PROGNOSTIC PREDICTION OF BILHARZIASIS-RELATED BLADDER CANCER BY NEURO-FUZZY CLASSIFIER

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Abstract - **Cancer prognostic prediction requires a classification system that is robust to the interaction and uncertainty of input factors, as well as being interpretable on the decision made. In this paper, a hybrid neuro-fuzzy classifier is applied to determine the long-term outcome of patients with bilharziasis-related bladder cancer. The same data set is also analysed by a Multi-Layer Percepton Neural Network (MLPNN) and logistic regression, which are both widely used in the area of medical decision-making. In order to better assess the value of this neuro-fuzzy classifier, a benchmark data set used in this area of oncology, the Wisconsin Breast Cancer Data (WBCD), is examined by the above three methods. The study demonstrates that the hybrid neuro-fuzzy classifier is efficient in cancer data analysis and it yields a high classification rate of 97.1% for WBCD, and 84.9% for the bladder cancer data, respectively.**
Keywords - **Medical decision-making, soft computing, Multi-Layer Perceptron neural networks, logistic regression.**

I. INTRODUCTION

Cancer prognostic analysis is the prediction of the future outcome for patients after diagnosis or treatment of the disease. One of the essential tasks is to enable the classification of the outcomes (survival or death) based on known respective outcomes, for subsequent patients whom the system has not been previously subjected to [1]. The major concerns are: (1) the identified prognostic markers for a specific cancer, for instance bladder cancer, are few. Current factors related to each patient to represent disease status may not fully support the classification procedure. If the given data set is comprised of those uncertainties and non-functional factors, the classification would encounter difficulty. Therefore, a requirement for extracting the significant factors in an appropriate manner for subsequent processing by any classification system must be a precondition; (2) the internal rules of the classification system should be clear and unambiguous in order to ease human communication and further medical decision making.

For some of the prognostic problems where some prognostic factors are a certainty, statistical classifiers are a conventional option, for instance Bayes classifiers [2], logistic regression [3], and K-NN algorithms [4]. Neural networks such as Multi-Layer Perception Neural Networks (MLPNNs) [5] and Radial Basis Function Neural Networks (RBFNNs), have also been applied in similar studies [6-7]. However, except for the common problem of the unavailability of the classification rules they encounter, statistical classifiers usually demand a distribution assumption for independent factors, and the tolerance of statistical classifiers to non-linear variation is not assured. Neural network classifiers are model-free estimators [8]. They tend to separate the cases by hard boundaries. Fuzzy technology is an encouraging solution to these problems [9]. The advantages of fuzzy classifiers have been clearly exhibited in at least two ways: they allow multiple gradual class membership to smooth the transition from one class to the other as the input changes [10], therefore result in a better response in those cases that may overlap over several classes; and they also favour interpretation. One of the important design issues of a fuzzy system is to construct a set of appropriate fuzzy rules. Because pure fuzzy systems cannot automatically acquire knowledge from data, the basic idea behind the design is to estimate fuzzy rules through learning from input-output data pair. Neural network is introduced to solve this problem [11].

In this paper, we apply an Adaptive Network-based Fuzzy Inference System (ANFIS), which has been previously proven to be efficient in relation to function approximation [12], to oncological data. Here we use its type III form as a classifier, with a specific function for its consequent part, in order to decide if a patient will die from bladder cancer, and to identify significant prognostic marker sets for prediction. In order to better assess the classification performance of ANFIS, we also apply the logistic regression model and MLP neutral network to the same data.

II. MATERIALS AND METHODS

A. Materials

The data set under examination consists of 238 patients in total, who have all been diagnosed with bladder cancer. Of those, 114 died from the disease, whereas 124 died from unknown causes. Eight prognostic factors were analysed and are shown in Table 1.

TABLE I
PROGNOSTIC FACTORS INDEX IN THE DATASET

Factors	***Index***
Histological Type	h
Tumour Grade	g
Lymph Nodes	l
Bilharziasis History	b
Tumour Stage	s
DNA Ploidy	d
Gender	e
Age	a

In order to evaluate the classification performance of ANFIS, a benchmark data set - the Wisconsin Breast Cancer Data (WBCD) set [13] - is also considered in addition to the above bladder cancer dataset (BCD). Since WBCD has been investigated in many studies, the ability of any new approach should be assessed against it. WBCD contains 9 prognostic factors and two outcome classes: benign and malignant. The total number of patients is 683.

B. Methods

The ANFIS in Fig. 1 implements a mapping from an *n*-dimensional space $U \subset R^n$ to the unit hypercube $[0,1]^P$ [14], based on inference rules in the form:

Rule j: If x_1 *is* A_{1j}, …, *and* x_n *is* A_{nj}, *Then* y *is* B_j.

where A_{ij} is the antecedent membership function and B_j the consequent membership function, which can be in any form from type I to type III [12]. For the classification system, we selected type III (Sugeno system) and a constant in particular to represent the output classes. Considering the restriction of ANFIS in demanding differentiable functions throughout the system, we further select a Gaussian membership function for fuzzification, product inference, and weighted average defuzzification for the above ANFIS architecture. Then the output is:

$$y = \sum_j \frac{B_j(\prod_i A_{ij})}{\sum_j(\prod_i A_{ij})}$$

Initially, the membership functions are produced by a fuzzy *c*-means algorithm (FCM) directly from the data [15]. FCM is an unsupervised clustering method. It groups the data into *c* clusters according to their spatial position. The output data is clustered together with the input data and then this adds an extra dimension to the clustering space. The parameters in A_{ij} and B_j are then adjusted by a hybrid learning procedure: Least Squares Estimate to obtain B_j in a forward pass of the cases, and then the Back-propagation algorithm to obtain A_{ij}. This learning procedure limits the structure of ANFIS to a feedforward type.

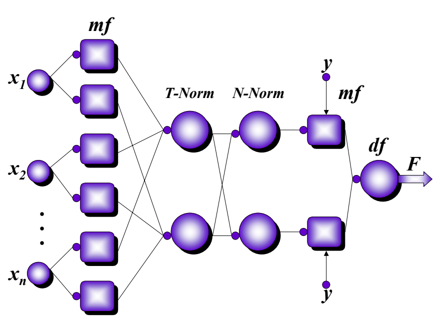

Fig. 1. ANFIS Reasoning

During the learning phase, the number of rules plays an important role in deciding the classification rates. Unlike some of the algorithms, this cannot be adjusted automatically during the learning phase [14]. Manual adjustment of the number of rules, therefore, has to be the first task to be undertaken when implementing the classification.

The entire factor set is presented to the system as well as factor subsets for identifying their predictive significance. The factor selection is based on their association with any improvement incurred in the classification rate [7].

For the purpose of a comparative analysis, a binary logistic regression model with backward stepwise feature selection procedure and a MLP neural network are adopted. For both ANFIS and the two comparative methods, the classification agreement between target and predicted classes has been tested by McNemar statistics. The corresponding p-values are provided.

III. RESULTS AND DISCUSSION

Data sets WBCD and BCD are divided on the basis of 50% for training and 50% for testing. All three models are implemented in the MATLAB environment, and the classification rates are obtained through the test set. From the classification matrix, sensitivity and specificity are calculated to show the medical significance of the prediction and supported by the corresponding p-values.

Table 2 shows the classification accuracy obtained by the three methods when applied to the two cancer data sets. For WBCD, all three methods yield high classification rates. This demonstrates that ANFIS as a classifier is suitable for cancer data analysis if it is properly presented. For BCD, ANFIS performs better than logistic regression and MLPNN, which means that for this dataset even though the data may not be properly presented, ANFIS is robust in such difficult situation and performs well, while logistic regression and MLPNN are unable to cope with this variation effectively. Meanwhile, MLP neural network tends to fit the more represented class in the data set, therefore leads to an unbalanced sensitivity and specificity. This unbalance is not desired in medical decision-making.

TABLE II
CLASSIFICATION OF CANCER DATA: LOGISTIC REGRESSION, MLPNN AND ANFIS

Method	Data	Sensitivity	Specificity	Classification Rate	P-value
Logistic	WBCD	95.0%	97.3%	96.5%	<.0001
	BCD	70.2%	75.8%	73.1%	<.0001
MLPNN	WBCD	97.5%	97.3%	97.4	<.0001
	BCD	100%	58.1%	78.2%	<.0001
ANFIS	WBCD	98.3%	96.4%	97.1%	<.0001
	BCD	89.5%	80.7%	84.9%	<.0001

In Table 3, the effect of factors on classification is evaluated by ANFIS. If histological type (h), or both histological type and gender (h and e), are removed from the analysis, the classifiers still perform well albeit with a classification rate slightly lower than that obtained for the entire factors presented. If the bilharziasis (b) factor is omitted, the classification rate decreases, but not too significantly (the p-value is still small). The above observation indicates that factors h and e are redundant for ANFIS classification, and factor b has a small impact on it. This conclusion is not readily apparent for the logistic regression model, since the entire factors remain in the logistic equation even after backward stepwise feature selection.

TABLE III
IMPACT OF FACTOR SETS ON CLASSIFICATION: ANFIS

Factors	Sensitivity	Specificity	Classification. Rate	p-value
{h,g,l,b,s,d,e,a}	89.4%	80.6%	84.9%	<0.0001
{g,l,b,s,d,e,a}	78.9%	88.7%	84.0%	<0.0001
{g,l,b,s,d,a}	92.9%	75.8%	84.0%	<0.0001
{h,g,l,s,d,e,a}	84.2%	80.7%	82.4%	<0.0001

As far as the number of rules is concerned, when these are changed over a relatively wide range, the effect is shown in Fig. 2 (considering that this curve is obtained by presenting the entire factors to the classifier). It can be observed that the middle section of the curve, which is the zone that represents the highest classification rate, is stable. This indicates that there exist redundant factors in the system that allow decisions to be made over multiple rules. The best number of rules is between 22 and 26 as shown in the figure. Values less than 10 or more than 30 have a definitely negative impact on reaching the right classification.

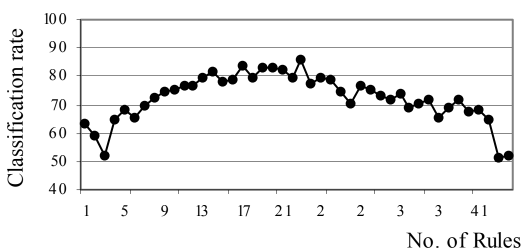

Fig. 2. Impact of rules on classification rate: ANFIS

VI. CONCLUSIONS

In this paper, ANFIS has been applied to a prognostic analysis of bilharziasis-related bladder cancer. The implementation of this method indicates its suitability as a classifier for oncological data in particular, and a potentially useful tool for medical decision making in general. In addition to identifying significant prognostic factors for bladder cancer prediction, it also outperforms the logistic regression model and MLP neural network. Histological type and patients' gender have been both recognised as redundant factors in this application. The highest classification rates obtained are 97.1% for WBCD, and 84.9% for the bladder cancer data, respectively.

REFERENCES

[1] R. M. Ripley, A. L. Harris, and L. Tarassenko, "Neural Network Models for Breast Cancer Prognosis", *Neural Computing and Applications*, **7**, pp. 367-375, 1998.

[2] C. H. Chen, J. D. Lee et al, "Colour Image Segmentation for Bladder Cancer Diagnosis", *Mathematical and Computer Modelling*, **27**(2), pp. 103-120, 1998.

[3] Y. H. Chou, C. M. Tiu, et al, "Stepwise Logistic Regression Analysis of Tumour Contour Features for Breast Ultrasound Diagnosis", *Ultrasound in Medicine and Biology*, **27**(11), pp. 1493-1498, 2001.

[4] S. S. Anand, A. E. Smith, et al, "An Evaluation of Intelligent Prognostic Systems for Colorectal Cancer", *Artificial Intelligence in Medicine*, **15**(2), pp. 193-214, 1999.

[5] L. Bottaci, P. J. Drew, et al, "Artificial Neural Networks Applied to Outcome Prediction for Colorectal Cancer Patients in Separate Institutions", *Lancet*, **350**, pp. 469-472, 1997.

[6] K. N. Qureshi, R. N. G. Naguib, et al, "Neural Network Analysis of Clinicopathological and Molecular Markers in Bladder Cancer", *Journal of Urology*, **163** (2)**,** pp. 630-633, 2000.

[7] W. Ji, R. N. G. Naguib et al, "Prognostic Value of Histology and Lymph Node Status in Bilharziasis-Bladder Cancer: Outcome Prediction Using Neural Networks", *CD ROM Proceedings of the 23rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, paper ID 844, 2001.

[8] R. P. Lippmann, "introduction to Computing with neural nets", *IEEE ASSP Mag,.* pp. 4-22, 1987.

[9] M. F. Abbod, D. G. Keyserlingk, et al, "Survey of Utilisation of Fuzzy Technology in Medicine and Healthcare", *Fuzzy Sets and Systems*, **120**, pp. 331-349, 2001.

[10] F. Steimann, "On the Use and Usefulness of Fuzzy Sets in Medical AI", *Artificial Intelligence in Medicine*, **21**, pp. 131-137, 2001.

[11] L. X. Wang, "Adaptive Fuzzy Systems and Control", Prentice-Hall, Englewood Cliffs, NJ, 1994.

[12] J. R. Jang, "ANFIS: Adaptive-Network-Based Fuzzy Inference System", *IEEE Trans. on SMC*, **23**(3), pp. 665-685, 1993.

[13] http://terra.acs.unt.edu/Rdoc/library/mlbench/html/BreastCancer.html

[14] L. Y. Cai and H. K. Kwan, "Fuzzy Classifications Using Fuzzy Inference Networks", *IEEE Trans. on SMC*, B, **28**(3), pp. 334-347, 1998.

[15] J. C. Bezdek., Pattern Recognition with Fuzzy Objective Function Algorithms, Plenum Press, 1981.