Capability of New Features from FTIR Spectral of Cervical Cells for Cervical Precancerous Diagnostic System Using MLP Networks

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Abstract*—The applicability and reliability of Infrared (IR) spectroscopy to distinguish normal and abnormal cells has opened this research to obtain new features from IR spectral of cervical cells to be fed into multilayered perceptrons (MLP) networks. In order for neural networks to be used as cervical precancerous diagnostic system, the features of cervical cell were used as inputs for neural networks and the classification of cervical cell types were used as output target. For cervical cell classification, this study proposes new features of cervical cell spectrum that are suitable and can be used as inputs for neural networks. The new cervical cell features were extracted from ThinPrep® spectrum and their applicability were tested by using seven types of MLP training algorithm. The MLP network trained using Levenberg-Marquardt Backpropogation (trainlm) algorithm presented the highest accuracy with percentage of 97.3%. The result shows that the proposed features i.e. area under spectrum at 1800-1500 cm^{-1}, area under spectrum at 1200-1000 cm^{-1}, area under spectrum at 1800-950 cm^{-1}, height of slope at 1650-1550 cm^{-1}, corrected area of protein band at 1590-1490 cm^{-1}, corrected area of glycogen band at 1134-985 cm^{-1}, corrected peak height protein (H1545) and corrected peak height glycogen (H1045) are applicable to be fed as input to neural network for cervical spectra classification in cervical precancerous diagnostic system.

Keywords-component; Fourier Transform InfraRed (FTIR); Cervical Cancer; Multilayered perceptrons (MLP); neural networks;

I. INTRODUCTION

Cervical cancer (especially invasive squamous cell carcinoma) is the second most prevalent cancer among women after skin cancer [1]. It is the most common cancer in many developing countries. There are over 370,000 new cases of cervical cancer each year, accounting for over 10% of cancers in women [2]. In United States of America, approximately 14,000 new cases of cervical cancer were diagnosed each year and over 5,000 women died each year, due to cervical cancer [3]. Cervical cancer progression may take many years for it to progress from pre-malignancy to invasive and or metastatic [4]. Hence, the incidence and mortality related to this disease can be significantly reduced through early detection and proper treatment.

Over the past 50 years, since the implementation of the Papanicolau (Pap) smear as a cancer-screening tool, there shown dramatic decrease in both the incidence and mortality rates of cervical cancer [5]. Despite its success in reducing mortality from cervical cancer, the Pap test has several limitations; one of them is false-negative results.

In 2004, a new technique, liquid-based cytology (LBC) using MonoPrep2™ and ThinPrep® Pap test, has emerged to improve the quality of smears for Cytopathologic evaluation [6]. This method uses a special preservative liquid which helps to remove some of the mucus, bacteria, yeast, and pus cells in a sample. It allows the cervical cells to be spread more evenly on the slide and keeps them from drying out and distorting. LBC produce a more representative sample of the specimens and reduce the chance that the Pap test will need to be repeated. However, it is much more expensive to be used as a routine screening test.

Past a decade, there are number of studies have been done to investigate the possibility used of Fourier Transform InfraRed (FTIR) technique as screening tool for cervical cancer. All this while, FTIR spectroscopy was utilized to measure and detect chemical compounds in many industrial

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fields. In recent times, it has been used to study the structural changes of cells at the molecular level in various human cancers [7]. The changes in term of spectral characteristics of cells and tissues as a result of carcinogenesis are due to different modes of vibration in the molecules of the cells and tissues induced by InfraRed light. Studies done by Shady *et al* [8] and Fung *et al* [9] proved that FTIR could overcome the limitations exist in either standard Pap or LBC in terms of sensitivity, specificity, false-negative rate and false-positive rate.

Therefore, this study proposes new features of cervical cell spectrum that are suitable and can be used as inputs for neural networks for cervical cell classification. The new cervical cell features were extracted from ThinPrep® spectrum and their applicability and capability were tested by using multilayered perceptrons (MLP) trained with several training algorithms. Although the MLP network has been applied in a number of researches as intelligent tool for cervical cancer diagnosis, they have not yet applied the proposed features extracted from IR spectrum of cervical cells for classification process. The capability and suitability of the proposed extracted feature for detecting of cervical cancer is established based on their accuracy percentage.

II. LITERATURE

A. Fourier Transform InfraRed (FTIR)

Fourier Transform Infrared Spectroscopy is a non-destructive analytical technique used to identify mainly organic materials. It can also be applied to the analysis of solids, liquids, and gasses. The term Fourier Transform Infrared Spectroscopy refers to the manner in which the data is collected and converted from an interference pattern to a spectrum [10]. FTIR analysis results in an absorption spectrum which provides information about the chemical bonds and molecular structure of a material. Perhaps, it is the most powerful tool for identifying types of chemical bonds where the wavelength of light absorbed is characteristic of the chemical bond producing an infrared absorption spectrum. The FTIR spectrum is equivalent to the "fingerprint" of the material. Therefore, it can be utilized in either quantitative or qualitative analysis.

B. FTIR in Cervical Cancer

FTIR have been used in various applications. It has emerged as a powerful tool for chemical analysis and shows its ability to provide detailed information on the spatial distribution of chemical composition at the molecular level [11]. FTIR spectroscopy also has been widely used by organic chemists to characterize the compounds synthesized by them [12]. In addition, it has become a powerful tool for investigation of the three-dimensional structure of various bio-molecules such as proteins [13], nucleic acids [14], and lipids [15]. Inspire by those outstanding results, there are many researchers who explore and apply FTIR in cervical cancer.

Shady *et al* (2008) [8] had evaluated Fourier Transform Infrared (FTIR) spectroscopy as new tool for screening of cervical cancer in comparison with cervical cytology. A total of 800 cervical scrapings were taken by cytobrush and placed in ThinPrep® medium. The samples were dried over infrared transparent matrix. Beams of infrared light were directed at the dried samples at frequency of 4000 to 400 cm71. The absorption data were produced using a Spectrum BX II FTIR spectrometer. Data were compared with the reference absorption data of known samples using FTIR spectroscopy software. FTIR spectroscopy was compared with cytology (gold standard). They concluded that FTIR spectroscopy could differentiate normal from abnormal cervical cells in the samples examined; with the sensitivity was 85%, specificity 91%, positive predictive value 19.5% and negative predictive value of 99.5%.

Fung *et al*. (1997) [9] had compared Fourier-transform infrared (FTIR) spectroscopy in screening cervical cytology and standard Papanicolaou (Pap) screening with colposcopic directed biopsy as a ‘‘gold standard’’. A total of 301 cases were used in their work. The results for cytologies were 196 positive and 105 negative with the sensitivity, specificity, false-negative rate, and false-positive rate for the Pap test were 86.6%, 90.5%, 13.4%, and 9.5%, respectively. However, FTIR results versus histology showed 215 positive and 86 negative with a sensitivity of 98.6% and specificity of 98.8%. False-negative and false-positive rates were 1.4 and 1.2%, respectively. In the 12 cervical cancers there were no false-negative FTIR results but 3 false-negative Pap smears. The positive and negative predictive values for FTIR were 99.5 and 96.5% while the Pap values were 95.9 and 72.3%.

Similarly, Ratana *et al* (2003) [16] also proposed Fourier-transform infrared (FTIR) spectrophotometry technique to be used as screening tool. The study was done among Thai women. The results were compared to the histologic diagnosis (gold standard). They discovered that this technique detects changes at the molecular level, structural changes of functional groups through the changes of the infrared absorption spectrum instead of detecting the morphological changes as used in Pap smear test. When the infrared light is passed through a cervical cell sample, a molecule absorbs infrared radiation of the appropriate frequency which excites it from one vibrational or rotational level to another. The FTIR spectra can be interpreted as normal and abnormal results. First, significant changes in the intensity ratios and, second, significant shifts of the peak frequencies were detected. FTIR results versus histology showed sensitivity of 96.3% and specificity of 96.4%. False-negative and false-positive rates were 3.7 and 3.6%, respectively.

Erick *et al* (2006) [17] concentrated in analyzing Fourier-Transform Infra-Red (FTIR) spectroscopy to offer the potential of improving the accuracy (i.e. sensitivity and specificity) and reduce false-negative rates of Pap smear tests. They detailed the application of the machine learning methodology of Support Vector Machines (SVM) using FTIR data to enhance and improve the standard Pap test. A cohort of 53 subjects was used to test the veracity of both the Pap smear results and the FTIR based classifier against the findings of the colposcopists. They managed an outstanding result with the Pap test achieved an overall classification of 43%, whereas their proposed method achieved a rate of 72%.

III. APPROACH/ METHODOLOGY

A. Sample Preparation

A total of 176 cervical scrapings collected in ThinPrep® solution (PreservCyt; Cytyc, USA) were taken from Gribbles Pathology laboratory Petaling Jaya, Selangor, Malaysia. These samples were from women undergoing routine cervical cancer screening between August 2008 and April 2009. The diagnosis results were recorded from Gribbles Pathology Laboratory Bukit Mertajam, Penang, Malaysia. The results were classified according to the Besthesda systems 2001. In this paper, the results were classified based on two classifications which are normal and abnormal. Abnormal were included HSIL, LSIL and Cancer. These results were then compared with FTIR spectral of ThinPrep® cervical cells. FTIR spectral of ThinPrep® were obtained by processing the samples using FTIR spectroscopy in School of Chemical Science, USM Minden.

Infrared spectra of the dried samples were obtained by placing a small amount (0.005 mL) of liquid ThinPrep® samples dried in a circular KRS 5 window which is an infrared transparent matrix cells. By using deuterated-telluride-triglycine-sulphate (DTGS) detector, Infrared spectra were measured with spectrum BX II Fourier transform spectrometer (Perkin Elmer, USA). For each spectrum several scans were taken at 400-4000 cm^{-1} range of frequencies. The spectral data was processed using FTIR spectroscopy software (Spectrum version 5.0.1, Perkin Elmer) i.e. baseline correction, smoothing, normalization for equal quality and standard. For analysis purposes, the highest Normalization absorbance constant is set to 1 and the lowest is set to 0.

B. FTIR Spectroscopy Characteristics

FTIR Spectroscopy software was used for measuring and obtaining some significants characteristics of FTIR spectral. The frequency range used for analyzing between normal and abnormal samples, demonstrated in previous studies by [1], [5], [8], [16]-[22], were approximately 1800-950 cm^{-1} in normalized spectra. There are 8 proposed features to differentiate between normal and abnormal spectral. Figure 1 depicts the features mentioned below. The proposed features are;

i) area under spectrum at 1800-1500 cm^{-1},

ii) area under spectrum at 1200-1000 cm^{-1},

iii) area under spectrum at 1800-950 cm^{-1},

iv) height of slope at 1650-1550 cm^{-1},

v) corrected area of protein at 1590-1490 cm^{-1},

vi) corrected area of glycogen at 1134-985 cm^{-1},

vii) corrected peak height protein (H1545) and

viii) corrected peak height glycogen (H1045).

Area under spectrum at 1800-1500 cm^{-1}, area under spectrum at 1200-1000 cm^{-1} and area under spectrum at 1800-950 cm^{-1} were three characteristics which distinguished between normal and abnormal cases. First, the intensity of the infrared band or absorbance intensity at every frequency was observed for any significant sign before the area under the spectrum was calculated. The absorbance intensity at every frequency was higher in abnormal cases spectral compared to in normal spectral. Furthermore, the area under the spectrum on each frequency was calculated using FTIR Spectroscopy software.

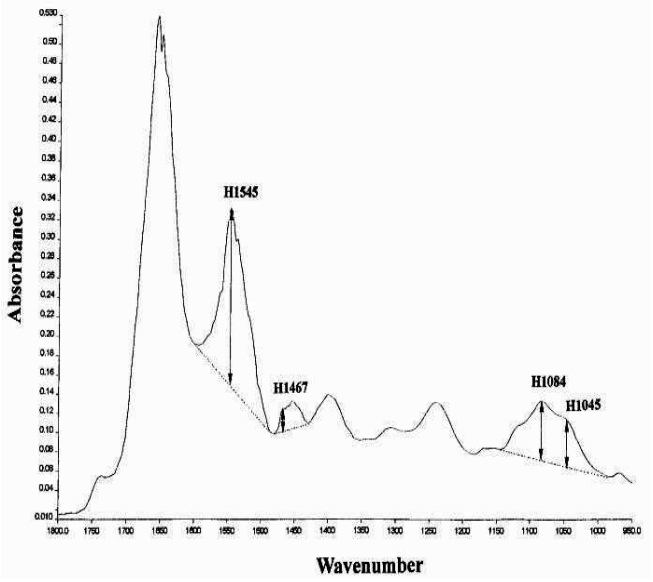

Fig. 1. Fourier-transform infrared spectral changes of cervical cancer and the 8 features.

A significant slope exists at frequency 1650-1550 cm^{-1} in normal spectrum, but no significant slope presents in abnormal spectrum at those respective range of frequencies. The height of the peak at the respective frequencies range was measured. Those values were characteristic for differentiating between abnormal and normal spectrums.

Based on the previous studies, Yano *et al* (2000) [18] used glycogen level to discriminated normal and abnormal human lung. They evaluated glycogen levels in the cancerous and noncancerous tissues of human lung by measuring the areas of glycogen at 1045 cm^{-1} due to the OH stretching coupled with bending [23] and reported that the glycogen levels in the cancerous tissues were significantly higher than those in the noncancerous tissues [24]. In human cervix [25] and liver [26], the amount of glycogen in tumor tissues is decreased compared with those in normal tissues, while in the colon [27], it is increased in tumor tissues. For this study, the corrected area under certain range of frequencies containing glycogen and protein level which are at 1134-985 cm^{-1} and at 1590-1490 cm^{-1} respectively were calculated. Again, value obtained were the marker to differentiate between normal and abnormal cells.

After the feature extraction process was completed, the suitability of eight extracted features in classifying the cervical cell in to two different categories (i.e. normal and abnormal) was tested by using neural network individually. The extracted features were fed as input data to the intelligent diagnostic part.

C. Neural Network

Multilayer perceptrons (MLP), the most popular architecture of artificial neural networks (ANNs) toolbox in Matlab 7.6 R2008 was used to simulate the training of data set. The capability of this data set was also tested using another high-performance learning algorithm called Extreme Learning Machine (ELM) [28]. The data were arranged to be 4 different sets of data. For training stage, 118 normal cervical spectrals and 5 abnormal cervical spectrals were used. While, for testing stage, 50 normal cervical spectrals and 3 abnormal cervical spectrals were used.

In this study there were 8 input neurons represent 8 features of FTIR cervical cells, 100 hidden neurons, 50 epochs, and 2 output neurons represent two targeted result i.e. normal and abnormal. The structure of a single hidden layer feed-forward network is considered in Figure 2.

In previous studies done by Mat-Isa *et al* (2003) [29], the standard MLP network trained using back propagation algorithm produced 76.0% accuracy when it was used to classify the cervical cells into normal, LSIL, and HSIL cells. Furthermore, they proved that a hybrid version of the MLP network called HMLP network, improved the diagnostic accuracy up 95.5%. Although the MLP network has been applied in a number of researches as intelligent tool for cervical cancer diagnosis, they have not yet applied the FTIR spectral of cervical cells for classification process.

There were 7 types of training algorithms were used in this study. There were Levenberg-Marquardt Backpropogation (trainlm), BFGS Quasi-Newton Backpropogation (trainbfg), Scaled Conjugate Gradient Backpropogation (trainscg), Conjugate Gradient Backpropogation With Powell Beale Restars (traincgb), Conjugate Gradient Backpropogation With Fletcher Reeves Updates (traincgf), Conjugate Gradient Backpropogation With Polak Ribiere Updates (traincgp), One Step Secant Backpropogation (trainoss). These algorithms generated different accuracy for each set of data. The results were discussed in subtopic below.

IV. RESULT AND DISCUSSION

All data were received from Gribbles Pathology laboratory Petaling Jaya, Selangor, Malaysia. The first 123 data were used as training data set and another 53 data were used as testing data set. The allocations for training data set are 118 normal cells, and 5 abnormal cells. While for testing, the allocations are 50 normal cells, and 3 abnormal cells. These data were reformed to be four training data sets and testing data sets individually. As mentioned before, eight features were extracted from each data sample that are; area under spectrum at 1800-1500 cm^{-1}, area under spectrum at 1200-1000 cm^{-1}, area under spectrum at 1800-950 cm^{-1}, height of slope at 1650-1550 cm^{-1}, corrected area of protein at 1590-1490 cm^{-1}, corrected area of glycogen at 1134-985 cm^{-1}, corrected peak height protein (H1545) and corrected peak height glycogen (H1045) and fed into MLP network. The network was trained with seven different types of training algorithm and ELM algorithm as mentioned in the previous subtopic. The diagnostic performances were based on accuracy of the proposed features within the respective algorithm. The results were tabulated in Table 1.

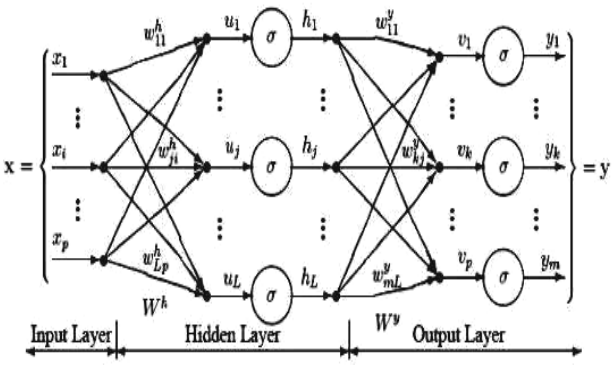

Fig. 2. One hidden layer MLP network.

TABLE 1
DIAGNOSTIC PERFORMANCE OF PROPOSED FEATURES WITHIN WITHIN SEVEN MLP ALGORITHM TYPES AND ELM

The Accuracy of MLP Algorithm Types and ELM (%)								
Algorithm	MLP							ELM
	Train LM	Train bfg	Train scg	Train cgb	Train cgf	Train cgp	Train oss	
Train1	96.7	95.9	95.1	95.9	95.9	94.3	95.9	95.7
Test1	96.2	96.2	98.1	96.2	96.2	98.1	96.2	96.7
Overall	96.5	96.1	96.6	96.1	96.1	96.2	96.1	96.2
Train2	98.4	95.9	95.1	97.6	95.9	95.9	94.3	96.2
Test2	96.2	94.3	96.2	94.3	96.2	96.2	96.2	95.7
Overall	97.3	95.1	95.7	96.0	96.1	96.1	95.3	95.9
Train3	97.6	97.6	96.7	95.9	95.9	95.9	95.9	96.5
Test3	96.2	94.3	94.3	94.3	94.3	94.3	94.3	94.6
Overall	96.9	96.0	95.5	95.1	95.1	95.1	95.1	95.5
Train4	98.4	95.9	95.9	95.9	95.9	95.9	95.9	96.3
Test4	96.2	94.3	94.3	94.3	94.3	96.2	94.3	94.8
Overall	97.3	95.1	95.1	95.1	95.1	96.1	95.1	95.6

Levenberg-Marquardt Backpropogation = trainlm, BFGS Quasi-Newton Backpropogation = trainbfg, Scaled Conjugate Gradient Backpropogation = trainscg, Conjugate Gradient Backpropogation With Powell Beale Restars = traincgb, Conjugate Gradient Backpropogation With Fletcher Reeves Updates = traincgf, Conjugate Gradient Backpropogation With Polak Ribiere Updates = traincgp, One Step Secant Backpropogation = trainoss, Extreme Learning Machine = ELM

The capability and suitability of the proposed extracted features for detecting of cervical cancer was established based on their percentage of accuracy [30]. Based on the result shown in Table 1, all data sets (i.e. 4 sets of data) consisting eight features trained (train1, train2, train3 and train4) and tested (test1, test2, test3, and test4) individually, had presented overall diagnostic performance of more than 95% average of percentage in all types of training algorithm used. The MLP network trained using Levenberg-Marquardt Backpropogation (trainlm) provided the highest percentage of overall accuracy with 97.3%. While the percentage of overall accuracy for other types of algorithm i.e. BFGS Quasi-Newton Backpropogation (trainbfg), Scaled Conjugate Gradient Backpropogation (trainscg), Conjugate Gradient Backpropogation With Powell Beale Restars (traincgb), Conjugate Gradient Backpropogation With Fletcher Reeves Updates (traincgf), Conjugate Gradient Backpropogation With Polak Ribiere Updates (traincgp), One Step Secant Backpropogation (trainoss) were 96.05%, 96.6%,

96.05%, 96.05%, 96.2%, and 96.05% respectively. Most probably, these results were influenced by small number of training and testing data sets for normal and abnormal cells.

Additionally, this study also provides the specification result for all sets of data. For train1 using Levenberg-Marquardt Backpropogation(trainlm) provided the highest accuracy with percentage of 96.7%. Whereas the percentage of accuracy for other algorithm i.e. BFGS Quasi-Newton Backpropogation (trainbfg), Scaled Conjugate Gradient Backpropogation (trainscg), Conjugate Gradient Backpropogation With Powell Beale Restars (traincgb), Conjugate Gradient Backpropogation With Fletcher Reeves Updates (traincgf), Conjugate Gradient Backpropogation With Polak Ribiere Updates (traincgp), One Step Secant Backpropogation (trainoss) were 95.9%, 95.1%, 95.9%, 95.9%, 94.3%, and 95.9%. Similar with train2, train3 and train4, the Levenberg-Marquardt Backpropogation (trainlm) algorithm had provided the highest accuracy with percentage of 98.4%, 97.6%, and 98.4% respectively. Although, the result portrayed that when Scaled Conjugate Gradient Backpropogation (trainscg) and Conjugate Gradient Backpropogation With Polak Ribiere Updates (traincgp) algorithms were used in test1, it gave the highest percentage of accuracy with 98.1%, but overall the percentage was dropped to 96.6% and 96.2% respectively. However, the highest accuracy percentage for test2, test3 and test4 were 96.2%, 96.2%, and 96.2% respectively with the Levenberg-Marquardt Backpropogation (trainlm) algorithm. Percentage of accuracy obtained with ELM as classifier tool for the four sets of data were 96.2%, 95.9%, 95.5% and 95.6% respectively.

V. CONCLUSION

This study proposed new features of cervical cell to be used for classification of cervical cells in cervical cancer diagnostic system. The features are area under spectrum at 1800-1500 cm^{-1}, area under spectrum at 1200-1000 cm^{-1}, area under spectrum at 1800-950 cm^{-1}, height of slope at 1650-1550 cm^{-1}, corrected area of protein at 1590-1490 cm^{-1}, corrected area of glycogen at 1134-985 cm^{-1}, corrected peak height protein (H1545) and corrected peak height glycogen (H1045). All the proposed features have been extracted using FTIR spectroscopy software manually before they can be fed as inputs to the MLP network using Levenberg-Marquardt Backpropogation(trainlm), BFGS quasi-Newton backpropogation (trainbfg), Scaled conjugate gradient backpropogation (trainscg), Conjugate gradient backpropogation with Powell Beale restars (traincgb), Conjugate gradient backpropogation with Fletcher Reeves updates (traincgf), Conjugate gradient backpropogation with Polak Ribiere updates (traincgp), One step secant backpropogation (trainoss). Based on the diagnostic performance of MLP network and ELM algorithm in classifying the cervical cells into normal and abnormal by using its FTIR spectrum reading, it is proven that the proposed 8 features of cervical cells' FTIR spectral are significant to be used as inputs to neural network for diagnosis purposes. The best intelligent classifier tool to classify the proposed features of FTIR spectral was The MLP network with Levenberg-Marquardt Backpropogation (trainlm) training algorithm. In a nutshell, the cervical precancerous cells could be classified by using FTIR spectral.

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