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Prediction of Nociceptive Responses during Sedation by Time-Frequency Representation

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***Abstract*— The level of sedation in patients undergoing medical procedures evolves continuously, such as the effect of the anesthetic and analgesic agents is counteracted by pain stimuli. The monitors of depth of anesthesia, based on the analysis of the electroencephalogram (EEG), have been progressively introduced into the daily practice to provide additional information about the state of the patient. However, the quantification of analgesia still remains an open problem. The purpose of this work is to analyze the capability of prediction of nociceptive responses based on the time-frequency representation (TFR) of EEG signal. Functions of spectral entropy, instantaneous power and instantaneous frequency were calculated in order to predict the presence or absence of the nociceptive responses to different stimuli during sedation in endoscopy procedure. Values of prediction probability of P_k above 0.75 and percentages of sensitivity and specificity above 70% and 65% respectively were achieved combining TFR functions with bispectral index (BIS) and with concentrations of propofol (Ce_{Prop}) and remifentanil (Ce_{Remi}).**

I. Introduction

The aggression that occurs on patient undergoing surgery triggers a series of responses in the body and in the tissue that may have implications on the outcome of the surgical process. To mitigate the intensity of these responses, a certain level of protection or "anesthetic state" must be achieved. The anesthetic state may be defined as the combination of pharmacological effects that minimize the impact of surgical aggression in the patient.

For several years, various methods have been developed for the noninvasive assessment of the level of consciousness during general anesthesia [1-5]. Since the main action of anesthetic agents occurs in the brain, a reasonable choice is to monitor the electroencephalographic signal (EEG). Changes on the EEG signal are directly related to biochemical variations of a drug induced in the brain and the effects on individual behavior. According to various methods, different EEG monitors have been developed. The three most important monitors consider bispectrum (BIS, A-2000 monitor, Aspect Medical, USA) [6,7], entropy (SE and RE - State and Response Entropy, S/5 Entropy Module, GE Healthcare, Finland) [8] and auditory evoked potentials (AAI, AEP Monitor/2, Danmeter, Denmark) [9,10] whereas the most recent is the qCON (Quantium Medical, Spain) [11].

However, it has not been possible to develop a system capable of quantifying analgesia. The classic methods include hemodynamic response, analysis of electrocardiographic waveforms variability, degree of respiratory sinus arrhythmia, plethysmographic response [12], pulse wave, skin conductance [13], and more recently the Surgical Stress Index (SSI ®) [14], and the ANI (Metrodoloris, France) [15], based on the heart rate variability. None of them has proven to be clinically useful methods because they are influenced by the response of the autonomic nervous system (ANS) and they are sensitive to other disturbances, such as changes in blood pressure or heart rate due to patient's baseline condition (hypertension, arrhythmias of diverse etiology), sympathomimetic drug delivery or unpredictable situations such as perioperative bleeding.

In this work, indexes based on Time-Frequency representation (TFR) were proposed in order to assess the prediction of the response to pain stimulation on the EEG signal during endoscopy procedure. Several variables were defined and statistical analysis was performed in order to evaluate the prediction of responding to the application of a painful stimulus such as nail bed compression or endoscopy tube insertion. EEG windows of 60 seconds were taken between 30 s and 90 s before the application of each stimulus in order to avoid the effect of the stimulation on the signal (evoked potential, movement artifact, EMG, etc.).

II. Materials and Methodology

A. EEG Database and Preprocessing

The database belongs to the Department of Anesthesiology, Hospital Clínic of Barcelona (Spain). This database contains data recorded from more than 300 patients undergoing sedation-analgesia for endoscopic procedures. For each patient, the following information is available: predicted concentrations of propofol (Ce_{Prop}) and remifentanil (Ce_{Remi}); bispectral Index (*BIS*) and electroencephalogram (EEG) signal. The observed categorical responses after applied nociceptive stimuli include the evaluation of the Ramsay Sedation Scale level (RSS) (see Table I) [16] after nail bed compression and the presence of gag reflex during endoscopy tube insertion (GAG).

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All the patients belong to 1-3 ASA classification. Patients with altered central nervous system, medicated with analgesics or drugs with central effects on the perception of pain, from moderate to severe cardiomyopathy, neuropathy or hepatopathy that needed control during the anesthetic process were not included in the database.

The EEG was recorded with a sampling frequency of 900 Hz, with a resolution of 16 bits and a recording time of about 60 min. All information Ce_{Prop}, Ce_{Remi}, BIS, RSS and GAG were annotated with a resolution of 1 second. After the application of a FIR band pass filter of 100th order, with cut-off frequencies of 0.1-45Hz, the EEG signals were resampled at 128 Hz. Then, the EEG signals were segmented in windows of length of 1 minute between 30 s and 90 s before the response annotation of RSS or GAG.

The annotated RSS was assigned to the previous 1 minute length window if the differences ΔCe_{Remi} and ΔCe_{Prop} between the first and the last second of the window were ΔCe_{Remi}<0.1 μg/ml and ΔCe_{Prop}<0.1 μg/ml. Otherwise, the window was cut at the sample where the conditions were satisfied. Windows of EEG containing high amplitude peak noise were processed with a filter based on the analytic signal envelope (ASEF) [17]. If the difference between adjacent samples were higher than 10% of the mean of the differences of the previous samples, the windows were cut. If the length of the window preprocessed was less than 5 seconds, the window was not analyzed.

TABLE I.
RAMSAY SEDATION SCALE

Score	Response
1	Anxious or restless or both
2	Cooperative, orientated and tranquil
3	Responding to commands
4	Brisk response to stimulus
5	Sluggish response to stimulus
6	No response to stimulus

B. Time-Frequency Representation

Time-Frequency Representation (TFR) based on Choi-Williams distribution (CWD) (1) is calculated by convoluting the Wigner distribution (WD) (2) and the Choi-Williams (CW) exponential (3), [18,19]

$$T_{xx}(t,f) = \iint_{-\infty}^{\infty} h(t-t', f-f')\, Wx(t',f')dt'df' \quad (1)$$

$$Wx(t,f) = \int_{-\infty}^{\infty} x(t+\tau/2)\; x^*(t-\tau/2)e^{-j2\pi f\tau}d\tau \quad (2)$$

$$h(t,f) = \sqrt{\frac{4\pi}{\sigma_c}}e^{-4\pi^2\frac{(tf)^2}{\sigma_c}} \quad (3)$$

In this work, σ_c was set to 0.005 [19]. For a more accurate analysis, the spectrum was divided into the characteristic frequency bands of the EEG signal: δ, 0.1-4 Hz; θ, 4-8 Hz; α, 8-12 Hz; β, >12 Hz; total frequency band (*TB*), 0.1-45 Hz.

The functions, instantaneous power (*IP*) and instantaneous frequency (*IF*), were obtained from $T_{xx}(t,f)$. *IP* was calculated for each window as the area under the curve of the $T_{xx}(t,f)$ at each instant. In each of the considered bands, this value was normalized by the total power. *IF* was defined as the mean frequency of the spectrum at each instant [19].

Instantaneous spectral entropies were calculated on $T_{xx}(t,f)$ as it is shown in (4) and (5).

$$SE\_Shan(t) = -\sum_{f=f_1}^{f_2} T_{xx}(t,f)log_2(T_{xx}(t,f)) \quad (4)$$

$$SE\_Re_q(t) = \frac{1}{1-q}log_2\left(\sum_{f=f_1}^{f_2} T_{xx}(t,f)^q\right) \quad (5)$$

where f_1 and f_2 are the limits of the frequency bands. $T_{xx}(t,f)$ was normalized by the total area. These non-linear measures were based on the traditional definition of Shannon (*Shan*) and Rényi (*Re*) entropies, where $T_{xx}(t,f)$, for each t, was used instead of the probability mass function. In this way, it is possible to have a measure of the complexity of the spectrum for each instant of time.

Several variables were defined on the TFR functions along the time: mean (*m*) and median (*med*) values of *IP* and *IF*; mean, median, maximum (*max*) and minimum (*min*) values of *SE_Shan* and SE_Re_q. In this work, different values of the control parameter of *Re* were taken into account: q = {0.1, 0.2, 0.5, 2, 3}.

C. Definition of Variables and Statistical Analysis

A non-parametric test, U of Mann-Whitney test, was applied and a significance level p-value <0.05 was taken into account. Variables that satisfy this condition were considered for building a discriminant function, in order to predict the pain responses. The leaving-one-out method was performed as validation method.

For the RSS evaluation, linear discriminant analysis was performed taking into account two groups: variables belonging to windows with responsive levels of RSS, RSS= {2, 3, 4, 5}, and variables belonging to windows with unresponsive level of RSS, RSS=6. The test was repeated 4 times; in each trial the group of responsive levels was progressively reduced by removing the windows of the lowest RSS level: trial1, (2≤RSS≤5) vs RSS=6; trial2, (3≤RSS≤5) vs RSS=6; trial3, (4≤RSS≤5) vs RSS=6; trial4, RSS=5 vs RSS=6. Another analysis was performed taking into account the presence or the absence of GAG, GAG 1 and GAG 0, respectively. Sensitivity (Sen) and specificity (Spe) were calculated for testing the performance of TFR variables. Sensitivity represents responsive states (RSS<6 and GAG 1) and specificity represents unresponsive states (RSS=6 and GAG 0).

The ability of the variables to describe pain responses was also evaluated using prediction probability (P_k), which compares the performance of indicators [20]. The P_k coefficient is a statistic commonly used to measure how well an index predicts the state of the patient. A P_k of 1 represents a perfect prediction and 0.5 is not better than tossing a fair coin. The P_k avoids the shortcomings of other measures being independent of scale units and it does not require knowledge of underlying distributions.

III. Results and Discussion

Tables II to V contain the results of the variables that give the best performances in the prediction of responding to the application of the painful stimulus (RSS or GAG). TFR variables that allow the best P_k for GAG stimulation were found to be mIP_α and $medSE_{\alpha}\_Re_{q=0.1}$ (Table II). These variables also describe the RSS states with $P_k > 0.7$ (Table IV). As it can be seen in Fig. 1a, mIP_α presents a higher median value for unresponsive states (RSS=6 and GAG 0) than responsive states (RSS<6 and GAG 1). These values are also reflected in reverse in the trends of the $medSE_{\alpha}\_Re_{q=0.1}$ (Fig. 1b). From the distributions shown in Figs. 1a and 1b, it can be deduced that the power in α frequency band increases and the complexity of the spectrum decreases when sedation level increases. The distribution of *BIS* values are shown in Fig. 1c.

Tables II and IV show the P_k values and the sensitivity and specificity of the best single variables for both studies of RSS and GAG. It can be noted that α frequency band better characterizes the prediction of stimulus response for RSS and GAG.

In order to increase the percentages of sensitivity and specificity, TFR variables were combined with *BIS*, Ce_{Remi} and Ce_{Prop}. All combinations considered a maximum of four uncorrelated variables. Tables III and V show those variables that give the best classification percentages. The combination of TFR variables with BIS improves the efficiency of the prediction both RSS and GAG. Furthermore, the contribution of drug concentration to the prediction of stimulus response is different in RSS and GAG. Particularly, Ce_{Remi} improves the prediction in GAG study, while Ce_{Prop} increases the efficiency in RSS study.

TABLE II
PRESENCE AND ABSENCE OF GAG REFLEX: ONE VARIABLE

Variables	P_k	Sen N=390	Spe N=122
mIP_α	0.7408	70.5	65.6
$medSE_{\alpha}\_Re_{0.1}$	0.7327	73.0	64.4
BIS	0.7342	72.1	62.3
$minSE_{\theta}\_Re_{0.2}$	0.6113	82.6	31.1

N= number of analyzed windows; P_k: prediction probability;
Sen: (%) sensitivity; Spe: (%) specificity; p-value<0.05

TABLE III
PRESENCE AND ABSENCE OF GAG REFLEX: MULTI VARIABLES

Variables *f(•)*	P_k	Sen N=390	Spe N=122
BIS, mIP_α	0.7591	71.3	66.4
BIS, $medSE_{\alpha}\_Re_{0.1}$	0.7636	74.6	64.9
mIP_α, $medSE_{\alpha}\_Re_{0.1}$	0.7641	71.3	66.7
Ce_{Remi}, mIP_α	0.7769	71.6	66.3
Ce_{Remi}, mIP_α, $minSE_{\theta}\_Re_{0.2}$	0.7956	74.5	69.3
BIS, Ce_{Remi}, mIP_α	0.8053	77.5	67.6
BIS, Ce_{Remi}, mIP_α, $minSE_{\theta}\_Re_{0.2}$	0.8163	74.5	71.9

N: number of analyzed windows; P_k: prediction probability;
Sen: (%) sensitivity; Spe: (%)specificity; p-value<0.05

IV. Conclusions

Time-frequency representation (TFR) function was applied to one-minute windows of EEG signals recorded during endoscopy procedure in order to predict the pain response. Several variables were defined from (TFR) function. The statistical analysis of single variables has not permitted to obtain values of P_k>0.8 for RSS and P_k>0.75 for GAG. In particular, the prediction of RSS decreased from trial1 to trial4.

Values of prediction probability of P_k>0.75 and percentages of sensitivity above 70% and specificity above 65 % could be achieved combining TFR functions with *BIS*. Concentrations of propofol (Ce_{Prop}) and remifentanil (Ce_{Remi}) improve even better the prediction in RSS and GAG tests, respectively. However, this work represents a preliminary study about the advantages taken from the application of TFR function on the prediction of pain response during sedation.

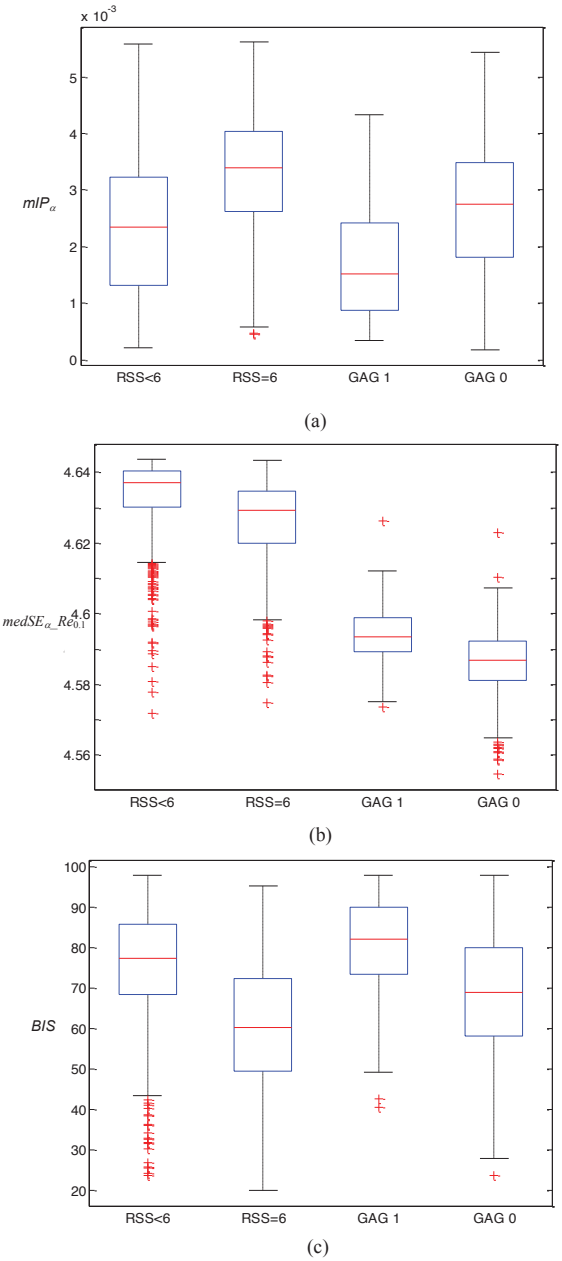

Fig. 1 Distribution of (a) mIP_α, (b) $medSE_{\alpha}\_Re_{0.1}$ and (c) *BIS*. On each box, the central mark is the median, the edges of the box are the 25th and 75th percentiles. The whiskers are lines extending from each end of the boxes to show the extent of the rest of the data. Values beyond the end of the whiskers are considered outliers and marked with a +.

TABLE IV
RSS RESPONSE TO NOCICEPTIVE STIMULATION: ONE VARIABLE

	trial1 (N1=1822, N2=774)			trial2 (N1=1411, N2=774)			trial3 (N1=776, N2=774)			trial4 (N1=354, N2=774)		
Variables	P_K	Sen	Spe	P_K	Sen	Spe	P_K	Sen	Spe	P_K	Sen	Spe
BIS	0.7988	75.5	68.6	0.7633	72.6	66.3	0.6878	67.3	60.7	0.6203	63.8	56.3
$medSE_{TB}\_Re_{0.2}$	0.7263	61.9	74.4	0.7238	60.4	73.4	0.6566	56.3	67.1	0.5929	54.0	61.2
mIP_{α}	0.7238	63.0	69.4	0.6752	60.2	65.5	0.5904	52.4	59.2	0.5817	48.0	56.1
$medSE_{\alpha}\_Re_{0.1}$	0.7290	74.8	53.5	0.7279	75.1	53.5	0.6813	70.2	51.0	0.6445	65.8	49.1
$maxSE_{\alpha}\_Re_{0.1}$	0.7692	78.6	54.8	0.7342	76.4	53.1	0.6644	71.9	49.5	0.6242	69.5	46.9
$minSE_{TB}\_Re_{2}$	0.6033	59.8	56.8	0.6423	61.4	61.9	0.6203	58.9	58.8	0.6015	57.6	55.4
mIP_{β}	0.7097	52.4	82.9	0.7213	51.9	81.7	0.6721	49.1	77.6	0.6129	45.2	74.3
$maxSE_{\alpha}\_Re_{0.5}$	0.7690	78.7	54.5	0.7340	76.3	53.0	0.6640	72.2	49.2	0.6248	69.5	45.8
$mSE_{\alpha}\_Re_{0.5}$	0.7136	73.7	53.2	0.7217	74.1	53.9	0.6813	69.6	52.1	0.6475	66.7	50.1

N1= number of analyzed windows RSS<6; N2= number of analyzed windows RSS=6; P_k: prediction probability; Sen: (%) sensitivity; Spe: (%) specificity; p-value<0.05

TABLE V
RSS RESPONSE TO NOCICEPTIVE STIMULATION: MULTI VARIABLES

	trial1 (N1=1822, N2=774)			trial2 (N1=1411, N2=774)			trial3 (N1=776, N2=774)			trial4 (N1=354, N2=774)		
Variables *f(•)*	P_K	Sen	Spe	P_K	Sen	Spe	P_K	Sen	Spe	P_K	Sen	Spe
BIS, $minSE_{TB}\_Re_{2}$	0.8060	75.6	68.9	0.7726	72.0	66.9	0.6977	67.7	62.0	0.6352	61.0	62.1
mIP_{α}, $medSE_{\alpha}\_Re_{0.1}$	0.7717	72.6	66.3	0.7423	72.4	62.8	0.6806	69.7	53.6	0.6433	65.8	48.4
Ce_{Prop}, mIP_{α}, $medSE_{\alpha}\_Re_{0.1}$	0.7942	75.6	66.5	0.7652	74.2	63.7	0.6920	70.2	55.3	0.6455	67.4	48.1
Ce_{Prop}, mIP_{β}, $maxSE_{\alpha}\_Re_{0.5}$	0.8066	75.1	69.6	0.7799	72.8	69.5	0.7020	65.5	62.9	0.6415	61.5	55.9
BIS, Ce_{Prop}, mIP_{α}, $medSE_{\alpha}\_Re_{0.1}$	0.8074	73.3	71.8	0.7780	71.8	70.0	0.6916	65.9	63.0	0.6225	61.8	58.5
BIS, Ce_{Prop}, mIP_{β}, $mSE_{\alpha}\_Re_{0.5}$	0.8301	77.2	70.0	0.8051	74.9	68.6	0.7292	69.4	63.6	0.6646	65.4	57.0

N1: number of analyzed windows RSS<6; N2:number of analyzed windows RSS=6; P_k: prediction probability; Sen: (%) sensitivity; Spe: (%) specificity; p-value<0.05

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