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What is myelin?

DANIEL K. HARTLINE

The evolution of a character is better appreciated if examples of convergent emergence of the same character are available for comparison. Three instances are known among invertebrates of the evolution of axonal sheaths possessing the functional properties and many of the structural properties of vertebrate myelin. Comparison of these invertebrate myelins raises the question of what structural features must a sheath possess in order to produce the two principal functional characteristics of impulse speed enhancement and energy savings. This essay reviews the features recognized by early workers as pertaining to myelin in vertebrate and invertebrate alike: osmiophilia, negative birefringence and saltatory conduction. It then examines common features revealed by the advent of electron microscopy: multiplicity of lipid membranes, condensation of those membranes, specialized marginal seals, and nodes. Next it examines the robustness of these features as essential components of a speed-enhancing sheath. Features that are not entirely essential for speed enhancement include membrane compaction, spiral wrapping of layers, glial cell involvement, non-active axonal membrane, and even nodes and perinodal sealing. This permissiveness is discussed in relation to the possible evolutionary origin of myelin.

Keywords: Evolution, invertebrates, saltatory conduction, crustaceans, oligochaetes

INTRODUCTION

In understanding the evolution of myelin, as with evolution of other characters, we need to examine what selective advantages might stimulate its emergence and what features endow it with those advantages. Its appearance has had a profound effect on the organisms possessing it, not only in vertebrates (Zalc and Colman, 2000; Zalc, 2006) but in several other taxa. Its impact derives from its enhancement of a number of key capabilities: success in escape from predators, success in predatory attacks, improved synchrony in muscle contraction, greater compactness of nervous systems and improved capability for rapid processing of complex information. The two last enable evolution of nervous systems with large numbers of neurons engaged in massively parallel computation (e.g. Bullock and Horridge, 1965; Zalc *et al.*, 2008). Myelin is hypothesized to enable a larger body size by maintaining timely communication between distant parts and to enhance precision in event timing by reducing the absolute travel time and thus absolute temporal variability in communication between two points. These advantages all derive from the enhanced speed of nerve impulse conduction that myelinated fibers enjoy relative to unmyelinated ones of the same diameter. Other advantages derived from the physical restriction in size of active membrane in myelinated fibers. This reduces cross-talk between adjacent nerve fibers, there being less chance that adjacent fibers will have active membrane regions (nodes) close enough to affect each other ephaptically. It also reduces energy requirements of an intrinsically energy-hungry system, and may thus enhance the ability of an organism to withstand low oxygen or periods of starvation.

Corresponding author:
D. K. Hartline
Email: danh@hawaii.edu

DEFINING THE QUESTION

What then, is this highly advantageous innovation, 'myelin'? Bullock (2004) defines it as 'Ranvier-type nodes and spirally-wrapped, single-cell-per-internode [glial] sheaths.' This is one possible, though narrow, meaning, and it limits the term to vertebrates. The same approach taken to classifying photoreceptor organs or walking appendages would deny that invertebrates have eyes or legs. As with eyes or legs, a more useful definition would be based on functional features and related structural ones. One that preserves historic observations associated with the term – osmiophilia and birefringence – yet focuses on functional properties might be 'a multilamellar axonal sheath that increases nerve impulse conduction speed significantly above that of fibers of the same outside diameter that lack the sheath' (see also Roots, 2009, this volume). This review will approach the issue of what myelin 'is' in three ways, starting with a brief overview of how early observations on structure became integrated with the developing understanding of function. We next turn to a functional examination of sheath structures contributing to conduction speed enhancement. Finally, we will assess the minimal structural requirements for speed enhancement and how they might relate to the evolutionary origins of myelin.

EMERGENCE OF MYELIN STRUCTURE–FUNCTION UNDERSTANDING

From the time early investigators focused their microscopes on the nervous system, their attention was attracted to a white fatty layer surrounding some but not all nerve fibers. The initial assumption was that the layer represented an internal structure, a 'medulla' within the fiber, hence our relic term 'medullated' from the Latin for marrow and its Greek root 'myelo', a sheath surrounding the axon core. Beginning with early studies in the

19th century, the term 'myelin' was applied to this multilamellar fatty sheath found in vertebrates, decapod shrimp and annelids, but missing from several other prominent and successful organisms (Virchow, 1858; Ranvier, 1871; Friedländer, 1889; reviewed by Rosenbluth, 1999). Comparisons among these taxa contributed to the developing understanding of sheath function. Its intense osmiophilic staining in the three groups was indicative of its fatty nature. Ranvier (1878) himself correctly interpreted this as suggesting an insulative role (quoted and translated in Ritchie, 1984). Birefringence studies led to the classification of sheaths as 'myelotropic' (strong negative birefringence with respect to the fiber axis) or 'proteotropic' (positive birefringence). Organisms with myelotropic sheaths include vertebrates (Ehrenberg, 1849 [cited in Schmitt, 1936], earthworms (Friedländer, 1889; Taylor, 1940) and decapod shrimp (Friedländer, 1889; Hao and Hsu, 1965). These fibers were considered to be myelinated, while those of the majority of invertebrates studied (including crabs, lobsters and squid) were proteotropic or 'non-myelinated' (Bear and Schmitt, 1937). The first electron microscopic observations validated the birefringence (and X-ray) studies, confirming the multilamellar osmiophilic ultrastructure of myelotropic axons in vertebrates (Fernández-Morán, 1950; Sjöstrand, 1953), earthworm (Hama, 1959), penaeid shrimp (Hsu and his co-workers: Yeh *et al.*, 1962) and palaemonid shrimp (Heuser and Doggenweiler, 1966; see the review by Roots, 2009, in this volume). Vertebrate and invertebrate sheaths were understood to be of similar structural nature, while differing in detail (e.g. Hama, 1959).

As physiological recording techniques were developed, it became apparent that conduction speed of nerve impulses was much higher in fibers with a fatty negatively birefringent sheath than in nerve fibers with a thin sheath. In 1938, Pumphrey and Young (1938) published a study establishing the now well-accepted square root dependence of conduction speed on fiber diameter in unmyelinated cephalopod axons. However, they also pointed out that myelinated fibers of annelids and vertebrates conduct faster than expected for a given diameter. The realization of the shared high conduction speed in fat-ensheathed axons of vertebrates, earthworms and decapod shrimp lent experimental support for the developing idea that the insulating myelin sheath was the factor in common that might explain the high speeds (e.g. Schmitt and Bear, 1939; Holmes *et al.*, 1941). By the 1940s, well before the advent of electron microscopy, higher conduction speeds for myelinated fibers relative to unmyelinated fibers of the same diameter had been established in earthworm (*Lumbricus*: Eccles *et al.*, 1932), vertebrates (Gasser and Grundfest, 1939) and palaemonid shrimp (*Leander*: Holmes *et al.*, 1941), albeit the speed advantage was acknowledged to be greatest in vertebrates. In 1961 Fan *et al.* (1961) made the startling discovery, confirmed by Kusano (1966), that the conduction speed in the myelinated giant axons of the Kuruma shrimp (a penaeid) is over twice that of the fastest known vertebrate axon (200–300 m s^{-1} versus ca. 100 m s^{-1}), a speed record that stands to this day. Most recently, a sub-group of copepods of the crustacean order Calanoida has been added to the list of organisms with myelinated axons (Davis *et al.*, 1999; Lenz *et al.*, 2000). Thus speed enhancing sheaths, while reported in relatively few groups to date, have evolved in phylogenetically very divergent taxa, including cases in each major branch of the bilateria. Each of the groups in which myelin has arisen is an important and successful member of its branch. The gnathostome vertebrates (those extant vertebrate taxa from the cartilaginous fishes – sharks, rays and their kin – on up) are dominant among the Deuterostomia. Oligochaetes (earthworms and their relatives) are fresh-water and terrestrial annelids sharing equal importance with their mostly marine polychaete counterparts. The annelids in turn collectively constitute a key taxon within the Lophotrochozoa. Decapod shrimp, including the basal Dendrobranchiata (to which the penaeids belong) and the more derived Caridea (to which the palaemonids belong) are myelinated representatives of the Ecdysozoa playing a prominent role in marine ecosystems. So, too, with copepods, which are among the more numerous metazoans. These small planktonic crustaceans vie for first place in marine metazoan biomass estimates, and the myelinate superfamilies of the Calanoida are major players in this. Interestingly, speed-enhancing sheaths have not been reported from three other highly successful branches of these same major lines, the Echinodermata (deuterostomes), the Mollusca (lophotrochozoans) and the Hexapoda (ecdysozoans). The great divergence between myelinated groups, with the exception of the two crustacean taxa, makes common ancestry of myelin in those groups unlikely. Their last common ancestor was presumably a basal bilaterian. Even the two myelinate crustacean taxa are phylogenetically widely separated by many basal non-myelinated forms. The patterns of myelin distribution are reviewed in detail elsewhere in this volume (Roots, 2009).

Turning to the nodes, now, understanding their importance to rapid conduction began with the first description of such structures in vertebrates by the man whose name they bear (Ranvier, 1871). Similar nodes were described in a caridean shrimp by Nageotte (1916), which observations, along with the similarity in the fat content of the sheath, helped establish the link between these two features. The role in saltatory conduction was first proposed by Lillie (1925), who showed in the iron wire nerve model, that conduction speed could be enhanced by increasing the resistance of the conducting medium adjacent to the wire using sections of glass tubing. Provided occasional gaps were left in the insulation through which electric current from the 'impulse' could flow, a faster saltatory mode of conduction was induced. He proposed that a similar mode could explain an early report by Yamada (1923) of a higher conduction speed for medullated compared to non-medullated nerve. This was confirmed in physiological experiments by Tasaki (1939) and Huxley and Stämpfli (1949) on vertebrates, by Hsu *et al.* (1964; as cited and reviewed in Xu and Terakawa, 1993, 1999) on penaeids and by Günther (1976) on earthworms. The similarities among the myelins of different taxa are greater than the differences. These will be examined in more detail next.

COMMONALITIES AMONG SPEED-ENHANCING SHEATHS

Figure 1 is a diagrammatic overview of the physiology of speed enhancement (see Hodgkin, 1964; Ritchie, 1984; Hartline and Colman, 2007 for fuller details). In unmyelinated fibers, current that enters at the active zone expends itself charging near-by regions ahead of the travelling impulse (Fig. 1A). The electrical insulation in the myelinated case (Fig. 1B) prevents this, allowing current to rapidly penetrate farther down the axon cylinder to the next node. The rapid charging of the distant node, by a net flow of electrical charge that is

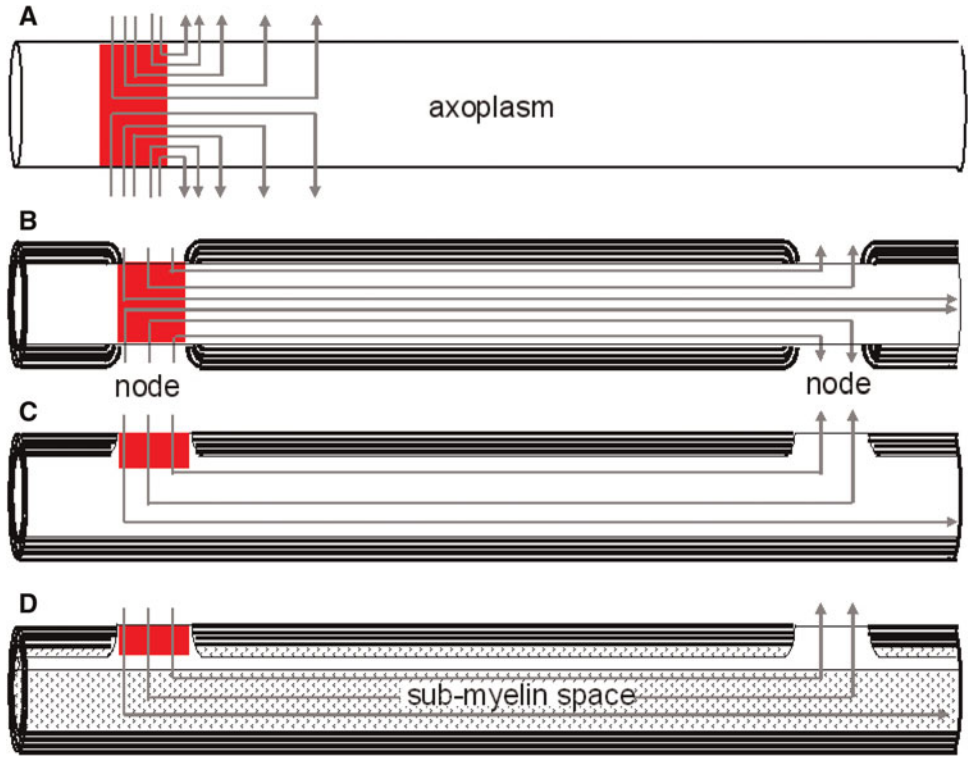

Fig. 1. Conduction in unmyelinated compared with myelinated nerve fibers. (A) In unmyelinated nerve, current entering the axon through open sodium channels in an active zone (shaded region) spreads electrotonically to charge (depolarize) immediately adjacent non-active membrane to initiate an impulse at the new site from which current spreads in turn. (B) In a myelinated axon of a vertebrate or a palaemonid shrimp, current entering through sodium channels at an active annular node charges adjacent (internodal) membrane more rapidly owing to the reduced capacitance afforded by the sheath. Electrotonic charging of the small capacitance of the next nodal membrane is also rapid, leading to a conduction speed an order of magnitude higher than that in a non-myelinated fiber of the same outside diameter. (C) In a myelinated axon of an oligochaete or a copepod, small openings that penetrate the sheath form 'focal' or 'fenestrated' nodes, with a current flow similar to that of a vertebrate. The axon fills most of the space within the sheath. (D) In a penaeid myelinated axon, the nodes are also focal, and sustain the nerve impulse as in other forms of myelin, but current entering at a node flows out of the axon again through surface-increasing convoluted membrane (Hsu and Terakawa, 1996) and travels in an enlarged sub-myelin space to the vicinity of the next node, where it enters the axon again and completes the circuit as before. Figures after www.pbrc.hawaii.edu/~danh/InvertebrateMyelin/invertebrate_myelin.html.

Table 1. Comparison of speed-enhancing features of multilamellar sheaths among taxa, as described in text. Mixed compaction refers to occurrence of both compact and semicompact myelin. Abbreviations: RAZ: radial attachment zone.

	Vertebrate	Oligochaete	Penaeid	Palaemonid	Calanoid
Wrap	Spiral	Spiral	Concentric	Concentric	Concentric
Compaction	Compact	Mixed	Mixed	Mixed	Mixed
Seams per layer	None	None	1–3	1	None
RAZs	None	Desmosome like	RAZ	RAZ	None
Axial current	Axoplasmic	Axoplasmic	Submyelinic	Axoplasmic	Axoplasmic
Myelin source	Glia	Glia	Glia	Glia	Neuron?
Node morphology	Annular	Fenestrated	Fenestrated	Annular	Fenestrated
Node seal	Septate junction	Desmosome like	?	Septate junction	Membrane compaction
Citation	Raine (1984)	Roots (1984)	Xu and Terakawa (1999)	Heuser and Doggenweiler (1966)	Weatherby *et al.* (2000)

smaller than in the unmyelinated case, produces a faster conduction speed as well as a smaller number of ions entering the fiber to be pumped out at metabolic cost. The primary speed-enhancing factor is the sheath's reduction of trans-fiber (radial) capacitance (secondarily leak conductance) – the capacitance between the interior and the exterior of the nerve fiber. Just halving the mean trans-fiber capacitance of an unmyelinated axon (one extra membrane lamella) produces an increase in speed of 50% (in contrast, halving its leak conductance produces only a 2% gain). Capacitance-reduction mechanisms are thus the first feature to be sought in examining speed-enhancing sheaths.

A comparison of sheath structures for the five cases mentioned above is presented in Table 1 and shown diagrammatically in Fig. 2. Four features are found in common in all five taxa: multiplicity of membranes, condensation of membrane, marginal seals and nodes.

Multiple membranes

In all groups, the most heavily ensheathed axons (almost ubiquitously those of greatest diameter – especially the 'giant' axons) are surrounded by dozens to a couple hundred nonconductive lipid membranes, spirally wound in vertebrates

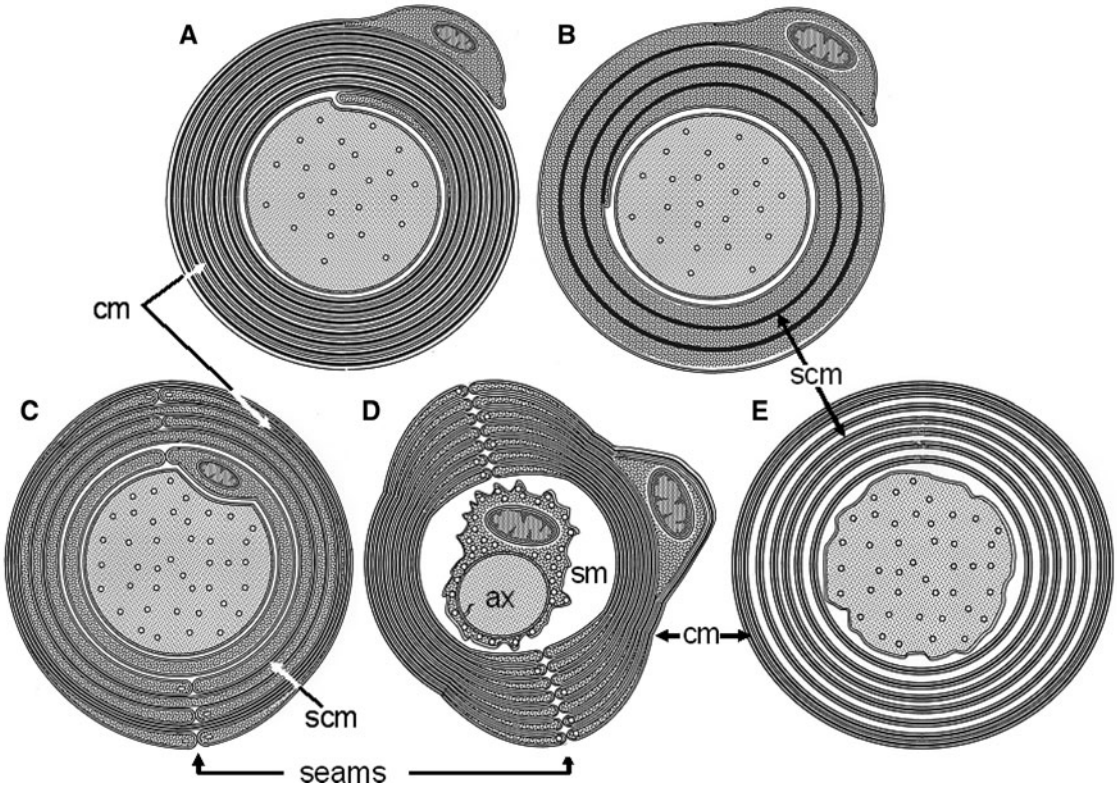

Fig. 2. Myelin architecture in cross-section. (A,B) Spiral myelin. (A) Vertebrate form, with fully compact layers (cm). (B) Oligochaete form with semi-compact layers (scm). The extracellular leaflets of the glial membranes are closely apposed, but there is some cytoplasm inside each glial cell. (C,D,E) Concentric myelin. (C) Palaemonid shrimp architecture. Some layers are compact (cm), some semi-compact (scm) and some non-compacted. As long as current passage is blocked through the seams at the margins of the surround glial layers, the myelin will serve its insulating (capacitance-lowering) purpose. Each layer has a single end loop at a seam, and the end-loop appositions alternate sides in successive layers. Nuclei may occur in any layer. (D) Penaeid shrimp architecture. Compact myelin is common, but semicompact regions exist near seams. Layers have from one to three sets of end loops at seams (two each are figured). Myelin surrounds a submyelin space (sm) filled with microtubule-containing cytoplasmic strands elaborated by an inner glial cell (nucleus figured) and containing a thin axon (ax). Figures after www.pbrc.hawaii.eedu/~danh/InvertbrateMyelin/; C and D modified from Heuser and Doggenweiler (1966) and Xu and Terakawa (1999), respectively.

(Fig. 2A) and oligochaete annelids (Fig. 2B), and concentric in all crustacean taxa (Fig. 2C–E; see Roots, 2009 for details). The intrinsically high capacitance of the axolemma ($\sim$1 μF cm^{-2}), which is the main restraint on conduction speed in an unmyelinated axon of given diameter, is reduced proportionately by electrically combining in series the additional membrane layers. The reduced capacitance decreases the charging time for the axolemma through the axial access resistance of the internode, and hence speeds the impulse as just described.

Condensed membrane

For the most part, adult vertebrate myelin is fully compact, and much oligochaete myelin described is at least semicompact: the extracellular but not always the intracellular faces of adjacent lamellae are closely apposed ('condensed' or 'compounded'), in a structure termed an 'external compound membrane' (Robertson, 1958; Fig. 2A,C,D, 'cm' labels). Myelin in copepods and both taxa of decapod shrimp typically show some regions of fully compact myelin, but much is semicompact, the latter retaining thin layers of glial cytoplasm (Fig. 2B,C,E 'scm' labels; Roots, 2009). In some myelin configurations, compaction can serve to seal extracellular (and intracellular) current paths that might short circuit the membrane insulation. In spiral myelin, a non-condensed mesaxon offers a ready escape route for current, and compaction eliminates this route (Fig. 3A). In the concentric myelin of palaemonid shrimp, the margins of each glial layer meet at 'seams', and the meeting points of successive layers alternate between opposite sides of the fiber (Fig. 2C). In such a case, current escaping along a resistive path from the central axon to the outside must follow a zig-zag course from one seam around half the circumference of the layer to the next on the opposite side, and thence into the next layer, so that compaction of the external faces of adjacent layers suffices to seal this escape route (Fig. 3B).

Marginal seals

The marginal border of a thin cellular sheet is another location where shunting of sheath insulation is possible. Spiral myelin, being a single long membranous sheet, and the seamless myelin of copepods, only possess such marginal borders at the nodes. In the concentric myelin of palaemonid and penaeid shrimp, tight seals of the end-loop contacts at seams provide an additional way to block shunt current, although details of their structure have not yet been worked out. At the myelin margins of the nodes, shunt-blocking specializations have evolved in all taxa (Fig. 4). The ubiquity of these features underscores their importance. Figure 4A indicates diagrammatically this vulnerability (dashed arrow). In vertebrates (Rosenbluth, 1984) and palaemonid shrimp (Heuser and Doggenweiler, 1966), terminal loops are attached to the axon by septate junctions that serve the sealing function. The

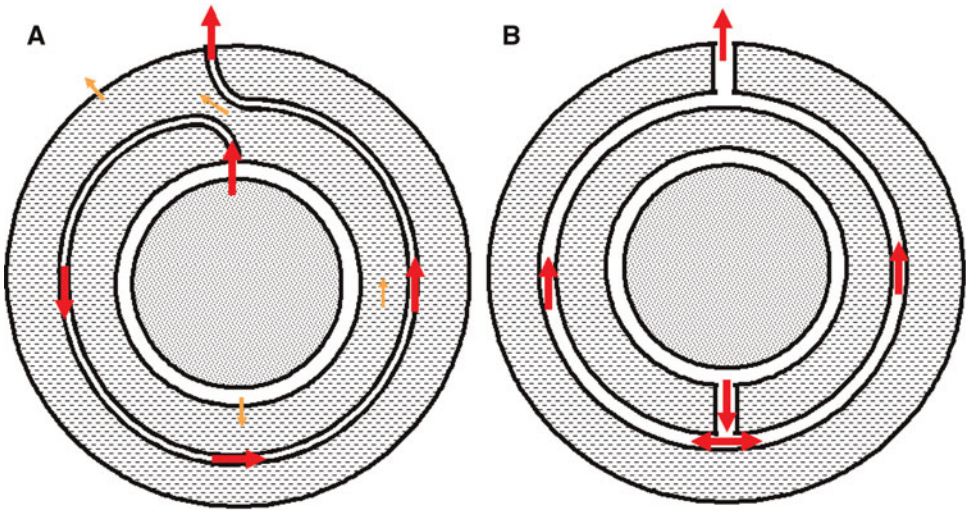

Fig. 3. Transverse shunt paths in non-compacted sheaths. (A) In a spirally wrapped sheath, current exiting through the axolemma can gain access to the external conducting medium by traveling along the spiral path between non-compacted layers. External compounding eliminates this path. Secondary paths (e.g. small arrows) cross the glial membrane capacitance and travel through non-compacted glial cytoplasm. (B) In a concentric sheath with marginal end loops meeting at seams on alternate sides of the fiber, current exiting through the axolemma can penetrate through short mesaxons past the margins, splitting to travel around both sides of the fiber between layers to meet at the opposite seam. Penetrating the layer at the seam, the process continues until the external medium is gained. Either blocking the mesaxon at the seams or compaction through external compounding eliminates this path. Figures after www.pbrc.hawaii.edu/~danh/InvertebrateMyelin/invertebrate_myelin.html.

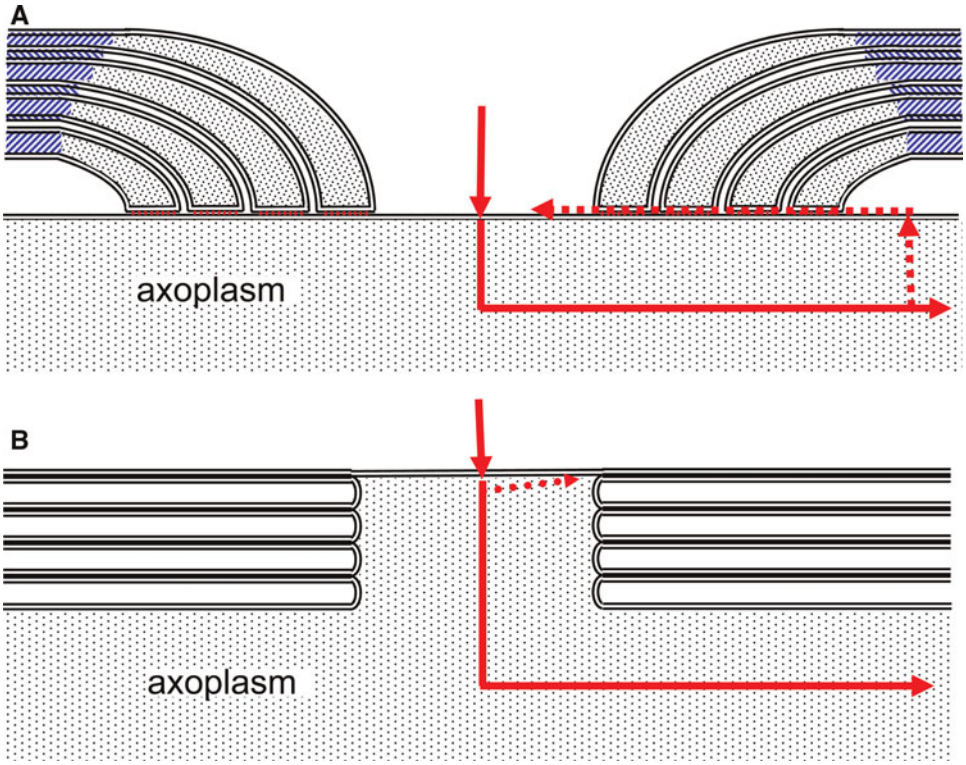

Fig. 4. Shunt pathways at nodes. (A) Ranvier-style node: Condensed myelin layers separate into 'terminal-loops' and become filled with glial cytoplasm. These come into close contact with the axolemma through extracellular junctional specializations of a septate form, but without forming membrane condensations. The end-loops of the outer-most myelin layer terminate nearest to the node. A key potential shunt path through the contacts between terminal loops and axolemma is shown with a dotted arrow. Vertebrates and palaemonid shrimp exhibit this type of node, and in basic organization, penaeid and annelid nodes are similar. In the invertebrate cases, desmosome-like structures termed 'radial attachment zones' bind the glial layers together (hatching). After Heuser and Doggenweiler (1966). (B) Copepod node: Suggested structure for copepod node showing the semicompact layers of myelin including the outermost condensed layer that appears to be continuous with the axolemma. The most vulnerable shunt path equivalent to that shown in A for Ranvier nodes (dotted arrow) is effectively closed by membrane condensation. Figures after www.pbrc.hawaii.edu/~danh/InvertebrateMyelin/invertebrate_myelin.html.

perinodal region of oligiochaetes contains numerous desmosome-like specializations, but no clear candidates for current-blocking specializations have yet been described (Roots, 2009, 1984). Desmosome-like structures have also been described at nodes in vertebrates (Rosenbluth, 1962; also at Schmidt-Lanterman incisures: Hall and Williams, 1970), palaemonid shrimp (Heuser and Doggenweiler, 1966) and penaeid shrimp (Kusano and LaVail, 1971; Hsu and Terakawa, 1996), and throughout the myelin, especially near end-loops, in the latter two cases (where they are termed 'radial attachment zones'). This cross-taxon pattern also bespeaks a strong convergently evolved need that is perhaps not as obvious as the ubiquity of the feature would lead one to expect. In a departure from the usual pattern, copepods appear to have no specialized structures at the lamellar margins at nodes. Close apposition of the membranes appears to leave little or no space through which shunting current can pass (Weatherby *et al.*, 2000; Fig. 4B).

Nodes

Nodes are ubiquitous in speed-enhancing sheaths. A key feature possessed by all is a greatly restricted area of exposed axolemma. The functional significance of the small area, and hence the likely selective force on minimizing nodal size, is the high specific capacitance of the exposed axolemma. The less area exposed, the less it will increase the overall capacitance of the fiber, which increase would slow the impulse. For example, in a fiber with a 1 mm long internode comprising 100 layers of double membranes, a 1 μm long annular node contributes 1/6 of the mean fiber capacitance per unit length. This contribution to capacitance produces an almost 10% lower conduction speed. The small size of nodes has made them hard to recognize in invertebrates, yet they are a hallmark of a speed-enhancing sheath. Their presence is evidence of a saltatory, and hence presumably rapid, mode of impulse propagation. Although the nodes themselves (or their equivalent) are ubiquitous, their geometry is not. In vertebrates and palaemonids, they are annular in form, encircling the axon, but in oligochaete, penaeid and copepod axons, they are restricted spots or 'fenestrated nodes'. It is of interest that even in the two myelinated decapod crustacean groups (palaemonid versus penaeid) there is a difference in the node form.

Nodes are key to the energy savings realized by myelinated fibers. Sodium channel densities reported in nodal membrane are only somewhat higher than those reported for un-myelinated fibers, e.g. 1200 μm^{-2} for vertebrate nodes (Rosenbluth, 2009); 530–5000 μm^{-2} for penaeid nodes (Terakawa and Hsu, 1991; Hsu and Terakawa, 1996); versus ca. 180–550 μm^{-2} for unmyelinated squid axons (Bekkers *et al.*, 1986). The small surface area of the node along with long internodal spacings gives ca. 1000-fold less active membrane, which even with a ten-fold increase in channel density gives over 100-fold fewer sodium ions entering per impulse. This translates into an energy savings of two orders of magnitude or more in restoring post-impulse ionic balances. Numerous studies of metabolic consumption of oxygen and/or production of carbon dioxide have been made on nervous tissue (review: Gerard, 1932). The increase in metabolic rate derived from neural activity has been well documented in vertebrate myelinated (e.g. Gerard, 1927) and unmyelinated (Ritchie, 1967) fibers and a few invertebrate unmyelinated fibers (Gerard, 1932). Ritchie (1967) estimated that the metabolic cost of an impulse in a single (very small) unmyelinated C fiber was about the same as that for a large myelinated fiber, which is an experimental illustration of the efficiency principle. Selective advantages gained from this efficiency do not receive the attention that those from speed-enhancement do, but under some ecological conditions, they may prove to be the more important.

REFINING THE QUESTION: MINIMAL MYELIN

In considering the purely functional aspects of speed-enhancing sheaths, little has been said yet about the relative merits of certain features of vertebrate myelin that are usually taken for granted: the high degree of compactness of the sheath, the spiral geometry of the layers, the glial cells that generate the myelin, the axoplasm through which internal current flows and even the existence of nodes of Ranvier. Exploration of these issues will help identify the essentials of functionally defined 'myelin.' We must ask 'which of these features are not essential to rapid conduction?'

Membrane compaction is not essential for speed enhancement

Although membrane compaction is found in all of the speed-enhancing sheaths reviewed above, the decreased capacitance producing the improvement depends on the number of insulating lipid layers, not on their state of compaction *per se*. Compaction was discussed above in the context of eliminating shunts, but there are alternatives. This can be clearly appreciated in concentric myelin, such as that of the two decapod shrimp taxa (Fig. 2C,D). Each concentric glial layer encircles the axon completely, with appositions – short mesaxons – at the meeting points of glial margins. If current through these mesaxons is blocked, the capacitances of all layers combine in series, shunt-free, producing the needed decrement to overall capacitance. This is independent of how much conducting space there is between layers. Compaction is not as big an issue in such concentric myelin. The issue is even further minimized in copepod myelin, which consists of continuous concentric rings (cylinders) of membrane with no seams and hence no resistive shunt paths for current escape in the internodes.

While compaction *per se* has little impact on conduction speed *for a given axon core size*, when performance is calculated in terms of the outer diameter of the sheath, a non-compact sheath will appear less efficient than a compact one. A possible reason for crustaceans and perhaps oligochaetes to be less affected by lack of sheath compaction than vertebrates is that their nervous systems have been geared to using small numbers of neurons, and no premium on space has emerged like that exemplified by the vertebrate cranium, as pointed out by Zalc *et al.* (2008).

Now suppose that the condition of blockage at the seams is relaxed, as it might be in the early stages of evolution or development of myelin. In palaemonids, the longer the zig-zag path between layers from inside to outside (i.e. the more glial layers: Fig. 3B), the greater the resistance in the path and hence the less its ability to shunt capacitance. Thus in principle, effective low-capacitance insulation might be provided by the normal

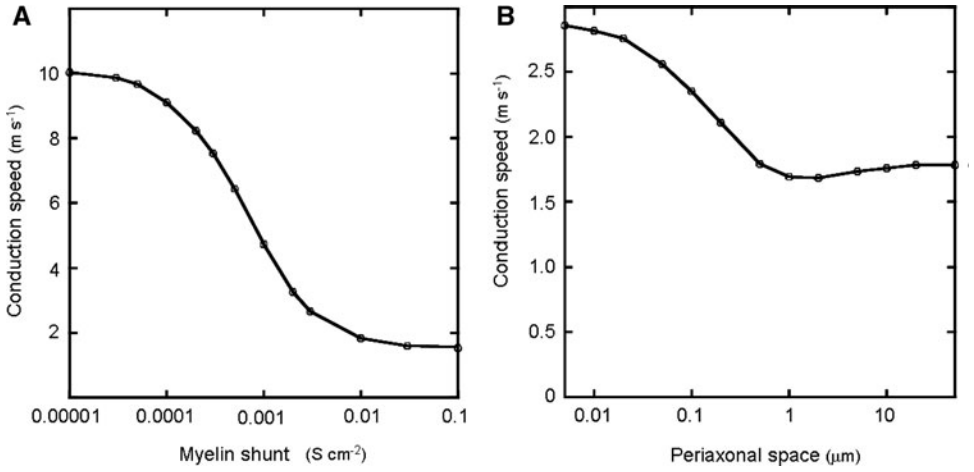

Fig. 5. Conduction speeds (ordinate) in a simulated 10 μm-diameter nerve fiber. (A) Effect of sheath shunting on speed: Simulation of a fiber with sheath-capacitance equivalent to 50 double layers of myelin but shunted by a conductance given in the abscissa. Node spacing in the model set at 1 mm, with a 1 μm node length and sodium and potassium channel densities elevated 1000× above those of squid axons (thus the *mean* channel conductances are the same as for squid axons). (B) Lillie transition: the onset of saltatory conduction. Simulation of a non-myelinated axon of 10 μm diameter placed inside an insulating tubular sheath of varying diameter. The sheath had simulated annular openings ('nodes') 10 μm in length, spaced at 1 mm intervals, giving access to an external medium of zero resistivity. Plot shows the dependence of impulse conduction speed on the width of the periaxonal space between axolemma and the inner surface of the sheath. As the periaxonal space decreases, speed at first decreases owing to the higher resistance of the more restricted extracellular space (a potential evolutionary bottleneck), then it increases abruptly for spaces $<10\%$ of the axon diameter as saltatory conduction sets in. Sheath consists of five double membrane layers. Note the logarithmic axis. Simulation by NEURON (Hines and Carnevale, 1997). Axolemma used default squid-axon parameters with an external medium resistivity of 20 Ω cm (A) or 35.4 Ω cm (B).

intercellular spaces between glial laminae, given enough laminae. It is true that condensation of the external membrane faces or impervious junctions between end-loops will block the shunt more readily, but it is not a requirement.

In a non-compact spiral wrap, the sheath capacitance is at risk for being shunted by the spiral conductive path afforded by the mesaxon (Fig. 3A). External compounding of membranes is an effective way to eliminate this path. However, the same reasoning that was applied to open-path concentric sheaths applies to a non-compact spiral: a long enough mesaxon, even without membrane condensation, can provide a resistive path that contributes to the insulating qualities of a glial investment. Figure 5A shows the effect of different levels of shunting of sheath capacitance (expressed in S cm^{-2}) on conduction speed in a simplified model of a 10 μm diameter myelinated axon having a sheath of fixed capacitance. Speed begins to be adversely impacted for shunts above 0.1 mS cm^{-2} (three times the leak conductance of the axolemma in this model) but even with a shunt 100 times greater, conduction speed is still elevated over that for a completely permeable sheath. This 'end point' corresponds to the insulating effect of a non-compacted mesaxon of 20 nm width wrapped only once around the axon.

Spiral wrapping is not essential for speed enhancement

Of the speed-enhancing sheaths considered so far, there is an even split in the geometry of the sheath wrapping, either spiral (vertebrates and oligochaetes) or concentric (shrimp and copepods). Thus there seems to be no evolutionary imperative for one form over the other. Spiral myelin, at least in vertebrates, forms by laying down and compacting a thin glial sheet that wraps progressively around the axon (Raine, 1984). Concentric myelin of penaeids forms from multiple layers of membrane elaborated by each glial cell and enveloping an axon from both sides (Xu *et al.*, 1994). Thus, different ways of laying down thin membranous sheets are possible. Spiral myelin is arguably not the most efficient design for blocking shunts. Concentric myelin with alternating seams has two options for eliminating shunts: external compounding and seam seals. Spiral myelin is largely dependent on external compounding, and does not achieve full design efficiency without internal compounding as well. What is important is not the geometry of the membranous wrapping but the ability of the structure to create low-capacitance high-resistance insulation.

Glia is not required for speed enhancement

As we have stressed, capacitance reduction utilizes a multiplicity of lipid-rich membrane layers, but functionally speaking, the origin of these layers is irrelevant. They need not be glial. Before the fine connections to oligodendrocyte perikarya were demonstrated and a glial origin for CNS myelin was confirmed (Bunge *et al.*, 1962), an axonal origin was a possibility considered (Scharf, 1951; Hild, 1957 cited in Bunge, 1968). Glial cells are prominently present in most of the cases of myelin heretofore investigated in detail (oligochaete, palaemonid and penaeid: Hama, 1959; Heuser and Doggenweiler, 1966; Kusano, 1966). However, they have never been seen to associate clearly with myelin in copepods (Weatherby *et al.*, 2000). Some evidence suggests that the multilamellar structures in copepods may be of neuronal origin (Wilson and Hartline, 2008). However that turns out to be, there is no intrinsic reason why a speed-enhancing insulating sheath composed of layers of lipid-rich cell membrane can only be generated by glial cells.

Most of the axon is inessential for speed enhancement

The role of the axolemma in saltatory conduction is to provide sodium channels at nodes. In most myelinated fibers, the

axonal core also serves as a convenient scaffold around which to wrap the myelin. In penaeid shrimp, however, a form of ensheathment has evolved which, except for nodes, has broken free of its dependence on a close association with the axon. Figure 1D shows a diagram of such a sheath. Here the axon makes internal contact with the edges of a fenestrated node. Hsu and Terakawa (1996) showed that this is where active sodium channels are located. These channels play a normal role in generating ion current for the impulse. However, the current passes out of the small-diameter axon and into the surrounding submyelin space, where it travels as it would have had the axon filled the space. There is no resting potential in the submyelin space. The action potential rises from a base of 0 mV and reaches a peak of over +65 mV! One advantage of this unusual arrangement is that the internal specific resistance of the submyelin space is close to that for sea water (23 Ω cm; Kusano, 1966) which is 2/3 that of squid axoplasm (Cole and Hodgkin, 1939) and 1/3 that of crab (Hodgkin and Rushton, 1946). This speeds conduction significantly. The selective pressure must be extremely high in penaeids to give them at ambient temperatures a much higher conduction speed than any warm-blooded mammal. In any event, involvement of an axon is only necessary at nodes.

Nodes are not essential for speed enhancement

A solid unbroken insulating membranous sheath would be incapable of sustaining nerve impulses by any mechanism currently known. The solution in all described cases of speed-enhancing sheaths has been to engineer periodic breaks in the sheath, where the axolemma, with its sodium channels, can gain access to the external conducting medium. We discussed nodes above, but axo-axonal synaptic sites can also serve as 'functional' nodes. At these sites the continuity of the sheath must be broken to permit juxtaposition of the pre- and post-synaptic membranes, giving a point for current to exit or enter the axon (Hsu and Terakawa, 1984). For a similar reason, branch points of the axon have also been implicated as functional nodes in saltatory conduction. This has been suggested for oligochaete (Günther, 1976) and penaeid shrimp giant fibers (Kusano and Lavail, 1971) as well as for Mauthner cells (Greef and Yasargil, 1980; see discussion in Roots, 1984). In all of these cases, the regions of exposed membrane are restricted. However there is another logical possibility, which is for a partial envelopment of the axon in sheath material, leaving a ribbon of axolemma exposed along its length. Such a configuration would still reduce the mean transverse capacitance significantly and hence would increase conduction speed. However, conduction would not be saltatory in such a situation – it would propagate continuously along the exposed axolemma, but at a higher speed than for an unmyelinated fiber of the same diameter. The interesting morphology of the myelin-like sheath of the phoronid, *Phoronis australlis*, the circumference of which is interrupted along a line of contact with subjacent connective tissue (Fernández *et al.*, 1996), suggests such a possibility. Certain situations with developing copepod myelin may fit this mode of conduction as well (Wilson and Hartline, 2007).

Sealing around nodes is not essential for speed enhancement

Normal myelin, be it vertebrate or invertebrate, is tightly sealed around the nodes or functional nodes (Kusano and LaVail, 1971). In vertebrates and palaemonids, this is accomplished by the paranodal terminal loops of glial cells, which contact the axolemma via septate junctions and are sealed to each other by tight junctions. A plethora of molecules has evolved to perform this function (e.g. Poliak and Peles, 2003; Susuki and Rasband, 2008). Although less well studied, the nodes of penaeids and oligochaetes also appear to have specializations that could reduce the insinuation of current at the glial margins. In copepods, the lamellae around nodes appear also to be compounded or tightly apposed (Weatherby *et al.*, 2000; Fig. 4B). However, it might be recalled that in the experiment of Lillie (1925), the insulating sections of tubing around the steel wire precipitated saltatory conduction without being tightly sealed. They were just tight enough to increase the longitudinal electrical resistance between the tube and the wire, favoring a return-current path outside the insulators rather than inside. A similar situation holds for the narrow but non-compound periaxonal space normally formed between the axolemma and the adjacent glial membrane, provided pathways for transverse (radial) current flow are limited. Figure 5B illustrates this 'Lillie effect' where a transition between continuous and saltatory conduction is produced by reducing the extracellular space enclosed by a segmented sheath without special seals at the segment margins. It shows the conduction speed of an unmyelinated fiber plotted against the separation between the axolemma and the surrounding sheath. The axon is 10 μm in diameter and has standard Hodgkin–Huxley squid membrane parameters (see caption). As the separation between axolemma and sheath decreases (right to left), conduction speed first decreases owing to the increasing external resistance in the periaxonal space, then reverses direction and increases steeply with the onset of saltatory conduction as the separation reaches a few tenths of a micron. To be sure, this form of insulation is not as effective as that of a well-sealed node, but like normal myelin, it provides high resistance in shunt paths and shows how saltatory conduction can arise under conditions that are more permissive than in fully formed myelin.

WHAT IS 'MYELIN' AND HOW MIGHT IT HAVE EVOLVED?

As I have tried to show, many of the features that might be thought to characterize myelin are not essential to its most basic function, that of speed enhancement. To generate low-capacitance energy-conserving characteristics, sheaths made of cell membrane require only extra layers placed without excessive shunting in series with the internodal axolemma, along with restricted areas of axolemma bearing sodium channels with easy access to the external conducting medium. All speed-enhancing sheaths reviewed here have had multiple layers of membrane with at least some membrane compaction as a sealing mechanism and some discrete nodal structures. Beyond this, the consistency ends. However, we have also seen that even these features are not required for speed enhancement. In both the evolution and the development of

myelin, shunt-reduction features may be as simple as long access channels to the outside. Unusual velocity–diameter relations have been noted in the developmental enlargement of at least one unmyelinated (though heavily ensheathed) reidentifiable crustacean giant axon (Govind and Lang, 1976). Exposed axolemma could have as little structure as small unsealed patches (protonodes), or continuous narrow (border-sealed) ribbons. Lowered capacitance can be provided even by small numbers of layers ('single layer' myelin has been reported in copepod chemosensory fibers: Lenz *et al.*, 2000). In the final analysis, 'minimal myelin' could require only a few (even just one) capacitance-reducing layers of membrane. Modest stretches of narrow, high-resistance extracellular spaces separating access points to low-resistance external current-return paths would produce significant increases in conduction speed. An incremental process might be envisioned in the evolution of myelin. Starting with speed-enhancement derived from properties already present in glial–axonal relations, innovative sealing mechanisms such as membrane condensation and specialized junctional proteins might be improvements added later. However, these seem not to be essential to the onset of the evolutionary process. All known myelin sheaths have had hundreds of millions of years to become fine tuned. Over this great span of time, additional refinements have been added almost ubiquitously to bring all myelins to their present-day high levels of performance. The evolution of myelin does not stand still. It will be fascinating and highly informative to see unfold the still largely obscure story of the molecular evolution of invertebrate myelin, for comparison with the remarkable vertebrate tale.

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Statement of interest

None.

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AUTHOR'S ADDRESS

Békésy Laboratory of Neurobiology
Pacific Biosciences Research Center
University of Hawaii at Manoa
Honolulu, HI
USA

Correspondence should be addressed to:
Daniel K. Hartline
Békésy Laboratory of Neurobiology
Pacific Biosciences Research Center
University of Hawaii at Manoa
Honolulu, HI 96822
USA
phone: 808-956-8003
fax: 808-956-6984
email: danh@hawaii.edu