PROVISIONAL APPLICATION FOR PATENT COVER SHEET

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☑ *Additional inventors are being named on the* 1 *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

METHOD AND APPARATUS FOR THE ESTIMATION OF THE ANESTHETIC DEPTH USING WAVELET ANALYSIS OF THE ELECTROENCEPHALOGRAM SIGNALS

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- ☐ Yes, the name of the U.S. Government agency and the Government contract number are: ____________

Respectfully submitted,

Date July, 10th 2002

SIGNATURE ____________

TYPED or PRINTED NAME Stéphane BIBIAN

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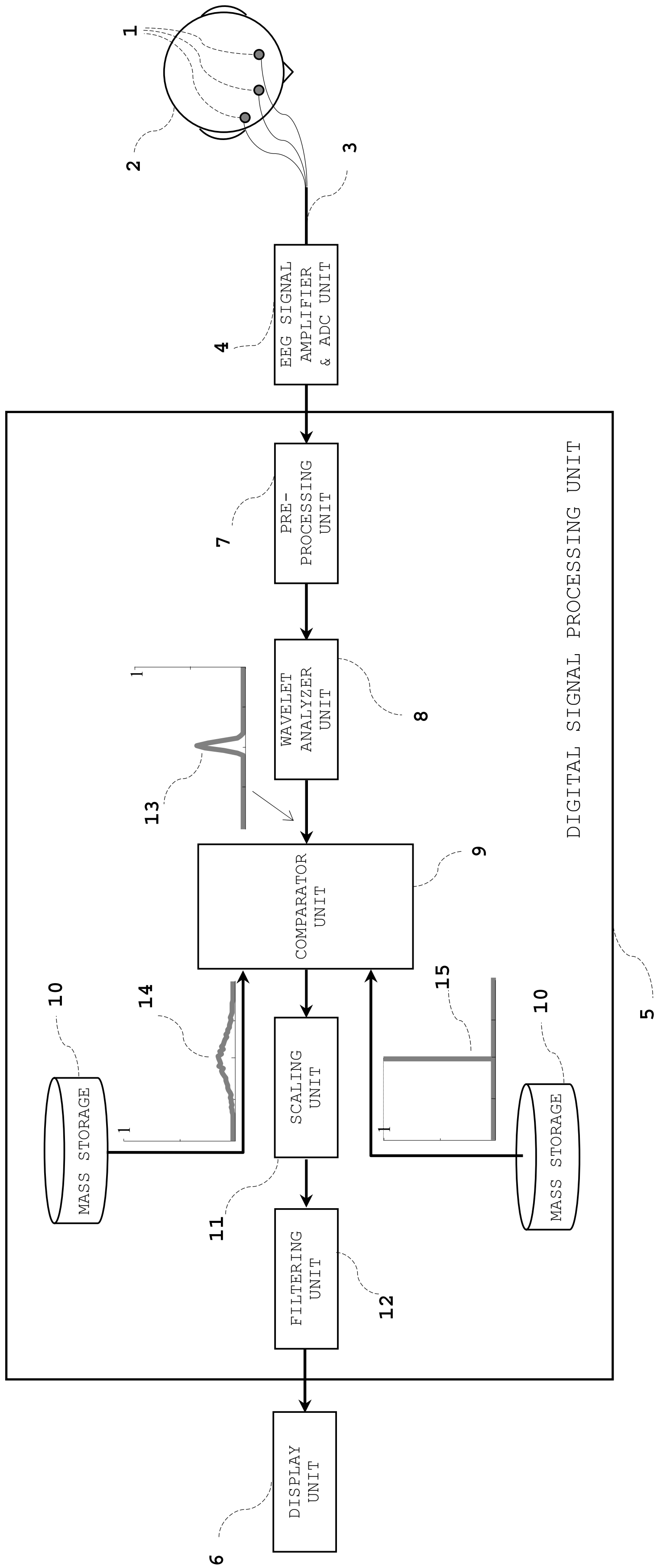

1
2
3
EEG SIGNAL AMPLIFIER & ADC UNIT
4
PRE-PROCESSING UNIT
7
WAVELET ANALYZER UNIT
8
13
COMPARATOR UNIT
9
DIGITAL SIGNAL PROCESSING UNIT
5
MASS STORAGE
10
14
SCALING UNIT
15
MASS STORAGE
10
11
FILTERING UNIT
12
DISPLAY UNIT
6

Figure 1:

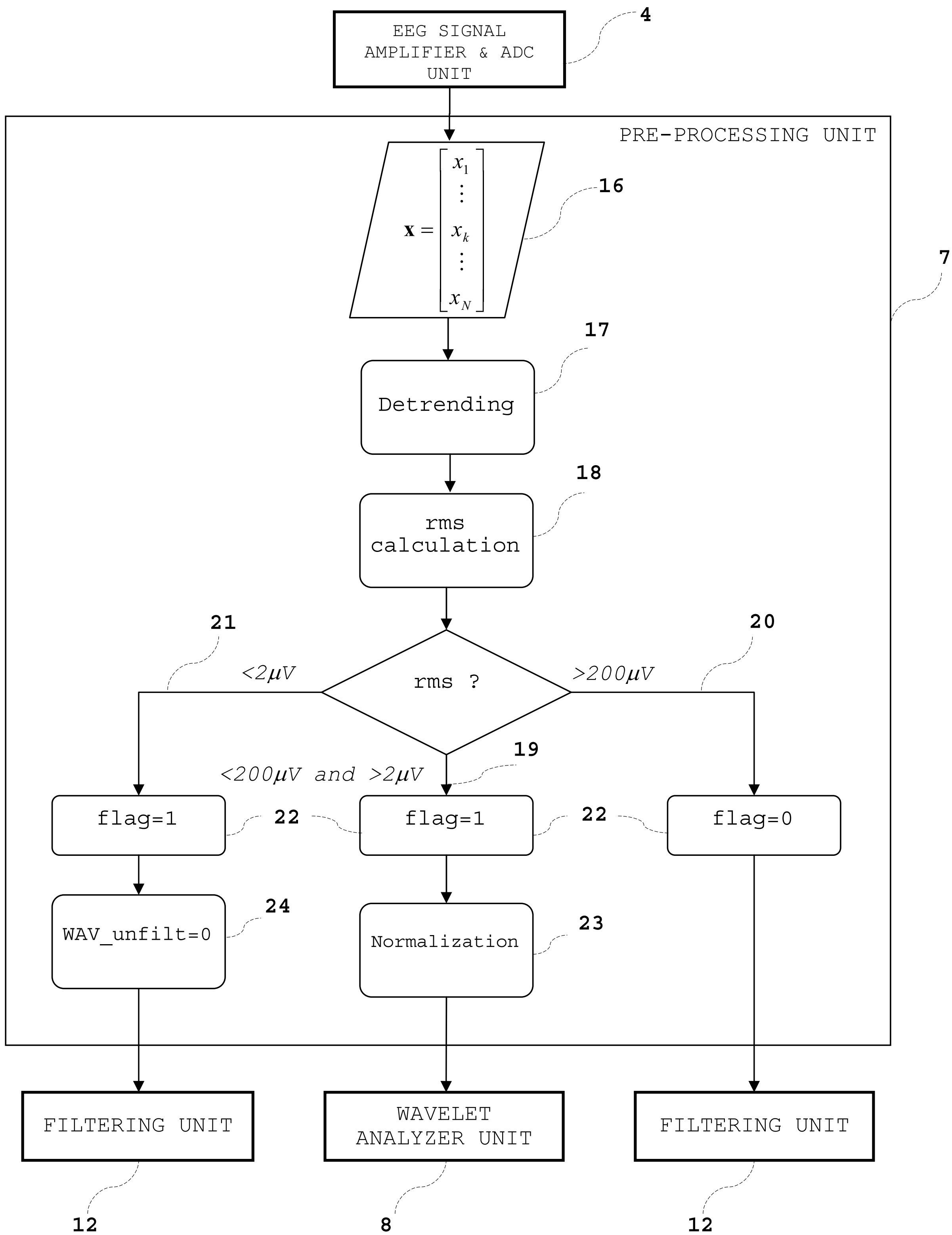

EEG SIGNAL
AMPLIFIER & ADC
UNIT
4
PRE-PROCESSING UNIT
$\mathbf{x} = \begin{bmatrix} x_1 \\ \vdots \\ x_k \\ \vdots \\ x_N \end{bmatrix}$
16
7
17
Detrending
18
rms
calculation
21
20
<2μV
rms ?
>200μV
19
<200μV and >2μV
flag=1
22
flag=1
22
flag=0
WAV_unfilt=0
24
Normalization
23
FILTERING UNIT
WAVELET
ANALYZER UNIT
FILTERING UNIT
12
8
12

Figure 2:

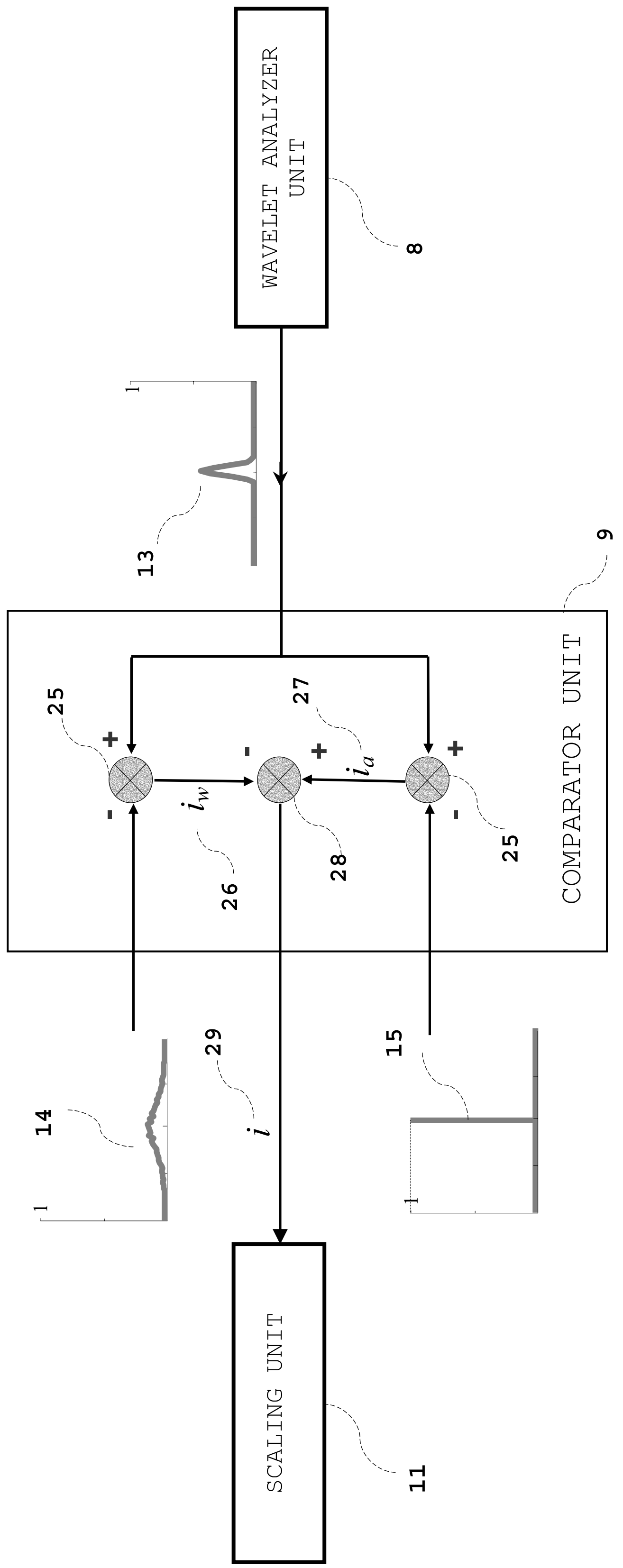
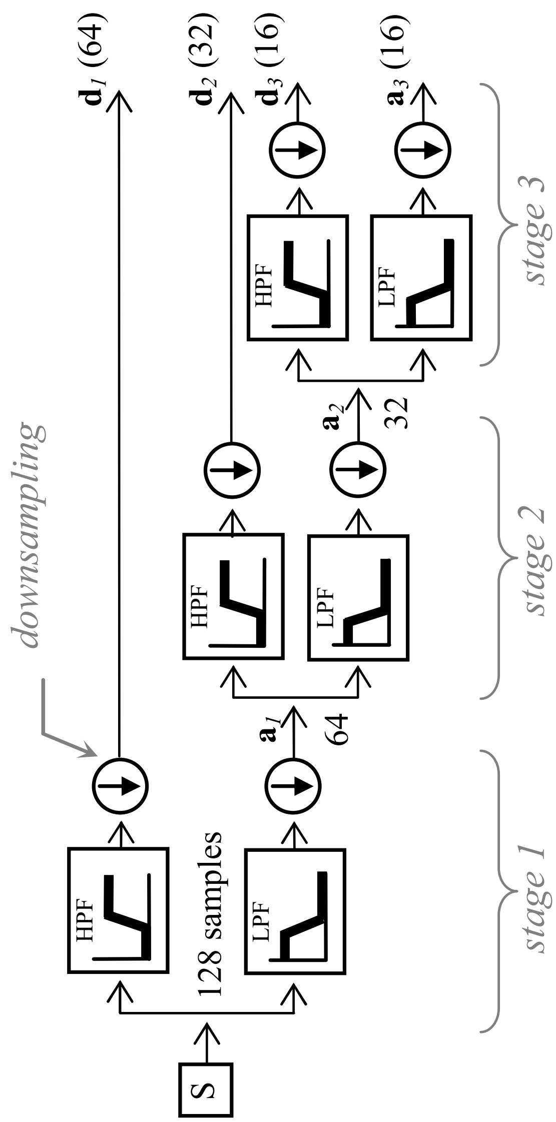

WAVELET ANALYZER UNIT
8
13
9
COMPARATOR UNIT
25
27
25
26
28
i_w
i_a
29
i
14
15
SCALING UNIT
11

Figure 3:



downsampling
S
128 samples
HPF
LPF
$\mathbf{a}_1$
64
$\mathbf{a}_2$
32
$\mathbf{d}_1$ (64)
$\mathbf{d}_2$ (32)
$\mathbf{d}_3$ (16)
$\mathbf{a}_3$ (16)
stage 1
stage 2
stage 3

Figure 4:

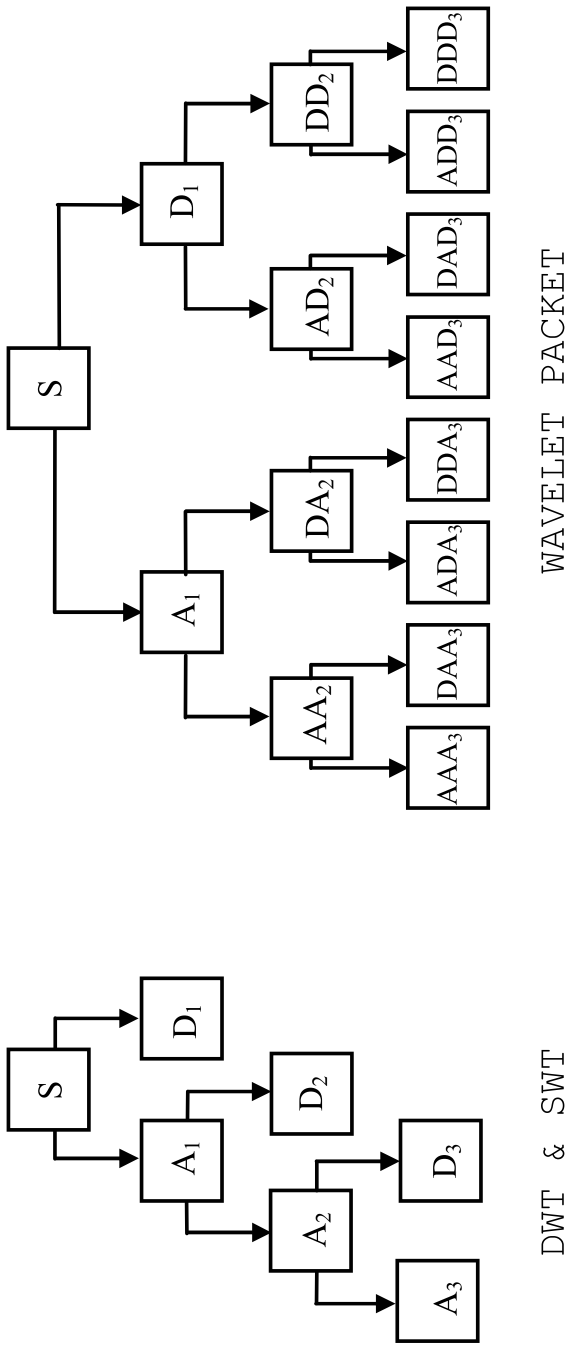

S
A_1
D_1
AA_2
DA_2
AD_2
DD_2
AAA_3
DAA_3
ADA_3
DDA_3
AAD_3
DAD_3
ADD_3
DDD_3
WAVELET PACKET
S
A_1
D_1
A_2
D_2
A_3
D_3
DWT & SWT

Figure 5:

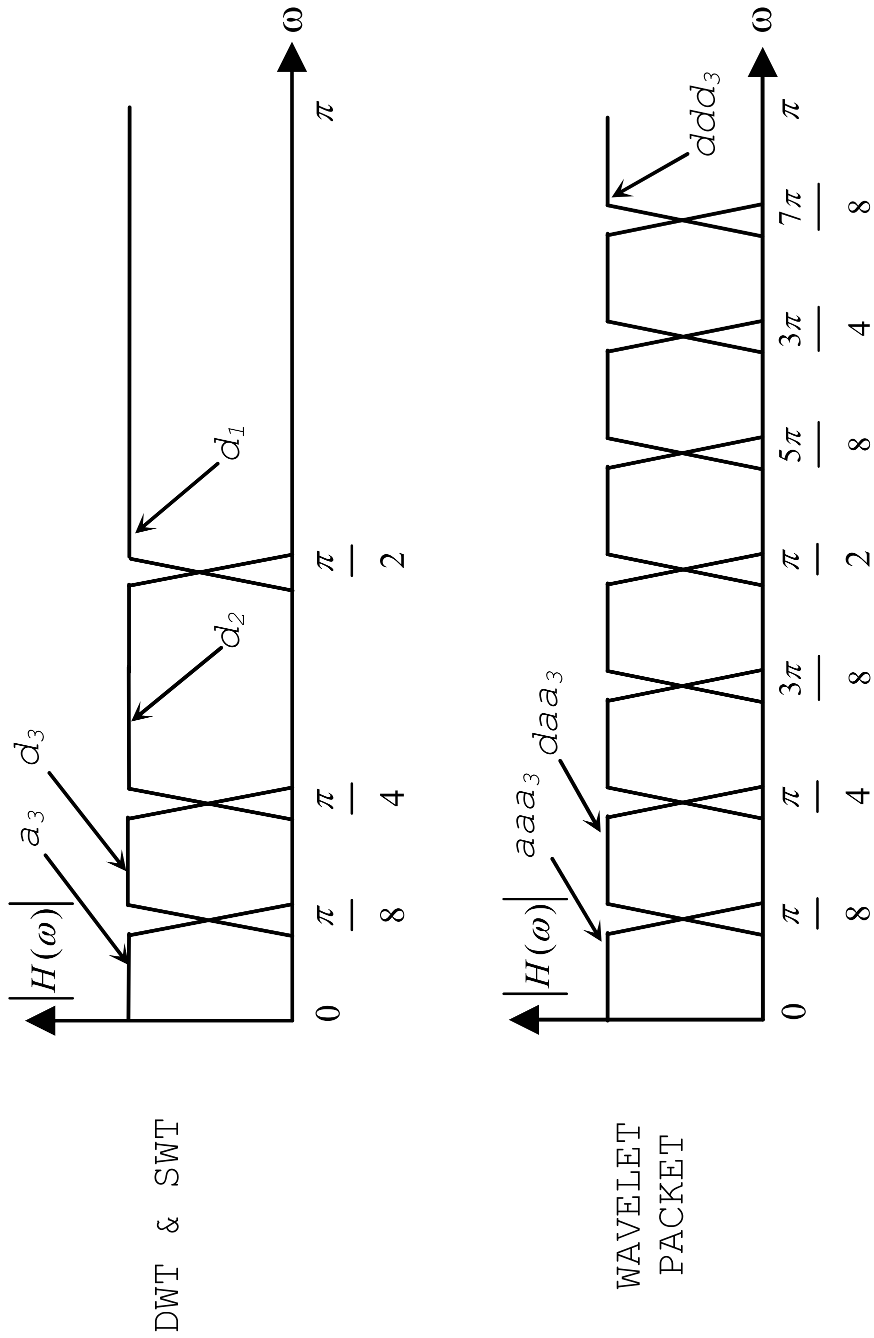

DWT & SWT
WAVELET PACKET
|H(ω)|
a3
d3
d2
d1
aaa3
daa3
ddd3
0
π/8
π/4
3π/8
π/2
5π/8
3π/4
7π/8
π
ω

Figure 6:

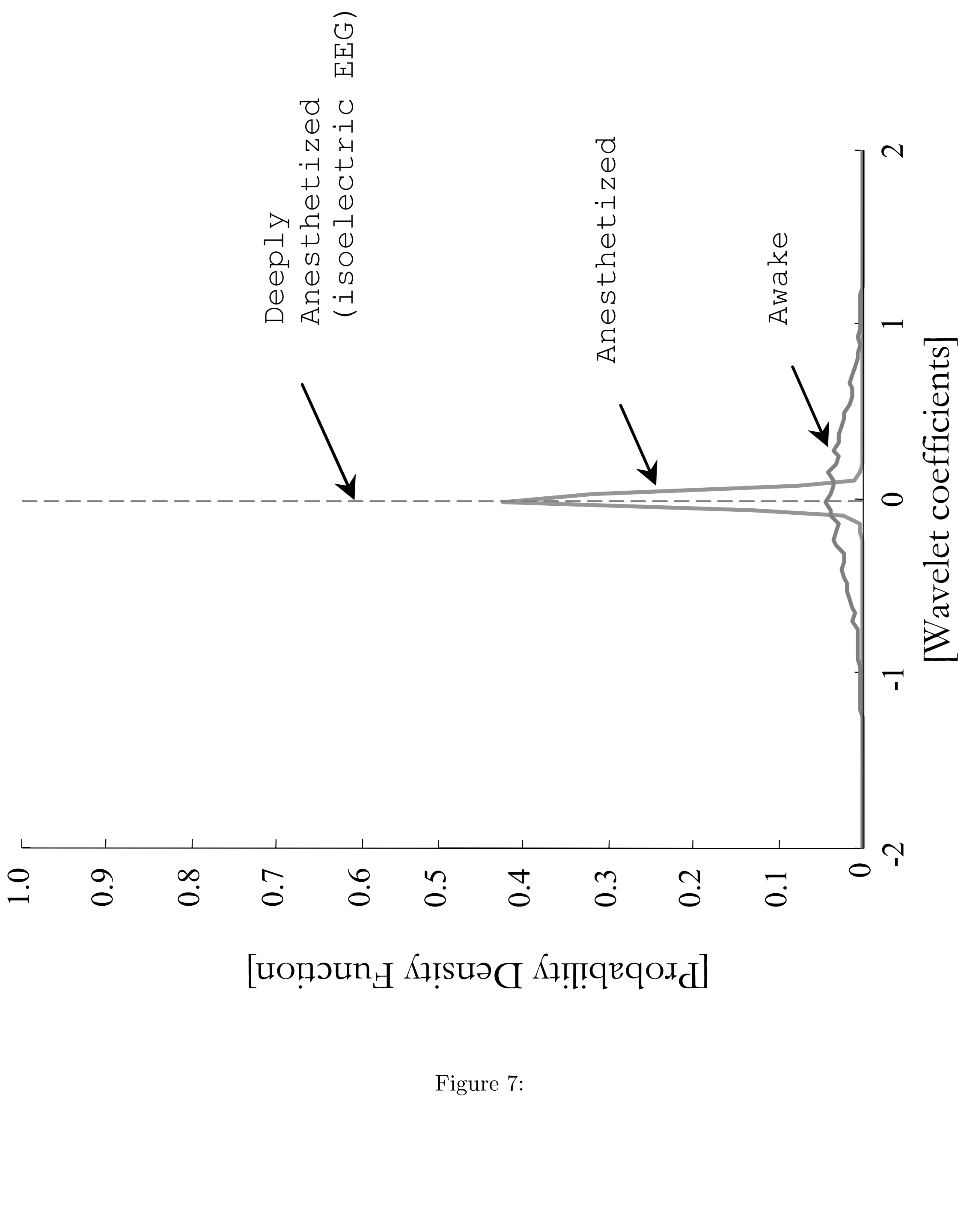

Deeply
Anesthetized
(isoelectric EEG)
Anesthetized
Awake
[Probability Density Function]
[Wavelet coefficients]
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-2
-1
0
1
2

Figure 7:

Method and apparatus for the estimation of the anesthetic depth using wavelet analysis of the electroencephalogram signals

1 Background of the Invention

The invention disclosed herewith relates to the field of clinical anesthesia, in particular to the intraoperative and postoperative monitoring of patients' hypnotic and cognitive states.

Members of industrialized societies have enjoyed the benefits brought by clinical surgery and modern medicine for over a century. Undergoing a surgical procedure has become nowadays a rather common event. However, this remarkable progress has only been made possible through the development of the practice of anesthesia.

The state of anesthesia is achieved by administering a combination of various anesthetic agents that render patients unconscious and insensitive to the trauma of surgery, while providing surgeons with a quiet surgical field. All general anesthetics lead to the loss of consciousness. At higher doses they also provide analgesia and muscle relaxation – two clinical end-points that can be independently achieved by analgesics and muscle relaxants. However, these drugs do not provide unconsciousness at clinical concentrations. Hence, although the mechanisms of anesthesia are still largely unknown, it is believed that *hypnosis* – i.e. drug-induced loss of consciousness and amnesia – is one of its major components.

Traditionally, anesthesiologists titrate drugs by assessing the anesthetic/hypnotic state of a patient based on observations of various clinical signs and their changes (such as blood pressure, heart rate, pupil dilatation, sweating, lacrimation, movement etc). However, these signs may not always be readily available, and furthermore, may be unreliable. The need for a monitor of hypnosis is especially strengthened by the use of neuromuscular blockade agents in modern clinical practice. It is therefore possible for a patient to be aware of the surgery, yet unable to communicate his or her awareness by movement to the anesthesiologist. Therefore, a monitor of hypnosis/consciousness will provide anesthesiologists with a guide for the precise titration of anesthetic drugs, thus avoiding both overdosing and intraoperative awareness. It is expected that a better titration will result in less side effects, faster discharge from intensive care unit, and long term savings in terms of the drug quantities administered during surgeries.

All hypnotic drugs depress the Central Nervous System (CNS). Therefore it is natural to assume that Electroencephalographic (EEG) changes in the brain's electrical activity carry relevant information about drug effects on the brain. Thus, the hypnotic state of a patient could, theoretically at least, be quantified by observing variations in EEG waveforms.

Numerous studies have explored this field since the first observation of the effect of narcotics or general depressant drugs on the EEG in the late 1930s. However, the interpretation of the unprocessed or raw EEG signal is very complex, time consuming and requires an experienced specialist. Therefore, many efforts have been put into deriving EEG-based indices that correlate with the hypnotic state of a patient.

A number of inventions related to monitoring of anesthesia using electroencephalographic signals have already been disclosed.

In John, US Pat. No 4,557,270 issued December 10, 1985 and US Pat. No 5,699,808 issued December 23, 1997, systems monitoring patients in postoperative care units are disclosed. These prior art systems are based on Brainstem Auditory Evoked Potentials (BAER) and Brainstem Somatosensory Evoked Potentials (BSER) which are extracted from the EEG signals after an auditory or somatosensory stimulus has been applied to the patient. The use of such signals suffer from a rather cumbersome setup and the heavy preprocessing of the EEG in order to extract the small evoked signals of interest from the background EEG. These systems also acquired other physiological quantities such as temperature, blood pressure, heart rate, etc...

Another invention using evoked potentials is described in John, US Pat. No 6,067,467 issued May 23, 2000. This invention further relies on the relative power in the band 3.5 to 7.5 Hz, which is used as an indication of blood flow and pain. A scoring algorithm is used to classify the patient's hypnotic state. The preferred embodiment for this invention is the close loop control of anesthetics drugs. A similar concept of close loop anesthesia using auditory evoked potentials was patented by Mantzaridis, WO 98/10701 issued September 10, 1997.

The use of time domain methods and frequency analysis to derive a number of parameters from spontaneous EEG has been thoroughly investigated. In Kangas, US Pat. No 5,775,330 issued July 7, 1998, the inventor discloses such a technique to classify hypnotic states during clinical anesthesia. This prior art system further relies on a neural network to reach a single univariate descriptor. Maynard, US Pat. No 5,816,247 issued October 6, 1998, also uses a similar analysis and a neural network for the classification of sleep states. Finally, in Schultz, US Pat. No 6,011,990 issued January 4, 2000, an autoregressive model of the EEG supplements the spectral analysis. A multivariate classification function is further used to generate an appropriate index representative of the patient's hypnotic state.

Ennen, US Pat. No 6,317,627 issued November 13, 2001, also uses spectral analysis. However, the disclosed invention uses additional observers that are further combined into a univariate index using component analysis.

Higher order spectral analysis have generated lots of interest since the early 1990s. Chamoun, US Pat. No 5,320,109 issued June, 1994, and US Pat. No 5,458,117 issued October 17, 1995, uses bispectral analysis combined with classical spectral analysis to derive an index of hypnosis. This invention's output is a weighted sum of the different measurements of which parameters are mainly derived using spectral and higher order spectral analysis.

In Merilainen, WO 01/24691 issued September 30, 2000, the inventor discloses a system that measures the patient's brain activity by means of a light directed towards the patient's forehead. The light is filtered by the patient's tissues and the analysis of the resulting optical signal gives an indication of the patient's cerebral state.

Finally, in Vierto-Oja, WO 02/32305 issued April 25, 2002, the inventor uses the entropy of patients' EEG to ascertain their cerebral state. In one embodiment, the inventor combines a parameter obtained from spectral analysis of the Electromyogram (EMG) to provide a fast indication of change of the patient's state.

While spectral and higher order spectral analysis are the key techniques used in the prior art to provide an accurate and reliable index of hypnosis, clinical practice has shown that some delay exists between the change of the patient's anesthetic state and the changes in the indices that are available today. Although the disclosed techniques of Chamoun and Ennen are already being used with success in the operating room, an index reacting faster to changes in a patient's state is desirable. This is particularly true in the context of close loop anesthesia where a fast index will increase the stability of the system, hence allowing for better performance. Spectral and high order spectral analysis are particularly suited for signals with repetitive patterns. However, the electroencephalogram is typically a noise-like signal that does not exhibit observable patterns.

The use of auditory or somatosensory evoked potentials has also been thoroughly investigated by the research community. These potentials are particular patterns embedded in the electroencephalogram itself, and resulting from the external excitation of sensory functions. These patterns are clearly different whether the sensory information can be processed by cognitive functions (e.g. awake patient) or not (e.g. anesthetized patients). However, the analysis of these signals suffer from poor signal to noise ratio. Hence, considerable averaging in necessary to extract these potentials, which makes this technique unreliable in detecting rapid changes in patients' state.

Wavelets have generated great interest in the biomedical field. Their very low computational complexity associated with excellent joint time-frequency resolution properties makes them particularly well suited for the analysis of time-varying, non-stationary signals such as the EEG. Wavelets have been successfully used as a diagnostic tool to capture small-scale transients and events within the EEG, as well as to extract various features and waveform patterns from the EEG. Also, wavelets have been used in pre-processing of the EEG, when used as input signal to a neural network, and for the de-noising and compression of EEG data. However, no prior patent addresses the use of wavelet analysis in the context of spontaneous EEG analysis and diagnosing for clinical anesthesia.

Prior art by Gillberg, WO 00/69517, proposes the analysis of heart rhythms using wavelet analysis applied to electrocardiogram (ECG) signals. The digitized signals are analyzed by transforming them into wavelet coefficients by a wavelet transform. The higher amplitude coefficients are identified and compared with corresponding sets of template wavelet coefficients, which are derived from signals of heart rhythms of known type. This method is used to discriminate normal from abnormal rhythms.

The object of the disclosed method and apparatus is the use of wavelet analysis to extract an univariate feature from a spontaneous EEG signal that correlates to the patient's hypnotic state (referred to throughout this patent as the ***WAV****elet index* - abbrev. WAV), hence avoiding the complex and time consuming discriminant analysis and/or neural network training done in the prior art.

Furthermore, prior art systems are characterized by a significant time delay between the patients' true hypnotic state and the computed indices. This time delay is either the result of the analysis technique itself – such as in spectral and higher order spectral analysis – or the consequence of the large averaging needed in case of evoked potential analysis. Therefore, it is the object of the present invention to significantly reduce this time delay by using a different analysis technique applied to spontaneous EEG. This makes of the WAV a more precise feedback quantity for the monitoring, and/or manual/automatic control of anesthesia.

Finally, while prior art systems rely on extensive tuning based on a large number of experimental data, it is an object of this invention to develop a method for diagnosing patients' hypnotic state which does not require neither a large subject pool, nor an extensive database of clinical EEG data.

2 Brief Summary of the Invention

The present invention comprises of a method and an apparatus for the reliable discrimination between various levels of a patient's hypnotic/consciousness state during general anesthesia. This is achieved by means of a wavelet transform based method for analyzing the patient's EEG signal. This signal can be acquired using any existing EEG recording device.

Wavelets are classes of functions with properties suitable for the analysis of non-stationary or transitory features that characterize most signals of interests found in biomedical applications. Wavelet analysis uses wavelets as basis functions for signal decomposition. Wavelet analysis can be viewed as a generalization of Fourier analysis since it introduces time localization in addition to frequency decomposition of a signal. Thus, wavelets are capable of capturing signal features such as small-scale transients, breakpoints, discontinuities as well as general trends and self-similarity, which cannot be measured by classical spectral techniques. For instance, Fourier analysis is not well suited for capturing such features, as it discards all the time information. Wavelets – classes of wave-like functions with a finite number of oscillations, an effective length of finite duration and no offset component – form a basis for the lossless decomposition of a given signal. Their shape further facilitates the analysis of fast transitory signals.

In the present invention the use of wavelet transform based techniques significantly reduces the computational complexity to perform the task of assessing the patients' hypnotic state based on their acquired EEG signal. Neither a large number of patients nor an extensive amount of clinical EEG data are needed to produce the index of hypnosis disclosed herewith. The methodology of the present invention may also be used to discriminate between different sleep stages, awareness levels in subjects performing safety critical activities, to predict seizure duration in Electroshock Therapy (ECT), to monitor the changes in the cerebral metabolic rate or to establish the blood characteristics at the cortical level. However, the preferred embodiment disclosed below is directed towards the assessment of the patient's hypnotic/consciousness level during general anesthesia.

The disclosed embodiment extracts, in real time, a *feature function* from a patient's EEG. This function characterizes patients in terms of their hypnotic state. It is further compared, in real time, with two *templates* that are characteristic of the awake and anesthetized hypnotic states. The comparison yields an index that is later referred to as ***WAV****elet index* (abbrev. WAV).

The feature function is a statistical representation of the wavelet coefficients obtained by applying a wavelet transform onto the signal. These coefficients may be obtained by standard dyadic discrete wavelet transform (DWT), by discrete stationary wavelet transform (SWT), or by wavelet packet transform. The choice of the wavelet transform (i.e. DWT, SWT or wavelet packets) determines the computational complexity of the method. In the disclosed embodiment, the feature function is the probability density function (PDF) of the wavelet coefficients in the frequency band that gives the best discrimination between the awake and anesthetized templates.

The templates are two feature functions representing the awake and anesthetized states. They are extracted off-line from two training data sets, corresponding to the awake and the anesthetized state. They are then stored for real time implementation. The selected family of wavelet bases maximizes the dissimilarity between the template feature functions of the awake and anesthetized states. Daubechies wavelet filters of higher order are particularly well suited for performing this task.

The comparison between the feature function of the unknown EEG waveform against the template feature functions of the awake and anesthetized states can be based on the computation of the correlation between these functions. However, a computationally less demanding solution is to quantify the similarity between these functions by computing the L1 (Manhattan), L2 (Euclidean), or any distance metrics. The result of this comparison yields two values, each expressing the likelihood of a patient being awake or anesthetized. These two values are further combined into a single value corresponding to a univariate index of hypnotic/consciousness state, the **WAV**elet index.

We claim that the **WAV**elet index (WAV), as derived from wavelet analysis of the electroencephalographic (EEG) is:

- able to distinguish the awake state of consciousness and the anesthetized state of consciousness during the various stages of general anesthesia,
- able to distinguish increasing and decreasing depths of general anesthesia,
- is able to immediately detect the loss of consciousness during the induction of general anesthesia, thus providing an endpoint for individual titration of intravenous induction agents.

3 Drawings

Fig. 1 Overview of the apparatus for estimating the hypnotic state based on wavelet analysis.

Fig. 2 Pre-processing function.

Fig. 3 Comparator function.

Fig. 4 3-level DWT filter bank.

Fig. 5 Analysis tree (approximations and details) for DWT/SWT and wavelet packet.

Fig. 6 Frequency bands for the analysis tree.

Fig. 7 Templates for the awake, anesthetized and deeply anesthetized (isoelectric EEG) states using the d_1 band and the Daubechie #14 wavelet filter.

4 Detailed Description of the Invention

This invention relies on the wavelet decomposition of a single channel EEG recorded from a patient. Figure 1 gives an overview of the present invention in its preferred embodiment.

The invention is based on the wavelet decomposition of the EEG epoch in the wavelet analyzer unit **8**. This unit **8** applies the wavelet transform onto the epoch delivered by the preprocessing unit **7**, and then extracts the feature function correlated to the hypnotic state from the corresponding wavelet coefficients. This feature function is further delivered to the comparator unit **9**, where it is compared with two template feature functions corresponding to the known hypnotic states - awake and anesthetized. These template functions are calculated off-line and stored in **10** for the real time comparison in the comparator **9**. The result of comparison is further integrated into an index of hypnosis, which is the input of the scaling **11** and filtering **12** units. Finally, the output of unit **12** is displayed by display unit **6**.

In order to make the description of the disclosed invention clear and precise, it is necessary to first review in brief the theory of wavelet analysis employed within.

4.1 Wavelet Analysis

Wavelet analysis represents a signal as a weighted sum of shifted and scaled versions of the original mother wavelet, without any loss of information. A single wavelet coefficient is obtained by computing the correlation between the scaled and time shifted version of the mother wavelet and the analyzed part of a signal. For efficient analysis, scales and shifts take discrete values based on powers of two (i.e. the *dyadic* decomposition). For implementation, filter bank and quadrature mirror filters are utilized for a hierarchical signal decomposition, in which a given signal is decomposed by a series of low- and high-pass filters followed by downsampling at each stage, see Figure 4. This analysis is referred to as Discrete Wavelet Transform (DWT). The particular structure of the filters is determined by the particular wavelet family used for data analysis and by the conditions imposed for a perfect reconstruction of the original signal.

The approximation is the output of the low-pass filter, while the detail is the output of the high-pass filter. In a dyadic multiresolution analysis, the decomposition process is iterated such that the approximations are successively decomposed. The original signal can be reconstructed from its details and approximation at each stage (e.g. for a 3-level signal decomposition, a signal S can be written as S=A3+D3+D2+D1), see Figure 5. The decomposition may proceed until the individual details consist of a single sample. The nature of the process generates a set of vectors (for instanced $\mathbf{a}_3$, $\mathbf{d}_3$, $\mathbf{d}_2$, and $\mathbf{d}_1$ in the three level signal decomposition), containing the corresponding coefficients. These vectors are of different lengths, based on powers of two, see Fig. 4. These coefficients are the projections of the signal onto the mother wavelet at a given scale. They contain signal information at different frequency bands (e.g. a_3, d_3, d_2, and d_1) determined by the filter bank frequency response. DWT leads to an octave band signal decomposition that divides the frequency space into the bands of unequal widths based on powers of two, see Fig. 6.

The Stationary Wavelet Transform (SWT) is obtained in a similar fashion, however, the downsampling step is not performed. This leads to a redundant signal decomposition with better potential for statistical analysis. The frequency space division is the same as for DWT, see Fig. 6.

Despite its high efficiency for signal analysis, DWT and SWT decompositions do not provide sufficient flexibility for a narrow frequency bandwidth data analysis (Fig. 4.a). Wavelet packets, as a generalization of standard DWT, alleviate this problem. At each stage, details as well as approximations are further decomposed into low and high frequency signal components. Figure 4.b shows the wavelet packet decomposition tree. Accordingly, a given signal can be written in a more flexible way than provided by the DWT or SWT decomposition (e.g. at level 3 we have S=A1+AD2+ADD3+DDD3, where DDD3 is the signal component of the narrow high frequency band ddd_3). Wavelet packet analysis results in signal decomposition with equal frequency bandwidths at each level of decomposition. This also leads to an equal number of the approximation and details coefficients, a desirable feature for data analysis and information extraction. Figure 6 illustrates frequency bands for the 3-level wavelet packet decomposition.

4.2 Method for the Estimation of the Hypnotic State Using Wavelet Analysis of the EEG

This invention discloses and implements a method based on the wavelet decomposition of the EEG signal recorded from a patient. Statistical information correlated to the hypnotic state is extracted from the wavelet coefficients and further compared with two template feature functions. These functions are extracted from two EEG signals corresponding to two different and known hypnotic states (awake and anesthetized).

The first signal corresponding to the awake state is a combination of EEG signals acquired from different awake subjects (population norming). The second signal corresponding to the anesthetized state is also a combination of EEG signals acquired from different anesthetized patients, but with the same known hypnotic level, evaluated according to the anesthesiologist's assessment.

These signals were pre-filtered to reject very low frequency components and very high frequencies, as well as the eventual electromagnetic interference due to the mains using a notch filter. Epochs of a fixed duration T_e were digitized by an ADC, and acquired at a fixed sampling rate f_s.

Both template signals contained M epochs with $N = f_s \cdot T_e$ samples and no apparent artifacts. These two signals form two training data sets that carry sufficient information to discriminate the awake baseline state from the anesthetized state. These data sets can be written as:

$$\begin{cases} T_w = \{\mathbf{x}_{w,k}, k = 1, 2, ...M\} & \text{(awake)}, \\ T_a = \{\mathbf{x}_{a,k}, k = 1, 2, ...M\} & \text{(anesthetized)} \end{cases} \tag{1}$$

where the vectors $\mathbf{x}_{\bullet,k}$ contain N samples representing the k^{th} epoch of either the awake or anesthetized data set. Subscripts w and a stand for "awake" and "anesthetized" states, respectively. To characterize the data sets, a particular feature can be extracted from each epoch. The feature extraction function, f is defined as:

$$f : \mathbf{x}_{\bullet,k} \longrightarrow f(\mathbf{x}_{\bullet,k}) = \mathbf{f}_{\bullet,k} \tag{2}$$

Each epoch $\mathbf{x}_{\bullet,k}$ is associated with a feature $\mathbf{f}_{\bullet,k}$. This feature can be either a scalar or a vector. Then, a particular state is characterized by averaging the set $\{\mathbf{f}_{\bullet,k}\}$ over the corresponding training data set. This results in two averaged features $\overline{\mathbf{f}_w}$ and $\overline{\mathbf{f}_a}$ defined as:

$$\begin{cases} \overline{\mathbf{f}_w} = \frac{1}{M} \cdot \sum_{k=1}^{M} \mathbf{f}_{w,k} \\ \overline{\mathbf{f}_a} = \frac{1}{M} \cdot \sum_{k=1}^{M} \mathbf{f}_{a,k} \end{cases} \tag{3}$$

These are representatives of the awake and the anesthetized state. In order to assess the hypnotic state of a patient, it is sufficient to record the patient's EEG and calculate the feature $\mathbf{f}$ for each epoch. Comparing this value to $\overline{\mathbf{f}_w}$ and $\overline{\mathbf{f}_a}$, it is possible to calculate the likelihood for the patient to be either awake or anesthetized. Hence, two indexes i_w (awake) and i_a (anesthetized) are defined such that:

$$\begin{cases} i_w = ||\mathbf{f} - \mathbf{f}_w||_1 \\ i_a = ||\mathbf{f} - \mathbf{f}_a||_1 \end{cases} \tag{4}$$

where the norm $|| \cdot ||_1$ is defined as:

$$||\mathbf{x}||_1 = \sum_{j=1}^{N} |x_j| \tag{5}$$

The norm $||\cdot||_1$ accurately quantifies the difference between $\mathbf{f}$ and $\overline{\mathbf{f}_\bullet}$ by integrating the distance between the two vectors. Higher degree norms can be used for this analysis, or the correlation function between two vectors. However, they would emphasize large differences and lead to a noisier index.

The main difficulty is obviously the selection of an appropriate function f. As mentioned in the previous section, each EEG epoch can be decomposed using SWT into a set of coefficients $\mathbf{a}$ and $\mathbf{d}_j$:

$$\mathbf{x} \longrightarrow \{\{\mathbf{a};\mathbf{d}_j\}, j = 1, 2 \cdots L\} \tag{6}$$

where L is the level of decomposition. Each vector $\mathbf{d}_j$ represents the detail of the signal in a specific frequency band d_j, and the vector $\mathbf{a}$ represents the signal approximation at the highest level of decomposition. As for the feature used to characterize each EEG epoch, the Probability Density Function (PDF) of a chosen wavelet detail band d_j is selected:

$$f : \mathbf{x} \longrightarrow f(\mathbf{x}) = \mathbf{f} = \mathrm{PDF}(d_j) \tag{7}$$

This choice is motivated by the fact that the probability density function does not emphasize large nor small coefficients but, conversely, tends to focus more on the general content of each wavelet decomposition band. This property is indeed used when dealing with noise-like signals such as the EEG. Other statistical functions, such as the variance or standard deviation of the wavelet coefficients, can also be considered.

Another difficulty arises when selecting an appropriate wavelet filter and choosing the best detail coefficient vector $\mathbf{d}_j$ for carrying out the analysis. To compare the effectiveness of different wavelets, it is necessary to introduce the discrimination parameter D:

$$D = ||\overline{\mathbf{f}_\mathbf{a}} - \overline{\mathbf{f}_\mathbf{w}}||_1 \tag{8}$$

The discrimination parameter, D, quantifies the difference between $\overline{\mathbf{f}_\mathbf{a}}$ and $\overline{\mathbf{f}_\mathbf{w}}$. Obviously, to better distinguish between the awake and anesthetized states, it is necessary to maximize D (i.e. select the wavelet filter and frequency band of decomposition that gives the highest value for D).

The wavelet selection method has been applied to training data sets obtained from awake subjects and anesthetized patients. The sets have been processed to derive the averaged features $\overline{\mathbf{f}_\mathbf{w}}$ and $\overline{\mathbf{f}_\mathbf{a}}$ and D. Using as an example a 128 Hz sampling frequency, the analysis using DWT and SWT and the Daubechies wavelet family has clearly singled out the probability density function of the band d_1 as the most discriminating. This result is interesting since the d_1 band corresponds to the detail in the 32-64 Hz frequency range of the EEG signal. In neurophysiology, this particular frequency band, referred to as the γ-band, often is discarded in classical power spectral analysis since it carries a very small amount of the EEG energy. Figure 7 illustrates the templates characterizing the awake and anesthetized states.

A similar conclusion using wavelet packets can be reached. Using a 3-level decomposition, the selection for the best wavelet yielded the band dda_3 (48-56 Hz) as the most discriminating, in conjunction with the wavelet filter Daubechies #8. Other bands can also be considered.

Note that any wavelet family (Daubechies, Coiflets, Symmlets, biorthogonal and reverse biorthogonal), and at any order, can be used for the analysis. The accuracy of the results will vary.

In the preferred embodiment, the signal is decomposed using the SWT, and the 32-64 Hz band is selected, along with the Daubechies #14 wavelet.

4.3 Apparatus for the Estimation of the Hypnotic State Using Wavelet Analysis of the EEG

While any EEG channel would be suited for the analysis, the electrodes **1** are preferably placed on the patient's **2** forehead. This implementation allows for a greater ease of use. Another reason is that the frontal and prefrontal lobes (which are at the origin of higher cognitive functions) are located directly behind the forehead.

Two electrodes, with a third electrode as a common reference, form a single frontal EEG channel. This signal is input **3** into the amplifier and an Analog/Digital Converter (ADC) unit **4**. After amplification, the signal is pre-filtered to reject low frequency components (e.g. $<$ 0.5 Hz) and very high frequencies (e.g. $>$ 100 Hz), as well as the eventual electromagnetic interference due to the power network (typically 50 Hz or 60 Hz) using a notch filter.

EEG epochs of a fixed duration T_e are digitized by the ADC and acquired at a fixed sampling rate f_s. In the preferred embodiment, the epoch length is typically 1 s and sampled at a frequency of 128 Hz. While it is possible to sample the signal at a higher sampling rate, the use of lower sampling rates is not recommended.

Digitized epochs containing $N = f_s \cdot T_e$ samples are then input, one at the time, into the digital signal processing unit **5**, where the **WAV**elet index is calculated in real time by means of a wavelet analysis based method. This resulting index is further displayed by the display unit **6**.

All parts of the digital signal processing unit **5** are described in details in the following.

4.3.1 Pre-processing Unit

Once an epoch has been acquired, it is sent to the pre-processing unit, see Figure 2. It is first stored as a vector **x** **16** of length N. The mean value $\overline{\mathbf{x}} = \sum_{k=1}^{N} x_k$ is removed **17**. This offset is due to the signal acquisition process as the EEG is a zero-mean signal. The root mean square amplitude **18** of the epoch is then calculated as:

$$rms = \sqrt{\frac{1}{N} \cdot \sum_{k=1}^{N} (x_k)^2} \tag{9}$$

Epochs with amplitudes greater than some maximum value (e.g. 200 μV) and less than some minimum value (e.g. 2 μV) are then rejected. It is indeed assumed that they contain either artifacts such as ocular and electrocautery artifacts or isoelectric EEG. If the amplitude is within the two bounds **19**, a flag **22** indicating that the epoch is not corrupted takes the value 1. In this case, the epoch is normalized **23** as:

$$x_k = \frac{x_k}{rms}, \qquad k = 1, \cdots, N \tag{10}$$

The amplitude normalization allows better focus on the phase and frequency content of the EEG, rather than its amplitude. Also, this eliminates the influence of electrodes' impedance on the calculation of the index.

The apparatus then proceeds to the next stage, (i.e. the wavelet analyzer unit denoted by **8** in Figure 1).

If an artifact is present **20**, the flag is put to 0 and the algorithm proceeds to the scaling unit **11**.

If an isoelectric EEG is detected **21**, it is indicative that the patient is in the deepest level of hypnosis. Hence the flag takes the value 1 and the variable `WAV_unfilt` **24** takes the value of 0. The apparatus then proceeds to send the signal to the filtering unit **12**.

Note that the pre-processing unit **7**, may also utilize more sophisticated artifact removal methods, such as described in Zikov *et al* [1].

4.3.2 Wavelet Analyzer Unit

After the pre-processing stage, the input of the wavelet analyzer unit **8** is a normalized epoch (rms amplitude of 1) that does not contain any large artifacts.

The wavelet analyzer unit **8** first calculates the wavelet coefficients applying the SWT and the wavelet filter Daubechies #14 to the pre-processed EEG epoch. The coefficients are obtained by convolution of the EEG epoch with the wavelet filter.

The coefficients corresponding to the band selected in the off-line analysis as the most discriminating (in this embodiment: d_1) are then stored in a vector $\mathbf{C}$. The probability density function is then obtained by calculating the histogram of the coefficients in vector $\mathbf{C}$. The vector of histogram contains b coefficients, where b is chosen number of bins (e.g. 100). Each element of this vector is then divided by the total number of coefficients in d_1 band, i.e. by the length of a vector $\mathbf{C}$. The result is a vector **pdf** of length b, which represents the probability density function of wavelet coefficients in d_1 band obtained by the wavelet decomposition of the epoch $\mathbf{x}$.

4.3.3 Comparator Unit

The resulting **pdf** vector is input into comparator unit **9**, see Fig. 3. This unit compares the **pdf** vector of a current epoch **13** with two template vectors $\mathbf{pdf_w}$ and $\mathbf{pdf_a}$ representing two known hypnotic states awake **14** and anesthetized **15**.

The awake template **14** is derived from a combination of EEG signals obtained from a group of healthy awake subjects (population norming). This template can be then stored on a mass storage device for future real time comparison. Another possibility is to record the patient's EEG while the patient is still awake, and then derive the awake template (self-norming).

The anesthetized template **15** is the PDF of the wavelet coefficients of an isoelectric signal, which corresponds to the deepest level of hypnosis. All coefficients are equal to 0. Hence, this particular PDF is a Dirac function centered at the origin.

The comparison **25** between the **pdf 13** calculated in the wavelet analyzer unit **8** and the two templates $\mathbf{pdf_w}$ **14** and $\mathbf{pdf_a}$ **15** is achieved using the L1 distance metric. This comparison yields two values i_w **26** and i_a **27** calculated as:

$$\begin{cases} i_w = \frac{1}{N} \cdot \sum_{k=1}^{b} |pdf_k - pdf_{w,k}|, \\ i_a = \frac{1}{N} \cdot \sum_{k=1}^{b} |pdf_k - pdf_{a,k}| \end{cases} \tag{11}$$

where pdf_k, $pdf_{w,k}$, and $pdf_{a,k}$ denote the $\mathrm{k^{th}}$ elements of the vectors **pdf**, $\mathbf{pdf_w}$, and $\mathbf{pdf_a}$ respectively.

Note again that while the L1 norm provides a computationally efficient method to compare the feature function against both templates, any norm of any order can also be used.

An index i **29** is then generated by calculating **28** the difference between i_w **26** and i_a **27**:

$$i = i_w - i_a \tag{12}$$

The output of the comparator unit is then input to the scaling unit **11**.

4.3.4 Scaling Unit

The index i is scaled in order to take values between 0% (corresponding to isoelectric signal) and 100% (corresponding to the awake baseline) with higher values indicating higher level of consciousness or awareness:

$$i = i \cdot scale + offset \tag{13}$$

$scale$ and $offset$ are two fixed values calculated in the offline analysis. In the preferred embodiment, values like $scale = 30$ and $offset = 56.4$ produced the best results. The result of the scaling is further stored into the variable `WAV_unfilt` **24**.

4.3.5 Filtering Unit

The variable `WAV_unfilt` **24** contains the unfiltered version of the final **WAV**elet index. The random character of the EEG dictates that in order to extract a meaningful trend of the patient's hypnotic state it is necessary to smooth this variable using a filter.

A new value `WAV_unfilt` is delivered by the scaling unit **11** for every epoch (i.e. every second in the preferred embodiment). However, note that if the current epoch is corrupted with an artifact (`flag=0` **22**), the variable `WAV_unfilt` can take an arbitrary value, as it will not be used to derive the final value of the index.

In the preferred embodiment, the variable `WAV_unfilt` is averaged over the past 30 seconds of data. The result of the averaging filter is stored in the variable `WAV`. However, when calculating the average, only uncorrupted epochs are taken into account (by investigating the corresponding `flag` variable).

Furthermore, in order to account for poor signal quality, if more than a certain number of previous epochs during last 30 seconds are corrupted due to numerous artifacts (e.g. 15), the monitor is unable to give an accurate estimate of the patient's hypnotic state. In that case, the variable `WAV` takes the value -100%.

The output variable `WAV` of the averaging filter is then sent to the display unit **6**. In case of poor signal quality, a message indicating the presence of numerous artifacts is sent to be displayed by the display unit.

Other techniques and filters such as moving average, Finite Impulse Response (FIR), Infinite Impulse Response (IIR) can also be used.

4.3.6 Display Unit

The `WAV` variable is finally displayed to the anesthesiologist using any standard display device (Cathode Ray Tube (CRT), Liquid Crystal Display (LCD), printer, etc...). In the preferred embodiment, the variable is displayed as a trend, or as a number, and can further be used as a measurement signal in the context of a feedback controller which does not make the object of the current disclosure.

5 Abstract of the Disclosure

The preferred embodiment proposes a method and apparatus to monitor the hypnotic state of a patient undergoing general anesthesia. The methodology of the present invention may also be used to discriminate between different sleep stages, predict the duration of ECT induced seizures, and awareness levels in subjects performing safety critical activities. It can also be used to monitor the changes in the cerebral metabolic rate. The index of hypnosis disclosed herewith (i.e. the **WAV**elet index) has the advantage of reacting within one second to changes in the patient's hypnotic state. Based on wavelet decomposition and statistical analysis, the computational complexity of the algorithm is low, making it implementable on a microprocessor. The proposed method is a single descriptor of the activity of the EEG signal within the gamma frequency band. Neither a large subject pool nor an extensive database of clinical EEG data are needed for tuning the index.