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Modeling to Guide Implantable Electrode Design

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Neuroprostheses are becoming widespread clinical solutions, addressing human nervous system at different levels. This technology can significantly improve the quality of life of people who have suffered from different neurological disabilities. Despite the large number of peripheral nervous system (PNS) electrodes available and their good performances, the ever-growing complexity of neuroprosthetic devices trying to mimic the natural hand implies a constant need to improve electrode selectivity. This is particularly true for stimulating electrodes whose aim is to mimic the natural sensory feedback from the hand arising from a very dense network of afferents serving different modalities (especially in the fingertips) by only stimulating at discrete, restricted locations on a given nerve (Riso, 1999). Hence, an important goal for a PNS electrode is to achieve the highest selectivity for a high number of nerve fascicles while minimizing the invasiveness and potential nerve damage. In this context, experimental studies have been conducted in order to compare the selectivity performances of different types of PNS electrodes (Badia et al., 2011). Animal models are common developmental tools for testing peripheral nerve interfaces. However, the complexity of the nerve tissue upon which stimulation is applied, as well as the anatomical differences between animal models and humans, induce great variability regarding the neural response (Grinberg et al., 2008). Furthermore, the wide range of design factors that can influence the outcome of the stimulation, such as electrode type and position or the stimulation pattern (amplitude, pulse width, frequency, monopolar, or multipolar stimulation), needs to be explored in order to optimize a stimulation protocol and the neural interfaces for a given application, thus requiring a large number of experimental trials and subjects. Even so, the interaction with living tissue induces an inevitable variability in experimental results due to several factors that cannot always be identified, thus rendering the problem even more complicated.

The use of computer models to study the electrical stimulation of neural systems appears to be an inexpensive and efficient way to tackle this issue and thus assist in the development of neural devices or applications, by exploring the high dimensional space of design parameters while minimizing animal use. Among the first explorations of an influence of external electrical fields on the neurons, by analytical modeling, was performed by McNeal (1976), who developed the concept of so-called "activating function." He used a fact that even though neural devices and neurons have different communicating currents, they both share same electric field. The modulation of it by the injected electrical currents can depolarize the external membrane of neurons, provoking the ionic currents flows, and finally the generation of spikes, which are the basic carriers of information in the human nervous system. Activation function is proposing that the likelihood of neural activation by external stimulation is proportional to the second derivative of external field respect to neuronal spatial extension. This idea is extended and analytically improved in Rattay's works (1986, 1989), which extended the concept from the point sources of current to the realistic, similar-to-electrode sources. Although the activation function is yet used as a most rapid and intuitive indicator of the approximate estimation of axonal responses to electrical stimuli, the recent works (Zierhofer, 2001; Moffitt et al., 2004) have shown that it is introducing the important mistakes. The main reasons for these errors were that approach based on the activation function, was neglecting of high nonlinearity present in axonal answers and the realistic anisotropy of a medium in which neurons are placed. Recent computational models do account for both the anisotropic extracellular conductivity present in the nerves, and for the dynamic response of neuronal cells and axons to the extracellular electrical stimulation. For calculating the voltages induced by means of electrical stimuli injected by electrode into the anisotropic medium, the finite element method (FEM) are exploited. The estimation of the axonal responses to the external stimuli was investigated by means of software dedicated for efficient calculus of neuronal dynamic (McIntyre, 2002) and cable equations, NEURON (Hines and Carnevale, 1997). Finally, the FEM results are interpolated into the NEURON model, obtaining together what can be called a "hybrid electro-neuronal model."

Initial concept of hybrid modeling was proposed in the studies regarding the electrical epidural stimulation (EES) of spinal cord (Coburn, 1985; Coburn and Sin, 1985). Then, similar idea has been exploited in works that model extracellular stimulation of central nervous system neurons, and in particular for the purpose of deep brain stimulation (DBS) modeling (McIntyre and Grill, 2002; Miocinovic et al., 2006). In the recent past, it has been also used in human peripheral nervous system to optimize the design of extraneural cuff electrodes (Schiefer et al., 2016) for the neural stimulation in effort to make a motor rehabilitation of spinal-cord-injured patients. Intraneural electrodes have been simulated (Raspopovic et al., 2011) and validated (Raspopovicet et al., 2012) in the rat nervous implants, using the same hybrid modeling approach. Successful translational use of models in the CNS, as the development of software CICERONE (Frankemolle et al., 2010), which is used in the DBS practice, or in model for spinal cord simulation (Moraud et al., 2016), which was the fundamental for the development of sophisticated stimulation paradigms, that enabled unseen level of mobility in fully Spinal Cord Injured (SCI) rats. These models were not only important from the translational viewpoint: by indicating the electrodes placement and paradigm of optimal stimulation, but also enabled the deep understanding of interactions, which is the fundamental of these intervention computer simulations (Rattay et al., 2000; Capogrosso et al., 2013) provided evidence that EES primarily engages large myelinated fibers associated with proprioceptive and cutaneous feedback circuits during the SCI rehabilitation.

Pivotal role of modeling in all these complex systems, increases the need for the implementation of similar realistic models also for the human PNS, to be exploited within the neuroprostheses (Raspopovic et al., 2014; Tan et al., 2014) development. Neural interfaces are an important component of these systems, which allow direct communication with the nervous system. Several neural interfaces for the PNS have been developed during the past year. They range from epineural electrodes, having low invasiveness and low selectivity, to regenerative electrodes, having higher selectivity but at the same time, also higher invasiveness (Navarro et al., 2005). A good trade-off between the two previous solutions can be found in intraneural interfaces (as transverse intrafascicular multichannel electrode (TIME) (Boretius et al., 2010) or self-opening intraneural peripheral interface electrode (SELINE)

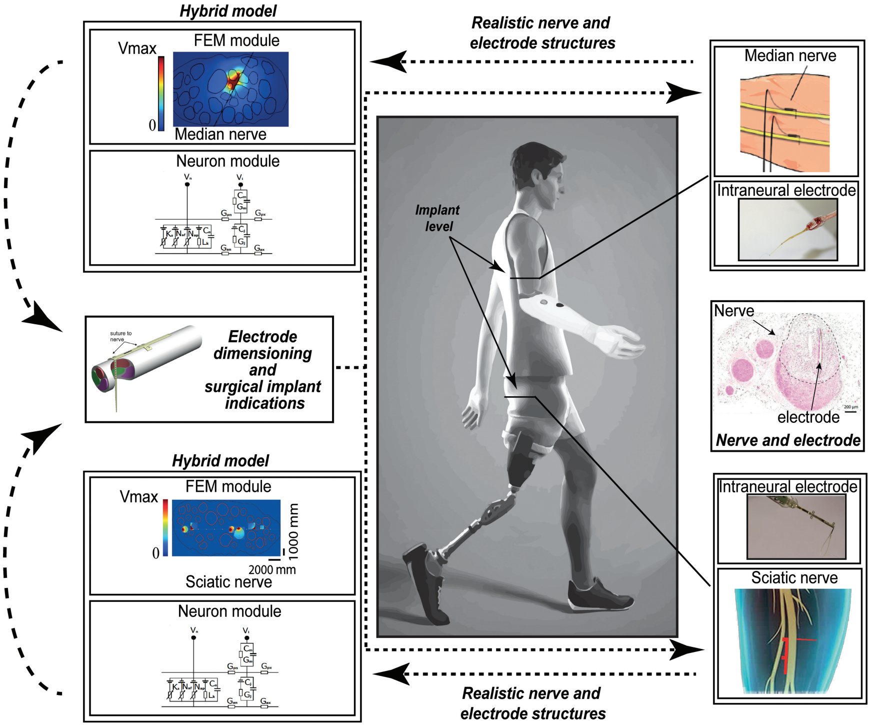


Figure 4.1 Hybrid modeling: nerves sections are taken at the appropriate level for the implantation, and then used within the hybrid electroneuronal models for the development of the optimized neural interfaces for selective, gradual, and minimally invasive use.

(Cutrone et al., 2015). Raspopovic and his collaborators (Raspopovic et al., 2017) were depicting the prominent use of models of human median and sciatic electrical nerves stimulation (ePNS) within the framework of development of innovative neuroprostheses (Figure 4.1).

The efficacy of neuroprostheses can be improved by increasing the possibility of neural interfaces used to stimulate specific subsets of neurons, while not stimulating the untargeted ones, the concept which is measured by the electrode's selectivity. Models could help to reach the scope of having devices that are enhancing selectivity, while reducing invasiveness and also decreasing the amount of current to be injected into the neural tissues. Selectivity is mainly influenced by interface design, and more in particular with dimensions of whole device, its shape, number, and distance of active contacts, used for the stimulation of the neural tissue. Models can indicate the optimal number of devices to be implanted into an individual nerve, and therefore they should give hints regarding how the neurosurgery should be performed (Raspopovic et al., 2017).

In the past years, the neural interfaces were tested in vitro or in animal preparation by single-channel stimulation and measurements of same type of output measure (Badia et al., 2011). This conceptual framework together with time limitation during the effective use, have restricted the clinical application of peripheral nerve stimulation to continuous, single active sites injected stimulation patterns. However, this strategy does not exploit optimally, all the possible capability offered by implanted devices, particularly does not allow to address subject-specific deficits which is pivotal to maximize the outcome of rehabilitation protocols. The use of more sophisticated stimulation paradigms (Fang and Mortimer, 1991; Grill and Mortimer, 1995, 1997; Vuckovic et al., 2004; Hennings et al., 2005), or combinations of single active sites stimulations into the complex multipolar stimulation, could be promising, and should be extensively explored by use of models (Schiefer et al., 2012; Saal and Bensmaia, 2015; Oddo et al., 2016; Saal et al., 2017).

Finally, among the biggest problems encountered during the use of different neural interfaces, is the temporal change of charge necessary to guarantee the therapeutic use. This is most probably due to the tissue complex reaction, and some aspects of it can be interpreted by use of models, rather than extensive animal sacrificing and following histological analysis.

Computer models can be useful for exploring the high dimensional space of design parameters with the goal to provide guidelines for the development of more efficient neural electrodes, with minimal animal use and optimization of manufacturing processes.

4.1 Hybrid Model

The use of computer models to study the electrical stimulation of neural systems appears to be an inexpensive and efficient way to assist in the development of neural devices or applications. The state of art in models accounts for anisotropy of extracellular conductivity, present in real nerves, and also for the nonlinear response of cells to the extracellular stimulation. Those two aspects are solved separately: by means of the FEM which solves the voltage distribution generated by injected currents, and by using calculations of neuronal dynamics to estimate the axonal response to the electrical stimulations. This kind of model has been called hybrid field-neuron models (or hybrid FEM/Neuron models). To couple the external electric fields with the fiber or cell, proper models to account for external stimulation were developed.

The state of the art most used approach is the so-called compartmental modeling of fibers, which is based on the subdivision of fibers and cells into elementary circuit representation used to model the different parts of the cell or fiber, like axons, somas, and nodes of Ranvier.

4.2 Finite Elements Model

As a first step, the correct heights of the nerve for implantation have to be determinate, and corresponding histological picture needs to be found. Considering upper and lower limb implants, the correct height to consider is above the elbow for the transradial (under-elbow) amputees, while the level at the ischial tuberosity for transfemoral (thigh-level) leg amputees.

Secondly, anatomically shaped geometrical model of the nerve and fascicles are segmented by using the freeware software ImageJ (by freeware software ImageJ with NeuronJ plug-in) obtaining an anatomically shaped geometrical model. Coordinates of the image segmentation are then exported to MATLAB (livelink COMSOL-MATLAB), where a 2D recreation of the nerve is constructed. Since the fascicles are surrounded with a connective tissue sheath called perineurium and it can influence the final results of potential distribution, it was crucial to separate it from the fascicles' contour. As reported in Grinberg et al. (2008) perineurium thickness being determined by the size of fascicle and it is equal to 3% of fascicle's radius. Then the coordinates were interpolated with interpolation curve. The segmented geometry is imported into the FEM software, COMSOL (COMSOL S.r.l., Italy) and extruded along the longitudinal axis achieving a 3D structure (Figure 4.2).

Very important aspect is a correct assignment of different electrical values to the separated tissue classes: epineurium, perineurium, and endoneurium. These values are available from literature, however, need to be critically revision, and adapted to the particular model. Indeed, the intrafasicular endoneurium, debt to the longitudinal disposal of axon within, has an anisotropic conductivity tensor with a longitudinal value of 0.571 S/m and a transverse value of 0.0826 S/m. The epineurium is assumed to be an isotropic medium with a conductivity of 0.0826 S/m (Schiefer et al., 2008). The perineurium is modeled as an isotropic conductor taking into account the thickness of the perineurium as 3% of the approximately diameter of the fascicle (Grinberg et al., 2008), and the difference temperature between frog and humans, with a value of 0.00088 S/m (Raspopovic et al., 2017). Generally, the surroundings of nerves are implemented as homogeneous saline solution (2 S/m), which is emulating the intraoperative environment, with

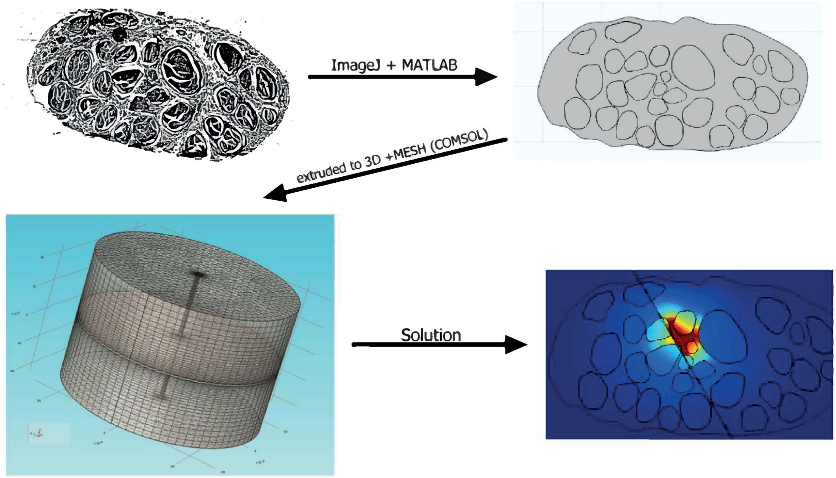


Figure 4.2 FEM solution. (a) Picture of cross-section of human median nerve. (b) 2D cross-section in COMSOL. (c) Final mesh of the entire structure in 3D. (d) Solution of the fem. Electric potential in plan xy (z = 0).

saline solution, but should be corrected in the future works about chronically implanted interfaces.

Models of electrodes are implemented separately and merged with the neural structure. Since the frequency range, which is of interest in sensing prosthetic applications, is low, we can assume a quasistatic approximation of Maxwell's equations within the nerve volume (Bossetti et al., 2008). Therefore, the electromagnetic problem can be expressed through Laplace formulation for the extracellular electric potential (Veltink et al., 1988; McIntyre and Grill, 2002):

$$\nabla \cdot \sigma \nabla Ve = 0 \tag{4.1}$$

To optimize the model from the computational load standpoint, an infinite-length/infinite-diameter to finite-length/finite-diameter approximation has to be considered. While in physics the 0-voltage is defined in infinity, within FEM model, in order to emulate the proper boundary conditions of the problem, the ground condition is set to the outermost surface of a finite model (McIntyre and Grill, 2002). Taking into account limited resources and time constraints, a minimal sufficient boundary dimensions had to be found calculating appropriated indexes (Raspopovic et al., 2011). Sufficient meaning the solution needs to be electromagnetically correct.

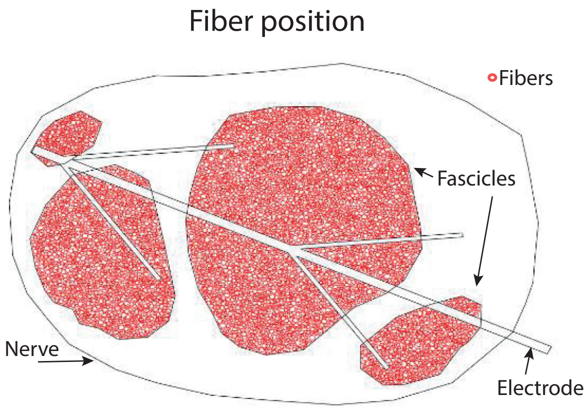
4.3 Neuron Fiber Model

To model the dynamics of nerve fiber, MRG (McIntyre Richardson Grill) model was used (McIntyre, 2002). This model represents the nonlinear modified Hodgkin–Huxley equations for the active compartment of the axons (the nodes of Ranvier) and a detailed realistic representation of the myelinated tracts. The success of this model is debt to its capability to reproduce several experimental aspects of cells dynamics, and to its availability: it can be found in model repository of NEURON. The difference between state-of-the-art models resides basically on two aspects: the first is the membrane dynamics and the second is the representation of the compartments. Membrane dynamics refers to differential equations of the membrane potential and extracellular potential relation (i.e., numbers of ion channels implemented). While compartment representations refer to the number and type of compartments. In this case, MRG model introduced Na+, K+, leakage channel, and nap channel for reproducing the hyperpolarization on the recovery cycle. The sensory axons population were simulated in NEURON 7.3 as implemented in (McIntyre, 2002). For a fiber of diameter *D*, a model made of 21 nodes of Ranvier with internodal spacing $L = 100$ D was built.

On the other side, it is unknown where are placed the fibers groups, which convey a specific sensation: either over the whole fascicle, or only within a very limited area of it. Fibers vary in diameter and position within the fascicle. To address this issue, multiple populations could be generated to account for fascicles' anatomical variability. In sensory human nerves, the probabilistic distribution for fibers diameter resulted in two Gaussian distributions, which differentiated nociceptive fibers from fibers responsible for pressure/touch sensation. Furthermore, nodal length was fixed at 1 um and nodal diameter was scaled from (McIntyre and Grill, 2002). A total amount of 100 fibers, were placed randomly in the specific target fascicle (Figure 4.3). Finally, we considered that fibers within a specific fascicle innervate the same portion of the hand (Jabaley et al., 1980).

4.4 Hybrid Model Solution

The FEM was solved with a stationary solver considering the quasistatic approximation for the electromagnetic problem, i.e., an electrostatic problem. The linear system obtained by FEM is symmetric and positive definite, therefore it can be solved by the Conjugate gradients method which applicable to sparse systems that are too large to be handled by a direct implementation.



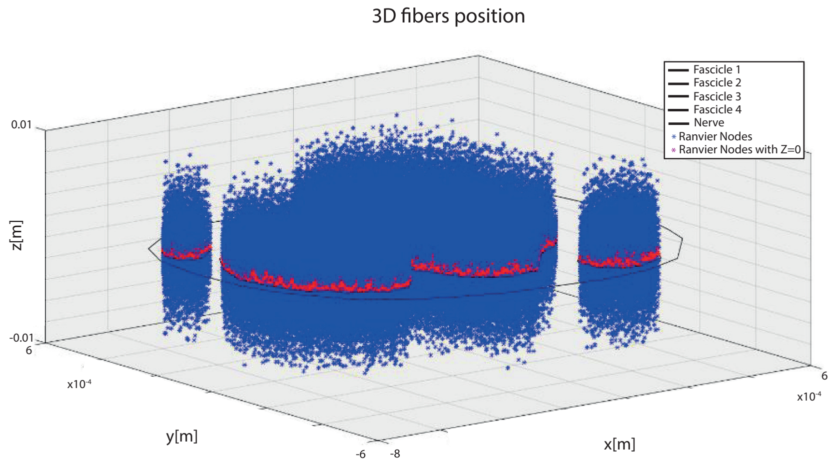


Figure 4.3 2D nerve cross-section with electrode and the fibers positioned inside the fascicles (red; left). 3D placement of Ranvier nodes for each fiber inside the nerve (right).

This method is an iterative solver that requires a preconditioner in order to improve its convergence. The preconditioner used was an algebraic multigrid, which is a numerical method that increases the computational speed by decreasing the complexity of the computations and then leading to a faster convergence. The convergence criterion is reached when the relative error becomes smaller than 1×10^{-6}.

Electric potentials generated inside the nerve by means of electrical stimulation were computed for the whole structure and then interpolated on the proper fibers positions and then neurons answer was computed

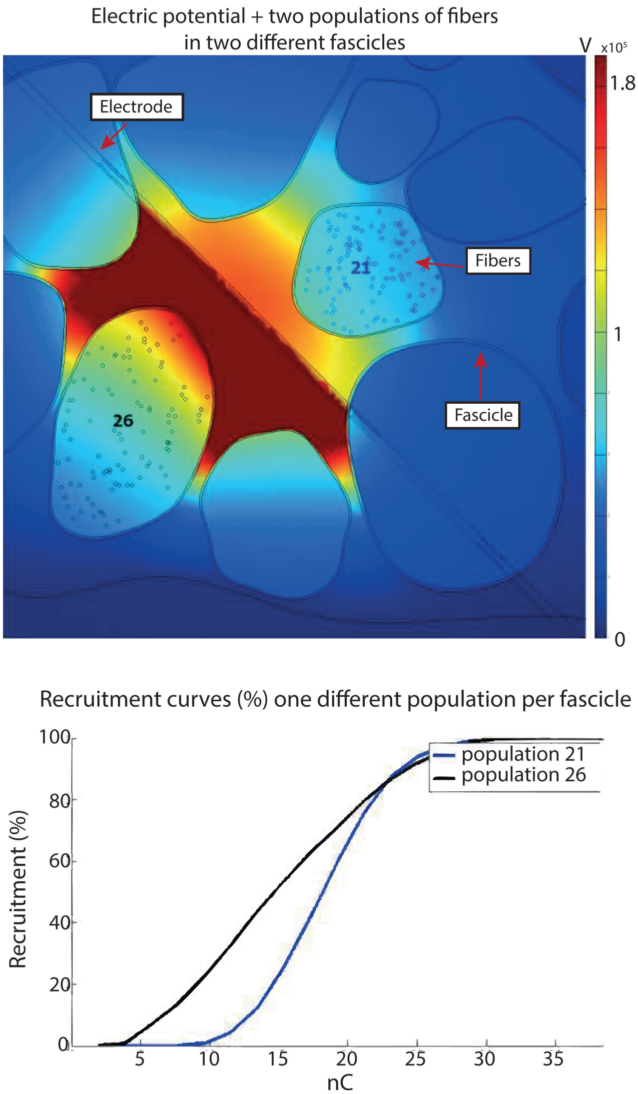


Figure 4.4 Active site of TIME close to three fascicles. (a) Recruitment curves (%). (b) Electric potential distribution (fixed 0–1.9 μV).

(Figure 4.4). Electric potentials were interpolated along the position of the nodes of Ranvier for each fiber in the model. Then, they were extracted from the FEM solutions and used as an extracellular mechanism for membrane depolarization. Fibers were stimulated by cathodal bipolar square current pulses of variable pulse-width (this is correct under quasistatic approximation). A fiber was considered recruited when a generated action potential traveled along its whole length (i.e., reached the last node of Ranvier).

4.5 Model-driven Electrode Design, Dimensions, and Number of Implants

The first, straightforward exploitation of models is for understanding of which type of electrode geometry is the most prominent for the selective stimulation of the discrete sensations. To do so, it is possible to implement different models of several electrodes type, which were successfully used in human applications, as intraneural and epineural electrode (Figure 4.5). Intraneural electrodes by design ensure closer distance to its targets then cuff-type electrodes. Results indicate that the most striking advantage of use of intraneural electrode is its one order of magnitude lower necessary charge threshold to elicit any fiber response respect to the case of epineural electrode (Raspopovic et al., 2017). On the other side, it is also possible to stimulate selectively the deep target fascicle by means of intraneural stimulation, while it is impossible to do so by means of epineural electrode. Finally, as regarding the dynamic of elicitable axonal response, it is possible to fine-modulate

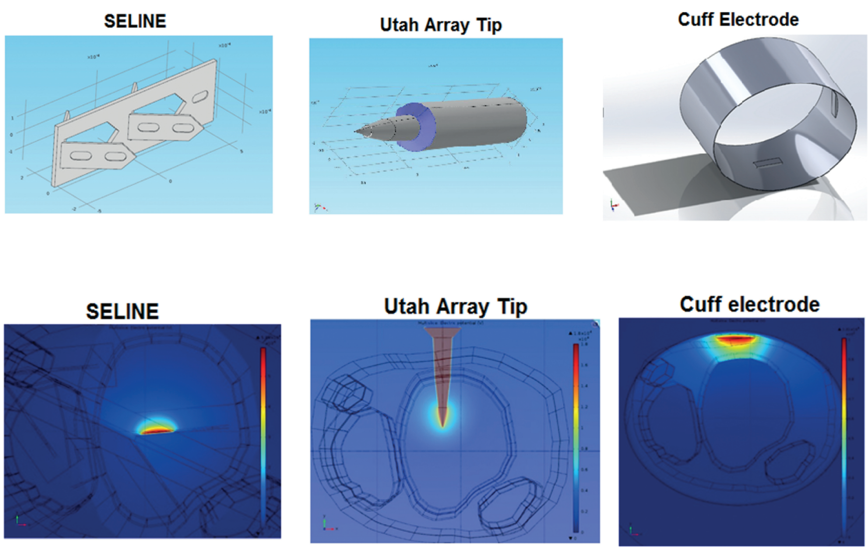


Figure 4.5 Different electrode geometries (top). FEM solutions according to different electrodes type (bottom).

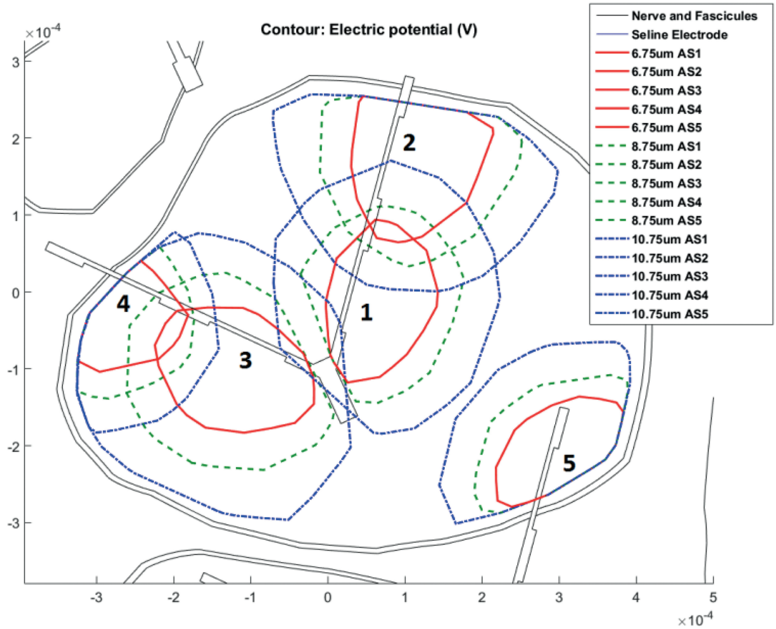


Figure 4.6 Isopotential curves regarding different fibers dimensions related for each active site inside the same fascicle (1–5).

the sensation by use of intraneural active site (TIME) and simple charge modulation, while the same is not feasible by epineural electrodes.

Appropriate electrode dimensions, number of active sites and their respective distances are essential for the manufacturing process. Models are ideal candidates for the proper addressing of this set of dimensions of electrodes. Total number of fascicles stimulated selectively is in a correlation with a number of contact sites, although some of them are recruited by more than one active site (Figure 4.6). The limiting factor, when having many active sites, is that the leads, necessary to connect them to the stimulator, are making the dimension of electrodes' substrate bigger, and therefore more invasive. The optimal number of electric active contacts for a neural electrode could be obtain using hybrid neuron model (Raspopovic et al., 2017).

In order to achieve the maximal performance (defined as the maximal possible number of fascicles elicited selectively) during the stimulation, with limited nerve damage, it is crucial to understand the optimal number of electrode for implant. This could be possible studying it with the models; indeed, it is possible to simulate different possible scenarios of implantation at the

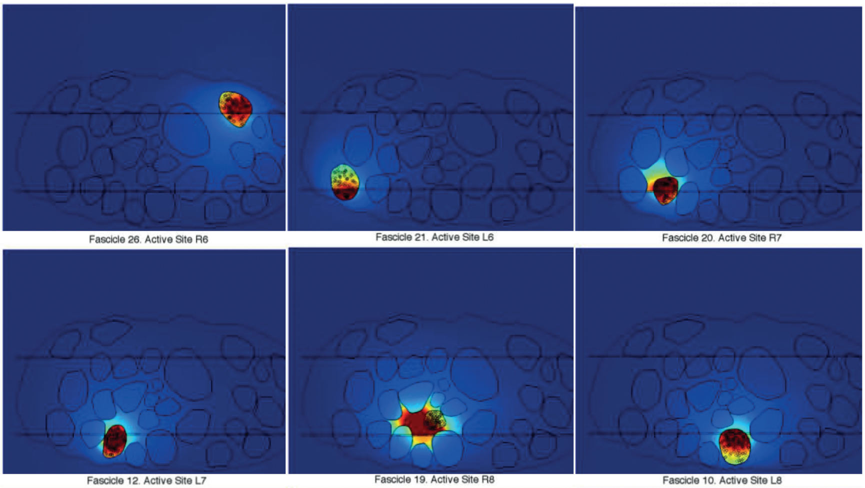


Figure 4.7 Double TIME implant in the same nerve and example of different stimulation positions.

same time (Figure 4.7). The most important goal is to reach the access to the maximal number of the fascicles using different active sites of the electrode. Technically, an implantation of many electrodes can be useful to stimulate every fascicle within the nerve, but too many electrodes could damage the nerve of the patient, put hard demand on the implantable electronics and transcutaneous communication implementation, and therefore this outcome of model is of essential value for neurosurgeon.

Using the hybrid computational model, it could be possible to design optimal configuration to stimulate the target nerve. Traditionally, the neural interface, even if having several stimulating contacts is generally used in paradigms concerning a single-channel: monopolar use. Monopolar stimulation consists in an activation of only one active site at time, while bipolar protocol enables to use two contacts in any configuration (with opposite or same polarity). This represents an example depicting the potentiality of the stimulation protocol design, guided by model findings.

4.6 Simulation of Biological Reaction to Electrode Optimization

Modeling framework is not only useful for the design of the neuroprostheses and their use. It can be successfully exploited also for the interpretation and investigation of scientific questions, which are not easy, or are impossible to face, by experimental empiric approach, that are of paramount importance for successful chronic use of neural interfaces.

One among the biggest issues with long-term use of neural interfaces in the neuroprosthetic devices is the decay/change of the stimulating capability over the time (Liu et al., 1999; Grill and Mortimer, 2000; Huang et al., 2004; McConnell et al., 2009; Polasek et al., 2009; Leach et al., 2010; Winslow

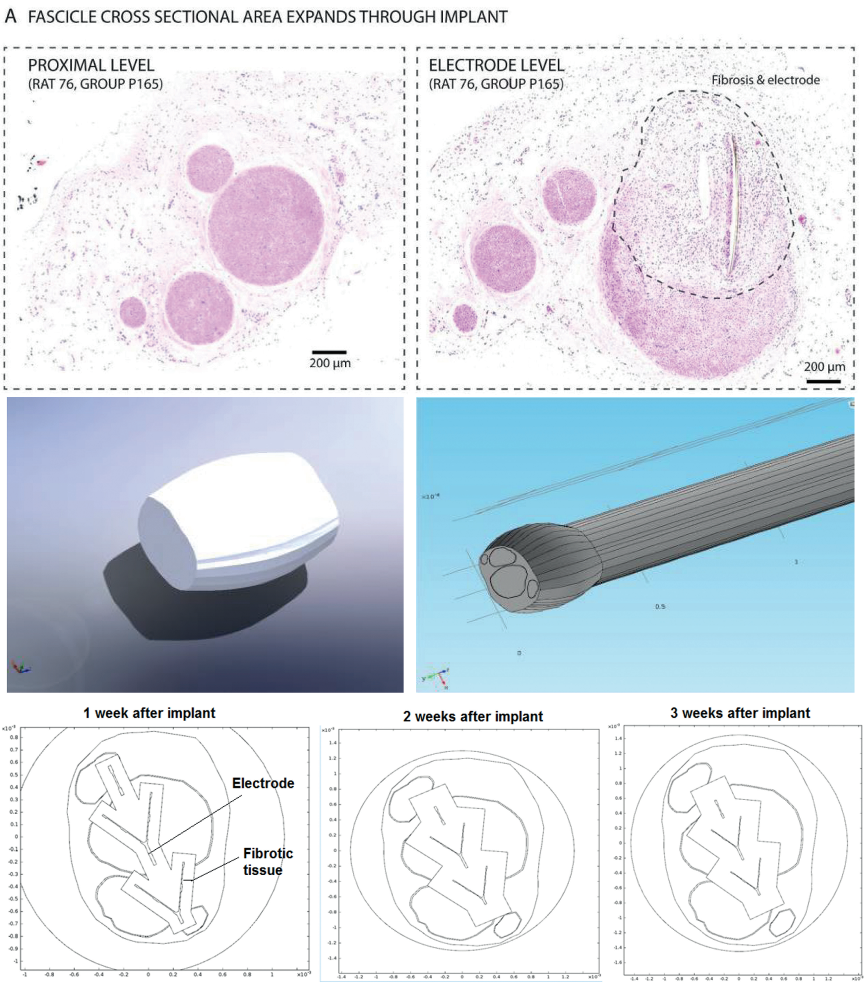


Figure 4.8 Modeling of the fibrotic tissue growth over weeks.

and Tresco, 2010; Raspopovic et al., 2014; Tan et al., 2014). Even though a significant amount of studies has been performed (Liu et al., 1999; Grill and Mortimer, 2000; Huang et al., 2004; McConnell et al., 2009; Polasek et al., 2009; Leach et al., 2010; Winslow and Tresco, 2010), the mechanisms of the thresholds change during the chronic neural stimulation are yet not elucidated. Between many possible hypothesis and interpretations, there is no consensus about the main factors; however, the nerve model can be an excellent instrument for testing some of these. It is possible to test several plausible hypotheses, which aim to explain the change of charge necessary to stimulate the nerve. For example: (i) Nerve fibers are in dysfunction/dying when electrode is placed intrafasciculary. (ii) Fibrotic tissue pushes electrode away from nerve fibers when electrode is placed intrafasciculary (Huang et al., 2004). (iii) Fibrotic tissue shifts electrode away from fascicle when placed extrafasciculary. (iv) Perturbation of the electric field by means of the fibrotic tissue generates the change in the axonal recruitment (Miocinovic et al., 2006). (v) Fibrotic encapsulation (Figure 4.8) changes over time the resistivity around the electrode.

4.7 Discussion

The hybrid modeling is a mandatory step in order to propose the optimized electrodes, and also to perform the most efficient manufacturing, avoid unnecessary animal experimentation, understand the unexpected changes and finally propose the hints for the neurosurgical procedure. It is of paramount importance to understand that, when dealing with models, they can be used properly only when addressing a clearly defined issue, and for what are tailored: it cannot be intended to explain all the aspects of such a complex system as neural system stimulation in every its aspect. Therefore, the models have to be customized toward the peculiar application of feature of interest. All of models account with specific limitations, and these should be clearly studied and stated, since could help in the correct interpretation of model results, their future exploitation and upgrading.

We believe that by the future development of the technologies, and specially imaging techniques, the sophisticated and widespread neuroprosthetic devices will go toward the ad hoc, ad personam modeling-based approach: starting from the high detailed images of structure of interest, and anatomical knowledge, by use of powerful computers, and efficient modeling computation we could have the patient-specific neural interface, and protocol of use.

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