Diagnosis of atherosclerosis from carotid artery Doppler signals as a real-world medical application of artificial immune systems

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Abstract

In this study, we have employed the maximum envelope of the carotid artery Doppler sonograms derived from Fast Fourier Transformation-Welch Method and artificial immune systems in order to distinguish between atherosclerosis and healthy subjects. In this classification problem, the used artificial immune system has reached to 99.33% classification accuracy using 10-fold Cross Validation (CV) method with only two system units which reduced classification time considerably. This success shows that whereas artificial immune systems is a new research area, one can utilize from this new field to reach high performance for his problem.

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1. Introduction

Atherosclerosis is the buildup of fatty deposits called plaque on the inside walls of arteries. Plaques can grow large enough to significantly reduce the blood’s flow through an artery. As an artery becomes more and more narrowed, less blood can flow through. The artery may also become less elastic (called “hardening of the arteries”). Atherosclerosis is the main cause of a group of cardiovascular diseases (Hirai, Sasayama, Kawasaki, & Yagi, 1989).

Atherosclerosis is usually diagnosed after symptoms or complications have arisen. There are a number of tests in diagnosing vascular diseases, including blood tests, electrocardiogram, stress testing, angiography, ultrasound, and computed tomography. Angiography is used to look inside arteries to see if there is any blockage and how much (Dart et al., 1991; Stefanadis, Stratos, Boudoulas, Kourouklis, & Toutouzas, 1990). This is the most accurate way to assess the presence and severity of vascular disease. On the other hand this technique involves injecting dye directly into the arteries. Therefore this is a much more invasive.

Since angiography is invasive and has a relatively high cost, noninvasive ultrasonic Doppler sonography is generally recommended. Recent advances in Doppler imaging technique have made the evaluation of the temporal and spatial flow characteristics in the different portions of the arterial system, such as aorta, coronary, carotid and peripheral arteries possible. Doppler signal analysis may lead to mean many things, including spectral analysis. The analysis of Doppler signals provides information about physiology and pathology, through applications of flow measurement and the detection of significant changes in “Doppler waveform” shape (Evans, 2000).

It is often useful to analyze the spectrum of the Doppler-shifted signal to assess the degree of a disease. The use of spectrum analysis to display Doppler frequency shifts provides not only the best means of measuring blood flow velocity but also information about the presence of disturbed flow (Saini, Nanda, & Maulik, 1993; Sigel, 1998). The Doppler sonograms describe how the power of a time...
series is distributed with frequency and in this way spectral analysis of the Doppler signal produces information concerning the velocity distribution in the artery (Evans, McDicken, Skidmore, & Woodcock, 1989; Muller, Cicotti, Reiche, & Hagen, 2001). In a sonogram, the horizontal axis (t) represents time, the vertical axis (f) frequency and the gray level represents the power level of the corresponding frequency at each point of time. As the color tone of the sonogram turns darker, the power level is increased and as it becomes lighter, the power level diminishes.

Several authors have reported good results in last decades using the diagnostic performance of ultrasound complex analysis of the carotid artery waveform (Currie, Wilson, Baird, & Lamont, 1995; Van Asten, Beijneveld, & Pieters, 1991). However, none of these methods have gained wide-spread use, mainly because of their complexity and need for additional equipment. Still, subjective visual examination of the carotid artery waveform profile has a potential for inter- and intra-observer variability. To overcome this, several methods of numerical analysis have been explored. Of these, the most straightforward are the waveform profile indices, such as the pulsatility index (PI) (Gosling & King, 1974) and the Pourcelot or resistance index (RI) from sonogram (Planiol & Pourcelot, 1973). More sophisticated methods have also been developed, such as the Laplace transform (Baird et al., 1980) and principal components analysis (PCA) (Macpherson, Evans, & Bell, 1984). But, neither the simple nor the more complex analytical techniques have yielded an acceptable diagnostic accuracy to make them common place in the vascular clinic.

The use of classifier systems in medical diagnosis is increasing gradually. There is no doubt that evaluation of data taken from patient and decisions of experts are the most important factors in diagnosis. But, expert systems and different artificial intelligence techniques for classification also help experts in a great deal.

Artificial immune systems (AISs) is a new artificial intelligence (AI) technique which is beginning to mature through the collaborative effort of many interdisciplinary researchers (Andrews & Timmis, 2005). By modelling some metaphors existing in natural immune system or by inspiring from these metaphors, successful applications have being conducted in AI literature. Classification is among these and there have been some promising studies in this branch of AISs. Considering medical diagnosis as an application domain for AISs, there are several studies like (Castro, Coelho, Caetano, & Von Zuben, 2005; Hamaker & Boggess, 2004; Polat, Sahan, Kodaz, & Gunes, 2005a; Polat, Sahan, & Gunes, 2006; Sahin, Polat, Kodaz, & Gunes, 2005) in AIS literature. But almost all of these studies use the datasets from UCI (University of California at Irvine) database (Blake & Merz, 1996) when conducting the classification process. While these datasets reflect real-world medical problems, they are recorded and processed datasets which are ready to use directly in a classification system and so they are mainly used for comparison of a proposed system with other studies in literature. This study therefore is the first attempt to apply an artificial immune system to a real-world medical classification problem which includes all of the stages ranging from recording data from subjects to the final classification of data.

In this study, a diagnostic system leading to more effective usage of the Doppler technique is presented. Our primary research motivation was to advance the research of atherosclerosis. We have employed the maximum envelope of the carotid artery Doppler sonograms derived Fast Fourier Transformation (FFT) based Welch Method and AISs in order to distinguish between atherosclerosis and healthy subjects.

2. Materials and method

2.1. Hardware and demographic acknowledgments

Carotid arterial Doppler ultrasound signals were acquired from 60 patients and 54 healthy volunteers. The patient group included 33 males and 21 females with an established diagnosis of atherosclerosis through coronary or aortofemoropopliteal (lower extremity) angiography (mean age: 45 years; range: 25–69 years). Healthy volunteers including 35 males and 14 females (mean age: 26 years; range: 20–39 years) were young non-smokers who appeared not to bear any risk of atherosclerosis. The two study groups represent the upper and lower extremes of the arterial compliance. We have utilized Toshiba Power-Vision 6000 Doppler Ultrasound Unit in the Radiology Department for data acquisition.

A linear ultrasound probe of 10 MHz was used to transmit pulsed ultrasound signals to the proximal left common carotid artery. In all tests performed on the patients and healthy subjects, the insonation angle and the presettings of the ultrasound were kept constant.

In order to obtain the Doppler responses at the carotid arteries, we used the audio output port on the ultrasound device. The audio signals from output of ultrasound unit was sampled at 44,100 Hz and then sent to a personal computer (PC) through an input/output card (Kara, 1995). The extracted data was digitized through Analog to Digital converter and transferred to a PC through input/output card. The audio output data delivered to PC.

2.2. Spectral analysis of carotid artery Doppler signals

Welch method of power spectrum estimation was applied on the Doppler data. Blood flow can only be considered statistically stationary for typically 10–20 ms. Therefore acquired Doppler data was grouped in frames of 512 data points and the method was applied on these frames. Welch’s method is one among the classical methods of spectrum estimation based on FFT.

2.2.1. Welch method of spectral analysis

FFT based Welch method is defined as classical (non-parametric) method. It is made the second modification
of periodogram spectral estimator, which is to window data segments prior to computing the periodogram (Evans, 2000; Saini et al., 1993; Sigel, 1998; Muller et al., 2001; Evans et al., 1989; Vaitkus, Cobbold, & Johnston, 1988). If available information on the signal consists of the samples \( \{x(n)\}_{n=1}^{N} \), the periodogram spectral estimator is given by:

\[
\hat{P}_{\text{PER}}(f) = \frac{1}{N} \left| \sum_{n=1}^{N} x(n) \exp(-j2\pi fn) \right|^2
\]  

(1)

where \( \hat{P}_{\text{PER}}(f) \) is the estimation of periodogram. In the Welch method, signals are divided into overlapping segments, each data segment is windowed, periodograms are calculated and then average of periodograms is found. \( \{x(n)\}, l = 1, \ldots, S \) are data segments and each segment’s length equals \( M \). Note that, the overlap is often chosen to be 50\%. The Welch spectrum estimate is given by:

\[
\hat{P}_{\text{w}}(f) = \frac{1}{S} \sum_{l=1}^{S} \hat{P}_{l}(f) \quad \text{and}
\]

\[
\hat{P}_{l}(f) = \frac{1}{M} \left| \sum_{n=1}^{M} v(n)x_{l}(n) \exp(-j2\pi fn) \right|^2
\]  

(2)

where \( \hat{P}_{l}(f) \) is the periodogram estimate of \( l^{\text{TH}} \) segment, \( v(n) \) is the data-window, \( P \) is total average of \( v(n) \) and given as \( P = 1/M \sum_{n=1}^{M} |v(n)|^2 \), \( \hat{P}_{w}(f) \) is the Welch PSD estimate, \( M \) is the length of each signal segment and \( S \) is the number of segments.

Then, evaluation of \( \hat{P}_{w}(f) \) at the frequency samples basically requires the computation of the following discrete Fourier transform (DFT):

\[
X(k) = \sum_{n=1}^{N} x(n) \exp \left( -j\frac{2\pi nk}{N} \right), \quad k = 0, \ldots, N - 1
\]  

(3)

where \( X(k) \) is expressed as the discrete Fourier coefficient, \( N \) is the length of available data and \( x(n) \) is the input signal on the time domain. The procedure that computes Eq. (3) is called as FFT algorithm. The Welch PSD can be efficiently computed by the FFT algorithm. Variance of an estimator is one of the measures often used to characterize its performance. For 50\% overlap and triangular window, variance for the Welch method is given by:

\[
\text{var}(\hat{P}_{w}(f)) = \frac{9}{8S} \text{var}(\hat{P}_{l}(f))
\]  

(4)

where \( \hat{P}_{w}(f) \) is the Welch PSD estimate and \( \hat{P}_{l}(f) \) is the periodogram estimate of each signal interval (Evans, 2000; Ubeysi & Güler, 2003; Vaitkus et al., 1988).

A sonogram is plotted with the frequency components and power spectral density values sequenced on the timeline. Time is on the x-axis, while frequency is on the y-axis and gray value of the display represents the corresponding power spectral density. Darker color tones in the sonogram indicate increased levels of power density and vice versa (Fig. 1a and b).

2.3. Extraction and processing of the maximum frequency envelope

The maximum-frequency envelope of the sonogram is plotted. Then, smoothing and curve-fitting operation is performed on the two dimensional graph (Fig. 2a and b) (Kara, 1995).

The data was smoothed by two-point and interpolant-cubic spline interpolation method in order to get curve-fitting.

Moving average acts like a low pass filter so that the discrete data is averaged out over a certain number of data points in the neighbourhood

\[
y_s(i) = \frac{1}{2N+1} \left( y(i+N) + y(i+N-1) + \cdots + y(i-N) \right)
\]  

(5)

In Eq. (5), \( y_s(i) \) stands for the averaged result of raw data \( y(i) \) and \( N \) is the number of data points, where averaging operation will extend to both before and after the data point in question. For our case, \( N \) was chosen as Matlab’s ‘smooth’ command with moving average method is used for averaging purposes.
Cubic spline: This method briefly interpolates two sequential data points with a cubic polynomial function, shown below in Eq. (6). For every trace between data pairs, the four parameters $a_i$, $b_i$, $c_i$ and $d_i$ are calculated. The Matlab command employed for this process is ‘fit’ with the spline library model

$$f_i(x) = a_ix^3 + b_ix^2 + c_ix + d_i,$$

$$i = 1, 2, \ldots, n \ (n: \text{number of data points}) \quad (6)$$

### 2.4. Artificial immune systems

The natural immune system is a distributed novel-pattern detection and defence system with several functional components positioned in strategic locations throughout the body. The immune system possesses the capability of extracting information from the infectious agents and making it available for future use in cases of re-infection by the same or a similar agent. From a biological and computational perspective, the presence of adaptive and memory mechanisms in the immune system is of great importance (De Castro & Timmis, 2002). By noticing these kinds of useful properties of natural immune system, researchers begun to interested in immunology as an inspiration source to form a new AI field now known as AISs. Like other fields in AI, first studies in AISs were resulted from the mathematical modelling of some mechanisms present in immune system to understand this biological system more detailed. After the link between the properties of this models and computational problem solvers had been noticed, today’s computational problem solvers have begun to come into existence. After a decade in this field, there are now lots of studies in a broad range of application areas ranging from the clustering/classification, anomaly detection, computer security to robotics, control, optimization, etc.

The main architects of adaptive immune response are lymphocytes, which divide into two classes as T and B Lymphocytes (cells), each having its own function. Especially B cells have a great importance because of their secreted antibodies (Abs) that take very critical roles in adaptive immune response.

The simplified working procedure of our immune system is illustrated in Fig. 3 Specialized antigen presenting cells (APCs) called macrophages circulates through the body and if they encounter an Antigen, they ingest and fragment them into antigenic peptides (I). The pieces of these peptides are displayed on the cell surface by major histocompatibility complex (MHC) molecules existing in the digesting APC. The presented MHC–peptide combination on the cell surface is recognized by the T-cells causing them to be activated (II). Activated T cells secrete some chemicals as alert signals to other units in response to this recognition. B cells, one of the units that take these signals from
the T cells become activated with the recognition of Antigen by their Antibodies occurred in the same time (IV). When activated, B cells turn into plasma cells that secrete bound Antibodies on their surfaces (V). Secreted Antibodies bind the existing Antigens and neutralize them signaling other components of immune system to destruct the antigen-antibody complex (VI) (De Castro & Timmis, 2002). For detailed information about immune system refer to (Abbas & Lichtman, 2003).

In the studies conducted in the field of AIS, B cell modeling is the most encountered representation type. Different representation methods have been proposed in that modelling. Among these, shape-space representation is the most commonly used one (De Castro & Timmis, 2002). The shape-space model (S) aims at quantitatively describing the interactions among antigens (Ags), the foreign elements that enter the body like microbe etc., and antibodies (Ag–Ab). The set of features that characterize a molecule is called its generalized shape. The Ag–Ab representation (binary or real-valued) determines a distance measure to be used to calculate the degree of interaction between these molecules. Mathematically, the generalized shape of a molecule ($m$), either an antibody or an antigen, can be represented by a set of coordinates $m = (m_1, m_2, \ldots, m_L)$, which can be regarded as a point in an L-dimensional real-valued shape-space ($m \in \mathbb{R}^L$). In this work, we used real strings to represent the molecules. Antigens and antibodies were considered of same length $L$.

2.4.1. Attribute weighted artificial immune system (AWAIS)

Shape-space model, which was proposed by Perelson and Oster (1979), is used as a representation mechanism modeling the interactions between two cells in the immune system. In the systems that use a distance criterion as a similarity metric, some shape-space related problems may exist in case of irrelevant attributes. One attribute value in shape space can cause two data in the same class to be distant from each other and therefore to be recognized and classified by different system units. If that attribute is irrelevant for class discrimination process, the algorithm may result in erroneous classes. In the study of Sahan, Polat, Kodaz, and Gunes (2004), it was aimed to reach higher classification accuracy by assigning weights to important attributes in classification. This was done with some modifications to affinity measures of AISs and then a system named attribute weighted artificial immune system (AWAIS) has come into existence (Sahan et al., 2004).

AWAIS is a simple, supervised AIS which uses weighted distance criteria while calculating the distance between system units (antibody-Ab) and input data (antigen-Ag). The system can be shown basically as in Fig. 4.

The training phase of the system consists of a pre-processing step which is used for determining the weights of attributes and a simple learning algorithm, AWAIS. In the pre-processing step, each attribute’s standard deviation in one class is calculated and reciprocal of this value is taken as the weight of that attribute for related class. In this way a weight matrix is obtained containing weights of each attribute in each column for each class in each row. This weight matrix is then used in AWAIS while calculating Euclidean distances of Abs to the presented data (Ag) in the following way:

$$D = \sqrt{\sum_{k=1}^{L} w_{j,k} (\text{Ab}_{j,k} - \text{Ag}_{j,k})^2}. \quad (7)$$

Here $\text{Ab}_{j,k}$ and $\text{Ag}_{j,k}$ are the $k$th attribute of $\text{Ab}$ and $\text{Ag}$, respectively; $w_{j,k}$ is the weight of $k$th attribute that belongs to the class of $\text{Ab}_{i}$.

The training procedure of the learning algorithm conducts the following steps:

1. For each $\text{Ag}_i$ do: ($i: 1, \ldots, N$)
   1.1 Determine the class of $\text{Ag}_i$. Call memory Abs of that class and calculate the distances between $\text{Ag}_i$ and these memory Abs with Eq. (7).
   1.2 If the minimum distance among the calculated distances above is less than a threshold value named as suppression value (supp) then return to step 1.
   1.3 Form a memory Ab for $\text{Ag}_i$.

   At each iteration do:
   1.3.1 Make a random Ab population with $\text{Ab} = [\text{Ab}_{\text{mem}}; \text{Ab}_{\text{rand}}]$ and calculate the distances of these Abs to $\text{Ag}_i$.

![Fig. 4. AWAIS system used for classification.](image-url)
(1.3.2) Select $m$ nearest Abs to $Ag_i$: clone and mutate these Abs ($Ab_{mutate}$).

(1.3.3) Keep the $m$ nearest Abs in the $Ab_{mutate}$ population to $Ag_i$ as $Ab_{mem}$ temporary memory population.

(1.3.4) Define the nearest Ab to $Ag_i$, as $Ab_{cand}$, candidate memory Ab for $Ag_i$ and stop iterative process if the distance of $Ab_{cand}$ to $Ag_i$ is less that a threshold value named as stopping criterion (sc).

(1.3.5) Concatenate $Ab_{cand}$ as a new memory Ab to memory matrix of the class of $Ag_i$.

(1.4) Stop training.

The mutation mechanism in the algorithm which is used in many AIS algorithms and named as hypermutation is performed proportional to distance between two cells (Eq. (8)):

$$Ab'_{i,k} = Ab_{i,k} \pm D_{i,j}(Ab_{i,k})$$

Here $Ab'_{i,k}$ is the new value and $Ab_{i,k}$ is the old value of $k$th attribute of $j$th Ab. $D_{i,j}$ stands for the distance between $Ag_i$ and $Ab_j$.

The resulted memory Abs form training samples in the algorithm of $k$-nearest neighbor method. That is, test instances are classified by the nearest memory Abs formed in training phase (the nearest Abs are determined by the weighted Euclidean distance).

While conducting the classification procedure, 10-fold cross validation method was used. For test results to be more valuable, $k$-fold cross validation (10-fold for our case) is used among the researchers. It minimizes the bias associated with the random sampling of the training (Delen, Walker, & Kadam, 2005). The whole data was randomly divided to 10 mutually exclusive and approximately equal size subsets. Because the whole dataset contains 60 patient data and 54 healthy data, each fold was to consist of 11 samples. Among these 11 samples, 6 were taken from recordings from patients while the remaining 5 samples were of healthy persons. Also, the last fold consisted of 6 patient, 8 healthy data (14 in total). The classification algorithm trained and tested 10 times. In each case, one of the folds is taken as test data and the remaining folds are added to form training data. Thus 10 different test results exist for each training-test configuration. The average of these 10 results gives the test accuracy of the algorithm (Delen et al., 2005).

The performance of AWAIS was evaluated by the following measures:

2.4.2. Classification accuracy

$$\text{accuracy}(T) = \frac{\sum_{t_i \in T} \text{assess}(t_i)}{|T|}, \quad t_i \in T$$

$$\text{assess}(t) = \begin{cases} 
1 & \text{if classify}(t) \equiv t.c \\
0 & \text{otherwise}
\end{cases}$$

where $T$ is the set of data items to be classified (the test set), $t_i \in T$. $t.c$ is the class of the item $t$, and classify($t$) returns the classification of $t$.

2.4.3. Sensitivity and specificity

$$\text{sensitivity} = \frac{TP}{TP + FN} (\%)$$

$$\text{specificity} = \frac{TN}{FP + TN} (\%)$$

where TP, TN, FP and FN denotes true positives, true negatives, false positives and false negatives respectively.

True positive (TP): An input is detected as a patient with atherosclerosis diagnosed by the expert clinicians.

True negative (TN): An input is detected as normal that was labelled as a healthy by the expert clinicians.

False positive (FP): An input is detected as a patient that was labelled as a healthy by the expert clinicians.

False negative (FN): An input is detected as normal with atherosclerosis diagnosed by the expert clinicians.

3. Results and discussion

Doppler signals reflected from the carotid artery in the time domain have not extra information about existence of the diseases. Therefore these signals were analyzed in the frequency domain to reveal differences between healthy and patient with atherosclerosis.

To assess the spectral analysis, we have employed sonograms from the carotid artery Doppler shift signals as seen Fig. 1a and b. The fuzzy appearance of the sonograms makes physicians suspicious about the existence of diseases and may causes false diagnosis. Our technique gets around this problem using AWAIS to decide and assist the physician to make the final judgment in confidence. Welch method of preprocessing was used to extract the sonogram, after that we plotted the curve-fitted maximum envelope of the sonograms, in this way a sonogram for one period was represented 61 sample. Afterwards 61 points of the matrices were used as the network inputs of AWAIS in this study.

When conducting experiments with AWAIS, the supp parameter was adjusted so that the maximum classification accuracy was obtained. The lower this parameter, the higher number of memory Abs is. Because the number of memory Abs affects classification accuracy of the system, adjustment of this parameter is very important. In out problem with Doppler sonograms, the best number of Abs was 2. That is, the system reached the highest classification accuracy with only two memory units. When we tried to lower supp parameter and thus caused the higher number of memory Abs to be formed, we observed that the classification accuracy had decreased. This is in contrast with other applications of AWAIS in that generally
when the number of memory units is increased, classification accuracy also increases because more units contribute to the classification process. But in this application the case is a bit different. In previous applications of AWAIS the experimented problems was containing samples with few number of attributes such as 4, 5, 9, 13, etc. However, Doppler sonograms involves samples with 61 attributes and the distance between two units can change considerably no matter most of the values of attributes are similar. In such a case, the minimum number of memory units is desirable not to confuse the classification decision.

As stated in above section, 10-fold CV method was utilized for training and test sets formation. For each fold, the size of training set was about 103 samples which consist of 54 patient data and 49 normal data. The test set on the other hand was 11 samples involving 6 patient, 5 healthy samples except the last fold. The classification accuracies of 9-fold were all 100%. But in the last fold the classification accuracy was 93.33%. This is because one sample in the last fold was classified as normal by the system whereas the sample belongs to a person with atherosclerosis in reality. Thus this misclassification resulted in the average classification accuracy of the system to be 99.33%. Considering that in cross validation method all of the samples in the whole dataset once become a test sample, this classification accuracy is highly reliable for such a problem because only one sample was misclassified by the system.

4. Conclusion

The aim of this study was 2-fold. The first one was to develop a diagnostic system leading to more effective usage of the Doppler technique and so to advance the research of atherosclerosis. The second objective was to use AISs in a real world medical classification system and so to show the effectiveness of this Artificial Intelligence field in this problem domain.

To assess the spectral analysis, the Doppler sonograms of carotid artery were firstly obtained by Fast Fourier Transform (FFT) based Welch Method. With curve-fitted maximum envelope of the sonograms, a sonogram for one period was represented 61 attributes. These sonograms were then used as the input data of AWAIS with 61 attributes to be distinguished between atherosclerosis and healthy subjects. Ten fold CV method was utilized for training and test sets formation.

In the applications, only one sample in the last fold was misclassified by AWAIS. The average classification of the system was found to be 99.33% and only two system units were formed to conduct this achievement. With this result, we have attained our objectives in a great deal. This classification accuracy is highly reliable for such a problem because only one sample was misclassified by the system. Also, the complexity of the system is quite low with regards to the formed system units. Thus, the system is capable of conducting the classification process with a good performance to help the expert while deciding the healthy and patient subjects. Our second aim was also reached by showing that AWAIS gained a success with a real-world medical classification problem even for a high-dimensional shape-space.

Table 1

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