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A distributed-parameter model of the myelinated nerve fiber

Halter, John Alan, Ph.D.

Rice University, 1989

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RICE UNIVERSITY

**A Distributed - Parameter Model of the
Myelinated Nerve Fiber**

by

John Alan Halter

A THESIS SUBMITTED
IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE

Doctor of Philosophy

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A Distributed - Parameter Model of the Myelinated Nerve Fiber

John Alan Halter

Abstract

This thesis is concerned with the development of a new distributed - parameter model of the myelinated nerve fiber that includes an adequate representation of the anatomical complexity present at the node of Ranvier, considers the peri-axonal conductance pathway and includes active ionic channels in the axolemmal membrane beneath the myelin sheath. A detailed review of the current anatomical and electrophysiological literature was performed and tables containing the biophysical properties of the amphibian and mammalian myelinated nerve fibers were compiled. Recent dynamics for the mammalian sodium channel were adopted and a non-linear parameter estimation method was applied to fit the dynamics of a fast and a slow amphibian potassium channel. Membrane action potentials were computed from the new space-clamped nodal and internodal membrane models.

A multi-axial electrical equivalent circuit was developed with intra-axonal, peri-axonal and extra-axonal longitudinal conduction paths and independent transverse elements for the axolemmal membrane and the myelin sheath. Non-uniform spatial step sizes were used, enabling detailed representation of the nodal region while minimizing the number of segments necessary to represent the entire fiber. An implicit integration method was developed for the resulting multiple cross-coupled parabolic partial differential equations as represented in finite difference matrix form. The solution was implemented on a Sequent Systems S81 parallel processor, dividing the

solution for the component ionic currents and the matrix operations across an arbitrary number of processors.

The model allowed for detailed examination of component potentials and currents. Physiological conduction velocities of 20.2 m/s at 20°C for a 15 μ m diameter amphibian fiber and 57.6 m/s at 37°C for a 17.5 μ m diameter mammalian fiber were achieved. An increase in conduction velocity of 32.3% was seen for a nodal constriction of 80%, contrary to previous modeling efforts. The peri-axonal space in the paranodal region was shown to have a strong influence on conduction velocity. Restriction of the extracellular volume resulted in slower conduction velocities for radii less than 25 μ m. Paranodal ionic channels were activated during conduction and there was model evidence for the possible generation of slow (0.06 m/s) propagating action potentials beneath the myelin sheath.

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Contents

Abstract	ii
Acknowledgments	iv
List of Illustrations	x
List of Tables	xiv
1 Introduction	1
1.1 Review of Previous Models	2
1.2 Old and New Questions Unanswered: Structure vs. Function	6
1.2.1 Nodal microanatomy	6
1.2.2 Distributed ionic channels	8
1.3 Objectives	8
2 Development of the Model Structure	11
2.1 Introduction	11
2.2 Anatomy	11
2.3 Equivalent Electrical Network	13
2.3.1 Coaxial equivalent network	13
2.3.2 Triaxial equivalent network	17
2.4 Summary	19
3 Properties of the Model Elements	20
3.1 Introduction	20
3.2 Passive Electrical Properties	21
3.2.1 Nodal properties	22

3.2.2	Internodal properties	22
3.3	Ionic Channel Properties	27
3.3.1	Sodium channels	28
3.3.2	Potassium channels	38
3.4	Membrane Action Potentials	45
3.4.1	Nodal model	47
3.4.2	Internodal model	48
3.5	Summary	48
4	Numerical Solution of the Model	54
4.1	Introduction	54
4.2	Development of Implicit Form Equation System	55
4.2.1	Geometric variables	56
4.2.2	Electrical relations for passive network elements	58
4.2.3	Nodal segment	63
4.2.4	Paranodal and internodal segments	68
4.2.5	Boundary conditions	73
4.2.6	Matrix form of the equation system	73
4.2.7	Computational molecule	78
4.2.8	Scaling	80
4.2.9	Stability and error measures	80
4.3	Computational Methods	81
4.3.1	Parallel versus sequential computation	81
4.3.2	Structure of the algorithm	81
4.3.3	Description of software	85
4.3.4	Performance	86
4.3.5	Stability	87
4.4	Summary	88

5	Simulation Results	91
5.1	Introduction	91
5.2	Conduction Studies	91
5.2.1	Computational aspects	91
5.2.2	Amphibian	97
5.2.3	Mammal	104
5.2.4	Effect of select properties on conduction velocity	110
5.3	Space-Clamped Node of Ranvier	121
5.3.1	Amphibian	123
5.3.2	Mammal	128
5.4	Summary	132
6	Discussion and Future Extensions	134
6.1	Model Development	134
6.1.1	Anatomy	135
6.1.2	Biophysical properties	135
6.2	Solution Technique	136
6.3	Simulation Results	137
6.3.1	Conduction studies	137
6.3.2	Space-clamped node of Ranvier	142
6.4	Future Extensions	143
A	Estimation Technique for Rate Constant Coefficients	145
B	Solution Technique for Space Clamped Membrane	149
C	Convolution Method for the Reduced Model	153
D	Explicit Solution Method	158

D.1	Derivation of Nodal Segment Expressions	158
D.1.1	Intra-axonal	158
D.1.2	Peri-axonal	159
D.2	MYSA Segment	161
D.2.1	Intra-axonal	161
D.2.2	Peri-axonal	163
D.3	Solution of Simultaneous Equations	166
E	Solution Technique for the Triaxial Case	167
	Bibliography	170

Illustrations

2.1	Basic anatomical features of the myelinated nerve fiber.	12
2.2	Longitudinal-section detail of the nodal region for a large ($17\mu m$) diameter nerve fiber.	14
2.3	Illustration of the cross-section of the nerve fiber.	16
2.4	Coaxial electrical equivalent network for the nerve fiber.	17
2.5	Form of the triaxial electrical equivalent network for the nerve fiber. .	18
3.1	Axolemmal membrane model.	21
3.2	Instantaneous rectification of the mammalian sodium channel.	32
3.3	Change in the amphibian and mammalian Na^+ rate constants as functions of transmembrane potential.	35
3.4	Change in the mammalian Na^+ activation and inactivation time constants with temperature.	36
3.5	Steady-state activation and time constants of the fast and slow gated potassium channels.	44
3.6	Model generated membrane action potentials and component currents for the amphibian and mammalian idealized node of Ranvier.	50
3.7	Model generated membrane action potentials and component currents in the amphibian and mammalian internode.	51
4.1	Volumes formed by the intra, peri and extra-axonal spaces for a single longitudinal segment.	57

4.2	Axolemmal membrane, the surrounding myelin sheath and the outer boundary membrane, represented by concentric thin cylindrical shells.	58
4.3	Component currents and potentials for a given longitudinal segment.	59
4.4	Equivalent network for the nodal region before consolidation of longitudinal resistances.	62
4.5	Equivalent network for the nodal region after consolidation of longitudinal resistances.	63
4.6	Equivalent network for the nodal, MYSA and FLUT segments.	69
4.7	Sealed end termination for the model.	74
4.8	Computational molecule for the equation system.	79
5.1	Segmentation of the nerve fiber for conduction studies.	93
5.2	Transfiber temporal action potentials at successive nodes of Ranvier for the amphibian fiber.	98
5.3	Transfiber spatial action potentials at successive points in time for the amphibian fiber.	99
5.4	Transfiber, transaxonal and transmyelin spatial action potentials for the amphibian fiber.	100
5.5	Transfiber, transaxonal and transmyelin temporal action potentials for the amphibian fiber.	101
5.6	Spatial distribution of the total transaxonal and component currents for the amphibian fiber.	102
5.7	Temporal plot of the transaxonal currents at the node, adjacent to the node and in the center of the internode for the amphibian fiber. .	103
5.8	Spatial distribution of the transmyelin currents for the amphibian fiber.	105
5.9	Temporal plot of the transmyelin currents at the node and internode for the amphibian fiber.	106
5.10	Spatial distribution of the longitudinal currents for the amphibian fiber.	107

5.11 Temporal plot of the longitudinal currents adjacent to the node of Ranvier and in the internode for the amphibian fiber.	108
5.12 Transfiber temporal action potentials at successive nodes of Ranvier for the mammalian fiber.	109
5.13 Transfiber spatial action potentials at successive points in time for the mammalian fiber.	110
5.14 Transfiber, transaxonal and transmyelin spatial action potentials for the mammalian fiber.	111
5.15 Transfiber, transaxonal and transmyelin temporal action potentials for the mammalian fiber.	112
5.16 Spatial distribution of the transaxonal currents for the mammalian fiber.	113
5.17 Temporal plot of the transaxonal currents at the node, adjacent to the node and in the center of the internode for the mammalian fiber.	114
5.18 Spatial distribution of the transmyelin currents for the mammalian fiber.	115
5.19 Temporal plot of the transmyelin currents at the node and internode for the mammalian fiber.	116
5.20 Spatial distribution of the longitudinal currents for the mammalian fiber.	117
5.21 Temporal character of the longitudinal currents for the mammalian fiber.	118
5.22 Conduction velocity versus the width of the peri-axonal space.	120
5.23 Conduction velocity versus the radius of the MYSA region.	121
5.24 Conduction velocity versus the radius of the extracellular volume. . .	122
5.25 Conduction velocity versus temperature.	123
5.26 Spatio-temporal perspective plot of the transaxonal potential for the space-clamped amphibian node of Ranvier.	124

5.27	Spatial distribution of the transaxonal potential, Na^+ , K_f^+ and K_s^+ currents with increasing width of the peri-axonal space.	125
5.28	Change in peak nodal action potential, Na^+ , K_f^+ and K_s^+ current amplitudes with peri-axonal space thickness.	127
5.29	Change in longitudinal peri-axonal currents as the width of the peri-axonal space is increased.	128
5.30	Spatio-temporal perspective plot of the transaxonal potential in an amphibian fiber with a $20nm$ thick peri-axonal space.	129
5.31	Spatio-temporal perspective plot of the transaxonal potential in a mammalian space-clamped fiber.	130
5.32	Spatio-temporal perspective plot of the transaxonal potential in a mammalian space-clamped fiber with a $4nm$ thick peri-axonal space.	131
C.1	Reduced model with a passive axolemmal membrane in the internode and no peri-axonal conductance pathway.	154
E.1	Equivalent network for the reduced model.	168

Tables

2.1	Morphometric Data	15
3.1	Passive Electrical Properties of Node	23
3.2	Nodal Gap Conductances	24
3.3	Axoplasmic Resistivities	24
3.4	Passive Properties of Internodal Axolemma	26
3.5	Passive Properties of Myelin Sheath	28
3.6	Sodium Permeability at the Node	30
3.7	Na^+ Rate Constant Coefficients	34
3.8	Q_{10} Temperature Coefficients	34
3.9	Sodium Permeability in the Internode	37
3.10	Potassium Permeability at the Node for the Amphibian	40
3.11	Potassium Permeability at the Node for the Mammal	41
3.12	K^+ Rate Constant Coefficients	45
3.13	Potassium Permeability in the Internode	46
3.14	Model Parameters for Node	49
3.15	Model Parameters for Internode	49
4.1	Geometric Variables	60
5.1	Model Parameters - Geometric	95
5.2	Model Parameters - Biophysical	96

Chapter 1

Introduction

The purpose of a mathematical model is to provide a tool for exploration of the normal and abnormal function of an existing or proposed system. In the case of the myelinated nerve fiber, at this point in time the motivation for modeling has been to facilitate basic understanding of the structure and function of these existing nerve fibers as well as to support efforts to understand the abnormal function of these nerve fibers when suffering from disease or injury. The latter application is fueled by hope that new forms of medical intervention can be guided more rapidly toward aiding the impaired nervous system. Perhaps in the future these mathematical models may guide the design of new neural systems but at present there are many functional and structural questions regarding the natural myelinated nerve fiber that remain unanswered.

The development of new models is driven both by the inadequacies of former models to address known properties as well as the discovery of new properties which the previous models cannot represent. In order to provide perspective for the motivation behind this development of a new model of the myelinated nerve fiber, previous mathematical models of the myelinated nerve fiber will be reviewed, old questions left unanswered by previous models will be presented and new questions stemming from new experimental findings will be proposed. The specific objectives of this thesis in developing a new distributed - parameter model of the myelinated nerve fiber will then be outlined.

1.1 Review of Previous Models

A mathematical model of the myelinated nerve fiber allowing for simulation of conduction using a Hodgkin - Huxley (HH) [63] characterization of the active neural membrane was first developed by Fitzhugh in 1962 [42] in order to better understand the phenomenon of excitation and generation of the propagating action potential in nerve fibers. The initial motivation for the effort came from interest in modeling the behavior of an unmyelinated fiber as described by the Hodgkin - Huxley parabolic partial differential equation [63]. However, the computational expense was considered too great, therefore Fitzhugh undertook to model the myelinated nerve fiber since it could be approximated by evenly spaced point sources of active membrane current separated by passive connecting segments which required less computational expense. The extrapolation of the HH model of the squid axon to the amphibian was necessary, since a quantitative description of the nodal membrane had yet to be published. The model took the form of a leaky coaxial cable punctuated by active nodal membrane. This is presented schematically in Section 2.3.1. The results of Fitzhugh's simulations were generation of conduction behavior similar to that seen in experimental studies on frog and toad as well as demonstration of stimulus strength - latency curves. Subsequently, Cooley and Dodge in 1966 [31] generated a computer model of the unmyelinated nerve fiber using the HH equations.

The structure established by Fitzhugh for the model of the myelinated nerve fiber remained essentially unchanged in works that followed. Goldman and Albus in 1968 [50] took the same structure established by Fitzhugh and inserted the nodal dynamics of *Xenopus laevis* as determined by Frankenhaeuser and Huxley in 1964 [46]. They explored the impact of the geometric parameters of internodal length, axon diameter and myelin sheath thickness on the conduction velocity and found that the results met with the predictions of Rushton [94] regarding the ratios of these parameters necessary to reproduce experimental fiber diameter - conduction velocity relations. This was followed by the work of Hutchinson, et al. in 1970 [66] who used the same

model developed by Goldman and Albus to explore the influence of fiber diameter on conduction velocity with the addition of examining the change in conduction velocity as a function of temperature. In the same year, Smith and Koles [111] also used the Goldman - Albus (GA) model to study the effect of myelin thickness on conduction velocity. They also confirmed the predictions of Rushton and got a basic indication of the slowing in conduction velocity that results from a very thin myelin sheath as an approximation to the demyelinated condition. Also in this time period, Dun [41] presented an analytic work using transmission line theory which indicated that the length and diameter present in the constricted nodal and paranodal region is a function of the fiber diameter. His reasoning was that the constriction may provide impedance matching and help prevent unwanted reflections of propagating action potentials.

The first detailed application of this type of model to the study of abnormal myelinated nerve fibers was performed by Koles and Rasminsky in 1972 [72]. They also used the GA model and simulated para and internodal demyelination. They found that conduction can still occur in cases of demyelination as long as an even layer of $1/3$ of the myelin sheath thickness remains uniformly across the internode, $2/9$ of the internode has at least one layer of myelin or $1/9$ of the internode has no myelin. They also showed production of conduction block in the demyelinated fibers at lower temperatures than in the normal fibers. They point out that their model does not distinguish between the myelin and the axolemmal membrane beneath and assume that they are similar in character. They also point out that their model does not account for any specialization of the nodal and paranodal structure and that their model assumes a constant axonal radius. In addition, they state that their model assumes that the internodal membrane is not electrically excitable.

Hardy in 1973 [54] undertook to examine the effects of temperature and extracellular Na^+ concentration on the conduction velocity in the myelinated nerve fiber. He followed the structure of Fitzhugh and employed the equations produced by Dodge

[35] to describe the nodal properties of the frog *Rana pipiens*. He found that the conduction velocity obtained with the fiber properties as taken from the experimental data derived from voltage clamp studies did not produce normal conduction velocities and therefore modified the Na^+ permeability, axoplasmic resistivity, myelin sheath conductance and capacitance and the nodal leakage conductance to achieve a faster conduction velocity. He found an exponential relation between conduction velocity and temperature as had been shown experimentally, at variance with a previous modeling study [66] which showed a linear relation.

Schauf and Davis in 1974 [98], interested in the study of impulse conduction in multiple sclerosis (MS), adopted the GA model with modifications by Koles and Rasminsky to simulate demyelination. The major variation on previous work was the examination of change in conduction as a function of extracellular Ca^{++} concentration and pH. This was accomplished by shifting of the voltage-dependent rate constants as described by Hille [59]. Decreasing the Ca^{++} concentration or reducing the pH resulted in an improvement in conduction velocity and restoration of conduction in blocked fibers.

Also adopting the form of Fitzhugh was the work of Brill, et al. in 1977 [15] which used a description of the node employing the HH equations with modification of the peak conductivities to match those determined by Dodge [34]. A significant feature of their work was the adoption of an implicit technique, Crank-Nicolson [32], for numerical integration of the parabolic partial differential equation as contrasted with the explicit techniques used in the former studies. This resulted in greater numerical stability and made it possible to use larger temporal step sizes in the computation of the solution. A companion paper was later produced by Waxman and Brill in 1978 [117] in which the possible role of short internodes as an aid in conduction through a demyelinated section of the nerve fiber was explored. The model was the same as in the previous publication. A study of the sensitivity of conduction to the various nodal and internodal properties was produced by Moore,

et al. in 1978 also [79]. In this work, a variant on the previous model was used, incorporating a new description based on scaled HH conductances as provided by Dodge through personal communication. The conclusion of their effort was that the conduction velocity was relatively insensitive to nodal properties, most sensitive to internodal myelin capacitance and axoplasmic conductance. They also claimed that the conduction velocity was insensitive to nodal constriction, showing evidence of only a 3.8% change with a reduction to $1/2$ the normal nodal area. Other works that followed have examined the effects of repetitive stimulation and impulse entrainment such as Wood, et al. in 1982 [119], but use the same model as presented in the work of Waxman in 1978 [117]. Also using the same basic model is the work of Waxman and Wood in 1984 on conduction in demyelinated fibers. A significant variation was the inclusion of active membrane in the demyelinated segment, showing the possible contribution to conduction in these regions.

A theoretical treatment of a segmented cable consisting of non-uniform spatial step sizes representing the nodal and internodal regions was produced by Andrietti and Bernardini in 1984 [1]. However, the work did not include any simulation of conduction, it was an analytic approach to the passive cable properties of various fibers, one of which was a myelinated nerve fiber. The method also presented the most error in representation of the myelinated nerve fiber as compared to other types of fibers. Another theoretical approach to modeling the behavior of the myelinated nerve fiber was that of Grindrod and Sleeman in 1985 [52]. Instead of the HH type of nodal description, Fitzhugh - Nagumo dynamics were employed which are simpler than the HH expressions and therefore amenable to an analytic treatment. To date, no other mathematical model simulating conduction behavior in the myelinated nerve fiber was located in the literature other than the work of Blight in 1985 [12] in modeling the experimental conditions of his studies into the mechanism of the depolarizing afterpotential.

Blight produced a significant variation on the previous models in that he included a separate description of the myelin and the underlying axolemmal membrane. In one internode he incorporated a peri-axonal conductance pathway to address its possible influence on the experimental data and in adjacent internodes he did not include a peri-axonal pathway and lumped the entire internode into one element. He did not allow for continuity of the peri-axonal space into the nodal region. A mammalian model was approximated by using the amphibian Frankenhaeuser - Huxley nodal description with a much reduced K^+ conductance. He used an explicit form solution versus an implicit form, claiming that the implicit form assumes that the myelin sheath and internodal membrane is collapsed together. The model could generate propagating action potentials. He was able to produce the depolarizing afterpotential which could not be generated by previous models and proposed that the myelin sheath is more conductive, the nodal membrane is less conductive than previously thought and the internodal axolemmal membrane is highly resistive.

1.2 Old and New Questions Unanswered: Structure vs. Function

1.2.1 Nodal microanatomy

The presence of a constriction in the nodal region has been noted since the time of the initial observations of the node of Ranvier by Ranvier [89]. After the development of electron microscopic methods, the fine detail of the node and paranode could begin to be examined. The work of Berthold [7, 8, 9] has been some of the most thorough in investigation of the anatomical character of the node of Ranvier. An impression of the detail can be gained from the information presented in Section 2.2. Regarding the possible functional implications of these anatomical features, Berthold comments, ‘...not only the nodal axon segment but the whole constricted axon segment together with its Schwann cell surroundings should be taken into consideration

when discussing the correlation between neurophysiological properties and structural organization of the node of Ranvier.' and '...detailed knowledge of nodal anatomy is a necessary element for the full understanding of the phenomena on which the fast propagation of information in all higher vertebrates depends.' [8]. The nodal constriction is also commented on in the initial work by Huxley and Stämpfli [67] on saltatory conduction in which they acknowledge its presence but assume that it does not present a significant contribution to the internal longitudinal resistance. No model has been developed that allows for representation of the fine architecture of the nodal region.

Regarding the surface area of the node, Berthold also makes reference to the area changing with fiber size from $4 \mu m^2$ in small to about $30 \mu m^2$ in large fibers. He also mentions that the nodal area in a ventral root fiber is about 25% larger than the area in a dorsal root fiber of comparable size, indicating a possible relationship to the differences between sensory and motor nerve fibers. No model has included an anatomical representation of the node of Ranvier allowing for examination of the current present across the node, independent of adjacent paranodal and internodal segments. Berthold also examines the nature of the nodal gap, which presents a significant constriction in the space between the nodal surface and the extracellular space. A model has yet to be developed that allows for inclusion of the nodal gap.

The presence of and dimension estimates for a space between the axolemmal membrane surface and the myelin sheath, referred to as the peri-axonal space, is also presented by Berthold. This space has been shown to be permeable to tracer elements such as lanthanum [74] and has been implicated in studies on the phenomenon of the depolarizing afterpotential [3]. No model has been developed that allows for inclusion of this space in continuity with the node of Ranvier.

1.2.2 Distributed ionic channels

K^+ channels have been shown to be present beneath the myelin sheath in the paranodal and internodal regions both in the amphibian [26, 97, 104] and mammalian [14, 18, 19, 23, 25, 103] myelinated nerve fibers. The work of Blight [12] did include a study of K^+ channels in the nodal and internodal axolemmal membrane, but no model has represented the paranodal channels without having first to remove the myelin which covers them.

Multiple types of K^+ channels have been identified [38, 39, 68, 73], some with slow gating characteristics and others with fast gating characteristics of two activation ranges [38]. The differential spatial distribution of the fast versus slow types of K^+ channels has also been documented experimentally in amphibian [53, 97] and mammal [2, 51, 102]. Models have yet to incorporate these different types of K^+ channels as well as their spatial distribution with the node, paranode and internode.

Na^+ channels have also been identified in the internodes of both the amphibian [104, 106] and the mammal [13, 77] and have been shown to contribute to action potential propagation in cases of demyelination [13, 106]. The possible role of these channels in demyelination has been examined in one study [118] but no model has allowed inclusion beneath the myelin sheath.

1.3 Objectives

The objectives of this thesis are as follows,

1. Development of a distributed - parameter model with the following properties.
 - Independent representation of the myelin sheath and the underlying axolemmal membrane.
 - Inclusion of intra-axonal, peri-axonal and extra-axonal spaces with independent dimensions and resistivities.
 - Inclusion of detailed description of the nodal region incorporating the anatomical detail as defined by Berthold [8].

- Inclusion of a description for the nodal gap.
 - Inclusion of Na^+ and K^+ channels in the node, paranode and internode with independent permeabilities.
 - Representation of both fast and slow gated K^+ channels.
 - Representation of both amphibian and mammalian myelinated nerve fibers.
 - Ability to taper fiber properties from one region to another.
 - Ability to extend the model to an arbitrary length.
2. Examination of the following behavior in both the amphibian and mammalian myelinated nerve fibers.
- Conduction of propagating action potentials.
 - (a) Influence of the peri-axonal space.
 - (b) Influence of the nodal - paranodal constriction.
 - (c) Influence of the extracellular properties.
 - (d) Influence of temperature.
 - Space - clamped conditions
 - (a) Influence of the peri-axonal space.
 - (b) Influence of the paranodal ionic channels.

This thesis addresses these objectives by first examining in Chapter 2 the anatomical literature to obtain quantitative information regarding the microanatomy of the nodal, paranodal and internodal regions followed with development of a model structure to represent these anatomical features. In Chapter 3, the passive electrical and active ionic properties of the component membranes are gathered from the current literature and combined to form representative membrane models for inclusion into the larger distributed - parameter model. Chapter 4 presents the development of the mathematical description of the distributed - parameter model with the numerical solution method and computational techniques utilized to form the numerical solution. Chapter 5 contains the results of the application of the model simulation to the study of conduction and a space - clamped node of Ranvier. The thesis then closes with discussion and proposals for future extensions in Chapter 6.

The following chapter continues with a description of the anatomical properties of the myelinated nerve fiber and the structure of the distributed - parameter model chosen to represent that anatomy.

Chapter 2

Development of the Model Structure

2.1 Introduction

In order to develop a representative model of the myelinated nerve fiber that is based on the current understanding of the morphology and electrophysiological behavior of the myelinated nerve fiber, this chapter will present a detailed review of recent morphological studies and formulate a discrete electrical equivalent model of the myelinated nerve fiber. The morphological review is guided by relatively recent examination of the microanatomy of neural tissue, such as with freeze-fracture methods [9, 70, 95, 96], revealing new quantitative data on the structure of the myelinated nerve fiber. This anatomical information will then be utilized in the formation of the model structure.

2.2 Anatomy

The basic anatomy of the myelinated nerve fiber is illustrated schematically in Fig. 2.1. As first described by Ranvier [89], the nodes of Ranvier can be seen as periodic constrictions in the nerve fiber. Adjacent to the nodal membrane is the paranodal region which is subdivided into the myelin sheath attachment segment (MYSA) and a crenated or fluted section (FLUT) in which the surface area of the axon is greater but with a relatively small cross sectional area (as detailed in Figs. 2.2 and 2.3). The majority of the internode is approximately cylindrical and is referred to as the stereotyped internodal region (STIN). The spacing between the nodes of Ranvier, as well as the thickness of the myelin sheath, vary with the diameter of the nerve

Figure 2.1: Basic anatomical features of the myelinated nerve fiber. The nerve fiber consists of long myelinated internodal sections, transitioning through paranodal regions to the nodes of Ranvier. The radial components consist of an axon core contained by the axolemmal membrane, the peri-axonal space between the axolemmal membrane and the myelin sheath (greatly exaggerated in this schematic diagram) and the myelin sheath which terminates at each node of Ranvier. This illustration is not to scale.

fiber; mammalian myelinated nerve fibers are typically of smaller diameter than those found in the amphibian [7, 48, 109]. Between the myelin sheath and the underlying internodal axolemmal membrane is the peri-axonal space. Under normal conditions, the width of this space has been reported to be on the order of 2 to 4 *nm* [8] although others have reported 10 to 20 *nm* [60]. In some abnormal cases, however this space can increase dramatically in size [11, 61]. The peri-axonal space is widest in the internodal region but it also extends to the node, thereby providing access to the perinodal region which lies just outside the surface of the nodal axolemmal membrane [60, 74].

Electron microscopy combined with the freeze-fracture technique has provided much detail on the morphology of the paranodal and nodal regions [9, 70, 95, 96]. Figure 2.2 provides a more detailed view of the node of Ranvier for a large fiber as seen in longitudinal cross-section. The most striking features are the pronounced constriction of the axon at the node and the presence of a constricted nodal gap region just outside of the nodal surface. Over the range of fiber diameters, the nodal width

stays relatively constant (1 to 1.5 μm) however other dimensions undergo significant changes [88, 96]. As fiber diameter increases, this nodal - paranodal structural complexity first develops in the 4 – 6 μm diameter fibers [9].

Figure 2.3 illustrates the cross-sectional profile for the nerve fiber at the internodal (STIN), paranodal (FLUT) and nodal regions. In the internodal portion the fiber is approximately cylindrical in shape, however as the node is approached the fiber develops a fluted shape, effectively reducing the cross-sectional area of the axon while increasing the surface area. When the node is reached, the shape suddenly returns to a cylindrical form. Outside of the nodal surface and filling the nodal gap are tightly packed Schwann cell microvilli whose function has yet to be determined. A summary of these characteristics and their respective dimensions for a typical large diameter fiber can be found in Table 2.1.

With this detailed description of the anatomy of the myelinated nerve fiber now presented, the task is to transfer form to function by accounting for the active and passive properties of these anatomical segments of the myelinated nerve fiber, develop a model equivalent structure to place them in and develop a mathematical method to explore their interactions.

2.3 Equivalent Electrical Network

In order to simulate the active processes in the myelinated nerve fiber, a discrete electrical equivalent network is formulated in this section to represent the myelinated nerve fiber.

2.3.1 Coaxial equivalent network

Previous models of the myelinated nerve fiber took the form shown in Fig. 2.4 [42, 50, 79]. These models are based on the assumption that the nerve fiber can be represented as an equivalent cylinder of constant radius by collapsing the myelin sheath into the underlying axolemmal membrane. No significant radial variation in

Figure 2.2: Longitudinal-section detail of the nodal region for a large ($17\mu m$) diameter nerve fiber. The longitudinal divisions are the STIN (STereotyped INternodal) region, FLUT (FLUTed) region, MYSA (MYelin Sheath Attachment) region and the CON (CONstricted) region as described by Berthold and Rydmark [8]. In the constricted region, the axon cross-sectional area reduces to about 20% of the STIN diameter. The nodal gap is about $0.25\mu m$ at its narrowest point. With the exception of the length of the FLUTed region and the thickness of the peri-axonal space, the illustration is approximately to scale.

Table 2.1: Morphometric Data

NODE Segment		
Segment length	1	μm
Axon diameter	5	μm
Axon cross section area	20	μm^2
Axon membrane surface area	24	μm^2
Nodal gap width (mean)	0.27	μm
MYSA Segment		
Segment length	4	μm
Axon diameter	4.8	μm
Axon cross section area	17.7	μm^2
Axon membrane surface area	60	μm^2
Peri-axonal space cross section area	0.06*	μm^2
Peri-axonal space thickness	0.004	μm
Mean myelin sheath surface area	101	μm^2
FLUT Segment		
Segment length	75	μm
Axon diameter (effective axial)	11.4	μm
Axon diameter (effective radial)	24.5	μm
Axon mean cross section area	102	μm^2
Axon membrane surface area	3680	μm^2
Peri-axonal space cross section area	0.2	μm^2
Peri-axonal space thickness	0.003	μm
Mean myelin sheath surface area	4128	μm^2
STIN Segment		
Segment length	1800	μm
Axon diameter	12.5	μm
Axon cross section area	122.7	μm^2
Peri-axonal space cross section area	0.16	μm^2
Peri-axonal space thickness	0.004	μm
Myelin thickness	2.5	μm

Derived from table in Berthold and Rydmark [8]

* Calculated from percentage of internodal value (38%) listed in original table.

Figure 2.3: Illustration of the cross-section of the nerve fiber. The axon is approximately circular in the internodal (STIN) region but changes into a fluted (FLUT) shape in the paranodal region reducing the cross-sectional area of the axon and increasing the surface area of the axon changing rapidly to an approximately circular form of reduced diameter at the node of Ranvier.

potential or current is assumed across the longitudinal spaces of the model (axoplasm, extracellular bathing medium, etc.) as defined by core conductor theory [55, 56, 57] for the simple cylindrical model. Axial symmetry is also assumed and the node of Ranvier is represented by an equivalent circuit that consists of a membrane capacitance shunted by ionic channels represented as time varying conductances in series with Nernst potentials for the relevant ionic species. The nodal circuit is coupled with distributed parallel passive conductances and capacitances representing the adjacent sections of the internodal regions. No separate distinction for the paranodal region is made in these models and the current passing through the narrow nodal region is effectively spread over a longer segment of the nerve fiber as determined by the spatial step size. The separate characteristics of the myelin sheath and the underlying axolemmal membrane are not represented, nor do these models provide for placement of ionic channels into the paranodal and internodal axolemmal membrane.

Figure 2.4: Form of the coaxial electrical equivalent network for the nerve fiber. This diagram illustrates the translation of the anatomical structure to the structure of the equivalent electrical network. The coaxial case assumes a constant radius for the equivalent cylinder and a homogeneous spatial step size. The internodal region is assumed to be passive, with no Nernst potential and collapses the myelin sheath into the axolemmal membrane to form an equivalent transverse admittance. Most significantly, the current and potential at the nodal membrane is distributed over a much longer segment of the nerve fiber than is present in practice. The box labeled Node represents the electrical equivalent circuit for the nodal axolemmal membrane.

2.3.2 Triaxial equivalent network

The new model structure is illustrated in Fig. 2.5 and takes on the appearance of a triaxial cable, possessing three longitudinally conductive pathways. A concentric cylindrical geometry is used employing axial symmetry. A triaxial core conductor model is adopted which assumes that there is no significant radial variation in potential or current across any of the longitudinal spaces in the model. A detailed representation of the nodal region is accomplished by allowing for longitudinal variation in radius of the axon, thickness of the peri-axonal space, thickness of the myelin

Figure 2.5: Form of the triaxial electrical equivalent network for the nerve fiber. The triaxial case does not assume a constant radius, uses a non-uniform spatial step size, represents the myelin sheath as separate from the axolemmal membrane, allows for the presence of a variable thickness peri-axonal space, inclusion of active membrane processes in the paranodal and internodal regions and includes a nodal gap resistive element. Three longitudinal conductance pathways are present, an intra-axonal, peri-axonal and extra-axonal, with two transverse elements, one for the myelin sheath and the other for the axolemmal membrane beneath. The terminology used for the the different segments is that defined in Fig. 2.2. Detail on the elements of the network can be found in Chapter 4.

sheath, passive electrical properties of the axolemmal and myelin membranes, densities and characteristics of the axolemmal ionic channels as well as inclusion of a nodal gap conductance. The longitudinal spatial step size of the distributed model can be non-uniform allowing the nodal region, paranodal region and internodal regions to be represented in greater detail without generation of a prohibitive number of discrete segments. This allows for representation of the distributed character of the axonal properties and, unlike previous models, a highly detailed representation of the node and paranode.

2.4 Summary

A detailed quantitative description of the myelinated nerve fiber anatomy was derived from the literature [9, 70, 95, 96], primarily from the work of Berthold [8]. These data were presented in compiled form as defined in Table 2.1. The coaxial cable structure which was assumed by previous modeling efforts was presented and shown to be insufficient in representing the morphology described by these anatomical studies. A triaxial cable form with non-uniform longitudinal spatial segments was proposed allowing for representation of more of the detail shown in the anatomical literature. The triaxial cable model contains representations for the nodal and paranodal regions, the peri-axonal conductance pathway, separate myelin sheath and axon elements, the extracellular medium and the nodal gap.

With this specification of the triaxial structure for the electrical equivalent network, characterization of the electrical properties of the various network elements is the next step in development of the model. This is presented in the following chapter.

Chapter 3

Properties of the Model Elements

3.1 Introduction

In order to develop a model that is truly representative of what is currently known regarding the myelinated nerve fiber, the most recent experimental data available regarding the biophysical character of the axon and the myelin sheath needs to be obtained from the literature. Characterizations of the specific conductivities, capacities, ionic channel permeabilities and dynamics of the various anatomical segments of the nerve fiber serve as important parameters to be utilized in the development of a distributed - parameter electrical equivalent model of the myelinated nerve fiber.

The electrical equivalent model adopted for the active axolemmal membrane has the structure shown in Fig. 3.1. The form is similar to that used by Dodge [35] which is based on the Hodgkin-Huxley formalism [63]. Here, the equivalent circuit model consists of five lumped parallel elements: a capacitor representing the capacitance of the membrane lipid bilayer, a sodium channel represented by a non-linear time-varying conductance in series with a sodium Nernst potential, fast and slow potassium channels similar in form to the sodium model element and a leakage channel attributed to potassium ions which consists of a constant conductance in series with a potassium Nernst potential. The myelin sheath is modeled as a lumped equivalent parallel conductance and capacitance for a given unit length. The characteristics of these model elements vary across species and segments of the nerve fiber being represented, as is presented in the following sections.

Figure 3.1: Axolemmal membrane model modified from that of Dodge [35]. This model follows the Hodgkin-Huxley convention, representing the ionic channels as variable conductances in series with a Nernst potential. In this case there is one type of sodium channel, two types of potassium channels (fast and slow), a leakage channel attributed to potassium and a membrane capacitance.

3.2 Passive Electrical Properties

The passive electrical properties of the myelinated nerve fiber were first examined systematically by Tasaki [115]. He reported values for the absolute nodal capacity and resistance and per unit length internodal capacitance and resistance as measured in large myelinated fibers of *Rana catesbeiana*. Some of these properties have been re-examined in the amphibian nerve fiber [27, 58, 80, 85, 86, 107, 110] and measured in the mammalian myelinated nerve fiber [17, 22, 27, 83, 101]. The nodal gap conductance has been measured in the amphibian and mammalian myelinated nerve fibers [23, 37, 40, 83, 114]. Various experimentally-induced demyelination studies

have provided information on the properties of the internodal axolemmal membrane [19, 25, 26, 28, 53, 97, 105].

3.2.1 Nodal properties

The capacitance and the resistance of the nodal membrane as measured in the amphibian and the mammalian fibers are summarized in Table 3.1. Here the leakage conductance values have been adjusted to a temperature of 20°C using a Q_{10} of 1.2 for the amphibian case [47] and 1.4 for the mammalian case derived from the recent work of Schwarz[101] for nodal properties at 20°C and 37°C . Prevailing opinion is that capacitance does not change significantly with temperature. The magnitude of the leakage conductance is similar for both amphibian and mammalian fibers with an increased value for larger fiber diameters, that corresponds to the larger nodal area involved.

The nodal gap series resistance values for amphibian and mammalian fibers are listed in Table 3.2. Indications are that the nodal gap is more conductive in the amphibian than the mammalian nerve fibers and exhibits a decrease in conductance for larger fiber diameters correlating with an observation of narrower gap widths for larger fiber diameters [8].

3.2.2 Internodal properties

The resistivity of the axoplasm which fills the interior of the axon has been most commonly considered to be on the order of $110\Omega\text{ cm}$ (see Table 3.3). Recent studies indicate however, that this may be a low estimate and show furthermore that the amphibian and mammalian resistivities are comparable [27, 83]. When necessary, a Q_{10} of 1.3 was used for temperature correction after the work of Moore, et al. [79]. This value is adopted for both the amphibian and the mammalian cases due to a lack of any comparative studies found in the literature.

Table 3.1: Passive Electrical Properties of Node

Amphibian					
Source	Species	Diameter (μm)	Type	Capacitance (pF)	Conductance (nS)
Tasaki '55 [115]	R.C.	12–15	motor	1.5 ± 0.45	24.4 ± 2.6
Dodge '63 [35]	R.P.	12–15	n.s.	2.2–2.5	25
Chiu '79 [27]	R.P.	17.5 ± 0.9	n.s.	•	41.3 ± 7.8
Palti '80 [85]	R.E.	11	sensory	•	21.0 ± 1.48
Palti '80 [85]	R.E.	11	motor	•	23.3 ± 3.9
Sigworth '80 [107]	R.P.	12–17	n.s.	$2.88 \pm .69$	15.3 ± 3.6
Smith '81 [110]	R.P.	16–20	n.s.	•	24.3 ± 0.05
Brismar '82 [21]	X.L.	10–12	n.s.	4.0 ± 1.5	18.0 ± 3.0
Schauf '87 [97]	R.P.	8–10,16–18	n.s.	1.4–1.6	21.7–29.4
Mammalian					
Source	Species	Diameter (μm)	Type	Capacitance (pF)	Conductance (nS)
Chiu '79 [27]	rabbit	14.6 ± 0.9	n.s.	2	37.9 ± 13.4
Brismar '80 [17]	rat	10–12	n.s.	•	24.5 ± 6.7
Neumcke '82 [83]	rabbit	12.3 ± 0.25	n.s.	•	23.9 ± 1.9
Brismar '85 [22]	rat	12–14	n.s.	•	30.8 ± 15
Schwarz '87 [101]	rat	n.s.	motor	•	23.7 ± 3.4
(37°C) [101]	rat	n.s.	motor	•	42.9 ± 4.8

R.C.: *Rana catesbeiana*R.E.: *Rana esculenta*R.P.: *Rana pipiens*X.L.: *Xenopus laevis*

n.s.: Not stated

• Not measured

Table 3.2: Nodal Gap Conductances

Amphibian			
Source	Species	Diameter (μm)	Conductance (μS)
Drouin '74 [37]	R.E.	11–14	4.34
Dubois '75 [40]	R.E.	n.s.	6.66
Stampfli '80 [114]	R.E.	n.s.	5–10
Mammalian			
Source	Species	Diameter (μm)	Conductance (μS)
Chiu '80 [23]	rabbit	18–22	1.3 ± 0.16
Neumcke '82 [83]	rabbit	12.3 ± 0.25	2.32 ± 0.28

R.E.: *Rana esculenta*

n.s.: Not stated

Table 3.3: Axoplasmic Resistivities

Amphibian		
Source	Species	Resistivity (Ωcm)
Stampfli '52 [112]	n.s.	110
Chiu '79 [27]	R.P.	158 ± 23
Mammalian		
Source	Species	Resistivity (Ωcm)
Chiu '79 [27]	rabbit	171 ± 23
Neumcke '82 [83]	rat	166

R.P.: *Rana pipiens*

n.s.: Not stated

Voltage clamp studies of experimentally demyelinated nerve fibers have allowed examination of the properties of the axolemmal membrane lying beneath the myelin sheath (see Table 3.4). The specific capacitance is on the order of the $1\mu F/cm^2$ expected for cellular membranes, with the exception of two studies [25, 28]. In the latter case, both the specific capacitance and the specific conductance are markedly higher than found in other studies. Possible explanations (though seemingly unlikely) are: (a) that an inaccurate assumption was made for the series axoplasmic resistance used for the absolute current measure or (b) the clamp voltage was less than expected due to an unaccounted series resistance. When taken into account, these factors could scale the specific conductance to a value near $1mS/cm^2$ and reduce the specific capacitance to $2\mu F/cm^2$, bringing both quantities closer to other published values. Potentially, the specific capacitance could be reduced even further if the possible contribution of the adjacent axolemmal membrane as coupled through the exposed peri-axonal space were considered.

The specific conductance of the axolemmal membrane is on the order of that approximated for a single layer of the myelin sheath ($1 - 2mS/cm^2$) [62]. It is indeed smaller than the specific conductance estimated for the nodal membrane ($130 - 150mS/cm^2$) [17, 22], as initially indicated by paranodal demyelination studies [19, 25]. These measures have been challenged by a recent study [12] on the underlying mechanism for the depolarizing afterpotential (DAP), which presents the hypothesis that the axolemmal membrane is much more resistive, in fact, on the order of the specific conductance of the entire myelin sheath ($0.0212mS/cm^2$).

The electrical properties of the myelin sheath itself stem almost exclusively from the work of Tasaki in 1955 [115]. Table 3.5 summarizes the parameters as found in the literature with one estimate derived from an illustration of currents resulting from voltage clamp of an intact internode by Grissmer [53]. The higher specific conductivity found from this study lends support to the conclusion of Blight [12] on the need for a higher specific conductivity of the myelin to account for the DAP. A

Table 3.4: Passive Properties of Internodal Axolemma

Amphibian				
Source	Species	Diameter (μm)	Specific Capacitance ($\mu F/cm^2$)	Specific Conductance (mS/cm^2)
Chiu '82 [26]	R.C.	20	2.3–3.4	2.1–3.1
Grissmer '86 [53]	R.E.	11–17	0.96 ± 0.52	0.55–1.65
Schauf '87 [97]	R.P.	8–18	•	1.0
Shrager '88 [105]	X.L.	20	•	0.5
Mammalian				
Source	Species	Diameter (μm)	Specific Capacitance ($\mu F/cm^2$)	Specific Conductance (mS/cm^2)
Chiu '81 [25]	rabbit	20	•	0.63
Brismar '81 [19]	rat	14–16	0.67–0.88	0.85–1.6
Chiu '87 [28]	rabbit	18–20	10.6	4.72

R.C.: *Rana catesbeiana*R.E.: *Rana esculenta*R.P.: *Rana pipiens*X.L.: *Xenopus laevis*

• Not measured

more recent work based on a thorough study of the morphology of the myelin sheath relative to the axon [48], proposes that the higher conductance could be due to a spiral conductive path between the layers of myelin. Furthermore, it claims that the individual layers of the myelin sheath may have a very low specific conductivity on the order of those found in artificial lipid bilayers ($0.001 - 0.00001 mS/cm^2$) [78]. We were unable to find any comparative studies in the literature regarding the electrical properties of the myelin sheath in mammalian versus amphibian nerve fibers.

3.3 Ionic Channel Properties

Examination of the properties of the ionic channels in the myelinated nerve fiber followed development of techniques for clamping the nodal membrane via multicompartamental chambers combined with feedback control circuitry [33, 84]. These techniques were first applied to study amphibian nodes of Ranvier [33, 35, 44] and subsequently mammalian nodes of Ranvier [65] after technical difficulties of examining the smaller diameter mammalian fibers were resolved. By disruption of the myelin to axolemmal seal in the MYSA region, the character of the paranodal membrane has been studied [18, 19, 20, 23, 25]. The axolemmal membrane in the internodal region of the nerve fiber was then studied by using lysing agents such as lysolecithin to remove the myelin sheath and expose the underlying membrane which was then placed in a voltage clamp assembly in the position the node would normally occupy [26, 53]. More recently, the patch clamp technique has been applied to the paranodal and internodal regions of the demyelinated nerve fiber allowing for examination of the behavior of these channels over smaller areas and display of activity during action potential propagation [29, 104, 105]. By combining these methods with the use of pharmacological agents such as tetrodotoxin (TTX) for blockage of Na^+ channels combined with tetraethylammonium (TEA) and 4-aminopyridine (4-AP) to block different types of K^+ channels selectively, the properties of these channels have been studied.

Table 3.5: Passive Properties of Myelin Sheath

Amphibian				
Source	Species	Fiber Diameter (μm)	Specific Capacitance ($\mu F/cm^2$)	Specific Conductance (mS/cm^2)
Tasaki '55 [115]	R.C.	12	0.005	0.01
Hodgkin '64 [62]	n.s.	14	0.0025–0.005	0.00625–0.01
Grissmer '86 [53]	R.E.	11–17	•	0.023–0.064

R.C.: *Rana catesbeiana*

R.E.: *Rana esculenta*

n.s.: Not stated

• Not measured

3.3.1 Sodium channels

Distribution

Early examination of the possible presence of Na^+ channels in the internode using a radioactive tracer technique indicated that few if any channels were present [92]. The presence of continuous conduction along the demyelinated internodes was then demonstrated by Bostock and Sears, arguing for the presence of viable Na^+ channels [13]. Further evidence has been presented recently supporting the presence of viable Na^+ channels in the internode, capable of supporting conduction [106]. Other studies have also examined the distribution of Na^+ channels at and near the nodes showing redistribution after disruption of the myelin sheath [77, 104].

Nodal peak permeability

Table 3.6 contains a summary of the peak permeabilities for amphibian and mammalian nodes of Ranvier. All values are presented as absolute permeabilities and conductances versus specific permeabilities and conductances due to reported uncer-

tainties in the previous estimates for the surface area of the node [96]. These values were either taken directly from the source articles when listed, or estimated from figures illustrating the I-V characteristics of the membrane. All values were adjusted to a temperature of 20°C with Q_{10} factors of 1.3 [47]. Variations across fiber diameters imply concomitant changes in the effective nodal surface areas. The values for the amphibian versus mammalian permeabilities are comparable for similar fiber diameters.

Nodal dynamics

In the case of the amphibian, thorough studies have been made of *Xenopus laevis* [34, 43, 44] and of *Rana pipiens* [35] which resulted in generation of expressions describing the dynamics of activation and inactivation in the Hodgkin-Huxley (HH) form. Subsequent studies have examined the differences in motor and sensory fiber inactivation [100] and also found evidence for two types of channels exhibiting fast and slow inactivation [4].

In the case of the mammal, detailed studies have been made of the rabbit [27] and rat [17] with a recent highly quantitative study also characterizing the Na^+ current at 20°C and 37°C resulting in production of HH form descriptions of the Na^+ activation and inactivation [101]. Recent studies indicate that there are only minor differences in amphibian versus mammalian Na^+ channel dynamics, supporting the argument that there have been few evolutionary modifications of Na^+ channels in the nerve fiber [81, 83].

Modeling the sodium channel

The Na^+ channel exhibits an instantaneous rectification that has been characterized by the Goldman-Hodgkin-Katz (GHK) constant field equation [49, 64],

$$I_{\text{Na}} = \bar{P}_{\text{Na}} \frac{VF^2}{RT} \frac{[\text{Na}]_o - [\text{Na}]_i \exp(FV/RT)}{1 - \exp(FV/RT)} \quad (3.1)$$

Table 3.6: Sodium Permeability at the Node

Amphibian					
Source	Species	Diameter (μm)	Type	Permeability ($cm^3/sec \times 10^{-9}$)	Conductance (nS)
Frank. '59 [43]	X.L.	25–30	n.s.	8.0 ^a	[3423]
Dodge '63 [35]	R.P.	12–15	n.s.	3.7	1594
Chiu '79 [27]	R.P.	17.5 $\pm$ 0.9	n.s.	[0.95]	420 $\pm$ 60
Chiu '79a [24]	R.P.	n.s.	n.s.	[0.68]	300
Sigworth '80 [107]	R.P.	14.5	n.s.	[0.48]	210 ^b
Smith '81 [110]	R.P.	9	M,S	[0.26]	114
Smith '81 [110]	R.P.	20	M,S	[1.4]	616
Brismar '82 [21]	X.L.	10–12	n.s.	0.94 $\pm$ 0.3	[413]
Schauf '87 [97]	R.P.	9	M,S	[0.2]	89
.	.	17	.	[1.13]	495
Mammalian					
Source	Species	Diameter (μm)	Type	Permeability ($cm^3/sec \times 10^{-9}$)	Conductance (nS)
Chiu '79 [27]	rabbit	14.6 $\pm$ 0.9	n.s.	[0.42]	250 $\pm$ 90
Chiu '79a [24]	rabbit	n.s.	n.s.	[0.59]	350
Brismar '80 [17]	rat	10–12	n.s.	0.84 $\pm$ 0.16 ^c	[498]
Chiu '80 [23]	rabbit	18–22	n.s.	[1.36]	810 ^d
Smith '81 [110]	rat	9–11	M,S	[0.28]	165
Neumcke '82 [83]	rabbit	12.3 $\pm$ 0.25	n.s.	[0.51]	300 ^d
Schwarz '87 [101]	rat	12–16 ^e	M	1.7 $\pm$ 0.064	[1007]
(37°C) [101]	rat	12–16	M	1.64 $\pm$ 0.094	[917]

Values in braces calculated from opposite entry.

All adjusted to 20°C with a Q_{10} of 1.3 unless stated otherwise.

M: Motor fiber

S: Sensory fiber

R.P.: *Rana pipiens*

X.L.: *Xenopus laevis*

n.s.: Not stated

^a Calculated from specific permeability using nodal area of 100 μm^2 .

^b Low value according to author

^c Calculated from specific permeability using nodal area of 22.6 μm^2 .

^d Calculated from single channel conductance and population.

^e Assumed value from previous work by Schwarz [99].

where $\overline{P}_{Na}$ is the peak permeability, V is the absolute potential present across the membrane, F is the Faraday constant, R is the gas constant, T is the absolute temperature ($^{\circ}K$) and $[Na]_o$ and $[Na]_i$ are the external and internal Na^+ concentrations respectively. Using the peak permeability and concentrations from Schwarz [101] for the mammalian case, Fig. 3.2 illustrates the change in the rectifying character as $[Na]_o$ is changed relative to $[Na]_i$.

The dynamics of the channel opening and closing is represented by an activation gating variable and an inactivation gating variable which operate on the peak permeability, effectively ‘gating’ the conductance of the channels. The activation gating variable is represented by m and inactivation by h . Each of these gating variables is described by a first order differential equation of this form,

$$\frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m. \quad (3.2)$$

The rate constants α_m and β_m are voltage-dependent and are used to define a voltage-dependent time constant τ_m and steady-state value m_{∞} ,

$$\tau_m = \frac{1}{\alpha_m + \beta_m} \quad (3.3)$$

$$m_{\infty} = \frac{\alpha_m}{\alpha_m + \beta_m}. \quad (3.4)$$

The expressions describing the inactivation gating variable h are of the same form. These rate constants are defined as functions of transmembrane potential by the following relations for amphibian [35],

$$\alpha_m = \frac{A(B - V)/C}{\exp((B - V)/C) - 1} + \acute{\alpha}_m, \quad (3.5)$$

where

$$\acute{\alpha}_m = \frac{A}{1 + ((V - B)/C)^2} \quad (3.6)$$

Figure 3.2: Change in character of the instantaneous rectification of the mammalian sodium channel as described by the Goldman-Hodgkin-Katz constant field equation as the external concentration of sodium ions $[Na]_o$ is changed from the normal level of 154mM to the internal concentration $[Na]_i$ of 8.71mM. Note the progressive diminution of the inward current as the external concentration is decreased. The peak effective conductance changes from 1007nS to 56.6nS.

and

$$\beta_m, \alpha_h = \frac{A(V - B)/C}{\exp((V - B)/C) - 1} \quad (3.7)$$

and

$$\beta_h = \frac{A(B - V)/C}{\exp((B - V)/C) - 1}. \quad (3.8)$$

With the following for mammalian case [101],

$$\alpha_m = \frac{A(V - B)}{1 - \exp((B - V)/C)}, \quad (3.9)$$

$$\beta_m, \alpha_h = \frac{A(B - V)}{1 - \exp((V - B)/C)} \quad (3.10)$$

and

$$\beta_h = \frac{A}{1 - \exp((B - V)/C)}. \quad (3.11)$$

Table 3.7 contains the rate constants coefficients as determined by Dodge [35] for the amphibian and Schwarz and Eikhof [101] for the mammal. Figure 3.3 illustrates the characteristics of the rate constants and the steady-state and time constants that they form as functions of transmembrane potential for the gating variables m and h .

These gating variables are then combined to form the following expression for transmembrane current as a function of transmembrane potential,

$$I_{Na} = \bar{P}_{Na} m^3 h \frac{VF^2}{RT} \frac{[Na]_o - [Na]_i \exp(FV/RT)}{1 - \exp(FV/RT)}. \quad (3.12)$$

The activation gating variable m is raised to the third power in order to represent the delay in activation found in voltage clamp studies. The variation of the time constants for the mammalian case as a function of temperature is illustrated in Fig. 3.4 resulting from the use of the Q_{10} factors shown in Table 3.8. The experimental data superimposed on that generated from the model is from the work of Schwarz and Eikhof [101].

Internodal peak permeability

Relatively few voltage clamp studies have been performed on the Na^+ channels present in the internode [19, 28, 53, 104, 105]. Estimates of the specific permeabilities derived from these studies are presented in Table 3.9. These studies propose internodal to nodal channel density ratios of 1:25 [104] and 1:500 [53] for the amphibian case and 1:30 [28] for the mammalian case.

Table 3.7: Na^+ Rate Constant Coefficients

Amphibian^a			
Constant	A ($msec^{-1}$)	B (mV)	C (mV)
α_m	1.6	37.5	3.8
α_h	6	23	17.5
β_m	4.05	37.5	13.2
α_h	0.08	75	4.9
β_h	0.6	49	9.7
Mammalian^b			
Constant	A ($msec^{-1}$)	B (mV)	C (mV)
α_m	0.49	25.41	6.06
β_m	1.04	21.00	9.41
α_h	0.09	-27.74	9.06
β_h	3.70	56.00	12.50

^a From Dodge [35]^b From Schwarz and Eikhof [101].**Table 3.8: Q_{10} Temperature Coefficients**

Amphibian^a							
α_m	β_m	α_h	β_h	α_n	β_n	$\overline{P}_{Na}$	$\overline{P}_K$
1.8	1.7	2.8	2.9	3.2	2.8	1.3	1.2
Mammalian^b							
α_m	β_m	α_h	β_h	α_n	β_n	$\overline{P}_{Na}$	$\overline{P}_K$
2.2	2.2	2.9	2.9	3.2 ^c	2.8 ^c	1.3 ^c	1.2 ^c

^a From Frankenhaeuser and Moore [47].^b From Schwarz and Eikhof [101].^c Adopted from the amphibian case [47].

Figure 3.3: Change in the amphibian and mammalian Na^+ rate constants α_m , β_m , α_h , β_h , time constants τ_m and τ_h and steady-state constants m_∞ and h_∞ as functions of transmembrane potential. The temperature was $22^\circ C$ for the amphibian and $20^\circ C$ for the mammalian case.

Figure 3.4: Change in the mammalian Na^+ activation (τ_m) and inactivation (τ_h) time constants versus transmembrane potential in relation to a change in temperature. The solid curves were computed using the mammalian coefficients presented in Table 3.7 combined with the Q_{10} factors for mammal presented in Table 3.8. The symbols $\bigcirc$ and $\triangle$ represent mammalian data with $\square$ representing amphibian data and are taken from the work of Schwarz and Eikhof [101].

Table 3.9: Sodium Permeability in the Internode

Amphibian					
Source	Species	Diameter (μm)	Type	Permeability ($cm/sec \times 10^{-3}$)	Conductance (mS/cm^2)
Grissmer '86 [53]	R.P.	12–15	n.s.	[0.0038]	1.7 ^a
Shrager '87 [104]	X.L.	n.s.	n.s.	0.174 ^b	[78]
Mammalian					
Source	Species	Diameter (μm)	Type	Permeability ($cm/sec \times 10^{-3}$)	Conductance (mS/cm^2)
Brismar '81 [19]	rat	14–16	n.s.	0.033–0.076 ^c	[20–45]
Chiu '87 [28]	rabbit	18–20	n.s.	[0.091]	54 ^d

Values in braces calculated from opposite entry.

All adjusted to 20°C with a Q_{10} of 1.3.

R.P.: *Rana pipiens*

X.L.: *Xenopus laevis*

n.s.: Not stated

^a Estimated from I-V curve in Figure 9 of article using an internodal surface area of 4700 μm^2 .

^b Calculated using a relative internodal to nodal density of 1:25 and the specific permeability for the node from Frankenhaeuser [43]

^c Derived from Table 1 of article, using the paranodal demyelination entries

^d Derived from authors' estimate of 0.238 μS for 10 μm of internode.

Internodal dynamics

The dynamics of these channels appear to be very similar to those located in the node, exhibiting the same inactivation characteristics [53], therefore the same rate constants used to represent the nodal Na^+ channels are adopted in this modeling effort to represent the dynamics of the internodal Na^+ channels.

3.3.2 Potassium channels

Distribution

In the amphibian there is a higher overall potassium permeability present at the node of Ranvier than there is in the mammal. Initially, studies on mammalian nerve fibers indicated that there were few if any K^+ channels present at the node [65, 71]. However, K^+ currents were noted in diseased mammalian nerve fibers [16] and subsequently shown to present in the paranode and internode of the mammalian [14, 18, 19, 23, 25, 103] and the amphibian [26, 97, 104] myelinated nerve fiber. Furthermore, evidence for a combination of fast and slow gated K^+ channels located at the node in the amphibian had been gathered [38, 39, 68, 73], with indication of two types of fast K^+ channels with different steady-state activation characteristics and inactivation time constants [38]. Multiple types of K^+ channels were later identified in the mammalian case with evidence for the slow channels being located primarily in the node and the fast channels in the paranodes [2, 51, 102]. This difference in distribution of fast versus slow channels is also evident in the amphibian [97] although Grissmer argues that there is a higher proportion of slow to fast channels in the internode than in the node [53].

Nodal peak permeability

The peak permeabilities for K^+ in the amphibian node of Ranvier are listed in Table 3.10 and for the mammalian case in Table 3.11. All have been adjusted to a temperature of $20^\circ C$ with a Q_{10} factor of 1.2 [47].

Table 3.10 reveals greater values of K^+ permeability for larger diameter fibers, a greater K^+ permeability in sensory versus motor fiber nodes and a greater proportion of fast to slow channels, as shown by Ilyin [68] and Dubois [39]. Table 3.11 illustrates the relatively small contribution of K^+ channels at the node in mammal, a quantitative study of the permeabilities of fast versus slow K^+ channels having yet to be published.

Nodal dynamics

For the amphibian case, Frankenhaeuser in 1963 [45] described a delayed outward potassium current in *Xenopus laevis* in a fashion similar to that of the sodium channel dynamics, using a GHK constant-field expression for the instantaneous rectifying character of the channels in combination with an activation (n) and inactivation (k) gating variable. The delayed character of the channel activation was represented by n^2 and it was determined that the inactivation was so slow ($> 200ms$) that it did not need to be included. On the other hand, in the same year Dodge [35] assumed that the permeability of K^+ was sufficiently linear with changes in membrane voltage to be adequately represented by a simple conductance, as in the HH case, and found a channel activation relationship best described by n^4 . In 1978, Krylov and Makovsky [73] proposed the presence of a slow gating K^+ channel represented by a constant peak conductance and an n^4 relation as in the case of Dodge [35]. The time constant employed by these investigators was about a factor of 10 slower (20ms peak) and the half-activation point of the steady-state activation curve occurred at rest potential. Ilyin, et al. in 1980 [68] published a description of both the fast and slow gating K^+ channels with an n^4 relation for both cases. Steady-state relationships similar to

Table 3.10: Potassium Permeability at the Node for the Amphibian

Source	Species	Diameter (μm)	Type	Permeability ($cm^3/sec \times 10^{-9}$)	Conductance (nS)
Dodge '63 [35]	R.P.	12–15	n.s.	[0.30]	130
Frank. '63 [45]	X.L.	large	n.s.	1.2 ^a	[527]
Ilyin '80 [68]	R.R.	15–20	n.s.	[1.34]	590 ^b (fast)
.	.	.	.	[0.36]	160 ^b (slow)
Neumcke '80 [82]	R.E.	n.s.	S	[0.57]	250 ^c
.	.	.	M	[0.36]	160 ^c
Palti '80 [85]	R.E.	11	S	[1.36]	600
.	.	.	M	[0.68]	300
Dubois '81 [38]	R.E.	n.s.	S	[0.84]	370 $\pm$ 31 ^d
.	.	.	.	[0.68]	302 (<i>fast</i>)
.	.	.	.	[0.42]	184 (<i>f1</i>)
.	.	.	.	[0.27]	118 (<i>f2</i>)
.	.	.	.	[0.15]	66 (<i>slow</i>)
.	.	.	M	[0.80]	355 $\pm$ 96 ^d
.	.	.	.	[0.65]	287 (<i>fast</i>)
.	.	.	.	[0.23]	101 (<i>f1</i>)
.	.	.	.	[0.27]	118 (<i>f2</i>)
.	.	.	.	[0.15]	67 (<i>slow</i>)
Smith '81 [110]	R.P.	9	n.s.	[0.10]	46
.	.	20	.	[0.38]	167
Brismar '82 [21]	X.L.	10–12	n.s.	0.31 $\pm$ 0.14	[136]
Conti '84 [30]	R.P.	15.5 $\pm$ 1.7	S	[0.59]	260 $\pm$ 86
.	.	15.5 $\pm$ 1.0	M	[0.39]	173 $\pm$ 60

Values in braces calculated from opposite entry.

All adjusted to 20°C with a Q_{10} of 1.2.

M: Motor fiber

S: Sensory fiber

R.P.: *Rana pipiens*

R.R.: *Rana ridibunda*

X.L.: *Xenopus laevis*

n.s.: Not stated

^a Calculated from specific permeability using nodal area of 100 μm^2 .

^b Estimated from I-V plots in Figure 7 of article.

^c Calculated from single channel conductance and population.

^d Total conductivity subdivided into fast and slow conductivities, with the fast subdivided into type 1 and type 2.

Table 3.11: Potassium Permeability at the Node for the Mammal

Source	Species	Diameter (μm)	Type	Permeability ($cm^3/sec \times 10^{-9}$)	Conductance (nS)
Brismar '80 [17]	rat	10–12	n.s.	0.0475 ± 0.014	[28]
Binah '81 [10]	rat	n.s.	M	[0.35]	80 ^a
Smith '81 [110]	rat	9–11	M,S	[0.12]	69
Brismar '85 [22]	rat	12–14	n.s.	0.065	[38]

Values in braces calculated from opposite entry.

All adjusted to 20°C with a Q_{10} of 1.2.

M: Motor fiber

S: Sensory fiber

n.s.: Not stated

^a Calculated from specific conductivity using author's assumed nodal area of 50 μm^2 .

Frankenhaeuser [45] were chosen for the fast channel and to Krylov and Makovsky [73] for the slow channel. Ilyin, et al. [68] also showed that the fast channel might be more sensitive to TEA. Subsequently in 1981, Dubois [39] presented a description of the gating characteristics in *Rana esculenta* using a single gating variable (x_∞) and accounting for the delayed character of the current by including an explicit delay parameter,

$$G_K = x_\infty \bar{G}_K \left[1 - e^{-(t-\delta t)/\tau} \right]. \quad (3.13)$$

He also showed evidence for the presence of three types of K^+ channels [38], a slow gating channel represented by a single gating variable (s) and a peak conductance ($\bar{G}_s$) unlike the n^4 relation with a GHK constant-field instantaneous rectification property of Ilyin, et al. [68] and two types of fast delayed channels. One fast channel (G_{Kf_1}) activates between -80 and -30 mV and inactivates very slowly ($\tau = 45$ sec at 0 mV). The other (G_{Kf_2}) activates between -40 and +30 mV and also inactivates slowly ($\tau = 2$ sec at 0 mV). Both are described as before, with a single gating variable and an explicit delay parameter. Dubois [38] also demonstrated that the fast channels were

blocked by 4-AP while the slow channel was not. Dubois also noted that while TEA blocked both types of channels, it affected the fast channels more than the slow as had been observed by Ilyin, et al. [68]. Future studies may benefit from the discovery of toxins that selectively block K^+ channels [5, 86], one blocking only one type of fast channel (G_{Kf1}) [5]. Regarding the functional implication of these channels, Poulter and Padjen in 1988 [87] report that intra-axonal administration of 4-AP and TEA decreases accommodation in the frog myelinated nerve fiber.

In the mammalian case, Binah and Palti [10] found a single gating variable relation to be between the order of n^1 to n^4 . Brismar found the best fit for the delay by n^4 and claimed that TEA provided only a partial block of the K^+ current and that 4-AP had less effect [22]. In none of these studies was a relation presented describing the full behavior of the K^+ channel dynamics or was enough detail provided in the voltage clamp studies to generate one.

Modeling the potassium channels

Due to the thorough description of the steady-state characteristics and time constants for the fast and slow channels, the work of Ilyin, et al. [68] was selected for the both the amphibian and mammalian model. Unfortunately, the work of Dubois [38] did not include complete information on the activation and inactivation characteristics, therefore only one fast (f) channel was modeled.

The steady-state and time constant curves presented by Ilyin, et al. [68] were digitized. The form for the rate constants as presented by Frankenhaeuser [45],

$$\alpha_n = \frac{A(V - B)}{1 - \exp((B - V)/C)}, \quad (3.14)$$

and

$$\beta_n = \frac{A(B - V)}{1 - \exp((V - B)/C)} \quad (3.15)$$

were selected for fit to the digitized data. A Gauss-Newton technique using a Levenberg parameter as described by Marquardt [75] was employed to solve for the coefficients

of each rate constant as is presented in Appendix A. The best least squares fits were obtained by generating coefficients for the steady-state relations independent from that for the time constants and are listed in Table 3.12. Both the resulting curves and the original data are presented in Fig. 3.5. The rate constants obtained were then used to form the slow K^+ gating variable n_s and the fast K^+ gating variable n_f utilized in the analytical expressions for the slow K^+ current,

$$I_{K_s} = \overline{P}_{K_s} n_s^4 \frac{VF^2}{RT} \frac{[K]_o - [K]_i \exp(FV/RT)}{1 - \exp(FV/RT)} \quad (3.16)$$

and fast current,

$$I_{K_f} = \overline{P}_{K_f} n_f^4 \frac{VF^2}{RT} \frac{[K]_o - [K]_i \exp(FV/RT)}{1 - \exp(FV/RT)}. \quad (3.17)$$

Due to the lack of data for the mammalian case, these same dynamics were employed to describe the mammalian K^+ channel characteristics.

Internodal peak permeability

Table 3.13 contains estimates for the peak permeabilities for K^+ in both the amphibian and mammalian cases. The presence of multiple types of K^+ channels in the amphibian (*Rana esculenta*) internode was confirmed by Grissmer [53]. However, it was only possible to block to 11% of normal conductance with external 110 mM TEA and in the study by Shrager [104] on *Xenopus laevis* reduction to only 15% was achieved with 7.4 mM TEA. There was no consistent correlation with position along the internode of the magnitude of the K^+ conductance [104]. In the mammalian case, Sherratt, et al. [103] and Bostock, et al. [14] showed the differential effects of TEA and 4-AP in that 4-AP was more effective, both allowing for recovery of conduction in damaged fibers.

Internodal dynamics

The work of Grissmer [53] shows that there are one slow and two fast K^+ channels in the amphibian internode as was shown by Dubois for the node [38]. In mammalian

Figure 3.5: Fit to data of Ilyin, et al. [68] for the steady-state activation and time constants of the fast and slow gated potassium channels.

Table 3.12: K^+ Rate Constant Coefficients

Steady-State			
Constant	A ($msec^{-1}$)	B (mV)	C (mV)
α_{n_f}	0.54	1.32	2.94
β_{n_f}	1.51	35.06	7.82
α_{n_s}	3.83	-15.73	16.44
β_{n_s}	2.11	45.56	18.85
Time Constant			
Constant	A ($msec^{-1}$)	B (mV)	C (mV)
α_{n_f}	0.0078	-20.17	38.85
β_{n_f}	0.0214	17.88	0.91
α_{n_s}	0.00092	-25.75	15.73
β_{n_s}	0.0042	0.24	8.54

myelinated nerve fibers, a recent study by Schwarz and Röper [102] indicates that the slow K^+ channels are located primarily at the node while the fast channels are found primarily in the paranode. Furthermore, the characteristics of the gating properties of the slow channel correlate well with those of Dubois [38] and Ilyin, et al. [68] in that there was 50% activation at rest potential. Since no published voltage clamp studies have provided sufficient details on steady-state and time constant curves and since the slow kinetics seem to correlate well with those of the mammal, the dynamics found in the work of Ilyin, et al. were adopted for the mammalian model.

3.4 Membrane Action Potentials

Assuming an ideal space-clamped condition, as did the investigators who measured the properties discussed in the previous section, membrane action potentials (MAP's) can be computed by numerical integration of the space-clamped membrane equation

Table 3.13: Potassium Permeability in the Internode

Amphibian					
Source	Species	Diameter (μm)	Type	Permeability ($cm/sec \times 10^{-3}$)	Conductance (mS/cm^2)
Chiu '82 [26]	X.L.	20	n.s.	[0.056–0.11]	25 – 50 ^a
Grissmer '86 [53]	R.E.	n.s.	S	[0.002–0.004]	9 – 18 ^b
.	.	.	.	[0.014–0.028]	6 – 12 (fast)
.	.	.	.	[0.006–0.012]	3 – 6 (slow)
Mammalian					
Source	Species	Diameter (μm)	Type	Permeability ($cm/sec \times 10^{-3}$)	Conductance (mS/cm^2)
Brismar '81 [20]	rat	12–16	n.s.	0.17–1.94 ^c	[100–1149]
Chiu '81 [25]	rabbit	20	n.s.	[0.065]	38.6 ^d

Values in braces calculated from opposite entry.

All adjusted to 20°C with a Q_{10} of 1.3.

S: Sensory fiber

R.P.: *Rana pipiens*

X.L.: *Xenopus laevis*

n.s.: Not stated

^a Estimated from I-V curve in Figure 8 of article using an internodal surface area of 1760–2640 μm^2 .

^b Estimated from I-V curve in Figure 2 of article using an internodal surface area of 3141–6242 μm^2 .

^c Derived from Table 1 in article.

^d Derived from authors' assumed value of 0.034 μS for a 2 μm section of internode,

in response to a simulated stimulus, as has been done by a number of investigators [35, 46, 63], foremost Hodgkin and Huxley [63]. The gating variables were estimated using a Rush-Larsen approximation technique [93] and then used in conjunction with the GHK constant field equations or peak conductances to form expressions for the component currents of the membrane equation at a given time interval. A description of the Rush-Larsen approximation technique and the solution method are described in Appendix B.

3.4.1 Nodal model

For the nodal case, the model parameters as shown in Table 3.14 were employed. The amphibian nodal model is derived from the model parameters presented by Dodge [35] with the single K^+ channel conductance used by Dodge replaced by fast and slow K^+ channel conductances as described by Ilyin, et al. [68]. A 4:1 ratio of the fast to slow K^+ conductances was taken from Ilyin, et al. [68]. To compensate for the addition of the slow K^+ channel, the leakage conductance was proportionally reduced. This is supported by the observation of Stämpfli in 1983 [113] in which he argues that currents once attributed to a simple leakage channel may actually be due to a slow gated K^+ channel. In keeping with the assumption of Dodge, the K^+ channels are represented by simple linear peak conductances versus the formulation utilizing peak permeabilities combined with non-linear GHK constant field expressions.

The mammalian nodal model is derived from the model parameters presented by Schwarz and Eikhof [101]. The fast and slow K^+ channel dynamics of Ilyin, et al. [68] also replace the single fast K^+ channel used by Schwarz and Eikhof, which was an adaptation of the dynamics of the K^+ channel used by Frankenhaeuser [45], using the peak permeability of $0.065 \times 10^{-9} \text{ cm}^3/\text{sec}$ of Brismar [22]. As was assumed by Frankenhaeuser, a GHK constant field expression is used in the calculation of each K^+ current. The ratio of fast to slow K^+ channels as determined by Ilyin, et al. was also adopted for the mammalian case, with the understanding that the relative

proportion of fast to slow K^+ channels in the node of Ranvier for mammalian nerve may be less than this figure as recently reported by Schwarz and Röper [102], however this has yet to be quantified.

Figure 3.6 presents the resulting MAP's generated for the mammalian and the amphibian cases. The discrete points shown in the figure for comparison represent the MAP's generated by the standard mammalian model of Schwarz and Eikhof [101], and the standard amphibian model of Dodge [35].

3.4.2 Internodal model

In similar fashion, simulations of the MAP's that might result in the internodal region were performed for the amphibian and mammalian cases. Table 3.15 contains the parameters used in the simulations and Fig. 3.7 illustrates the resulting MAP's and currents from stimulation of a unit length of internodal axolemmal membrane.

This indicates that, within the range of parameters specified in the literature, MAP's can be generated by the internodal axolemmal membrane. This correlates with studies showing the generation and propagation of action potentials within demyelinated internodes [13, 104].

3.5 Summary

In order to provide data for a new distributed - parameter model of the myelinated nerve fiber, a comprehensive review of the literature was undertaken with regard to the biophysical properties of amphibian and mammalian myelinated nerve fibers. These data were compiled in tabular form and categorized by property, i.e. passive conductance, by location, i.e. nodal and internodal, and by species. Standard data sets were then adopted from these tables for the nodal and internodal properties of the amphibian and mammalian myelinated nerve fiber.

New data was used to represent the dynamics of the Na^+ channels in the mammalian node of Ranvier [101]. The presence of multiple types of K^+ channels, which

Table 3.14: Model Parameters for Node

Parameter	Units	Amphibian	Mammal
$[Na]_o$	mM	110	154
$[Na]_i$	mM	16.6	8.71
$\bar{P}_{Na}$	cm^3/sec	3.9×10^{-9}	1.7×10^{-9}
$[K]_o$	mM	.	5.9
$[K]_i$	mM	.	155
$\bar{P}_{Kf}$	cm^3/sec	.	0.054×10^{-9}
$\bar{G}_{Kf}$	nS	580	.
$\bar{P}_{Ks}$	cm^3/sec	.	0.0135×10^{-9}
$\bar{G}_{Ks}$	nS	125	.
G_{leak}	nS	22	24
C_m	pF	2	2
V_{rest}	mV	-75	-78
T	$^{\circ}C$	22	20

Table 3.15: Model Parameters for Internode

Parameter	Units	Amphibian	Mammal
$[Na]_o$	mM	110	154
$[Na]_i$	mM	16.6	8.71
$\bar{P}_{Na}$	cm/sec	0.039×10^{-3}	0.05×10^{-3}
$[K]_o$	mM	.	5.9
$[K]_i$	mM	.	155
$\bar{P}_{Kf}$	cm/sec	.	0.04×10^{-3}
$\bar{G}_{Kf}$	mS/cm^2	12	.
$\bar{P}_{Ks}$	cm/sec	.	0.02×10^{-3}
$\bar{G}_{Ks}$	mS/cm^2	6	.
G_{leak}	mS/cm^2	1	1
C_m	$\mu F/cm^2$	1	1
V_{rest}	mV	-75	-78
T	$^{\circ}C$	22	20

Figure 3.6: Model generated membrane action potentials (MAP's) and component currents for the amphibian and mammalian idealized node of Ranvier. The discrete points represent the MAP's generated by the standard models for the amphibian by Dodge [35] and the mammal by Schwarz and Eikhof [101].

Figure 3.7: Model generated membrane action potentials (MAP's) and component currents in the amphibian and mammalian internode. Note the reduced peak potential and increase in action potential duration in comparison to the nodal case.

have not been included in previous models of the axolemmal membrane, was also taken into account. A fast and slow-gated K^+ channel were modeled from the data of Ilyin, et al. [68] on frog by performing parameter estimation of the coefficients describing the rate constants. A Gauss-Newton parameter estimation technique was employed for this estimate using a Levenberg parameter as described by Marquardt [75]. The resulting parameter estimates were used in the individual K^+ channel models and were subsequently incorporated into a larger membrane model similar to that of Dodge [35] for the amphibian case. The K^+ channel conductivities used in this model were taken from Ilyin, et al. [68]. Given the experimental evidence for the presence of multiple types of K^+ channels with very similar characteristics in the mammalian myelinated nerve fiber by Schwarz and Röper [102], these same dynamics were utilized for the mammalian axolemmal membrane model. In keeping with the work of Dodge [35], the K^+ channels were represented by peak conductances modulated by a gating variable of the form n^4 for the amphibian case. For the mammalian case, the K^+ channels were represented by peak permeabilities multiplied by instantaneous non-linearities as described by the Goldman-Hodgkin-Katz (GHK) constant field equations and then modulated by a gating variable of the form n^4 . Subsequently, these properties were incorporated into an electrical equivalent model of the nodal axolemmal membrane (Fig. 3.1) and membrane action potentials (MAP's) were generated via numerical integration of an expression relating the displacement to component ionic currents. The relative magnitudes of the leakage conductances versus slow K^+ conductances were manually adjusted to achieve close fits of the new model-generated MAP's for the amphibian node in comparison to the model-generated MAP of Dodge [35] and the mammalian node in comparison to the model-generated MAP of Schwarz and Eikhof [101].

A model of the internodal axolemmal membrane was then formed by modifying the parameters for the Na^+ and K^+ channel permeabilities and the leakage conductances for the amphibian and mammalian cases. Simulation results indicate that the

internodal axolemmal membrane can generate an MAP which is slower and of lower peak potential and current density than that seen at the node of Ranvier. This result lends support to experimental findings regarding action potential propagation in the demyelinated internode [13].

These model parameters and dynamics for the axolemmal membrane can now be incorporated into an overall distributed - parameter model of the myelinated nerve fiber, seen as a multi-axial core conductor equivalent circuit. The development of the solution method for the distributed - parameter model is presented in the following chapter.

Chapter 4

Numerical Solution of the Model

4.1 Introduction

Given the multi-axial structure of the model, alternatives were first explored for approaching the problem analytically. A review of the literature produced only one example of an approach to the problem, this was the work of Taylor [116] in which the problem of stimulation of a nerve enclosed by a nerve sheath was addressed. He developed an analytic method for dealing with the case of an unmyelinated nerve fiber encased in a nerve sheath, the so-called, ‘double - cable model’. However, he was primarily interested in models of electrical stimulation and his approach to the case of the myelinated nerve fiber was extremely constrained and did not provide much promise in addressing the fine details of the node and paranodal region. The discontinuous nature of the myelinated nerve fiber presents difficulties in formulation of an analytic solution, therefore numerical methods were pursued.

The next approach considered was a reduced model possessing no peri-axonal conductance pathway and a passive internodal region with the myelin sheath characterized as independent from the axolemmal membrane. This approach is detailed in Appendix C. A solution was achieved by deriving an equivalent admittance for the internodal transverse elements using Laplace transforms followed by application of an inverse transform to move back into the time domain. The resulting expressions included convolutions which were merged into a Crank-Nicolson [32] form algorithm. This approach was able to produce the afterpotential phenomena described by Barrett and Barrett [3] as well as Blight [12], but was not able to address the possible im-

pact of the peri-axonal conductance pathway or the presence of ionic channels in the axolemmal membrane beneath the myelin sheath.

An attempt was then made to represent the triaxial case as a set of cross-coupled partial differential equations using the transmyelin and transaxonal potentials as primary state variables. The solution took the form of two cross-coupled Crank-Nicolson algorithms which took advantage of a tridiagonal form for the transmyelin and transaxonal coefficient matrices. This approach was also shown to be flawed in that it failed to produce conduction velocities which were sufficiently high and therefore was abandoned. The difficulty lay in representing the intra-axonal potential versus the outside reference potential as the sum of the transmyelin and transaxonal potentials. The solution is not unique in that a given intra-axonal potential can be represented by an arbitrary combination of transmyelin and transaxonal potentials. Subsequently, an approach was taken using the intra, peri and extra-axonal potentials as primary state variables.

In this development, an implicit technique would be preferred due to its documented stability in comparison to an explicit technique [108]. However, due to possible computational advantages offered by an explicit approach, it was developed as is described in Appendix D. In preliminary tests, the explicit method was found to be much less stable than the implicit method. For example, solutions could easily be obtained for the case of a uniform homogeneous internodal region. However, when a node of Ranvier was included, the explicit method was rendered unstable regardless of temporal step size. The implicit method was therefore chosen and the development and implementation of the technique follow.

4.2 Development of Implicit Form Equation System

The nerve fiber was sectioned into longitudinal segments which have the equivalent cylindrical geometries illustrated in Figs. 4.1 and 4.2. Figure 4.1 addresses the longitudinal electrical resistive properties of the nerve fiber, showing the intra-axonal

cylindrical volume, the peri-axonal annular volume and the extra-axonal annular volume. Included in the structure but not shown, is an outer-region volume of infinite extent and high conductivity, providing a reference for the intra, peri and extra-axonal potentials. Applying Ohm's law, there is a potential drop along the length of each concentric cylindrical section which is a function of the specific conductivity and geometry of the medium, and the current passing through it. Figure 4.2 addresses the transverse electrical properties of the axolemmal membrane, the myelin sheath that surrounds it and a high impedance outer boundary membrane, represented as thin cylindrical shells. Again, applying Ohm's law, the potential drop across each shell, measured interior relative to exterior, is a function of the specific conductance of the equivalent membrane and the current per unit length (i^{ax} , i^{my} or i^{ob}) through it. In addition, each of the axolemmal and myelin membranes possesses a significant specific capacitance ($1\mu F/cm^2$ for the axon and $0.0025 - 0.005\mu F/cm^2$ for the myelin sheath) which necessitated their inclusion in the model. The outer boundary membrane is chosen to be a highly resistive barrier, possessing a very low specific conductance and a specific capacitance of zero. As outlined in the previous chapter, the axolemmal membrane possesses resistive ionic channels (Fig. 3.1) each channel characterized by a current-voltage relationship. Kirchoff's current and voltage laws were then applied to couple these elements as shown in Fig. 4.3. Using these fundamental principles, the model equivalent network was constructed.

4.2.1 Geometric variables

The variables describing the parameters of the equivalent cylindrical geometry are presented in Table 4.1, with the subscript X identifying the related segment, where N = NODE segment, M = MYSA segment, F = FLUT segment or S = STIN segment. Other geometric terms such as the thickness of an individual myelin lamellae (mt) are fixed, where $b_X = (a_X + \delta_X + nl_X mt)$.

Figure 4.1: Volumes formed by the intra, peri and extra-axonal spaces for a single longitudinal segment. The concentric elements are represented in an 'exploded' form, with the intra-axonal space on the left, peri-axonal space in the middle and extra-axonal space on the right. The diameter of the axon is shown as $2a$, the width of the peri-axonal space as δ and the diameter of the outer boundary of the extracellular space as $2c$. The length of the segment is Δz . The potential across the length of the each section is a function of the conductivity of the medium and the longitudinal current passing through it.

Figure 4.2: Axolemmal membrane, the surrounding myelin sheath and the outer boundary membrane, represented by concentric thin cylindrical shells also in ‘exploded’ form. In order to represent the transverse properties of the axon, myelin sheath and outer boundary, a shell with a length of Δz and diameter of $2a$ is formed for the axolemmal membrane, a shell of diameter $2b$ for the myelin sheath and a shell of diameter $2c$ for the outer boundary membrane. The potentials across the axon ($V^{ax} = V^i - V^p$), the myelin sheath ($V^{my} = V^p - V^o$) and the outer boundary ($V^{ob} = V^o - V^r$) where V^r is an outer-region iso-potential, are functions of their respective specific electrical properties and the currents $i^{ax}\Delta z$, $i^{my}\Delta z$ and $i^{ob}\Delta z$ present across them. The intra, peri and extra-axonal potentials are also shown for reference.

4.2.2 Electrical relations for passive network elements

Longitudinal coupling elements

The longitudinal resistive elements that represent the volumes presented in Fig. 4.1 are now formed. Using the nodal segment as an example, the magnitude of the longitudinal coupling resistances for the intra and peri-axonal spaces is a function of both the resistivity of the medium, where ρ^i = intra-axonal resistivity, ρ^p = peri-axonal resistivity, ρ^o = extra-axonal resistivity and the effective cross-sectional area presented

Figure 4.3: Component currents and potentials for a given longitudinal segment. This illustration shows the summation nodes and segments with their respective currents and potentials as used to employ Kirchoff's current and voltage laws to form the network relations. Note the sense of the currents, particularly the transverse currents as being positive outward and that the potentials are also referenced to the outer-region space. The peri-axonal potential, intra-axonal and extra-axonal potentials are referenced to the outer-region potential which is assumed to be iso-potential.

Table 4.1: Geometric Variables

Parameter	Definition
a_X	Radius of axon
b_X	Radius of outer surface of myelin sheath
c_X	Radius of outer boundary
δ_X	Width of peri-axonal space
nl_X	Number of myelin lamellae
ΔZ_X	Length of segment

at that longitudinal segment to generate per-unit-length resistances ($k\Omega/cm$),

$$r_N^o = \frac{\rho^o}{\pi(c_N^2 - b_N^2)} \quad (4.1)$$

$$r_N^p = \frac{\rho^p}{\pi((a_N + \delta_N)^2 - a_N^2)} \quad (4.2)$$

for the peri-axonal space and

$$r_N^i = \frac{\rho^i}{\pi(a_N)^2} \quad (4.3)$$

for the intra-axonal space, with $r_M^o, r_M^p, r_M^i, r_F^o, r_F^p, r_F^i, r_S^o, r_S^p, r_S^i$ formed in similar fashion. The absolute longitudinal coupling resistances ($k\Omega$) for this segment are formed by multiplying the per-unit-length resistance by the length of the segment

$$R_N^o = r_N^o \Delta Z_N, \quad (4.4)$$

$$R_N^p = r_N^p \Delta Z_N \quad (4.5)$$

and

$$R_N^i = r_N^i \Delta Z_N \quad (4.6)$$

with incorporation into the network as shown in Fig. 4.4. These longitudinal elements are then combined to form single elements

$$R_{NM}^o = r_N^o \frac{\Delta Z_N}{2} + r_M^o \frac{\Delta Z_M}{2}, \quad (4.7)$$

$$R_{NM}^p = r_N^p \frac{\Delta Z_N}{2} + r_M^p \frac{\Delta Z_M}{2} \quad (4.8)$$

and

$$R_{NM}^i = r_N^i \frac{\Delta Z_N}{2} + r_M^i \frac{\Delta Z_M}{2} \quad (4.9)$$

as shown in Fig. 4.5 with $R_{MF}^o, R_{MF}^p, R_{MF}^i, R_{FS}^o, R_{FS}^p, R_{FS}^i, R_{SS}^o, R_{SS}^p$ and R_{SS}^i formed likewise. Since the cross-sectional geometry is non-cylindrical in the fluted region, separate radii are used to calculate the cross-sectional area versus the surface area.

Transverse coupling elements

As seen in Fig. 4.2, equivalent cylindrical shells represent the axolemmal membrane and surrounding myelin sheath for a given longitudinal segment. The surface area is the important parameter in formation of the transverse elements. Axolemmal capacitances are formed by multiplication of the specific capacitances by the effective circumference of the segment to produce per-unit-length values ($\mu F/cm$),

$$C_N^{ax} = 2\pi a_N c_N^{ax} \quad (4.10)$$

with C_M^{ax}, C_F^{ax} and C_S^{ax} likewise. The myelin capacitances are formed in similar fashion,

$$C_M^{my} = 2\pi \left[a_M + \delta_M + \frac{nl_M mt}{2} \right] \frac{c^{my}}{nl_M} \quad (4.11)$$

for the FLUT and STIN segments also, using the specific capacitance of a single layer of the myelin sheath divided by the number of layers. The myelin conductances (mS/cm) are formed in the same way,

$$G_M^{my} = 2\pi \left[a_M + \delta_M + \frac{nl_M mt}{2} \right] \frac{g^{my}}{nl_M} \quad (4.12)$$

with G_F^{my} and G_S^{my} likewise. For the nodal segment, the myelin sheath is not present and the outer transverse element is represented by a conductance alone which reflects the resistance presented by the nodal gap constriction shown in Fig. 2.2. The outer boundary possesses a single conductance with the value,

$$G_M^{ob} = 2\pi c_M g^{ob}. \quad (4.13)$$

Figure 4.4: Equivalent network for the nodal region before consolidation of longitudinal resistances. The longitudinal and transverse elements for the nodal and adjacent MYSA segments are shown, with the Δz increments for the nodal and MYSA segments noted. The multi-axial form is evident, the outer-region longitudinal pathway is assumed to be of low enough resistance to be set to an iso-potential, the extra, peri and intra-axonal longitudinal resistances (R_N^o , R_N^p , R_N^i , R_M^o , R_M^p and R_M^i) are included and split, placing the transverse element in the center of the segment. The transverse elements for the outer-boundary membrane are simple conductances. The myelin sheath transverse elements shown for the MYSA segment are a paralleled capacitance and conductance, with only a single conductance present in the nodal gap region. For the axolemmal membrane, the transverse elements are shown as boxes containing the circuit equivalents for the ionic channels and a passive capacitance and conductance.

Figure 4.5: Equivalent network for the nodal region after consolidation of longitudinal resistances. The longitudinal resistive elements for the separate segments are combined to form single elements R_{NM}^o , R_{NM}^p , R_{NM}^i , R_{MF}^o , R_{MF}^p and R_{MF}^i . The spatial indices are $k - 1$, k and $k + 1$.

As mentioned in Section 4.2.2 a separate radius is defined for the surface versus cross-sectional area computations allowing for representation of the increased surface area seen in the fluted region.

4.2.3 Nodal segment

Using the network shown in Fig. 4.5, expressions can now be formed for the model which represent the distributed-parameter properties. Focusing first on the nodal region, the following expressions can be formed using a modified implicit form, utilizing both present and future temporal values of the intra-axonal and peri-axonal

potentials. The indices used for the difference expressions are k for the longitudinal spatial index and j for the temporal index.

Intra-axonal expressions

First, forming expressions for the longitudinal currents as functions of the potentials along the intra-axonal space at the j th time instant,

$$I_L^i(k, j) = \frac{V_{k-1,j}^i - V_{k,j}^i}{R_{NM}^i} \quad (4.14)$$

and

$$I_L^i(k+1, j) = \frac{V_{k,j}^i - V_{k+1,j}^i}{R_{NM}^i} \quad (4.15)$$

For the subsequent time step:

$$I_L^i(k, j+1) = \frac{V_{k-1,j+1}^i - V_{k,j+1}^i}{R_{NM}^i} \quad (4.16)$$

and

$$I_L^i(k+1, j+1) = \frac{V_{k,j+1}^i - V_{k+1,j+1}^i}{R_{NM}^i}. \quad (4.17)$$

These are combined to form an expression centered around the $j+1/2$ time point,

$$I_L^i(k, j+1/2) = \frac{V_{k-1,j}^i - V_{k,j}^i}{2R_{NM}^i} + \frac{V_{k-1,j+1}^i - V_{k,j+1}^i}{2R_{NM}^i} \quad (4.18)$$

and

$$I_L^i(k+1, j+1/2) = \frac{V_{k,j}^i - V_{k+1,j}^i}{2R_{NM}^i} + \frac{V_{k,j+1}^i - V_{k+1,j+1}^i}{2R_{NM}^i}. \quad (4.19)$$

Using Kirchoff's current law (KCL) by taking the difference of these longitudinal currents to form the transverse current,

$$I_{k,j+1/2}^{ax} = i_{k,j+1/2}^{ax} \Delta Z_N = I_L^i(k, j+1/2) - I_L^i(k+1, j+1/2) \quad (4.20)$$

a second order averaged spatial difference expression about the time point at $j+1/2$ results,

$$I_{k,j+1/2}^{ax} = \frac{(V_{k-1,j}^i - 2V_{k,j}^i + V_{k+1,j}^i) + (V_{k-1,j+1}^i - 2V_{k,j+1}^i + V_{k+1,j+1}^i)}{2R_{NM}^i}. \quad (4.21)$$

Setting this equivalent to a temporal difference expression describing the current present across the axolemmal membrane as a function of the capacitance of the membrane and the component ionic currents and passive leakage,

$$I_{k,j+1/2}^{ax} = i_{k,j+1/2}^{ax} \Delta Z_N = \left[C_N^{ax} \frac{(V_{k,j+1}^i - V_{k,j+1}^p) - (V_{k,j}^i - V_{k,j}^p)}{\Delta t} + i_N^{ionic} \right] \Delta Z_N \quad (4.22)$$

results in

$$\begin{aligned} & \frac{(V_{k-1,j}^i - 2V_{k,j}^i + V_{k+1,j}^i) + (V_{k-1,j+1}^i - 2V_{k,j+1}^i + V_{k+1,j+1}^i)}{2R_{NM}^i} \\ &= \left[C_N^{ax} \frac{(V_{k,j+1}^i - V_{k,j+1}^p) - (V_{k,j}^i - V_{k,j}^p)}{\Delta t} + i_N^{ionic} \right] \Delta Z_N. \end{aligned} \quad (4.23)$$

Note that the potential across the transverse element V^{ax} is expressed as the difference between the intra-axonal potential V^i and the peri-axonal potential V^p .

Rearranging the coefficients yields,

$$\begin{aligned} & V_{k-1,j+1}^i - \left(2 + \frac{2R_{NM}^i C_N^{ax} \Delta Z_N}{\Delta t} \right) V_{k,j+1}^i + V_{k+1,j+1}^i \\ &+ \left(\frac{2R_{NM}^i C_N^{ax} \Delta Z_N}{\Delta t} \right) V_{k,j+1}^p = \\ &- \left[V_{k-1,j}^i - \left(2 - \frac{2R_{NM}^i C_N^{ax} \Delta Z_N}{\Delta t} \right) V_{k,j}^i + V_{k+1,j}^i \right] \\ &+ \left(\frac{2R_{NM}^i C_N^{ax} \Delta Z_N}{\Delta t} \right) V_{k,j}^p + 2R_{NM}^i \Delta Z_N i_N^{ionic}. \end{aligned} \quad (4.24)$$

Note also that the use of both V^i and V^p to describe the axolemmal transmembrane potential results in the appearance of V^p on both sides of the equation.

This can be reduced to a general form,

$$\Psi_N^i V_{k-1,j+1}^i + \Theta_{N,j+1}^i V_{k,j+1}^i + \Lambda_N^i V_{k+1,j+1}^i + \Gamma_{N,j+1}^i V_{k,j+1}^p = \Phi_{N,j}^i \quad (4.25)$$

where

$$\Phi_{N,j}^i = -(\Psi_N^i V_{k-1,j}^i + \Theta_{N,j}^i V_{k,j}^i + \Lambda_N^i V_{k+1,j}^i) + \Gamma_{N,j}^i V_{k,j}^p + \Upsilon_{N,j}^{ionic}, \quad (4.26)$$

with the following coefficients,

$$\Psi_N^i = 1, \quad (4.27)$$

$$\Theta_{N,j+1}^i = -2 - \frac{2R_{NM}^i C_N^{ax} \Delta Z_N}{\Delta t}, \quad (4.28)$$

$$\Theta_{N,j}^i = -2 + \frac{2R_{NM}^i C_N^{ax} \Delta Z_N}{\Delta t}, \quad (4.29)$$

$$\Lambda_N^i = 1, \quad (4.30)$$

$$\Gamma_{N,j+1}^i = \Gamma_{N,j}^i = \frac{2R_{NM}^i C_N^{ax} \Delta Z_N}{\Delta t}, \quad (4.31)$$

and

$$\Upsilon_N^i = 2R_{NM}^i \Delta Z_N. \quad (4.32)$$

Peri-axonal expressions

In like fashion, a second order spatial difference equation can be formed to describe the currents across the nodal gap outside the node of Ranvier using the central summing node,

$$\Psi_N^p V_{k-1,j+1}^p + \Theta_{N,j+1}^p V_{k,j+1}^p + \Lambda_N^p V_{k+1,j+1}^p + \Gamma_{N,j+1}^p V_{k,j+1}^i + \bar{\Gamma}_{N,j+1}^p V_{k,j+1}^o = \Phi_{N,j}^p \quad (4.33)$$

with

$$\Phi_{N,j}^p = -(\Psi_N^p V_{k-1,j}^p + \Theta_{N,j}^p V_{k,j}^p + \Lambda_N^p V_{k+1,j}^p) + \Gamma_{N,j}^p V_{k,j}^i + \bar{\Gamma}_{N,j}^p V_{k,j}^o + \Upsilon_N^p i_N^{ionic} \quad (4.34)$$

where

$$\Psi_N^p = 1, \quad (4.35)$$

$$\Theta_{N,j+1}^p = -2 - \frac{2R_{NM}^p C_N^{ax} \Delta Z_N}{\Delta t} - G_N^{my} R_{NM}^p \Delta Z_N, \quad (4.36)$$

$$\Theta_{N,j}^p = -2 + \frac{2R_{NM}^p C_N^{ax} \Delta Z_N}{\Delta t} - G_N^{my} R_{NM}^p \Delta Z_N, \quad (4.37)$$

$$\Lambda_N^p = 1, \quad (4.38)$$

$$\Gamma_{N,j+1}^p = \Gamma_{N,j}^p = \frac{2R_{NM}^p C_N^{ax} \Delta Z_N}{\Delta t}, \quad (4.39)$$

$$\bar{\Gamma}_{N,j+1}^p = G_N^{my} R_{NM}^p \Delta Z_N, \quad (4.40)$$

$$\bar{\Gamma}_{N,j}^p = -G_N^{my} R_{NM}^p \Delta Z_N, \quad (4.41)$$

and

$$\Upsilon_N^p = -2R_{NM}^p \Delta Z_N. \quad (4.42)$$

As in the intra-axonal case, note the use of V^i and V^p to describe the potential across the axolemmal membrane, necessary in this case to represent the current through the transverse element of the axolemmal membrane at the central summing node. This results in an expression similar to that seen for the intra-axonal case with the roles of V^p and V^i reversed.

Extra-axonal expressions

For the outer-boundary membrane a similar relation is formed, the exception being the lack of a capacitative term and the contribution of ionic currents.

In general form,

$$\Psi_N^o V_{k-1,j+1}^o + \Theta_{N,j+1}^o V_{k,j+1}^o + \Lambda_N^o V_{k+1,j+1}^o + \Gamma_{N,j+1}^o V_{k,j+1}^p = \Phi_{N,j}^o \quad (4.43)$$

where

$$\Phi_{N,j}^o = -(\Psi_N^o V_{k-1,j}^o + \Theta_{N,j}^o V_{k,j}^o + \Lambda_N^o V_{k+1,j}^o) + \Gamma_{N,j}^o V_{k,j}^p, \quad (4.44)$$

with the following coefficients,

$$\Psi_N^o = 1, \quad (4.45)$$

$$\Theta_{N,j+1}^o = \Theta_{N,j}^o = -2 - (G_N^{ob} + G_N^{my}) R_{NM}^o \Delta Z_N, \quad (4.46)$$

$$\Lambda_N^o = 1, \quad (4.47)$$

$$\Gamma_{N,j+1}^o = G_N^{my} R_{NM}^o \Delta Z_N \quad (4.48)$$

and

$$\Gamma_{N,j}^o = -G_N^{my} R_{NM}^o \Delta Z_N. \quad (4.49)$$

This completes the expressions required to represent the nodal segment.

4.2.4 Paranodal and internodal segments

The MYSA segment requires a different form due to the spatial variation in the longitudinal coupling resistance values. This is presented in Fig. 4.6, showing the adjacent nodal, MYSA and FLUT segments.

Intra-axonal expressions

As in the nodal case, longitudinal currents for each segment are formed from the potential difference present across the longitudinal resistive elements, a transverse current is formed from their difference and set equivalent to the transverse current formed from the temporal difference of potential across the axolemmal membrane,

$$\begin{aligned} & \frac{1}{2} \left[\frac{(V_{k-1,j}^i - V_{k,j}^i)}{R_{NM}^i} - \frac{(V_{k,j}^i - V_{k+1,j}^i)}{R_{MF}^i} \right] + \frac{1}{2} \left[\frac{(V_{k-1,j+1}^i - V_{k,j+1}^i)}{R_{NM}^i} - \frac{(V_{k,j+1}^i - V_{k+1,j+1}^i)}{R_{MF}^i} \right] \\ &= \left[C_M^{ax} \frac{(V_{k,j+1}^i - V_{k,j+1}^p) - (V_{k,j}^i - V_{k,j}^p)}{\Delta t} + i_M^{ionic} \right] \Delta Z_M. \end{aligned} \quad (4.50)$$

As in the nodal case, this can be reduced to the following general form,

$$\Psi_M^i V_{k-1,j+1}^i + \Theta_{M,j+1}^i V_{k,j+1}^i + \Lambda_M^i V_{k+1,j+1}^i + \Gamma_{M,j+1}^i V_{k,j+1}^p = \Phi_{M,j}^i \quad (4.51)$$

Figure 4.6: Equivalent network for the nodal, MYSA and FLUT segments. There are different longitudinal coupling resistances for each segment, R_{NM}^o , R_{NM}^p , R_{NM}^i , R_{MF}^o , R_{MF}^p , R_{MF}^i , R_{FS}^o , R_{FS}^p and R_{FS}^i .

and

$$\Phi_{M,j}^i = -(\Psi_M^i V_{k-1,j}^i + \Theta_{M,j}^i V_{k,j}^i + \Lambda_M^i V_{k+1,j}^i) + \Gamma_{M,j}^i V_{k,j}^p + \Upsilon_M^i i_M^{ionic}, \quad (4.52)$$

using more complicated coefficients,

$$\Psi_M^i = \frac{2R_{MF}^i}{R_{NM}^i + R_{MF}^i}, \quad (4.53)$$

$$\Theta_{M,j+1}^i = -2 - \frac{4R_{NM}^i R_{MF}^i C_M^{ax} \Delta Z_M}{(R_{NM}^i + R_{MF}^i) \Delta t}, \quad (4.54)$$

$$\Theta_{M,j}^i = -2 + \frac{4R_{NM}^i R_{MF}^i C_M^{ax} \Delta Z_M}{(R_{NM}^i + R_{MF}^i) \Delta t}, \quad (4.55)$$

$$\Lambda_M^i = \frac{2R_{NM}^i}{R_{NM}^i + R_{MF}^i}, \quad (4.56)$$

$$\Gamma_{M,j+1}^i = \Gamma_{M,j}^i = \frac{4R_{NM}^i R_{MF}^i C_M^{ax} \Delta Z_M}{(R_{NM}^i + R_{MF}^i) \Delta t}, \quad (4.57)$$

and

$$\Upsilon_M^i = \frac{4R_{NM}^i R_{MF}^i \Delta Z_M}{R_{NM}^i + R_{MF}^i}. \quad (4.58)$$

Peri-axonal expressions

In like fashion, the expressions for the transverse currents found across the myelin sheath can be formed,

$$\begin{aligned} & \frac{1}{2} \left[\frac{(V_{k,j-1}^p - V_{k,j}^p)}{R_{NM}^p} - \frac{(V_{k,j}^p - V_{k+1,j}^p)}{R_{MF}^p} \right] + \frac{1}{2} \left[\frac{(V_{k-1,j+1}^p - V_{k,j+1}^p)}{R_{NM}^p} - \frac{(V_{k,j+1}^p - V_{k+1,j+1}^p)}{R_{MF}^p} \right] \\ &= \left[C_M^{my} \frac{(V_{k,j+1}^p - V_{k,j+1}^o) - (V_{k,j}^p - V_{k,j}^o)}{\Delta t} + G_M^{my} \frac{(V_{k,j}^p - V_{k,j}^o) + (V_{k,j+1}^p - V_{k,j+1}^o)}{2} \right] \Delta Z_M \\ & \quad - \left[C_M^{ax} \frac{(V_{k,j+1}^i - V_{k,j+1}^p) - (V_{k,j}^i - V_{k,j}^p)}{\Delta t} - i_M^{ionic} \right] \Delta Z_M. \end{aligned} \quad (4.59)$$

This also reduces to a general form,

$$\Psi_M^p V_{k-1,j+1}^p + \Theta_{M,j+1}^p V_{k,j+1}^p + \Lambda_M^p V_{k+1,j+1}^p + \Gamma_{M,j+1}^p V_{k,j+1}^i + \bar{\Gamma}_{M,j+1}^p V_{k,j+1}^o = \Phi_{M,j}^p \quad (4.60)$$

and

$$\Phi_{M,j}^p = -(\Psi_M^p V_{k-1,j}^p + \Theta_{M,j}^p V_{k,j}^p + \Lambda_M^p V_{k+1,j}^p) + \Gamma_{M,j}^p V_{k,j}^i + \bar{\Gamma}_{M,j}^p V_{k,j}^o + \Upsilon_M^p i_M^{ionic}, \quad (4.61)$$

with the following coefficients,

$$\Psi_M^p = \frac{2R_{MF}^p}{R_{NM}^p + R_{MF}^p}, \quad (4.62)$$

$$\Theta_{M,j+1}^p = -2 - \frac{4R_{NM}^p R_{MF}^p (C_M^{my} + C_M^{ax}) \Delta Z_M}{(R_{NM}^p + R_{MF}^p) \Delta t} - \frac{2R_{NM}^p R_{MF}^p G_M^{my} \Delta Z_M}{(R_{NM}^p + R_{MF}^p)}, \quad (4.63)$$

$$\Theta_{M,j}^p = -2 + \frac{4R_{NM}^p R_{MF}^p (C_M^{my} + C_M^{ax}) \Delta Z_M}{(R_{NM}^p + R_{MF}^p) \Delta t} - \frac{2R_{NM}^p R_{MF}^p G_M^{my} \Delta Z_M}{(R_{NM}^p + R_{MF}^p)}, \quad (4.64)$$

$$\Lambda_M^p = \frac{2R_{NM}^p}{R_{NM}^p + R_{MF}^p}, \quad (4.65)$$

$$\Gamma_{M,j+1}^p = \Gamma_{M,j}^p = \frac{4R_{NM}^p R_{MF}^p C_M^{ax} \Delta Z_M}{(R_{NM}^p + R_{MF}^p) \Delta t}, \quad (4.66)$$

$$\bar{\Gamma}_{M,j+1}^p = \frac{4R_{NM}^p R_{MF}^p C_M^{my} \Delta Z_M}{(R_{NM}^p + R_{MF}^p) \Delta t} + \frac{2R_{NM}^p R_{MF}^p G_M^{my} \Delta Z_M}{(R_{NM}^p + R_{MF}^p)}, \quad (4.67)$$

$$\bar{\Gamma}_{M,j}^p = \frac{4R_{NM}^p R_{MF}^p C_M^{my} \Delta Z_M}{(R_{NM}^p + R_{MF}^p) \Delta t} - \frac{2R_{NM}^p R_{MF}^p G_M^{my} \Delta Z_M}{(R_{NM}^p + R_{MF}^p)} \quad (4.68)$$

and

$$\Upsilon_M^p = \frac{4R_{NM}^p R_{MF}^p \Delta Z_M}{R_{NM}^p + R_{MF}^p}. \quad (4.69)$$

Extra-axonal expressions

Unlike the nodal case, the MYSA segment couples in a capacitative term contributed by the myelin sheath.

$$\begin{aligned} \frac{1}{2} \left[\frac{(V_{k-1,j}^o - V_{k,j}^o)}{R_{NM}^o} - \frac{(V_{k,j}^o - V_{k+1,j}^o)}{R_{MF}^o} \right] + \frac{1}{2} \left[\frac{(V_{k-1,j+1}^o - V_{k,j+1}^o)}{R_{NM}^o} - \frac{(V_{k,j+1}^o - V_{k+1,j+1}^o)}{R_{MF}^o} \right] \\ = \left[C_M^{my} \frac{(V_{k,j+1}^p - V_{k,j+1}^o) - (V_{k,j}^p - V_{k,j}^o)}{\Delta t} \right. \\ \left. + G_M^{my} \frac{(V_{k,j+1}^p - V_{k,j+1}^o) + (V_{k,j}^p - V_{k,j}^o)}{2} - G_M^{ob} \frac{(V_{k,j+1}^o + V_{k,j}^o)}{2} \right] \Delta Z_M. \end{aligned} \quad (4.70)$$

Reducing to the general form yields,

$$\Psi_M^o V_{k-1,j+1}^o + \Theta_{M,j+1}^o V_{k,j+1}^o + \Lambda_M^o V_{k+1,j+1}^o + \Gamma_{M,j+1}^o V_{k,j+1}^p = \Phi_{M,j}^o \quad (4.71)$$

and

$$\Phi_{M,j}^o = -(\Psi_M^o V_{k-1,j}^o + \Theta_{M,j}^o V_{k,j}^o + \Lambda_M^o V_{k+1,j}^o) + \Gamma_{M,j}^o V_{k,j}^p, \quad (4.72)$$

with the following coefficients,

$$\Psi_M^o = \frac{2R_{MF}^o}{R_{NM}^o + R_{MF}^o}, \quad (4.73)$$

$$\Theta_{M,j+1}^o = -2 - \frac{4R_{NM}^o R_{MF}^o C_M^{my} \Delta Z_M}{(R_{NM}^o + R_{MF}^o) \Delta t} - \frac{2R_{NM}^o R_{MF}^o (G_M^{my} + G_M^{ob}) \Delta Z_M}{(R_{NM}^o + R_{MF}^o)}, \quad (4.74)$$

$$\Theta_{M,j}^o = -2 + \frac{4R_{NM}^o R_{MF}^o C_M^{my} \Delta Z_M}{(R_{NM}^o + R_{MF}^o) \Delta t} - \frac{2R_{NM}^o R_{MF}^o (G_M^{my} + G_M^{ob}) \Delta Z_M}{(R_{NM}^o + R_{MF}^o)}, \quad (4.75)$$

$$\Lambda_M^o = \frac{2R_{NM}^o}{R_{NM}^o + R_{MF}^o}, \quad (4.76)$$

$$\Gamma_{M,j+1}^o = \frac{4R_{NM}^o R_{MF}^o C_M^{my} \Delta Z_M}{(R_{NM}^o + R_{MF}^o) \Delta t} + \frac{2R_{NM}^o R_{MF}^o G_M^{my} \Delta Z_M}{(R_{NM}^o + R_{MF}^o)} \quad (4.77)$$

and

$$\Gamma_{M,j}^o = \frac{4R_{NM}^o R_{MF}^o C_M^{my} \Delta Z_M}{(R_{NM}^o + R_{MF}^o) \Delta t} - \frac{2R_{NM}^o R_{MF}^o G_M^{my} \Delta Z_M}{(R_{NM}^o + R_{MF}^o)}. \quad (4.78)$$

The expressions for the FLUT segments and STIN segments are similar in form to that of the MYSA segment. The transition from one type of segment to another requires the same treatment, due to alteration in the longitudinal coupling values. This derivation presents the MYSA and FLUT segments as being single segments in the triaxial model, in practice these portions of the paranodal region are represented by multiple discrete segments which are tapered from region to region.

4.2.5 Boundary conditions

Sealed-end conditions are assumed for the model. As can be seen in Fig. 4.7, the transaxonal current can be made equivalent to the longitudinal intra-axonal current, the transmyelin current can be equivalenced to the difference in the longitudinal peri-axonal and extra-axonal currents and the transverse outer-boundary current can be set equal to the outer region longitudinal current.

A point of concern is the effect of the end conditions on the performance of the model, influencing the results of the simulation. In this case, the sealed-end offers advantages to the shorted end termination, in that there is not a resulting depolarization of the active membrane near the termination point. However, the potentials at the end of the model tend to be larger than those seen in other portions of the model due the lower effective load presented by the sealed-end.

4.2.6 Matrix form of the equation system

As can be seen in the previous sections, the form of the equation system falls into three principle finite difference expressions, one describing the relation of the longitudinal to transverse currents in the intra-axonal space, one describing the relation of the longitudinal to transverse currents in the peri-axonal space and the other describing the relation of the longitudinal to transverse currents in the extra-axonal space.

Figure 4.7: Sealed end termination for the model. The extremes of the model are terminated by an open circuit, or sealed end. This results in the longitudinal outer region current being equivalenced to the transboundary current, the difference in the longitudinal outer boundary and extra-axonal currents being equivalenced to the transmyelin current and the intra-axonal longitudinal current being equivalenced to the transaxonal current. This termination occurs in an internode of the nerve fiber as indicated by the STIN labels.

Each of these expressions is in the form of a second order spatial difference expression equivalenced to a first order temporal difference. The primary state variables are the intra-axonal potential V^i , the peri-axonal potential V^p and the extra-axonal potential V^o . Each expression has terms containing at least one of the other state variables, therefore this system of equations must be solved simultaneously. The coefficients in these expressions are constant with any given geometry and passive electrical properties. The non-linearities are present within the expression for i^{ionic} which drives the

solution for the new values of the state variables intra and peri-axonal potential at each discrete time step. The system takes on the appearance of a cross-coupled set of parabolic partial differential equations. Forming vectors for the intra and peri-axonal potentials, these coefficients can be put in matrix form where,

$$A \underline{V} = \underline{\Phi}. \quad (4.79)$$

A represents the matrix of coefficients, $\underline{V}$ represents the vector of potentials at the future time step with $\underline{\Phi}$ driving the solution. Taking a total number of n segments in the model, A becomes a $3n \times 3n$ matrix. In the reduced case, where the extracellular resistance is sufficiently low to set the extracellular potential to be iso-potential, the system of equations can be reduced to that of two state variables, V^i and V^p . This takes the form of a $2n \times 2n$ matrix as shown in Appendix E.

The basic structure of the matrix A consists of three divisions of the diagonal representing the coefficients operating on the local state variables with the off-diagonal blocks representing the cross-coupling between state variables as seen in the following representation,

$$A = \left[\begin{array}{c|c|c} \Theta^o & \Gamma^o & 0 \\ \hline \bar{\Gamma}^p & \Theta^p & \Gamma^p \\ \hline 0 & \Gamma^i & \Theta^i \end{array} \right]. \quad (4.80)$$

The following illustrates the extremes of the matrix equation, reflecting the end conditions,

$$A = \begin{bmatrix} \Theta_E^o & 1 & \dots & 0 & 0 & \Gamma_{SS}^o & 0 & \dots & 0 & 0 & 0 & 0 & \dots & 0 & 0 \\ 1 & \Theta_{SS}^o & \dots & 0 & 0 & 0 & \Gamma_{SS}^o & \dots & 0 & 0 & 0 & 0 & \dots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \dots & \Theta_{SS}^o & 1 & 0 & 0 & \dots & \Gamma_{SS}^o & 0 & 0 & 0 & \dots & 0 & 0 \\ 0 & 0 & \dots & 1 & \Theta_E^o & 0 & 0 & \dots & 0 & \Gamma_{SS}^o & 0 & 0 & \dots & 0 & 0 \\ \Gamma_{SS}^p & 0 & \dots & 0 & 0 & \Theta_E^p & 1 & \dots & 0 & 0 & \Gamma_{SS}^p & 0 & \dots & 0 & 0 \\ 0 & \Gamma_{SS}^p & \dots & 0 & 0 & 1 & \Theta_{SS}^p & \dots & 0 & 0 & 0 & \Gamma_{SS}^p & \dots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \dots & \Gamma_{SS}^p & 0 & 0 & 0 & \dots & \Theta_{SS}^p & 1 & 0 & 0 & \dots & \Gamma_{SS}^p & 0 \\ 0 & 0 & \dots & 0 & \Gamma_{SS}^p & 0 & 0 & \dots & 1 & \Theta_E^p & 0 & 0 & \dots & 0 & \Gamma_{SS}^p \\ 0 & 0 & \dots & 0 & 0 & \Gamma_{SS}^i & 0 & \dots & 0 & 0 & \Theta_E^i & 1 & \dots & 0 & 0 \\ 0 & 0 & \dots & 0 & 0 & 0 & \Gamma_{SS}^i & \dots & 0 & 0 & 1 & \Theta_{SS}^i & \dots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \dots & 0 & 0 & 0 & 0 & \dots & \Gamma_{SS}^i & 0 & 0 & 0 & \dots & \Theta_{SS}^i & 1 \\ 0 & 0 & \dots & 0 & 0 & 0 & 0 & \dots & 0 & \Gamma_{SS}^i & 0 & 0 & \dots & 1 & \Theta_E^i \end{bmatrix} \quad (4.81)$$

with

$$A \bullet \begin{bmatrix} V_{1,j+1}^o \\ V_{2,j+1}^o \\ \vdots \\ V_{n-1,j+1}^o \\ V_{n,j+1}^o \\ V_{1,j+1}^p \\ V_{2,j+1}^p \\ \vdots \\ V_{n-1,j+1}^p \\ V_{n,j+1}^p \\ V_{1,j+1}^i \\ V_{2,j+1}^i \\ \vdots \\ V_{n-1,j+1}^i \\ V_{n,j+1}^i \end{bmatrix} = \begin{bmatrix} \Phi_1^o \\ \Phi_2^o \\ \vdots \\ \Phi_{n-1}^o \\ \Phi_n^o \\ \Phi_1^p \\ \Phi_2^p \\ \vdots \\ \Phi_{n-1}^p \\ \Phi_n^p \\ \Phi_1^i \\ \Phi_2^i \\ \vdots \\ \Phi_{n-1}^i \\ \Phi_n^i \end{bmatrix} \quad (4.82)$$

where $\Theta_E^o = \Theta_{SS}^o - 1$, $\Theta_E^p = \Theta_{SS}^p - 1$ and $\Theta_E^i = \Theta_{SS}^i - 1$. The subscript SS denotes the coefficients for a STIN-STIN segment.

The change in coefficients as the node is approached can be seen as,

$$A = \begin{bmatrix} \vdots & \vdots & \vdots & \vdots & & \vdots & \vdots & \vdots & \vdots & & \vdots & \vdots & \vdots & \vdots \\ \dots & \Theta_S^o & \Lambda_S^o & 0 & 0 & \dots & \Gamma_S^o & 0 & 0 & 0 & \dots & 0 & 0 & 0 & 0 & \dots \\ \dots & \Psi_F^o & \Theta_F^o & \Lambda_F^o & 0 & \dots & 0 & \Gamma_F^o & 0 & 0 & \dots & 0 & 0 & 0 & 0 & \dots \\ \dots & 0 & \Psi_M^o & \Theta_M^o & \Lambda_M^o & \dots & 0 & 0 & \Gamma_M^o & 0 & \dots & 0 & 0 & 0 & 0 & \dots \\ \dots & 0 & 0 & \Psi_N^o & \Theta_N^o & \dots & 0 & 0 & 0 & \Gamma_N^o & \dots & 0 & 0 & 0 & 0 & \dots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \\ \dots & \Gamma_S^p & 0 & 0 & 0 & \dots & \Theta_S^p & \Lambda_S^p & 0 & 0 & \dots & \Gamma_S^p & 0 & 0 & 0 & \dots \\ \dots & 0 & \Gamma_F^p & 0 & 0 & \dots & \Psi_F^p & \Theta_F^p & \Lambda_F^p & 0 & \dots & 0 & \Gamma_F^p & 0 & 0 & \dots \\ \dots & 0 & 0 & \Gamma_M^p & 0 & \dots & 0 & \Psi_M^p & \Theta_M^p & \Lambda_M^p & \dots & 0 & 0 & \Gamma_M^p & 0 & \dots \\ \dots & 0 & 0 & 0 & \Gamma_N^p & \dots & 0 & 0 & \Psi_N^p & \Theta_N^p & \dots & 0 & 0 & 0 & \Gamma_N^p & \dots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \\ \dots & 0 & 0 & 0 & 0 & \dots & \Gamma_S^i & 0 & 0 & 0 & \dots & \Theta_S^i & \Lambda_S^i & 0 & 0 & \dots \\ \dots & 0 & 0 & 0 & 0 & \dots & 0 & \Gamma_F^i & 0 & 0 & \dots & \Psi_F^i & \Theta_F^i & \Lambda_F^i & 0 & \dots \\ \dots & 0 & 0 & 0 & 0 & \dots & 0 & 0 & \Gamma_M^i & 0 & \dots & 0 & \Psi_M^i & \Theta_M^i & \Lambda_M^i & \dots \\ \dots & 0 & 0 & 0 & 0 & \dots & 0 & 0 & 0 & \Gamma_N^i & \dots & 0 & 0 & \Psi_N^i & \Theta_N^i & \dots \\ \vdots & \vdots & \vdots & \vdots & & & \vdots & \vdots & \vdots & \vdots & & \vdots & \vdots & \vdots & \vdots & \end{bmatrix} \quad (4.83)$$

with

$$A \bullet \begin{bmatrix} \vdots \\ V_{S,j+1}^o \\ V_{F,j+1}^o \\ V_{M,j+1}^o \\ V_{N,j+1}^o \\ \vdots \\ V_{S,j+1}^p \\ V_{F,j+1}^p \\ V_{M,j+1}^p \\ V_{N,j+1}^p \\ \vdots \\ V_{S,j+1}^i \\ V_{F,j+1}^i \\ V_{M,j+1}^i \\ V_{N,j+1}^i \\ \vdots \end{bmatrix} = \begin{bmatrix} \vdots \\ \Phi_S^o \\ \Phi_F^o \\ \Phi_M^o \\ \Phi_N^o \\ \vdots \\ \Phi_S^p \\ \Phi_F^p \\ \Phi_M^p \\ \Phi_N^p \\ \vdots \\ \Phi_S^i \\ \Phi_F^i \\ \Phi_M^i \\ \Phi_N^i \\ \vdots \end{bmatrix} \quad (4.84)$$

This coefficient matrix is quindagonal in form, with two diagonals immediately adjacent to the principal diagonal and two diagonals at a distance of n from the principal diagonal. As a node of Ranvier is approached, the coefficients change asymmetrically along each of the two off-center diagonals. The two outer diagonals are composed of different coefficients and also contribute to the asymmetry of the matrix. The solution method must therefore deal with a matrix which is asymmetric and quindagonal with two of the diagonals being distant from the principal diagonal. Possibilities are application of decomposition techniques applicable to general matrices, such as an LU decomposition followed by a Gaussian elimination methods to solve for the vector $\underline{V}$. Also possible, if the matrix A is non-singular and well conditioned, is formation of the inverse A^{-1} with performance of a matrix multiplication versus a back-substitution method in formation of the solution for $\underline{V}$ at each time interval.

4.2.7 Computational molecule

This system of finite difference expressions can be viewed schematically in a spatio-temporal form that illustrates the operations performed on the three state variables V^i , V^p and V^o . Figure 4.8 shows the computational molecules for the intra-axonal, peri-axonal and extra-axonal expressions present in the space-time plane for each state variable. This form of presentation helps in visualizing the implicit nature of the solution, in that multiple values of each state variable at the future time point are used in solving for those values. The molecule can also be looked upon as a combination of an explicit method, where three present-time points are used to solve for one future time point, and a basic version of the implicit method, using one present time point and three future time points. For each time increment j , the span of the spatial dimension is traveled by the second order spatial difference expression,

Figure 4.8: Computational molecule for the equation system. The space-time domain of the state variables V^i , V^p and V^o are represented by a grid of points for each variable. The spatial index is k and the temporal index is j . A second-order spatial difference expression is formed by three spatial points for both the present j and future $j+1$ temporal step for each case. This results in a computational molecule which is centered about the $k, j+1/2$ point for each state variable and is also balanced between the domain of each state variable.

operating on three adjacent spatial points. The ‘balanced’ nature of this technique can be seen by the use of both present and future time values of these spatial points to generate the future time values, effectively balanced around the $j + 1/2$ time step. Furthermore, the intra, peri and extra-axonal computational molecules are balanced about a central point since that each uses present and future time values of the other state variable to determine a new value for it’s own. In this way, the philosophy of the Crank-Nicolson [32] method for the finite difference approximation to the parabolic partial differential equation was employed to insure computational stability.

4.2.8 Scaling

A very important aspect of solving a large matrix expression, such as the one describing this model, is proper scaling of the matrix equation to insure that difficulties will not be encountered in the numerical solution. The fundamental units adopted for the model simulation are as follows; time - ms , space - cm , potential - mV , current - μA and temperature - $^{\circ}C$. The derived units are; specific capacitance - $\mu F/cm^2$ ($\mu F = (\mu A ms)/mV$), resistivity - $K\Omega-cm$ ($K\Omega = mV/\mu A$) and specific conductance - mS/cm^2 ($mS = \mu A/mV$).

4.2.9 Stability and error measures

As a numerical solution of this expression is formed for each time increment, a measure of the error present at each time interval is desired in order to monitor the accuracy of the algorithm and adequacy of the computational parameters. As there is no analytic expression against which to compute a strict error measure, assessment of the stability of the solution is a practical means of determining whether the temporal and spatial step sizes used are appropriate. A sensitive monitor of stability is the spatial character of the state variables V^i , V^p , V^o and the tranverse currents formed

by the second-order spatial difference of these potentials. By examining the these currents during the formation of the solution, oscillations resulting from instabilities should be evident. An estimate can also be made of the error in forming the ionic currents by comparing the magnitude of the time constants used for the dynamics of the Na^+ and K^+ channels versus the temporal step size used in solution of the overall problem. The implementation of the numerical solution is now presented in the following section.

4.3 Computational Methods

Given the mathematical structure of the model and the nature of the options for achieving a numerical solution, selection and development of a computational algorithm is the next task.

4.3.1 Parallel versus sequential computation

The application of new parallel processor computer systems to these types of mathematical models is a very active area of current research. Since the physical structure of this model is distributed, it is well suited for solution on a computer based upon a parallel architecture. Initial development was performed on a single-processor system (Sun Microsystems 3/260) which worked very well, however, since a parallel processor (Sequent Systems model S81) was available for use, the model algorithm was restructured and implemented on this machine. In this light, relevant portions of the algorithm will be described as implemented on the parallel processor.

4.3.2 Structure of the algorithm

The solution of the expressions describing the distributed - parameter model entails,

- Construction of the A coefficient matrix from the given geometric and biophysical properties,
- Decomposition and inversion of the matrix in preparation for solution of the matrix equation,
- Initialization of the V^i, V^p, V^o, m, h, n_f and n_s state variables for each segment,
- Execution of the following steps for each time increment,
 1. Determination of the ionic currents for each axon segment. (Parallel)
 2. Construction of the Φ matrix, including injection of a stimulus current if indicated. (Parallel)
 3. Solution of the matrix equation to find new $\underline{V}$. (Parallel)
 4. Output of the new V^i, V^p, V^o and component ionic currents.
- Termination.

The major steps are described in the following sections.

Construction of the coefficient matrix

The detailed geometry present in this model, along with the distributed character of the biophysical properties of the respective model elements, requires careful formulation of the elements of the coefficient matrix A . As is evident in Sections 4.2.3 and 4.2.4 the algebraic expressions can be complex. An algorithm was developed allowing for representation of a myelinated nerve fiber that possesses nodes spaced at even intervals with stereotyped internodal and nodal properties but allowing for representation of the complexity present in the nodal and paranodal regions. This was achieved by representing the transitions from the nodal to MYSA to FLUT to

STIN segments with coefficients for these sections calculated by assuming a linear variation in parameters such as axon radius. In this way, a ‘tapered’ cylindrical model can be formed and the ability to represent changes in other parameters such as the permeability of ionic channels with position along the axon realized. An aid to accomplishing this was definition of the geometric and biophysical properties in a single file which could be easily modified, thereby avoiding the need for time delays caused by recompilation of the program code. Two versions of the algorithm were developed, one for the quadaxial structure containing the outer boundary as derived in Section 4.2 and the other for the reduced triaxial structure presented in Appendix E. These two versions required the formulation of different coefficients and necessitated the inclusion of different numbers of vectors representing the state variables. There were only minimal changes to the format of the input parameter files.

Solving for the component ionic currents

The solution technique used for the generation of the component ionic currents present at each time interval was identical to that presented in Section 3.4. The Rush-Larsen [93] technique was used and vectorized, in that each axonal segment was given a separate representation for the state of the gating variables. The solution was parallelized by dividing the number of axonal segments present in the model across the number of processors designated for use. Each processor then computed the new values for the gating variable as well as solved the GHK or conductance expressions necessary to form the current densities and total transmembrane ionic current for each axonal segment.

Formation of the Φ vector

Φ was formed from the ionic currents and the combination of other coefficients and state variables by using a parallelized routine as well. This routine also provided injection of the stimulus currents as defined by the input file.

Solving the matrix equation

LINPACK [36] was selected for manipulation of the A matrix by utilizing the routines for general matrices, DGECCO (Double precision GEneral factorization and COndition estimation) for LU factorization of A using Gaussian elimination with partial pivoting as well as estimation of the reciprocal condition number and DGEDI (Double precision GEneral factorization and Determinate and Inverse computation) to form A^{-1} . Initially, when the single-processor system was utilized, the DGECL (Double precision GEneral SoLution) routine was used to solve the matrix equation. The parallelization of this method, which entails formation of the solution of $A \underline{V} = \Phi$ by performing solution of $\underline{L} \underline{y} = \Phi$ and $\underline{U} \underline{V} = \underline{y}$, was investigated and necessitated modification of the basic linear algebra subroutines (BLAS) in order to take advantage of the parallel architecture. Consideration was given to making these modifications, however it was discovered that J.J Dongarra of Argonne National Labs and others were actively working on development of a parallel version of the LINPACK routines, therefore the decision was made to defer this effort. As an alternative, gains could definitely be made by implementation of a parallel matrix multiplication method on the parallel processor by forming A^{-1} and using it as a means to compute the new values for $\underline{V}$ at each time increment.

The possible advantages of the banded matrix routines were examined, which conserve memory resources as well as offer advantages in execution speed, but unfortunately the lateral bands in A are too distant from the principle diagonal to benefit

from this approach. The breakpoint is reached however for problems using one or more outer shells than presently used in the model. As more concentric shells are added to the model structure, the lateral bands in A become proportionally closer to the principle diagonal and therefore begin to gain from the implementation of the banded algorithm.

4.3.3 Description of software

The C programming language was selected for use in implementation of the algorithm. The rational behind selection of C was due to the relatively superior development tools available on the Unix-based Sun and Sequent systems. The main C code was then linked to the Fortran code of LINPACK. A large system global memory space was used to contain all state variables, including A and the other matrices.

QUAD and TRIAX routines

Two versions of the algorithm were coded into programs. QUAD was the name of the routine implementing the mathematical form of the model as described in Section 4.2. The TRIAX routine was an implementation of the reduced problem as presented in Appendix E. Each of these routines performed initialization of local variables, obtained the model parameters from the input file containing the geometric and biophysical data through the INPUT routine, constructed the A matrix and called the LINPACK routines DGECCO and DGEDI to form A^{-1} . A computation loop was then initiated which performed initial computation of the component ionic currents from the parallelized IONIC routine and constructed the Φ matrix necessary to drive the solution. A parallel matrix multiplication operation was then performed by the MATRIX routine and the resulting new value of V was output to relevant files

along with other state variable information such as the component currents for each segment, etc.

Parallel features

The Sequent machine possesses 20 Intel 386 processors each with a Weitek floating point accelerator which are based on a shared memory architecture currently configured with 80 megabytes of random access memory. The operating system is referred to as the Dynix operating system which coordinates the system resources of the multiple processors. A parallel data structure approach was taken towards implementation of the software, in that the functions to be performed are identical in nature but are operating on separate segments of data. The QUAD or TRIAX routines would initiate a 'fork' operation to begin a parallel process, upon return the processors would 'spin' briefly while the next parallel process was initiated and would then be placed in a 'parked' condition during file I/O to allow the processors to be utilized by other tasks. After completion of the simulation, the processors would be released with a 'kill' command.

4.3.4 Performance

A test case of 221 segments in the models was used, resulting in a size for the A matrix of 663 x 663 elements for the QUAD routine and 442 x 442 elements for the TRIAX routine. The parameters used are identical to those listed in Tables 5.1 and 5.2 for the mammalian case with a radius for the outer boundary of $100\mu m$ for the QUAD case.

Condition of the A matrix

The resulting reciprocal condition number was 1.09×10^{-11} for the QUAD case and 3.1×10^{-9} for the TRIAX case.

Solution time

Using a run of 1000 iterations as a test case, the execution time for the QUAD routine was 937.6 seconds (15.6 minutes) for factoring the A matrix and generating the inverse, all of which were single processor tasks. The multiprocessor tasks took 22.58 seconds for computation of the ionic currents, 4.29 seconds to load the Φ matrix and 647.15 seconds for matrix multiplication, totaling to 674 seconds (11.2 minutes) of time per processor. When accounting for the use of 10 processors, this is a total computation time of 6740 seconds (112 minutes). The TRIAX routine had the following performance specifications; 190 seconds (3.2 minutes) for factoring the A matrix and generating of the inverse. For multiprocessor computation, 22.77 seconds were for computation of the ionic currents, 2.74 seconds for loading the Φ matrix and 293.4 seconds for matrix multiplication, totaling to 319 seconds (5.3 minutes) per processor. The total combined computation time was 3190 seconds (53 minutes). So, excluding the time for computation of the inverse, the QUAD routine takes about twice as long as the TRIAX routine. For a computation of 1ms of data, the real time is 127.6 minutes (2.13 hours), equivalent to 18.9 hours of cumulative computation time for the QUAD routine versus 56.2 minutes real time and 8.88 hours cumulative time for the TRIAX routine.

4.3.5 Stability

The stability of the solution was checked by alteration of the temporal step size and examination of the resulting spatial currents and potentials for evidence of oscillations

indicating instability. As a test case, the TRIAX routine was used for the mammalian case at 37°C using temporal step sizes of 0.1, 0.2, 0.5, 1, 2, 5 and $10\ \mu\text{s}$. Only minor differences in the simulation results were evident for the cases of 0.1 - $0.5\ \mu\text{s}$ step sizes. At $1\ \mu\text{s}$ a variation was seen in the spatial distribution of the intra-axonal potential and at $2\ \mu\text{s}$ marked perturbations were noted.

4.4 Summary

In this chapter, the development of the numerical solution for the distributed - parameter model of the myelinated nerve fiber was presented. Several mathematical approaches to the model were considered; an analytical approach using a variation of the method described by Taylor [116], solution of a reduced model possessing no peri-axonal conductive pathway and a passive internodal axolemmal membrane, solution of a full triaxial model with a difference equation approximation to a pair of coupled PDEs using the transmembrane and transmyelin potentials for the primary state variables and an explicit technique using the intra and peri-axonal potentials as primary state variables. All of these methods were found to either be too restrictive, flawed in performance or computationally unstable, therefore it was decided to pursue development of a stable implicit technique.

A form for the model was developed based on the geometric structures illustrated in Figs. 4.1 and 4.2. This geometry was then used as a guide for formation of equivalent electrical networks shown in Figs. 4.4, 4.5, 4.6 and 4.7. This form allowed for inclusion of the extracellular volume and examination of its influence on the behavior of the myelinated nerve fiber. Sealed ends (open circuit) were used for boundary conditions. Expressions were developed by performing successive application of Kirchhoff's current (KCL) and voltage (KVL) laws. These expressions took the form of a difference equation approximation to a set of cross-coupled parabolic partial differential

equations. As mentioned, an implicit form for the numerical solution was selected. This implicit method followed the philosophy of the Crank-Nicolson approach to the parabolic PDE, in that a centered computational molecule was developed, utilizing both present and future time values to compute the new values for the state variables as seen in Fig. 4.8. The system of equations was expressed in matrix form, resulting in a coefficient matrix which was quindagonal and asymmetric in form with two of the diagonals immediately adjacent to the principal diagonal and the other two located laterally, at a distance of n from the principal diagonal. The structure of the formulation allows for relatively easy extension to greater numbers of concentric shells representing other membrane layers.

The computational solution technique was then described. The program was developed in the C language and implemented on a Sequent Systems parallel processor. A major portion of the software entailed building the A coefficient matrix which was then inverted to be used in the formation of the new potential values for each time increment. LINPACK routines were used for factoring and inversion of the matrix. Two main programs were developed. The first, QUAD, solved for the full structure presented in the figures mentioned earlier, the second, TRIAX, solved a reduced problem which assumes that the extracellular space is of significant extent such that it can be set to an iso-potential. The structure of the code involved initialization of the state variables, formation and inversion of the A coefficient matrix followed by execution of a loop which produced new values for the trans-axonal ionic currents using a Rush-Larsen [93] approximation method, formation of the knowns for the matrix equation (Φ) and performance of multiplication of the A^{-1} all in parallel to form the solution for $\underline{V}$ for the next time interval. 10 processors were used in formation of the solution, providing solution times on the order of 10 times less than with only a single processor.

The A coefficient matrix was found to have reciprocal condition numbers on the order of 10^{-8} to 10^{-11} and presented no difficulties in formation of an inverse. Using a stringent test case of the mammalian fiber conducting at the physiological temperature of $37^{\circ}C$, the solution was found to be well behaved for temporal step sizes of $0.5 \mu s$ and below. Small signs of abnormal behavior began for temporal step sizes of $1 \mu s$ with definite errors present for step sizes above $1 \mu s$.

The following chapter demonstrates the utility of this technique as developed to represent the functional behavior of the myelinated nerve fiber.

Chapter 5

Simulation Results

5.1 Introduction

The distributed - parameter model can now be employed to examine the functional implications of the microanatomy of the nodal region, the peri-axonal space, the relative properties of the myelin sheath versus the underlying internodal axolemmal membrane and the internodal ionic channels. First to be explored are the conduction properties of the amphibian and mammalian nerve fiber. Specifically, the impact of the characteristics of the nodal region are studied, in particular the effect of the nodal constriction, the peri-axonal conductive pathway and the properties of the extracellular volume. The other demonstrated application of the model is an examination of the behavior of a single node of Ranvier when space - clamped over a length of $100 - 200\mu m$.

5.2 Conduction Studies

5.2.1 Computational aspects

Model structure

Two fiber lengths were simulated, the first was a fiber containing 20 nodes of Ranvier, providing approximately 4 cm of fiber length and the other was half the length, containing 10 nodes of Ranvier. As shown in Fig. 5.1, one segment was used to represent the nodal compartment, 4 segments were used to represent the MYSA

section, 4 segments were used for the FLUT region and 5 segments were used for the STIN section. This segmentation was selected to provide representation of the rapid spatial gradients of potentials and currents present near the node, without including so many segments as to become too computationally intensive. This resulted in 22 segments between successive nodes of Ranvier, totaling to 441 segments for the long fiber. The fiber was stimulated at the rightmost node of Ranvier by current injection.

The triaxial form of the model was used for the baseline studies, assuming a large extracellular volume conductor. The quadaxial form was used in the studies of the influence of the extracellular volume. The resulting coefficient matrix for the 20 node triaxial model had dimensions of 882 by 882 double precision real elements. The 10 node triaxial model had 442 by 442 elements and the 10 node quadaxial model 663 by 663. A step size of $0.2\mu s$ was used for the amphibian case at $20^{\circ}C$ and $0.1\mu s$ was used for the mammalian case at $37^{\circ}C$. Duration of the simulation was $2.5ms$ for the amphibian case and $1ms$ for the mammalian case, equivalent to 12,500 and 10,000 iterations respectively. To save on disk resources, the temporal resolution of the output for the 20 and 10 node models was $20\mu s$ versus $10\mu s$ for the amphibian and $5\mu s$ versus $2\mu s$ for the mammalian case. The 10 node model was used to provide higher resolution in the temporal plots necessary for the longitudinal and transverse currents.

Figure 5.1: Segmentation of the nerve fiber for use in conduction studies. The nodal section is divided into one nodal compartment, the MYSA section into 4 segments, the FLUT section into 4 segments and the STIN section into 5 segments.

Model parameters

Tables 5.1 and 5.2 contain the standard model parameters adopted for the amphibian and mammalian cases as derived from the properties presented in Chapters 2 and 3. The geometric parameters were taken directly from those presented in Table 2.1 for the mammalian case and scaled to represent an amphibian fiber with an axon diameter of $10\mu m$ versus $12.5\mu m$ to enable comparison to previous modeling efforts [50, 54, 72, 79, 118, 119].

Initially, the parameters were selected from those shown in Table 3.14 for the nodal properties and Table 3.15 for the internodal parameters with the passive properties of the axoplasm and the myelin sheath adopted from those studies more recently published. These parameters are listed in parentheses within Table 5.2. However, when these were placed into the model, the resulting conduction velocities were below those expected, 8 m/s in the case of amphibian and 0 m/s in the case of the mammal. A similar phenomenon was observed by Hardy [54] while modeling the influence of external Na^+ and temperature upon the conduction velocity in an amphibian myelinated nerve fiber. He initially used the nodal characteristics described by Dodge [35] for *Rana pipiens* and adopted properties for the myelin sheath from Tasaki [115]. The conduction velocity he initially obtained was 9.5 m/s , about half of what he had expected. He therefore increased the Na^+ permeability, decreased the specific capacitance of the myelin sheath, increased the specific resistance of the myelin sheath, decreased the axoplasmic resistivity and the leakage conductance at the node. After these modifications he obtained a conduction velocity of 18.9 m/s . In this work, similar modifications were made to the parameters for the amphibian myelinated nerve fiber model and a conduction velocity of 20.2 m/s was achieved.

Table 5.1: Model Parameters - Geometric

NODE		
Parameter	Amphibian	Mammal
<i>Length</i> – μm (typ.)	1.5	1.5
a_N	2.5	2.5
δ_N (effective)	0.03	0.03
MYSA Section		
Parameter	Amphibian	Mammal
<i>Length</i>	4	4
a_M^1	2.2	2.2
a_M^2	2.4	2.4
δ_M	0.001	0.001
FLUT Section		
Parameter	Amphibian	Mammal
<i>Length</i>	75	75
$a_F^{axial_1}$	5.1	5.1
$a_F^{axial_2}$	5	6.25
$a_F^{radial_1}$	9	9
$a_F^{radial_2}$	5	6.25
δ_F	0.003	0.003
STIN Section		
Parameter	Amphibian	Mammal
<i>Length</i>	1800	1800
a_S	5	6.25
δ_S	0.004	0.004

Table 5.2: Model Parameters - Biophysical

Amphibian 20°C			
Parameter	Units	Node	Internode
$[Na]_o$	mM	110	110
$[Na]_i$	mM	16.6	16.6
$\bar{P}_{Na}$	$cm/sec \times 10^{-3}$	25 (16.6)	0.039
$\bar{G}_{Kf}$	mS/cm^2	2468	12
$\bar{G}_{Ks}$	mS/cm^2	266 (532)	6
g^{ax}	mS/cm^2	53 (106)	1
c^{ax}	$\mu F/cm^2$	1	1
$G^{nodalgap}$	mS	0.0075	.
nl	.	0	200
g_M^{my}	mS/cm^2	.	1
c_M^{my}	$\mu F/cm^2$	.	0.5 (1.0)
ρ	Ωcm	100 (158)	100 (158)
V_{rest}	mV	-75	-75
V_{leak}	mV	-76.475	-75.125
Mammalian 37°C			
Parameter	Units	Node	Internode
$[Na]_o$	mM	154	154
$[Na]_i$	mM	8.71	8.71
$[K]_o$	mM	5.9	5.9
$[K]_i$	mM	155	155
$\bar{P}_{Na}$	$cm/sec \times 10^{-3}$	33.9 (7.2)	0.0781
$\bar{P}_{Kf}$	$cm/sec \times 10^{-3}$	0.375	0.0625
$\bar{P}_{Ks}$	$cm/sec \times 10^{-3}$	0.0937	0.0312
g^{ax}	mS/cm^2	156 (182)	1
c^{ax}	$\mu F/cm^2$	1	1
$G^{nodalgap}$	mS	0.003	.
nl	.	0	175 (140)
g_M^{my}	mS/cm^2	.	1
c_M^{my}	$\mu F/cm^2$	.	0.5 (1.0)
ρ	Ωcm	70 (106)	70 (106)
V_{rest}	mV	-78	-78
V_{leak}	mV	-77.9625	-76.48

(): Initial value as determined from literature

For the mammalian case, modification of the parameters was also necessary in order to achieve conduction velocities in the range of those documented experimentally. A velocity of $57.6m/s$ was achieved for a temperature of $37^{\circ}C$. This corresponds very well to that seen experimentally in rat ventral root fibers by Rasminsky [90] of about $57m/s$. This also correlates well with the simulation of Blight [12] for ventral spinal tract fibers in rat who reported a conduction velocity of $56m/s$.

5.2.2 Amphibian

Figures 5.2 and 5.3 illustrate the propagating action potentials as generated by the distributed - parameter model. Figure 5.2 shows the transfiber potentials present at successive nodes of Ranvier, demonstrating the temporal character of the action potentials and showing the time delay between arrival at each node. This is a traditional presentation of the propagating action potential (PAP). A less familiar, but very important and powerful way of viewing the same information is as a spatial distribution of potential. Figure 5.3 illustrates the spatial action potential, i.e., the distribution of potential along the fiber, at several discrete points in time. The PAP can be seen to move from the right to the left aspect of the nerve fiber and the inhomogeneous nature of the myelinated nerve fiber can be seen in the peaks of potential which occur each node of Ranvier. This spatial distribution is similar to that demonstrated indirectly by the measurement of extracellular potentials and currents as performed by Huxley and Stämpfli [67] in their initial treatise on saltatory conduction as well as that produced in coaxial cable simulations of the myelinated nerve fiber by a number of investigators [42, 50, 54, 72].

A unique feature of this model that is not possible with previous models is the decomposition of the transfiber potential into a transaxonal and transmyelin potential as shown in Figs. 5.4 and 5.5. The most striking features are the sharp peaks of

Figure 5.2: Transfiber temporal action potentials at successive nodes of Ranvier of a $15\mu m$ amphibian fiber. The potentials are taken from node numbers 11 to 15 with node 15 activating first. The conduction velocity is $20.2m/s$.

transaxonal depolarization at and near the nodes with very little in the internodes, with the complementary distribution of transmyelin potential at the node versus the internode. This is expected, in that the impedance presented by the myelin sheath is significantly greater than that presented by the axolemmal membrane both in the reactive ($0.003\mu F/cm^2$ versus $1.0\mu F/cm^2$) and the conductive ($0.005mS/cm^2$ versus $1.0mS/cm^2$) components. A 1% change in the myelin specific capacitance has been shown by Moore, et al. [79] to cause a 0.5% change in conduction velocity, while a 1% change in the myelin specific conductance resulted in a 0.01% change in conduction velocity.

The transaxonal current and its components are shown in Figs. 5.6 and 5.7. Figure 5.6 presents the spatial distribution of the currents present along the axon. On the left portion of the axon outward currents are visible which result from the longitudinal intra-axonal currents sourced by the active regions to the right. The

Figure 5.3: Transfiber spatial action potentials at successive points in time ($0.2ms$). Each spatial potential represents the state of the transfiber potential at each of the five time instants. The movement of the propagating action potential can be seen in the movement from the right to the left portion of the figure. Note the discontinuous character of the transmembrane potential with peaks located at the nodes of Ranvier with intermediate potentials present in the internodal regions.

inward sodium currents are the largest, followed by the outward fast potassium currents. The slow potassium current follows a profile similar to the leakage current, with a slightly different profile resulting from the slow gating action. The temporal character of these currents can be seen in Fig. 5.7 at the node and in the center of the internode. The time course of the PAP at the node is similar to the MAP presented in Section 3.4.1. In the internode, there is no evidence of an MAP on the order of that produced in Section 3.4.2, but there is a slight activation of both the sodium and potassium currents. The majority of the current is displacement current coupling through the myelin sheath.

Figure 5.4: The potential present along the amphibian fiber 1.5 ms after initiation of the propagating action potential. The transfiber potential is that seen in the intra-axonal space relative to the external volume, the transaxonal and the transmyelin potentials sum to form the transfiber potential.

Figure 5.5: The temporal action potentials present at the node, $1\mu\text{m}$ to the right of the node and at mid-internode in the amphibian fiber. At the node, the transfiber potentials is essentially equivalent to the transaxonal potential, with transmyelin potential reflecting the current present in the nodal gap. Adjacent to the node, the beginnings of the change in proportion of the transmyelin to transaxonal potential are present. In the center of the internode, the contribution of the myelin sheath is evident in the transmyelin potential versus the transaxonal potential which only shows a small deviation from rest potential.

Figure 5.6: Spatial distribution of the transaxonal component currents. Taken at the same time instant as that in Fig. 5.4, the phases of depolarization and repolarization can be seen as they occur along the length of the fiber.

Figure 5.7: Temporal plot of the transaxonal currents at the node, 1 μm to the right of the node and in the center of the internode.

The transverse currents present across the myelin sheath are similar in form to those present across the underlying axon in the internodal region, but differ in the nodal region. Figure 5.8 presents the spatial distribution of the total and component capacitative and leakage currents. The nodal gap leakage is dominant, at the point where the myelin sheath terminates. The displacement currents are about 3 orders of magnitude lower in current density compared to that seen at the node, however the total displacement current is five times that present at a single node. The differences in the currents as the node is reached are shown in Fig. 5.9.

The transverse currents are related to the difference in the longitudinal currents seen in Fig. 5.10. The sense of the currents, as was presented in Fig. 4.3, is positive right. The current is largest in the region just to the left of the segment undergoing the leading edge of depolarization. As the Na^+ current enters the fiber, current is drawn from ahead of the depolarizing region in the extra-cellular space and forced forward along the intra-axonal space, resulting in depolarization of the next segments. A longitudinal current can also be seen entering the peri-axonal space, resulting from the large spatial potential gradient present along the length of the axon. Figure 5.11 presents the temporal character of the longitudinal currents as seen on both sides of the node of Ranvier. Current can be seen entering the peri-axonal space, although the relative amplitude is less than that seen either intra or extra-axonally and diminishes rapidly on either side of the node.

5.2.3 Mammal

The mammalian myelinated nerve fiber simulation produced higher conduction velocities and a different character for the temporal and spatial action potentials and currents to those seen in the amphibian. Figure 5.12 illustrates the transfiber temporal action potential over a series of nodes of Ranvier. The action potential amplitude

Figure 5.8: Spatial distribution of the transmyelin currents.

is higher than that seen in the amphibian and has a 'double hump' character as well as a shorter duration, on the order of $0.4 - 0.5\text{ms}$ versus about 1.5ms for the amphibian. The transfiber spatial action potentials also exhibit a similar character in comparison to the amphibian case as seen in Fig. 5.13.

The decomposition of the transaxonal and transmyelin potentials are similar in character to those of the amphibian (Fig. 5.14 and 5.15). There is a greater sag in the internodal region due to the higher drive and faster dynamics of the sodium currents.

The higher magnitude of the sodium current is evident in Fig. 5.16. The spatial distribution of the currents are also different from those seen in the amphibian,

Figure 5.9: Temporal plot of the transmyelin currents at the node, $1\mu\text{m}$ to the right of the node and at mid-internode. There is no myelin present at the node and therefore the displacement current is zero, the leakage current represents the current flowing through the nodal gap resistance.

Figure 5.10: Spatial distribution of the longitudinal currents. Also taken at the same time instant as that in Fig. 5.4, the extra-axonal, peri-axonal and intra-axonal longitudinal currents are shown. The sense of the currents is positive right.

Figure 5.11: Temporal plot of the longitudinal currents adjacent to the node of Ranvier and in the center of the internode. The extra-axonal, peri-axonal and intra-axonal longitudinal currents are shown. Note the change in magnitude of the left versus right side extra and intra-axonal current and that the peri-axonal currents are directed toward the node. Also note the relatively consistent shape of the extra and intra-axonal currents, diminishing in amplitude as the distance from the sourcing node increases.

Figure 5.12: Transfiber temporal action potentials at successive nodes of Ranvier of a $17.5 \mu\text{m}$ mammalian fiber. Conduction velocity is 57.6m/s .

reversing from inward to outward over a shorter distance. The temporal plots of the transverse currents also emphasize the rapid dynamics of the sodium channels (Fig. 5.17).

The displacement currents at the node and in the internode are of higher amplitude than that seen in the amphibian case. Figure 5.18 shows more rounding of the displacement currents about the active node, presumably due to the fact that the sodium dynamics are approaching the time constant for the myelin sheath. The temporal plots also show the higher amplitudes and shorter time course compared to the amphibian (Fig. 5.19).

The longitudinal currents are also larger and of a different distribution than those found in the amphibian (Fig. 5.20). A higher peri-axonal current is evident. The temporal plots of the longitudinal currents (Fig. 5.21) exhibit some interesting differences from those seen in the amphibian case. One feature is the larger hump in the post-spike portion of the extra and intra-axonal currents but the most intriguing is

Figure 5.13: Transfiber spatial action potentials at $0.05ms$ intervals.

the small spike present in the right portion of the node which is on the proximal side of the PAP. At first the character of this small spike led to a concern about possible instabilities in the solution method. The temporal step size was reduced to $0.25\mu s$ from the $0.1\mu s$ initially used, without a discernable difference. Upon reviewing the literature, the initial work of Huxley and Stämpfli [67] demonstrated the same phenomenon, although of lower amplitude presumably due to the lower temperature and therefore lower conduction velocity present in the amphibian versus the mammalian case. This component is visible both in figure 8 and figure 10 of their publication and is also on the proximal aspect of the node. Upon closer scrutiny of Fig. 5.11, a small perturbation can also be seen in the amphibian simulation results.

5.2.4 Effect of select properties on conduction velocity

The effect of the peri-axonal space width on conduction in amphibian myelinated fibers was explored, with attention focused on the MYSA region. The amphibian

Figure 5.14: The potential present along the mammalian fiber 0.55 ms after initiation of the propagating action potential. The transfiber potential is that seen in the intra-axonal space relative to the external volume, the transaxonal and the transmyelin potentials sum to form the transfiber potential.

Figure 5.15: The temporal action potentials present at the node, $1\mu m$ to the right of the node and at mid-internode in the mammalian fiber. At the node, the transfiber potentials is essentially equivalent to the transaxonal potential, with transmyelin potential reflecting the current present in the nodal gap. Adjacent to the node, the beginnings of the change in proportion of the transmyelin to transaxonal potential are present. In the center of the internode, the contribution of the myelin sheath is evident in the transmyelin potential versus the transaxonal potential which only shows a small deviation from rest potential.

Figure 5.16: Spatial distribution of the transaxonal currents. The spatial extent of the sodium current is less than that seen in the amphibian case and the relative contribution of potassium current is less.

Figure 5.17: Temporal plot of the transaxonal currents at the node, $1\mu\text{m}$ to the right of the node and in the center of the internode. Note the stronger sodium current at the node and the relatively small amount of potassium current in comparison to the amphibian.

Figure 5.18: Spatial distribution of the transmyelin currents.

model was also employed to examine the effect of the nodal constriction on the conduction velocity. The mammalian model was used to study the influence of the extracellular volume and temperature on conduction velocity.

Peri-axonal space

The conduction velocity was sensitive to the size of the peri-axonal space pathway present in the MYSA and the adjacent FLUT and STIN segments. Figure 5.22 shows the effect of expanding the peri-axonal space in the MYSA segment and along the length of the fiber. As the myelin sheath in the MYSA region is loosened, the conduction velocity slows due to the increase capacitive load presented to the node and shows evidence of reaching a lower limit due to the $3nm$ peri-axonal space still

Figure 5.19: Temporal plot of the transmyelin currents at the node, $1\mu\text{m}$ to the right of the node and at mid-internode.

Figure 5.20: Spatial distribution of the longitudinal currents. The sense of the currents is positive right.

Figure 5.21: Temporal character of the longitudinal currents. The extra-axonal, peri-axonal and intra-axonal longitudinal currents are shown for the segments immediately adjacent to a node of Ranvier and in the center of the internode. Note the spike on the second phase of the extra and intra-axonal currents at the right of the node as discussed in the text.

remaining in the FLUT section. In the other case, the peri-axonal space is uniformly increased in the MYSA, FLUT and STIN regions from a width of $0.01nm$, approximating zero, and opened to a maximum of $20nm$ which is in the range of that reported in the STIN region. In this case, the velocity continues to decrease as the axon becomes effectively demyelinated.

Nodal constriction

Regarding the constriction seen in the anatomical studies of the myelinated nerve fiber, a very interesting result can be seen in Fig. 5.23. The radius of the component sections near the node of Ranvier were varied. First the FLUT radius was set equal to the radius of the STIN region. No effective change in conduction velocity was noted ($20.62m/s$ vs. $20.51m/s$). However, when the radius of the MYSA section was increased, the conduction velocity decreased. This seemed counter-intuitive, since the longitudinal resistance was decreasing and should provide for a larger space constant. When the radius was increased to that equivalent to the STIN region, the conduction velocity reached $16.66m/s$. As the radius was decreased, a peak conduction velocity of $22.04m/s$ was noted for a radius of $1\mu m$ and then the conduction velocity dropped rapidly as expected. $22.04m/s$ represents a 32.3% increase in conduction velocity from that without the constriction.

Extracellular volume

The size of the extracellular volume was varied to explore the impact on conduction. The mammalian model was employed, at the physiological temperature of $37^{\circ}C$. Figure 5.24 presents the results of that study, showing the slowing of conduction as the radius of the extracellular volume is decreased. The specific conductivity of the outer boundary layer was set to a very low value, that of $10^{-9} mS/cm^2$. The

Figure 5.22: Conduction velocity versus the width of the peri-axonal space in the amphibian myelinated nerve fiber. The upper curve shown the effect of increasing the peri-axonal space width in the MYSA region alone. The conduction velocity slows as the node is loaded by the adjacent exposed axolemmal membrane and approaches a constant velocity due to the remaining 3nm space in the FLUT section. In the second case the space in the MYSA, FLUT and STIN regions are increased uniformly.

conduction shows no change until the radius of $25\ \mu\text{m}$ is reached, then the velocity decreases dramatically as the outer-boundary radius approaches that of the outer surface of the myelinated nerve fiber. Conduction block occurs at a radius of $9.125\ \mu\text{m}$, a thickness for the extracellular volume of $0.375\ \mu\text{m}$.

Temperature

By varying the temperature of the mammalian fiber, a measure of the change in conduction velocity was made (Fig. 5.25). The results of the simulation match the

Figure 5.23: Conduction velocity versus the radius of the axon in the MYSA region in the amphibian myelinated nerve fiber. As the radius of the axon in the MYSA segment is increased to the radius of the STIN section, the conduction velocity decreases. As the radius is decreased, the conduction velocity increases and then falls rapidly as the internal longitudinal resistance increases to the point of conduction block.

experimental findings of a study performed by Rasminsky [90] on ventral root fibers in rat.

5.3 Space-Clamped Node of Ranvier

Experimental conditions for the space-clamped node of Ranvier can be simulated by reducing the length of the fiber represented by the model to that on the order of 100 – 200 μm . The model can then be applied to the question of what influence nodal and paranodal properties such as the peri-axonal space, paranodal ionic channels, etc.

Figure 5.24: Conduction velocity versus the radius of the extracellular volume for the mammalian myelinated nerve fiber. The conduction velocity shows little change as the extracellular volume decreases until the radius of the outer surface of the nerve fiber ($8.75 \mu m$) is approached. Conduction block occurs at a radius of $9.125 \mu m$, a thickness of $0.375 \mu m$.

may have on the observations made on the node. A fundamental question is how iso-potential the node is relative to the paranode and internode and whether para and internodal ionic channels are being activated.

The model was configured to a length of $200 \mu m$ containing one node of Ranvier centered in the model. The spatial step sizes for the fluted section and the portion of the STIN section present were reduced to $1 \mu m$ to allow for a detailed examination of the distribution of potentials and currents along the fiber. The model therefore consisted of 201 segments total. The same characteristics listed in Tables 5.1 and 5.2

Figure 5.25: Conduction velocity versus temperature in the mammalian myelinated nerve fiber. The solid line with circles represents the results of the simulation and the experimental data of Rasminsky [90] are shown as triangles.

were used for the other properties unless otherwise stated. Since the extracellular space is assumed large in these single fiber studies, the triaxial form of the model was employed for the simulation.

5.3.1 Amphibian

Figure 5.26 presents the results of the simulation as seen in a perspective plot of the transaxonal potential present along the length of the model versus time. The temporal character of the action potential is evident in the right portion of the diagram presenting the voltage across the axon versus time. An impression of the spatial

Figure 5.26: Spatio-temporal perspective plot of the transaxonal potential for the space-clamped amphibian node of Ranvier. Standard data were used in the simulation.

Figure 5.27: Spatial distribution of the transaxonal potential, Na^+ , K_f^+ and K_s^+ currents with increasing width of the peri-axonal space. The width of the space varies from 1 to 5nm in increments of 1nm, followed by 10 and 20nm. The amplitude scale has been selected to show the distribution of the paranodal ionic currents

distribution of the action potential can be seen from the side labelled 'position'. Note that portions of the axon adjacent to the node are depolarized to levels that can activate ionic channels present there. This is seen more clearly in Fig. 5.27 in which the spatial distribution of transaxonal potential, Na^+ , K_f^+ and K_s^+ currents are presented. This figure shows the change in distribution present in the paranodes when the peri-axonal space width is increased. The inner curves are those present in the model for narrow peri-axonal space thicknesses, with the distribution of transaxonal potential and activation of more ionic channels extending as the width is increased. These plots do not show the magnitude of the currents present at node due to their relatively high current densities. The change in these levels with modification of the peri-axonal space thickness can be seen in Fig. 5.28. Note that the amount of Na^+ current increases as the transaxonal potential decreases. The K^+ current density decreases at the node as the transaxonal potential decreases. However, the paranodal K^+ channels are progressively more active with the spread of potential along the axon.

The effect of the wider peri-axonal space is readily seen in the change in longitudinal currents present along the peri-axonal space, spreading progressively down the axon as the space expands (Fig. 5.29). This effect can be seen in the perspective plot in Fig. 5.30 in which the peri-axonal space width was $20nm$. The diminution of the height of the action potential can be seen in comparison to Fig. 5.26 as well as the spreading of the depolarization along the axon. Note the evidence for activation of the paranodal Na^+ channels as seen in Fig. 5.28 with a hint of formation of an internodal action potential.

Figure 5.28: Change in amplitude of the transaxonal nodal potential, Na^+ , K_f^+ and K_s^+ currents with increasing width of the peri-axonal space. The perturbations in the curves are due to slight variations in the stimulation parameters used to initiate the action potentials.

Figure 5.29: Change in longitudinal peri-axonal currents as the width of the peri-axonal space is increased. The transition from the MYSA region to the FLUTed region can be seen in the discontinuity near the node. Taken at the time of the peak amplitude.

5.3.2 Mammal

The same procedure was followed for the mammalian model, using two cases for study. The initial case, using the standard model parameters, as seen in Fig. 5.31 illustrates the faster kinetics of the mammalian node of Ranvier at 37°C and resulting higher peak potentials versus the amphibian node. In the repolarization phase, evidence for some paranodal depolarization is present. In this simulation, the concentration of internodal Na^{+} channels was doubled from that used in the previous mammalian simulations, still well within the range of what are assumed to be normal values. In this case, when the peri-axonal space at the MYSA segment was increased to a

Figure 5.30: Spatio-temporal perspective plot of the transaxonal potential in an amphibian fiber with a $20nm$ thick peri-axonal space. Note the broader character of the spatial distribution and lower amplitude peak for the nodal action potential.

Figure 5.31: Spatio-temporal perspective plot of the transaxonal potential in a mammalian space-clamped fiber.

Figure 5.32: Spatio-temporal perspective plot of the transaxonal potential in a mammalian space-clamped fiber with a $4nm$ thick peri-axonal space.

$4nm$ width from $1nm$, a strong secondary action potential was initiated, propagating beneath the myelin sheath. $4nm$ is also within a normal range of values, judging from the cross-sectional areas provided by Berthold [8]. The conduction velocity of this secondary action potential was on the order of $0.06 m/s$.

5.4 Summary

In this chapter, the distributed - parameter model was first applied to simulation of the conduction of action potentials in the myelinated nerve fibers of the amphibian and the mammal. Standard parameters were selected from the tables that were generated by the literature review performed in Chapter 3. When these parameters were used to drive the model, conduction velocities were obtained that were well below those expected for fibers of the diameters simulated, $8m/s$ for the $15 \mu m$ amphibian fiber at $20^\circ C$ and $0m/s$ for the $17.5 \mu m$ diameter mammalian fiber at $37^\circ C$. Adjustment of these parameters as listed in Tables 5.1 and 5.2 were made in order to produce conduction velocities in the physiological range of $20.2m/s$ for the amphibian fiber and $57.5m/s$ for the mammalian fiber. The capacity of the model to provide decomposition of the component currents and potentials such as the transaxonal versus the transmyelin potentials and currents was demonstrated.

The effect of the new features of the model on conduction revealed that the peri-axonal space is a sensitive parameter in establishment of higher conduction velocities. Although the peri-axonal space width was set to $1nm$ in the MYSA region, an increase in conduction velocity was seen when this width was reduced down to $0.01nm$. As expected, the conduction velocity diminished when the peri-axonal space was increased in size.

The effect of the nodal constriction was one of the major results of the simulation studies. The constriction at the MYSA segment was found to promote higher

conduction velocities than without a constriction. A radius of $1\mu m$ at the MYSA segment of an amphibian myelinated nerve fiber with a radius of $5\mu m$ in the STIN segment resulted in a conduction velocity of $22.04m/s$ as compared with $16.66m/s$. This is a relative constriction of 80%.

The influence of the extent of the extracellular volume was to reduce the conduction velocity in the mammalian myelinated nerve fiber with an outer radius of $8.75\mu m$ for external radii less than $25\mu m$. Conduction block occurred at a radius of $9.125\mu m$, an equivalent annular space of $0.375\mu m$.

The change in conduction velocity with temperature matched the experimental results of Rasminsky [90] on ventral root fibers in the rat.

The results of the simulation of space-clamp conditions, in which the length of the fiber was set to $200\mu m$ with one node of Ranvier centrally placed, demonstrated the presence of transaxonal potentials sufficient enough to active Na^+ and K^+ channels present in the adjacent paranodal axolemmal membrane. A study of the effect of varying widths of the peri-axonal space demonstrated the additional load place on the node of Ranvier as well as the increase in potential presented on the paranodal membrane. In the case of the mammalian fiber, when the internodal Na^+ channel permeability was set to $0.066 \times 10^{-3}cm/sec$ and the peri-axonal space width was set to $4nm$, in the range of possible normal values, a secondary action potential was initiated, propagating beneath the myelin sheath at a conduction velocity of $0.06m/s$.

Chapter 6

Discussion and Future Extensions

The primary objective of this thesis was met, in that a distributed - parameter model of the myelinated nerve fiber based on detailed anatomical data and recent biophysical properties was created and a stable numerical solution method was developed and successfully implemented. The ability of the model to simulate the behavior of actual myelinated nerve fibers was demonstrated, in that physiological conduction velocities were achieved both for the amphibian case at $20^{\circ}C$ (20.2 m/s) and the mammalian case at $37^{\circ}C$ (57.6 m/s). The ability of the model to allow for close examination of the nodal and paranodal region was demonstrated in space-clamp simulations. Secondary objectives, such as the influence of various model parameters on these behaviors were accomplished in the case of conduction studies. Discussion of the model development, solution technique and simulation results follow.

6.1 Model Development

A major contribution of this work was the development of a model which can detail the structural and biophysical properties of the node of Ranvier while allowing for representation of macroscopic behavior such as the conduction of action potentials. The use of non-uniform spatial step sizes proved to be a viable practical means of accomplishing high definition of the nodal and paranodal region without becoming too computationally expensive in memory and time resources. This enabled fine spatial resolution in regions where the amount of spatial variation was greatest, both

in the fiber properties as well as the associated potentials and currents representing the functional behavior of these fibers.

6.1.1 Anatomy

This model provides for the anatomical detail suggested by Berthold [8] as quoted in Chapter 1 for the nodal and paranodal region. In this work, the anatomical detail for the amphibian fiber was adopted from the detail provided by Berthold on mammalian fibers. The geometry of the model can be readily adapted to represent the normal or abnormal anatomy of other fibers as they are defined.

6.1.2 Biophysical properties

This model is the first known to incorporate the Na^+ dynamics as described by Schwarz and Eikhof [101] in a mammalian myelinated fiber model simulating propagating action potentials. It is also the first known to include Na^+ and fast and slow gated K^+ channels in the paranodes and internodes of a full myelinated fiber model. The authors of a recent abstract claims to have modeled the presence of multiple types of K^+ channels in the node in order to study their effect on accommodation, but no detail is provided or mention made of incorporation into a larger fiber model or the paranodal and internodal region [87].

Regarding the attempt to be as quantitative as possible in definition of the biophysical properties, this thesis has attempted to address the issue with detailed review of the literature. This has been touched on by previous modeling efforts but not to this extent. As can be noted in Chapter 3, there is an imbalance in information available on amphibian versus mammalian, large versus small and sensory versus motor fibers. In particular, more information is needed on the properties of the internodal and paranodal axolemmal membrane. It would also be very useful for the myelin

sheath characteristics to be re-examined, preferably with a new method that might be able to address the hypothesis of Friede [48] claiming that the myelin sheath is highly resistive and that the leakage path is along the spiral path between the layers of the myelin sheath. Given that the model did not produce physiological conduction velocities when nominal values from the tables in Chapter 3 were used, the question of accuracy in these measures is raised.

6.2 Solution Technique

The development of an implicit method of the form described in Chapter 4 is believed to be an original contribution to this class of mathematical models. The symmetry seen in the matrix form for the equation system and ease of extension to higher orders of multiaxial geometries is an attractive feature of the model. The numerical condition of the $\underline{A}$ coefficient matrix was good and the matrices were invertible without difficulty, indicating that the problem was well scaled. The work of Blight [12], in which one internode was modeled with a similar geometry but without continuity of the peri-axonal space to the node, stated that, ‘Explicit integration was used....because the implicit model assumes that the impedances of the internodal axolemma and myelin can be lumped together,...’. An implicit technique is more stable than an explicit method [108] and is an obvious advantage when considering that the explicit method was unable to accommodate the node of Ranvier in a triaxial form with a series nodal gap conductance. Another reason to select an implicit method over an explicit one is that the implicit method can represent the instantaneous distribution of potential along the longitudinal portions of the multi-axial model since it solves for the system simultaneously, whereas the explicit method does not. Again, the ease of extension of the technique is straightforward; should it be desired, separate concentric shells could be produced as approximations to each wrap of myelin, producing a high

definition two dimensional model of the myelinated nerve fiber as contrasted with the one dimensional coaxial cable model.

The inclusion of an extracellular volume whose properties can be altered to examine their influence on the behavior of the nerve fiber is also believed to be an original contribution to this class of models and demonstrated the power of the formulation to be easily extended, allowing for relatively rapid addition of this feature in the model.

The application of parallel processing methods to the solution of these types of models is another contribution of this thesis and an indication of the advantage and power that these types of computers provide to the study of distributed - parameter models. A welcome addition will be the development of parallelized linear algebraic routines that can assist in forming solutions for this class of problems. In light of the rapid proliferation of this technology and the resulting cost-performance advantages, it appears to be wise to become familiar with this class of computers.

6.3 Simulation Results

A true test of the model was in the simulation of propagating action potentials. In addition, the simulation of a short section of nerve fiber in a space-clamp, testifies to the flexibility of the model and the ease in extension of the model to the study of several phenomena.

6.3.1 Conduction studies

The ability of the model to provide both spatial and temporal detail regarding the character of the component potentials and currents is evident in Sections 5.2.2 and 5.2.3. The adjustment of the biophysical parameters necessary to achieve these conduction velocities is evidence that there are inconsistencies between the parameters obtained through clamp studies and those present in the normal *in vivo* condition

of the nerve fibers, or that there is still some factor not properly considered in formation of these models. The adjustments made were similar to those made by Hardy [54] in which the Na^+ permeabilities were increased a factor of 1.28, the nodal leakage conductances were decreased by a factor of 2, the axoplasmic resistivity decreased by a factor of 1.07, the myelin sheath capacitance reduced by a factor of 1.6 and the conductance by 1.38. In the amphibian case the Na^+ permeability was increased by a factor of 1.5 while for the mammalian case, if the original value of Schwarz and Eikhof [101] is used for the fiber at $37^\circ C$, a ratio of 4.7 was used to scale the permeability. If the value at $20^\circ C$ is used and a Q_{10} factor of 1.3 applied, the ratio was 3. The resulting total permeability was on the same order as that used by Blight [12] to represent the mammalian myelinated nerve fiber. The slow K^+ and the passive leakage conductances were decreased by a factor of 2 for the amphibian case and the passive leakage was decreased by a factor of 1.2 for the mammalian case. In both cases the axoplasmic resistivities were decreased a factor of 1.5. The myelin capacitance was decreased by a factor of 2 in the amphibian case and 2.5 for the mammalian case.

Aside from the generation of physiological conduction velocities, the character and magnitudes of the amphibian longitudinal currents correlated well with those published by Huxley and Stämpfli in their original work [67]. They present data in Figure 8 for the longitudinal currents found just proximal and distal to the node with the proximal amplitude of about 3nA which correlates well with the 3nA seen in Fig. 5.11 for the column labeled 'Left of node'. Likewise, the trace for the distal side measures at about 2nA, also closely matching the trace labeled 'Right of node' in Fig. 5.11. The character of the longitudinal current waveform is seen best in the mammalian case as the notched waveshape labeled 'Right of node' in Fig. 5.21 as compared to the current seen for the distal case in their work.

Peri-axonal space

The peri-axonal space in the MYSA section was found to profoundly influence the conduction velocity of the amphibian nerve fiber (Fig. 5.22) over a range of thicknesses that are considered to be in a normal range [8]. It is reasonable that the additional capacitative load presented by the peri-axonal conductive path to a wider axonal surface area should slow conduction. It is surprising however, that it has as much effect as it does for thicknesses on the order of $0.1 - 1nm$, equivalent to $1 - 10\text{\AA}$ s. This is supported by the evidence for measurable amounts of peri-axonal longitudinal current flow local to the node as seen in Figs. 5.10, 5.11, 5.20 and 5.21. In addition, the disparity in the displacement current density seen across the axolemmal membrane $1\mu m$ to the right of the node versus that present across the segment of myelin sheath just surrounding the axon, argues for longitudinal current flow in the peri-axonal space and a greater effective capacitative load at the node. This is the result of such large longitudinal spatial gradients in potential, on the order of $15KV/m$. This appears to be a sensitive parameter and may therefore be one that is either exploited by the fiber itself for minor adjustments in performance or one that could have a significant influence on the conduction properties of nerve fibers suffering from trauma or other pathology.

Nodal constriction

The influence of the nodal-paranodal constriction on the conduction properties was the most surprising finding (Fig. 5.23). The results indicate that the constriction provides a possible 32.3% increase in conduction velocity over no constriction at all in the MYSA section. Compared to the radius of the MYSA section in the normal condition, averaging $2.3\mu m$, this provides a 23.1% speed-up over the non-constricted case. This is at variance with the finding of Moore, et al. [79] who claimed that the

nodal constriction has very little influence on conduction velocity. They referenced a case of reducing the *nodal area* to one-half the normal amount and saw only a 3.8% reduction in conduction velocity. This points out a fundamental distinction between the two models. The only adjustment Moore, et al. made was to the nodal area within a Δz step on the order of $200 - 400\mu m$ in length, not to the cross-sectional area of the $4\mu m$ length MYSA section just adjacent to the nodal compartment. This provides a theoretical stand for the functional purpose of what has been a noted anatomical feature of the nerve fiber for some 118 years.

A piece of theoretical work that lends support to this phenomenon, although applied only to the case of a single step change in diameter, is that of Joyner, et al. [69] in which they modeled differences in diameters of various cylindrical cells. In their Figure 6 the effect of a step reduction in diameter is shown, resulting in a conduction velocity increase in the region just before change in diameter occurs and the conduction velocity decreasing as the action potential enters the smaller diameter fiber. In their Figure 7 the diameter increases and the conduction velocity shows a short region of higher velocity just beyond the change in radius. In the case of the myelinated nerve fiber, this effect may be exploited in combination, where the reduction and expansion may combine to aid in increasing the conduction velocity. The effect of this 'throttle' phenomenon is to increase the longitudinal current density present in MYSA region and also increase the effective impedance present in that region. This may act as a 'valve' of sorts in that the load provided by the relatively leaky node of Ranvier may be minimized and the difference made up by the surplus current drive capacity present at the node, i.e. the 'safety factor' of the sourcing current being more than needed to activate the next node down the line. If this is occurring, it seems sensible that the more constricted region would be on the distal side of the node relative to the direction of propagation, so the current sourcing could

be done efficiently. Indeed, this is supported by the anatomical literature in which indications are that the paranode is larger on the proximal side of the node versus the distal side [6]. This may mean that the proximal-distal difference in degree of constriction is acting as a *rectifier*, in other words, encouraging conduction in the ortho versus antidromic direction.

When the radius of the MYSA segment is reduced further, the conduction velocity begins to decrease rapidly as the longitudinal resistance becomes too great for the current sourced by the previous node to depolarize the following node. Also noted during this study was the increase in the transaxonal potential at the node that was being stimulated. This is expected, as the load of the remainder of the fiber is being progressively cut off, approximating an isolated space-clamp condition for the node.

Extracellular volume

The capacity to explicitly include the size of the extracellular volume as well as the resistivity in the model of the myelinated nerve fiber is a feature that is also a major contribution of this thesis. Inclusion of this space allows for examination of the functional implication on conduction as seen in Fig. 5.24 as well as the potential for coupling with field-theoretic techniques. The influence of this space on the conduction velocity seen in the mammalian myelinated nerve fiber was explored and found to effect the conduction behavior only for radii less than $25\mu m$. As the radius of the extracellular space outer-boundary approached that of the outer edge of the myelinated nerve fiber, the conduction velocity slowed and stopped at a radius of $9.125\mu m$, a thickness of $0.375\mu m$ for the extracellular volume. The conduction block occurred when the extracellular resistance per-unit-length approached that of the intra-axonal resistance per-unit-length.

Temperature

The relation of conduction velocity to temperature seen in Fig. 5.25 is supported both by the data of Rasminsky [90] as presented in the graph as well as that of Hardy [54] in that a non-linear relation of conduction velocity to temperature is evident for the model-generated results. Hardy reports a theoretical Q_{10} of 1.5 for the conduction velocity. An estimated Q_{10} for the results shown in Fig. 5.25 is 1.56, close to that found by Hardy [54]. At some variance with this, but not extreme is the work of Moore et al. [79], reporting a Q_{10} of 1.68 when the axoplasmic resistivity was given a Q_{10} of 1.3 (the value used in computation of Fig. 5.25).

6.3.2 Space-clamped node of Ranvier

The results of the simulation of a space-clamped node of Ranvier indicate that the peri-axonal space width may play an important role in the effective electrical load seen by the node during clamp studies. This has been noted in previous studies in which the myelin sheath was disrupted [17]. Simulation results also lend support to the hypothesis that paranodal ionic channels are activated during nodal depolarization and repolarization. The possibility for propagating action potentials occurring beneath the myelin sheath was also demonstrated. This was a possibility posed by Huxley and Stämpfli [67] but was considered by them to be a minor mechanism of conduction in the myelinated nerve fiber if at all, the saltatory form of conduction being dominant.

This technique of simulating the space-clamp conditions of the nodal region can be expanded upon, offering a detailed method of modeling the behavior of the node of Ranvier under these conditions.

6.4 Future Extensions

When more experimental data becomes available on the differences in kinetics between two type of fast K^+ channels, this could easily be included in the nodal and internodal regions of the model. If desired, the steady-state and time constant relations of the existing fast K^+ could simply be shifted and the permeabilities scaled according to Dubois [38].

The next major enhancement to the distributed-parameter model suggested is the inclusion of compartments for modification of the ionic concentrations during activity. The work of Dubois and Bergman [40] cites the accumulation of K^+ in the perinodal space, the space just outside of the nodal membrane, during long periods of depolarization. The subsequent work of Moran, et al. [80] investigated this phenomenon in more detail and found that an unstirred layer model provided the best results. A desired attribute of this addition would be the possibility of modeling diffusion along the length of the fiber as well as across the nodal and internodal membranes. This, coupled with the addition of $Na^+ - K^+$ pumps, would allow the exploration of the behavior seen at the growth cone in fibers that are undergoing growth or recovery from injury. This is becoming an area of great interest due to the hope for guidance of nerve fibers in stages of recovery.

As mentioned earlier, the coupling of this type of model which can account for the presence of an extracellular volume with field-theoretic techniques can provide a tool for study of potentials generated by these nerve fibers as well as offer some new options for the study of stimulation of these myelinated nerve fibers. Existing models such as that by McNeal [76] or by Reilly [91] are limited in their structure and assumptions in that they can only address the threshold issue, McNeal with a single modeled node and Reilly with several. The myelin sheath is assumed to be of

infinite impedance and the structure of these models is such that the propagation of action potentials cannot be simulated.

These extensions, along with application of the existing model to multiple issues such as repetitive activity and the possible ‘information processing’ aspects of these myelinated nerve fibers both individually and in tandem as networks of neurons are formed and studied, provide ample opportunities and challenges for the future.

Appendix A

Estimation Technique for Rate Constant Coefficients

As was presented in Section 3.3.2, the form adopted for the rate constants modeling the kinetics of the slow and fast K^+ channels described by Ilyin, et al. [68] were those used by Frankenhaeuser [45],

$$\alpha_n = \frac{A(V - B)}{1 - \exp((B - V)/C)}, \quad (\text{A.1})$$

and

$$\beta_n = \frac{A(B - V)}{1 - \exp((V - B)/C)}. \quad (\text{A.2})$$

Using these to form expressions for the steady-state n_∞ and time constant τ_n relations,

$$n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n} \quad (\text{A.3})$$

and

$$\tau_n = \frac{1}{\alpha_n + \beta_n} \quad (\text{A.4})$$

these were fit to the experimental data of Ilyin, et al to form values for the rate constant coefficients, A, B and C. The method used for the fit was the Gauss-Newton quasilinearization technique.

In brief, the Gauss-Newton technique consists of a procedure for minimization of an error measure in the least squares sense across an interval of interest for a given function of multiple parameters. For this case, a discrete set of data points existed for the functions $n_\infty(\underline{\phi}, V_k)$ and $\tau_n(\underline{\phi}, V_k)$; where $\underline{\phi}$ represents the vector of rate constant parameters: A_α , B_α , C_α , A_β , B_β and C_β . V_k indicates the use of discrete values

of transmembrane potential. Using the steady-state case as an example, an error measure was formed,

$$e(\underline{\phi}, V_k) = n_\infty(\underline{\phi}, V_k) - \hat{n}_\infty(V_k) \quad (\text{A.5})$$

where $\hat{n}_\infty(V_k)$ is the experimental steady-state value for a given voltage V_k . Represented across the range of discrete potentials,

$$\underline{e}(\underline{\phi}) = \begin{bmatrix} e(\underline{\phi}, V_1) \\ e(\underline{\phi}, V_2) \\ \vdots \\ e(\underline{\phi}, V_N) \end{bmatrix} = \begin{bmatrix} n_\infty(\underline{\phi}, V_1) \\ n_\infty(\underline{\phi}, V_2) \\ \vdots \\ n_\infty(\underline{\phi}, V_N) \end{bmatrix} - \begin{bmatrix} \hat{n}_\infty(\underline{\phi}, V_1) \\ \hat{n}_\infty(\underline{\phi}, V_2) \\ \vdots \\ \hat{n}_\infty(\underline{\phi}, V_N) \end{bmatrix} \quad (\text{A.6})$$

a least squares sense error measure was then formed,

$$E(\underline{\phi}, \underline{V}) \equiv \frac{1}{2} \underline{e}^T(\underline{\phi}, \underline{V}) \underline{e}(\underline{\phi}, \underline{V}). \quad (\text{A.7})$$

The following condition was used for the minimization of $E(\underline{\phi})$,

$$J(\underline{\phi}) \underline{e}(\underline{\phi} + \Delta \underline{\phi}, \underline{V}) = 0. \quad (\text{A.8})$$

$J(\underline{\phi})$ is the Jacobian matrix formed from the following partial derivatives,

$$\frac{\partial n_\infty}{\partial A_\alpha} = \frac{\beta \frac{\partial \alpha}{\partial A_\alpha}}{(\alpha + \beta)^2} \quad (\text{A.9})$$

with $\frac{\partial n_\infty}{\partial B_\alpha}$ and $\frac{\partial n_\infty}{\partial C_\alpha}$ of similar form and

$$\frac{\partial n_\infty}{\partial A_\beta} = -\frac{\alpha \frac{\partial \beta}{\partial A_\beta}}{(\alpha + \beta)^2} \quad (\text{A.10})$$

with $\frac{\partial n_\infty}{\partial B_\beta}$ and $\frac{\partial n_\infty}{\partial C_\beta}$ likewise. $\frac{\partial \alpha}{\partial A_\alpha}$, $\frac{\partial \alpha}{\partial B_\alpha}$ and $\frac{\partial \alpha}{\partial C_\alpha}$ are defined as,

$$\frac{\partial \alpha}{\partial A_\alpha} = \frac{(V - B)}{1 - \exp((B - V)/C)}, \quad (\text{A.11})$$

$$\frac{\partial \alpha}{\partial B_\alpha} = \frac{A((1 + (V - B)/C) \exp((B - V)/C) - 1)}{(1 - \exp((B - V)/C))^2} \quad (\text{A.12})$$

and

$$\frac{\partial \alpha}{\partial C_\alpha} = \frac{A(V - B)^2 \exp((B - V)/C)}{C^2(1 - \exp((B - V)/C))^2} \quad (\text{A.13})$$

with $\frac{\partial \beta}{\partial A_\beta}$, $\frac{\partial \beta}{\partial B_\beta}$ and $\frac{\partial \beta}{\partial C_\beta}$ of similar form. The Jacobian for τ_n was produced in the same way.

This Jacobian was then used to compute a change in $\underline{\phi}$ as follows,

$$\Delta \underline{\phi} = -(JJ^T + \lambda I)^{-1} J \underline{e}(\underline{\phi}, \underline{V}) \quad (\text{A.14})$$

where λ is the Levenberg parameter as discussed by Marquardt [75]. This parameter was modified at each iteration of the algorithm based on the results of a performance index,

$$\rho = \sum_{i=1}^m E(\phi_i, \underline{V}) \quad (\text{A.15})$$

where m is the number of parameters being estimated, 6 in this case. If the performance index was less than in the previous iteration, λ was decreased by a given amount, typically 1/2. If the performance index was greater than in the previous iteration, the λ was increased by a factor of 2. The effect of increasing λ was to drive the algorithm from Gauss step sizes to smaller step sizes like that for the gradient method. Stopping conditions were set by setting a limit on the performance index or by limiting the number of iterations.

The algorithm was coded in the C language and executed on a Sun 3/260 processor with floating point acceleration hardware. The LINPACK linear algebraic software library Gaussian elimination routines DGECCO and DGESL were used to solve the matrix equation. The time to compute 500 iterations of the algorithm was on the order of 15 seconds.

The rate constant coefficients for each case were usually reached in multiple stages. An initial guess for the coefficients of 1.0 often reached a good initial estimate for the A multiplicative coefficient as well as the B and C coefficients which are in the

exponent and more unpredictable as a result. Some experimentation with the λ values, of which there was one for each coefficient, proved necessary to parse out each case. This proved very useful in the sense that λ could be set to an initially large value for one or more coefficients, allowing for others to vary more rapidly.

Appendix B

Solution Technique for Space Clamped Membrane

The space-clamped membrane equation representing the equivalent circuit shown in Fig. 3.1 is as follows,

$$C \frac{dV}{dt} = I_{Na} + I_{Kf} + I_{Ks} + G_L(V - V_L) + I_{stim}. \quad (B.1)$$

For the amphibian and mammalian cases, I_{Na} is represented by a Goldman-Hodgkin-Katz (GHK) constant field expression,

$$I_{Na} = \bar{P}_{Na} \frac{VF^2}{RT} \frac{[Na]_o - [Na]_i \exp(FV/RT)}{1 - \exp(FV/RT)}. \quad (B.2)$$

In the case of I_{Kf} and I_{Ks} , these are represented by the following expressions in the amphibian case,

$$I_{Kf} = \bar{G}_{Kf} n_f^4 (V - V_K) \quad (B.3)$$

and

$$I_{Ks} = \bar{G}_{Ks} n_s^4 (V - V_K) \quad (B.4)$$

with the following for the mammalian case,

$$I_{Kf} = \bar{P}_{Kf} n_f^4 \frac{VF^2}{RT} \frac{[K]_o - [K]_i \exp(FV/RT)}{1 - \exp(FV/RT)}. \quad (B.5)$$

and

$$I_{Ks} = \bar{P}_{Ks} n_s^4 \frac{VF^2}{RT} \frac{[K]_o - [K]_i \exp(FV/RT)}{1 - \exp(FV/RT)}. \quad (B.6)$$

I_L is the leakage current which is a function of a simple constant conductance and an offset potential V_L . I_{stim} is the injected stimulus current used to initiate the membrane action potential.

The gating variables follow the ordinary differential equation relations presented in Chapter 3, restated here for completeness,

$$\frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m, \quad (\text{B.7})$$

with the equations for the other gating variables of the same form. This can be rewritten in terms of the steady-state m_∞ and time constant τ_m as follows,

$$\frac{dm}{dt} = \frac{m_\infty - m}{\tau_m} \quad (\text{B.8})$$

In the case of the Na^+ rate constants, the expressions by Dodge [35] are used for the amphibian,

$$\alpha_m = \frac{A(B - V)/C}{\exp((B - V)/C) - 1} + \alpha_{\bar{m}}, \quad (\text{B.9})$$

where

$$\alpha_{\bar{m}} = \frac{A}{1 + ((V - B)/C)^2}, \quad (\text{B.10})$$

$$\beta_m, \alpha_h = \frac{A(V - B)/C}{\exp((V - B)/C) - 1} \quad (\text{B.11})$$

and

$$\beta_h = \frac{A(B - V)/C}{\exp((B - V)/C) - 1}. \quad (\text{B.12})$$

For the mammalian case, those adopted by Schwarz and Eikhof [101] are used,

$$\alpha_m = \frac{A(V - B)}{1 - \exp((B - V)/C)}, \quad (\text{B.13})$$

$$\beta_m, \alpha_h = \frac{A(B - V)}{1 - \exp((V - B)/C)} \quad (\text{B.14})$$

and

$$\beta_h = \frac{A}{1 - \exp((B - V)/C)}. \quad (\text{B.15})$$

In the case of the fast n_f and slow n_s K^+ gating variables, the rate constants use the following relations,

$$\alpha_n = \frac{A(V - B)}{1 - \exp((B - V)/C)}, \quad (\text{B.16})$$

and

$$\beta_n = \frac{A(B - V)}{1 - \exp((V - B)/C)}. \quad (\text{B.17})$$

In order to minimize computation time as much as possible during the solution of the larger problem involving multiple segments of active membrane distributed along the model, it was decided to implement a simple and efficient algorithm for generation of the component currents present across the membrane for each temporal step. The integration of the membrane currents occurs during the implicit integration for the entire model. Since a single temporal step is used in the implicit integration, a simple Euler's method was selected to integrate the space-clamped membrane equation B.1. In order to speed the determination of the new values for the gating variables, a Rush-Larsen approximation method [93] was employed to effectively integrate these simple first order ordinary differential equations. The approximation is of the following form,

$$m(V_{k+1}, t_{k+1}) = m_\infty(V_k) - [m_\infty(V_k) - m(V_k, t_k)] \exp\left(-\frac{\Delta t}{\tau_m(V_k)}\right) \quad (\text{B.18})$$

with the expressions for the other gating variables in similar form. This approximation is predicated on the assumption that the α 's and β 's can be assumed to be constant over the Δt interval.

Programs were written in the C language to solve this system of equations and implemented on a Sun 3/260 computer system with floating point acceleration hardware. The main routine performed integration of equation B.1 using ionic currents provided by a subroutine which evaluated the rate constants for the respective ionic channels, performed the Rush-Larsen approximation to obtain a new value for each gating variable, evaluated the new GHK or conductance equations as necessary and

returned the transmembrane ionic currents to the main routine. This process necessitated maintaining the state of each gating variable resident in memory during determination of the MAP. The main routine was driven by input conditions residing in an ASCII file which was easily edited to allow for modification of the model parameters. The only modifications necessary to represent the internodal versus the nodal membrane was alteration of this input file.

Both the amphibian and mammalian MAPs as illustrated in Figs. 3.6 and 3.7, were calculated for 20°C using temporal step sizes of $2\mu\text{s}$ for the integration. The 2ms of data computed for the mammalian case, equivalent to 1000 iterations, took less than 4 seconds of computation time including storage of the output. To check for accuracy, a comparison was made of the results obtained with a step size of $0.2\mu\text{s}$ versus $2\mu\text{s}$. The resulting percentage total rms error was less than 1%.

Appendix C

Convolution Method for the Reduced Model

An alternative for the full form model that can address the issue of charge storage both in the myelin and underlying axolemmal membrane is a reduced model consisting of a passive axolemmal membrane consisting of solely a parallel conductance and capacitance as illustrated in Fig. C.1. This reduced model also assumes that the periaxonal conductance pathway is of sufficiently high impedance that it can be ignored. The equivalent network is of the same form as that seen in the simple coaxial case with the significant difference of the transverse impedance seen in the internodal region not collapsing to a simple form amenable to formation of a simple expression for the transverse current as a function of total transverse potential. Indeed, the series combination of two parallel elements provides for several paths of possible current flow and an equivalent impedance characteristic that is dominated by the series capacitive element as the frequency approaches infinity and by the series conductive elements as the frequency approaches zero, with a transition region between these two extremes dependent on the ratio of component values.

An approach to the problem that results in a difference expression that can be put into the Crank-Nicolson implicit form for the partial differential equation solution is to find the Laplace transform equivalent for this transverse impedance and then use the inverse transform technique to form the desired difference expressions. Using the Laplace transform equivalent of the internodal network elements we have:

Figure C.1: Reduced model with a passive axolemmal membrane in the internode and no peri-axonal conductance pathway. The peri-axonal conductance pathway is assumed to be of high enough impedance to be ignored.

$$Y(s) = \frac{(C_m s + G_m)(C_{my} s + G_{my})}{(C_m s + G_m) + (C_{my} s + G_{my})} \quad (C.1)$$

Collecting terms:

$$Y(s) = \frac{C_m C_{my} s^2 + (G_m C_{my} + G_{my} C_m) s + G_m G_{my}}{(C_m + C_{my}) s + (G_m + G_{my})} \quad (C.2)$$

In order to determine the form of the inverse transform the order of the numerator needs to be reduced. First factor out leading coefficient in the denominator.

$$Y(s) = \frac{C_m C_{my}}{C_m + C_{my}} \left[\frac{s^2 + \left[\frac{G_m C_{my} + G_{my} C_m}{C_m C_{my}} \right] s + \frac{G_m G_{my}}{C_m C_{my}}}{s + \frac{G_m + G_{my}}{C_m + C_{my}}} \right] \quad (C.3)$$

Next add and subtract terms to isolate the s^2 term.

$$Y(s) = \frac{C_m C_{my}}{C_m + C_{my}} \left[\frac{s^2 + \frac{G_m + G_{my}}{C_m + C_{my}} s}{s + \frac{G_m + G_{my}}{C_m + C_{my}}} - \frac{\frac{G_m + G_{my}}{C_m + C_{my}} s}{s + \frac{G_m + G_{my}}{C_m + C_{my}}} + \frac{\left[\frac{G_m C_{my} + G_{my} C_m}{C_m C_{my}} \right] s + \frac{G_m G_{my}}{C_m C_{my}}}{s + \frac{G_m + G_{my}}{C_m + C_{my}}} \right] \quad (C.4)$$

Cancelling terms:

$$Y(s) = \frac{C_m C_{my}}{C_m + C_{my}} \left[s + \frac{\left[\frac{G_m C_{my} + G_{my} C_m}{C_m C_{my}} - \frac{G_m + G_{my}}{C_m + C_{my}} \right] s + \frac{G_m G_{my}}{C_m C_{my}}}{s + \frac{G_m + G_{my}}{C_m + C_{my}}} \right] \quad (C.5)$$

Results in this form for $Y(s)$.

$$Y(s) = \frac{C_m C_{my}}{C_m + C_{my}} s + \frac{\left[\frac{G_m C_{my} + G_{my} C_m}{C_m + C_{my}} - \frac{C_m C_{my} (G_m + G_{my})}{(C_m + C_{my})^2} \right] s + \frac{G_m G_{my}}{C_m + C_{my}}}{s + \frac{G_m + G_{my}}{C_m + C_{my}}} \quad (C.6)$$

Finding $I(s)$:

$$I(s) = Y(s)V(s) \quad (C.7)$$

Yields:

$$\begin{aligned} I(s) = \frac{C_m C_{my}}{C_m + C_{my}} s V(s) + \frac{\left[\frac{G_m C_{my} + G_{my} C_m}{C_m + C_{my}} - \frac{C_m C_{my} (G_m + G_{my})}{(C_m + C_{my})^2} \right] s}{s + \frac{G_m + G_{my}}{C_m + C_{my}}} V(s) \\ + \frac{\frac{G_m G_{my}}{C_m + C_{my}}}{s + \frac{G_m + G_{my}}{C_m + C_{my}}} V(s) \end{aligned} \quad (C.8)$$

Taking the inverse transform:

$$i(t) = \frac{C_m C_{my}}{C_m + C_{my}} \delta(t) * \frac{dV(t)}{dt} + \alpha e^{-\beta t} * \frac{dV(t)}{dt} + \gamma e^{-\beta t} * V(t) \quad (C.9)$$

Where the coefficients α, β , and γ equal:

$$\alpha = \frac{G_m C_{my} + G_{my} C_m}{C_m + C_{my}} - \frac{C_m C_{my} (G_m + G_{my})}{(C_m + C_{my})^2} \quad (C.10)$$

$$\beta = \frac{G_m + G_{my}}{C_m + C_{my}} \quad (C.11)$$

$$\gamma = \frac{G_m G_{my}}{C_m + C_{my}} \quad (C.12)$$

Placing the convolution in discrete form and substituting V and i for the equivalent discrete membrane terms:

$$i_{k,j}^m = \frac{C_m C_{my}}{C_m + C_{my}} \frac{V_{k,j+1}^m - V_{k,j}^m}{\Delta t} + \alpha \sum_{i=1}^{j-1} e^{-\beta(j-i)\Delta t} \frac{V_{k,i+1}^m - V_{k,i}^m}{\Delta t} \Delta t + \gamma \sum_{l=1}^{j-1} e^{-\beta(j-l)\Delta t} V_{k,l}^m \Delta t \quad (C.13)$$

Rearranging for integration into the Crank-Nicolson form:

$$i_{k,j}^m = \left[\frac{C_m C_{my}}{C_m + C_{my}} + \alpha \Delta t \right] \frac{V_{k,j+1}^m - V_{k,j}^m}{\Delta t} + \sum_{i=1}^{j-1} e^{-\beta(j-i)\Delta t} \left[\alpha \frac{V_{k,i+1}^m - V_{k,i}^m}{\Delta t} + \gamma V_{k,i}^m \right] \Delta t + \gamma V_{k,j}^m \Delta t \quad (C.14)$$

The complete expression of the Crank-Nicolson form solution for the internodal region can now be formed:

$$\begin{aligned} & V_{k+1,j+1}^m - \left[2 + (r_i + r_o) \Delta z^2 \left[\frac{C_t}{\Delta t} + \alpha \right] \right] V_{k,j+1}^m + V_{k-1,j+1}^m \\ &= -V_{k+1,j}^m + \left[2 - (r_i + r_o) \Delta z^2 \left[\frac{C_t}{\Delta t} + \alpha - \gamma \Delta t \right] \right] V_{k,j}^m + V_{k-1,j}^m \\ &+ (r_i + r_o) \Delta z^2 \left[\sum_{i=1}^{j-1} e^{-\beta(j-i)\Delta t} \left[\alpha \frac{V_{k,i+1}^m - V_{k,i}^m}{\Delta t} + \gamma V_{k,i}^m \right] \Delta t \right] \end{aligned} \quad (C.15)$$

Where: $C_t = \frac{C_m C_{my}}{C_m + C_{my}}$

The results obtained from this model reproduce phenomena such as the depolarizing afterpotential that cannot be generated by the standard form coaxial cable equivalent for the myelinated nerve fiber. Disadvantages of this technique are that active processes cannot be represented in the internodal region and the peri-axonal space effect cannot be examined. The method also becomes computationally burdensome depending on the time of the simulation run that is necessary. As the simulation

duration increases, the time to perform the necessary convolution at each time iteration also becomes greater. In addition, this convolution is required for each segment represented in the model. An attempt to truncate this convolution was attempted, hoping that only the early components were significant, however instability resulted.

In summary, this method can provide a means of examining phenomena such as the depolarizing afterpotential which is predicated on the independence of charge storage across the myelin sheath versus the axolemmal membrane. However, it becomes computationally burdensome for long time simulations and cannot allow for representation of active processes in the internodal axolemmal membrane or the presence of a peri-axonal conductance pathway.

Appendix D

Explicit Solution Method

D.1 Derivation of Nodal Segment Expressions

D.1.1 Intra-axonal

Starting with the expression equating the currents dependent on the intra-axonal spatial potential distribution with the transmembrane currents,

$$\frac{V_{k-1,j}^i - 2V_{k,j}^i + V_{k+1,j}^i}{R_{N-M}^i} = \left[C_N^a \frac{(V_{k,j+1}^i - V_{k,j+1}^p) - (V_{k,j}^i - V_{k,j}^p)}{\Delta t} + i_{ionic} \right] \Delta Z_N, \quad (D.1)$$

This is then rearranged to equate the new time step values to the old,

$$\begin{aligned} V_{k,j+1}^i - V_{k,j+1}^p &= \frac{\Delta t}{C_N^a \Delta Z_N R_{N-M}^i} (V_{k-1,j}^i - 2V_{k,j}^i + V_{k+1,j}^i) \\ &\quad + (V_{k,j}^i - V_{k,j}^p) - \frac{\Delta t}{C_N^a} i_{ionic}. \end{aligned} \quad (D.2)$$

Rearranging to clarify the coefficients for each component,

$$\begin{aligned} V_{k,j+1}^i - V_{k,j+1}^p &= \frac{\Delta t}{C_N^a \Delta Z_N R_{N-M}^i} V_{k-1,j}^i + \left[1 - \frac{2\Delta t}{C_N^a \Delta Z_N R_{N-M}^i} \right] V_{k,j}^i \\ &\quad + \frac{\Delta t}{C_N^a \Delta Z_N R_{N-M}^i} V_{k+1,j}^i - V_{k,j}^p - \frac{\Delta t}{C_N^a} i_{ionic}. \end{aligned} \quad (D.3)$$

Rearranging into a general form yields,

$$V_{k,j+1}^i + \beta_N^i V_{k,j+1}^p = \Phi_N^i \quad (D.4)$$

and

$$\Phi_N^i = \Psi_N^i V_{k-1,j}^i + \Theta_N^i V_{k,j}^i + \Lambda_N^i V_{k+1,j}^i + \Gamma_N^i V_{k,j}^p + \Upsilon_N^i i_{ionic} \quad (D.5)$$

with the following coefficients,

$$\beta_N^i = -1 \quad (D.6)$$

$$\Psi_N^i = \frac{\Delta t}{C_N^a \Delta Z_N R_{N-M}^i} \quad (D.7)$$

$$\Theta_{N,j}^i = 1 - \frac{2\Delta t}{C_N^a \Delta Z_N R_{N-M}^i} \quad (D.8)$$

$$\Lambda_N^i = \frac{\Delta t}{C_N^a \Delta Z_N R_{N-M}^i} \quad (D.9)$$

$$\Gamma_N^i = -1 \quad (D.10)$$

$$\Upsilon_N^i = -\frac{\Delta t}{C_N^a}. \quad (D.11)$$

D.1.2 Peri-axonal

Proceeding in like fashion for the peri-axonal space yields,

$$\begin{aligned} \frac{V_{k-1,j}^p - 2V_{k,j}^p + V_{k+1,j}^p}{R_{N-M}^p} &= \left[\frac{G_N^{my}(V_{k,j}^p + V_{k,j+1}^p)}{2} \right] \Delta Z_N \\ &- \left[C_N^a \frac{(V_{k,j+1}^i - V_{k,j+1}^p) - (V_{k,j}^i - V_{k,j}^p)}{\Delta t} + i_{ionic} \right] \Delta Z_N. \end{aligned} \quad (D.12)$$

Following the same procedure of manipulation to produce expressions for the new time step values,

$$\begin{aligned} \left(\frac{G_N^{my}}{2} + \frac{C_N^a}{\Delta t} \right) V_{k,j+1}^p - \frac{C_N^a}{\Delta t} V_{k,j+1}^i &= \frac{(V_{k-1,j}^p - 2V_{k,j}^p + V_{k+1,j}^p)}{\Delta Z_N R_{N-M}^p} \\ &+ \left(\frac{C_N^a}{\Delta t} - \frac{G_N^{my}}{2} \right) V_{k,j}^p - \frac{C_N^a}{\Delta t} V_{k,j}^i + i_{ionic}, \end{aligned} \quad (D.13)$$

with re-arrangement of coefficients,

$$\begin{aligned} V_{k,j+1}^p - \frac{C_N^a}{\left(\frac{G_N^{my}}{2} + \frac{C_N^a}{\Delta t} \right) \Delta t} V_{k,j+1}^i &= \frac{(V_{k-1,j}^p - 2V_{k,j}^p + V_{k+1,j}^p)}{\left(\frac{G_N^{my}}{2} + \frac{C_N^a}{\Delta t} \right) \Delta Z_N R_{N-M}^p} \\ \frac{\left(\frac{C_N^a}{\Delta t} - \frac{G_N^{my}}{2} \right)}{\left(\frac{G_N^{my}}{2} + \frac{C_N^a}{\Delta t} \right)} V_{k,j}^p - \frac{C_N^a}{\left(\frac{G_N^{my}}{2} + \frac{C_N^a}{\Delta t} \right) \Delta t} V_{k,j}^i &+ \frac{1}{\left(\frac{G_N^{my}}{2} + \frac{C_N^a}{\Delta t} \right)} i_{ionic}, \end{aligned} \quad (D.14)$$

results in the following final form,

$$\begin{aligned} V_{k,j+1}^p - \frac{C_N^a}{\left(\frac{G_N^{my}}{2} + \frac{C_N^a}{\Delta t} \right) \Delta t} V_{k,j+1}^i &= \frac{1}{\left(\frac{G_N^{my}}{2} + \frac{C_N^a}{\Delta t} \right) \Delta Z_N R_{N-M}^p} V_{k-1,j}^p \\ &+ \left[\frac{\left(\frac{C_N^a}{\Delta t} - \frac{G_N^{my}}{2} \right)}{\left(\frac{G_N^{my}}{2} + \frac{C_N^a}{\Delta t} \right)} - \frac{2}{\left(\frac{G_N^{my}}{2} + \frac{C_N^a}{\Delta t} \right) \Delta Z_N R_{N-M}^p} \right] V_{k,j}^p \\ &+ \frac{1}{\left(\frac{G_N^{my}}{2} + \frac{C_N^a}{\Delta t} \right) \Delta Z_N R_{N-M}^p} V_{k+1,j}^p - \frac{C_N^a}{\left(\frac{G_N^{my}}{2} + \frac{C_N^a}{\Delta t} \right) \Delta t} V_{k,j}^i + \frac{1}{\left(\frac{G_N^{my}}{2} + \frac{C_N^a}{\Delta t} \right)} i_{ionic}. \end{aligned} \quad (D.15)$$

Expressing this in general form yields,

$$V_{k,j+1}^p + \beta_N^p V_{k,j+1}^i = \Phi_N^p \quad (D.16)$$

and

$$\Phi_N^p = \Psi_N^p V_{k-1,j}^p + \Theta_N^p V_{k,j}^p + \Lambda_N^p V_{k+1,j}^p + \Gamma_N^p V_{k,j}^i + \Upsilon_N^p i_{ionic} \quad (D.17)$$

with the following coefficients,

$$\beta_N^p = -\frac{C_N^a}{\left(\frac{G_N^{my}}{2} + \frac{C_N^a}{\Delta t}\right) \Delta t} \quad (\text{D.18})$$

$$\Psi_N^p = \frac{1}{\left(\frac{G_N^{my}}{2} + \frac{C_N^a}{\Delta t}\right) \Delta Z_N R_{N-M}^p} \quad (\text{D.19})$$

$$\Theta_{N,j}^p = \frac{\left(\frac{C_N^a}{\Delta t} - \frac{G_N^{my}}{2}\right)}{\left(\frac{G_N^{my}}{2} + \frac{C_N^a}{\Delta t}\right)} - \frac{2}{\left(\frac{G_N^{my}}{2} + \frac{C_N^a}{\Delta t}\right) \Delta Z_N R_{N-M}^p} \quad (\text{D.20})$$

$$\Lambda_N^p = \frac{1}{\left(\frac{G_N^{my}}{2} + \frac{C_N^a}{\Delta t}\right) \Delta Z_N R_{N-M}^p} \quad (\text{D.21})$$

$$\Gamma_N^p = -\frac{C_N^a}{\left(\frac{G_N^{my}}{2} + \frac{C_N^a}{\Delta t}\right) \Delta t} \quad (\text{D.22})$$

$$\Upsilon_N^p = \frac{1}{\left(\frac{G_N^{my}}{2} + \frac{C_N^a}{\Delta t}\right)} \quad (\text{D.23})$$

D.2 MYSA Segment

For the MYSA segment adjacent to the node of Ranvier, changes in the values of longitudinal coupling elements require the following treatment.

D.2.1 Intra-axonal

As before, equating the currents resulting from the longitudinal potential distribution with the transmembrane current produces,

$$\frac{V_{k-1,j}^i - V_{k,j}^i}{R_{N-M}^i} - \frac{V_{k,j}^i - V_{k+1,j}^i}{R_{M-F}^i}$$

$$= \left[C_M^a \frac{(V_{k,j+1}^i - V_{k,j+1}^p) - (V_{k,j}^i - V_{k,j}^p)}{\Delta t} + i_{ionic} \right] \Delta Z_M. \quad (D.24)$$

Rearranging,

$$\begin{aligned} V_{k,j+1}^i - V_{k,j+1}^p &= \frac{\Delta t}{C_M^a \Delta Z_M} \left[\frac{V_{k-1,j}^i - V_{k,j}^i}{R_{N-M}^i} - \frac{V_{k,j}^i - V_{k+1,j}^i}{R_{M-F}^i} \right] \\ &\quad + (V_{k,j}^i - V_{k,j}^p) - \frac{\Delta t}{C_M^a} i_{ionic}, \end{aligned} \quad (D.25)$$

to form coefficients for each value of potential result in,

$$\begin{aligned} V_{k,j+1}^i - V_{k,j+1}^p &= \frac{\Delta t}{C_M^a \Delta Z_M R_{N-M}^i} V_{k-1,j}^i \\ &\quad + \left[1 - \frac{\Delta t}{C_M^a \Delta Z_M} \left(\frac{1}{R_{N-M}^i} + \frac{1}{R_{M-F}^i} \right) \right] V_{k,j}^i \\ &\quad + \frac{\Delta t}{C_M^a \Delta Z_M R_{M-F}^i} V_{k+1,j}^i - V_{k,j}^p - \frac{\Delta t}{C_M^a} i_{ionic}. \end{aligned} \quad (D.26)$$

Placing this in general form yields,

$$V_{k,j+1}^i + \beta_M^i V_{k,j+1}^p = \Phi_M^i \quad (D.27)$$

$$\Phi_M^i = \Psi_M^i V_{k-1,j}^i + \Theta_M^i V_{k,j}^i + \Lambda_M^i V_{k+1,j}^i + \Gamma_M^i V_{k,j}^p + \Upsilon_M^i i_{ionic} \quad (D.28)$$

with the following coefficients,

$$\beta_M^i = -1 \quad (D.29)$$

$$\Psi_M^i = \frac{\Delta t}{C_M^a \Delta Z_M R_{N-M}^i} \quad (D.30)$$

$$\Theta_{N,j}^i = 1 - \frac{\Delta t}{C_M^a \Delta Z_M} \left(\frac{1}{R_{N-M}^i} + \frac{1}{R_{M-F}^i} \right) \quad (\text{D.31})$$

$$\Lambda_M^i = \frac{\Delta t}{C_M^a \Delta Z_M R_{M-F}^i} \quad (\text{D.32})$$

$$\Gamma_M^i = -1 \quad (\text{D.33})$$

$$\Upsilon_M^i = -\frac{\Delta t}{C_M^a}. \quad (\text{D.34})$$

D.2.2 Peri-axonal

In like fashion, the expression for the MYSA peri-axonal space results in,

$$\begin{aligned} & \frac{V_{k-1,j}^p - V_{k,j}^p}{R_{N-M}^p} - \frac{V_{k,j}^p - V_{k+1,j}^p}{R_{M-F}^p} = \\ & \left[C_M^{my} \frac{(V_{k,j+1}^p - V_{k,j}^p)}{\Delta t} + G_M^{my} \frac{V_{k,j}^p + V_{k,j+1}^p}{2} \right] \Delta Z_M \\ & - \left[C_M^a \frac{(V_{k,j+1}^i - V_{k,j+1}^p) - (V_{k,j}^i - V_{k,j}^p)}{\Delta t} + i_{ionic} \right] \Delta Z_M, \end{aligned} \quad (\text{D.35})$$

$$\begin{aligned} & \left[\frac{C_M^{my} + C_M^a}{\Delta t} + \frac{G_M^{my}}{2} \right] V_{k,j+1}^p - \frac{C_M^a}{\Delta t} V_{k,j+1}^i = \\ & \frac{1}{\Delta Z_M} \left[\frac{V_{k-1,j}^p - V_{k,j}^p}{R_{N-M}^p} - \frac{V_{k,j}^p - V_{k+1,j}^p}{R_{M-F}^p} \right] \\ & - \frac{G_M^{my}}{2} V_{k,j}^p - \frac{C_M^a}{\Delta t} (V_{k,j}^i - V_{k,j}^p) + i_{ionic} \end{aligned} \quad (\text{D.36})$$

and

$$\begin{aligned}
V_{k,j+1}^p - \frac{C_M^a}{\left[\frac{(C_M^a + C_M^{my})}{\Delta t} + \frac{G_M^p}{2}\right] \Delta t} V_{k,j+1}^i = \\
\frac{1}{\left[\frac{(C_M^a + C_M^{my})}{\Delta t} + \frac{G_M^{my}}{2}\right] \Delta Z_M} \left[\frac{V_{k-1,j}^p - V_{k,j}^p}{R_{N-M}^p} - \frac{V_{k,j}^p - V_{k+1,j}^p}{R_{M-F}^p} \right] \\
- \frac{G_M^{my}}{\left[\frac{(C_M^a + C_M^{my})}{\Delta t} + \frac{G_M^{my}}{2}\right] 2} V_{k,j}^p - \frac{C_M^a}{\left[\frac{(C_M^a + C_M^{my})}{\Delta t} + \frac{G_M^p}{2}\right] \Delta t} (V_{k,j}^i - V_{k,j}^p) \\
+ \frac{1}{\left[\frac{(C_M^a + C_M^{my})}{\Delta t} + \frac{G_M^{my}}{2}\right]} i_{ionic} \tag{D.37}
\end{aligned}$$

with the following final form,

$$\begin{aligned}
V_{k,j+1}^p - \frac{C_M^a}{\left[\frac{(C_M^a + C_M^{my})}{\Delta t} + \frac{G_M^p}{2}\right] \Delta t} V_{k,j+1}^i = \frac{1}{\left[\frac{(C_M^a + C_M^{my})}{\Delta t} + \frac{G_M^{my}}{2}\right] \Delta Z_M R_{N-M}^p} V_{k-1,j}^p \\
+ \left[\frac{C_M^a}{\left[\frac{(C_M^a + C_M^{my})}{\Delta t} + \frac{G_M^p}{2}\right] \Delta t} \right] V_{k,j}^p \\
+ \left[\frac{1}{\left[\frac{(C_M^a + C_M^{my})}{\Delta t} + \frac{G_M^{my}}{2}\right]} \left[-\frac{G_M^{my}}{2} - \frac{1}{\Delta Z_M R_{N-M}^p} - \frac{1}{\Delta Z_M R_{M-F}^p} \right] \right] V_{k,j}^p \\
+ \frac{1}{\left[\frac{(C_M^a + C_M^{my})}{\Delta t} + \frac{G_M^{my}}{2}\right] \Delta Z_M R_{M-F}^p} V_{k+1,j}^p \\
- \frac{C_M^a}{\left[\frac{(C_M^a + C_M^{my})}{\Delta t} + \frac{G_M^p}{2}\right] \Delta t} V_{k,j}^i + \frac{1}{\left[\frac{(C_M^a + C_M^{my})}{\Delta t} + \frac{G_M^{my}}{2}\right]} i_{ionic}. \tag{D.38}
\end{aligned}$$

Expressing it in general form produces,

$$V_{k,j+1}^p + \beta_M^p V_{k,j+1}^i = \Phi_M^p \quad (\text{D.39})$$

$$\Phi_M^p = \Psi_M^p V_{k-1,j}^p + \Theta_M^p V_{k,j}^p + \Lambda_M^p V_{k+1,j}^p + \Gamma_M^p V_{k,j}^i + \Upsilon_M^p i_{ionic} \quad (\text{D.40})$$

with the following coefficients,

$$\beta_M^p = -\frac{C_M^a}{\left[\frac{(C_M^a + C_M^{my})}{\Delta t} + \frac{G_M^p}{2}\right] \Delta t} \quad (\text{D.41})$$

$$\Psi_M^p = \frac{1}{\left[\frac{(C_M^a + C_M^{my})}{\Delta t} + \frac{G_M^{my}}{2}\right] \Delta Z_M R_{N-M}^p} \quad (\text{D.42})$$

$$\begin{aligned} \Theta_{N,j}^p &= \frac{C_M^a}{\left[\frac{(C_M^a + C_M^{my})}{\Delta t} + \frac{G_M^p}{2}\right] \Delta t} - \frac{G_M^{my}}{\left[\frac{(C_M^a + C_M^{my})}{\Delta t} + \frac{G_M^{my}}{2}\right] 2} \\ &\quad - \frac{1}{\left[\frac{(C_M^a + C_M^{my})}{\Delta t} + \frac{G_M^{my}}{2}\right] \Delta Z_M R_{N-M}^p} - \frac{1}{\left[\frac{(C_M^a + C_M^{my})}{\Delta t} + \frac{G_M^{my}}{2}\right] \Delta Z_M R_{M-F}^p} \end{aligned} \quad (\text{D.43})$$

$$\Lambda_M^p = \frac{1}{\left[\frac{(C_M^a + C_M^{my})}{\Delta t} + \frac{G_M^{my}}{2}\right] \Delta Z_M R_{M-F}^p} \quad (\text{D.44})$$

$$\Gamma_M^p = -\frac{C_M^a}{\left[\frac{(C_M^a + C_M^{my})}{\Delta t} + \frac{G_M^p}{2}\right] \Delta t} \quad (\text{D.45})$$

$$\Upsilon_M^p = \frac{1}{\left[\frac{(C_M^a + C_M^{my})}{\Delta t} + \frac{G_M^{my}}{2}\right]} \quad (\text{D.46})$$

The expressions for the remaining segments, FLUT and STIN fall into the same form with modification of the coefficients.

D.3 Solution of Simultaneous Equations

For each of these segments the value of the intra-axonal and peri-axonal potentials must be determined by simultaneous solution of expressions derived from the summation of currents at their respective summation points.

For the intra-axonal space,

$$V_{k,j+1}^i + \beta_X^i V_{k,j+1}^p = \Phi_X^i. \quad (\text{D.47})$$

For the peri-axonal space,

$$\beta_X^p V_{k,j+1}^i + V_{k,j+1}^p = \Phi_X^p. \quad (\text{D.48})$$

Multiplying equation D.48 by $-\beta_X^i$ and eliminating $V_{k,j+1}^p$,

$$V_{k,j+1}^i - \beta_X^i \beta_X^p V_{k,j+1}^i = \Phi_X^i - \beta_X^i \Phi_X^p \quad (\text{D.49})$$

results in,

$$V_{k,j+1}^i = \frac{\Phi_X^i - \beta_X^i \Phi_X^p}{1 - \beta_X^i \beta_X^p}. \quad (\text{D.50})$$

Substituting the expression for $V_{k,j+1}^i$ back into equation D.48 yields,

$$V_{k,j+1}^p = \Phi_X^p + \frac{\beta_X^i \beta_X^p \Phi_X^p - \beta_X^p \Phi_X^i}{1 - \beta_X^i \beta_X^p}. \quad (\text{D.51})$$

This method was able to solve for the behavior of the uniformly-sampled internode but was unstable irregardless of the temporal step size when a node of Ranvier was included.

Appendix E

Solution Technique for the Triaxial Case

By assuming that the extra-axonal volume is of large diameter ($> 1mm$) in comparison to that of the myelinated nerve fiber and that the resistivity of the medium is not abnormally high, the model can be reduced in form to that of a triaxial core conductor equivalent with the extracellular potential V^o set to an iso-potential. This assumption has been typical in previous coaxial equivalent core conductor models [42, 50, 79]. Figure E.1 illustrates the form of the electrical equivalent network that can be contrasted with the network shown in Fig. 4.5.

The matrix equation is of a reduced order in comparison to that seen in Chapter 4. The A coefficient matrix is of the form,

$$A = \left[\begin{array}{c|c} \Theta^p & \Gamma^p \\ \hline \Gamma^i & \Theta^i \end{array} \right]. \quad (E.1)$$

Figure E.1: Equivalent network for the reduced model. Note the lack of longitudinal resistive elements in the extra-axonal portion of the network as contrasted with those seen in Fig. 4.5. The spatial indices are $k - 1$, k and $k + 1$.

The following illustrates the extremes of the matrix equation, reflecting the end conditions,

$$\begin{bmatrix}
 \Theta_E^p & 1 & \cdots & 0 & 0 & \Gamma_{SS}^p & 0 & \cdots & 0 & 0 \\
 1 & \Theta_{SS}^p & \cdots & 0 & 0 & 0 & \Gamma_{SS}^p & \cdots & 0 & 0 \\
 \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\
 0 & 0 & \cdots & \Theta_{SS}^p & 1 & 0 & 0 & \cdots & \Gamma_{SS}^p & 0 \\
 0 & 0 & \cdots & 1 & \Theta_E^p & 0 & 0 & \cdots & 0 & \Gamma_{SS}^p \\
 \Gamma_{SS}^i & 0 & \cdots & 0 & 0 & \Theta_E^i & 1 & \cdots & 0 & 0 \\
 0 & \Gamma_{SS}^i & \cdots & 0 & 0 & 1 & \Theta_{SS}^i & \cdots & 0 & 0 \\
 \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\
 0 & 0 & \cdots & \Gamma_{SS}^i & 0 & 0 & 0 & \cdots & \Theta_{SS}^i & 1 \\
 0 & 0 & \cdots & 0 & \Gamma_{SS}^i & 0 & 0 & \cdots & 1 & \Theta_E^i
 \end{bmatrix} \cdot \begin{bmatrix} V_{1,j+1}^p \\ V_{2,j+1}^p \\ \vdots \\ V_{n-1,j+1}^p \\ V_{n,j+1}^p \\ V_{1,j+1}^i \\ V_{2,j+1}^i \\ \vdots \\ V_{n-1,j+1}^i \\ V_{n,j+1}^i \end{bmatrix} = \begin{bmatrix} \Phi_1^p \\ \Phi_2^p \\ \vdots \\ \Phi_{n-1}^p \\ \Phi_n^p \\ \Phi_1^i \\ \Phi_2^i \\ \vdots \\ \Phi_{n-1}^i \\ \Phi_n^i \end{bmatrix} \quad (E.2)$$

where $\Theta_E^p = \Theta_{SS}^p - 1$ and $\Theta_E^i = \Theta_{SS}^i - 1$. The subscript SS denotes the coefficients for a STIN-STIN segment.

The change in coefficients as the node is approached can be seen as,

$$\begin{bmatrix}
 \vdots & \vdots & \vdots & \vdots & & \vdots & \vdots & \vdots & \vdots & \\
 \dots & \Theta_S^p & \Lambda_S^p & 0 & 0 & \dots & \Gamma_S^p & 0 & 0 & 0 & \dots \\
 \dots & \Psi_F^p & \Theta_F^p & \Lambda_F^p & 0 & \dots & 0 & \Gamma_F^p & 0 & 0 & \dots \\
 \dots & 0 & \Psi_M^p & \Theta_M^p & \Lambda_M^p & \dots & 0 & 0 & \Gamma_M^p & 0 & \dots \\
 \dots & 0 & 0 & \Psi_N^p & \Theta_N^p & \dots & 0 & 0 & 0 & \Gamma_N^p & \dots \\
 \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \vdots & \\
 \dots & \Gamma_S^i & 0 & 0 & 0 & \dots & \Theta_S^i & \Lambda_S^i & 0 & 0 & \dots \\
 \dots & 0 & \Gamma_F^i & 0 & 0 & \dots & \Psi_F^i & \Theta_F^i & \Lambda_F^i & 0 & \dots \\
 \dots & 0 & 0 & \Gamma_M^i & 0 & \dots & 0 & \Psi_M^i & \Theta_M^i & \Lambda_M^i & \dots \\
 \dots & 0 & 0 & 0 & \Gamma_N^i & \dots & 0 & 0 & \Psi_N^i & \Theta_N^i & \dots \\
 \vdots & \vdots & \vdots & \vdots & & \vdots & \vdots & \vdots & \vdots & \vdots &
 \end{bmatrix} \bullet \begin{bmatrix} \vdots \\ V_{S,j+1}^p \\ V_{F,j+1}^p \\ V_{M,j+1}^p \\ V_{N,j+1}^p \\ \vdots \\ V_{S,j+1}^i \\ V_{F,j+1}^i \\ V_{M,j+1}^i \\ V_{N,j+1}^i \\ \vdots \end{bmatrix} = \begin{bmatrix} \vdots \\ \Phi_S^p \\ \Phi_F^p \\ \Phi_M^p \\ \Phi_N^p \\ \vdots \\ \Phi_S^i \\ \Phi_F^i \\ \Phi_M^i \\ \Phi_N^i \\ \vdots \end{bmatrix} \quad (\text{E.3})$$

This coefficient matrix is quindagonal in form, with two diagonals off the principal diagonal and two diagonals at a distance of n from the principal diagonal. The solution technique is the same as that outlined in Section 4.3.

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