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A New 3D Finite Element Model of Extracellular Action Potentials Recording with a Microelectrode in a Tissue Slice

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***Abstract* - A new transient finite element model of extracellular action potentials recording with a microelectrode in a tissue slice is presented. The neuron model is based on the Hodgkin-Huxley equations implemented with a thin film approximation of the neuron membrane. The computations of the membrane potential and currents, as well as that of the intra and extracellular potential fields, are performed at the same time, within a single finite element software.**

The neuron membrane model is validated by comparison with a NEURON simulation. It is shown that the finite element model is able to properly represent the neuron behavior in terms of membrane currents and potential.

Moreover, it is demonstrated that an ideal measurement system model can be used, provided that the electronic recording system is adapted to the electrode-tissue interface impedance.

A brief study of the influence of the relative position of the neuron and recording microelectrode on the recorded signal is presented. It is shown that the maximum recorded extracellular action potential is obtained when the electrode is placed below the neuron soma and hillock-initial segment areas.

I. Introduction

MICROELECTRODE arrays (MEAs) provide a useful tool for neuroscientists to study the bioelectrical activity of small neuron networks. Despite a large body of literature on extracellular action potential (AP) recordings, there is still a lack of knowledge on how the extracellular potential is related to the much better known intracellular potential. A better understanding of the influence of the bioelectrical and geometrical properties of the neuron, the extracellular medium, and the microelectrode on the AP parameters is needed. First, it would give useful insights to neuroscientists on how to extract information on the intracellular state of the neuron from the extracellular recordings. Secondly, it would help designing MEAs according to the neuronal sample properties (e.g. microelectrodes and grid sizes corresponding to the neurons sizes and estimated positions).

Toward these goals, several models of microelectrodes AP recordings have been proposed. Lumped circuit elements models have been used to simulate AP recordings of cultured neuron or tissue slice on a microelectrode [1, 2]. These models are easily implemented but cannot always accurately predict the measurements, as they do not properly take into account complex geometries. Two more sophisticated models, coupling the finite element (FE) method with an externally solved active neuron model, have been proposed to date. The first one uses a reciprocal FE formulation coupled to a NEURON neuron model to simulate AP recordings with a needle-like microelectrode array in a rat brain [3, 4]. The second one addresses the problem of the AP recording of neurons cultured on a planar MEA [5]. It couples the FE simulation of the current conduction in the extracellular medium with the solution of differential equations for the neuron and electrode descriptions in Matlab.

This paper is dedicated to the presentation of a new FE model of extracellular AP recording based on the thin film approximation. The results are obtained by the means of a single transient computation performed within a single FE software. In the next section, the model of a structured and active neuron embedded in a tissue slice is presented. Then two recording microelectrode models are proposed and compared. In the last section, the neuron model is validated. It is also shown that an ideal measurement system model can be used if the electronic recording system is adapted to the electrode-tissue interface impedance. Finally, as an example of the model analysis, the influence of the neuron-electrode relative positions on the AP recording, is presented.

II. Models

The model presented here aims at providing a tool to study the relationship between the neuron signal and the extracellular signal recorded with a microelectrode. In order to model our system, composed of a neuron, an electrode and the surrounding medium, the general framework of the Maxwell's equations is used. Considering the values of time and length scales, and physical properties, these equations can be simplified and replaced by the current conservation law (1):

$$\nabla(-\sigma\nabla\Phi) = 0 \qquad (1)$$

where Φ is the electrical potential field (V/m) and σ the medium conductivity (S/m) [6]. The solution of this equation by the FE method is straightforward but in our context special care must be taken to model the neuron membrane as well as the measurement electrode and acquisition system (see Section II.A and II.B).

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In this paper, the following geometry and bioelectrical parameters are used: the nervous tissue is represented by a small cylindrical volume of 1 mm diameter and 0.6 mm height with a single active neuron; the base of this cylinder represents the passivation layer of the MEA with one recording microelectrode (Fig. 1.A). With these dimensions, the cylinder is large enough to avoid its top and side boundaries to be submitted to potential change due to neuron activity. The MEA substrate is insulating and the tissue boundaries (top and side of the cylinder) are grounded to simulate a distant reference electrode. The extracellular and intracellular media are supposed homogeneous and isotropic, as they are usually assumed to be [3, 5], and their conductivities are respectively set to 0.3 S/m and 3 S/m. The neuron is represented by a 20 µm diameter circular soma, a 10 µm long hillock, with diameter tapering from 4 µm to 1µm, a 10 µm long initial segment, and a 60 µm long axon, both with a 1 µm diameter (Fig. 1.B). The geometry of the neuron structures are set according to the neuron described by Mainen et al. [7].

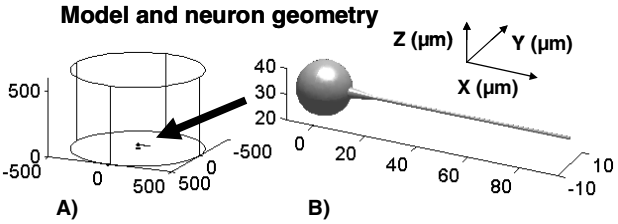

Fig. 1. Three dimensional model and neuron structure. A: model geometry. The neuron and microelectrode can be seen in the lower part of the cylinder. B: close up of neuron geometry at the default position.

A. Thin film Approximation of the Neuron Membrane

A neuron can be described as a semi permeable membrane with active, nonlinear, and inhomogeneous electrical properties, which separates the intracellular medium from the extracellular medium. The neuronal membrane is very thin (a few nanometers thick) compared to the other problem typical dimensions, which are in the micrometer and above ranges (e.g. neuron, microelectrode, etc.). The thin film approximation can be used to solve problems where, due to large length scale differences between a thin layer and the surrounding media, meshing the geometry would result in unrealistic requirements in terms of computer processing power and memory resources. This approximation is valid under the assumptions that (i) the layer thickness is negligibly thin and (ii) the electrical current or thermal flux flows perpendicularly through it. It is classically used to model the electrical or thermal contact resistance which occurs at an interface between two solids [8]. The thin film approximation is extended as follows in this paper to the simulation of the neuron membrane: the neuron membrane is replaced by the interface separating the intracellular and extracellular media and the transmembrane potential jump is related to the membrane current through a set of coupled differential equations. The equations classically used to link the neuron membrane currents and potential are the Hodgkin-Huxley (HH) equations [9]. These equations express the transient nonlinear relation between ionic, capacitive and leakage membrane currents, and the membrane potential. The thin film approximation of the membrane allows the simultaneous computation of the active membrane electrical parameters (currents and potentials) and of the extracellular potential field as well as the intracellular potential field.

The equations used in this paper to link the membrane currents and potential are those described by Hodgkin and Huxley in 1952, but with the present membrane potential convention (i.e. membrane potential equals intracellular potential minus extracellular potential, membrane resting potential equal to -60 mV). Bioelectrical properties of the membrane are described by the usual HH parameters except for the hillock and initial segment structures where the maximum potassium and sodium conductivities are set to ten times the normal ones, in order to simulate greater concentrations of voltage gated ionic channels. Other types of equations or ionic channels distribution, as well as neuron morphology and dimensions, can be easily implemented within the same finite element framework.

B. The MicroElectrode Model

Two different models of the microelectrode interface were implemented and compared. In the first one, the measurement system is considered to be ideal, that is to say the microelectrode current is null. In the second model, the microelectrode and recording system impedance are taken into account.

1) Ideal measurement system

The microelectrode is modeled by an insulating Neumann boundary condition (the ideal recording system input impedance is equivalent to an infinite impedance). The recorded extracellular potential is determined as the mean voltage over the non equipotential microelectrode surface.

2) Nonideal microelectrode and recording system

The measurement system impedance and the microelectrode-tissue interface impedance are incorporated in the model (Fig. 2). In a first approximation the microelectrode interface impedance is supposed to be purely capacitive (Cdl) and the measurement system equivalent input impedance is supposed to be purely resistive (Re). The microelectrode is connected on its metal side to the recording system input impedance, which is connected to the electronic ground.

The electrode potential Velectrode is the mean voltage over the non equipotential microelectrode surface area. The measured potential Vmeasured is the simulated recorded potential, equal here to the multiplication of the electrode current by the recording system input impedance. The difference between the electrode potential and the measured potential is the potential drop Vc across the microelectrode

interface impedance.

More sophisticated electrode-electrolyte interface and measurement system impedances, for instance a constant phase impedance model of the electrode interface, could be implemented.

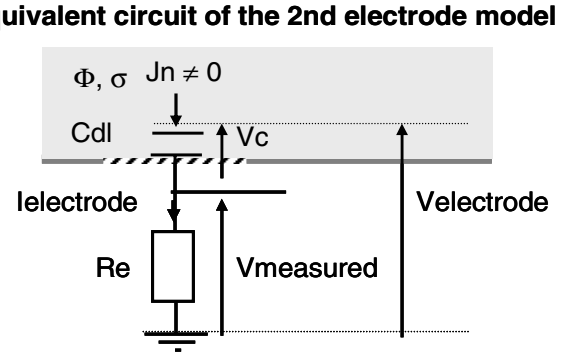

Fig. 2 Equivalent circuit of the second electrode model. It includes the electrode double layer capacitance Cdl and the recording system equivalent input impedance Re. Velectrode is the mean voltage calculated over the electrode surface area.

III. Results and Discussion

The FE simulations were performed with the software COMSOL version 3.2a. Each model was solved in a single transient computation using a nonlinear time dependent solver. In the simulations presented here the initial intracellular potential is set to 10 mV above the intracellular resting potential, in order to release an AP. Note that it is also possible to stimulate the neuron extracellularly with a current injected through the microelectrode. This paves the way to the study of devices designed to both stimulate neurons and record APs, and to the study of stimulation artifacts.

A. Neuron Model Validation

The neuron presented in section II.A is placed at the center of the cylinder of homogeneous surrounding tissue. In this section, the outer boundaries of the extracellular volume are all grounded in order to focus only on the neuron and not on the boundary conditions.

The thin film approximation based model allows the simulation of the neuron behavior consistently with what can be found in the literature in terms of membrane currents and potentials, action potential propagation, and initiation locus. The three dimensions model results are compared to simulations obtained with NEURON 5.8 for the same neuron structures and dimensions, with an AP initiation due to a current injection at the soma. The two simulations provide very similar results in terms of APs and currents shapes and amplitudes (Fig. 3). In both cases, the AP propagation velocity in the axon is found to be 5.5 m/s, and the AP initiation locus to be located at the end of the initial segment, close to the axon.

The thin film approximation allows not only to compute the transient variations of the membrane potential and currents but also the intracellular and extracellular potential fields. Moreover, it gives the possibility to implement inhomogeneous conductivities in the extra as well as in the intracellular mediums, and to represent the neuron with realistic geometries.

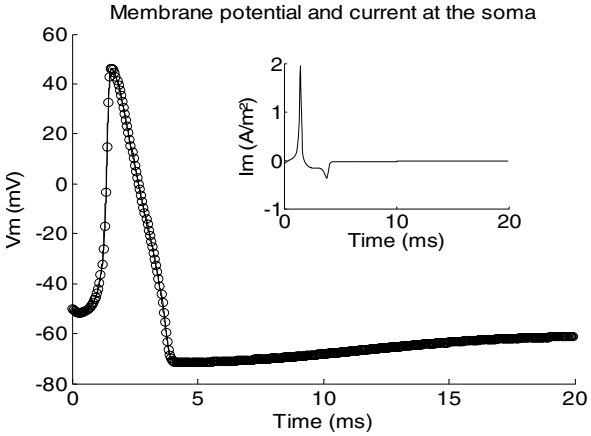

Fig. 3 The main figure represents the membrane potential Vm at the soma for the FE model (straight line) and for the NEURON model (circular markers). The NEURON potential was delayed 280 µs to compensate for the different AP initiation methods. The inset represents the FE modeled membrane current Im at the soma.

B. MicroElectrode Model Validation

The neuron presented in section II.A is placed in the three dimensional conductive domain with its main axis parallel to the passivation layer (Fig. 1). The center of the spherical soma is placed 30 µm above the passivation layer and centered on the (x,y) plane, while the main neuron axis is parallel to the x axis. The microelectrode is represented by a circular boundary of 30 µm diameter, and centered below the hillock-initial segment structures at (x=20 µm, y=z=0).

The microelectrode-tissue interface impedance value used in the second model is 192 pF (0.271 F/m²). This value is the equivalent capacitance at 1 kHz of a 30 µm diameter circular platinum microelectrode from Ayanda Biosystems (MEA 100 Pt), calculated from impedance measurements (BiStat, Bio-Logic). The second model was solved for several values of the measurement system equivalent input impedance Re (Ω): [10^{12}, 10^{9}, 10^{7}, 10^{6}].

First, the results show that there is no significant difference between the two models for the electrode potentials, whatever the value of the recording system input impedance. This means that the current going through the microelectrode is so small that it does not change significantly the potential field in the vicinity of the microelectrode for our model configuration. The results also show that, as long as the measurement system impedance is much larger than the maximum electrode-tissue interface impedance (e.g. Re=10^{9} Ω for a 100 Hz-10 kHz bandwidth), there is no significant difference between the electrode potential and the measured potential, the maximum potential drop in the interface capacitance being then five order of magnitude smaller than the electrode potential, which is in

the µV range. On the contrary, when the input impedance is of comparable value or smaller than the interface capacitance, that is to say when the input impedance of the measurement system is not adapted to the microelectrode interface capacitance, the error between the electrode potential and the measured one, is important (as much as 50% error when the input impedance is equal to 10^6 Ω).

To conclude, as long as the measurement system is adapted to the microelectrode impedance, the ideal model of the measurement system consisting in applying an insulation boundary condition to the electrode surface can be used. The measured extracellular action potential can then be assimilated to the mean voltage over the microelectrode surface area.

C. Influence of the Neuron – Electrode Relative Positions

Several extracellular potential recordings were simulated for different positions of the electrode below the neuron. The model is composed of the neuron model presented in the precedent sections, but with its soma centered 15 µm above the passivation layer, and of a 20 µm by 20 µm square microelectrode connected to an ideal electronic measurement system. The microelectrode is centered at different (x, y) positions on a 20 µm by 20 µm grid below the neuron. For each position, the maximum amplitude of the extracellular AP recording is represented on Fig 4.

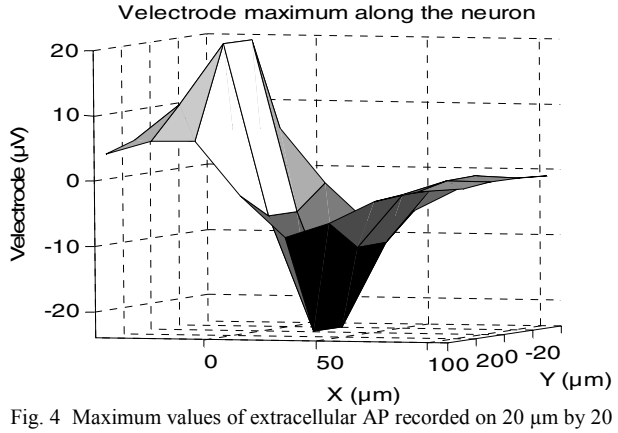

Fig. 4 Maximum values of extracellular AP recorded on 20 µm by 20 µm electrodes positioned below the neuron. The neuron is parallel to the passivation layer and its soma center is placed at (0, 0, 15 µm)

The results obtained with the model are consistent with the experimental measurements obtained by Claverol-Tinture and Pine [10]. The signal amplitudes, shapes, and duration are in the range of those observed experimentally with small neurons in a tissue slice (a few tens of µV). The recorded APs are of the same shape and duration (1 ms) as the membrane current presented in Fig. 3. Then the simulation results show that the maximum extracellular signal amplitudes are located below the soma (the largest neuron structure and also the closest to the electrode plane), and below the hillock-initial segment structures where the sodium and potassium maximum conductivities, hence currents, are larger than for the other membrane sections. It is also shown that the extracellular potential becomes rapidly very small when going farther from the initial segment along the axon. It would then be difficult to record extracellular potentials coming from the axon with MEA as the noise level on this type of recording is usually larger than 10 µV peak to peak. Let us also remark that the extracellular potential sign depends on the microelectrode-neuron relative position. The extracellular AP are positive near the soma (current source), and negative near the hillock-initial segment (current sink).

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REFERENCES

[1] S. Martinoia, P. Massobrio, M. Bove, and G. Massobrio, "Cultured Neurons Coupled to Microelectrode Arrays: Circuit Models, Simulations and Experimental Data," *IEEE Transactions on Biomedical Engineering*, vol. 51, pp. 859-864, 2004.

[2] P. Fromherz, "Sheet conductor model of brain slices for stimulation and recording with planar electronic contacts," *European Biophysics Journal*, vol. 31, pp. 228-231, 2002.

[3] M. A. Moffitt and C. C. McIntyre, "Model-based analysis of cortical recording with silicon microelectrodes," *Clinical Neurophysiology*, vol. 116, pp. 2240-2250, 2005.

[4] M. L. Hines and N. T. Carnevale, "NEURON: A tool for neuroscientists," *Neuroscientist*, vol. 7, pp. 123-135, 2001.

[5] J. R. Buitenweg, W. L. C. Rutten, and E. Marani, "Geometry-based finite-element modeling of the electrical contact between a cultured neuron and a microelectrode," *IEEE Transactions on Biomedical Engineering*, vol. 50, pp. 501-509, 2003.

[6] K. A. Lindsay, J. R. Rosenberg, and G. Tucker, "From Maxwell's equations to the cable equation and beyond," *Progress in Biophysics and Molecular Biology*, vol. 85, pp. 71-116, 2004.

[7] Z. F. Mainen, J. Joerges, J. R. Huguenard, and T. J. Sejnowski, "A model of spike initiation in neocortical pyramidal neurons," *Neuron*, vol. 15, pp. 1427-1439, 1995.

[8] COMSOL, "Thin film approximation," *COMSOL Knowledge Base # 902, http://www.comsol.fr/support/knowledgebase/902.php*, 2006.

[9] A. L. Hodgkin and A. F. Huxley, "A quantitative description of membrane current and its application to conduction and excitation in nerve," *journal of physiology*, vol. 117, pp. 500-544, 1952.

[10] E. Claverol-Tinture and J. Pine, "Extracellular potentials in low-density dissociated neuronal cultures," *Journal of Neuroscience Methods*, vol. 117, pp. 13-21, 2002.