Modeling Workflow for Study of Functional Electrical Stimulation in Peripheral Nerves

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Abstract: Urinary dysfunctions are among the most devastating consequences of spinal cord injuries (SCI). Neurostimulation of intact sacral nerve roots innervating bladder is potentially a good alternative to the treatments using drugs and catheterization. A finer control over the electrical stimulation of sacral roots can be an enabling technology for developing advanced neurostimulation matching the patient needs. In this paper a modeling workflow to study axon behaviour in sacral nerve roots is presented. Simulation results show that the width and the amplitude of the stimulation electric pulses can be tuned to selectively recruit axons in sacral roots. A selective recruitment of axons innervating bladder is shown to be possible for pulse widths above 9 ms.

1 INTRODUCTION

Spinal cord injuries (SCIs) are estimated to affect 330,000 people (with about 11,000 new cases every year) in Europe (Social and F.A.C, 2002), and about 300,000 in the USA (with also about 12,000 new cases every year) (National Institute of Neurological Disorders and Stroke, 2012). Among the most traumatic consequences of an SCI event are the urinary dysfunctions (e.g., incontinence) due to lesions above the level of sacral nerve roots (bundle of nerves innervating bladder and urethral sphincter). In the conservative medical approach, drugs and catheters are used to manage the lower urinary system in cases of SCIs. However, side effects of medication and the unwilling of patients to use catheters have driven research in the pursuit of electrical devices for neurostimulation of sacral roots innervating bladder.

Sacral nerve roots have become a preferential site to elicit bladder voiding by neurostimulation (Rijkhoff et al., 1997); (Brindley, 1977). The sacral roots are made out of several sub-units, known as fascicles. Each fascicle is derived from neural cells in the spinal cord with certain degree of specificity for their function (Probst et al., 1997). Somatic and parasympathetic are the two fiber types present in the fascicles of sacral roots - the parasympathetic fibers are the smaller fibers innervating bladder, while the somatic fibers are the larger fibers innervating sphincter.

Even there are differences between individuals in terms of histology of sacral roots, still fascicular trends in specificity are observed. This fact raises the potential that a focal stimulation can selectively stimulate the neural unit (fiber/nerve) for a certain function, e.g., parasympathetic stimulation for bladder contraction (Hauck et al., 2009). Hence, the steering of electric current applied in neurostimulation of sacral roots can yield a selective recruitment of parasympathetic fibers resulting in bladder voiding. The selective control of muscles activation can be achieved using a multipolar nerve cuff electrode (Schiefer et al., 2010). In terms of design and optimization of multipolar electrodes for functional electrical stimulation (FES) of peripheral nerves two factors are crucial: 1) anatomical trends and 2) nerves response. Indeed, modeling nerve response to a given external stimulation parameters (e.g. pulse width, pulse amplitude) allows to predict whether a neuron will or will not be activated. In this work, axonal response in sacral roots is studied - axon is the most excitable part of a peripheral nerve. The hypothesis of this study is that a multipolar cuff electrode placed proximally on the sacral root with a fixed number of contacts can selectively stimulate smaller parasympathetic axons that are preferentially grouped by specialized fascicles. Stimuli is defined

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a priori as a simple monopolar, square and cathodic waveform. Through the use of finite element models and nonlinear axonal models, the presented study investigates selectivity for given combinations of pulse width/pulse amplitude.

2 METHODS

Selective stimulation effect of a multipolar cuff electrode on sacral roots was investigated using a modeling workflow based on 3 different software tools: ANSYS Multiphysics, MATLAB and NEURON. First, a finite element model (FEM) of a sacral root together with a multipolar cuff electrode was developed and implemented in ANSYS Multiphysics. Steady-state electric potential field was calculated in ANSYS for several electrode configurations. The potentials were exported to MATLAB. In MATLAB, ordered pairs (x, y) were randomly generated inside a circle with radius of 300 µm and centered at the origin – this circle defines the contour of the sacral root. Longitudinal points representing different segments of each axon were randomly generated. Voltages were interpolated at each (x, y, z) position representing a specific anatomical compartment of each axon. As its output MATLAB returned a matrix of [M x N], where M is the number of axons inside each fascicle and N is the number of axon's segments (nodes of Ranvier + internodal positions). In NEURON, electric potential at each axon position is applied as an extracellular field to an axon model representing the mammalian motor axon. Each node of Ranvier is checked for action potential (AP) events indicating that the extracellular field invoked axonal activation. Results from simulations in NEURON were analyzed in MATLAB to determine selectivity. The modeling workflow to determine selectivity is schematically shown in Fig. 1.

In the presented design, the multipolar electrode is made out of 18 electrode contacts (six tripoles) that were placed in direct contact with the sacral root. Each tripole is positioned around the sacral root at positions {30, 90, 150, 210, 270, and 330 deg}. The stimulating surface of each electrode is 100 µm x 50 µm (length x width) and its thickness is 2 µm. Thickness of the electrodes is derived from the fabrication process which was used to fabricate the first prototype of a flexible multipolar cuff (Rodrigues et al., 2012). Figure 2 shows a schematic of the contact spacing in the multipolar electrode in its unrolled state. The simulated sacral root was 600 µm in diameter and 16 mm in length (z axis). Part of the model is shown in Fig. 3. It comprises sacral root, 18 metal contacts, insulating cuff, cephalo raquidian fluid and a highly resistive boundary layer. Geometric and electric properties of the various elements within the model were reported previously (Rodrigues et al., 2012). The electrode contacts are modeled as current sources and a zero voltage boundary condition is added to the outer surfaces of the boundary layer. Steady-state simulations were performed for several electrode configurations. The two electrode configurations presented here are shown in Fig. 4 and Fig. 5.

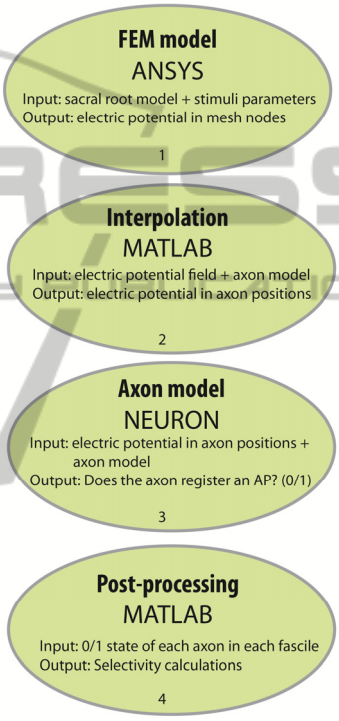

Figure 1: The modeling workflow used to determine selectivity of multipolar cuff electrode in sacral roots stimulation.

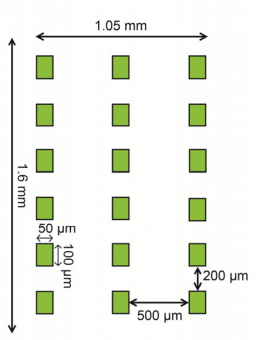

Figure 2: Schematic of the multipolar electrode in its unrolled state.

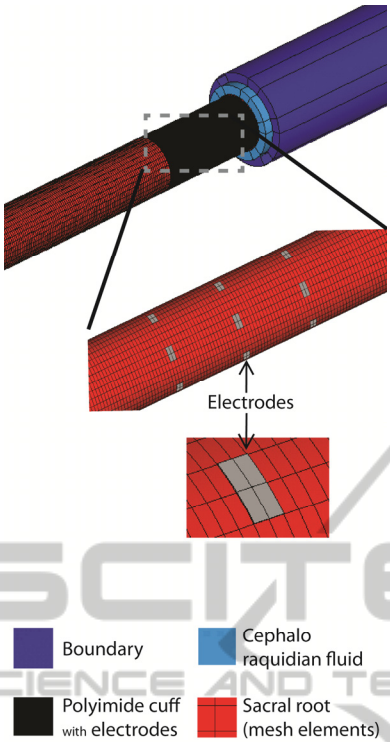

Figure 3: Parts of the FEM model. Note that the mesh elements in the sacral root are half width of the electrode.

To shorten the time of modeling iterations it is favourable to introduce a pulse amplitude factor (PAF). This factor is multiplied by electric potential field solution in each axonal position. So, assuming V=1 as the electric potential at a given node/internode position of the axon, if PAF = 0.1, then V=0.1 will be the electric potential solution at the same coordinate.

Indeed, simulations were run in NEURON for all combinations of pulse widths (PW) of 0.01, 0.05, 0.1, 0.2, 0.5, 1, 2, 5, 7, 8, 8.33, 8.66, 9, 10 and 11 ms and pulse amplitude factors of 0.1, 0.2, 0.5 and 1. Axonal results from NEURON simulations were analyzed to determine which stimulation case (electrode configuration vs. PW vs. PAF) produced the greatest selectivity. Adapted from Choi (Choi et al., 2001), muscular selectivity, *S*, was defined as the fraction of axons activated within all fascicles innervating a target muscle (the "recruitment benefit" or "RB") minus the fraction of axons not innervating the target muscle that were activated (the "recruitment cost" or "RC") – Eq. 1.

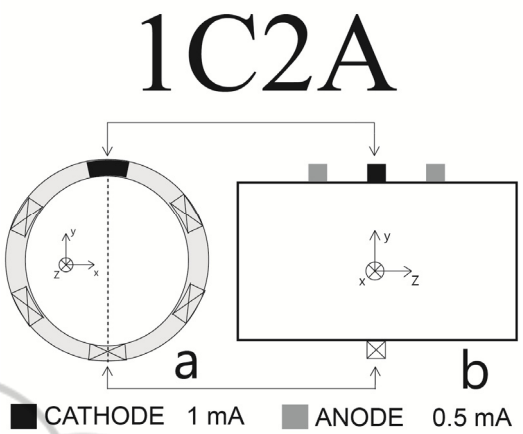

Figure 5: Electrode configuration 1C2A: (a) a transverse cross section under the central row of electrodes; (b) a longitudinal cross section with tripole at the top (position 90 deg). Cathode drains 1 mA and each anode injects 0.5 mA.

$$S = RB - RC \quad (1)$$

In the case of targeting bladder muscle to elicit bladder voiding, *S* will be higher when parasympathetic fibers (innervating bladder) will be recruited in larger ratio (higher RB) than somatic fibers innervating the sphincter (lower RC).

For the anatomy of sacral root presented in Fig. 6, selectivity for bladder muscle (activation of parasympathetic fibers in red color) was calculated for the considered electrode configurations: 1C2A and 2C6A.

2.1 Anatomical and Physiological Considerations

2.1.1 Anatomy of Sacral Nerve Roots

Sacral roots have a mixed population of fibers with diameters ranging from 1 µm (smaller fibers) to 14 µm (larger fibers). In the present study, a ventral sacral root, known as S3 is selected to analyze the effect of the multipolar electrode on axonal selectivity. S3 has a bimodal axon distribution with peaks at 4 and 14 µm (Anon, 1996). Inside peripheral nerves (e.g. sacral nerve roots) the sub-structures giving support to the axons/fibers are known by fascicles. In the terminology of Hauck (Hauck et al., 2009), fascicles mostly carrying parasympathetic fibers are called vegetative fascicles and fascicles with predominance of somatic fibers are called somatic fascicles. In our analysis, 21 fascicles were considered, which is in agreement with the reported number of fascicles in S3 sacral

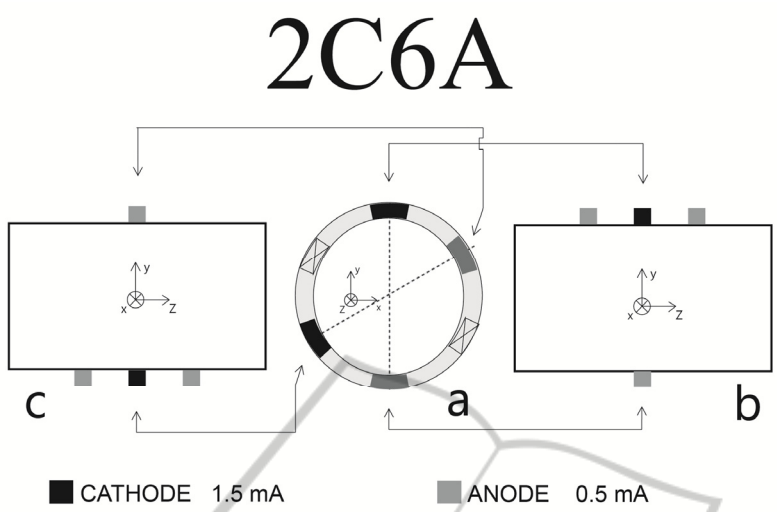

Figure 4: Electrode configuration 2C6A: (a) a transverse cross section under the central row of electrodes; (b) a longitudinal cross section with tripole at the top (position 90 deg) and steering anode at the bottom (position 270 deg); (c) longitudinal cross section with steering anode at the top (position 30) and tripole in the bottom (position 210 deg). Each cathode drains 1.5 mA and each anode injects 0.5 mA.

nerve root (Hauck et al., 2009). Distribution in vegetative and somatic fascicles was previously set and it is represented in Fig. 6. Each somatic fascicle contains 50 axons of 14 µm in diameter (somatic axons innervating sphincter) and each vegetative fascicle has 50 axons of 4 µm in diameter (parasympathetic axons innervating bladder).

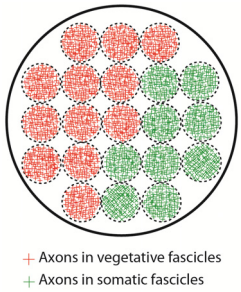

Figure 6: Sacral nerve roots anatomy considered in the presented study.

2.1.2 Physiology of the Axon

Myelinated axons are modeled using an active electrical network to simulate the dynamics of each node of Ranvier and of internodal sections of the axon (McIntyre et al., 2002). A simulation procedure was developed in NEURON to integrate the NEURON's open source axon model of McIntyre (McIntyre et al., 2002). Axonal excitation is generated by extracellular potentials (potentials generated outside node of Ranvier and outside myelinated internodes). These potentials are assumed to be unaffected by the fiber response and thus determined only by the stimulus electrodes and the conductivity of the extracellular space.

Axon model from McIntyre is shown in Fig. 7. This model used 10 segments between successive nodes with an explicit representation of the myelin attachment segment (MYSA), paranode main segment (FLUT), and internode segment (STIN) regions of the fiber. Extracellular potentials interpolated in MATLAB and exported to NEURON were assigned to these compartments.

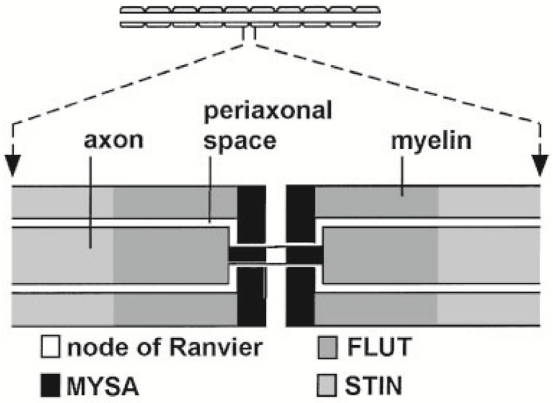

Figure 7: Multi-compartment axon model. Axon and nodes of Ranvier are at the top. Physiological compartments are in the bottom. Figure adapted from McIntyre (McIntyre et al., 2002).

3 RESULTS

In NEURON, action potentials (APs) were used as a measure to evaluate if the axon has fired for a given combination of "electrode configuration / PW / PAF". It was assumed that if each axon has registered more than 11 APs (1 AP / 1 node of Ranvier), axon activation would be assumed. An example of an action potential registered in NEURON is plotted in Fig. 8.

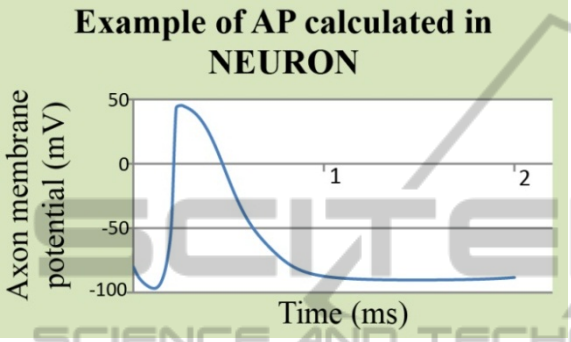

Figure 8: Plot of action potential from NEURON.

Selectivity results are shown in Fig. 9. For each electrode configuration – 1C2A and 2C6A – selectivity index is plotted for 4 different pulse amplitude factors (PAF), along the different pulse widths (PWs).

In case of 1C2A, the activation of any fiber (parasympathetic or somatic) only occurs for PW>9 ms. A hypothesis can be that because of the limitation of electric current (1 mA @ PAF=1), the pulse width required to inject a sufficient charge is high. For PW>9 ms, the selectivity shifts from 0 to 1. This means that all the parasympathetic fibers (4 µm in diameter) were activated and none of the somatic fibers (14 µm) was. As suggested by McIntyre (McIntyre et al., 2002), the smaller diameter fibers have longer chronaxies (i.e. smaller fibers may need longer time to be electrically stimulated) than the larger diameter ones. This can explain the observation that after a 9 ms long pulse, only the 4 µm fibers are depolarized (i.e. only the parasympathetic fibers register an action potential).

In case of 2C6A, there is also complete selectivity (S=1) for PW>9 ms. However, for lower PWs intermediate selectivity values are registered. These intermediate values of selectivity were due to the activation of smaller parasympathetic as well as to the activation of larger somatic. As it could be expect, for larger input current levels (3 mA for 2C6A) it is possible to lower the pulse width required for activation (activation was registered for PW = 5 ms).

Lowering pulse width is a trade-off. If on the one side, the lowering of pulse width also lowers the required power to achieve axonal stimulation; on the other side, it matches the chronaxie values for larger somatic fibers, which contributes to lower the selectivity.

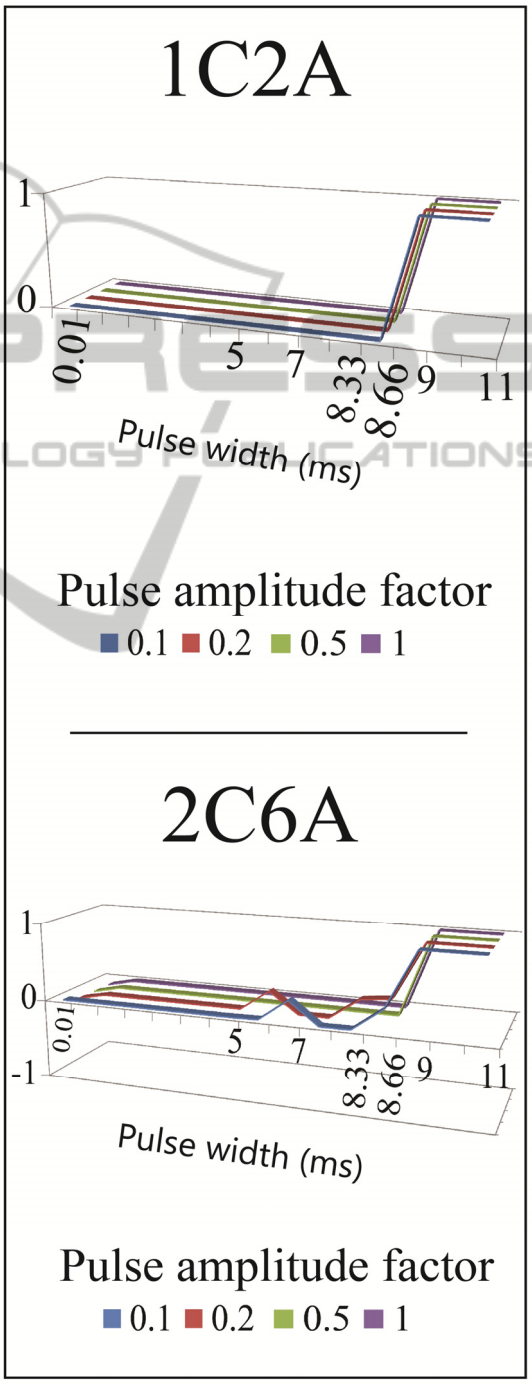

Figure 9: Selectivity for electrode configurations – 1C2A and 2C6A. Selectivity varies between -1 and 1.

Figure 10 shows the complete selectivity of axons for PW > 9 ms. One can observe that only the smaller parasympathetic fibers are active.

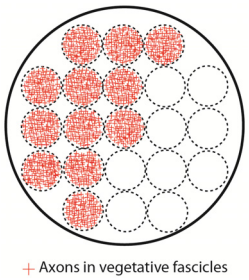

Figure 10: Activated axons for PW > 9 ms.

4 CONCLUSIONS

In this work design and testing of a multipolar cuff electrode for peripheral nerve is presented. For that purpose, a modeling workflow to study selectivity in sacral nerve roots was implemented using ANSYS Multiphysics, MATLAB and NEURON. Anatomical studies were used to define a representative distribution of fascicles in the sacral root. These anatomical features were used to carry a study on the effect of a multipolar cuff electrode on selective stimulation of different fiber diameters. For pulse widths higher than 9 ms, the selectivity is maximum (most probably because of a "chronaxie effect"). However to lower the need for electric power in the electrical stimulation of sacral roots, further studies have to be done in order to achieve selectivity for lower pulse widths – e.g. increasing number of electrode contacts, increasing number of rows of electrodes in order to "reshape" the external stimulation potential on each axon.

Modeling workflow showed to be effective for the element size used in ANSYS. However, further simulations are required for finer meshes in order to study on effectiveness and stability of the workflow. For that, a real anatomic mesh derived from a histological cross section of the sacral roots will be used.

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REFERENCES

Anon, 1996. Morphometric data of canine sacral nerve roots with reference to electrical sacral root stimulation. *Neurourology Urodynamics*, 15, pp.235–248.

Brindley, G. S., 1977. An implant to empty the bladder or close the urethra. *Journal of Neurology, Neurosurgery, and Psychiatry*, 40, pp.358–369.

Choi, A., Cavanaugh, J. & Durand, D., 2001. Selectivity of Multiple-Contact Nerve CuffElectrodes: A Simulation Analysis. *IEEE Transactions on Biomedical Engineering*, 48, pp.165–172.

Hauck, E. F. et al., 2009. Measurements and mapping of 282,420 nerve fibers in the S1-5 nerve roots. *Journal of neurosurgery. Spine*, 11(3), pp.255–63. Available at: http://thejns.org/doi/full/10.3171/2009.3.SPINE17684 [Accessed November 2, 2011].

McIntyre, C., Richardson, A. & Grill, W., 2002. Modeling the Excitability of Mammalian Nerve Fibers: Influence of Afterpotentials on the Recovery Cycle. *Journal Neurophysiology*, 87, pp.995–1006.

McIntyre, C. et al, 2002. No Title. Available at: http://senselab.med.yale.edu/ModelDb/.

National Institute of Neurological Disorders and Stroke, 2012. Spinal Cord Injury: Hope Through Research. Available at: http://www.ninds.nih.gov/disorders/sci/detail_sci.htm [Accessed August 20, 2012].

Probst, M. et al., 1997. Neurostimulation for bladder evacuation: is sacral root stimulation a substitute for microstimulation? *British Journal of Urology*, 79, pp.554–566.

Rijkhoff, N. et al., 1997. Selective Detrusor Activation by Electrical Stimulation of the Human Sacral Nerve Roots. *Artificial Organs*, 21, pp.223–226.

Rodrigues, F. et al., 2012. Flexible Multipolar Cuff Microelectrode For FES Of Sacral Nerve Roots. In *Smart Machines – Neural Evolution*. Banff, Canada: IFESS .

Schiefer, A. et al., 2010. Selective stimulation of the human femoral nerve with a flat interface nerve electrode. *Journal Neural Engineering*, 7.

Social, H. and F. A. C., 2002. Towards concerted efforts for treating and curing spinal cord injury. Available at: http://assembly.coe.int/ASP/Doc/XrefViewHTML.asp?FileID=17004&Language=EN [Accessed August 20, 2012].