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Research article

# What is the optimal distribution of myelin along a single axon?

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ABSTRACT

The myelin sheath that insulates some axons in the central nervous system allows for faster signal conduction. Previously, axons were thought to be either unmyelinated or fully myelinated. Recent experimental work has discovered a new pattern of myelination (intermittent myelination) along axons in the mouse brain, in which long unmyelinated axon segments are followed by myelinated segments of comparable length. We use a computational model to explore how myelin distribution (in particular intermittent myelination) affects conduction velocity. We find that although fully myelinated axons minimize conduction velocity, varying the spatial distribution of a fixed amount of myelin along a partially myelinated axon leads to considerable variation in the conduction velocity for action potentials. Whether sodium ion channel number or sodium ion channel density is held constant as the area of the unmyelinated segments increases has a strong influence on the optimal pattern of myelin and the conduction velocity.

## 1. Introduction

Some axons in the vertebrate nervous system are wrapped with layers of myelin, which insulate these axons allowing for faster conduction of action potentials. The myelin sheath is produced by Schwann cells in the peripheral nervous system and oligodendrocytes in the central nervous system (CNS) [18,19]. Unlike Schwann cells, which act on single peripheral axons, oligodendrocytes in the CNS ensheath up to 50 axons [7], allowing them to exert influence on neural processing on a larger scale. An individual oligodendrocyte, or a cluster of neighbouring oligodendrocytes, can have a large number of nearby axons available to myelinate, but experimental data [7] supports the proposition that the choice of which axons to myelinate is not made at random [27]. Moreover, myelination has been shown to be a dynamic process that responds to environmental cues [6,14].

In a recent study, Tomassy et al. [25] analysed high-resolution maps of myelination by tracing high-throughput electron microscopy reconstructions of single axons of pyramidal neurons in the mouse brain. Analysing neurons in layers II/III from a publicly available dataset of a region of the mouse visual cortex [2,3], they observed a new pattern of myelination. Historically, axons were thought to be either fully myelinated or unmyelinated. However, when tracing neurons in layers II/III, Tomassy et al. found that 17 out of 22 neurons displayed a pattern of myelination in which myelinated axon segments are interspersed with long unmyelinated segments, and they called this newly identified pattern “intermittent myelination” (IM). In this myelination pattern, unmyelinated sections of these axons were observed to be up to 55 μm long, much longer than typical nodes of Ranvier (approximately 1 μm long).

Since the discovery of intermittent myelination of (excitatory) pyramidal neurons by Tomassy et al. [25], Micheva et al. [15] also observed that the distribution of myelin in layer II/III inhibitory neurons was “patchy” with myelinated segments preferentially located near the cell body. Tomassy et al. [25] noted that neurons in layer II/III are involved in more complex cortical functioning than those found in layers V and VI, where IM was not observed. This raises the possibility that IM may be facilitating more complex neural functioning.

Whilst the evidence that signalling between electrically active axons and oligodendrocyte progenitor cells provides an important cue for inducing OPCs to differentiate into myelinating oligodendrocytes is firmly established, see [16], and the evidence that myelin provides more than just insulation to maximise conduction velocity (CV) continues to mount [9], the mechanisms controlling active myelination remain largely unknown (reviewed in Snaidero and Simons [23]).

The discovery of IM by Tomassy et al. raises several questions. What is the purpose of IM? Does an IM distribution provide any advantages to signal propagation over a fully myelinated pattern? Obviously, the shortest conduction time will be for a fully myelinated axon. However, it is not obvious which distribution of myelin will maximise CV when only a fixed fraction of the length of an axon is to be myelinated. In this instance, the distribution of ion channels also becomes important.

We examine the consequences for CV of the partial myelination of axons. The geometry of our model depends crucially on one parameter, $L$, which is the length of both the myelinated segments and the

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unmyelinated segments. This pair is repeated periodically over a fixed length of axon. We only study the effects of myelin distribution on signal CV but we note that there are several other facets of neural information processing that depend on myelin distribution, such as the reliability of action potential (AP) propagation [8] and the energy consumption [11,20,21].

## 2. Materials and methods

Our modelling was based on the NEURON [4,5] implementation of a highly influential model of spike initiation in a myelinated mammalian axon by Mainen et al. [12]. We simplify this model by removing the dendrites but keep the ion channel kinetics characteristics, based on recordings of neocortical pyramidal neurons from the rat brain. Mainen et al. [12] used this kinetic model to simulate experimental measurements of rat pyramidal neurons [24].

Our simplification of this model consisted of a single axon, with inner diameter $d = 1$ μm, which is approximately twice the diameter of the axons examined by Tomassy et al. [25], and outer diameter (inner axon plus myelin lamellae) of 1.5 μm. This yields a realistic ratio of internal to external axon diameter, the g-ratio, of 0.66. In Mainen et al. [12], internodes of length 100 μm were periodically interrupted by nodes of Ranvier of length 1 μm. The resting potential of the axon was taken to be $-70$ mV. At the nodes of Ranvier, modified Hodgkin–-Huxley (HH) type ion channels were present.

To minimize any boundary effects, we broke the axon into three regions (as shown in Fig. 1): a pre-analysis region (Region 1), an analysis region (Region 2) and a post-analysis region (Region 3). The current is injected at the left boundary of Region 1. To create Region 1, we generated a sequence of 20 node–myelin pairs, each pair with combined length 100 μm (a 99 μm internode and a 1 μm node of Ranvier). Region 1 is joined to Region 2, a 4000 μm long axon segment made up of (a variable number of) node–myelin pairs of variable length. Region 2 is the analysis region where we calculate the CV, and is joined to Region 3, which is created in the same way as Region 1.

The uniformity of Regions 1 and 3, across all our models, facilitates cross-model comparison by ensuring each model has identical initial conditions whilst maintaining accurate results (by calculating CV in Region 2, far from the outer boundaries). If the IM pattern in Region 2 is replicated in Region 3 only a slight numerical change in conduction time (CT) results. A schematic of this setup is shown in Fig. 1. Note that Region 2 is much longer than the axons traced by Tomassy et al. [25]. This was necessary to distinguish signal arrival times to high precision. It must be emphasized that we do not attempt to build a replica of the short thin axons examined in Tomassy et al. [25] but rather simulate their salient features (an IM pattern for thin pyramidal neurons). This guided our choice to use the model of Mainen et al. [12].

The left boundary node is stimulated by a 40 nA pulse, of 0.1 ms duration, which initiates an AP which travels to the right along the axon. The CT is calculated by recording the time taken, in ms, for the AP to depolarize the beginning of the twentieth node to a voltage of $-15$ mV, which we call $t_1$, and the time taken to depolarize a spatial point 4000 μm upstream of node 20, to a voltage of $-15$ mV, $t_2$ say. The CT over this interval is then simply $(t_2 - t_1)$ ms, and CV $= 4/\text{CT}$ (in units of m/s).

Modelling axons displaying IM, such as the axons analyzed by Tomassy et al. [25], presents a unique challenge. The usual periodic pattern of short (approximately 1 μm) nodes of Ranvier (with a high density of sodium channels that ensures depolarization), followed by a much longer myelin internode (typically one hundred times the length of the node) is replaced by a pattern of unmyelinated and myelinated regions of comparable length. In myelinated axons, potassium channels are mostly found beneath the myelin sheath (more specifically in the juxta-paranodal region that is separated from the node of Ranvier by the paranode). Since we are not modelling repetitive firing of APs, it is assumed that sodium channel kinetics dominate AP conduction. We compare the CVs obtained by varying the IM pattern characteristic length $L$ under two sodium ion channel assumptions.

The main reason for the increased CV of myelinated axons is that it reduces effective membrane capacitance [26]. Following Mainen et al. [12], the myelin sheath is characterized by increasing the outer diameter, reducing the specific membrane capacitance $C_m$ and increasing the membrane resistance $R_m$ (both of which are independent of geometry). These values are presented in Table 1. The relative simplicity of this representation of the myelin internodes facilitates the inclusion of sodium ion channels in the internodal regions, reflecting experimental evidence [26]. Internodal channels have been omitted from more detailed models of myelinated axons, such as [13].

Our first model assumes that the density of the sodium ion channels is constant as the length of the unmyelinated segments $L$ is increased. Our second model assumes that the number of sodium channels in the unmyelinated segments is constant (i.e. that it matches the number

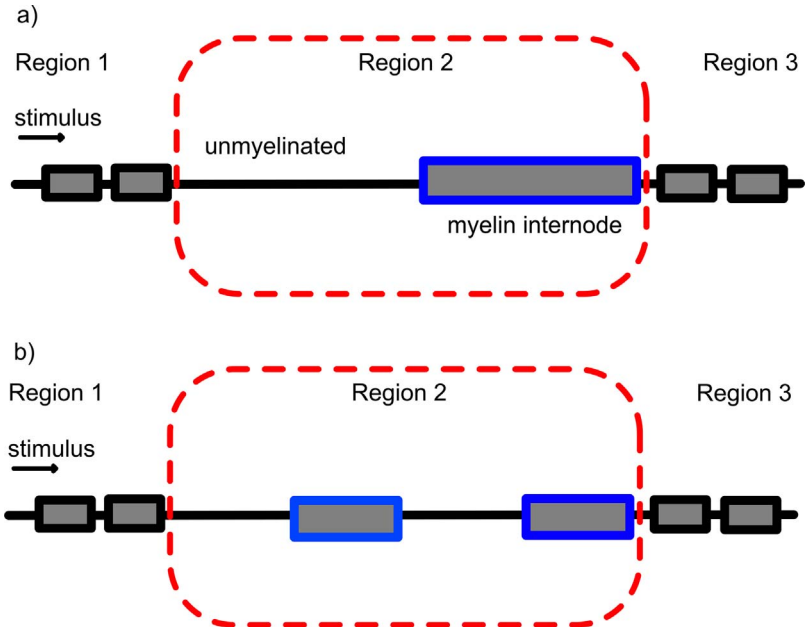


**Fig. 1.** Schematic displaying the spatial setup of the IM simulation model. The left boundary of the axon is stimulated by a pulse which travels along a typical periodic node–internode region (Region 1) before reaching Region 2, which is the analysis region, where IM distribution is varied and conduction time (CT), measured in ms, is calculated. This region is 4000 μm in length (so conduction velocity CV $= 4/\text{CT}$ m/s. For illustration, panel (a) displays an intermittent myelination pattern corresponding to $L = 2000$ μm, whilst panel (b) displays an intermittent myelination pattern corresponding to $L = 1000$ μm (in our analysis we never consider an intermittent pattern with $L > 400$ μm). Region 3 is identical to Region 1 and is included to avoid spurious boundary effects in the calculation of CV.