MicroRNA Expression Profile Selection for Cancer Staging Classification Using Backpropagation

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MicroRNA Expression Profile Selection for Cancer Staging Classification Using Backpropagation

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Abstract. Ovarian cancer, breast cancer, and lung cancer are deadly diseases and require serious treatment. The cancers are among the fifth most common causes of cancer-induced deaths especially for woman. The high mortality rate of cancer is caused by the lack of effective strategies for early detection of the cancer, whereas if its detected in the early stages, the life survival of cancer patients will be 90%, otherwise the survival rate only 30% when the cancers detected on metastasis stages or cancer cells have spread from a primary site of cancer. MicroRNAs can be used as potential biomarkers for cancer due to their profile expression on the cancers. In this paper, we proposed the feature selection of microRNA expression profiles for classification of the cancers stages using Backpropagation Neural Network. The Cancer stages are classified into before metastasis and after metastasis. Several combinations of the microRNA expression profiles from medical references are compared to find the best features for the classification. The accuracy and the mean square errors are used as basis testing the comparison.

1. Introduction

Ovarian, breast, and lung cancer are deadly disease and need serious treatment. Ovarian cancer and breast cancer ranked by number 5 common cause of women death due to cancer. While lung cancer causes men died more often than any other cancer, due to the smoking habits [1]. Unfortunately, the cancers only show few specific initial symptoms, while most cases are diagnosed when the cancer is already at an advanced stage. When, the cancer patient is detected on an advanced stage, the 5-year survival rate is below 30%. In other way, early diagnosed in stadium I, 5-year survival rate increased by the number of 90% [2]. The high value of cancer mortality rate among provinces is due to the lack of effective strategies for early detection of the disease, whereas if it is found at an early stage life expectancy of cancer patients will be considerably increased [3]. Therefore, early detection is important as it is having high value for people to make important decisions on the medical treatment.

Early detection and better interpretation of molecular values in cancer are needed to identify new targets in the early detection and improve treatment prior to the spread of cancer cells to other organs. Metastatic is cancer cell invasion at distant which allow the growth of cancer cells in the same or a new organ [4]. The spread may result in brain, bones, lungs, or liver. MicroRNA is encoding RNA family and helps to translate the DNA into proteins [5-6]. MicroRNA are also detected and correlated with clinical cancer behaviors, but thousands microRNA variety in ovarian cancer, breast cancer and lung cancer may result in costly medical test if it must be detected in all expressions [7].

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Backpropagation Neural Network is an algorithm that can be used to analyze data based on a decision or target to be achieved. Research on this method has been done by several researchers, including Rahman et.al. using Neural Network to recognize pre-miRNA to set the positive and negative analysis of ovarian cancer [8]. Jiang et.al proved the backpropagation algorithm is superior to several machine learning algorithms in detecting novel microRNAs [9]. Other studies also used Neural Networks to develop detection of ovarian cancer in serum miRNA [10]. However, research related to the classification of the stage of cancer is still a molecular analysis, therefore, it's important to get the necessary information corresponding microRNA features profiles of the expression pattern for the classification stage of the cancer. Moreover, the most of the study in the classification of ovarian cancer, breast cancer, and lung cancer is only to identify microRNA expression, had not yet reached the stage of the cancer stage classification.

In this paper, we implement Backpropagation Neural Networks to determine the most appropriate profile of MicroRNA features for cancer stages classification in ovarian cancer, breast cancer, and lung cancer. The Cancer stages are classified into before metastasis and after metastasis. Several combinations of the microRNA expression features from medical references are compared to find the best features for the classification. The accuracy and the mean square errors are used as basis testing the comparison.

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2. Literature and Method Review

2.1. MicroRNA

MicroRNA (miRNA) is an RNA family that not encoding function. MicroRNA can be either oncogenes or tumor suppressor genes, which depends on the miRNA target and it serves as a translational and stable microRNA modulator, as well as potentially affecting the various pathways of proliferation, differentiation, and apoptosis [5]. MiRNA has a profile of features that can be used as a cancer-detecting biomarker. The biomarker is an upregulated and decreased expression (downregulated) in profiles of certain microRNA features that depend on the type of cancer experienced.

2.2. Backpropagation Neural Network

Artificial neural networks are information processing systems that have characteristics similar to biological neural networks. Artificial neural network is determined by three things: the network architecture, the method for determining the weight, as well as the activation function [11].

Backpropagation is one of artificial neural network model. Backpropagation trains the network to get a balance between networking capabilities to recognize patterns used during training, and networking capabilities to provide the correct response to the similar input pattern but not the same as patterns used during training [12]. The backpropagation architecture consists of one or more input units plus one bias unit, one hidden screen consisting of one or more units plus one bias unit, as well as one or more output units as shown in Fig 1.

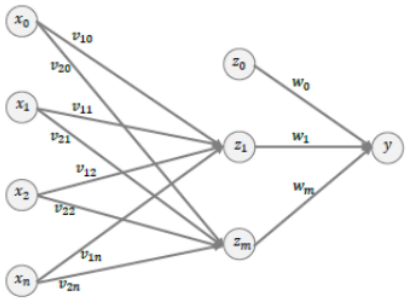

Figure 1. Backpropagation Neural Network Architecture

3. Experiment and Discussion

3.1. Data Collection

In this research, the data obtained from the paper [6]. The data obtained in the form of excel file (.xls) contains data columns of patient ID, age, gender, type of cancer, cancer metastasis classes, some information about cancer suffered by patients, and 48 miRNAs. The details of the dataset are 14 data for ovarian cancer with 7 data in metastasis stage, 28 datasets for lung cancer with 14 data in metastasis stage, and on 6 datasets for the breast cancer with 3 data in metastasis stage.

Preprocessing data is used to create raw data into ready-to-process data using the Backpropagation method. The preprocessing data has three stages; data mapping, data normalization and separation between training data and test data with K-Fold method.

3.2. Experiment and Discussion

The first experiment was aimed for finding the best architecture of the propagation method in cancer stage classification using all features of cancer miRNA. The analysis processes are performed in combination with alpha and the number of hidden neurons. Alpha is a parameter that controls the weight of hidden neuron for each input and the number hidden neuron has functions to fit the pattern of input based on the output classification. In this experiment the alpha value had a range of 0.1 to 0.9 and the number of hidden neurons layer from 1 to 5. The maximum epoch value was 100 and the target value error was 0.0001. Based on the combination of alpha and hidden neuron parameters, the processes were performed in 45 times. Ovarian, breast and lung cancer datasets were studied in this experiment.

In the ovarian cancer dataset, based on lowest MSE value we obtained the best model on backpropagation with 0.8 for the alpha value and 1 hidden neuron. The experiment for lung cancer dataset, the best configurations was obtained with 0.5 for the alpha and 1 hidden neuron. Moreover, for breast cancer dataset, the best configurations were 0.7 for alpha and 3 hidden neurons. In this case the value of miRNA expressions were high variances of values, therefore a big alpha value can accelerate the process of convergences to achieve network stability. In the next experiment, we used the best architecture for comparing the feature set of miRNA for the classifications.

3.2.1. Ovarian Cancer

In this experiment, nine feature sets of miRNA were used for the stages of ovarian cancer classification. The features sets were obtained based on references [5] [13-16]. Based on Table 1, the results demonstrate that the highest accuracy of our method is 85.71% for feature sets number 7 however with 48 miRNAs feature. Due to the goal of this study is obtaining the smalless feature sets with high accuracy, the best feature set is number 5 with three miRNAs features (miR-200a, miR-

200C, and miR-141). Based on the references [16], the feature set number 5 is the miRNA biomarker for prognosis in ovarian cancer.

3.2.2. Lung Cancer

In the lung Cancer dataset, we used seven (7) features sets based on the references. By using the best setting of the backpropagation on previous experiment, Table 2 show the accuracy that using each feature set. Based on the goal, feature set number 6 is the best feature sets for the classification with six miRNAs features (miR-92, let-7e, let-7i, miR-29a, miR-29b and miR-29c). The best profile features miRNA for the lung cancer classification is the abnormal miRNA expression profiles that found in tumor specimens and cancer cell lines when compared with normal tissue control [13]. In many types of cancer, an abnormal regulation of miRNAs indicates that miRNA affects the target genes involved in cell proliferation, apoptosis, differentiation, invasion, and mortality that are essential for cancer progression. Therefore, by using abnormal miRNA expression profiles can provide cancer staging classification for lung cancer for before and after metastasis based on this data.

Table 1 Comparison of miRNA Feature Sets in the Cancer stages of ovarian

No	miRNA Feature Sets	References	Accuracy	MSE
1.	miR-92, miR-29a	[13] [14]	50%	0.259
2.	miR-141, miR-200a, miR-205, miR-214	[13]	57.15%	0.129
3.	miR-9, miR-200a	[13]	71.43%	0.161
4.	miR-200a, miR-200c, let-7e, let-7i, miR-29a, miR-92, miR-214, miR-182, miR-205	[13]	50%	0.100
5.	**miR-200a, miR-200c, miR-141**	**[13]**	**71.43%**	**0.142**
6.	miR-181a, miR-181b	[13]	50%	0.256
7.	miR-29b, let-7e, let7i, miR-106b, miR-10b, miR-122a, miR-124a, miR-130a, miR-138, miR-141, miR-142-3p, miR-146a, miR-148b, miR-151 , miR-181a , miR-181b , miR-182 , miR-187 , miR-192 , miR-193a , miR-193b , miR-194 , miR-196a , miR-19b , miR-200a , miR-200c , miR-205 ,miR-210, miR-214, miR-27b, miR-29a, miR-29b, miR-29c, miR- 31, miR- 345 , miR-34a , miR-34b , miR-363 , miR-372 , miR-373 , miR-375 , miR-382 , miR-509 , miR-649 , miR-661 , miR-9 , miR-92 , miR-99a	[6]	85.71%	0.005
8.	miR-373, let-7e, let7i, miR-9, miR-34a, miR-34b, miR-29a, miR-29b, miR-181b	[15]	64.29%	0.084
9.	miR-214, miR-34b, miR-200a, miR-200c	[16]	71.43%	0.152

Table 2 Comparison of miRNA Feature Sets in the Cancer stages of Lung

No	miRNA Feature Sets	References	Accuracy	MSE
1.	miR-19b, miR-29c	[13]	50%	0.241
2.	miR-372, miR-182, miR-142-3p	[13]	50%	0.247
3.	miR-141, miR-200c, miR-205	[13]	53.57%	0.216
4.	miR-192, miR-205, miR-210, miR-214	[13]	46.43%	0.227
5.	miR-205, miR-210	[13]	46.43%	0.240
6.	**miR-92, let-7e, let-7i, miR-29a, miR-29b, miR-29c**	**[15]**	**71.43%**	**0.155**
7.	miR-29b, let-7e, let7i, miR-106b, miR-10b, miR-122a, miR-124a, miR-130a, miR-138, miR-141, miR-142-3p, miR-146a, miR-148b, miR-151 , miR-181a , miR-181b , miR-182 , miR-187 , miR-192 , miR-193a , miR-193b , miR-194 , miR-196a , miR-19b , miR-200a , miR-200c , miR-205 ,miR-210, miR-214, miR-27b, miR-29a, miR-29b, miR-29c, miR- 31, miR- 345 , miR-34a , miR-34b , miR-363 , miR-372 , miR-373 , miR-375 , miR-382 , miR-509 , miR-649 , miR-661 , miR-9 , miR-92 , miR-99a	[6]	78.57%	0.014

3.2.3. Breast Cancer

In the breast cancer datasets, we used six (6) feature set of miRNAs profile for the classification. The experiment using previous the method setting, table III shows that feature set number 3 is the highest accuracy with 83.33%. The profile of feature sets is four (4) miRNAs feature (miR-29b, miR-196a, miR-34b, and miR-205). Based on the paper [13], the best pprofile features is an example of miRNAs profile in abnormal FFPE samples in breast cancer. The abnormal expression profile of the miRNA are upregulated expression for miR-29b and miR-196a, then downregulated expression for miR-34b and miR-205. Abnormal microRNA expression profiles are found in tumor specimens and cancer cell lines when compared with normal tissue control. While the data in this experiment were provided from the FFPE sample, therefore, by using the profile of abnormal expression on the FFPE sample can provide the best classification of breast cancer stage on this data.

Table 3 Comparison of miRNA Feature Sets in the Cancer stages of Breast

No	miRNA Feature Sets	References	Accuracy	MSE
1.	miR-10b, miR-141, miR-210	[13]	66.67%	0.162
2.	miR-10b, miR-373, miR-210	[13]	66.67%	0.154
3.	**miR-29b, miR-196a, miR-34b, miR-205**	**[13]**	**83.33%**	**0.129**
4.	miR-373, miR-34a, miR-29a	[13]	50%	0.221
5.	miR-10b, miR-210, miR-373, let-7e, let-7i, miR-9, miR-31, miR-200a, miR-200c, miR-205	[15]	66.67%	0.099
6.	miR-29b, let-7e, let7i, miR-106b, miR-10b, miR-122a, miR-124a, miR-130a, miR-138, miR-141, miR-142-3p, miR-146a, miR-148b, miR-151 , miR-181a , miR-181b , miR-182 , miR-187 , miR-192 , miR-193a , miR-193b , miR-194 , miR-196a , miR-19b , miR-200a , miR-200c , miR-205 ,miR-210, miR-214, miR-27b, miR-29a, miR-29b, miR-29c, miR- 31, miR- 345 , miR-34a , miR-34b , miR-363 , miR-372 , miR-373 , miR-375 , miR-382 , miR-509 , miR-649 , miR-661 , miR-9 , miR-92 , miR-99a	[6]	66.67%	0.008

4. Conclusion

We show the feature selection of microRNA expression profiles for classification of the cancers stages using Backpropagation Neural Network. The Cancer stages are classified into before metastasis and after metastasis. The best ccombinations of the miRNA expression profiles that obtained on this study are; ovarian cancer (miR-200a, miR-200c, and miR-141), lung cancer (miR-92, let-7e, let-7i, miR-29a, miR-29b, and miR-29c) and breast cancer (miR-29b, miR-196a, miR-34b, and miR-205)**.** Based on the medical references, the selected feature sets are high related to the cancer stages classification. In the future, the analysis for more number of sample and details of the cancer stages are changing for improvement the classification.

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