Approximate Entropy and Densely Connected Neural Network in the Early Diagnostic of Patients with Chagas Disease

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Abstract

It is estimated that in the world there are between 6 and 8 million people infected with Chagas disease, mainly in endemic areas of 21 Latin American countries, and in recent years it is slowly becoming a health problem in more urban areas and countries. In that sense, developing diagnosis methods is primordial. That is why this work used a deep neural network to classify 292 subjects (volunteers and patients) composed of 83 health volunteers (Control group); 102 asymptomatic chagasic patients (CH1 group) and 107 seropositive chagasic patients with incipient heart disease (CH2 group). Approximate Entropy ApEn was calculated from the tachograms of the circadian profiles of 24 hours every 5 minutes (288 frames) of each subject, and part of this data were used to train the network. The classification work done by the deep neural network had 98% of accuracy and 98% of precision, validated with the ROC curve, whose AUC values were approximately the unit for each group. Taking into account the good performance, we can consider this deep neural network and approximate entropy as useful tools to have a good early diagnosis about Chagas disease and its cardiac compromise.

1. Introduction

Chagas disease, also called American trypanosomiasis, is caused by the protozoan parasite Trypanosoma cruzi. According to the Pan American Health Organization, there are currently between 6 and 8 million people in the Americas with T. cruzi infection, with approximately 30,000 new cases per year due to vector transmission, and 8,000 new cases per year due to congenital transmission mainly in endemic areas of 21 Latin American countries. About 65 million people live in the region at risk of contracting the infection and the disease is estimated to cause about 12,000 deaths each year [1].

Chagas disease is considered by World Health Organization as a tropical neglected disease, and in recent decades, it began to be detected in other non-endemic regions of America [2]. The disease presents in an acute form and, if not diagnosed and treated in a timely manner, it transforms into a chronic disease; in other words, it has two phases: acute (often asymptomatic) and chronic. The most important consequence of Chagas disease is chronic Chagas cardiomyopathy, which occurs in 20-40% of infected persons [3–5], and it can be potentially lethal. Although there are some detection ways, which involve various analyzes and antigen tests [6], these are expensive, limited and invasive. In this context, a new early diagnostic tool becomes essential.

It is known that the analysis of heart rate variability has prognostic importance, and specifically, the use of Approximate Entropy has proven to be a very useful statistic in the treatment of clinical data, especially time series [7–9]. A previous study even used the HRV analysis with this entropy for Chagas disease [10], finding significant differences in different periods of the day between the groups of patients analyzed.

Also, deep neural networks are widely used for disease detection, and Chagas disease has not been the exception [11–14] although they mostly involve image analysis. That is why the present work proposes a deep neural network that uses an analysis of heart rate variability based on the Approximate entropy of a database of patients with Chagas disease in order to create a highly efficient and non-invasive tool for early diagnosis of this disease.

2. Method

2.1. Database

In this work, the ECG database of the Institute of Tropical Medicine of the Central University of Venezuela was used, made up of 292 subjects (volunteers and patients), who underwent various tests with their respec-

tive informed consent: clinical evaluation, test positive Machado-Gerreiro serology, chest X-rays, echocardiogram, electrocardiogram and Holter recording (24 hours). All patients and volunteers are classified into three groups: the Control group made up of 83 healthy people (volunteers), the CH1 group made up of 102 patients infected only with a positive Machado-Gerreiro serological test (clinical evaluation test, chest X-ray, echocardiogram, electrocardiogram and Holter were normal), and the CH2 group made up of 107 seropositive patients with incipient heart disease, first-degree atrioventricular block involvement, sinus bradycardia, or His right bundle branch block, were not receiving treatment or medication. The ECG signals in this database were recorded at a frequency of 500 Hz with 12-bit resolution.

2.2. Data preprocessing

The obtaining of the QRS complexes from the ECG data was made with the Pan-Tompkins algorithm [15], then generating the 288 tachograms of 5-minute RR for each subject of the database. Additionally, a filter used in [10] was implemented to remove noise.

Taking into account that we are working with time-series data, Approximate Entropy (ApEn) is precisely a technique that measures their irregularity and complexity. That is why this stadistic tool was applied to each 5-minute RR subsegment of each subject according to the definition given by Steve Pincus [16], in which if the time-series data consists on N elements:

$$ApEn(m, r, N) = -\frac{1}{N-m} \sum_{i=1}^{N-m} \log\left(\frac{A_i}{B_i}\right) \quad (1)$$

where m is the embedding dimension, r is a threshold and A_i and B_i are the measures of proximity between embedding vectors in m and $m+1$ dimensions respectively. So ApEn compares embedding vector elements with others of the time series to measure the similarity between them.

After having tried values of m from 1 to 4, and r from 10% to 50% of the standard deviation, the parameters $m = 2$ and $r = 40\%$ of standard deviation were selected for the good discrimination they achieved between the three groups and each group with another.

Finally, some missing Approximate Entropy data (produced by noise filtering and the database itself) were interpolated using the fillgaps algorithm that uses autoregressive models [17] to predict the missing data. Therefore, each subject had 288 ApEn values.

2.3. Proposed NN architecture

The great capacity of artificial neural networks to carry out classification or prediction tasks is widely known. First of all, for the implementation of a neural network, all data was randomly divided as follows: 70% of 292 subjects made up the training set and the other 30% made up the test set. In addition, a validation set was considered to evaluate the ability of the model while adjusting the most optimal hyperparameters in the training phase. This was 20% of the training set during the network training.

A Densely Connected Neural Network was implemented in Pyhton, using Keras and Scikit-learn library, with a sequential model and dense layers. 288 values of ApEn were the input layer nodes, which were previously standardized in order to obtain an optimal performance. Three hidden layers were included with 15, 10 and 8 nodes respectively, and the output layer had 3 nodes (corresponding to each group).

To train the model, the activation function was sigmoid in all layers, except the output layer, which was softmax due to multiclass output. The Adam optimizer was used with a learning rate of 0.002 and the loss function was categorical cross entropy. Finally, a batch size of 10 was used, and 200 was the epoch limit. No cross validation was performed.

3. Results

With the proposed architecture it was possible to obtain some graphs that describe the evolution of the training. One of those is the loss function represented in Figure 1, it shows the error made by the network at the end of each epoch. It is observed that the validation curve are following the same behavior of the training curve. Both curves are getting closer to cero, without characteristics of overfitting thanks to the early stopping function implemented to stop the model training when the validation loss does not reach smaller values in 5 consecutive epochs.

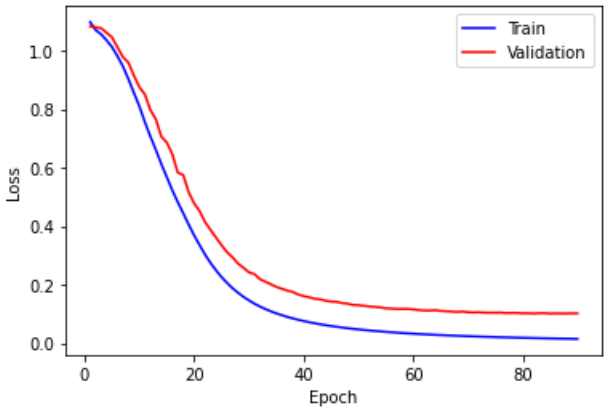

Figure 1. Evolution of the Loss function through the epochs

The ratio of correctly classified subjects to the total number of them in each epoch is represented in Figure 2, which shows the evolution of the accuracy through the epochs. It can be seen that both curves (training and validation) follow the same tendency to increase their value (closer and closer to 1) as the number of epochs increases, and in the same way as the previous graph, it does not show signs of overfitting, so its evolution is satisfactory.

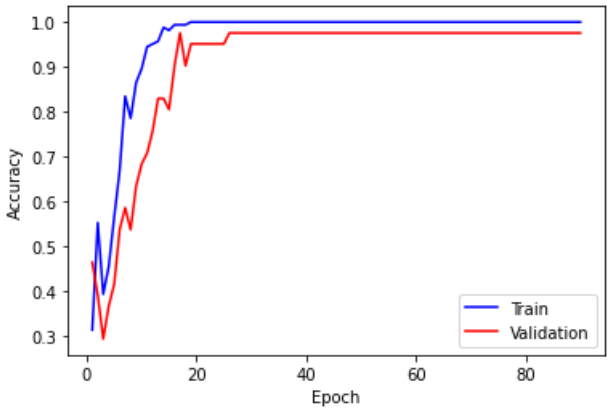

Figure 2. Evolution of the Accuracy through the epochs

In order to visualize the performance of the model, Figure 3 shows the confusion matrix. This matrix is an object that shows what types of successes and errors our trained model has had, through relevant information obtained with the test set, like the total number of true positive, true negative, false positive and false negative classifications. From this table we can obtain the best known performance evaluation metrics of a neural network, such as precision, recall and the F1-score for each class, as well as the accuracy, macro average and weighted average of the total classification. Therefore, with these evaluation metrics, the classification results of our model were as follows: for the Control group we got a precision of 96%, a recall of 96% and a F1-score of 96%. For the CH1 group the precision was 97%, the recall was 100% and the F1-score was 98%. And for the CH2 group the results were 100% for precision, 97% for recall and 98% for F1-score. On the other hand, the overall precision of the model was calculated using the number of subjects in each group as a weight for each class and it was about 98%.

In order to clarify and observe the success rate, the receiver operating characteristic curve (ROC curve) was plotted with the true positives rate (sensitivity) on the y-axis and the false positives rate (1 - specificity) on the x-axis. Since a ROC curve is normally used in binary classification, in order to evaluate the output of our multiclass classifier, an extended version of the ROC curve had to be applied with the micro and macro averaging algorithm in

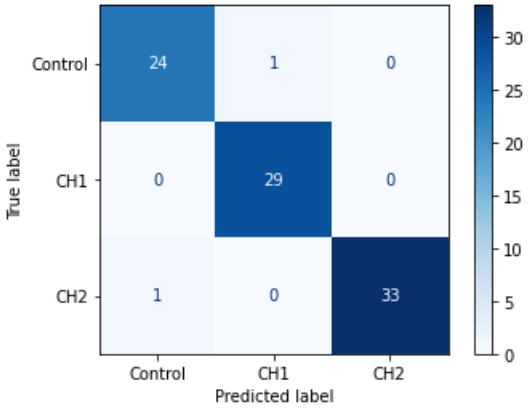

Figure 3. Confusion matrix

the scikit-learn library. Thus, Figure 4 shows the following ROC curves: one curve for each group (one-vs-all) and two general curves for the whole classification. Likewise, the area under the curve (AUC) values for each curve are also shown. It is known that while the AUC value is higher, the performance of the model is better at distinguishing between classes. As all the AUC values are approximately 1, we can say that the classification results were really remarkable.

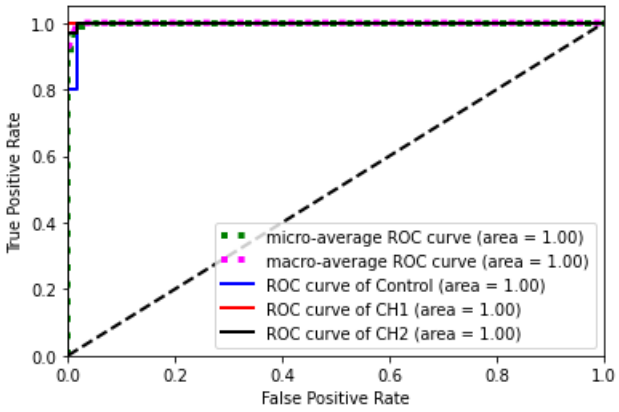

Figure 4. ROC curve

4. Discussion and conclusions

Considering the differences in the circadian profiles obtained with the use of ApEn between the three groups of the database used of patients with Chagas disease, it was possible to implement a densely connected neural network to classify them.

Although the number of subjects was limited (292) and no data augmentation algorithm was used, the results obtained in this work for the model evaluation were remarkable.

From the training graphs, which did not present overtraining characteristics, a satisfactory evolution in network learning could be evidenced. Thus, an excellent performance of the model was obtained, corroborated by the best-known evaluation metrics. All precision values were greater than 95% in all groups, with 98% of accuracy and 98% of overall precision in classification. ROC curves also validated this excellent performance, since in all cases the AUC values are 1.

Due to the need for early identification of patients with Chagas disease who do not yet have symptoms (CH1 group) but who could potentially be part of the CH2 group, we can consider the proposed network, as an effective detection tool for early non-invasive diagnosis of this disease. Other works have considered the application of neural networks based on clinical and sociodemographic data for the prediction of Chagas disease [13], but in particular, the focus of the present work, which is based only on the analysis of heart rate variability with ApEn, achieves higher diagnostic accuracy.

Finally, despite the excellent results obtained, since it is a neural network, it could be possible to increase its robustness by considering a larger number of patients by being exposed to a more precise representative sample and, of course, updated.

Acknowledgements

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