Neural Networks to Evaluate Morphological Features for Breast Cells Classification

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Summary

Rapid technology advancement has contributed towards achievements in medical applications. Cancer detection in its earliest stage is definitely very important for effective treatments. Innovation in diagnostic features of tumours may play a central role in development of new treatment methods. Thus, the purpose of this study is to evaluate proposed morphological features to classify breast cancer cells. In this paper, the morphological features were evaluated using neural networks. The features were presented to several neural networks architecture to investigate the most suitable neural network type for classifying the features effectively. The performance of the networks was compared based on resulted mean squared error, accuracy, false positive, false negative, sensitivity and specificity. The optimum network for classification of breast cancer cells was found using Hybrid Multilayer Perceptron (HMLP) network. The HMLP network was then employed to investigate the diagnostic capability of the features individually and in combination. The features were found to have important diagnostic capabilities. Training the network with a larger number of dominant morphological features was found to significantly increase the diagnostic capabilities. A combination of the proposed features gave the highest accuracy of 96%.

Key words: *Morphological features, Breast cancer, Fine needle aspirates, Neural network, Classification.*

1. Introduction

Breast cancer is the most commonly diagnosed cancer and it is the leading cause of cancer-related death among women. It is estimated that approximately one in 12 women will develop breast cancer in their lifetime. The majority of breast cancers (95%) are sporadic. Only a small proportion, particularly those diagnosed in young women, are due to a highly penetrant autosomal-dominant trait. There has been considerable progress in the identification and localization of the morphological features of tumors responsible for hereditary breast cancer. Early detection is the key to recognize the stage of the disease in order to implement a proper treatment (Sunil, 1999).

An alternative diagnostic method to mammography is using fine needle aspiration (FNA) technique. Conventionally, FNA smear slides are viewed under the microscope to determine malignancy. Specific morphological patterns or features are investigated before diagnoses are given. The characteristics of individual cells and important contextual features for instance the size of cell clumps are examined. However, many different features are thought to be correlated with malignancy and the process remains highly subjective, depending upon the skill and the experience of the pathologists. The diagnosis process takes a long time and it is costly.

Neural network methods and its application in medical field have enabled diagnosis of the cancer cells easier. The ability some of those methods have been reported more accurate as compared to conventional methods. Consequently, breast cancer diagnosis systems based on artificial intelligence have been implemented widely as an alternative as described in reference (Subramaniam et al. 2006). In order to evaluate the morphological features diagnostic ability, therefore, this work was carried out.

2. Some Related Works

A detailed study of breast cancer classification based on morphological features of breast cells had been done by many researchers (Demir & Yener 2005, Lo et al. 2003, Tozaki et al. 2005, Wedegartner et al. 2001). According to the recent discovery, many algorithms had been applied for the detection of breast cancer cells classification using neural networks. Applying the watershed morphological segmentation algorithm on the digital mammogram image could assist the detection of breast cancer tumor

Manuscript received September 5, 2008.
Manuscript revised September 20, 2008.

(Sheshadri & Kandaswamy 2005). Support Vector Machine algorithm could create a hyperplane that differentiate the inputs data of Multi Layer Perceptron network into two classes with the maximum-margin for breast masses classification (Bottigli et al. 2006).

In another research, Abbass (2002) introduced evolutionary multi-objective approach to artificial neural networks (ANNs) for breast cancer diagnosis. The approach was based on pareto differential evolution algorithm which was named memetic pareto artificial neural network. Besides using evolutionary algorithms, genetic algorithms can also be used to select features for neural networks inputs. However, evolutionary algorithm was argued to be more efficient than genetic algorithms for evolving ANNs.

Recent studies emphasized the usefulness of morphological features in breast cancer detection. Various types of morphological features had been used for breast cancer diagnosis and prognosis. A research studied the usefulness of four morphological features such as lesion shape, irregularity of contour, homogeneity of contrast enhancement and presence of ring enhancement in differentiating between benign and malignant lesions on MR-mammography was conducted by Wedegartner et. al. (2001). Irregularity of contour was the most significant feature as it gave the best result with the highest specificity of 76%.

In a research by Tozaki et. al. (2005), a combination of morphological features and kinetic information such as visual washout were used. The combination was very useful in differentiating between benign and malignant lesions of high-spatial-resolution magnetic resonance imaging of focal breast masses. Eight novel features were developed by Sheta et. al. (2005) for breast cancer automated detection. Those features were utilized to characterize the linear structures in regions of interest (ROI) during screening mammograms by using linear genetic programming. The same method, characterizing ROI of feature selection by some morphological lesion differences in mammographic images were done by a group of researchers from Italy (Bottigli et al. 2006b). The best performance of about 88% area under Receive Operating Characteristic curve was obtained using Feed Forward Neural Network.

Another study on automated analysis of breast masses based on morphological features was presented by Bottigli et al. (2006a). In the paper, twelve morphological features extracted from segmented mammographic images were used for the study. The search for objects in the image was characterized by peculiar shapes. The extracted features were fractal index, eccentricity, average intensity, average radial length (ARL), entropy of intensity distribution, inertial momentum, area, contour gradient entropy, standard deviation of intensity, standard deviation of ARL, anisotropy and circularity. The Principal Component Analysis and Independent Component Analysis were employed for features reduction process. The analysis gave promising results as it was able to provide a better performance to differentiate pathological ROIs. In addition, Evans (2003) claimed that granular calcifications with irregularity in density, shape and size are the most common morphological features of calcifications for the detection and diagnosis of ductal carcinoma in situ (DCIS). Based on past studies, these features were presented in over 90% of cases of DCIS.

In detection of other types of cancer, morphological features have also been identified as a valuable marker. In 2002, Kroll reported his findings on molecular rearrangements and morphology in thyroid cancer. A study by Mosquera et. al. (2007) demonstrated that there was a significant association between common morphological features of prostate cancer (phenotype) and *TMPRSS2-ERG* fusion prostate cancer (genotype). A total of eight morphological features were studied. According to the paper, any of the significant features could potentially be utilized for diagnosis of a fusion positive prostate cancer.

3. Morphological Features

In this study, the description morphological features refer to the form or structure of morphology of breasts cells. The morphological features provide information about the size, shape and texture of a cell. The breast cells are those obtained from fine needle aspirations cytology which consists of benign and malignant cases. In general, common features of malignant patterns are:

1. High cell yield.
2. A single population of atypical epithelial cells.
3. Irregular angulated clusters of atypical cells.
4. Reduced cohesiveness of epithelial cells.
5. Nuclear enlargement and irregularity of variable degree.
6. Single cells with intact cytoplasm.
7. Absence of single bare nuclei of benign type.
8. Necrosis - important if present.

On the other hand, benign tissues will have overall low cell yield. Sheets of ductal cells with small uniform nuclei would appear with myoepithelial nuclei visible among epithelial cells in aggregates. There will also be single,

bare, oval nuclei separated from epithelial aggregates (Trott, 1996).

4. Methodology

In this study, a preliminary investigation on the suitable network type has been carried out to evaluate the suitable network for classifying breast cancer cells. The morphological features data obtained from FNA smears were used as input markers to train the artificial neural networks. The input markers chosen were those suggested by pathologists who are involved in breast cancer management. The markers were based on diagnostic features commonly looked for during diagnostic procedures. Suggested features were a mix between continuous and categorical values which were standardized according to respective categories.

There are five numbers of morphological features which were used in this evaluation. The features comprises of Cellularity of Cells, Cells in Cluster, Cells in Discrete, Xlength and Ylength. Cellularity or cell density is a measure of distribution of breast cells on a smear. A smear with poor cell yield generally indicates normal breast gland tissue. Cellularity has been divided into three categories, ranked between 1 (poor density) up to 3 (highly dense). Cells visualized on a smear could be in clusters (grouped) or in discrete (individually placed, separated from other cells). Irregularity in distribution generally indicates abnormality. An estimated count of cells in discrete and cells in clusters are included as two separate inputs to the neural network. Xlength refers to the shortest while Ylength refers to the longest cells visualized. Both measurements were made in micrometers (μm).

The best networks' architecture was determined based on results on testing set in terms of:

1. Classification accuracy, false positive, false negative, sensitivity and specificity percentage.
2. Mean Squared Error (MSE) nearest or equal to 0. For ease of comparison, the values of MSE were quoted in the unit of decibel (dB).

The optimum network identified is then used to utilize the morphological features effectively. During this stage, individual and various combinations of breast features were applied to the network to produce classification. Each of the features was then omitted respectively to evaluate the impact on network diagnostic performance.

4.1 Dataset Acquisition

A clinical dataset of 804 cases was employed for this study. Those dataset was extracted from FNA smears of breast cell. The standard Papanicolou staining method as described in reference (Bancroft & Stevens 1982), was implemented to the smears before the cell images were viewed by using Leica Qwin Image Analyser software (Leica, Cambridge, United Kingdom). The software was hosted by a computer which was attached to a digital microscope. The smears were generally viewed to identify its overall picture and its relative position was noted when a region of interest was identified. After that, magnification was fixed at x40 and constant light source was set before measurements were taken. Then, calculations were made on all smear slides. Only one experienced cytotechnologist involved in capturing the images. This purpose is to eliminate variations in visual subjectivity.

4.2 Training and Testing Data

Morphological features obtained from FNA of breast cells were used to train and test the neural networks. A total of 804 FNA samples of breast cells were analyzed and each data was considered as individual cases. There were 538 (67%) benign and 266 (33%) malignant cases. For preliminary investigation of the suitable network type, the cases were randomly selected and grouped into two data sets. The first set was further partitioned into two subsets. The first subset was used for estimation of the network parameters (network training) while the second subset was used for evaluation of the performance of the model (network testing). In other words, the training and testing data sets were used to assess the performance of various candidate model structures. The second set is to validate (network validation) the resulting of the best network type for breast cells classification. When the network with best performing parameter values has been chosen, its generalization capability is assessed using the validation set. Division of the data sets is given in Table 1. In the training set, there are 152 (30%) malignant cases and 352 (70%) benign cases. In both the testing and validation sets, each has 57 (38%) malignant cases and 93 (62%) benign cases.

Table 1: Divisions of morphological features data sets for investigation

Total Cases = 804			
Data Set	**Training**	**Testing**	**Validation**
Benign	352	93	93
Malignant	152	57	57
Total	504	150	150

4.3 Optimum Neural Network Investigation

To investigate the optimum neural network architecture for breast cancer cells diagnosis, morphological features data were preliminary applied to six types of neural network and their performance compared. The trained networks were Multilayer Perceptron (MLP), Multilayer Perceptron Sigmoid (MLPSig), Hybrid Multilayer Perceptron (HMLP), Radial Basis Function (RBF), Hybrid Radial Basis Function (HRBF) (Mat Sakim et al. 2005) and Self-Organizing Maps (SOM).

The optimum network structure is different for the different neural network types. To avoid complex network architecture and assure better run-time performance, each of the neural networks was constructed based on standard network architecture. Therefore, the neural networks established, only consisted of three layers that were input layer, hidden layer and output layer. There was only one output node, which corresponds to classification of breast cancer cells. The network's output was graded to range from 0 to 1 and determined due to cut-off point of 0.5. A probability of high output ($\geq$0.5) was considered to indicate malignancy, while a probability of low output (<0.5) indicated benignity (normal cell). The input layer has five nodes, which corresponds to the five morphological features under study.

Corresponding diagnostic results given by pathologist were assigned to 1 for malignant and 0 for benign. The actual output of neural network is compared to these values (0s and 1s) for comparative measurements. The number of training epochs and nodes in the hidden layer needs to be investigated to find the optimum network structure. Therefore, the trial and error method was carried out.

In general, each network type was initially trained with fixed number of hidden nodes while the epoch was varied. Then, training and testing were repeated for increasing numbers of hidden nodes. Determining the optimum number of hidden nodes is crucial. In the literature, there is no specific rule on determining the number of nodes in the hidden layer. A network with a small number of hidden nodes will not have enough capability to represent the input-output mapping. While a network with a large number of hidden nodes will increase the error and lead to a problem of overfitting. The network simply memorizes the training data (Masters, 1993). Table 2 shows proposed morphological features for classification and corresponding values for neural network inputs.

The optimum neural network architecture (and network type) identified was then validated and employed to investigate classification capabilities of features. Individual and various combinations of breast features were applied to the network to produce classification. During this investigation, all 804 data were employed.

Table 2: Variables proposed for classification network

Input Marker	Categories	Neural Network Inputs
Cellularity	High	3
	Moderate	2
	Poor	1
Cells in Discrete	>100	3
	50-100	2
	<50	1
Cells in Cluster	>51	4
	31-50	3
	10-30	2
	<10	1
X Length	Mean of shortest length of cells in μm	
Y Length	Mean of longest length of cells in μm	
Output	Malignant	1
	Benign	0

5. Results and Discussion

The performance of all networks trained using the morphological data is tabulated in Table 3. The table shows the best number of hidden node (HN) and epoch for each type of network investigated. From this table, it can be seen that all the networks investigated were able to give more than 90% training and testing data accuracy. However, only SOM network presented below 90% (84%) for testing data accuracy. During training, HMLP network performed the best with 96% accuracy and MSE of -30.81dB. During testing, the highest accuracy was 99% with least MSE of -36.66dB.

Table 3: Performance of all networks trained using morphological features

Network Type	No. of HN	No. of Epoch	Training		Testing	
			MSE (-dB)	ACC (%)	MSE (-dB)	ACC (%)
MLP	10	11	27.43	94	33.35	98
MLPSig	8	6	29.26	95	34.21	98
HMLP	7	6	30.81	96	36.66	99
RBF	7	4	23.23	94	26.42	98
HRBF	13	2	27.84	94	32.58	98
SOM	10	50	14.09	92	12.05	84

Based on results tabulated in Table 3, HMLP network was presented with the validating data set. HMLP network was able to give 96% accuracy, 91% sensitivity, 99% specificity, 1% false positive and 9% false negative. This shows that HMLP network is capable of classifying the breast cancer cells. Figure 1 illustrates the output of

optimum structured HMLP network as compared to actual diagnosis of patients in the validation data set.

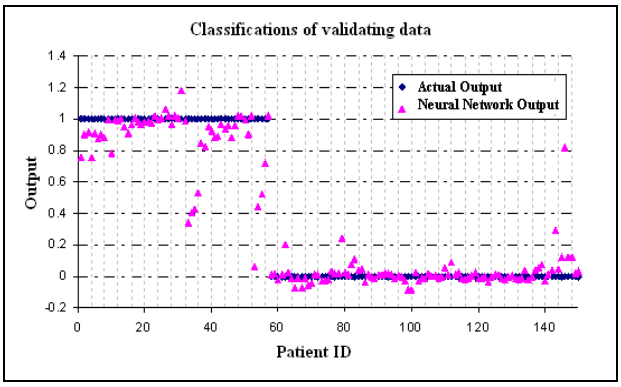

Figure 1. Actual and neural network output of patients in the validation data set

The HMLP network was employed with 7 hidden nodes and trained using 6 epochs to analyze the morphological features. When the input features were omitted one at a time, the classification results are as shown in Table 4. FP%, FN%, SN%, SP% and ACC% are percentage of False Positive, False Negative, Sensitivity, Specificity and Accuracy respectively. From Table 4, some observations could be made. They were:

1. The network specificity and accuracy reduced the most when Ylength was omitted (using all features but Ylength). The increased in MSE and false positive percentage are too large. The network cannot identify benign cases correctly. Ylength is considered an important diagnostic feature.
2. Omitting Xlength affects the classification such that only benign cases were correctly identified. The network cannot detect any of malignant cases (100% false negative), thus reducing overall accuracy. The MSE was increased the most.
3. Omitting Cluster enabled the network to identify all malignant cases. However, there was a reduction in benign cases identified, thus reducing overall accuracy.
4. Omitting Discrete has positive effect on sensitivity but negative effect on specificity. The overall accuracy was not affected. Discrete can be considered comparatively, not to be a significant feature. However, MSE was increased. The feature Discrete may be useful for difficult cases.

Table 4: Results of classification when input features were omitted one at a time

Input Nodes	FP (%)	FN (%)	SN (%)	SP (%)	ACC (%)	Final MSE (-dB)
All features included	3	6	94	97	96	29.52
Cellularity omitted	3	18	82	97	92	23.9
Cluster omitted	26	0	100	74	83	18.31
Discrete omitted	4	3	97	96	96	28.13
Xlength omitted	0	100	0	100	67	3.94
Ylength omitted	93	3	97	7	37	9.42

Various combinations of input markers were then presented to the HMLP network. The classification results on all the data are as shown in Table 5. Applying single inputs at a time to HMLP network gave classification results as shown in Table 6. Some observations made were:

1. Combination of the features Xlength and Ylength improved classification accuracy. The network achieved 100% sensitivity and no false negative presented. All malignant cases were correctly identified.
2. Combination of the features Cluster, Xlength and Ylength were able to correctly classify most of the patients. Compared to network with Xlength and Ylength only, more benign cases were correctly identified, although some malignant cases were missed.
3. Network with combination of Discrete, Xlength and Ylength was able to identify many of the malignant cases. However, many benign cases were missed, thus reducing overall accuracy.
4. Combination of Cellularity and Xlength was identified to be the lowest classification accuracy for two input nodes category. While combination of Cellularity, Discrete and Xlength was identified to be the lowest classification accuracy for three input nodes category. However, both of the combinations were more sensitive towards malignant cases than benign cases.
5. The feature Xlength on its own has positive effect on sensitivity and negative effect on specificity. Combination of this feature with others is important to detect malignancy.
6. Single input application for instance Cellularity, Cluster, Discrete or Ylength, was not sensitive towards malignant cases (only identified benign cases).

Table 5: Results of classification when using combination of input features

Input Nodes	FP (%)	FN (%)	SN (%)	SP (%)	ACC (%)	Final MSE (-dB)
3 Input Nodes						
Cell,Clust&Discrete	0	100	0	100	67	7.80
Cell,Clust & XL	85	4	96	15	42	10.80
Cell,Clust & YL	0	100	0	100	67	4.95
Cell,Discrete & XL	96	3	97	4	35	8.58
Cell,Discrete & YL	0	100	0	100	67	6.73
Cell,XL&YL	34	0	100	66	77	16.18
Clust,Discrete &XL	47	3	97	53	67	14.43
Clust,Discrete &YL	26	100	0	74	50	-0.63
Clust,XL&YL	3	13	87	97	94	24.35
Discrete,XL&YL	22	2	98	78	85	19.08
2 Input Nodes						
Cell & Clust	0	100	0	100	67	8.15
Cell & Discrete	0	100	0	100	67	8.26
Cell & XL	92	4	96	8	37	9.00
Cell & YL	0	100	0	100	67	7.39
Clust & Discrete	0	100	0	100	67	6.58
Clust & XL	42	3	97	58	71	14.73
Clust & YL	26	100	0	74	49	-0.07
Discrete & XL	60	3	97	40	59	13.52
Discrete & YL	16	100	0	84	56	1.44
XL & YL	36	0	100	64	76	16.41

Cell=Cellularity, Clust=Cluster, XL=Xlength, YL=Ylength.

Table 6: Results of classification when using one feature at a time

Input Nodes	FP (%)	FN (%)	SN (%)	SP (%)	ACC (%)	Final MSE (-dB)
Cellularity only	0	100	0	100	67	9.05
Cluster only	0	100	0	100	67	6.13
Discrete only	0	100	0	100	67	7.02
Xlength only	53	3	97	47	63	13.87
Ylength only	0	100	0	100	67	2.17

6. Conclusion

In this study, the morphological features were found to have diagnostic capabilities. The individual features were able to give correct classifications. This shows that the features are able to indicate tumor aggressiveness at cellular level. Although the features were independently insignificant, the features were able to give high accuracies collectively. This is shown when the features were employed individually; they did not give high classification results as expected. Most of the features only identified benign cases well. For example, the feature Xlength on its own classified many of the malignant cases but at the expense of many misclassified benign cases. When combined with Ylength, all the malignant cases could be classified and more benign cases were identified.

Although the feature Ylength was able to correctly classify all benign cases on its own, none of the malignant cases was identified. However, employing all the morphological features except Ylength degrades the overall network performance. Ylength can be considered to be relatively, the most significant morphological feature. When the combination of the features Cellularity, Cluster, Xlength and Ylength were used as inputs to the HMLP network, the highest accuracy, 96% was achieved. Although this accuracy percentage was similar during all features employment, but its sensitivity and specificity were higher. This shows that a combination of markers could be more useful in classification although they do not seem to be that important on their own. Therefore, other morphological features that are thought to be unimportant should also be included so that its impact when combined with other markers could be studied. In term of accuracy percentage as presented in the result section, this study achieved slightly better performance compare to other previous researches.

In other words, training the network with a small number of morphological features can significantly reduce its prediction capabilities. The networks classification would perform better when more dominant features were employed. This indicates that morphological features play an important role in network classification.

7. Future Work

Since choice and number of morphological features are important criterion in improving accuracy of network classification, more potential morphological features must be investigated. Information on cellular bindings of breast cells may be considered as inputs to network. These features may be useful for development of an early breast cancer detection system.

Acknowledgments

A clinical dataset of this study has been provided by the Pathology Department, School of Medical Sciences, USM, Kubang Kerian, Kelantan, Malaysia. The authors are very grateful to competent reviewers for their constructive comments and valuable suggestions which timely helped to improve the quality level of this paper.

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