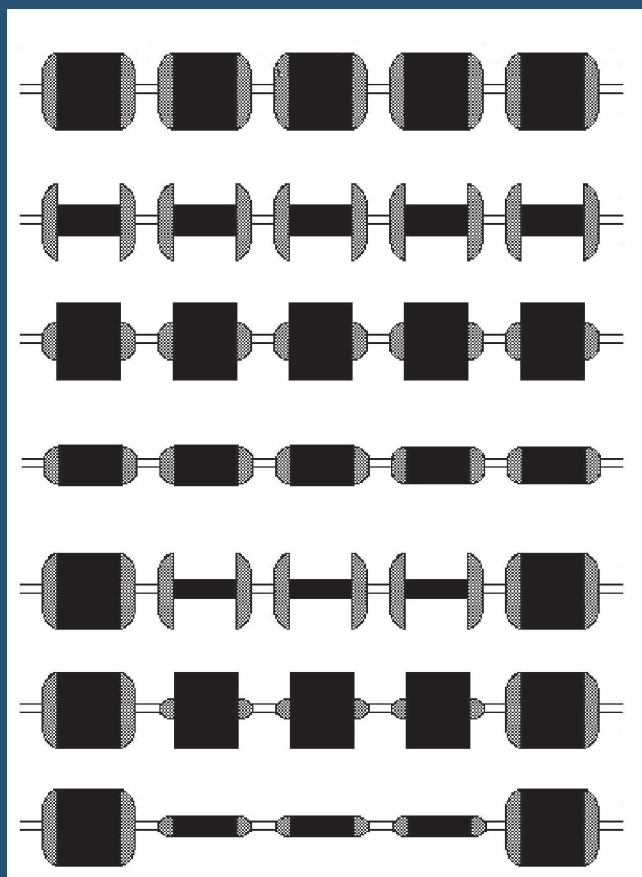


Computational Neuroscience

Simulated Demyelinating Neuropathies and Neuronopathies



Diana I. Stephanova
Bozhidar Dimitrov

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COMPUTATIONAL NEUROSCIENCE:
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Preface

In the field of computational neuroscience, this book is an attempt: (1) to summarize demyelinating neuropathies such as Charcot-Marie-Tooth Disease Type 1A (CMT1A), Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), CIDP subtypes, Guillain-Barré Syndrome (GBS), Multifocal Motor Neuropathy (MMN) and neuronopathies such as Amyotrophic Lateral Sclerosis (ALS), simulated by our own models; (2) to compare the abnormalities in their axonal excitability properties; and (3) to explain the mechanisms underlying these abnormalities. The book, as a huge review, contains Introduction (Chapter I), Methods (Chapter II), Results, Discussions (Chapters III, IV) and References.

A brief description of the objects under the simulation and clinical studies of the nerve excitability properties, investigated by a threshold tracing technique in control groups and patients with CMT1A, CIDP, CIDP subtypes, GBS, MMN, ALS as well as a brief chronology of the models used for the simulation of nerve fibres are given in Chapter I.

Our multi-layered model used in computations is described in detail in Chapter II. Methods for both stimulation of human myelinated motor nerve axons and the calculation of their excitability properties such as potentials (action, electrotonic, extracellular), strength-duration time constants, rheobasic currents and recovery cycles are also given in this chapter.

Abnormalities in the multiple investigated axonal excitability properties and their mechanisms, for simulated normal and abnormal (CMT1A, CIDP, CIDP subtypes, GBS, MMN, ALS) cases are described, compared and discussed in detail in Chapter III. The complex structure of the myelin sheath is not taken into account in these simulations. The results confirm that the changes obtained in simulations replicate those recorded *in vivo* in control groups and patients with corresponding diseases. The results also confirm that axonal excitability properties are not identical, and they can be used as specific indicators for these disorders. The analysis shows that: (1) mild internodal systematic demyelination (ISD) is a specific indicator for CMT1A; (2) mild paranodal systematic demyelination (PSD) and paranodal internodal systematic demyelination (PISD) are specific

indicators for CIDP and its subtypes; (3) severe focal demyelinations, each of them internodal and paranodal, paranodal-internodal (IFD and PFD, PIFD), are specific indicators for acquired demyelinating neuropathies such as GBS and MMN; (4) simulated progressively greater degrees of axonal dysfunctions termed ALS1, ALS2 and ALS3 are specific indicators for ALS Type1, Tape2 and Type3; and (5) the obtained excitability properties in simulated demyelinating neuropathies are quite different from those in simulated ALS subtypes, because of the different fibre electrogenesis. The results show that the abnormalities in the axonal excitability properties in the ALS1 subtype are near normal. The results also show that in simulated hereditary, chronic and acquired demyelinating neuropathies, the slowing of action potential propagation, based on myelin sheath dysfunctions, is larger than this, based on the progressively increased uniform axonal dysfunctions in simulated ALS2 and ALS3 subtypes. Conversely, abnormalities in the accommodative and adaptive processes are larger in the ALS2 and ALS3 subtypes than in demyelinating neuropathies. The increased axonal superexcitability in the ALS2 and ALS3 subtypes leads to repetitive discharges (action potential generation) in the nodal and internodal axolemma beneath the myelin sheath along the fibre length in response to applied long-duration subthreshold polarizing current stimuli (accommodative processes) and to applied long-duration suprathreshold depolarizing current stimuli (adaptive processes). Moreover, in the case of adaptation, the axonal superexcitability leads to blockage of each applied third (testing) stimulus in the recovery cycle of the ALS2 case and to blockage of each applied second (testing) stimulus in the recovery cycle of the ALS3 case. This is a result of repetitive firing caused by the preceding applied stimulus [i.e., by the applied first (conditioning) and second (testing) stimuli in the ALS3 and ALS2 cases, respectively]. The resulting superexcitability of the nodal and internodal axolemma beneath the myelin sheath, caused by repetitive discharges based on the continuous activation and reactivation of ionic (mainly “transient” Na^+) channels in these compartments can be regarded as a prelude to cell (neuron) death. And it is probably the reason for motor neuron degeneration in this disease.

The complex structure of the myelin sheath is taken into account in the simulations presented in Chapter IV. And the effect of the myelin sheath aqueous layers on the excitability properties in simulated hereditary and chronic demyelinating neuropathies are investigated and compared. The results show that aqueous layers have an additional effect on the simulated cases. All excitability properties, except for refractoriness and strength-duration time constants, worsen in simulated hereditary demyelinating neuropathies such as CMT1A and Dejerine-Sottas syndrome (DSS) when

the myelin lamellae and their corresponding aqueous layers are reduced. Myelin sheath aqueous layers improve all axonal excitability properties in simulated CIDP. Aqueous layers do not modulate the axonal excitability properties in the simulated CIDP subtypes. This is because the reciprocally opposed effects of the aqueous layers on these properties are neutralized when demyelinations are heterogeneous.

This book should be of great interest to computational neuroscientists, neurologists, neurophysiologists, biophysicists, biologists, pharmacologists, lecturers and students in these fields.

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Abbreviations

PNS	:	Peripheral Nervous System
CNS	:	Central Nervous System
NGF	:	Nerve Growth Factor
CMT	:	Charcot-Marie-Tooth Disease
CMT1A	:	Charcot-Marie-Tooth Disease Type 1A
DSS	:	Dejerine-Sottas Syndrome
CIDP	:	Chronic Inflammatory Demyelinating Polyneuropathy
GBS	:	Guillain-Barré Syndrome
MMN	:	Multifocal Motor Neuropathy
ALS	:	Amyotrophic Lateral Sclerosis
TCC	:	Terminal Cytoplasmic Cord
ISD	:	Internodal Systematic Demyelination
PSD	:	Paranodal Systematic Demyelination
PISD	:	Paranodal Internodal Systematic Demyelination
IFD	:	Internodal Focal Demyelination
PFD	:	Paranodal Focal Demyelination
PIFD	:	Paranodal Internodal Focal Demyelination

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Nerve Fibres

Myelinated Axons

Studies during the last decades have focused on the intricate structure of myelinated axons, mainly by exploring the build-up, development, maturation and, eventual their degradation in genetically modified mice. Thanks to increasingly fine and revealing techniques in biochemistry, biophysics and micro-imaging we are now in possession of a completely new picture and thorough knowledge of many fine details for the structure of myelinated axons (Kirschner and Caspar 1972, Kirschner et al. 1984, Quarles et al. 2006, Zu Hörste and Nave 2006, Heredia et al. 2007, Douglas and Popko 2009, McGregor et al. 2010, Dučić et al. 2011). Since this book goes in a slightly different direction, we will not present the subject in great depth. Instead, we will review the general principles and gross outcome of accumulated knowledge for myelinated axons, diagnostics and differentiation between several forms of demyelination.

Axons of the peripheral nervous system (PNS) and the central nervous system (CNS) are highly specialized structures, and they are endowed with excitable membranes capable of electrogenesis. Myelin is built either of Schwann cells, surrounded by a basal lamina in the conducting axons of PNS, or of oligodendroglial cells, the so-called white matter, in the CNS. This structure is valid for both motor and sensory fibres (Peles and Salzer 2000). Myelination in the CNS has many similarities, but also points of difference, with respect to myelination in the PNS. CNS nerve fibres are not separated by connective tissue nor are they surrounded by cell

cytoplasm, and specific glial nuclei are not obviously associated with particular myelinated axons. Unlike the peripheral nerve, where the sheath is surrounded by Schwann cell cytoplasm on the inside and outside, the cytoplasmic tongue in the CNS is restricted to a small portion of the sheath. This glial tongue is continuous with the plasma membrane of the oligodendroglial cell through slender processes. One oligodendrocyte can myelinate as many as 40 or more separate axons (Salzer 2003, Simons and Trotter 2007, Ndubaku and de Bellard 2008).

According to the organization of Schwann cells matured peripheral axons are classified either as unmyelinated or myelinated. In mammals (including humans), unmyelinated axons comprise approximately 75% of axons in cutaneous nerves and dorsal spinal roots, approximately 50% in muscle nerves (Ochoa 1976), and approximately 30% in ventral roots (Coggeshall et al. 1974, Risling and Hildebrand 1982). Unmyelinated axon diameters range from 0.1 to 2 μm (to approximately 3 μm in humans). The axons are more or less completely submerged in longitudinal troughs formed along the Schwann cell surface. In PNS myelinated nerve fibre, a single axon is associated with a train of longitudinally arranged Schwann cells.

In general, myelinated fibres are organized into several different structural parts (domains): an initial segment, deriving from the axonal hillock of the neuron; the axon, tightly covered by a myelin sheath (internode); a discontinuation with lack of cover (node of Ranvier); and two adjoining regions—paranodal (immediately adjoining the node; each region corresponding to 2% to 3% of the internode) and juxtaparanodal [further away alongside the sheath; stereotype internodal region (STIN) –95% of the internode] (Bhat et al. 2001, Bhat 2003, Nave and Salzar 2006, Birchmeier and Nave 2008, Nave 2010, Trapp and Kidd 2004). The length of a node ranges around 1 μm , and nodes are interposed several hundred μm s apart. The internodal length, approximately from 200 to 2,000 μm , is correlated to axon size. The diameter of a peripheral myelinated axon is measured in the STIN region, and it is in the interval of 1 to 20 μm . The numerical relations between the axon diameter, myelin sheath thickness and internodal length are based on the studies of many authors (Yates et al. 1976, Berthold 1978, Arbuthnott et al. 1980, Friede et al. 1981, Friede and Bischhauser 1982, Berthold et al.