Title: Simulating perinodal changes observed in immune-mediated neuropathies – Impact on conduction in a model of myelinated motor and sensory axons

Running head: Impact of perinodal changes on conduction

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Abstract:

Immune-mediated neuropathies affect myelinated axons, resulting in conduction slowing or block which may affect motor and sensory axons differently. The underlying mechanisms of these neuropathies are not well understood. Using a myelinated axon model, we studied the impact of perinodal changes on conduction. We extended a longitudinal axon model (41 nodes of Ranvier) with biophysical properties unique to human myelinated motor and sensory axons. We simulated effects of temperature and axonal diameter on conduction, and strength-duration properties. Then, we studied effects of impaired nodal sodium channel conductance, paranodal myelin detachment by reducing periaxonal resistance, and their interaction on conduction in the nine middle nodes and enclosed paranodes. Finally, we assessed the impact of reducing the affected region (five nodes) and adding nodal widening. Physiological motor and sensory conduction velocities and changes to axonal diameter and temperature were observed. The sensory axon had a longer strength-duration time constant. Reducing sodium channel conductance and paranodal periaxonal resistance induced progressive conduction slowing. In motor axons conduction block occurred with a 4-fold drop in sodium channel conductance or a 7.7-fold drop in periaxonal resistance. In sensory axons block arose with a 4.8-fold drop in sodium channel conductance or a 9-fold drop in periaxonal resistance. This indicated that motor axons are more vulnerable to develop block. A boundary of block emerged when the two mechanisms interacted. This boundary shifted in opposite directions for a smaller affected region and nodal widening. These differences may contribute to the predominance of motor deficits observed in some immune-mediated neuropathies.
New and noteworthy:

Immune-mediated neuropathies may affect myelinated motor and sensory axons differently. By the development of a computational model we quantitatively studied the impact of perinodal changes on conduction in motor and sensory axons. Simulations of increasing nodal sodium channel dysfunction and paranodal myelin detachment induced progressive conduction slowing. Sensory axons were more resistant to block than motor axons. This could explain the greater predisposition of motor axons to functional deficits observed in some immune-mediated neuropathies.

Keywords:
Computational model, myelinated motor and sensory axon, conduction slowing and block, nodal sodium channel disruption, paranodal myelin detachment.
Introduction

Immune-mediated polyneuropathies may affect myelinated nerve fibers including the myelin sheath, the node of Ranvier, the adhesion molecules binding the axonal membrane to the Schwann cell membrane, and the axonal membrane itself (Kieseier et al. 2018). These neuropathies include the acute inflammatory demyelinating polyneuropathy (AIDP) and acute motor axonal neuropathy (AMAN) variants of the Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN), and anti-myelin associated (MAG) glycoprotein neuropathy. Developing disease-specific treatments poses a significant challenge as the selective vulnerability of motor or sensory nerve fibers and corresponding downstream mechanisms have not been fully elucidated. As the primary function of myelinated nerve fibers involves efficient transmission of action potentials, their damage will eventually present clinically by loss of muscle strength, loss of sensation, or both. A better understanding of the key mechanisms that hamper impulse transmission via saltatory conduction may potentially help to develop more targeted treatments aimed at prevention of irreversible nerve damage.

Studying the underlying pathology in patients with standard nerve conduction studies may not always provide sufficient detail as conduction slowing and block may originate from the malfunctioning of a variety of components in myelinated nerve fibers (Burke et al. 2001; Franssen 2015). Nerve excitability testing is an attractive translational method in which threshold changes, induced by various conditioning stimuli, can be ascribed to changes in ion channel activity at one site of a group of axons. However, detailed aspects of the relation between pathological and heterogeneous pathophysiological disease processes at single axon level cannot be adequately assessed in ex-vivo models such as voltage-clamp experiments (Franssen and Straver 2014). Animal models that accurately mimic human pathology specifically in motor and sensory axons are available for AMAN (Yuki et al. 2001) and to a
limited extent for AIDP, but not for CIDP and MMN. Studying computational models of myelinated axons have emerged to provide a quantitative view on the vital mechanisms for adequate saltatory conduction (Blight 1985; Fitzhugh 1962; Goldman and Albus 1968; Halter and Clark 1991; Koles and Rasminsky 1972; McIntyre et al. 2002; Moore et al. 1978; Smit et al. 2009; Stephanova and Bostock 1995). By systematically investigating pathological processes that cannot be examined otherwise, they may assist in defining avenues for developing disease-specific treatments.

Emerging insights into the pathology of immune-mediated neuropathies have shown specific targeting of molecular complexes that characterize the distinct geometrical domains surrounding the node of Ranvier, including the paranode and juxtaparanode (Delmont et al. 2017; Devaux et al. 2016; Susuki 2013; Uncini and Kuwabara 2015). Physiologically, these perinodal domains also have a vital role in saltatory conduction and recovery following action potentials (Barrett and Barrett 1982; Halter and Clark 1991; McIntyre et al. 2002). Moreover, biophysical differences between motor and sensory axons have often been proposed as potentially contributing to the varied degree of functional impairment in immune-mediated neuropathies (Burke et al. 2017). However, the interplay of these biophysical differences and the pathological processes related to immune-mediated neuropathies with the occurrence of conduction block remains yet unclear. This emphasizes the need for a computational model with a sufficient geometrical and biophysical description to systematically study pathological processes and their impact on conduction in motor and sensory axons.

Our study presents an extended longitudinal myelinated axon model, modified from McIntyre et al. (McIntyre et al. 2002) by including axonal ion channel properties under the myelin sheath, based on experimental mammalian (Waxman et al. 1995) and human nerve excitability studies (Howells et al. 2012; Jankelowitz et al. 2007; Kiernan et al. 2005). Our model allows biophysical characteristics unique to human myelinated motor and sensory
axons to be implemented (Berthold and Rydmark 1995; Bostock et al. 1994; Bostock and
Rothwell 1997; Howells et al. 2012; Kiernan et al. 2004; Mogyoros et al. 1996; Mogyoros et
al. 1997; Ritchie 1995; Schwarz and Eikhof 1987; Schwarz et al. 1995). We simulated various
physiological conditions, and have shown that these are in agreement with experimental
studies. In addition, we explored how saltatory conduction will be affected by some putative
mechanisms associated with immune-mediated neuropathies focussing on loss of functioning
nodal sodium channels and disruption of the surrounding paranodal seal (Susuki 2013; Uncini
and Kuwabara 2015).
Methods

Model structure and anatomical properties of the myelinated axon model

We applied the double cable structure described by McIntyre et al. (McIntyre et al. 2002). As starting point, we used the Matlab implementation of this model as published by Danner et al. (Danner et al. 2011a; Danner et al. 2011b; Krouchev et al. 2014). The model accurately describes the anatomy of a myelinated axon where a successive node-internode configuration consists of a node (1 segment), paranode (1 segment), juxtaparanode (1 segment), standard internode (6 segments), and again a juxtaparanode (1 segment) and paranode (1 segment). Except for the nodal segments, the non-nodal (paranode, juxtaparanode and standard internode) segments are surrounded by a myelin sheath in which the periaxonal space was connected to the extracellular space by a myelin capacitance and conductance. Using Kirchoff’s first law, each segment $k$ was coupled with the previous segment $(k-1)$ and next segment $(k+1)$, where the non-nodal segments required calculation of the potential across the inner-axonal/periaxonal and periaxonal/extracellular space. As the nodal segment did not involve the periaxonal space, it included the potential across inner-axonal/extracellular space, which equals the nodal membrane potential (Danner et al. 2011b). For the longitudinal model, we used a total of 41 nodes of Ranvier separated by 40 internodes. The membrane potential was clamped at its resting membrane potential. Table 1 gives a detailed summary of the morphological and electrical parameters of these segments (McIntyre et al. 2002) based on microscopic-anatomical mammalian studies (Waxman et al. 1995).
Similar to the original model (McIntyre et al. 2002), the node of Ranvier consists of voltage-gated transient and persistent sodium channels, voltage-gated slow potassium channels, a leak channel, and nodal membrane capacitance. Their conductances are given in Table 2 and the gating kinetics in the Appendix.

To accurately simulate internodal membrane dynamics, the original passive description was modified by implementing juxtaparanodal and internodal voltage-gated fast potassium channels, internodal voltage-gated sodium, slow potassium, and hyperpolarizing-activated nucleotide-gated-cation (HCN) channels. Density of nodal sodium channels is significantly higher (1000-2000/µm²) than at the internode (<25/µm²) (Waxman et al. 1995). By taking a physiological ratio of 100 (2000/µm² divided by 20/µm²), the internodal sodium conductance was set at 1/100 of the nodal sodium conductance. To reduce complexity, internodal sodium channels in a persistent state were omitted. Since the density of internodal slow potassium channels was suggested to be approximately 1/30 of their nodal density, internodal/nodal conductance ratio was set at 1/30 (Waxman and Ritchie 1993). Based on the same study, internodal fast potassium conductance was set at 1/6 of juxtaparanodal conductance (Waxman and Ritchie 1993). The location of Na⁺/K⁺-pumps is still ambiguous. Early work suggested a nodal location but subsequent electrophysiological and staining experiments an internodal location (Kleinberg et al. 2007; Waxman et al. 1995). Therefore, an electrogenic pump current was implemented in the internode. Based on the above modifications, a conductance for HCN channels was applied to satisfy internodal ionic equilibrium at the resting membrane potential which was set at -84.9 mV (see Table 2 and Appendix). A schematic view of the new model is shown in Figure 1.
Sensory axons were suggested to have greater inward rectifying current (Bostock et al. 1994). Responses to long-lasting hyperpolarization revealed that a major part of this greater current originates from changes in gating kinetics of HCN channels, which was best modeled by depolarizing their half-activation potential (Howells et al. 2012). In our model, this half-activation was depolarized by 6.3 mV. Furthermore, a reduced slow potassium channel expression was hypothesized to contribute to the increased susceptibility of ectopic activity in sensory axons (Baker et al. 1987; Howells et al. 2012; Kocsis et al. 1987). This was modeled by reducing the slow potassium conductance in the sensory axon model by 20% relative to the motor axon. Subsequently, broadening of the sensory action potential due to a reduction in slow potassium channel was compensated by accelerating the activation gate and slowing the inactivation gate of sensory sodium channels (Honnou et al. 1994; Howells et al. 2012; McIntyre et al. 2002; Mitrovic et al. 1993; Schwarz et al. 1983) (see Appendix). With these biophysical differences, an ionic equilibrium was achieved when setting sensory resting membrane potential at -81.8 mV (see Table 2 and Appendix). Without altering the amount of sodium channels in persistent state, the depolarized membrane potential of 3.1 mV in sensory axons (motor vs. sensory: -84.9 mV vs. -81.8 mV) approximately doubled the persistent sodium current at resting membrane potential, which was also suggested to be an important biophysical difference (Bostock and Rothwell 1997; Howells et al. 2012).

**Simulation and stimulation settings**

Numerical integration of the differential equations was performed within Matlab (R2014b; The MathWorks, Natick, MA) using the SUNDIALS CVode package ((Hindmarsh et al. 2005); version 2.6.1) with time steps of 10 µsec. To calculate the conduction velocity, first,
the derivative of the membrane potential was taken in every node, and from this the time
divisions with maximum gradient were determined. To provide an estimate of conduction
velocity, the distance between nodes 11 and 31 was divided by the time interval with
maximum gradient at these nodes. The nodal excitation threshold and severity levels of
pathological conditions that blocked saltatory conduction were determined using a binary
search algorithm based on Hennings et al. (Hennings et al. 2005). These severity levels,
expressed as % of normal, were determined with a binary search stop criteria of 0.5% and
subsequently rounded down to the integer that induced a block. Similar to a previous study
(Hales et al. 2004), when the membrane potential reached a target level (0 mV in our
simulations) a generated action potential was detected. To avoid boundary effects of the
model, results of the simulations were derived from the middle nodes (nodes 11 to 31). Single
intracellular stimuli were delivered with a stimulus duration of 1 ms and a fixed stimulus
intensity set at three times the excitation threshold at node 11.

Simulating effects of temperature, axon diameter and strength-duration properties

The relation between conduction velocity and myelinated axon diameter was simulated by
increasing axon diameter from 10 µm (= default) to 14 µm, and 16 µm. In conjunction, other
parameters were also scaled (see Table 1 from (McIntyre et al. 2002)) including the nodal (3.3
µm, 4.7 µm and 5.5 µm), paranodal (3.3 µm, 4.7 µm and 5.5 µm), juxtaparanodal (6.9 µm,
10.4 µm and 12.7 µm), standard internodal diameter (6.9 µm, 10.4 µm and 12.7 µm), node-
to-node distance (1150 µm, 1400 µm, and 1500 µm), and number of myelin lamellae (120,
140, and 150). The effect of temperature on conduction velocity was modeled by varying
temperature from 30°C to 36°C (= default temperature) in steps of 2°C. Rheobase and
strength-duration time constant were determined using Weiss’s law (Bostock 1983;
Mogyoros et al. (1996) and assessing excitation thresholds at five different stimulus durations
(1 ms, 0.8 ms, 0.6 ms, 0.4 ms and 0.2 ms) at the middle node (node 21).

Simulating nodal sodium channel disruption and loss of paranodal seal

Several mechanisms in immune-mediated neuropathies have been suggested in which the
node of Ranvier and its surrounding structures play an important role (Kieseier et al. 2018).
For instance, in MMN half of the patients have high titers of serum antibodies against
ganglioside GM1 which is expressed on the axolemma of the nodes of Ranvier and perinodal
Schwann cells. Ganglioside GM1 was suggested to contribute to nodal sodium channel
clustering and paranodal stabilization (Susuki et al. 2007a; Susuki et al. 2007b; Susuki et al.
2012). Disrupted sodium channel clustering and paranodal myelin detachment at both sides of
the nodes may contribute to the development of conduction slowing and eventually block.
Simulations were performed to quantify how these mechanisms affect saltatory conduction.
Disrupted sodium channel clustering may result in decreased inward sodium current density
(reviewed by (Kaji 2003)). In the present study, this was simulated by decreasing maximum
transient and persistent sodium channel conductances (Fig. 1 – nodal $N_a$ and $N_p$). Broken
paranodal seals were simulated by decreasing the periaxonal resistance across the paranodal
region such that juxtaparanodal fast potassium channels also become exposed to the
extracellular medium (Fig. 1 – increasing the periaxonal paranodal conductance $G_{peri,p}$ and the
juxtaparanodal conductance $G_{peri,jp}$). The resulting effective increase in nodal area was
simulated by increasing nodal capacitance (Fig. 1 – $C_n$). The affected region involved the nine
middle nodes (nodes 17 – 25) and the paranodal structures between them.
Results

Validation of motor and sensory axon model

Figure 2 illustrates an action potential in a myelinated motor and a myelinated sensory axon obtained at the middle node (node 21) after applying a single pulse at node 11. The excitation thresholds at node 11 were 577 pA for the motor axon and 403 pA for the sensory axon. The action potential was followed by the physiologically characteristic depolarizing after potential (DAP) and hyperpolarizing after potential (HAP) (zoomed part in Fig. 2A). Action potential duration (half-way resting and peak potential) was longer for the motor axon (0.34 ms) than for the sensory axon (0.29 ms). With a modeled diameter of 10 µm, the action potential propagation (nodes 11 to 31) was in the physiological range with a conduction velocity of 47.9 m/sec for the motor axon (Fig. 3) and 50.0 m/sec for the sensory axon (Boyd and Kalu 1979).

Conduction velocity increased approximately linearly with axon diameter to 70.0 m/sec (14 µm) and 83.3 m/sec (16 µm) in motor axons and to 73.7 m/sec (14 µm) and 88.2 m/sec (16 µm) in sensory axons (Fig. 4A). Conduction velocities also increased linearly with temperature (Fig. 4B), the increase being 1.60 m/sec/°C for the motor and 1.58 m/sec/°C for the sensory axon. Converting to Q_{10} with the conduction velocities at 30°C and 36°C, Q_{10} was 1.45 for the motor axon and 1.43 for the sensory axon, thereby falling within the range of physiologically observed temperature dependence (Davis et al. 1976; Lowitzsch et al. 1977; Paintal 1965; Rasbinsky 1973).

Figure 5 illustrates the strength-duration properties for motor and sensory axons determined at the middle node. It must be emphasized that simulations with intracellular stimulation results in a shorter strength-duration time constant (SDTC) compared to experiments with transcutaneous stimulation due to the large nerve/electrode distance (Kuhn
et al. 2009). The motor rheobase was 476 pA and the motor SDTC was 205 µs, which closely matches previous modeling studies (Bostock 1983; Daskalova and Stephanova 2001; McIntyre et al. 2002). In agreement with experimental studies, the SDTC in the sensory axon (304 µs) was higher and the rheobase was lower (308 pA) compared to the motor axon. This results in a ratio of 1.5 for sensory/motor SDTC (304/205 µs), which matches with experimental observations (Kovalchuk et al. 2018; Mogyoros et al. 1996).

**Disruption of nodal sodium channel clusters in motor and sensory axon**

Figure 6 shows motor action potential propagation from node 11 to 31 for a 70% of normal nodal sodium channel conductance (Fig. 6A). A small drop of the maximal membrane potential can be observed at the affected middle nodes with a slowed conduction velocity to 43.4 m/sec. Failure of motor action potential propagation occurred at nodal sodium channel conductance of 25% of normal (4-fold drop, Fig. 6B). To determine the effect of disruption of nodal sodium channel clusters on motor and sensory conduction velocities, nodal sodium channel conductance was reduced from 100% (normal), 70%, 50%, 30% up to conduction block. In sensory axons, action potential propagation failure occurred at a conductance of 21% of normal (4.8-fold drop). Decreasing nodal sodium channel conductance induced progressive slowing towards block in the motor and sensory axon with slightly higher conduction velocities and more resistance to conduction block for the sensory axon (Fig. 7).

**Paranodal myelin loop detachment in motor and sensory axon**

Detachment of paranodal myelin loops from the axonal membrane in motor and sensory axons was simulated by decreasing the periaxonal resistance to 70%, 50%, 30% and 20% of normal. Motor conduction velocity decreased to 44.2 m/sec (70% of normal), 41.1 m/sec
(50% of normal), 35.4 m/sec (30% of normal; Fig. 8A) and 28.0 m/sec (20% of normal) until conduction block occurred at a periaxonal resistance of 13% of normal (Fig. 8B). Sensory conduction velocity decreased to 46.9 m/sec (70% of normal), 44.2 m/sec (50% of normal), 37.7 m/sec (30% of normal) and 30.7 m/sec (20% of normal) until conduction block occurred at a periaxonal resistance of 11% of normal (9-fold drop). Decreasing periaxonal resistance induced progressive slowing towards block in the motor and sensory axon, where the sensory axon had slightly faster conduction velocities and was more resistant to conduction block (Fig. 9).

Interaction of disrupted nodal sodium channel clusters and paranodal myelin loop detachment

More sophisticated simulations were subsequently performed to the interaction of nodal sodium channel disruption and detachment of paranodal myelin loops on conduction slowing and block. Figure 10A shows that a boundary of block emerges, representing the percentage of normal where this interaction induces conduction block. Outside this boundary (lower left), there is failure of saltatory conduction and within this boundary (upper right of Fig. 10A), saltatory conduction is still maintained, albeit at lower conduction velocities. The sensory axon compared to the motor axon had consistently higher resistance to the emergence of block. Finally, for the motor axon, we completely mapped the conduction velocity distribution within the boundary of block in 2-dimensional (Fig. 10B, top) and projected 3-dimensional representations (Fig. 10B, bottom), which also encompasses the results of Figures 7 and 9.
Sensitivity of the boundary of block to enlarged nodal area

Depending on various pathophysiological conditions and their severity levels, the boundary of block shifts changing the areas covered by conduction slowing and block. To investigate the sensitivity of this boundary, two additional conditions were simulated in the motor axon. As damage may appear more focally, the affected region was reduced to five nodes (node 19 to 23). Also, paranodal myelin detachment may, as an additional consequence, effectively enlarge the exposed nodal area. An enlarged nodal area was simulated by increasing the nodal capacitance that reflects widening of nodal length from 1 µm to 3 µm. Figure 10C shows that the two conditions shifts the boundary of block in opposite directions. When only five nodes are affected the area covered by conduction block reduces, while for nodal widening this area increases.
Discussion

In this study we successfully implemented a mathematical model to simulate saltatory conduction along peripheral myelinated motor and sensory axons in circumstances resembling those hypothesized in immune-mediated neuropathies. The simulations with the model generated action potentials followed by the physiological depolarizing and hyperpolarizing afterpotentials. Our model further corresponded with experimental and simulation studies on motor and sensory conduction velocities that scaled linearly with temperature and axonal diameter (Boyd and Kalu 1979; Davis et al. 1976; De Jesus et al. 1973; Franssen and Wieneke 1994; Lowitzsch et al. 1977). Also the motor and sensory strength-duration properties followed the behaviour as observed in human peripheral myelinated nerves (Howells et al. 2013; Kiernan et al. 2000; Kiernan et al. 2001; Kovalchuk et al. 2018; Mogyoros et al. 1996; Sleutjes et al. 2018). Subsequently, we were able to quantitatively determine that saltatory conduction progressively slows prior to conduction block when inducing pathology associated with immune-mediated neuropathies by focusing on disrupted nodal sodium channel clusters and paranodal detachment (Franssen and Straver 2014; Kieseier et al. 2018; Susuki et al. 2012; Uncini and Kuwabara 2015). A boundary of block emerged when simulating the interaction of both mechanisms with block occurring outside this boundary and slowing when remaining within this boundary. Simulations provided a link between the biophysical differences characteristic for motor and sensory axons and their varied impact on the emergence of conduction block. This provides quantitative evidence of their differential susceptibility to conduction block (Burke et al. 2017), which may also consequently induce a varied degree of functional impairment.
The implemented biophysical differences between motor and sensory axons are based on experimental evidence and simulations obtained from human nerve excitability studies (Bostock et al. 1994; Bostock and Rothwell 1997; Howells et al. 2012). Using these differences, our findings support the studies suggesting that sodium gating kinetics may underlie the narrower sensory action potential compared to motor action potential (Burke et al. 1997; Howells et al. 2012; McIntyre et al. 2002), despite the larger persistent sodium current and smaller slow potassium conductance in normal sensory, compared to motor axons. Sensory conduction velocity was also previously found to be slightly higher than the motor nerve conduction velocity (Nielsen 1973). The slopes of the conduction velocity (1.6 m/sec/oC) due to temperature changes were approximately linear and fell within the experimentally observed ranges for motor and sensory axons (1.1 m/sec/oC – 2.3 m/sec/oC) (Davis et al. 1976; De Jesus et al. 1973; Franssen and Wieneke 1994; Halar et al. 1980; Lowitzsch et al. 1977; Rasminsky 1973). Modeled strength-duration properties were in agreement with previous modeled values (Bostock 1983; Daskalova and Stephanova 2001; McIntyre et al. 2002). Single intracellular stimuli applied at a node results in shorter simulated strength-duration time constants compared to experiments with large nerve/electrode distance (Kuhn et al. 2009). Uniform stimulation over all nodes and internodes has been suggested to more closely approximate external stimulation with large surface electrodes (Daskalova and Stephanova 2001). It should be further noted that studying single axons (Mogyoros et al. 1996; Sleutjes et al. 2018) result in a larger physiological range for strength-duration properties compared to assessing a group of axons. The sensory to motor SDTC ratio of 1.5 (304 / 205 µs) was also in accordance with previous studies (Howells et al. 2012; Kiernan et al. 2000; Kiernan et al. 2001; Kovalchuk et al. 2018; Mogyoros et al. 1996). Although the excitation threshold depends on many factors, the order of magnitude (≈ 0.1- 1 nA) to
generate an action potential resembled that of other modeling results (Bostock 1983; Danner et al. 2011b; Stephanova and Bostock 1995). With the implemented biophysical differences between motor and sensory axons, our simulations showed that they responded differently to conduction slowing and emergence of block induced by nodal and paranodal dysfunction at various severity levels. Differences in motor and sensory axons are likely not limited to axonal membrane dynamics, but might also include microstructural components. This may further contribute to the varied susceptibility and selectivity of motor and sensory involvement in immune-mediated neuropathies. Although more difficult to elucidate, adequate implementation of these differences may further improve computational models to study immune-mediated neuropathies more specifically.

Emergence of conduction block

Inducing conduction block required considerable blockage of sodium channels (4 to 5-fold) and reducing of the paranodal seal resistance (8 to 9-fold ) emphasizing that the safety factor for impulse generation is generally high. Normal axons have a safety factor, defined as the ratio of available/required driving current to excite a node, in the same order of magnitude (about 5 – 7) (Tasaki 1953). Our simulations further suggest that the smaller the area (Fig 10B, top) or volume (Fig. 10B, bottom) in the multidimensional diagrams covered by conduction slowing, relative to that of conduction block, the more susceptible the myelinated axon becomes to the occurrence of a conduction block. As a result, additional, either internal or external, perturbations (e.g. membrane hyperpolarization or voluntary activity) that negatively affect the condition is likely to reduce this area or volume and may result in crossing the slowing/block boundary inducing failure of action potential propagation. Being close to this boundary is comparable to a reduced safety factor just above unity, where conduction is still possible, but slower. When it falls below unity by crossing the boundary,
conduction failure eventually occurs (Franssen and Straver 2014; 2013). Interestingly, our
findings further indicate that if conduction is still possible at the affected region, the
membrane potential recovers outside such a region (Fig 6A and Fig. 8A). This implies that
multifocally affected regions within a myelinated axon do not necessarily lead to block,
provided they are separated by sufficient distance. Nevertheless, as long as conduction is
preserved, nerve function potentially varies depending on the distance from the affected region,
which may explain the excitability studies in patients with MMN showing both abnormal
(Garg et al. 2019) and normal excitability indices outside the affected region (Cappelen-Smith
et al. 2002). Further experimental evidence of this longitudinal recovery is also present in a
study in which a rat myelinated fiber was partly exposed to anti-galactocerebroside serum and
internodal conduction time normalized adjacent to the affected region (Lafontaine et al.
1982).

Simulating pathology

In various human neuropathies the modeled pathology, including nodal sodium channel
abnormalities and paranodal myelin loop detachment, was suggested to be of significant
relevance. In CIDP, excitability changes in median nerve motor axons distal to sites with
conduction block were consistent with increased current leakage between node and internode;
furthermore, sera of these patients were shown to bind to nodal and paranodal regions of
teased rat nerve fibers (Garg et al. 2019). In anti-MAG neuropathy, electron microscopy of
sural nerve biopsy sections revealed loosening of paranodal Schwann cell microvilli
(Kawagashira et al. 2010). Axonal excitability studies of median nerve motor axons showed
decreased threshold changes during the supernormality period of the recovery cycle which
were consistent with increased juxtaparanodal fast potassium channel activation due to loss of
paranodal sealing (Garg et al. 2018). In diabetic neuropathy, latent addition revealed
decreased nodal persistent sodium currents; this method allows for separation of changes in
strength-duration properties due to passive from those due to active nodal properties (Misawa
et al. 2006). Axonal excitability studies in type 1 diabetes patients without neuropathy showed
changes consistent with loss of sodium permeability and decreased fast and slow potassium
conductances (Kwai et al. 2016). Finally, staining of nodal sodium channels was shown to be
dehased or lost in a rabbit model of human AMAN (Susuki et al. 2007b). Supporting our
simulations, an experimental study showed that targeting sodium channels with lidocaine
slows conduction, and therefore dysfunction of sodium channels should be considered as a
mechanism of slowing, also in absence of block (Yokota et al. 1994). Similarly, exposure to
anti-galactocerebroside antibodies was suggested to disrupt the outermost paranodal myelin
loops from the paranodal axon, thus inducing slowing and block (Lafontaine et al. 1982). At a
microstructural level, abnormalities in various proteins (Kieseier et al. 2018) may contribute
to altered sodium channel conductance and paranodal seal resistance. GM1 gangliosides are
enriched in the nodal and paranodal axolemma and maintain nodal sodium channel clustering
and paranodal stabilization (Susuki et al. 2007b). Additionally, the septate-like junctions at
the paranode are formed by axonal contactin-associated protein (Caspr1) and contactin 1 that
are tightly connected to neurofascin-155 at the paranodal myelin loops. Nodal sodium
channels are anchored to spectrin of the cytoskeleton via ankyrin-G, to gliomedin of the
Schwann cell microvilli via neurofascin-186. As such, changes in functioning of these
proteins may potentially be reflected within the model by dysfunction of sodium channels and
detachment of paranodal myelin loops.
Sensitivity of the model to parameter choices

Besides altering parameters to simulate pathology, it must be noted that small variations in any parameter within the model, e.g. dimensionality of the myelinated axon, ion channel conductances, gating kinetics, and longitudinal characteristics will cause fluctuations in excitability properties, levels of conduction slowing or block depending on the parameter’s sensitivity within the model. Therefore, with the specific parameterization applied, the model structure, and simulation and stimulation settings, our findings should not be interpreted as rigid and absolute cut-off points regarding conduction slowing, block and varied response of the motor and sensory axon. More extensive and advanced probabilistic approaches are required to determine the contribution of these sources of variability (Mirams et al. 2016). Nevertheless, our simulation study provides a broad and quantitative insight into how single or interaction of multiple pathophysiological mechanisms may affect saltatory conduction, which otherwise cannot be systematically studied with experimental techniques.

Model limitations

The model includes the most prominent voltage-gated ion channels whose functioning has been experimentally studied in detail. As completely capturing the functioning of a human peripheral myelinated axon in a computational model is impossible, these models always come with certain simplifications. It has also been suggested that ion channel types are present in the myelin membrane (Baker 2002; Chiu 1987). The myelin sheath in our model involved a myelin conductance and capacitance, which has also previously been applied (McIntyre et al. 2002; Stephanova and Bostock 1995) generating physiological conduction velocities and excitability properties. Besides the gating kinetics, temperature also affects conductance, the electrogenic pump, and resting membrane potential (Franssen et al. 2010;
Howells et al. 2013; Kovalchuk et al. 2018; Smit et al. 2009; Stephanova and Daskalova 2014). For convenience, we kept these parameters constant, as their values are less unambiguously defined to set properly. In the simulated temperature range (30°C – 36°C), results matched experimental studies well, indicating the validity of our approach. The dynamics of extracellular and intracellular ion concentrations has not yet been incorporated into the model. The electrogenic pump represents a constant current, where more sophisticated models take into account its dependence on ion concentrations (Dijkstra et al. 2016). Repetitive nerve stimulation can result in potassium accumulation in the periaxonal space, which may also induce conduction block (Brazhe et al. 2011), or affect resting membrane potential and excitability of the nerve (Hageman et al. 2018). As we restricted our study to simulations of action potential propagation after applying single stimuli, the expectation is that the above factors will have only a limited effect on our findings. Simulations of pathology were implemented homogenously in the affected region. When myelinated axons are pathologically targeted, they are likely to be affected more heterogeneously. Disturbed sodium channel clustering may not only be reflected by blockage of channel conductance, but potentially also accompanies changes in gating kinetics. In pathological conditions, also implementing the expression of other sodium channel subtypes (e.g. Nav1.8) may become relevant to further refine the model as there is some evidence of their presence in some nodes of Ranvier (Han et al. 2016). As the membrane potential of the model is clamped changes to conductances do not affect the resting membrane potential. As such, the model allows studying changes to resting membrane potential as a separate mechanism. The above aspects can be further addressed in more detail in subsequent studies and provide interesting opportunities for improvements, depending on the research question posed.
Conclusion

With its current implementation, the presented model contains the most prominent biophysical aspects that appear necessary and sufficient to simulate saltatory conduction in motor and sensory axons. The link between these biophysical aspects and their varied impact on the emergence of block provides support that they may also partly contribute to the selective susceptibility in immune-mediated neuropathies. It further explains how action potential propagation becomes affected due to pathological mechanisms involved in immune-mediated neuropathies by focusing on perinodal changes. In various human neuropathies, such as anti-MAG neuropathy, these mechanisms may not remain restricted to the perinodal region, but may also involve morphological changes associated with demyelination (Kawagashira et al. 2010). It therefore also provides a valuable platform that enables the implementation of e.g. segmental, paranodal or juxtaparanodal demyelination (Franssen and Straver 2014; Stephanova et al. 2007; Stephanova et al. 2006) to further study their individual and composite impact on saltatory conduction. In CIDP and MMN, next to the morphological changes, also the interaction with increased or decreased currents through specific ion channels (e.g. juxtaparanodal fast potassium channels) is of clinical relevance to corporate into the model (Garg et al. 2019). It may help to understand how these abnormalities can potentially be counteracted by specific pharmacological ion channel modifiers to prevent the occurrence of conduction block and restore action potential propagation. Computational models (Stephanova and Daskalova 2008), in conjunction with techniques to reliably assess the physiology and pathology in single human myelinated axons (Howells et al. 2018; Sleutjes et al. 2018), are valuable tools for providing insights into vital mechanisms that affect saltatory conduction, and into which component may potentially be targeted in immune-mediated neuropathies.
Appendix

In this section, we present the basic equations in the model underlying the ionic currents including their dynamics. For a more extensive description of the double cable structure with the corresponding differential equations, we would like to refer to the work of Danner et al. (Danner et al. 2011b). The specific ionic currents including their gating properties were modeled according to the Hodgkin-Huxley formulation (Hodgkin and Huxley 1952). The transient and persistent sodium, slow and fast potassium, inward rectifying, and leak currents are described by

\[ I_{Na} = g_{Na} m^3 h (V_{mem} - E_{Na}) \]  
\[ I_{Na_p} = g_{Na_p} p^3 (V_{mem} - E_{Na}) \]  
\[ I_{K_s} = g_{K_s} s (V_{mem} - E_K) \]  
\[ I_{K_f} = g_{K_f} n^4 (V_{mem} - E_K) \]  
\[ I_{H} = g_{HCN} q (V_{mem} - E_H) \]  
\[ I_{L_k} = g_{L_k} (V_{mem} - E_{L_k}) \]

The conductances \( g_{Nat}, g_{Nap}, g_{Ks}, g_{Kf}, g_{HCN}, \) and \( g_{Lk} \) are given in Table 2. The variables \( m, h, p, s, n, \) and \( q \) are the dimensionless gates involving the transient sodium activation and inactivation, persistent sodium activation, and slow and fast potassium activation, and HCN activation, respectively. \( V_{mem} \) represents the membrane potential. The ionic reversal potentials are given by (Howells et al. 2012; Jankelowitz et al. 2007)

\[ E_{ion} = \frac{RT}{F} \log \left( \frac{[K]_{ex} + Sel_{ion}[Na]_{ex} - Sel_{ion}[K]_{ex}}{[K]_{i} + Sel_{ion}[Na]_{i} - Sel_{ion}[K]_{i}} \right) \]
with $E_{ion}$ the reversal potentials for sodium $E_{Na}$, potassium $E_{K}$ and inward rectifier $E_{IL}$ is set to $V_{rest}$. The applied channel selectivities, $Sel_{ion}$ were for $Sel_{Na} = 0.9$, $Sel_{K} = 0$, and $Sel_{IL} = 0.097$ (Howells et al. 2012). The applied intracellular and extracellular potassium and sodium concentrations were comparable to previous studies (Kiernan et al. 2005; Schwarz et al. 1995; Smit et al. 2009) with $[K]_{ex} = 5.6$ mM, $[K]_{i} = 155$ mM, $[Na]_{i} = 9$ mM, $[Na]_{ex} = 144.2$ mM, and $F$ and $R$ were Faraday’s constant, $96485000 \frac{C}{mol}$ and the gas constant, $8315 569.8 \frac{J}{K \cdot mol}$.

The dynamics of the channel gates were described by:

$$\frac{dy}{dt} = [\alpha_{y}(1 - y) - \beta_{y}y]Q_{10}^{\frac{T_{sim} - T_{ref}}{10}}$$

with $y$ the channel gates (i.e. $m$, $h$, $p$, $s$, $n$, $q$), where $\alpha_{y}$ and $\beta_{y}$ were derived using the equations shown in Table 3 and corresponding parameters shown in Table 4 (Howells et al. 2012; Jankelowitz et al. 2007; Kiernan et al. 2005; McIntyre et al. 2002).

The temperature dependencies are given by $Q_{10}$ ($Q_{10} = 2.2$ for $m$-and $p$-gate, $Q_{10} = 2.9$ for $h$-gate, and $Q_{10} = 3.0$ for $n$-, $s$-, and $q$-gate). The default simulated temperature ($T_{sim}$) was $36^\circ C$ and the reference temperature ($T_{ref}$) was $20^\circ C$. At $t = 0$, the initial conditions for the gating kinetics satisfied (Hodgkin and Huxley 1952):

$$y_{t=0} = \frac{\alpha_{y}}{\alpha_{y} + \beta_{y}}$$

where $y_{t=0}$ represents the initial state of the gates. To ensure a net zero current at resting membrane potential across the axonal membrane in the compartments with voltage-gated ion channels, a small auxiliary current is implemented to initialize the model (Carnevale and Hines 2009).
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**Disclosures**

None of the authors has potential competing interests to disclose.
Table 1. Overview of morphological and electrical parameters of model (obtained from McIntyre et al. (McIntyre et al. 2002)).

<table>
<thead>
<tr>
<th>Morphological parameters</th>
<th>Nerve fiber</th>
<th>Node-to-node</th>
<th>Node</th>
<th>Paranode</th>
<th>Juxtaparanode</th>
<th>Standard internode</th>
<th>Myelin</th>
<th>Longitudinal resistivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter</td>
<td>10 [µm]</td>
<td>1150 [µm]</td>
<td>3.3  [µm]</td>
<td>3.3 [µm]</td>
<td>46 [µm]</td>
<td>175.2 [µm]</td>
<td>0.1 [µF/cm²]</td>
<td>70 [Ωcm]</td>
</tr>
<tr>
<td>Node length</td>
<td>1 [µm]</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter</td>
<td>3.3 [µm]</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Periaxonal space width</td>
<td>0.004 [µm]</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Juxtaparanode length, per segment</td>
<td>46 [µm]</td>
<td></td>
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<td></td>
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<tr>
<td>Diameter</td>
<td>6.9 [µm]</td>
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<tr>
<td>Periaxonal space width</td>
<td>0.004 [µm]</td>
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<tr>
<td>Standard internode length, per segment</td>
<td>175.2 [µm]</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Diameter</td>
<td>6.9 [µm]</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periaxonal space width</td>
<td>0.004 [µm]</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myelin c&lt;sub&gt;myelin&lt;/sub&gt;</td>
<td>0.1 [µF/cm²]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>g&lt;sub&gt;myelin&lt;/sub&gt;</td>
<td>0.001 [S/cm²]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of myelin lamella</td>
<td>120 [-]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longitudinal resistivity</td>
<td>Axoplasmatic, 70 [Ωcm]</td>
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<tr>
<td></td>
<td>Periaxonal, 70 [Ωcm]</td>
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</tbody>
</table>
Table 2. Maximum conductances, specific capacitances and resting membrane potential of motor and sensory axon model. Unless indicated, parameters were obtained from McIntyre et al. (McIntyre et al. 2002). Absolute values were calculated using diameter and length of the regions (Table 1) by assuming circular symmetry.

<table>
<thead>
<tr>
<th>Node</th>
<th>Parameters</th>
<th>Motor</th>
<th>Sensory$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient sodium conductance</td>
<td>$g_{Na,t}$</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Persistent sodium conductance</td>
<td>$g_{Na,p}$</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Slow potassium conductance</td>
<td>$g_{Ks}$</td>
<td>0.08</td>
<td>0.064</td>
</tr>
<tr>
<td>Leak conductance</td>
<td>$g_{Lk}$</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Nodal capacitance</td>
<td>$c_{node}$</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

**Paranode**

| Paranodal capacitance        | $c_p$      | 2       |             |
| Paranodal conductance        | $g_p$      | 0.001   |             |

**Juxtaparanode**

| Juxtaparanodal capacitance   | $c_{jp}$   | 2       |             |
| Juxtaparanodal conductance   | $g_{jp}$   | 0.0001  |             |
| Fast potassium conductance   | $g_{Kf}$   | 0.02    |             |

**Standard internode**

| Sodium conductance$^c$       | $g_{Na,t}$ | 0.03    |             |
| Slow potassium conductance   | $g_{Ks}$   | 0.0027  | 0.0022      |
| Fast potassium conductance   | $g_{Kf}$   | 0.0033  |             |
| Leak conductance             | $g_{Lk}$   | 0.0001  |             |
| HCN conductance$^d$          | $g_{HCN}$  | 0.0014  |             |
| Electrogenic pump current$^e$| $I_{pump}$ | 100     |             |
| Internodal capacitance       | $c_i$      | 2       |             |

| Resting membrane potential   | $V_{rest}$ | -84.9   | -81.8       |

$^a$ Biophysical differences between motor and sensory axons (see text and Appendix)

$^b$ Resting membrane potentials achieved with the new models (see text)

$^c$ Internodal conductances relative to nodal conductances (see text)

$^d$ Determined to satisfy internodal ionic equilibrium at resting membrane potential.

$^e$ Pump current similar to that previously applied (Stephanova and Bostock 1995)
Table 3. Ion channel gating variables with their corresponding equations.

<table>
<thead>
<tr>
<th>Ion channel gating variables</th>
<th>Equations</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_m, \alpha_p, \alpha_n, \alpha_s$</td>
<td>( \frac{A(V+B)}{1-e^{-\frac{V-B}{c}}} )</td>
</tr>
<tr>
<td>$\alpha_h, \beta_m, \beta_p, \beta_n, \beta_s$</td>
<td>( \frac{A(-V-B)}{1-e^{-\frac{V+B}{c}}} )</td>
</tr>
<tr>
<td>$\beta_h$</td>
<td>( \frac{A}{1+e^{-\frac{-V-B}{c}}} )</td>
</tr>
<tr>
<td>$\alpha_q$</td>
<td>( Ae^{-\frac{-V-B}{c}} )</td>
</tr>
<tr>
<td>$\beta_q$</td>
<td>( \frac{A}{e^{-\frac{-V-B}{c}}} )</td>
</tr>
</tbody>
</table>
Table 4. Rate constants (A), half-activation potentials (B), and slope factors (C) for motor and sensory axon.

<table>
<thead>
<tr>
<th></th>
<th>A (ms(^{-1}); T(_{\text{ref}}) = 20°C)</th>
<th>Half-activation potential, B (mV)</th>
<th>Slope factor, C (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Motor</td>
<td>Sensory(^a)</td>
<td>Motor</td>
</tr>
<tr>
<td>(\alpha_m)</td>
<td>1.86</td>
<td>1.778</td>
<td>20.4</td>
</tr>
<tr>
<td>(\beta_m)</td>
<td>0.0861</td>
<td>0.0824</td>
<td>25.7</td>
</tr>
<tr>
<td>(\alpha_p)</td>
<td>0.01</td>
<td>0.0096</td>
<td>27.0</td>
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<tr>
<td>(\beta_p)</td>
<td>0.00025</td>
<td>0.00024</td>
<td>34.0</td>
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<tr>
<td>(\alpha_h)</td>
<td>0.0619</td>
<td>0.075</td>
<td>113.8</td>
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<tr>
<td>(\beta_h)</td>
<td>2.294</td>
<td>2.800</td>
<td>31.8</td>
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<tr>
<td>(\alpha_n)</td>
<td>0.008</td>
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<td>83.2</td>
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<tr>
<td>(\beta_n)</td>
<td>0.0142</td>
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<td>66</td>
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<tr>
<td>(\alpha_s)</td>
<td>0.00097</td>
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<td>23.5</td>
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<tr>
<td>(\beta_s)</td>
<td>0.00059</td>
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<td>91.1</td>
</tr>
<tr>
<td>(\alpha_q, \beta_q)</td>
<td>0.0009</td>
<td></td>
<td>107.3</td>
</tr>
</tbody>
</table>

\(^a\) Changes of sensory to motor sodium channel activation gate \((m, p)\) and inactivation gate \((h)\) similar to that in Howells et al. (Howells et al. 2012)

\(^b\) Depolarization of the half-activation of HCN-channels by 6.3 mV (see text)
Figures and Legends

Figure 1. The longitudinal myelinated axon model. A schematic view of a myelinated axon (modified from Franssen et al. (Franssen and Straver 2013) with permission from © 2013 Wiley Periodicals, Inc) with an electric circuit diagram of the new model showing the nodal, paranodal, juxtaparanodal and internodal regions. The nodal domain (1 segment) contains persistent (Na_p) and transient sodium (Na_t) channels, slow potassium (K_s) and leak (L_k) channels, and the nodal capacitance (C_n) in the axonal membrane. The paranodal domain (two segments, one left and right) contains, in the axonal membrane, a linear conductance with, in parallel, a capacitance (G_p and C_p). The juxtaparanodal domain (two segments, one left and right) contains in the axonal membrane fast potassium channels (K_f), and in parallel, a linear conductance (G_jp) and capacitance (C_jp). The internodal domain (six segments, three left and right) contains sodium channels (Na), fast (K_f) and slow (K_s) potassium channels, a leak (L_k) conductance, I_h-channels (H), an electrogenic pump (I_pump), and an internodal capacitance (C_i) in the axonal membrane. The myelin sheath is represented by a linear conductance with, in parallel, a capacitance in the paranode (G_m,p and C_m,p), the juxtaparanode (G_m,jp and C_m,jp) and internode (G_m,i and C_m,i) (See Table 2). Longitudinally, the model contains axonal (G_ax) and periaxonal (G_peri) resistivities (see Table 2).
Figure 2. Motor and sensory action potential generation. Generated action potential for the motor (black) and sensory (gray) myelinated axon up to 100 ms (A) and up to 3 ms (B) at node 21 after a 1 ms intracellular stimulus pulse of three times the excitation threshold at node 11. In (A), the action potential close to the resting membrane potential is also shown. Dotted lines represent resting membrane potential.
Figure 3. **Motor action potential propagation.** Action potential propagation of the motor myelinated axon model up to 3 ms from node 11 to 31. The dots at node 11 ($T_1 = 0.10$ ms) and 31 ($T_2 = 0.58$ ms) define the time points with the highest gradient of membrane potential from which the conduction velocity was derived ($[20 \times 1150 \, \mu m] / [T_2 - T_1] = 47.9$ m/sec).
Figure 4. Effect of axon diameter and temperature on conduction velocity. (A) Effect of increase in myelinated fiber diameter - motor (black) and sensory (gray) - on conduction velocity. (B) The relation between temperature and conduction velocity for the motor (black) and sensory (gray) myelinated axon.
**Figure 5. Motor and sensory strength-duration properties.** (A) Stimulus duration curve for motor (black) and sensory (gray) myelinated axon. In (B) the same result as in (A), but after converting to the charge-duration curve. The vertical arrows indicate the cross-sections with the x-axis, which correspond with the strength-duration time constant (motor $= 205 \mu$sec; sensory $= 304 \mu$sec).
Figure 6. Motor action potential slowing and conduction block due to disrupted nodal sodium channel clusters. Action potential propagation of the motor myelinated axon model up to 3 ms from node 11 to 31, with (A) 70% of normal nodal sodium channel conductance resulting in a slight drop of the maximum membrane potential around the affected region and conduction slowing \((20 \times 1150 \, \mu m) / [T_2 - T_1] = 43.4 \, m/s\), and (B) 25% of normal nodal sodium channel conductance inducing a conduction block when stimulating at node 11 at three times the excitation threshold. Insets in (A) show a schematic view of the myelinated axon with the affected region and the characteristics of the myelinated axon being modeled – the persistent \((N_{ap})\) and transient \((N_{at})\) sodium channel conductances.
Figure 7. Relation of motor and sensory conduction slowing towards block with increasing nodal sodium channel cluster disruption. Relation between nodal sodium channel cluster disruption simulated by decreasing the sodium channel conductance from 100% (normal), 70%, 50%, and 30% and decreasing conduction velocities in motor (black) and sensory (gray) axons until conduction block (motor = 25% of normal; sensory = 21% of normal). Note the logarithmic scaling of the x-axis.
Figure 8. Motor action potential slowing and conduction block due to paranodal myelin loop detachment. Action potential propagation of the motor myelinated axon model up to 3 ms from node 11 to 31 with (A) 30% of normal paranodal seal resistance resulting in a slight drop of the maximum membrane potential around the affected region and conduction slowing \( \frac{[20*1150 \text{ µm}]}{[T_2 - T_1]} = 35.4 \text{ m/sec} \), and (B) 13% of normal paranodal seal resistance inducing a conduction block when stimulating at node 11 at three times the excitation threshold. Insets in (A) show a schematic view of the myelinated axon with the affected region and the characteristics of the myelinated axon being modeled – the periaxonal paranodal \( G_{\text{peri,p}} \) and juxtaparanodal conductance \( G_{\text{peri,jp}} \).
Figure 9. Relation of motor and sensory conduction slowing towards block with increasing detachment of paranodal myelin loops. Relation between detachment of paranodal myelin loops simulated by decreasing the paranodal seal resistance from 100% (normal), 70%, 50%, 30%, and 20% of normal and the decreasing conduction velocities in motor (black) and sensory (gray) axons until conduction block (motor = 13% of normal; sensory = 11% of normal). Note the logarithmic scaling of the x-axis.
Figure 10. Emergence of a boundary of block in motor and sensory axon due to the interaction of nodal sodium channel cluster disruption, paranodal myelin loop detachment, and effects of enlarged nodal area and a reduced affected region. (A) The interaction of nodal sodium channel cluster disruption (as % of normal nodal sodium channel conductance) and paranodal myelin loop detachment (as % of normal paranodal seal resistance) in motor and sensory axon (nine middle nodes) when stimulating at three times the excitation threshold. (B) A 2D (top) and 3D (bottom) map of motor conduction slowing towards block from (A). (C) Boundary of block in motor axon – 9 middle nodes (black solid square – dashed, Fig. 10A), 9 middle nodes with enlarged nodal area (black open square – continues), and 5 middle nodes (gray solid square - dashed). Note the logarithmic scaling of the axes.
A. Motor Sensory

B. Temperature [°C]

Conduction velocity [m/sec]
A. Motor

Stimulus duration [ms]

Stimulus duration [ms]

Stimulus charge [pC]

B. Sensory

Stimulus charge [pC]
A. 70% of normal nodal sodium channel conductance

Membrane potential [mV]

Time [ms]

$T_1 = 0.1 \text{ ms}$  $T_2 = 0.63 \text{ ms}$

B. 25% of normal nodal sodium channel conductance

Membrane potential [mV]

Time [ms]
Nodal sodium channel conductance [% of normal]

Conduction velocity [m/sec]

Motor

Sensory

Conduction velocity [m/sec] vs. Nodal sodium channel conductance [% of normal]
A. 30% of normal paranodal seal resistance

Membrane potential [mV]

Time [ms]

B. 13% of normal paranodal seal resistance

Membrane potential [mV]

Time [ms]