Myelin as longitudinal conductor: a multi-layered model of the myelinated human motor nerve fibre

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Abstract. The myelin sheath is normally regarded as an electrical insulator. Low values of radial conductance and capacitance have been measured, and in electrical models of myelinated axons the contribution of longitudinal conduction within the sheath has been ignored. According to X-ray diffraction studies, however, myelin sheaths comprise alternate lipid and aqueous layers, and the latter may be expected to have a low resistivity. We propose a new model of myelinated axons in which the aqueous layers within the myelin provide appreciable longitudinal and radial conductance, the latter via a spiral pathway. We have investigated the likely contribution of these conductive paths within the myelin to the electrical properties of a human motor nerve fibre by computer simulation, representing the myelin sheath as a series of interconnecting parallel lamellae. With this new model, action potential conduction has been simulated along a 20-node cable, and the electrotonic responses to 100-ms depolarizing and hyperpolarizing current pulses have been simulated for a uniformly polarized fibre. We have found that the hypothesis of a longitudinally conducting myelin sheath improves our previous model in two ways: it is no longer necessary to make implausible assumptions about the resistivity or width of the periaxonal space to simulate realistic electrotonus, and the conduction velocity is appreciably faster (by 8.6%).

1 Introduction

Studies of native myelin by X-ray and neutron diffraction have demonstrated that the typical picture we have from electron microscopy of fixed tissue is rather misleading: the myelin lamellae are not tightly compacted but separated by cytoplasmic and extracellular spaces of about 4–5 nm, respectively, so that up to half the volume fraction of myelin is taken up by water (Kirschner et al. 1984). Moreover, the water in both aqueous layers contains salts that can be washed out or exchanged with the extracellular solution. Calcium ions in the extracellular compartment (intermediate dense line) have a special role in maintaining myelin structure by electrostatic interaction with fixed negative charges on the membranes (Roppe et al. 1990), but other ions can be shown to diffuse readily throughout both aqueous compartments (Blaurock 1971). It is reasonable to suppose, therefore, that ions can move within these aqueous layers under the influence of a potential gradient and endow the myelin sheath with a longitudinal conductance much greater than its radial conductance.

This hypothesis, that the myelin sheath is a longitudinal conductor, might help to account for some of the properties of myelinated axons that have been difficult to reconcile with their morphology. For example, the longitudinal conductance of the periaxonal space appears to be much higher than expected. When Barrett and Barrett (1982) presented evidence that the depolarizing afterpotential is generated passively by the internodal axolem- ma, they could not fully account for the low access resistance to this membrane [i.e. the ‘Barrett–Barrett resistance’ (Ritchie 1995)] in terms of typical fibre morphology. Blight (1985) found that to model the depolarizing afterpotential in rat spinal cord axons he had to assume a low value for the longitudinal resistance of the periaxonal space, corresponding to a width of 170 nm, and we had to assume a similar figure to reproduce electrotonus in our double-cable model of human motor axons (Stephanova and Bostock 1995, 1996). These difficulties might be overcome if the myelin sheath itself provided a longitudinal conductive path. Barrett and Barrett (1982) actually did consider the contribution that conduction through the aqueous layers of the myelin sheath might make to its radial conductance but apparently did not consider the consequences of longitudinal conduction through the same medium. A second weakness of present computer models of myelinated nerves is that it is commonly found necessary to modify some parameters arbitrarily to make the models conduct as

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fast as real fibres (Hardy 1973; Blight 1985; Halter and Clark 1991). We conjectured that longitudinally conducting myelin might speed conduction, by effectively reducing the longitudinal axonal resistance from one node to the next, since current could penetrate partly into the myelin sheath, travel longitudinally within it, and then return to the axon before the next node.

The aim of the research reported in this article was therefore to test the hypothesis that the striking structural anisotropy of the myelin sheath results in electrical anisotropy, so that it functions to a significant extent as a longitudinal conductor. Previous electrical models have actually made the contrary assumption, representing the double myelin structure by resistances and capacitances of the lipid layers only. As we have already proposed a model that accounts very well for the membrane currents and electrotonus of mammalian myelinated axons (Stephanova and Bostock 1995, 1996), we have tested the hypothesis by seeing whether it enables us to improve our assumptions, bringing them more into line with the known morphology of the fibres, and by its effects on the conduction velocity. To do this, we have programmed a new multi-layered model and two cases are explored. In the first, the myelin sheath is presented by alternating high-resistance and low-resistance layers, so that its radial properties remain unchanged, but it has a new property of longitudinal myelin resistance. In the second case, the aqueous layers do not end blindly but curve simultaneously at the paranodal ends. The computations have shown that the new model is a good one, since it substantially improved the assumptions required to model the electrical behaviour of real axons, and the anticipated effect on conduction velocity is appreciable.

2 Methods

The new multi-layered model was derived from a previous double-cable model (Stephanova and Bostock 1995, 1996), in which the myelin sheath and internodal axolemma were treated as concentric cables. The geometric and membrane parameter values were the same as in the cited papers and in brief, the full model fibre comprised 20 nodes of Ranvier and 19 internodes. Each space between the nodes was divided into 2 paranodal and 5 internodal segments. All calculations were carried out for a fibre with an axon core diameter \( d \) of 12.5 \( \mu \)m and a myelin thickness of 2.4 \( \mu \)m, giving an external diameter \( D \) of 17.3 \( \mu \)m. The lengths of node, paranode, and nodal centre to nodal centre were 1.5, 200, and 1400 \( \mu \)m, respectively. Stimulation, to produce propagation along the fibre, was simulated by adding a \( (6 \, \text{nA} \times 0.1 \, \text{ms}) \) rectangular current pulse to the centre of the first node. (The first node at the space origin is numbered 0.) Subthreshold stimulation, to produce electrotonus, was simulated by injecting a 100-ms rectangular current pulse to the centre of each axon segment (with return path via the external medium), to correspond to the case of a uniformly polarized fibre. Electrotonic data are presented for depolarization with 0.24 nA per internode and hyperpolarization with −0.48 nA per internode, which correspond respectively to 0.6 and −1.2 times the threshold for a 1-ms current pulse. The temperature was 37 °C.

Unlike in previous work (Stephanova and Bostock 1995, 1996), the myelin sheath was simulated by \( N = 150 \) interconnected parallel lamellae, and their double structure was simulated by alternating \( N = 150 \) aqueous and \( N = 150 \) lipid layers, and two cases were explored (Fig. 1).

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Fig. 1. Equivalent electric circuit of the multi-layered myelinated human motor nerve fibre. One node (\( N \) box) and internodal segments, each including internodal axolemma (\( \text{In boxes} \)), and the multi-layered myelin sheath are presented. The longitudinal axoplasmic \( (R_{ax}) \), periaxonal \( (R_{pa}) \) and paranodal seal \( (R_{sa}) \) resistances are also illustrated. The length of each internodal segment is one-fifth of the overall length (998.5 \( \mu \)m). The equivalent electric circuit for the multi-layered myelin sheath contains, respectively, myelin-layered capacitance and resistance \( (C_{myN}, R_{myN} \) for \( N = 1, 150 \)), as well as aqueous-layered longitudinal and radial resistances \( (R_{axN}, R_{adN} \) for \( N = 1, 150 \)). The equivalent circuits for each of the \( N \) and \( \text{In boxes} \) are given earlier (Stephanova and Bostock 1995).