A novel dengue fever (DF) and dengue haemorrhagic fever (DHF) analysis using artificial neural network (ANN)

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Summary Dengue fever (DF) is an acute febrile viral disease frequently presented with headache, bone or joint and muscular pains, and rash. A significant percentage of DF patients develop a more severe form of disease, known as dengue haemorrhagic fever (DHF). DHF is the complication of DF. The main pathophysiology of DHF is the development of plasma leakage from the capillary, resulting in haemoconcentration, ascites, and pleural effusion that may lead to shock following defervescence of fever. Therefore, accurate prediction of the day of defervescence of fever is critical for clinician to decide on patient management strategy. To date, no known literature describes of any attempt to predict the day of defervescence of fever in DF patients. This paper describes a non-invasive prediction system for predicting the day of defervescence of fever in dengue patients using artificial neural network. The developed system bases its prediction solely on the clinical symptoms and signs and uses the multilayer feed-forward neural networks (MFNN). The results show that the proposed system is able to predict the day of defervescence in dengue patients with 90% prediction accuracy.

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1. Introduction

Artificial neural network (ANN) is a powerful non-linear statistical paradigm for recognition of complex patterns with the ability to maintain accuracy...
even when some input data are missing. ANN is able to perform certain specific task that mimics the acts of human brain, with its neurons and synaptic connections [1–3]. In ANN, the output performance for particular input variables of the network is optimised by adjusting the weights during the training process. The back propagation-training algorithm is commonly used for ANN in medical databases and has been shown by many researchers to be a powerful tool for prediction, prognosis and diagnosis in medical applications [4–9]. The outcome of these research findings showed promising result and enable a more effective resource planning and patient management. However, the use of ANN as a prognostic tool in dengue fever (DF) and dengue haemorrhagic fever (DHF) diseases has not been reported in the literature. Hence, this paper will be the first attempt to apply ANN for prognostic purpose in DF and DHF.

DF is an acute febrile viral disease frequently presenting with sign and symptoms that include headache, myalgia, macular rash, loss of appetite, nausea, vomiting, abdominal pain, metallic taste of food, change in psychological state and moderate thrombocytopenia [10]. A significant number of DF patients will progress to dengue haemorrhagic fever (DHF). DHF is the complication of DF around the day of defervescence of fever. The mechanism of progression from DF to DHF is related to immune mediated injury to the endothelium of the capillary, leading to plasma leakage from the capillary system, resulting in haemoconcentration, ascites, and pleural effusion and shock. It has been well documented that these serious complications usually set in following the day of defervescence of fever [11–13]. Since the early clinical features of DHF are indistinguishable from DF [11,14–16], the major pathophysiological changes that determine the severity of disease in DHF and also differentiate it from DF is plasma leakage resulting in increasing haematocrit (20% absolute rise from the baseline) leading to haemoconcentration, and a serious effusion that may lead to hypotension [11,17,18]. Defervescence is defined as the day when a patient has no fever or the disappearance of a fever. Fever is defined as the state when the body temperature rises above 37.5 °C [19]. Furthermore, patients who progress to shock will suddenly deteriorate at the time of, or shortly following defervescence of fever. These patients are in danger of dying if appropriate treatment is not promptly administered. Septic shock syndrome with vasodilatation, abnormal haemostasis and plasma leakage are the three pathophysiological hallmarks of DHF [11,14,15]. These characteristic features typically occur at the onset of defervescence of fever [11,14–16]. Thus, the final diagnosis of severity of any dengue infection is unfortunately a retrospective one, after the progression of the illness has come to its end. Although most patients recover without sequel but a small minority may die from dengue shock syndrome (DSS). As a result, the mainstay of treatment remains as early diagnosis, close monitoring and aggressive fluid replacement therapy when indicated. The majority of patients were probably admitted for close monitoring and aggressive treatment merely due to anticipation of DSS. Decision making on when to admit or discharge patient has been a great challenge for the managing physician because there are very few clinical studies that address these issues. If the potentially ill patients can be identified confidently in time, a lot of unnecessary admission can be avoided. This will definitely have major impact on health care cost saving in view of the huge incident of dengue fever in this region. Thus, it is very crucial to know the day of defervescence of fever. If this information is made known beforehand to the clinician, early and proper clinical management and treatment can be planned to avoid mortality. This paper describes the development of a prognostic system to predict the day of defervescence of fever in DF and DHF patients using Matlab’s neural network toolbox [20]. The data have been collected from a total of 252 hospitalised patients (4 DF and 248 DHF patients).

2. Dengue fever (DF) and dengue hemorrhagic fever (DHF)

The dengue viruses are members of the Flavivirus family. They consist of four serotypes and are transmitted by Aedes aegypti and Aedes albopictus mosquitoes. It is the commonest arthropod-borne viral infection in man [21]. It is estimated that as many as 100 million dengue virus infections occur annually in the tropics, with over 10,000 deaths from DSS and many as 100 million dengue virus infections occur annually in the tropics [20]. Besides a rapid global increase in incidence, there has been an increase in severe cases as well [12,23]. Malaysia had its largest outbreak in the year 1996; a total of 14,255 dengue cases were notified of which 533 were DHF with 32 deaths [24,25].

Adult DF is typically a flu-like illness characterized by fever, headache, eye pain, myalgia, arthralgia, and rash, which last from 5 to 7 days. DHF has been graded according to the WHO specifications into four grades of severity, where grades III and IV are considered to be DSS. Grade I is defined as patients having a fever accompanied by non-specific constitutional symptoms, the only haem-
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orrhagic manifestation is a positive tourniquet test that result in petechial rash. Grade II is defined as patients having a spontaneous bleeding from any site of their body skin. Grade III (DSS) is where a patient has circulatory failure manifested by rapid and weak pulse, narrowing of pulse pressure (20 mmHg or less) or hypotension, with the presence of cold clammy skin and restlessness. Grade IV (DSS) is defined as patients having profound shock with undetectable blood and pulse [11].

The characteristics of DF and DHF described above provide features that are amenable for a non-linear modeling especially using ANN.

3. Artificial neural networks (ANNs)

Artificial neural networks (ANNs) have been widely applied to non-linear modeling problems, and they are highly suitable for modeling complex databases of medical information. The work carried out in this paper employed a multilayer feed-forward neural network (MFNN) trained via steepest descent back propagation algorithm [3,4,8,26–39]. At each iteration of this algorithm the sum-squared-error (SSE) of the network prediction is used as the cost function. Many literatures refer to the SSE as the error goal [27—30,32—34]. The hyperbolic tangent function was used for the ANN activation [27]. Since the training algorithm may produce over fittings, pruning technique was employed.

3.1. Reducing network size using weight elimination cost function

Thenetwork pruning technique called ‘weight elimination cost function’ was implemented and a complexity term was added to the cost function. The weight-elimination cost function includes a penalty term (in addition to the average squared error) that serves to reduce the small weights to zero or near zero, thereby removing their influence from the network. The weight-elimination cost function is defined as [35–39].

$$E(W) = E_0(W) + \lambda \sum_{ij} \frac{\omega_0}{1 + \omega_0 |\omega_{ij}|}$$

where $E(W)$ is the combined cost function that includes the initial cost function $E_0(W)$ and the weight elimination term (the second term). $W$ represents the weight vector, $\lambda$ is the weight decay constant, $\omega_0$ is a scale parameter, which defines the size of the weight, and $\omega_{ij}$ is the individual weight of the ANN. The role of the weight decay constant, $\lambda$, is to determine the relative important of the weight-elimination term. Larger values of $\lambda$ mean that a weight must be closer to zero to be considered a part of the ‘noise’ distribution and increase the ‘pressure’ on small weights to further reduce the size. Choosing a value of $\lambda$ that is too small will not affect the network. When $\lambda$ is too large, all weights are forced to zero [35,38]. The value of $\lambda$ is generally chosen ad hoc. Several trials need to be run to observe how the network is responding. The value is increased if the weights are not diminishing or decreased if all the weights are forced to zero [38]. On the other hand, the scale parameter $\omega_0$ must be chosen by the user. When $\omega_0$ is small, the small weights will be forced to zero resulting in fewer larger weight (i.e. weight elimination). A large $\omega_0$ causes many small weights to remain and limits the size of large weights (i.e. weight-decay) [35,38].

4. Methodology

Initially, the subjects were interviewed and physical examinations were carried out as detailed in the study protocol below. Then SPSS software was employed for the data analysis. Finally, the ANN was applied via the Matlab toolbox.

4.1. Subjects and study protocol definition

Two hundred and fifty two adult patients aged 12 years old and above, with serological confirmation [11] of acute dengue infection, admitted in Hospital Universiti Kebangsaan Malaysia (HUKM), Malaysia, during the years of 2001–2002, were prospectively studied. Ethics approval code (D-004-2002, HUKM) and informed consent was obtained from each patient.

Clinical and epidemiological data were recorded on admission by an investigator using standardized questionnaires designed for the study [40]. The clinical data comprises of data onset of fever, 37 daily surveillance of symptoms and signs, and blood results from laboratory tests. Since the patients were admitted at different stages of their illness, the daily progress of the patients were dated with reference to the day of onset of fever. ‘Fever day 1’ is defined as the first day of the onset of fever, when the body temperature reaches above 37.5°C. Days after ‘fever day 1’ is designated as ‘fever day 2’, ‘fever day 3’, and onwards. The history of fever is recorded based on the patients’ recalls: it has been shown elsewhere that this technique is reliable and accurate [41—44].
At present, the knowledge acquisition to present pattern to predict day of defervescence of fever are limited to the clinical symptoms and signs. Thus, only clinical symptoms were used as the input data for predicting the day of defervescence of fever in DF and DHF patients while the output data was defined as the number of days the fever will subside. For example, if a patient experienced 4 days of fever during his infection of dengue virus, on the first day of his onset of fever (‘fever day 1’) all the symptoms were recorded and the output was declared as 4 days before the fever subside, on ‘fever day 2’ the output was declared as 3 days before the fever subside and so on.

In the application of the study, we reduced the total output categories from multiple output state (i.e. 0—7 days) to binary output state (i.e. 2 days below or 2 days above the day of defervescence of fever). It is important to highlight here that the prediction of 2 days before the day of defervescence of fever is vital in preventative clinical patient management. The prediction of the day of defervescence of fever is divided into three categories, i.e. (i) 2 days (equivalent to 0.3 normalized values), (ii) 3 days (equivalent to 0.4 normalized values), and (iii) 4 days (equivalent to 0.6 normalized values) before the day of defervescence of fever.

4.2. Data pre-processing and analytical method

The DF and DHF clinical symptoms were analysed using SPSS 10.0.1 for Windows. Sensitivity study on the assessment of the ANN input variables has been conducted using multinomial logistic regression (MLR) method. The MLR was applied to identify the most significant variables from the 37 input symptoms and signs. Any of the variables will be considered as statistically significant if the p-value is ≤0.01. As a result of this analysis, eight most sensitive signs and symptoms (headache, nausea, vomiting, epigastric pain, petechia rash, chill and rigor, throat injection and bleeding tendency) were selected [45]. However, considering ‘fever day 1’ to ‘fever day 8’ as an important reference to the physiological changes in the clinical symptoms and signs, it was included as the ninth input of the ANN.

The descriptive statistic frequencies for each of the nine input variables were further analysed for data cleaning. From the sample obtained, it was found out that the ‘fever day’ ranges from ‘fever day 1’ to ‘fever day 12’. But due to the lack of sample for ‘fever day 9’ onwards, this study only considers data inclusive of ‘fever day 1’ to ‘fever day 8’.

Two hundreds and fifty two patients were monitored over an average of 4.6 succeeding days depending on their severity and duration of stay in the hospital. The patient’s symptoms were monitored daily to form a unique set of samples; hence a total of 1923 samples were obtained. All the data were normalized from ‘0’ to ‘1’. Then, these data were divided randomly between two sets: a training set consisting of 1244 samples, and a testing set of 279 samples.

4.3. Multilayer feed forward neural network (MFNN)

In this study, a feed-forward ANN was trained using the standard back propagation algorithm [3,28,30]. The system had a simple three-layer network comprising of 9, 5 and 1 neurons in the input, hidden and output layers, respectively. The three-layer network was chosen because of its relative ease of implementation and success in completing various classification tasks, as demonstrated by other researchers [4,32–34].

Experimental determination of optimal multi-layer perceptron that involves varying the number of neurons in the hidden layer, learning rate, and momentum term has been implemented [3]. The transfer function for neurons in the hidden layers is set as hyperbolic tangent sigmoid and the single neuron in the output layer has a linear transfer function. The feed forward ANN was trained using Matlab’s neural network toolbox [20].

4.4. Optimising ANN

The ANN application was optimised via four steps. Each of these steps was implemented to find optimum value or setting for number of neurons, momentum, learning rate, and training iterations. At each step, the parameter to be optimised is varied while the other three were fixed; SSE and the total prediction accuracy were observed. Once optimised, a further four experiments were carried out to prune the ANN using the weight-elimination technique. Then, the best model for the experiment was selected for the final application.

4.5. Model validation

In this study, the correlation test is used to justify the fitted network model. A non-linear model is considered as unbiased if the residual, r(t) is unpredictable or uncorrelated with all linear and non-linear combinations of past inputs and outputs.
Billings and Voon [46,47] proved that for a certain class of non-linear systems the following residual correlation conditions should hold if the fitted non-linear model is adequate:

\[ \phi_1(r) = E(\varepsilon(t-r)|\varepsilon(t)) = \delta(r), \quad \text{for all } r \quad (2) \]

\[ \phi_2(r) = E(\varepsilon^2(t-r)|\varepsilon(t)^2) = \delta(r), \quad \text{for all } r \quad (3) \]

\[ \phi_3(r) = E(\bar{\varepsilon}(t-r)|\varepsilon(t)) = 0, \quad \text{for all } r \quad (4) \]

\[ \phi_4(r) = E(\bar{\varepsilon}^2(t-r) - \bar{\varepsilon}^2(t)|\varepsilon(t)^2) = 0, \quad \text{for all } r \quad (5) \]

where \( \bar{\varepsilon}(t) \) and \( E[ ] \) are the mean value of \( \varepsilon(t) \) and the expectation, respectively; \( r(t) \) the residual between the measured output and prediction output. Eqs. (2) and (3) are the autocorrelation tests for the residual. Eqs. (4) and (5) are the cross-correlation tests between the measured output and residual. In practice, the correlation will never be exactly zero for all lags but the model is considered as adequate if the correlation tests lie within the 95% confidence limits, \( \pm 1.96/\sqrt{N} \), where \( N \) is the number of sample [46,47].

5. Results and discussions

Figs. 1–8 illustrate the results for the optimisation of the MFNN. Figs. 1 and 2 show the results for optimising the hidden layer size. Hidden layer sizes of 1, 3, 5, 6, 8, 9, 10, 15, 20, and 25 were used. From these figures, it can be seen that the ANN with hidden layer sizes 3, 5 and 15 may produced good prediction result. However, due to parsimony principle, the network with hidden layer size 5 was selected. This network produced a SSE of 0.0387 with a predictive accuracy rate of 79.3%.

Figs. 3 and 4 show the results for finding the optimum momentum. From these figures, it can be seen that momentum value of 0.4 and 0.9 produced good outcomes. Since, the momentum constant value of 0.4 has the highest predictive accuracy of 81% and lowest SSE of 0.0379, this setting was chosen to be the optimal momentum value.

Figs. 5 and 6 show the results for finding the optimum learning rate and it is shown that learning rates of 0.5 and 0.6 produced good predictions due to its highest accuracy of 81% and low SSE of 0.0377, the learning rate of 0.6 was found to be the optimum.

Figs. 7 and 8 show the results for finding the iteration rate. It can be observed that increasing
Fig. 4 The prediction accuracy of the day of defervescence of fever in DF and DHF varying with momentum.

Fig. 7 The training performance of the MFNN with varying number of iterations.

Fig. 5 The training performance of the MFNN with varying learning rate.

Fig. 8 The prediction accuracy of the day of defervescence of fever DF and DHF varying the iterations.

Fig. 6 The prediction accuracy of the day of defervescence of fever in DF and DHF varying with learning rate.

Fig. 9 The training of MFNN SSE convergence goal plot over 25,000 iterations for the network with five hidden neurons, 0.6 learning rate and 0.4 momentum.
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Fig. 10 MFNN prediction result for multiple output. State (normalized data at y-axis: 0, 0.1, 0.4, 0.6, 1 represent the 0, 2, 3, 4, and 7 days before the day of defervescence of fever. Solid line = targeted output, dotted line = predicted output).

The number of iterations has little reduction on the SSE except that it takes more time to converge. Iteration rate of 20,000 and 25,000 produced good prediction. Iteration of 25,000 was selected due to its highest prediction accuracy rate and low SSE of 0.0377.

Finally, a network defined by 5 hidden neurons, momentum of 0.4, and learning rate of 0.6 was employed. Its SSE convergence goal plot over 25,000 iterations is shown in Fig. 9.

Fig. 10 illustrates the MFNN prediction results for multiple output states (from 7 days to 0 day before the day of defervescence) in comparison to the target outputs, while Fig. 11 shows the MFNN prediction errors. The MFNN prediction model is validated using the correlation tests as shown in Fig. 12. It can be observed that all of the correlation tests are sufficient, however, in $\phi_{\omega}(t)$ test, the model crosses the confidence limits at lag interval from $\pm 10$ to $16$. For $\phi_{\omega,\epsilon}(t)$, the test crosses the confidence limits at lags 5 and 13. Since other tests are satisfactory, the model can be considered as adequate [46,47].

The MFNN prediction results for 2 days before and after the day of defervescence of fever are 77% and 94%. The other predictions according to their categories are 3 days (prediction accuracy of 76%), and 4 days (prediction accuracy of 91%) before the day of defervescence of fever, respectively. Table 1 tabulates the summary of MFNN prediction results before and after pruning. On average, the prediction accuracy of the network is 81.3%. The pruning
exercise improved the prediction of 2 days before the day of defervescence from 77% to 85%. The detail pruning predictions accuracy results according to the 3 and 4 days before the day of defervescence of fever categories are 92% and 93%, respectively. On average, the pruning technique improved the prediction rate for all categories from 81.3% to 90%.

### 6. Conclusion and future work

Network architecture of nine input neurons, five hidden neurons and one output neuron with 25,000 iterations was found suitable for predicting the day of defervescence of fever in DF and DHF patients. The ANN presented in the study had successfully adapted itself to the non-linear mechanism of the training data and yielded promising results with the prediction error of only 10%.

It was also found that, even though the application of the MFNN, trained using the back-propagation algorithm, was successful, the weight-elimination technique to prune the MFNN has tremendously improve the network prediction capability (90% prediction accuracy).

The results shown in this paper indicates that it is highly possible to predict the day before the defervescence of fever. The system can be used as a tool to aid clinicians in early prognosis and in outlining the management plan of the patients. Since, it has been shown that most of the patients were sick during or around the defervescence of fever, the ability to predict the day before the defervescence of fever will be very helpful to the clinician.

In future, this application can be extended for actual application in the hospital to assist the clinician in an efficient management and treatment especially to the outpatients DF and DHF.

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