Wireless Thermal Neuromodulator for Long-term in Vivo Cooling Performance Assessment

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Abstract: Focal cooling is considered a potential solution to stop or control epileptic activity. However, despite the available proof of concept studies, such approach requires further validation before being used in humans. One hindering factor is the lack of suitable devices to enable large-scale validation of such methodology. This paper presents a wireless thermal neuromodulator that can wirelessly record the rat's brain electrical activity and temperature. At the same time, the temperature is reduced without the need to use cumbersome liquid pipes. The proposed device has two modules: one headstage with a cooler and sensors, and one backpack with acquisition electronics and wireless communication capability. It is possible to record the brain temperature, the EEG at 16 kbps, and to control the cooler's temperature, with an autonomy of 1 day.

1 INTRODUCTION

Thermal neuromodulation has been proposed as a solution to handle medication resistant neurological disorders, being epilepsy one of such diseases. It has been demonstrated that focal cooling is a potential solution to stop epileptic activity (Fujii, 2010). Despite such validation in controlling neuronal activity, and before becoming an effective solution, further tests are required to demonstrate the large scale and long-term efficacy of focal cooling on epilepsy control. However, the available cooling devices are not suitable to perform the required large scale, long-term testing in vivo. Such tests may be performed using rats and will require the development of a suitable device to control the rats' brain temperature in specific spots (Fernandes, 2018). To be placed on a rats' brain, the cooler must satisfy size and biocompatibility constraints (Mata, 2005). To be transported by the rodent, the system must be wireless and must not be oversized or overweighed.

In this paper, the design of a wireless, small, low-power thermal neuromodulator is presented in order to reduce the rodent's brain temperature, while EEG, and focus temperature is being recorded.

2 COOLER ARCHITECTURE

The proposed cooling device uses two modules to reduce at maximum the weight and volume on top of the rats' head. Placed in contact with the brain, is the thermal neuromodulator. This component is connected to the unit of acquisition which is inserted in a bag on the rat's back. Fig.1 shows the proposed system architecture.

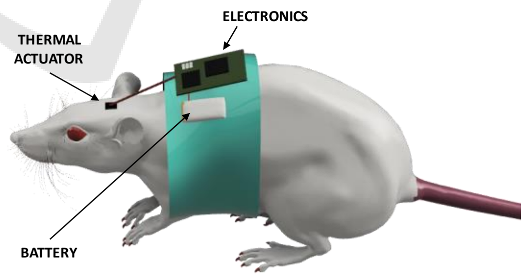

Figure 1: Wireless neuromodulator system overview.

The two modules were designed taking into account their specific constraints. Their design will be explained next.

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3 ACQUISITION AND CONTROL SYSTEM

The acquisition and control system on the rats' back should communicate wirelessly with the outside world using a low power solution. The proposed device is shown below, in Fig.2.

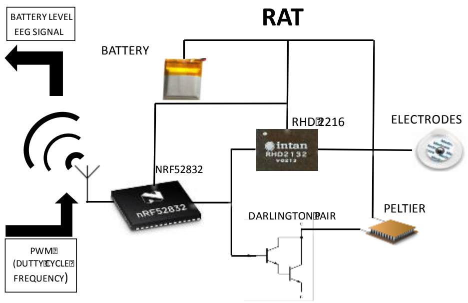

Figure 2: Block diagram of the proposed system.

The system has two fundamental parts. The first one, placed on the freely moving rat, and the second one attached to the PC. The rats' module integrates a small and thin battery, a Bluetooth 5 (BL5) module (ISP1507), a low-power electrophysiology signal acquisition chip (RHD2216) and a Peltier module used to cool down the epileptic focus.

Since it must sit on the back of a rat, this device must be lightweight, and have a small volume, so it will not become uncomfortable for the rodent. If so, the animal will try to remove the device with its paws. According to literature, a rat heavier than 250 g (an adult rodent often is heavier than this) can carry 60 g on its back and move freely without any inconvenience on locomotion or motivation (Hampson, 2009). Hence, the rat can have, positioned on its back, a board with a size of 2.5x5 cm^2 without any disturbance. Nevertheless, the size and the weight should be reduced to the maximum possible (Ativanichayaphong, 2008).

Our device will have near 10 g and will occupy a volume of 4 x 4 x 0.3 cm^3.

The second part uses also a BL5 module, which will be connected to the PC to record and process the data sent wirelessly from the rats' device.

BL5 was selected, since it offers improvements in numbers of bytes that can be sent in each connection, allowing higher speed without compromising energy efficiency (DiMarco, 2017). The Bluetooth 5 module ISP1507 consumes only 7,5 mA on tx with 4 dBm or 5,3 mA with 0 dBm and 5,4 mA when working on rx. It allows, also, for better range. BL5 grants a data packet to be sent at a rate of 2 Mbps between 2 devices and communication in a range of 200 m outdoors and 40m indoors (Collotta, 2017). However, the ISP1507 reports only 100 m free open space which is more than necessary for this application since we only need a range of 3 to 5 meters for the system to work correctly.

The main disadvantage of using this type of communication standard is the difficulty to achieve high data rate communications. However, since we want to record an EEG at sampling rates between 250 and 2000 Hz the data rate is enough. Since we have an 8-bit resolution ADC, we only need a data rate of 8*(sampling rate) bits per second (bps). For instance, if we select a sampling rate of 2000 Hz, the data rate of 16 kbps will be feasible with BL5.

The ISP1507 is from Insight Sip and it is based on nRF52832 integrated with decoupling and loading capacitors, 2 crystals (32 MHz and 32,768 kHz) and a RF matching circuit and antenna. The integration of the antenna is important, since it allows for full system size reduction (8x8x1 mm^3).

3.1 System Main Features

The implemented device allows to record both the temperature and the EEG, and to control Peltier temperature. Since the device runs on batteries, it also sends the battery levels to recharge or to replace it. Temperature and EEG will be described next with more details.

3.1.1 Temperature Control

When desired, a command can be sent from the PC to the device, to turn on the Peltier positioned on the rat's brain. It activates one PWM unit that digitally encodes an analog signal level. This modulation technique uses a square wave in which the time the signal is on (high) or off (low) can be controlled. To characterize the amount of time the signal is on we can set the duty cycle to the percentage aimed. For instance, if the duty cycle is set to 75%, then the output from the PWM would be a square wave with high voltage 75% of the time. If, for example, the supply is 3 V, the resulting analog signal would be of 2.25 V (Barr, 2001). The frequency of the square wave can also be controlled. Finally, since the output current from the PWM generated by the chip is low and not enough to power the peltier, it was amplified using a Darlington pair connected between the PWM and the Peltier. A Darlington pair acts as a single transistor and generates a high current gain. This way, the Peltier can be turned on and off wirelessly using the BL5 module.

3.1.2 EEG Acquisition

To detect when the rat is having a seizure, its frequency and duration, it is necessary to record its electroencephalogram (EEG). This is done using 3 electrodes placed on its cortical surface. These electrodes will be connected to the electrophysiology chip on the device. The selected chip was the RHD2216 from Intan Technologies. It integrates 16 amplifiers, analog and digital filters and a multiplexed analog-to-digital converter (ADC). Its miniature size (4.8x4.1 mm^3) and low-power make it ideal for this application. It can sample 16 differential amplified channels at a maximum data rate of 30 kSamples/s each.

This chip communicates with the BL5 module over a digital Serial Peripheral Interface bus (SPI). Each digital signal sent over this bus is transmitted on a single wire. So, this communication consists of 4 standard signals. An active-low chip select ($\overline{CS}$) and a serial data clock (SCKL) provided by the BL5 module (master device); a MOSI (master out, slave in) data line in which a 16-bit command word flows from the BL5 module to the Intan chip and a MISO (master in, slave out) data line where the response from the Intan chip (also a 16-bit word) flows to the BL5 module.

3.2 Software Description

There are two possible network configurations in BL5 specification: connection (bidirectional communication), and broadcast (unidirectional communication). Since we need both BL5 modules to communicate with each other, a connection topology will be implemented.

In connection mode, a peripheral device sends advertising packets. The central device receives the advertisement and accepts the connection. Once this is established, the peripheral stops advertising and both devices start trading data (Collotta, 2017).

The peripheral's data can be classified in services and characteristics. The service is a collection of characteristics describing a function of the peripheral. A peripheral can have multiples, or only one service, and a service can, also, have only one or multiple characteristics. Each service and characteristic uses an UUID (universally unique identifier) to identify itself.

Only two services were created on the peripheral device, the Biosignals service and the Battery service. The Biosignals service has the EEG level characteristic and the Temperature characteristic. The Battery service has the Battery level characteristic. The first one is responsible of sending both the data acquired with the Intan chip and the temperature values and receiving the configuration of the PWM. The second one sends a notification of low battery when its levels reach 2V.

On the central device it was created the service PWM with the characteristic PWM values. This characteristic is responsible for sending the frequency and the duty cycle for the PWM. These values are set on the PC side and the sent over BL5.

The peripheral device will send the data as a notification which the central device will be able to read immediately as it changes (Hortelano, 2017). This attribute data has a Maximum Transmission Unit of 247 bytes, i.e., for each notification, 247 bytes are transferred from the peripheral to the central device.

After a connection between both BL5 modules is established, the BL5 module connected to the PC receives the data from the rat and sends it to the PC using the universal asynchronous receiver-transmitter (UART).

4 MICROCOOLER DESING

The previous sections describe the system's overall concept, as well as the control hardware. This section will explain the cooler and heatsink design process. To be able to perform the required thermal neuromodulation the cooler must guarantee that the neuronal cells temperature does not exceed 43 ºC, to ensure cellular integrity (Yarmolenko, 2011). On the other hand, the cold side must reach temperatures lower than 30 ºC to suppress epileptic seizures.

Hou et al. (2011) present the project and development of a thermal neuromodulator to epilepsy control. In this work, the chip permits the EEG acquisition so that the epilepsy event can be detected and the neuromodulator can actuate and suppress it. The chip's dimensions are 1.4 x 0.95 mm^2. So, we can deduce the possible dimensions of an implantable device on the brain.

So that the cooling in situ is able to interfere with the cerebral activity a solid-state cooler using a Peltier component (Micropelt MPC-D403) was selected. The device is only 2x2x1 mm^3 in volume and allows to reach a net cooling up to ~50 K, depending on current and heat loading.

4.1 Heatsink and Packaging Design

It is important to refer that once the device is implanted in the brain, it is in direct contact with the neuronal cells. Thus, triggering an electric current in the Peltier results in a temperature gradient being generated between the cold and the hot sides of the Peltier device. Therefore, the cold side enables neural cooling while the hot side is responsible for dissipating the heat that is being generated to cool down the brain.

However, it is necessary to control the temperatures reached at the hot side of the Peltier, to ensure the thermal modulation of the brain does not induce irreversible damage to the cells near the hot plate. Moreover, the continuous increase of the temperature on the Peltier's hot side causes a consequent increase in the temperatures reached at the cold end after a certain time, due to the Joule effect. So, it is necessary to include in the heat modulating device a heatsink that needs to be in direct contact with the hot end side of the Peltier. The reason to choose aluminum as the heatsink was because, despite having a lower thermal conductivity than copper, it is a viable and a low-cost alternative in the manufacture of heatsinks.

For heatsink design, shown in Fig.3, special constraints were considered: the volume required to efficiently dissipate the heat being generated; the need to miniaturize the device dimensions without compromising heat dissipation.

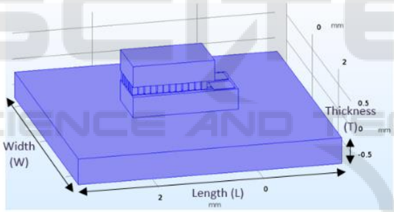

Figure 3: Model used to simulate the microcooler (Peltier and heatsink).

Is also important to ensure the safety and viability of the implantable device. To do so, it is important to meet certain requirements, namely concerning its biocompatibility. Biocompatibility is an essential feature that ensures the device's long-term implantation, avoiding the induction of irreversible damage. Therefore, the device was isolated with a biocompatible material. Several options like flexible polymer substrates such as polydimethylsiloxane (PDMS), polyimide (PI) or parylene (Patil, 2016), ensure that the device can be embedded without compromising its structure or mode of operation.

Among the options presented, PDMS is a silicone elastomer with excellent physicochemical properties that make it an attractive and promising material in the development of MEMS and numerous components in biomedical applications. PDMS has been traditionally used as a biomaterial in catheters and other drainage tubes, ear and nose implants and also as insulation material in pacemakers (Mata, 2005).

In addition, PDMS handling and manipulation is rather easy and since it is a non-toxic and biocompatible material it can be implanted in vivo. Also, its elastic properties permit this polymer to recover its initial shape after undergoing long cycles of deformation, with the particularity of standing strong strain deformations before breaking. Concerning thermal properties, this material is thermally stable, acting as a thermal insulation (thermal conductivity of 0.2 W/mK), since it does not allow resistive heat dissipation (Mata, 2005).

Hence, in order to simulate the PDMS embedding device, a tri-dimensional CAD model for the PDMS structure was planned and designed.

This structure, besides protecting the cold side of the Peltier, which is in direct contact with brain cells, also fills the spaces between the Peltier tellurium bismuth pellets and covers the hot side plate of the PDMS that is not in direct contact with heatsink. Furthermore, since the heatsink is also coated with PDMS, the PDMS structure should be adapted to the dimensions and shape of the heatsink.

In the next set of tests, the PDMS thickness relationship on the thermal performance of the device was subsequently tested (Mata, 2005).

4.2 Temperature Control Modelling

To understand how the brain temperature changes with the control current it was necessary to model the cooling system behavior. Such behavior will be highly dependent on the heatsink and its dimensions. The temperature control modelling was studied using COMSOL, which allows modelling all systems previously described

A tri-dimensional block of 180x110x130 mm^3 was used to model the brain, since studies state that the human brain volume ranges from 650 cm^3 to 1260 cm^3 (Lahr, 2004). Thus, a parallelepiped with the reported dimensions was designed and the previously presented Peltier device was included inside, simulating an implantable neuronal device, as can be seen in Fig. 4.

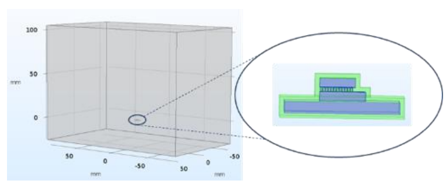

Figure 4: Simulated brain block with implanted device.

The Peltier device was simulated considering the materials that compose the semiconductor pellets (bismuth telluride Bi_2Te_3), the conductive bond-pads (copper Cu) and the materials that compose the cold and hot sides of the plates of the device (alumina or aluminum oxide Al_2O_3) above mentioned.

4.3 Heatsink and PDMS Cover Performance Assessment

In this section are presented simulation results for several heatsink dimensions and PDMS thicknesses.

Initially, it was only simulated the Peltier device and the heatsink when implanted inside the brain. The main goal of this study is to find the minimum dimensions of heatsink that allow maximum heating dissipation without the temperature in cerebral cells being higher than the threshold of 43 °C. In order to analyze the maximum temperature (T_{max}) and the minimum temperature (T_{min}) resulting from heat transfer between the device and the brain, different combinations of L, W and T values (L, W, T) were considered for the heatsink dimensions. These form the parallelepiped seen in table 1.

The simulation time was set to 20 minutes, where only from 10 s<t≤1200 s was applied a 50 mA current. Furthermore, it should be noted that the initial temperature of the device considered for all simulations (at t=0 s) was 37 °C. The reason to do it so was since this temperature is the basal temperature of the human body and the device is totally integrated in the brain tissue.

From the simulation results for the 18 different combinations tested, the following table was obtained.

Table 1: Results of simulations with different dimensions of heatsink (length unit is mm).

L	W \ T		0.5	1	1.5
3	3	T_{min} (°C)	30.4	29.8	29.3
		T_{max} (°C)	44.9	44.1	43.5
	4	T_{min} (°C)	29.7	29.1	28.7
		T_{max} (°C)	43.9	43.3	42.8
	5	T_{min} (°C)	29.1	28.7	28.3
		T_{max} (°C)	43.3	42.7	42.3
4	4	T_{min} (°C)	29.0	28.6	28.3
		T_{max} (°C)	43.1	42.6	42.2
	5	T_{min} (°C)	28.6	28.2	27.9
		T_{max} (°C)	42.6	42.1	41.8
5	5	T_{min} (°C)	28.2	27.9	27.6
		T_{max} (°C)	42.1	41.7	41.4

From the previous results, one can conclude that increasing L and W values lead to a decrease in the T_{min} and T_{max} values. These results went according to what was expected, since a larger heatsink area implies a greater efficiency when heat dissipation is occurring and, consequently, the temperatures recorded will be lower.

Regarding the thickness relationship, it has been observed that an increase in the thickness of the heatsink (T), for fixed values of L and W, results in decreasing temperature values for T_{min} and T_{max}, as expected, since larger thickness values lead to a higher volume of heat dissipation. Concluding, the larger the heatsink (5x5x1.5 mm^3), the lower the reached temperature is.

However, since it is desirable to miniaturize the device, the smallest heatsink should be used, while still respecting the requirements for T_{min} and T_{max} temperatures that do not compromise the integrity of neuronal cells. Since the device behavior is being simulated, it is advisable to ensure a margin of safety for the maximum temperature that can be reached with respect to the critical temperature, T_{max}, of 43 °C. It was, therefore, chosen a safety margin of approximately 1 ºC.

By observing the simulation results presented in Table 1, it is possible to conclude that 5x5x0.5 mm^3 heatsink results in a T_{max} of 42.1°C. Compared with other feasible dimensions that achieved approximately the same critical temperature, these are the dimensions for which the volume of heat dissipation is lower and therefore were the chosen dimensions for the heatsink.

In Fig. 5, it is possible to observe the temperature profile of the device being tested for the chosen heatsink dimensions. In the coloring bar presented at the right side of the image are the maximum and minimum temperatures registered after the simulation has been performed.

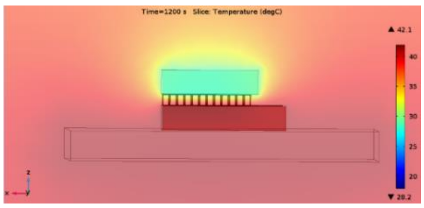

Figure 5: Temperature profile of the device with the 5x5x0.5 mm^3 heatsink.

The 5x5x0.5 mm^3 heatsink was tested with different PDMS thicknesses to analyze the influence of the referred thicknesses in achieved temperatures. Followingly are presented the device's temperature profiles for PDMS thicknesses of 20, 50 and 100 µm, respectively.

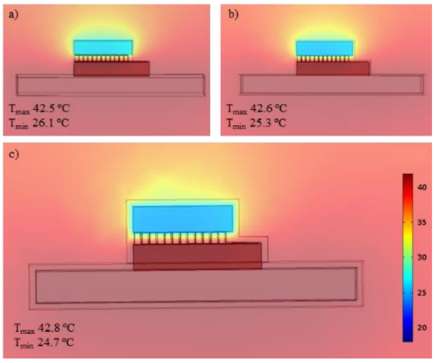

Figure 6: Temperature profile of the device with the 5x5x0.5 mm^3 heatsink for PDMS thicknesses: a) 20 µm, b) 50 µm, c) 100 µm.

It was observed that increasing PDMS thickness results in an increase T_{max}, which is explained by the thermal insulation behavior of PDMS. It was also noted that T_{min} value decreased with increasing PDMS thickness. However, lower T_{min} values was observed specially on the cold plate of Peltier and not on the brain. It should also be referred that with the increasing PDMS thickness the neuronal cells cooling region is closer to the Peltier's cold end.

It is also noteworthy that, ideally, the thinnest PDMS thickness that guarantees biocompatibility is desirable.

5 CONCLUSIONS

This work presents the design and implementation of wireless thermal neuromodulator, small and light enough to be used for long-term in-vivo testing on rats. The proposed device records brain temperature, EEG, and allows to control the current that will switch the cooling element on and off. The electronics were fully assembled and tested, while the heatsink and cooler were fully designed and are undergoing testing in laboratorial conditions.

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