

CAPABILITY OF NEW FEATURES OF CERVICAL CELLS FOR CERVICAL CANCER DIAGNOSTIC SYSTEM USING HIERARCHICAL NEURAL NETWORK

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Abstract: *Currently, Pap test is the most popular and effective test for cervical cancer. However, Pap test does not always produce good diagnostic performance. This problem has encouraged several studies to develop diagnosis system based on neural networks to increase the diagnostic performance. In order for neural networks to be used as cervical cancer diagnostic system, the features of cervical cell are used as inputs for neural networks and the classification of cervical cell type are used as output target. This study proposes new features of cervical cell that are suitable and can be used as inputs for neural networks for cervical cell classification system. The new cervical cell features are extracted from ThinPrep[®] images and their suitability are tested by using hierarchical hybrid multilayered perceptron (H²MLP). The results shows that the proposed features which are size, grey level, perimeter, red, green, blue, intensity1, intensity2 and saturation are suitable to be fed as input to neural network for cervical cell classification in cervical cancer diagnostic system.*

Keywords: Cervical cancer, ThinPrep[®] image, feature extraction, neural network

1. INTRODUCTION

Cervical cancer is the second most common type of cancer that affects women, ranked after breast cancer. Cervical cancer is largely preventable if precancerous lesions are detected by effective screening and then adequately treated [Noorani et al, 2003]. The most popular and preferred screening

test for cervical cancer is Pap test [Cronjé, H. S., 2004]. Pap test begins with a wooden scraper (spatula) and/or a small brush that is used to collect a sample of cells from cervix and upper vagina. The cells are placed on a glass slide and any abnormal changes of cervical cells are determined. Based on Bethesda System, cells are classified into normal, low grade squamous intraepithelial lesion (LSIL)

and high grade squamous intraepithelial lesion (HSIL). However, Pap test does not always produce good diagnostic performance due to bad samples, technical and human errors, and small size of cancer development area [Othman et al, 1997; Tay, 1996; Hislop et al, 1994].

Due to limitations of diagnosis performance by Pap test, automated or semi-automated screening systems based on computer aided visualization and intelligent diagnosis have been developed to increase the diagnostic performance of the Pap test. Example of systems based on computer aided visualization and intelligent diagnosis are PAPNET[®], AutoPap[®] Primary Screening, AutoCyte SCREEN and NeuralPAP [Medical Services Advisory Committee, 2003]. Besides, there is also a few system designed to improve the cervical cell

sample obtained from patients. The prominent systems in this category are ThinPrep[®], PrepStain[™], CytoScreen[®] and Labonord Easy Prep[®] [Karnon et al, 2004]. These systems use liquid based cytology (LBC) technique to improve the quality of the conventional smear through an improved slide preparation technique following the collection of the sample in the standard way.

Normally, cervical cancer diagnosis systems are developed based on algorithmic image analysis [Mashor et al, 2003]. Most of these systems help the experts to perform better diagnosis by improving cell images quality so that the morphological features can be seen easily. Recently, there is a few study has work on cervical cancer diagnostic system based on neural network in order to increase the diagnosis performance [Tan et al, 2003; Mat-Isa et al, 2002; Li and Najarian, 2001; Mitra et al, 2000; Balasubramaniam et al, 1998]. In order for neural networks to be used as cervical cancer diagnostic system, features of cervical cell which are extracted by human expert could be used as neural networks inputs and the classification of cervical cells type could be the output [Mat-Isa et al, 2003a].

Biologically, the size of nucleus increases while size of cytoplasm decreases as the cervical cell is in the transformation process from normal cell to HSIL cell. As a result, the nucleus to cytoplasm ratio (NC ratio) increases from normal cell to HSIL cell [Thiran et al, 1994]. In addition, normal and abnormal cell (refer to LSIL and HSIL cell) yield different reaction during preservation with a fixative and staining with stain processes. Nucleus and cytoplasm of abnormal cells create darker colour [WebMD, 2002]. Therefore, features of cervical cell such as nucleus size, cytoplasm size, nucleus grey level and cytoplasm grey level are commonly used by the pathologists or in diagnostic systems to classify cervical cell into normal or abnormal cells. In NeuralPAP system, four features have been selected to be used as input to the hierarchical hybrid multilayered perceptron (H²MLP) neural network for classification of cervical cell into normal and abnormal [Mat-Isa, 2003]. Instead of neural networks, the classification of cervical cells also could be done by using the grey level co-occurrence matrix textural features and wavelet [Walker et al, 2004, Raad, 2003].

Based on the biological changes mentioned above, this study proposes a few new features to be extracted from the cervical cells in ThinPrep[®] images. The features are perimeter, red, green, blue, intensity1, intensity2 and saturation. Then, the

suitability of these features in classifying the cervical cell into normal, LSIL and HSIL cells will be tested by using neural network. For this purpose, the H²MLP network [Mat-Isa, 2003] has been chosen.

2. APPROACH /METHODOLOGY

The image of cervical cells has been captured from ThinPrep[®] slides using a computerised microscope. A total of 508 data (each data of ThinPrep[®] image consists of a cervical cell) were collected from Hospital University Sains Malaysia. First, the captured images were revised by the pathologist to determine appropriateness and type of the cervical cell. The cervical cells are classified into three categories; normal, LSIL and HSIL. Then, the proposed features of cervical cell of each ThinPrep[®] images have been manually extracted by using image analyzer. This process has been done by experienced cytotechnologists with assistance and supervision by experienced pathologists.

The proposed features are perimeter, red, green, blue, intensity1, intensity2 and saturation. Intensity1, intensity2 and saturation were then computed using Equation (1), (2) and (3) respectively [Zhang and Wang, 2000; Weeks, 1996]. Besides, this study has also extracted some conventional features such as size and grey level. Therefore, the total numbers of features that have been extracted from nucleus and cytoplasm components of cervical cell in ThinPrep[®] images were nine.

$$\text{Intensity1} = \frac{1}{3} (\text{Red} + \text{Green} + \text{Blue}) \quad (1)$$

$$\text{Intensity2} = (0.299 * \text{Red}) + (0.587 * \text{Green}) + (0.114 * \text{Blue}) \quad (2)$$

$$\text{Saturation} = \sqrt{c_1^2 + c_2^2} \quad (3)$$

$$\text{where } c_1 = \text{Red} - 0.5 * \text{Green} - 0.5 * \text{Blue} \quad (4)$$

$$c_2 = -\frac{\sqrt{3}}{2} * \text{Green} + \frac{\sqrt{3}}{2} * \text{Blue} \quad (5)$$

After the feature extraction process was completed, the suitability of the nine extracted features in classifying the cervical cell into three different categories (i.e. normal, LSIL and HSIL) was tested by using neural network individually. The extracted features will be fed as input data to the intelligent diagnostic part. For this purpose, H²MLP network

[Mat-Isa, 2003] was used to test the suitability of each extracted features. The H²MLP network has been chosen because it provide the best diagnostic performance and yielded the simplest network structure compared to other artificial neural network (ANN) architecture such as multilayered perceptron (MLP), radial basis function (RBF) and hybrid multilayered perceptron (HMLP) [Mat-Isa et al, 2008]. Moreover the H²MLP network is more efficient than the other networks where it gives better results with less hidden node.

The 508 data obtained were then divided into training data set and testing data set where the distributions of these data are as shown in Table 1. 255 samples, which consisted of 192 normal cells, 40 LSIL cells and 23 HSIL cells, were used to train the neural network. The remaining 253 were used as testing data that consisted of 192 normal cells, 39 LSIL cells and 22 HSIL cells.

Table 1 . Distribution of training and testing data sets

Category of cervical cell	Training data	Testing data
Normal	192	192
LSIL	40	39
HSIL	23	22
Total	255	253

2.1 Hierarchical Hybrid Multilayered Perceptron

Although the MLP network has been applied in a number of researches as intelligent tool for cervical cancer diagnosis, from literature review no attempt was carried out to use the MLP network to further classify the abnormal cervical cells into more specific stages. In previous studies done by [Mat-Isa, 2003; Mat-Isa et al, 2003b], 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. With additional linear connection between input nodes and output nodes, they proved that a hybrid version of the MLP network called HMLP network, improved the diagnostic accuracy up to 95.5%.

2.1.1 Hybrid Multilayered Perceptron

It has been shown in [Mashor, 2000] that modeling a linear model using the standard nonlinear MLP network is not the best solution. An optimum performance of modeling both linear and nonlinear

systems could be achieved using hybrid multilayered perceptron (HMLP) network [Mashor, 2000]. Nonlinear system is modeled by the standard connections (i.e. represented by line connection in Figure 1) as of the standard MLP network, and the linear system could be modeled by additional direct connections between input nodes to output nodes (i.e. represented by dotted line connections in Figure 1). For *m* output nodes, the output of the HMLP network is given by:

$$\hat{y}_k(t) = \sum_{j=1}^{n_h} w_{jk}^2 F \left(\sum_{i=1}^{n_i} w_{ij}^1 x_i^0(t) + b_j^1 \right) + \sum_{i=1}^{n_i} w_{ik}^l x_i^0(t)$$

for $1 \leq k \leq m$ (6)

where w_{ij}^1 , w_{jk}^2 and w_{ik}^l denote the weights of the connection between input and hidden layer, weights of the connection between hidden and output layer, and weights of the linear connection between input and output layer respectively. b_j^1 and x_i denote the thresholds in hidden nodes and inputs that are supplied to the input layer respectively. $F(\bullet)$ is an activation function and is normally be selected as sigmoid function.

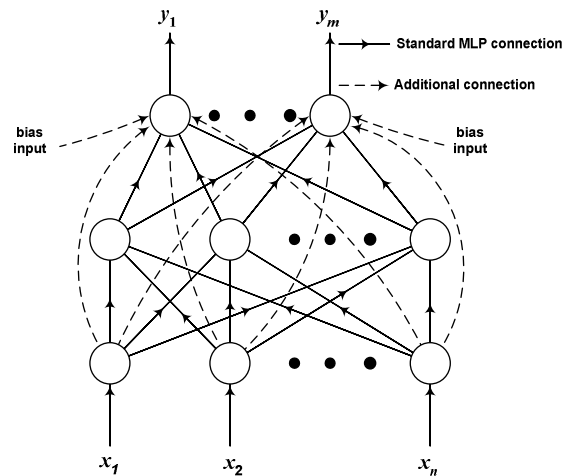


Figure 1: One hidden layer HMLP network

Learning algorithm for the HMLP network to determine the values of w_{ij}^1 , w_{jk}^2 , w_{ik}^l and b_j^1 have been proposed in [Mashor, 2000]. To handle the additional linear connections, a modified version of recursive prediction error (RPE) (the detailed RPE algorithm could be found in [Chen et al, 2003], namely modified recursive prediction error (MRPE) is introduced [Mashor, 2000]. By optimizing the way the momentum and the learning rate are assigned, the MRPE algorithm is able to improve the convergence rate of the RPE algorithm. This section will briefly explain the MRPE

algorithm. The detailed MRPE algorithm can be found in [Mashor, 2000].

The standard RPE algorithm proposed in [Chen et al, 2003] minimizes the following cost function:

$$J(\hat{\Theta}) = \frac{1}{2N} \sum \varepsilon^T(t, \hat{\Theta}) \Lambda^{-1} \varepsilon(t, \hat{\Theta}) \quad (7)$$

by updating the estimated parameter vector, $\hat{\Theta}$ (consists of w 's and b 's), recursively using the Gauss-Newton algorithm:

$$\hat{\Theta}(t) = \hat{\Theta}(t-1) + P(t)\Delta(t) \quad (8)$$

and

$$\Delta(t) = \alpha_m(t)\Delta(t-1) + \alpha_g(t)\psi(t)\varepsilon(t) \quad (9)$$

where $\varepsilon(t)$ and Λ are the prediction error and a $m \times m$ symmetric positive definite matrix respectively, and m is the number of output nodes; $\alpha_m(t)$ and $\alpha_g(t)$ are the momentum and the learning rate respectively. $\alpha_m(t)$ and $\alpha_g(t)$ can be

arbitrarily assigned to some values between 0 and 1, and the typical values of $\alpha_m(t)$ and $\alpha_g(t)$ are closed to 1 and 0 respectively. In [Mashor, 2000], $\alpha_m(t)$ and $\alpha_g(t)$ are varied to further improve the convergence rate of the RPE algorithm according to:

$$\alpha_m(t) = \alpha_m(t-1) + a \quad (10)$$

and

$$\alpha_g(t) = \alpha_m(t)(1 - \alpha_m(t)) \quad (11)$$

where a is a small constant (typically $a = 0.01$); $\psi(t)$ represents the gradient of the one-step-ahead predicted output, \hat{y} with respect to the network parameters:

$$\psi(t, \Theta) = \left[\frac{d\hat{y}(t, \Theta)}{d\Theta} \right] \quad (12)$$

$P(t)$ in equation (8) is updated recursively according to equation (13):

$$P(t) = \frac{1}{\lambda(t)} \left[P(t-1) - P(t-1)\psi(t)(\lambda(t)I + \psi^T(t)P(t-1)\psi(t))^{-1} \psi^T(t)P(t-1) \right] \quad (13)$$

where $\lambda(t)$ is the forgetting factor, $0 < \lambda(t) < 1$, and has been updated using the following scheme:

$$\lambda(t) = \lambda_0\lambda(t-1) + (1 - \lambda_0) \quad (14)$$

where λ_0 and the initial forgetting factor, $\lambda(0)$ are the design values. The initial value of the $P(t)$ matrix, $P(0)$ is set to αI where I is the identity

matrix and α is a constant, typically between 100 and 10000.

The gradient matrix, $\psi(t)$ can be modified to accommodate the extra linear connections for a one-hidden-layer HMLP network model by differentiating equation (12) with respect to the parameters, θ_c , to yield $\psi_k(k)$ as shown in equation (15).

$$\psi_k(k) = \frac{dy_k(t)}{d\theta_c} = \begin{cases} u_j & \text{if } \theta_c = w_{jk}^2 & 1 \leq j \leq n_h \\ x_i & \text{if } \theta_c = w_{ik}^l & 0 \leq i \leq n_i \\ u_j(1-u_j)w_{jk}^2 & \text{if } \theta_c = b_j^1 & 1 \leq j \leq n_h \\ u_j(1-u_j)w_{jk}^2x_i & \text{if } \theta_c = w_{ij}^1 & 1 \leq j \leq n_h, 1 \leq i \leq n_i \\ 0 & \text{otherwise} \end{cases} \quad (15)$$

The MRPE algorithm to determine the output $y_k(t)$ for a one-hidden-layer HMLP network can be implemented as follows [Mashor, 2000]:

1. Initialize weights, thresholds, $P(0)$, a , b , $\alpha_m(0)$, λ_0 and $\lambda(0)$. (b is a design parameter that has a typical value between 0.8 and 0.9).
2. Present inputs to the network and compute the network outputs according to equation (6).
3. Calculate the prediction error according to:

$$\varepsilon_k(t) = y_k(t) - \hat{y}_k(t) \quad (16)$$

where $y_k(t)$ is the actual output.

4. Compute matrix $\psi(t)$ according to equation (15). Note that, elements of $\psi(t)$ should be calculated from the output layer down to the hidden layer.
5. Compute matrix $P(t)$ and $\lambda(t)$ according to equations (13) and (14) respectively.
6. If $\alpha_m(t) < b$, update $\alpha_m(t)$ according to equation (10).
7. Update $\alpha_g(t)$ and $\Delta(t)$ according to equations (11) and (9) respectively.
8. Update parameter vector $\hat{\Theta}(t)$ according to equation (8).
9. Repeat steps (2) to (8) for each training data sample.

2.1.2 Hierarchical Hybrid Multilayered Perceptron

The MRPE algorithm can only be applied to one output node HMLP network. Although in the MRPE algorithm, it is denoted that it can be applied to any output node (i.e. $y_k(t)$) but from the algorithm, the output for each output node must be implemented separately. Thus, for the proposed cervical pre-cancerous diagnostic system, three separate HMLP networks are required to detect the normal, low grade squamous intra-epithelial lesion (LSIL) and high grade squamous intra-epithelial lesion (HSIL) cells respectively.

The original structure of the HMLP network has to be modified for effective diagnostic process. Two HMLP networks are cascaded together to form hierarchical HMLP (H^2 MLP) network. The details of the H^2 MLP can be found in [Mat-Isa et al, 2007]. Figure 2 shows the first HMLP network classifies the Pap smear into normal and abnormal cervical cells. Only the input data for the abnormal cervical cells will be fed into the second HMLP network,

which will further classify the abnormal Pap smear into LSIL and HSIL cells. The H^2 MLP network approach reduces the number of the neural networks adopted if the standard HMLP network is used for diagnosing the cervical pre-cancerous stage.

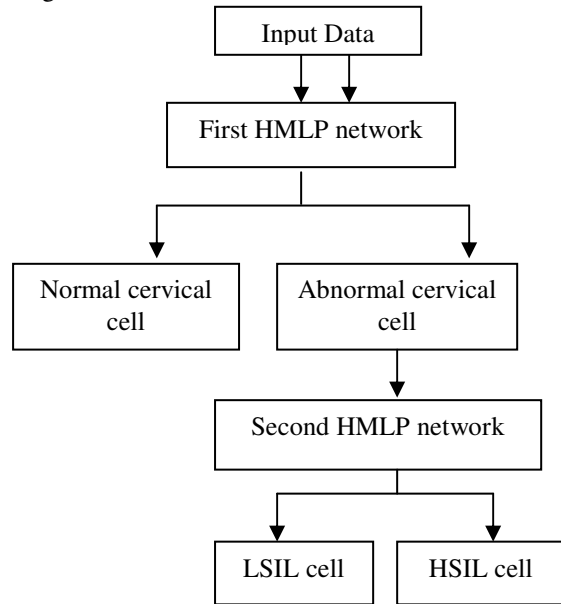


Figure 2: The H^2 MLP network

3. RESULTS AND DISCUSSION

A total of 508 data were collected from Hospital University Sains Malaysia. The first 255 data were used as training data set and another 253 data were used as testing data set. The distribution for training data set are 192 normal cells, 40 LSIL cells and 23 HSIL cells. While for testing data set the distribution are 192 normal cells, 39 LSIL cells and 22 HSIL cells. Nine features were extracted from each data sample that are size, perimeter, grey level, red, green, blue, intensity1, intensity2 and saturation and fed into H^2 MLP network. The diagnostic performance of the proposed features are summarised in Table 2. The performance was done based on accuracy, sensitivity, specificity, false negative and false positive. The definition and procedure of those analysis in [Merriam, 1995] was closely followed.

The suitability of the proposed extracted feature in detecting of cervical cancer is determined based on their accuracy percentage. Based on the results in Table 2, all nine features including the proposed features have provided high accuracy with average percentage of more than 80% in classifying the cervical cells into normal, LSIL and HSIL. Size and perimeter provided the highest accuracy with the percentage of 88.98%. While accuracy percentage

for other features such as grey level, red, green, blue, intensity1, intensity2 and saturation are 81.89%, 81.89%, 81.49%, 81.50%, 81.69%, 84.25% and 80.31% respectively. The average sensitivity percentage and average false negative percentage for all features are moderate. Most probably, these results are influenced by the small number of training and testing data sets for LSIL and HSIL cells. Perhaps the average sensitivity percentage and average false negative percentage could be increased by adding more training and testing data sets for LSIL and HSIL cells to be balanced with normal training and testing data set number. The average specificity percentage for all features is more than 90% except for 'saturation' that only achieved 89.07%. The average false positive percentage for all features is below 10.92%. These results show that all the proposed features are suitable to be fed as individual input to neural network system for cervical cancer diagnostic system.

This study also provides the result when all the nine features were fed as inputs to the H²MLP network simultaneously. Table 3 shows the diagnosis performance for all features. It is discovered that, the system achieved high accuracy with an average of 94.29%. The average percentage for sensitivity and specificity are 78.23% and 99.48%, respectively. While the average percentage for false negative and false positive are as low as 2.42% and 0.52%, respectively. The results show that the combination of all nine features which are size, grey level, perimeter, red, green, blue, intensity1, intensity2 and saturation provided better performance in classifying the cervical cells into the three categories compared to individual feature performance. Overall diagnostic performance shows that all the proposed features including the conventional features are suitable to be used in classification of cervical cell for cervical cancer diagnostic system.

Table 2 . Diagnostic performance of individual feature

Feature	Phase	Acc (%)	Sens (%)	Spec (%)	FN (%)	FP (%)
Size	Train	91.76	76.19	96.88	4.76	3.13
	Test	86.17	65.57	92.71	1.63	7.29
	Overall	88.98	70.97	94.80	3.22	5.21
Grey level	Train	85.88	42.86	100.00	28.57	0.00
	Test	77.87	31.15	92.71	52.46	7.29
	Overall	81.89	37.10	96.36	40.32	3.64
Perimeter	Train	92.55	80.95	96.35	3.17	3.65
	Test	85.38	62.30	92.71	3.28	7.29
	Overall	88.98	71.78	94.53	3.22	5.47
Red	Train	85.88	42.86	100.00	28.57	0.00
	Test	77.87	31.15	92.71	52.46	7.29
	Overall	81.89	37.10	96.36	40.32	3.64
Green	Train	87.45	57.14	97.40	6.35	2.60
	Test	75.49	37.70	87.50	39.34	12.50
	Overall	81.49	47.58	92.45	22.58	7.54
Blue	Train	83.14	33.33	99.50	34.92	0.52
	Test	79.84	24.59	97.40	67.20	2.60
	Overall	81.50	29.03	98.45	50.80	1.56
Intensity1	Train	88.63	58.73	98.44	9.52	1.56
	Test	74.70	44.26	84.38	37.70	15.63
	Overall	81.69	51.61	91.41	23.38	8.58
Intensity2	Train	88.63	53.97	100.00	20.63	0.00
	Test	79.84	34.43	94.27	49.18	5.73
	Overall	84.25	44.36	97.14	34.67	2.86
Saturation	Train	87.45	58.73	96.88	14.29	3.13
	Test	73.12	47.54	81.25	32.79	18.75
	Overall	80.31	53.23	89.07	23.39	10.92

Note : Acc=accuracy, Sens=sensitivity, Spec=specificity, FN=false negative, FP=false positive

Table 3 . Diagnostic performance for the combination all nine features

Analysis	Train (%)	Test (%)	Overall (%)
Accuracy	97.65	90.91	94.29
Sensitivity	90.48	65.57	78.23
Specificity	100.00	98.96	99.48
False Negative	0.00	4.92	2.42
False Positive	0.00	1.04	0.52

4. CONCLUSION

This study has proposed new features of cervical cell to be used for classification of cervical cells in cervical cancer diagnostic system. The features are perimeter, red, green, blue, intensity1, intensity2 and saturation. All the proposed features have been extracted using image analyzer manually before they can be fed as inputs to the H²MLP network. Based on the good diagnostic performance of the H²MLP network in classifying the cervical cells into normal, LSIL and HSIL, it is proved that the proposed features can be used as inputs to neural network to improve its diagnostic performance.

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BIOGRAPHY



Nazahah Mustafa obtained her B.Eng Hons in Electronic Engineering from Universiti Sains Malaysia in 2004 and M.Sc in Electrical and Electronic Engineering (Medical Image Processing) from the same university in 2007. She is currently a lecturer and lecturing at the School of Mechatronic, Universiti Malaysia Perlis, Malaysia. She specializes in the area of image processing and algorithms.



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Assoc. Prof. Dr. Mohd Yusoff Mashor was born on 3rd August 1967 in Pasir Putih, Kelantan. He obtained his Bachelor of Engineering in Control and Computer Engineering from University of Westminster, London in 1990.

Under USM's RLKA scheme he pursued his M.Sc in Control Engineering and Information Technology at University of Sheffield, in 1991. In 1995 he obtained his PhD specialized in Neural Network from the same university. He started his service in USM in the School of Electrical and Electronic Engineering in December 1999. He is currently a Dean of Postgraduate Studies, University Malaysia Perlis. Since his PhD time, he is actively involved in research. Over the years he has developed his expertise in Neural Network, System Identification, Fuzzy Logic, Control System, Intelligent Forecasting/Prediction, Image Processing and Medical Diagnostic Systems. He has authored or co-authored more than 70 research publications in form of book chapters, refereed journals and conferences at international and national level.



Professor Dr. Nor Hayati Othman obtained her medical degree, MBBS, from University of Malaya in 1981. Upon graduation she worked as House Officer and Medical Officer in 2 main hospitals in the country, Hospital Kuala

Lumpur and Hospital Pulau Pinang, mainly in the department of general surgery. She would be a surgeon now, but family commitment made her changed her career. She obtained the degree of Master of Pathology from University of Malaya in 1987 upon which she serves as a lecturer in pathology department, Universiti Sains Malaysia (USM). When the medical school of USM was in Pulau Pinang, she served as Pathologist for Pulau Pinang General Hospital. When the school moved to Kelantan in 1990, her pathology practice moved to Hospital Universiti Sains Malaysia. In 1994, she has promoted to associate professor and in year 2000, to a professor.