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A BIOLOGICALLY INSPIRED MYELINATED NEURON AXON MODEL USING A SYSTEM IDENTIFICATION APPROACH

BIOLOŠKI INSPIRISAN MODEL MIJELINIZIRIANOG NERVNOG AKSONA PRIMENOM SISTEMSKE IDENTIFIKACIJE

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Abstract
A method to modeling and simulating neural action potential (AP) propagation along the length of an axon containing a number of Ranvier nodes is proposed in this paper. A system identification approach is employed to determine a transfer function representation of the input-output relationship, based upon the classical Hodgkin-Huxley equations, for membrane voltage potential [1]. The identified transfer function model is applied to a site-of –stimulus introduction, of which cascading segments of internodal regions and nodal regions represent the remaining downstream axon. This cascading network is used to simulate "cable" properties and signal propagation along the length of the axon. This work proposes possible solutions to attenuation losses inherited in the classical myelinated cable models and accounts for neuronal AP velocity of propagation as well as introducing signal attenuation and transient delays associated with internodal demyelination.

INTRODUCTION

Mammalian neural demyelination has been linked to a variety of neurological disorders such as multiple sclerosis (MS) and Guillian Barre Syndrom. The formation of myelin is critical for the normal function of the mammalian nervous system. While effects of demyelination can lead to action potential (AP) attenuation and negative transient response along the length of the axon, current models utilizing the so-called cable models [2-4] have been unable to reproduce such phenomena. In fact, simulations of the current cable models have shown a failure to eliminate attenuation losses and as such, modeling AP propagation along the length of a myelinated axon model has proven difficult. A benefit to creating a more "biologically" relevant model could lead to a better understanding of demyelinating diseases by allowing one to study effects on AP magnitude and transient response due to losses in the number of myelin layers present within a particular internodal region.

Historical and more recent models have focused primarily on the modeling of the NR either by passive lumped circuit realizations describing ionic channel conductance or resistivity, as well as ionic potential gradients, or cascaded transmission line segments of the previously mentioned lumped circuit realization separated by axonal membrane and myelin sheath resistances [2,3,5,6]. In this study, it is desired to create a model capable of reproducing AP propagation, observable at each Node of Ranvier (NR), along the length of the axon. The axon will be modeled as a state dependent logical transmission line incorporating transfer function realizations for axonal membrane potential response to an externally applied current stimulus. This model incorporates a number of axon dimensional features which directly influence AP propagation velocity and radial leakage current phenomena. The radial leakage current can negatively influence the ability to generate an AP as a result of demyelination, as indicated in Figure 1. The proposed model is capable of estimating/representing maintained AP signal integrity for the case of healthy myelin sheaths, as well as introducing transient and attenuation effects for cases where demyelination has been introduced into the axonal myelinated internodal (IN) regions.

2 METHODS

2.1 System Identification

In an effort to reduce the mathematical complexity associated with the implementation of the original Hodgkin-Huxley equations for ionic channel dynamics of the axonal membrane, a system identification approach was taken to

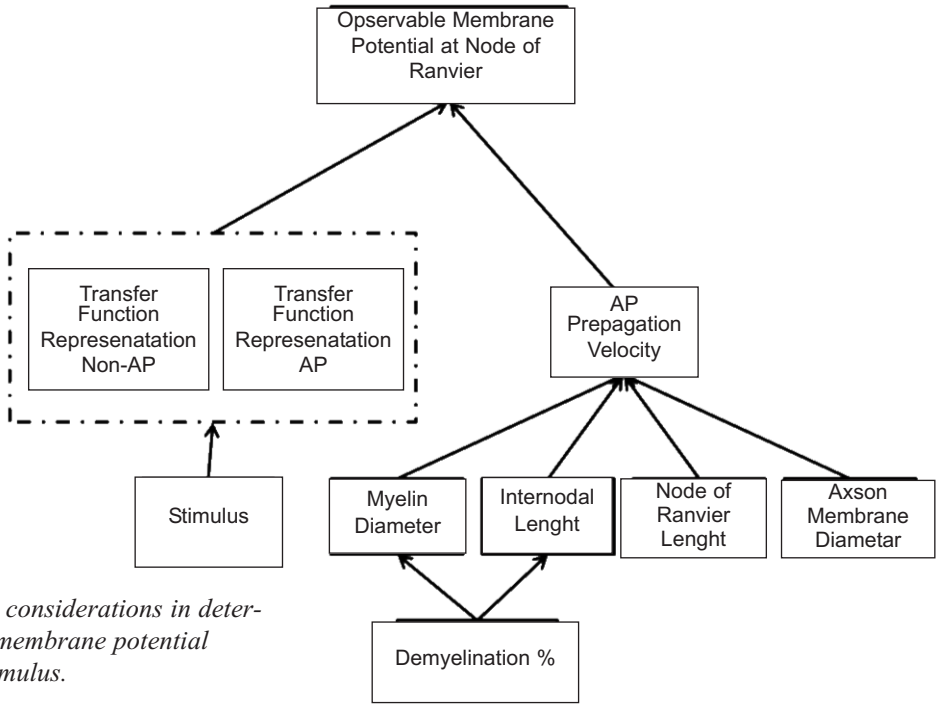

Figure 1: Model considerations in determination of NR membrane potential response to a stimulus.

represent membrane potential response to a known current pulse input. However, the nonlinearity of membrane response to a stimulus makes it difficult to represent the axon by one simple transfer function representation. It is argued that each NR can be expressed by one of the two states:

1) A sufficient stimulus is presented to the NR to generate an AP (termed Excited), or

2) An insufficient stimulus is presented to the NR failing to generate an AP (termed Non-Excited).

These state representations allow for a transfer function representation to be identified for each state. As such, a mathematical model of the system response to a known stimulus is made possible by observation of the system's input-output relationships in a process known as system identification [7].

Using the Hodgkin-Huxley equations as described in [5], axonal membrane potential response to a variety of stimulus was observed for the two states described earlier. The two states were then identified for a super-threshold stimulus of 55μA and an insufficient stimulus of 8μA current pulse of a 1ms lasting duration. Given the input-output relationships of these two states of the system, one can then attempt to identify a low-order process model representation of observable NR membrane potential for each individual state.

The process involved in application of system identification is typically associated with a minimization of fitting error to the known system response given a known input. If we assume a grey-box representation of our system, being the NR region under observation, one assumes that little to nothing is known of the underlying system parameters. Description of the system can be accomplished by application of a difference equation [7]:

$$\nu(t+1)-a_1\nu(t)-a_2\nu(t-1)-a_2\nu(t-2) + b_1u(t)=\theta^{\tau}\phi\,(t)$$

Equation 1

where, a_1, a_2, a_3 and b_1 are the unknown system parameters written in the form of a parameter vector,

$$\theta^{\tau}=[a_1, a_2, a_3, b_1]$$

Equation 2

with the observation vector being described as:

$$\phi\,(t)^T=[-\nu(t),\ -\nu(t-1),\ -\nu(t-2),\ u(t)]$$

Equation 3

The predictive model of the system can be described as:

$$\hat{\nu}(t+1)=\hat{\theta}\,(t+1)^{\tau}\ \phi\ (t)$$

Equation 4

The prediction error is defined as the difference between the known system output and that of the predictive model of our system:

$$r(t,\hat{\theta}) = \nu(t) - \hat{\nu}(t)$$

Equation 5

Implementation of an error minimization criteria on the parameter vector (Equation 2), often leads to a nonlinear least squares problem, of which a variety of approaches can be taken to minimize the prediction error given in Equation 5.

2.2 Gauss-Newton Method

Iterative solutions towards minimization of fitting errors inherit within the prediction model for our system is made possible by application of the Gauss-Newton method. This method has advantages in that it is possible to reduce the number of iterations of linear approximations of the calculated prediction error, given as Equation 5, thereby aiding in fast local convergence on mildly nonlinear and nearly consistent problems. The observation function, defined as the sum of squares of *m* nonlinear functions, $f(\hat{\theta})$, is provided as [8,9]:

$$f(\hat{\theta}) = \sum_{i=1}^{m}[r_1(\hat{\theta})]^2$$

Equation 6

where, $r_1(\hat{\theta}) = r(t\hat{\theta})$ is interpreted as the residuals of the m nonlinear equations.

With the axonal membrane potential response being represented by the original Hodgkin-Huxley equations as described within [5], and knowing the axonal membrane potential response to a provided stimulus an effort is now undertaken to represent the excited and non-excited states by curve-fitting. The system to be modeled is an over-determined system as the number of known data samples, *m*, exceeds the process order model of order, n. Solutions to the over-determined system of nonlinear equations is made possible by application of the Gauss-Newton method. For reasons of brevity, the reader is pointed to description and application of this method within the works of [9]. The application of this method point the membrane potential response to a stimulus being treated as a linear time invariant (LTI) system for both the excited and non-excited states and represented as a set of linear difference equations with constant coefficients of the form [10]:

$$\sum_{i=0}^{p} a_i y[t-i] = \sum_{i=0}^{q} b_i u[t-i] \qquad a_0 \neq 0$$

Equation 7

Application of the Laplace transformation to the differential equation representation of the LTI system is straightforward and the transfer function representation of the myelinated membrane potential can now be obtained.

2.3 Transfer Function Identification

The continuous-time transfer function representation of the system utilizes a static gain and characteristic time constants associated with system poles and zeros. For the purpose of this model, underdamped or complex poles are used. As previously mentioned, a low-order process model is used to represent the axonal membrane potential response to a stimulus. This transfer function is represented as a three-pole, one-zero, underdamped model as described by [11]:

$$H(S) = \frac{K(1 + T_z s)}{1 + (2\zeta T_w)s + (T_w s)^2(1 + T_{p3} s)}$$

Equation 8

where, K is a static gain, and ζ, T_z, T_w and T_{p3} are time related system constants.

As indicated in Figure 2, there are two transfer function representations generated. While the indication of model P3IZU indicates a better data fit with a minimization of residuals, this model represents the introduction of an integrator term within the denominator and results in a pole location at zero. This introduces instability to the system and as such its use is omitted in favor of the more stable model without the integrator term represented by P3ZU. A similar method is applied to the Non-Excited state of axonal membrane potential resulting in an additional transfer function representation of a three-pole, one-zero underdamped model.

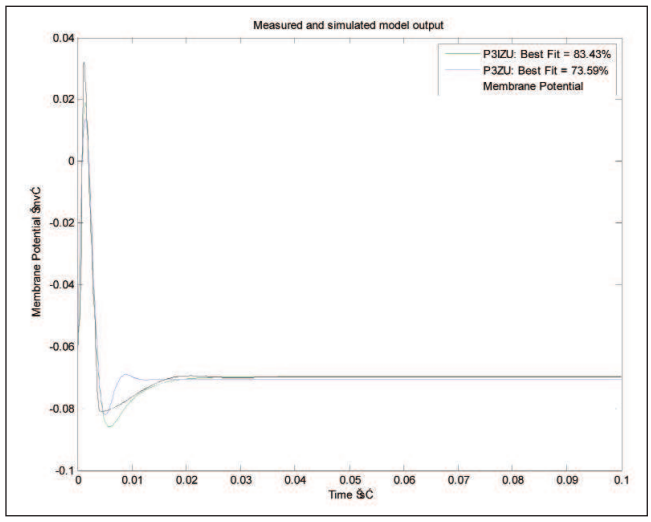

Figure 2: Transfer Function Model of Axonal Membrane Potential in Excited State

2.4 A*P Velocity of Propagation*

Using the dimensions of internodal length, nodal length and total fiber diameter, as outlined in [2] a cascaded model of IN and NR regions is created. This model is created within the Simulink environment and is conditioned by an external conditioning m-file using MATLAB. A high-level view of the cascaded network is provided in Figure 4. The velocity of AP propagation is also dependant on the presence or absence of myelin [12]. A relationship between myelin thickness and conduction velocity of the AP has been found to exist and as such, this relationship is incorporated within this model. The velocity of AP propagation has been experimentally expressed as [6]:

$$\nu_m = 4.5 * D_m$$

Equation 9

$$\nu_u = 1.1 \sqrt{D_u}$$

Equation 10

where, ν_m and ν_u are the propagation velocities of an AP along an axon in units of [m/s], and D_m and D_u are for a myelinated and non-myelinated axon diameter, respectively. The introduction of this relationship aids in simulation efforts to represent transient delay characteristics associated with demyelination.

3 DISCUSSION/RESULTS

The objective of this study is to create a myelinated neuron model that is capable of simulating AP propagation along the length of the axon where the membrane potential is observed at each NR. By incorporating biologically relevant features, the model should be able to represent AP propagation along the length of the axon in accordance with signal fidelity and transient response for a healthy, myelinated

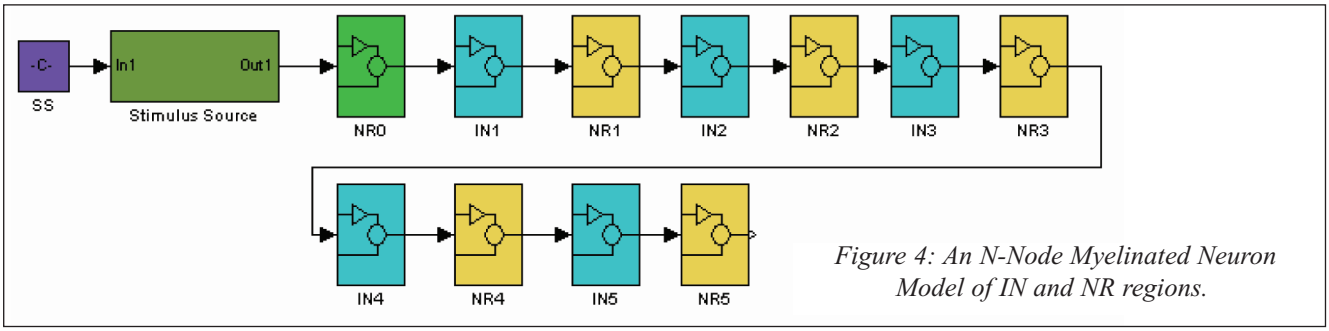

Figure 4: An N-Node Myelinated Neuron Model of IN and NR regions.

axon. Furthermore, this model incorporated attenuation and transient shifts of membrane potential in accordance with the introduction of demyelination at specific IN regions. As mentioned earlier, the NR response is dependent on a sufficient stimulus which elicits an AP or an insufficient stimulus. A transfer function representation of each state is identified and implemented based upon the axial current stimulus presented to the NR.

3.1 Three-Port Network Considerations

The determination of whether or not sufficient axial current is presented to each NR is handled by treating each IN region as a three-port network. Figure 3 illustrates a variety of scenarios in which axial current is affected by a particular degree of demyelination.

With the variety of wounding states that may be introduced into the model, as indicated in Figure 3, the axial current seen at the NR under observation must be capable of producing an AP in order to utilize the transfer function representation of the "Excited" state. The validity of this approach is similar to conduction studies shown in demyelinated fibers

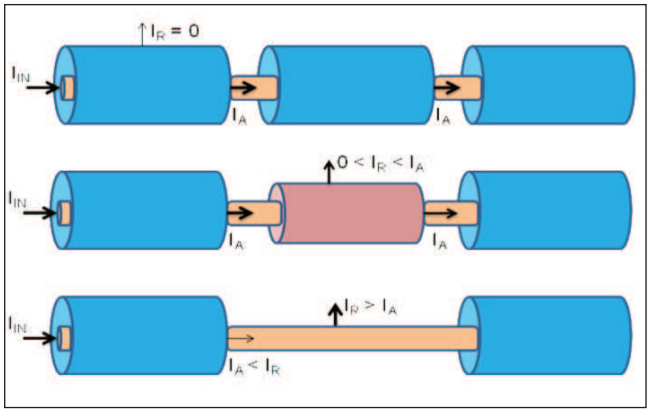

Figure 3: (Top) Healthy Internodes, (Middle) Wounded Internodal Region, (Bottom) Severely Wounded IN. Where I_{IN} is the input axial current seen at the IN, I_A is the axial current seen at the NR and I_R is the radial leakage current through the IN.

[13] as well as keeping in accordance with current flow in axonal conduction studies [12,14]. Furthermore, by treating each NR as exposed to a sufficient or insufficient stimulus, we can eliminate the need for complex differential equation representations at each NR region and rather focus on the overall effects of demyelination on eventually switching the state of a NR from what should be an excited state to a non-excited state. Additionally, interdependencies between previous IN regions not adjacent to the observed NR also play a role in available axial current flow to elicit an AP response [13].

It is theorized that demyelination introduction at any of the IN regions would result in increased AP propagation latencies at "downstream" NR where the AP would be observed. Naturally, the AP should not only appear time-delayed with respect to observable point of reference, which we assume to be the peak of the AP waveform, but transient affects should also be seen with changes in the slope of the AP waveform. The changes in AP waveform slope will undoubtedly be seen in signal generated as a result of a smaller axial current being seen at the affected NR with the transfer function representation serving as the mapping between the reduced stimulus and the expected membrane potential response to such a stimulus.

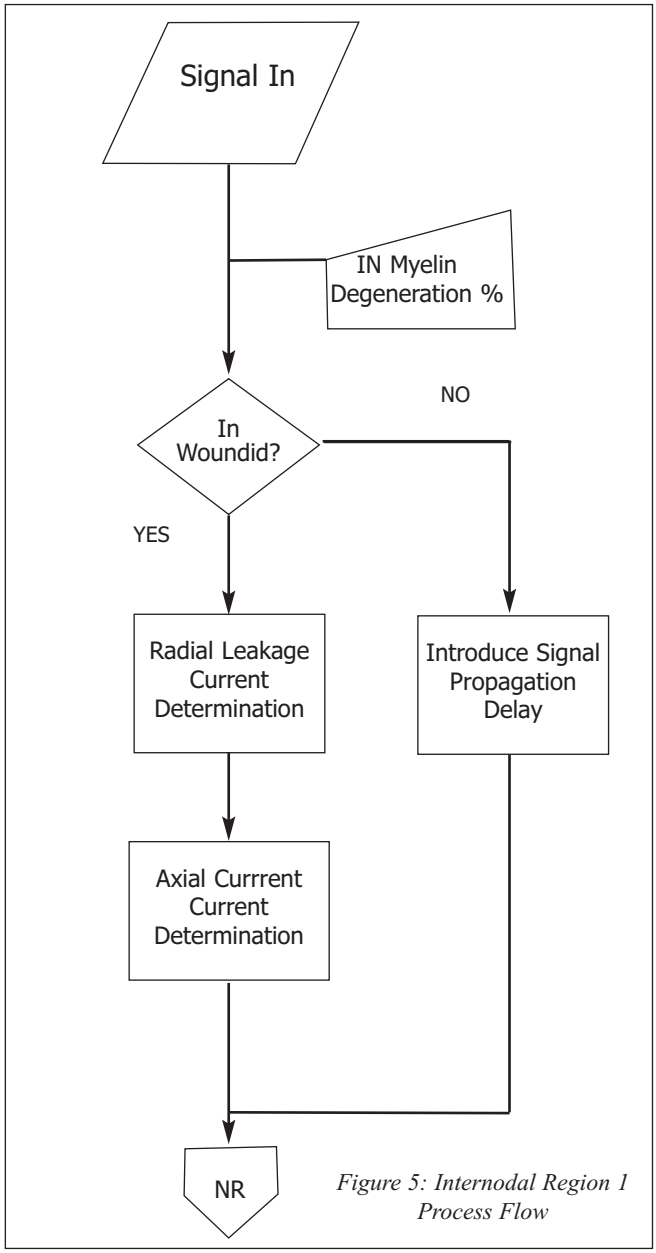

Figure 5: Internodal Region 1 Process Flow

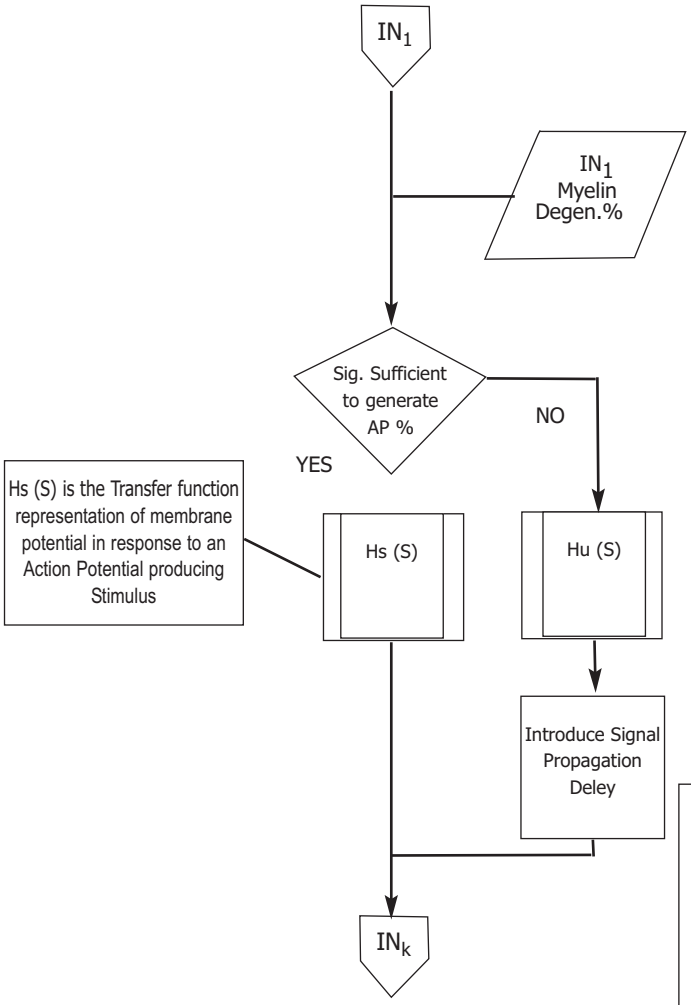

Figure 6: Node of Ranvier 1 Process Flow

3.2 Theory of Operation/Process Flow Assessment

Each IN and NR region undergoes a series of processes in order to propagate the AP along the axon, However, the process is relatively straight-forward in the sense that we introduce logic checks and switching statements, based on the severity of demyelination at the IN regions as well as the axial current seen at each NR. While the subsystem representation of the IN and NR regions are not depicted within this study, flowchart representations of the logic employed within these subsystems are provided as Figures 5 - 8.

Figure 5 represents IN_1, which is directly downstream to the stimulation site of NR_0. This is the first IN segment of the model and can be affected by demyelination. As such, the myelin sheath diameter can be reduced and a conditional check is necessary to introduce radial leakage current associated with the pathology of demyelination. It is assumed that any reduction in myelin diameter greater than 15% is sufficient to term the IN region as "wounded" and the calculation and introduction of leakage current is performed. Finally, the axial current is determined and simply routed to the adjacent-downstream NR_1. Alternatively, if IN_1 is not "wounded" the propagation delay time is calculated and radial leakage currents are considered negligible.

As indicated in Figure 6, axial current flow from IN_1 serves as the input stimulus to NR_1. The severity of demyelination at NR_1 creates a mechanism for switching NR_1's state from either "excited" to "non-excited". This allows for the proper state transfer function representation to be presented

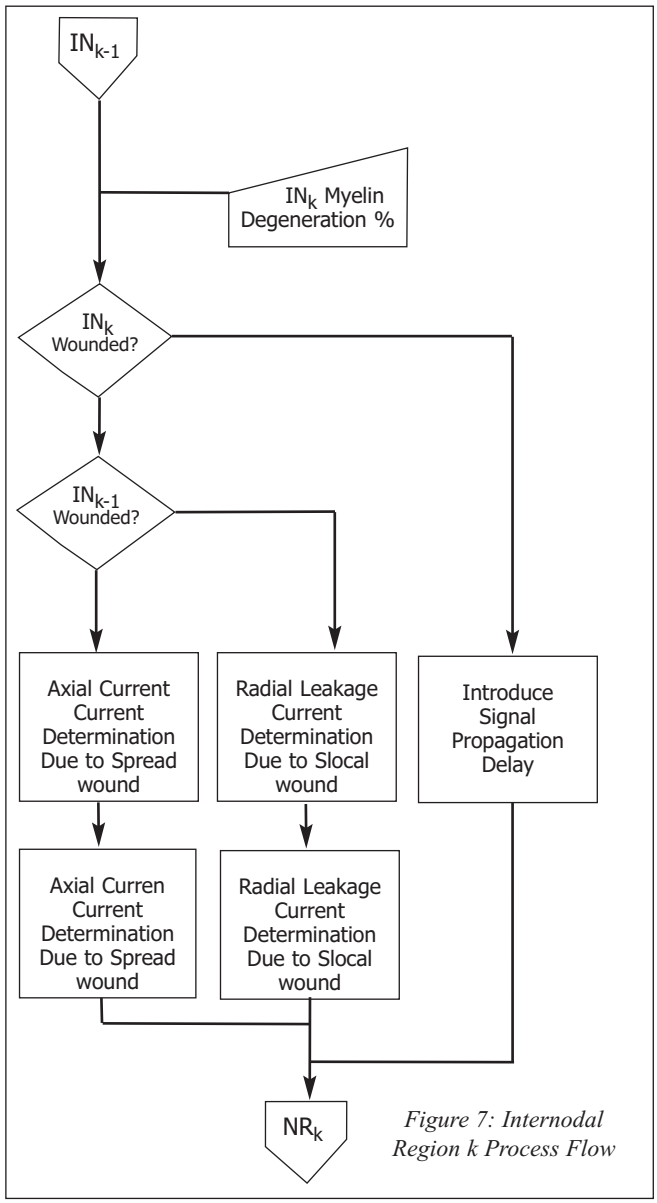

Figure 7: Internodal Region k Process Flow

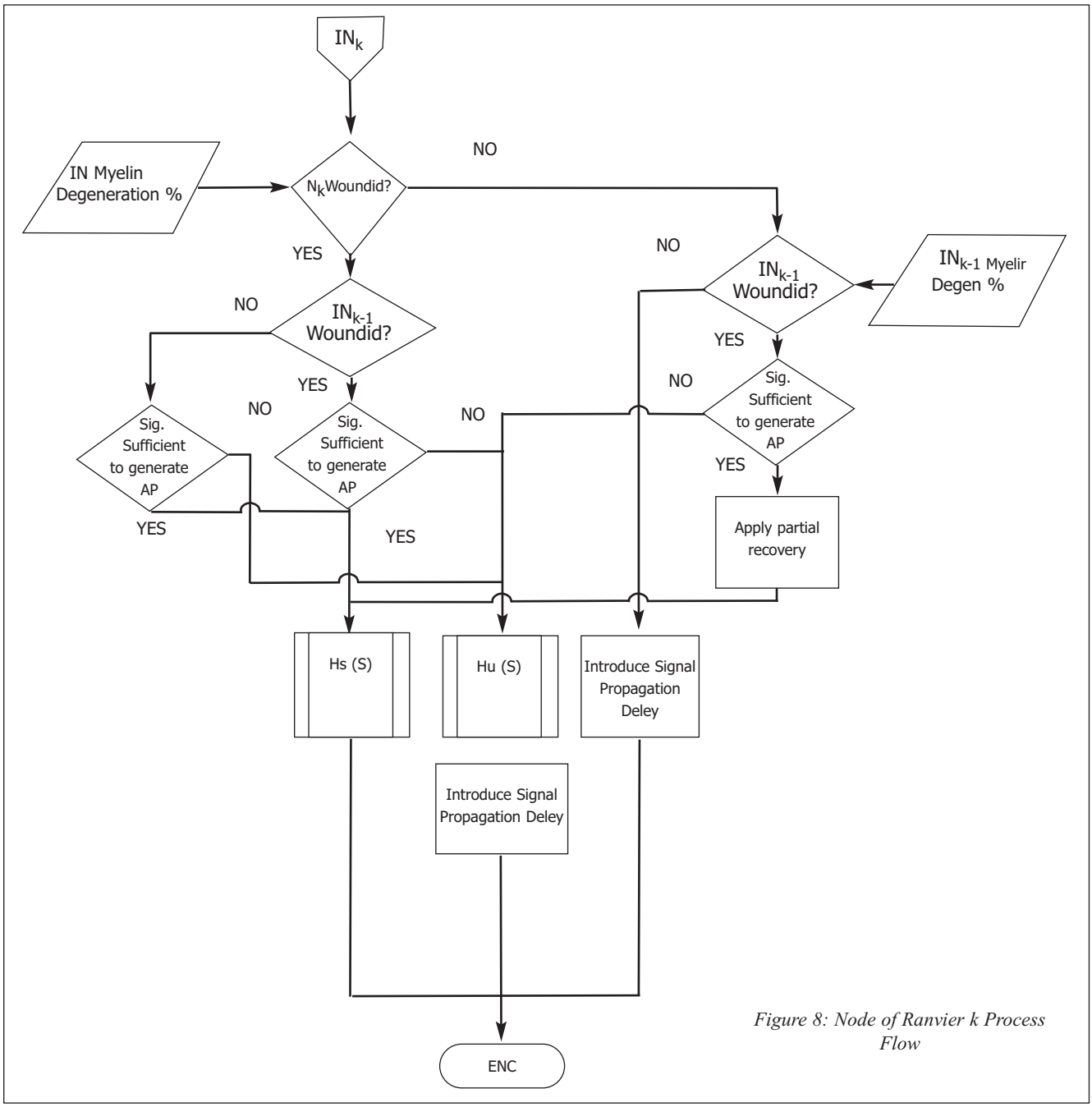

Figure 8: Node of Ranvier k Process Flow

with the axial current stimulus from IN_1. If a sufficient stimulus is presented to NR_1, then the transfer function representation for AP generation, $H_s(S)$, is utilized. Otherwise, the non-AP producing transfer function, $H_u(S)$, is used and the transient effects of signal propagation delay due to demyelination is introduced. Both $H_s(S)$ and $H_u(S)$ have the form given in Equation 8 with their appropriately calculated constants.

The complexity and decision process involved in IN_k and NR_k, illustrated in Figures 7 and 8, show the interdependencies not only on the severity of demyelination at their respective location, but also at a previous location k-1. Furthermore, an introduction of AP recovery is made possible in the case of intact myelin structure at a k^{th} internode so long as the AP has not been lost due to large radial current losses associated with severe demyelination. While this recovery mechanism is not well understood, it is proposed that a nonlinear amplifier may serve as a model of recovery within the NR.

3.3 Targeted Demyelination Pathologies

Implementation of the rule-sets as shown in Figures 5 – 8 within the Simulink environment have yielded favorable results to date. Currently, the overall model representation, as depicted in Figure 4, is capable of simulating AP propagation along the axon and is observed at subsequent NR regions in a unidirectional manner. There are three conditions that each NR region may respond to their predecessor IN regions: healthy, wounded, and severely wounded. Below are series of snap shots of variations of the three listed conditions as well as a brief description. Note that these generated outputs illustrate observable membrane potentials response to a super-threshold stimulus introduction at the site NR_0. AP propagation flows in ascending IN-NR order.

As indicated in Figure 9, the healthy condition is defined in the case where all IN regions have intact myelin structures resulting in no loss of myelin sheath diameter at each IN. In this condition, a sufficient stimulus is applied at NR_0 and an AP propagates without attenuation along the axon and is

observable at subsequent NR regions in accordance with the velocity of propagation as defined in Equation 9. Simulations indicate that for this axon, with axon properties as outlined in [2], the time delay between peaks in the AP waveform observed at each NR is 14.84 ± .01 μs. This indicates that the proposed model is capable of reproducing an AP at subsequent NR without the attenuation effects seen in the passive circuit models of the myelinated axon. Figure 10

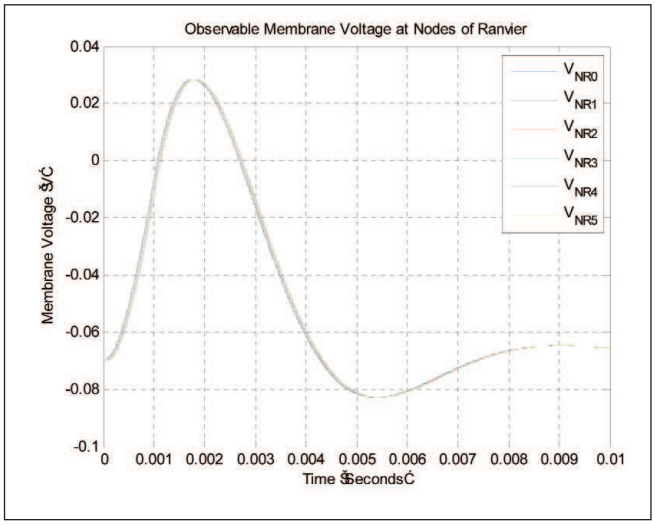

Figure 9: Healthy Condition - IN regions do not exhibit demyelination

provides a zoomed in view of the AP rising edge for the healthy axon condition.

The second condition of the axon is termed "wounded". This condition exists once an IN region has started to undergo a demyelination process. This model introduces demyelination as a pathology that decreases IN myelin sheath diameter and length. While the introduction of demyelination throughout the axon is possible in this model, Figure 11 illustrates a targeted demyelination of the fifth IN to reduce the myelin sheath diameter by 30%. To further define the "wounded" condition, it is assumed that the level of demyelination introduced is not of a severe nature as to result in high radial leakage current, thereby allowing for the AP propagation along the axon but introducing attenuation affects and transient delays associated with a decrease in AP propagation velocity.

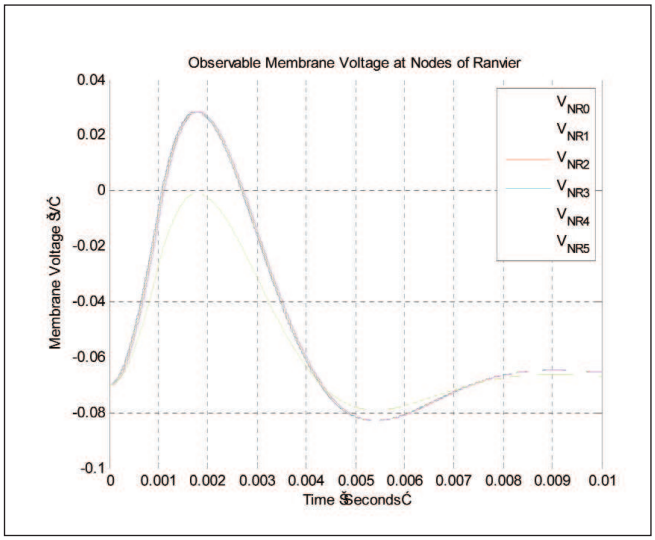

Figure 11: Wounded Condition IN_5 myelin diameter reduced by 30%

The third condition of the axon is termed, "severely wounded". This condition is defined as a severe demyelination event has occurred and the axial current flow through the affected IN is insufficient to elicit an AP at the subsequent NR. All remaining NR regions are affected and the axon is no longer capable of AP propagation past the severely wounded IN site. Results of severe demyelination introduced into the third IN are shown in Figure 12.

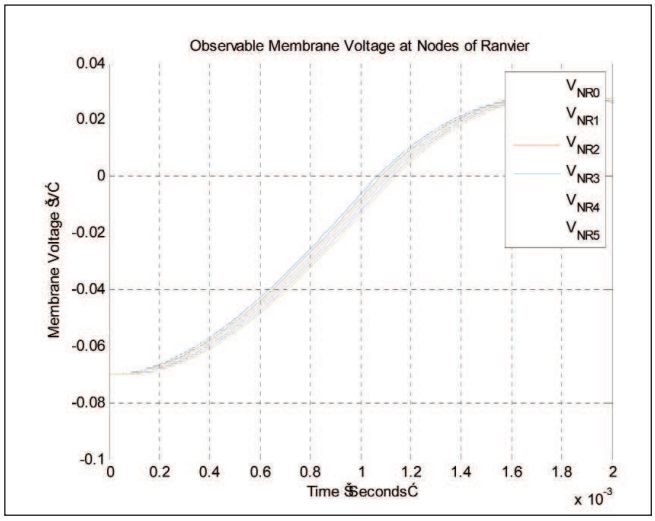

Figure 10: AP rising edge for healthy axon condition

4 CONCLUSION

As expected, the model is capable of simulating AP propagation for the three axonal conditions: healthy, wounded, and severely wounded. These conditions are triggered by the severity of the demyelination pathology affecting a particular IN. In this study, a targeted demyelination approach was taken verify the process maps as outlined in Figures 5 – 8. Furthermore, the proposed model is capable of simulating the interdependencies between a local wound, defined as a targeted IN is affected, provided as Figure 3; or a more spread wound, defined as a distributed demyelination along adjacent IN regions. However, the present model introduces a conditional recovery mechanism that is simply modeled as a state dependent linear amplifier to simulate some recovery

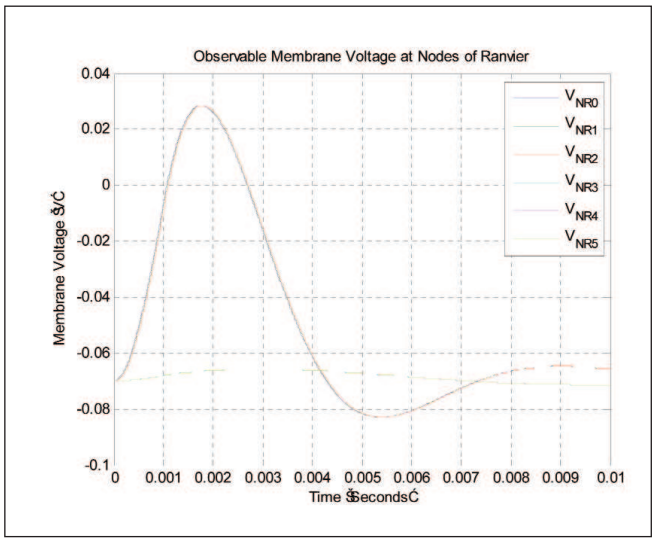

Figure 12: Severely Wounded Condition - IN_3 myelin diameter reduced past threshold

or rectification of the AP waveform, if the axon has not been negatively affected to the level of severely wounded condition. Further investigation into application of a non-linear amplifier representation of NR recovery properties is necessary at this time.

The utilization of a transfer function representation for membrane potential response to an introduced stimulus served as a mechanism to:

1) Simplify NR ion channel dynamics represented by the Hodgkin-Huxley equations, and

2) Provide a two state solution towards radial leakage currents associated with demyelination responsible for "switching" the subsequent NR responses from an "excited" to a "non-excited" state.

While the low-order process model provided a satisfactory estimate of the NR membrane potential response, efforts to increase process model system order to reduce fitting errors to the original Hodgkin-Huxley equations could increase accuracy of the transfer function estimate.

Finally, while the initial results show the capability of the model to simulate the three axon conditions of healthy, wounded and severely wounded, it is strongly desired to introduce a more progressive demyelination process. By introducing a slow demyelination process into the model, it may be possible to create a better mechanism towards understanding and predicting membrane potential signal integrity over the course of the specific demyalinating disease. Future work on this model will incorporate an iterative process towards simulation of this gradual and complex demyelination pathology by mimicking situations in MS and ALS.

Apstrakt

U ovom radu predložena je metoda za modelovanje i simuliranje propagacije akcionog potencijala (AP) neurona niz akson, koji sadrži određen broj Ranvierovih suženja. Primenjen je pristup sistemske identifikacije, da bi se odredio transfer funkcionalne reprezentacije na relaciji input-output, baziran na klasičnoj jednačini Hodgin-Hyxley-a, koja važi za membranski voltažni potencijal (1). Identifikovani model s transferskom funkcijom primenjen je za introdukciju (uvođenje) stimulusa u tački (regionu) iz koje vode kaskadni segmenti internodalnih i nodalnih regiona, predstavljeni ostatkom silaznog aksona. Ova kaskadna mreža iskorišćena je za simulaciju "kablovskih" osobina i propagacije signala niz sam akson. Rad predlaže moguća rešenja za atenuaciju gubitaka ugrađenih u klasičnim modelima mijelinizovanog kabla i doprinos je propagaciji brzine neuronskog AP kao i introdukciji signalne atenuacije i prolaznog zakašnjenja vezanog za internodalnu demijelinizaciju.

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