A Novel Approach to Predict Risk in Dengue Hemorrhagic Fever (DHF) using Bioelectrical Impedance Analysis

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Abstract: The purpose of this study was to validate a single BIA for predicting the risk in DHF in dengue patients in the Hospital Universiti Kebangsaan Malaysia (HUKM). The BIA technique based on the passing of low-amplitude electrical current less than 1 mA (500 to 800µA) with frequency 50kHz. During hospitalization, 210 patients who are 119 males and 91 females serologically confirmed DF and DHF patients were tested using single BIA. By using multiple regression analysis, race, reactance, complication, headache and the day of fever were found independent determinants of predicting the risk. Hence, this novel approach of BIA technique can provide rapid, non-invasive, and promising method for classifying and evaluating the status of the DHF patients.

Key words: Modeling, Bioelectrical Impedance, Dengue Fever, Dengue Hemorrhagic, Hemoglobin, Multivariate Analysis.

1. INTRODUCTION

Dengue infections are due to several types of dengue viruses. Initially, it was difficult to differentiate dengue fever since its characteristics is similar to some other diseases. An early study reported that between the years 1780 to 1940, a unique characteristic associated with dengue-like illness was the relatively infrequent but often large epidemics [1]. New dengue virus strains and serotypes were identified (DEN-1 in 1977, a new strain of DEN-2 in 1981, DEN-4 in 1981, a new strain of DEN-3 in 1994) [1]. They belong to the genus Flavivirus, family Flaviviridae, which contains approximately 70viruses [1]. All flaviviruses have common group epitopes on the envelope protein that result in extensive cross-reactions in serological test. These make unequivocal serological diagnosis of flaviviruses difficult. Infection with one dengue serotype provides lifelong immunity to that virus, but there is no cross-protective immunity to other serotypes. Thus, persons living in an area of endemic dengue can be infected with three, and probably four, dengue serotypes during their lifetime [1].

Typical case of DHF is characterized by acute fever associated with reflecting a mild degree of plasma leakage; when the plasma loss is critical, it develops shock, which can lead to mortality. Several additional unique symptoms belong to DHF such as petechiae, ecchymoses, bleeding from the mucosa, injection sites and haematemesis can only be discriminated by medical experts. The cases of DHF have been graded, according to the WHO specification, into four grades [2]. Grade I is defined as having a fever accompanied by non-specific constitutional symptoms, the only haemorrhagic manifestation is a positive touniquet test that results in petechial rash. Grade II is defined as patients having a spontaneous bleeding from any site of their body, i.e. skin. Grade III is patients with circulatory failure manifested by rapid and weak pulse, narrowing of pulse pressure (20mmHg or less) or hypotension, with the presence of cold clammy skin and restlessness. Grade IV is defined as patients having profound shock with undetectable blood and pulse.

DHF with plasma leakage may lead to dengue shock syndrome (DSS). The condition of patients who progress to shock suddenly deteriorates after a fever of 2-7 days duration. This deterioration occurs at the time of, or shortly after, the fall in temperature-between the third and the seventh day of the disease. There are the typical signs of circulatory failure: the skin becomes cool, blotchy and congested; circumoral cyanosis is frequently
observed; the pulse becomes rapid. Patients may initially be lethargic, then become restless and rapidly enter a critical stage of shock. Acute abdominal pain is a frequent complaint shortly before the onset of shock.

1.1. Epidemiology

The first major outbreak of DHF in Malaysia occurred in 1973. DEN-3 was considered to be the main causal type [3]. In 1998, the country experienced a large epidemic with 15493 notified cases, where 799 were cases of DHF with 99 deaths [4]. It was thought that the El Nino weather phenomenon may have influenced the dengue infection [5]. It was warned that global warming has affected the pattern of dengue fever in several ways. Figure 1 shows the trend of dengue situation in Malaysia from the year 1988 to 2001 [4][6]. The incidence rate of clinically diagnosed DF and DHF reported shows an upward trend from 8.5 cases/100,000 populations in 1988 to 123.4 cases/100,000 population in 1998. Out of the 16,368 cases reported in the year 2001, 22% were among children 14 years and below. Similarly the case fatality rate (CFR) for DF is high, ranging from 5% to 6% per annum for both children and adults. As expected, there have been more cases of DF than DHF, with a ratio of 16–25:1 over the last 5 years. In the year 2001, the DF:DHF ratio in children was 6.7:1 as compared to 27.3:1 in adults.

1.2. Bioelectrical Impedance Analysis

The BIA measurements were conducted by way of a tetrapolar configuration [7] using the BIA 450 analyzer as shown in Figure 2. The four electrode technique used by this system largely avoided the aforementioned difficulties faced when using the two electrode technique. Four surface electrodes were used: two electrodes were placed on the subject’s right hand, one at the base of knuckles and another slightly above the wrist joint. Another two electrodes were placed on the right foot, one near the base of the toes and the other slightly above the ankle joint.

The BIA 450 analyzer delivered constant current less than 1mA at 50 kHz into the tissue via the electrodes attached at base of the knuckles and base of the toes (current electrodes between points A and B) and the signal was picked up by the other two sensor electrodes (voltage electrodes between points C and D) slightly above the ankle and wrist joints as shown in Figure 3.

2. PATIENTS AND METHODS

Two hundred ten adult patients aged 12 years old and above, suspected of DF and DHF admitted to the Universiti Kebangsaan Malaysia Hospital (HUKM), were monitored. For the first group, the severity of the DHF is classified into grade I to IV, according to WHO recommendation [2]. Acute dengue infection was confirmed subsequently by the use of ELISA to detect elevated dengue specific IgM (primary infection) and IgG (secondary infection) [9]. Patient serum samples were tested for hemoglobin determination using an automated counter (Coulter STKS machine). The second group is the control group for healthy female and male subjects.

Figure 1: Number of Cases, Deaths and Incidence Rates (per 100,000) in Malaysia, 1988-2003 [6]

Figure 2: Principle of Bioelectrical Impedance Measurement using the Four Electrode Technique. A and B are the Current Source Electrodes (Less than 1mA) While C and D are Detecting Electrodes
All patients were required to follow the following guidelines to ensure accurate body composition results, no drinking and eating intake for 4 hours prior to the test, no alcohol consumption for 24 hours prior to the test, no physical exercise for 12 hours prior to the test. The subjects were required to expose their right ankle and wrist during the BIA measurement. Two electrodes were placed on the patient’s right hand, one the base of the knuckles and another slightly above the wrist joint. Another two electrodes were placed on the right foot, one near the toes and the other slightly above the ankle joint. A constant current less than 1 mA and single frequency of 50 kHz was produced by a biodynamic Model 450 bioimpedance analyzer and injected to the base of the knuckles and base of the toes and the signal was picked up by the other two sensor electrodes. Resistance, reactance, body capacitance and phase angle were measured by the BIA analyzer. The clinical data were recorded using the standardized questionnaire data collection.

The second groups of patients (control subjects) who do not have past medical history of dengue were recruited and studied using the same guidelines as in the BIA subject preparation used for the first group. The BIA safety measurements procedure and other safety precautions were made known to the subjects and their informed consent was obtained from each subject prior to the BIA measurement.

For the control subject, the weight was taken once. However for subjects with dengue infection, the weight was measured daily until upon discharged.

3. STATISTICAL ANALYSIS
Statistics were calculated with SPSS version 16.0, using non-parametric test because variables were not always normally distributed. Correlations between variables were analyzed using Spearman’s rank correlation coefficient (p) and multiple linear regression analysis was used to determine the independent effect of parameters related with DHF risk. Statistical significance was defined as p<0.05 for all tests.

Subjects were 210 patients, 119 males and 91 females with men age of 30.65 years. Correlations between variables were analyzed using Spearman’s correlation coefficient. It is a standardized measure of the strength of the relationship between two variables that does not rely on the assumptions of a parametric test.

Linear regression was used to identify the most significant variable among the bioelectrical impedance analysis parameters. A significant variable were reactance, race, complication, headache and the day of fever (p<0.05).

4. GENERATING ROC CURVES FOR ARTIFICIAL NEURAL NETWORKS
Receiver operating characteristic (ROC) analysis is an established method of measuring diagnostic performance in medical imaging studies. Traditionally, artificial neural networks (ANN’s) have been applied as a classifier to find one “best” detection rate. Recently researchers have begun to report ROC curve results for ANN classifiers. The current standard method of generating ROC curves for an ANN is to vary the output node threshold for classification. Better ROC curves are in the sense of having greater area under the ROC curve (AUC).

One method of specifying the performance of a classifier is to note its true positive (TP) rate and false positive rate (FP) rate for a data set. The TP rate is the percentage of target samples that are correctly classified as target samples. The FP rate is the percentage of no target samples that are incorrectly classified as target samples. For particular applications, we may require the classifier to operate at some point other than the one to which it naturally trained. Statistical classifiers have parameters that can be varied to alter the TP and FP rates. Each set of parameter values may result in a different (TP, FP) pair, or operating point.
An ROC curve is a plot of operating points showing the possible trade off between a classifier’s TP rate versus its FP rate. The TP rate is commonly referred to as “sensitivity,” and (1 - FP rate) is called as “specificity. Typical ROC curve are shown in Figure.

In practice, the errors that can be made by the classifier [FP and false negative (FN)] often have different “costs”. In such cases, “profits” can be maximized by selecting the appropriate operating point on the ROC curve. In practical application, this requires that the underlying parameters of the classifier be easily manipulated to facilitate selection of the operating point [11]. The generation of ROC curves for traditional statistical classifiers is well understood. Analogues techniques are not so well understood for nonparametric classifiers, such as artificial neural networks (ANN’s).

![Typical ROC Curve and the Performance Level that could be Expected from Random Guessing. The Greater the Area of the Unit Square that Lies below the ROC Curve, the Greater the Power of the Classifier](Figure 4)

The ANN must be trained before the ROC curve can be generated. The resulting network is referred to as a “basic trained network.” This initial instance of the ANN provides one operating point. Based on the training data, it manipulates one or more parameters of the basic trained network to give additional instances of the ANN. The result is a set of instances of the network chosen to represent points on the ROC curve. The goodness of this set of network instances is then evaluated using separate test data. So, ANN training involves both the learning of the network connection weights, and the estimation of classifier parameter settings for the purpose of generating an ROC curve.

Generally, an ANN for a two-class problem has a single output node. The commonly accepted method of generating ROC points [12-13] is to vary a threshold over the range of the output node activation (0.0 – 1.0). For each value of threshold, any feature vector which produces an output greater than or equal to the threshold is classified as target, otherwise it is classified as non target.

An optimal set of threshold values, which correspond to successively higher level of sensitivity, can be found by sorting the set of network outputs found when every training sample from the target class is input to the trained network. Each distinct value in this sorted set corresponds to a threshold that results in a new point in a ROC plot for the training data. Additional points, if desired, could be found by interpolation. For example, assume the training data provides threshold values of 0.6 and 0.7 corresponding to sensitivity levels of 40% and 50%, but nothing in between. A threshold of 0.65 might be assumed to produce an interpolated ROC point with a sensitivity of 45%. Note that this newly estimated value of threshold will not result in a new sensitivity level for the training data, but it may for a different data set with a similar distribution (such as the test data).

Standard ANN training algorithms are not designed to vary the strength of the output according to a training sample’s proximity to the final decision surface. Ideally, all target samples would produce identical outputs of “1”, and all non target samples would produce identical outputs of “0.”

The typical ANN implementation contains an inherent weakness which may cause problems when the standard method is used to generate ROC curves. Since the sigmoid activation function asymptotically approaches zero and one, all inputs above a saturation value generate an output of one, while all output less than another saturation value generate an output zero. These saturation values depend on the precision of the ANN implementation. For example, using the activation function of (1), all inputs greater than 14 generate outputs identical to six significant digits. The overall effect is that many different input samples appear identical to a hidden node, even with a double precision floating-point implementation. This grouping together of samples due to saturation occurs at all nodes in the network, resulting in multiple samples having the same network output.
regardless of proximity to the decision surface. As a result, varying a threshold on the output node activation may not generate many distinct ROC points [14].

5. RESULTS

Subjects were 210 patients, 119 males and 91 females with mean age of 30.65 years. Correlations between variables were analyzed using Spearman’s correlation coefficient. It is a standardized measure of the strength of the relationship between two variables that does not rely on the assumptions of a parametric test. Linear regression was used to identify the most significant variable among the bioelectrical impedance analysis parameters. A significant variable were reactance, race, complication, headache and the day of fever (p<0.05).

Table 1 shows the model parameters. This model includes 19 variables predicting the risk, but only five variables are highly significant.

Finally linear regression was used to identify all significant variables and adjusted R2 to 29% (Table 2). Hence the final model can be written as follows:

Risk = 0.926 + 0.099 (race) - 0.037 (complication) + 0.045 (the day of fever) – 0.013(reactance) + 0.20 (headache).

From the SPSS model, five predictors such as race, reactance, complication, headache and the day of fever were the best predictive factors for modelling the risk in dengue patients. These results are used as the input to the Neural Network model, while the output is risk. The input-output data sets were then imported into MATLAB Workspace and the programming was written into Matlab’s M-File.

The Neural Network system consists of three parts; training, testing and validation. Feed forward back propagation algorithm with Levenberg-Marquardt (trainlm) training was used in this system because; it has the fastest convergence, very accurate training and lower mean squared error (MSE). Function tansig and purelin were used as the activation function for the input and output respectively.

For the training part, all other parameters were set to their default value except for number of hidden neurons, epochs and also the learning rate. These parameters were varies in order to find the optimal values.

<table>
<thead>
<tr>
<th>Model</th>
<th>R</th>
<th>R Square</th>
<th>Adjusted R Square</th>
<th>Std. Error</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>0.539</td>
<td>0.291</td>
<td>0.212</td>
<td>0.441</td>
</tr>
</tbody>
</table>

Figure 5: Optimal Number of Hidden Neurons
The optimal parameters obtained by training are used in the training data set and the result is shown below. For the training part, MSE is equals to 0.0215 and the system accuracy is equals to 95.33%.

Next, the optimal parameters is used in the testing data set and the result shows that MSE is equals to 0.0353 while the accuracy for the testing part is equals to 92.67%.

For the validation part, receiver operating characteristic (ROC) curve was used. ROC curves is a plot of test sensitivity (plotted on the y axis) versus its 1- specificity (plotted on the x axis). Each point on the graph is generated by using a different threshold. The set of data points generated from the different thresholds is the empirical ROC curve.

The ROC plot has many advantages over single measurements of sensitivity and specificity. The scales of the curve, that is, sensitivity and 1-specificity are the basic measurement of accuracy and are easily read from the plot; the values of the threshold are often labelled on the curve as well.

One of the most popular measures of the accuracy of diagnostic test is the area under (AUC) the ROC curve. The ROC curve area can be chosen between the ranges of 0.0 to 1.0. The closer the ROC curve area is to 1.0, the better the diagnostic test. The percentage for diagnostic accuracy (DA) refers to the percentage of samples that have been correctly diagnosed. In any test with a fixed threshold, it is desirable for a decision model to produce TPR and FPR pair nearby to this point. Therefore, measurement of Euclidean Distance (ED) of any coordinate pairs in the plot to this ideal point would distinctively differentiate performance between models for a fixed threshold.

The area under the receiver operating characteristic (ROC) curve (AUC) is then calculated and the result shows that the AUC is equals to 0.583.
(58.3%). Based on the table above, this system can be classified as fail and could not predict the risk of DHF patients effectively.

Figure 10: System’s ROC Curve

6. CONCLUSIONS

The goal of this research was to develop a rapid, non-invasive and simple to use tool to predict risk in DHF in dengue patients in the Hospital Universiti Kebangsaan Malaysia (HUKM) by using Artificial Neural Network (ANN). Five independant determinants of predicting risk that is race, reactance, complication, headache and the day of fever were found using multiple regression analysis and were used as the input to the neural network system.

REFERENCES


