

Chapter 1

WAVELET ANALYSIS OF EVENT RELATED POTENTIALS FOR EARLY DIAGNOSIS OF ALZHEIMER'S DISEASE

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Abstract Alzheimer's disease, a neurological disorder claiming hundreds of thousands of lives every year, is the most common of all cortical dementias. Neurologists usually identify the disease from various symptoms; however, misdiagnosis is not uncommon. An autopsy is the only method for a definite diagnosis. Additional techniques to increase the accuracy of ante-mortem diagnoses are therefore necessary. In this study, evoked potentials of the electroencephalograms (EEGs) of a group of patients were analyzed, half of whom had been diagnosed with early Alzheimer's disease. The EEGs were analyzed and processed using multiresolution wavelet analysis techniques, and processed signals were then used to train a neural network to distinguish the signals that belonged to patients with Alzheimer's disease from those that belonged to patients without Alzheimer's disease. We discuss why wavelet analysis is particularly well suited for these kind of signals, along with results demonstrating the feasibility of the approach.

Keywords: Multiresolution wavelet analysis, Alzheimer's disease, electroencephalography, event related / evoked potentials.

1. Introduction

Event related potentials (ERPs), also known as evoked potentials, are segments of the electroencephalogram generated by the brain when an external stimulus is perceived by an individual, and he/she deliberately responds to that stimulus. These potentials have been used for several years in diagnosing dementia, a condition of deteriorated mentality. Dementia is a general term used to characterize a group of diseases which affect a person's ability to think, remember, and make judgments. Dementia is defined by the American Psychiatric Association as a syndrome that consists of a decline in cognitive and intellectual abilities occurring in awake and alert patients. The decline is sometimes severe enough to interfere significantly with work, routine social activities, or relationships with others [1].

Senile dementia of Alzheimer's type (SDAT), or simply, Alzheimer's disease, is the most common cortical dementia, the first symptoms of which usually appear in later stages of life. Today, it is estimated that there are over 4 million patients suffering from Alzheimer's disease, and typically over 100,000 Alzheimer's disease patients die every year in the United States alone [2, 3]. These statistics make the Alzheimer's disease the fourth leading cause of death among the elderly, behind heart disease, cancer and stroke.

Alzheimer's disease has devastating effects on its victims, as well as on those people who care for them. In the early stages of this disease, the victims start having difficulty in remembering recent events, as their memory skills start deteriorating. The deterioration becomes more severe in later stages, as these patients forget where they are, why they are doing what they are doing, how to get back home, etc. They then start forgetting prior events as well, as hallucinations, disorientation and confusion become part of their daily life. As the deterioration of their mental abilities continue, they lose major motor skills as well as the basic skills to eat, write, read, etc. [3]. The victims become more and more dependent on care givers, and eventually they become completely dependent and confined to bed.

The disease is characterized by the unusually large concentrations of plaques and neurofibrillary tangles in the brain. In addition to plaques and tangles, an unusual protein, called *the Alzheimer's disease associated protein (ADAP)*, appears in the memory related portions of the brain [2]. Patients with Alzheimer's disease are also known to lose a significant

number of neurons especially from the frontal and temporal lobes of their brains. A definitive diagnosis can therefore be made only through an autopsy procedure after the patient has died. To date, no antemortem technique is available to diagnose the Alzheimer's disease with 100% confidence.

Research efforts to find more robust, reliable and accurate ways of diagnosing, as well as for curing this disease have intensified over the last decade. In particular, researchers in the fields of signal and image processing, pattern recognition, and artificial intelligence have recently combined their efforts with those of neurophysiologists for this common goal. Many of the approaches recently developed employ some form of an automated pattern classification algorithm. The selection of the classification algorithm is very important and depends on the particular application. However, equally important is the set of features that are used with the classifier, since the success of any pattern classification algorithm is subject to the robustness and relevance of the features used.

Many features have been tried, with varying success, to distinguish patterns obtained from Alzheimer's disease patients from those obtained from normal controls. Such features include positron emission tomography images [4], cerebral blood flow measurements [5], infrared spectra of the brain tissue [6], neuropathological test results of the patients [7], magnetic resonance images of the brain [8], event related / evoked potentials [9, 10, 11], and EEG signals themselves [12]. Among these, event related potentials are particularly interesting because numerous studies have established a strong relationship between patterns of the event related potentials and mental ability [13, 14, 15]. Neurologists have used these patterns, as well as various physiological and emotional symptoms to determine whether the patient has Alzheimer's disease; however, the pattern that distinguishes the disease is not always obvious from visual pattern recognition. These potentials therefore need to be analyzed in such a way that a subset of features that are more robust and more descriptive of the underlying physiological phenomenon can be obtained.

Time-frequency representations, in particular multiresolution wavelet analysis, provide such a tool to obtain a better set of features as described in the following sections of this paper. The goal of this study was therefore to investigate the feasibility of a pattern recognition based approach using the time-frequency representations of event related potentials for early diagnosis of Alzheimer's disease.

Frequency domain analysis using Fourier transform has been a popular tool for analyzing EEG signals, since the spectral components of the ERPs may, and usually do, contain valuable information. In fact, neurophysiologists typically look for existence or lack of certain patterns

at specific frequencies in the 0 ~ 100 Hz range when analyzing EEGs. These patterns, such as so-called alpha waves at 8 ~ 13 Hz, beta waves at 14 ~ 30 Hz, theta waves at 4 ~ 7 Hz and delta waves at frequencies below 3.5 Hz have all been linked to various specific neurophysiological activities. However, Fourier analysis provides only limited information by identifying which spectral components reside in the signal. As discussed later in this paper, time localizations of the spectral components also carry important information, which can only be extracted using a time-frequency representation based technique, such as the short time Fourier transform, continuous wavelet transform or discrete wavelet transform. This paper describes the application of the discrete wavelet transform (DWT), to the Alzheimer's disease diagnosis problem.

The relationship between the ERPs and Alzheimer's disease is first discussed, along with the experimental procedure used to obtain the relevant signals. Reasons for using a time-frequency representation (TFRs) based scheme is then described, along with a brief overview the DWT. A brief overview is also provided for the multilayer perceptron type neural network classifier used in this study, followed by results and discussion of results.

2. Experimental Method

2.1. Background

The effect of dementia on the EEG was first studied by Goodin *et al.* [13, 14] in 1978. Goodin and his colleagues demonstrated that dementias have a distinct effect on the so-called P300 component of the event related potential (ERP). The P300 component of event related potentials is a positive peak occurring at a latency of approximately 300 ms following the stimulus. This component is generated when an individual is asked to respond to a specific stimulus from a series of stimuli, where the target stimulus appears rather infrequently compared to other stimuli. A procedure called *the oddball paradigm* is commonly used to obtain the event related potentials and consequently record the P300 component (typically abbreviated as the P3 component).

In the oddball paradigm procedure the subject is asked to respond to a target tone of 2000 Hz, the "oddball tone", which occurs less frequently than the non-target tone of 1000 Hz. Although different types of stimuli, such as visual, electrical or tactical stimulations can be used for this procedure, auditory stimuli have been found to be advantageous, since they are easy to produce and they do not cause electrooculogram (EOG) artifacts [1].

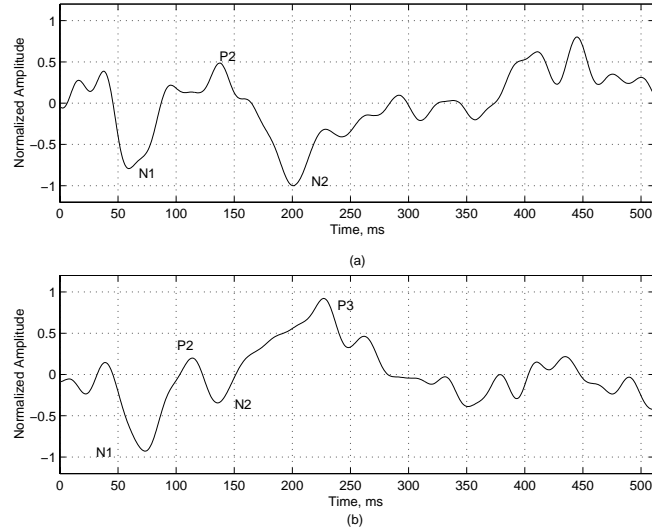


Figure 1.1. Typical ERPs (a) in response to a non-target tone, (b) in response to an oddball tone.

Four major peaks are observed in a typical ERP: N1, P2, N2 and P3. N1 is a negative peak that occurs at a latency of approximately 100 ms following the stimulus. P2 is a positive peak and N2 is a negative peak both appearing approximately at a latency of 200 ms. Finally, P3 (P300) is a positive peak that appears approximately at a latency of 300 ms. The distinguishing property of P3 is that it only occurs in response to an oddball stimulus. Figure 1.1 shows typical ERPs acquired for this study from a control (normal) subject. The landmarks N1, P2, N2, and P3 are all labeled on corresponding peaks. Figure 1.1(a) is the ERP in response to a non-target tone, and Figure 1.1(b) is the ERP in response to the oddball target tone. Note that the P3 component is only present in the ERP in response to the oddball tone.

Many studies have shown that this experimental procedure can be used to distinguish patients with dementias from patients with other neurological disorders [13, 15], in particular differentiating cortical dementias (such as Alzheimer's disease, Pick's disease) from other sub-cortical dementias (such as Huntington's disease, Parkinson's disease). Two indicators, the amplitude and the latency of the P3 component, are identified as the most influential, since they have been linked to the mental performance of individuals affected by dementia. These indicators are, however, closely dependent on various parameters of the oddball paradigm experiment, such as the intensity of the stimuli, the interval

between stimuli, and especially the probability of occurrence of the two sets of stimuli [14, 16, 17, 18, 19, 20] and therefore care must be taken in designing the experiment. For example, it has been observed that there is a close relationship between the information provided by the stimulus and the amplitude of the P300; if the frequency of occurrence of the target stimulus decreases, the amplitude of the P300 component increases in control patients. This complies with the well known rule of information theory that a less likely event has more information. As another example, the amplitude of the P300 component also increases when the interval between the stimuli increases [17].

Other studies [21, 22, 23] have shown that the latency and the amplitude of the P300 component are susceptible to changes due to age and the presence of dementias. These studies showed that the amplitude of the P300 component increases with better memory performance. In other words, whenever attentional resources, such as mental capability, are available to recognize a stimulus that is different from other stimuli, an ERP (*P300*) occurs at a latency of 300 ms. Generally speaking, shorter latencies, and higher amplitudes of the P300 component indicate better mental performance.

It should, however, be noted that although a strong relationship has been found between mental performance and the P300 component, large variations in amplitude and latency have been reported in different experiments [1]. Therefore, a generalization regarding the relationship between amplitude and latency of the P300 component and the mental performance of an individual is difficult.

2.2. Experimental Setup and Methodology

The study presented in this paper was performed on electroencephalograms obtained from 28 subjects. Fourteen of these subjects were diagnosed with early forms of the Alzheimer’s disease, whereas the remaining 14 (control) were known to be free of this disease. All subjects were elderly individuals with a mean age of 72.6 and standard deviation of 5.3. The diagnosis of Alzheimer’s disease was made through extensive clinical screenings and evaluations by neuropsychologists at the Emory University School of Medicine.

The EEG data were obtained from auditory oddball tests in which the subjects listened to a sequence of oddball and non-target tones. Each tone was 200 ms in duration, repeating at an interval of 1500 ms. The non-target tones were 1 kHz, and the oddball tones were 2 kHz. The subjects were asked to respond to oddball tones by pressing a button. Eighty six percent of the tones were non-target tones, whereas

the remaining 14% were oddball tones. Multiple recordings (over forty) were acquired for each subject.

EEG recording began 250 ms before each stimulus, and continued for 1000 ms after the stimulus, giving a total recording of 1250 ms per patient. A sampling rate of 600 Hz was used. In all experiments, the EEG was recorded from frontal and parietal locations. After sampling, data were hand-scored by neuropsychologists, and the artifactual trials were removed [24].

The important parameters of the oddball paradigm experiment that are used to obtain the recordings in this study are summarized in Table 1.1.

3. Multiresolution Wavelet Analysis of ERPs

The main objective of this study was to develop a robust technique to detect Alzheimer's disease by analyzing the ERPs of patients. Artificial neural networks (ANNs) are used extensively for various signal classification problems, since they are able to differentiate patterns of different classes, if they are trained with correct features. For diagnosis of Alzheimer's disease, existence, amplitude and/or latency of a particular peak (the P300 component) are considered to be the most relevant features of an ERP. However, this information may not be obvious in the original time domain signal due various sources of noise. Such sources can be other signals of biological origin, such as the electrocardiogram, electrooculogram, electromyogram, as well as thermal and 60 Hz noise.

It is quite likely that there may be features other than the P300 component in the ERP that are relevant to the Alzheimer's disease. Therefore, a classifier that analyzes the entire signal could be of benefit, as opposed to visual analysis of the ERP exclusively searching for the P300 component. On the contrary, however, signals often times contain features that are not relevant to the specific problem at hand. Apart from providing data reduction, removing such irrelevant features can significantly simplify the classification task. Therefore, a feature extraction scheme that analyzes the data to identify the minimum set of most relevant features is necessary. The information that is relevant to this application can be either in time domain (latency of the peak), or in frequency domain (existence of the peak and its amplitude). Therefore, a time-frequency analysis would be appropriate for analyzing ERPs.

Fourier transform has been used extensively in the past for analyzing various forms of EEG signals, however, Fourier transform is not always very appropriate for analyzing nonstationary signals, such as EEGs whose spectral content changes in time. This is because the Fourier

Table 1.1. Parameters of the oddball paradigm experiment used in this study

Parameter	Value
<i>Stimulus parameters</i>	
Non-target tone frequency	1000 Hz.
Probability of occurring	86%
Oddball tone frequency	2000 Hz.
Probability of occurring	14%
Rise time/fall time	< 1 ms.
Tone duration	200 ms.
Non-target tone intensity	62 dB
Target tone intensity	72 dB
Interstimulus interval	1500 ms.
<i>Subjects</i>	
Mean age	72.6 (SD: 5.3)
Gender	16 F, 12 M
<i>Task</i>	
Position	Seated
Eyes	Open
Task	Button press
<i>Recording parameters</i>	
Electrodes	Fz, Cz, Pz, EOG
Bandpass	0.01-0.5 to 30 Hz.
Sampling rate	600 Hz.
Artificial rejection	$\pm 100 \mu V$
Average number of target trials	30+

transform analyzes the signal globally, which allows identification of the spectral components residing in the signal. However, Fourier transform provides no information regarding the time localizations of the spectral components, that is, when in time spectral components appear. In many

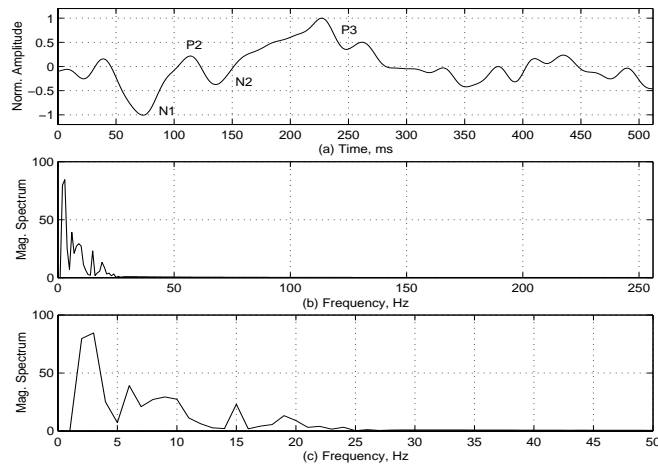


Figure 1.2. Fourier analysis of ERPs. (a) ERP of a control subject to a target tone (b) Fourier spectrum of the ERP (c) detail view of 0 ~ 50 Hz band.

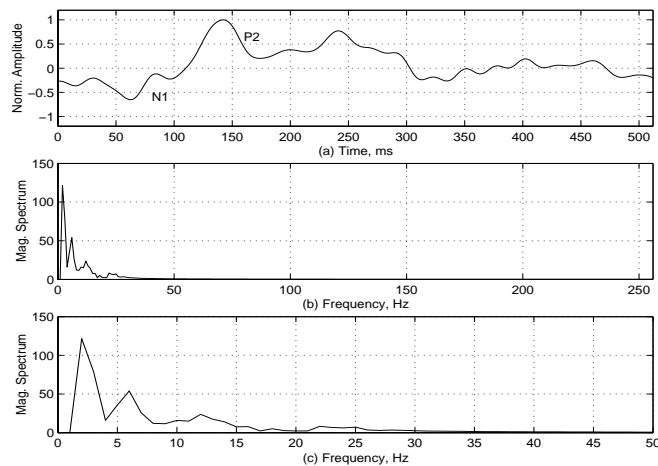


Figure 1.3. Fourier analysis of ERPs. (a) ERP of an Alzheimer's patient to a target tone (b) Fourier spectrum of the ERP (c) detail view of 0 ~ 50 Hz band.

applications, including EEG analysis, time localizations of the spectral components provide valuable information.

Figures 1.2 and 1.3 illustrate spectral analysis of event related potentials used in this study. Figure 1.2(a) and (b) show a typical ERP and the corresponding Fourier spectrum of a control subject, whereas Figures 1.3(a) and (b) provide the same information for an Alzheimer's patient. Figures 1.2(c) and 1.3(c) provide detailed views of the first 50 Hz.

We note that due to high sampling rate of the signal, Fourier transform provides substantial data reduction, since Fourier coefficients beyond 25 Hz do not carry any significant information. However, the data reduction in this case is too severe. Although some difference can be observed in the Fourier spectra of two ERPs, the difference proves to be insufficient in providing adequate discriminatory information to distinguish an Alzheimer's patient's ERP from that of a control patient.

Clearly, a time-frequency representation can provide the time localizations of the spectral components, which may provide necessary distinguishing information. In fact, since we are interested in the existence and latency of the P300 component, time-frequency representation seems to be the logical choice.

Recently, promising results have been reported [25, 26, 27, 28, 29] regarding the use of time-frequency analysis in various applications of biological signals, such as evoked potential analysis using wavelets, EEG spike detection, or compression of ECG signals. A collection of papers on a diverse set of biomedical applications of time-frequency analysis can be found in [30].

In this study, the multiresolution subband coding implementation of the discrete wavelet transform was chosen from a number of time-frequency analysis techniques due to many of its nice properties. DWT is a fast and simple algorithm, it provides a substantial amount of data reduction, yet it still provides the discriminatory information necessary to distinguish Alzheimer's patient's ERPs from those of control subjects.

Discrete wavelet transform was developed to efficiently compute the time-scale representation of non-stationary signals. A detailed coverage of the discrete wavelet transform and the multiresolution wavelet analysis can be found in [31, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42] as well as other chapters of this book, but a filter bank implementation of the DWT used to analyze the ERPs in this study is briefly explained in the following paragraphs. Further details of the wavelet theory can be found elsewhere in this book, as well as in a number of excellent other texts [31, 32, 33, 34, 35, 36]. The DWT coverage in this paper will suffice with describing the subband coding algorithm as applied to the event related potentials.

The discrete wavelet transform analyzes the signal at different frequency bands with different resolutions, hence the name *multiresolution analysis*. This is particularly important in analysis of event related potentials, since distinct pieces of information lie at different frequency bands. The multiresolution analysis is achieved by repeatedly decomposing the signal into a coarse approximation and detail information using a series of successive low pass and highpass filters. One level of

DWT decomposition is obtained simply by passing the original signal $x[n]$ through a halfband highpass filter $g[n]$ and a lowpass filter $h[n]$, followed by subsampling. Note that after the filtering, half of the samples can be eliminated according to the Nyquist's rule, since the signal now has a highest angular frequency of $\pi/2$ rad/s instead of π rad/s. The signal is therefore subsampled by 2, simply by discarding every other sample. One level of decomposition can therefore be expressed as

$$y_{high}[k] = \sum_n x[n] \cdot g[2k - n] \quad (1.1)$$

$$y_{low}[k] = \sum_n x[n] \cdot h[2k - n] \quad (1.2)$$

where $y_{high}[k]$ and $y_{low}[k]$ are the outputs of the highpass and lowpass filters, respectively, after subsampling by 2.

This decomposition in effect halves the time resolution, since the entire signal is now characterized by half the number of samples compared to the original signal. However, this operation doubles the frequency resolution, since the frequency band of the signal now spans only half the previous frequency band. The above procedure, which is also known as subband coding, can be repeated for further decomposition. Figure 1.4 illustrates this procedure on a typical ERP of length 512 points, sampled at a rate of 600 Hz. The frequency bands analyzed at each level (denoted as B), along with the number of coefficients available are provided on the figure.

The outputs of the highpass filters constitute the DWT coefficients (also referred to as *detail coefficients*), and they are denoted as d_i , $i = 1, 2, \dots, \log_2 N$, where N is the total number of samples in the signal. The outputs of lowpass filters are referred to as approximation coefficients, a_i , and they represent the approximation of the original signal at the current resolution level. The original signal can then be reconstructed by simply summing coefficients at all levels.

The DWT coefficients can be displayed in various forms. One approach for displaying DWT coefficients is concatenating all coefficients starting with the last level of decomposition. The DWT will then have the same number of coefficients as the original signal. Figure 1.5, which shows a typical response of an Alzheimer's disease patient to an oddball tone along with the concatenated DWT coefficients, illustrate this approach. The original signal (Figure 1.5(a)), normalized to unit amplitude, has 512 samples. The horizontal axis is the number of samples, whereas the vertical axis is the normalized amplitude.

Figure 1.5(b) shows the 8 level DWT of the signal, where all DWT coefficients are concatenated. The last 256 samples (d_1 coefficients) cor-

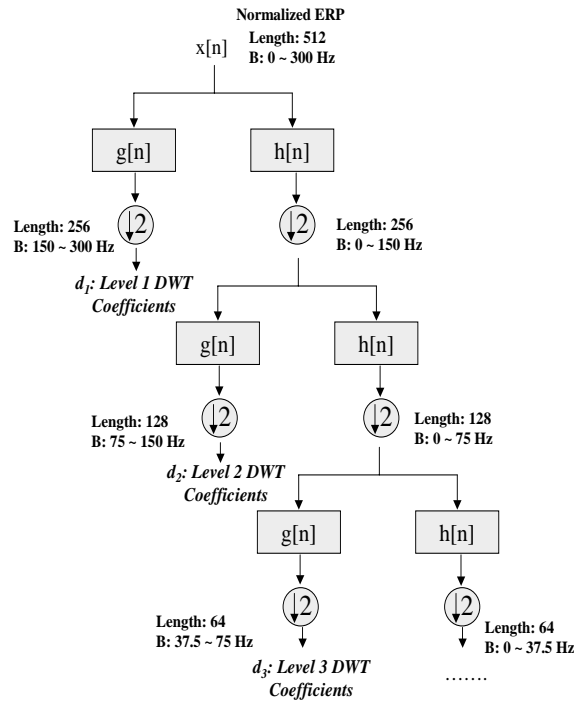


Figure 1.4. Subband coding scheme for computing the DWT.

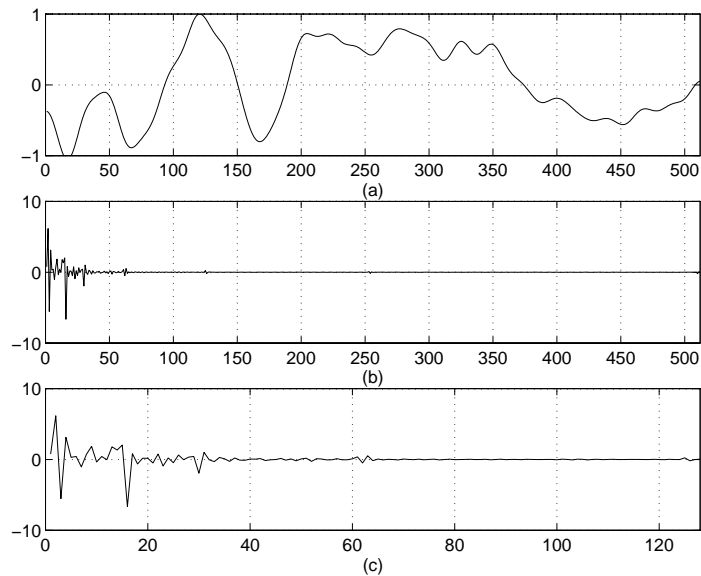


Figure 1.5. DWT and data reduction. (a) A typical ERP from an AD patient, (b) 8 level DWT, (c) first 128 samples of the DWT.

respond to the lowest scale (highest frequency) band in the signal, the previous 128 samples (d_2 coefficients) correspond to the next scale (previous frequency) band and so forth. We observe from Figure 1.5(b) that only the first 30 to 40 samples carry a substantial portion of the information. Therefore, all but the first 40 samples can be discarded without loss of any significant information. Figure 1.5(c) shows the first 128 samples of this particular DWT signal. This representation of the DWT is useful when data reduction is important, since only those bands with significant energies can be retained for further analysis. This representation of DWT coefficients allows us to use them very easily with a neural network classifier, as explained in the next section. However, this representation is difficult to interpret.

The second approach for displaying DWT is plotting individual DWT coefficients at each level, i.e., plotting $d_i, i = 1, 2, \dots, \log_2 N$. Plotting individual detail coefficients allows easy interpretation of the time - frequency plane for visual analysis. We note that upper levels of d_i include fewer and fewer coefficients, due to subsampling. These coefficients can be interpolated to make sure that all d_i have the same N coefficients. Figure 1.6 illustrates this approach on an Alzheimer's disease patient's ERP.

The top plot, s , shows the normalized ERP, whereas the remaining plots show all coefficients in full decomposition: a_7 are the approximation coefficients at level 7 (highest scale - lowest frequency), which represent the coarsest approximation of the signal. The remaining plots illustrate the detail coefficients $d_1 \sim d_7$, the sum of which, along with a_7 , reconstructs the original signal. In this decomposition, d_1 represents the signal in the (approximately) 150 ~ 300 Hz range, d_2 in the 75 ~ 150 Hz range, d_3 in the 37.5 ~ 75 Hz range, and so on. We note that d_5, d_6 and d_7 , which correspond to roughly 2.5 ~ 20 Hz range, carry most of the information since they have the largest amplitudes, and their sum resembles the original signal the most. This fits perfectly to the range of frequencies that are commonly seen in event related potentials of EEGs. We note that detail coefficients d_1 through d_4 , corresponding to highest frequencies, largely represent the noise inherent in the signals (and therefore omitted in the subsequent plots).

Clinical studies have shown that the spectrum of the P300 component typically lies around 3 Hz [1] which, at the given sampling rate, corresponds to d_7 level. Therefore, we would expect to see the P300 component at around the 200 ~ 300 ms range of the d_7 coefficients. Figure 1.7 illustrates the last three levels ($d_5 \sim d_7$) of decomposition of a control subject's ERP. We observe the peak around 230 ms at level 7, which clearly indicates the presence of the P300 component.

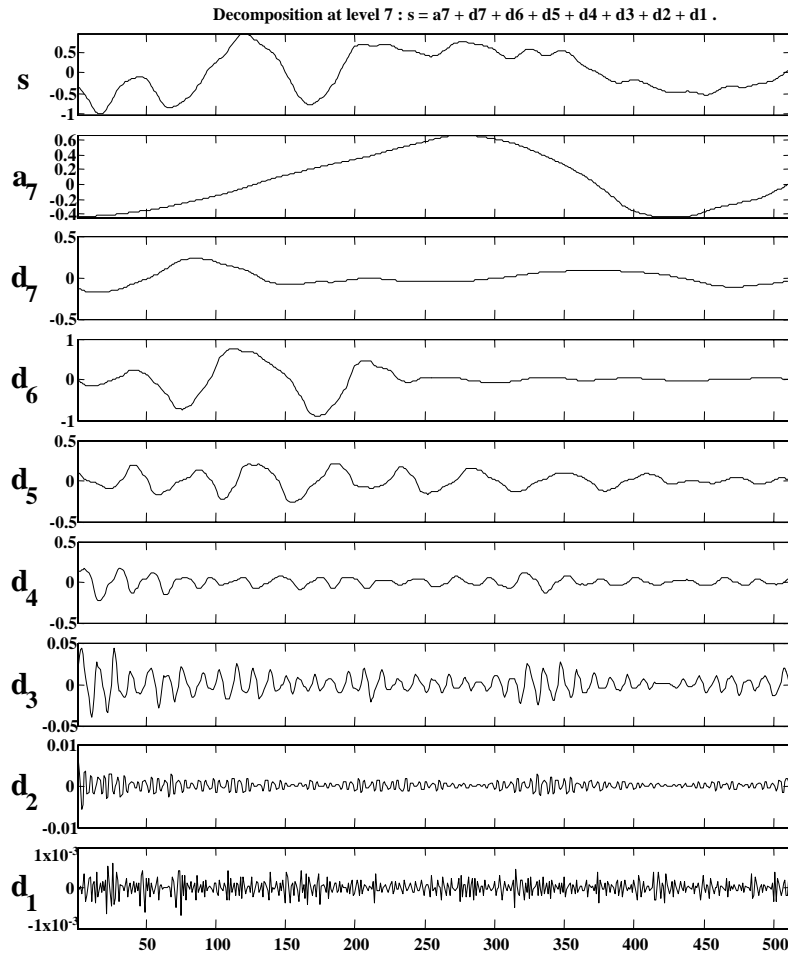


Figure 1.6. Alzheimer's disease patient's ERP, full decomposition using subband coding: s original signal, a_7 approximation coefficients, $d_1 \sim d_7$ detail DWT coefficients.

Comparing the decompositions of two signals in Figures 1.6 and 1.7, the additional information provided by the wavelet analysis becomes even more evident. In particular, note in Figure 1.6 that the original time domain signal s (from an Alzheimer's patient) does include peaks in the 200 ~ 300 ms range, which might mistakenly be interpreted as the P300 component. However, the detail coefficients at level 7 clearly show that the signal has no indicators that characterize the P300 component. In contrast, level 7 coefficients in Figure 1.7 clearly indicate signs of evidence of the P300 component.

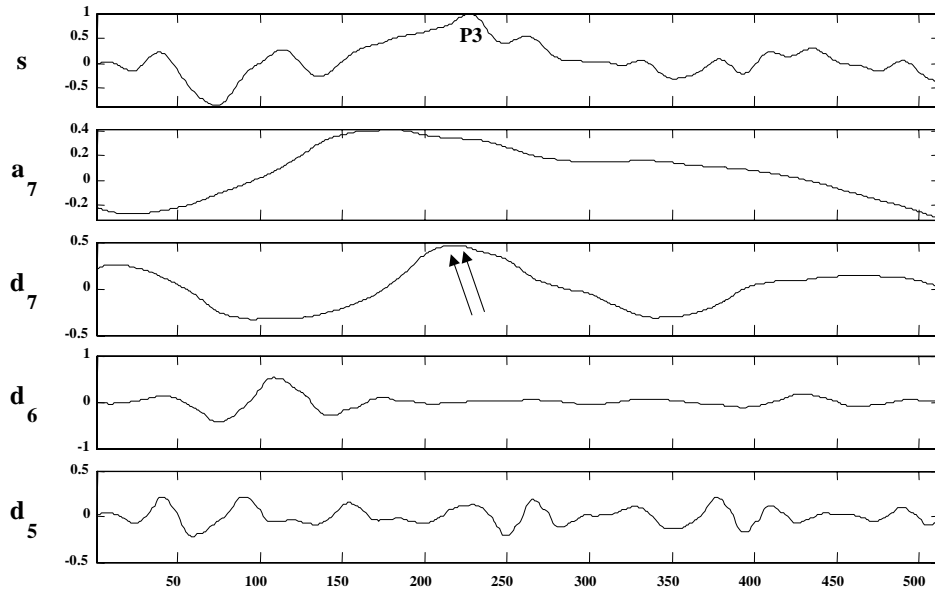


Figure 1.7. Control subject's ERP, partial decomposition using subband coding: s original signal, a_7 approximation coefficients, $d_5 \sim d_7$ detail DWT coefficients.

4. Preprocessing and Classification of Data

4.1. Preprocessing

The original data acquired for this study consisted of 56 files, two files for each of the 28 patients, corresponding to their responses to oddball tones and non-target tones. Each file had 8 recordings corresponding to 8 different electrode configurations. However, recordings only from the Pz channel of the international 10-20 electrode placement system were used in the analysis, since recordings from this electrode show the most robust P300 component [1, 24].

Each patient's stimulus set included approximately 40 oddball tones, and since the discriminating information is embedded in responses to oddball tones, all responses to oddball tones were extracted for the analysis.

The recording for each tone lasted 1250 ms and was sampled at 600 Hz, resulting in 750 samples. These 40 recordings of 750 samples each per patient were then averaged to obtain robust components of ERPs [1].

Since the recording started 250 ms before the beep, the first 150 samples of each recording constituted the prestimulus recording. These 150 samples were therefore removed. The last 150 ms (about 88 samples)

of the signals were also removed because those sections included post-recording artifacts. The mean of the prestimulus recording was then subtracted from each recording to remove the DC offset.

The resulting 28 files, each 512 samples long, corresponding to 28 patients' responses to oddball tones, were then decomposed by using the subband coding scheme, and the DWT coefficients were computed for full decomposition. The first 24 coefficients with the highest amplitudes from each patient were retained for training and testing a neural network classifier. Note that the first 24 coefficients constitute detail coefficients d_5 and below, including all coefficients corresponding to d_7 . Note that a significant data reduction is obtained, since a 512 long vector represented by only 24 coefficients corresponds to a 95 % data reduction.

4.2. Classification: Multilayer Perceptron

A number of supervised and unsupervised pattern recognition algorithms have been developed over the years for the classification of multidimensional signals, including discriminant analysis based classifiers, clustering algorithms [43], neural networks [44], and support vector machines [45].

Among these, neural networks have enjoyed significant attention, and various neural network architectures and learning algorithms have been developed for different applications. Multilayer perceptron neural networks using the backpropagation learning algorithm have traditionally been the method of choice for most classification problems. This can be attributed to their simple architecture and powerful performance in generating multidimensional nonlinear decision boundaries.

In this study, we have used the multilayer perceptron which was trained with the supervised backpropagation learning rule to distinguish the signals from patients with Alzheimer's disease from those of control subjects. A multilayer perceptron (MLP) is a feed-forward network with one or more hidden layers between the input and output nodes. The number of input nodes is chosen as the dimensionality of the signals to be classified, and the number of output nodes is chosen as the number of classes. The number of layers in between and the number of nodes at each layer are application dependent. All nodes are fully interconnected to the nodes of adjacent layers by a set of weights. Figure 1.8 illustrates the architecture of the one-hidden layer MLP network used in this study, where I_i , $i = 1, 2, \dots, 24$ is the 24 samples long input vector, H_j , $j = 1, 2, \dots, 64$ are the values of the hidden layer nodes, and O_k , $k = 1, 2$ are the values of the output nodes.

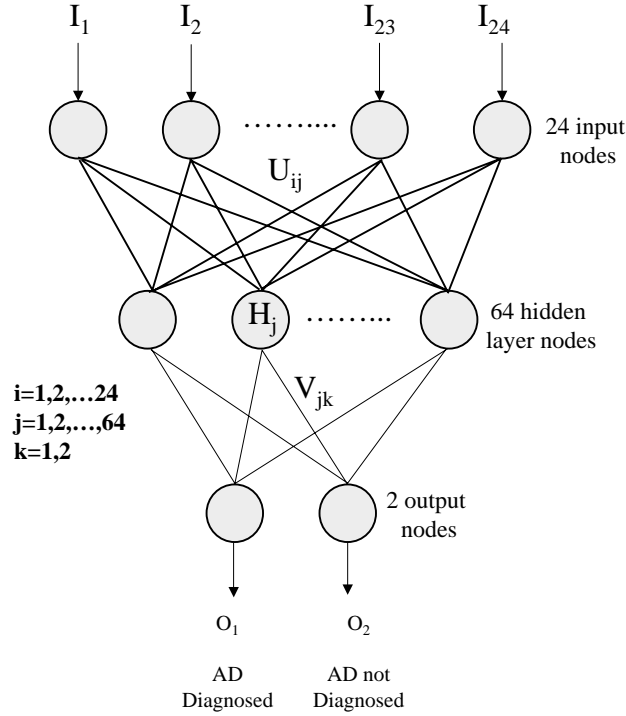


Figure 1.8. One hidden layer MLP neural network

The weights connecting the input nodes to the first hidden layer nodes are denoted by U_{ij} , and the weights connecting the second hidden layer nodes to the output nodes are denoted by V_{jk} . The procedure for determining these weights is called *training* the network. MLP type neural networks are often trained using the backpropagation learning algorithm. The details of this algorithm are beyond the scope of this paper, and can be found in [44], along with a comprehensive coverage of other network architectures.

A training database is required for training the network, and this database should ideally include representative examples of all patterns the network is likely to encounter when it is used to classify unknown patterns. Therefore, it is common practice in neural network applications to divide the existing database into at least two subsets. The first set is used for training the network and the second set is used to evaluate the network performance on patterns that were not seen during training. The classification performance of the network on the evaluation set is called the *generalization performance* of the network.

We used half of the available signals for training the network, and the rest for testing the generalization performance of the trained network. Fourteen patients' signals, 7 from Alzheimer's disease patients, were randomly chosen for training. The MLP had 24 input nodes (corresponding to the 24 DWT coefficients), one hidden layer with 64 nodes and 2 output nodes corresponding to two classes: 1) patient has Alzheimer's disease 2) patient does not have Alzheimer's disease.

5. Classification Results

Classification was initially performed on the raw time domain signals as well as on Fourier transformed signals to compare with the multiresolution wavelet analysis. For time domain analysis all 512 samples and, for Fourier analysis, the first 30 coefficients were used as features. Recall that the signal was sampled at 600 Hz, and 512 Fourier coefficients were computed. According to Nyquist's criterion, the 512th sample corresponds to the sampling frequency of 600 Hz. Therefore, the first 30 samples span the 0 ~ 35 Hz frequency range, which constitutes the frequency range of interest for most event related potentials.

Over many trials using various network architectures and learning parameters, the correct classification performance of the network on the raw data was generally around 50 % (7 out of 14 of test dataset). The best performance ever obtained using the raw data was 71 % (10 out of 14).

The typical correct classification performance using the Fourier coefficients was only a little better than that of the raw data, around 57% (8 of 14 test signals correctly classified). The best performance obtained using Fourier coefficients was also 71 %.

Classification was then performed using the DWT coefficients of the data. Average classification performance using DWT coefficients was significantly better at 80 % for various network architectures. The network described above (24 input nodes, 64 hidden layer nodes, 2 output nodes, with an error goal of 0.05) achieved the best classification performance by classifying 13 of 14 test signals (93%).

Figure 1.9 shows the only signal in the test set that was misclassified, and Figure 1.10 shows its decomposition. We note that level 7 detail coefficients indicate a transition region from a dip to a peak around 300 ms. This may be part of the reason why this signal was misclassified. However, other features that are considered by the network probably contributed to its decision as well.

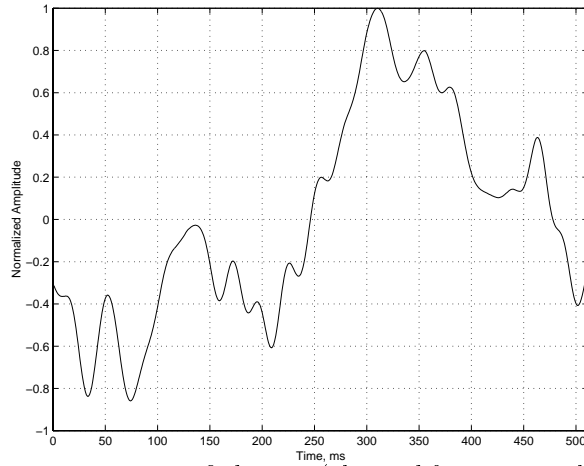


Figure 1.9. The misclassified signal (obtained from a control subject).

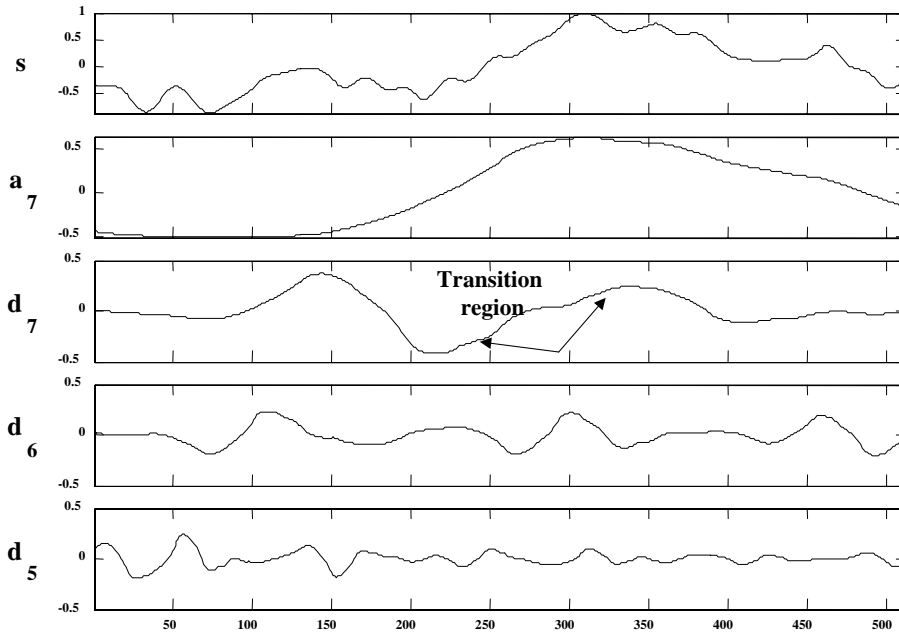


Figure 1.10. Decomposition of the misclassified signal.

6. Discussion and Conclusions

Although event related potentials have been used to assist in diagnosing Alzheimer's disease, their assistance have been of limited value. This is because a visual analysis of ERPs is often inconclusive. It is not

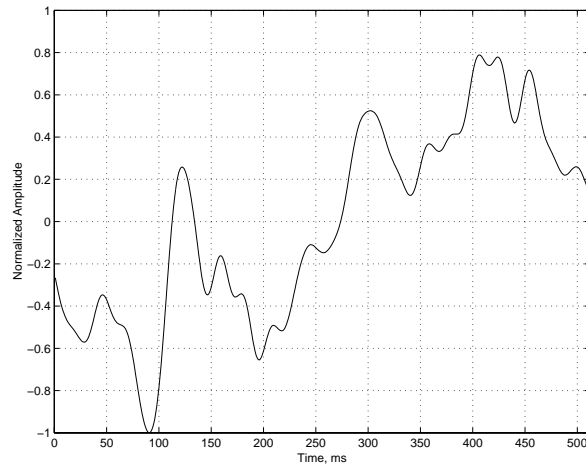


Figure 1.11. Response of an Alzheimer's patient to an oddball tone

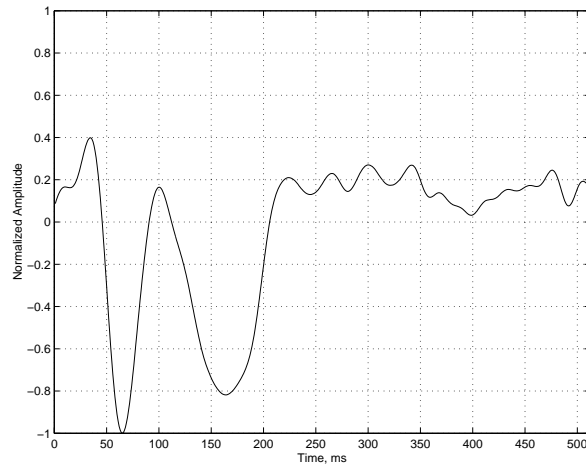


Figure 1.12. Response of a control subject to an oddball tone.

unusual for P300-like peaks to appear in Alzheimer's patients ERPs, nor it is unusual for such peaks to be absent or inconspicuous in the ERPs of normal people. Figures 1.11 and 1.12 illustrate two such cases.

Figure 1.11 shows the ERP of an Alzheimer's disease patient, which clearly indicates a P300-like component at 300 ms. However, the wavelet analysis indicated that this peak was not at the expected frequency range, and the neural network correctly determined that this signal came from an Alzheimer's disease patient. Alternatively, Figure 1.12 shows the ERP of a control subject. Note that no P300 component can be clearly identified in this signal.

These examples demonstrate that not only it is difficult to visually identify the P300 component, but also there may be other features in an ERP that characterize the disease. Since ERPs are highly nonstationary signals, multiresolution wavelet analysis followed by a nonlinear classifier, such as a neural network, address both of these issues. First of all, it is easier to identify the P300 component using wavelet analysis, because this technique provides us time localizations of spectral components. Knowing that P300 component should lie around 3 Hz, wavelet analysis allows us look at the signal from a scale window that corresponds to the frequencies of interest. Second, if there are other features in the signal that may characterize the disease, the wavelet coefficients will preserve those features, and the neural network will be able to use them in assessing to which class a given signal should belong.

In this paper, we introduced the above described automated ERP analysis and identification scheme for early diagnosis of the Alzheimer's disease, which makes use of multiresolution wavelet decomposition followed by neural network classification. We showed that multiresolution analysis fits naturally for analyzing nonstationary biological signals, such as EEGs, when time localizations of certain spectral components are of interest.

Our initial results indicate that with adequate training data, it is possible to train a neural network to be used as an aid to neurologists for detecting the various features used in the diagnosis of Alzheimer's disease. Discrete wavelet transform provides a very systematic and compact way to represent the event related potentials to allow a neural network classifier to correctly identify these signals.

We note that two levels of data reduction is achieved by using the described approach. First, the results reported above were obtained by using ERPs from one channel of EEG only. In most clinical examinations, several channels of EEG are recorded, requiring the neuropsychologists to analyze volumes of data. Second, only 5 % of each recording (24 of 512 coefficients) was adequate for correctly classifying ERP patterns.

Therefore, the availability of fast algorithms for computing DWT coefficients, along with the data reduction obtained using this procedure, can provide the classification results in real time while the ERPs are being recorded. Future work on this study will concentrate on verifying the results obtained with additional data, and implementing the described system in hardware as a prototype system.

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