PREOPERATIVE OVARIAN CANCER DIAGNOSIS USING NEURO-FUZZY APPROACH

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ABSTRACT

In this paper, we propose a neuro-fuzzy model for preoperative prediction of malignancy in ovarian tumours. The model is intended to form part of a reliable preoperative tool to discriminate between benign and malignant ovarian tumours to help clinicians decide the most appropriate form of treatment for patients. An aim of our work is to find a model that is understandable, practicable and capable of achieving accurate diagnosis. In this paper, we present our initial attempts to develop such a model using the Adaptive Network based Fuzzy Inference System (ANFIS). Our model predicts ovarian cancer malignancy using demographic, serum tumour marker and ultrasound-derived criteria. An evaluation of the classification performance of the model suggests that an accuracy of about 84% is obtainable with an area under the receiver operating characteristic curve of 0.85.

Keywords: ovarian cancer, medical diagnosis, neural networks, neuro-fuzzy, partitioning, ROC analysis, malignancy, prediction.

INTRODUCTION

Ovarian cancer is one of the most common cancers among women in Europe. In the UK alone, there are about 6,800 new cases of ovarian cancer each year, but only 25% of these are diagnosed at an early stage [4]. Early detection of malignancy is important for the survival of the patient, but because a large number of cases are only diagnosed at an advanced stage the rate of mortality for this type of cancer is high.

The treatment and management of different types of ovarian tumours also differ significantly. For patients with a benign tumour, a conservative management or minimally invasive surgery will suffice whereas for those with suspected malignancy timely referral to a gynaecologic oncologist [11, 18] is necessary. Thus, a reliable preoperative test to discriminate between benign and malignant ovarian tumours would be of considerable help to clinicians [18] in deciding the most appropriate form of treatment for patients.

Over the years, significant attempts have been made to perform preoperative detection of malignancy and this has led to the development and use of the Risk of Malignancy Index (RMI). The RMI combines values of the CA 125 with ultrasonographical parameters and the menopausal status of the patient [8] and provides better results than most other methods. The RMI is widely used, but it has some limitations (e.g. when it is applied to borderline cases of ovarian tumours and to stage I invasive cancers) and there is a need to achieve a higher rate of performance than RMI can provide.

Various statistical and machine learning techniques have been used with some success for preoperative prediction of ovarian tumour. These include multi-layer perceptrons, least squares support vector machines [11], combined genetic algorithm and fuzzy logic model [14], and Bayesian believe networks [2, 19]. However, some of these are seen as ‘black boxes’ and some are time consuming to design or simply not easy to understand. In this paper, we have used the neuro-fuzzy approach to exploit the benefits of both neural networks and fuzzy logic. Fuzzy logic enables the model to capture expert knowledge and neural networks make it possible to learn and to optimise results. A key feature of this approach is the ability to capture knowledge from data that is inherently imprecise and to maintain a high level of performance in the presence of uncertainty. This is important because medical tests and data are inherently imprecise because of individual differences, measurement errors and noise [13]. Another important advantage is the interpretability of the resulting model, which is important for widespread acceptance in ovarian cancer diagnosis. Thus, the combined use of fuzzy logic and neural networks provides an inference approach with learning capability and a reasoning model that is not only understandable but accurate.

Our model is based on the Adaptive Network Fuzzy Inference System (ANFIS) which has been shown to provide a more accurate result compared to other methods [13]. ANFIS has been successfully used in modelling, control and in different areas of biomedicine, including breast cancer and diabetes [5].

The remainder of the paper is organized as follows. In the next section we explain the methodology used in the study. This includes a description of the ovarian cancer data base, a brief introduction to the Adaptive Network Fuzzy Inference System (ANFIS) which formed the basis for the diagnostic model we have developed. Thereafter, we discuss the implementation and then present the results of the study. Finally, we present the conclusions.

METHODOLOGY

A. Ovarian cancer database

The data used in this study was provided by the Katholieke Universiteit Leuven, University Hospital, Leuven, Belgium. The database includes the information for 525 patients who were referred for an ultrasonographic examination between 1994 and 1999. The classification output was binary: malignant (1) or benign (0) tumour, [11]. The database contains information about demographic, serum marker, colour Doppler imaging and morphological variables (see Table I). The results of histological examination were considered as the "gold standard" for discrimination of benign and malignant tumours. The database consists of 26 variables, 6 of which are continuous variables: age, CA 125, pulsatility index, resistance index, peak systolic velocity and time-averaged mean velocity. The remaining variables are categorical (see Table I). Several studies have been carried out at Katholieke Universiteit Leuven using the data set [11].
Transvaginal ultrasound examination was performed on all patients. Morphological assessment of the tumour includes: presence of abdominal fluid, presence of papillary structures (more than 3mm), smoothness of internal wall, tumour on both pelvic sides. The presence of a symptom was assigned a value of 1; the absence of a symptom was assigned a value of 0. All tumours were examined by colour Doppler imaging (CDI), and a colour score was used for subjective semiquantitive assessment of the amount of blood flow. The outcome (pathology) was assigned a binary value, 0 for benign and 1 for malignant. The level of serum CA 125 tumour marker was measured. Serum CA 125 is a specific protein for which the elevated value has been shown to detect 80% of epithelial ovarian cancers. Demographic variables (age and menopausal status) were also considered and included.

The initial database was pre-processed to remove cases with missing values and to logarithmically transform the variable CA 125. After removing records with missing values the database contains 425 cases (see Table II).

TABLE I - Description of the initial data set (n = 525 cases)

Type	Variable description (short name)	Groups			
		N_M	Malignant	N_B	Benign
Demographic	Age (Age)	141	56.8 ± 14.7	384	45.6 ± 15.2
	Menopause (Meno)	141	65.2%	384	31.3%
CDI – Colour score	Moderate blood flow (Col3)	141	34.0%	384	15.4%
	Strong blood flow (Col4)	141	44.0%	384	3.4%
Serum marker	Logarithm of CA 125 (Ln_CA125)	137	5.2 ± 1.9	295	3.0 ± 1.2
CDI – blood flow indices	Pulsatility index (PI)	129	0.96 ± 0.60	234	1.34 ± 0.94
	Resistance index (RI)	129	0.54 ± 0.17	234	0.64 ± 0.16
	Peak systolic velocity (PSV)	129	27.22 ± 16.54	234	19.85 ± 14.62
	Time-averaged mean velocity (TAMX)	129	17.41 ± 11.48	234	11.35 ± 9.69
B-mode Ultrasonography	Ascites (Asc)	141	60.3%	384	13.3%
	Unilocular cyst (Un)	141	4.3%	384	46.1%
	Unilocular solid (UnSol)	141	16.3%	384	6.3%
	Multilocular cyst (Mul)	141	5.7%	384	28.6%
	Multilocular solid (MulSol)	141	36.2%	384	10.7%
	Solid tumour (Sol)	141	37.6%	384	8.3%
	Bilateral mass (Bilat)	141	39.0%	384	13.3%
	Smooth wall (Smooth)	141	5.7%	384	56.8%
	Irregular wall (Irreg)	138	73.2%	373	33.8%
	Papillations (Pap)	141	53.9%	384	12.2%
	Septa > 3 mm (Sept)	141	31.2%	384	13.0%
	Acoustic shadows (Shadows)	141	5.7%	384	12.2%
Echogenicity	Anechoic cystic content (Lucent)	141	28.4%	384	43.5%
	Low level echogenicity (Low-level)	141	20.6%	384	11.7%
	Mixed echogenicity (Mixed)	141	13.5%	384	20.3%
	Ground glass cyst (G.Glass)	141	8.5%	384	19.8%
	Hemorrhagic cyst (Haem)	141	0.7%	384	3.6%

Note: N_M – number of malignant cases; N_B – number of benign cases; for continuous variables the mean ± standard deviation were calculated; for binary variables, the occurrence (%) of symptoms were counted.

TABLE II – Distribution of patients in the pre-processed data set

Group	Frequency	Percentage (%)
Malignant	134	31.5
Benign	291	68.5
Total	425	100.0

B. Neuro-fuzzy modelling and the adaptive network fuzzy inference system.

Fuzzy systems are characterised by fuzzy sets and fuzzy *if-then* rules of the form:

"IF x is A THEN y is B", where *A* and *B* are fuzzy sets and *x* and *y* are members of the sets.

The fuzzy sets *A* and *B* will each have a membership function associated with it which defines the distribution of the membership grades for the set. An example of the membership functions for a fuzzy set, *Menopause Status*, is depicted in Figure 1. In this case, the menopause status is determined by the age of the patient.

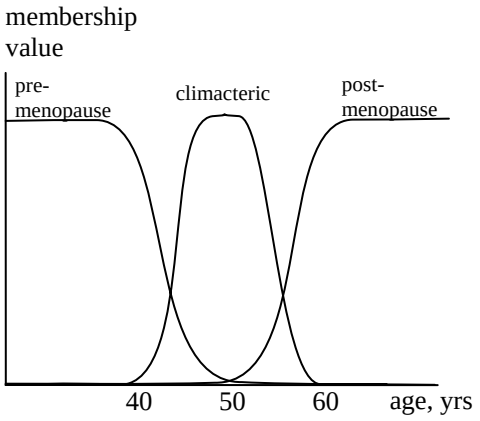


Fig. 1. Membership functions for a fuzzy set "Menopause status".

In conventional fuzzy system, the fuzzy rules are obtained from human experts. The parameters of the fuzzy system (e.g. parameters of the membership functions and the rules) are then optimised either manually or by using a suitable optimisation technique [6]. This can be time consuming. The neuro-fuzzy approach used in our work is data-driven. In this case, the fuzzy rules are generated directly from the input-output data sets. The neuro-fuzzy model learns the salient features in the data and automatically adjusts the system parameters in order to meet a specified error criterion.

Our neuro-fuzzy model is based on the Adaptive Network based Fuzzy Inference System (ANFIS) [10]. The ANFIS embeds the fuzzy inference model within the framework of an adaptive network and this provides a systematic way to generate and optimize the parameters of the model using a suitable learning algorithm [10] in a way that is not directly dependent on expert knowledge as in conventional fuzzy system.

To understand the link between ANFIS and conventional fuzzy system, consider a simple fuzzy inference system with two inputs, *x* and *y*, one output, *f*, and two fuzzy rules of the form:

Rule1: IF x is A_1 *and y is* B_1*, THEN* $f_1=p_1x+q_1y+r_1$
Rule2: IF x is A_2 *and y is* B_2*, THEN* $f_2=p_2x+q_2y+r_2$

The fuzzy reasoning and processing required to generate the output, f, from a given set of inputs *x*, *y* is depicted graphically in Fig 2(a). The inputs, *x* and *y*, are first fuzzified to generate appropriate membership grades using the membership functions for the fuzzy sets, *A* and *B*. This essentially provides the values for the antecedent (the IF) part of the rule. The "firing strength", i.e. the THEN part of the rule, is then obtained as the product of the membership grades in the premise part of the rule suitably weighted.

The equivalent ANFIS architecture is depicted in Figure 2(b). The ANFIS consists of adaptive nodes represented as squares and fixed nodes represented as circles. Using a learning rule the parameters in these nodes are adjusted to minimize a specified error measure.

As can be seen, the ANFIS consists of five layers. The first layer is used to generate the membership grades for each set of input data vectors. For example, if the fuzzy sets A_1 and A_2 in Figure 2(a) each has a membership function which is bell shaped, the membership grades are obtained as:

$$\mu_{A_i}(x) = \frac{1}{1+\left[\left(\frac{x-c_i}{a_i}\right)^2\right]^{b_i}}$$

where a_i, b_i, c_i is the parameter set which is used to alter the shape of the membership function.

The second layer of ANFIS calculates the firing strengths of the rules as a product of the membership grades:

$$w_i = \mu_{A_i}(x) \times \mu_{B_i}(y), \ \mathrm{i} = 1,2$$

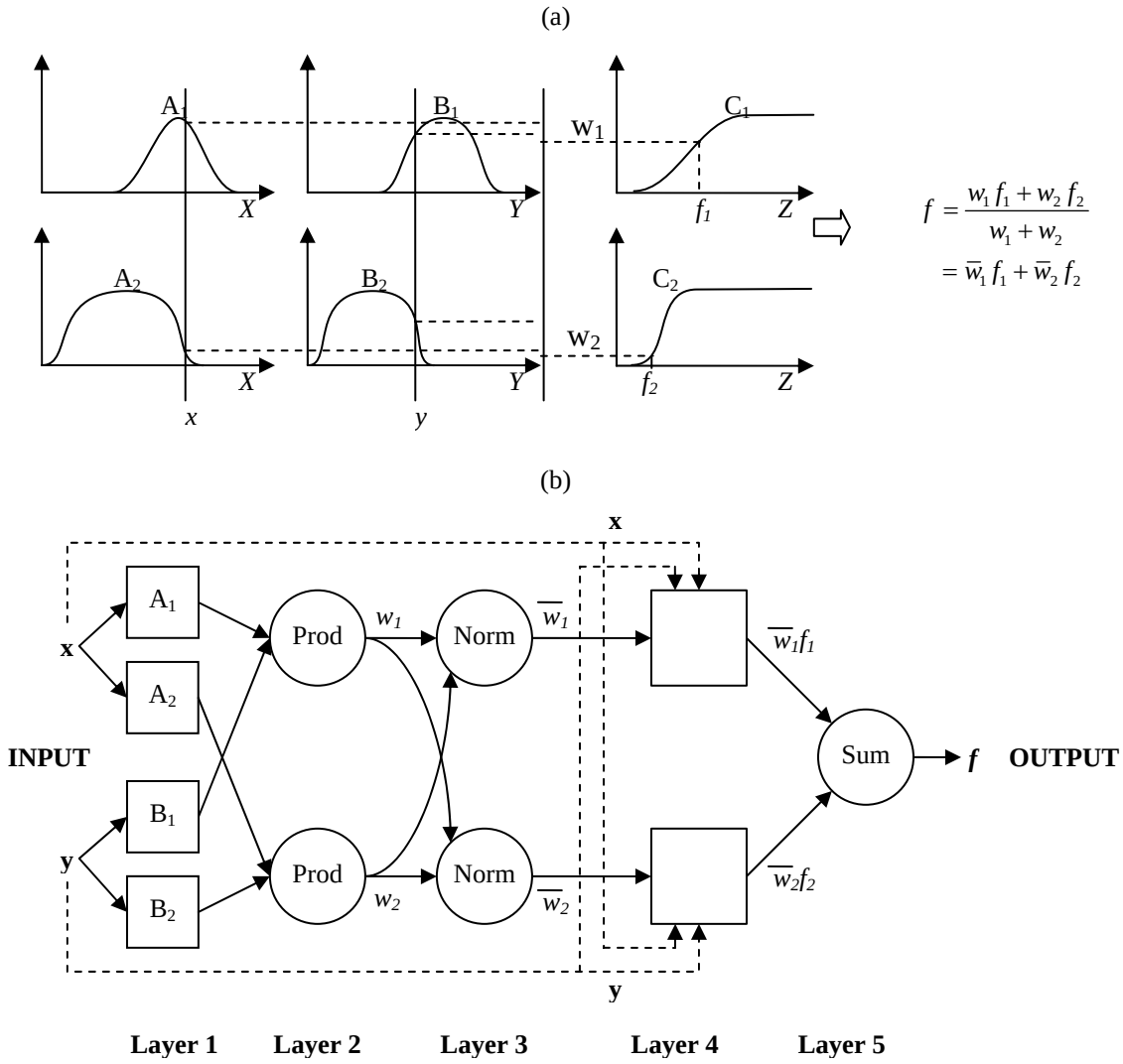


Fig. 2. (a) A 2-rule fuzzy inference process, (b) Equivalent ANFIS architecture.

In layer 3, the normalized firing strengths of the rules (i.e. the ratio of the i-th rules firing strength to the sum of all rules' firing strengths) are calculated as:

$$\bar{w}_i = \frac{w_i}{w_1 + w_2} \quad , \text{i} = 1,2$$

Layer 4 yields the parameters of the consequent part of the rule. In this layer, every node i is characterized by a function of the form:

$$\bar{w}_i \cdot f_i \text{, where: } \bar{w}_i \text{ - the output of layer 3}$$

The fifth layer calculates the overall output as the sum of the contributions of each rule, i.e.

$$= \sum_i \bar{w}_i \cdot f_i = \frac{\sum_i w_i \cdot f_i}{\sum_i w_i}$$

It is evident that the adaptive network is functionally equivalent to the fuzzy inference system in Figure 2(a).

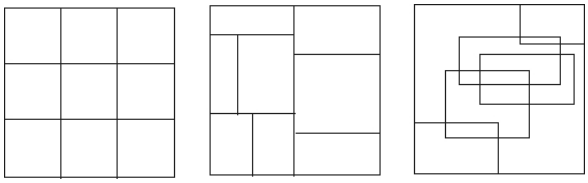
In summary, the first and fourth layers in the ANFIS are adaptive layers. The first layer contains three adjustable parameters [a_i, b_i, c_i] which characterize the shape of the input membership functions. These parameters are associated with the IF part of the rule (the so-called premise parameters). The fourth layer also has three adjustable parameters, [p_i, q_i, r_i], the consequent parameters, which are associated with the THEN part of the rule.

Suitable learning rules are used to tune the model parameters. A hybrid learning algorithm is used in the ANFIS. This combines the gradient descent and the least squares method for an effective search for the optimal parameters.

IMPLEMENTATION

A. Initialization of the input space

Successful design of the neuro-fuzzy model requires the division of the input into rule patches. This could be done using a variety of methods, e.g. grid, tree or scatter partitioning methods (see Fig. 3).



(a) Grid partition (b) Tree partition (c) Scatter partition

Fig. 3. Input Space partitioning.

Grid partitioning involves partitioning the input space (i.e. the number of rules which are used in the fuzzy inference system) into all the logical number of membership functions and this makes it easy to put all the parameters together. The drawback of this approach is that the number of rules grows rapidly as the input dimension increases. For m input variables and C partitioned fuzzy subset for each input, the number of possible rules is C^m. As the number of variables increases, the number of rules increases exponentially. It has also been found that this often leads to over fitting. Thus, in order to reduce the problems associated with grid-partitioning, the input space is divided into rule patches, e.g. scatter partitioning. This permits arbitrary positioning of the IF-parts of the fuzzy rules into sites in the input space. Scatter partitioning requires specification of a radius. This radius has a spherical neighbourhood in which the centre of each cluster will have an influential range. In MATLAB grid and scatter partition are implemented to generate the inference system. Grid partitioning is implemented as *GENFIS1* and scatter partitioning as *GENFIS2*.

B. Diagnostic model

Membership functions building involves either the use of an expert knowledge or a measure to obtain the relevant classes. The measure uses the significant attributes in the data to generate clusters. Extensive research has developed many variants of clustering techniques. For example, Mapping-Constrained Agglomerative (MCA) Algorithm [20] was used to partition breast cancer data set into a set of classes. However, different clusters produce different results and each has its own advantages and disadvantages. A comparative study of clustering techniques has been especially difficult since each technique offers different results [9]. Subtractive clustering introduced by *Chiu (1994)* is a technique which extends the mountain clustering technique, where the potential is calculated for the data rather than the grid points. The advantage of this technique is that it produces a minimum number of fuzzy rules. This has been applied in ANFIS to generate initial parameters (GENFIS2).

ANFIS requires the user to make a priori decisions about the type and number of linguistic terms per variable and the number of rules. Here we analyse two common types of membership functions: Gaussian and generalised bell membership functions since they model uncertainty of real measurements very well. Secondly, ANFIS extracts rules only where the premises are connected through differentiable t-norms and generates as many rules as the product of the number of linguistic terms per variable. These two membership functions fall into this category.

We carried out the study using MATLAB version 7.0 running on a Pentium 4 (2.8GHz, 512MB RAM) PC. We divided the data set into two subsets: 283 cases (two thirds) for raining and 142 cases (one third) for testing. The data set comprises different features (e.g. linguistic labels and semantic symptoms) and therefore was normalized to produce stable convergence. Normalisation enables the data to have an average of zero and a standard deviation of one (unit variance). We started by using candidate features consisting of 10 variables which were already obtained by feature selection using LS-SVM with RBF kernels as described in [11]. The training set for the model, containing 283 cases, was chosen randomly while maintaining the ratio $\lambda \approx 0.46$ of malignant to benign (134 malignant cases: 291 benign cases). The number of variables was changed from 2 to 4. The performance index, the Root Mean Square Error (RMSE), was measured at each step. Each combination was used to test predictive accuracy. Four variables were selected using grid partitioning of the input space to initialise the membership function parameters. In this set, all possible combinations of the input/output mapping were used. Two different membership functions (Gaussian and generalised bell) were tested during the run. We then obtained the system generated by the training data over 100 epochs and the accuracy with a threshold of 0.5. Four combinations from the subset of the 10 variables with the minimum RMSE were chosen, i.e. from all possible combinations of 4 from 10 $C_{10}^4 = 210$. The combination with the minimum RMSE was used as the variables set to predict the diagnosis.

In the second method scatter partitioning was used to generate the initial membership function parameters and involves applying subtractive clustering algorithm (in MATLAB as *GENFIS2*). It generates a FIS structure from data using subtractive clustering. A Receiver Operating Characteristic (ROC) analysis was carried out to evaluate the performance of the neuro-fuzzy classification.

TABLE III - Selecting features for the model

No. of features	Variables	RMSE	Accuracy (%)
(4)	Meno/Sol/Pap/Shad	2.47×10^{-8}	75.45
(3)	Meno/Sol/Pap	1.74×10^{-8}	75.35
(2)	Meno/Irreg	2.83×10^{-9}	71.84

RESULTS

The initial concern was to identify the core attributes needed in order to enable the model to classify accurately. The selection of variables procedure was produced using the root mean square error, RMSE. The minimum RMSE for four variables is 2.47×10^{-8} and 75.45% accuracy, when the combination, Meno/Sol/Pap/Shad variable is used (see Table III). The test for accuracy of diagnosis was compared using Gaussian and generalised bell membership functions. The number of membership function was varied between 2 and 3.

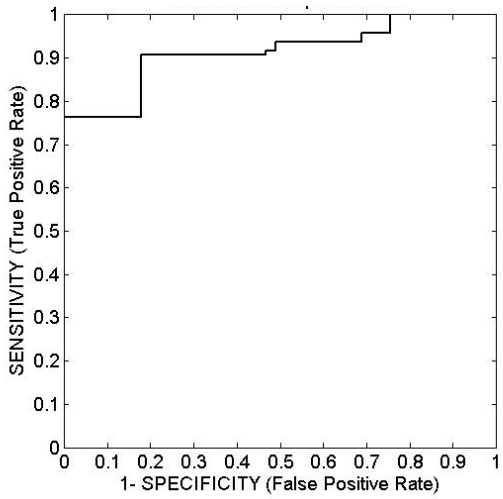


Fig. 4. ROC curve for the model with a grid partitioning (r = 0.4).

In order to draw conclusions from the model, a threshold mechanism that can produce a non-fuzzy (numerical crisp) output was used. Here we use a variable threshold ξ ranging from 0 to 1. Also since the training data was set to a target of 1 and 0, the algorithm compares each output *y* for example to 0.3, and equates each of the outputs to 1(malignant) if *y* is greater than 0.3 and otherwise 0 (benign). The issue of threshold is important and must be explicit, particularly in relation to sensitivity and specificity. If a positive test has a high cut-off point it ultimately results in a low sensitivity and high specificity, and a low cut-off point results in a high sensitivity and low specificity. ROC analysis evaluates performance over the entire range of cut-off points. The ROC curve (see Figure 4) shows the relationship between false positive rate (*x*-axis) and true positive rate (*y*-axis) when changing the threshold point for decision-making.

The grid partition performance is lower than the scatter partitioning, because scatter partitioning covers only a subset of the whole input space which describes a region of possible occurrence of the input vectors. The model predictions show high specificity, but a relatively low sensitivity. Table IV shows the results for a test set (142 patients). The models used four input variables: menopausal status (Meno), presence of solid tumour (Sol), papillarities (Pap) and presence of acoustic shadows (Shad).

Table IV - Summary of results based on four variables (cut-off = 0.3)

Technique			Acc (%)	Se (%)	Sp (%)
Grid Partitio-ning	2 MF	Gaussian MF	83.19	84.74	82.47
		Generalised bell MF	83.19	84.74	82.47
	3 MF	Gaussian MF	84.65	87.41	83.37
		Generalised bell MF	84.65	87.41	83.37
Scatter Partitioning		r = 0.2	80.14	65.19	87.08
		r = 0.4	80.94	69.19	86.39
		r = 0.6	80.85	68.74	86.46
		r = 0.8	80.94	69.19	86.39

The result using grid partitioning gives an average accuracy of 83.19% for models with two membership functions, and 84.65% for models with three membership functions. The same values of ROC for different types of membership functions may be explained by the fact that only binary variables were included in the models so that parameters of membership functions with the shape do not affect performance of the model. However, the number of the membership functions has an influence on the model's sensitivity and specificity.

Scatter partitioning gives a high specificity, but low sensitivity (average Sp ≈ 86%, average Se ≈ 67%). The average accuracy of the models based on scatter partitioning was lower than for grid partitioning-based models.

To assess the impact of different membership functions on the operating characteristics for grid partitioning we used first four variables considered in [11] as the best: CA 125, Pap, Sol, and Col3. The results are presented in the Table V. The overall accuracy for this combination of parameters is lower, but not as much as the sensitivity. However, specificity for both sets of input variables was merely the same.

Table V - Summary of results based on four variables (CA 125, Pap, Sol, Col3) for cut-off = 0.3

Technique			Acc (%)	Se (%)	Sp (%)
Grid Partitio-ning	2 MF	Gaussian MF	74.93	55.33	84.02
		Generalised bell MF	74.58	55.11	83.61
	3 MF	Gaussian MF	79.23	64.22	86.19
		Generalised bell MF	76.34	54.89	86.29
Scatter Partitioning		r = 0.2	77.66	64.44	83.79
		r = 0.4	74.39	52.12	84.72
		r = 0.6	69.21	57.17	74.79
		r = 0.8	69.01	57.58	74.32

A conclusive model should be reliable and reproducible. Thus the test was run for 15 times, each time randomly selecting the cases.

Patient Result Diagram (PRD)

There is a need to relate the result to the model. We have used a Patient Result Diagram to graphically show the result of the diagnosis on a set of patients. This diagram made of bars and no-bars, shows an evaluation of patients and the category which they belong after the prediction has been done by the classifier. The bars represent patients with malignant tumour; whereas no-bars represent patients with benign tumour. Figure 7 gives an illustration of the technique. The top diagram (in Figure 75) represents data obtained by "Gold standard", while the bottom diagram shows results obtained from the model. This research uses a selected number of patients chosen randomly from the test data and predicts their diagnosis based on the trained model.

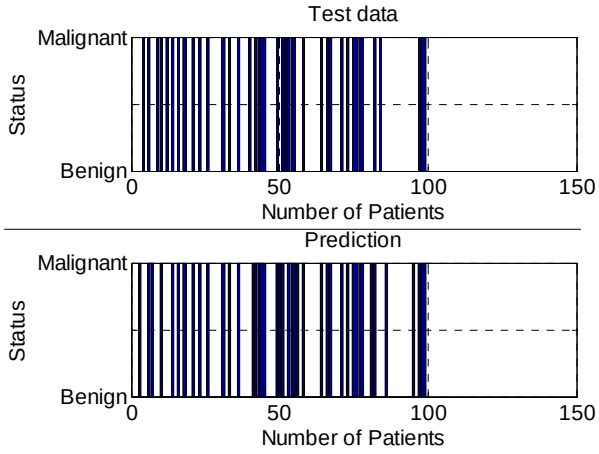


Fig. 5. Patient Result Diagram of prediction.

CONCLUSIONS

In this paper we have introduced the use of neuro-fuzzy methodology for preoperative ovarian tumour prediction. The main advantage of the model is its simplicity and good accuracy. The overall result is interesting for two reasons. firstly, the technique returns a relatively small number of false positive results. The variables selection process was performed by permutation-based approach, which selects the best combinations of features in terms of the room means square error. Another interesting point is that conventional markers such as age, serum CA 125 were not included in the final model. The variables selected include a combination of ultrasound characteristics of the tumour and menopausal state of patient. Future work will extract and examine the rules and fuzzy sets associated with the final model to gain a better understanding of the underlying workings of the model. More work is needed to study and evaluate the importance of certain rules and their contributions to model output. An understanding of this should help to develop strategies for improving the performance of the model.

The study has made use of common data obtained from ovarian cancer tests, although it is not possible to detect all malignant cases using the variables. In future, the inclusion of genomic data may improve the diagnostic accuracy and provide better a decision support for tasks such as treatment course management.
This work has focused on preoperative diagnosis of ovarian cancer using neuro-fuzzy approach. Extensive comparison with other statistical and machine learning techniques would also need to be done, including a study of the impact of the missing values on the diagnostic accuracy. Extensive comparison with statistical and machine learning techniques such as MLP, LS-SVM will be carried out to provide a benchmark for ovarian tumour diagnostics. We will also investigate the use of neuro-fuzzy methodology in other cancer areas. This work will be integrated into a web-based decision support system as part of BIOPATTERN Cancer special interest group (subproject SP09).

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