Acta Neurochir (2011) 153:2351–2355
DOI 10.1007/s00701-011-1151-x

EXPERIMENTAL RESEARCH

The role of electrode direction during axonal bipolar electrical stimulation: a bidomain computational model study

Emmanuel Mandonnet · Olivier Pantz

Received: 9 June 2011 / Accepted: 26 August 2011 / Published online: 11 September 2011

Abstract
Background Direct electrical stimulation of cortical and axonal areas is widely used for brain mapping of functional areas during intraparenchymatous resections. However, there are very few data (be they experimental or computational) regarding the exact volume of activated axons surrounding the bipolar electrodes. The aim of this study was to provide a computational model to estimate the regions in which electrical stimulation will generate an action potential in the axons.
Methods An axonal fasiculus was modeled as a homogenized bidomain medium. Passive membrane dynamics was implemented at the interface between the two domains. The resulting set of equations was numerically solved by the finite element method.
Results Simulations show that the activated volumes are located in the vicinity of each electrode. The volume of the activated regions grows linearly with intensity. The direction of the bipolar tips (parallel or orthogonal to the fibers' axis) does not significantly influence the size of activated regions.
Conclusions This computational study suggests that directing the bipolar electrodes orthogonal to the axis of a fasciculus should facilitate its identification, as the chances are higher in this configuration that at least one of the electrode tips will be in contact with a fasciculus. Experimental studies are needed to confirm this model prediction.

Keywords Computational model · Bidomain model · Brain mapping · Axonal electrical stimulation · Ojemann's bipolar

E. Mandonnet (✉)
Department of Neurosurgery, Lariboisière Hospital,
2 rue Ambroise Paré,
75010 Paris, France
e-mail: mandonnet@mac.com

E. Mandonnet
Paris Diderot University,
Paris, France

E. Mandonnet
IMNC, UMR 8165,
Paris, France

O. Pantz
CMAP, Ecole Polytechnique,
Palaiseau, France

Introduction

Ojemann's stimulation (bipolar 60 Hz current-constant biphasic 1-ms pulse) is considered to be the "gold standard" for brain function mapping during awake surgery [5]. Whereas this method has been validated by more than 40 years of neurosurgical practice, it is amazing to realize that we do not know how it works—a situation somehow similar to the case of deep brain stimulation for movement disorders. In this latter field, considerable efforts have been recently devoted to develop mathematical models, with the aim to get a better understanding of the effect of electrical stimulation by deep electrodes (see for example [8]). Comparatively, very little attention has been paid to the setting of Ojemman's stimulation (OS) during surgical removal of brain parenchyma (tumoral or epileptic tissue). During the past decade, the use of this methodology has been progressively spreading among the neurosurgical community [2], and also among neuroscientific researchers [3]. Indeed, in addition to its clinical utility in performing a functionally safe resection, direct electrical stimulation (DES) offers a powerful tool to investigate brain functioning and to map the neural substrates of various cognitive

processes. At present, the imprecise knowledge of the interaction between brain elements and electrical currents generated by a bipolar electrode hampers the inference of brain functioning from DES observations [3].

In this paper, we propose a first step in the computational modeling of the complex processes involved in OS. For the sake of simplicity, we will restrict our analysis to the case of axonal stimulation: the anatomical geometry of an axonal fiber tract is far more simple to implement in a numerical model than the seven intermingled cortical layers. Our approach is based on a bidomain model, and we consider only passive membrane dynamics. Within the limitations due to these oversimplifications, we will address an issue of practical interest for the neurosurgeon: how does the direction of the bipolar tips—with respect to the axons—influence the effects of the stimulation?

Methods

We developed a bidomain model of a large number of axons, constituting a fasciculus. This model, based on an homogenization of the medium, is well known in the field of cardiac tissue excitation [1, 9], and has been more recently applied in the context of electrical nerve stimulation [6]. Briefly, the homogenized extra-axonal and intra-axonal potentials, u_e and u_i obey the following equations:

$$-\nabla.\left(M_e^*\nabla u_e\right) - C^*\frac{\partial[u]}{\partial t} - R^*([u]-\delta V) = 0$$

$$-\nabla.\left(M_i^*\nabla u_i\right) - C^*\frac{\partial[u]}{\partial t} + R^*([u]-\delta V) = 0$$

where $[u]=u_i\text{-}u_e$. M_e^* and M_i^* are the homogenized conductivities, R^* is the homogenized conductivity of the membranes of the axons and C^* their homogenized capacity. Because of the anisotropic geometry of the bundle of axons, M_e^* and M_i^* are non-diagonal tensors. Expression of these homogenized constants from their non-homogenized counterparts (and density and diameter of axons) can be found in [4].

Boundary conditions at the contact surface between electrodes and tissue is

$$M_e^*\nabla u_e.n = g$$

where g is the applied current per surface unit and n the outward normal to the tissue.

Outside the contact surface, boundary condition is

$$M_e^*\nabla u_e.n = 0$$

Moreover, we set $u_e=0$ and $M_i^*\ \nabla u_i=0$ at infinity. Numerical values [7, 10] are given in Table 1.

Table 1 Values for axonal bipolar electrical stimulation

Radius of the medium	1.5 cm
Length of the medium	4.0 cm
Inter-electrodes distance	7 mm
Radius of the contact	1 mm
Pulse time	500 μs
Stimulation period	0.02 s
Applied intensity	0.5–5 mA
Extra-axonal conductivity	1/3 Sm^{-1}
Intra-axonal conductivity	1 Sm^{-1}
Membrane conductivity	0.15 Sm^{-2}
Membrane capacitance	0.6 μFm^{-1}
Axon diameter	2 μm
Axon density	1.e5 mm^{-2}

This system of equations is numerically solved by a finite element discretization in space and a finite difference in time (see [4] for more details). Finally, the total activated volume was defined as the set of elements of the medium for which the jump of the potential u exceeded the activation threshold δV (set at 30 mV) at least once during the whole biphasic pulse. Simulations were performed for two configurations of stimulation: orthogonally to the direction of axons (Fig. 1a) and parallel to this direction (Fig. 1b).

Results

Figure 2a and b represent the isopotentials, at a stimulation intensity of 5 mA, for the orthogonal and parallel configurations respectively. Note the asymmetry of the isolines in the orthogonal case, that reflects the anisotropy of the bidomain model.

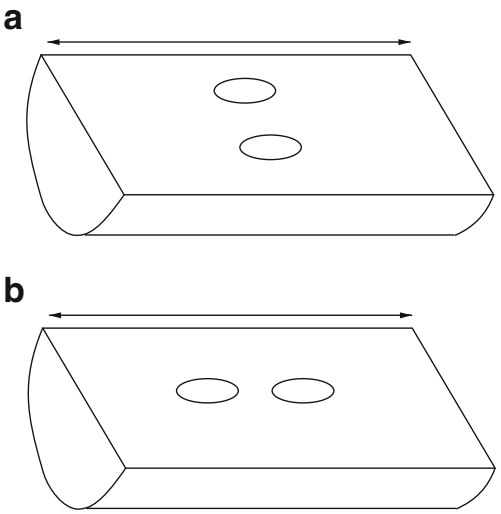

Fig. 1 Schematic view of the contact between bipolar tips and axonal fasciculus. **a** Orthogonal setting. **b** Parallel setting

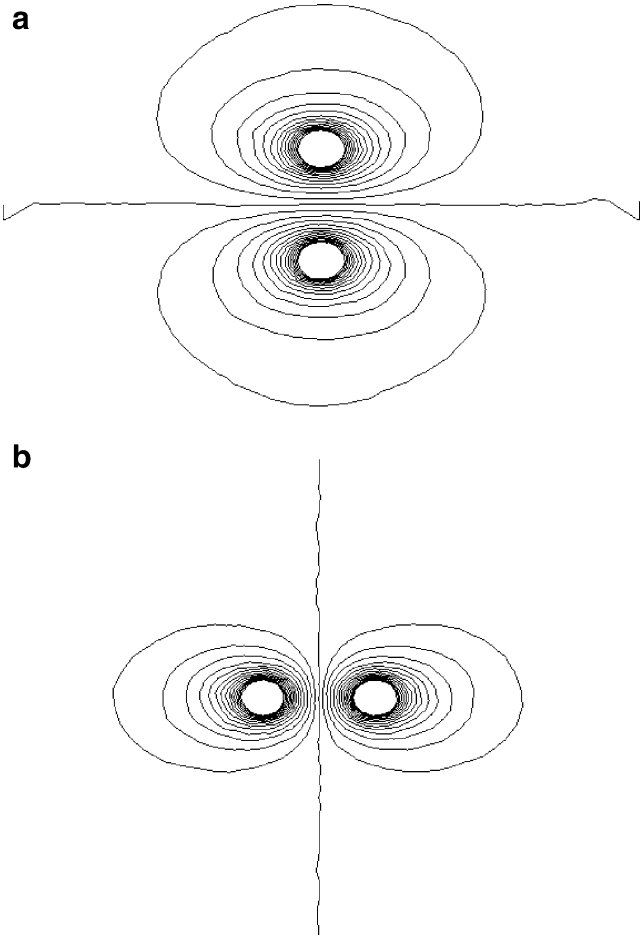

Fig. 2 Isopotentials at a stimulation intensity of 5 mA. **a** Orthogonal setting. **b** Parallel setting

In Fig. 3, we plotted, for the orthogonal setting, the activated areas for increasing current intensity, from 0.5 mA to 5 mA. The activated volume is represented as a function of intensity on Fig. 4: it appears to grow linearly with intensity.

Finally, a comparison of the total activated volume at an intensity of 5 mA can be made between the orthogonal (Fig. 5a) and parallel (Fig. 5b) cases. Interestingly, the volumes are located in both cases in the vicinity of each electrode tips, with no significant difference.

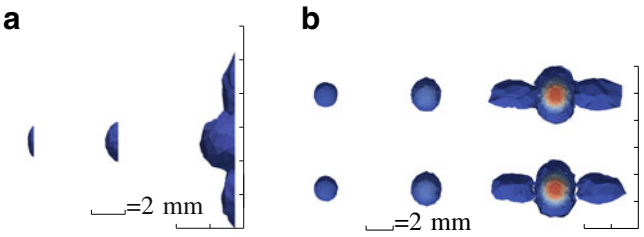

Fig. 3 Activated volumes at stimulation intensity of 0.5 mA, 2 mA and 5 mA. **a** Side view. **b** Superior view

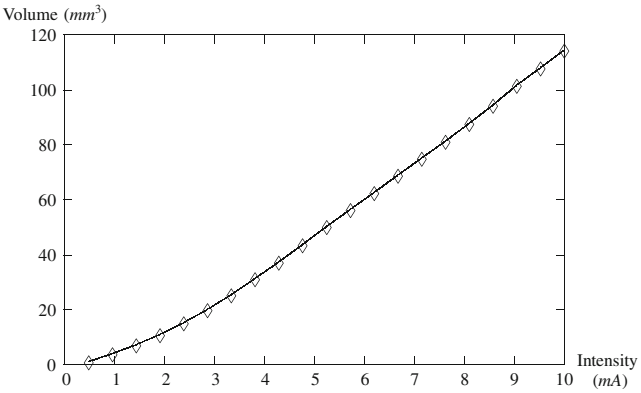

Fig. 4 Evolution of activated volume as a function of stimulation intensity

Discussion

Analysis of the potentials

Note that in the present study, the extracellular and intracellular compartments are both assumed to be isotropic. This is not the case for the global medium, which is anisotropic as a consequence of the homogenization process. Accordingly, in Fig. 2a showing the potentials,

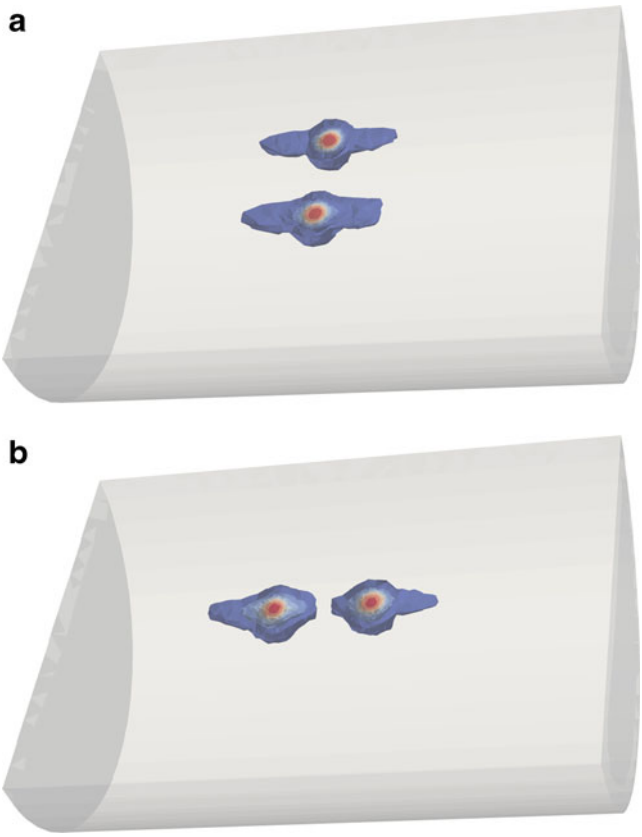

Fig. 5 Activated areas at a stimulation intensity of 5 mA. **a** Orthogonal setting. **b** Parallel setting

one observes an elongated form of the isopotential along the axonal axis.

Analysis of stimulus intensity

As shown in Fig. 4, the activated volume grows linearly with the intensity of the stimulation. This curve also shows that the activated volume becomes greater than 10 mm^3 above 2 mA of stimulating intensity, which corresponds more or less to the intensity used during awake surgery. In this activated volume of 10 mm^3, the number of stimulated axons is approximately ten times the axonal density expressed in mm^{-2}. For a density of $10^5/mm^2$ (which is a high density of axons, as in the corpus callosum), one gets that a transient cognitive deficit is generated when about 1 million axons are activated.

Analysis of the activated volumes

A striking feature of our simulation results is that activated volumes are located around each electrode, whereas in between the two electrodes, there is virtually no activation. In other words, nothing is happening in the middle of the two electrodes. Consequently, there is no major difference in the activated volume between the orthogonal and parallel cases, as illustrated on Fig. 5.

Role of the bipolar direction

Based on the present results, one can assume that the sensitivity of OS to detect functional fibers will be enhanced when the bipolar electrode is directed orthogonally to the fiber tracts. Indeed, there will be a greater chance that one of the two electrode tips will interact with the functional pathway, whereas in the parallel configuration, stimulation occurs only when the two electrodes are in contact with the fasciculus. Theses theoritical results are in good agreement with surgical experience: it has been indeed observed that transient neurological deficit were more easily elicited in the orthogonal rather than parallel settings (Hugues Duffau, personal communication).

Advantages and limitations of the present model

As stated in [6], the bidomain approach contrasts with the commonly used two-step method, in which the extra-axonal electrical field is first derived, and then injected in the membrane equation of an axon. Actually, the two-step framework is an approximation of the bidomain model in the case of a low density of axons. With the numerical values used in this paper, we have shown that in comparison with the bidomain model, the two-step method gives qualitatively similar results, but with significant differences in the quantitative values (see [4]).

On the other hand, the total activated volume computed in this study is a crude approximation of the real processes involved in electrical stimulation. In particular, we neglected the influence of the propagation of an action potential away from its generation site. The influence of areas of hyperpolarization during the first period of the pulse, which may block action potential propagation, has also been discarded. However, it should be possible to implement full non-linear membrane dynamics (Hodgkin-Huxley-like) using the bidomain framework.

Conclusion

Our modeling study suggests that the neurosurgeon can indifferently choose a direction of the bipolar electrodes, orthogonal or parallel to the fibers, during the mapping of white matter pathways. However, the identification of the tract could be facilitated by attempting to be orthogonal to the expected direction of the tract: there is a higher chance that one the two electrodes will be in contact with the fasciculus. Experimental studies are needed to confirm these computational results.

Finally, the present model can be generalized, by introducing non-linear Hodgkin-Huxley-like membrane dynamics. This would allow to better depict the interaction between OS and axons, which in turn would enable to improve inferences about brain function from brain stimulation data.

Conflicts of interest None.

References

1. Basser PJ, Roth BJ (2000) New currents in electrical stimulation of excitable tissues. Annu Rev Biomed Eng 2:377–397
2. July J, Manninen P, Lai J, Yao Z, Bernstein M (2009) The history of awake craniotomy for brain tumor and its spread into Asia. Surg Neurol 71:621–624, discussion 624–625
3. Karnath HO, Borchers S, Himmelbach M (2010) Comment on "Movement intention after parietal cortex stimulation in humans". Science 327:1200, author reply 1200
4. Mandonnet E, Pantz O (2011) On the activation of a fasciculus of axons. Rapport interne CMAP Numero 714:http://www.cmap.polytechnique.fr/preprint/. Accessed 8 Jun 2011.
5. Mandonnet E, Winkler PA, Duffau H (2010) Direct electrical stimulation as an input gate into brain functional networks: principles, advantages and limitations. Acta Neurochir (Wien) 152:185–193
6. Martinek J, Stickler Y, Reichel M, Mayr W, Rattay F (2008) A novel approach to simulate Hodgkin-Huxley-like excitation with COMSOL Multiphysics. Artif Organs 32:614–619

7. McIntyre CC, Grill WM (1999) Excitation of central nervous system neurons by nonuniform electric fields. Biophys J 76:878–888
8. McIntyre CC, Hahn PJ (2010) Network perspectives on the mechanisms of deep brain stimulation. Neurobiol Dis 38:329–337
9. Neu JC, Krassowska W (1993) Homogenization of syncytial tissues. Crit Rev Biomed Eng 21:137–199
10. Rattay F (1999) The basic mechanism for the electrical stimulation of the nervous system. Neuroscience 89:335–346

Comment

The authors proposed a computational model of the complex processes involved in direct brain electrostimulation using a bipolar probe (60 Hz, current-constant biphasic stimulation, 1-ms pulse). They restricted their study to the case of axonal stimulation, i.e., to the estimation of the regions in which electrical stimulation will generate an action potential in the axons. They observed that the activated volumes were located in the vicinity of each electrode, whereas in between the two electrodes, there was virtually no activation. They also found that the volume of the activated regions grew linearly with intensity, and that the direction of the bipolar tips did not significantly influence the size of activated regions.

This is a very interesting article. The rationale is original, and the methodology is robust. Very few data are currently available about the mechanisms underlying electrostimulation mapping. Computational modeling represents an elegant solution to improve our understanding of the interaction between neuronal elements and electrical stimulation, with the aim to optimize the clinical results. The authors show that, if during the past decade huge efforts have been devoted for developing computational models in the field of deep brain stimulation, the situation is somehow similar in the settings of axonal stimulation during awake mapping. In practice, it means that the surgeon has to direct the bipolar probe orthogonally and not parallel to the axis of a fascicle in order to optimize the chances to detect the functional fibers during the mapping of the subcortical connectivity. As a consequence, this paper may have useful surgical implications, even if experimental studies are, of course, needed to validate the model prediction.

Hugues Duffau
Montpellier, France