Thermal Effect of Dielectrophoresis Manipulation on Cerebrospinal Fluid*

Amine Miled, *IEEE member*[1]

***Abstract*— This paper introduces an investigation on the thermal effects of dielectrophoresis on cerebrospinal fluid (CSF). It highlights the temperature propagation in CSF according to applied voltage and generated electrical field in a limited area of the brain. Through the described study, the temperature increase is considerable in the close surrounding area of electrodes where applied voltage goes up to 20 V_{rms} in order to generate dielectrophoretic forces for CSF sampling. Matlab simulations detailed in this work are based on the assumption that the propagation of temperature in CSF is linear. The objective of this research is to study the thermal side effects of direct measurements and manipulations of neurotransmitters in the brain versus in-channel measurement of neurotransmitter concentration. Indeed, according to simulation results, if the temperature in the top of electrodes is 46.85 $^{\circ}C$ then it will decrease only to 45.35 $^{\circ}C$ at 1 mm away from electrode surface.**

I. INTRODUCTION

Temperature fluctuation in brain is critical as its variation far from 37 $^{\circ}C$ can lead to severe diseases and alterations in brain electrical and chemical activities. However the temperature dependency of brain tissue is complex as it affects its electrical conductivity and consequently its electrical activity [1]. Indeed, electrical conductivity is temperature dependant and conductivity of biological tissues increases with temperature as it influences ion concentration, motion and diffusion. The biological conductivity depends also on frequency as shown in [2]. In fact according to Kraszewski et al., the conductivity of grey matter rises from 9 $S.m^{-1}$ to 67 $S.m^{-1}$ when frequency increases from 0.1 GHz to 8 GHz [3]. But such high frequency is not commonly used for biological manipulations. From another side, Baumann et al., showed that the conductivity rises from 1.789 S.m^{-1} to 1.802 S.m^{-1} when frequency increases from 10 Hz to 10 MHz [1]. Usually biological manipulations occur at low frequencies, making the impact of frequency change at body temperature (37$^{\circ}C$) be $\Delta\sigma$ = 0.014 S.m^{-1}), which is negligible.

However, the same study shows that a considerable change of CSF conductivity occurs if temperature increases from 25 $^{\circ}C$ to 37 $^{\circ}C$ which leads to a conductivity change from 1.454 $S.m^{-1}$ to 1.793 $S.m^{-1}$. Consequently, the use of intensive electrical fields in direct contact with brain tissue leads to a temperature increase which may have an impact on the conductivity of CSF and other side effects.

*This work was supported by Laval University

[1]A. Miled is with LABioTRON bioengineering research laboratory at electrical and computer engineering department at Laval University, Faculty of Science and Engineering, Adrien-Pouliot Build. 1065 Av. de la médecine, Québec (Qc), Canada amine.miled at gel.ulaval.ca

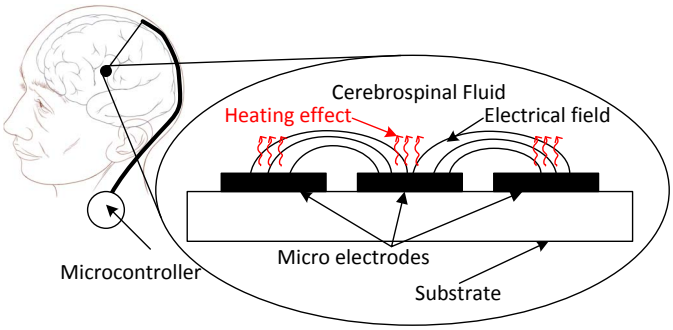

Fig. 1. Diagram of proposed electrodes showing their arrangement

In fact, recent advances in microfabrication has resulted in very compact microelectrodes which can produce intensive electrical fields with a lower voltage as in the case with recent dielectrophoresis-based devices to monitor neuronal activities [4]. Indeed Honegger et al., showed in their work that it was possible to dynamically control axonal growth in cultured rat hippocampal neurons through the use of AC electrokinetics. They applied a 3 V signal on interdigitated electrodes; consequently, the temperature increased by 7$^{\circ}C$ for in-vitro experiments. Such temperature increase for in-vivo experiment with brain tissue can cause major side effects even if applied locally. Indeed, according to Haveman et al., the maximum temperature that can be supported by brain tissue is 42 $^{\circ}C$ to 42.5 $^{\circ}C$ for 40 min to 60 min and 43 $^{\circ}C$ for 10 min to 30 min [5], [6]. Then, while the use of low voltage dielectrophoresis resulted in many advantages such as generation of high electrical fields with a low voltage using microelectrodes to manipulate small particles as described by Miled et al., serious heating side effects emerged when this technique is used with brain tissue [7].

In this paper, we describe an investigation on the local thermal effect of high intensity electrical fields on CSF. The objective of this study is to estimate how localized dielectrophoretic manipulations can affect brain temperature.

Then, section II details the theoretical background and environment of the application. In section III, the microfabricated electrodes and devices are presented. Section IV presents details of used models and simulation results related to thermal effect of dielectrophoretic manipulation with CSF

II. THEORETICAL BACKGROUND

The proposed system consists of an implantable device for neurotransmitter manipulation as shown in Fig. 1.

978-1-4244-7929-0/14/$26.00 ©2014 IEEE

In order to study side effects of intensive electrical fields applied on a local area of brain with CSF, we confine this research to square electrodes whose dimensions are $l \times l$ and manipulated molecules are neurotransmitters (NT) whose diameter a is extremely small compared to the electrodes, i.e $a \ll l$. Then dielectrophoretic forces generated by AC voltage on electrodes can be expressed based on equation 1.

$$\overrightarrow{F}_{DEP} = 2\pi a^3 Re(\frac{\epsilon_0 \varepsilon_1^*(\omega)(\varepsilon_2(\omega) - \varepsilon_1(\omega))}{2\varepsilon_1(\omega) + \varepsilon_2(\omega)}) \nabla |E|^2 \quad (1)$$

where, $\varepsilon_1(\omega)$ and $\varepsilon_2(\omega)$ are the complex permittivity of particle and medium respectively, $\varepsilon_1^*$is the complex conjugate of ε_1, ϵ_0 is the permittivity of air, E is the external electrical field, a the radius of the spherical particle, ∇ the differential vector operator and Re the real part of the complex number and $\omega = 2.\pi.f$ where f is the frequency of applied AC voltages on electrodes.

Furthermore, equation (1) shows that the amplitude of the dielectrophoretic (DEP) force also depends on the electric field which is related to the applied voltage. Then, DEP forces that are applied on particles depend on frequency and phase shift between applied signal on electrodes as well [8].

In order to manipulate CSF in brain we propose to use DEP forces whose effects are equivalent to a magnetic field. Indeed depending on the frequency of applied signals, two DEP effects can be observed which are called negative DEP (nDEP) and postive DEP (pDEP) which are related to electrode attraction or repulsion effects, respectively. The frequency shift which moves nDEP to pDEP is defined by the clausius mossotti factor f_{cm} as detailed in equation 2.

$$f_{CM}(\varepsilon_1(\omega), \varepsilon_2(\omega)) = \frac{(\varepsilon_2(\omega) - \varepsilon_1(\omega))}{2\varepsilon_1(\omega) + \varepsilon_2(\omega)} \quad (2)$$

However, the complex permittivity depends not only on the frequency but also on the electrical conductivity as shown in equation 3.

$$\varepsilon(\omega) = \varepsilon^{'} + i\frac{\sigma}{\omega} \quad (3)$$

where $\varepsilon^{'}$ refers to the in-phase permittivity [9]. σ refers to the electrical conductivity of the medium. As applied signals are in the range of 0 MHz to 1.5 MHz, the conductivity variation versus frequency is negligible [1]. Consequently, we focus in this work only on side effects of DEP forces on CSF temperature.

The thermal effect of DEP forces is originally coming from the electrical field intensity due to the applied voltage and electrode dimension. Indeed the power generation W of electrical field is based on equation 4.

$$W = \sigma E^2 \quad (4)$$

The power dissipation leads to a temperature increase. In order to estimate the temperature variation, the energy balance is detailed in equation 5 and shows the contribution of different parameters to power dissipation and heating effect.

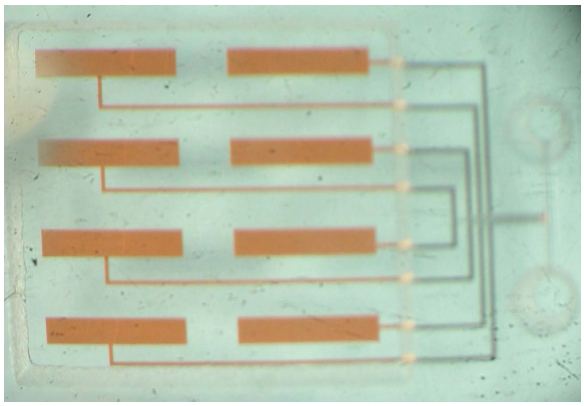

Fig. 2. Fabricated device with 8 in-channel electrodes

$$\rho_m c_p \overline{v} \nabla T + \rho_m c_p \frac{\partial T}{\partial t} = k\nabla^2 T + \sigma E^2 \quad (5)$$

where v is the velocity, T is the temperature, ρ_m is the mass density, c_p is the specific heat (at constant pressure) and k is the thermal conductivity. If we assume that the fluid is static, i.e. v=0 $m.s^-1$, then equation 5 becomes.

$$0 = k\nabla^2 T + \sigma E^2 \quad (6)$$

Then the temperature change can be approximated by the following equation

$$\Delta T = \sigma \frac{V_{rms}^2}{k} \quad (7)$$

where V_{rms} is the potential difference across the electrodes.

This study does not take into account the conductivity change according to temperature as the temperature coefficients, for both permittivity and conductivity, are tissue-type and frequency dependent [2].

III. Microfabricatced Electrode

Through this work, the objective is to investigate the temperature diffusion of DEP forces through the use of microelectrodes in direct contact with tissue or through in-channel microelectrodes. In-channel microelectrodes, shown in Fig. 2 are fabricated using sensonit technology (Micronit, The Netherlands). They are made from 180 nm of gold and 10 nm of tantalum as adhesive to attach electrodes on borosilicate (glass). The electrode dimensions are 10 μm $\times$ 10 μm. Two glass thickness's are used which are 1.5 mm and 170 μm. The microchannel depth is 40 μm. Electrodes are planar and applied voltage range is 1.7 V to 24 V. Used liquid is CSF from Tocris bioscience (Bristol, United Kingdom) with the following ion concentration in mM: Na 150; K 3.0; Ca 1.4; Mg 0.8; P 1.0; Cl 155.

IV. Modeling and Simulation Results

Simulation results are achieved using Matlab 2014 with the PDE toolbox. We assume that only the convection effect takes part as shown in equation 8. In addition, electrical field

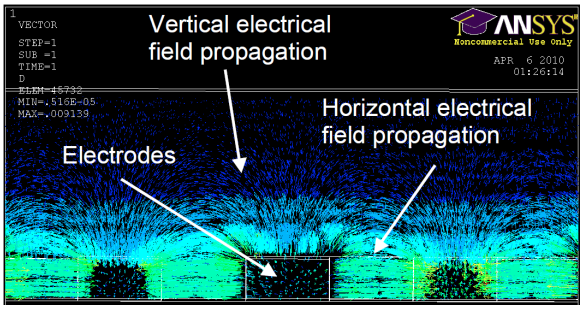

Fig. 3. Electrical field propagation with square electrodes

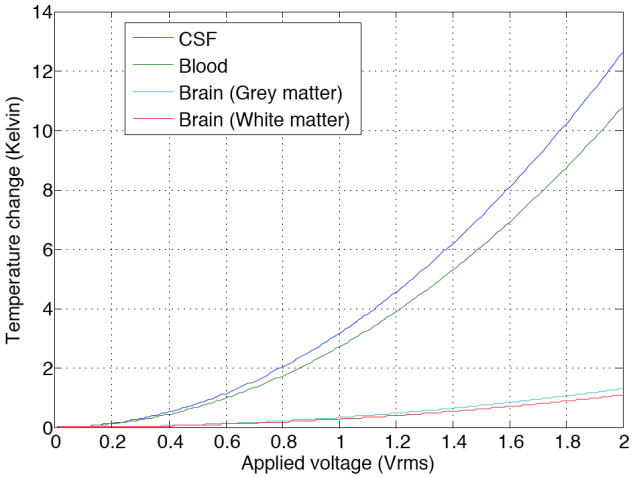

Fig. 4. Temperature change versus applied voltage for CSF, blood, brain (grey and white matter)

is stronger in the close area of microelectrodes as it can be seen in Fig. 3.

$$Q_c = h(T - T_a) \tag{8}$$

where T_a is the ambient temperature, T is the temperature at a particular x and y location and h is a specified convection coefficient. Thermal conductivity of CSF is 0.57 $(W/m/^{\circ}C)$, CSF density 1007 kg/m^3, heat capacitance 4096 $J/(kg - K)$.

Fig. 4 shows the temperature change profile for brain liquid and tissue and blood. As it can be observed, the brain is more sensitive to temperature change. Indeed starting from 1.4 V temperature increases more than 6 $^{\circ}C$ which is the maximum tolerable increase in temperature in the brain, however in the case of blood, temperature change is not critical as it stays below 2 $^{\circ}C$ even when 2 V are applied on electrodes.

Fig. 5 shows the diffusion of the temperature in the CSF when the temperature at the top of the electrode is 46.85 $^{\circ}C$ (320 $^{\circ}C$) . As it can be seen the temperature is high even at 1 mm far from electrodes. Then if we assume that the width of a synapse is around 4 nm to 10 nm and electrode dimensions are 10 $\mu m \times 10$ μm, then the propagation of the temperature will affect a large number of neurons if

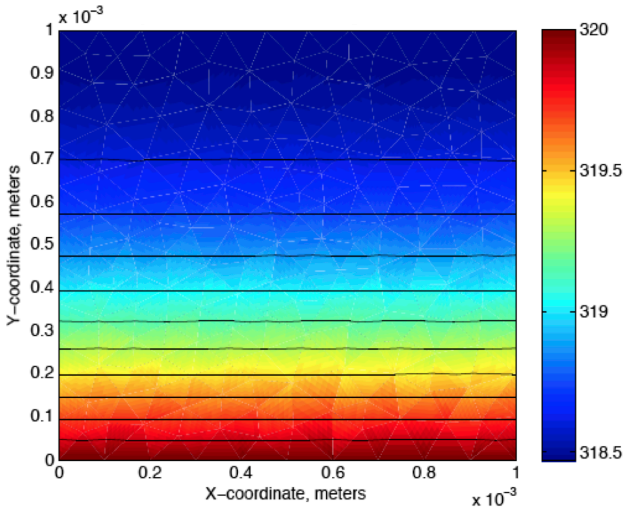

Fig. 5. Temperature diffusion in CSF when the temperature on the top of the electrode is 46.85$^{\circ}C$

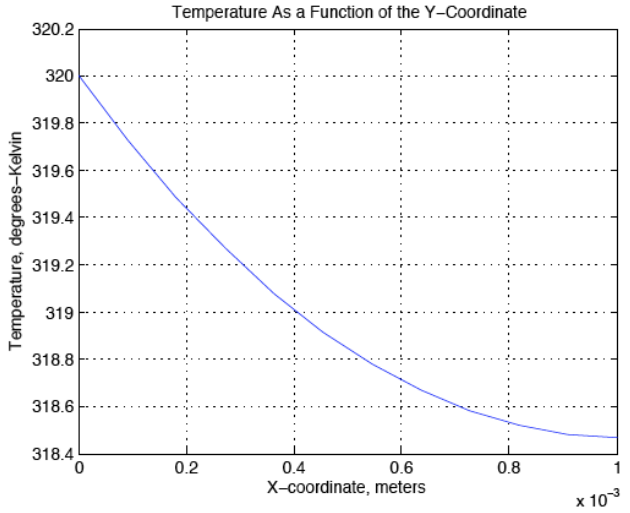

Fig. 6. Temperature diffusion in CSF through Y-axis

electrodes are in direct contact with brain tissue as seen in Fig. 6. The temperature decrease in the brain is very slow especially for deep brain areas compared to superficial brain areas close to the skull.

Fig. 7 shows the transient propagation of temperature in CSF. It can be noticed that there is a sharp increase of temperature during the first seconds if we assume that we are applying a continuous voltage on the electrodes,.

In order to reduce side effects of high intensity electrical fields, we used in-channel electrodes as shown in Fig. 2 covered by a microchannel in a borosilicate plate. The top plate reduces considerably the temperature propagation as it can be seen in Fig. 8 and 9. However, glass considerably reduces temperature down to to 37.85 $^{\circ}C$ (311 $^{\circ}K$), the needed glass thickness to eliminate thermal propagation is 7 mm which is too much in order to place the device in

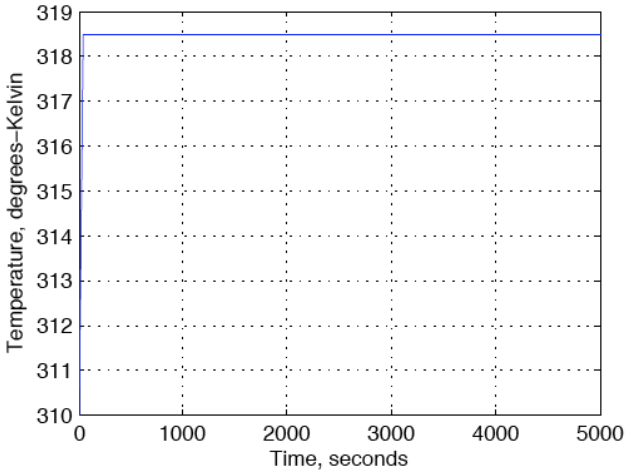

Fig. 7. transient propagation of temperature in CSF

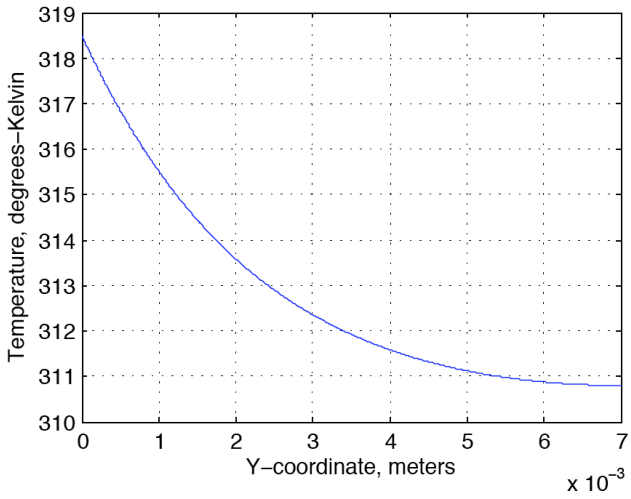

Fig. 9. Temperature diffusion in CSF through X-axis

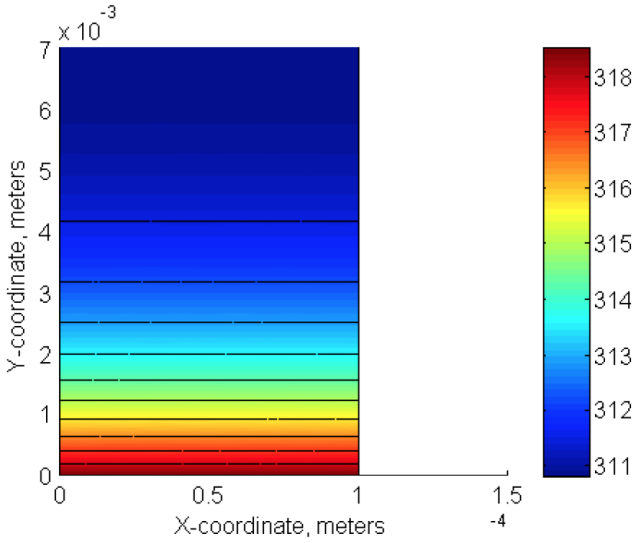

Fig. 8. Temperature diffusion in CSF when the temperature on the top of the electrode is 46.85°C

the deep brain region. Despite this disadvantage, the use of glass top plate can be considered for cortical placement of the device.

In addition, in this study, we neglected the radiation effect as the goal is primarily to investigate on thermal conductivity of CSF when a high temperature is observed close to electrodes and how it is propagated through the CSF. A more complete study is undertaken in order to propose a more concise model for thermal propagation within brain tissue.

V. CONCLUSIONS

In this work, we highlighted the influence of high intensity electrical fields on the temperature of CSF. According to literature review, 43°C for more than 30 min is considered as a firm barrier not to go further in order to avoid serious brain injury. With actual simulation results we can see that temperature increases to more than 9.85°C. However, there is no major study to investigate on the detailed impact of such high temperatures on brain tissue when applied for a long time through few micrometers, this study brings into attention the major side effect that may be generated through the use of high intensity electrical field.

ACKNOWLEDGMENT

The author acknowledge the financial support from Laval University, and he is grateful for the design and simulation tools supplied by CMC Microsystems and Laval University.

REFERENCES

[1] S. B. Baumann, D. Wozny, S. Kelly, and F. Meno, "The electrical conductivity of human cerebrospinal fluid at body temperature," *IEEE Trans. Biomedical Engineering*, vol. 44, no. 3, pp. 220–223, Mar. 1997.

[2] C. Gabriel, S. Gabriel, and E. Corthout, "The dielectric properties of biological tissues: I. literature survey," *Physics in Medicine and Biology*, vol. 41, no. 11, p. 2231, 1996.

[3] A. Kraszewski, M. A. Stuchly, S. S. Stuchly, and A. M. Smith, "In vivo and in vitro dielectric properties of animal tissues at radio frequencies," *Bioelectromagnetics*, vol. 3, no. 4, pp. 421–432, May. 1982.

[4] T. Honegger, M. A. Scott, M. F. Yanik, and J. Voldman, "Electrokinetic confinement of axonal growth for dynamically configurable neural networks," *Lab on a Chip*, vol. 13, no. 4, pp. 589–598, Jan. 2013.

[5] C. Childs, "Human brain temperature: regulation, measurement and relationship with cerebral trauma: Part 1," *British Journal of Neurosurgery*, vol. 22, no. 4, pp. 486–496, Aug. 2008.

[6] J. Haveman, P. Sminia, J. Wondergem, J. van der Zee, and M. C. C. M. Hulshof, "Effects of hyperthermia on the central nervous system: What was learnt from animal studies?" *International Journal of Hyperthermia*, vol. 21, no. 5, pp. 473–487, Aug. 2005.

[7] M. Miled and M. Sawan, "Dielectrophoresis-based integrated lab-on-chip for nano and micro-particles manipulation and capacitive detection," *IEEE Trans. Biomed. Circuits. Syst.*, vol. 6, no. 2, pp. 120 –132, Apr. 2012.

[8] X. Wang, X.-B. Wang, F. F. Becker, and P. R. C. Gascoyne, "A theoretical method of electrical field analysis for dielectrophoretic electrode arrays using green's theorem," *J. Phys. D: Appl. Phy.*, vol. 29, no. 6, pp. 1649–1660, 1996.

[9] K. Kaler and H. A. Pohl, "Dynamic dielectrophoretic levitation of living individual cells," *Industry Applications, IEEE Transactions on*, vol. IA-19, no. 6, pp. 1089–1093, Nov. 1983.