Mini-Symposia Title:

Computational Models of Neuromodulation

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Theme:

- ○ 01. Biomedical Signal Processing
- ○ 02. Biomedical Imaging and Image Processing
- ○ 03. Micro/ Nano-bioengineering: Cellular/ Tissue Engineering &
- ◉ 04. Computational Systems & Synthetic Biology; Multiscale modeling
- ○ 05. Cardiovascular and Respiratory Systems Engineering
- ○ 06. Neural and Rehabilitation Engineering
- ○ 07. Biomedical Sensors and Wearable Systems
- ○ 08. Biorobotics and Biomechanics
- ○ 09. Therapeutic & Diagnostic Systems and Technologies
- ○ 10. Biomedical & Health Informatics
- ○ 11. Biomedical Engineering Education and Society
- ○ 12. Translational Engineering for Healthcare Innovation and Commercialization

Mini-Symposia Synopsis— Max 2000 Characters

The field of Neuromodulation continues to grow and encompass a wide array of therapies using implanted and external devices that interface with the nervous system. Computational modeling can be used hand-in-hand with these developments to help determine mechanism of action and improve design and efficiency of electrodes, batteries, waveform generators, and targets. New developments continue apace in both commonly-used devices and established therapies such as spinal cord stimulation for pain and vagus nerve stimulation for epilepsy, and the neuromodulation frontier, such as non-invasive transcranial stimulation for a growing number of treatments. Understanding the underlying biophysics and neurophysiology in the use of new protocols (e.g. novel waveforms and neural targets) and devices has become the province of computational modeling efforts. This Invited Session will include international speakers using computational methods to unravel the fascinating, diverse array of mechanisms underlying neuromodulation therapies. Modeling efforts presented will range from the microcosm – e.g. axon and neuron ionic channel subcomponents and flux dynamics – to the macrocosm of larger scale circuitry models of entire spinal cord segments, and include sophisticated axonal models using novel waveforms such as high frequency (10kHz) and 'burst', vagus nerve stimulation and novel 'closed-loop' systems involving evoked compound action potentials. Attendees will hear expert modelers' first-hand experience in the benefits, challenges, and limitations of identifying and capturing critical elements of neuromodulation phenomena in a computational approach. Speakers will present glimpses of the future of modeling the nervous system and the 'electroceutical' goal of modulating nervous system functions via electromagnetic stimulation as an alternative to pharmaceutical modulation.

Applications of Modeling Axon Ion Chanel Sub-Components

Jay L. Shils, PhD[1], Jeffrey E. Arle, MD PhD[2], Longzhi Mei MS[2], Kristen W. Carlson[2]

***Abstract*—Starting with Hodgkin and Huxley, numerical axon models resolved at the ion channel level have proved useful to capture phenomena that cannot be represented with a less-detailed model. We describe the development of two active axon models and their strengths and weaknesses compared to other models. One model has been implemented in the COMSOL finite element program so that electric potential from a neurostimulation device can be solved along with its effects on axons.**

I. INTRODUCTION

Hodgkin and Huxley created the first numerical model of an axon including its sodium, potassium, and leak ion gates with their various time constants. In the modern era of neuromodulation electroceuticals [1].

To study the effects of various neuromodulation devices we have built several different passive and active axon models and explored different device parameters (e.g. waveform, amplitude, pulse width) on the electric field between the device and its target tissues, and the resulting effect on the target axons [2-4].

II. METHODS

We implemented the Wesselink et al. and Schwarz et al. active fiber models in C++, and additionally implemented the Wesselink et al. model in COMSOL Multiphysics finite element program (Burlington, MA USA) via customized equation-based modeling [5, 6].

Calibrating the resulting set of sensitively coupled differential equations and supporting equations and parameters and modifying them.is not a simple procedure [7].

III. RESULTS

Extensive modeling of fiber threshold activation and blocking thresholds using both active models showed threshold blocking amplitudes significantly in excess of reported clinical values, supporting a study using a third active fiber model [8].

IV. DISCUSSION & CONCLUSION

Given that the models predicted fiber blocking thresholds in excess of clinical values, we concluded that fiber threshold blocking of the fibers producing paresthesia in spinal cord stimulation could not be an explanation of the lack of paresthesia in two new SCS protocols, 'burst' and high frequency.

Funding was provided by the Sydney Family Foundation.

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Can Fiber Threshold Accommodation Explain the Lack of Paresthesia in Burst and High Frequency Spinal Cord Stimulation?

Jeffrey E. Arle, MD PhD[3], Longzhi Mei MS[1], and Kristen W. Carlson[1]

Abstract— **The newer modes of spinal cord stimulation using 10 1-ms pulse width 'bursts' and 30 – 50 μs pulse width, 10 KHz waveforms produce analgesia *sans* the paresthesia present in low frequency stimulation, yet the different mechanisms of action are unknown. We built a numerical model based on empirical studies of fiber threshold change in dorsal column axons to elucidate the MoA of the 3 waveforms.**

V. INTRODUCTION

In contrast to low frequency spinal cord stimulation (SCS) (LFS, < 200 Hz), 'burst' and high frequency SCS reduce neuropathic pain without the side effect of paresthesia. The mechanism of action (MoA) of these SCS protocols has eluded researchers. We used empirically-based computational models of fiber threshold accommodation (increase and decrease of threshold in response to stimulation) to examine the three MoA [1].

VI. METHODS

Empirical studies of human peripheral sensory nerve fibers show different accommodation effects occurring in response to cathodic, anodic and 0-amplitude ('rest phase') SCS [2, 3]. Larger diameter fibers accommodate significantly more than smaller fibers. We developed a numerical axon model in *Mathematica* (WRI, Inc., Champaign, IL USA) to replicate fiber threshold accommodation behavior for diameters from 5 to 15 μm in each phase. We then examined fiber threshold response to variations of burst, high frequency, and LFS waveforms.

VII. RESULTS

The accommodation model showed 1) inversion of larger and smaller diameter fiber thresholds produce a therapeutic window in which smaller fibers fire while larger ones do not; 2) the anodic pulses increase accommodation and perpetuate threshold inversion from burst to burst and between cathodic pulses in burst, high frequency, and variations, resulting in an amplitude 'window' in which larger fibers are inactivate while smaller fibers fire. No threshold inversion was found for traditional LFS.

VIII. DISCUSSION & CONCLUSION

The fiber threshold accommodation theory predicts that burst and high frequency SCS do not activate large-diameter fibers that produce paresthesia while driving medium-diameter fibers, likely different from LFS, that produce analgesia via different populations of dorsal horn neural circuits. We outline the clinical parameter ranges predicted to produce analgesia without paresthesia, point to energy-efficient parameter combinations, and hypothesize on the different dorsal horn circuits possibly activated by burst and HFS vs. LFS.

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Syncing Neural Circuitry Models with Empirical Connectome Data

Kristen W. Carlson[4], Jay L. Shils, PhD[2], Jeffrey E. Arle[1], MD PhD[1], Longzhi Mei MS[1]

Abstract— **We built the first large-scale computational model of the human spinal cord (SC) connectome. This first draft provides a template for building innumerable large and small-scale SC models to dissect the neural circuitry involved and understand SC disorders and how to treat them with pharmaceuticals and electroceuticals.**

I. INTRODUCTION

We have entered the age of the connectome. Many brain connectomes are underway but few of the spinal cord, and none, to our knowledge, of the full human spinal cord, the most ancient and in some ways, evolved, component of the central nervous system [1].

Toward that end we built a detailed model of the human spinal cord connectome from data in the literature and performed some initial calibrations [2].

II. METHODS

A thorough search of the literature revealed extensive connectivity data to constrain the connectivity, yet with considerable gaps as well. A similar situation was found with existing data on connection density at the target, neurotransmitters, and other indicators of connection strength from source to target group.

In many cases human data was not available, so we selected as close a phylogenetic species as possible.

The final model consists of over 500 neural and fiber groups and 11,000 connections. The vastness of this model dispelled initial expectations that one or two calibrations (e.g. of the well-known H-reflex) would suffice for broad use of the model.

While it is possible to construct simple connectomes through a graphical user interface [3], it became clear that this is unfeasible for a model of this complexity. Thus, we designed a datasheet in Excel (Microsoft, Inc., Redmond, WA USA) to facilitate compiling all the connectome data, and a translator program to re-write the data into the format for our neural circuitry simulation software [2].

III. RESULTS

As an exemplar of an application of the spinal cord connectome, we replicated known normal and neuropathic pain circuitry, and its treatment with spinal cord stimulation [4]. This model supported suspected and reported discrepancies between theoretical neuropathic pain models [5] and elucidated possible mechanisms of action underlying neuropathic pain signaling in the dorsal horn and its treatment with neuromodulation.

IV. DISCUSSION & CONCLUSION

Empirical techniques to elucidate the data required to construct connectomes are advancing rapidly [2]. We discuss the various ways to synchronize computational models with empirical connectome data, such as functional connectivity derived by MRI and blood oxygen level imaging, and top-down calibration to further constrain and validate connectome models.

Funding was provided by the Sydney Family Foundation.

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Computational Models of the Dose Response Relationship for Spinal Cord Stimulation for Pain Management and Other Disorders

John Parker, PhD[5]

***Abstract*— Closed loop spinal cord stimulation has been shown to provide superior pain relief when compared with open loop devices. The control loop maintains dorsal column recruitment levels constant, within the capabilities of the system, whereas open loop devices do not. The difference in efficacy between open and closed loop can be explained by considering the overlap of recruitment histograms with model dose and side effect response curves.**

V. INTRODUCTION

Pain relief has been demonstrated with closed loop SCS[1] and more recently a double blinded randomized control trial has been published [2] which demonstrates superiority of closed loop spinal cord stimulation to open loop stimulation. The device used in the study allowed continuous recording of evoked dorsal column potentials which were analyzed.

VI. METHODS.

The statically distribution of recorded compound action potentials over fixed time intervals were compared between patients in the open loop arm with those in the closed loop arm. A model of the statistical distribution was derived and compared with a theoretical dose response relationships for both benefit and side effect.

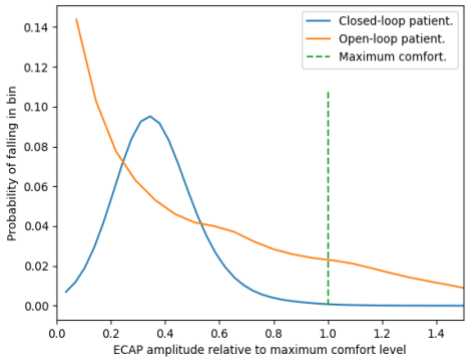

Figure 1. Histograms from an open-loop and a closed-loop patient from the 3 month visits for the Evoke trial. These are normalized to the patient maximum comfort level. These histograms show that the open-loop patient experienced a significantly greater percentage of stimuli above the maximum comfort level indicated by the dashed green bar.

VII. RESULTS.

Overlapping the measured histogram response with the models of dose and side effect curves allows estimation of the net therapeutic benefit by integration and simple subtraction. (ie Net benefit = Overlap of therapy – Overlap of side effect).

VIII. CONCLUSION.

The results suggest a possible mechanism by which SCS can be therapeutic but, also over time, result in loss of efficacy. This leads to a set of hypotheses which can be tested further.

1. SCS therapy and side effects are the result of activation of Aβ fibers.
2. Stimuli below the ECAP activation threshold provide no therapy.
3. Stimuli above the ECAP activation threshold provide therapy which increases with the degree to which they exceed the threshold and with the frequency of occurrence.
4. Stimuli above the ECAP maximum comfort threshold provide side effects which increase with the degree to which they exceed the side effect threshold and frequency of occurrence.
5. The net effect is the sum of the net therapy and the net side effect.
6. At high ECAP amplitudes, the net side effect exceeds the net benefit, and may lead to intolerance.

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Computational Modelling of Vagus Nerve Stimulation

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Abstract—**Vagus nerve stimulation (VNS) is a neuromodulation therapy being used as the treatment of several chronic disorders. We want to maximize the desired and minimize the undesired effects of VNS in order to achieve function and/or organ-specific vagal neuromodulation. The desired and undesired effects of VNS are mediated by activation of nerve fibers of different types (A, B and C type). Assessing the activation of these different vagal fiber types is essential for developing fiber-selective VNS therapies. Therefore, we conducted *in silico* investigations using functionally-distinct nerve fiber computational models based on COMSOL software. This model can be used to design optimal stimulation parameters distinguishing functionally-distinct vagus nerve fibres.**

I. INTRODUCTION

Vagus nerves can be classified as myelinated A and B fibers, as well as unmyelinated C-fibers based on conduction velocity and nerve fiber morphology. These subtypes control different nervous system functions [1]. Assessing the differential activation of these vagal fiber types is essential for developing fiber-selective VNS therapies.

II. METHODS

Our nerve fiber model formulations are based on McIntyre, Richardson and Grill (MRG) model [2] Schwarz, Reid and Bostock (SRB) model [3]. The membrane dynamics follows Hodgkin-Huxley type formulation. A 3D cylinder (radius: 20um, length: 1cm) is reconstructed to present extracellular environment of nerve fibers. All nodes and myelins on the 1-cm nerve fiber are modelled as 1D line geometry [4]. Model parameters are optimized to produce experimental recording from typical fibers A, B and C. Bipolar 50-µm and 60° center cuff stimulating electrodes are located 20 µm above the first node. All simulation are implemented in COMSOL Multiphysics. (COMSOL Inc., Burlington, MA). Intracellular potential (Vi) in node and myelin was modelled by PDEs:

$$-\nabla\left(\frac{r_{node}}{\rho_i}(\nabla V_i)\right)+2C_{node}\frac{\partial V_i}{\partial t}=-2\left(i_{ion}-C_{node}\frac{\partial V_e}{\partial t}\right) \quad (1)$$

$$-\nabla\left(\frac{r}{\rho_{myelin}}(\nabla V_i)\right)+2C_{myelin}\frac{\partial V_i}{\partial t}=2C_{myelin}\frac{\partial V_e}{\partial t} \quad (2)$$

where ρ_n and ρ_{my} are the intracellular resistivity in the nodes and myelin respectively. Extracellular potential (V_e) is modelled as

$$\nabla\left(-\frac{1}{\rho_i}\nabla(V_e-V)\right)=0 \quad (3)$$

The ionic model includes a generic sodium current, a fast potassium channel, a slow potassium channel and a leakage current [3].

III. RESULTS

With fiber-specific model settings, the simulated action potential velocity are all within the experimentally-measured range (see Table 1), these model fibers have physiological characteristics and are able to reflect part of physiological properties of VN fibers. In addition, During electrical simulation (monophasic stimulation with a pulse width of 5 ms and a amplitude of 0.2 mA), the fiber recruitment starts from A and B fiber to C fiber, and only long pulse width (> 0.5 ms) can effectively activate C fiber. These results all agree with the recent experimental recordings in vagus nerve fibers in rat.

Simulation of different Nerve Fibers			
Model type	***Myelin diameter***	***Node Diameter***	***Simulated Conductive velocity (CV)***
Fiber A	2~5 µm	1 µm	9.1 ~ 18.7 m/s
Fiber B	1~3 µm	1 µm	5.7 ~ 7.9 m/s
Fiber C	N/A	0.3 ~ 1.3 µm	0.54 ~ 0.87 m/s

Table 1 Model parameters settings and outputs of three nerve fibers

IV. CONCLUSION

Our computational model approach can predict optimal stimulation parameters that accurately control different vagus nerve fibre types, without detailed experimental investigations, providing insights into stimulation strategies that may contribute further to fiber-selective VNS therapies

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Modelling the Response of Retinal Networks to Electrical Stimulation

Socrates Dokos, PhD[7]

Abstract— **Retinal prostheses aim to provide artificial vision to RP patients by electrically stimulating the surviving retinal neurons. Recent retinal studies has demonstrated the ability to preferentially recruit different retinal ganglion cells (RGCs), using a wide range of high frequency electrical stimulation (from 1-kHz to 8-kHz). However, it is still largely unclear how well does ON/OFF preferential activation scale up for clinical translation in a diseased, remodelled retina? And does our previously optimised parameter space shown to be effective in a healthy retina apply to a diseased retina, or does it need re-optimisation? In answering these questions, we conducted *in silico* investigations supported by in vitro whole-cell patch-clamping recordings, to explore the generalizability of HFS to differentially active ON and OFF RGCs.**

I. INTRODUCTION

Existing retinal studies demonstrated the ability to differentially recruit ON and OFF retinal ganglion cells (RGCs) in a healthy retina over a wide range of electrode locations and stimulation parameters using a high frequency electrical stimulation (HFS) paradigm. Spontaneous and stimulated activities of RGCs from degenerated retina were investigated in this study. Recent experiments in degenerating mouse (rd1) retina suggested that the intrinsic firing property of RGCs was not significantly altered compared with the wild-type mouse [1, 2]. However, the observed 10-Hz rhythmic resting spike activity in rd1 ON and OFF RGCs may alter their response to electrical stimulation.

II. METHODS

ON and OFF RGC clusters were implemented using the computational software NEURON. Techniques used to model individual RGCs have been described in detail previously [3]. , the morphological structures of different RGCs were simulated by a neural morphology generator. RGC dendritic morphological parameters were adjusted based on published data for ON and OFF RGC morphologies in guinea pig retina [4]. The simulated synaptic currents are injected to ON and OFF RGC soma to reproduce cell-specific spontaneous oscillatory activities. The time and frequency properties of rhythmic synaptic currents in ON and OFF RGC are reconstructed based on the published data observed in rd1 retina [2].

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III. RESULTS

Our simulations demonstrated that the parameter space for differential activation can be influenced by characteristic rhythmic activity occurring in retinal degeneration. Frist, both simulated ON and OFF RGCs showed strong 10-Hz oscillatory activities, which influence their response to electrical stimulation. Second, HFS pulse trains were still able to induce robust differential activation of the ON RGC with stimulation parameters similar to that measured in healthy retina (5 ~ 10 kHz, 100 ~ 150 μA), but cannot preferentially activate the OFF RGC with the given stimulation parameter space.

IV. CONCLUSION

The simulation results suggest the possibility of differential neural activation in clinically relevant conditions by achieving HFS-based differential activation in a degenerated condition. One advantage of the computational approach is that the model-generated response space map can be made arbitrarily large and fine-grained for thorough exploration of stimulus parameters. This is difficult, if not impossible, to achieve through biological experiments due to the invasiveness of intracellular recordings.

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