DOKUZ EYLÜL UNIVERSITY

GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES

AUTOMATIC PRIORITY SCORING SYSTEM FOR CORNEAL TRANSPLANTATION USING SOFT COMPUTING TECHNIQUES

by

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October, 2015

İZMİR

AUTOMATIC PRIORITY SCORING SYSTEM FOR CORNEAL TRANSPLANTATION USING SOFT COMPUTING TECHNIQUES

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by
Vahid BEHROUZ

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M.Sc. THESIS EXAMINATION RESULT FORM

We have read the thesis entitled **"AUTOMATIC PRIORITY SCORING SYSTEM FOR CORNEAL TRANSPLANTATION USING SOFT COMPUTING TECHNIQUES"** completed by **VAHID BEHROUZ** under supervision of **ASST. PROF. DR. MUSTAFA ALPER SELVER** and we certify that in our opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Science.

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ABSTRACT

Corneal blindness is one of the most important reasons of blindness worldwide. The corneal transplantation surgery is currently the only effective solution for this disease. The selection of the adequate transplantation candidates for an available cornea relies on the decision of the surgeon, who generally uses features including but not limited to the age, interval of vision loss, and visual acuity as the decision criteria. Due to the severe lack of donors, the large number of candidates causes long waiting lists, which makes the selection process tedious, time consuming and error-prone. Therefore, the development of an automatic priority system for determining a set of appropriate candidates for an available cornea is necessary. In this study, such a system is developed using a new neural network based approach. Several features are used as the input of the system during the training. For the application phase, a tournament based classification strategy, which allows fast and reliable selection of the best candidates, is developed. The application of the system to an expert generated waiting list shows promising results in terms of decision performance and speed.

Keywords: Corneal transplantation, classification, tournament strategy, artificial neural networks

KORNEA NAKLİ İÇİN ESNEK HESAPLAMA TEKNİKLERİ İLE OTOMATİK ÖNCELİK BELİRLEME SİSTEMİ

ÖZ

Kornea nedenli körlükler genel olarak körlüğün en önemli nedenlerinden biridir. Kornea nakli ameliyatı günümüzde bu hastalık için tek etkili çözümdür. Kullanılabilir bir kornea nakli için uygun adayların seçimi genellikle karar kriteri olarak yaş, görme kaybı, görme keskinliği gibi öznitelikleri kullanan sorumlu cerrahın inisiyatifindedir. Donör sayısındaki ciddi eksiklik nedeniyle adayların çok uzun bekleme listeleri oluşturması seçim sürecini yorucu, zaman alıcı ve hataya açık hale getirmektedir. Bu nedenle, mevcut kornea için bir dizi uygun aday belirlemek üzere otomatik bir öncelik sisteminin geliştirilmesi gereklidir. Bu çalışmada, bu tür bir sistem, yeni bir sinir ağı tabanlı yaklaşım kullanılarak geliştirilmiştir. Çeşitli özniteliklerin sistemin girdisi olarak kullandığı sistemde adayların hızlı ve güvenilir seçilmesini sağlayan bir turnuva tabanlı sınıflandırma stratejisi geliştirilmiştir. Uzmanlar tarafından oluşturulmuş bir bekleme listesi ile yapılan uygulama sonucunda sistemin başarımı ve uygulama hızı ümit verici sonuçlar göstermektedir.

Anahtar kelimeler: Kornea nakli, sınıflandırma, turnuva stratejisi, yapay sinir ağları

CONTENTS

LIST OF FIGURES

Pages

LIST OF TABLES

Pages

CHAPTHER ONE

INTRODUCTION

Approximately, 6 to 10 million people are suffering from corneal blindness, which is about 10% of total blindness worldwide. The only possible treatment for corneal blindness is the corneal transplantation (Whitcher et al., 2001). Corneal transplantation, the removal of diseased corneal tissue and replacement with healthy tissue from a deceased donor by a corneal expert is the important treatment. Since the first successful full thickness human corneal transplantation, which was performed in 1905 (Zirm, 1906), there are several progresses about corneal transplantation surgery such as the development of preservative solutions for the corneal tissue, immunosuppressive agent usage for increasing the clinical success after the surgery, eye-banking organization all over the world (Filatov, 1935; Paton, 1991; Maumenee, 1941; Maumenee & Kornbluet, 1948; Doughman et al., 1976; Anderson & Ehlers, 1986).

The first successful human corneal transplant was performed in 1905 by an Austrian surgeon Dr. Eduard Zirm, who gave a labor worker his sight back after having been blinded accidentally by burning his eyes with caustic lime (Zirm, 1989). Almost 50 years later in 1954 the first kidney transplant was achieved (Merrill, et al., 1956). In the 1960s, lung, pancreas, liver, and heart transplants were successfully accomplished (Barnard, 1967; Kelly et al., 1967; Hardy et al., 1963; Cooley et al., 1969; Starzl et al., 1968).

In the 1970s, meaningful advancements in postoperative immunosuppressant medication was achieved by the introduction of cyclosporine which was given as part of a “cocktail,” together with steroids (Murray et al., 1963).

The United Network for Organ Sharing (UNOS) website (http://www.unos.org) reports that in 2009 more than 19,000 organ transplants were performed in the USA, while the number of candidates awaiting transplantation was 118,000. The gap between the number of available donor organs and the number of people who need organs still grows (http://optn.transplant.hrsa.gov).

In order to deal with this ongoing issue, most countries have developed formal systems to determine, control, and allocate available donor organs. Transplant calculators have long become the gold standard guideline in deciding which candidate has preference over another for a certain organ transplant.

Each tissue or organ has its own designated calculator with relevant parameters. An example of such a calculator is the Lung Allocation Score (LAS), a numerical calculation used for allocating lungs to candidates who are 12 years of age or older (Davis & Garrity, 2007).

Similar calculators are available for other types of organ transplants such as liver, kidney, and others (Davis & Garrity, 2007; Cholongitas et al., 2010; Leffell, 2011; Cecka, 2009). Only a few countries around the world, most of which are in Europe and North America, have institutionalized corneal banks with corneal reserves which are available for transplantation surgery at almost any time. Furthermore, some of these countries offer the selling of available corneas from their banks to worldwide institutes.

In most countries, there is a great lack of corneas for transplantation. Long waiting lists translate to long waiting times. Even in Europe, the request to draw a post-mortem blood sample within 24 h post-mortem (EU-Directive requirement) led to shortage of transplants (Technical Guidelines for Ocular Tissue, 2013).

Once a cornea becomes available, the cornea specialist is faced with a difficult decision in determining which of his candidates to appoint the cornea to. The decision making may be long and hard, needing to go through the medical history of each patient, and estimating who will benefit from the transplant the most.

In the study which was published in 2002 (Saunders et al., 2002), a prioritization system was based on the assumption that patients who can achieve the best improvement in visual acuity, visual function, or reduction in pain, should be the ones who should receive the highest priority for surgery. Their study concluded that patients who had a high preoperative priority score were more likely to have a good outcome, and that their priority system was accurately identifying patients at greatest need for surgery.

In contrast to the requirements of other transplantation surgeries, the evaluation process of corneal transplantation candidates does not require blood group similarity and cross match (HLA antigen) competition. The selection of the adequate transplantation candidate for an available cornea relies on the decision of the surgeon, who will perform the operation. Albeit being dependent on the surgeon, the decision criteria usually depends on the age, interval of vision loss, visual acuity and related features (George & Larkin, 2004). Considering the gap between the number of available donor organs and the number of people who are waiting, the decision process of the surgeon becomes tedious, time consuming and error-prone. Therefore, the development of a priority system for determining the appropriate candidates for an available cornea is necessary and suggested by several studies (Rosenfeld, & Varssano, 2013; Courtrigh, et al. 1997; Saunders, et al. 2002). Although, there are standard methods for the candidate evaluation of other tissue and/or organ transplantations, there is still no commonly accepted corneal candidate evaluation method (Rosenfeld & Varssano, 2013).

The concept of artificial intelligence today has reached a significant level of technology, which can mimic many important features of human thinking and learning ability. One of the well-developed fields of artificial intelligence is the Artificial Neural Networks (ANN), which can be used to realize an intelligent black box model performing classification, non-linear regression and other tasks requiring nonlinear approximation property, adaptability and generalization ability. Using ANN's capacity on non-linear regression, several different scoring systems for various applications are proposed. These include medical applications such as sleep stage scoring (Schaltenbrand et al., 1996; Kim & Park, 2000) hepatic fibrosis grading ultrasonic imaging (Zhang et al., 2012), radiotherapy treatment planning, evaluation and scoring (Willoughby et al., 1996). Some of these scoring systems (Pacelli & Azzollini, 2011) are also integrated into software solutions in different areas such as credit scoring in economics (http://www.alyuda.com; http://www.plug-n-score.com). In all those systems, the output of the ANN is a score, which is clearly determined by the experts or using some certain rules. Then, all of these developed systems actually perform a regression process in order to find the output score.

In the introduced corneal transplant surgery scoring system, the parameters, which surgeons interpret to decide the appropriate candidates, can be used as the input features of an ANN. These features include but not limited to visual acuity, visual function, reducing pain, sex, and risk of infection. Thus, the organization of the input can be constructed as a traditional ANN scheme. However, in the selection of the candidates, the output of the ANN cannot be evaluated by a score. Since the experts only select a set of potential candidates and then chose the most appropriate one for the transplantation, there is no score for the output variable. Therefore, the problem can naturally be posed as a classification problem rather than regression.

On the other hand, the design of an ANN as a classifier in order to select the best one among many candidates faces another challenge. If the number of patients, who are waiting for the transplantation, is high, the output of the ANN must have too many outputs in order to encode the winner. This requires a much more complex ANN design. Moreover, it reduces generalization capability and robustness of the system.

In order to overcome this challenge, in this study, the candidate selection is posed as a binary classification problem. Instead of finding the best candidate at once, the proposed system utilizes a tournament strategy. The designed system takes features of a pair of transplantation candidates, i.e. two patients, as its inputs, and binary classification decides who wins among the pair of candidates. Systematic application of this approach to whole data set finally ends up with a single winner, who is the best candidate among all candidates.

CHAPTER TWO

REVIEW ON ARTIFICAL NEURAL NETWORKS

2.1 Definition of Artificial Intelligence

Since the invention of computers the possibility of intelligent machines allured many, and as will be shown in the historical review, the precursors of an Artificial Intelligence precede those of the invention of computers. What do they refer to by the term Artificial Intelligence, even when the word intelligence is very hard to describe? Much debate was focused on the exact definition for the term intelligence, and more for the Artificial Intelligence, and a heap of confusion was the result. Even a single dictionary contains as much as four definitions for Artificial Intelligence:

Artificial intelligence is an area of study in the field of computer science which concerned with the development of computers able to entertain in human-like thought processes such as learning, reasoning, adapting, self- correction and self-correction.

The deploy of human intelligence through the use of computers, as in times past physical power was extended through the use of mechanical tools. In a restricted sense, the study of techniques to use computers more effectively by improved programming techniques (*The New International Webster's Comprehensive Dictionary of the English Language, Encyclopedic Edition*).

In the wake of rapid advances, the definitions changed, too. More recent definitions include phrases like "imitating intelligent human behavior", a definitively more striking definition compared to the previous. Artificial Intelligence community, for a considerable period, has been engaged with trials on imitation of intelligent behavior through computer programs. This, however, is not quite simple, for the program should be capable of a wide range of different activities to be referred to as intelligent.

Rather than the more encompassing definitions of Artificial Intelligence, one may focus on the definition of artificially intelligent systems as well. A number of definitions for such are available, but the general bit can be confined within the four following categories:

- systems which imitate human behavior
- systems which contemplate rationally
- systems which imitate human-like contemplation
- systems which act rationally

2.2 Introductory Remarks

Conventional designing methods for intelligent systems, such as the rule-based ones, not really quite delivered the outcome which was anticipated in a period where people became aware that computers could be applied in occupations with more variety than numeral calculations. Hitherto, the construction of a series of rules capable of displaying true intelligent behavior has not been achieved.

Certain specialist systems were able to compete on an expert-level in confined fields, but no general AI ever managed to function in daily-life occurrences. It is said that "Expert systems know everything about almost nothing", meaning that other than certain subjects there is a salient difference from human experts. However, numerous systems use AI techniques, and from this point AI community made a rather significant effect despite the fact that actual goal has not been reached (for now). Also remember that someone who can play high level chess is generally considered very intelligent, regardless of their success in other fields.

Neural Network is a specific branch of the Artificial Intelligence. Overall, Neural Networks are set of mathematical methods created to complete a variety of duties. Neural Networks utilize a set of processing components (nodes) scarcely analogous to cerebral neurons (the name is thus neural networks) In a network these components are interconnected which can detect patterns in perceived data. In a respect, the network learns as humans do through experience. Neural networks allow different configuration in a number of settings to achieve tasks like pattern recognition, classification, process modeling and data mining.

Neural networks are structural models and algorithms used to arrange the model in accord with certain data. A neural network is potentially capable of intelligent control systems since they can perform adaptation and learn through experience, offer approximations on nonlinear functions, are fitting to perform parallel and distributed processing, and model naturally multivariable systems. Neural network models are alternatives, in the case that a physical model is not available.

There are a lot of neural network architectures such as the perceptron, multilayer perceptron, networks with feedback loops, self-organizing systems, and dynamical networks, along with several different learning methods such as error-correction learning, competitive learning, supervised and unsupervised learning (Haykin, 1994). Neural network types and learning methods have been arrayed into a brief classification schema, a taxonomy (Figure 2.1).

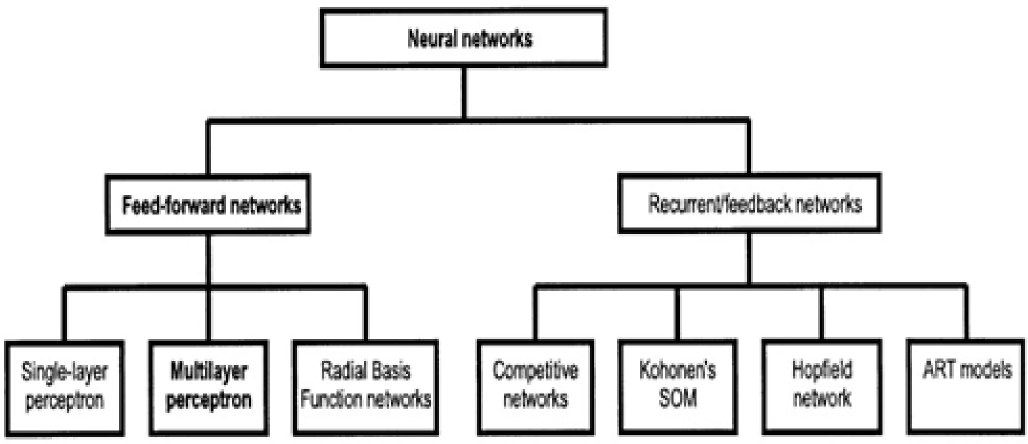

Figure 2.1 A taxonomy of neural network architectures (Gardner & Dorling, 1998).

2.3 Why Study Neural Nets?

These networks are mostly employed in statistical analysis and data modeling, where their function is regarded as an alternative to standard nonlinear regression, or cluster analysis techniques (Cheng & Titterington, 1994). Their typical employment include mostly the areas where the problems included classification and forecasting. Some examples are image and speech recognition, textual character recognition, and disciplines of human specialists such as medical diagnosis, oil survey on a geographical level, and financial market indicator prediction. Such problems are also included in the fields where classical artificial intelligence (AI) were used, so that engineers and computer scientists observe natural nets as offering a style of parallel distributed computing, consequently offering an alternative to the traditional algorithmic methods with wide influence over machine intelligence. Practitioners of this field are not interested in biological realism, mostly heeding the ease with which a solution will be implemented in a digital hardware or the efficacy and accuracy of specific methods.

2.3.1 Why Use Neural Networks?

As opposed to traditional problem-solving methods, artificial neural networks possess a series of specialties which make them gripping alternatives. Development of algorithmic solutions and application of an expert system are of the basic alternatives to neural nets.

Adequate information on the data and an underlying theory are perquisite to the arising of algorithmic methods. From the problem space incognito solutions can be calculated, if the data and the theoretical relationship between the data is understood. Conventional von Neumann computers may be used to calculate such relationships rapidly with efficacy from a numerical algorithm.

On the contrary, expert systems are applied under conditions in which there is inadequate data and theoretical background to form any sort of reliable problem model. In such cases, human knowledge and rationale human experts possess is codified into an expert system. These systems imitate the deductive processing of an actual expert through information gathering and traversing the solution space in a directed way. Even when an accurate problem model and full data is unavailable these systems perform rather well overall. Nonetheless, expert systems are not ideal in the case that adequate data or an algorithmic solution can be reached.

Artificial neural networks are useful with abundant data, and little underlying theory. Data gathered by immense experimentation can be non-linear, non-stationary, or disorderly Input-output spaces can be in such intricacy that any logical traversal with an expert system would remain insufficient. Significantly also, neural nets do not have any perquisite of an a priori assumption relating to the problem space, and, even, information regarding statistical distribution. Though there is no need for such presumptions, it was found that adding a priori information such as the statistical distribution of the input space may assist to accelerate the training. Mathematical problem models are prone to assume the data lies in a standardized distribution patterns, like those of Gaussian or Maxwell-Boltzmann distributions. No such assumption is required in neural networks. In the course of training, neural network achieve the needed analytical task, which if other methods were to be applied would take significant effort from the analyst's respect.

2.4 Structure of a Neuron

The main unit of computation in the nervous system is the nerve cell - neuron**.** A neuron has:

- Dendrites (inputs)
- Cell body (soma)
- Axon (output)

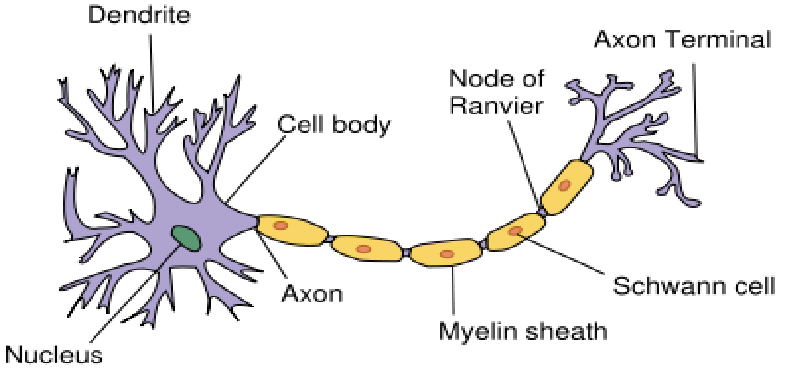

Figure 2.2 Typical neuron (Cheng & Titterington, 1994)

A neuron has an almost spherical cell body called soma (Figure 2.2). Other neurons receive the signals generated in soma by the way of an extension upon the cell body named *axon* or *nerve* fibers. *Dendrites* is another type of extension seen around the cell body resembling a bushy tree, which are tasked as recipients of the incoming signals generated by other neurons (Cheng & Titterington, 1994).

2.4.1 Models of a Neuron

A neuron is a unit which processes information, being vital to the operation of neural networks. Three general components of the neuron model are given below:

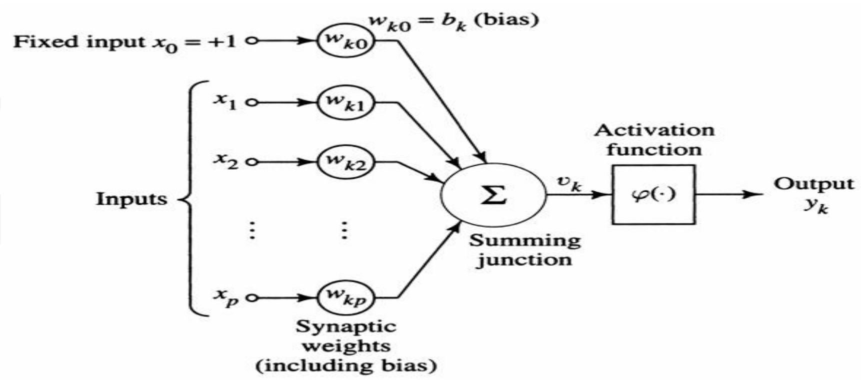

Figure 2.3 Nonlinear model of a neuron (Hajek, 2005).

In Figure 2.3:

1. If the related synapse is excretory the weight $\boldsymbol{w_{kj}}$ is positive; and if inhibitory negative.

2. An adder to sum the input signals, weighted by the respective synapses of the neuron.

3. An activation function used in limitation of the amplitude the output of a neuron has. The activation function is referred to as squashing function because of the permissible amplitude range of the output signal it squashed (limited) to a finite value.

The normalized amplitude range of the neuron's output is written as the closed unit interval [0, 1] or alternatively [-1, 1].

Also included in a neuron model is a bias (threshold) applied from outside $\boldsymbol{w_{k0}}$ $=b_k$, which has an impact of diminishing or augmenting the net input from the activation function. Mathematically, the neuron represented by k can be described by writing the equations given below:

$$v_k = \sum_{j=0}^{p} w_{kj} x_j \tag{2.1}$$

$$y_k = \varphi(v_k) \tag{2.2}$$

or in a matrix form:

$$v_k = \begin{bmatrix} w_{k0} & w_{k1} & \cdots & w_{kp} \end{bmatrix} \begin{bmatrix} x_0 \\ x_1 \\ \vdots \\ x_p \end{bmatrix} = w_k^T x \tag{2.3}$$

2.4.2 Types of Activation Functions

2.4.2.1 Threshold Activation Function (McCulloch–Pitts Model)

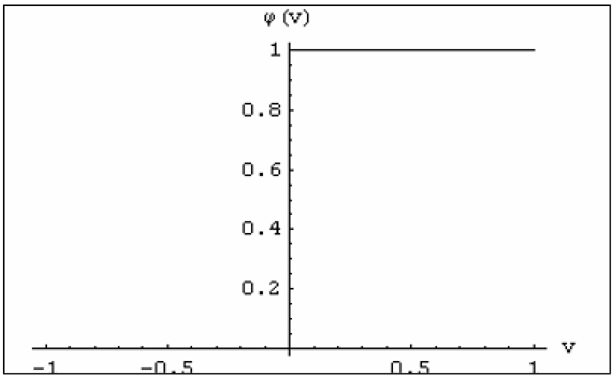

Figure 2.4 Threshold activation function (Hajek, 2005)

This model contains neuron whose output receives the value of 1 in the case total internal activity level of that neuron is nonnegative or 0. All-or-none feature of the McCulloch-Pitts model (Figure 2.4).

The McCulloch–Pitts model of a neuron is used along with the outputs of -1 or +1:

$$\varphi(v) = \begin{Bmatrix} 1, & v \geq 0 \\ -1, & v < 0 \end{Bmatrix} \tag{2.4}$$

2.4.2.2 Piecewise-Linear Activation Function

Inside the linear area the amplification factor is thought to be unity (Figure 2.5). The two solutions displayed below can be thought of as exquisite forms of the piecewise linear function:

$$\varphi(v) = \begin{Bmatrix} 1, & v \geq \frac{1}{2} \\ v + \frac{1}{2}, & -\frac{1}{2} < v < \frac{1}{2} \\ 0, & v \leq -\frac{1}{2} \end{Bmatrix} \tag{2.5}$$

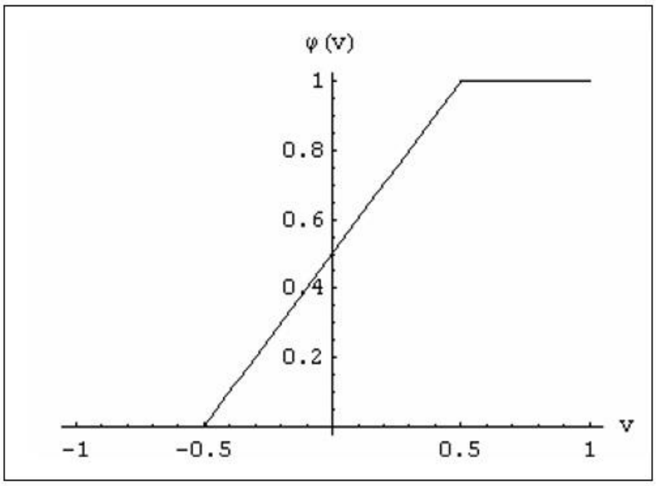

Figure 2.5 Piecewise-linear activation function (Hajek, 2005)

1. A linear combiner occurs when the linear operation area is maintained without saturation.

2. When the amplification factor of the linear area is made large infinitely, the piecewise-linear function shrinks to a threshold function.

2.4.2.3 Sigmoid (Logistic) Activation Function

Most common activation function form applied in constructing the artificial neural network is the sigmoid function. Whilst a threshold function takes on the value of 0 or 1, a sigmoid function assumes a continuous range of values (from 0 to 1. Also noteworthy is the differentially of the sigmoid function, which is quite a significant property neural network theory has offered (Figure 2.6).

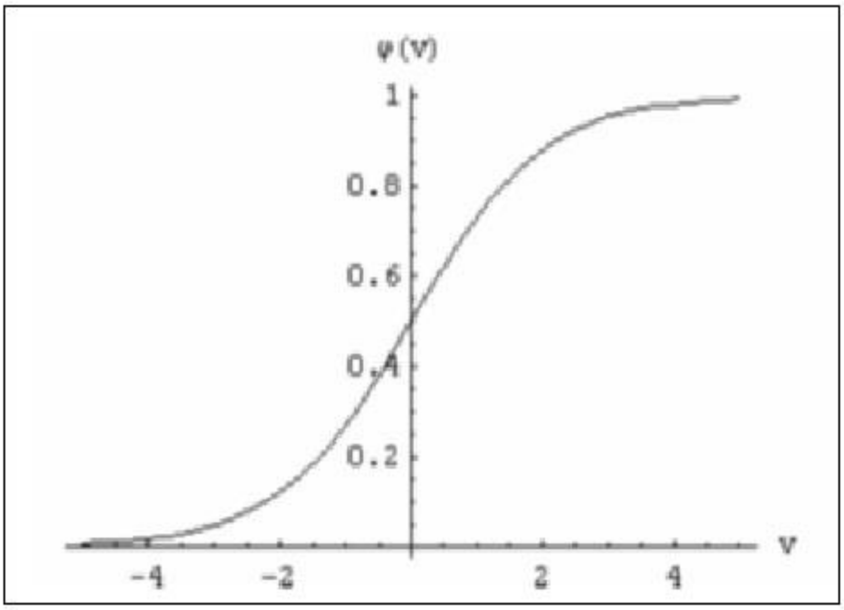

Figure 2.6 Sigmoid (logistic) activation function (Hajek, 2005)

Sigmoid function:

$$\varphi(v) = \frac{1}{1+\exp(-v)} \tag{2.5}$$

Sigmoid function has a nice property as a derivative, easing the calculation:

$$\frac{\partial\varphi(v)}{\partial v} = \varphi(v)(1-\varphi(v)) \tag{2.6}$$

2.4.2.4 Hyperbolic Tangent Function

Hyperbolic tangent function is expressed with ease with respect the logistic function: (2 x logistic function - 1) (Figure 2.7).

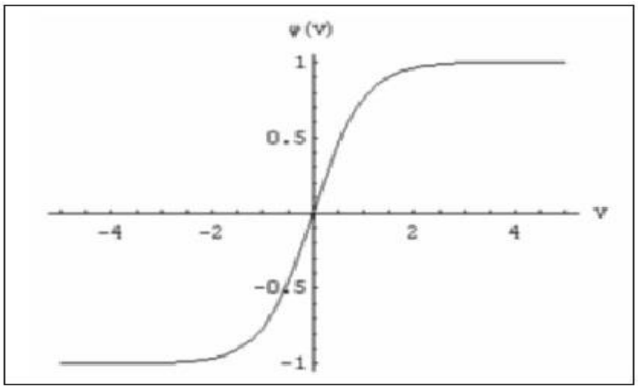

Figure 2.7 Hyperbolic tangent activation function (Hajek, 2005)

Definition of hyperbolic tangent activation function:

$$\varphi(v) = \tanh\left(\frac{v}{2}\right) = \frac{1-\exp(-v)}{1+\exp(-v)} \tag{2.7}$$

Its derivative is also easy to calculate:

$$\frac{\partial\varphi(v)}{\partial v} = \frac{1}{2}(1+\varphi(v))(1-\varphi(v)) \tag{2.8}$$

2.5 Multilayer Feedforward Network

Respective components of the activation pattern (input vector), which display input signals applied on the neurons (computation nodes) in the second layer (i.e. the first hidden layer), are supplied by the source nodes within input layer of the network supply. As inputs to the third layer output signals from the second layer are used, and this went on for the remainder of the network.

Usually the neurons contained in each of the layers of the network have output signals of the precedent layer only as their inputs. The set of output signals from the neurons of the output layer in the network forms the general response of the network to the activation pattern, which is supplied by the source nodes of the input layer (Figure 2.8).

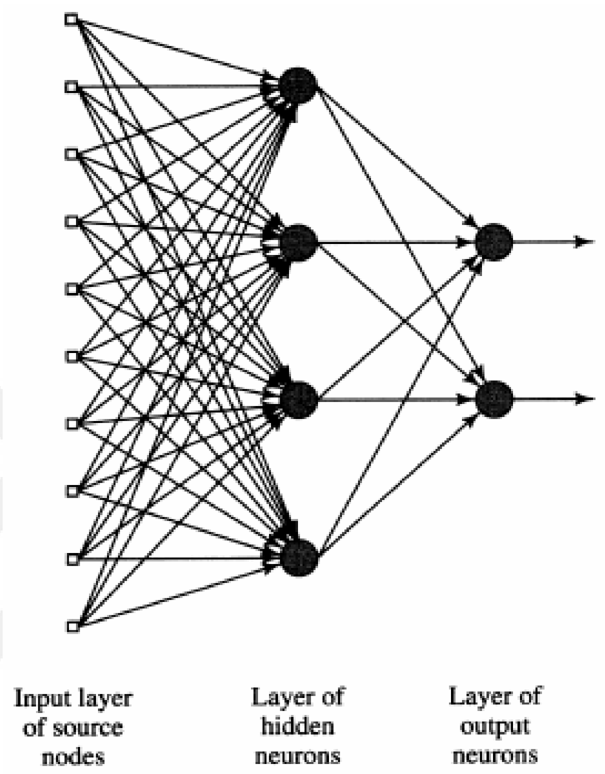

Figure 2.8 Fully connected feedforward network (Hajek, 2005)

A neural network is presumed in complete connection if all the nodes in every layer of the network is connected to every other node in the neighboring forward layer (Figure 2.8). On the other hand, if a portion of the communication links (synaptic connections) are absent in the network, the network can be presumed partially connected.

2.6 Perceptron

Utilized in classifying a particular type of linearly separable patterns, the perceptron is the simplest form of a neural network. It is made of a single McCulloch-Pitts neuron with synaptic weights and bias (threshold) adjustable. Rosenblatt (1958) demonstrated that if the patterns (vectors) applied in training of the perceptron are drawn from linearly separable classes, then the perceptron algorithm converges on and positions the decision surface in the form of a hyperplane between the classes. The single-layer perception demonstrated in Figure 2.9 contains a single neuron.

For instance: Considering a classification problem, the set of data *U* is to be classified into the classes *C1* and *C2*. A neural network is able to learn from data and better its performance.

The most basic form of a neural network can classify data into two different classes. Essentially it exists of a single neuron which has a variety of adjustable weights. The fundamental processor of a neural network is the neuron (Figure 2.9); consisting of three main components:

1. A set of intermediary links (or synapses); each link carrying a wait (or gain) w_0, w_1, w_2.

2. A summation (or adder) has the function to sum the input singles once they are multiplied by their respective weights.

3. An activation function f(x), restricts the neuron's output. Generally the output is restricted the interval [0, 1], or interchangeably [-1, 1].

The summation inside the neuron includes an offset as well to lower or raise the net input to the activation function. In mathematical terms a vector $U = (1, u_1, u_1, \dots, u_n)^T$ represents the input to the neuron, and the output is a scalar y = f (x). The vector where the offset is placed represents the weights $w = (w_0,\ w_1, \dots, w_n)^T$ of the connections: The output calculation is as follows:

$$y = f\,(w^T u) \tag{2.11}$$

Figure 2.9(a) is a perceptron with two inputs and an offset. The neuron yields an output of +1 or -1, with a hard limiter such as activation function (b), which can be associated with and, respectively:

$$w^T u \geq 0 \text{ for every input vector } \boldsymbol{U} \text{ belonging to class } C1$$
$$w^T u < 0 \text{ for every input vector } \boldsymbol{U} \text{ belonging to class } C2 \qquad (2.12)$$

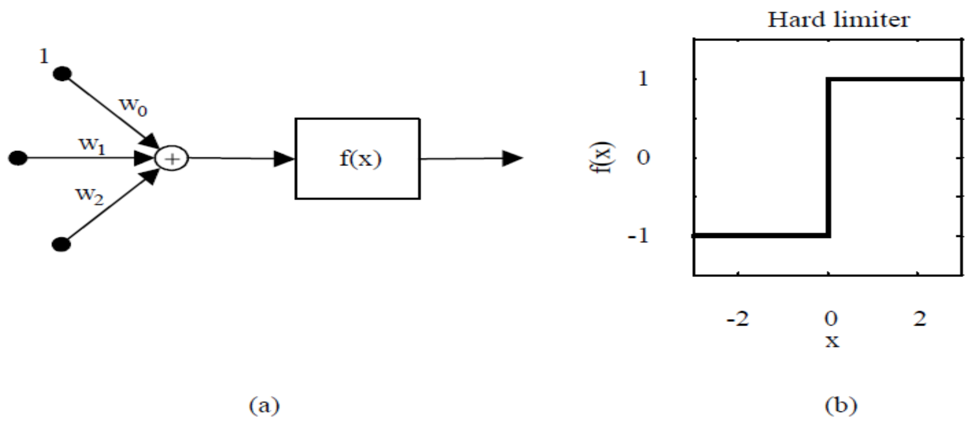

Figure 2.9 (a) Perceptron consisting of a neuron with an offset $\boldsymbol{w_0}$ (b) An activation function f(x), which is a hard limiter (Jantzen, 1998).

2.6.1 Multilayer Perceptrons in Neural Networks

In taxonomy in Fig. 2.1 one of the neural networks illustrated is multilayer perception. Recently, the utilization of neural networks, and specifically the multilayer perceptrons, have been demonstrated to be efficient alternatives to more conventional statistical methods (Schalkoff, 1992). Initially, that the multilayer perceptron is open to training to approximate any smooth, measurable function has been shown (Hornik et al., 1989). Unlike other statistical methods the multilayer perceptron has no beforehand assumption in regard to the distribution of the data. It can model highly non-linear functions and be trained to generalize spot-on if presented with new, unknown data. It then becomes a heeded alternative through these features in development of numeric models, along with the process of deciding between statistical approaches.

In order to be capable of solving non-linearly separable problems a range of neurons are in connection with layers so that a multilayer perceptrons can be constructed. Each perceptron is used to define small linearly separable portions of the inputs. To offer a final output, outputs of the perceptrons are gathered into another perceptron. The hard-limiting (step) function used in production of output prohibits information on the real inputs streaming toward inner neurons. For this to be solved, the step function is replaced by a continuous function.

In a multilayer perceptrons, the neurons are arranged into an input layer, an output layer, and one or more hidden layers as in Figure 2.10.

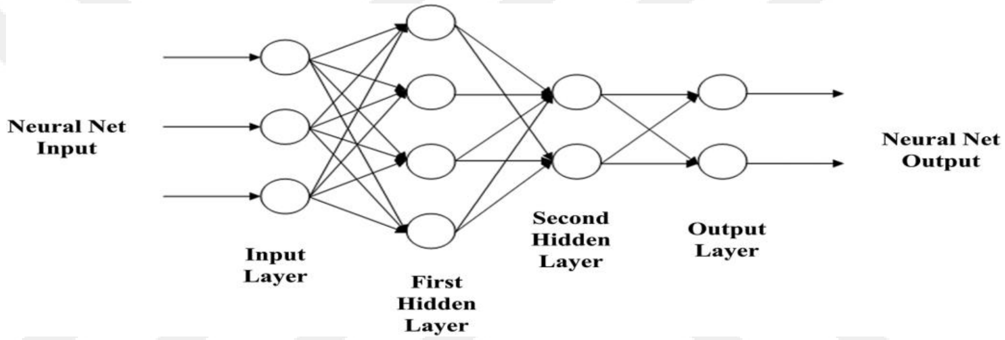

Figure 2.10 A multilayer perceptrons with two hidden layers (Mohammed et al., 2014).

2.6.2 Applications of Multilayer Perceptrons

The multilayer perceptrons with back-propagation has been used in a series of applications from Optical Character Recognition to medicine. Short definitions of some are offered below.

2.6.2.1 Speech Synthesis

A well acquainted application of the multilayer perceptron is NET talk, a system that makes text-to-speech conversions, developed by Sejnowski and Rosenberg in 1987. Consisting of 203 input units, 120 hidden units as well as 26 output units with more than 27000 synapses. Each unit of output stands for a simple unit of sound called a phoneme. Utilization of the context is achieved through a prevention of seven consecutive letters to the input and the net learns how to pronounce the middle letter. Training set had a 90% correct pronunciation and the unseen set achieved a ratio of 80-87%. It has damage resistance and shows graceful degradation.

Multilayer perceptrons are being used as well in speech recognition systems which are designed to function in voice activated control systems.

2.6.2.2 Financial Applications

Examples comprise of bond rating, loan application evaluation and stock market prediction. Bond rating is involved with categorization of the issuer's capability. No hard and fast rules exist in determination of such ratings. A statistical regression is out of place since the factors to be applied are poorly defined. Neural networks with back-propagation training have persistent outperformances in coping with standard statistical techniques.

2.6.2.3 Pattern Recognition

For numerous applications relating to neural networks, the principle behind is that of a pattern recognition. A target identification system using sonar echoes has been developed. With only a day of training, the net yielded a 100% correct identification when compared to the 93% scored by a Bayesian classifier.

There exists a series of commercially related application options in networks available in character recognition. An example of such systems performs signature verification for bank cheques.

Certain networks have found use in applications to problems concerning aircraft identification and to terrain matching for automatic navigation.

2.7 Principles of Artificial Neural Networks

2.7.1 The Basic Principles of ANNs

The perks of the ANNs are represented in general by the network's architecture and the algorithms. Currently neural network studies are concentrated on these aspects. An ANN consists of a series of units of processing, also referred to as neurons and are connected with one another. This might be described as an oriented graph, and every neuron is a transfer function. A neuron is mostly a multi-input and single-output nonlinear element. The Neural Network's architecture is set by all the connections in the network as well as the transfer function the neurons have.

2.7.2 The Learning Process in ANNs

The learning process of an ANN usually goes through a set of examples; it is also referred to as "training", since the process of learning is completed by repetitive adjustment of the connection weights. Leaning process of the ANNs are sectioned into three types: supervised, unsupervised and reinforcement learning. Supervised learning finds its basis on the flat-out comparison performed between the actual output and expected output. Algorithms used for optimization are stemmed from gradient descent like back-propagation algorithm, and they can be used in iterative adjustment of the connection weights and thus minimizing the error ratio. Reinforcement learning is a particular portion pertain to supervised learning; this is not just based on the accuracy of the actual output. Unsupervised learning on the other hand solely set upon the correlation of the input data. The fundamentals of an algorithm proposed for education is the rule of learning, which thus determines the weight update rule. A number of popularized rules for learning are delta rule, Hebbian rule and competitive learning rule.

2.7.3 Encoding Scheme and Determine the Expression of the Connection Weights of the ANN

In order to encode connection weights and the threshold values for the ANNs two ways exist. The first is binary encoding and the second is real encoding. Binary encoding (Whitley et al., 1990) is a one in which each weight is expressed by fixed length 0-1 string. Once the encoding length is restricted, expression precision in binary encoding becomes insufficient; if certain, any, precision limit is met the area of the search will be extended in accordance and will affect the rapidity of the evolutionary process. Real encoding is referred to as the expression of each weight through a real number (Ren and San, 2007); overcoming the demerit of binary encoding, yet requires to re-design the operators.

2.7.3.1 The Evolution to the Learning Rules of ANNs

Differing activation functions possess different features and different rules of learning have differing performance rates. For instance, the activation functions can evolve through selection among certain popular nonlinear functions such as the Heaviside, sigmoidal, and Gaussian functions (Alvarez, 2002). The learning rate and the momentum factor of the Back-Propagation (BP) algorithm might evolve (Kim et al., 1996), and learning rules may as well be evolved to produce new leaning rules. EAs also participated in the selection of appropriate input variables for neural networks from a raw data field of a larger dimension, that is, to evolve input properties (Guo, 1992).

CHAPTER THREE
LITERATURE REVIEW

3.1 System 1: Priority Criteria for Corneal Transplantation

The Eye Bank of British Columbia (EBBC) corneal transplantation waiting list has grown from 500 in 1991 to almost over 1,000 in early 1995. Patients with conditions requiring emergency correction (e.g. corneal perforation) were excluded from the list. Prior to 1995, patients' prioritization took into account the number of months spent on the waiting list, and the list was kept by the surgeon. Factors like number of patients on the list, time spent in waiting, available surgical time and the attempts of persistence by the patient impacted greatly the surgeon's decision process for the surgery.

Responding to the acceleration of the number of patients added to the wait list, in January 1995 the EBBC established certain criterion to determine priority based on a series of clinical factors and on months waited, in order to forma an overall score of priority for the patients.

Table 3.1 Priority listing scheme for corneal transplantation in British Columbia in January 1995 (Courtright et al., 1997).

Priority Items	Allocation of Points		
Progressive corneal condition	Yes = 5	No = 0	
Vision in one eye only	Yes = 10	No = 0	
Legal blindness	Yes = 10	No = 0	
Good potential result	Yes = 5	No = 0	
Pain	Constant = 10	Intermittent = 5	No = 0
Each month on the wait list	1 point		

The criterion (in the Table 3.1) were offered by the participating surgeons. Like before, patients who had conditions requiring urgent intervention were excluded on the wait list. The criterion for priority required the approval of all corneal surgeons involved before the implementation; the motive behind the formation of a prioritization criteria was generated by a few surgeons with extensive patient list. Allocation of corneal tissue to surgeons was not related to the general priority score the patients performed. Rather, surgeons were provided individually with a list of their patients ordered by the priority scores. And although criteria of standard priority criterion is quite vital a first step in the provision of services to the ones who had the most eminent requirement of it, it is also important to evaluate the application of a priory scheme and to decide whether the scheme correspond both with the patient's needs and, in the end, improved life quality. Little information exists regarding the application of priority criteria predicted which patients had surgery. In addition, they wanted to better the criteria so that the patient's surgical needs would be met accurately.

All patients added on the April 1995 (EBBC) waiting list for corneal transplantation (n=882) consisted of potential subjects for study. Because the priority criteria effectuated in January 1995 they waited till April to ascertain that it was properly in place prior the start of the study. Patients' names are put on the EBBC wait list by individual British Columbia corneal surgeons (n=19). All transplant tissue in British Columbia is handled through the EBBC.

In February 1996 (10 months after study's start and 14 months after the priority scheme was effected) patients in the April 1995 wait list were traced through the EBBC to elucidate surgical status. Surgical status was described as follows: had surgery, did not have surgery (still on wait list), or did not have surgery (removed from the wait list). Analysis includes no data on the last group removed from the list.

Due to the large numbers of corneal surgeons who take tissue from the EBBC, this research has grouped them in accord with the size of their waiting list. Low volume surgeons (n=15) had less than 50 patients put on the waiting list whilst high volume ones (n=4) had more than 50 patients on the list. Relative risks and 95% confidence intervals were calculated for surgical coverage in accordance with particular baseline characteristics. For continuous variables, Student's *t* tests were calculated. A non-parametric statistic (Mann-Whitney *U* test) was calculated when the data were not normally distributed. As multiple factors were associated with surgery, a multiple regression model was constructed to determine the independent contribution of factors to surgical correction.

3.1.1 Results

In 1995, of all the 882 patients on the waiting list, 98 were taken off of the list by the surgeon. Patients were removed from the waiting list consisted of those who died (n=3) or those whom the surgeon regarded no more as an "active" case (n=95). Hence, 784 patients constituted the list of possible surgical cases. The median age in the patients was 59.2 years is as follows: 47% were males and 53% were females. 28% of the patients were from visible minority groups, primarily from South and East Asia. Bilateral blindness (<20/200 in the better eye) was recorded in 62 patients (8%), and blindness in the affected eye was recorded in 405 patients (52%). At the 10-month follow-up, of all the patients, 312 (40%) listed had surgery. Univariate analysis on demographic and clinical factors showed that age, sex, minority status, diagnosis, best-corrected vision, and surgeon predicted which patients had surgery (Table 3.2). Patients who underwent surgery had acquired an overall priority score of 29.0 (median=29, range 9-69) whereas patients who did not undergo surgery had obtained an overall priority score of 26.8 (median=24, range 6-71).

Table 3.2 Demographic and clinical factors associated with selection of patients for corneal transplantation from April 1995 to February 1996 (Courtright et al., 1997).

Parameter		Patient Had Surgery		Patient Still on Wait List		Relative Risk (95% CI) *p* value
		No.	(%)	No.	(%)	
Mean age (SD):		61.9	19	57.4	20	p<0.001
Sex:	Female	189	46	223	54	1.0 (reference group)
	Male	119	33	243	67	0.72 (0.6-0.9)***
Group†:	Non-minority	232	42	323	58	1.0 (reference group)
	Visible minority	70	34	138	66	0.81 (0.6-1.0)*
Clinical diagnosis:	Bullous keratopathy Fuch's endothelial	70	54	59	46	1.0 (reference group)
	dystrophy/other dystrophy	100	40	152	60	0.73 (0.6-0.9)**
	Injury	15	31	33	69	0.58 (0.4-0.9)**
	Keratoconus Herpes simplex	57	34	111	66	0.63 (0.5-0.8)***
	Keratitis	16	35	30	65	0.64 (0.4-0.9)*
	Graft rejection	33	36	60	65	0.65 (0.5-0.9)**
	Other	18	43	24	57	0.79 (0.5-1.2)
Vision in eye to be operated	Not visually impaired (>20/55)	28	37	47	63	1.0 (reference group)
	Visually impaired (20/200-20/55)	113	39	179	61	1.04 (0.7-1.4)
	Blind (<20/200)	167	41	238	59	1.10 (0.8-1.5)
Best corrected vision (in better eye‡)	Not visually impaired	192	37	325	63	1.0 (reference group)
	Visually impaired	83	44	108	57	1.17 (0.9-1.4)
	Blind (<20/200)	33	53	29	47	1.43 (1.1-1.9)*
Surgeon§	High volume	210	34	407	66	1.0 (reference group)
	Low volume	102	61	65	39	1.79 (1.5-2.1)***

SD = Standard deviation, CI = Confidence interval. Statistical significance at * p<0.05, ** p<0.01, or *** p<0.001.
† Visible minority defined as East Asian, South Asian or other; non-minority defined as Caucasian and First Nations.
‡ Information missing on other eye in 2 patients.
§ Low volume defined as <50 patients on the wait list; high volume defined as ≥ 50 patients on the wait list.

An analysis performed on the elements of the priority score suggested that only two among the six of the criteria, namely pain and the presence of vision in one eye only, contributed greatly to the recipient of the operation (Table 3.3) Of all criteria, those regarding the potential clarity of the cornea and time spent on the list had no contribution; faint contribution came from legal blindness and progressing diseases. With multiple logistic regression two models were constructed.

Table 3.3 Eye Bank of British Columbia priority score associated with selection of patients for corneal transplantation from April 1995 to February 1996 (Courtright et al., 1997).

Priority Item		Patient Had Surgery		Patient Still on Wait List		Relative Risk (95% CI) p value
		No.	(%)	No.	(%)	
Progressive disease:	No	52	31	114	69	1.0 (reference group)
	Yes	256	42	352	58	1.34 (1.1-1.7)*
Vision in one eye only:	No	253	36	442	64	1.0 (reference group)
	Yes	55	70	24	30	1.91 (1.6-2.3)***
Legally blind:	No	259	38	416	62	1.0 (reference group)
	Yes	49	50	50	51	1.29 (1.0-1.6)*
Pain:	No	219	37	373	63	1.0 (reference group)
	Intermittent	68	45	82	55	1.23 (1.0-1.5)
	Constant	21	66	11	34	1.77 (1.4-2.3)**
Potential for clear cornea:	Not good	31	48	33	52	1.0 (reference group)
	Good	277	39	433	61	0.81 (0.6-1.1)
Mean number of months on list [SD]:	High volume Low volume	15.2	[10.3]	15.8	[11.7]	NS †
Median [Range]:		13	[1-42]	14	[1.56]	
Mean priority score without months [SD]:		13.8	[6.7]	11.1	[5.1]	p<0.001 †
Mean priority score with months included [SD]:		29.0	[9.8]	26.8	12.8]	p=0.008 †

SD = Standard deviation, CI = Confidence interval. Statistical significance at * p<0.05, ** p<0.01, and *** p<0.001; NS = not statistically significant at p<0.05.
† Variances significantly different at p<0.05, Mann Whitney U test used to test statistical significance.

The initial model contained only the criteria from the priory scheme. Findings suggested that only pain, vision in one eye and the existence of a progressing disease were independent predictors for the operation (Table 3.4). With other factors from the model (those which display statistical significance by univariate analysis) showed that surgeon, gender, pain, progressive ocular disease and vision in one eye only contributed dominantly in prediction of the surgery’s recipients.

Table 3.4 Findings from logistic regression model (Courtright et al., 1997).

Model #1: Priority grading score:		
Priority Score Factor	**Adjust Odds Ratio (95% CI)**	***P* Value**
Progressive disease	1.09 (1.06, 1.14)	0.02
Vision in one eye only	1.14 (1.12, 1.18)	<0.001
Legal blindness	1.03 (1.00, 1.05)	NS
Pain	1.08 (1.05, 1.12)	0.006
Potential clear cornea	1.01 (0.95, 1.07)	NS
Months	1.00 (0.99, 1.01)	NS
Model #2: All factors associated (univariate) with surgery:		
Priority Score Factor	**Adjust Odds Ratio (95% CI)**	***P* Value**
Progressive disease	1.12 (1.07, 1.17)	0.01
Vision in one eye only	1.17 (1.14, 1.21)	<0.001
Pain	1.08 (1.05, 1.12)	0.01
Sex (=female)	1.70 (1.44, 2.01)	0.001
Surgeon (=low volume)	3.41 (2.78, 4.19)	<0.001
Age	1.00 (0.99, 1.01)	NS
Diagnosis (=bullous keratopathy)	1.10 (0.86, 1.41)	NS
Ethnic group (=non-immigrant)	1.07 (1.00, 1.12)	NS
Best corrected vision	1.23 (1.00, 1.40)	NS
NS=not significant, CI=confidence interval.		

Surgeon's stance as a top predictor brought certain suggestion indicating a rather significant variation in the way the priority system was employed by individual surgeons (Figures 3.1, 3.2 and 3.3) Some of those kept employing months spent on the waiting list as the primary criterion for the decision of operation and only age was associated with surgery as a factor. Mean patient age to undertake this operation was 81.6 and of those who did not it was 55.3 (p<0.001). This research evaluates the priority system to decide the weight of each factor.

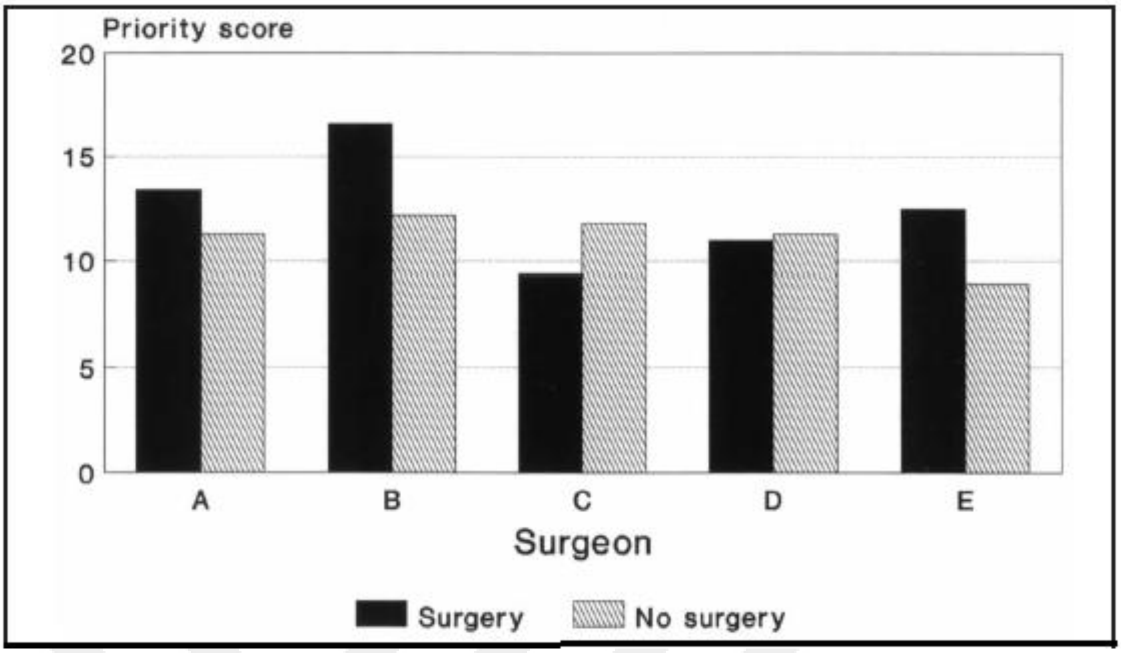

Figure 3.1. Clinical priority score (first 5 parameters in Table 3.1) of patients who did and did not have surgery by surgeon. Surgeons A-D are high volume surgeons; all low volume surgeons are grouped as E. Differences for surgeons A, B, and E are statistically significant at p<0.01 (Courtright et al., 1997).

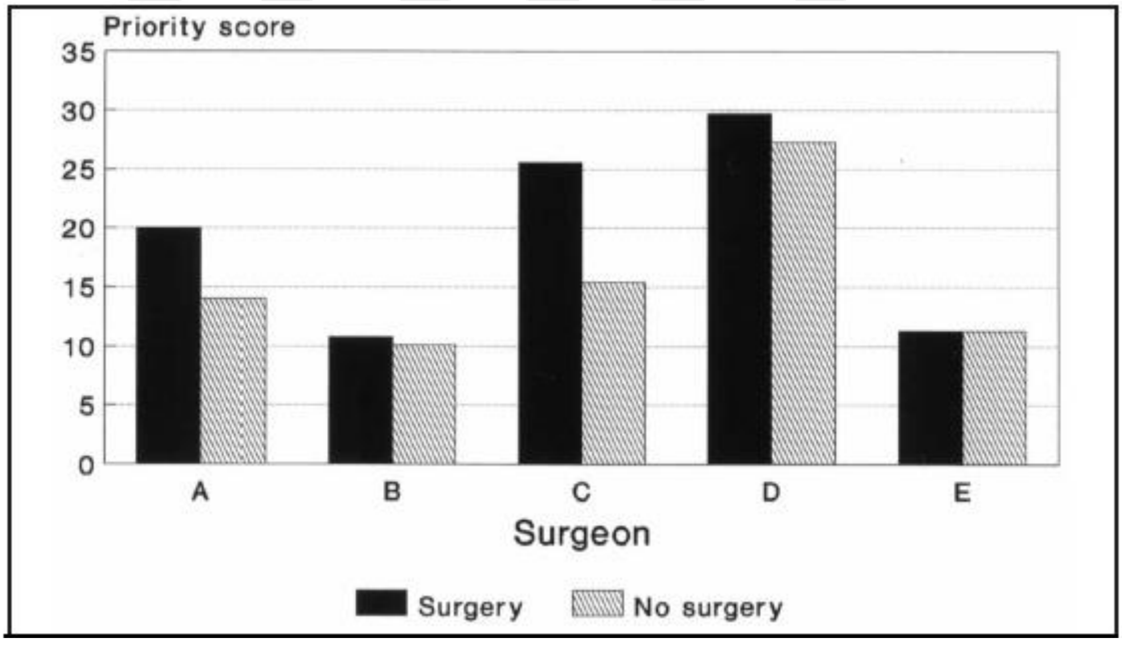

Figure 3.2 Months on the wait list for patients who did and did not have surgery. Differences for surgeons A and C are statistically significant at p<0.01 (Courtright et al., 1997).

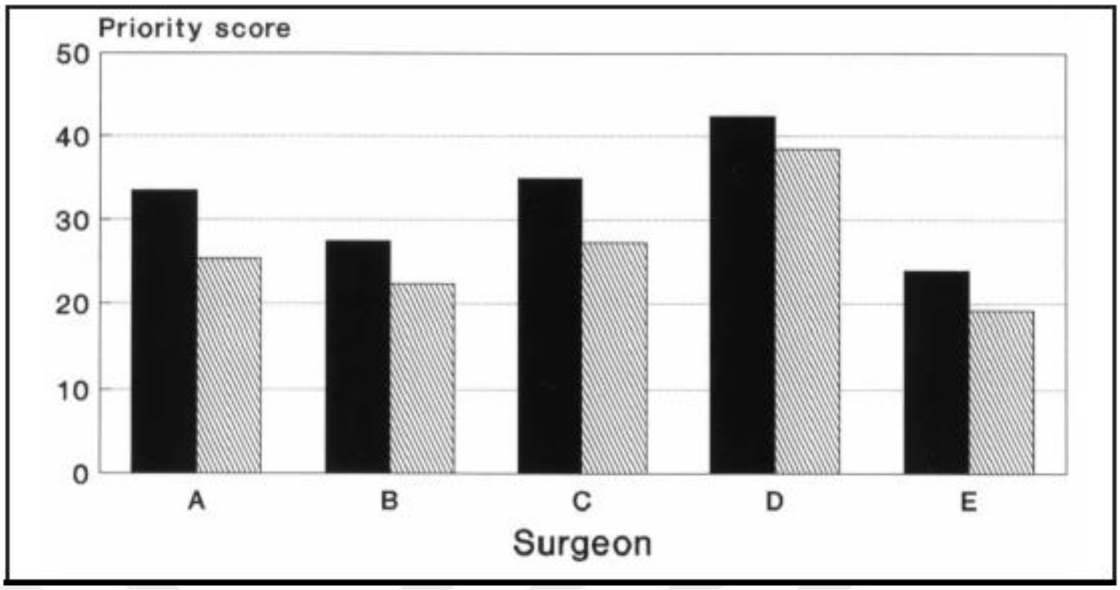

Figure 3.3 Priority score (clinical score + months on wait list) of patients who did and did not have surgery. Differences for surgeons A, B and E (low volume surgeons) are statistically significant at $p<0.01$ (Courtright et al., 1997).

Table 3.5 Comparison of 1995 and 1996 (updated) EBBC priority grading of patients wait-listed for corneal transplantation (Courtright et al., 1997).

Parameter	1995 Score System	1996 Score System	% of Total Score	
			1995	1996*
Vision in one eye only	No = 0 Yes = 10	No = 0 Yes = 25	3.8%	7.3%
Legal blindness	No = 0 Yes = 10	≥20/50 = 0 20/60-20/80 = 8 20/100-20/200 = 16 <20/200 = 25	4.4%	8.4%
Pain	No = 0 Intermittent = 5 Constant = 10	No = 0 Intermittent = 20 Constant = 50	4.9%	16.1%
Progressive disease	No = 0 Yes = 10	No = 0 Yes = 5	13.5%	10.4%
Potential for good outcome	No = 0 Yes = 5	[removed]	15.6%	0
Months on list	1 for each month	0.5 for each month	58.0%	22.3%
Visual function assessment	(not included in priority score)	VF score x 5†	0	35.5%

* 1996 value calculated using 1995 waiting list.

† Visual function (VF) assessment includes 15 items; scoring is similar to the VF-14 (Steinberg et al., 1994).

Duration waited in the list contributed approximately to 58% of the weight of the waiting list priority score (Table 3.5) One clinical parameter with potential for a good outcome was reported as favorable in 93% of patients, adding little practical value to the priority score while contributing 16% of the overall weight.

The results and their assessment on patient-derived visual function assessment have led to alterations on the priority system, listed as well in Table 3.4. Shortly, they encompass increasing the general weight of particular clinical factors, specifically pain, vision in one eye only and best corrected visual acuity.

Clinical factors will keep contributing approximately 42% of the total score. The contribution based on months waiting has been reduced from 58% of the total score to around 22%. Lastly, the new priority criteria has a standardized patient-derived visual function assessment.

3.2 System 2: Prioritization System for Predict Outcome

From May 1997 until April 1998 including all patients (save emergencies) who received a transplant by one of the 16 EBBC surgeons (one surgeon did not participate in the outcome assessment) were enrolled in the outcome assessment program held routinely. When a surgeon decided that an individual required a corneal transplant, the surgeon would fill out a waiting list form; this short form includes patient demographics, visual acuity in both eyes, primary corneal diagnosis, level of pain, and whether the condition is to progress. The patient is given a visual function form (Dam OM, et al., 2001) available in English and Chinese, reliability completed. Twelve months postop surgeons are given a clinical follow-up form to gather postop data on visual acuity, complications, other ocular morbidity, and other variables.

Patients are asked to fill-out a visual function assessment (VFA) questionnaire beforehand and 12 months after the operation. The preoperative questionnaires are usually completed in the surgeon's office when a patient is added to the corneal transplant waiting list of the EBBC. Postoperative questionnaires on the other hand are filled out either in the surgeon's office 12 months postop or are e-mailed to the patient's account asked to be resent in a self-addressed stamped envelope.

The VFA is a version of the VF-14 (Steinberg et al., 1994) which was revised to become more appropriate to the lifestyles and visual demands of Vancouver's multicultural, multilingual population (Courtright et al., 1998). For every question within the VFA five choices are offered: no difficulty (4), a little difficulty (3), a moderate amount of difficulty (2), a great deal of difficulty (1), and unable to do the activity (0). An overall score is calculated by taking the median scores from all answered items and multiplying by 25; possible scores range from 0 to 100 with 100 as the best imaginable score.

The best corrected Snellen visual acuity was recorded for each eye when each patient was placed on the waiting list and in their follow up appointment, generally 12 months following surgery. Prior to the operation, surgeons ask patients whether they currently feel any eye pain and this is recorded as either no, sometimes, or constantly. After the operation a question was placed in the end of the VFA questionnaire asking patients whether any experience of severe eye pain occurred during the operation and the options no, sometimes, or constantly were.

The three indices chosen to monitor the outcome were visual acuity (operative eye best corrected assessed by surgeon), visual function (assessed by patient via questionnaire), and pain. They considered a patient "preop complete" if all three measures were available preoperatively. Similarly, they considered a patient "postop complete" if all three measures were available postoperatively.

In the analysis patients with completed data were compared with those without complete data; Student's *t* test was used to compare the means of the continuous variables (age, VFA score, priority points, etc.) and a test was used to compare proportions in the categorical data (pain, visual acuity, sex, etc.). For each of the three improvement indices patients were classified at worse, same, and improved and these categories were compared in terms of clinical and demographic factors. Next, patients were classified by the number of categories they improved in 0, 1, 2, or 3 and the clinical and demographic factors were compared between these categories.

3.2.1 Results

In 12 months of enrollment, the 269 patients who have undergone a corneal transplant were either on the existing waiting list (n = 126) at the beginning of the period or were placed on the waiting list within the period (n = 143). During this, an additional 26 patients had corneal transplantation surgery on an emergency basis; this group is not given in data.

Among the 269 potentially enrolled 216 (80.3%) offered extensive and all-inclusive preoperative information. A comparison of the patients with complete information with those who did not showed that there were no differences in these two regarding age, sex, pain, visual function, or visual acuity.

Complete postoperative information was acquired successfully on 159 patients (59.1%) of the total of 269 and 63.0% (136/216) of 216 with complete preoperative information). Patients who had no complete postoperative history did not differ from those who had complete information with respect to age, pain, or visual function. Males were mildly more prone to have a flawed follow up. The single factor relating to completeness was the surgeon; some surgeons were not successful in provision of complete information on all patients (data not shown). Since there was no significant difference between the two groups, they used findings taken from all of the 269 patients.

3.2.2 Outcome

In accordance with surgeon criteria, an expected outcome was descried as improvement in one of three indicators: visual acuity (operative eye), pain, and visual function (person). According to these criterion patients whom were improved in at least one of these categories constituted an 88.2% of all (Table 3.6). Patients who showed the most improvement had *aphakic* or *pseudophakic* bullous keratopathy whilst the poorest improvement rate was associated to patients with a history of Fuchs' dystrophy. Overall, there have been a striking relation between the outcome and priority scores prior surgery (Fig 3.4).

Table 3.6 Number of outcome categories improved (Saunders et al., 2002).

	None (n=16)	1 Improved (n=65)	2 Improved (n=47)	3 Improved (n=8)	
Mean age(SD)	66.4 (16.1)	64.4 (17.7)	70.9 (14.5)	79.0 (2.6)	0.103
Sex					
Female	6 (6.7%)	46 (51.7%)	31 (34.8%)	6 (6.7%)	
Male	10 (21.3%)	19 (40.4%)	16 (34.0%)	2 (4.3%)	0.083
Diagnosis					
Corneal degen	1 (16.7%)	3 (50.0%)	2 (33.3%)		
Trauma		2 (40.0%)	3 (60.0%)		
Scar/oedema		7 (70.0%)	3 (30.0%)		
Fuchs'	3 (15.8%)	8 (42.1%)	7 (36.8%)	1 (5.3%)	
Keratitis	1 (7.7.%)	10 (76.9%)	2 (15.4%)		
Keratoconus	2 (13.3%)	10 (66.7%)	2 (13.3%)	1 (6.7%)	
PBK/ABK	5 (10.2%)	20 (40.8%)	19 (38.8%)	5 (10.2%)	
Regraft	4 (21.1%)	5 (26.3%)	9 (47.4%)	1 (5.3%)	0.524
Preop visual acuity (best eye)					
>20/40	13 (15.3%)	44 (53.7%)	25 (30.5%)		
20/60–20/80	2 (8.0%)	8 (32.0%)	12 (48.0%)	3 (12.0%)	
20/100–20/200		10 (41.7%)	9 (37.5%)	5 (20.8%)	
<20/200	1 (20.0%)	3 (60.0%)	1 (20.0%)	0 (0.0%)	0.003
Preop pain					
None	13 (16.7%)	51 (65.4%)	14 (17.9%)		
Intermittent	2 (4.7%)	10 (23.3%)	27 (60.5%)	5 (11.6%)	
Constant	1 (6.7%)	4 (26.7%)	7 (46.7%)	3 (20.0%)	<0.001
Mean preop VFA (SD)	74.4 (23.1)	64.8 (26.1)	63.9 (20.4)	48.4 (23.5)	0.095
Mean priority points	24.9 (20.5	30.1 (20.8)	42.7 (14.8)	63.1 (15.6)	<0.001
Mean months waited	9.2 (11.3)	8.4 (10.1)	7.9 (9.5)	1.9 (1.1)	0.336
Surgeon					
A	1 (6.3%)	7 (43.8%)	7 (43.8%)	1 (6.3%)	
B	5 (12.2%)	15 (36.6%)	16 (39.0%)	5 (12.2%)	
C	4 (13.8%)	16 (55.2%)	9 (31.0%)		
D	1 (8.3%)	7 (58.3%)	4 (33.3%)		
E	2 (10.0%)	12 (60.0%)	6 (30.0%)		
F	3 (14.3%)	8 (38.1%)	7 (33.3%)	3 (14.3%)	0.644

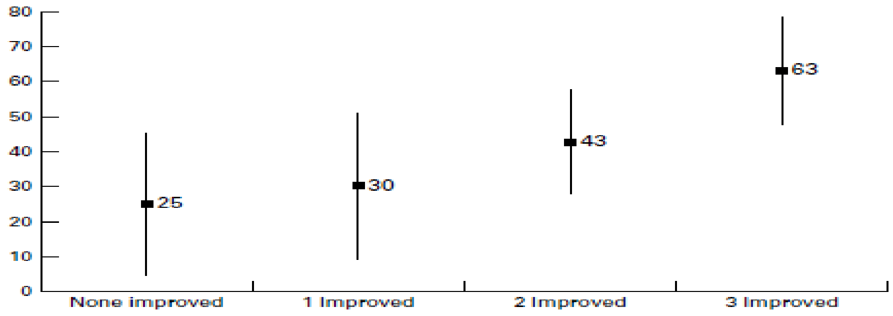

Figure 3.4 Mean preoperative priority points ($p < 0.001$) (Saunders et al., 2002).

3.3 System 3: The Corneal Transplant Scoring

3.3.1 Methods

Scoring system was formed on an electronic spreadsheet. Data of each candidate was entered into the system. The seven parameters are listed in Table 3.7. Age, gender, socioeconomic status, and general health were excluded. Seven parameters were used in calculation of other interim arguments (Table 3.8). Six components in equal weight were thereafter summed to form a single score, which is the Priority Index. Values for the Priority Index ranged between 0 (lowest priority) to 18 (highest priority). Cohort Forty sets of data on candidates were formed through an electronic spreadsheet randomly and divided into 20 pairs sequentially.

Table 3.7 Program input parameters (Rosenfeld & Varssano, 2013).

Parameter	Abbre viation	Minimal value	Maximal value
BSCVA* in operated eye	V1	Hand motion (0.001)	20/20 (1.00)
BSCVA* in fellow eye	V2	Hand motion (0.001)	20/20 (1.00)
Potential **BSCVA* operated eye**	PV1	Hand motion (0.001)	20/20 (1.00)
Pre-operative discomfort level	D	No discomfort (0)	Severe pain (Barnard CN, 1967)
Pre-operative risk of infection	I	No apparent risk (0)	Very high (Barnard CN, 1967)
Months since current disease onset	T	0 (0)	36 and more (36)
Estimated success rate	S	Very low (0)	Very high (Barnard CN, 1967)

*Best spectacle-corrected visual acuity

Table 3.8 Computed arguments (Rosenfeld & Varssano, 2013).

Argument	Computation	Abbreviation	Minimal value	Maximal value
BSCVA* **in eye score**	LOG10(V1)	V1S	-3	0
BSCVA* in fellow score	LOG10(V2)	V2S	-3	0
Potential **BSCVA*** in eye score	LOG10(PV1)	PV1S	-3	0
BSCVA* both eyes score	MAX(V1S,V2S)	VS	-3	0
Potential **BSCVA*** both eyes score	MAX(PV1S,V2S)	PVS	-3	0
Vision Benefit Score	PV1S-V1S	VB	0	3
Binocular Vision Benefit Score	PVS-VS	BVB	0	3
Priority Index	VB+BVB+D+I+T/12+S		0	18

*Best spectacle-corrected visual acuity

Assessment of one pair of candidates was performed by a cornea surgeon (David, 2013). The surgeon was asked to determine, based on the randomly generated parameters of the two candidates who should take the next corneal donation at hand. The decision was recorded. For every 20 pairs this process was repeated. After completion of the surgeon assessment, Priority Index was computed for each candidate. Selection between the two candidates in each one of the pairs was performed in regard to the Priority Index: the candidates of the higher index were designated to receive the next donated cornea in line. Comparison then was concluded between the human and the computed decisions.

3.3.2 Results

The scoring system offers values that range between 0 (lowest priority) and 18 (highest priority) for each candidate. Mean value of score in this randomly formed cohort was 6.35±2.38 (mean ±SD), range 1.28 to 10.76. Mean score difference between the candidates in each pair was 3.12±2.10 (mean ± SD), range 0.08 to 8.45. The manual scoring process, although theoretical, was mentally and emotionally demanding for the surgeon. Agreement was shown between the human decision and the value calculated in 19 out of 20 pairs (Table 3.9). Disagreement was seen in the pair that has the lowest score difference (0.08).

Table 3.9 Candidates and results (Rosenfeld & Varssano, 2013).

Case	Vision in operated eye	Vision in fellow eye	Potential vision eye	Discomfort level	Risk of infection	Waiting time	Estimated Success rate	Human choice	Priority Index	Pair difference	Agreement
1.	0.732	0.826	0.738	2	3	6	2	✓	7.504	2.336	Yes
2.	0.283	0.752	0.284	1	0	26	2		5.168		
3.	0.717	0.997	0.771	1	0	3	0		1.282	8.449	yes
4.	0.601	0.851	0.934	3	2	30	2	✓	9.731		
5.	0.538	0.929	0.562	3	2	13	2	✓	8.102	1.299	Yes
6.	0.111	0.244	0.312	2	1	27	1		6.803		
7.	0.045	0.721	0.162	0	1	36	1		5.552	2.749	Yes
8.	0.185	0.291	0.584	2	1	30	2	✓	8.301		
9.	0.922	0.412	0.965	3	3	17	2	✓	9.456	4.007	Yes
10.	0.122	0.619	0.192	1	1	15	2		5.449		
11.	0.102	0.695	0.283	2	1	35	3	✓	9.360	0.469	Yes
12.	0.646	0.910	0.895	2	1	33	3		8.892		
13.	0.040	0.960	0.093	0	0	21	1		3.114	5.622	Yes
14.	0.674	0.646	0.973	2	2	29	2	✓	8.736		
15.	0.645	0.537	0.962	0	2	25	2		6.419	2.920	Yes
16.	0.630	0.857	0.773	1	3	27	3	✓	9.339		
17.	0.470	0.468	0.666	1	0	25	0		3.386	5.069	Yes
18.	0.445	0.405	0.512	3	1	28	2	✓	8.455		
19.	0.269	0.109	0.467	0	2	2	1		3.645	3.929	Yes
20.	0.568	0.316	0.825	1	3	27	1	✓	7.574		
21.	0.418	0.040	0.564	2	3	30	3	✓	10.761	6.307	Yes
22.	0.585	0.558	0.611	1	2	5	1		4.454		
23.	0.149	0.273	0.164	0	2	8	2		4.707	2.536	Yes
24.	0.375	0.061	0.545	3	0	35	1	✓	7.243		
25.	0.234	0.602	0.330	0	0	31	2		4.732	3.836	Yes
26.	0.697	0.942	0.965	3	2	29	1	✓	8.568		
27.	0.234	0.655	0.354	2	1	30	1	✓	6.681	1.035	Yes
28.	0.502	0.093	0.791	0	0	27	3		5.646		
29.	0.733	0.259	0.929	0	3	28	2	✓	7.540	3.735	Yes
30.	0.465	0.734	0.829	2	1	6	0		3.805		
31.	0.086	0.131	0.454	2	0	30	3	✓	8.760	3.092	Yes
32.	0.164	0.497	0.355	1	2	28	0		5.668		
33.	0.308	0.520	0.492	0	0	16	0		1.536	0.904	Yes
34.	0.176	0.229	0.185	1	0	5	1	✓	2.440		
35.	0.598	0.274	0.719	1	1	28	3		7.493	0.082	No
36.	0.519	0.054	0.688	2	0	26	3	✓	7.411		
37.	0.166	0.322	0.400	2	3	0	1	✓	6.477	2.304	Yes
38.	0.526	0.248	0.530	3	1	2	0		4.173		
39.	0.962	0.388	0.979	1	1	0	2		4.015	1.734	yes
40.	0.662	0.310	0.727	1	3	20	0	✓	5.749		

CHAPTER FOUR
MATERIALS AND METHOD

In our study an artificial data set of 50 patients was created by two ophthalmologists, who are experts on corneal transplantation surgery. These patients are assumed to be waiting for an adequate cornea for transplantation and their specifications are determined according to the real clinical findings. Then, 20 corneas were created similarly. For each of the 20 corneas, the surgeon needs the best candidate patient for transplantation. Among 50 patients, this creates 20 winners (i.e. the best candidates).

The only attribute related to the cornea is defined as the age of it. On the other hand, patient features include many attributes such as age, vision in the diseased eye (visual acuity), vision in the other eye (visual acuity, other eye), impairment of visual system that defines us the sum of the vision loss in both eyes, preoperative pain in the diseased eye (pain), potential success rate of the surgery according to the nature of the corneal disease such as recurrence risk of the disease on the donor cornea (potential clinical result), the progressive nature of the disease that affects the vision of the eye during the waiting period (progressive nature of the disease), the time duration on the waiting list that explains us how long the patient is waiting for the surgery (the time duration on the waiting list), systematical drug usage such as anticoagulants that affects the surgery timing (systematical drug usage), need for transportation and time for transportation that also affect the surgery timing.

The mentioned parameters are listed in Table 4.1. The first four criteria scores (age, visual acuity, visual acuity of the other eye, pre-operative pain score) were evaluated by the corneal surgeons as a demonstrative application for the selection of the patient.

Table 4.1 Data set of 50 patients and 20 cornea

Patient No	Age	Waiting Period (Month)	Visual Acuity	Visual Acuity (Other Eye)	Need for Transport	Systematic drug usage	Pre-operative pain (1 to 4)	progressive sick	Potential Clinical Result (%)	Transport Time (hours)
1.	35	36	0.1	0.9	-	-	1	+	70	1
2.	49	24	0.05	1	-	-	1	-	100	1
3.	62	23	0.2	1	-	-	1	-	100	2
4.	33	13	0.03	0.4	-	-	2	+	80	3
5.	43	12	0.1	1	-	-	2	-	100	1
6.	45	15	0.05	1	-	-	1	+	100	5
7.	65	5	0.02	0.5	-	-	4	-	100	4
8.	28	7	0.04	0.1	+	-	4	+	100	2
9.	64	34	0.02	1	-	+	4	-	100	1
10.	62	5	0.05	0.9	-	-	3	-	90	1
11.	61	15	0.2	1	-	-	1	-	100	1
12.	60	17	0.1	1	-	-	4	-	90	1
13.	50	7	0.05	0.2	-	-	2	-	90	1
14.	51	3	0.05	0.3	+	-	3	+	90	2
15.	52	9	0.2	1	+	+	1	-	100	3
16.	53	19	0.03	1	-	-	1	-	80	1
17.	29	4	0.04	0.4	-	-	1	+	80	3
18.	58	24	0.05	1	-	-	3	-	90	1
19.	61	13	0.1	0.7	-	-	4	-	90	4
20.	57	17	0.2	0.5	-	-	3	+	80	1
21.	55	22	0.04	1	-	-	1	+	60	1
22.	44	29	0.05	0.4	-	+	1	+	80	1
23.	43	25	0.03	1	-	-	1	+	60	2
24.	24	11	0.05	0.3	+	-	1	+	90	1
25.	27	21	0.1	0.6	-	-	1	+	90	3
26.	29	2	0.2	1	-	-	1	-	100	1
27.	37	10	0.04	0.2	-	-	1	+	90	5
28.	43	21	0.2	0.9	+	-	1	-	100	2
29.	48	14	0.05	0.2	-	-	3	+	80	5
30.	54	14	0.3	0.6	-	-	4	+	90	6
31.	29	4	0.3	0.4	-	-	2	+	90	6
32.	65	12	0.1	0.8	-	-	4	-	90	1
33.	53	5	0.2	0.5	+	-	3	+	90	2
34.	39	12	0.3	0.8	-	-	2	+	90	1
35.	70	36	0.2	0.9	-	-	4	-	90	2
36.	54	6	0.1	0.7	-	-	4	-	100	2
37.	50	13	0.3	0.9	-	+	1	-	100	3
38.	32	28	0.04	0.4	-	-	1	+	90	2
39.	29	14	0.03	0.3	-	-	2	+	90	1
40.	44	15	0.3	1	-	-	1	-	100	2
41.	46	8	0.1	1	-	-	1	+	70	3
42.	48	5	0.05	1	-	-	1	-	90	1
43.	65	11	0.2	0.9	-	+	4	-	90	3
44.	56	12	0.1	0.6	-	-	4	-	90	6
45.	46	33	0.3	1	+	-	1	-	100	3
46.	48	28	0.03	1	-	-	1	-	90	2
47.	61	13	0.02	0.7	-	-	4	-	90	1
48.	56	29	0.02	1	-	-	2	+	70	5
49.	57	36	0.03	0.7	-	-	4	-	90	4
50.	53	12	0.05	0.2	-	-	4	+	90	2

4.1 Classification Based Tournament Strategy

The ANN system developed in this study has been designed for priority ranking of the candidates, who are waiting for corneal transplantation surgery. With the use of the developed system, it is aimed to select appropriate candidates in a fast, reliable, and accurate manner. Moreover, the workload of the surgeon will be reduced and the efficiency in the workflow will be increased. Thus, the developed ANN design should satisfy all these requirements in order to be practically useful.

A data set of 50 patients, who are waiting for the transplantation surgery, and a data set of 20 corneas, which are ready for transplantation, have been generated by the ophthalmologists. For each of the 20 corneas, the surgeon needs to determine the best candidate for transplantation. Among 50 patients, this creates only 20 winners (i.e. the best candidates). This small number of winners limits the opportunities for the training of the ANN. Moreover, the error risk at the ANN output becomes very high. This is illustrated in Table 4.2 as a demonstrative case including 50 patients and 20 corneas which constitute complete data set.

In order to generate a more suitable data set for training, the corneal surgeon picked and ordered (namely ranked) 6 patients for each corneal tissue. This is illustrated in Table 4.3, where the numbers represent the rank of a patient for the corresponding cornea. In other words, the surgeon listed the six potential candidates for the corresponding cornea in the order of priority. The patients, who are not in the first six selections, are represented by zero.

Table 4.2 The best candidates for each cornea

	Cornea 1	Cornea 2	Cornea 3	Cornea 4	Cornea 5	Cornea 6	Cornea 7	Cornea 8	Cornea 9	Cornea 10	Cornea 11	Cornea 12	Cornea 13	Cornea 14	Cornea 15	Cornea 16	Cornea 17	Cornea 18	Cornea 19	Cornea 20
Patient 1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0
Patient 2	0	1	0	0	0	0	0	0	0	1	1	0	1	1	1	0	1	0	1	0
Patient 3	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	1	0	0	0	0
Patient 4	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Patient 5	1	1	0	0	0	0	0	0	0	1	0	0	1	1	0	0	0	1	1	0
Patient 6	1	1	0	0	0	0	0	0	0	1	1	0	1	1	0	0	0	0	1	0
Patient 7	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Patient 8	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 9	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Patient 10	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	1	0	0	0	0
Patient 11	0	0	0	0	0	1	1	0	0	0	0	1	0	0	0	1	0	0	0	0
Patient 12	0	0	1	0	0	1	1	1	0	0	0	1	0	0	0	1	0	0	0	1
Patient 13	0	1	1	0	0	0	0	1	0	1	1	0	0	1	1	0	1	0	1	1
Patient 14	0	0	1	0	0	0	1	1	0	0	1	0	0	1	1	0	1	0	1	1
Patient 15	0	0	0	0	0	0	1	1	0	0	1	0	0	1	1	1	1	0	1	1
Patient 16	0	0	1	0	0	0	1	1	0	0	1	0	0	1	1	1	1	0	0	1
Patient 17	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 18	0	0	1	0	0	1	1	1	0	0	0	1	0	0	0	1	0	0	0	1
Patient 19	0	0	0	0	0	1	1	0	0	0	0	1	0	0	0	1	0	0	0	0
Patient 20	0	0	1	0	0	1	1	1	0	0	0	1	0	0	0	1	1	0	0	1
Patient 21	0	0	1	0	0	0	1	1	0	0	0	0	0	0	1	1	0	0	0	1
Patient 22	1	1	0	0	0	0	0	0	0	1	1	0	1	1	0	0	0	1	1	0
Patient 23	1	1	0	0	0	0	0	0	0	1	0	0	1	1	0	0	0	1	1	0
Patient 24	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 25	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 26	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 27	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0
Patient 28	1	1	0	0	0	0	0	0	0	1	0	0	1	1	0	0	0	1	1	0
Patient 29	1	1	0	0	0	0	0	0	0	1	1	0	1	1	1	0	1	0	1	0
Patient 30	0	0	1	0	0	0	1	1	0	0	1	0	0	0	1	1	1	0	0	1
Patient 31	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 32	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	1	0	0	0	0
Patient 33	0	0	1	0	0	0	1	1	0	0	1	0	0	1	1	0	1	0	0	1
Patient 34	1	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	1	0	0
Patient 35	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Patient 36	0	0	1	0	0	0	1	1	0	0	1	0	0	0	1	0	1	0	0	1
Patient 37	0	1	1	0	0	0	0	1	0	1	1	0	0	1	1	0	1	0	1	1
Patient 38	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Patient 39	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 40	1	1	0	0	0	0	0	0	0	1	1	0	1	1	0	0	0	1	1	0
Patient 41	1	1	0	0	0	0	0	0	0	1	1	0	1	1	1	0	0	0	1	0
Patient 42	1	1	0	0	0	0	0	0	0	1	1	0	1	1	1	0	1	0	1	0
Patient 43	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Patient 44	0	0	1	0	0	1	1	1	0	0	0	1	0	0	1	1	1	0	0	1
Patient 45	1	1	0	0	0	0	0	0	0	1	1	0	1	1	1	0	0	0	1	0
Patient 46	1	1	0	0	0	0	0	0	0	1	1	0	1	1	1	0	1	0	1	0
Patient 47	0	0	0	0	0	1	1	0	0	0	0	1	0	0	0	1	0	0	0	0
Patient 48	0	0	1	0	0	1	1	1	0	0	0	1	0	0	1	1	1	0	0	1
Patient 49	0	0	1	0	0	1	1	1	0	0	0	1	0	0	0	1	1	0	0	1
Patient 50	0	0	1	0	0	0	1	1	0	0	1	0	0	1	1	1	1	0	0	1

Although Table 4.2 and Table 4.3 create a better data distribution for training of the ANN, it requires the output to be encoded based on the number of candidates (i.e. six in Table 4.3). Extensive simulations show that this causes generalization and performance problems as the number of candidates increases. Thus, in this study, we present an alternative organization of the candidates.

Table 4.4 and illustrate our approach using the same demonstrative examples in Table 4.2 and 4.3. Table 4.4 presents candidate patient matrix for a single cornea (i.e. Cornea 1 as an example). Each cell of the matrix shows the pairwise decision of the surgeon, or in other words, which one would the surgeon choose between two patients. For instance, in Table 4.3, the surgeon has ranked the first six candidates for cornea 1 as winner 1 (P29), winner 2 (P22), winner 3 (P5), winner 4 (P23), winner 5 (P45), and winner 6 (P6), respectively (see the first column of Table 4.3). According to this priority ranking, patient matrix in Table 4.4 is constructed as follows.

P29 is ranked as the best candidate for cornea 1. So, for any pairwise competition of P29 with another candidate, the surgeon would select P29 (see the first column of Table 4.3). P22 is selected as the second best candidate and P22 will be chosen at any pairwise competition except its competition with P29. The upper half of the matrix is not filled in because of the symmetry property of the data (i.e. P29-P22 competition is equivalent to P22-P29 competition).

Table 4.3 The first six candidates for each cornea

	Cornea 1	Cornea 2	Cornea 3	Cornea 4	Cornea 5	Cornea 6	Cornea 7	Cornea 8	Cornea 9	Cornea	Cornea	Cornea	Cornea	Cornea	Cornea	Cornea	Cornea	Cornea	Cornea	Cornea
Patient 1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	5	0	0
Patient 2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 4	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Patient 5	3	0	0	0	0	0	0	0	0	6	0	0	0	0	0	0	0	4	0	0
Patient 6	6	6	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Patient 7	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 8	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 11	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0
Patient 12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 13	0	2	3	0	0	0	0	3	0	2	4	0	0	4	4	0	4	0	3	3
Patient 14	0	0	2	0	0	0	2	2	0	0	0	0	0	3	3	0	3	0	2	2
Patient 15	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 16	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 17	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 18	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 19	0	0	0	0	0	5	0	0	0	0	0	5	0	0	0	5	0	0	0	0
Patient 20	0	0	6	0	0	6	0	0	0	0	0	6	0	0	0	6	0	0	0	0
Patient 21	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 22	2	3	0	0	0	0	0	0	0	3	5	0	2	5	0	0	0	2	4	0
Patient 23	4	4	0	0	0	0	0	0	0	4	0	0	0	0	0	0	0	3	5	0
Patient 24	0	0	0	2	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 25	0	0	0	3	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 26	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 27	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	1	0	0
Patient 28	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 29	1	1	0	0	0	0	0	0	0	1	2	0	1	2	2	0	2	0	1	0
Patient 30	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 31	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 32	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 33	0	0	5	0	0	0	0	6	0	0	0	0	0	6	6	0	0	0	0	6
Patient 34	0	0	0	0	0	0	0	0	4	0	0	0	3	0	0	0	0	6	0	0
Patient 35	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 36	0	0	0	0	0	0	0	5	0	0	6	0	0	0	0	4	0	0	0	5
Patient 37	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 38	0	0	0	0	4	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0
Patient 39	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 40	0	0	0	0	0	0	0	0	0	5	0	0	0	0	0	0	0	0	0	0
Patient 41	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 42	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 43	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 44	0	0	4	0	0	4	5	4	0	0	0	4	0	0	0	0	6	0	0	4
Patient 45	5	0	0	0	0	0	0	0	0	0	0	0	6	0	0	0	0	0	0	0
Patient 46	0	5	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0	6	0
Patient 47	0	0	0	0	0	2	3	0	0	0	0	2	0	0	0	1	0	0	0	0
Patient 48	0	0	0	0	0	0	6	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient 49	0	0	0	0	0	3	4	0	0	0	0	3	0	0	0	2	0	0	0	0
Patient 50	0	0	1	0	0	0	1	1	0	0	1	0	0	1	1	3	1	0	0	1

For only a single cornea (Cornea 1)	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15	Patient 16	Patient 17	Patient 18	Patient 19	Patient 20	Patient 21	Patient 22	Patient 23	Patient 24	Patient 25
Patient 1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient 2	NA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient 3	NA	NA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient 4	NA	NA	NA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient 5	5	5	NA	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient 6	6	5	NA	6	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient 7	P1	NA	NA	NA	5	6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient 8	NA	NA	NA	NA	5	6	NA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient 9	NA	NA	NA	NA	5	6	NA	NA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient 10	NA	NA	NA	NA	5	6	NA	NA	NA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient 11	NA	NA	NA	NA	5	6	NA	NA	NA	NA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient 12	NA	NA	NA	NA	5	6	NA	NA	NA	NA	NA	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient 13	NA	NA	NA	NA	5	6	NA	NA	NA	NA	NA	NA	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient 14	NA	NA	NA	NA	5	6	NA	NA	NA	NA	NA	NA	NA	-	-	-	-	-	-	-	-	-	-	-	-
Patient 15	NA	NA	NA	NA	5	6	NA	NA	NA	NA	NA	NA	NA	NA	-	-	-	-	-	-	-	-	-	-	-
Patient 16	NA	NA	NA	NA	5	6	NA	NA	NA	NA	NA	NA	NA	NA	NA	-	-	-	-	-	-	-	-	-	-
Patient 17	NA	NA	NA	NA	5	6	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	-	-	-	-	-	-	-	-	-
Patient 18	NA	NA	NA	NA	5	6	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	-	-	-	-	-	-	-	-
Patient 19	NA	NA	NA	NA	5	6	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	-	-	-	-	-	-	-
Patient 20	NA	NA	NA	NA	5	6	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	-	-	-	-	-	-
Patient 21	NA	NA	NA	NA	5	6	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	-	-	-	-	-
Patient 22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	-	-	-	-
Patient 23	23	23	23	23	5	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	-	-	-
Patient 24	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	22	23	-	-
Patient 25	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	22	23	NA	-

Table 4.4 Competition matrix for a single cornea

For only a single cornea (Cornea 1)	Patient 26	Patient 27	Patient 28	Patient 29	Patient 30	Patient 31	Patient 32	Patient 33	Patient 34	Patient 35	Patient 36	Patient 37	Patient 38	Patient 39	Patient 40	Patient 41	Patient 42	Patient 43	Patient 44	Patient 45	Patient 46	Patient 47	Patient 48	Patient 49	Patient 50
Patient 26	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient 27	NA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient 28	**28**	**28**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient 29	**29**	**29**	**29**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient 30	NA	NA	**28**	**29**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient 31	NA	NA	**28**	**29**	NA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient 32	NA	NA	**28**	**29**	NA	NA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient 33	NA	NA	**28**	**29**	NA	NA	NA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient 34	**34**	**34**	**NA**	**39**	**34**	**34**	**34**	**34**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient 35	NA	NA	**28**	**29**	NA	NA	NA	NA	**34**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient 36	NA	NA	**28**	**29**	**30**	**36**	NA	NA	**34**	NA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient 37	NA	**29**	**28**	**29**	NA	NA	NA	NA	34	NA	NA	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient 38	NA	NA	**28**	**29**	NA	NA	NA	NA	**34**	NA	NA	NA	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient 39	NA	NA	**28**	**29**	NA	NA	NA	NA	**34**	NA	NA	NA	NA	-	-	-	-	-	-	-	-	-	-	-	-
Patient 40	**40**	**40**	NA	**29**	**40**	**40**	**40**	**40**	NA	**40**	**40**	**40**	**40**	**40**	-	-	-	-	-	-	-	-	-	-	-
Patient 41	**41**	**41**	NA	**29**	**41**	**41**	**41**	**41**	NA	**41**	**41**	**41**	**41**	**41**	NA	-	-	-	-	-	-	-	-	-	-
Patient 42	**42**	**42**	NA	**29**	**42**	**42**	**42**	**42**	NA	**42**	**42**	**42**	**42**	**42**	NA	NA	-	-	-	-	-	-	-	-	-
Patient 43	NA	NA	**28**	**29**	NA	NA	NA	NA	**34**	NA	NA	NA	NA	NA	**40**	**41**	**42**	-	-	-	-	-	-	-	-
Patient 44	NA	NA	**28**	**29**	NA	NA	NA	NA	**34**	NA	NA	NA	NA	NA	**40**	**41**	**42**	NA	-	-	-	-	-	-	-
Patient 45	**45**	**45**	NA	**29**	**45**	**45**	**45**	NA	**45**	**45**	**45**	**45**	**45**	**45**	**45**	**45**	**42**	**45**		-	-	-	-	-	-
Patient 46	**46**	**46**	NA	**29**	**46**	**46**	**46**	**46**	NA	**46**	**46**	**46**	**46**	**46**	NA	NA	NA	NA	NA	**45**	-	-	-	-	-
Patient 47	NA	NA	**28**	**29**	NA	NA	NA	NA	**34**	NA	NA	NA	NA	NA	**40**	**41**	**42**	NA	NA	**45**	**46**	-	-	-	-
Patient 48	NA	NA	**28**	**29**	NA	NA	NA	NA	**34**	NA	NA	NA	NA	NA	**40**	**41**	**42**	NA	NA	**45**	**46**	NA	-	-	-
Patient 49	NA	NA	**28**	**29**	NA	NA	NA	NA	**34**	NA	NA	NA	NA	NA	**40**	**41**	**42**	NA	NA	**45**	**46**	NA	NA	-	-
Patient 50	NA	NA	**28**	**29**	NA	NA	NA	NA	**34**	NA	NA	NA	NA	NA	**40**	**41**	**42**	NA	NA	**45**	**46**	NA	NA	NA	-

Table 4.4 Competition matrix for a single cornea (continue)

4.2 Tournament Method

The competition results are only available for the pairs, one of which is in the first six candidates selected by the surgeon. For instance, considering cornea 1, P7 is not elected inside the first six candidates. Its competition with P45 would result with selection of P45, because P45 is ranked as the sixth possible candidate. However, the competition of P2 with P7 is unknown, because both of them are not ranked. These are illustrated with NA (i.e. Not Applicable) in Table 4.4. Thus, the matrix is filled in with competition results wherever the winner is known.

The constructed matrix generates 232 competitions and winners for each cornea, which are formulated as a pairwise classification problem. Thus, the output of an ANN should have two output variables to encode the winner. For instance, in P1-P2 competition, P1 and P2 features are fed to the ANN as the input, and the result would generate $[1\ 0]^T$ if P1 is the winner and $[0\ 1]^T$ if P2 is the winner.

After the creation of patient matrices for each cornea, different methods can be employed for training and testing phases. In this study, conventional training strategy is used: Features that belong to a portion of the available competition are used as the ANN input, while the competition results are used as the desired targets.

On the other hand, the testing (or application) phase is designed by using a new approach called the tournament strategy. Considering the problem of determining six candidates for a cornea, the first level of the tournament determines the winners of pairwise competitions of all patients. These winners are shown in Figure 2 as with Winner 1.1, 1.2, 1.3, 1.4 and 1.5. Then, at the second level of the tournament, the winners of the first level are paired and the winners of their competitions are determined (Winner 2.1 and 2.2 in Figure 4.1). This procedure continues until the last winner is determined at the final competition level. The final winner is chosen as the best candidate for transplantation and ranked as 1. In order to determine the second best candidate for the transplantation, the previous winner is removed from the data set and the same tournament strategy is applied again. The winner of the second tournament is chosen as the second best candidate for the surgery and ranked as 2. This procedure goes on iteratively until all six candidates are determined.

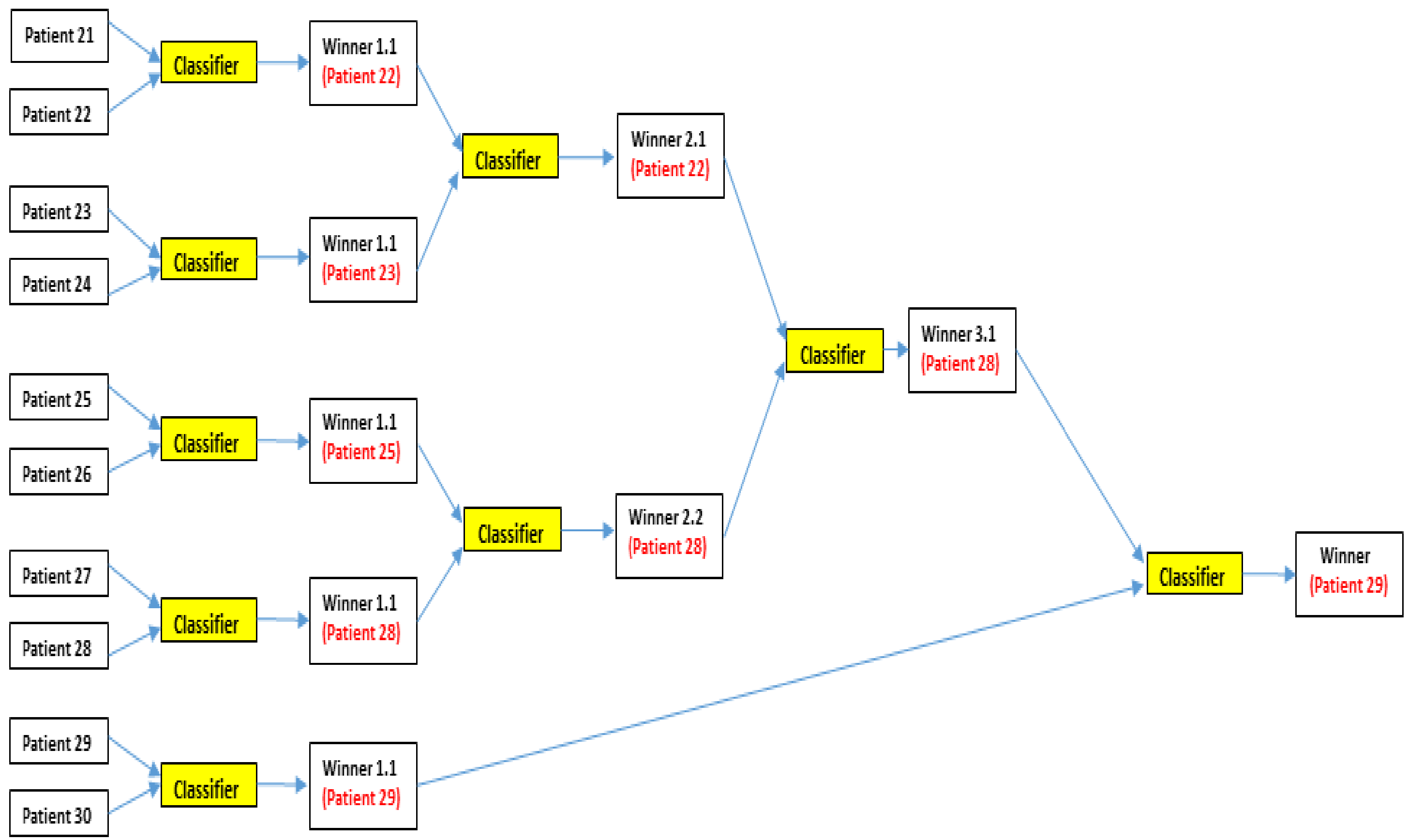

Figure 4.1 Part of all pairwise competition item of cornea 1

4.3 Application and Results

The classifier of the system is chosen as a Multi-Layer-Perceptron (MLP) (Haykin, 1998) due to its wide and effective use in several applications. The MLP is trained using back-propagation with adaptive learning rate. The employed MLP has 20 inputs (i.e. 10 features from each patient), one hidden layer with 36 neurons with trainlm activation functions and an output layer with 2 neurons with linear activation functions. The network goal for mean square error is chosen to be 0.001 and the maximum number of iterations is determined as 1000 epochs. The adaptive learning rate is initialized to 0.01. If the performance decreases below the goal, the learning rate increases with a ratio of 1.05, otherwise it decreases with a ratio of 0.7.

First of all, the donor age is used as a filter to eliminate all the candidates, whose ages difference to donor is more than ±5. For the remaining patients, the proposed strategy, which is described in detail in the previous section, is applied to the data set using a similar technique to leave-one out (Kearns & Ron, 1999). Considering 20 corneas and 50 patients in the data set, the ANN is trained with pairwise competition results of 19 corneas. Then the remaining cornea is used for testing using the tournament strategy. This procedure is repeated for all corneas and the results are presented in Table II, which provides a color code for better illustration of the performance. For each cornea presented in Table 4.6 the left column show the expert ranking while the right column show the six candidates selected by the system. If a row in both columns has the same color, it indicates that the system has chosen the same candidate with the same rank as the expert. If the selection is compatible with the expert but the rank is different, then the difference can be observed by following the corresponding color.

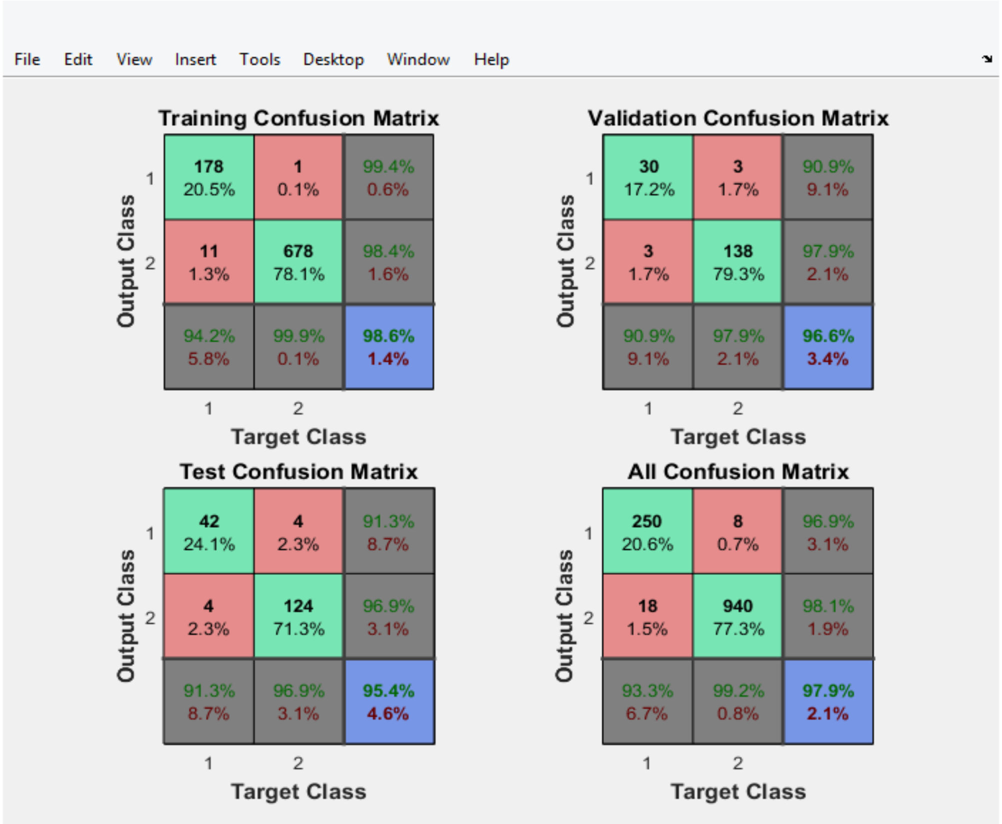

Figure 4.2 Confusing matrix results for simulink 19 corneas

There were 1216 pairwise competitions matrix for cornea 1 which is remained cornea in leave-one-out phase, has illustrated in Figure 4.2.

"All Confusion matrix" in this figure shows:

TP: 250 pairwise that were correctly selected winners as $[1\ 0]^T$ or $[0\ 1]^T$, which must be winners as $[1\ 0]^T$ or $[0\ 1]^T$, (True Positive).

TN: 940 pairwise that were correctly selected not winners as $[0\ 0]^T$, which must be not winners as $[0\ 0]^T$, (True Negative).

FP: 8 pairwise that were incorrectly selected as winners as $[1\ 0]^T$ or $[0\ 1]^T$, which must be not winners as $[0\ 0]^T$, (False Positive).

FN: 18 pairwise that were incorrectly selected as not winners $[0\ 0]^T$, which must be winners as $[1\ 0]^T$ or $[0\ 1]^T$, (False Negative).

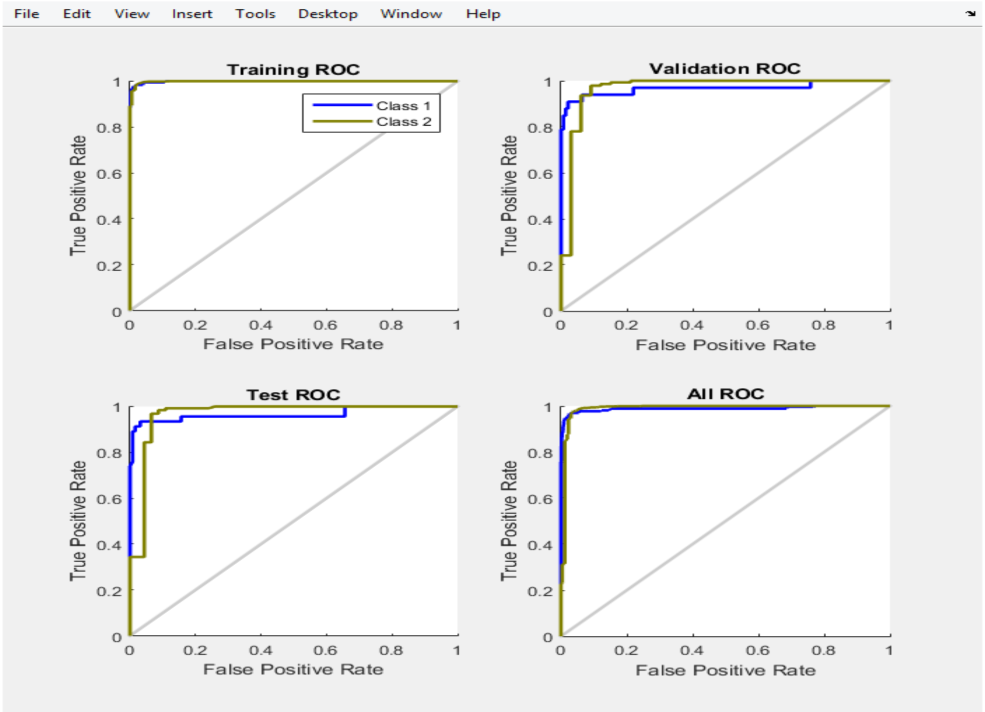

Figure 4.3 Receiver Operating Characteristic for Simulink 19 corneas which Cornea 1 is remained

Receiver operating characteristic (ROC), or ROC curve, is illustrated in Figure 4.2 the curve is created by plotting the true positive rate (TPR) against the false positive rate (FPR) at various threshold settings. The true-positive rate is also known as sensitivity. The true negative rate (TNR) is also known as specificity.

$$\text{Sensitivity} = \frac{TP}{TP + FN} = \frac{250}{250+18} = \%93 \tag{4.1}$$

$$\text{Specificity} = \frac{TN}{FP+TN} = \frac{940}{8 + 940} = \%99 \tag{4.2}$$

Overall, 94 of the 114 candidates are found by the system, which corresponds approximately to 82% of the all possible candidates. More importantly, the system achieves to find the best four candidates for each donor cornea. Although, the ranks assigned by the system are slightly different than the expert ranking, the system successfully narrows down the long list of candidates to the adequately selected four.

In light of these results, the system is found to be significantly effective by the surgeons, who have selected the candidates manually.

First row in Table 4.5 shows 30% of the candidates who were in the first rank as the expert's decision, has been found at the first rank in system, and 100% of the candidates who were in the first rank, has been found but in different rank (except first rank) by the scoring system. Other ranks results is also shown in this table as the second, third, fourth, fifth and sixth.

Table 4.5 Compare system ranks with experts ranks

Rank	Scoring System	
	Same Rank	Different Rank
First	30%	100%
Second	40%	100%
Third	25%	95%
Fourth	21%	90%
Fifth	21%	75%
Sixth	12%	30%

Table 4.6 Pairwise result of the system

	Cornea 1		Cornea 2		Cornea 3		Cornea 4	
	Expert	System	Expert	System	Expert	System	Expert	System
1.	29	22	29	13	50	13	8	8
2.	22	29	13	29	14	14	24	24
3.	5	23	22	22	13	50	25	25
4.	23	46	23	23	44	49	----	---
5.	45	42	46	46	33	44	---	---
6.	6	41	5	45	20	48	---	---

	Cornea 5		Cornea 6		Cornea 7		Cornea 8	
	Expert	System	Expert	System	Expert	System	Expert	System
1.	8	8	7	7	50	14	50	13
2.	39	17	47	47	14	50	14	14
3.	17	24	49	19	47	49	13	50
4.	38	25	44	44	49	48	44	49
5.	24	38	19	49	44	47	36	48
6.	25	39	20	48	48	36	33	44

	Cornea 9		Cornea 10		Cornea 11		Cornea 12	
	Expert	System	Expert	System	Expert	System	Expert	System
1.	4	4	29	13	50	13	7	47
2.	27	27	13	22	29	14	47	7
3.	38	38	22	29	14	22	49	49
4.	34	1	23	46	13	29	44	44
5.	1	34	46	23	22	50	19	19
6.	---	---	5	45	36	46	20	48

	Cornea 13		Cornea 14		Cornea 15		Cornea 16	
	Expert	System	Expert	System	Expert	System	Expert	System
1.	29	29	50	13	50	13	50	50
2.	22	22	29	14	29	14	47	44
3.	23	46	14	22	14	29	49	47
4.	46	5	13	29	13	50	36	49
5.	45	45	22	50	21	48	19	36
6.	---	---	33	23	33	46	20	19

	Cornea 17		Cornea 18		Cornea 19		Cornea 20	
	Expert	System	Expert	System	Expert	System	Expert	System
1.	50	13	27	22	29	13	50	13
2.	29	14	22	27	14	14	14	14
3.	14	29	23	23	13	29	13	50
4.	13	50	5	40	22	22	44	49
5.	42	49	1	34	23	23	36	44
6.	44	44	34	1	46	46	43	48

CHAPTER FIVE
DEVELOPED SOFTWARE

5.1 User Guide of the Developed GUI

The first step of the GUI is to input private username and password which belongs to ophthalmologist (Figure 5.1).

Figure 5.1 Login menu

"User ID" and "Password" must be input during 15 seconds in case of vanishing "Log in" menu after 15 Seconds. After Inputting "User ID" and "log in" correctly, user see "Patients Information" menu (Figure 5.2).

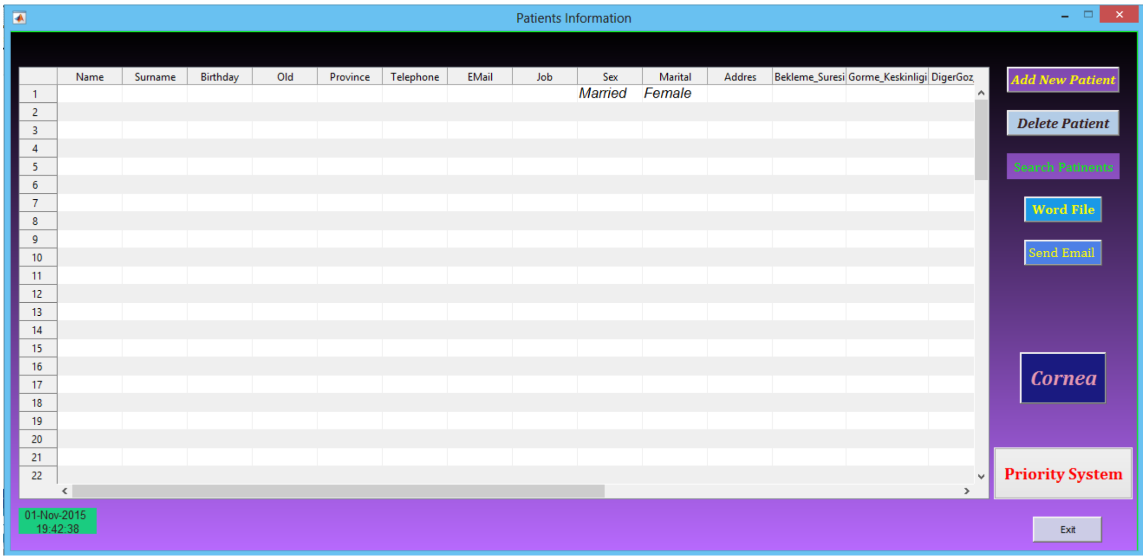

Figure 5.2 Patient information

- "Add New Patient": add a new patients features.
- "Delete Patient": delete a patients which maybe has died or refuse cornea transplantation.
- "Word File"; view data set as word format in Microsoft office.
- "Send Email": send word file to an E-mail address.
- "Cornea": properties of cornea (Figure 5.5).
- "Rank": creating rank for each cornea (Figure 5.7).
- "Priority System": priority patients by system.
- "Exit": close "Patients Information" menu.

5.1.2 Create New Patient Menu

For importing a new patient information and feature:

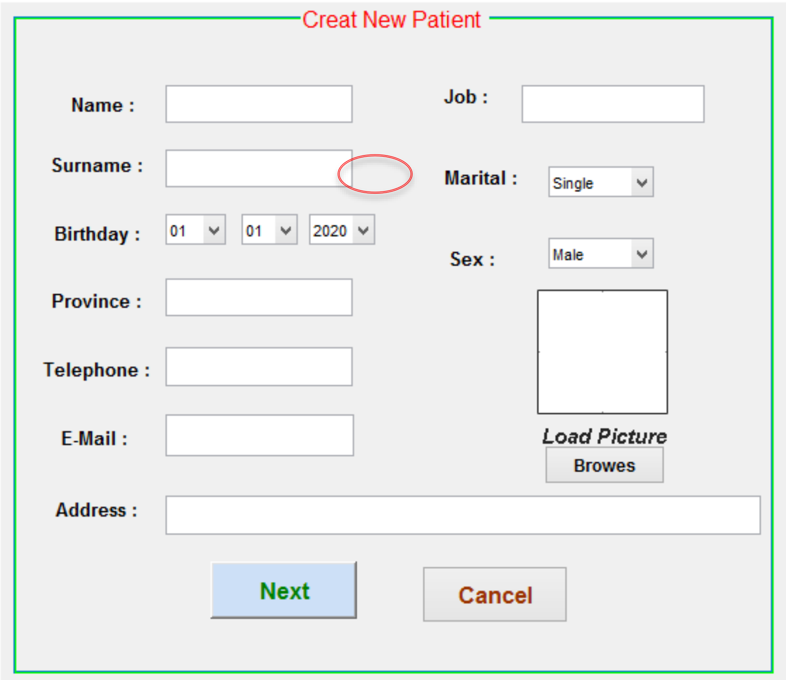

Figure 5.3 Create new patient

In "Birthday" part the program calculate Age of Patient by years. For example; if the data of patient is "1980" his/her age is '35' (in 2015 year).

In the above table:

These are general properties of patients:

- “Name”: Name of patient.
- “Surname”: Surname of patient.
- “Birthday”: Birthday of patient
- “Province”: Province of patient.
- “Telephone”: Patient’s telephone number.
- “Email”: Patient Email-address.
- “Job”: Patient job.
- “Sex”: Patient Sexuality (Male or Female).
- “Marital”: Patient marital (Single or married).
- “Address”: Patient residence.

In the next step (Figure 5.4)

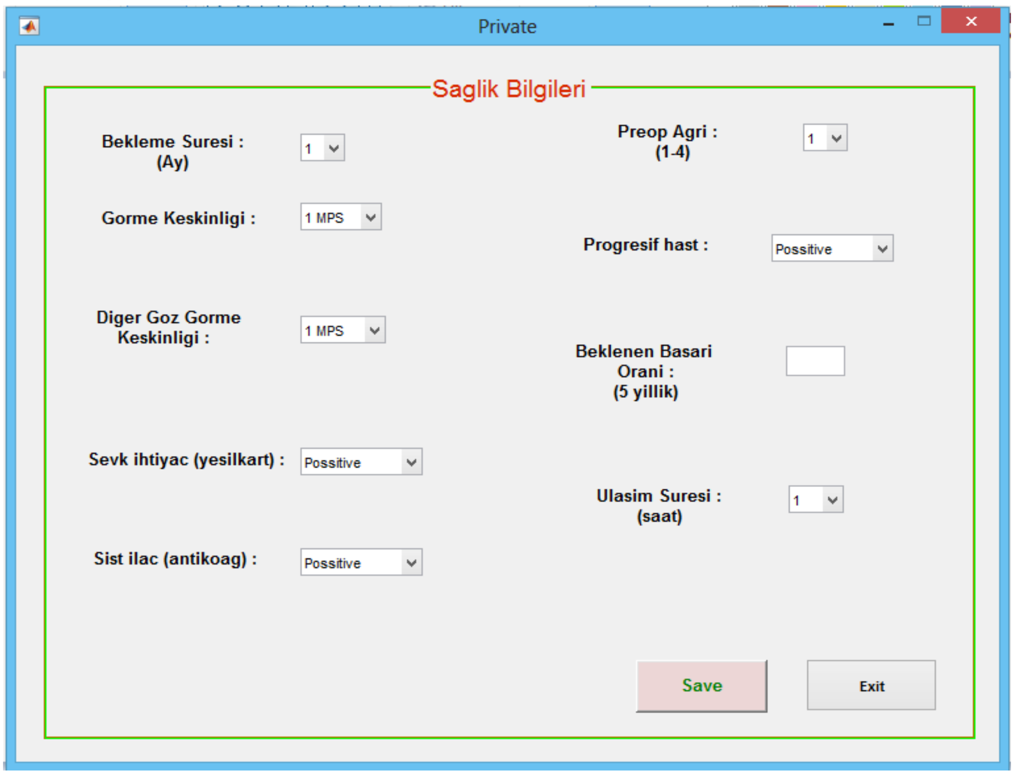

Figure 5.4 Patient features

- "Bekleme Suresi (Ay)": Patient who is waiting for operating (month).
- "Gorme Keskinligi": Visual Acuity.
- "Diger Goz Gorme Keskinligi": Visual Acuity of other eye.
- "Sevk ihtiyacı (yesilkart)": Referral requirement or need for transport
- "Sist ilac (antikoag)": Systematic drug usage.
- "Proep Agri (1-4)": Pre-operative (1 to 4).
- "Prograsivf hast": Progressive sick.
- "Beklenen Basari Orani (% yillik)": Potential clinical results (%).
- "Ulasim suresi (saat)": Transport time (hours).

5.1.3 Create New Cornea List

By clicking on "Cornea" user can input dataset of cornea (Figure 5.5)

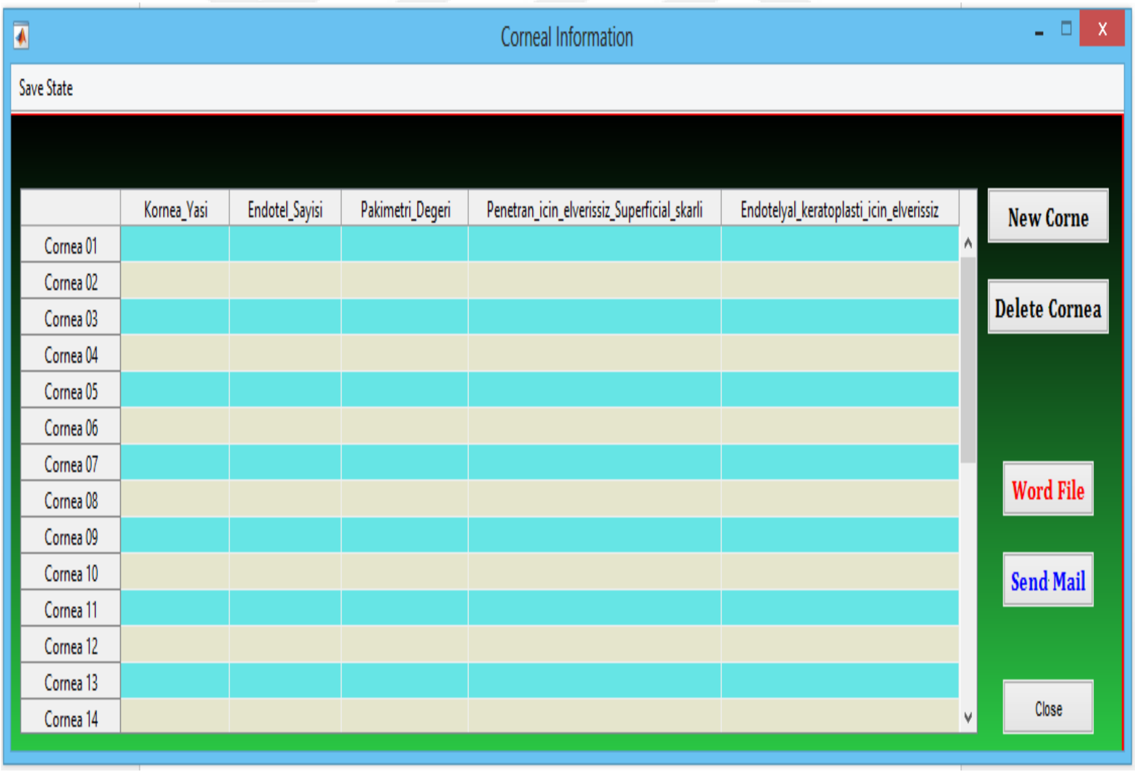

Figure 5.5 Cornea features

5.2.1 New Cornea

User can adjust features of cornea in Figure 5.6 :

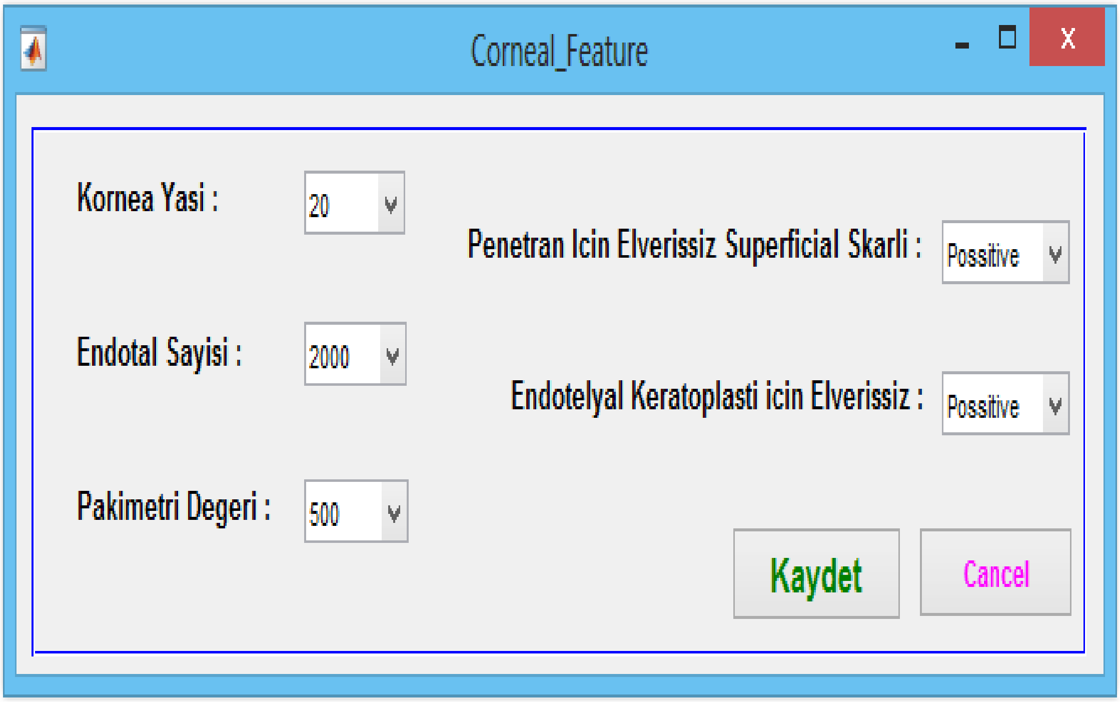

Figure 5.6 Cornea features

Cornea has 5 features (Figure 5.6)

- "Kornea Yaşı": Corneal Age.
- "Endotel Sayısı": The number of endothelial.
- "Pakimetri Değeri": Pachymetry Value.
- "Penetran_icin_elverissiz_Superficial_skarli": Penetrating on the unfavorable superficial scars.
- "Endotelyal_keratoplasti_icin_elverissiz"

5.2.2 Ranking

In this menu expert can make a rank list for each cornea (Figure 5.7).

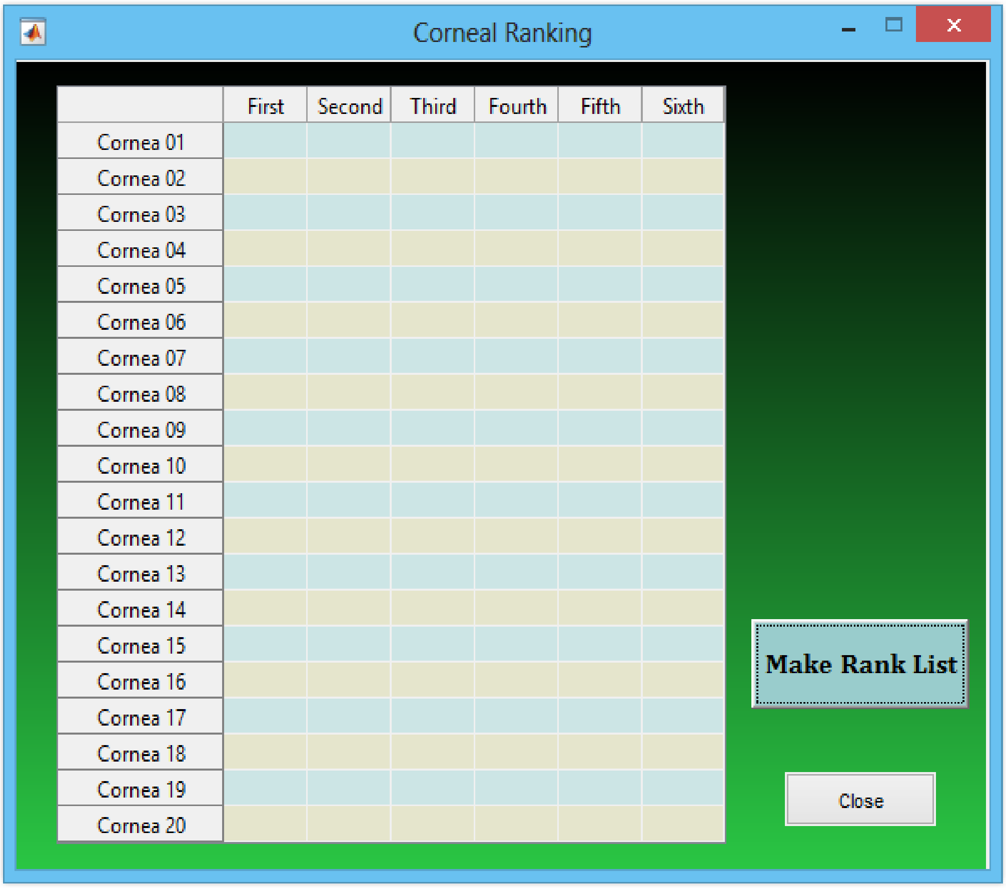

Figure 5.7 Ranking menu

CHAPTER SIX
CONCLUSIONS AND DISCUSSIONS

In this study, a tournament based ANN classification system has been designed for priority ranking of the patients, who are possible candidates for corneal transplantation surgery. Using the developed system, the selection of the appropriate candidates can be done in a fast, reliable, and accurate manner. Moreover, the workload of the surgeon is reduced and the workflow efficiency can be increased by automatic selection of the corneal transplant candidates among a long waiting list. The automation also prevents the possible error-prone decision making due to the tedious manual selection process.

Expert selected features, which are analyzed in the project, consist of information from two sources:

1) Data of the patient.
2) Information about the donor cornea.

In contrast to the studies presented in the literature, which consist of only a limited number of patients and mostly based on heuristic scoring methods, our approach implements a learning scheme, which tries to mimic the decision criteria of the surgeon.

The system has flexible properties in order to adapt its decision rules to different experts by using various features of the donor corneal tissue as the inputs of the ANN. This will allow further possibilities on deciding whether to use a single cornea for more than one transplantation surgery.

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