Evolution of rapid nerve conduction*

Ann M. Castelfranco

Daniel K. Hartline

Békésy Laboratory of Neurobiology

Pacific Biosciences Research Center

University of Hawai^o i at Manoa

1993 East-West Rd

Honolulu, HI 96822

Corresponding author:

Dan Hartline

danh@hawaii.edu

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* Dedicated to the memory of David Colman who was the inspiration for our long-standing interest in myelin evolution.

1. INTRODUCTION

1.1 Rapid conduction in nerve.

The pinnacle of speed in rapid nerve impulse conduction is clearly reached by large myelinated nerve fibers. Wrapped in multiple layers of condensed membrane and conducting up to speeds over 200 m s^{-1} , the morphological as well as the physiological differences between myelinated and non-myelinated nerve fibers could hardly be greater. Figure 1 vividly illustrates this with electron micrographs of fibers (A vs B) from the same nerve trunk in an amyelinate and a myelinate species of calanoid copepod. But why and how myelinate species diverged from amyelinate kin, some possibly as recently as 270 million years ago (Bradford-Grieve, 2002), to evolve such an elaborate structure is less clear. Ancestral species had to go from amyelinate Point A (Figure 1A, *Gaussia*) to myelinate Point B (Figure 1B, *Undinula*) without degrading function. The "why" and the "how" of this will be explored in our review. We first examine the "ultimate" causes for evolution of rapid signaling -- the selective advantages that can be deduced from observing speed in action.

1.2 Why care about conduction velocity?

The ultimate cause of an evolutionary advance is the adaptive value or advantage of the evolved trait. It is usually taken for granted that conduction speed in the nervous system has adaptive value, and the faster the better. This is supported by several specific potential advantages it could have, any one or more of which might provide the selective pressure driving the evolution of higher speeds: 1) Timely reaction to predatory attack is perhaps the most often-cited and obvious advantage. The sooner an organism can recognize the signs of such an attack, the more likely it will be able to take effective evasive measures. 2) More rapid conduction decreases reaction times in launching and coordinating predatory attacks when opportunity arises suddenly and/or precise timing is critical (Zalc and Colman, 2000; Zalc et al., 2008). 3) Greater speed can serve to better synchronize contraction of a distributed muscle sheet, all regions of which must contract at the same time to be effective (e.g. in cephalopod mantle: Pumphrey and Young, 1938). 4) It improves precision in temporal discrimination, since it reduces the impact of natural variations in the rate of conduction (Hartline, 2008; Wang et al., 2008). 5) Speed allows

timely integration of information from spatially-dispersed sensors and better coordination of dispersed muscles, which thus allows evolution of more complex sophisticated nervous systems. 6) It permits evolution of larger body sizes, since faster speeds are needed to keep in timely communication with increasingly distant parts.

1.3 Proximate issues in the evolution of rapid conduction.

Granted the value of rapid signal conduction, it is less obvious how its underlying mechanisms evolved and were fine-tuned over the eons of geologic time. The millisecond reaction times of some organisms, and conduction velocities of over 100 meters per second in myelinated axons, had humble beginnings. Life forms have had to set a myriad of novelties in place. What were these, and how did they evolve without adversely affecting organismal fitness -- indeed enhancing it at each step? The evolutionary trajectory culminating in such speeds thus depends strongly on the "building blocks" made available through evolution. Furthermore, each evolved novelty constrains the possible sequence of future innovations within a given line, while nevertheless satisfying the underlying principles. Comparison between lines should thus illuminate both basic design principles and likely evolutionary pathways. These paths lead from improvements over chemical communication speeds through the invention of electrical signaling, to channels with integrated voltage sensors for impulse generation, then to core-conductor axons capable of reaching more distant points and optimized for speed. At this point the paths diverge as the different forms of the complex insulation of myelin are added. The first several innovations appeared before the rise of the Bilateria. Myelin, on the other hand, has arisen independently in four different groups since the bilaterian radiation. In what follows, we will take up this sequence of innovations as a rough guide to a logical trajectory followed in the evolution of rapid conduction.

2. Non-regenerative mechanisms

2.1 Chemical signaling by diffusion.

Starting with the very small, the size of single-celled organisms allows slower communication modalities to suffice, and these appear to have been the first to evolve. In the

Bacteria, Archaea and unicellular Eukaryota, communication is often by chemical diffusion and reaction (Na^+ , H^+ , Mg^{2+} , signal proteins, etc.), as in the control of flagellar movement (Blair, 2003) and turning responses in chemotactic or phototactic bacteria (Zusman et al., 2007) and motile algae (Jékely, 2009). While the speed of diffusional communication in cells of bacterial size (μm) involves timescales of milliseconds for key small signaling molecules such as calcium, this timescale lengthens with the square of distance, which is a rapidly-increasing disadvantage as cells enlarge. Diffusion-dependent signaling still remains an important modality in "higher" organisms, as in the spread of calcium waves in astrocytes (Table I; see below), at synapses and in parasympathetic (retrograde) transmission (Fitzsimons and Poo, 1995), but the key to diffusional speed is employing small molecules over short distances. The need to circumvent this diffusional constraint as an organism evolves toward larger and more complex morphologies is likely to have provided the evolutionary impetus for the early emergence of faster conduction mechanisms.

2.2 Faster signaling by chemical transport.

As the limits for rapid communication by diffusion are reached, chemical communication can still be speeded through special adaptations for transporting the signal (or effector) molecules. These include "advective" bulk transport of the fluid in which the chemical signal is embedded, as in cyclosis (cytoplasmic streaming) in certain plant cells (Wayne, 1994) and unicellular organisms, and carrier-based transport as in axonal transport in animals with nervous systems (Fitzsimons and Poo, 1995) and circulatory-system-based communication using hormones. The relative effectiveness of transport vs diffusional chemical conduction can be represented by the "Péclet number," $\text{Pe} \equiv T_{\text{diffusion}}/T_{\text{transport}} = UL/D$, where U is the transportation velocity, L is the size of the communication dimension (e.g. cell length) and D is Fick's diffusion coefficient (Verchot-Lubicz and Goldstein, 2010). $\text{Pe} \approx 1$ is the dividing line between diffusion-dominated and transport-dominated signaling. With D for small molecules $\sim 10^{-6} \text{ cm}^2 \text{ s}^{-1}$ ($100 \mu\text{m}^2 \text{ s}^{-1}$) and intracellular transport processes reaching up to $100 \mu\text{m s}^{-1}$ (Table I), diffusion can dominate in organisms below $\sim 1 \mu\text{m}$ (bacterial size). However, for even small molecules traveling at the slow rates of axonal transport ($1 \mu\text{m s}^{-1}$ when in motion: Roy et al., 2007) over

distances of centimeters, Pe is much greater than 1, and transport becomes by comparison a "rapid conduction" modality (e.g. Mignot et al., 2007).

2.3 Voltage-based passive signaling.

Transport-based communication even as high as $100 \mu\text{m s}^{-1}$ will only suffice for organisms as large as small protozoans (cyclosis is not found in prokaryotes, although other transport processes are: Zusman et al., 2007). Given that many predators can react in a matter of milliseconds, a faster means of communication is needed for organisms larger than *ca.* $10 \mu\text{m}$ (e.g. Hartline 2015). This speed barrier was broken by the invention of voltage-based signaling. Voltage perturbations, even passively ("electrotonically") conducted, spread much more rapidly along cell membranes than chemical diffusion or transport (Table I). Various protozoans have achieved this by employing membrane-localized electrical signaling in the control of their locomotion. In the 100-200 μm -long protozoan ciliate, *Paramecium*, a mechanical stimulus applied posteriorly activates a non-regenerative hyperpolarizing potassium current with a concomitant speeding of the forward propulsion by the cilia (Naitoh and Eckert, 1973; review: Martinac et al., 2006). The use of electrical signaling enhances the protozoan's capability for responding rapidly and correctly along its whole elongate ciliated body to predatory attack from behind. While electrical signals are intrinsically fast-conducting, they are also intrinsically slowed by the capacitance of the lipid membranes upon which they depend for the separation of charge needed to sustain a voltage signal. They also lack the richness that chemical signaling offers. For evolution to optimize an electrical modality of signaling, it must adjust the parameter controlling timing and response speed in passive membrane, i.e. the membrane time constant. Reducing membrane resistance shortens this time constant. However, the ability to conduct voltage signals over distance in an elongate cell depends on the length constant, which is also shortened by reducing membrane resistance resulting in greater spatial attenuation of the signal. The interaction between the two is subject to evolutionary mediation, and these same parameters are important in controlling the speed of conduction in myelinated nerves. Although typically slower than action potentials, passive conduction of non-spiking electrical signals is nevertheless retained in key roles even in nervous systems with well-developed spike-generating properties. The "all-or-none" nature of conventional spikes has the disadvantage of requiring intensity to be

encoded in spike timing (e.g. frequency), which provides only intermittent rather than continuous information transfer. Passive graded signal conduction in electrotonically short processes, as for example in many dendritic trees, permits continuous but still timely spatial and temporal integration of local information prior to the spike generation used for long-distance communication. Vertebrate photoreceptors, bipolar and horizontal cells operate rapidly over short distances without spikes entirely, and even long-distance voltage-based signaling can be achieved without spikes, in neurons with elevated membrane resistance (Mirolli, 1979).

3. Regenerative voltage-based mechanisms.

As cells evolve more elongated forms, electrical communication between increasingly distant points becomes difficult with passive electrical processes, owing to electrotonic decrement. Surmounting this impediment, while also assuring timely communication of the information that a critical (threshold) level of input has been reached, are likely selective forces that promoted the evolution of regenerative signaling. This solution was based on coupling a voltage sensor to an ion channel. The coupling came in two forms, a "graded" form in which a voltage perturbation of extrinsic origin was augmented by intrinsic mechanisms without being self-sustaining, and a self-sustaining action potential, typically of an "all-or-none" character. As an early example, also from *Paramecium*, the same mechanical stimulus that elicits a non- (or weakly) regenerative voltage signal when applied to the posterior end, when applied to the anterior end, elicits a regenerative (albeit not all-or-none) calcium action potential in the cilia, which causes ciliary reversal (Figure 2A; Eckert et al., 1972; Naitoh et al., 1972; review: Eckert and Brehm, 1979). This enables the protozoan to respond within milliseconds by rapidly backing away from collisions with objects in a manner again coordinated along its entire body. Calcium diffusion by itself from end to end of this 100 μm organism would take ~10 seconds, and transport-based signaling ~1 second. Although most reported regenerative spike-producing mechanisms depend on depolarizing (positive-going) membrane mechanisms, hyperpolarization-activated regenerative hyperpolarization can be produced in *Paramecium* in a potassium-free medium (Eckert and Brehm, 1979), in *Necturus* inner segments amplifying the

negative-going primary receptor potential (Werblin, 1975) and mediating rapid relaxation in *Ascaris* oesophageal muscle (del Castillo and Morales, 1967) among others (Grundfest, 1961).

3.1 Signal conduction in multicellular organisms.

With the arrival of the key evolutionary leap of multicellularity, the need arose to coordinate activity among multiple individual cells by extending impulse conduction to intercellular communication. The most widely-used solution has been the evolution of special channels directly bridging between adjacent cells. Such a bridge probably evolved initially to pass small signaling molecules of different kinds. Throughout much of the animal kingdom such bridges are provided by gap junctions, which are broadly produced by the pannexin family of proteins (also connexins in chordates and plasmodesmata in plants) (White et al., 1995). Such systems evolved in basal metazoans (Mackie, 1965) and, with a few notable exceptions, are nearly ubiquitous between cells in physical contact, whether or not dependent on electrical signaling. Gap junctions in vertebrate brain have recently come into focus as the means by which waves of ATP-activated calcium entry into astrocytic networks spread. While still only partially understood, these slowly-propagating waves are limited by the central role played by chemical diffusion (Table I; e.g. Charles, 1998; Stout et al., 2002). However, the same gap junctions enable communication through the flow of ionic current and hence electrical signals. In such a role, these become "electrotonic connections" or "electrical synapses" according to the time-scale of signals being passed. Gap-junction-mediated spread of electrical signals among epithelial cells has been identified as the modality for producing coordinated swimming behavior in certain basal metazoans including ctenophores (Satterlie and Case, 1978) and jellyfish (Figure 2B; Mackie, 1965, Mackie and Passano, 1968; review: Mackie, 2004). Electrically-mediated excitation in epithelia of various jellyfish spreads at $0.15 - 0.55 \text{ m s}^{-1}$; that among heart muscle cells in a range between 0.05 to 4 m s^{-1} (Table I).

3.2 Impulse conduction in plants.

It has long been known that motor activity in plants is accompanied by electrical signals, which have now been shown to mediate the activity. Galvanometric responses from stimulated Venus fly traps were described by Burdon-Sanderson (1873), including their activation by

electrical stimulation. More recently, it has become increasingly clear that other higher plants also use propagating all-or-none ionic-current-based electrical signals to mediate key physiological processes, not restricted to rapid movements as in the fly trap or *Mimosa* (review: Fromm and Lautner, 2007). These tend to be prolonged (seconds) and slowly propagating (cm per second: see Table I), but have all the basic features of nerve action potentials including a specialized conducting system in the phloem, as a plant equivalent of a nerve trunk (Figure 2C). In plants as in animals propagating impulses are often an evolutionary response to attack, injury or stress. Selective forces for rapid conduction may not yet have produced the conduction speeds found in animals (Table I), but speeds being reported are increasing (e.g. Volkov et al 2013) and animals may not hold on to the speed record. What we learn from examining the plant situation is that voltage-dependent mechanisms modifying the conductance state of ion channels in conjunction with an electrical conducting system situated in elongate cells with specialized "electricity-friendly" connections to other cells seem to be the design features utilized to best effect in long-distance rapid (as plants go) signal conduction.

3.3 Speeding voltage-based regenerative processes.

Certain green algae with elongate cells provide added insight into rapid conduction principles. These are among the more basal organisms to have employed the voltage-regenerative modality of conduction to communicate over their length (e.g. Findlay, 1959). For producing the inward currents of regenerative impulses, neuroscientists are used to thinking solely in terms of Na^+ and Ca^{2+} , both cations, as charge carriers, with voltage-gated cation-selective channels as their conduits. However, the stonewort alga *Nitella* (and the related *Chara*) respond to predator-induced injury with action potentials that communicate information on the injury along the several centimeter-long cell to coordinate the response: halting protoplasmic streaming to minimize damaging cytoplasmic loss (Wayne, 1993). The main depolarizing inward current sustaining this action potential is provided not by Na^+ or Ca^{2+} entry but by Cl^- exit through chloride/anion-selective channels. The signal propagates at rates comparable to those for calcium spikes in cnidarian epithelia and axons (Table I). Thus at some level, choice of ionic species has little intrinsic impact on impulse speed. The ubiquity of calcium channels as charge carriers in many cells may be largely owed to the role for calcium established early in

evolutionary history as a diffusion-conducted messenger within cells. Voltage changes originally produced as a byproduct of receptor or stimulus-based calcium permeability may have facilitated evolution of faster voltage-gated processes.

Nor is there an intrinsic necessity for voltage signals to be depolarizing (positive-going), as the regenerative hyperpolarizations in *Paramecium*, *Ascaris*, and vertebrate rods illustrate. The few cases of regenerative hyperpolarization that have been investigated identify potassium ions as the primary charge carrier (del Castillo and Morales, 1967; Eckert and Brehm, 1979; Werblin, 1975,). While a few voltage-based signals involve conductance decreases (e.g. vertebrate photoreceptors, Werblin, 1975), the lengthening of overall membrane time constant makes this an unlikely mode for the most rapid communication. Further investigation of these issues could be informative.

3.4 Molecular substrates.

Accompanying the evolutionary changes in the morphological and physiological traits that underlie more rapid conduction is of course much molecular evolution, most of which we will not deal with here. However the evolution, diversification, and activation mechanisms of inward current channel proteins are particularly relevant to speed issues. In a departure from the "standard" molecular channel model, the chloride channels of *Nitella* do not themselves contain a voltage sensor. Conduction requires a two-step process: depolarization gates the entry of calcium ions from extracellular (or tonoplast) sources, which ions in turn activate the chloride channels internally (Wayne, 1994). This two-step process slows it (Castelfranco, 1988). However, a two-step process was once considered possible for the rapid conduction of nerve impulses through local acetylcholine release followed by short-distance diffusion and receptor binding before the current picture emerged (Nachmanson, 1961; Ritchie, 1967). Single-step activation of voltage acting on a voltage sensor that is intrinsic to the channel protein is potentially more rapid. However, that in itself is not sufficient to assure the fastest channel kinetics. When expressed in mammalian cell lines, the bacterial sodium channel, which contains such a sensor, is much slower to activate than eukaryote sodium channels (Na_v ; Ren et al., 2001). Further, the closely-related (some have suggested ancestral to Na_v) calcium channels for

all of their diversity in the service of a variety of functions, are slow compared with Na_vs . It has been suggested that this ability to utilize rapidly-conducting electrical signals, in particular the voltage-sensitive variety, arose during evolution from a non-voltage-sensitive ancestral ion-channel molecule consisting of two trans-membrane segments (S5 and S6) connected by an ion-selective pore-lining "p-loop." To this was then added a voltage-sensor complex consisting of four trans-membrane segments (S1-S4) (Moran et al., 2015). This strategy has been retained (or convergently evolved) and elaborated upon (as with the joining of four such subunits to form calcium and sodium-selective channels) to produce the principal voltage-gated channels of more rapidly-conducting metazoan nerve.

4. Origins of the nervous system

Multicellular structures for rapid conduction have evolved independently in the lateral giant axons of decapods (Payton et al., 1969) and the medial giants of earthworms (Oesterle and Barth, 1981). In these, the lengths of active portions of each cell, joined end-to-end, are electrotonically short (<100 axon diameters), with strong electrical coupling between cells provided by gap junctions. Generally, however, the multicellular cell-to-cell "bucket brigade" approach to signal conduction tends to be slow as it typically involves circuitries with high access resistances and capacitances (e.g. Lieberman et al., 1973). Also, electrical synapses, while more rapid than chemical ones, still produce a synaptic delay. Such delays may be acceptable or inevitable for some communication, especially local, but timely signaling to remote parts requires the invention of long-distance pathways along which electrical impulses can travel unimpeded by junctional delays. This doubtless contributes to the remarkable early evolutionary innovation of a long thin filiform cell specialized for communication: a "neuron."

4.1 Metazoan electrical communication.

Surviving examples of the neuronal communication system that arose early on are found in ctenophores and cnidarians. Their nervous system includes regenerative impulses capable of traveling long distance through interconnected networks of axons from sites of input to effector organs (Satterlie, 2015). The communication is, however, generally slower than in nerve fibers

of more advanced groups (Figure 3, starred points). Part of the explanation for this appears to be the inheritance from protist ancestors of relatively slow voltage-gated channels. The particularly slow ones are permeable to calcium rather than sodium, but even axons with sodium-gated channels fall below the curve for more advanced groups in conduction speed for a given diameter (Meech and Mackie, 1993). Indeed, the employment of calcium as a charge carrier in long-distance axonal conduction is rare, even among cnidarians. Sodium is by far the dominant charge carrier in rapidly-conducted metazoan action potentials, probably in part, at least, due to its adaptability to more rapid gating (see discussion in Meech, 2004). Nevertheless, the early evolution of a voltage-gated calcium channel molecule is a major advance in communication, since it has allowed linking of four previously separate subunits into a single molecule capable of forming a channel on its own, the different portions of which can be tailored to different functions, such as inactivation, within the same molecule (Moran et al., 2015).

5. Cables as substrates for rapid propagation of regenerative signals

5.1 Theoretical considerations: the Huxley function.

The application of core-conductor theory (Kelvin, 1855; Figure 4) to passive signal spread in axons by Rushton (1951) and others was followed by the seminal research of Hodgkin and Huxley (1952) on the biophysics of action potential propagation along such cables. It is with these advances that additional factors affecting conduction speed became apparent. Huxley (1959) analyzed solutions of the Hodgkin-Huxley (HH) equations as a general case of a wave traveling along a uniform cable at constant velocity and showed that the velocity can be represented as the product of two factors dependent on the 5 basic parameters describing the active cable:

$$(1) \quad v = \alpha^{1/2} f(\beta), \text{ for } \alpha \equiv k d / (R C) \text{ and } \beta \equiv \gamma / (k C),$$

where k is a scaling parameter for the rate constants of the active channels, d is the diameter of the axon, R is the specific resistance of axoplasm, C is the specific membrane capacitance of the axon, and γ is a scaling parameter for the conductance density of the active channels. The

"Huxley function", $f(\beta)$, is a unitless empirically-determined function, which is plotted, normalized to squid axon parameters (indicated by the subscript "0"), in Figure 5A (see caption for details). Multiplying $f(\beta)$ by $\alpha^{1/2}$ for any set of values of the 5 parameters yields a predicted velocity for that set. Three such (normalized) plots are superimposed in Figure 5B: varying the activation rate constant factor (k_0 ; broken line), varying the membrane capacitance factor (C_0 ; dotted line) and varying peak channel conductance factor (γ_0 ; solid line). Note that the latter line coincides with the $f(\beta)$ line, since conductance does not contribute to α . Thus the analysis predicts a maximum of $f(\beta) = 1.16$ for $\beta = 6.5$, which gives a peak in the velocity vs conductance relation (Figure 5B). Hodgkin (1975) and others have recognized that the sodium channel density in the squid giant axon may have evolved to maximize conduction velocity. However, the maximum for the Huxley function predicts a channel density much greater than that actually observed (Figure 5; Castelfranco and Hartline, 2015), and even carefully refined models of the squid action potential including voltage-dependent gating currents predict an optimal sodium channel density significantly larger than the densities observed in nature (Sangrey et al., 2004). A solution was proposed by Crotty et al. (2006), who found that when the metabolic cost of conduction velocity was included in the optimization the squid channel densities minimize the metabolic cost of the action potential for a given conduction velocity and axon diameter. Thus the adaptive impetus to evolve faster conduction is tempered by adaptive forces from other sources, and these must be quantitatively assessed before a clear model for the evolution of rapid conduction can be established with confidence.

5.2 Enhancing cable conduction: Rate kinetics.

In addition to optimizing channel densities, another way to increase conduction speed is to speed the kinetics of the active channels. The Huxley formulation shows, and model runs and experimental manipulations confirm, that conduction velocity of the squid axon can be increased by increasing the rate constants (principally the opening rate for sodium; increasing temperature is one way to increase channel rate kinetics uniformly). However, the increase in speed obtained is only modest, as the $f(\beta)$ curve is nearly flat for axons with squid parameters, so conduction speed only increases with the square root of the rate-constant factor.

5.3 Enhancing cable conduction: r_i -based mechanisms.

Basal metazoans invented a third mechanism for speeding communication, exploiting the fact that a lowered internal core resistance, r_i , of an axon enhances the electrotonic spread of current and hence increases the velocity of nerve impulses. Two strategies have evolved over time for doing this: increasing the inner diameter of the axon core and decreasing the specific resistance of the electrolyte contained in that core.

5.3.1 Axon diameter

Enlarging axon diameter operates on the fact that internal axial resistance decreases rapidly as the square of diameter. For unmyelinated fibers, impulse propagation velocity increases with diameter, usually with close to a square root dependence (Figure 3; Pumphrey and Young, 1938; but for deviations, see e.g. Hoffmeister et al., 1991; Govind and Lang, 1976). In terms of evolution, this should be a relatively easy route, since the mechanisms for increasing axonal diameter already exist for the developmental program. The principle is taken to an extreme in the evolution of "giant axons" several times larger than other large axons in a nervous system. Such giant axons occur throughout the Metazoa, often associated with escape or other rapid reactions in organisms possessing them. The most basal phylum in which giant fibers have been described is Cnidaria. Studies by Mackie and Meech (1985) found two types of swimming behavior in the hydrozoan *Aglantha*, both mediated by propagating all-or-none spikes in giant (40 μm) axons. One is a slow swim mediated by slow calcium spikes (Figure 2E); the other a fast escape swim elicited by faster-conducting sodium spikes (Figure 2D; Table I). The remarkable feature of this giant fiber system is that both types of spikes, sodium and calcium, are carried in the same axon! The separation between the two systems is based on threshold and amplitude partitioning that allows the sodium spike and fast swim to be elicited only by strong stimulation evoking large depolarizations. Despite the size of these axons, propagation velocities for both spike types are well below the norm for unmyelinated axons of comparable diameter in more advanced taxa, as mentioned above (§4.1; Figure 3; this and subsequent work reviewed by Meech 2004). Giant-fiber-mediated escape systems are found in Reptantia (lobsters and crayfish) triggering the "tail-flip" response in this group (e.g. Johnson 1924; Wiersma 1948;

Wine and Krasne 1972). A similar system of giant fibers has been found in copepods, both myelinate and amyelinate (Lowe 1935; Park 1966) and are presumed to mediate their extremely rapid escape reactions (Lenz et al 2000). Those of polychaetes have been extensively reviewed by Nicol (1948), mediating among tube worms the dramatically-fast withdrawal of gills and retreat to cover. Goldman and colleagues availed themselves of the large size of the giant axon in the sabellid, *Mixicola*, to study ionic mechanisms of impulse conduction as a parallel to squid studies (e.g. Goldman and Schauf 1973; Goldman 1991). Among insects the collection of giant fibers in the ventral nerve cord have been shown to underlie the rapid directional response of a cockroach to air puffs, such as would be produced by a predatory attack (Camhi and Tom, 1978). Figure 6 shows an example of such a "giant" fiber in a predatory caterpillar, an inchworm relative, to illustrate the size differential in such rapidly-conducting axons. The best-known of the cases is undoubtedly the giant axon in the mantle nerve of squid, brought to light by J. Z. Young (1936) and made famous by Hodgkin and Huxley (1952) among others, which mediates the escape jetting of that organism (adaptive, perhaps, as much for its synchronization of muscle contraction as for its quick reaction: Pumphrey and Young, 1938). The Mauthner-cells mediating startle behavior in amyelinate lampreys provide a classic vertebrate example (Rovainen, 1967; Currie and Carlsen 1987). Thus while basal metazoans were the first to invent "giant" axons (e.g. Satterlie, 2015), these axons remain a recurrent feature of rapid-response circuitry throughout the animal kingdom.

Speeding communication by enlarging core-conductor (axon) size has implications for long-distance communication in organisms against the backdrop of an evolutionary trend toward larger body size (also relevant to developmental changes). Because of its square root dependence, scaling of conduction speed with axon dimensions is allometric, obeying a power function with an allometric coefficient (exponent) less than 1.0 (negative allometry). Thus, if a neuron in which it takes a certain time for an impulse to propagate its length doubles in size in all dimensions with growth or evolution, it will take $2^{1/2}$ times or ~40% longer for impulses to reach the terminals. This means that if an organism doesn't increase the relative size of its axons (and as it turns out, other neuron metrics) as it evolves to larger size, it is increasingly sluggish in its ability to communicate with its distant parts. One solution is "isoelectrotonic" growth, in which

unmyelinated axon diameters increase as the square of the growth in length, as has been documented in cricket (Olsen et al., 1996), but such growth in a vertebrate would lead toward unmanageably large heads. Two ways around this impediment have evolved.

5.3.2 Core specific conductivity.

An additional method for reducing r_i , is to provide the core conductor with more highly-conducting medium. This has been the case for marine invertebrates, which, in order to maintain body fluids isotonic with the surrounding sea water, maintain a high axoplasmic ionic strength giving a specific resistance of 35 Ω cm (Hodgkin and Huxley, 1952) or above. With much lower ionic strengths in vertebrates and non-marine invertebrates, axoplasmic specific resistances are typically 3-fold higher, so a marine invertebrate axon of a given size can conduct almost twice as fast (a correction for this has been made in the plots of Figure 3). This principle has been carried even further by penaeid shrimp, in which the heavy myelin sheath surrounds a large extracellular tube (Xu and Terakawa, 1999; Figure 7D). Instead of axoplasm, much of the interior of the tube is filled with fluid having conductivity close to that of sea water (23 Ω cm: Kusano, 1966) as the core conductor, which in turn is predicted to increase conduction speed by 25% above that of squid axons of comparable diameter.

In principle, altering the external medium could have a similar effect on conduction, either by altering its conductivity or especially by increasing the electromotive driving force (EMF) on the inward current carriers as has been shown by artificial manipulation (e.g. Katz, 1947; Hardy 1973). While such a mechanism is utilized to amplify mechanoreceptive signals in the ear (Ochs, 1965), we are unaware of examples of its being used to specifically speed nerve impulse conduction. However, in a related phenomenon, the specialized perineurium of insects provides their nervous system with an assured supply of the necessary sodium ions required for reliable conduction speeds in the face of highly variable and potentially disruptive ionic compositions of hemolymph (Treherne and Schofield, 1981).

6. Myelination

The final step in the evolution of increasing conduction speeds in nervous systems, and the major one that frees axons from the 1/2-power allometry, is the invention of myelin. It is presently known in four widely-separated taxa: vertebrates of course, but also in oligochaetes (earthworms), decapod shrimp and copepods (Davis et al., 1999; Roots, 1984; Schweigreiter et al., 2006). While its form in invertebrates differs from that in vertebrates, its function, based on physiology and morphology, is identical. The myelinate taxa are separated phylogenetically by major amyelinate taxa (Figure 8A). Except for the two well-separated crustacean taxa, the last common ancestor of the myelinate groups appears to be a basal bilaterian, leading to the conclusion that it has emerged through evolutionary processes independently at least four times. As with other convergently-evolved structures with the same function, such as legs on crabs and mammals or wings on insects and birds, we regard it as "myelin" independent of taxon (Hartline, 2008).

6.1 Myelinate taxa and myelin organization.

Evidence for oligochaete myelin was first reported by Taylor (1940) and has been examined in detail at the electron microscopic level by Roots (1984). It consists of a spiral wrapping of 20 to 200 layers by a glial cell or cells (Figure 8D). It has a mixture of compact and less-compact regions with thin sheets of cytoplasm included in the latter. Myelination is confined to the giant axons in the earthworm, which conduct at speeds double that of unmyelinated axons of the same diameter and temperature (Eccles et al., 1932; Günther, 1976) (Figure 3). Myelin in decapod shrimp was reported by Friedländer (1889) thirty years after its first description in vertebrates by Virchow (1858) (extensively reviewed in a monograph by Xu and Terakawa, 2013). Over a hundred years later it was described in another crustacean group, the more derived superfamilies of the copepod order Calanoida (Davis et al., 1999). A contrasting organization is afforded by these two crustacean taxa, consisting of concentrically rather than spirally-arranged membrane layers. Each layer encircles the fiber with few if any discernable connections between layers. In decapod shrimp, margins of each myelin layer abut where they meet, forming a "seam" built up from the enlarged and aligned marginal contacts

(Heuser and Doggenweiler, 1966; Xu et al., 1994; Xu and Terakawa, 1999; Figure 8B, C). A concentric layering more easily insulates the inner axon than does a spiral one since tight seals are only needed at the margins of the layers, if any, to prevent short circuiting. In copepods, even marginal contacts are eliminated, the layers being formed from cisternae internally-deposited layer by layer against the inside of the nerve fiber with no breaks or gaps in fully-formed myelin (Wilson and Hartline, 2011b; Figure 1B). The concentric geometry in shrimp and copepods reduces the need for compactness, which is potentially required in spirally-wrapped myelin to prevent current escape to the outside along spiral pathways between uncompacted layers. Thus crustacean myelin is sometimes compact and sometimes not, with little consequence for its insulating properties. Permitting thin layers of cytoplasm within myelin layers likely facilitates supplying nutrients and other metabolic requirements for maintaining healthy myelin layers. It has the negative effect of increasing sizes of a myelinated fiber for a given amount of insulation, which can be a disadvantage where space is limited.

6.2 Node structure

Most mature myelins possess nodes, functionally equivalent to nodes of Ranvier in vertebrates (Figure 7). Vertebrates and caridean shrimp have circumferential nodes, meaning nodes that encircle the axon core and provide a short cylindrical segment of axolemma with electrical access to the surrounding conducting medium (Figure 7B). Earthworms and penaeid shrimp utilize a structure termed a "focal" or "fenestrated" node in the two groups respectively (Günther, 1976; Hsu and Terakawa, 1996). In these nodes, a small opening occurs in the myelin, giving a patch of axolemma access to the outside medium. In earthworms, an axoplasmic process penetrates the myelin to form a surface more or less even with the outer layers (Figure 7C). In penaeids, a depression is carved in the myelin layers penetrating to the underlying axon (Figure 7D). Copepods, possessing internal myelin, form abrupt "cliffs," where all myelin layers terminate in a line roughly perpendicular to the encircling axolemma. Their myelin in some cases only partially covers the inside of the fiber. Conduction is continuous (non-saltatory) but presumably fast in these axons (Wilson and Hartline, 2011b). The copepod architecture highlights the fact that nodes and saltatory conduction are not rigid requirements for reaping the benefits of increased conduction speed from myelin.

6.3 Advantages and disadvantages.

In addition to augmenting conduction speed, the evolution of myelin confers a few more advantages on myelinate species. At some trade-off cost to the extra speed that it promotes, it provides the possibility of a more compact nervous system. This has been singled out as particularly helpful for craniates, which encase their nervous systems in a heavy bony protection that is less costly in weight if its size is limited (Ochs 1965). By reducing the number of channels participating in the impulse, myelin potentially greatly reduces the energetic cost of activity by decreasing the number of ions that have to be pumped out after an impulse passes. By having nodes out of register in space, myelin restricts the points for ephaptic interaction, allowing such to be better controlled than in unmyelinated axons (Hartline, 2008; Debanne et al., 2011). Myelin also potentially generates a thermal tolerance for conduction safety factor, the failure temperature in simulated myelinated axons being above that in unmyelinated ones (Castelfranco and Hartline, 2015; Moore et al., 1978). Myelin also comes with certain disadvantages, chief of which is nutritional. It requires a lot of lipid-rich membrane and associated membrane proteins. In particular, protostomes (most invertebrates) don't make their own cholesterol, a key ingredient of the membranes that then has to be obtained from the diet, so this may be particularly limiting in myelinate taxa (Hartline and Kong, 2007; Lenz, 2012).

7. Theoretical considerations: effects of myelin structure on conduction velocity

We now examine the consequences on conduction velocity of several morphological features of myelin common to all taxa in which it has evolved. By taking advantage of the underlying biophysical properties of nerve conduction, computational modeling and simulation provide a technique for examining the effects on conduction velocity of individual changes in the structure of the myelin sheath. While the approaches most often used for such studies involve varying one, or at most two, parameter(s) at a time, it should be kept in mind that it is unlikely that only one parameter at a time would be optimized by natural selection. Rather, the collection of parameters that control the sheath properties influencing conduction velocity would be varied together. Nevertheless, this approach provides a way of evaluating whether a predicted

evolutionary pathway could have proceeded without introducing traits that are disadvantageous to a functioning nervous system. The myelin sheath reduces the capacitance of the axon in several ways: in the multi-layered membrane coating investing the internodes, in the small size of the regions of exposed axolemma, reduced in some organisms to “focal” nodes and in the wide separation between the exposed nodal regions. Hence increasing the number of membrane layers in the sheath, elongating the internodal segments covered by the sheath and reducing the area of the exposed nodes all have the effect of speeding the charging of the membrane, resulting in increased conduction velocity.

7.1 Capacitance reduction through sealing glial shunts

Unmyelinated axons come nevertheless with a membranous glial sheath. This sheath fails to have much effect on conduction velocity because the 20 nm periaxonal gap in combination with the mesaxon gives ion current flowing between axon and surrounding glial layer ready access to the external conducting spaces. Both calculations and measurements suggest this ensheathment presents little impediment to escaping current (Binstock et al., 1975; Frankenheuser and Hodgkin, 1956; Kuffler, 1967). If the innermost glial cell were to completely seal the axon off from access to the external conducting spaces, the external longitudinal resistance, being then determined solely by the limited periaxonal space, would rise and impulse conduction would slow (e.g. Young et al., 2013b). If, however, gaps are left in the glial sealing (“protonodes”), at some point saltatory conduction commences and even with just one or two unit membranes of capacitance-reduction, conduction speeds (Castelfranco and Hartline, 2015). Relocation of ion channels to the protonodes then increases the molecular economy of the axon and the path to further evolution of myelin is open.

7.2 Capacitance reduction through multi-layering

Adding multiple layers of sealed membrane reduces the transverse capacitance and increases the transverse resistance of a sealed region (internode) of a cylindrical fiber in proportion to the number of layers. Simply increasing the thickness of the myelin sheath without constraining the fiber diameter results in an increase in conduction velocity that saturates at large fiber diameters or thick sheaths provided other parameters such as node size and channel density

are kept constant (Figure 9A; Moore et al., 1978; Smith and Koles, 1970). Even very small-diameter axons will experience an increase in conduction velocity if myelin is added with no other constraints, although the speed-up will saturate with fewer layers than for larger axonal cores. If instead fiber diameter is fixed, as for example with a constraint on available space (e.g. an enclosed and heavy cranium: Zalc and Colman, 2000), there is a thickness that maximizes conduction velocity (Goldman and Albus, 1968; Rushton, 1951). This observation has led to the concept of an optimal ratio of axon core diameter to overall fiber diameter (including the sheath), termed the g-ratio. The optimal g-ratio of 0.6 predicted by Rushton agreed with physiological observations primarily taken from the vertebrate peripheral nervous system (Gasser and Grundfest, 1939; Waxman and Bennett, 1972). If the impact of increasing fiber diameter on the volume of the nervous system is included as an explicit constraint in the optimization, the optimal g-ratio is shifted toward larger values (i.e. thinner sheaths) the greater the cost of increasing nervous system size. This provides a possible explanation of the difference between the g-ratios observed in the vertebrate peripheral and central nervous systems (Chomiak and Hu, 2009). The g-ratio of 0.6 – 0.7 cannot be maintained for fibers less than the *ca.* 0.06 μm diameter set by the thickness of a single myelin lamella (~ 12 nm in vertebrates, Raine, 1984; ~ 9 nm in penaeid shrimp, Xu and Terakawa, 1999; ~ 18 nm in copepods, Weatherby et al., 2000), which likely contributes to the observed lower limit on myelinated fiber diameter. Below this, a layer of myelin rapidly loses its speed-enhancing advantage. If one allows the possibility that active channel densities co-evolved with the addition of multiple layers of myelin, then the analysis based on Huxley's (1959) relation (*viz* §5.1) predicts that if active conductance densities decrease in proportion to the decrease in capacitance, the conduction velocity will continue to increase until further myelin expansion is blocked by other physiological constraints (see Figure 9B; Castelfranco and Hartline, 2015). The resistance of a layer of myelin also in principle affects the conduction velocity, although variation in myelin resistance between brain regions may have a relatively small effect on it (Bakiri et al., 2011).

7.3 Capacitance reduction by restriction of node size

Reducing the area of the axolemma exposed at the node is another mechanism for decreasing overall trans-fiber capacitance and hence one that likely impacts the evolution of

conduction velocity. In general, it results in an increase in conduction velocity as long as the conductance density required to generate an impulse isn't compromised (Castelfranco and Hartline, 2015; Moore et al., 1978; Young et al., 2013b). In a fully-myelinated fiber, a significant proportion of the conduction-slowing trans-fiber capacitance is localized at the node, relative to that of the internode. Thus, for equal specific capacitances of a unit membrane for myelin and axolemma, nodal and internodal capacitances will be equal for internodes that are n_m times the length of the flanking nodes, where n_m is the number of myelin unit membranes in the sheath (i.e. twice the number of lamellae). For example, a node 1 μm long has approximately the same capacitance as an internode of 0.1 mm with 50 myelin lamellae, which would correspond to a 30% lower conduction velocity than with an infinitesimally small node (Castelfranco and Hartline, 2015), and 10% the capacitance of a more standard 1 mm-long internode (6% lower velocity). Thus decreasing the size of an already small node can have a significant effect on conduction velocity, which effect may be presumed to approach optimal in the evolution of different species. For vertebrates, these nodes have further reduced capacitance by decreasing the diameter of the axon core passing through the node and hence the exposed surface area (Robertson, 1959; Rydmark, 1981). In contrast, however, an expansion of surface area at nodes has been reported in caridean shrimp by Heuser and Doggenweiler (1966; confirmed in unpublished studies by one of us [Orcine and Hartline]), which should slow the conduction owing to the increased capacitance. The expansion may have other benefits such as allowing a higher channel density at nodes.

Modeling studies have confirmed the basics of small size enhancing conduction speed. Moore et al. (1978) found that the increase in conduction velocity due to a 50% reduction in the nodal specific capacitance was almost canceled out by a similar reduction in the nodal specific maximum conductances. Hence, reducing the nodal area, which results in changes in both the nodal capacitance and conductance, had only a small effect on conduction velocity in their model. However, if channel densities averaged over the whole fiber were to remain constant then as nodal area was reduced conduction velocity would increase even with only one myelin layer (Castelfranco and Hartline, 2015). Halter and Clark (1993) found that conduction velocity was quite sensitive to nodal area in their model of a mammalian myelinated nerve fiber. In

particular, for a range of fiber diameters, conduction velocity increased when the diameter of the axon core was constricted along the node and paranode while keeping the nodal length and specific permeabilities of the ionic channels fixed. This trend didn't begin to reverse due to the associated increase in longitudinal axonal resistance until the radius was reduced to one sixth of the internodal radius. The nodal and paranodal radii that gave peak conduction velocities agreed well with measurements of cat myelinated fibers (Rydmark, 1981).

7.4 Capacitance reduction by extension of internode length

The relationship between internode length and conduction velocity is more complex, and depends on the other assumptions being made in the model (or on the details of the situation being studied). If the node size is assumed to be fixed, Rushton (1951) found that for the class of fibers satisfying the condition that dimensions scale in proportion to internode length, there is an optimal ratio of internode length to fiber diameter (~ 100), which agreed with observations from physiological studies on mammalian nerves and modeling studies (Basser, 2004; Goldman and Albus, 1968; Hursh, 1939). Even myelinated fibers of *Penaeus* shrimp have been observed to conform to this optimal ratio, the internode length being in the range from 70-100 times the fiber diameter (Hsu and Terakawa, 1996). Huxley and Stämpfli (1949) argued that near the maximum the dependence of conduction velocity on internode length might be nearly flat, with even relatively large reductions in internode length having but a small effect on conduction velocity. Brill et al. (1977) examined the effect of internode length on conduction velocity for a wide range of ratios of internode length to fiber diameter. By varying the internode length while holding all other parameters, including diameter, fixed, they found that conduction velocity increased rapidly with increasing internode length for short internodes, reached a broad maximum for intermediate lengths and finally slowed with conduction failing for very long lengths. The optimal internode length (i.e. the length that corresponds to the maximum conduction velocity) was found to depend on the thickness of the myelin sheath with the optimal length shifting to larger internodes as the thickness increased (and capacitance dropped) (Castelfranco and Hartline, 2015). Another condition that affects the theoretical results is whether the models describe the myelin sheath as distinct from the axolemma, including current flow in the submyelin space as in "double cable" models (Blight, 1985; Halter and Clark, 1991;

Hines and Shrager, 1991; McIntyre et al., 2002). Overall these detailed models show a relationship between conduction velocity and internode length similar to that described by Brill et al. (1977), but the predictions of the effect on conduction velocity of a specific change in internode length can differ (Lasiene et al., 2008; Young et al., 2013a; Young et al., 2013b). In particular, the optimal internode length depends on the amount of sealing around the margins of the myelin sheath at the nodes, with the peak conduction velocity occurring at shorter internodes the tighter the seal as shown in Figure 10. The shift to longer optimal internode lengths as the access resistance at the paranode is decreased reflects the compensatory effect of increasing longitudinal resistance by lengthening the path of the submyelin current from the node to the internode. This shift corresponds to a change in the shape of the conduction velocity versus internode length curve with the peak becoming broader and flatter as the seals are reduced. Hence, depending on the tightness of the sheath a given change in the internode length might result in an increase or a decrease or little change in conduction velocity (see Figure 10; Lasiene et al., 2008; Young et al., 2013a). Allowing other parameters such as node size to co-vary along with the internode length can also modify the effect on conduction velocity, e.g. if the node increases in proportion to the increase in the internode then there is no optimal internode length and the velocity declines with increasing internode length from an elevated initial velocity (Castelfranco and Hartline, 2015).

While it is difficult in experimental preparations to separate the individual effects on conduction velocity of these capacitance reducing changes, there have been several studies that have succeeded in varying one property of the myelin sheath without changing others. The basic relationship between conduction velocity and internode length described by Brill et al. (1977) has been supported by physiological studies that have varied internode length without significant changes in axon diameter and myelin thickness. Mice expressing mutant forms of periaxin, a protein required for Schwann cell elongation, have shortened internodes with normal axon diameters and g-ratios. At three weeks, the average internode length in quadriceps nerve fibers in the mutants was 250µm compared with ~450 µm in the wild type and the conduction velocity was reduced by more than 50% (Court et al., 2004; Wu et al., 2012). As the nerves and internodes lengthened this effect was reduced in mutants having a less severe phenotype, at 16

weeks the internode length was still significantly shorter than in the wild type (479 μm compared with the wild type average length of $\sim 700 \mu\text{m}$) but there was no significant difference in conduction velocity (Wu et al., 2012). In a study of limb lengthening in rabbits the internode length was increased $\sim 35\%$ above normal but there was no significant difference in conduction velocity, although the velocity was slightly reduced in the lengthened limbs ($36.0 \pm 1.6 \text{ m s}^{-1}$ compared with $39.2 \pm 2.2 \text{ m s}^{-1}$ in the controls) (Simpson et al., 2013). Court et al. (2004) verified that the dependence of conduction velocity on internode length that they had observed was consistent with theoretical predictions by simulating a model, based on that of McIntyre et al. (2002), with geometric parameters taken from their experimental measurements (Court et al., 2004; supplementary Fig. 3). In addition to showing the steep dependence of conduction velocity on internode lengths in their experimental range (250 μm to 500 μm), they found that there was only a small change in velocity (1 m s^{-1} or $\sim 4\%$) for internode lengths between 750 μm and 1500 μm . Hence, these physiological studies confirm the theoretical prediction that if the normal internode length is close to the optimal internode length then there is a broad range of internode lengths (both shorter and longer than normal) for which the conduction velocity is nearly normal (see Figure 10, e.g. curves corresponding to $\delta_p = 1 \text{ nm}$ or 0.1 nm). Neuregulin-1(Nrg1) regulates sheath thickness, Michailov et al. (2004) found that mutant mice with reduced Nrg1 had significantly thinner myelin (and larger g-ratios) in sciatic nerve axons with no significant change in internode length nor axon size distribution, but the conduction velocity of the tail nerve was reduced from $34 \pm 0.65 \text{ m s}^{-1}$ in the wild type to $26 \pm 1.34 \text{ m s}^{-1}$ in the mutant. This supports the model predictions that thinner myelin sheaths result in decreased conduction velocity (Moore et al., 1978; Smith and Koles, 1970).

7.5 Sheath integrity and sealing capacitance shunting currents

The addition of an insulating myelin sheath, with just mesaxonal seals, is sufficient to increase nerve conduction velocity without the evolution of specialized paranodal structures to restrict the shunting of nodal currents under the myelin sheath and between the myelin lamellae (Castelfranco and Hartline, 2015; Hartline, 2008; Young et al., 2013b). However, with the exception of copepod myelinated fibers in which the stack of myelin lamellae is condensed against the axolemma providing no access to the extracellular medium (Wilson and Hartline,

2011b), such specialized structures are required to fully exploit the speed enhancing properties the sheath (see Figure 10, increased seals are represented by smaller δ_p values). In vertebrates, palaemonid and penaeid shrimp, the terminal loops of the myelin layers at the paranodes are attached to the axon by septate junctions, which contribute to the sealing function (Heuser and Doggenweiler, 1966; Hsu and Terakawa 1996; Rosenbluth, 1984). Although the vertebrate paranodal junction serves to electrically isolate the node, the seal is far from tight, instead there is a narrow pathway along the transverse bands that runs the length of the paranode and allows slow diffusion of metabolites. This pathway is so narrow and the junction is so long that the resistance is sufficiently high relative to the extracellular current path to block most of the shunt current (Rosenbuth, 2009). The importance of blocking these shunt currents for rapid conduction velocity has been confirmed in modeling studies that use a double cable model to include the submyelin space along the internode (Castelfranco and Hartline, 2015; Halter and Clark, 1993; Hines and Shrager, 1991; Stephenova and Dashkolova, 2005). The thicker the myelin sheath, the more critical the sealing around the nodes is for conduction velocity. For thin sheaths consisting of a few myelin layers (<10 lamellae for a 10 μm diameter axon), the addition of seals at the paranode had little effect on conduction velocity (Castelfranco and Hartline, 2015). This implies that for fully developed myelin sheaths conduction velocity is quite sensitive to the disruption of the paranodal seals due to disease or injury. It also suggests that paranodal seals might have been relatively late in evolving, as the myelin itself became optimized. Another source of disruption of the myelin sheath is shunting between the myelin lamellae. Devaux and Gow (2008) found the tight junctions between myelin layers of the optic nerve were absent in *Claudin 11*-null mutant mice. Although the mutants had normal myelin sheaths in terms of g-ratio and internode length, the conduction velocity for small axons ($\sim 0.7 \mu\text{m}$ in diameter) was reduced by more than 50% while that of large diameter axons ($\sim 2.1 \mu\text{m}$) was normal. The effect on the conduction velocity of small diameter axons was confirmed by simulations of a model that included the tight junctions as a resistance in series with the axolemmal and myelin cables in a double cable model (Devaux and Gow, 2008; Gow and Devaux, 2008). This illustrates the principle that the conduction velocity of fibers with small axon core diameter is more susceptible to disruptions in the integrity of the myelin sheath and the shunting of currents between the sheath and the axolemma or through the sheath than those with

large core diameters. It supports the speculation arising from other studies (e.g. Young et al., 2013b) that myelination might have evolved first in larger axons when its parameters were first being adjusted by evolution and then extended to smaller axons as the effectiveness of the sheath was improved.

7.6 Channel density and kinetics

Ionic channel densities must have co-evolved with the elongation of the myelin sheath resulting in enriched sodium channel densities in the nodes and decreased densities in the internodes with an overall reduction in the mean number of sodium channels per length of axon compared with an unmyelinated axon (Hartline, 2008; Vabnick and Shrager, 1998). In particular, increasing the ionic channel densities doesn't necessarily result in increased conduction velocity, as might be inferred from the Huxley relation described in §5.1. By adjusting densities to maintain the Huxley parameter, β , fixed at 6.5, we showed for a simple model of myelination that channel densities should decrease along with increases in sheath thickness in order to maintain maximal conduction velocity (Figure 9B; Castelfranco and Hartline, 2015). This predicts that myelination should result in decreased overall channel densities – increased densities in the nodes but decreased total densities in the axon - and reduced metabolic costs of impulse conduction. Another prediction of this analysis is that sodium channel kinetics might co-evolve with myelination, since as myelination proceeds, the charging of distant membrane becomes more rapid and hence activation kinetics could become the limiting factor for conduction velocity. For example, figure 9A shows that increasing activation kinetics 3-fold, e.g. from $k_0 = 1$ to $k_0 = 3$, results in a greater relative increase in conduction velocity for thicker sheaths (e.g 100 vs 10 unit myelin membranes). Indeed activation of penaeid channels, which underlie action potentials that propagate even faster than those in vertebrates, is even faster than vertebrate channels at the same temperature (130 vs 150-180 μ s; Terakawa and Hsu, 1991). Thus, myelination could provide selective pressure for the evolution of fast-activating sodium channels.

8. Evolution of myelin

Putting all of this together, what might the likely scenario be for the evolutionary sequence leading to rapid conduction in ultimately myelinate organisms? One key constraint, as mentioned in the introduction (§1.1), is the need to retain a functioning nervous system. How can this be assured? Several lines of reasoning point to the initiation of myelin evolution occurring in larger diameter axons: larger axons are less affected by imperfections in a newly-evolving sheath since the access and shunting produced by an electrolyte-filled periaxonal shell of a given gap size are proportionately less the larger the axon. Further, in simulations in which a pre-formed sheath was tightened around an unmyelinated axon as a way of progressively increasing insulation, conduction velocity slowed a bit before speeding up with the onset of saltatory conduction. This slowdown would present a barrier to this route for myelin evolution. However the slowdown, and hence the barrier, was minimal for larger axons (Young et al., 2013b). The occurrence of giant axons in pre-myelin ancestors is likely in any event, since the selective forces promoting myelin evolution will presumably have already caused the evolution of giant axons. Availability of such giant axons would then provide the opportunity for myelin to evolve under more permissive conditions. In fact as mentioned, in some organisms, such as earthworms, only the giant axons are myelinated (Günther, 1976; Hama, 1959). An additional possibility, for how the process might avert a slow-down altogether, might be termed a "nodes first" hypothesis: myelin sheaths might first arise as small patches of myelin membrane closely apposed to the axolemma, either externally from the attachment of a glial process (as at modern-day nodes in most taxa) or by the tight apposition of an internal cisternal membrane (as in copepods: Wilson and Hartline, 2011b). For glial myelin, a "mesaxonal seal first" hypothesis is an alternative possibility in which sheaths would form by sealing (e.g. condensing) mesaxons over short longitudinal segments, the diverted external current being carried in a compensatory expansion of extracellular pathways around the submyelin space "isolated" thereby. In either case, Huxley's relation (Eqn. 1) predicts a resulting speed gain since the increase due to capacitance reduction will be greater than the loss from conductance decreases, for parameters centered around squid axon values (Figure 5). Furthermore, channel loss to patch isolation could be easily compensated in immediately-adjacent membrane. Once such an isolated patch forms a

ring around an axon, conduction becomes technically saltatory. Strong selective pressure would then act to elongate or add layers to the myelin of the initial ensheathed patch. It is possible that lengthening and thickening of the sheath would occur in close succession, since both result in large increases in conduction velocity initially (Figures 9A and 10). As a thicker sheath evolves the need for developing specialized seals at the margins of the nodes would become more pressing. Ultimately the node spacing, sheath thickness and blocking of shunt currents would co-evolve to produce a myelin sheath that supports conduction at nearly maximal velocity. Not surprisingly these steps are consistent with the process of myelin development in many organisms (Carpenter and Bergland, 1957; Simons and Lyons, 2013; Snaidero et al., 2013; Vabnick and Shrager, 1998; Wilson and Hartline, 2011a; Xu et al., 1994.) The development of myelinated fibers in the rat sciatic nerve provides one example of the dramatic increase in conduction velocity that occurs with myelination (Figure 11). At birth the fibers of the rat sciatic nerve are unmyelinated and impulses propagate slowly by continuous conduction (e.g. the fastest component of the compound action potential propagates at $\sim 0.66 \text{ m s}^{-1}$ at room temperature; Vabnick and Shrager, 1998). During the first three postnatal weeks, conduction speed increases rapidly and propagation transitions from continuous to saltatory. Over the course of development, mammalian myelinated fibers undergo a 10-fold increase in diameter, a 6 to 8-fold increase in internodal length, and conduction velocity increases 10- to 100-fold (Vabnick and Shrager, 1998).

9. CONCLUSIONS

We have outlined several observations on the factors needed to achieve a maximal speed of impulse conduction in nerve based in part on comparisons with invertebrate or non-neuronal conduction systems. These provide a useful set of hypotheses relevant to the constraints on evolutionary trajectories leading to increased conduction speed: 1) Rapid conduction must be based on voltage-dependent mechanisms. Sound and light, while widely used in inter-organismal communication seems not to be used intraorganismally, and we might ask "why not?" Pressure is used in some plants (Stahlberg et al., 2005), but apparently not animals, perhaps because of lack of rigid cell walls. This illustrates the point raised earlier (§1.3) that once started along a

path, the evolution of conduction speed is constrained by past history. 2) The voltage-based mechanisms open aqueous-core ion channels in the membrane. 3) This leads to voltage-regulated facilitated diffusion of ions down concentration gradients. 4) The voltage-sensing mechanism must be intrinsic to the "voltage-gated" channel to achieve the most rapid activation. 5) Such activation leads to regenerative feedback producing "all-or-none" impulses. 6) This endows the process with threshold characteristics and post-impulse refractoriness. 7) The most rapid conduction is realized in an electrical "core-conductor" system with a single elongate "cable" (usually an "axon"; *cf* penaeids), but a system of tubular elements connected by low-resistance junctions, as in giant axons of lobsters and earthworms and phloem cells of plants, can provide an acceptable alternative. 8) The core conductor is ideally cylindrical and unbranched. The velocity of impulses along the cylinder is maximized by: 9) adjusting the activation rate of the regenerative voltage-gated channels in the membranes; 10) optimizing channel density and distribution (e.g. increasing internodal transfiber resistance and tuning nodal conductance magnitudes); 11) increasing the EMF of the ionic battery driving the current; 12) reducing the capacitance of the fiber walls (increasing myelin thickness and decreasing nodal area); 13) optimizing the distribution of the capacitance reduction along the core conductor (node/internode geometry for node-possessing myelin); and 14) decreasing the resistance of the medium inside and outside the core-conductor (e.g. enlarging diameter). All of these factors are susceptible to selective pressure, and their effects interact with each other and with other adaptive requirements and physical/chemical constraints (space availability; energetic costs) so that optimization involves simultaneous (within evolutionary timescales) tuning of many factors. Changes in these parameters as an organism develops may provide a useful model for the evolutionary pathway they followed. No clear intrinsic reason is evident for why a rapid signal-conducting system needs to be sodium-based, and yet the most rapid systems -- myelinated axons in both vertebrates and invertebrates -- are so based despite the wide evolutionary divergence among myelinate taxa and the presence of alternative signaling mechanisms in other parts of their nervous systems.

Further, as we have noted before (Hartline, 2008), some of the more prominent features of vertebrate myelin are *not* crucial to the speed-enhancing properties of myelin. In particular: 1) compaction of layers contributes primarily to space conservation, but to speed only weakly, as

each successive layer of the thickening sheath, being of slightly larger surface area, makes a slightly smaller per-layer contribution to capacitance reduction. Compaction reduces trans-fiber shunts via the mesaxon and/or cytoplasmic paths in spiral myelin with few layers, but this contribution decreases with increasing numbers of layers as the mesaxon lengthens. 2) Spiral forms, characteristic of vertebrate myelin, are also of little (or more likely negative) value to speed. 3) Glial origins from which myelin arises in three of the four independently-evolved cases is similarly not essential to speed. Indeed, the internal generation of myelin by copepods may be viewed as a superior design, as it produces neither shunt-prone mesaxons at contacting cell margins, nor a conductive space between the axolemma and the first myelin layer, which is the interlaminar space that is most detrimental to rapid conduction in glial myelin. 4) Nodes, which provide periodic impulse-regeneration access spots (which need not be circumferential) along an otherwise insulated fiber, are not the only solution to the access problem. Once again, this is demonstrated by copepods. Their "partial myelin" (Wilson and Hartline 2011a) covers a fiber with thick capacitance-reducing insulation but incompletely so. 5) Finally, as penaeid shrimp show, there are viable alternatives to axoplasm-filled axons as core conductors for impulses. These cases show that axons, nodes and saltatory conduction are not the only evolutionary pathway to rapid conduction.

On the other hand, the linear relationship between fiber diameter and conduction speed that ultimately governs all compact myelin turns the allometric ($1/2$ -power) relation to size into an isometric relationship, freeing it from limits imposed by allometry. In this way, myelin has contributed to moderating the diminishing returns of increasing organismal size. These originally appeared as organismal size increased from that of a bacterium, in which the constraints diffusion placed on speed had to be broken by the invention of electrical signaling. Then in turn the constraints electrotonic decrement placed on long-distance electrotonic conduction had to be broken by the invention of propagating all-or-none action potentials. Action potentials in unmyelinated cylinders were still impeded by the allometric dependence of conduction speed on the square root of diameter, but this limitation was finally surmounted by the invention of myelin with its linear dependence. In addition, serendipitously or some would argue seminally (Stiefel et al., 2013), myelination gave options for reduced energetic costs,

enabling evolution of compact nervous systems with complex high-speed energy-cost-effective computational capabilities (Wang et al., 2008). The limits myelin places on organism size may be few (e.g. whales and dinosaurs) -- perhaps nutritional. Thus we hope this review has indicated how a comparison of the different structural and molecular solutions to tuning for high-speed conduction by different taxa illuminates the underlying principles driving the adaptations observed in its evolution. While most current attention is focused on vertebrate myelin, it should be clear that vertebrates exhibit only one version of this solution to the speed problem. Indeed the speed record for impulse conduction is not held by a vertebrate. Understanding the designs used for the different versions contributes significantly to appreciating the vertebrate one and leads to a better understanding of the ways it could have evolved and may be affected by injury and disease.

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FIGURE CAPTIONS

Figure 1. Homologous nerves in amyelinate and myelinate copepods. Transmission electron micrographs of cross sections through the antennular nerve of (A) adult amyelinate *Gaussia princeps*; note the numerous mitochondria (*cf* (B)), indicative of the greater metabolic cost of activity in non-myelinated axons; (B) adult myelinate *Undinula vulgaris* (motor branch). Virtually every axon in *U. vulgaris* is myelinated to some extent, the sheath being thicker in larger axons. Mitochondria are scarce. Scale bar: 5 μm . From Lenz et al. (2000), with permission pending.

Figure 2. Diversity of action potentials. Representative voltage responses of various excitable tissues from non-bilaterian taxa. (A) Intracellular recording of a response of a *Paramecium* to an abrupt mechanical stimulus (S) to the anterior end. The initial rapid depolarization is the receptor potential, which triggers a regenerative calcium potential (from Eckert et al., 1972, with permission pending). (B) Two examples of exumbrellar epithelial potentials recorded with extracellular suction electrodes from a scyphozoan, *Chelophyes*, following electrical stimulation (S), of which the deflection labeled P1 is the most consistent (from Mackie, 1965, with permission pending). (C) Electrical response of an unspecified plant to electrical stimulus at the apex (top) recorded extracorporally with 4 electrodes spaced along the stem. Note the inter-electrode time delay. Time, amplitude and distance scales not given. From Fromm and Lautner (2007), with permission pending. (D) and (E) Intracellularly-recorded action potentials from giant axons of *Aglantha digitale* during a fast swim (D) and an endogenously-generated slow swim (E). Two recording sites (labeled "A" and "B" on records) spaced respectively 2.5 and 6.9 mm apart. Calculated conduction velocity of the two spike types respectively 1.4 m s^{-1} and 0.3 m s^{-1} . From Mackie and Meech (1985) with permission pending.

Figure 3. Conduction velocity for nerve fibers vs fiber diameter. Lines indicate general relations over a range of diameters, many taken from Bullock and Horridge (1965) but adjusted to a

standard temperature of 20 °C using a Q_{10} of 1.8 (Chapman and Pankhurst, 1967) and an internal and external ionic conductivity of a squid axon (35.4 Ω cm). Thus $v_{\text{plot}} = v_{\text{meas}} \times 1.8^{(20-T)/10} \times \sqrt{(35.4/R_{\text{axoplasm}})}$ where T is the temperature in °C for the measured velocity v_{meas} and R_{axoplasm} is the specific resistance of the axoplasm, if available, or the extracellular medium if otherwise. Specific labeled points or lines from the following sources: Squid: Hartline and Young, 1936 cited in Pumphrey and Young (1938); Earthworm: Eccles, Granit & Young (1932); *Penaeus* and *Macrobrachium*: Kusano (1966). Crayfish: Govind and Lang (1976); Hydromedusa: Mackie and Meech (1985). Reprinted from www.pbrc.hawaii.edu/~danh/InvertebrateMyelin/ with permission (Original from Dan/RES-Myelin/Myelin-theory&modeling/)

Figure 4. Core-conductor circuitry of (A) an unmyelinated fiber and (B) a myelinated fiber. Arrows indicate the current flow for impulses generated in the membrane patch labeled ①. Current of the rapidly-rising voltage upstroke predominantly flows out through capacitances of adjacent membrane ②, which provides accessible paths in unmyelinated fibers (A), but which carry little of the current in myelinated axons because of the lowered capacitance of the internode. The current is instead directed farther down the fiber to charge the capacitance of the next node ③. Reprinted with permission from www.pbrc.hawaii.edu/~danh/InvertebrateMyelin..

Figure 5. Huxley function, $f(\beta)$. (A) Log-log plot of the empirically-derived function normalized to squid axon parameters as a function of the parameter $\beta \equiv \gamma_0 / (k_0 C_0)$ where the subscripts "0" indicate normalization with respect to squid values: γ_0 is the scaling factor for ionic conductances ($g_{\text{barNa}} = 0.12 \text{ S cm}^{-2}$; $g_{\text{barK}} = 0.036 \text{ S cm}^{-2}$ $g_{\text{leak}} = 0.002 \text{ S cm}^{-2}$); k_0 is the scaling factor for conductance rate constants α and β for m, n and h in the HH model relative to their value at 6.3 °C (Hodgkin and Huxley, 1952) and C_0 is the specific capacitance of the axolemma relative to 1 $\mu\text{F cm}^{-2}$ for squid. Symbols are points for particular model runs of a uniform cable having HH channels and electrical constants normalized with respect to those in the HH squid model. Dotted line is a best-fit parabola through the points having the equation $\log f(\beta) = 0.015673 + 0.14659 \log(\beta) - 0.11828 \log^2(\beta)$ and from which the curves in (B) were computed. (B) The Huxley development predicts a conduction velocity, v_0 , relative the that of the squid axon (12.3

m s^{-1}) given by $v_0 = \alpha^{1/2} f(\beta)$, where $\alpha \equiv k_0 d_0 / (R_0 C_0)$, d_0 is the axon diameter relative to that of the HH squid unmyelinated axon ($476 \mu\text{m}$) and R_0 is the specific conductance of axoplasm relative to the squid value ($35.4 \Omega \text{cm}$). The panel shows log-log plots of normalized velocity, v_0 , as the normalized parameters k_0 (coarse broken line), γ_0 (solid line) and C_0 (dotted line) are varied from their standard value of 1.0 (abscissa). Decreasing C_0 or increasing k_0 from this value increases conduction velocity, but sensitivity is greater for C_0 at this starting level. Effects of decreasing C_0 plateau out at $\sim 8\times$ squid values while increasing k_0 plateaus at $< 2\times$ without altering other parameters (indeed conduction fails at the right edge of the graph). Increasing γ_0 above 1.0 increases conduction velocity of axons but this reaches a maximum with v_0 16% above the normal squid value. Sensitivity to k_0 is even less for initial $\beta < 1$ (fine-broken line labeled $\beta_{\text{init}} = 0.1$). Reprinted with permission. from www.pbrc.hawaii.edu/~danh/InvertebrateMyelin

Figure 6. Giant fiber from the ventral nerve cord of a carnivorous caterpillar, *Eupithecia orichloris*. The caterpillar, a member of the geometrid family (inch worms), when contacted on posteriorly-located hairs by a small insect, launches a rapid attack with the anteriorly-located grasping appendages, possibly mediated by this fiber. Scale bar: $2 \mu\text{m}$. Image by J. Kong, reproduced from www.podbases.net with permission. All rights retained by the author.

Figure 7. Current flow from nerve impulses. Comparison of that in an unmyelinated fiber (A) with those in several different forms of myelinated fibers (B - D). (A) In unmyelinated axons, inward current enters at an active zone through voltage-gated sodium channels (shaded). The resulting depolarization spreads electrotonically to immediately adjacent non-active membrane, which it raises to threshold to initiate a regenerative impulse, which spreads in turn to the next patch of membrane. The impulse thereby propagates along the axon as a wave of constant temporal and spatial shape. (B) In a vertebrate or a palaemonid shrimp, the voltage-gated sodium channels of myelinated axons are located in annular nodes that occur at intervals along each fiber. Current entering at a node charges adjacent membrane more rapidly than in an unmyelinated fiber owing to the capacitance-reducing insulation of the internode provided by the sheath. Charging of the capacitance of the next node along the chain is also rapid owing to its

reduced capacitance, leading to a much higher conduction speed (see Figure 4). (C) In oligochaetes and copepods, a myelinated fiber possesses small openings in the sheath that form 'focal' or 'fenestrated' nodes. Current flow similar to that of (B). (D) In the mature myelin of penaeid shrimp, the axons are much reduced in diameter, but come to lie inside an enlarged submyelin space (stippled). Nodes are also fenestrated, and access an enlargement of the underlying axon that becomes tightly attached to the myelin margins around the node. Current that enters at a node flows out of the axon again through convoluted, surface-increasing axonal membrane (Hsu and Terakawa, 1996) and travels in the low-resistance submyelin space to the vicinity of the next node, where it reenters the axon and activates the node as before. Reprinted from www.pbrc.hawaii.edu/~danh/InvertebrateMyelin/invertebrate_myelin.html with permission.

Figure 8. Myelin phylogeny and diversity. (A) Simplified phylogeny of myelinate (underlined) and closely related amyelinate taxa. The Hyperaortia are lampreys while the Gnathostomata are the remaining vertebrate clades (fish and higher including extinct placoderms but not ostracoderms). The Reptantia are crabs, lobsters, and their kin while the Natantia are shrimp. The order Calanoida of the crustacean subclass Copepoda contains two major divisions of several superfamilies each, the Amyelinata lacking myelin in the nervous system and the Myelinata possessing it. Finally, the Hirudinea are leaches while the Oligochaeta are earthworms and their kin, both grouped under the class Clitellata in the phylum Annelida. (B), (C), (D) transmission electron micrographs of myelin from nerve fibers of, respectively, a caridean shrimp (*Palaemonetes vulgaris*), a dendrobranchiate shrimp (*Litopenaeus vannamei*), and an earthworm (*Lumbricus terrestris*). Micrographs from: (B) Heuser and Doggenweiler (1966), with permission pending; (C) courtesy of M. Orcine and D. Hartline, reproduced from www.podbases.net with permission, all rights retained by the authors. (D) Günther (1976) with permission pending.

Figure 9. Effects of adding multiple myelin membranes predicted by a simplified model (the "UC Model" of Castelfranco and Hartline, 2015) that mimics the primary effect of myelin as an axonal covering with decreased capacitance and increased resistance but evenly distributed

channels and no nodes. (A) Effect of increasing sheath thickness on conduction velocity for active rate constants scaled by multiples of k_0 . Changing the parameter k_0 corresponds to changing the temperature since k_0 can represent the temperature-dependence of HH channel kinetics with a Q_{10} of 3. The value $k_0=1$ corresponds to HH squid channel kinetics at 6.3 °C; $k_0=3$ that at 16.3 °C and $k_0=9$ that at 26.3 °C. The conductance densities are kept fixed at squid densities ($\gamma_0=1$) allowing β to vary. (B) Effects of reducing trans-fiber capacitance (thickening the sheath) on optimized velocity. Log-log plot of normalized conduction velocity (v_0 : solid line; left ordinate axis) and conductance adjustment that keeps β fixed at the optimum value of 6.5 (γ_0 : broken line; right ordinate; see Figure 5) against the total number of unit membrane layers (axolemma plus myelin) in the fiber, computed from $f(\beta)$ as given in Figure 5. Velocity increases indefinitely with the square root of the number of membranes in this simplified model. Modified from Castelfranco and Hartline (2015).

Figure 10. Effect of sealing the margins of the myelin sheath (paranodes) on the relationship between conduction velocity and the spacing between the nodes. The amount of sealing in the 1 μm compartments flanking the nodes is indicated by δ_p with smaller values of δ_p corresponding to tighter seals (for details see Castelfranco and Hartline, 2015). The bottom curve ($\delta_p = 10$, broken line with filled circles) has no additional sealing beyond the close apposition of the sheath along the internode. The top curve (solid line, filled triangles) with $10^{10} \text{ M}\Omega \text{ cm}^{-1}$ seals adjacent to the nodes approaches the behavior of a model with lumped axolemma and myelin sheath at the internodes and no submyelin shunt currents. The simulated fiber had a 10 μm diameter axon core, 0.5 μm nodes, 1.0 μm paranodes, 100 myelin lamellae (g-ratio = 0.73) and HH sodium and potassium conductances at the nodes. As the node spacing increased, the internode length increased and the channel density was adjusted to keep the Huxley parameter β fixed at 2.0. The simulations were run at 6.3°C using NEURON (Hines and Carnevale, 1997).

Figure 11. Increase in conduction velocity with myelination in a developing mammalian nerve. Conduction velocity measured by suction electrode recording from representative single fibers of the rat sciatic nerve 37 °C (filled squares); curve is a sigmoidal fit to the data. Letters indicate

stages in myelin development: “A” - fiber is unmyelinated at birth, continuous conduction of impulses; “B” - initiation of myelination, clusters of Na^+ channels appear at borders of Schwann cells, node formation begins, “C” - formation of paranode; K^+ channel clusters localize with paranode, expansion of myelin; “D” - saltatory conduction occurs in larger fibers; K^+ channels cluster in juxtaparanode; “E” - sealing of axoglial junction at paranode and “F” - mature myelin (Vabnick and Shrager, 1998; Vabnick et al., 1999). The movement of delayed rectifier K^+ channels out of the node and into the juxtaparanode during development is a mammalian adaptation that has not been reported in other taxa. Modified from Vabnick and Shrager (1998) with permission pending.

TABLE I - Conduction speeds in selected systems

Speeds of signal conduction (m s^{-1} ; Column 2) from published sources (last column) or calculated from data therein. Column 5 (Size) gives the characteristic dimension in μm unless otherwise indicated: diameter of cylindrical structures (nerve fibers; *Nitella*); communication distance for other measures. Abbreviations: lat.: lateral; myel.: myelinated; unmyel.: unmyelinated.

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

Figure 6

Figure 7

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Figure 8

Figure 9

Figure 10

Figure 11

TABLE I - Conduction speeds in selected systems

Organism	Speed (m s ⁻¹)	Propagation modality	System	Size (μm)	Reference
Rat	15-22×10 ⁻⁶	Chemical (ATP) diffusion	hippocampal astrocytes - Ca ²⁺	150	Cornell-Bell, 1990 Charles, 1998
Caracean algae	0.0001	Transport: cyclosis	cytoskeletal (actomyosin)	3-10 cm	Verchot-Lubicz & Goldstein, 2010
Sponge	0.0027	trabecular reticulum Ca ²⁺ spike	aggregated		Leys et al., 1999
Poplar tree	0.004-0.008	Ca ²⁺ /Cl ⁻ spike	phloem		Fromm & Lautner, 2007
Caracean algae	0.01 - 0.4	Ca ²⁺ /Cl ⁻ spike	nodal cell	3-10 cm	Wayne, 1994
Venus fly trap	0.02	Ca ²⁺ /Cl ⁻ spike			Hodick & Sievers 1989
<i>Mimosa</i>	0.02-0.03	Ca ²⁺ /Cl ⁻ spike	phloem		Fromm & Lautner, 2007
Metazoans	0.02-0.04	Acetylcholine	synaptic cleft	0.02-0.04	
Human	~0.03	Transport: hormones	blood vessel		Milnor, 1968ab
Medusozoan (Cnidarian)	0.15-0.5	Electrical synapse	epithelial		Mackie & Passano, 1968 Mackie, 1965
Human heart	0.05 0.5 2 4	Electrical synapse	AV node Atrial Bundle of His Purkinje fiber		Klabunde, 2008
Hydrozoan (Cnidarian)	0.3 1.4	Ca ²⁺ spike Na ⁺ spike	unmyelinated giant	40	Mackie & Meech, 1985
Frog	1 - 2	Na ⁺ spike	unmyel. C-fibers	0.5 - 2.0	Ochs, 1965
Lamprey	2 - 3	Na ⁺ spike	unmyel. Mauthner	20 - 40	Rovainen, 1967
Frog	10-20	Saltatory Na ⁺ spike	myel. B fibers	3	Ochs, 1965
Lobster	10	Na ⁺ spike	unmyel. lat. giant	100	Govind & Lang, 1976
Squid	20	Na ⁺ spike	unmyelinated giant	500	Pumphrey & Young, 1938
Earthworm	80	Saltatory Na ⁺ spike	myel. medial giant	70	Günther, 1976
Zebrafish	45±9.6	Saltatory Na ⁺ spike	myelinated		Hatta & Korn, 1998
Goldfish	100		Mauthner cell	<100	
Frog	15 - 90	Saltatory Na ⁺ spike	myel. A fibers	2.5 - 16	Ochs, 1965
Penaeid shrimp	>200	Saltatory Na ⁺ spike	myel. lateral giant	120	Kusano, 1966

Speeds of signal conduction (m s⁻¹; Column 2) from published sources (last column) or calculated from data therein. Column 5 (Size) gives the characteristic dimension in μm unless otherwise indicated: diameter of cylindrical structures (nerve fibers; *Nitella*); communication distance for other measures. Abbreviations: lat.: lateral; myel.: myelinated; unmyel.: unmyelinated.