Differential Diagnosis of Hemorrhagic Fevers Using ARTMAP

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Abstract. The differential diagnosis of endemic hemorrhagic fevers in tropical countries is by no means an easy task for medical practitioners. Several diseases often overlap with others in terms of signs and symptoms, thus making this diagnosis a difficult, error-prone process. Machine Learning algorithms possess some useful qualities to tackle this kind of pattern recognition problems. In this paper, a neural-network-based approach to the differential diagnosis of Dengue Fever, Leptospirosis and Malaria, using the Adaptive Resonance Theory Map (ARTMAP) family is discussed. The use of an Artificial Immune System (CLONALG) led to the identification of a subset of symptoms that enhanced the performance of the classifiers considered. Training, validation and testing phases were conducted using a dataset consisting of medical charts from patients treated in the last 10 years at Napoleón Franco Pareja Children Hospital in Cartagena, Colombia. Results obtained on the test set are promising, and support the feasibility of this approach.

Keywords: machine learning, neural networks, ARTMAP, hemorrhagic fever, dengue, leptospirosis, malaria, differential diagnosis.

1 Introduction

Dengue, Leptospirosis and Malaria are diseases belonging to a group known as Hemorrhagic Fevers [16,23]. The initial manifestations of such diseases may be consistent with indeterminate febrile illnesses, and because of that they can be easily confused with other conditions or even between them [22]. Despite similar symptoms, etiologies and treatment are very different for each one of these diseases, and that makes it especially important to achieve high performance, clearly defined diagnostic mechanisms, since early diagnosis improves patients prognosis. In order to perform diagnosis, medical practitioners rely on semiological attributes discussed in the relevant literature, but the highly variable characteristics of this diseases imply high variability in terms of signs and symptoms present in patients; making it very hard to come up with a plausible

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diagnostic hypothesis. Besides, laboratory tests available to confirm potential diagnoses have variable confidence and sometimes it takes too long for results to be available. All these issues play against an accurate and opportune diagnosis, and lead often to the wrong ones. Several studies [1,13,18,19] point out situations where an epidemic outbreak of one disease masks out a significant portion of cases from some other disease. On the other hand in tropical countries like Colombia, Dengue, Leptospirosis and Malaria are diseases with mandatory notification to disease control public entities, since they are considered public health risks, making it even more pressing to find ways to obtain accurate early diagnoses. Machine learning techniques have historically offered important resources in the form of Computer Aided Diagnosis software, by considering diagnosis as a pattern recognition problem. The idea behind this kind of applications is not to replace medical personnel but to provide additional tools for decision making, and contributing to enhanced patient care.

Among machine learning techniques, a particular family of neural networks based on the Adaptive Resonance Theory (ART) have been used with positive results, reported in the specialized literature [12,14,20]. In this paper, we state the use of an Adaptive Resonance Theory Neural Network (ARTMAP) to perform differential diagnosis of Dengue, Leptospirosis and Malaria, with a subset of inputs identified by means of an Artificial Immune System based on Clonal Selection Theory (Clonalg).

2 Dengue, Leptospirosis and Malaria

Dengue, Leptospirosis and Malaria are febrile diseases which are endemic in tropical countries, and in Colombia they are subject to mandatory notification to government health institutions, and considered public health risks, because of their contagion dynamics and the possible mortal consequences of their most severe forms. An important characteristic of these three diseases (and other hemorrhagic fevers) is that in their mild forms they can be practically indistinguishable (in terms of clinical signs) from common cold, or even between themselves. Hemorrhagic manifestations can be present in severe forms, contributing to death of the patient. Despite all similarities regarding symptoms and clinical signs, these diseases are very different in terms of etiology, transmission vectors and infection mechanisms; all of this implies different treatments. It is worth noting that an early and correct treatment improves patient prognosis.

2.1 Dengue Fever

Dengue fever is a syndrome caused by several viruses transmitted by arthopodes (aedes aegypti mosquito mainly), characterized by biphasic fever, myalgia and/or arthralgia, leucopenia and lymphadenopathy. Severe dengue with hemorrhagic manifestations is an often fatal complication that can lead to Dengue Shock Syndrome (DSS), characterized by abnormalities in hemostasis and capillary permeability [15]. There is a general consensus regarding existence of four antigenically

distinct members into into the Dengue subgroup, inside Flavivirus genus. Dengue fever is an illness characterized by high fever, absence of chills, frontal headache, myalgia, arthralgia, retro-ocular pain, exanthema (petequial, specially), "white islands in a sea of red" sign, facial erythema (blush), leukopenia with lymphocytosis, thrombocytopenia, among others symptoms [23], with severity varying according to patient age.

2.2 Leptospirosis

Leptospirosis is a zoonosis present worldwide, caused by spirochaete of the genus Leptospira. Leptospira infect a variety of wild and domestic animals that excrete the microorganism in their urine. Humans, which get infected by contact with sick animals or through exposition to water contaminated with urine of infected animals, develop an acute febrile illness which can be followed by a more severe and sometimes fatal condition (Weils disease), that may include jaundice, renal failure, meningitis, myocarditis, hemorrhagic pneumonia and hemodynamic collapse. Until discovery of the agent causing Leptospirosis, it was diagnosed erroneously as Yellow Fever or Malaria [22]. Even today confusion persists between Leptospirosis and other febrile illnesses as Dengue, Hepatitis, Malaria and Influenza, to mention a few.

2.3 Malaria

Malaria is a disease caused by any of the following microorganisms: Plasmodium Falciparum, Plasmodium Vivax, Plasmodium Ovale and Plasmodium Malariae. From those, in Colombia only P. Falciparum and P. Vivax are found. Cyclic fever is the hallmark of malaria, and occurs shortly after or during rupture of red cells and the release of merozoites into the bloodstream. In the case of infection by P. Ovale or P. Vivax, this release cycle occurs every fourty-eight hours, producing the malignant tertians (fever each third day); and in the case of infection by P. Malarie each 72 hours, giving rise to the malignant quartans (fever each fourth day). P. Falciparum tends to produce continuous fever with intermittent peaks, instead of the well-defined cycles of P. Vivax and P. Ovale. Malaric crisis has some very well defined characteristics, to the extent that it is a definitive clinical manifestation of the disease. After a prodrome of variable duration, malaric crisis has three stages: Chills that can last from fifteen minutes to several hours, high fever for several hours and coinciding with the release of merozoites to the blood stream; and finally sweating, fatigue and defervescence.

2.4 Differential Diagnosis of Dengue, Leptospirosis and Malaria

Diseases considered in this work share a series of symptoms and signs that can make diagnosis difficult. However, according to a systematic revision of the relevant literature [10,19,21], and expert opinions from staff in Napoleón Franco Pareja Children Hospital - Casa del Niño, a preliminary symptoms and signs list

for the differential diagnosis between the three diseases was constructed. The list was used to construct a dataset for the training, validation and testing of the proposed classifiers. Table 1 describes the structure of the list and shows the included symptoms and signs and the disease for which they are predictors.

Table 1. Signs and symptoms for the differential diagnosis and the importance relative to each disease

Sign/Symptom	Dengue	Leptospirosis	Malaria
Age	x	x	x
Fever type (continuous or cyclic)	x	x	x
Positive tourniquet sign	x		
Anorexia	x		
Chills		x	x
Headache type (frontal or global)	x	x	
Retro-ocular pain	x		
Arthralgia	x		
Myalgia	x	x	
Exanthema localization	x	x	
White islands in a sea of red	x		
Itch	x		
Facial erythema (blush)	x		
Hyponatremia		x	
Opportunistic infections			x
Elevated CPK		x	
Renal compromise		x	x
Jaundice		x	
Pharyngitis		x	
History of contact with dogs or rodents		x	
Contact with rainwater/stagnant water		x	
Calf pain		x	
Hemoglobin level			x
Leukocyte count	x	x	
Lymphocyte count	x	x	
Neutrophil count	x	x	
Month of medical consult	x	x	x
Days of fever	x	x	x
Hematocrit level	x		x

3 Adaptive Resonance Theory (ART) and ARTMAP Neural Networks

3.1 Adaptive Resonance Theory - ART

Adaptive Resonance Theory (ART) was initially proposed by Grossberg as an attempt to resolve the stability-plasticity dilemma [4]. With neural networks as

the Multilayer Perceptron, there is the risk of forgetting already memorized patterns when learning new ones, and the solution proposed by Grossberg included a similarity measure designed to avoid this catastrophic forgetting of patterns. ART networks are a special type of competitive network, where neuron activation depends on the similarity between the pattern stored in its weights and the input being considered, similarly to a Kohonen Self-Organizing Map [17]. ART spans a family of neural networks that includes ART1 [4] (binary values), ART2 [5], ART3 [6] and Fuzzy ART [8] among others, which use unsupervised learning; and FuzzyARTMAP [7], ARTMAP-IC [9] and Default ARTMAP [3] among others, which use supervised learning. ART is inspired in the mechanisms of the mammal visual system, and specifically in the way the brain interprets signals coming from the retina.

3.2 ART1

An ART1 network is composed by two layers of neurons. The first layer represents the network Short Term Memory (STM), and the second represents the network Long Term Memory (LTM). When a pattern is presented to the network, it is stored in the STM, and then each neuron in LTM receives a copy of the pattern stored in STM and a competition takes place between the neurons, which results in only one neuron with non-zero activation. This kind of competition is called a Winner-Take-All (WTA) competition, and it is inspired in the activation of certain zones of the cerebral cortex in response to certain stimulus. The connection between STM and LTM layers is filtered by the Bottom-Up weight matrix and the Top-Down weight matrix, which communicate, respectively STM layer with LTM layer (Bottom-Up) and in the opposite way, closing a circuit (Top-Down).

Learning in ART1. ART1 (and in general all models in the ART family) can operate under two modes of learning: Slow learning and fast learning. In slow learning mode (Grossberg models original mode of learning), convergence of weights requires several presentations for each pattern, since in each iteration just a fraction of the pattern is actually learnt (the learning rate β is less than 1); whereas in fast learning mode it is assumed that the pattern is presented during a sufficient time to guarantee convergence in only one iteration (learning rate is equal to one). In practice fast learning is often preferred, since it allows learning in few iterations, with the possible disadvantage of getting different internal memories depending of the order of presentation of the inputs. In any case, ART1 learning mechanisms guarantee that the learning weights will converge after a finite number of iterations.

3.3 ARTMAP

ARTMAP is a neural model that consists of an ART network and an associative memory (map) for supervised training applications. The internal ART network

attempts to predict the class where the input vector belongs, and if the prediction is not correct, the vigilance parameter is raised (its value increases to the minimum needed to cause the inhibition of the selected neuron plus a small value ϵ) according to an algorithm called Match-Tracking (MT) and the input pattern is presented again forcing the network to make a correct prediction. This process is repeated until the ART network selects a memory/neuron that predicts correctly the input vector class or (if every neuron in LTM is inhibited) until the creation of a new category in LTM, adding a new neuron that will code the new pattern; and at this point, vigilance returns to its original value. For a detailed description, the interested reader can consult [7].

4 Training, Validation and Testing of the ARTMAP Classifiers

4.1 Dataset Construction

In order to construct a dataset for training, validation and testing, medical charts from the last ten years were collected at Napoleón Franco Pareja Children Hospital in Cartagena, Colombia. The medical chart was selected for inclusion if there were laboratory confirmed diagnosis of dengue, Leptospirosis or Malaria or a very strong confirmatory opinion from senior medical staff.The resulting dataset is comprised by medical charts of 136 patients, and it was divided in three parts, one for training, one for model selection (validation) and one for testing. Stratified random sampling with proportional assignment was used to populate the sets. The final distribution is shown in table 2.

Table 2. Data distribution between training, validation and test sets

Set	Dengue	Leptospirosis	Malaria	Total
Training	51	11	8	70
Validation	24	5	4	33
Test	23	5	5	33

4.2 Training

After partition, the classifiers were trained using the training set. The training mode chosen for the networks was fast learning, which guarantees perfect learning (zero percent error) in few iterations. To reduce the possibility of overfitting the training set, only one training iteration was performed (early stopping).

4.3 Validation

The validation process was centered in finding a subset of symptoms and signs that maximized the performance of the classifiers (feature selection). The idea

Table 3. Parameter values used in each network

Neural network	alpha	initial epsilon	MT	Q	CAM Power
FuzzyARTMAP	0,1	0	-0,01	N/A	N/A
ARTMAP-IC	0,1	0	-0,001	9	N/A
DefaultARTMAP2	0,1	0	-0,001	N/A	4

was to reduce model complexity in order to minimize computational times and improve the generalization bounds. This problem was formulated as an combinatorial optimization problem, and an artificial immune system (CLONALG) was used. Clonalg [11] is an optimization algorithm based on the Clonal Selection Theory [2].

During validation (operating with the whole set of predictors) the parameter values maximizing model performance on the validation set were identified (table 3). Model performance on the validation set is shown in table 4.

Table 4. Results (Recall) on the validation set using all predictors

Neural network	Dengue	Leptospirosis	Malaria
FuzzyARTMAP	91,67% (22/24)	80% (4/5)	50% (2/4)
ARTMAP-IC	87,5% (21/24)	100% (5/5)	50% (2/4)
DefaultARTMAP2	87,5% (21/24)	100% (5/5)	50% (2/4)

Feature Selection. Optimization algorithms seek to minimize (or maximize) an objective function. Solutions can be restricted to certain feasible region (constrained optimization) or not, according to the problem. In this work, the objective function is the classifier performance, and the search space is given by all possible subsets of symptoms and signs that can be used as input; and no restrictions were considered. Every B-cell (immune agent) used a binary encoding, where one represented the presence of a particular sign/symptom, and zero its absence. Measures used to assess performance are a fundamental issue here, and in this case precision, recall and F1-score were chosen as performance measures, since the dataset classes are skewed in favor of Dengue. The formula used to calculate F1-Score is shown in equation 3. It is worth noting that the F1-Score is used in binary classification problems, and since the problem stated in this work is not binary (multi-class classification), the macro-averaging [24] technique to handle multiclass problems was used.

$$precision = \frac{truepositives}{truepositives + falsepositives} \tag{1}$$

$$recall = \frac{truepositives}{truepositives + falsenegatives} \tag{2}$$

$$F1 = 2 * \frac{precision * recall}{precision + recall} \tag{3}$$

After execution of the artificial immune system (10 iterations, 30 B-cells, 300 clones per B-cell) using each neural network, several subsets of symptoms and signs that maximized the performance of each classifiers were obtained (100% F1 score). A specific subset of nineteen symptoms and signs was particularly good, since it maximized the performance of the three classifiers used (Fuzzy, IC and DefaultARTMAP).

4.4 Final Tests

Once validation determined the parameter values and the subset of symptoms and signs that maximized the classifiers performance, final tests were conducted using the test set. Results are shown in table 5.

Table 5. Test set results (recall per class and Macro F1-Score) using symptoms and signs determined by validation

Neural Network	Dengue	Leptospirosis	Malaria	Macro F1-Score
FuzzyARTMAP	91,30% (21/23)	80% (4/5)	40% (2/5)	0,725
ARTMAP-IC	91,30% (21/23)	60% (3/5)	80% (4/5)	0,768
DefaultARTMAP2	91,30% (21/23)	60% (3/5)	60% (3/5)	0,736

4.5 Analysis of the Results Obtained

Test set results obtained by the networks show ARTMAP-IC with a slight advantage in terms of F1-score and accuracy. In general, performance of the three classifiers appears to be very good discriminating Dengue cases from the rest (91,30% of correct diagnoses), which can be explained by the higher amount of Dengue data available for training. On the other hand, models present greater performance variability for class Leptospirosis (60% - 80% of correct diagnoses), and this phenomena is even more pronounced for class Malaria (40% - 80% of correct diagnoses); this variability can be explained also by the limited amount of training cases available for these two clases.

It is interesting to note that distributed prediction models (ARTMAP-IC and Default ARTMAP) offer better results, outperforming FuzzyARTMAP. This is consistent with results available in the relevant literature. Each trained classifier generated 13 categories in layer LTM, which corresponds to a compression factor of 81%, which suggests that results obtained in the test set are not due to overfitting, and offer a reliable estimator for the generalization performance of the classifiers.

5 Conclusions

Dengue, Leptospirosis and Malaria are zoonosis that prevail in tropical countries, even having very different etiological nature, they share several symptoms

and clinical signs at different stages, and that makes the differential diagnose a complicated one. This paper stated an ARTMAP based approach to the diferential diagnosis of these three diseases, and the use of an Artificial Immune System for the identification of a set of symptoms and signs that maximized the performance of the classifiers. Test set results obtained show that an ARTMAP-IC classifier is able to perform differential diagnosis with confidence enough to be used by medical staff as a computational aid.

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