Neuro-Fuzzy Nets in Medical Diagnosis: The DIAGEN Case Study of Glaucoma

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Abstract. This work presents an approach to the automatic interpretation of the visual field to enable ophthalmology patients to be classified as glaucomatous and normal. The approach is based on a neuro-fuzzy system (NEFCLASS) that enables a set of rules to be learnt, with no a priori knowledge, and the fuzzy sets that form the rule antecedents to be tuned, on the basis of a set of training data. Another alternative is to insert knowledge (fuzzy rules) and let the system tune its antecedents, as in the previous case. Three trials are shown which demonstrate the useful application of this approach in this medical discipline, enabling a set of rule bases to be obtained which produce high sensitivity and specificity values in the classification process.

1. Introduction

Glaucoma is a disease characterized by the existence of a chronic and progressive lesion of the optic nerve caused by damage to the ganglion cells in the retina. This disease causes anatomic damage to the optic nerve and impairment of the visual function. The importance of this disease lies in its serious implications, since it causes progressive and irreversible loss of vision and is one of the most common causes of blindness in developed countries [10,12].

Consequently, measurement of the visual field (perimetry) is one of the most important ophthalmologic tests for the diagnosis of glaucoma. However no satisfactory solution has been found yet for addressing the problem of making an objective interpretation of the visual field (VF) results, and there are no standard criteria that, taking into account the distribution of the incipient glaucomatous lesions, enable them to be distinguished from lesions caused by other factors. Most of the research carried out into analyzing the perimetry results is based on clinical experience, and is inevitably influenced by pre-existent criteria on glaucomatous defects and their evolution. As a result, it may prove useful to carry out initial research, on an objective basis, into the

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characteristics of the glaucomatous defects, using mathematical database analysis methods which provide automatic VF analysis systems and in which the medical expert's involvement is minimal.

2. Patient Characteristics

A group of 218 glaucomatous patients and 62 individuals with no ocular pathology (normal) were used. In order to proceed to train the neuro-fuzzy network, 2/3 of each class were separated (145 pathological and 42 normal), and the remaining 1/3 (73 pathological and 20 normal) were used to check the resulting network. In both cases, training and test, the VF analysis was performed using the Octopus G1X program (Interzeag AG, Schilieren, Switzerland) and the first VF was ignored to rule out errors caused by the learning effect [4].

3. Data Processing

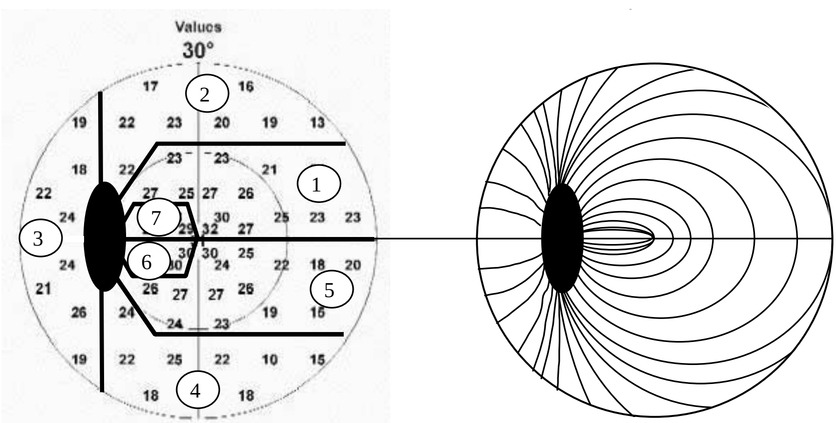
The information obtained when performing a VF analysis depends on the type of perimeter, the type of program, the matrix of points analyzed and the perimetric strategy employed. Generally, threshold determination is performed on a set of points of the VF for a particular stimulus of a determined size, display time and fundus illumination. Basically the stimuli are projected onto a spatial localization (which may vary depending on the matrix used) and their intensity is modified to determine the sensitivity threshold of the retina for each point. Eventually a set of threshold sensitivity measurements is obtained which the expert analyzes in order to assess the patient's condition. In an effort to automate and standardize the process of diagnosis, a series of numerical indices is used which manage to summarize the vast amount of information furnished by an ophthalmologic test of this kind.

Mean sensitivity (MS) is one of the most frequently used indices which, as its name implies, evaluates the mean value of all the sensitivity measurements (one for each point), each of which represents the minimum luminous intensity that the patient can perceive in each point of the VF analyzed. If a defect is considered to be the difference between the sensitivity value measured and that of a person of the same age considered to be statistically normal, the *mean defect* (MD) is defined as the mean of all these differences. Finally, another frequently used index corresponds to the calculation of the so-called *loss variance* (LV), which is simply the statistic variance applied to the previous defect values.

A database was created with the VF information furnished by Octopus. Each point tested (59 points altogether) was represented by the threshold sensitivity value in decibels (dB). The central 30º visual field area was divided into seven zones as shown in Figure 1(a). The choice of these areas was made by analyzing the correlation between each of the points with all the others and by choosing groups of points with a maximum degree of correlation between one another [5]. As can be seen, the zones eventually chosen are closely connected with the routes taken by the bundle of nerve fibers on their way from the different points of the retina to the papilla (emergence zone of the bundle of nerve fibers of the optic nerve), Figure 1(b). In [1, 3] VF valuation studies were performed which were also based on zones but with a different distribution to the one chosen in this instance.

Initially, 17 input variables were chosen: the mean defect and the loss variance in each of the seven zones chosen (MD1, MD2, MD3, MD4, MD5, MD6 and MD7, LV1, LV2, LV3, LV4, LV5, LV6 and LV7, respectively), the mean defect (MD) and the total loss variance (LV) and, finally, the number of points with a mean defect of over 5 dB ("Points>5dB").

If each variable is displayed on a coordinate axis opposite the others and when, in each case, a greater or lesser degree of overlapping between the normal and the pathological population is observed, the discriminating power of each of the input variables chosen can be established. This is relatively easy to perform given the limited number of classes involved in this particular classification: normal and glaucomatous patients. After performing this approximate study, the mean defect of zones 1, 2, 3, 4 and 5 and the number of points with a mean defect of over 5 dB proved to be the variables with most power of discrimination.



(a) (b)

Figure 1. Seven zones into which the VF was divided (a) according to the evolution of the bundle of nerve fibers in the retina (a) An approximate diagram (b).

4. Method: Neuro-fuzzy Approach

The decade from 1965-1975 witnessed the first applications of fuzzy logic in the field of medicine. Specifically, in 1968 L.A. Zadeh presented the first article on the possibility of developing applications based on fuzzy sets for use in the field of biology [13]. Since then, fuzzy logic and other disciplines related to it (neuro-fuzzy systems, fuzzy clustering) have undergone increasing application in the field of medicine and biology [11].

Within the framework of taxonomy, as proposed in [7], for combining neural networks and fuzzy systems (fuzzy neural networks, concurrent neuro-fuzzy models, cooperative neuro-fuzzy models and hybrid neuro-fuzzy models), we have focused on the last approach, which consists in combining a fuzzy system and the work of a neuronal network in a homogeneous architecture. This system can be interpreted either as a special neuronal network with fuzzy parameters or as a fuzzy system implemented in distributed and parallel form.

The case studies of Nauck, Kruse and their collaborators should be encompassed here. This research group from the University of Magdeburg focuses its work on a fuzzy perceptron as a generic model for neuro-fuzzy approaches [6]. The idea is to use this fuzzy perceptron to provide a generic architecture which can be initialized with a priori knowledge and can be trained using neuronal learning methods. The training is performed in such a way that the learning result can be interpreted in the form of fuzzy linguistic if-then rules. Finally, in addition to the advantage of having a generic model for comparing neuro-fuzzy models, the fuzzy perceptron can be adapted to specific situations. In this case study, the NEFCLASS tool [8] is used to classify the VF data. Basically, NEFCLASS enables fuzzy rules to be obtained from data for classifying patterns in a specific number of classes. It uses a supervised learning algorithm based on fuzzy error backpropagation.

5. Learning

Learning can be performed in two facets: on the one hand, if a priori knowledge is not introduced into the network, the system tries to find the set of fuzzy rules that adapt best to the training patterns; on the other hand, once the best rules have been selected, the learning focuses on adapting the parameters that define each of the membership functions associated with the fuzzy sets that feature in the antecedent of each of the rules chosen.

When a priori knowledge exists, it is fed into the system in the form of fuzzy rules. The rule-learning stage is no longer necessary and the system focuses only on tuning the membership functions. There is a third option which involves the combination of the previous two options, that is to say, introducing a priori knowledge and letting the system add new rules to the rules that already exist so that, eventually, it tunes the precedents of them all.

Whichever option is chosen, NEFCLAS also obliges the user to choose the number of fuzzy sets with which each input variable will be partitioned, i.e. this magnitude is not learnt. Also, when the no a priori knowledge learning option is chosen, the user has the option of leaving the system with only the best n rules, before going on to the membership function adaptation stage, in which case there is one more parameter to initialize before launching the learning.

6. Results

Since it is possible to train the network with and without a priori knowledge, both cases were studied and produced the following results.

6.1 Without a Priori Knowledge

Various different trials were performed in this category, juggling with different input variables, using different fuzzy partitionings of each of the variables chosen and with the maximum number of rules. The best results were obtained for the configuration of parameters shown in Table 1, labeled as trial 1 and 2. Despite the fact that four rules less were used in trial 2 than in trial 1, the classification results are very similar, at the expense of increasing the partition of variable MD3 by just one more fuzzy set. The rule bases obtained after the network had been trained are shown in Figure 2 and Figure 3 for trial 1 and 2 respectively.

6.2 With a Priori Knowledge

In this case, the system starts with a set of rules (see Figure 4) which are input beforehand and are based on the expert's knowledge. That is to say, the training stage now only involves the tuning of the parameters associated with the membership functions of each of the precedents of the rules considered initially. Several tests were also carried out as regards the choice of the number of partitions of each of the variables selected. At the same time, the variable "Points>5dB" was included, which produced better results than in the previous case. Of all the trials carried out, the best is shown in Table 1, in the line labeled trial 3, where the classification results obtained are indicated. It can be seen how now, with a priori knowledge, there is a considerable improvement on those obtained in the previous two trials.

Table 1. Results of classifications for each trial

Trial	Input/MF	Know ledge	Nº Rules	Errors		
				Training	Test	Total
1	MD1, MD2, MD4 = 3MF MD3, MD5 = 2MF	No	10	12 (6N+6P)	6 (1N+5P)	18 (7N+11P)
2	MD1, MD2, MD3, MD4 = 3MF MD5 = 2MF	No	6	12 (5N+7P)	5 (1N+4P)	17 (6N+11P)
3	MD1, MD2, MD4 = 2MF MD5, Ptos5dB = 2MF	Yes	6	6 (4N+2P)	2 (0N+2P)	8 (4N+4P)
MF = Membership function, N = Normal Patients, P = Pathological Patients Total pattern = 280 (62N/218P), Training Pattern = 187 (42N/145P), Test pattern = 93(20N/73P)						

IF MD_1 is small and MD_2 is small and MD_3 is small and
MD_4 is small and MD_5 is small THEN NORMAL

IF MD_1 is medium and MD_2 is large and MD_3 is small and
MD_4 is small and MD_5 is small THEN GLAUCOMA

IF MD_1 is large and MD_2 is large and MD_3 is small and
MD_4 is small and MD_5 is small THEN GLAUCOMA

IF MD_1 is large and MD_2 is large and MD_3 is small and
MD_4 is medium and MD_5 is small THEN GLAUCOMA

IF MD_1 is medium and MD_2 is medium and MD_3 is small and
MD_4 is medium and MD_5 is small THEN GLAUCOMA

IF MD_1 is medium and MD_2 is large and MD_3 is small and
MD_4 is medium and MD_5 is small THEN GLAUCOMA

IF MD_1 is large and MD_2 is large and MD_3 is large and
MD_4 is medium and MD_5 is small THEN GLAUCOMA

IF MD_1 is medium and MD_2 is medium and MD_3 is large and
MD_4 is medium and MD_5 is small THEN GLAUCOMA

IF MD_1 is medium and MD_2 is large and MD_3 is large and
MD_4 is medium and MD_5 is small THEN GLAUCOMA

IF MD_1 is large and MD_2 is large and MD_3 is large and
MD_4 is large and MD_5 is large THEN GLAUCOMA

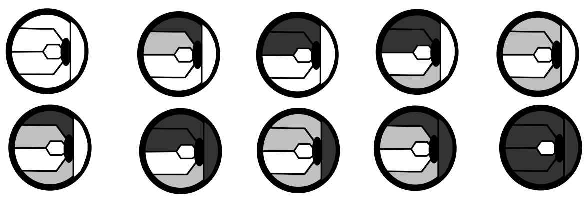


Figure 2. Rule base for trial 1 (no a priori knowledge)

IF MD_1 is small and MD_2 is small and MD_3 is small and
MD_4 is small and MD_5 is small THEN NORMAL

IF MD_1 is medium and MD_2 is medium and MD_3 is medium and
MD_4 is medium and MD_5 is small THEN GLAUCOMA

IF MD_1 is medium and MD_2 is large and MD_3 is medium and
MD_4 is medium and MD_5 is small THEN GLAUCOMA

IF MD_1 is large and MD_2 is large and MD_3 is medium and
MD_4 is medium and MD_5 is small THEN GLAUCOMA

IF MD_1 is large and MD_2 is large and MD_3 is large and
MD_4 is large and MD_5 is large THEN GLAUCOMA

IF MD_1 is large and MD_2 is large and MD_3 is medium and
MD_4 is large and MD_5 is large THEN GLAUCOMA

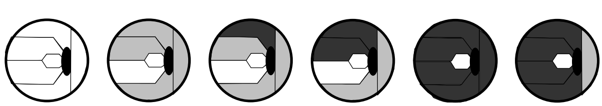


Figure 3. Rule base for trial 2 (no a priori knowledge)

IF MD_1 is small and MD_2 is small and MD_4 is small and
MD_5 is small and Ptos>5dB is small THEN NORMAL

IF MD_1 is large and THEN GLAUCOMA

IF MD_2 is large and THEN GLAUCOMA

IF MD_4 is large THEN GLAUCOMA

IF MD_5 is large THEN GLAUCOMA

IF Ptos>5dB is large THEN GLAUCOMA

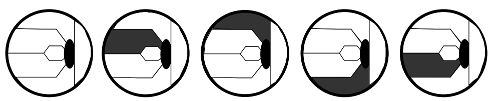


Figure 4. Selected rule base (a priori knowledge) for performing trial 3

7. Conclusions

Interpretation of the VF by the medical community is not yet based on a series of standards that allow a clear and precise classification of each of the pathologies that influence the deterioration of the VF to be made. Fortunately, different heuristics make it possible to orientate the decision-making process in one direction or another, so that a diagnosis can be made that is as reliable as possible. Nevertheless, the VF values obtained for a particular patient may not discriminate well enough to enable a reliable diagnosis to be made, meaning that the doctor has to resort to information furnished by other ophthalmologic tests. In this context, the use of systems that learn from data seem appropriate, as on the one hand they enable the diagnosis heuristics to be used and refined and on the other hand they enable new heuristics to be established.

The apparently large difference between the rule antecedents obtained from the trials performed with a priori knowledge training, or without it, is due mainly to a limitation of the NEFCLASS tool. When the system learns rules without a priori knowledge, all their antecedents have to participate on the basis of all the input variables, and it is only when a set of a priori rules is inserted that this possibility can be altered. In any case, the rule bases learnt in trial 1 and 2 express in a very similar manner what was inserted as a priori knowledge in the rule base of trial 3.

The VF indices referred to at the beginning, and which are calculated globally from 59 points on, could have been used directly as input variables. However the drawback in this case is that it is not possible to discriminate between a few abnormal points scattered over the VF and those grouped in localizations typical of glaucoma. As a result, we chose to work with those indices but calculated on the basis of the points that belonged to each of the zones into which the VF had been divided and which are highly related to the typical zones where scotomas appear in glaucoma.

As can be seen, on the basis of the results obtained, the network learning produces a set of fuzzy rules whose membership functions have been tuned on the basis of the set of training data. The great advantage of fuzzy rules compared with the possibility of using neural networks to solve the problem of classification is the high degree of linguistic interpretability of the former compared with the low interpretability of the learning result of the latter (black boxes). This high degree of interpretability has been maintained due to the NEFCLASS option of not permitting the learning of weights of the different rules obtained [9]. From the medical viewpoint, this is all crucial. In effect, when automatic diagnosis systems are used, doctors not only need to know what the pathology associated with the patient is, but also the reason for the classification performed by the system.

Table 2 shows the sensitivity and specificity associated with each of the tuned fuzzy rule bases and obtained in each of the three experiments. In all three cases it shows that the ability to detect glaucomatous pathology is greater than the ability to detect normal persons (higher sensitivity than specificity). But very good classification percentages are obtained in all cases (almost all of them above 90%). Finally, as might be expected, it should be stressed that the best sensitivity and specificity ratios are obtained when a priori knowledge (experiment 3) was used.

Table 2. Sensitivity and specificity for each rule base

Trial	**Sensibility**	**Specificity**
1	94.9%	88.7%
2	94.9%	90.3%
3	98.2%	93.5%

Although it is not always easy to compare case studies with different designs, the results obtained here can be compared with those contained in [2] based on expert systems, discriminating analysis and on neuronal networks. As can be seen, the results obtained in this instance are an improvement or are equal to the results shown there.

To summarize, this case study shows once again the important contribution of neuro-fuzzy systems to the field of medicine and, specifically, in this case, to the field of ophthalmology, by obtaining a set of rules that enable good classification results to be obtained among patients with glaucomatous pathology and normal individuals. Trials underway focus on the discrimination capacity of the neuro-fuzzy approach in terms of patients with VF disorders and who suffer from a different pathology to glaucoma.

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