Microcooling solution development and performance assessment for thermal neuromodulation applications

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***Abstract*— Miniaturization and integration technologies are well known for unveiling solutions where the device volume is a restriction. The biomedical field eagers such solutions because they bring relevant benefits, namely achieving faster results, requiring less reagent quantities, increasing sensitivity, having less noise by operating very close to the measurement source, and allowing access to otherwise inaccessible places.**

Some neuronal diseases are known to be resistant to medication and intractable by surgery, which pushes the development of new treatments to improve patients' quality of life. In epilepsy, up to 30% of patients suffer from seizures that can't be controlled with medication. Consequently, thermal neuromodulation was proposed as method that can be used in these cases. Cooling the seizure focal point to 20 ºC can suppress seizures without inducing irreversible damage. However, available devices are too big, both for research with animals and for use on patients. In this paper, a miniaturized microdevice is developed and its performance as thermal neuromodulator is evaluated.

Keywords – microdevice, thermal neuromodulation, epilepsy, microcooler, seizure control.

I. Introduction

Neuromodulation is the ability to manipulate the neurons' behavior, altering their biochemical processes or their electric signals. Such techniques are used to modify, normalize or modulate the electrical signals in order to accomplish different objectives, which are achieved by suppressing or improving the flow of action potentials. This is an expanding research area and three major applications are described in [1] as the three main purposes of neuromodulating devices: Prosthetics – Some devices can replace or improve the neural function. Therapeutics – the devices regulate neural activity for medical benefits. Neuroscience – Investigate the neural functions, observe their behavior and understand how they work. To change the electrical behavior of neurons, some different approaches are being studied for application in distinctive scenarios [1, 2]. Devices for Functional Electrical Stimulation (FES), where a current or a voltage is applied to a neuron, starting or changing is electrical activity, are the most common, and a well-known application is Deep Brain Stimulation [3].

Nervous system pathologies prevalency is increasing, with some of them requiring new and revolutionary treatment solutions. A recent approach that is growing is the use of optogenetic neuromodulation. This principle uses light sensitive proteins that can change the electrical signal or the biochemical process of the cells. Some aproaches inject these proteins (that are either activated or inhibited) into cells in order to allow this neuromodulation method [1]. Another way to modulate neuronal activity is based on magnetic fields, where the neuron's magnetic fields is changed, therefore changing their electric activity. The most evident advantage of this technique, known by micro-TMS (transcranial magnetic stimulation), is its non-invasiveness. [4]. Chemical neuromodulation is also being implemented in some research topics. Injecting microfluids with chemicals such as neurotransmitters or ions can also change the electrical potential of the neurons and, therefore, normalize or change their behavior [1]. Acoustic neuromodulation is also an emerging technique. The use of ultrasound waves can interfere with some action potentials and alter the electric potentials [5]. Thermal neuromodulation is being used for different applications and was also proposed as a solution for treatment of neuronal diseases resistant to medication, like epilepsy [6], or stimulations of single neurons in vitro [7]. This method can change the cells' behavior through temperature control. Despite having the potential hazard of inducing irreversible thermal damage to the cells, therefore requiring full control of exposure temperatures and times in order to avoid thermal ablation, there are many different applications where increasing or decreasing the temperature can promote modulation of the electrical neuronal activity without inducing any permanent neuronal damage.

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II. Objectives

It is well known that 30% of patients with epilepsy have no medication or surgery that can help them overcome their disease. However, manipulating the brain cells' temperature on the epileptic event focus can prevent seizures without major consequences to the patient [6]. Despite the immense potential of thermal neuromodulation, a device that meets the needs for such an application is not yet available, as such device must be small enough to be applied, for example, on rat brains, without interfering with the daily life activity of subjects undergoing tests or treatments. The proposal in this paper is to have an external device to monitor implant activity and, more importantly, to enable the use of wireless power transfer technology. Such capability will allow a significant size reduction of internal batteries, contributing to further implant miniaturization. The proposed solution is schematically shown in Fig. 1.

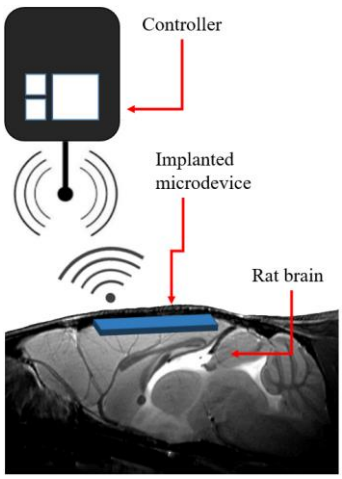

Figure 1. Proposed neuromodulation system architecture .

The miniaturized implant includes a microcooler, a small rechargeable battery based on wireless power transfer technology, a wireless link for communications, and a miniaturized heat sink that also supports one antenna. Since the implant is being developed for rat studies, this paper investigates the performance of a system to fit in a small volume (bellow 1 cm^3), while being able to cool down one side to around 20 ºC, and simultaneously guaranteeing the hot side doesn't heat above 40 ºC. Cooling speed and the cooled volume are also studied in this paper.

III. Materials and Methods

A. Neuromodulator architecture

For the sake of miniaturization, the modules are integrated using microtechnologies such as multichip module technology and wire bonding, avoiding individual packaging of each element and promoting size reduction. Fig. 2 shows the proposed neuromodulator architecture.

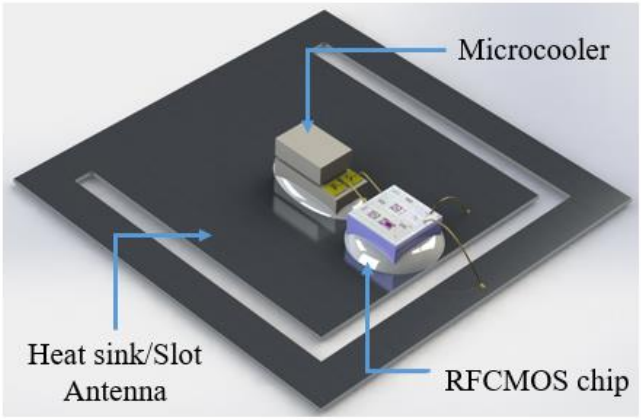

Figure 2. Proposed thermal neuromodulator.

The thermal neuromodulator is built around a microcooler (Micro MPC-D403), an in-house RFCMOS circuit, and a metallic heat sink, which is designed to integrate an antenna for wireless communications and wireless power transfer. Considering a not yet optimized heat sink, the full system volume was designed to be smaller than 10 x 10 x 3 mm^3.

B. Brain modeling

To evaluate the neuromodulator's thermal performance, brain modeling was required to allow the full thermal problem analysis. The three main variables considered for brain heat transfer simulations are shown in table I.

TABLE I. Materials used in simulation. Heat capacity – *Cp*, density – ρ and thermal conductivity – λ

Variable	Value	Reference
Cp	3700	[8]
ρ	1050	[8]
λ	0.527	[9]

Also, due to the brain's thermal regulation mechanism, the convective heat generated by blood perfusion was considered, 0.029 W/cm^3/K, as well as the metabolic heat, 0.025 W/cm^3 [10]. Those values represent the temperature control due to the brain blood vessels, responsible to maintain 37 ºC on the brain cells at all times. Since brain cells are known to be at a temperature of 37 ºC, the model starts with that temperature.

C. Microcooler modeling

The temperature controller, and core of the proposed microsystem, is a commercially available microcooler (Micro MPC-D403), which is based on the thermoelectric effect. It will be the element in contact with the neural cells, and must be able to drive the cold side down to 20 ºC (from 37 ºC). To assess the temperature control of brain cells, a model was developed using the proposed microcooler datasheet and the knowledge about standard constitutive materials (Bi2Te3 and copper for the thermoelectric center, and alumina for the device plates). Fig. 3 shows the simulation results when the model was used to evaluate its ability to predict temperature control in brain tissue.

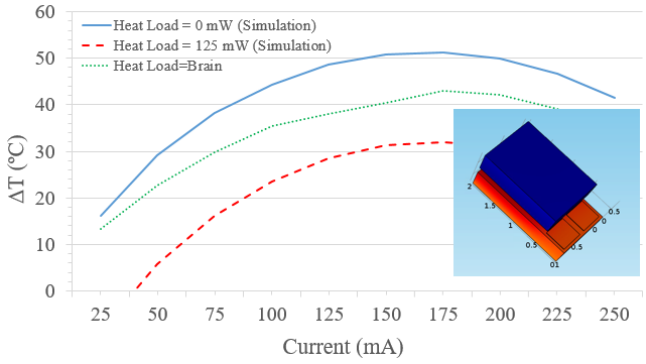

Figure 3. Microcooler thermal performance as a function of supply current, and for diferent heat loads.

Fig. 3 shows the simulations considering different scenarios: with two ideal heat loads (0 mW and 125 mW), and when the microcooler is loaded with brain tissue. The results lead to the conclusion that the brain behaves as a heat load between 0 mW and 125 mW, as expected. It's also possible to observe that, for a temperature difference of ~20 ºC, the microcooler requires a current of ~50 mA.

D. Neuromodulation analysis

After modeling the two main intervenients, the effect of using the proposed microcooler to achieve neuromodulation was simulated to understand how the microcooler can affect the brain cells' temperature, and how a small heat sink handles overheating. Two different aspects were under analysis: how the temperature changes with time and with applied current, and how far from the microcooler is it possible to cool down the activity focus without breaking the limit temperature on the hot side, which was controlled through a 10 x 10 x 0.1 mm^3 plate of aluminum, acting as a heat sink over a large surface.

For such analysis, four microcooling solutions were assessed: single or double microcooler, and with and without spikes. The aluminum heat sink was unchanged in order to compare and discuss the effect of changing the cooling device alone. The analysis was evaluated at three different instants, while using a current of 50 mA to drive the microcooler. This current value was used since, both from Micro MPC-D403 datasheet and fig. 3, a temperature differential of ~20 ºC is achieved when the device is powered by ~50 mA.

IV. Results and Discussion

This section shows the results expected for the aforementioned scenarios.

A. Temperature control over time

The temperature evolution with time is important because it impacts how long the device needs to operate in order to stop seizures, therefore influencing how much energy is required to stop the seizure. This translates directly on battery dimensions and/or device lifetime between recharges. Also, exposing brain cells to high temperatures for long time periods may lead to cell damage. Fig. 4 shows the results

when one or two microcoolers were used, at time stamps 5, 30 and 100 seconds.

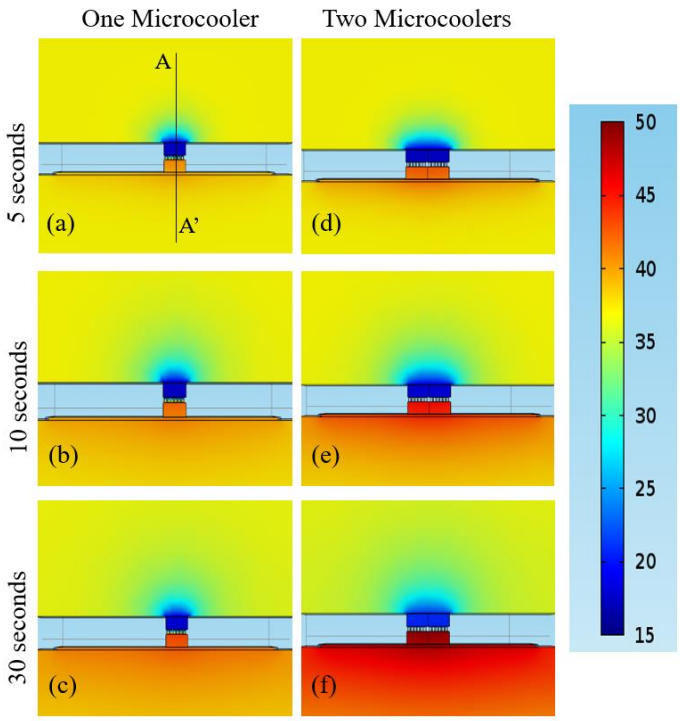

Figure 4. Simulation of the effect of: one microcooler in 5s (a), 30s (b) and 100s (c); two microcoolers in 5s (d), 30 (e) and 100s (f).

Observing the 100 s instant, it can be observed that the volume of cooled cells is not significantly bigger than the volume at 30 s, but the hot side shows higher values of temperature, which may be harmful to cells. So, this exposure time has increased damage risks without any benefits to the experiment. So, turning on the microcooler for 30 s is enough guarantee the required temperature in the cold side, without exceeding the hot side temperature limits.

Looking at the results for two devices, at 30 s, and regarding achieved temperatures versus distance from the microcooler, similar results can be observed as those for one device (see Fig. 5 for a cross-section view).

However, the required power doubles, since each device requires 50 mA to operate. As it does not cool down two times faster, this means more energy required to achieve the same temperature, therefore larger batteries are necessary and more device volume would come as a consequence.

B. Volume affected by temperature changes

In focal cooling, achieving greater depths can be interesting and more important than getting bigger areas, because seizures can begin in nerve cells that are some millimeters bellow the gray matter of the brain [6]. Fig. 5 shows the temperature variations in the cross section A to A' (shown on figure 4). The cooled area may double when using two coolers, but the depth of brain cells that are cooled is not significantly larger, as is shown in figure 5.

Since the neuromodulation obtained will depend on the depth of the cooled region, it is important to provide solutions to control the volume affected by temperature changes. To overcome the problem of low cooling depths, it was proposed to add some spikes that can get inside the gray matter, and more easily reduce cells temperature. So, in each microcooler device, one small spike with 1000 µm of length and 200 µm of diameter was added to assess if the cooled area and depth can be increased. This small spike was simulated as aluminum because this material is a good thermal conductor.

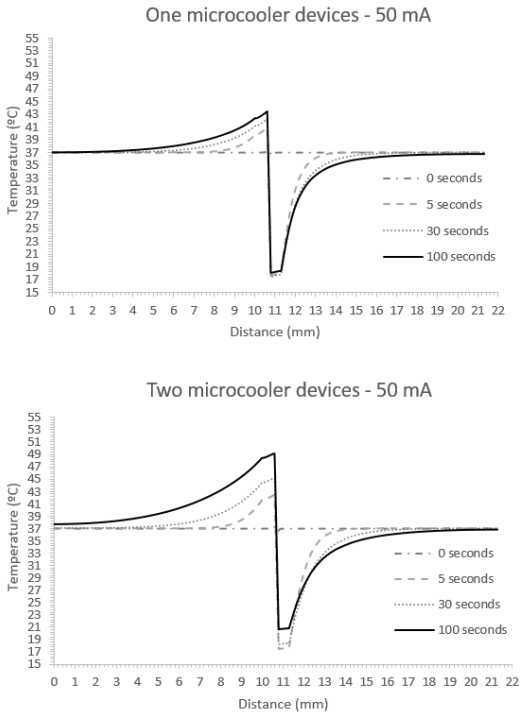

Figure 5. Temperature variation from the bottom of the brain cells to the top, passing on the middle of the microcooler device.

Fig. 6 shows the effect of using spikes on the temperature distribution.

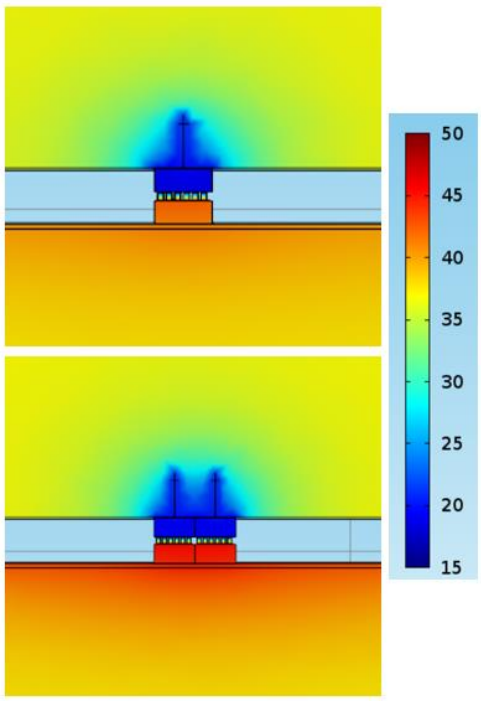

Figure 6. Simulation results for temperature when spikes are used on top of the microcooling device.

Observing the obtained results, it's obvious that the spikes increased the depth of cooled tissue, both with one and two microcoolers, while the hot side was mostly unaltered. To check and compare the areas and volumes of cooled tissue, fig. 7 may be used.

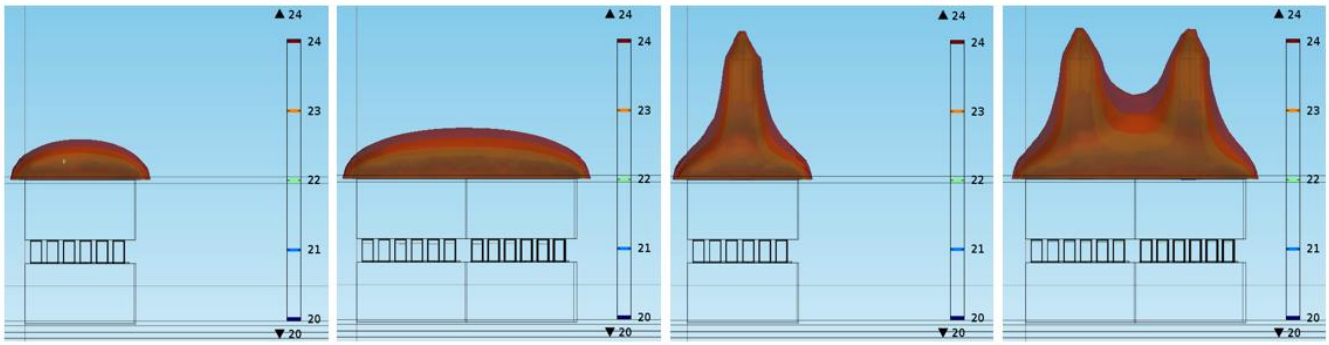

Figure 7. Cooling volumes for diferent microcoolers: one element, two elements, one element with spike, and two elements with spikes.

In fig. 7 it's possible to make a final comparison on the volume of tissue that is indeed cooled bellow 25 ºC for each simulation that was made in this work. As it can be seen, the introduction of spikes produces a big effect, even considering that part of the volume that is occupied by the spikes themselves. These results show that the cooling depth can be increased resorting on the use of spikes on the top of the microcoolers.

V. Conclusions and Future Work

This paper proposes the use of microfabrication technologies to obtain a microsystem for thermal neuromodulation. The core device size, a microcooler, is in the mm scale, where the expected full device volume is expected to be bellow 10 x 10 x 3 mm^3. Thermal simulations were used to conclude that the proposed device was able to cool down brain tissue to the required temperature to stop seizures, ~20 ºC, without exceeding the critical value of 43 ºC in the hot side.

Since different brain tissue thicknesses are under consideration, solutions to control the cooling depth that may achieved by the microcooler, were also investigated. Solutions with multiple coolers were analyzed, as well as the use of spikes, instead of flat coolers. Equally important was the analysis of the time that the microcooler must be kept switched on. It was essential to understand how to avoid exceeding the temperature threshold in the hot side, how long it may take to stop seizures, and to provide guidelines about the required rechargeable battery size. In this paper the biocompatibility is not discussed but in the future the heat sink material has to be changed. Gold or titanium are two good options that can be discussed and used with the same objectives.

It may be concluded that the proposed device is suitable for use in neuromodulation studies, and the next step will be testing with rats. A protocol to induce epileptic activity will be used, while the proposed neuromodulator will control the brain temperature to stop seizures.

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