Search for a Suitable Numerical Model for Electrical Stimulation: From the Electric Double Layer to Electrokinetics, Confrontation with Impedance Measurements.

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Abstract: Electrical Stimulation is widely used today for Deep Brain Stimulation treatments and retinal prostheses. At present, no experimental technique is available for measuring the distribution of the electric current delivered by electrodes inside tissues. Numerical simulation is a promising solution to investigate this question. The choice of the underlying mathematical model is the fundamental step for having a predictive tool. The Electrical Double Layer (EDL) formed between the electrode surface and the extracellular medium is considered through the linear Gouy-Chapman model and the nonlinear more realistic Modified Poisson Boltzmann model. The EDL is coupled to the bulk using the thin layer approximation. The bulk electric field distribution is computed from the electrokinetic equation, solved using both the complex and the temporal form. Numerical simulations, solved using Comsol Multiphysics, are compared with Electrochemical Impedance Spectroscopy (EIS) for a Medtronic 3389 DBS electrode and a Micro Electrode Array (MEA) retinal prosthesis immersed in a 137mM NaCl solution. The impedance measurement-calculation confrontation clearly shows that the EDL cannot be neglected for frequencies lower than the kHz. The full temporal electrokinetic equation is in better agreement than the complex one.

Keywords: Electrical stimulation, numerical modeling, Electric Double Layer, electrokinetic equation.

1. Introduction

Electrical stimulation consists of injecting currents via electrodes implanted in the vicinity of excitable tissues or cells to control or replace their electrical activity. For Deep Brain Stimulation (DBS) in humans, millimetric electrodes are implanted in subcortical structures to treat a variety of disabling neurological symptoms, most commonly the debilitating symptoms of Parkinson's disease (PD) [1]. DBS stimuli are usually voltage pulses of -3V amplitude, 90µs width, and 130Hz repetition frequency. In degenerative retinal diseases, such as Age-Related Macular Degeneration, the photoreceptor cells slowly degenerate, but many of the inner retinal neurons that transmit signals from the photoreceptors to the brain are preserved. Electrical stimulation of the remaining retinal neurons can produce perception of light. Current retinal prostheses involve a very small number of electrodes, while several thousands of them are required for functional restoration of sight [2]. Number of electrodes in the array is limited by such physical factors as heating of the retina, cross-talk between neighboring electrodes and electrochemistry at the electrode-liquid interface. All these factors are strongly dependant on the distance between the electrodes and the target cells. A broad range of current waveforms, durations, and amplitudes has been successfully used to stimulate the retina. Current waveforms might range from µs to ms in duration and from hundreds of nA to mA in amplitude.

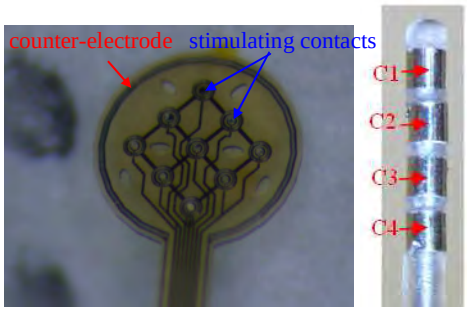


Figure 1: Photos of retinal MEA (left) and DBS 4 platinum iridium contacts Medtronic 3389 electrode (right).

Electrical stimulation is today an interdisciplinary question. New devices or optimization of existing ones need to identify the phenomena that strongly influence the electric field distribution inside the target tissue. Most numerical studies in DBS and retinal prosthesis applications consider the tissue environment of

the stimulating electrode as conductive media. This conductive representation is not sufficient if one needs to understand the temporal response of tissues to a temporal stimulus. As tissues or target cells are surrounded by extracellular liquid, the electrode surface is wetted by a thin film of this liquid [3]. Electrode polarization allows the formation of an Electric Double Layer (EDL) at the electrode-liquid interface [4]. If the EDL is known to be the center of possible electrochemical reactions, it may strongly influence the electric field distribution inside target tissues because of its capacitive behavior. Few recent papers consider the EDL in DBS or retinal electrical stimulation studies [5-7]. In those papers, the EDL is represented using the empirical equivalent circuit approach which is not satisfactory if we want the numerical tool to be predictive for any types of *in vivo* electrical stimulation applications. The use of theoretical models for representing the EDL is possible as it has already been done for other applications such as electroosmosis [8-9] or fuel cells [10]. Our final goal is to find a capacitance model that represent reasonably well the EDL for *in vivo* electrical stimulation conditions, i.e.: non sinusoidal applied potentials of several Volts, metallic (mainly platinum) electrodes, extracellular liquid, excitable cells in the vicinity of the electrode surface. Comparisons of numerical simulations with measurements must be carried out to determine the adequacy of the chosen EDL theoretical model. As a first step, we compare numerical simulations with sinusoidal low potentials impedance measurements performed using a commercial potentiostat (Bio-Logic VPM2).

2. Governing equations

The mathematical model should represent all the objects/phenomena influencing the electric field/potential distribution during the electrical stimulation. Four of them are actually identified: (i) the applied electrical stimulus which is usually time dependant voltage or current squared pulses, (ii) the tissues or neurons composed of both dielectric matter (lipid membrane cells) and conductive aqueous electrolyte (intra and extracellular media), (iii) the electrical activity of neurons and (iv) the extracellular liquid film supposed to wet the electrode [3] and to form an EDL at the electrode surface [4]. Those four independent contributions can be represented mathematically using electrical models. The influence of each on the electrical field/potential distribution during electrical stimulation can be studied by numerical simulation. As a first step, this paper addresses the particular question of the EDL influence. In this work, EDL models are confronted to impedance measurements performed in a saline solution of composition close to the extracellular medium one (137mM NaCl) and using sinusoidal low amplitude voltages (< 1V). The resulting equations to solve are composed of the electrokinetic equation for the electrolyte bulk (electrolyte region outside the EDL) and two capacitance models for the EDL considered using the thin layer approximation.

2.1 Temporal or complex electrokinetic equation for the bulk

If the quasi-static assumption is valid, the temporal electrokinetic equation [11] can be used as the governing equation to calculate the electric potential distribution inside the living matter:

$$\vec{\nabla}.\left(-\sigma\vec{\nabla}V(t) - \frac{\partial\varepsilon\vec{\nabla}V(t)}{\partial t}\right) = 0 \qquad (1)$$

where σ and ε are respectively the conductance and the permittivity of media crossed by the applied electric field.

Under the linear assumption, when sinusoidal potentials of angular frequency ω (rad/s) are applied, the temporal electrokinetic equation (1) can be expressed using the complex formalism. With

$$V(t) = V_0^* e^{i\omega t} \qquad (2)$$

V_0^* being the complex amplitude potential, then (1) then becomes:

$$\vec{\nabla}.\left(-\sigma^*\vec{\nabla}V_0^*\right) = 0 \qquad (3)$$

where the frequency dependent complex conductivity σ^* is such that:

$$\sigma^* = \sigma + i\omega\varepsilon \qquad (4)$$

In this study, both the temporal and the complex electrokinetic equation (1) and (3) are

used in computations to model the electric potential inside a saline 137mM NaCl solution where no living matter is present.
In equation (1), the ratio between conduction current $\vec{J}_C$ and displacement current $\vec{J}_D$ is given by:

$$\frac{\left|\vec{J}_C\right|}{\left|\vec{J}_D\right|} = \frac{\sigma}{\varepsilon\,\omega} \tag{5}$$

For the particular case of the 137mM NaCl solution, σ ~ 1.6S/m and $\varepsilon = 78.5\,\varepsilon_0$: for frequencies lower than 0.1GHz equation (1) can simplify into

$$\vec{\nabla}.\left(-\sigma\vec{\nabla}V(t)\right) = 0 \tag{6}$$

The electrokinetic equation is associated to homogenous Neumann boundary conditions (BCs) for insulated surfaces. Due to the very small thickness of the EDL comparing the electrode size (see next section), the EDL is represented using a thin layer approximation. The following BC expresses the normal current conservation at the interface bulk/EDL:

$$\vec{J}_{bulk}.\vec{n}\Big|_{EDL-bulk} = J_{EDL}(t) \tag{7}$$

The EDL is assimilated to a Diffuse Layer (DL) capacitance C_{DL} (F/m^2) (see next section) then:

$$J_{EDL}(t) = -\frac{\partial\left(\varepsilon_{water}\,\vec{\nabla}V_{EDL}\right)}{\partial t} = C_{EDL}\frac{\partial(\Delta V_{DL})}{\partial t} \tag{8}$$

where $\Delta V_{DL} = V_E(t) - V(t)$ is the potential drop across the diffuse layer, $V_E(t)$ is the time-varying potential applied to the electrode and V(t) the resulting potential at the interface EDL-bulk (unknown). Boundary condition (8) is of Robin type which is a linear combination of Dirichlet and Neumann boundary conditions.
For the complex electrokinetic equation (3), the corresponding Robin BC for the EDL is:

$$-\sigma^*\vec{\nabla}V^*.\vec{n} = i\omega\; C_{EDL}\;\Delta V_{DL} \tag{9}$$

As DBS Medtronic electrode is composed of 4 contacts, an EDL is formed even on contacts that are not connected to the pulse generator. For non connected contacts, the EDL is still represented by the capacitance C_{EDL} but treated using the Comsol 'contact pairs'.

2.2 Capacitance models for the EDL

A capacitive EDL is formed at the electrode-electrolyte interface because of the electrostatic interaction between charges inside the polarized electrode and electrolyte free ions. Several capacitance models are available in literature [4,8,12]. The most accomplished EDL model is the Gouy-Chapman-Stern model where the EDL is composed of two contributions: the compact (Stern) layer and a Diffuse Layer (DL). For high voltages and/or low concentrations, the compact layer effect becomes insignificant comparing to the DL one [4,12]:

$$C_{EDL} \approx C_{DL} \tag{10}$$

The DL is assimilated to a capacitor which thickness is estimated using the Poisson-Boltzmann equation [9]: for small potentials, the EDL thickness is given by the Debye length λ_D which, for a 137mM NaCl solution, is about 8nm.

Two capacitance DL models are tested in this work: the simplest Gouy-Chapman (GC) linear capacitance (F/m^2) model and the Modified Poisson Boltzmann (MPB) nonlinear capacitance model. The GC capacitance is deduced from the Gouy-Chapman theory [4,8]:

$$C_{GC} = \frac{\varepsilon_{water}}{\lambda_D}\cosh\left(\frac{ze\,\Delta V_{DL}}{k_B T}\right) \tag{11}$$

This non linear capacitance can be linearized under low potential conditions ($V_E << \frac{k_B T}{ze}$):

$$C_{DL} = C_{GC} \approx \frac{\varepsilon_{water}}{\lambda_D} \tag{12}$$

For high electrode potentials, the GC model (11), solution of the Poisson-Boltzmann (PB) equation, fails because it doesn't consider ion size which limits their accumulation inside the DL. Many authors have proposed modifications in order to consider this steric limit inside the DL. In particular, Kilic et al. [12] proposed the MPB nonlinear capacitance model:

$$C_{DL} = C_{MPB} = \frac{\frac{\varepsilon_{water}}{\lambda_D}\sinh\left(\frac{ze}{k_B T}\Delta V_{DL}\right)}{\left[1+2\nu\sinh^2\left(\frac{ze}{2k_B T}\Delta V_{DL}\right)\right]\left[\frac{2}{\nu}\ln\left(1+2\nu\sinh^2\left(\frac{ze}{2k_B T}\Delta V_{DL}\right)\right)\right]} \tag{13}$$

where $\nu = 2a^3C_0$ is the packing parameter of the concerned ion of effective size a and C_0 its bulk concentration. As a first approximation, we consider the parameter a as the ion hydrated diameter: for a sodium chloride aqueous solution, $a_{Na^+} = 0.368nm$ and $a_{Cl^-} = 0.242nm$ [13].

3. Computation domain

If some retinal prostheses consist of MEA with flat contacts of characteristic dimension of tens of microns, DBS Medtronic electrodes are millimeter-sized (figure 1). Those two devices are interesting to study with the same mathematical model because of the varying characteristic dimension. Computational geometry for retinal MEA is 3D as DBS electrode can be represented using a 2D axi-symmetric geometry because of the homogeneous surrounding liquid (137mM NaCl solution) used for the impedance measurements.
For the retinal MEA case, the outer MEA ring of 15 µm wide (figure 1 left) is used as the working electrode (WE) whereas an external 3mm diameter platinum electrode is immersed in the NaCl solution and used as the counter-electrode (CE):

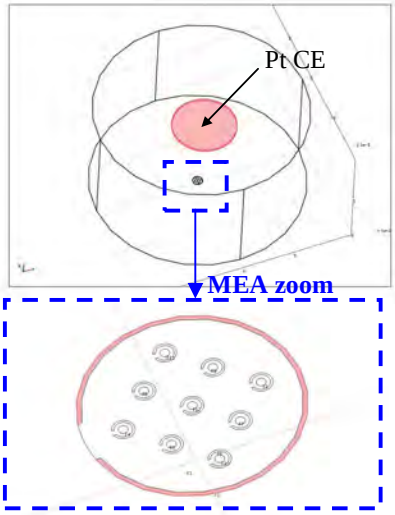


Figure 2: Computational 3D geometry for the retinal MEA. A 3mm diameter platinum electrode immersed in NaCl is the CE (upper). Colored ring contact of MEA (lower) is the WE.

The Medtronic DBS electrode is used with the bipolar mode, i.e. contact C1 (figure 1 right) is the WE and contact C2 is the CE:

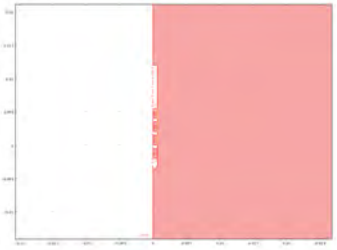


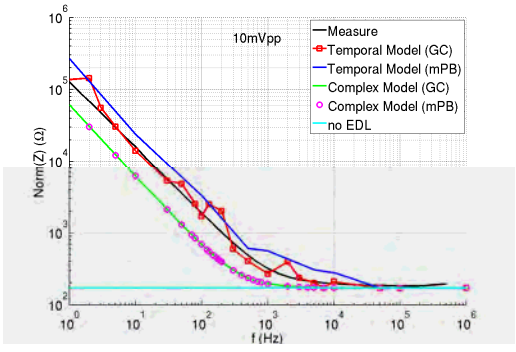
Figure 3: Computational 2D axi-symmetric geometry for the DBS Medtronic electrode.

4. Numerical and measured impedance spectra comparisons

Impedance measurements were performed using a Bio-Logic VPM2 potentiostat. Low voltages (much lower than the ones used for electrical stimulation) were applied so no electrochemical gas release was visible at the polarized contact surface.

4.1 Medtronic DBS electrode

Figures 4 and 5 compare Bode impedance spectra for measurements and numerical simulations of the DBS electrode. Computations were done using the temporal (1) or the complex electrokinetic equation (3) coupled to the linearized GC (12) or the MPB capacitance (13) to represent the EDL formed on the 4 contacts. The applied voltage was 10mVpp and 200mVpp.



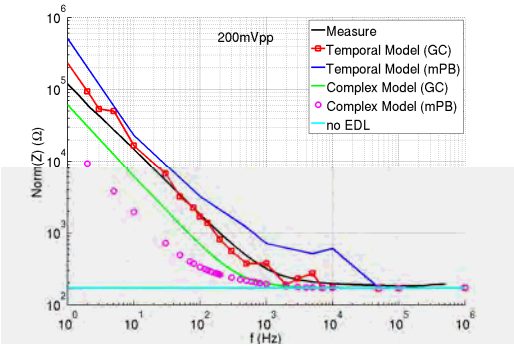
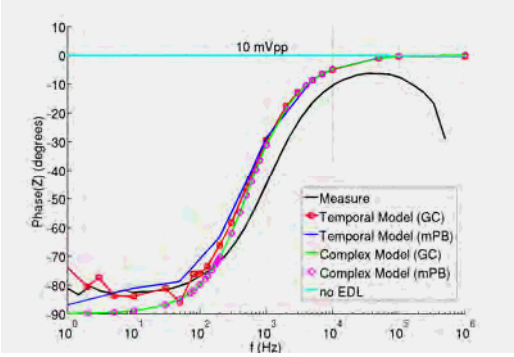


Figure 4: Bode Impedance norm spectra comparison between measurements (black line) and numerical simulations (coloured lines) for a bipolar Medtronic 3389 electrode immersed in a NaCl 137mM solution at 25°C. The applied voltage is 10mVpp (upper), and 200mVpp (lower).

As expected, while neglecting the EDL in models (cyan line), the computed impedance gave no frequency dependance and fitted with the resistive regime obtained at high frequencies for models which consider it. For both voltages, the best agreement with measures was obtained using the temporal GC model (red line). When coupled with the GC linear capacitance, the complex model underestimateds norm(Z). Although theoretically the complex model couldn't be used with the non linear MPB capacitance, we still did the calculations to show the importance of the resulting error which increased with the voltage (200mVpp, purple circles). Unexpectingly, when the voltage is increased, the temporal resolution showed that the MPB capacitance (blue line) increased the mismatch with measures comparing to the GC capacitance (red line).



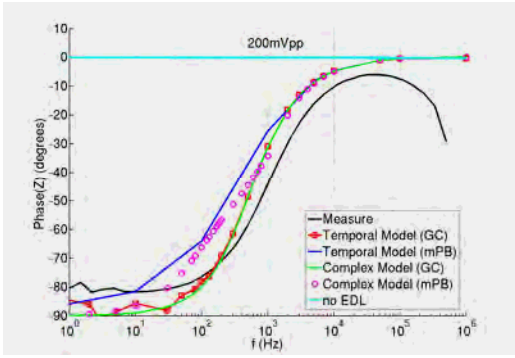


Figure 5: Bode Impedance phase spectra comparison between measurements (black line) and numerical simulations (coloured lines) for a bipolar Medtronic 3389 electrode immersed in a NaCl 137mM solution at 25°C. The applied voltage is 10mVpp (upper), 200mVpp (lower).

The high frequencies phase decrease in measures (black line for f > 2kHz, figure 5), is attributed to the Bio-Logic VMP2 limitations. When comparing the phase spectra, the temporal GC model gave the best fits. The temporal GC model was also able to predict the capacitance phase shift measured to -80° for lower frequencies. This unexpected good result was obtained only at low voltage (10mVpp). As for the norm spectra, the MPB capacitance model increased the error comparing to the GC model.

4.2 Retinal MEA

As the MEA contacts are much smaller than the DBS electrode, the corresponding mesh was much refined than the one used for the DBS electrode. The needed memory was a limiting parameter for temporal simulations which couldn't be done using our 4GB ram 64 bits linux computer. So no temporal results are presented here and we hope to run those computations with a more powerful computer.
Next figure shows the comparison between simulations using the complex GC model and measures for an applied voltage of 20mVpp. As for the DBS electrode, the complex GC model still underestimates the impedance norm. Numerical simulation of norm(Z) doesn't match also at high frequencies (>10kHz) for the resistive regime. This mismatch comes from the geometric description of the polarized contact which doesn't correspond with the real device. This was confirmed with Scanning Electron

Microscopy photos which attest for the presence of remaining oxide coating spots on the contact surface.

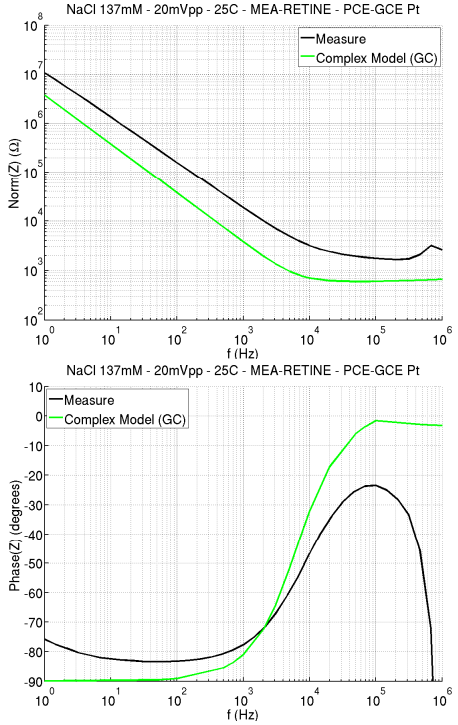


Figure 6: Bode Impedance phase spectra comparison between measurements (black line) and numerical simulations (green line) for a retinal MEA immersed in a NaCl 137mM solution at 25°C. MEA polarization is described in figure 2. The applied voltage is 20mVpp. Impedance norm (upper), impedance phase (lower).

5. Conclusions

Our goal is to find a theoretical model able to represent the EDL electrical behavior in the range of frequencies and voltages used for *in vivo* electrical stimulation. The advantage of using a theoretical model instead of a circuit element approach is that it is applicable to any type of electrodes and stimulation conditions.

As a first step, we worked with sinusoidal signals of low amplitude to compare models with impedance measurements. The use of a theoretical model for representing the EDL formed at the electrode surface showed a good correspondance with impedance measurements. Unexpectingly, the nonlinear MPB capacitance model appeared to be in less agreement with measures than the linear GC model. This non linear model is also difficult to compute, specially at high frequencies (>10kHz) where problems of convergence may appear.

For the two electrode geometries, the linear GC EDL capacitance shows the same discrepancies: at very low frequencies, where the capacitance dominates, norm(Z) is understimated by a factor of 2 and phase(Z) shows a ten degrees gap with measure. The EDL capacitance model could be refined by adding the compact layer influence [10].

For the DBS electrode, the temporal formalism (red line) of the electrokinetic equation gave a better correlation with measures (black line) than the complex formalism.

Although the temporal formalism is heavy to implement and solve, this approach is well suited to electrical stimulation signals that are usually non-sinusoidal. In addition, it is suited to develop models with more biological plausibility, for instance that incorporate model of neurons (e.g. Hodgkin-Huxley temporal equations) bathed in the extracellular medium.

For the case of real stimuli (square waveform, high potentials) the electrochemical reactions will have to be added in models. The next step is to perform impedance measurements using real stimuli. This requires developing a suitable impedance measuring system. To model square waveform stimuli a Fast Fourier Transform (FFT) approach is necessary for the complex formalism [14].

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