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Recognition and Inhibition of Dorsal Horn Nociceptive Signals within a Closed-loop System

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***Abstract*—We implemented an integrated system that can acquire neuronal signals from spinal cord dorsal horn neurons, wirelessly transmit the signals to a computer, and recognize the nociceptive signals from three different mechanical stimuli (brush, pressure and pinch). Positive peak detection method was chosen to distinguish between signal spikes. The inter spike intervals (ISIs) were calculated from the identified action potentials (APs) and fed into a numerical array called cluster. When the sum of the ISIs in the cluster reached a critical level, the program recognized the recorded signals as nociceptive inputs. The user has the flexibility to tune both the cluster size and critical threshold for individual's need to reach optimization in pain signal recognition. The program was integrated with a wireless neurostimulator to form a feedback loop to recognize and inhibit nociceptive signals.**

I. Introduction

Harmful stimuli to the skin or subcutaneous tissue (joints or muscle) are received by nociceptors (thermal, mechanical, and polymodal). The nociceptive stimulus travels to the dorsal horn of the spinal cord through Aδ and C fibers. The response of the spinal cord dorsal horn neurons are typically classified as low threshold (LT), high threshold (HT), and wide dynamic range (WDR) neurons according to their response to graded mechanical stimuli [1]. Among these types of neurons, WDR neurons are the only ones that respond to both Aδ and C fibers. In addition, WDR neurons have the capacity to precisely encode the intensity of a nociceptive stimulus [2]. Therefore, they can be used effectively to recognize the nociceptive signals.

It has been shown that electrical stimulation of the deep brain structures could be beneficial in pain treatment [3]–[5]. Areas of the brain that are examined for neurostimulation pain management include thalamic nuclei such as ventroposterolateral (VPL) or ventroposteromedial (VPM), and periaqueductal gray (PAG) [3]. All currently available brain stimulators perform in an open-loop fashion. After implantation, physician tunes the intensity of the stimulator based on patient's understanding of pain [6]. Currently, doctors cannot physiologically document the pain signals in a quantitative manner. However, several researchers have proposed the need for a closed-loop real-time system in deep brain stimulator (DBS) treatments [3], [6]. The closed-loop approach can provide more physiological data for the doctor, hence increase the efficiency and efficacy of the neurostimulator [3]. The efficiency of the system can be increased in terms of reduction in battery power consumption that will allow the implant to stay longer inside the patient's body.

In order to achieve the mentioned benefits, we have developed an automatic real-time feedback system that could record the neural activities from spinal cord dorsal horn neurons, recognize signals from three different mechanical stimuli, and inhibit the detected noxious signals by applying electrical stimulation to the brain. Brush (Br.), pressure (Pr.) and pinch (Pi.) were used as graded mechanical stimuli in this study. For neural stimulating and recording in a closed loop, we utilized our wireless system that was demonstrated by [7]. The system was tested on a Sprague-Dawley rat.

II. Method

A. System Overview

A wearable, wireless module that was developed in our group [7] was utilized in this study. This module is an integrated platform that can be used for recording extracellular neuronal signals and electrical stimulation of the nervous system. The system consists of a receiver station and a transmitter station. Neuronal signals were acquired at the spinal cord, and transmitted wirelessly to the receiver station that was connected to two data acquisition units: USB-6008 (National Instrument) and CED 1401Plus (Cambridge Electronic Design). The CED 1401Plus was connected to a computer (#1) and acquired data into a commercial signal-processing program Spike 2 (Cambridge

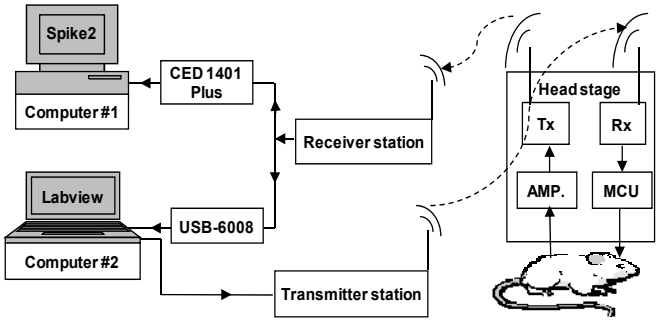

Fig. 1. The block diagram of the system for automatic, real-time recognition and inhibition of the nociceptive signals. Action potentials were recorded from the spinal cord and transmitted wirelessly to the computers #2 where received signals were processed, and electrical pulses commands were initiated and transmitted to the wearable module on the rat to stimulate the PAG area. Computer #1, which also acquired neural signals in real-time, was used for further off-line processing and comparison of the signals.

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Electronic Design). The data acquisition unit USB-6008 was connected to another computer (#2). A custom made program extracted the demodulated neuronal signals, processed the data, made decision on stimulation and wirelessly sent the stimulation commands through the transmitter station to the wearable module to initiate brain stimulation. The second data acquisition system (computer #1) was also used for further off-line verification of the performance of our software. The real-time processing of the recorded signals, including detection of the action potentials, an algorithm to distinguish the nociceptive ones from non-nociceptive signals, and decision making for stimulation closed the feedback loop in the computer #2. LabVIEW (National Instrument) was used for programming of our signal-processing algorithm in the computer #2. The block diagram of the system is shown in Fig. 1.

B. Spike Detection

A sampling rate of 10k Hz was chosen for signal acquisition assuming that the duration of an action potential was in the millisecond range [8]. Because a single microelectrode typically records from several nearby neurons that each could fire different forms of spikes, the recognition method has to differentiate between the desired action potentials and redundant spikes. In order to detect the desired spike, the simple positive threshold method was chosen [9] due to its acceptable accuracy and simplicity [10]. The program applied a positive threshold to the raw recorded data and detected action potentials above the threshold. Generally, the closer the microelectrode was to the recording neuron, the higher the threshold should be set to detect the desired action potentials.

C. Neural Activity Detection

In order to identify different levels of neural activities, WDR neurons that respond to a wide range of stimuli were recorded from the spinal cord, by a tungsten microelectrode mounted on a micromanipulator. The more noxious the stimulus is, the higher the frequency of the neuronal responses will be [11].

Inter spike interval (ISI) was used as the main feature [12], for differentiating the various mechanical stimuli (i.e. brush, pressure and pinch in our experiments). ISIs of the recognized action potentials were saved in a floating numerical array called cluster. The cluster size (CS) could be selected by the user for post-collection processing. Assuming a fixed size for the cluster, if the sum of the ISIs in the cluster became equal or smaller than a critical threshold (CT), the program defined the series of action potentials as nociceptive.

Once the WDR neuron was identified, in order to find the optimized values for CS and the correspondent CT, an algorithm shown in Fig. 2 was developed for the off-line analysis. Responses to a 10-s baseline of brush, pressure and pinch stimuli were recorded. As shown in Fig. 3, there was a discontinuity between neural signals obtained from the brush stimulus, because it had a periodic rhythm due to manual strokes. The signals of pressure and pinch stimuli did not have the periodic rhythm. The numbers of spikes before and after the first brush stroke were counted and considered for setting the cluster size (step 1). Setting this CS, the summations of the ISIs inside the first cluster of each signal were calculated as CT_{Br}, CT_{Pr}, and CT_{Pi} for brush, pressure and pinch, respectively (step 2). If the resulted CT_{Pi} happened to be smaller than both CT_{Br} and CT_{Pr} (step 3), then the current value of CT_{Pi} (with the corresponding CS) was chosen in the system (step 4) to distinguish between the nociceptive and non-nociceptive signals. Otherwise, the cluster size would be increased with a step of 5 units (step 5) to repeat the same procedure until the CT_{Pi} became smaller than CT_{Br} and CT_{Pr}.

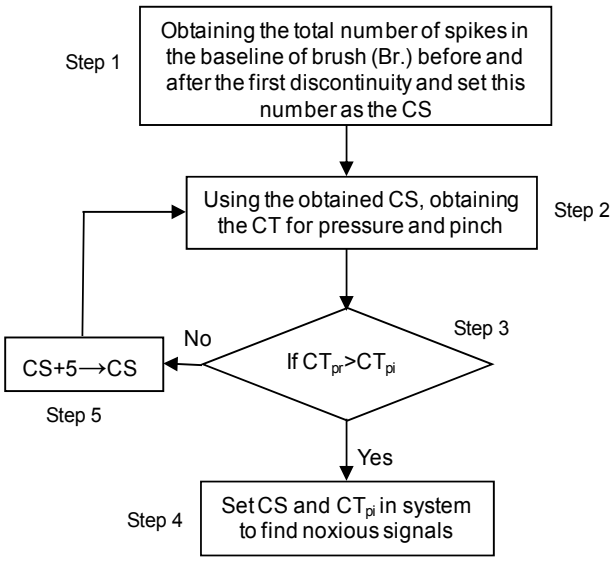

Fig. 2. The flowchart for finding the cluster size (CS) and critical threshold (CT) to distinguish different mechanical stimuli.

After the noxious signals were detected, the program closed its feedback loop by initiating an electrical stimulation command and the hardware transmitted it wirelessly to the wearable module to trigger the neurostimulator.

D. Animal Experiment

In vivo testing of the device and algorithm was conducted in an anesthetized male Sprague-Dawley (520 g) rat. The aims of these tests were two fold. First, we examined the accuracy of the system in recognizing the nociceptive from non-nociceptive spikes. Second, we assessed the efficacy of the feedback system in applying the stimulus signals. The recordings were obtained from WDR neurons at the L5 level in the spinal cord. The mechanical stimuli, using camel hair for brushing as well as two different bulldog clamps for pressure (31 N/m) and pinch (57 N/m) stimuli, were administered to the animal's left hind paw, each for 10 s with intervals of 20 s. Brain stimulation was applied in the periaqueductal gray (PAG) area at 100 Hz, ±1 V, with a pulse width of 100 μs. All procedures were approved by the University of Texas at Arlington Institutional Animal Care and Use Committee. The procedures were in accordance with the guidelines published by the Committee for Research and Ethical Issues of the International Association for Study of Pain [13].

III. *In Vivo* Testing and Results

Three experiments were conducted on the two spinal cord WDR neurons, WDR neuron #1 and #2. The first two experiments demonstrated the feasibility of the algorithm (Fig. 2) used in this paper. The third experiment showed the performance of the system using the WDR #1 in real time. The desired signals (with larger amplitudes) from both WDR neurons were separated from the background signals (smaller amplitudes) with the positive thresholds. The action potential patterns of the WDR neuron #1 in response to three different mechanical stimuli (brush, pressure and pinch) and the positive threshold (horizontal dashed line in Fig. 3) that was used to reveal the desired signals are shown in Fig. 3. The discontinuities in the brush signals due to the rhythmic manual strokes were specifically distinguished in this figure.

Experiment 1. It was conducted on the WDR neuron #1, the first discontinuity (from the brush signal) was chosen and the numbers of action potentials before and after the discontinuity were counted (step 1). A cluster size of 10 was obtained. The ISIs of the first ten APs were calculated as the first cluster as shown in Fig. 4. The critical thresholds were calculated for brush (CT_{Br}), pressure (CT_{Pr}) and pinch (CT_{Pi}) as 0.73 s, 0.21 s and 0.11 s, respectively (step 2). Because the CT_{Pr} was greater than CT_{Pi} (step 3) which means the program could recognize the pinch from pressure, the critical threshold was then set with CS of 10 to find the nociceptive signals in the third experiment (step 4).

To investigate alternate ways of analyzing the WDR neuron #1, the cluster size was arbitrarily chosen to be four. The results of four consecutive ISIs (chosen arbitrarily among all ISIs) are shown in Fig. 4 as the second cluster. CT_{Br}, CT_{Pr} and CT_{Pi} were obtained as 0.06, 0.13 and 0.10 respectively. CT_{Br} was smaller than both CT_{Pr} and CT_{Pi}, which meant the nociceptive signals were not recognized and the CS had to be chosen according to the step 1 (i.e. ten in the previous case) of the flowchart (Fig. 3). This suggests that the cluster size may not be chosen arbitrarily.

Experiment 2. In the experiment on the WDR neuron #2, the step 1 of the flowchart was followed and a CS of eight and corresponding CT_{Pr} of 0.08 s and CT_{Pi} of 0.10 s were obtained (step 2). Because the CT_{Pi} was greater than the CT_{Pr} (step 3), five units were added to the CS (step 5) and the critical threshold was calculated for the CS=13. The resulted

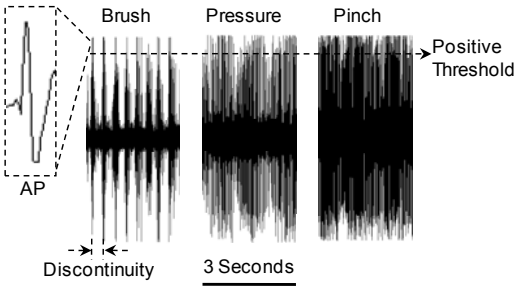

Fig. 3. Typical forms of the signals that were resulted from mechanical stimulations of brush, pressure and pinch. The positive threshold was used to distinguish different action potentials. The discontinuity in the brush signals was periodic due to rhythmic strokes.

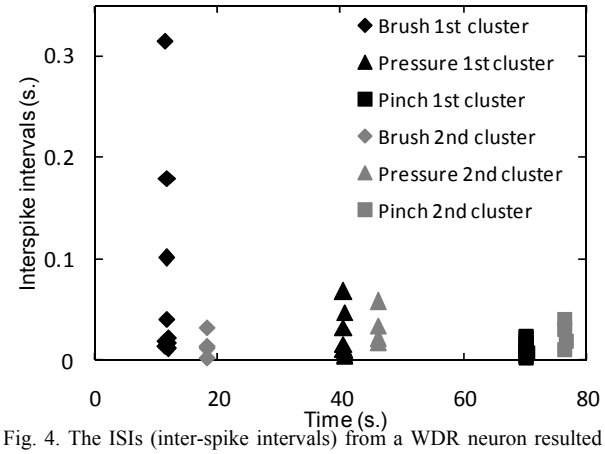

Fig. 4. The ISIs (inter-spike intervals) from a WDR neuron resulted from the mechanical stimuli (brush, pressure and pinch). The ISIs were in two different clusters. Black labels show data from a CS of 10 and the gray ones show data from a CS of 4.

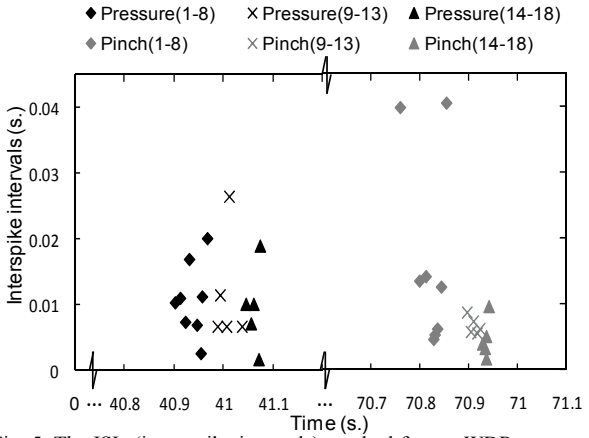

Fig. 5. The ISIs (inter-spike intervals) resulted from a WDR neuron during pressure (black) and pinch (gray) stimuli. The ISIs were clustered in consecutive CSs of 8, 5 and 5 for both pressure and pinch stimuli.

critical thresholds were 0.14 s, and 0.13 s for pressure and pinch, respectively. CT of 0.13 together with CS of 13 then were set (step 4) to differentiate the nociceptive and non-nociceptive signals. However, the difference between the CT_{Pr} and CT_{Pi} was 10 ms, which provided a very narrow boundary between the pressure and pinch signals. Adding another five units to the CS, CT_{Pr} of 0.19 s and CT_{Pi} of 0.17 s were obtained and provided a greater difference (20 ms) between CT_{Pr} and CT_{Pi}. Fig. 5 shows the resulted ISIs for the pressure (in black) and pinch (in gray) signals in the above mentioned iterations.

Experiment 3. In this experiment, the performance of the system in differentiating the nociceptive from non-nociceptive signals in real time was examined. This experiment was conducted on the WDR neuron #1. CS and CT were set as 10 and 0.11 s according to the results obtained in *Experiment 1*. For this experiment, the signals were also simultaneously recorded by Spike 2 (Fig. 6, bottom trace). The system triggered electrical stimulations (Fig. 6, middle trace) only during the pinch stimuli, but not the brush or pressure stimuli. The rates of action potentials were calculated in the bins of 500 ms (Fig. 6, top panel). The bins, which contain the clusters that satisfied the condition of CT less than 0.11 s are labeled with the numbered arrows.

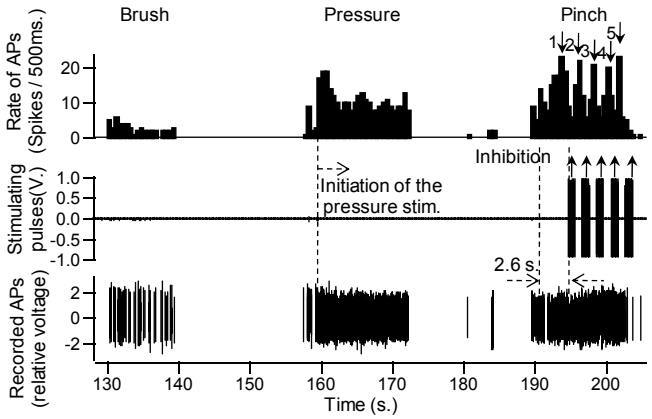

Fig. 6. A real-time experiment with the feedback system. Top trace - rate of action potentials; middle trace - electrical stimulation; bottom trace - the action potentials generated by the WDR neuron.

The rate of APs decreased (shown by solid vertical arrows) when the electrical pulses (shown in the middle panel) were triggered by the system. There was a time delay of 2.6 s between the initiation of pinch stimulation and the stimulation pulses generated by the feedback system. There were also time delays of 500 ms between the numbered bins and the initiation of electrical pulses.

IV. Discussion and Conclusions

In this study, we developed a system that can automatically recognize nociceptive signals resulting from three different mechanical stimuli in real time. Furthermore, the system generated electrical pulses using nociceptive signal as feedback to stimulate the PAG that could potentially inhibit the nociceptive signals. As shown in the flowchart for recognizing the nociceptive signals (Fig. 2), our results demonstrate the necessity of the step 1 in the flowchart for choosing the CS based on the brush signals (Figs. 4 and 5). The discontinuity in the brush signals (Fig. 3) provides a valuable signature and the value chosen makes sure that both the CT_{Pr} and CT_{Pi} are greater than CT_{Br}. They also show that if the cluster size is chosen correctly, CT_{Pr} would be greater than CT_{Pi} giving a criterion to distinguish between the pressure and pinch signals (Fig. 4). However, if the CT_{Pi} happens to be greater than the CT_{Pr}, it may give the wrong impression that the pinch stimulus causes less neuronal firing than the pressure does. Then, the CS needs to be increased in order to include more pulse samples to be considered (by five units, in this case, as in the step 5 of the flowchart in Fig. 2). Fig. 5 shows an example in which the CT_{Pi} happened to be greater than the CT_{Pr}. In this case, increasing the CS to 13 or 18 corrected the situation and CT_{Pi} became smaller than the CT_{Pr}. The increase of CS size can be adjusted to provide desired precision in distinguishing the stimuli. However, a large size of CS might cause excessive delay in finding nociceptive signals since it would require more time to fill the cluster. Therefore, a tradeoff between the CS size and the delay time is needed. We chose the smallest possible CS to minimize the time delay, due to the short period (10 s) of the mechanical stimuli in our experiment protocol.

The performance of the whole system was examined and shown in Fig. 6. System recognized five clusters (with the size of 10) that satisfied the condition (CT < 110 ms), only during pinch stimuli. It meant that the system correctly distinguished pinch as noxious but did not recognize brush and pressure stimuli as nociceptive. In addition, there was a delay of several seconds between the initiation of the mechanical stimuli and electrical pulses triggered by the system. The reason for the delay is that the system did not find any cluster that satisfied the criteria immediately after the pinch stimulus was initiated. The delay of 500 ms between the nociception recognition and stimulation initiation was also contributed partially by the delay in wireless communication and signal processing time. In a real-time system, such a delay will not be an issue for applications since the system should be able to find the optimal size of cluster in continuous uses, and the limited delay will be acceptable for chronic pain management. In order to demonstrate the reliability of our feedback system and its use in human as the next step the efficacy of the system will be examined in awake animals.

Acknowledgment

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