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# REVIEW

# REGULATION OF CONDUCTION TIME ALONG AXONS

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**Abstract—Timely delivery of information is essential for proper functioning of the nervous system. Precise regulation of nerve conduction velocity is needed for correct exertion of motor skills, sensory integration and cognitive functions. In vertebrates, the rapid transmission of signals along nerve fibers is made possible by the myelination of axons and the resulting saltatory conduction in between nodes of Ranvier. Myelin is a specialization of glia cells and is provided by oligodendrocytes in the central nervous system. Myelination not only maximizes conduction velocity, but also provides a means to systematically regulate conduction times in the nervous system. Systematic regulation of conduction velocity along axons, and thus systematic regulation of conduction time in between neural areas, is a common occurrence in the nervous system. To date, little is understood about the mechanism that underlies systematic conduction velocity regulation and conduction time synchrony. Node assembly, internode distance (node spacing) and axon diameter – all parameters determining the speed of signal propagation along axons – are controlled by myelinating glia. Therefore, an interaction between glial cells and neurons has been suggested. This review summarizes examples of neural systems in which conduction velocity is regulated by anatomical variations along axons. While functional implications in these systems are not always clear, recent studies on the auditory system of birds and mammals present examples of conduction velocity regulation in systems with high temporal precision and a defined biological function. Together these findings suggest an active process that shapes the interaction between axons and myelinating glia to control conduction velocity along axons. Future studies involving these systems may provide further insight into how specific conduction times in the brain are established and maintained in development.**

**Throughout the text, conduction velocity is used for the speed of signal propagation, i.e. the speed at which an action potential travels. Conduction time refers to the time it takes for a specific signal to travel from its origin to its target, i.e. neuronal cell body to axonal terminal.**

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**Key words: conduction velocity regulation, neuronal isochronicity, internode distance, auditory system, coincidence detection, neuron–glia interaction.**

Contents



## INTRODUCTION

When signals are conveyed from one neuron to another, temporal accuracy is essential for proper information processing in the nervous system. Exertion of fine motor skills, sensory processing and higher integrative functions require precise regulation of nerve conduction velocity. If the speed of conduction in nerves is altered by illness, impairments of motor, sensory (Compston and Coles, 2002) and possibly cognitive skills follow (Nave, 2010). In the peripheral and central nervous system a specialization of glial cells, the myelin sheath enwrapping of axons, was the last major evolutionary invention for the nervous system of vertebrates (Bullock et al., 1984; Zalc et al., 2008). Myelination of axons, first described in 1854 (Virchow, 1854), increases the speed of conduction significantly by saltatory nerve conduction between nodes of Ranvier (Ranvier, 1871). Qualitative differences of myelination along axons, such as variations in internode distance and myelin sheath thickness, enable systematic regulation of conduction velocity.

Precise temporal signal transmission is of particular importance for the processing of auditory information. One of the important functions of the auditory system is spatial hearing, which enables us to localize sound and

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*Abbreviations:* AIS, axon initial segment; IID, interaural intensity difference; IO, inferior olive; ITD, interaural time difference; LSO, lateral superior olive; MNTB, medial nucleus of the trapezoid body; MSO, medial superior olive; NL, nucleus laminaris; NM, nucleus magnocellularis.

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to extract acoustic information in a noisy environment (sound segregation or ''cocktail party effect'') (Blauert, 1997), a task that fails with aging. The two main acoustic cues used for these tasks are interaural time differences (ITDs) and interaural intensity differences (IIDs). Processing ITDs and IIDs requires binaural inputs that are temporally correlated. Abnormal timing and synchrony in the auditory brainstem have been suggested to contribute to auditory neuropathy (Oertel, 2005; Zeng et al., 2005), a form of hearing impairment with normal cochlear conduction but disordered neural conduction (Starr et al., 1996, 2000). Likewise, patients with demyelinating diseases like MS display loss of hearing acuity and impaired temporal processing in the auditory brainstem (Noffsinger et al., 1972; Levine et al., 1993; Rappaport et al., 1994; Jones et al., 2002). At a cellular level, dysmyelination has been shown to cause increase in spike jitter and failures (Kim et al., 2013). Similarly, temporal and speech processing is diminished in elderly listeners who have normal hearing thresholds (Gordon-Salant and Fitzgibbons, 1993; Anderson et al., 2012).

Systematic timing of signal propagation is a common occurrence in the nervous system and is required for proper neural function. A particularly precise timing of neuronal fibers is displayed by the circuits in the auditory brainstem, detecting time disparities in the microsecond range and providing binaural inputs in temporal register. The auditory brainstem of birds and mammals presents a unique opportunity to study the development and mechanisms of CV regulation. The sound localization circuits in the auditory brainstem have temporally precise axonal projections, and a well-defined function. Future experiments may utilize these systems to study the regulation of conduction time in the nervous system, both during development and at an advanced age. The results will contribute to the understanding and treatment of myelin-related diseases – from hereditary leukodystrophies to multiple sclerosis and the degeneration of myelin with age.

## DETERMINANTS OF CONDUCTION VELOCITY REGULATION

Measurements of conduction velocity in axons attracted attention very early in the history of neuroscience. Empirical (Zotterman, 1937; Hursh, 1939; Gasser and Grundfest, 1939; Hutchinson et al., 1970) and theoretical studies (Rushton, 1951) showed a linear relationship between diameter and conduction velocity in myelinated axons. The myelin sheath is provided by specialized glial cells: the oligodendrocytes in the central nervous system (CNS) and Schwann cells in the peripheral nervous system (PNS). The myelin sheath is interrupted in regular intervals by the nodes of Ranvier, where sodium channels are present in high density, thereby enabling saltatory conduction (Tasaki, 1939), the basis of fast signal propagation along myelinated axons.

Conduction velocity is influenced by myelin sheath thickness and internode distance (i.e. the distance along the axon between the nodes of Ranvier) (Hursh, 1939), and both parameters are linearly related to axon diameter. Conduction velocity increases with increasing internode distance up to 2000 μm (Brill et al., 1977). Another factor influencing the speed of signal propagation is the composition and density of sodium channels at the nodes of Ranvier (Waxman, 1975) as they influence the onset of the action potential generated at the node. Thus, speed of conduction in myelinated axons is dependent on a number of parameters and variation of any of those parameters can regulate signal propagation speed. These parameters and their influence on conduction velocity have been described in a number of reviews (Waxman, 1975, 1980, 1997; Waxman and Swadlow, 1977).

## CONDUCTION VELOCITY VARIATIONS IN AXONS

Evolutionary pressures have lead to a maximization of conduction velocity in some axons. However, optimizing nerve fiber function means more than maximizing conduction velocity: certain neural functions require adjustment of conduction velocity to regulate the relative timing of inputs, which in some cases entails a slowing down or a delay of signal propagation along axons relative to other axonal inputs.

One of the earliest studies on differential conduction velocity described systematic variations in axon diameter of motor axons innervating the mantle of the squid (Pumphrey and Young, 1938). These variations reduced temporal discrepancies as the longer fibers conducted more quickly than the shorter ones. While these differences in diameter do not achieve isochronicity of inputs (the concurrent arrival of inputs at the target), they do ensure nearly simultaneous contraction of the mantle muscles, resulting in a faster reaction time.

Another well-studied example is found in the classical model of the electromotor system in electric fish. In this organ, so-called electrocytes on the body surface provide an electrical discharge used to incapacitate prey. In order to fully deploy its potential, electrocyte discharges need to be synchronized. The electrocytes are connected to a pacemaker nucleus controlling their deployment and due to their location along the body, the axons providing input from the pacemaker nucleus differ in length. Internode distance along those axons is adjusted so that conduction velocity compensates for different axon lengths and simultaneous firing is achieved (Bennett, 1970; Waxman, 1971; see Fig. 1 in Waxman, 1997). In the electric fish Sternarchus, two types of nodes of Ranvier exist: a small, typical type that actively generates spikes, and a larger electrically passive node type that adds capacitance to delay the propagation of action potentials along the axon and modify the waveform of the voltage spike (Waxman et al., 1972). Hence, in addition to the number of nodes of Ranvier along an axon, the structure of nodes can influence conduction velocity.

A particularly elegant example of systematic regulation of conduction velocity in mammals is found in

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