Task 2

SENN Model Evaluations

Task Report
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Acronyms

Acronym	Definition
HEMI	Human Electromuscular Incapacitation
JHU/APL	Johns Hopkins University Applied Physics Laboratory
JIFCO	Joint Intermediate Force Capabilities Office
SENN	Spatially Extended Nonlinear Node
MRG	McIntyre Richardson Grill
DAP	Depolarizing Afterpotentials
AHP	After Hyperpolarization
MRI	Magnetic Resonance Imaging
IEEE	Institute of Electrical and Electronics Engineers
ICNIRP	International Commission on Non-Ionizing Radiation Protection

Executive Summary

The goal of this task is to determine which electrostimulation model is best suited for the study of human electromuscular incapacitation (HEMI) devices. To accomplish this goal, we perform a comparative review of broadly used electrostimulation models.

Electrostimulation models are used to simulate nerve impulse generation under various forms of electrical stimulation. They can be used in conjunction with electromagnetic computational models to determine whether particular neurons are brought to an excited state given the electric field along the neuron as described by Reilly (2016). The determination of whether a neuron is excited given the electrical field that it is exposed to is based upon several interdependent factors such as membrane dynamics, fiber geometry, electrode configuration, myelin impedance and neuronal terminations. We examine these key properties across multiple electrostimulation model types to determine which one best suites the study of HEMI devices.

Key points of this study are summarized below:

- This report specifically focuses on models of myelinated nerves exposed to external electrical stimulation with a focus on neurons that are most relevant to the evaluation of HEMI devices.
- Some of the most widely used electrostimulation models of myelinated neurons include the McNeal model, the Spatially Extended Nonlinear Node (SENN) model, the McIntyre Richardson Grill (MRG) model, and the Sweeney model.
- The McIntyre Richardson Grill (MRG) model has the most detailed representation of membrane electrodynamics. However, that is not necessarily ideal for the study of human exposure limits with HEMI devices, because this approach is much more computationally expensive without providing much benefit in studying the excitability of neurons in relation to HEMI devices.
- The different electrostimulation models vary substantially in excitation thresholds. This difference may be accounted for by the electrodynamics of the individual models. These models differ based on whether they assume finite impedance for the myelin sheath, and their representation between the nodes of Ranvier, and paranodal and intermodal sections of the axon.
- The SENN model was the only model that has been extensively leveraged in the establishment of human safety limits for electromagnetic exposure, and is able to study a broad range of stimulus parameters.

1. INTRODUCTION

1.1 Overview

Electrostimulation models are used to simulate nerve impulse generation under various forms of electrical stimulation. They can be used in conjunction with electromagnetic computational models to determine whether particular neurons are brought to an excited state given the electric field along the neuron [1]. These computational models can be used to study a range of anatomical fidelity, and serve to define the distribution of electric fields by an external source [1]. Electric field distribution calculated by the models can then serve as an input to the electrostimulation model to evaluate whether a neuron would fire under the applied electrostimulation. Neuronal excitability is dependent on multiple factors including, but not limited to, membrane dynamics, nerve fiber geometry, electrode configuration, myelin properties, and neuronal terminations [2]. To determine which electrostimulation model is most relevant for the study of human electromuscular incapacitation (HEMI) devices, we perform a comparative review of widely used electrostimulation models.

2. BACKGROUND

2.1 Membrane Model Fundamental Equations

In the case of a myelinated fiber (illustrated in Figure 1) subjected to electrical forces, the current travels from the stimulus electrode, through the conducting medium, and to the neural fiber where it produces a voltage disturbance at the nodes of Ranvier. These voltage disturbances at the nodes of Ranvier force current across the membrane, which either depolarizes, or hyperpolarizes the membrane. The equations governing membrane electrodynamics broadly vary across electrostimulation models. However, most of these models are based on adaptations of the same core set of equations.

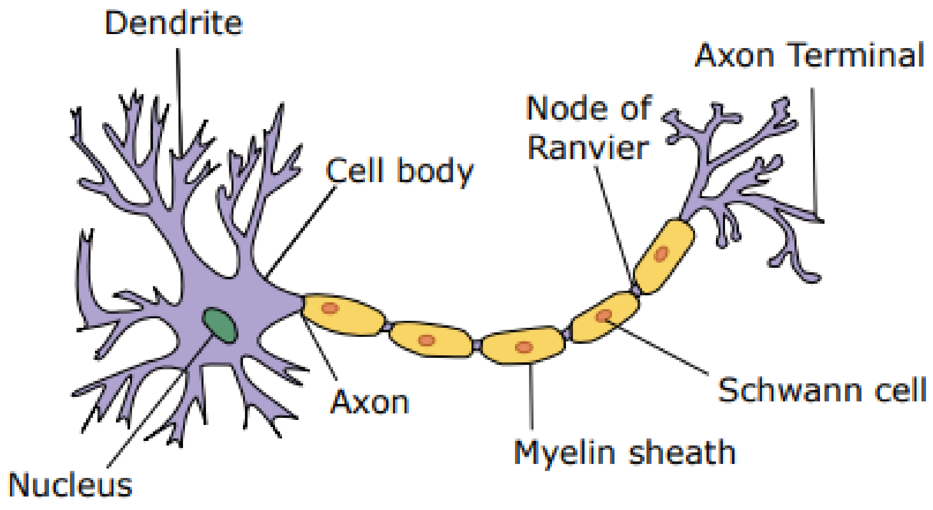

Figure 1: Illustration of one type of myelinated nerve fiber [3].

Hodgkin and Huxley provided the first detailed mathematical equations describing the electrodynamics of an unmyelinated axon in a squid [4]. Frankenhaeuser and Huxley (FH) extended this work to apply to myelinated nerve fibers of a toad [5]. Frankenhaeuser and Huxley use a set of nonlinear differential equations to describe neuron electrodynamics, which include voltage sensitive variables that control the opening and closing of ion specific channels in the membrane at each node of Ranvier. The membrane dynamics of many electrostimulation models of myelinated nerves are based on the Frankenhaeuser and Huxley equations [5] with various adaptations.

2.1.1 Membrane Model Types

Whether a neuron is excited given the electrical field that it is exposed to is dependent on several interdependent factors such as membrane dynamics, fiber geometry, electrode configuration, myelin impedance, and neuronal terminations [2]. It was found that neuronal excitability is greatly impacted by the membrane electrodynamics and the location of the neural terminations [2]. For this reason, it is critical to select an electrostimulation model with membrane and neural termination properties that are relevant to the type of exposure being examined.

A key factor distinguishing between electrostimulation models is the method by which membrane dynamics are modeled. There are a few main categories of axonal membrane dynamics. The first category includes electrostimulation models in which the myelin sheath acts as a perfect insulator. In this case, the axon is modeled as a single cable and the behavior of the model is only dependent on the membrane dynamics at the nodes of Ranvier [6]. In the second category, the myelin sheath has finite impedance, so some current can flow through the myelin sheath. This type of axon is also modeled as a single cable [6]. The final axon type, with the most detailed membrane dynamics, is where the axon is modeled as a double cable structure with finite impedance. The double cable structure allows for separate electrical representations of the myelin and the underlying intermodal axolemma. This type of electrostimulation model allows for explicit representation of the nodes of Ranvier, and paranodal and intermodal sections of the axons, as well as the myelin sheath with finite impedance.

2.1.2 Mechanisms of Reaction specific to HEMI devices

Stimulation by an external electrical source can involve several mechanisms of reaction based on nerve fiber orientation relative to the electrodes. There are three main mechanisms of motor reaction relative to HEMI devices: (a) direct stimulation of muscle, which occurs closest to the stimulating electrodes [7]; (b) stimulation of the motor neurons; the motor neurons have a much lower excitation threshold for short duration pulses than the muscles that they innervate [7]; and (c) reflex activity due to stimulation of afferent neurons (Figure 2) [7].

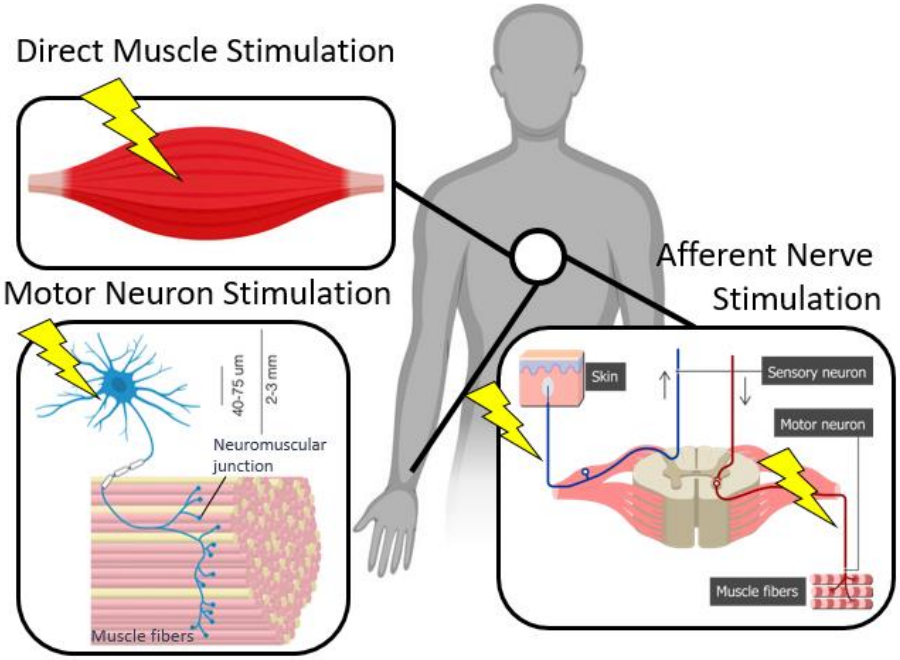

Figure 2: Mechanisms of reaction to HEMI devices include direct muscle stimulation from the external electrical source, activation of motor neurons through the electrical stimulation, or even activation of peripheral nerves connected to spinal reflex pathways pertaining to incapacitation [7, 8, 9].

3. MATERIALS AND METHODS

3.1 Electrostimulation Models

Some of the most widely used electrostimulation models of myelinated neurons include the McNeal model [10], the Spatially Extended Nonlinear Node (SENN) model [7], the McIntyre Richardson Grill (MRG) model [6], and the Sweeney model [11, 2].

The McNeal model was the first computational model of nerve excitation for extracellular electrostimulation of a myelinated neuron [10]. The myelin is assumed to act as a perfect insulator, such that the membrane electrodynamics are defined only at the nodes of Ranvier. The membrane dynamics model originally used by McNeal considered only single node depolarization [12]. Each node of Ranvier is represented as a linear electric circuit, except for the excitation node which is represented by the nonlinear equations of Frankenhaeuser and Huxley [5]. With this framework, it is possible to study the effects of arbitrary distributions of stimulus current external to the fiber [13]. Similar to many other models, the SENN model is based upon the McNeal model, and it has been adapted over time.

With the SENN model, all nodes of Ranvier can be represented by the nonlinear equations of Frankenhaeuser and Huxley [5]. As in the McNeal model, the myelin sheath is treated as a perfect insulator such that the dynamics of the model are solely defined by the membrane dynamics at the nodes of Ranvier [7]. The SENN model permits the study of neuronal dynamics in response to different stimulus parameters such as polarity, waveshape, and geometric properties of the neuron [5].

The Sweeney model is another electrostimulation model for myelinated nerve fibers. However, this model has been adapted for mammalian nerve fiber properties rather than those of a toad [11]. The Sweeney model replaced the Frankenhaeuser and Huxley electrodynamics of the McNeal model with equations appropriate to the rabbit myelinated nerve to simulate a spatially extended fiber similar to the SENN model [7]. Also similar to the SENN model, the myelin sheath is treated as a perfect insulator.

The McIntyre Richardson Grill model has the most complex membrane electrodynamics of the four models examined here. It has a double cable structure that allows for explicit representation of the nodes of Ranvier, the paranodal and internodal sections of the axon, as well as finite impedance of the myelin sheath [6]. Membrane electrodynamics are based upon experimental measurements from human, cat and rat neurons [6]. The MRG model was developed to evaluate mechanisms of the recovery cycle of a mammalian myelinated motor axon following action potential [6]. In order to study the mechanisms of depolarizing afterpotentials (DAPs) in myelinated axons, it is necessary to have a more complex representation of an axon, thus this model employs a double cable structure, as discussed in Section 2.1.1, rather than the typical single cable of many other models.

4. RESULTS

4.1 Down Selection of Electrostimulation Models

The selection of an ideal electrostimulation model for use in evaluation of HEMI devices requires consideration of many factors. These factors include the availability of the model, membrane electrodynamics, excitation threshold, treatment of the neural end organ, and relevance in human exposure limits.

Wide availability of the model is important such that study results may be compared across researchers. For this reason, publicly available electrostimulation models were favored. The SENN model is publicly available both as FORTRAN code and in the NEURON environment, and a detailed user’s guide is publicly available. The MRG model is also publicly available through the NEURON environment. The Sweeney model is not publicly available, and uses MATLAB and SIMULINK, which are not open source. The McNeal model is publicly available in FORTRAN.

Table 1: Summary of Nerve Excitation Models

	Publicly Available?	Code Used	Available In NEURON?
MRG	Yes	NEURON	Yes
SENN	Yes	FORTRAN	Yes
McNeal	Yes	FORTRAN	No
Sweeney	No	MATLAB & SIMULINK	No

Although the MRG model has the most in depth membrane electrodynamics, that is not necessarily ideal to the study of human exposure limits with HEMI devices. The double cable structure of the MRG model is most useful for physiological research where the structure of the myelinated axon is under specific consideration [6]. In addition, the MRG model has features of reproducing the depolarizing afterpotentials (DAPs) and after hyperpolarization (AHP). However, the DAP and AHP have no direct impact on nerve excitability indices [2]. The double cable structure is much more computationally expensive, without adding much benefit in studying the excitability of neurons in relation to HEMI devices. In contrast, the McNeal model has the simplest membrane dynamics of the models examined here, with only one node being treated as nonlinear. The SENN model is a middle ground between the McNeal model and the MRG model, which makes it a good candidate for studying a wide variety of electrostimulation problems.

When measuring nerve excitation, another factor to consider is the variation of excitation thresholds among the neural stimulation models. This variation is expressed via a strength-duration curve shown in Figure 3 and Figure 4 [1]. The full list of neural stimulation models shown in these Figures can be found in Appendix A, but most notably (A) SENN model, (B) MRG model (E and F) SENN model with temperature adjustments to 22° C and 37° C, respectively, and (J) Sweeney model. The strength duration relationship is a useful way to characterize neural excitation sensitivity. Figures 3 and 4 demonstrate the strength-duration curve of various neuronal stimulation models for a point electrode on the surface of a semi-infinite medium and a nerve fiber in a constant E-field, respectively. This demonstrates how the different models vary significantly in excitation thresholds. In Figures 3 and 4, it is apparent that the MRG model has a significantly different threshold, especially where approaching rheobase, as compared to the SENN models and Sweeney model. This significant difference may be explained by the electrodynamics of the MRG model, having finite impedance of the myelin sheath and representation between the nodes of Ranvier, paranodal, and intermodal sections of the axon.

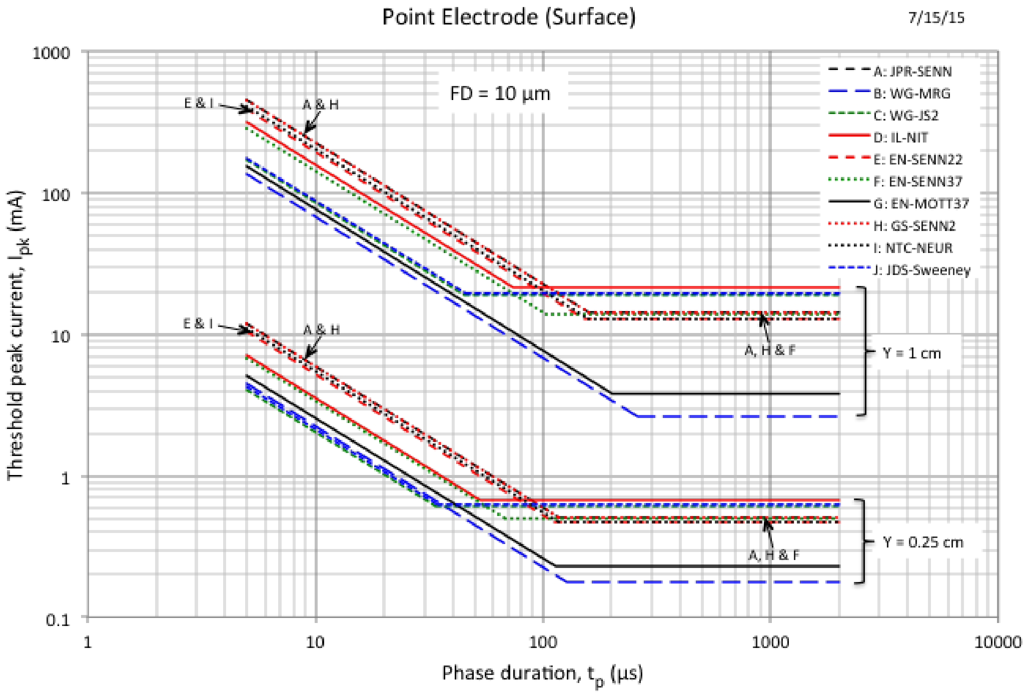

Figure 3. Graphical representation of strength-duration curves (asymptotes) for point electrode stimulation.

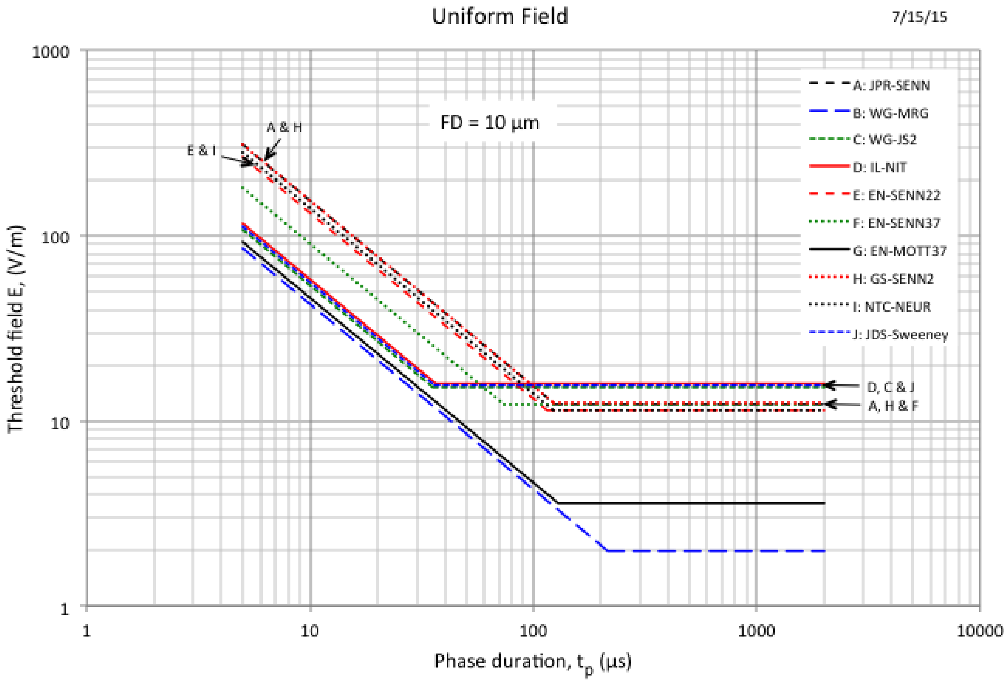

Figure 4. Graphical representation of strength-duration curves (asymptotes) for constant E-field stimulation.

Another factor taken into consideration was the relevance of the electrostimulation model for use in determining human exposure limits. The SENN model has a long history in relation to human exposure limits, starting with MRI exposure limits. The SENN model was the first use of an electrostimulation model to derive human exposure limits on MRI switched gradient fields. In these studies, it was found that with magnetic induction from an MRI switched gradient field, the spatial derivative of an induced E-field would be too weak to initiate an action potential at a location along the neuronal axon. To study this scenario, the McNeal model was adapted to apply to stimulation at neural end organs. For stimulation at the neural end organs, the magnitude of the induced E-field at the neural terminus was the relevant exposure metric, rather than its spatial derivative [1]. In addition to its role in the derivation of human exposure limits for the use of MRI, the SENN model also played a critical role in the development of guidelines for human exposure to electromagnetic fields. The SENN model is widely used by researchers to study electrostimulation of myelinated fibers, and plays a key role in standards developed by IEEE [14] and the International Commission on Non-Ionizing Radiation Protection (ICNIRP) [15, 16].

As discussed above, for an electrostimulation model to respond to both significant and insignificant spatial derivative of the E-field, the model should be able to demonstrate excitation at the neural terminus within an extracellular field that is relatively constant along the axon [1]. Under some conditions, excitation may be initiated at a neural end organ rather than along the axon. All of the models examined here model the terminus as ending at a node of Ranvier [1]. Therefore, all models considered demonstrate this necessary capability.

Another main advantage of the SENN model is that the spatial and temporal properties of the extracellular stimulus current can be arbitrarily selected. This allows one to simulate a variety of electrode and neuron geometries [13], allowing the researcher to study a wide variety of stimulus parameters include electrode configuration, waveshape, and polarity. Having control over these parameters is crucial in studying HEMI devices, for which electrode placement can vary greatly, together with variations in stimulus waveshapes and polarity.

5. SUMMARY and CONCLUSIONS

Electrostimulation models allow for the study of a broad range of electrostimulation problems, and therefore, are critical for tools in the investigation of human exposure to HEMI devices. Many electrostimulation models have been developed and utilized across a variety of investigations. However, this report specifically focuses on models of myelinated nerves with external electrical stimulation with a focus on neurons that are most relevant to the evaluation of HEMI devices. The SENN model was the only model that has been extensively leveraged in the establishment of human safety limits for electromagnetic exposure, and is able to study a broad range of stimulus parameters. Given these considerations, the SENN model is a reasonable choice for the investigation of human exposure to HEMI devices, although we recognize the need for further validation of electrostimulation models.

6. REFERENCES

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7. APPENDIX A (from [1])

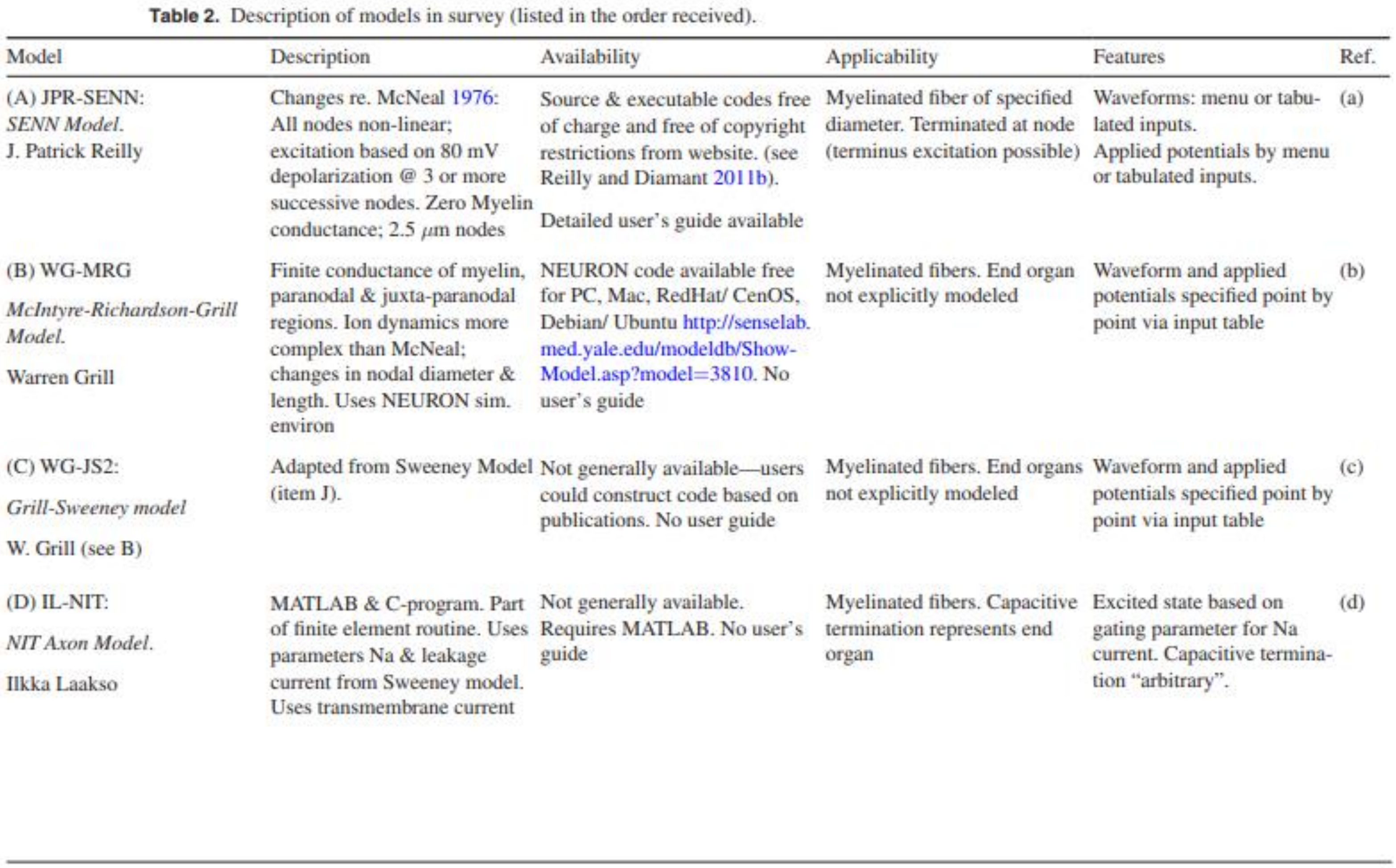

Table 2. Description of models in survey (listed in the order received).

Model	Description	Availability	Applicability	Features	Ref.
(A) JPR-SENN: *SENN Model.* J. Patrick Reilly	Changes re. McNeal 1976: All nodes non-linear; excitation based on 80 mV depolarization @ 3 or more successive nodes. Zero Myelin conductance; 2.5 μm nodes	Source & executable codes free of charge and free of copyright restrictions from website. (see Reilly and Diamant 2011b). Detailed user's guide available	Myelinated fiber of specified diameter. Terminated at node (terminus excitation possible)	Waveforms: menu or tabulated inputs. Applied potentials by menu or tabulated inputs.	(a)
(B) WG-MRG *McIntyre-Richardson-Grill Model.* Warren Grill	Finite conductance of myelin, paranodal & juxta-paranodal regions. Ion dynamics more complex than McNeal; changes in nodal diameter & length. Uses NEURON sim. environ	NEURON code available free for PC, Mac, RedHat/ CenOS, Debian/ Ubuntu http://senselab.med.yale.edu/modeldb/ShowModel.asp?model=3810. No user's guide	Myelinated fibers. End organ not explicitly modeled	Waveform and applied potentials specified point by point via input table	(b)
(C) WG-JS2: *Grill-Sweeney model* W. Grill (see B)	Adapted from Sweeney Model (item J).	Not generally available—users could construct code based on publications. No user guide	Myelinated fibers. End organs not explicitly modeled	Waveform and applied potentials specified point by point via input table	(c)
(D) IL-NIT: *NIT Axon Model.* Ilkka Laakso	MATLAB & C-program. Part of finite element routine. Uses parameters Na & leakage current from Sweeney model. Uses transmembrane current	Not generally available. Requires MATLAB. No user's guide	Myelinated fibers. Capacitive termination represents end organ	Excited state based on gating parameter for Na current. Capacitive termination "arbitrary".	(d)

Table 2. *(Continued)*

Model	Description	Availability	Applicability	Features	Ref.
(E) EN-SENN(22) *SENN model,* 22 °C Esra Neufeld	Essentially SENN model, implemented in NEURON, with $T = 22$ °C.	SENN is available from JPR as Model (A) above. This implementation is part of the commercial Sim4Life platform (special licenses avail. for non-commercial)	Myelinated fibers	Fashioned from JPR-SENN, but with differences in discretization & numerical scheme.	(e)
(F) EN-SENN(37) *SENN model,* 37 °C Esra Neufeld	SENN model, implemented in NEURON with temperature adjustment to 37 °C	See (E)	See (E)	See (E)	(f)
(G) EN-MOT(37) *Motor Neuron model* Esra Neufeld	Finite impedance of myelin sheath, paranodal & inter-nodal segments; very different ion channel dynamics from McNeal	Part of commercial Sim4Life platform (special licenses available for non-commercial research); user's manual	Myelinated motor neuron	Pre-/user-defined pulse shapes, coupled to comput-able phantoms for *in vivo* field determ., support for inhomogeneous. & aniso-tropic tissue distribution.	(g)
(H) GS-SENN *SENN model* Gernot Schmid	SENN Model for PC	See (A)	See (A)	See (A)	(h)
(I) NTC-NEUR N. T. Carnevale	'NEURON' model, largely based on McNeal formulation	OSX, MSWin, UNIX, Linux. www.neuron.yale.edu/	Myelinated fibers	AP propagation electronic + manual exam.	(i)
(J) JDS-Sweeney J.D. Sweeney	McNeal with rabbit peripheral nerve shifted to 37 °C, empirically adjusted for AP cond. Velocity 57 m s^{-1}	Not publically available in MATLAB & SIMULINK. Users could construct code based on publication. No user guide	PNS myelinated fibers. End organs not explicitly modeled	Applied field created point by point in MATLAB. Majority of model then in SIMULINK.	(j)