 2012)	Urinary Tract Infection	Treatment	FCM
(Papageorgiou, E. I. & Froelich, 2012)	Pulmonary Infection	Detection	FCM

Table 3.3 (cont.) Publications with chronological order

Publication	Field	Objective	Method
(Papageorgiou, E. I. & Salmeron, 2012)	Urinary Tract Infection	Treatment	FCM
(Papageorgiou, E. I. & Salmeron, 2012)	Radiation Therapy	Treatment	FCM
(Salmeron & Papageorgiou, 2012)	Radiation Therapy	Treatment	FCM
(Bevilacqua et al., 2013)	Drug Administration	Treatment	FCM
(Bourgani et al., 2013)	Radiation Therapy	Other	FCM
(De Brito et al., 2013)	Dysmorphic Disorder	Detection	FCM
(Georgopoulos, V. C. & Stylios, 2013)	Emergency Room Admissions	Other	FCM
(Papageorgiou, E. I. et al., 2013)	Urinary Tract Infection	Treatment	FCM
(Papageorgiou, E. I. & Iakovidis, 2013)	Pneumonia	Detection	IFCM
(Anninou & Groumpos, 2014)	Parkinson's Disease	Detection	FCM
(Bhatia et al., 2014)	Classification	Other	FCM
(Bourgani et al., 2014)	Pulmonary Diseases	Diagnosis	FCM
(Douali et al., 2014)	Urinary Tract Infection	Diagnosis	FCM
(Georgopoulos, V. C. et al., 2014)	Education	Other	FCM
(Gürsel, 2014)	Healthcare Applications	Other	FCM
(Borracci & Arribalzaga, 2015)	Cardiac Surgery	Detection	FCM
(Bourgani et al., 2015)	Obstetrics	Detection	FCM
(Buyukavcu et al., 2016)	Breast Cancer	Detection	FCM
(Chandiok & Chaturvedi, 2016)	Disease Severity	Diagnosis	FCM
(Amirkhani et al., 2018)	Celiac	Diagnosis	FCM

3.3.2 MDR-TB Risk Factors Assessment

TB is an infectious disease caused by the bacillus Mycobacterium tuberculosis. It is one of the top 10 causes of death worldwide and the leading cause from a single infectious agent (above HIV/AIDS) (WHO, 2018). A preventive treatment is available with vaccination of children with the bacille Calmette-Guérin (BCG). The risk factors of the disease, shown in Figure 3.3, are known and investigated continuously in various countries with high TB rates.

In the scope of the project “End TB Strategy” of WHO, all TB data is collected from countries (usually by The Health Ministry), driven by WHO, and reported annually as “Global Tuberculosis Report”. In addition, according to the latest research, “Treatment Guidelines” are also prepared and published each year by WHO as a key reference for TB healthcare practitioners, experts, physicians and patients (www.who.int/tb/en).

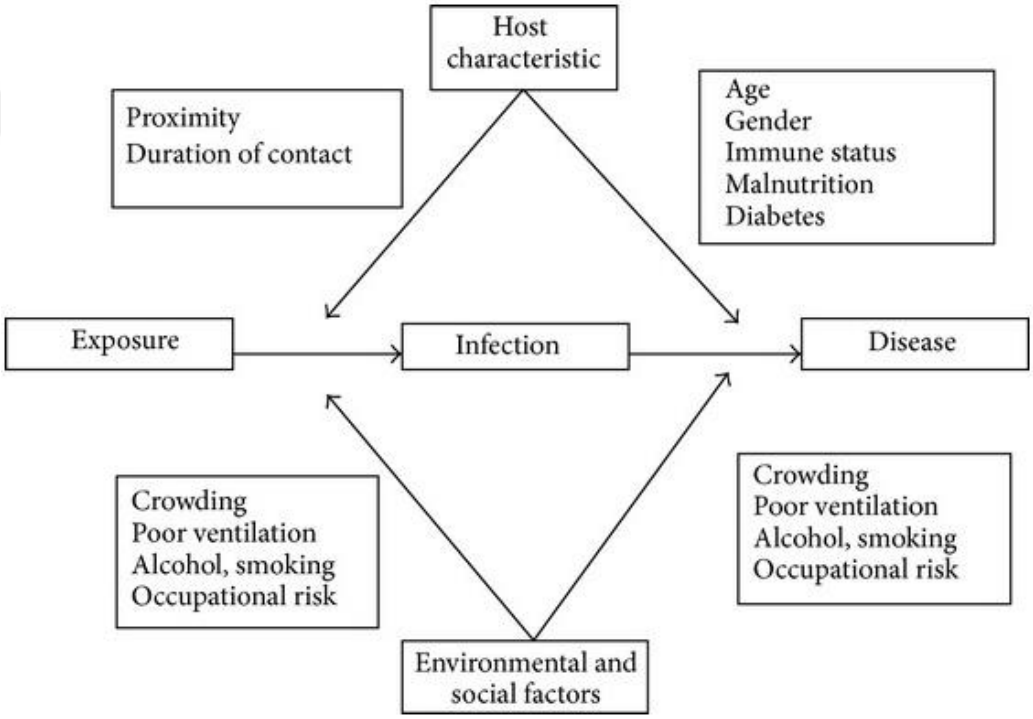

Figure 3.3 Risk Factors of TB (Narasimhan et al., 2013)

The types of TB are defined by the drug-susceptibility condition of bacteria causing the disease. There are two types of anti-TB drugs currently in use: First-line drugs and second-line drugs. The five first-line anti-TB drugs are (WHO, 2017):

- Isoniazid (H/Inh)
- Rifampicin (R/Rif)
- Pyrazinamide (Z/Pza)
- Ethambutol (E/Emb)
- Streptomycin (S/Stm)

The first-line antitubercular drugs provide the most powerful and effective treatment of TB. These are cost-efficient drugs with few side effects. Drug-susceptible TB has a standard treatment regimen of 6 months with high intensity phase (Inh, Rif, Ebm and Pza) of 2 months and continuity phase (Inh and Rif) of 4 months. Standard regimen has shown high efficacy rates (90% - 95%) (Shin & Kwon, 2015), and low toxicity in TB patients. The second-line antitubercular drugs are shown in Table 3.4. Groups A, B and C are the core second-line drugs and Group D is additional drugs that cannot be used without core second-line drugs in a treatment plan.

If the TB bacteria are only resistant to Rifampicin, the type of TB is called Rifampicin Resistant-TB (RR-TB). If the TB bacteria are resistant to Rifampicin and Isoniazid, the two most effective anti-TB drugs, the type of TB is called MDR-TB. If the TB bacteria have, in addition to MDR-TB, resistance to at least one drug in both of the two most important classes of medicines in an MDR-TB regimen; fluoroquinolones (Group A) and second-line injectable agents (Group B), the type of TB is named as Extensively Drug Resistant TB (XDR-TB). Average treatment success rate of these resistant TB cases is 55% globally (WHO, 2018).

Table 3.4 Second-line anti-TB drugs (WHO, 2016b)

Group A: Fluoroquinolones	**Group B: Second-Line Injectable Drugs**
Levofloxacin (Lfx)	Amikacin (Am)
Moxifloxacin (Mfx)	Capreomycin (Cm)
Gatifloxacin (Gfx)	Kanamycin (Km)
	(Streptomycin)
Group C: Other Core Second-Line Drugs	**Group D: Add-on Drugs**
Ethionamide/Prothionamide (Eto/Pto)	D1 Pyrazinamide
Cycloserine / Terizidone (Cs/Trd)	D1 Ethambutol (E)
Linezolid (Lzd)	D1 High-dose isoniazid (H^h)
Clofazimine (Cfz)	D2 Bedaquiline (Bdq)
	D2 Delamanid (Dlm)
	D3 p-aminosalicylic acid (PAS)
	D3 imipenem-cilastatin (lpm)
	D3 Meropenem (Mpm)
	D3 Amoxicillin-clavulanate (Amx-Clv)
	D3 Thioacetazone (T)

In RR-TB and MDR-TB, recommended treatment is a bundle of five effective TB drugs during the intensive phase: pyrazinamide and four core second-line drugs – one from Group A, one from Group B, and at least two from Group C. If the minimum number of effective drugs cannot be reached as given, one additional drug from Group D2 and other drugs from Group D3 is included to bring the total to five (WHO, 2016b). Recommended total treatment duration is 18 months and more, up to two years. In

XDR-TB, according to drug-susceptibility test results of the bacteria, the most effective treatment bundle is constructed by using the drugs to which the bacteria are not resistant. High-dose of first line drugs can be used also when there is no other chance of completing the treatment bundle.

A patient with tuberculosis may have resistance in two main ways; by contacting a resistant TB patient (i.e. Primary Resistance) or by failing in the previous TB treatment (i.e. Secondary Resistance). Globally, 3.5% of new TB cases and 18% of previously treated cases have MDR/XDR/RR-TB (WHO, 2018). If a patient has the history of previous TB treatment, it is relatively uncomplicated to foresee the current drug-resistance pattern since the drugs of the previous treatment are known. However, the diagnosis of primary resistant TB is highly challenging. Considering the primary resistant cases are only 3.5% of the total, until the drug-susceptibility test results are ready (in nearly 45 days), all new TB cases start with the standard TB treatment regimen. If the patient has primary resistance in the test results, the treatment is re-organized using second-line drugs and the patient returns to the beginning with 45 days of loss and a fatigued liver.

Determining the risk factors of resistance development in a TB patient is important to detect a patient with primary resistance without waiting for the results of the drug-susceptibility test. When the risk factors are detected, a decision support system can be constructed as a predictive model.

3.3.3 Risk Factors of Resistance

In order to assess the risk of multi-drug resistance, the factors that influence the resistance development are determined. These factors are not the risk factors of being infected with TB, but the risk factors of having primary resistance in a newly diagnosed TB patient. First, an in-depth literature research is conducted to find all the risk factors that have been investigated previously, and then three chest diseases experts are

interviewed, risk factors are classified and defined. Nine factors are determined as system concepts:

- *Age* (Chung-Delgado et al., 2011; da Silva Garrido et al., 2012; Talay et al., 2008): The patient's age in years. The resistance is more likely to develop in younger ages.
- *Substandard housing conditions* (Aibana et al., 2017; Franke et al., 2008): Substandard means homelessness, excessive household crowding etc. Housing conditions can be related to strength of immune system.
- *BMI* (Chung-Delgado et al., 2011; Franke et al., 2008): Low Body-Mass Index represents potential risk for many diseases.
- *History of MDR-TB Exposure* (Gler et al., 2012; Shariff et al., 2016): MDR-TB is reported as an infectious disease.
- *Presence of comorbidities* (Bastos et al., 2012; Tierney et al., 2014): All comorbid diseases as diabetes, hypertension etc., especially HIV, is associated with TB resistance risk.
- *Previous use of TB antibiotics* (Bastos et al., 2012): There exist the risk of resistance development for each antibiotic previously used.
- *Being an immigrant* (Elmi et al., 2015): Migration represent many risks like low income, poor health-care, etc.
- *History of imprisonment* (Aibana et al., 2017; Shariff et al., 2016): Prisons are dangerous in terms of infectious diseases.
- *History of travel to high-risk country* (Dessalegn et al., 2016): The 30 high MDR-TB burden countries are determined by WHO (WHO, 2015) to provide a focus for global action on the MDR-TB crisis in the countries where progress is most needed. The 20 countries with the highest estimated numbers of incident MDR-TB cases are: Bangladesh, China, DPR Korea, DR Congo, Ethiopia, India, Kazakhstan, Kenya, Indonesia, Mozambique, Myanmar, Nigeria, Pakistan, Philippines, Russian Federation, South Africa, Thailand, Ukraine, Uzbekistan, and Viet Nam. The additional 10 countries by estimated rate per 100 000 population and with a minimum number of 1000 cases per year are:

Angola, Azerbaijan, Belarus, Kyrgyzstan, Papua New Guinea, Peru, Republic of Moldova, Somalia, Tajikistan, and Zimbabwe.

3.3.4 Numerical Application

To obtain a conceptual map of the system and calculate the final values of the factors, three chest disease specialists of Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital are interviewed: Assoc. Prof. Esin Tuncay MD, Assoc. Prof. Gülfidan Aras MD and Tuğba Mandal MD. Relation and hesitation matrices of each expert are constructed as 9x9 matrices for pair-wise causal relations between each of the 9 concepts.

4 questions are asked to decision makers to define each causal relationship:

1) With respect to resistance development in a TB patient, does a positive change in Concept 1 create a change in Concept 2? (Yes or No)
2) Is this change positive or negative?
3) What is the strength of this change? (Low, Fair, High, Very High)
4) How much hesitation do you have on the information that you give? (Low, Fair, High, Very High)

The first three questions are common with FCM. In IFCM, an additional question is asked in order to represent hesitation degrees of the decision makers in the model.

Relation and hesitation degrees of Decision Maker 1 are given in Table 3.5. The diagonal elements of the matrix is zero, by definition, to avoid creating reinforce loops in the algorithm. For example, Decision Maker 1 responded that, a positive change in Age creates a *positively fair* change in Substandard Housing Conditions with respect to resistance development in a TB patient, and that she has *high* level of hesitation on this information. Linguistic terms of decision makers' responses are represented with intuitionistic fuzzy scales given in Figure 3.4 and Figure 3.5.

Table 3.5 Relation and hesitation degrees matrix of Decision Maker 1 (NVH: Negatively Very High, NH: Negatively High, NF: Negatively Fair, NL: Negatively Low, Z: Zero, PL: Positively Low, PF: Positively Fair, PH: Positively High, PVH: Positively Very High)

	Age		Sub.Hous. Cond.		BMI		MDR-TB.Exp		Comorb.		Prev.use. anti.		Immig.		Imprison.		Tra.high-risk.cou.	
	μ	π	μ	π	μ	π	μ	π	μ	π	μ	π	μ	π	μ	π	μ	π
Age	Z	Z	PF	H	PF	F	Z	L	PF	F	Z	Z	Z	Z	Z	Z	Z	Z
Sub.Hous. Cond.	Z	Z	Z	Z	PH	L	PH	L	PF	F	Z	L	PH	Z	PL	H	Z	Z
BMI	Z	Z	Z	L	Z	Z	Z	Z	PH	L	Z	L	Z	L	Z	Z	Z	Z
MDR-TB.Exp	Z	Z	PF	F	NL	F	Z	Z	Z	F	PF	L	Z	F	Z	F	Z	Z
Comorb.	Z	Z	Z	H	NL	H	Z	H	Z	Z	PF	Z	Z	H	Z	F	Z	Z
Prev.use. anti.	Z	Z	PL	H	NL	L	Z	L	NF	H	Z	Z	Z	H	Z	H	Z	Z
Immig.	Z	Z	PVH	Z	NF	L	PF	L	Z	H	PF	F	Z	Z	PL	F	PF	L
Imprison.	Z	Z	PF	L	NL	H	PF	L	PF	Z	PL	F	PL	F	Z	Z	Z	Z
Tra.high-risk.cou.	Z	Z	Z	L	Z	Z	PH	Z	Z	L	Z	L	Z	L	Z	L	Z	Z

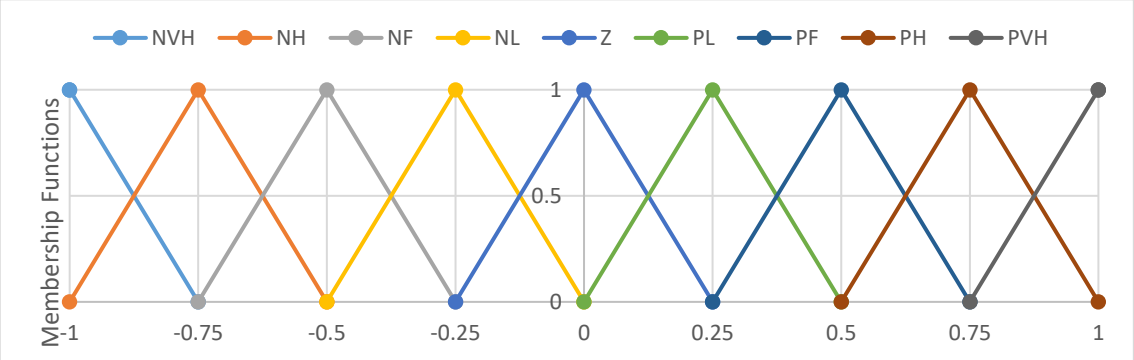

Figure 3.4 Linguistic variables of relation degrees (NVH: Negatively Very High, NH: Negatively High, NF: Negatively Fair, NL: Negatively Low, Z: Zero, PL: Positively Low, PF: Positively Fair, PH: Positively High, PVH: Positively Very High)

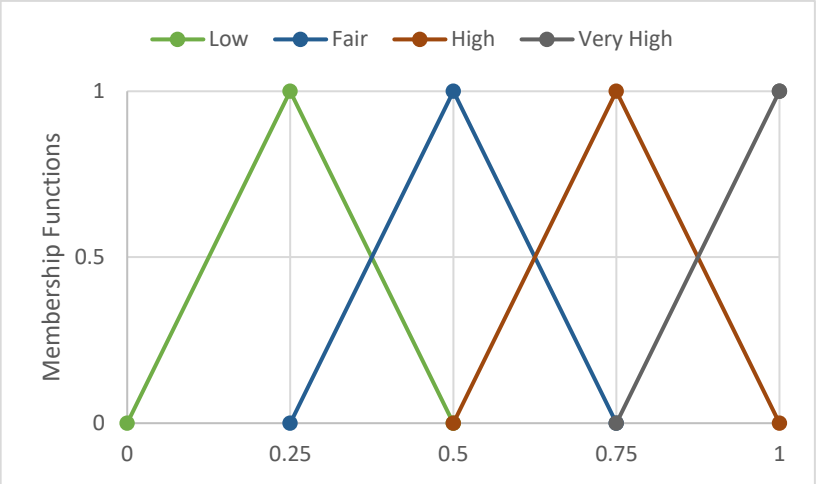

Figure 3.5 Linguistic variables of hesitation degrees

Three relation matrices and three hesitation matrices of three decision makers (DMs) are aggregated and defuzzified using max aggregation and centroid defuzzification methods. For example for the row “Age” and the column “BMI”, DMs responses are:

- DM1: Positively Fair Relation, Fair Hesitation
- DM2: Positively Fair Relation, Fair Hesitation
- DM3: Positively Low Relation, High Hesitation

The aggregated and defuzzified relation and hesitation values for the causal relationship of these two factors are 0.3750 and 0.6250, respectively.

For the row “Immigration” and the column “BMI”, DMs responses are:

- DM1: Negatively Fair Relation, Low Hesitation
- DM2: Negatively Low Relation, Fair Hesitation
- DM3: Negatively High Relation, Low Hesitation

The aggregated and defuzzified relation and hesitation values for the causal relationship of these two factors are -0.5000 and 0.3750, respectively. Hence, the influence weight and hesitancy weight matrices are obtained with aggregated and defuzzified values.

The weights of the map are calculated considering the concept weights defined in Equation (3.2) as w_{ji}^{μ}.(1-w_{ji}^{π}). Hence for the causal relation edges (Age → BMI) and (Immigration → BMI), the weight values are calculated as 0.1406 and -0.3125, respectively. Using the weight matrix, a conceptual map of the system is obtained as shown in Figure 3.6. An IFCM is a directed graph therefore; outdegree, indegree and centrality values of the system concepts/nodes can be evaluated through the weights of the edges, as given in Table 3.6.

Table 3.6 Outdegree, indegree and centrality values of the concepts

Concept	Outdegree	Indegree	**Centrality**
Age	0.99	0.00	0.99
Sub.Hous.Cond.	2.21	2.39	4.60
BMI	0.85	1.01	1.86
MDR-TB.Exp	1.63	3.08	4.71
Comorb.	1.52	1.84	3.36
Prev.use.TB anti.	1.05	2.33	3.38
Immig.	2.75	2.54	5.29
Imprison.	2.44	1.77	4.21
Tra.high-risk.co.	1.76	0.23	1.99

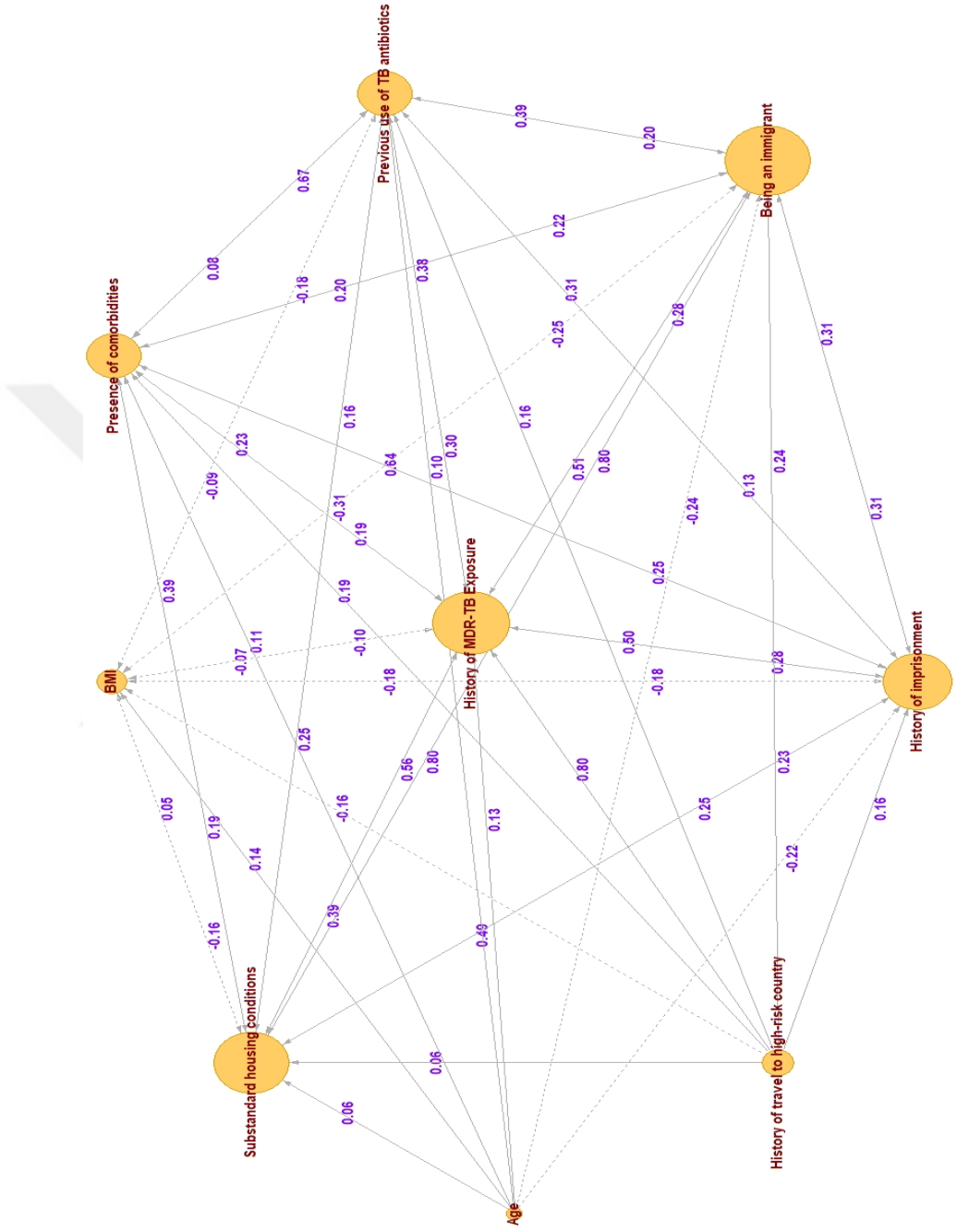

Figure 3.6 IFCM of MDR-TB Risk Factors

Briefly, in directed graphs, indegree is the number of arrows arriving to the node, outdegree is the number of those departing from the node, and centrality is the total number of edges that a node possesses. Centrality can be interpreted as the popularity of a concept in the system. In Figure 3.6, the sizes of concept nodes are adjusted by their centrality degrees.

“Being an immigrant” has the greatest centrality degree, 5.29, which shows that it is the most interacting node with other system concepts. Migration is one of the most important factors in the spread of infectious diseases. Migration brings poor living conditions and puts immigrants in a vulnerable position in terms of contagious diseases. Migration creates every kind of reason that will expose a person to the infection by weakening his/her immune system. In this respect, it is expected that this factor have the highest centrality in this system.

“Age” has the lowest centrality degree, 0.99. It is mostly because its indegree equals to zero, by definition. “Age” is a scale variable that only changes with time. None of the factors in the system can make any change to the age of a person. “Age” is a transmitter variable in the system that affects other concepts but not affected by them. It is predictable that the factor “Age” has a low degree of popularity in the network because of its constant increase in years.

Centrality degree should not be confused with node influence in the network. Centrality is calculated using influence weights and hesitancy weights of the edges. However, node influences are calculated using Equation (3.2) and the weights of the edges. It is an iterative process, which is terminated by the convergence of final values of all the nodes in the system.

For the iterations, the initial state vector is chosen as the vector of ones, assuming each concept is on state in the system, which means all the factors are equally active in the initial state of the network. The threshold function is chosen as tanh(x) providing an output interval of [-1, 1], which allows to observe positive and negative effects of the factors in the resistance development system. All the iterations are operated using

MATLAB Software and the final values are converged in 20 iterations, as shown in Table 3.7 with the ranking order of absolute values.

Table 3.7 Final values of the concepts and the ranking order

Concept	Value	**Concept**	Value
Age	0.2616	MDR-TB.Exp.	0.9989
Sub.Hous.Cond.	0.9973	Sub.Hous.Cond.	0.9973
BMI	-0.9221	Prev.use.TB.anti.	0.9967
MDR-TB.Exp.	0.9989	Immig.	0.9963
Comorb.	0.9910	Comorb.	0.9910
Prev.use.TB anti.	0.9967	Imprison.	0.9842
Immig.	0.9963	BMI	-0.9221
Imprison.	0.9842	Tra.high-risk.co.	0.7580
Tra.high-risk.co.	0.7580	Age	0.2616

“History of MDR-TB Exposure” has the greatest final value, and hence the greatest influence in the resistance development system. MDR-TB exposure means that the body recognizes resistant bacteria. If the body’s immunity is powerful when exposure occurs, resistant bacteria are inactivated in the lung but not excreted. Resistant bacteria may remain in the lung for many years asleep. When the immunity of the body, especially of the lungs, decreases due to weight loss, stress, pneumonia etc. these bacteria become active and start to multiply. Thus, if a patient with TB diagnosis has previously encountered resistant bacteria, it is highly likely to be MDR-TB. It is the most influencing factor of the resistance. However, it is challenging to determine the

occurrence of MDR-TB exposure if the patient has not exact information on a MDR-TB infected relative, colleague or acquaintance. In tuberculosis disease, a contact is defined as breathing the same air in a closed area for a long time with an active, infected and non-treated patient. If the patient does not reveal his/her condition, it is not possible to notice the exposure in the daily life. Since tuberculosis is an infectious disease, patients tend to hide their medical condition at work in order not to lose their jobs. According to chest disease specialists, if a TB patient knows exactly an acquaintance previously infected with MDR-TB, they usually have similar resistance conditions. If there is not a known case, then it is unlikely to estimate whether there is history of MDR-TB exposure or not. It is the most effective factor in the system and the most problematic to determine. On the other hand, it creates a critical advantage in estimating the resistance pattern, if there is a pre-determined case of exposure.

“Substandard housing conditions” has the second greatest influence in the system because it gathers many components that might weaken the immune system. Substandard housing conditions represent homelessness, excessive household crowding, lack of heating system, coldness, humidity, lack of hygiene and poverty. Homelessness, where housing conditions are considered the worst, makes a person vulnerable to all kind of diseases. In addition, homeless people are more likely to drink alcohol to stay warm outside, which yields serious problems as comorbid diseases by damaging the liver. Excessive household crowding increases the likelihood of disease transmission and decreases hygiene. Lack of heating system and humidity creates an environment that allows the bacteria to multiply easily. Moreover, poverty is usually the essential reason for not reaching proper healthcare. “Substandard housing conditions” has an extensive influence in the system by depressing the immune system and it is very simple to detect. The presence of this factor might be an advantage for the physician in predicting resistance with its power in the system and its simplicity in detection.

“Previous use of TB antibiotics” has the third rank of influence. Some of anti-TB drugs are commonly used is the treatment of other lung diseases, especially in chronic and recurrent pneumonia. There is a probability of resistance development in the body, for each type of antibiotic previously used. Hence, if the patient has a history of treatment

of a lung disease with TB antibiotics in his/her medical records, then the physician considers the probability of resistance to that group of antibiotics. Previous use of TB antibiotics is vital information for the TB patient's resistance pattern. Since antibiotics are not sold without prescription, the patients usually have the list of previously used antibiotics in their medical records. The existence of this factor in a patient is relatively effortless to notice.

"Being an immigrant", "presence of comorbidities" and "history of imprisonment" are following factors by means of influence. These three factors have relatively more indirect effects than the first group of three factors. Being an immigrant increases the probability of having substandard housing conditions. Presence of comorbidities, especially HIV, weakens the immune system of the body. History of imprisonment provides an environment for MDR-TB exposure. The effects of these three factors are less direct in the resistance development system however, they should not be eliminated from the conceptual map because their final values are greater than 0.98. An indirect effect is still an effect.

"BMI" is the only factor that has negative effect on resistance development. As the BMI falls below normal values, the body's immunity decreases, which makes the person vulnerable to development of resistance. In other words, when the BMI is reduced, the probability of resistance development increases. This situation creates an opposite influence of BMI in the system. The negative final value of BMI is a marker of the reliability of the numerical application.

"Travel to high risk country" is also related to the most influencing factor, MDR-TB exposure. Since it does not guarantee the occurrence of exposure, it has a smaller influence in the system.

"Age" has the smallest influence. 0.2616 is not a negligible value however; it is relatively very small when compared to other factors of the system. If the aim is to conduct a new statistical study with these factors, the presence of "Age" factor can be questioned.

3.3.5 Scenario Analyses

Scenario analysis is one of the most important advantages of cognitive mapping methods. Once the map is constructed and the final values are calculated, one or more concepts can be set as off state (to the value zero) to observe the rest of the system. Setting a concept as off state can be interpreted as elimination of the factor from the system by cancelling its influence. If only one factor is set as off state, more information about the system can be obtained by examining how the final values of the remaining factors change. Scenario analysis allows decision makers to ask "What if?" questions about the system.

Scenario analyses in this study are performed using FCMapper software, which is an Excel based mapping & modelling program freely available online at www.fcmappers.net.

Scenario 1: "Age" is off state.

Since "Age" has the smallest influence in the system, the first scenario is on its elimination from the map. Changes in other factors are shown in Table 3.8.

Table 3.8 Changes of Scenario 1 (1: Strong, 2: Medium, 3: Weak, 4: Very Weak)

Positive Changes	Strength	**Negative Changes**	Strength
Immig.	3	Sub.Hous.Cond.	4
Imprison.	2	BMI (-)	2
Tra.high-risk.co.	4	MDR-TB.Exp	4
		Comorb.	3
		Prev.use.TB.anti	3

According to Table 3.8, none of the factors showed a strong change after the elimination of “Age”. The factors, which interact with “Age”, have lost little influence that the others have gained. “History of imprisonment” and “BMI” had positive medium change in their influence. “Age” has more effect on other factors than “History of imprisonment”, therefore it gains most of the power that the others factors lose by interacting with “Age”. “BMI” gains importance because “Age” and “BMI” change in parallel direction in time. With elimination of “Age”, “BMI” gains power because it starts to represent two of them together. However, apart from these minor changes, the ranking order of the final values did not change. Hence, according to Scenario 1, the elimination of the factor “Age” does not affect the system significantly.

Scenario 2: “History of MDR-TB Exposure” is off state.

What will happen if the most influencing factor in the system is eliminated? This question is important for the chest disease specialists because in addition to resistance development, this factor has a certain influence on other factors too. Which one of the remaining factors will gain or lose power is valuable to understand the system thoroughly. Table 3.9 shows the changes in other factors in the absence of “History of MDR-TB Exposure”

When “History of MDR-TB Exposure” is off state, all the other factors lose power with mostly strong and medium strength. Being exposed to resistant bacteria means the body can recognize and reproduce resistance, hence it is a pillar of the resistance development system. It is a reinforcing concept. In its absence, the ranking order of the remaining concepts does not change however, their final values decrease dramatically.

Table 3.9 Changes of Scenario 2 (1: Strong, 2: Medium, 3: Weak, 4: Very Weak)

Positive Changes	Strength	**Negative Changes**	Strength
BMI	1	Age	1
		Sub.Hous.Cond.	2
		Comorb.	2
		Prev.use.TB anti.	2
		Immig.	2
		Imprison.	1
		Tra.high-risk.co.	3

Apart from elimination of the concepts, cognitive mapping allows for the individual analysis of each patient's condition in medical decision-making. For example, if a patient claims that he/she has never used any of the anti-TB drugs and has never been in prison, these two factors can be set as off state and the most influencing factors for this patient can be determined for a customized treatment planning. Scenarios 3 and 4 are two examples based on previous patient stories given by chest disease specialists.

Scenario 3: “Being an immigrant”, “History of imprisonment” and “History of travel to high-risk country” is off state.

Scenario 4: “Substandard housing conditions”, “Presence of comorbidities” and “Previous use of TB antibiotics” is off state.

For the patients in Scenarios 3 and 4, the final values and the ranking orders of the remaining concepts are given in Table 3.10. At first glance, it is observed that final values of the concepts are smaller than the values given in Table 3.7. The factors of the

system empower each other. When some of the factors are eliminated, the influence of the other factors on resistance development decreases.

Table 3.10 Final values of the concepts and the ranking order

Scenario 3		**Scenario 4**	
Concept	**Value**	**Concept**	**Value**
Prev.use.TB anti.	0.9769	MDR-TB.Exp	0.9901
MDR-TB.Exp	0.9668	Immig.	0.9569
Sub.Hous.Cond	0.9516	Imprison.	0.9439
Comorb.	0.9242	Tra.high-risk.co.	0.7510
Age	0.1212	Age	0.1212
BMI	-0.6029	BMI	-0.9145

The most noticeable change in Scenario 3 is that “MDR-TB Exp.” has regressed to second rank. The eliminated factors in Scenario 3 are all the most affecting factors of “MDR-TB Exp.”. In their absence, “MDR-TB Exp.” loses its power on the resistance development system and “Prev. use of TB anti.” becomes stronger. Hence, for the patients with these conditions, “Prev. use of TB anti.” might be the reason of having primary resistance. The drugs previously used, should not be included in the new treatment.

In Scenario 4, “MDR-TB Exp” is still the most influencing factor however, its final value is decreased. The patient in Scenario 4 is more difficult to diagnose than the patient in Scenario 3 is, because of the difficulty in determining the occurrence of exposure in a patient’s life.

3.3.6 Discussions on the Results

Tuberculosis is a growing problem of the world, especially with increasing rates of antibiotic resistance. There are two types of resistance in TB: primary resistance and secondary resistance. Primary resistance is developed by contacting an active, non-treated and resistant TB patient. Secondary resistance is developed by failing in a previous TB treatment. In this chapter, an intuitionistic fuzzy cognitive map model is applied in order to assess the risk factors of primary resistance in a newly diagnosed TB patient.

By means of an in-depth literature survey and many interviews with three chest disease specialists, 9 factors are determined and defined as the concepts of resistance development system: Age, substandard housing conditions, BMI, history of MDR-TB exposure, presence of comorbidities, previous use of TB antibiotics, being an immigrant, history of imprisonment and history of travel to high risk country. Using linguistic terms, the relation and hesitation degrees of the causal relationships among these concepts are identified by the decision makers. The degrees are represented by Atanassov's intuitionistic fuzzy numbers in the numerical application and three matrices are formed for three decision makers. For each element of the matrix, in other words for each causal relationship, the relation and hesitation degrees are aggregated and defuzzified. A conceptual map of the resistance development system is obtained. To find the influences of the concepts, the iterative procedure of IFCM is initiated and the final values of the concepts are calculated. History of MDR-TB exposure, substandard housing conditions, and previous use of TB antibiotics had the greatest influence values in the system.

IFCM method is a structuring tool and it is highly useful in putting the information that exists in human brain on paper. The decision makers not only reflect their experience on the system but also they can express their hesitations on the information that they give. Especially in medical decision-making, the physicians are used to work with statistical information. Since no data is required in IFCM, the physicians feel more comfortable when hesitation degrees are considered in the model.

When the results are discussed with the decision makers, they stated their total agreement with the results. The results and the ranking order were expected however, the ability of analyzing new scenarios for each patient was unexpected. They pointed out the usefulness of the model in daily decisions of newly diagnosed TB patients.

IFCM method is advantageous in structuring human knowledge however, it is subjective and its results cannot be validated if it remains at this stage. As further research, statistical data should be collected in order to demonstrate the influences of the factors and to construct predictive models.

4. LENGTH OF STAY PREDICTORS ASSESSMENT IN COPD WITH THE NOVEL STATISTICAL-BASED FUZZY COGNITIVE MAPS

COPD is one of the most common chronic respiratory diseases with various clinical presentations, which is characterized by airflow limitations because of diverse problems in airways and other components of the lung. It is a multicomponent disease with extra-pulmonary effects (Pauwels et al., 2001). COPD, which defines an umbrella term to diagnose “chronic bronchitis” and “emphysema”, is not a completely curable disease and airflow limitations are progressive, however, the disease is preventable and several treatments exist that help enlarge major air passages and improve respiration of COPD patients. The widespread symptoms are a long-term cough, producing excessive sputum, and shortness of breath. According to the latest WHO report, COPD has the second highest prevalence among chronic respiratory diseases after asthma, it affects 210 million people (WHO, 2007) and it is projected to be the third cause of mortality by 2030 (Mathers & Loncar, 2006).

COPD is a global burden which induces many decision-making problems such as healthcare system management (Adeyemi et al., 2013), diagnostic classification (Badnjevic et al., 2015; Moghadas-Dastjerdi, Ahmadzadeh, Karami, et al., 2017), disease progression monitoring (Exuzides et al., 2017; Tabberer et al., 2017), risk assessment (Demir, 2014), hospital organization (Alshabanat et al., 2017), forecasting (Ryynänen et al., 2013) etc.

The COPD publications involving decision support systems in the last decade are listed and classified in Table 4.1.

Table 4.1 Publications of Medical Decision-Making in COPD

Title	**Field**	**Journal**	**Method**
(Akl et al., 2007)	Steroid Therapy	BMC Medical Informatics and Decision Making	Expected Utility Theory
(Hajizadeh et al., 2010)	Patient Informing	BMC Medical Informatics and Decision Making	Decision Tree
(Smidth et al., 2012)	Diagnosis	BMC Medical Informatics and Decision Making	Statistics
(Adeyemi et al., 2013)	System Management	Decision Support Systems	Random Effects Modeling
(Burkow et al., 2013)	Patient Acceptability	BMC Medical Informatics and Decision Making	Statistics
(Ryynänen et al., 2013)	Mortality	BMC Medical Informatics and Decision Making	Bayesian Model
(Demir, 2014)	Readmission Risk	Decision Sciences	Statistics
(Vemer et al., 2014)	Patient Heterogeneity	Medical Decision Making	Markov Model
(Badnjevic et al., 2015)	Classification	BMC Medical Informatics and Decision Making	Fuzzy Logic and Neural Networks
(Elkhenini et al., 2015)	Clinical Trials	BMC Medical Informatics and Decision Making	Statistics
(Hardinge et al., 2015)	Mobile Application	BMC Medical Informatics and Decision Making	Statistics
(Rosenbek Minet et al., 2015)	Counselling	BMC Medical Informatics and Decision Making	Statistics
(Hoaas et al., 2016)	Tele-rehabilitation	BMC Medical Informatics and Decision Making	Statistics
(Briggs et al., 2017)	Data Extraction	Medical Decision Making	Statistics and Risk Model
(Exuzides et al., 2017)	Data Extraction	Medical Decision Making	Statistics
(Hajizadeh et al., 2017)	Information Communication	Medical Decision Making	Statistics
(Middlemass et al., 2017)	Home tele-monitoring	BMC Medical Informatics and Decision Making	Statistics
(Moghadas-Dastjerdi, Ahmadzadeh, Karami, et al., 2017)	GOLD Stage Assessment	Expert Systems with Applications	Naive Bayes Classification
(Moghadas-Dastjerdi, Ahmadzadeh, & Samani, 2017)	Classification	Expert Systems with Applications	Image Thresholding
(Tabberer et al., 2017)	Disease Progression	Medical Decision Making	Delphi Method
(Velardo et al., 2017)	Digital Health System	BMC Medical Informatics and Decision Making	Statistics

Medical decisions are naturally originated from personal experience of the physician and statistical analysis of previous data. If perceived as a process, Medical Decision Making involves three main steps: (1) Using statistical methods to understand general behavior of the system, (2) consulting other physicians, and (3) making the final decision with personal opinion. A decision made using only the statistics of the collected data would be incomplete and overly objective without the physician's interpretation, on the other hand, a decision made using only the physician's opinion would be overly subjective and incomplete. Thereupon, a proper medical decision must be a combination of expert judgment and data analysis for accurate detection, certain diagnosis and effective treatment.

In mostly cited COPD literature, statistical methods are used for COPD management aiming to analyze the global burden (Lozano et al., 2012), construct a global disease management strategy (Rabe et al., 2007), set the treatment standards (Celli, MacNee, et al., 2004), predict the risk of death (Celli, Cote, et al., 2004), observe drug's effect on survival (Calverley et al., 2007), and examine the pathological effects (Hogg et al., 2004). Statistical information coming from the past has a key role in medicine in terms of knowledge management and physicians are accustomed to working with statistical results. Statistical methods are usually preferred in medical literature based on their advantage of simplicity and objectivity. However, previous data are hardly projected to the future unless they are merged with actual information originated from the physician's experience and personal opinion.

On the other hand, because of its structural advantages in revealing the behavior of complex systems, and in capturing human judgment by means of fuzzy information, FCM and its extensions are widely used in medical decisions. In the last two decades, FCM is used in radiation therapy planning (Papageorgiou, E. I. et al., 2003), bladder tumor grading (Papageorgiou, E. I., Stylios, et al., 2007b), thyroid diagnosis (Papageorgiou, E. I., Papandrianos, et al., 2008), brain tumor characterization (Papageorgiou, E. I., Spyridonos, et al., 2008), pneumonia severity assessment with intuitionistic extension (Iakovidis & Papageorgiou, 2011) and, breast cancer risk factors assessment (Buyukavcu et al., 2016). FCM is a useful decision-making tool regarding

medical problems however; it is solely based on expert judgment and intrinsically subjective. Lack of statistical information and the difficulty of collecting expert opinion data can be considered as major drawbacks of FCM method.

In this chapter, a novel approach called Statistical-Based Fuzzy Cognitive Map is proposed which aggregates the power of statistical analysis with dynamical nature FCMs. SBFCM method conducts statistical analysis to prepare preliminary information for the experts and then collects expert opinions accordingly, in order to define a conceptual map of the system. It first extracts the relationships from the data, and then inserts expert opinion to construct a frame so that the resulting system becomes semi-subjective. SBFCM is the very first method that unites two effective methods in medicine; statistics and fuzzy cognitive mapping. In brief, the contribution of this study arises from its integrated approach as a decision support system.

Altogether, the SBFCM method is developed in this chapter in order to evaluate the factors that affect the length of hospital stay of COPD patients that apply to the hospital with an acute exacerbation. Fifty factors, including LoS, are adopted as system concepts and observed under four groups: Socio-Demographics (age, gender, exposures etc.), Clinical Findings (blood tests, respiratory function tests etc.), Comorbidities (diabetes, heart diseases etc.), and Medical Records (years of illness, respiratory machine usage etc.). Medical data of 154 patients for all system concepts are collected in Yedikule Chest Diseases and Thoracic Surgery Training & Research Hospital in Istanbul / Turkey. Statistical analysis is conducted to determine the relationships between the system concepts and statistical tests are performed to extract all significant relationships. Statistical results are prepared as a preliminary data for the experts. Afterwards, three experienced physicians of the hospital provided medical support with their expert opinion. Experts defined the causalities among the significant relationships thus, a conceptual map of the system is provided. System behavior is observed, the most powerful factors on LoS are determined through iterative steps and different scenarios suggested by the experts are generated for an in-depth understanding of the system.

4.1 Length of Stay in Acute Exacerbation of COPD

Due to its growing morbidity and mortality, COPD is an economic burden on the world (Lozano et al., 2012). High use of resources and costs are associated to COPD (Mannino et al., 2015). In 2016, total health expenditure of Turkey amounted to 119.756 million TL, which is 4.6% of the gross domestic product, and 53% of these expenditures appertain to hospitals (TurkStat, 2017). Coupled with this fact, COPD is reported as one of the most costly diseases in 2017, along with diabetes and ischemic heart disease (Kılıç, 2017).

An acute exacerbation of COPD is defined as sudden development of respiratory symptoms with malfunctioning of airways. Acute exacerbations frequently result in hospital admission of patients. It is estimated that hospital expenditures correspond to 70% of total costs of COPD management and the length of hospital stay is directly related to these expenditures (Diamantea et al., 2014). Aiming to reduce LoS, guidelines are developed (Kong et al., 1997), predicting factors are observed (Diaz-Peromingo et al., 2004), protocols (LaRoche et al., 2016), programs (Alshabanat et al., 2017) and care bundles (Parikh et al., 2016) are proposed, however in such a complex system, it is critical to differentiate between simultaneous changes in variables and cause-and-effect relationships. For example, on a patient level, a longer LoS for COPD hospitalizations was associated with higher risk for readmission which is likely confounded by the severity of the illness (Rinne et al., 2017).

In this chapter, for a clear understanding of the system behavior, all the factors that might have an effect on the LoS of a COPD patient are derived from COPD literature and classified into four groups: Socio-Demographics, Clinical Findings, Comorbidities and Medical Records. Since patient data would be collected for all the factors, their units (years, days, cm, etc.) and variable types (Nominal, Ordinal, and Scale) are determined. A variable can be treated as nominal (N) when its values represent categories with no intrinsic ranking, as ordinal (O) when its values represent categories with some intrinsic ranking and as scale (S) when its values represent ordered categories with a meaningful metric.

Group 1: Socio-Demographics

- Age (Years): Patient's age in years. (S) (Agboado et al., 2012)
- Male Gender: This variable is 1 if the patient is male, and 0, otherwise. (N) Previously, women are seen to stay longer periods than men (Pérez-Hoyos et al., 2000) and elderly women have the longest inpatient periods (Saynajakangas et al., 2004).
- Occupational Exposure: This variable is 1 if the patient has ever been exposed to hazardous substances in the air of workplace, and 0, otherwise. (O)
- Height (cm): Patient's height in centimeters. (S)
- Weight (kg): Patient's weight in kilograms. (S) Nutritional supplementation may be associated with reduced LoS (Snider et al., 2015).
- Smoking: This variable is 1 if the patient is a current smoker, 0.5 if the patient is an ex-smoker and 0 if the patient has never smoked. (O) Longer LoS is demonstrated for the current and former smokers (Rezaei et al., 2016).
- Biomass Exposure: This variable is 1 if the patient has ever been exposed to household air pollution caused by biomass fuel (coal, animal dung, wood, crop residues etc.) especially in rural areas, and 0, otherwise. (O) [33](Diette et al., 2012)
- Passive Smoker: This variable is 1 if the patient is usually exposed to any kind of tobacco smoke, and 0, otherwise. (O)
- Pack-Years: This variable is calculated by multiplying the number of packets of cigarettes the patient smokes/smoked in a day by the number of years the patient has been smoking. (S)

Group 2: Clinical Findings

- Glucose/Blood Test: The glucose level in the blood of the patient. (S)
- Urea/Blood Test: Urea level in the blood of the patient. (S)
- Creatinine/Blood Test: Creatinine level in the blood of the patient. (S)
- TOT PROT/Blood Test: Total protein level in the blood of the patient. (S)
- ALB/Blood Test: Albumin level in the blood of the patient. (S) Low serum albumin level has been associated with a prolonged LoS (Wang et al., 2014).
- CRP/Blood Test: C-reactive protein level in the blood of the patient. (S)
- ESR/Blood Test: Erythrocyte sedimentation rate of the blood of the patient. (S)
- WBC/Blood Test: White blood cell count of the patient. (S)
- HGB/Blood Test: Hemoglobin level in the blood of the patient. (S)
- HCT/Blood Test: Hematocrit level in the blood of the patient. (S)
- PLT/Blood Test: Platelet count in the blood of the patient. (S)
- AST/Blood Test: Aspartate aminotransferase level in the blood of the patient. (S)
- ALT/Blood Test: Alanine aminotransferase level in the blood of the patient. (S)
- FEV-1 Test Result: FEV-1 (Forced Expiratory Volume in 1 second) respiratory function test results of the patient. (S)
- FEV-1/FVC Test Result: FEV-1/Forced Vital Capacity respiratory function test results of the patient. (S)
- GOLD Stage: Patient's airflow limitation severity in COPD according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) scale. Stage 1: Mild, Stage 2: Moderate, Stage 3: Severe, Stage 4: Very Severe. (O) [2] Longer LoS has been associated with GOLD Stage (Ruparel et al., 2016; Wong et al., 2008).

- PH/Blood Gas: pH (the degree of acidity) of the blood of patient measured with blood gas test. (S)
- CO2/Blood Gas: Amount of carbon dioxide in the blood of patient measured with blood gas test. (S)
- O2/Blood Gas: Amount of oxygen in the blood of patient measured with blood gas test. (S)
- SPO2/Blood Gas: Oxygen saturation of the blood of the patient. (S)
- Cyanosis: This variable is 1 if the patient has cyanosis in examination findings, and 0, otherwise. (O)
- Breaths per minute: The number of breaths the patient takes in one minute. (S)
- Number of pulses per minute: The number of heartbeats of the patient in one minute. (S)

Group 3: Comorbidities

- Pretibial Myxedema: This variable is 1 if the patient has pretibial myxedema in examination findings, and 0, otherwise. (O)
- Charlson Comorbidity Index Score: The degree of comorbid conditions which may have an influence on mortality of the patient according to Charlson Comorbidity Index (CCI) (Charlson et al., 1987). (S) CCI has been used as a predictor of LoS (Diamantea et al., 2014).
- Other Lung Disease: This variable is 1 if the patient has other lung diseases than COPD (lung cancer, tuberculosis etc.), and 0, otherwise. (O)
- Hypertension: This variable is 1 if the patient has hypertension problem, and 0, otherwise. (O)

- Diabetes Mellitus: This variable is 1 if the patient has diabetes, and 0, otherwise. (O) It is suggested that comorbid DM prolongs LoS of COPD patients (Parappil et al., 2010).
- Ischemic Heart Disease: This variable is 1 if the patient has ischemic heart disease, and 0, otherwise. (O)
- Cardiac Insufficiency: This variable is 1 if the patient has cardiac insufficiency, and 0, otherwise. (O)

Group 4: Medical Records

- Years of illness: The number of years that the patient is suffering from COPD. (S)
- Having treatment properly: This variable is 1 if the patient claims that he/she is taking his/her COPD treatment properly, and 0, otherwise. (Right medication at the right time) (S)
- Nebulizer at home: This variable is 1 if the patient has a nebulizer machine at home, and 0, otherwise.(O)
- O2 at home: This variable is 1 if the patient has an oxygen concentrator machine at home, and 0, otherwise. (O)
- BiPAP at home: This variable is 1 if the patient has a Bi-level Positive Airway Pressure machine at home, and 0, otherwise. (O)
- Re-hospitalization in 15 days: This variable is 1 if the patient has ever been re-hospitalized in 15 days, after being discharged from the hospital, and 0, otherwise. (O)
- Emergency admissions in the last year: The number of emergency service visits of the patient by COPD related causes in the last 12 months. (S)
- Need of NIMV in hospital (Days): Total number of days that the patient needs Non-Invasive Mechanical Ventilation machine during the hospital stay. (S)

- Total number of hospitalization: The total number of hospitalization of the patient by COPD related causes. (S)

- Dyspnea Level - mMRC Survey: Dyspnea severity of the patient according to modified Medical Research Council scale [33] which is a questionnaire that consists of five statements about perceived breathlessness of the patient: Grade 1, “I only get breathless with strenuous exercise”; Grade 2, “I get short of breath when hurrying on the level or up a slight hill”; Grade 3, “I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level”; Grade 4, “I stop for breath after walking 100 yards or after a few minutes on the level”; Grade 5, “ I am too breathless to leave the house”. (O) Dyspnea level has been used as a predictor of LoS (Diamantea et al., 2014; Quintana et al., 2015).

- Length of Stay (Days): The number of days the patient spent in the hospital. (S)

4.2 The Proposed SBFCM Methodology

Every linear regression contains a correlation; however, not every correlation implies a regression relation. Especially in medical decision making, it is fundamental to collect, analyze and interpret data. Accordingly, it is vital to distinguish between correlation and cause-effect relationships while processing this data. There exists a certain prevalence of the correlation coefficient in the medical literature. Even though correlation provides information on linear dependence of two factors, it does not fully attain to clarify the causal interrelations. Correlation needs to be interpreted by experienced physicians.

On the other hand, conventional FCMs are solely based on expert opinion and they ignore all previous statistical results, which are imperative in medical research. SBFCM has an integrated methodology that collects and analyzes patient data, finds correlations and then consults experienced physicians to construct a conceptual map of the system.

Incorporating statistical data into the method has two major advantages; first, as mentioned earlier, statistical data provides objectivity to FCMs. Furthermore, in FCMs, if the system has n number of concepts, an expert must fill in an n-by-n matrix for double-sided causal relationships. As the number of systems concepts increases, it becomes much more difficult for experts to express their opinion clearly. In complex systems, expert information tends to be blurred and out-of-focus. SBFCM method conducts statistical tests to analyze the correlations between concepts and eliminates insignificant relationships from the matrix; hence, it primarily reduces the number of cells that the expert must fill. It also helps the expert by revealing all the correlation coefficients between concepts. Flow-chart of SBFCM methodology is given in Figure 4.1 and its process in two parts is as follows:

Process 1: Statistical Analyses

1) The elements of the system are determined by an in-depth literature survey and experts' opinion. Essentially, all the risk factors for the disease and all the indicators (tests, clinical findings, comorbidities etc.) observed by physicians while diagnosing are adopted as the concepts of the system.

2) For every concept, patients' data are collected in the hospital. Linguistic data are converted to numeric data and defined as scale, ordinal or nominal variables. Let n be the number system concepts and m be the number of patients, then a data matrix with m rows and n columns is obtained. In order to have a decent statistical analysis, sample size m must be greater than 30. (In this study, m=154 and n=50.)

3) Bi-variate Pearson correlation coefficients between n concepts are calculated and an n-by-n symmetric matrix, namely the *Correlation Matrix*, is obtained. Statistical tests are conducted with 0.05 significance level using SPSS software.

4) Correlations with P-value greater than 0.05 are eliminated from the matrix and all significant correlations in the nxn matrix are prepared as preliminary data for the experts.

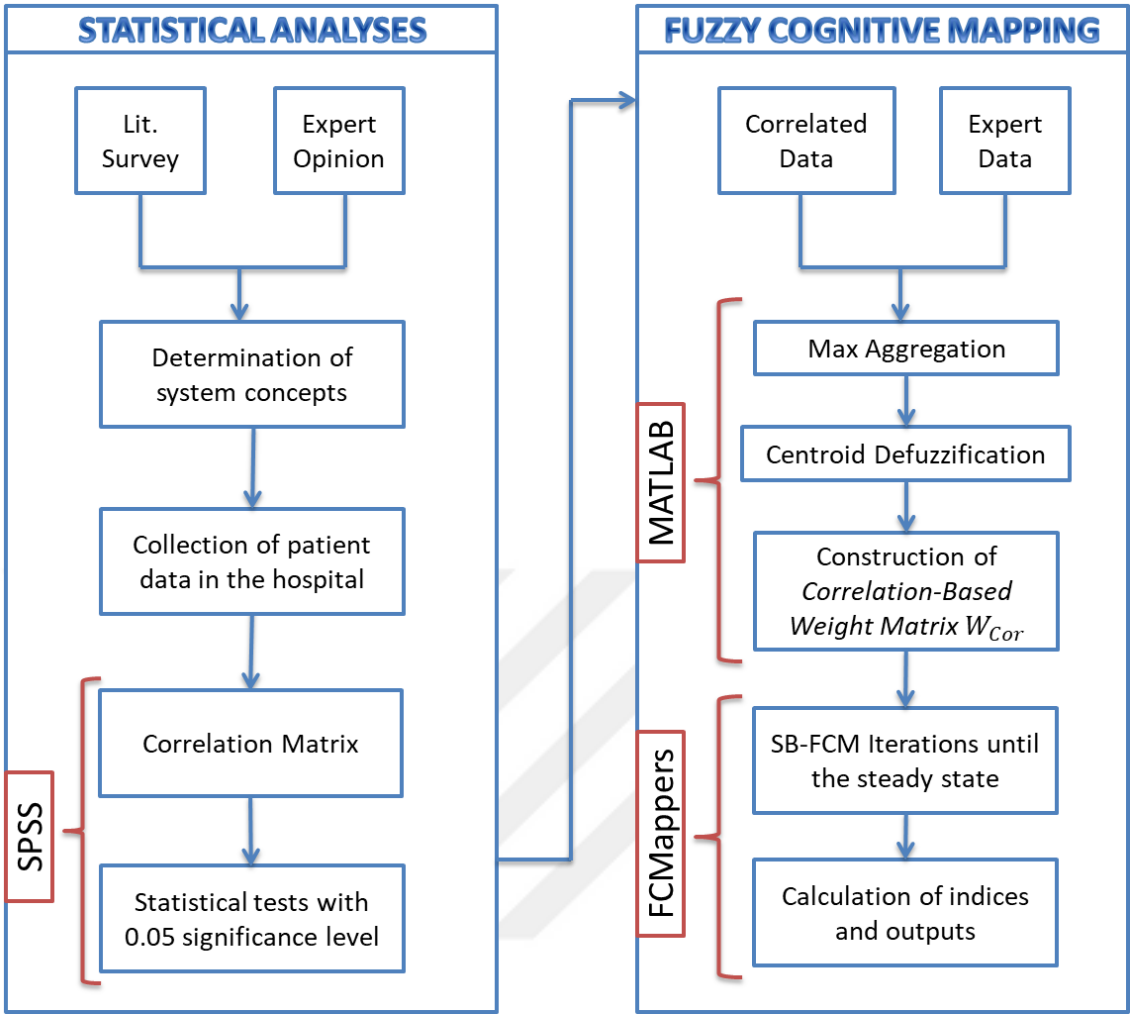

Figure 4.1 Flow-chart of SBFCM Methodology

Process 2: Fuzzy Cognitive Mapping

1) In the nxn matrix, the experts evaluated only the cells with significant correlations. Given the information of correlation coefficients between two concepts, the experts determine the existence (relation-no relation), direction (positive-negative) and importance (Weak-Medium-Strong-Very Strong) of causal relationships regarding the domain variable (LoS).

2) In each expert's decision matrix, linguistic terms are replaced with fuzzy numbers using a pre-determined fuzzy linguistic scale. Using max aggregation and centroid

methods, all experts' opinion is aggregated and defuzzified with MATLAB software. Hence, the *Correlation-Based Weight Matrix* W_{Cor} is constructed and SBFCM of the system is obtained.

3) SBFCM indices (indegree, outdegree, and centrality) are calculated using FCMappers software (www.fcmappers.net).

4) Iteration process starts with unit vector, which means initially all concepts are "on state", and the values of the concepts are updated using Equation (4.1):

$$V^i = f(V^{i-1}W_{Cor} + V^{i-1}) \tag{4.1}$$

where V^i is the state vector of all concept values at iteration i, V^{i-1} is the state vector of all concept values at iteration i-1, and f is the threshold function tanh(x). When the iterations reach the steady state, final values of concepts are determined.

4.3 Real-Case Numerical Application

Aiming to determine the most critical factors affecting the LoS of a patient suffering from COPD and measuring the strength of their effect, the first application of SBFCM method is conducted in Yedikule Chest Diseases and Thoracic Surgery Training & Research Hospital with 154 patients that applied to the hospital with an acute exacerbation between November 2011 and August 2012. Three experienced physicians of the hospital, Assoc. Prof. Esin Tuncay MD, Assoc. Prof. Gülfidan Aras MD and Zehra Dilek Kanmaz MD gave countenance to the application with their expert opinion.

Process 1: Statistical Analyses

1) First, the COPD literature is reviewed and all risk factors for the disease that may have an influence on the LoS are listed. 63 factors are determined and then experts

excluded 13 dependent factors. 50 factors including LoS (domain) defined in Section 4.1 are adopted as system concepts.

2) Patients' data for all system concepts are collected as shown in Table 4.2 and converted to numeric data in SPSS (154x50 matrix) as shown in Table 4.3.

Table 4.2 Sample Patient Data

	1) Age	2) Gender	3) Occ.Exp.	4) Heig.	5) Weig.	…	49) Car. Insuf.	50) LoS
Patient 1	73	Male	Yes	173	60	…	Yes	4
Patient 2	65	Male	Yes	165	65	…	No	9
Patient 3	42	Male	No	164	50	…	No	3
…	…	…	…	…	…	…	…	…
Patient 153	57	Female	No	160	90	…	No	5
Patient 154	50	Male	Yes	157	97	…	Yes	10

Table 4.3 Sample Numeric Data

1) Age	2) Male Gender	3) Occ.Exp.	4) Heig.	5) Weig.	…	49) Car. Insuf.	50) LoS
73	1	1	173	60	…	1	4
65	1	1	165	65	…	0	9
42	1	0	164	50	…	0	3
…	…	…	…	…	…	…	…
57	0	0	160	90	…	0	5
50	1	1	157	97	…	1	10

3) In SPSS software, Correlation Matrix is calculated, coefficients are tested and significant correlations with P-value lower than 0.05 are flagged as shown in Table 4.4.

Table 4.4 A Part of Correlation Matrix (SPSS Output)

	Age	Male	Occ.Exp.	Heig.	Weig.	…	Car.Ins	LoS
Correlation	1	-.024	.023	-.099	-.197*	…	.077	.039
P-value		.770	.781	.223	.014	…	.344	.630
Sample Size	154	154	154	154	154	…	154	154
Correlation	-.024	1	.358*	.632*	-.041	…	-.223*	.118
P-value	.770		.000	.000	.616	…	.006	.143
Sample Size	154	154	154	154	154	…	154	154
Correlation	.023	.358*	1	.155	-.053	…	-.108	.067
P-value	.781	.000		.055	.517	…	.182	.406
Sample Size	154	154	154	154	154	…	154	154
Correlation	-.099	.632*	.155	1	.234*	…	-.065	-.031
P-value	.223	.000	.055		.004	…	.422	.704
Sample Size	154	154	154	154	154	…	154	154
Correlation	-.197*	-.041	-.053	.234*	1	…	.404*	-.112
P-value	.014	.616	.517	.004		…	.000	.166
Sample Size	154	154	154	154	154	…	154	154
	…	…	…	…	…	…		
Correlation	.077	-.223*	-.108	-.065	.404*	…	1	-.004
P-value	.344	.006	.182	.422	.000	…		.960
Sample Size	154	154	154	154	154	…	154	154
Correlation	.039	.118	.067	-.031	-.112	…	-.004	1
P-value	.630	.143	.406	.704	.166	…	.960	
Sample Size	154	154	154	154	154	…	154	154

4) Insignificant correlations are eliminated from the matrix and preliminary data is prepared as shown in Table 4.5.

Table 4.5 Significant Correlations (P-value<0.05)

	Age	Male	Occ.Exp.	Heig.	Weig.	…	Car.Insuf.	LoS
Age	1				-.197	…		
Male		1	.358	.632		…	-.223	
Occ. Exp.		.358	1			…		
Heig.		.632		1	.234	…		
Weig.	-.197			.234	1	…	.404	
…	…	…	…	…	…	…		
Car.Insuf.		-.223			.404	…	1	
LoS						…		1

Statistical tests revealed that LoS have significant correlations with 7 factors: Nebulizer at home (.258), O2 at home (.239), Need of NIMV in hospital (.435), Total number of hospitalization (.246), ALB (-.258), WBC (.197), and Dyspnea Level – mMRC Survey (.231). This information might be useful while envisaging LoS of a patient, yet it is not sufficient to structure the whole system. Expert opinion is needed in order to observe cause-and-effect relationships and make predictions that are more accurate.

Process 2: Fuzzy Cognitive Mapping

1) Three experts filled three matrices given with preliminary information as shown in Table 4.6. (NVS: Negatively Very Strong Causal Relation, NS: Negatively Strong, NM: Negatively Medium, NW: Negatively Weak, Z: Zero – No Causal Relation,

PW: Positively Weak, PM: Positively Medium, PS: Positively Strong, PVS: Positively Very Strong)

Table 4.6 A Part of Expert Opinion Matrix of Expert 1

	Age	Male	Occ.Exp.	Heig.	Weig.	…	Car.Insuf.	LoS
Age					-.197 **NM***	…		
Male			.358 PS	.632 PM		…	-.223 Z	
Occ. Ex		.358 Z				…		
Heig.		.632 Z			.234 P M	…		
Weig.	-.197 Z			.234 Z		…	.404 PM	
	…	…	…	…	…	…		
Car. Ins.		-.223 Z			.404 Z	…		
LoS						…		

2) Linguistic influence degrees are replaced with triangular fuzzy numbers according to the scale (Buyukavcu et al., 2016) given in Figure 4.2.

As marked in Table 4.6, Expert 1 claims a “Negatively Medium” causal relationship from the concept “Age” to the concept “Weight”. Expert 2 and Expert 3 claim “Negatively Weak” and “No Relation”, respectively. Three experts’ opinion is aggregated and defuzzified for all the causal relations as shown in Figure 4.3.

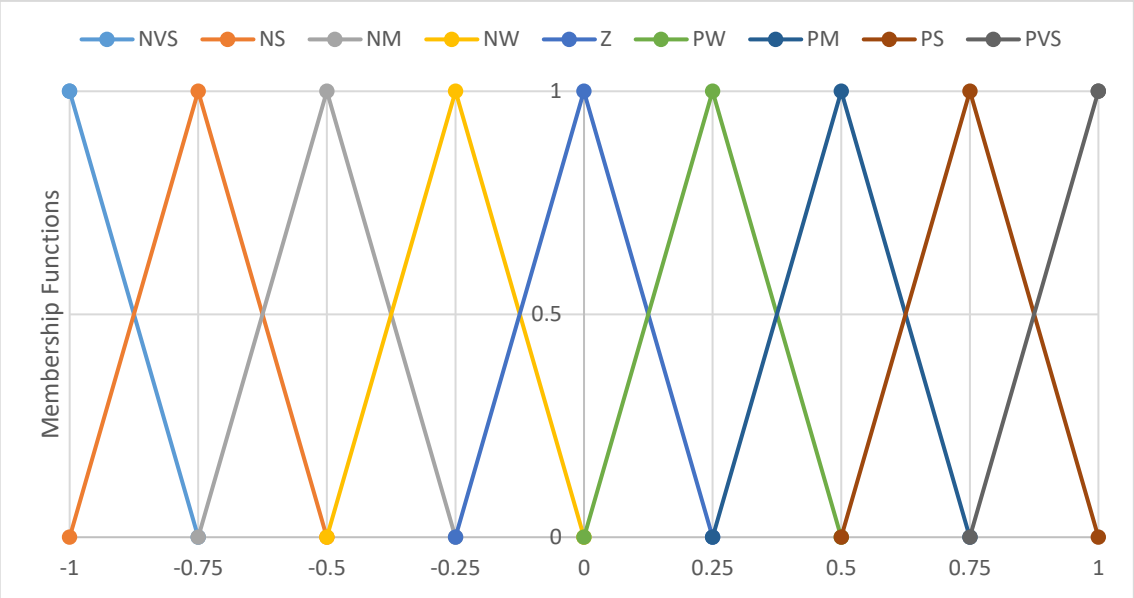

Figure 4.2 Fuzzy Linguistic Scale

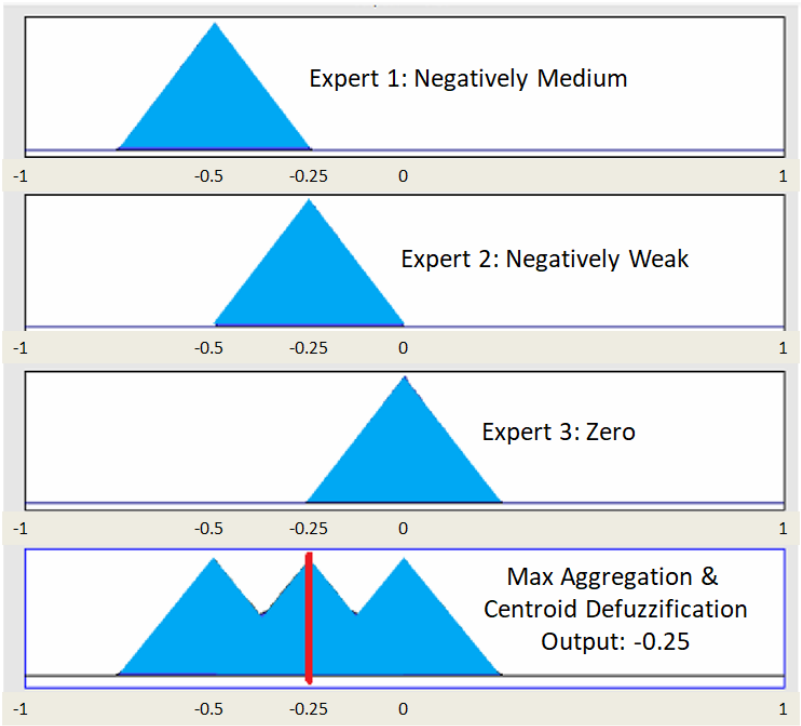

Figure 4.3 Max Aggregation and Centroid Defuzzification

Correlation-Based Weight Matrix W_{Cor} is constructed using MATLAB with defuzzification outputs (Output of Figure 4.3 is marked):

$$W_{Cor} = \begin{bmatrix} 0 & 0 & 0 & 0 & \mathbf{-0.25}^{*} & \dots & 0 & 0 \\ 0 & 0 & 0.35 & 0.25 & 0 & \dots & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \dots & 0 & 0 \\ 0 & 0 & 0 & 0 & 0.40 & \dots & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \dots & 0.25 & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & 0 & 0 & \dots & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \dots & 0 & 0 \end{bmatrix}$$

SBFCM is obtained as shown in Figure 4.4 (Node sizes are drawn up based on the centrality degrees and edges are colored with a grey-scale based on the W_{Cor} values).

3) SBFCM indices are calculated: The total number of factors is 50 and the total number of connections is 183 on the map. Outdegree, indegree, and centrality indices are shown in Table 4.7.

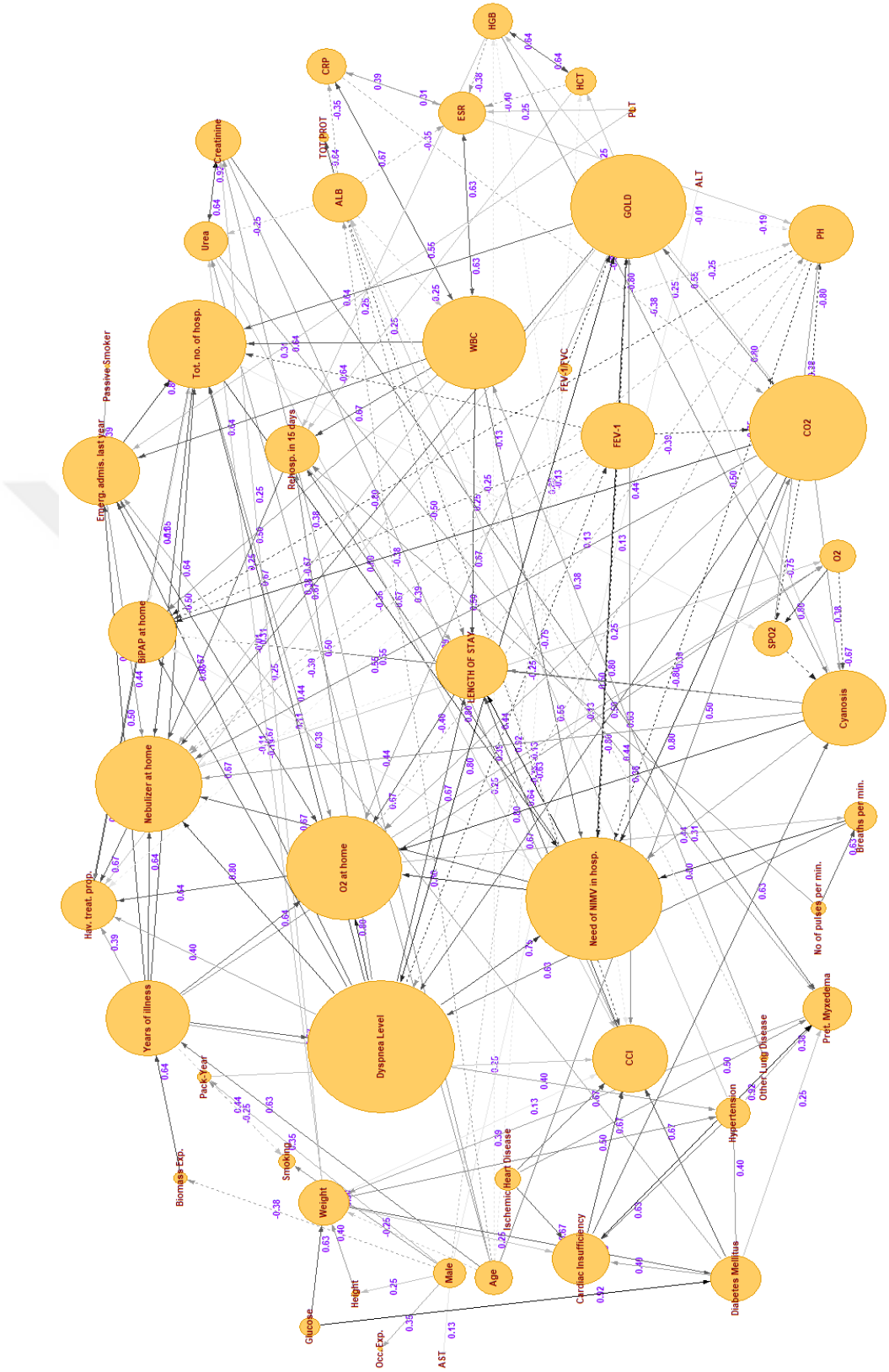

Figure 4.4 SBFCM of LoS of COPD Patients

Table 4.7 SBFCM Indices

Concepts	**Outde.**	**Inde.**	**Centr.**	**Concepts**	**Outde.**	**Inde.**	**Centr.**
Age	2.75	0.00	2.75	WBC	5.53	1.80	7.34
Male	2.33	0.00	2.33	HGB	1.89	1.02	2.91
Occ. Exp.	0.00	0.35	0.35	HCT	1.29	1.02	2.31
Height	0.40	0.25	0.65	PLT	0.56	0.00	0.56
Weight	2.00	1.66	3.66	AST	0.00	0.13	0.13
Smoking	0.44	0.75	1.19	ALT	0.00	0.13	0.13
Biomass Exp.	0.64	0.38	1.02	FEV-1	4.56	0.75	5.31
Passive Smoker	0.39	0.00	0.39	FEV-1/FVC	0.80	0.25	1.05
Pack-Year	0.25	0.80	1.05	GOLD	4.91	3.39	8.30
Years of illness	4.76	1.27	6.03	PH	2.33	2.25	4.58
Hav. treat. prop.	0.35	3.62	3.97	CO2	5.98	2.42	8.40
Nebulizer at home	0.92	6.67	7.59	O2	1.47	1.14	2.60
O2 at home	2.23	6.04	8.27	SPO2	1.17	1.67	2.84
BiPAP at home	0.64	4.22	4.87	Cyanosis	2.99	2.97	5.95
Rehosp. in 15 days	1.01	2.84	3.85	Breaths per min.	1.42	0.93	2.35
Emerg.admis.la. ye	1.91	3.55	5.46	No of PPM	1.13	0.00	1.13
Need of NIMV	3.17	6.52	9.69	Pret. Myxedema	0.39	3.11	3.50
Tot. no. of hosp.	2.65	4.39	7.04	CCI	1.09	4.27	5.36
Glucose	1.54	0.00	1.54	Other Lung Disease	0.63	0.00	0.63
Urea	1.61	1.52	3.13	Hypertension	1.25	1.30	2.55
Creatinine	1.66	1.55	3.20	Dyspnea Level	7.46	3.09	10.55
TOT PROT	0.13	0.64	0.77	Diabetes Mellitus	2.09	1.55	3.64
ALB	2.97	0.88	3.85	Ischemic Heart Dis.	1.84	0.00	1.84
CRP	1.49	1.41	2.90	Cardiac Insuffici.	2.22	1.94	4.16
ESR	1.01	2.31	3.32	LoS	0.79	4.29	5.08

4) All the concept values converged after 22 iterations and final values are given in Table 4.8 with descending order.

Table 4.8 Outputs of SBFCM

System Concept	Final Value	System Concept	Final Value
Need of NIMV in hosp.	1.00000	Pack-Years	0.86801
Nebulizer at home	0.99999	Smoking	0.81314
O2 at home	0.99998	O2/Blood Gas	0.77924
BiPAP at home	0.99992	ESR/Blood Test	0.71499
GOLD Stage	0.99929	Occ. Exposure	0.60966
Having treatment properly	0.99922	Height	0.55645
Pretibial Myxedema	0.99862	AST/Blood Test	0.46101
CCI Score	0.99828	ALT/Blood Test	0.46101
Total number of hospitalization	0.99796	SPO2/Blood Gas	0.46099
Re-hospitalization in 15 days	0.99785	TOT PROT/Blood Test	0.28164
Dyspnea Level	0.99377	Age	0.26164
Cardiac Insufficiency	0.98112	Male Gender	0.26164
CO2/Blood Gas	0.97800	Passive Smoker	0.26164
Creatinine/Blood Test	0.97506	Glucose/Blood Test	0.26164
WBC/Blood Test	0.96413	PLT/Blood Test	0.26164
Urea/Blood Test	0.95310	No of pulses per min	0.26164
CRP/Blood Test	0.94797	Other Lung Disease	0.26164
Diabetes Mellitus	0.94372	Ischemic Heart Disease	0.26164
Emerg. admis. in the last year	0.94332	ALB/Blood Test	0.25134
HGB/Blood Test	0.94222	FEV-1/FVC Test Result	-0.55304
HCT/Blood Test	0.93936	Biomass Exposure	-0.61961
Weight	0.92737	Years of illness	-0.75664
Hypertension	0.89224	FEV-1 Test Result	-0.93260
Cyanosis	0.89044	PH/Blood Gas	-0.97341
Breaths per minute	0.87401	LoS (Domain)	0.99980

The final value of a concept can be interpreted as the strength of that factor on the domain variable, and the final value of the domain variable is expected to converge to one. On the other hand, centrality is related to the importance of the factor in the system. 11 factors have more than 99% strength, which can be considered as predictors of LoS. Given these points, the results of SBFCM are significant according to the experts:

- "Need of NIMV in the hospital (days)" has the greatest power on LoS, because the patient must stay in the hospital when this need occurs. The need of NIMV has a certain observable effect on LoS; a unit change in this factor causes a unit of change in LoS in the same direction, consequently Need of NIMV is the only factor that has the greatest possible strength, 1.
- "Nebulizer at home", "O2 at home", and "BiPAP at home" factors are the next predictors of a longer LoS. Having one of these inhaling machines at home indicates a greater probability of need of NIMV in the hospital and that prolongs LoS. Since the effect is observable but indirect, final values are slightly less than 1.
- "GOLD Stage" and "Dyspnea Level" factors state the severity of COPD from different point of views. GOLD Stage is an objective indicator that is determined by the patient's FEV1 and FEV1/FVC test results. Dyspnea Level, on the other hand, is a subjective indicator that is determined based on the patient's statement. As the severity of the disease increases, the patient is expected to have a greater readmission rate and stay longer in the hospital.
- "Having treatment properly" factor has a substantial positive strength on LoS. If a patient who claims to follow his/her treatment regimen regularly is still hospitalized with an acute exacerbation, either he/she does not have his/her treatment properly or his/her treatment regimen needs to change. In both cases, the patient must be kept under observation in the hospital.
- "Pretibial Myxedema" and "CCI Score" are the most powerful factors of the Comorbidities group. CCI Score regards all possible comorbidities and contains more information than individual comorbidity factors. In like manner, Pretibial

Myxedema is a predictor of cardiac insufficiency proceeding with COPD in later stages.

- "Total number of hospitalization" and "Re-hospitalization in 15 days" factors are considered as readmission rate indicators. Aiming to decrease the readmission probability, physicians tend to make more observations before the patient is discharged which is likely to extend LoS.
- Dyspnea Level, Need of NIMV in hosp., CO2, GOLD Stage and O2 at home factors have the greatest centrality degrees. Among these, CO2 is not one of the greatest final values, which can be interpreted as; CO2 is one of the most important factors in the system however, it is not as powerful as on LoS.
- In negative direction, "Blood pH" and "FEV1 Test Result" are the most powerful factors on LoS. Weakened lung function increases the amount of carbon dioxide in the blood, which causes a decrease in pH value. The pH balance must be provided for the patient to be discharged. Likewise, FEV1 is an important measurement of pulmonary functions. The increased FEV1 result is expected to reduce LoS.

Moreover, when the factor groups are observed, the ranking of average strengths is Medical Records (99%), Comorbidities (76%), Clinical Findings (75%), and Socio-Demographics (57.5%). Socio-Demographics comprises well-known risk factors of COPD however, regarding the results, Medical Records of a patient would be more efficient while predicting his/her LoS. Comorbidities are slightly more powerful than Clinical Findings; conversely, Clinical Findings have greater average centrality degree. Hence, Clinical Findings have greater importance in the system and less strength on LoS, which is meaningful for COPD management.

4.4 Scenario Analyses

Having the conceptual map of a complex system provides many advantages; as the capability of further analysis of concepts for different scenarios and a better comprehension of the dynamic structure. While establishing the scenarios, the final

values of certain concepts are re-adjusted. If the concept value is set to zero, it means this concept becomes “off state” which can be construed with the elimination of that concept from the system. In medical problems, most of the variables are binary (Yes or No), setting a few pre-defined concepts to “off state” and analyzing the rest, would create an edge in the disease management.

After analyzing the results, experts constructed four different scenarios to observe. In Table 4.9, the results of four scenarios are shown and the final values of the concepts (previously ranked in Table 4.8) are given under the No Change column for comparison.

Positive and negative changes are analyzed for each scenario. For all factors with positive final values, a positive change means that the factor gains power on LoS in that scenario. For all factors with negative values, it is vice-versa: a positive change in negative final values means a decrease of power on LoS. The scale used for strengths of changes is as follows: 1 – Strong Change, 2 – Medium Change, 3 – Weak Change, 4 – Very Weak Change.

Scenario 1: In the first scenario, “Smoking” factor is reduced to off state. Smoking is not only an important risk factor of COPD, but also it lies behind many of other diseases and metabolic problems. As shown in Table 4.10, switching off the smoking concept strongly affected the system; 96% of variables changed. The effect of exposure factors, such as Biomass, Passive Smoker etc., that accompanies smoking and prolongs LoS by triggering the disease is diminished because smoking becomes risky, along with other exposure factors, rather than a risk factor alone. Consequently, a Medium Change (Strength: 2) is observed in the domain variable in favor of the shortening of LoS. The 96% change in this scenario indicates that the smoking factor, by influencing the entire system, has become a very strong factor on LoS. On the other hand, the removal of the smoking factor from the system reduces the effects of all factors of comorbidity group (diabetes, hypertension) on the LoS. Lastly, the power to determine LoS of respiratory function tests (FEV1, FEV1/FVC) is reduced with the blood tests (CO2,TOT PROT etc.) gaining power.

Table 4.9 Concept Values for Different Scenarios

Concepts	No Change	Scene 1	Scene 2	Scene 3	Scene 4
Age	0.26164	0.05464	**0**	0.05464	0.05464
Male	0.26164	0.05464	**0**	0.05464	0.05464
Occ. Exp.	0.60966	0.37595	**0**	0.37595	0.37595
Height	0.55645	0.33761	**0**	0.33761	0.33761
Weight	0.92737	0.89271	**0**	0.89271	0.68662
Smoking	0.81314	**0**	**0**	0.74194	0.74194
Biomass Exp.	-0.61961	-0.38336	**0**	-0.38336	-0.38336
Passive Smoker	0.26164	0.05464	**0**	0.05464	0.05464
Pack-Year	0.86801	0.37595	**0**	0.82597	0.82597
Years of illness	-0.75664	-0.74181	0.05464	-0.74181	-0.74181
Hav. treat. prop.	0.99922	0.99538	0.99951	0.99537	0.99923
Nebulizer at home	0.99999	0.99857	0.99994	0.99856	0.99999
O2 at home	0.99998	0.99901	0.99991	0.99900	0.99995
BiPAP at home	0.99992	0.99925	0.99936	0.99925	0.99986
Rehosp. in 15 days	0.99785	0.96204	0.96214	0.96204	0.99734
Emerg.admis.last year	0.94332	-0.90254	-0.74769	-0.90254	0.81755
Need of NIMV in hos.	1.00000	0.99986	0.99999	0.99986	1.00000
Tot. no. of hosp.	0.99796	-0.78139	0.83500	-0.78198	0.99755
Glucose	0.26164	0.05464	0.05464	0.05464	0.05464
Urea	0.95310	0.92319	0.85799	0.92319	0.95297
Creatinine	0.97506	0.96810	0.93884	0.96810	0.96644
TOT PROT	0.28164	0.86998	0.86730	0.86998	-0.76762
ALB	0.25134	0.71937	0.70652	0.71937	-0.38336
CRP	0.94797	-0.97909	-0.97889	-0.97909	0.96877
ESR	0.71499	-0.99369	-0.99361	-0.99369	0.81698
WBC	0.96413	-0.98025	-0.98012	-0.98025	0.97134
HGB	0.94222	0.94652	0.94699	0.94652	0.94437
HCT	0.93936	0.94634	0.94212	0.94634	0.92652
PLT	0.26164	0.05464	0.05464	0.05464	0.05464
AST	0.46101	0.27079	0.05464	0.27079	0.27079
ALT	0.46101	0.27079	0.05464	0.27079	0.27079
FEV-1	-0.93260	-0.93258	-0.93302	-0.93258	-0.93255
FEV-1/FVC	-0.55304	-0.33761	0.05464	-0.33761	-0.33761
GOLD	0.99929	0.99900	0.99812	0.99758	0.99752
PH	-0.97341	-0.98990	-0.97153	-0.98989	-0.97552
CO2	0.97800	0.99374	0.99338	0.99373	0.97207
O2	0.77924	0.78086	0.91937	0.78085	0.78132
SPO2	0.46099	-0.74941	0.59485	-0.74946	0.35892
Cyanosis	0.89044	0.98697	0.81961	0.98697	0.42241
Breaths per min.	0.87401	0.82201	0.82215	0.82201	0.82215
No of pulses per min.	0.26164	0.05464	0.05464	0.05464	0.05464
Pret. Myxedema	0.99862	0.99816	0.99701	0.99816	**0**
CCI	0.99828	0.99263	0.97837	**0**	**0**
Other Lung Disease	0.26164	0.05464	0.05464	0.05464	**0**
Hypertension	0.89224	0.88475	0.74936	0.88475	**0**
Dyspnea Level	0.99377	0.99366	0.99763	0.99364	0.99338
Diabetes Mellitus	0.94372	0.90806	0.50346	0.90806	**0**
Ischemic Heart Disea.	0.26164	0.05464	0.05464	0.05464	**0**
Cardiac Insufficiency	0.98112	0.97307	0.92630	0.97307	**0**
LENGTH OF STAY	0.99980	0.99571	0.99492	0.98433	0.99936

Table 4.10 Changes in Scenario 1 & Scenario 2

SCENARIO 1				SCENARIO 2			
Positive Changes	**Str**	**Negative Changes**	**Str**	**Positive Changes**	**Str**	**Negative Changes**	**Str**
Biomass Exp.	**1**	Age	1	Years of illness	1	Nebulizer at home	4
Years of illness	1	Male	1	Hav. treat. prop.	3	O2 at home	4
TOT PROT	**1**	**Occ. Exp.**	**1**	**TOT PROT**	**1**	BiPAP at home	3
ALB	**1**	Height	1	**ALB**	**1**	Rehosp. in 15 days	1
HGB	**2**	Weight	1	**HGB**	**2**	Emerg. admis. last year	1
HCT	**2**	**Passive Smoker**	**1**	**HCT**	**2**	Need of NIMV in hosp.	4
FEV-1	**4**	**Pack-Year**	**1**	FEV-1/FVC	1	Tot. no. of hosp.	1
FEV-1/FVC	**1**	Hav. treat. prop.	2	PH	2	Glucose	1
CO2	1	Nebulizer at home	2	CO2	1	Urea	1
O2	2	O2 at home	3	O2	1	Creatinine	1
Cyanosis	1	BiPAP at home	3	SPO2	1	CRP	1
		Rehosp. in 15 days	1	Dyspnea Level	2	ESR	1
		Emerg. admis. last year	1			WBC	1
		Need of NIMV in hosp	3			PLT	1
		Tot. no. of hosp.	1			AST	1
		Glucose	1			ALT	1
		Urea	1			FEV-1	3
		Creatinine	2			GOLD	2
		CRP	1			Cyanosis	1
		ESR	1			Breaths per min.	1
		WBC	1			No of pulses per min.	1
		PLT	1			**Pret. Myxedema**	**2**
		AST	1			**CCI**	**1**
		ALT	1			**Other Lung Disease**	**1**
		GOLD	3			**Hypertension**	**1**
		PH	1			**Diabetes Mellitus**	**1**
		SPO2	1			**Ischemic Heart Disea.**	**1**
		Breaths per min.	1			**Cardiac Insufficiency**	**1**
		No of pulses per min.	1			**LENGTH OF STAY**	**2**
		Pret. Myxedema	**3**				
		CCI	**2**				
		Other Lung Disease	**1**				
		Hypertension	**2**				
		Dyspnea Level	3				
		Diabetes Mellitus	**1**				
		Ischemic Heart Disea.	**1**				
		Cardiac Insufficiency	**2**				
		LENGTH OF STAY	**2**				

Scenario 2: In Scenario 2, in addition to Scenario 1, eight more socio-demographic factors (which shows strong change - Strength: 1- in Scenario 1) are set to off state, in other words, it is assumed that LoS is, for example, independent of the gender or weight of the patient. According to the results obtained, actual clinical findings factors such as TOT PROT, ALB, HBG, and HCT become important in influencing the patient's LoS. Exposures and demographic factors are leading actors not only in the development of COPD but also in other comorbid diseases. Setting these factors to off state also reduces the effect of comorbidities (Strong Change – Strength: 1) on LoS. In addition, in both scenarios (1&2), a Medium Change (Strength: 2) is observed in the domain variable LoS, which means there is no significant difference between setting smoking alone to off state and setting all socio-demographic factors to off state.

Scenario 3: CCI Score is reduced to off state. The effect on LoS of biochemical blood test factors evaluating COPD (CO2, O2, and ALB) was increased, while the effect of blood test factors evaluating comorbid diseases (Glucose, urea, etc.) was significantly reduced as shown in Table 4.11. The socio-demographics group, which consists of risk factors for all comorbid diseases, also showed a significant decrease (Strength: 1) in the strength on LoS. At the same time, the absence of any comorbid disease significantly reduces the domain variable LoS (Strength: 1).

Scenario 4: All comorbidities are set to off state, in other words, it is presumed that the patient has no comorbid disease or even if the patient has comorbid disease, it has no effect on LoS. With the intention of determining the most effective predictors of LoS, Scenario 3 and Scenario 4 indicate that CCI score in fact comprises all other factors in Comorbidities group; no significant difference was observed between the results of the last two scenarios. Therefore, while estimating the LoS of a new patient, only the CCI Score variable will suffice for the group of comorbidities.

Table 4.11 Changes in Scenario 3 & Scenario 4

SCENARIO 3				SCENARIO 4			
Positive Changes	**Str**	**Negative Changes**	**Str**	**Positive Changes**	**Str**	**Negative Changes**	**Str**
Biomass Exp.	**1**	**Age**	**1**	Biomass Exp.	1	Age	1
Years of illness	**1**	**Male**	**1**	Years of illness	1	Male	1
TOT PROT	1	**Occ. Exp.**	**1**	Hav. treat. prop.	4	Occ. Exp.	1
ALB	**1**	**Height**	**1**	CRP	1	Height	1
HGB	2	**Weight**	**1**	ESR	1	Weight	1
HCT	2	**Smoking**	**1**	WBC	2	Smoking	1
FEV-1	4	**Passive Smoker**	**1**	HGB	2	Passive Smoker	1
FEV-1/FVC	1	**Pack-Year**	**1**	FEV-1	4	Pack-Year	1
CO2	**1**	Hav. treat. prop.	2	FEV-1/FVC	1	Nebulizer at home	4
O2	**2**	Nebulizer at home	2	O2	2	O2 at home	4
Cyanosis	1	O2 at home	3			BiPAP at home	4
		BiPAP at home	3			Rehosp. in 15 days	3
		Rehosp. in 15 days	1			Emerg. admis. last year	1
		Emerg. admis. last year	1			Need of NIMV in hosp.	4
		Need of NIMV in hosp	3			Tot. no. of hosp.	3
		Tot. no. of hosp.	1			Glucose	1
		Glucose	**1**			Urea	3
		Urea	**1**			Creatinine	2
		Creatinine	**2**			TOT PROT	1
		CRP	**1**			ALB	1
		ESR	**1**			HCT	1
		WBC	**1**			PLT	1
		PLT	**1**			AST	1
		AST	**1**			ALT	1
		ALT	**1**			GOLD	2
		GOLD	2			PH	2
		PH	1			CO2	2
		SPO2	1			SPO2	1
		Breaths per min.	1			Cyanosis	1
		No of pulses per min.	1			Breaths per min.	1
		Pret. Myxedema	3			No of pulses per min.	1
		Other Lung Disease	1			Dyspnea Level	3
		Hypertension	2			LENGTH OF STAY	3
		Dyspnea Level	3				
		Diabetes Mellitus	1				
		Ischemic Heart Disease	1				
		Cardiac Insufficiency	2				
		LENGTH OF STAY	**1**				

4.5 Discussions on the Results

COPD is a growing problem of the world. In COPD management and hospital organization, the length of hospital stays of patients is a major issue because of its economic aspect. Although the risk factors of COPD are well known, their individual effects on LoS still remain uncertain. At this point, the purpose of this chapter is to develop a medical decision support system for evaluating the factors, which have influence on LoS of COPD patients with acute exacerbation, and to determine the most efficient predictors of LoS.

FCMs are convenient tools to structure such a complex system however, when the number of factors increases, it becomes difficult to gather the expert data. Hence, for medical decision-making problems involving numerous factors, the novel SBFCM method is proposed in this chapter. SBFCM method integrates objective statistical data and subjective expert data; thereby it facilitates the acquisition of expert data and reduces the criticized subjectivity of conventional FCM.

The first application of SBFCM method for COPD management is conducted in Yedikule Chest Diseases and Thoracic Surgery Training & Research Hospital located in İstanbul / Turkey with 154 patients and 50 factors including LoS. In the first part of the study, patient data is analyzed, statistical tests are conducted and preliminary data for the experts is prepared. In the second part, expert data is used to construct the SBFCM of the system. After the SBFCM iterations, the most efficient predictors of LoS are determined. The results stated that Need of NIMV in hospital, Nebulizer at home, O2 at home, BiPAP at home, GOLD Stage, Having treatment properly, Pretibial Myxedema, CCI Score, Total number of hospitalization, Re-hospitalization in 15 days and Dyspnea Level factors have more than 99% strength in determining LoS of a COPD patient with acute exacerbation.

For a deeper observation of the system, different scenarios are generated. First, smoking factor is eliminated from the system and 96% of variables are changed, which revealed that smoking was influential on nearly all other factors. Second, when all socio-

demographic factors are removed, comorbidities lost strength and actual clinical findings gained power on LoS. Then, CCI Score is set to zero, which caused a strong negative change on the domain variable LoS. Lastly, all comorbidities are excluded from the system and the results showed no significant change from the previous scenario, which asserted that CCI Score was the representative of the entire comorbidities group.

The results of SBFCM methodology were significant in the real-case numerical application, which indicates that SBFCM can be a useful decision making tool for physicians and hospital managers. As future research, predictor factors of LoS determined in this chapter can be used with artificial intelligence techniques such as neural networks for more structured medical decisions, which can accelerate medical decision processes and accordingly increase the capacity of hospitals.

5. LENGTH OF STAY PREDICTION IN COPD WITH ARTIFICIAL NEURAL NETWORKS

Today's technological developments have made it possible to collect and process large amounts of data for medical decision-making. The interest in artificial intelligence techniques is increased because of their learning capabilities. One of the most studied techniques of artificial intelligence is artificial neural networks. Essentially, artificial neural networks are mathematical models that are able to capture the knowledge contained in the data by imitating human neurons. They are useful in detecting nonlinear and complex relationships between different kinds of variables where conventional statistical methods may fail to detect.

As mentioned in previous chapter, COPD is a global burden, which is estimated to be the third leading cause of death worldwide by 2030 (WHO, 2007). COPD needs proper management because of its long and difficult process. The economic burden of COPD grows continuously because it is not a curable disease. These conditions make COPD an important research field of artificial intelligence techniques in medicine. In Table 5.1, use of artificial neural networks in COPD literature is summarized with authors, years, fields and sources of publication. Since 1998, there exist many publications, which use artificial neural networks in COPD management. 20 years later, in 2018, it is still an interesting field for researchers, medical doctors and academics, which reveals the power of artificial neural networks in medical decision support.

Table 5.1 Artificial Neural Networks in COPD

Publication	Field	Source
(Agarwal et al., 2018)	Hospital Readmissions	IEEE Journal of Biomedical and Health Informatics
(Laskar et al., 2018)	Air Quality	Journal of the Indian Society of Remote Sensing
(Andrés-Blanco et al., 2017)	Sleep Apnea	PLoS ONE
(Filho et al., 2017)	Classification	Neural Computing and Applications
(Pramono et al., 2017)	Respiratory Sounds	PLoS ONE
(Raja & Babu, 2017)	Classification	International Journal of Pure and Applied Mathematics
(Shakerkhatibi et al., 2015)	Hospital Admissions	International Journal of Environmental Science and Technology
(Badnjevic et al., 2015)	Classification	BMC Medical Informatics and Decision Making
(Moretz et al., 2015)	Classification	Journal of Managed Care Pharmacy
(Alemzadeh et al., 2015)	Classification	Critical Reviews in Biomedical Engineering
(Ramalho et al., 2014)	Classification	Revista Brasileira de Engenharia Biomedica
(Bhuvaneswari et al., 2014)	Classification	Journal of Theoretical and Applied Information Technology
(Dias et al., 2014)	Classification	Methods of Information in Medicine
(Amaral et al., 2013)	Smoking	Computer Methods and Programs in Biomedicine
(Morillo et al., 2013)	Classification	Journal of the American Medical Informatics Association
(Hosseini et al., 2013)	Classification	Acta Medica Iranica
(Işik et al., 2013)	Tracking System	Telemedicine and e-Health
(Cengiz & Terzi, 2012)	Air Quality	Central European Journal of Public Health
(Flores-Fernández et al., 2012)	Classification	Expert Systems with Applications
(Gueli et al., 2012)	Antibiotic Therapy	Archives of Gerontology and Geriatrics
(Amaral et al., 2012)	Classification	Computer Methods and Programs in Biomedicine
(Raoufy et al., 2011)	Arterial Blood Gas Values	Journal of Medical Systems
(Er et al., 2009)	Classification	Journal of Medical Systems
(Mehrabi et al., 2009)	Classification	Expert Systems with Applications
(Er & Temurtas, 2008)	Classification	Journal of Medical Systems
(Veezhinathan & Ramakrishnan, 2007)	Flow-volume Spirometry	Journal of Medical Systems
(Coppini et al., 2007)	Emphysema	Medical Engineering and Physics
(Bibi et al., 2002)	Emergency Admissions	Chest
(Bright et al., 1998)	Goiter	American Journal of Respiratory and Critical Care Medicine

In addition, several studies make predictions of length of hospitalization stay of patients with various diseases using artificial neural networks. Mobley et al. predicted LoS of patients in post-coronary care unit with nearly 72% accuracy (Mobley et al., 1995), Kim et al. predicted LoS of patients in post-anesthesia care unit with 81.4% accuracy (Kim, W. O. et al., 2000), Launay et al. predicted prolonged LoS of older emergency department users with 62.7% sensitivity and 96.6% specificity (Launay et al., 2015), LaFaro et al. predicted LoS in the cardiac surgical intensive care unit based on pre-incision patient characteristics and demonstrated that the results are significantly better in artificial neural networks than automatic linear modeling module of IBM-SPSS software (LaFaro et al., 2015), and Tsai et al. predicted LoS of cardiology patients with 88.07% accuracy (Tsai et al., 2016). In medical decision support, artificial neural networks are often compared with linear regression models and logistic regression models.

5.1 Artificial Neural Networks Methodology

As an inspiration from human nerves, artificial neural networks are computational models with learning and generalization capabilities. They are able to acquire knowledge from experience, generalize the acquired knowledge and make predictions of further unknown factors. The networks consist of computational units (artificial neurons) and their interconnections (artificial synapses). Each unit produces a function of its inputs and transfers it as an output to other connected units. Graphical presentation of a unit as a threshold element is shown in Figure 5.1.

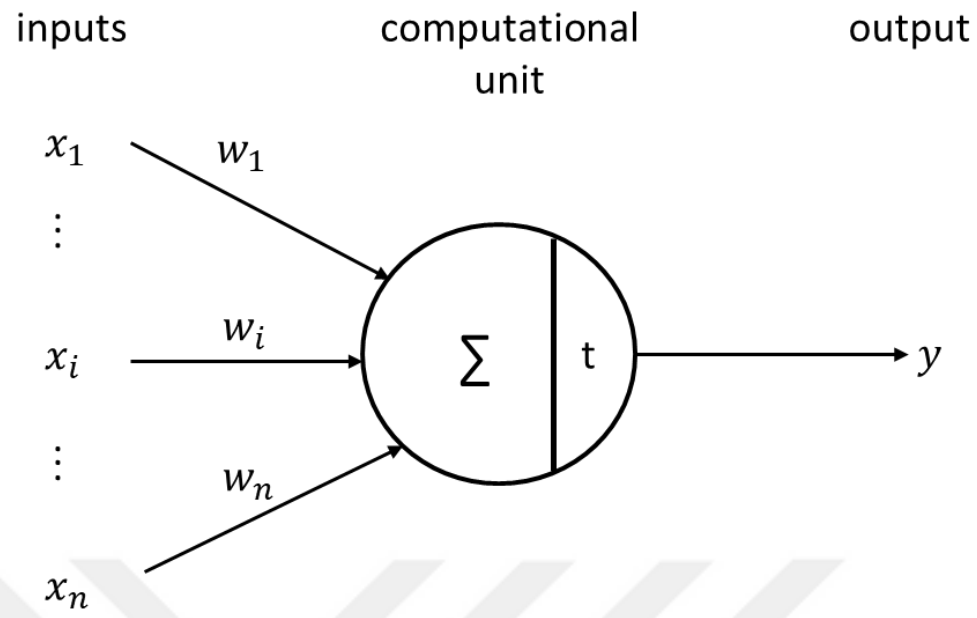

Figure 5.1 An Artificial Neuron (Ross, 2010)

Each neuron creates a nonlinear function of its input values and synaptic weights as given in Equation (5.1).

$$y = f(\sum w_i x_i - t) \tag{5.1}$$

where x_i is the signal input ($i = 1,2, \dots, n$), w_i is the synaptic weight associated with x_i, t is the threshold level and f is a nonlinear function as the sigmoid function ($f(a) = 1/(1 + e^{-a})$).

In Figure 5.2, a simple neural network of one input layer, two hidden layers and one output layer with the architecture (1x3x2x1) is shown.

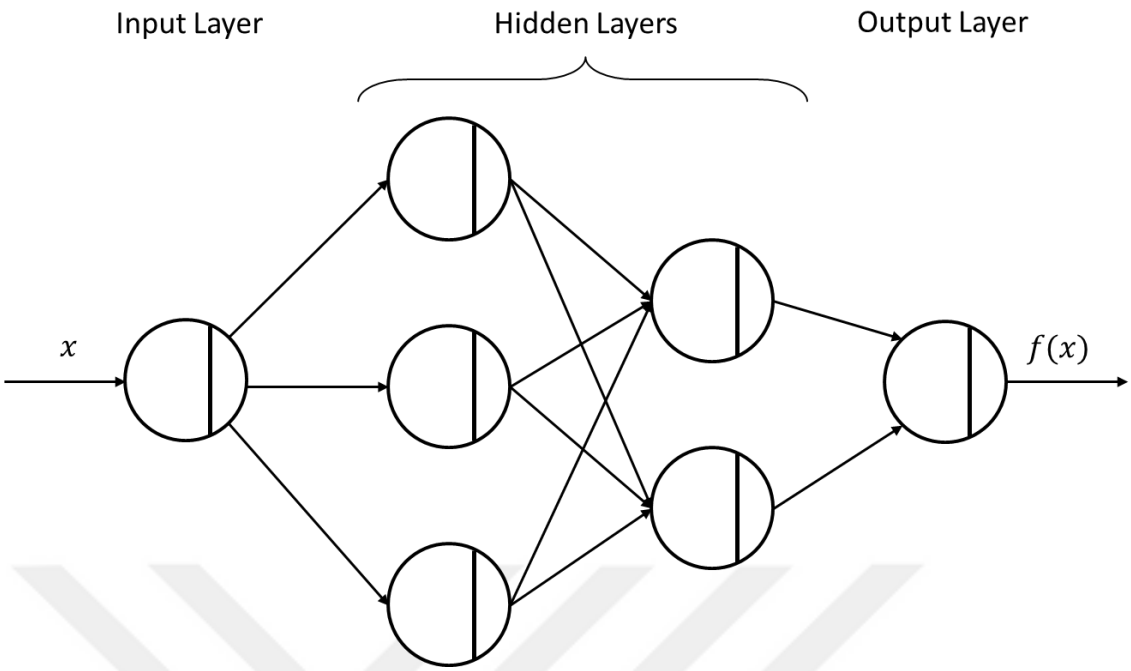

Figure 5.2 A (1x3x2x1) Neural Network

In artificial neural network models, the data is usually divided into three parts:

1. *Training data:* Usually training data is 70%-80% of the data. Training data is used to train the model in adjusting synaptic weights of the system with the error measure and back-propagation algorithm.
2. *Cross-validation data:* This data is usually 15%-20% of the data. It is used to determine the parameters of the model in order to prevent overfitting.
3. *Testing data:* This data is usually 15%-20% of the data. Test data is used to measure the performance of the artificial neural network model.

The portions of training, cross-validation and testing data is determined by the modelers according to the amount of data set that they have. In addition, if the parameters of the model are pre-adjusted by the modeler, the data can be divided into two parts as training data and testing data, without a cross-validation process.

The initial step is a random assignment of all synaptic weights. Then an input of the training data is passed through the network to calculate the value $f(x)_{output}$. The error

measure E is determined, which is the difference between the real (target) value and the calculated output value as given in Equation (5.2) (Ross, 2010).

$$E = f(x)_{target} - f(x)_{output} \tag{5.2}$$

This error measure belongs to the last layer of the network; therefore, it should be distributed to the elements of the hidden layer. This distribution process is named as back-propagation algorithm, which uses the Equation (5.3) and Equation (5.4) (Ross, 2010).

$$E_n = F'(I)w_{nj}E_j \tag{5.3}$$

where E_j is the error associated with the j'th element, w_{nj} is the weight associated with the line from element n to element j, I is the input to unit n and $F'(I) = F(I)(1 - F(I))$ if $F(I)$ is the sigmoid function.

In the next step, synaptic weights are updated using the error measures of each node with Equation (5.4).

$$w_i(new) = w_i(old) + \propto Ex_i \tag{5.4}$$

where $\propto$ is the learning constant (given by the modeler), E is the associated error measure and x_i is the input to the element.

Back-propagation algorithm is repeated for all of the training data and then the training process is completed. An optional cross-validation process can be operated to adjust the parameters and lastly the testing data is used to measure the performance of neural network model.

The architecture of the neural network model is still a curious research field for computer scientists. The number of hidden layers and the number of hidden neurons change depending on input layer, output layer and the quantity of acquired data. However, certain effects are demonstrated by researchers. If there are too many hidden neurons that increase the complexity of the model, it might cause overfitting. If the number of hidden layers is not sufficient to fulfill the complexity of the data, then it might cause underfitting (Panchal & Panchal, 2014). To detect these effects, fitting and prediction performance of training, cross-validation and testing data should be observed. In this study, try and error method with a forward approach will be applied, which means a small number of hidden neurons will be chosen initially and by adding more hidden neurons, the performance indicators will be observed and the best results of testing data will be used as the final model.

5.2 Construction of the Artificial Neural Network Prediction Model

For the first step of the construction of an artificial neural network prediction model, the nodes in input and output layers should be ascertained. The output layer is relatively simple. Since the model targets to predict LoS of a COPD patient with acute exacerbation, the output layer will consist of a single node: LoS as a scale variable.

As already stated in previous chapter, the study is conducted in Yedikule Chest Diseases and Thoracic Surgery Training & Research Hospital with 154 patients that applied to the hospital with an acute exacerbation between November 2011 and August 2012. Fifty factors, including LoS, of each patient is recorded. Hence, forty-nine factors are input candidates of the model.

In artificial neural network models, input nodes selection has a major role in the model's success. Input variables should be carefully selected for a better performance in prediction. The factors that are statistically related to LoS are used in numerous studies since they have more chance in predicting.

For the selection of input nodes, two different approaches will be adopted in this study and their performances will be compared:

1. The factors that are significantly correlated with LoS (p=0.05) are selected, as proposed in medical decision making literature (LaFaro et al., 2015; Tsai et al., 2016).
2. The most powerful factors on LoS are selected with respect to the results of SBFCM method, calculated in the previous chapter, as a novel and integrated approach.

The most important difference in these two approaches is the intervention of expert opinion on the cause-and-effect relationships. The first approach is data-driven and solely based on correlation coefficients between the factors, however in SBFCM approach, experts incorporate their experience in the model.

Two different artificial neural network models will be constructed for a comparative observation; Model I and Model II. In order to determine the inputs of Model I, correlation coefficients between the 49 input candidate variables and LoS are obtained using SPSS 23.0 for Windows software. Spearman correlation coefficients are used because LoS is a non-parametric variable (Test of normality, $p < 0.001$). Correlations are given in Table 5.2 with decreasing order.

According to Table 5.2, seven variables have significant ($p < 0.05$) correlations with LoS. These seven variables can be used as input variables of the model if they are not collinear. To avoid multi-collinearity in the model, collinearity statistics are analysed and checked using SPSS 23.0 software; none of the input candidates were collinear. Therefore in the Model I, input layer has seven nodes and output layer has one node as shown in Figure 5.3. The number of nodes in hidden layer will be decided in the numerical application, using performance indicators.

Table 5.2 Correlations between LoS and input candidates

Input Candidates	**Correlation Coefficient**	**P-value**
Need of NIMV in hospital (Days)	0.4352*	0.0000
Nebulizer at home	0.2581*	0.0012
ALB/Blood Test	-0.2581*	0.0012
Total number of hospitalization	0.2463*	0.0021
O2 at home	0.2391*	0.0029
Dyspnea Level - mMRC Survey	0.2313*	0.0039
WBC/Blood Test	0.1972*	0.0143
BiPAP at home	0.1552	0.0546
TOT PROT/Blood Test	-0.1453	0.0723
O2/Blood Gas	0.1447	0.0733
Cyanosis	0.1445	0.0738
SPO2/Blood Gas	0.1432	0.0765
Charlson Comorbidity Index Score	0.1429	0.0770
Non-smoker/Former/Current	-0.1407	0.0817
Emergency admissions in the last year	0.1342	0.0972
Rehospitalization in 15 days	0.1214	0.1337
Occupational Exposure	0.1208	0.1356
HGB/Blood Test	-0.1160	0.1520
Urea/Blood Test	0.0871	0.2829
Other Lung Disease	0.0868	0.2845
Packet in a day x Years	-0.0822	0.3110
Weight (kg)	-0.0810	0.3179
HCT/Blood Test	-0.0799	0.3243
Height (cm)	-0.0799	0.3245
Diabetes Mellitus	0.0792	0.3287
PLT/Blood Test	0.0745	0.3585
ESR/Blood Test	-0.0730	0.3683
Gender	0.0722	0.3735
FEV-1 Test Result	-0.0690	0.3952
CO2/Blood Gas	0.0653	0.4212
AST/Blood Test	-0.0598	0.4610
Passive Smoker	0.0571	0.4819
Cardiac Insufficiency	0.0473	0.5600
ALT/Blood Test	0.0460	0.5714
CRP/Blood Test	0.0435	0.5919
Pretibial Myxedema	0.0412	0.6122
Biomass Exposure	-0.0372	0.6466
Creatinine/Blood Test	0.0368	0.6507
Ischemic Heart Disease	0.0337	0.6778
Hypertension	-0.0327	0.6869
FEV-1/FVC Test Result	-0.0298	0.7135
Having treatment properly	0.0261	0.7475
Glucose/Blood Test	0.0198	0.8076
Age (Years)	0.0149	0.8543
Number of pulses per minute	-0.0055	0.9457
Years of illness	0.0054	0.9466
GOLD Stage	-0.0049	0.9519
Breaths per minute	0.0017	0.9838
PH/Blood Gas	0.0008	0.9926

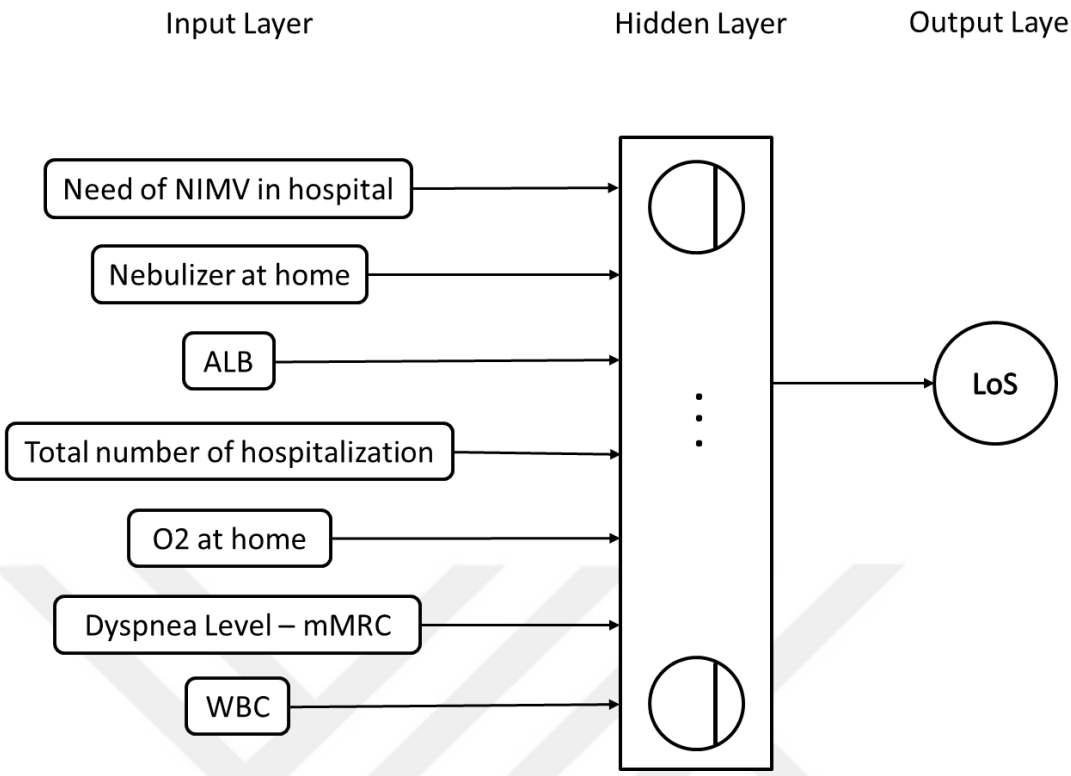

Figure 5.3 Architecture of the Model I

To determine the input variables of Model II, the final values of SBFCM application will be used. The final values of SBFCM can be interpreted as the strength of factors in the system. These values include statistical results and expert opinion. The final values range between -1 and 1, since tanh(x) function is used as the threshold function. Hence, the absolute strength of factors can be determined with absolute final values and the factors can be ranked with decreasing strengths as shown in Table 5.3.

An important research question arises while using SBFCM results; where is the cut-off point? The most common approach would be to determine a cut-off percentage for final values, 95% for example, which means the factors with final values greater than 0.95 would be the inputs of the model. Alternatively, in this study a sequential difference approach is proposed to consider relative powers of the input candidates. Sequential differences are calculated and given in Table 5.3.

Table 5.3 SBFCM final values of input candidates and sequential differences

Input Candidates	Final Value	Difference
Need of NIMV in hospital	1.00000	-
Nebulizer at home	0.99999	0.00001
O2 at home	0.99998	0.00001
BiPAP at home	0.99992	0.00006
GOLD Stage	0.99929	0.00063
Having treatment properly	0.99922	0.00007
Pretibial Myxedema	0.99862	0.00060
Charlson Comorbidity Index Score	0.99828	0.00034
Total number of hospitalization	0.99796	0.00033
Rehospitalization in 15 days	0.99785	0.00011
Dyspnea Level	0.99377	0.00408
Cardiac Insufficiency	0.98112	0.01265
CO2	0.97800	0.00312
Creatinine	0.97506	0.00294
PH	(-) 0.97341	0.00165
WBC	0.96413	0.00928
Urea	0.95310	0.01103
CRP	0.94797	0.00513
Diabetes Mellitus	0.94372	0.00425
Emergency admissions in the last year	0.94332	0.00040
HGB	0.94222	0.00110
HCT	0.93936	0.00286
FEV-1 Test Result	(-) 0.93260	0.00676
Weight	0.92737	0.00523
Hypertension	0.89224	0.03513
Cyanosis	0.89044	0.00180
Breaths per minute	0.87401	0.01643
Pack-Year	0.86801	0.00600
Smoking	0.81314	0.05488
O2	0.77924	0.03390
Years of illness	(-) 0.75664	0.02259
ESR	0.71499	0.04166
Biomass Exposure	(-) 0.61961	0.09538
Occupational Exposure	0.60966	0.00995
Height	0.55645	0.05320
FEV-1/FVC Test Results	(-) 0.55304	0.00341
AST	0.46101	0.09203
ALT	0.46101	0.00000
SPO2	0.46099	0.00002
TOT PROT	0.28164	0.17935
Age	0.26164	0.02000
Male	0.26164	0.00000
Passive Smoker	0.26164	0.00000
Glucose	0.26164	0.00000
PLT	0.26164	0.00000
Number of pulses per minute	0.26164	0.00000
Other Lung Disease	0.26164	0.00000
Ischemic Heart Disease	0.26164	0.00000
ALB	0.25134	0.01030

The proposed approach is to set the cut-off point where a sequential difference greater than 1% is observed. This approach creates a bundle of the most powerful factors in the system while setting a distance from the rest (cut-off point) as represented in Figure 5.4. With this approach, the factors whose final values differ less than 1% are prevented from being excluded.

As given in Table 5.3, the first sequential difference that is greater than 1% is the difference between “Dyspnea Level” and “Cardiac Insufficiency” factors. Hence, the cut-off point is set before “Cardiac Insufficiency”, multi-collinearity is checked and, Model II is constructed with 11 inputs in the input layer as shown in Figure 5.5.

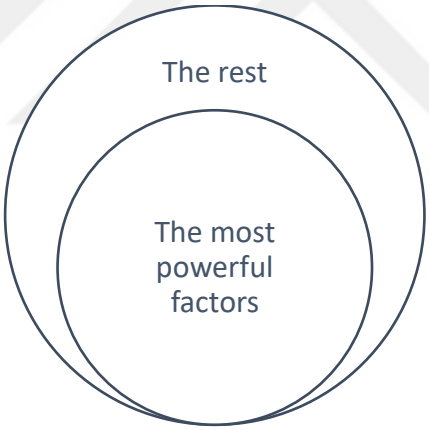

Figure 5.4 Representation of the proposed approach

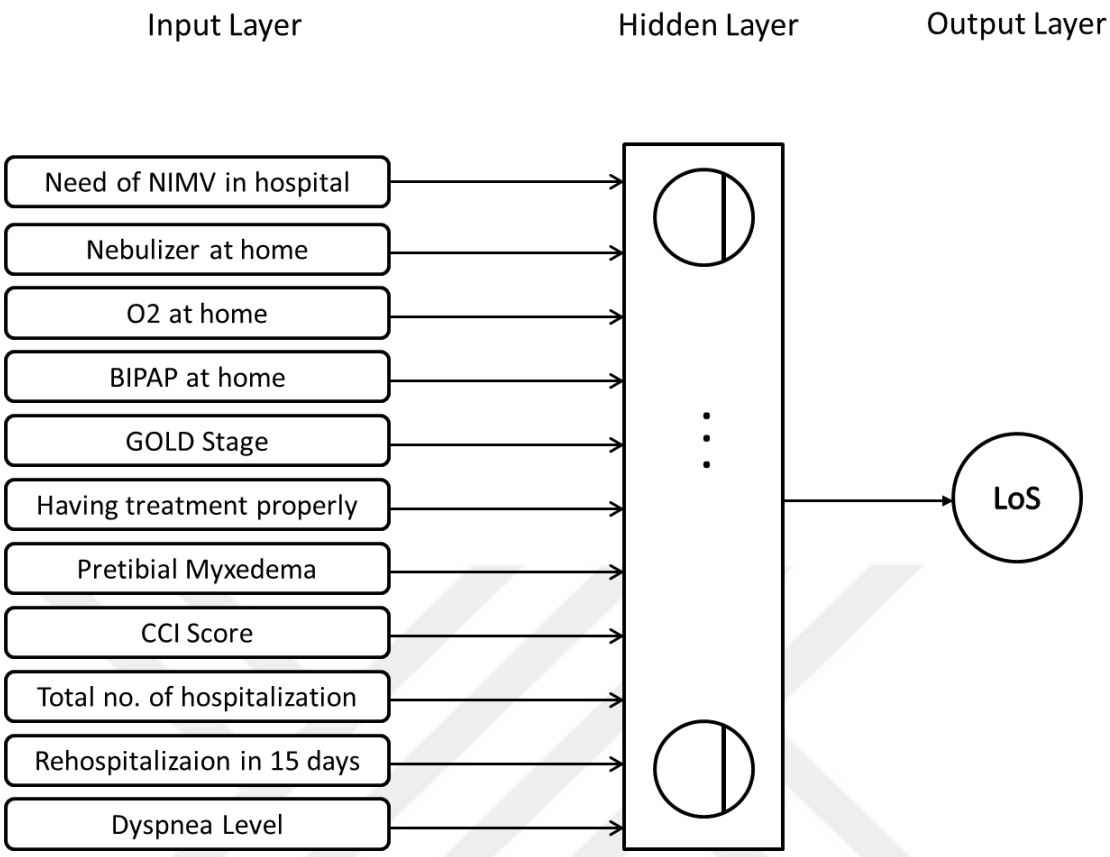

Figure 5.5 Architecture of the Model II

Thereby, the architecture of two models are determined with two different points of view. Their prediction performances can be compared in the numerical application.

5.3 Numerical Application of Artificial Neural Networks

The objective of the numerical application is to predict LoS of COPD patients that applied to the hospital with an acute exacerbation and to compare the prediction performances of two models. Two different performance indicators will be applied, which are frequently used in medical decision-making and engineering applications for prediction performance.

1) Mean Absolute Percentage Error (MAPE):

Let y_i be the model output values and t_i be the actual target values, then

$$MAPE = \frac{1}{N}\sum_{i=1}^{N}\left(\frac{|y_i - t_i|}{t_i}.100\right) \quad (5.5)$$

MAPE is widely used because it can be easily interpreted. For example, if MAPE is 30%, it means the model approximates the target value with an average of 70% accuracy (by subtracting from 100%). MAPE is an error measure, hence smaller MAPE indicates better prediction. MAPE cannot be used if there is zero in target values because it would make a division by zero.

2) Root Mean Square Error (RMSE):

Let y_i be the model output values and t_i be the actual target values, then

$$RMSE = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(y_i - t_i)^2} \quad (5.6)$$

RMSE is the square root of the variance of the differences between outputs and targets. It is also an accuracy indicator and it can be interpreted as the closeness between outputs and targets. The most important aspect of RMSE is the property of being in the same units as target values. Smaller RMSE indicates better prediction and better fit. RMSE is always non-negative and if RMSE is zero, it means a perfect fit to the data, which is nearly impossible in practice. Hence, it is highly useful in observing overfitting in artificial neural network models.

In the application, MAPE is used as the primary performance indicator because of its frequent use in medical decision-making and ease of interpretation by the physicians. RMSE is used as secondary indicator. All prediction models are implemented using MATLAB R11b - Neural Network toolbox. As a supervised learning algorithm, back-propagation is used. The original data of 154 COPD patients is randomly separated into three parts with proportions of 70%, 15%, 15%. Training, cross-validation and test data includes 108, 23 and 23 COPD patients, respectively.

For both models, the quantity of neural nodes in hidden layer will be decided using performance indicators. Trials will start with 2/3 times of the size of the input layer as suggested in previous studies (Karsoliya, 2012; Tsai et al., 2016; Walczak & Cerpa, 1999), and will stop when signs of overfitting occur.

5.3.1 Application of Model I

Since Model I has 7 inputs, trials for the number of nodes in hidden layer starts with 5 nodes. MAPE is chosen as the primary performance indicator and epochs are trained with back-propagation algorithm until no difference is observed in the cost function of fitting.

The algorithm of artificial neural network always begins with randomly assigned synaptic weights, therefore the code should be operated multiple times, the interval of performance indicators should be determined and the best model (the model with minimum MAPE in testing data) should be chosen.

Initially, with 5 neural nodes in hidden layer, the code is operated 1000 times and for each iteration MAPE and RMSE values are calculated for testing data. Scatter plots are shown in Figure 5.6 and Figure 5.7 to observe their intervals. For each of the 1000 models, MAPE varies between 20% and 180%, and RMSE varies between 3 and 15 days.

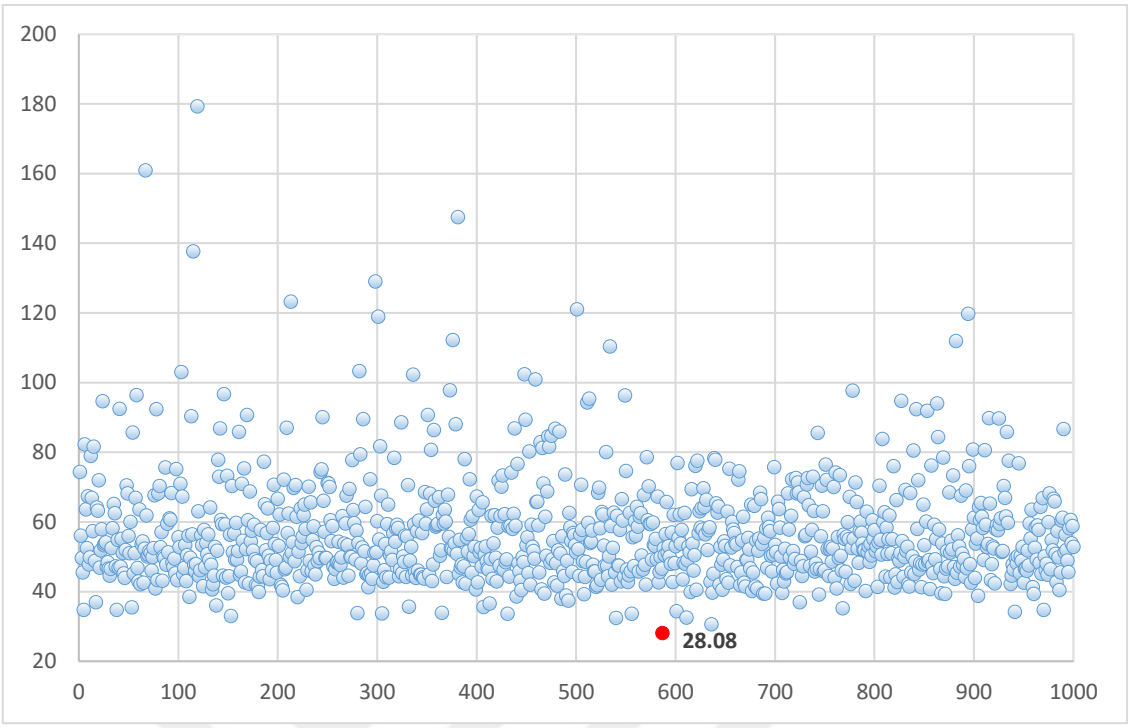

Figure 5.6 MAPE values of testing data in 1000 iterations for 5 nodes in hidden layer

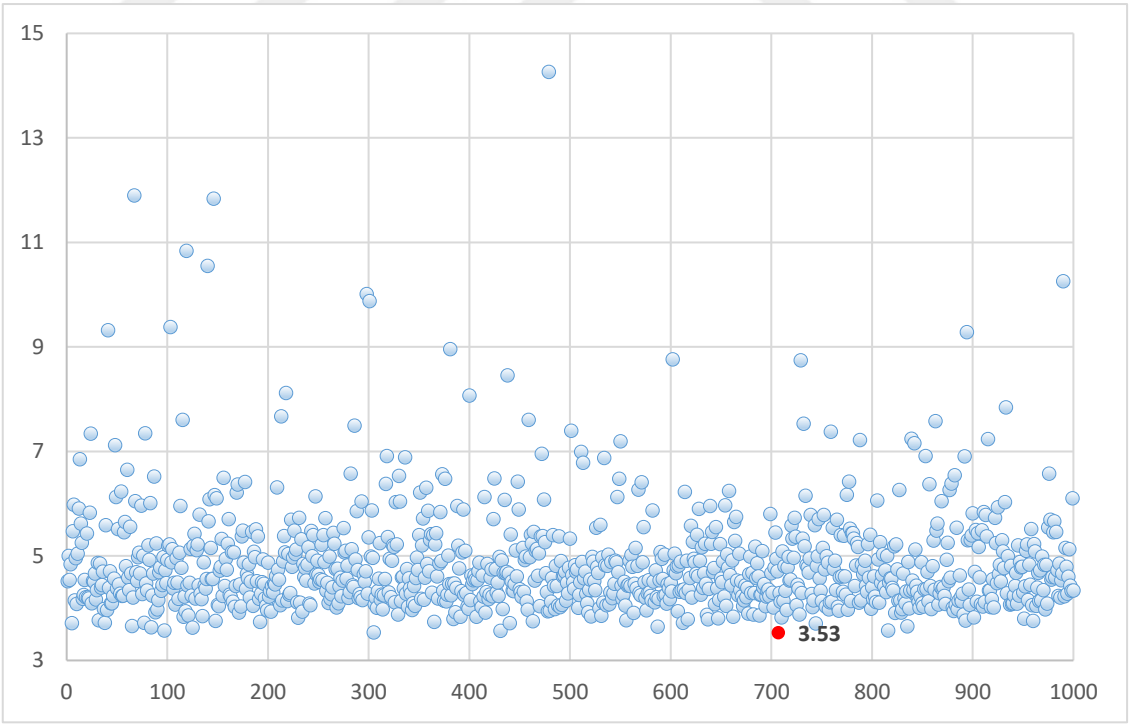

Figure 5.7 RMSE values of testing data in 1000 iterations for 5 nodes in hidden layer

1000 iterations mean 1000 different artificial neural network models and one of them should be chosen for the application. It is uncommon for all performance indicators to choose the same model. Therefore, one of the indicators is given priority and all choices are made accordingly. For example, as indicated in Figure 5.6 and Figure 5.7 with red dots, minimum MAPE (28.08%) is observed in Iteration 587 and minimum RMSE (3.53) is observed in Iteration 707. Since MAPE is the primary indicator, model of the Iteration 587 is chosen as the representative of the model with 5 nodes in hidden layer.

The next step is to repeat this selection process for increasing number of neural nodes in hidden layer until overfitting is observed and find the optimal number of nodes. To detect overfitting, performance indicators of training and cross-validation sets are needed. In Figure 5.8 and Figure 5.9, MAPE and RMSE values of training, cross-validation and testing sets are given for 5 to 12 number of nodes in hidden layer.

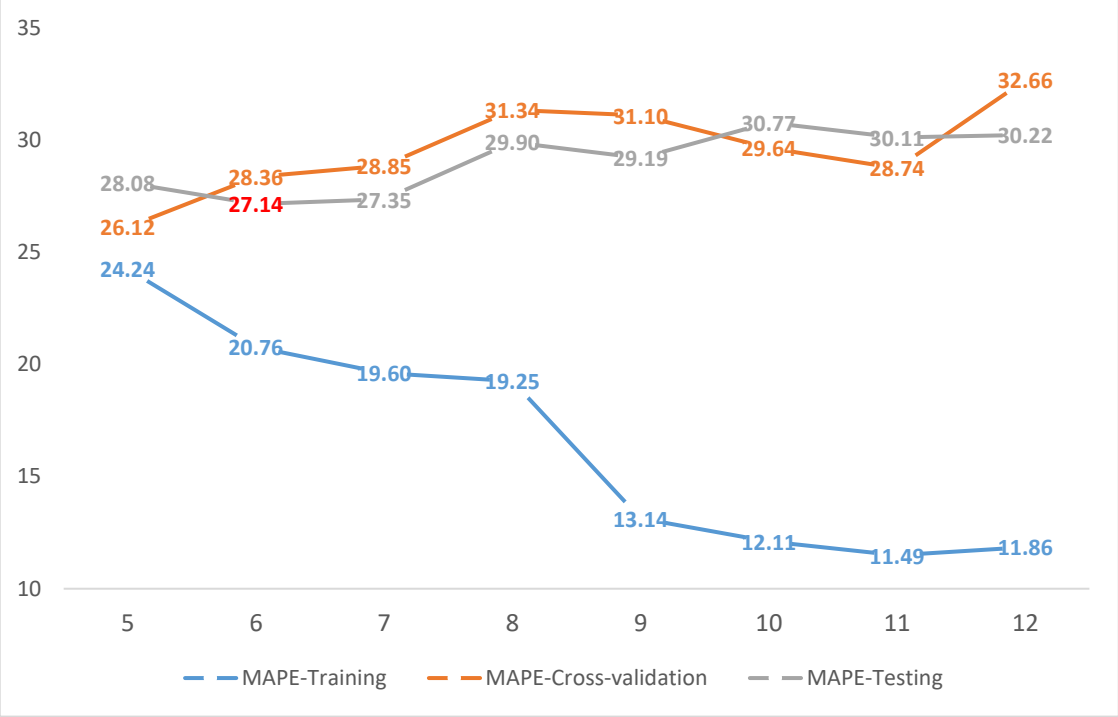

Figure 5.8 MAPE values of training, cross-validation and testing sets for 5-12 number of nodes in hidden layer

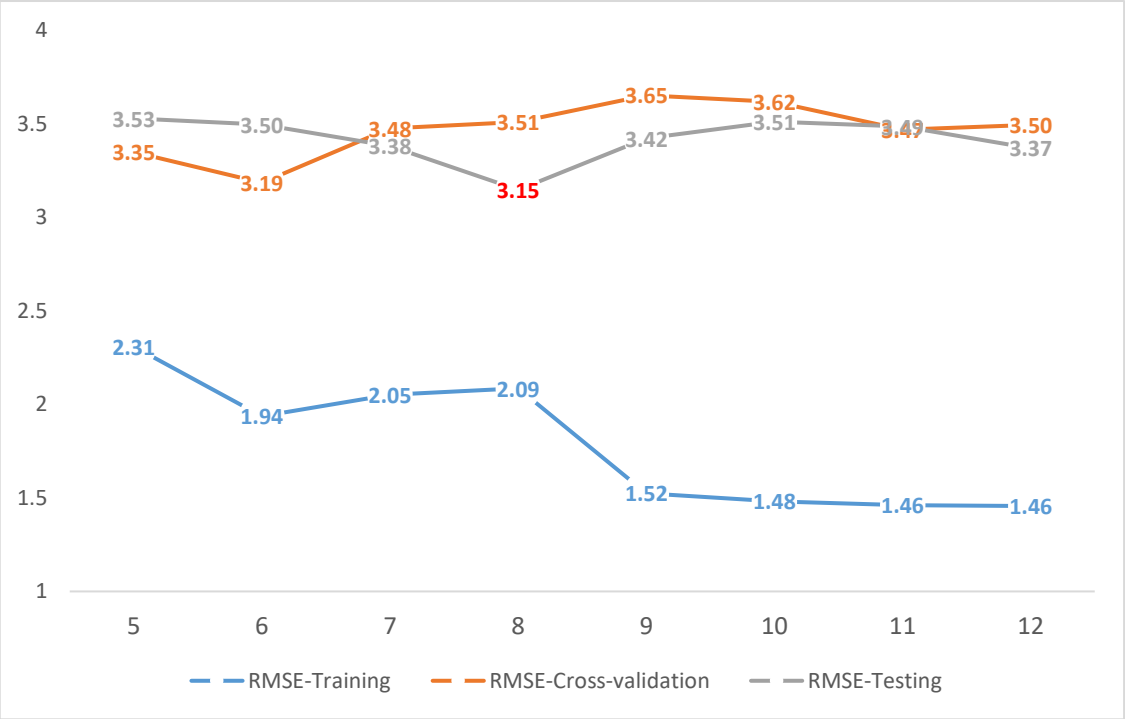

Figure 5.9 RMSE values of training, cross-validation and testing sets for 5-12 number of nodes in hidden layer

In both indicators, overfitting can be easily observed because between 8 and 9 nodes, errors in training set decrease drastically. Simultaneously, errors in cross-validation and testing set increase. These are the signs of overfitting. To be sure, trials are pursued until 12 nodes and no improvements are observed in testing set errors.

According to MAPE values, the optimal number of nodes is 6. However, RMSE values indicate 8 nodes. As MAPE is the primary indicator, the model with minimum MAPE value should be chosen, which has 6 nodes in hidden layer.

Consequently, in the architecture of Model I, given in Figure 5.3, the number of neural nodes in hidden layer is 6. It is a 7x6x1 prediction model. The best performance of Model I has 27.14% MAPE value and 3.50 days RMSE value in testing set.

5.3.2 Application of Model II

Model II has 11 nodes in input layer as presented in Figure 5.5. If the input layers of two models are compared, it is observed that 5 input nodes are common:

- Need of NIMV in hospital (days)
- Nebulizer at home
- Total number of hospitalization
- O2 at home
- Dyspnea Level – mMRC

Two inputs are only included in Model I:

- ALB (Blood Test)
- WBC (Blood Test)

Six inputs are only included in Model II:

- BiPAP at home
- GOLD Stage
- Having treatment properly
- Pretibial Myxedema
- Charlson Comorbidity Index score
- Rehospitalization in 15 days

The presence of 11 nodes in the input layer entails that the trials for the number of nodes in hidden layer start with 8 nodes. In Figure 5.10 and Figure 5.11, scatter plots of MAPE and RMSE values of 1000 iterations are shown. It is observed that MAPE varies between 20% and 140%, and RMSE varies between 2 and 12 days.

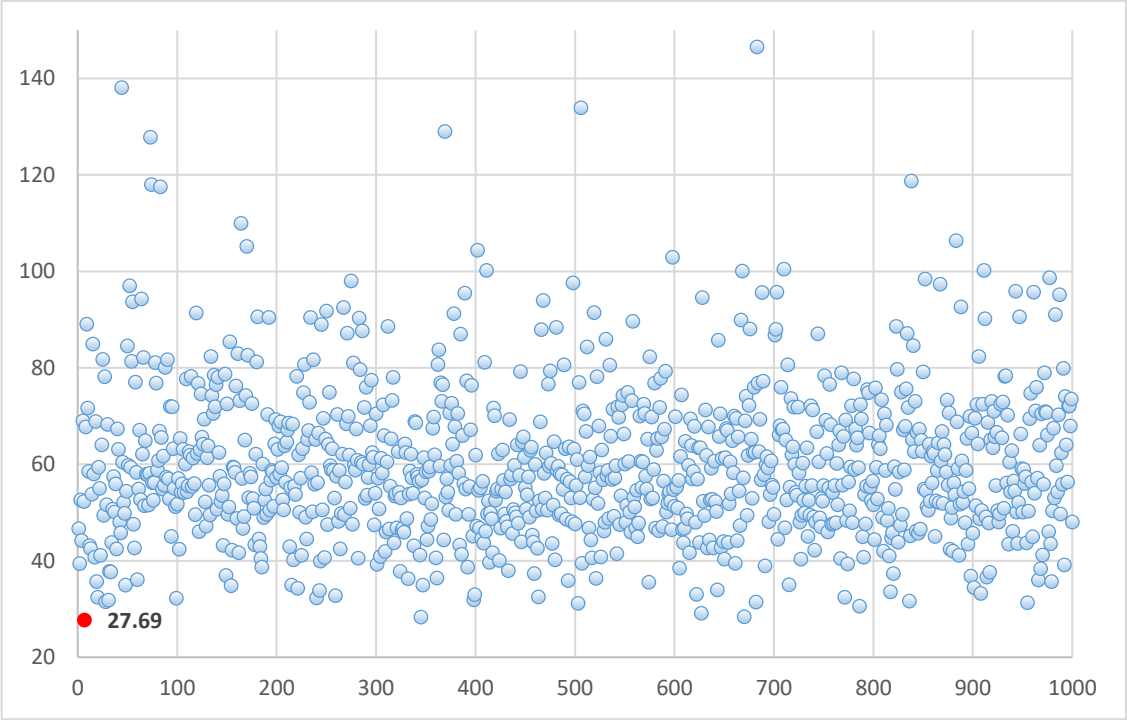

Figure 5.10 MAPE values of testing data in 1000 iterations for 8 nodes in hidden layer

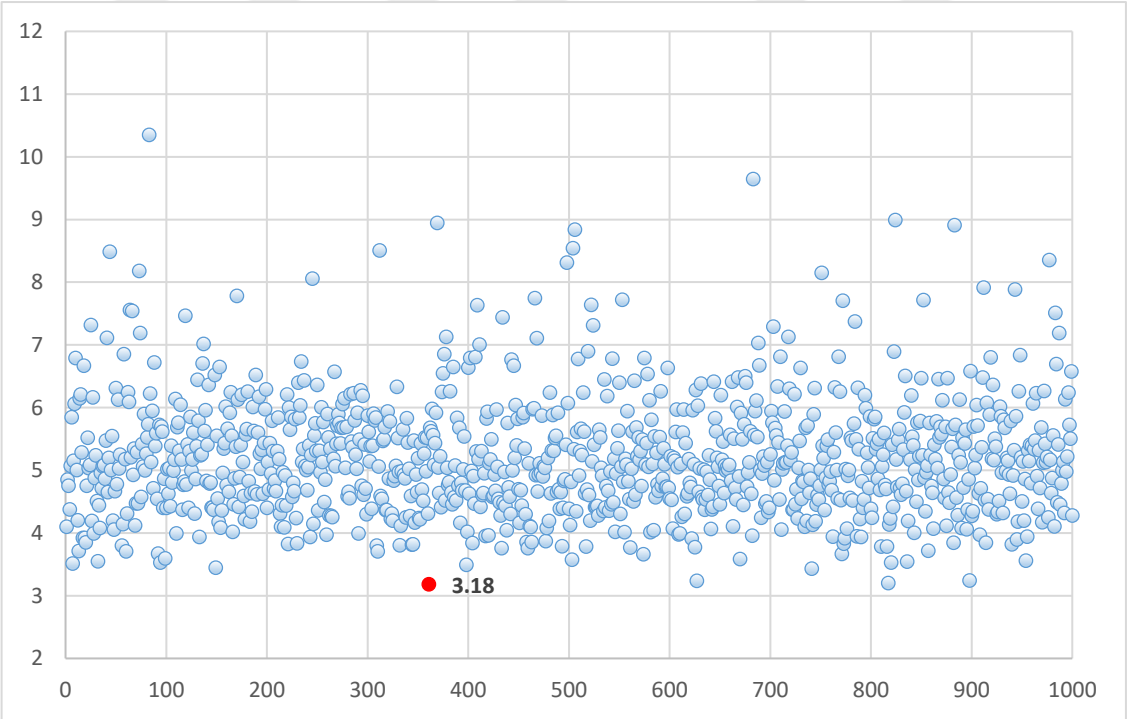

Figure 5.11 RMSE values of testing data in 1000 iterations for 8 nodes in hidden layer

As indicated in Figure 5.10 and Figure 5.11 with red dots, minimum MAPE (27.67%) is observed in Iteration 7 and minimum RMSE (3.18) is observed in Iteration 361. Since MAPE is the primary indicator, model of the Iteration 7 is chosen as the representative of the model with 8 nodes in hidden layer.

This selection process is repeated process for increasing number of neural nodes in hidden layer until overfitting is observed. To detect overfitting and find the optimal number of nodes in hidden layer, MAPE and RMSE values of training, cross-validation and testing sets are given for 8 to 19 number of nodes.

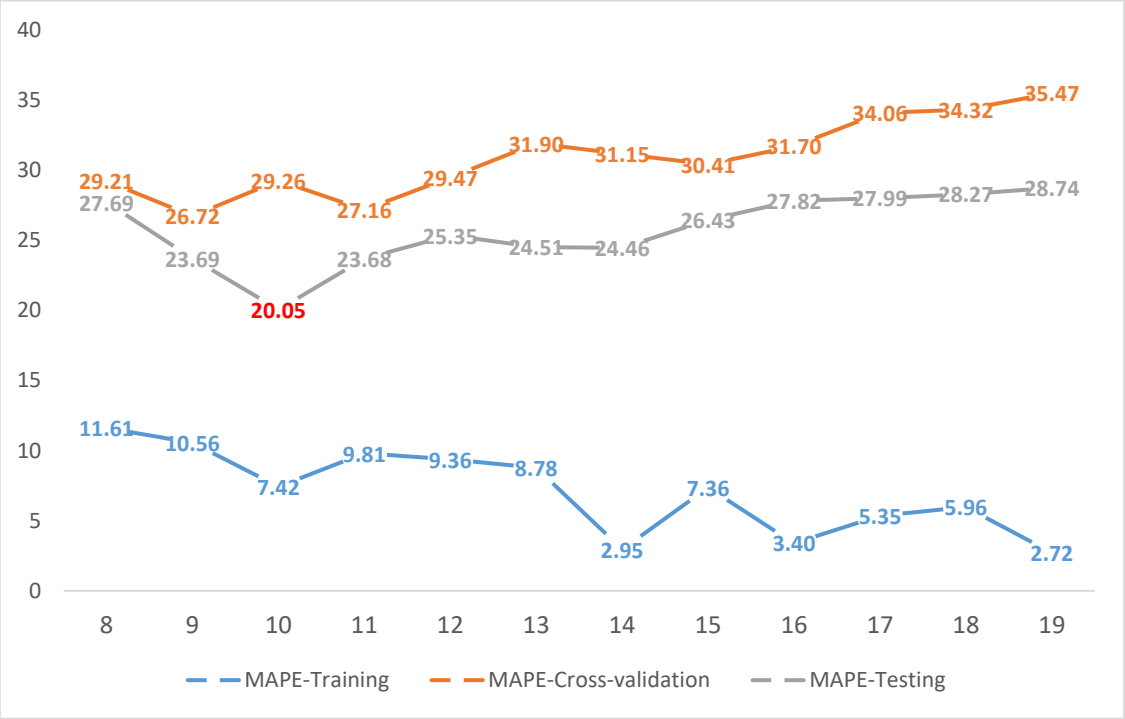

Figure 5.12 MAPE values of training, cross-validation and testing sets for 8-19 number of nodes in hidden layer

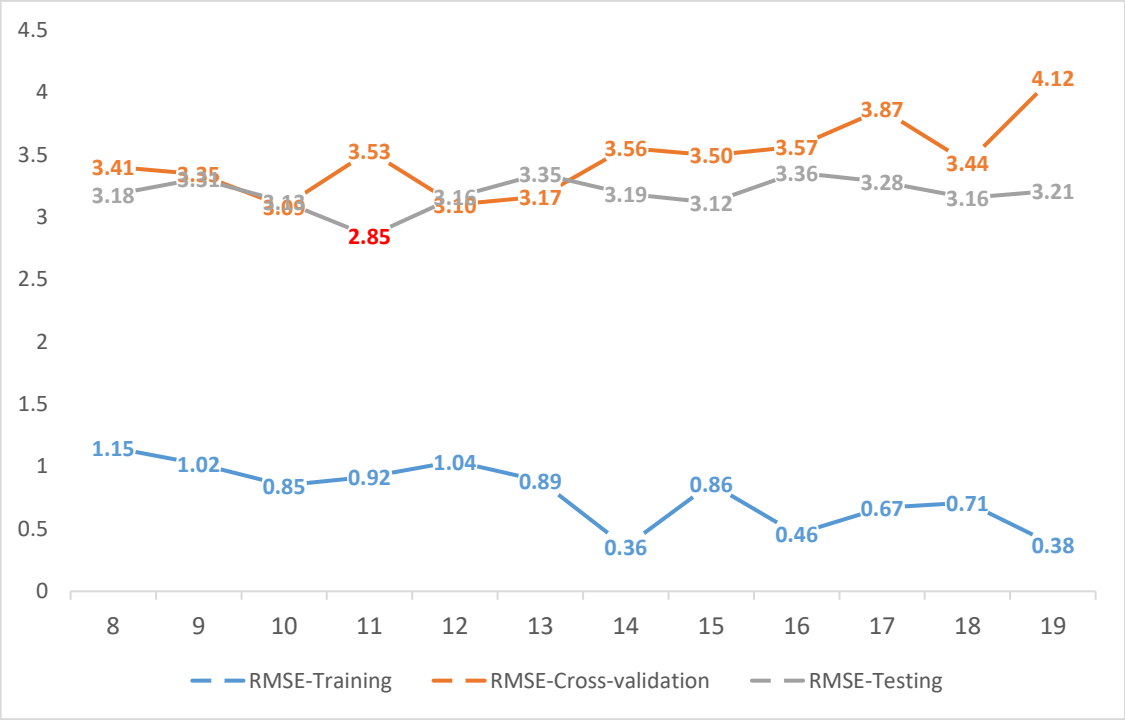

Figure 5.13 RMSE values of training, cross-validation and testing sets for 8-19 number of nodes in hidden layer

In both indicators, overfitting is observed after 13 nodes because of the steep decline in errors of training set. In addition, after 13 nodes, the errors in cross-validation and testing sets begin to escalate, especially in MAPE values.

While executing the application of artificial neural networks, the problems of underfitting and overfitting are observed through the trends in performance indicators. To determine overfitting, a single point or a steep decline is not sufficient. Therefore, even if the steep decline is realized after 13 nodes, the trials continued until 19 nodes with the purpose of observing the trends in all three parts of data sets.

As the primary indicator, MAPE indicates that the best version of Model II has 10 nodes in hidden layer with 20.05% MAPE and 3.13 days RMSE as shown in Figure 5.14 and Figure 5.15. Model II, shown in Figure 5.5, has a 11x10x1 architecture.

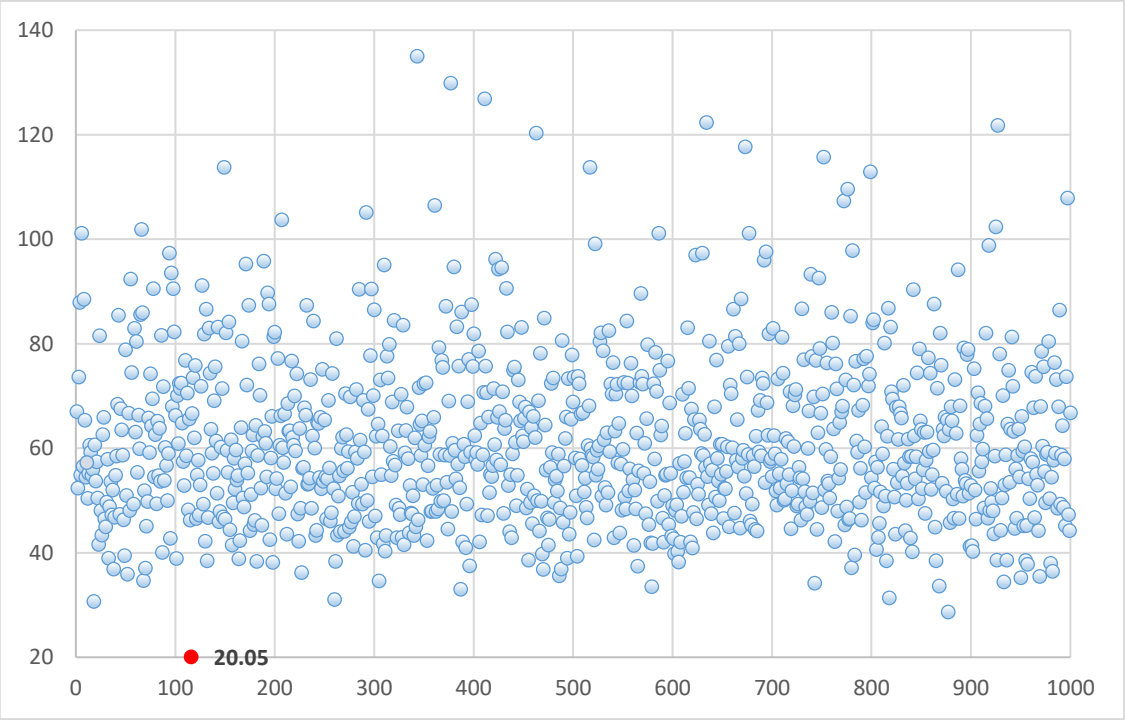

Figure 5.14 MAPE values of testing data in 1000 iterations for 10 nodes in hidden layer

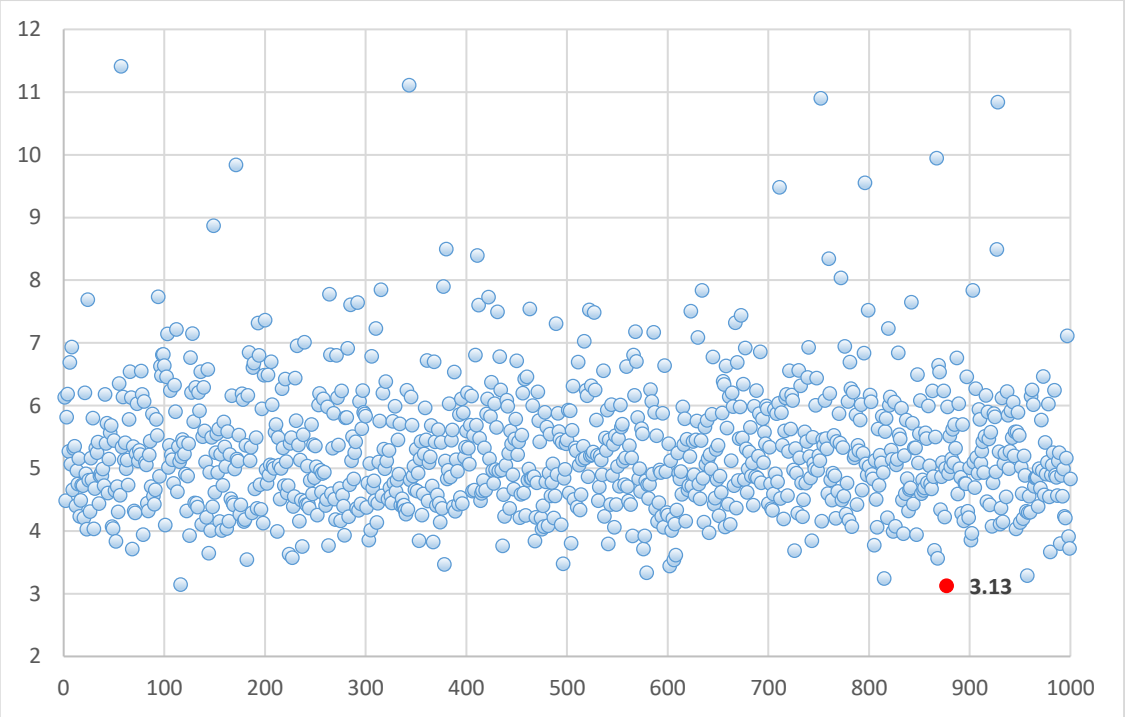

Figure 5.15 RMSE values of testing data in 1000 iterations for 10 nodes in hidden layer

5.4 Discussions on the Results of Model I and Model II

It is worth highlighting that the essential difference between these two models is involvement of expert opinion (opinion of the physicians). The objective of these applications is to predict LoS of COPD patients with maximum accuracy. In daily life, physicians are the only authority to decide on the discharge of patients. Therefore, in this application it is expected that Model II have better results than Model I. In this study, Model II is proposed instead of Model I, which is commonly used in previous studies.

To have a better insight on the results of both models, all performance indicators of training, cross-validation and testing data sets of Model I and Model II are listed side by side in Table 5.4. Model I has the results of 5 to 12 nodes in hidden layer and Model II has 8 to 19 nodes.

Table 5.4 Performance indicators of Model I and Model II

Model I						**Model II**					
MAPE (Percentage)			RMSE (Days)			MAPE (Percentage)			RMSE (Days)		
Train	Cr-V	Test	Train	Cr-V	Test	Train	Cr-V	Test	Train	Cr-V	Test
24.24	26.12	28.08	2.31	3.35	3.53	11.61	29.21	27.69	1.15	3.41	3.18
20.76	28.36	27.14	1.94	3.19	3.50	10.56	26.72	23.69	1.02	3.35	3.31
19.60	28.85	27.35	2.05	3.48	3.38	7.42	29.26	20.05	0.85	3.09	3.13
19.25	31.34	29.90	2.09	3.51	3.15	9.81	27.16	23.68	0.92	3.53	2.85
13.14	31.10	29.19	1.52	3.65	3.42	9.36	29.47	25.35	1.04	3.10	3.16
12.11	29.64	30.77	1.48	3.62	3.51	8.78	31.90	24.51	0.89	3.17	3.35
11.49	28.74	30.11	1.46	3.47	3.49	2.95	31.15	24.46	0.36	3.56	3.19
11.86	32.66	30.22	1.46	3.50	3.37	7.36	30.41	26.43	0.86	3.50	3.12
						3.40	31.70	27.82	0.46	3.57	3.36
						5.35	34.06	27.99	0.67	3.87	3.28
						5.96	34.32	28.27	0.71	3.44	3.16
						2.72	35.47	28.74	0.38	4.12	3.21

In Table 5.4, the models with best performances are marked with red and the primary indicator values are underlined. In their best performances, Model I has 27.14% MAPE and 3.50 days RMSE, Model II has 20.05% MAPE and 3.13 days RMSE. Since MAPE and RMSE are error measures, smaller values indicates better accuracy.

For further analyzing the prediction performances of testing sets, statistical analysis approach is required. Testing sets' performance indicator values of Model I and Model II are considered as two independent samples. To compare their average performances with 95% confidence interval, independent sample t-tests are conducted with SPSS 23.0 for Windows software. While comparing MAPE and RMSE values of two samples, Levene's test for equality of variances neither suggest a significant difference in variances of MAPE ($F = 3.215$, $p = 0.090$) and nor in variances of RMSE ($F = 0.005$, $p = 0.945$). Therefore, t-tests are conducted with equal variances assumed. SPSS 23.0 independent samples t-test outputs are shown in Table 5.5.

Table 5.5 Independent samples t-test statistics for equality of means

Group Statistics			N	Mean	Std. Deviation	Std. Error Mean
MAPE-Testing	Model I		8	29.095	1.397	0.494
	Model II		12	25.723	2.579	0.745
Independent Samples Test / t-test for Equality of Means						
					95% Confidence Interval of the Difference	
t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
3.363	18	.003	3.372	1.003	1.265	5.478
Group Statistics			N	Mean	Std. Deviation	Std. Error Mean
RMSE-Testing	Model I		8	3.419	0.124	0.044
	Model II		12	3.192	0.136	0.039
Independent Samples Test / t-test for Equality of Means						
					95% Confidence Interval of the Difference	
t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
3.780	18	.001	.227	.060	.101	.353

Table 5.5 indicates that an independent sample t test reported a significant difference in MAPE of Model I and Model II, *t (18) = 3.363, p = 0.003, 95% C.I. [1.265 – 5.478]*. Model II has lower MAPE (*Mean=25.723, Std. Deviation=2.579*) as compared to Model I (*Mean=29.095, Std. Deviation=1.397*). In addition, an independent sample t test reported a significant difference in RMSE of Model I and Model II, *t (18) = 3.780, p = 0.001, 95% C.I. [0.101 – 0.153]*. Model II has lower RMSE (*Mean=3.192, Std. Deviation=0.136*) as compared to Model I (*Mean=3.419, Std. Deviation=0.124*).

In fact, the difference between the performance indicator averages of the two models is not important in terms of model selection. The final decision is about the minimum MAPE obtained. If the average of one model were larger than the other's average, but if its minimum value were smaller than the minimum value of the other, then that model would be chosen. The statistical test was conducted to measure the overall success of Model II, since it has been already preferred by minimum MAPE.

In the application, both performance indicators state that Model II has a better prediction accuracy than Model I. Moreover, statistical tests indicate a significantly higher average performance. The model that involves expert opinion has significantly better results than the model that only considers statistical data.

The use of artificial neural networks in medical decision support is an increasing trend among researchers. Machine learning techniques provide numerous advantages in deeply understanding and summarizing data.

In this study, a novel and integrated prediction model is proposed and its first application is conducted for the prediction of LoS of COPD patients who admitted the hospital with acute exacerbation. Prediction of LoS has a major role in effective scheduling of available hospital rooms and therefore in hospital management.

Artificial neural networks technique has been already recognized as a successful prediction and classification tool in the medical decision support literature. However, many details in its practical application affect its precision and performance. In particular, the selection of inputs is directly related to the performance of the model. There exist many factor analysis methods as principal component analysis, maximum

likelihood, weighted and unweighted least squares etc. that can be implied by data analysis programs.

On the other hand, in medical studies concerning artificial neural networks, the variables that are significantly correlated with the output variable, are selected as input variables and the results are usually compared with multivariate regression methods. These methods have a property in common; they are all data-driven methods.

In this chapter, SBFCM method is proposed for the selection of inputs of the artificial neural network model. SBFCM method considers the data and the expert opinion simultaneously. With the purpose of predicting LoS of patients, among 49 variables, 7 variables are selected by their correlation coefficients with LoS and data-driven Model I is constructed as the common method in the literature. Then, through SBFCM method, 3 experts' opinion is included and 11 variables are selected to construct Model II, which is the proposed model.

MAPE and RMSE are used as performance indicators and after the numerical application; it is observed that Model II outperforms Model I for both indicators. The best version of Model II has 20.05% MAPE and 3.13 days RMSE. It means the integration of SBFCM and artificial neural network methods approximate the LoS of a patient with an average of 79.95% accuracy.

At first glance, 79.95% accuracy may not seem like an outstanding performance. In the literature, comprehensive studies of artificial neural networks are closer to 100% accuracy. However, these studies have spread over a long period and have collected a large amount of data. In this first application, 154 patients who were admitted to a single hospital within one year were used. Therefore, the accuracy is very successful for this amount of data. Training algorithm of artificial neural networks works better with large amounts. The integrated model proposed in this study has not given perfect results yet, but it definitely has a promising future for broader research projects.

6. CONCLUSIONS

Medical science is very receptive to the support and integration of technological developments, and artificial intelligence has a major role in technological advancements of this era. It is not a coincidence that the first applications of artificial intelligence technology are conducted in healthcare. A large amount of diseases still exists in the world and breeds social inequality and poverty. These diseases have higher prevalence in low- and middle-income countries, and threaten the future by mostly affecting children. In addition, the economic burden of these diseases prevents the development of countries. Therefore, scientists strive with these diseases with the latest technology that they have; artificial intelligence.

In this thesis, three serious diseases are examined in detail, using four different artificial intelligence techniques in order to construct medical decision support systems.

First technique was fuzzy c-means and it is used for faster diagnosis of diabetes mellitus via other patient information in an emergency. Fuzzy c-means is an extension of conventional k-means clustering method that uses the fuzzy sets. To develop the method in clustering, a family of fuzzy sets is defined a fuzzy c-partition on a data points' universe. Since fuzzy sets accept for membership degrees, the crisp classification idea can be extended into a fuzzy classification concept, which makes the method more suitable for medical applications. Diagnosis of diabetes is not difficult however; its process needs time and consciousness of the patient. When an unconscious patient is brought to emergency for a reason that is not related to DM, it is highly problematic to understand if he/she had DM as a comorbid disease. This information is vital because it might change the treatment given in the emergency.

Patient data is gathered in a full-fledged state hospital in Istanbul. A sample of 100 patients admitted to hospital with diverse complaints is prepared. After an interview with the physicians, mostly demographic factors and blood test results are included in application for a faster diagnosis. 23 types of patient data are observed: Age, gender, height, weight, glucose, urea, creatinine, total protein, ALB, CRP, ESR, WBC, HGB, HCT,PLT, AST, ALT, PH, CO2, O2, SPO2, breaths per minute (BPM) and number of pulses per minute (PPM). Numerical application is performed with MATLAB Software Fuzzy Logic Toolbox. Fuzzy c-means reached an accuracy of 81%. As a medical decision support model, 81% accuracy is interpreted as useful by the physicians.

Second technique was intuitionistic fuzzy cognitive maps and it is used in risk assessment of multi-drug resistant tuberculosis. Fuzzy cognitive map is a causal knowledge-driven methodology for modeling complex decision systems, coming out from the combination of fuzzy logic and neural networks. It allow fuzzy numbers or linguistic terms to be used to describe the degree of the relationship between concepts. IFCM is an extension of FCM with Atanassov's intuitionistic fuzzy sets, which differ from fuzzy sets with their ability of representing hesitation degrees of decision makers in the mathematical model. Therefore, in medical decision making, where decision makers claim that they are hesitant about the information they give, IFCM is preferred.

MDR-TB is a type of TB that does not respond to the two most powerful first-line anti-TB drugs: rifampicin and isoniazid. MDR-TB can be treated with second-line TB drugs with an extensive treatment up to two years. It is continuously emerging and spreading around the world. Utilization of incorrect or low quality medications, poor healthcare conditions, poor quality of life, and dropping the treatment prematurely may lead to drug resistance, which is transmitted especially in crowded areas as hospitals and prisons. After a patient is diagnosed with TB, a number of drug-susceptibility tests are performed to determine whether it is TB or MDR-TB and the test results are completed in approximately 45 days. Since the prevalence of TB is higher than the prevalence of MDR-TB, standard TB treatment is given to the patient during this process. If the patient is MDR-TB, it is a waste of time and an unnecessary load of chemicals to the patient's body, especially to the liver. Considering that liver health is essential to the

effectiveness of the rest of the treatment, it is vital for the patient to predict resistance quickly in a TB patient.

In order to assess the risk of multi-drug resistance, the factors that influence the resistance development are determined. These factors are not the risk factors of being infected with TB, but the risk factors of having primary resistance in a newly diagnosed TB patient. First, an in-depth literature research is conducted to find all the risk factors that have been investigated previously, and then three chest diseases experts are interviewed, risk factors are classified and defined. Nine factors are determined as system concepts: Age, substandard housing conditions, BMI, history of MDR-TB exposure, presence of comorbidities, previous use of TB antibiotics, being an immigrant, history of imprisonment and history of travel to high-risk country. To obtain a conceptual map of the system and calculate the final values of the factors, three chest disease specialists evaluated the concepts. Relation and hesitation matrices of each expert are constructed as 9x9 matrices for pair-wise causal relations between each of the 9 concepts. Three relation matrices and three hesitation matrices of three decision makers are aggregated and defuzzified using max aggregation and centroid defuzzification methods. Using the weight matrix, a conceptual map of the system is obtained. Then the iterations are operated using MATLAB Software and the final value of the concepts are calculated. “”History of MDR-TB exposure”, “Substandard housing conditions”, and “Previous use of TB antibiotics” had the greatest influence values in the system. When the results are discussed with the decision makers, they stated their total agreement with the results. The results and the ranking order were expected however, the ability of analyzing new scenarios for each patient was unexpected. They pointed out the usefulness of the model in daily decisions of newly diagnosed TB patients.

When the first two applications are summarized, both fuzzy c-means technique and intuitionistic fuzzy cognitive maps obtained favorable results. However, fuzzy c-means is a data-driven technique and IFCM is an expert opinion-based method. Fuzzy c-means is totally objective and IFCM is very subjective. Then the research question raised; can the powers of statistical analysis and human experience be combined?

At this point, the third technique, statistical-based fuzzy cognitive maps is proposed for the assessment of length of hospital stay predictors of chronic obstructive pulmonary disease patients that admitted to the hospital with acute exacerbation. COPD is one of the most common chronic respiratory diseases with various clinical presentations, which is characterized by airflow limitations because of diverse problems in airways and other components of the lung. An acute exacerbation of COPD is defined as sudden development of respiratory symptoms with malfunctioning of airways. Acute exacerbations frequently result in hospital admission of patients. It is estimated that hospital expenditures correspond to 70% of total costs of COPD management and the length of hospital stay is directly related to these expenditures.

To determine the most important predictors of LoS, the novel SBFCM method is developed, which aggregates the power of statistical analysis with dynamical nature FCMs. SBFCM method conducts statistical analysis to prepare preliminary information for the experts and then collects expert opinions accordingly, in order to define a conceptual map of the system. It first extracts the relationships from the data, and then inserts expert opinion to construct a frame so that the resulting system becomes semi-subjective. SBFCM is the very first method that unites two effective methods in medicine; statistics and fuzzy cognitive mapping.

Fifty factors, including LoS, are adopted as system concepts and observed under four groups: Socio-Demographics (age, gender, occupational exposure, height, weight, smoking, biomass exposure, passive smoker and pack-years), Clinical Findings (glucose, urea, creatinine, total protein, ALB, CRP, ESR, WBC, HGB, HCT, PLT, ALT, AST, FEV-1 Test Result, FEV-1/FVC Test Result, GOLD Stage, PH, CO2, O2, SPO2, cyanosis, breaths per minute and number of pulses per minute), Comorbidities (pretibial myxedema, Charlson Comorbidity Index score, other lung disease, hypertension, diabetes mellitus, ischemic heart disease and cardiac insufficiency), and Medical Records (years of illness, having treatment properly, nebulizer at home, O2 at home, BiPAP at home, re-hospitalization in 15 days, emergency admissions in the last year, need of NIMV in hospital, total number of hospitalization, dyspnea level, and LoS). Medical data of 154 patients for all system concepts are collected. Statistical

analysis is conducted to determine the relationships between the system concepts and statistical tests are performed to extract all significant relationships. Statistical results are prepared as a preliminary data for the experts. Afterwards, three experienced physicians of the hospital provided medical support with their expert opinion. Experts defined the causalities among the significant relationships thus, a conceptual map of the system is provided. System behavior is observed, the most powerful factors on LoS are determined through iterative steps and different scenarios suggested by the experts are generated for an in-depth understanding of the system. The results stated that Need of NIMV in hospital, Nebulizer at home, O2 at home, BiPAP at home, GOLD Stage, Having treatment properly, Pretibial Myxedema, CCI Score, Total number of hospitalization, Re-hospitalization in 15 days and Dyspnea Level factors have more than 99% strength in determining LoS of a COPD patient with acute exacerbation. The results of SBFCM methodology were interpreted as significant by chest disease specialists in the real-case numerical application, which indicates that SBFCM can be a useful decision making tool for physicians and hospital managers.

Fourth technique was artificial neural networks and it was used to predict LoS of COPD patients, which was examined in detail with SBFCM application. Essentially, artificial neural networks are mathematical models that are able to capture the knowledge contained in the data by imitating human neurons. They are useful in detecting nonlinear and complex relationships between different kinds of variables where conventional statistical methods may fail to detect.

As a further research on the novel SBFCM method and, with the purpose of predict LoS of COPD patients with maximum accuracy, two different artificial neural network models are constructed. The first model (Model I) represented the conventional approach, which has been widely used in medical literature and the second model (Model II) represented the novel approach of integration with SBFCM method. The difference between these two models was involvement of expert opinion (opinion of the physicians). To measure the prediction performances, two different performance indicators are observed: MAPE and RMSE. MAPE is used as the primary performance indicator because of its frequent use in medical decision-making and ease of

interpretation by the physicians. RMSE is used as secondary indicator. All prediction models are implemented using MATLAB R11b - Neural Network toolbox. As a supervised learning algorithm, back-propagation is used. The original data of 154 COPD patients is randomly separated into three parts with proportions of 70%, 15%, 15%. Training, cross-validation and test data included 108, 23 and 23 COPD patients, respectively. For both models, the quantity of neural nodes in hidden layer are decided using performance indicators.

Among 49 variables, 7 variables are selected by their correlation coefficients with LoS and data-driven Model I is constructed as the common method in the literature. Then, through SBFCM method, 3 experts' opinion is included and 11 variables are selected to construct Model II, which was the proposed model. After the applications, in the architecture of Model I, the number of neural nodes in hidden layer was 6. It was a 7x6x1 prediction model. The best performance of Model I had 27.14% MAPE value and 3.50 days RMSE value in testing set. In the architecture of Model II, the number of neural nodes in hidden layer was 10. It was a 11x10x1 prediction model. The best performance of Model II had 20.05% MAPE value and 3.13 days RMSE value in the testing set.

For a better insight on the results of both models, statistical tests are conducted. To compare the average performances with 95% confidence interval, independent sample t-tests are conducted with SPSS 23.0 for Windows software. An independent sample t test reported a significant difference in MAPE of Model I and Model II, *t (18) = 3.363, p = 0.003, 95% C.I. [1.265 – 5.478]*. Model II has lower MAPE (*Mean=25.723, Std. Deviation=2.579*) as compared to Model I (*Mean=29.095, Std. Deviation=1.397*). In addition, an independent sample t test reported a significant difference in RMSE of Model I and Model II, *t (18) = 3.780, p = 0.001, 95% C.I. [0.101 – 0.153]*. Model II has lower RMSE (*Mean=3.192, Std. Deviation=0.136*) as compared to Model I (*Mean=3.419, Std. Deviation=0.124*).

Consequently, both performance indicators stated that Model II has a better prediction accuracy than Model I. Moreover, statistical tests indicated a significantly higher

average performance. The model that involves expert opinion had significantly better results than the model that only considers statistical data.

Briefly, the main contributions of this thesis are:

1) A medical decision support framework is constructed for faster diagnosis of diabetes mellitus disease and the usefulness of data-driven fuzzy c-means algorithm is shown.

2) A medical decision support framework is constructed for the detection of multi-drug resistant tuberculosis disease and the practicability of expert opinion-based intuitionistic fuzzy cognitive maps are shown, by means of their ability of representing the hesitation degrees of decision makers in the mathematical models.

3) The novel statistical-based fuzzy cognitive maps method is proposed, its first application is conducted in COPD management and its effectiveness is shown by analyzing different scenarios.

4) A medical decision support framework is constructed for prediction of length of hospital stay of COPD patients, using the integration of SBFCM and artificial neural network techniques. The integrated approach proved to be better than the conventional approach.

To conclude, artificial intelligence is one of the most promising technological developments of this era. With big data implications, its effectiveness and simplicity of implementation will further increase. However, it cannot replace human intuition and human knowledge in a near future. The methods that would empower artificial intelligence with human knowledge will probably have the most successful outcomes. It is still early for computers to replace human, but these are best times for human and computer to combine their powers.

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