Integrated Protocol for Objective Pain Assessment

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Abstract: In the absence of any standardized objective aid for measuring pain levels in human body, a manifold of subjective tools have been developed to monitor chronic pain patients and intra-/post-operative analgesic drug management. However, due to the subjective nature of the evaluation methods and tools, pain remains a challenging phenomenon to be characterised for objective assessment and monitoring. In this paper we briefly describe a protocol and methodology for non-invasive evaluation of pain as result of nociceptor stimulation via skin impedance measurements. Both time-frequency domain analysis is performed, providing interesting observations.

1 INTRODUCTION

Clinical literature, as well as biomedical engineering literature, have identified the need of a non-invasive medical device to measure the pain level in an objective manner for patients. Pain is very important phenomena in medicine and biology that includes physiological, sensory, affective, cognitive, behavioural and sociocultural aspects (Copot, 2018). The subjective perception of pain is hard to quantify and the most commonly used measures of pain intensity are subjective methods, such as: numerical rating scale (NRS), visual analogue scale (VAS) and verbal rating scale (VRS) (Shieh, et al., 2018). All tools currently available have a number of limitations: i) they are not based on a mathematical; ii) do not deliver an objective evaluation index, iii) require the intervention by medical staff, iv) not responsive to postoperative efforts of the patient, v) not suitable for time-frequency domain dynamic analysis, vi) do not provide continuous monitoring and vii) they are often not reliable in all measurement conditions (Shieh, et al., 2018). Despite all those limitations, the perception of pain is assessed in conscious awake patients from their personal feedback information. The NRS is the most commonly used pain scale, and patients are asked to rate their pain level on a 0–10 scale.

Recommendations on pain management strategies are based on the index provided by those ratings and/or on caregiver's opinion when patients are not conscious or awake (e.g. infants, children, anesthetized or delirious patients). Evaluating the postoperative pain in intensive care units is a necessary part of the overall treatment plan (Czaplik, et al., 2012). According with recent studies, pain is identified by the American Pain Society (APS) as the fifth vital indicator in diseases and diagnosis chart along with temperature, blood pressure, pulse and respiration rates (Shieh, et al., 2018; Yang, et al., 2017; Merboth and Barnason, 2000; McCaffery and Pasero, 1997).

Ideally, a pain detection and evaluation device should be non-invasive, applicable on any individual and monitor changes in real time and in correlation with the administered medication. To meet the requirements of an objective pain assessment, the concept of a continuous pain measurement by means of non-invasive skin impedance measurements enables clinicians to provide personalized and effective pain management.

The scope of this paper, is to present and discuss such a system. The ANSPEC-PRO prototype has been validated in awake participants with self-induced nociceptor excitation (Copot and Ionescu, in print). Currently, it undergoes a clinical trial on post-operatory awake patients in ICU at Ghent University Hospital, Belgium (B670201734377).

Apart from the studies related to correlations to NRS and other features enabled by such a device, it

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is interesting to investigate memory of pain as part of extracellular tissue dynamics and latency in perception process. This gives an in-depth information that could explain changes in thresholds for pain management decision makers, such as in chronic pain patients.

The paper is organized as follows. The available measurement tools are briefly described in the second section, along with the prototype developed at Ghent University in our lab. Section 3 describes the protocol and methodology proposed to be followed in this study. The results are given in the fourth section along with a short discussion of their usefulness and limitations. A conclusion section summarizes the main outcome of this work and points to further steps.

2 AVAILABLE DEVICES

2.1 Commercial Devices

Objective tools developed for pain measurement during consciousness and unconsciousness of the patients in intensive care units (ICU) are one of the main subject for further research. None of the commercial devices can accurately measure pain levels, despite the efforts to demonstrate the validity and reliability of tested data. The following devices for pain assessment have been developed in the last fifteen years.

Med-Storm Pain Monitor is a medical device intended to determine a patients' sensitivity to pain (http://www.med-storm.com/). The system uses real-time data measurements to measure pain/nociceptive stimuli and awakening during anaesthesia, intensive care, in adults, children and infants. Hence, the exosomatic electrodermal activity is measured in terms of conductance. After different studies, there was developed a standard index (not-standardized method): The Skin Conductance Algesimeter index, which is represented by the skin conductance responses (SCR) per second. The company has already delivered and sold the equipment for clinical research projects or for diagnostic purposes, but is not used by critical care clinicians because Med-Storm Pain Monitor is not considered proper to be a substitute for the medical stuff judgement and it cannot be liable for the results obtained using it (www.med-storm.com). This device is not suitable for awake patients, nor for chronic pain patients.

AlgiScan monitors depth of analgesia in sedated and unconsciousness patients using pupillary reflex dilation (PRD). This method has been studied for the evaluation of the level of sensibility to nociception and in the prediction of the haemodynamic reactions to nociceptive stimuli in volunteers and surgical patients (www.medica.de). The pilot studies relate that in anesthetized patients the pupil increase in size due to an incision/tetanic electrical simulation, measurements that can be highlighted by AlgiScan device which indicates a pain pupillary index (PPI). However, further research is required in order to use AlgiScan as a standardised "objective "device for pain measurement. This device is not suitable for awake patients (discomfort due to blocked eyelid).

MEDASENSE is based on changes in physiological parameters (heart rate, temperature, skin conductance level and more) affected by pain and analgesic medications. The technology combines a non-invasive, finger-mounted probe for collecting the physical data with artificial intelligence algorithms that convert the data into a Nociception Level Index (NOL). The pain-related index is between 0 (no pain) and 100 (extreme pain). This device is not available in Europe.

2.2 ANSPEC-PRO Prototype

ANSPEC – PRO device is a prototype developed with the scope of continuously monitoring the pain in patients who are conscious or not, by measurements of changes in skin impedance (Juchem and Ionescu, in review). An overview is given in Figure 1.

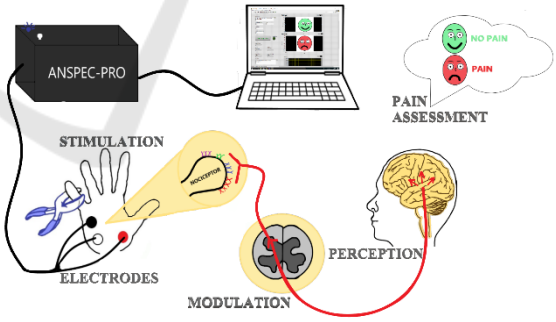

Figure 1: ANSPEC-PRO prototype and afferent components of the system.

The elements of the ANSPEC – PRO device are listed here below.

- *Disposable standard electrodes* – are interfacing the skin and the device and are temporarily attached in the palm of the hand. This is a three-electrode system, two current-carrying electrodes and one pick-up electrode, which picks up the voltage without carrying any currents for no

polarization. The electrodes are disposable (single use only).

- *Data-acquisition circuit* – essentially consists of a power supply for the electrodes and interfaces the microprocessor of the device with the signals acquired by the electrodes. A carefully designed voltage signal is sent to excite a part of the skin using a National Instruments (Texas, USA) device (cRIO9074 with NI9201- and NI9263-slots). The current induced in the circuit by this voltage is related to the bio-impedance of the human skin. A voltage buffer limits the supplied current to +/- 20mA, well below the maximum allowed for *in vivo* studies (5A).

- *DELL Laptop computer* – is used for capture, save and display measured data in real time; is interconnected through Ethernet with the data-acquisition circuit. The laptop is a standard laptop with the operating system Windows 7 Enterprise 64-bit and a INTEL® Core ™ i7-6600U CPU@2.80 GHz processor.

- *User interface* – is developed in LabView.

In short, ANSPEC-PRO device is a non-invasive method for continuously measurements of changes in skin impedance caused by an applied stimulus (pain). The changes in skin impedance reflect changes in the extracellular fluid matrix composition which facilitates the electro-chemical channel communication for pain signalling pathway. Electrical variability in the electrical carrier throughout the signalling pathway, originated by mechanical nociceptor stimulation, affect the response of the skin related in impedance values. The device measures the current $i(t)$ coming from the skin. Also, it acquires the measured signal $v(t)$ with a 15KHz sampling frequency, f_s, and sends it to an analogue output port, using zero-order hold protocol for digital signal processing (Copot, 2018). As part of the signal conditioning step, the current is transformed to a voltage, using a transimpedance amplifier (TIA), which can be then interpreted by the algorithms, as in the Figure 2.

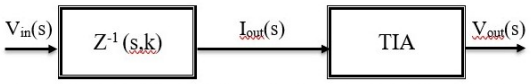

Figure 2: Block diagram with the skin impedance Z(s,k) as black box system.

The bio-electrical-impedance is the Laplace transform equivalent model $Z(s)$, with $s=d/dt$ the Laplace operator, of the ratio of the Laplace transformed voltage $V(s)$ and current $I(s)$ signals. The impedance can be evaluated using spectral identification methods, and further parametric model identification as given in (Ionescu and De Keyser, 2003). The impedance is further evaluated using moving averaged windows over time, such that it depicts a both time- and frequency- domain variability index $Z(s,k)$, with k denoting the discretized time (Pintelon and Schoukens, 2012).

3 PROTOCOL AND METHODOLOGY

3.1 Hypothesis

In this paper, we discuss the two major hypothesis for our study:

1. that a latency exist which implies a minimum time elapsed for nociception stimulation to fade under the threshold for pain pathway to be open – if measurement time between nociception stimulation time intervals is not adequately chosen, one gets residual pain/memory effect. The clinical implication of this is over-dosing.
2. that the impedance of extracellular fluid changes is not dependent on sensor location. The clinical relevance of this hypothesis is that the location of the electrodes may be chosen freely and does not affect the impedance values.

Both hypotheses are made under the further assumption that no other device/sensor/monitor is present on the patient/volunteer at the time of testing.

3.2 Protocol

The participants were the authors of this paper. The biometric information of two volunteers are:

Volunteer #1 – weight 70 kg, height 1.80 cm, age 24 years, female

Volunteer #2 – weight 66 kg, height 1.79 cm, age 24 years, female.

The volunteers approved with the protocol and procedures prior to data collection. Both participants were eligible and reliable for this study, especially because their biometric data are similar and it is expected to have virtually no effect on results. Subjects are clinically healthy, awake and without prior pain or related medications.

The protocol has been designed for 36 minutes and was conducted indoors, as follows.

Case A: participants were asked to sit on a chair and act normally without affecting the sensors attached to the left hand. Data acquisition starts with a reference range of

- 2 minutes when no pain is applied (NP1).

The activity continues with pain/no pain alternation:

- 1 minute nociceptor stimulation applied with a clip on the right hand (P1),
- 1 minute no pain applied (NP2),
- 1 minute nociceptor stimulation applied with a clip on the left hand – same location with the sensors (P2),
- 1 minute no pain applied (NP3),
- 1 minute nociceptor stimulation applied with a clip on the right ear – totally different location with the sensors (P3),
- 2 minutes no pain applied (NP4).

The total period of time for following the procedure in **Case A is 9 minutes**.

Case B: participants were asked to take the same sitting position as in case A. The measuring session starts (NP1) and ends (NP2) also with a period of 2 minutes when no pain is applied to have a reference for the measurements.

Between the reference range of measurements, the procedure has been realised continuously:

- 1 minute nociceptor stimulation applied with a clip on the right hand (P1),
- 1 minute nociceptor stimulation applied with a clip on the left hand – same location with the sensors (P2),
- 1 minute nociceptor stimulation applied with a clip on the right ear – totally different location with the sensors (P3).

The total period of time for following the procedure in **Case B is 7 minutes.**

The time interval elapsed between the two cases for measurement on the same individual was 20 minutes.

In order to investigate the existence of a memory effect of pain or residual pain, the protocol procedures enables to observe differences in data between Case A and Case B (sensors placement is on the left hand, pain location is maintained: right hand (P1), left hand (P2), right ear (P3)).

3.3 Analysis Tools

The recorded data were post-processes and analysed in MATLAB (The MathWorks, Inc. USA) version R2017b (9.3).

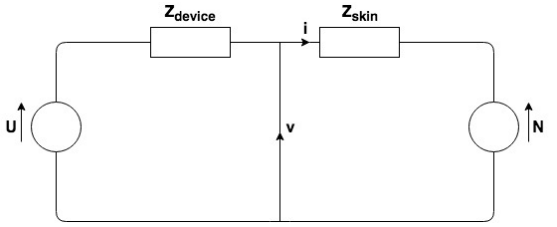

Figure 3: Electrical Scheme Analogy.

The system has 2 inputs: the multisine excitation signal $U(s)$ and the nociceptor stimulus $N(s)$:

$$\begin{bmatrix} V(s) \\ I(s) \end{bmatrix} = Z(s) \begin{bmatrix} U(s) \\ N(s) \end{bmatrix} \quad (1)$$

with V(s) and $I(s)$ the measured signals. Define now the vectors:

$$S_{YU} = \begin{bmatrix} S_{VU} \\ S_{IU} \end{bmatrix}, \text{ and } S_{UU} = \begin{bmatrix} S_{UU} \\ S_{NU} \end{bmatrix} \quad (2)$$

containing the cross-power spectra $S_{YU}(j\omega)$ between two distinct signals and auto-power-spectra $S_{UU}(j\omega)$ of a signal. It follows that:

$$S_{YU}(j\omega) = Z(j\omega)S_{UU}(j\omega) \quad (3)$$

If the nociceptor stimulation signal is not correlated with the multisine excitation signal, then the impedance can be directly estimated from (3).

Every 60 sec, the impedance is calculated and plotted against frequency, by means of its real and imaginary parts. The complex impedance is then normalized and analysed per interval of pain (P) or no pain (NP), as the response of the nociceptor excitations.

The variability within individual is observed with ANOVA method, using absolute individual impedance values. Boxplot analysis is the procedure used for determining whether variation in the response variable arises within the same individual, for both protocols.

One way anova has been used to compare among the group of values. The function ANOVA1 has been used in Matlab which returns box plots of the observations in data y, by group. Box plots provide a visual comparison of the group location parameters. If y is a vector, then the plot shows one box for each value of group. If y is a matrix then the plot shows one box for each column of y. On each box, the central mark is the median and the edges of the box are the 25th and 75th percentiles (1st and 3rd quantiles). The whiskers extend to the most extreme

data points that are not considered outliers. The outliers are plotted individually. The interval endpoints are the extremes of the notches. The extremes correspond to:

$$\frac{q2 \pm 1.57(q3 - q1)}{\sqrt{n}} \quad (4)$$

where q2 is the median (50th percentile), q1 and q3 are the 25th and 75th percentiles, respectively, and n is the number of observations (excludes NaN values).

Confidence intervals have been calculated at 95\%, and significant differences defined for p-values<0.05. The function TTest in Matlab has been used.

4 RESULTS

4.1 Bio-electrical-impedance as Function of Frequency

The frequency response of the bio-electrical-impedance for every protocol interval in **Case A** is depicted in Figure 4, using experimental data from volunteer #1.

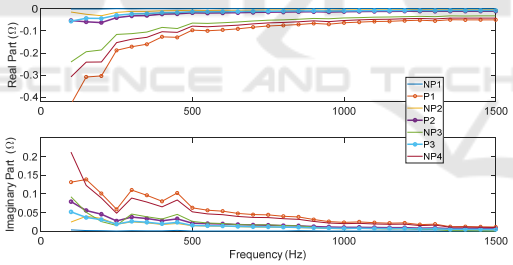

Figure 4: Individual frequency response of the normalized impedance, evaluated for "pain"/"no pain applied" intervals for case A.

It is observed that the bold lines that denote the second (P2) and third (P3) pain interval responses overlap the corresponding non-pain intervals: NP2 and NP3. This suggests that NP2 and NP3 indicate the presence of pain latency (i.e. memory pain). Hence, even in absence of nociceptor stimulation, the impedance indicates presence of pain pathways because of the pain memory effect. Also, since the nociceptor stimulus is applied in different locations and still detected with our non-invasive measurement device, we conclude that the device is sensitive to any stimulation through the physiological pathway of pain.

At this point, the first hypothesis of our study is demonstrated.

In the protocol for **Case B**, the pain is applied continuously to different places on the volunteer #1 and the responses are evaluated per interval, as depicted in Figure 5.

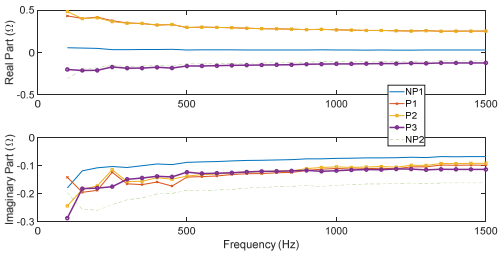

Figure 5: Individual frequency response of the normalized impedance, evaluated for "pain"/"no pain applied" intervals for case B.

From the three locations of the nociceptor stimulation tested, it can be seen that the first two pain responses (P1 and P2) seem to give the same result. This relates to the left and right hand, respectively. The third one (P3) suggests some differences (the bold line with circle marks) – on the ear. Further analysis will clarify whether or not the location on the ear provides biased results due to electrical activity of other nearby sources (e.g. brain).

Therefore, the bio-impedance is sensitive to any nociceptor stimulation location. While the impedance has different values for each interval, the amplitude value cannot be correlated to the stimuli location.

The second hypothesis of our study is also demonstrated.

4.2 Variability within Individual

From the two protocols analysed above, the variability within the same individual is described by means of boxplot in Figure 6. Instead of complex (real and imaginary parts), we now introduced the absolute values of the impedance |Z| obtained for each nociceptor stimulation interval.

For the first pain interval (P1), there are no statistical significant differences within individual per protocol ($p<0.7$). By contrast, the second (P2) and third (P3) pain interval, significantly differences are observed ($p<0.05$). Despite the fact that all nociceptor stimulation amplitudes are equal, the P2 and P3 data are clearly higher in amplitude for case B than for case A. This is due to overlapping of electrochemical ions channel activity in case B,

since in the proposed protocol the no-pain intervals are not performed.

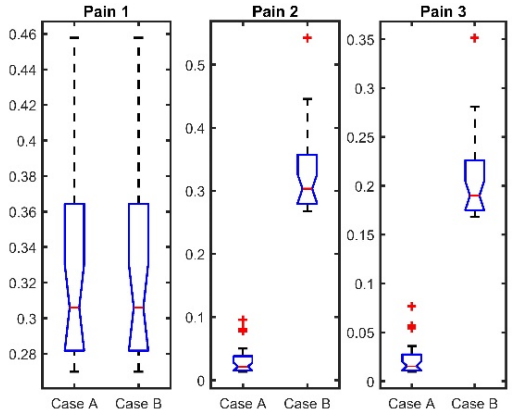

Figure 6: Absolute values of frequency response complex impedance in one individual per protocol (Case A and Case B). Each figure depicts boxplot analysis in all pain intervals during both protocols.

5 CONCLUSIONS

This work describes the first steps towards a novel non-invasive pain detection, evaluation and monitoring in chronic pain patients. Ideally, the same index would be valid also for analgesic drug dose management in general anaesthesia. The protocol and biosignal processing methodology proposed here lead to results to support the claim that latency of pain pathway exists (i.e. memory pain). Additionally, the tests indicated the technical soundness of the measurements, by accurate detection of nociceptor stimulation intervals through skin impedance evaluation. The location of nociceptor stimulation has no effect to the the accuracy of the device.

The evaluation of the ANSPEC-PRO prototype in clinical environment for patients experiencing post-operative pain is currently ongoing. Major challenges are expected by evaluating a “pain index” that can be correlated with patient information, in order to make ANSPEC -PRO clinically useful.

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