Determinants of Neuronal Conduction Velocity: A Mechanistic and Biophysical Analysis

Introduction

The computational power of the human brain, with its estimated 100 billion neurons, is fundamentally constrained by the speed and fidelity with which its constituent cells transmit electrical signals.[1] Neuronal conduction velocity, the speed at which the fundamental unit of neural information—the action potential—propagates along an axon, is not a fixed parameter. Instead, it is a highly regulated and exquisitely optimized variable, shaped by immense evolutionary pressure to meet the diverse functional demands of the nervous system, from rapid motor reflexes to complex cognitive processing. Understanding the factors that govern this speed is paramount to understanding brain function in both health and disease. This report will provide an exhaustive, mechanistic examination of the determinants influencing the speed and efficiency of action potential propagation.

This analysis will proceed in a structured, hierarchical manner. We will begin by deconstructing the action potential itself, the fundamental electrochemical event that constitutes the neural signal. We will then explore the axon as a biological cable, analyzing the intrinsic biophysical properties, such as resistance and capacitance, that govern the passive flow of electrical current according to cable theory. Subsequently, we will investigate the transformative impact of myelination, a key evolutionary innovation that dramatically enhances conduction speed and metabolic efficiency, and the biophysical trade-offs involved in its optimization. The report will then delve into the profound molecular heterogeneity of the ion channels that orchestrate the action potential, revealing how the expression and strategic localization of specific channel subtypes fine-tune neuronal firing properties. Finally, we will consider system-level modulators like temperature, explore how different neural pathways are specialized for different conduction speeds based on their function, and examine the devastating consequences of conduction failure in

demyelinating diseases, with a focus on the pathophysiology of multiple sclerosis.

Section 1: The Action Potential: The Fundamental Unit of Neural Communication

The action potential is a transient, regenerative electrical impulse that serves as the primary mode of long-distance communication in the nervous system.[2] It is a rapid, all-or-nothing sequence of changes in the voltage across the neuronal membrane, driven by the precisely coordinated opening and closing of voltage-gated ion channels.[3] The generation and propagation of this signal are predicated on the neuron's ability to maintain a delicate electrochemical balance.

1.1 The Electrochemical Landscape: Resting Membrane Potential and Ion Gradients

The capacity for electrical signaling is born from the establishment of a stable electrical potential difference across the neuronal membrane, known as the resting membrane potential. In a typical neuron, this potential is approximately -60 to -70 millivolts (mV), with the inside of the cell being negative relative to the outside.[5] This potential is not a static state but a dynamic equilibrium generated by two primary factors.

First, distinct ion concentration gradients are established and actively maintained by the energy-dependent Na+/K+-ATPase pump. This integral membrane protein utilizes ATP to transport three sodium ions (Na+) out of the cell for every two potassium ions (K+) it transports in.[3] This tireless activity results in a high concentration of

Na+ in the extracellular fluid and a high concentration of K+ in the intracellular fluid (cytosol).[3]

Second, the neuronal membrane at rest exhibits differential permeability to these ions. It is significantly more permeable to K+ than to Na+ due to the presence of constitutively open or "leak" potassium channels.[8] This allows

K+ ions to diffuse out of the cell down their steep concentration gradient, carrying positive charge with them and leaving behind a net negative charge inside the cell.

The movement of any given ion is governed by the interplay of two opposing forces: the chemical force, driving the ion down its concentration gradient, and the electrical force, which is the attraction or repulsion exerted by the membrane potential itself.[3] The specific membrane potential at which these two forces perfectly balance for a single ion species is known as its Nernst equilibrium potential. For a typical neuron, the equilibrium potential for

Na+ (ENa) is approximately +60 mV, while the equilibrium potential for K+ (EK) is approximately -85 mV.[3] Because the resting membrane is most permeable to

K+, the resting membrane potential lies much closer to EK than to ENa.[5] This stored potential energy, embodied in the electrochemical gradients, is the battery that powers the action potential.

1.2 Initiation and Depolarization: The All-or-Nothing Event

An action potential is triggered only when an incoming stimulus, such as neurotransmitter binding at a synapse, depolarizes the membrane from its resting state to a critical threshold voltage, typically around -55 mV at the axon hillock.[3] Any depolarization that fails to reach this threshold is considered sub-threshold and will not elicit a full action potential; the event is "all-or-nothing".[4]

Upon reaching the threshold potential, a population of voltage-gated sodium channels (Nav) undergoes a rapid conformational change and opens.[3] These channels are complex transmembrane proteins. Their structure includes four domains, each containing six alpha-helical segments. The fourth segment (S4) in each domain is rich in positively charged amino acids (lysine or arginine) and acts as the voltage sensor. When the membrane depolarizes, the negative charge inside the cell is reduced, repelling the positive S4 helices. This repulsion forces a conformational change that opens the central pore of the channel.[3]

The opening of Nav channels allows Na+ ions to flood into the cell, driven powerfully by both their strong concentration gradient and the negative electrical potential inside the neuron. This influx of positive charge causes a rapid and explosive further depolarization of the membrane. This, in turn, triggers the opening of even more

nearby Nav channels, creating a regenerative, positive-feedback loop that is the hallmark of the action potential's rising phase.[3] This entire depolarization process is incredibly swift, with the membrane potential soaring from -70 mV to a peak of around +30 to +40 mV in approximately 1 millisecond.[3] The peak of the action potential approaches, but never quite reaches, the sodium equilibrium potential (

ENa) because the membrane retains some permeability to other ions.[5]

1.3 Repolarization and Firing Rate Limitation: The Role of Kv Channels and the Refractory Period

The explosive depolarization phase is self-terminating. Crucially, about 1 millisecond after opening, the very same depolarization that activated the Nav channels also triggers a second, slightly slower process: fast inactivation. An intracellular loop of the channel protein, often called the "inactivation gate," swings into the pore and physically blocks it, halting the influx of Na+ ions.[3] This inactivation is a distinct molecular state from the channel simply being closed (deactivated) and is essential for bringing the depolarization phase to a swift end.

Coincident with the inactivation of Nav channels, a separate class of channels—the "delayed rectifier" voltage-gated potassium channels (Kv)—become fully activated.[3] These channels also sense the depolarization, but their kinetics are inherently slower. The opening of these Kv channels creates a large outward current as

K+ ions rush out of the cell, driven by their electrochemical gradient. This efflux of positive charge rapidly drives the membrane potential back down towards its negative resting state, a process known as repolarization or the "falling phase" of the action potential.[3]

The kinetics of the Kv channels are not only slow to activate but also slow to deactivate. Consequently, many Kv channels remain open even after the membrane potential has returned to its resting level of -70 mV. This continued efflux of K+ causes the membrane to temporarily become even more negative than the resting potential, a phase known as hyperpolarization or the "undershoot".[4] This phase ends as the slow-closing Kv channels finally deactivate, allowing the constant work of the Na+/K+-ATPase pump to restore the precise resting ion concentrations and membrane potential.[3]

This entire sequence of events creates a refractory period during which the neuron's excitability is altered. The **absolute refractory period** occurs during the depolarization and repolarization phases. Because the Nav channels are in their inactivated state, they cannot be reopened by any stimulus, no matter how strong, making it impossible to fire a second action potential.[10] The

relative refractory period occurs during the hyperpolarization phase. Because the membrane is more negative than rest, a stronger-than-normal stimulus is required to reach the threshold for firing another action potential. Together, these refractory mechanisms are critical: they ensure that action potentials are discrete, all-or-nothing events that propagate in only one direction (away from the site of initiation) and they place an upper limit on the frequency at which a neuron can fire.[10]

The speed and efficiency of the action potential are not merely a function of ion flow but are the direct result of a precisely timed kinetic ballet between different ion channel families. The Nav channels are molecularly engineered for speed—fast activation to initiate the signal and fast inactivation to terminate it—creating a brief, powerful depolarizing pulse. In contrast, the Kv channels are designed as "delayed rectifiers" with slower activation and deactivation kinetics. This temporal mismatch is a fundamental design principle. If both channels were equally fast, their opposing ion flows would be inefficiently simultaneous. The observed kinetics, however, represent an optimized solution for creating a brief, self-terminating digital signal. This allows neurons to encode information not in the amplitude of the signal (which is constant) but in its frequency, with some neurons capable of firing up to 1000 times per second.[4]

It is a common misconception that the Na+/K+ pump is responsible for actively repolarizing the membrane after each individual spike. The research clarifies that the pump is far too slow for this role. For any single action potential, the number of ions that cross the membrane is minuscule relative to the total concentrations in the cytosol and extracellular fluid.[5] The repolarization of a single spike is a passive process, driven entirely by the electrochemical gradients flowing through the open Kv channels. The pump's crucial role is one of long-term maintenance, working constantly in the background to preserve the ion gradients over the course of thousands or millions of action potentials, ensuring the "battery" remains charged for future signaling.[3] This distinction underscores the remarkable metabolic efficiency of the action potential on a per-spike basis.

Table 1: Key Properties of Ion Channels in Action Potential Propagation

Channel Family	Key Subtypes (in CNS)	Voltage Dependence	Activation/Inactivation Kinetics	Primary Role in AP	Key Locations
Voltage-Gated Sodium (Nav)	Nav1.1, Nav1.2, Nav1.6	Opens at threshold (~-55mV)	Fast activation (<1ms), Fast inactivation (~1ms)	Depolarization (Rising Phase)	Axon Initial Segment, Nodes of Ranvier
Voltage-Gated Potassium (Kv)	"Delayed Rectifier" types (e.g., Kv2, Kv3)	Opens with delay at depolarized potentials	Slow activation, Slow deactivation	Repolarization (Falling Phase) & Hyperpolarization	Axonal membrane, Juxtaparanodes

Section 2: The Axon as a Conductor: Intrinsic Biophysical Properties

Once an action potential is initiated, typically at the axon hillock, it must propagate along the length of the axon to the presynaptic terminals.[1] The speed and efficiency of this propagation are governed by the intrinsic biophysical properties of the axon, which can be understood by modeling the axon as a biological electrical cable.

2.1 Principles of Cable Theory: The Interplay of Resistance and Capacitance

The passive spread of electrical signals in an axon is described by cable theory, which quantifies how a voltage change dissipates over distance and time. Conduction velocity is determined by two key composite parameters: the length constant (λ) and the time constant (τ).[11] A faster conduction velocity is achieved with a larger length constant and a smaller time constant.[11] These parameters are, in turn, determined by three fundamental electrical properties of the axon:

- **Membrane Resistance (Rm):** This property reflects the resistance to ion flow *across* the axonal membrane. It is inversely related to the density of open ion

channels; a membrane with many open "leak" channels has low resistance and is considered "leaky." A high membrane resistance (a well-insulated, non-leaky membrane) forces the electrical current to travel farther *down the length* of the axon rather than leaking out. This increases the length constant, λ, promoting faster propagation.[11]

- **Axial Resistance (Ri):** Also known as internal or axoplasmic resistance, this is the resistance to the longitudinal flow of ions *within* the axon's cytoplasm.[11] It is determined by the resistivity of the axoplasm and the axon's diameter. A lower axial resistance allows for more efficient and rapid flow of current down the axon, which also increases the length constant, λ.[14]
- **Membrane Capacitance (Cm):** The lipid bilayer of the membrane acts as a capacitor, storing electrical charge by separating the intracellular and extracellular conductive fluids. A higher capacitance means that more charge (and thus more time) is required to change the voltage across the membrane. Therefore, to achieve rapid depolarization, a low membrane capacitance is desirable. A lower Cm results in a smaller time constant, τ, and thus faster conduction.[12]

2.2 The Influence of Axon Diameter: A Direct Modifier of Axial Resistance

Of these properties, axon diameter is a key structural variable that directly and powerfully influences conduction velocity. Its primary effect is on the axial resistance (Ri). The cross-sectional area available for current flow increases with the square of the axon's radius (Area=πr2), while the membrane surface area through which current can leak only increases linearly with the radius (Circumference=2πr).[17] Consequently, increasing the axon's diameter causes a disproportionately large decrease in the internal axial resistance.[14]

This reduction in Ri allows the longitudinal current generated by an action potential to flow more easily and with less internal obstruction from the crowded milieu of cytoplasmic proteins and organelles.[21] According to cable theory, this lower internal resistance increases the length constant (

λ), allowing the depolarizing current to spread much farther down the axon before decaying. This brings more distant regions of the axonal membrane to their threshold

potential more quickly, thereby increasing the overall conduction velocity.[11]

This biophysical principle has been a major driver of evolutionary adaptation. Invertebrates, such as the squid, which lack myelination, evolved giant axons to achieve the rapid conduction speeds necessary for escape reflexes.[22] In vertebrates, the fastest conducting nerve fibers, such as those responsible for proprioception (the sense of body position), are invariably those with the largest diameters.[21] The relationship between diameter and speed is dramatic: in monkeys, a large 20 µm diameter axon can conduct signals at 120 m/s, whereas a tiny 0.1 µm axon conducts at a mere 0.3 m/s—a 400-fold difference in speed.[24] The geometry of the axon is not merely a structural feature; it is a primary determinant of its fundamental electrical character. However, the non-linear scaling presents a problem. To double the velocity in an unmyelinated axon, one must quadruple its diameter, which leads to an unsustainable increase in volume and metabolic cost.[11] This biophysical reality created a strong evolutionary pressure for a more space- and energy-efficient solution to the problem of rapid signaling.

2.3 Continuous Conduction: The Propagating Wave in Unmyelinated Axons

In axons that lack a myelin sheath, the action potential must be actively regenerated at every immediately adjacent point along the entire membrane.[25] This process is known as continuous conduction. The influx of

Na^+ at one location creates a local electrical current that passively spreads to and depolarizes the neighboring patch of membrane to its threshold. This triggers the opening of Nav channels in that new patch, generating a "new" action potential, which in turn depolarizes the next patch. This process repeats in a continuous, self-propagating wave down the length of the axon, analogous to a line of falling dominoes or a trail of gunpowder igniting along its length.[11]

This mode of propagation is inherently slow and inefficient. Conduction velocities in unmyelinated axons are limited to a range of approximately 0.5 to 10 m/s.[22] The slowness arises from the cumulative time required to execute the full sequence of ion channel opening and closing at every single point along the axon. Furthermore, the process is metabolically expensive. Because the bare axonal membrane is intrinsically "leaky" (low

Rm) and has high capacitance (Cm), the passive electrical current cannot spread very far before dissipating.[15] This necessitates a high density of voltage-gated channels all along the axon to ensure constant regeneration, and consequently, requires the Na+/K+ pump to work continuously along the entire length of the axon to restore ionic gradients after each signal passes.[25] Continuous conduction thus represents a "brute force" method of signaling, a baseline strategy that effectively highlights the biophysical problems of leakiness and capacitance that a more advanced mechanism like myelination was evolutionarily selected to overcome.

Section 3: Myelination: An Evolutionary Leap for Speed and Efficiency

The evolution of myelination represents one of the most significant innovations in the history of the nervous system. By wrapping axons in an insulating sheath, glial cells fundamentally re-engineered the biophysical properties of the axon, enabling a new mode of conduction that is orders of magnitude faster and more metabolically efficient.

3.1 The Myelin Sheath: A High-Resistance, Low-Capacitance Insulator

The myelin sheath is a multi-layered, lipid-rich membrane formed by specialized glial cells: Schwann cells in the peripheral nervous system (PNS) and oligodendrocytes in the central nervous system (CNS).[25] These cells wrap themselves tightly around segments of the axon, known as internodes, creating a compact, insulating layer.[1]

The biophysical impact of this structure is profound. Myelin dramatically alters the axon's passive cable properties in two crucial ways:

1. **Increased Membrane Resistance (Rm):** The many layers of lipid membrane act as a superb electrical insulator, increasing the transverse resistance across the axonal membrane by a factor of up to 5,000.[12] This effectively "plugs the leaks" along the internodal axon, preventing the ionic current from escaping into the extracellular fluid. This forces the current to flow longitudinally down the axoplasm.[15]

2. **Decreased Membrane Capacitance (Cm):** The thickness of the myelin sheath physically separates the conductive intracellular and extracellular fluids, acting like a thick dielectric layer in a capacitor. This increased separation reduces the membrane's ability to store charge, decreasing its capacitance by as much as a factor of 50.[12] A lower capacitance means that the membrane potential can be changed much more rapidly for a given amount of current flow, significantly reducing the time constant (τ) of the membrane.[16]

Myelination is not just "insulation" in a colloquial sense; it is a biophysical transformation of the axon. By simultaneously increasing Rm and decreasing Cm, it converts the axon from a poor, leaky cable that requires constant, slow, active signal boosting into a high-fidelity transmission line optimized for rapid, passive current flow.

3.2 Saltatory Conduction: Regenerative "Leaping" of the Action Potential

The myelin sheath is not a continuous covering. It is periodically interrupted by short (≈1 μm), unmyelinated gaps called the Nodes of Ranvier.[30] These nodes are the linchpin of myelinated nerve conduction.

The mechanism, known as saltatory conduction (from the Latin *saltare*, "to leap"), proceeds as follows: An action potential is generated at a Node of Ranvier, causing a massive and rapid influx of Na+. Because the adjacent internode is exceptionally well-insulated (high Rm) and has low capacitance (low Cm), this bolus of positive charge spreads as a passive electrical current through the axoplasm with remarkable speed and minimal signal decay.[3] When this near-instantaneous wave of depolarization reaches the next Node of Ranvier, it is still strong enough to bring the nodal membrane to its threshold potential.

The membrane at the Nodes of Ranvier is not like the rest of the axon; it is a highly specialized domain packed with an extremely high density of voltage-gated sodium channels.[3] This dense concentration of Nav channels ensures that the action potential is robustly and reliably regenerated at each node, "refreshing" the signal to its full amplitude before it continues its rapid passive journey to the next node.[26] This apparent "jumping" of the action potential from node to node is the essence of saltatory conduction.

This mechanism confers enormous advantages.

- **Speed:** By replacing the slow, sequential process of channel gating along the entire membrane with rapid passive current flow in the internodes, saltatory conduction achieves velocities of up to 150 m/s, more than an order of magnitude faster than the fastest unmyelinated axons.[22]
- **Efficiency:** The action potential is only regenerated at the tiny surface area of the nodes. This means that the ion channels, and more importantly, the metabolically expensive Na+/K+-ATPase pumps, are largely confined to these discrete locations. This conserves a tremendous amount of cellular energy compared to the alternative of maintaining ionic gradients along the entire length of the axon.[25]

3.3 The Optimal g-Ratio: A Biophysical Compromise

The efficiency of saltatory conduction is not simply a matter of making the myelin sheath as thick as possible. There is an optimal thickness of myelin relative to the axon's own diameter that maximizes conduction velocity. This relationship is quantified by the **g-ratio**, defined as the ratio of the inner axon diameter to the total outer fiber diameter (axon diameter + myelin sheath thickness).[37]

The existence of an optimum arises from a fundamental biophysical trade-off. For a given total fiber diameter, two opposing factors influence speed:

- **Thicker Myelin (Lower g-ratio):** A thicker myelin sheath provides better insulation (higher Rm, lower Cm), which promotes faster passive current spread along the internode.
- **Thicker Axon (Higher g-ratio):** A thicker axon has a lower axial resistance (Ri), which also promotes faster passive current spread.

For any fixed total volume, making the myelin thicker necessitates making the axon thinner, and vice versa. The pioneering theoretical work of Rushton demonstrated that there is a single g-ratio value that perfectly balances these two factors to achieve the maximum possible conduction velocity.[38] If speed were the only evolutionary pressure, this optimal g-ratio would be approximately 0.6.[38]

However, biological systems are subject to multiple constraints. More recent and comprehensive biophysical models have shown that the optimization problem also includes the metabolic cost of building and maintaining large volumes of tissue and,

especially in the brain, the severe constraints on physical space.[39] While conduction speed continues to increase with ever-thicker myelin, the overall

efficiency of the system—balancing speed, energy, and volume—shows a clear optimum that is context-dependent.[42]

This multi-objective optimization provides a powerful explanation for the observed differences in myelination across the nervous system.

- **In the CNS**, where neurons are densely packed and space is at a premium, the optimal g-ratio is higher, around **0.77**. This reflects a compromise that favors slightly thinner myelin sheaths to allow for larger axons and greater packing density of fibers within a fixed volume.[39]
- **In the PNS**, where space constraints are less severe and raw speed for long-distance motor and sensory signals is often paramount, the g-ratio is closer to the speed-optimized value of **≈0.6**, favoring thicker myelin sheaths to achieve maximal velocity.[39]

The existence of an optimal g-ratio, and its variation between different parts of the nervous system, is a clear demonstration that neuronal design is a product of competing evolutionary pressures. The nervous system does not simply maximize for speed at any cost; it arrives at elegant, optimized solutions that balance the demand for speed with the biological costs of energy and space. The g-ratio of a given nerve fiber is a quantitative window into how evolution has solved this complex trade-off for a specific functional context.

Table 2: Comparative Analysis of Continuous vs. Saltatory Conduction

Feature	Continuous Conduction	Saltatory Conduction
Myelination	Absent	Present (in internodes)
Location of V-gated Channels	Distributed along the entire axon length	Highly concentrated at Nodes of Ranvier
Mechanism of Propagation	Sequential regeneration of AP at every point	Rapid passive spread in internodes, AP regeneration at nodes
Key Biophysical Limitation	Low Rm and high Cm (leaky, slow to charge)	High Rm and low Cm (well-insulated, fast to

		charge)
Conduction Velocity	Slow (0.5–10 m/s)	Fast (up to 150 m/s)
Metabolic Efficiency	Low (Na+/K+ pumps active along entire axon)	High (pumps concentrated at nodes)
Example Fibers	C-fibers (slow pain, temperature)	Aα-fibers (proprioception, motor commands)

Section 4: Molecular Heterogeneity and Its Functional Consequences

The action potential is not a monolithic entity. Its precise waveform, firing frequency, and propagation characteristics are sculpted by a rich diversity of ion channel subtypes. The specific "cocktail" of channels a neuron expresses and, just as importantly, where it strategically places them along its membrane, defines its unique electrical personality and computational role within a circuit. This molecular heterogeneity is a primary determinant of signaling speed and efficiency.

4.1 The Voltage-Gated Sodium (Nav) Channel Family: Subtype-Specific Contributions

While all Nav channels mediate the rapid influx of Na+ that drives depolarization, the nine functional mammalian subtypes (Nav1.1–Nav1.9) have distinct properties and distributions that are critical for specialized functions and are often implicated in disease.[45]

Key CNS Subtypes:

- **Nav1.1:** This channel is predominantly expressed in the cell bodies and dendrites of inhibitory GABAergic interneurons. Its properties are tailored to support the high-frequency firing patterns characteristic of these cells, which are essential

for regulating and synchronizing circuit activity. Consequently, loss-of-function mutations in the *SCN1A* gene encoding Nav1.1 lead to reduced inhibition and are a major cause of severe epilepsy syndromes, such as Dravet syndrome.[45]

- **Nav1.2:** This subtype is crucial for action potential propagation and is primarily located in unmyelinated axons and at the axon initial segment (AIS) during early development. As neurons mature, it is largely replaced by Nav1.6. Mutations in the *SCN2A* gene are linked to a spectrum of neurodevelopmental disorders, including early-onset epilepsy and autism.[45]
- **Nav1.6:** This is the workhorse sodium channel of the mature CNS. It is highly concentrated at two critical locations for high-speed signaling: the nodes of Ranvier in myelinated axons and the distal part of the AIS where action potentials are initiated. Its biophysical properties, including the ability to generate a small, non-inactivating "persistent" current, are essential for both saltatory conduction and repetitive firing. Mutations in the *SCN8A* gene are associated with severe epilepsy and intellectual disability.[45]

Key PNS Subtypes:

- **Nav1.7, Nav1.8, and Nav1.9:** These subtypes are primarily expressed in the peripheral sensory neurons of the dorsal root ganglia and are central to the sensation of pain. They have different sensitivities to the toxin tetrodotoxin (TTX) compared to their CNS counterparts. Their importance in pain is dramatically illustrated by human genetics: gain-of-function mutations in the *SCN9A* gene (Nav1.7) cause debilitating inherited pain syndromes, whereas rare loss-of-function mutations result in a complete inability to feel pain, highlighting this channel as a key therapeutic target for analgesics.[45]

4.2 The Voltage-Gated Potassium (Kv) Channel Superfamily: Sculpting the Action Potential

The diversity of the Kv channel superfamily, with nearly 100 genes, is even greater than that of Nav channels.[52] This vast repertoire allows for the precise sculpting of the action potential waveform, regulation of firing frequency, and control of neuronal excitability. The channels can be broadly classified based on their voltage-dependence and gating kinetics, which directly determine their functional role.[54]

Key Subfamilies and Their Roles:

- **Kv1 Family (Low-voltage activated, slow inactivation):** These channels begin to activate at potentials just above rest, near the action potential threshold. This allows them to act as a "brake" on excitability, helping to set the firing threshold and limit the frequency of repetitive firing. They are strategically located at the AIS, presynaptic terminals, and, critically, at the juxtaparanodes flanking the nodes of Ranvier, where they help maintain the resting potential and ensure rapid repolarization between spikes.[55]
- **Kv2 Family (High-voltage activated, slow kinetics):** These channels require a strong depolarization to open and are very slow to activate and inactivate. Their primary role is to contribute to action potential repolarization during periods of sustained, high-frequency firing, preventing excessive depolarization. They are typically found in large clusters on the soma and proximal dendrites, distinct from other channel domains.[49]
- **Kv3 Family (High-voltage activated, fast kinetics):** These are the specialists for high-speed signaling. Kv3 channels activate only at very positive potentials (near the peak of the action potential) but, crucially, they deactivate extremely rapidly upon repolarization. This unique combination allows for an exceptionally brief action potential and a very short afterhyperpolarization, enabling the neuron to recover quickly and fire again. This property is essential for neurons that must sustain firing at very high frequencies (up to 1000 Hz), such as fast-spiking inhibitory interneurons in the cortex and neurons in the auditory brainstem that encode temporal information.[59]
- **Kv4 Family (Low-voltage activated, fast inactivation):** These channels generate a transient, rapidly inactivating current known as the "A-type" current. They are predominantly located in the dendrites and soma. By activating in response to sub-threshold synaptic inputs, they can dampen incoming signals and regulate whether an action potential is generated. They also play a critical role in controlling the backpropagation of action potentials from the axon into the dendritic tree, a key mechanism for synaptic plasticity.[49]

4.3 Strategic Localization: The Axon Initial Segment (AIS) and Nodal Architecture

The function of these diverse ion channels is critically dependent on their precise placement in specific subcellular domains. This localization is not random but is orchestrated by a complex molecular machinery that anchors channels to the

cytoskeleton at strategic sites.

- **The Axon Initial Segment (AIS):** This unmyelinated, ~40 µm segment where the axon emerges from the soma is the primary site of action potential initiation in most neurons.[64] Its unique excitability stems from its distinct molecular architecture. The master scaffolding protein Ankyrin-G forms a submembranous matrix that specifically recruits and anchors a high density of Nav1.6 channels and low-threshold Kv7 (M-current) channels. This specific channel composition creates a local hotspot with a lower voltage threshold for firing than any other part of the neuron, ensuring that integrated synaptic inputs trigger an action potential here first.[54]
- **The Node of Ranvier:** The node is far more than a simple gap in the myelin; it is a highly structured, multi-domain micro-machine engineered for the faithful regeneration of the action potential.[33]
    - **Node:** The central 1 µm gap is densely packed with Nav1.6 channels to mediate rapid depolarization.
    - **Paranode:** This is the region where the myelin loops terminate and form tight junctions with the axonal membrane (the axolemma). These junctions, containing proteins like Caspr and Contactin, create a physical and electrical barrier. This seal is critical; it prevents the nodal Nav channels from diffusing away and stops the ionic current from leaking out from under the myelin, thereby forcing it to flow towards the next node.[33]
    - **Juxtaparanode:** Located immediately adjacent to the paranode, under the final myelin loop, this domain is enriched with Kv1 family channels. Their placement here is perfect for rapidly repolarizing the nodal membrane after an action potential and clamping the internodal potential at a hyperpolarized level, which helps to maintain the driving force for the next spike.[34]

The functional identity of a neuron is thus dictated by a "molecular zip code" system for its ion channels. The vast diversity of Nav and Kv subtypes is not redundant; rather, the specific combination of channels a neuron expresses (its molecular "cocktail") and where its cellular machinery delivers and anchors them (its "zip code"—AIS, node, dendrite, or soma) precisely defines its electrical behavior. A fast-spiking interneuron achieves its characteristic firing pattern because its genetic program includes Kv3 channels and its trafficking machinery places them in the axon and terminals. A pyramidal neuron that performs complex integration of synaptic inputs does so because it expresses Kv4 channels in its dendrites. This demonstrates a direct and elegant link, where function at the circuit level is determined by molecular identity and localization at the subcellular level.

Table 3: Functional Roles and Properties of Key Voltage-Gated K+ (Kv) Channel Subfamilies

Kv Subfamily	Activation Voltage	Gating Kinetics	Primary Functional Role	Typical Location
Kv1	Low-voltage	Fast activation, slow inactivation	Sets AP threshold, limits firing frequency	Axon Initial Segment, Juxtaparanodes
Kv2	High-voltage	Slow activation, slow inactivation	Repolarization during high-frequency firing	Somatic/proximal dendritic clusters
Kv3	High-voltage	Very fast activation, very fast deactivation	Enables rapid repolarization for sustained high-frequency firing	Axons/terminals of fast-spiking neurons
Kv4	Low-voltage	Fast activation, fast inactivation (A-type)	Regulates dendritic signal integration and AP backpropagation	Dendrites and soma

Section 5: System-Level and Environmental Modulators

Beyond the intrinsic properties of the axon and its ion channels, conduction velocity is also influenced by extrinsic variables like temperature and is tailored at a system-wide level to meet the specific demands of different neural pathways.

5.1 The Impact of Temperature on Neuronal Conduction

Temperature is a potent, global modulator of neuronal function because it directly affects the kinetics of all underlying biochemical and biophysical processes.[27]

- **Mechanism of Action:** The conformational changes that constitute ion channel gating, as well as the enzymatic activity of the Na+/K+ pump, are all temperature-sensitive processes.[66]
    - **Increasing Temperature:** Warmer temperatures accelerate the rates of ion channel opening, closing, and inactivation.[66] This leads to action potentials that are shorter in duration and have a briefer refractory period, as Nav channels recover from inactivation more quickly. This allows for higher maximum firing frequencies. The increased kinetic energy also enhances the rate of ion diffusion. The cumulative effect is a significant increase in nerve conduction velocity, which rises in a roughly linear fashion by about 2 m/s, or approximately 5%, for every 1°C increase in temperature within the physiological range.[66]
    - **Decreasing Temperature:** Conversely, cooling slows all these kinetic processes. This prolongs the action potential duration and lengthens the refractory period, resulting in a marked decrease in conduction velocity.[66]
- **Optimization of Energy Efficiency:** Intriguingly, there appears to be an optimal temperature for the metabolic efficiency of action potential generation. At the warmer physiological temperatures of mammals (e.g., 37°C), the faster inactivation kinetics of Nav channels result in less temporal overlap between the inward Na+ current of depolarization and the outward K+ current of repolarization. This minimizes the simultaneous, counteracting flow of ions, reducing the amount of "wasted" ionic flux that the Na+/K+ pump must later correct. Computational models suggest that the total energy cost per signal reaches a global minimum in the temperature range of 37–42°C.[72] This finding suggests that the evolution of endothermy (warm-bloodedness) was not just a metabolic adaptation but also a critical neurocomputational one. It provided a massive advantage by making the energetically expensive brain "cheaper" to run on a per-signal basis, potentially being a key permissive step in the evolution of the large, complex mammalian brain.

5.2 Functional Specialization: Conduction Velocities in Motor and Sensory Pathways

The nervous system is not a homogenous network; it is a highly differentiated one

where the biophysical properties of axons are precisely matched to the functional requirements and informational priority of the pathway they serve.[73] This is vividly illustrated by the stark differences in conduction velocities among major motor and sensory pathways.

- **High-Speed Pathways for Survival and Control:**
  - **Proprioception:** The sense of body and limb position, which is critical for real-time motor control and balance, is transmitted by the fastest fibers in the body. These are the Type Aα (also classified as Ia and Ib) fibers, which are heavily myelinated and have the largest diameters (13–20 µm). They achieve blistering conduction velocities of 80–120 m/s, ensuring that feedback from the muscles and joints reaches the CNS with minimal delay.[74]
  - **Somatic Motor Commands:** The corticospinal tract, the primary descending pathway for voluntary movement, is also composed of large, myelinated axons (Aα fibers). It conducts signals from the motor cortex to the spinal cord at an average velocity of approximately 60 m/s, allowing for the swift and precise control of muscles, especially for fine digital movements.[76]
  - **Discriminative Touch:** The ability to precisely locate and identify tactile stimuli is carried by myelinated, relatively large Type Aβ fibers (6–12 µm), which conduct at a rapid 33–75 m/s.[74]
- **Slower Pathways for Awareness and Alerting:**
  - **Sharp Pain and Cold Temperature:** The initial, sharp, well-localized sensation of pain (often called "first pain") and the sensation of cold are transmitted by thinly myelinated, small-diameter Type Aδ fibers (1–5 µm). Their conduction velocities are much slower, in the range of 3–40 m/s.[74]
  - **Dull, Aching Pain and Warmth:** The subsequent, more diffuse, and persistent sensation of pain ("second pain") and the sensation of warmth are carried by the slowest fibers in the nervous system. These are the unmyelinated, very small-diameter Type C fibers (0.2–1.5 µm), which conduct at a leisurely 0.5–2 m/s.[75]

This differentiation reflects a sophisticated, resource-efficient design. The nervous system allocates its most metabolically and spatially "expensive" resources—large, heavily myelinated axons—to transmit information with the highest temporal priority, that which is critical for immediate physical survival and interaction. In contrast, information that is important for awareness but less time-critical is sent along more "economical," slower pathways.

5.3 From Axon to Axon: The Influence of Synapse Type

The final step in signal propagation is the transmission from one neuron to the next at a synapse. The type of synapse used introduces another factor that affects the overall speed and nature of communication.

- **Chemical Synapses:** These are the most common type of synapse in the mammalian nervous system. Communication is indirect. The arrival of an action potential at the presynaptic terminal triggers the release of chemical messengers called neurotransmitters. These molecules must diffuse across a physical gap—the synaptic cleft (≈20 nm)—to bind to receptors on the postsynaptic neuron. This entire process introduces a significant **synaptic delay**, typically ranging from 0.5 to 4.0 milliseconds.[80] While slower, this chemical step provides immense computational flexibility. It allows for signal amplification, the conversion of an excitatory signal into an inhibitory one, and complex forms of modulation and plasticity that are the basis of learning and memory.[80]
- **Electrical Synapses (Gap Junctions):** In these synapses, the pre- and postsynaptic neurons are physically connected by channels called gap junctions. These channels allow for the direct, passive flow of ions (and thus electrical current) from one cell to the next. Transmission is therefore nearly instantaneous, with virtually no synaptic delay.[81] This mode of transmission is ideal for functions that require extremely rapid and highly synchronized activity among a population of neurons, such as the coordination of escape reflexes or the generation of rhythmic firing patterns in the brainstem.[80] However, they lack the modulatory flexibility of their chemical counterparts.[81]

Table 4: Conduction Velocities and Fiber Properties of Major Neural Pathways

Pathway/Function	Primary Fiber Type(s)	Typical Diameter (µm)	Myelination	Conduction Velocity (m/s)	Functional Significance
Proprioception (Joint Position)	Aα (Ia, Ib)	13–20	Heavy	80–120	Extremely rapid feedback for motor control and balance.

Somatic Motor (Corticospinal)	Aα	13–20	Heavy	~60–80	Fast voluntary commands for fine motor control.
Discriminative Touch	Aβ	6–12	Medium	33–75	Rapid identification of tactile stimuli.
Sharp Pain / Cold ("First Pain")	Aδ	1–5	Thin	3–40	Fast, localizing signal for acute threat detection.
Dull Pain / Warmth ("Second Pain")	C	0.2–1.5	None	0.5–2	Slower, persistent signal for ongoing tissue damage awareness.

Section 6: Pathophysiological Insights: Conduction Failure in Demyelinating Disorders

The critical importance of the mechanisms governing conduction velocity is starkly illustrated by diseases in which these processes fail. Multiple sclerosis (MS) serves as a profound clinical model of demyelination, revealing the catastrophic consequences of disrupting the finely tuned architecture of the myelinated axon.

6.1 Multiple Sclerosis (MS) as a Model of Demyelination

Multiple sclerosis is a chronic, inflammatory autoimmune disease of the CNS in which the body's own immune system mistakenly attacks and destroys the myelin sheath and the oligodendrocytes that produce it.[85] This destructive process leaves behind focal areas of demyelination and scarring known as lesions or "plaques".[85]

The primary physiological consequence of demyelination is the profound disruption of saltatory conduction.[89] When the insulating myelin is stripped away, the previously protected internodal membrane is exposed to the extracellular environment. This has two devastating biophysical effects: membrane resistance (

Rm) plummets, and membrane capacitance (Cm) increases. The axon reverts to being a very "leaky" cable. As a result, the passive current generated at a node of Ranvier now rapidly dissipates as it travels along the exposed, demyelininated segment. By the time the current reaches the next intact node, it is often too weak to depolarize the membrane to threshold. This results in a complete failure of action potential propagation, a phenomenon known as **conduction block**.[90] This abrupt cessation of signaling is believed to be the primary cause of the acute neurological symptoms—such as vision loss, weakness, or paralysis—that characterize an MS relapse.[85] Even if the signal is not entirely blocked, its propagation is severely slowed as it is forced to travel in a continuous, inefficient manner across the demyelinated region.[93]

6.2 Molecular Mechanisms of Axonal Dysfunction and Degeneration

In the face of demyelination, the axon is not entirely passive. It initiates adaptive, albeit ultimately maladaptive, changes in an attempt to restore function.

- **Ion Channel Reorganization:** A remarkable form of plasticity occurs where voltage-gated sodium channels, particularly the Nav1.6 subtype, which were once exclusively clustered at the nodes, begin to redistribute and express themselves along the length of the newly denuded internodal membrane.[50] This allows the demyelinated axon to regain some ability to conduct action potentials, albeit in a slow, continuous fashion, as it now has the molecular machinery for regeneration along its length. This adaptive reorganization of channels may be one of the key mechanisms underlying periods of clinical remission, where symptoms partially or fully resolve after a relapse.[90]

- **The Energy Crisis and Axonal Degeneration:** This attempted compensation, however, sets the stage for long-term failure. The clinical course of MS can be viewed as a two-act tragedy. Act I is the acute biophysical failure: demyelination causes conduction block and relapses, a process that is potentially reversible if remyelination can occur. Act II is a chronic bioenergetic failure. The shift from the highly efficient saltatory conduction to the inefficient continuous mode places an immense and unsustainable metabolic burden on the axon. The Na+/K+-ATPase pumps, now required to operate over a much larger surface area of excitable membrane, must consume vast amounts of ATP to extrude the excess Na+ that enters during each action potential.[50]

This chronic energy demand often outstrips the axon's mitochondrial capacity, leading to a state of virtual hypoxia and energy failure. This energy crisis has a fatal downstream consequence: it can cause the Na+/Ca2+ exchanger, a transporter that normally uses the sodium gradient to extrude calcium, to reverse its function. This leads to a slow, toxic influx and accumulation of intracellular calcium (Ca2+).[50] Persistently elevated intracellular

Ca2+ is a potent death signal, activating a cascade of destructive enzymes, including proteases like calpain, that degrade the axonal cytoskeleton and other essential proteins. This ultimately leads to the physical transection of the axon and irreversible neuronal loss.[90] This progressive axonal degeneration, not the initial demyelination itself, is the primary pathological correlate of the permanent, accumulating disability seen in the progressive stages of MS.

This tragic cascade reveals a deeper, more intimate role for myelin. It is not merely a passive insulator; the oligodendrocyte and its myelin sheath act as a crucial metabolic partner to the axon, providing trophic support and energy-rich substrates like lactate to help the axon meet its high energy demands.[50] The loss of myelin is therefore a double blow: it cripples conduction electrically while also severing a vital metabolic lifeline. The ultimate failure of the axon in progressive MS is thus a failure of this critical axon-glia partnership, underscoring that they operate as a single, interdependent functional unit.

Conclusion: A Synthesis of Speed and Efficiency

The speed and efficiency of electrical signaling in the human brain are not governed

by any single factor but emerge from a beautifully orchestrated, multi-layered hierarchy of determinants. This analysis has traced the origins of conduction velocity from the fundamental biophysics of the action potential to the complex architecture of neural pathways and the devastating consequences of its failure in disease.

At the most basic level, the rapid kinetics of voltage-gated sodium and potassium channels create the brief, all-or-nothing action potential, the digital currency of the nervous system. At the structural level, the axon's intrinsic properties, governed by cable theory, set the stage for propagation. While a larger axon diameter can increase speed by reducing internal resistance, this strategy is inefficient. The evolutionary innovation of myelination provides a far more elegant solution, transforming the axon into a high-speed, energy-efficient transmission line by enabling saltatory conduction. At the molecular level, the remarkable diversity of Nav and Kv channel subtypes, combined with their precise strategic localization at domains like the axon initial segment and the nodes of Ranvier, allows for the fine-tuning of firing patterns, tailoring each neuron to its specific computational role.

A central, recurring theme throughout this analysis is that of optimization and trade-offs. The nervous system continuously and dynamically balances the relentless demand for speed against the unyielding biological constraints of metabolic energy and physical space. The existence of an optimal g-ratio for myelin thickness, the differential investment in high-speed axons for different functional pathways, and the evolution of maximally energy-efficient action potentials at warm body temperatures all exemplify this powerful principle of optimized biological design.

A deeper understanding of these fundamental mechanisms is not merely an academic exercise; it illuminates the path toward novel therapeutic strategies. By targeting the specific ion channel subtypes that drive hyperexcitability in epilepsy or pain, by developing therapies that promote the regeneration of myelin and restore the critical metabolic partnership between axons and glia in diseases like multiple sclerosis, or by modulating pathway-specific conduction to restore function after injury, the future of clinical neuroscience lies in harnessing the very mechanisms that govern the speed and fidelity of the brain's electrical signals.

Works cited

1. 6.2: The Structure Of The Neuron - Social Sci LibreTexts, accessed July 12, 2025, https://socialsci.libretexts.org/Bookshelves/Psychology/Introductory_Psychology/General_Psychology_for_Honors_Students_(Votaw)/06%3A_Neurons/6.02%3A_The_Structure_Of_The_Neuron
2. What is a neuron? - Queensland Brain Institute, accessed July 12, 2025,

https://qbi.uq.edu.au/brain/brain-anatomy/what-neuron
3. Physiology, Action Potential - StatPearls - NCBI Bookshelf, accessed July 12, 2025, https://www.ncbi.nlm.nih.gov/books/NBK538143/
4. Action Potentials – Foundations of Neuroscience - Open Textbook Publishing, accessed July 12, 2025, https://openbooks.lib.msu.edu/neuroscience/chapter/action-potentials/
5. Ionic Mechanisms and Action Potentials (Section 1, Chapter 2) Neuroscience Online, accessed July 12, 2025, https://nba.uth.tmc.edu/neuroscience/m/s1/chapter02.html
6. Neuroanatomy, Neurons - StatPearls - NCBI Bookshelf, accessed July 12, 2025, https://www.ncbi.nlm.nih.gov/books/NBK441977/
7. 12.5 The Action Potential – Anatomy & Physiology - Oregon State University, accessed July 12, 2025, https://open.oregonstate.education/aandp/chapter/12-5-the-action-potential/
8. Ion Channels and the Electrical Properties of Membranes - Molecular Biology of the Cell - NCBI Bookshelf, accessed July 12, 2025, https://www.ncbi.nlm.nih.gov/books/NBK26910/
9. Voltage-gated ion channels: Structure, types and function - Kenhub, accessed July 12, 2025, https://www.kenhub.com/en/library/physiology/voltage-gated-ion-channels
10. Saltatory conduction in neurons (video) - Khan Academy, accessed July 12, 2025, https://www.khanacademy.org/science/biology/human-biology/neuron-nervous-system/v/saltatory-conduction-neurons
11. Propagation of the Action Potential (Section 1, Chapter 3 ..., accessed July 12, 2025, https://nba.uth.tmc.edu/neuroscience/m/s1/chapter03.html
12. Why is saltatory conduction in myelinated axons faster than continuous conduction in unmyelinated axons? - Biology Stack Exchange, accessed July 12, 2025, https://biology.stackexchange.com/questions/8282/why-is-saltatory-conduction-in-myelinated-axons-faster-than-continuous-conductio
13. Unlocking Action Potentials in Neuroscience - Number Analytics, accessed July 12, 2025, https://www.numberanalytics.com/blog/ultimate-guide-action-potentials-computational-neuroscience
14. www.frontiersin.org, accessed July 12, 2025, https://www.frontiersin.org/journals/cellular-neuroscience/articles/10.3389/fncel.2019.00413/full#:~:text=(B)%20Conduction%20can%20be%20improved,space%20constant%20and%20faster%20conduction.
15. Saltatory conduction : r/askscience - Reddit, accessed July 12, 2025, https://www.reddit.com/r/askscience/comments/1m2uq5/saltatory_conduction/
16. How does the thickness of myelin affect the speed of action potential propagation? - Reddit, accessed July 12, 2025, https://www.reddit.com/r/askscience/comments/2x9yae/how_does_the_thickness_of_myelin_affect_the_speed/
17. Why do axons with a larger circumferences transmit action potentials faster? -

Reddit, accessed July 12, 2025, https://www.reddit.com/r/askscience/comments/lcoop/why_do_axons_with_a_larger_circumferences/
18. 1neuroscienceL04 Flashcards - Quizlet, accessed July 12, 2025, https://quizlet.com/584327189/1neuroscience104-flash-cards/
19. pmc.ncbi.nlm.nih.gov, accessed July 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC6131297/#:~:text=In%20summary%2C%20increasing%20axon%20diameters,the%20spread%20of%20action%20potential.
20. pmc.ncbi.nlm.nih.gov, accessed July 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC6772175/#:~:text=In%20myelinated%20axons%20conduction%20velocity,due%20to%20larger%20surface%20area.
21. Action potential velocity (article) - Khan Academy, accessed July 12, 2025, https://www.khanacademy.org/test-prep/mcat/organ-systems/neuron-membrane-potentials/a/action-potential-velocity
22. Increased Conduction Velocity as a Result of Myelination ... - NCBI, accessed July 12, 2025, https://www.ncbi.nlm.nih.gov/books/NBK10921/
23. Thicker nerve fibres enable faster reactions in mice - Max-Planck-Gesellschaft, accessed July 12, 2025, https://www.mpg.de/15409874/axons-cmtm6
24. Axon diameter and conduction velocity - Monkey - BNID 110607, accessed July 12, 2025, https://bionumbers.hms.harvard.edu/bionumber.aspx?s=n&v=2&id=110607
25. Saltatory conduction: mechanism and function | Kenhub, accessed July 12, 2025, https://www.kenhub.com/en/library/physiology/saltatory-conduction
26. Saltatory conduction - Wikipedia, accessed July 12, 2025, https://en.wikipedia.org/wiki/Saltatory_conduction
27. Saltatory conduction of nerve impulses - Biology Stack Exchange, accessed July 12, 2025, https://biology.stackexchange.com/questions/14249/saltatory-conduction-of-nerve-impulses
28. Conduction Velocity and Myelin – Introduction to Sensation and Perception, accessed July 12, 2025, https://pressbooks.umn.edu/sensationandperception/chapter/conduction-velocity-and-myelin/
29. Effects of axon diameter and myelination (video) - Khan Academy, accessed July 12, 2025, https://www.khanacademy.org/test-prep/mcat/organ-systems/neuron-membrane-potentials/v/effects-of-axon-diameter-and-myelination
30. Anatomy of a neuron (video) | Human biology - Khan Academy, accessed July 12, 2025, https://www.khanacademy.org/science/biology/human-biology/neuron-nervous-system/v/anatomy-of-a-neuron
31. www.britannica.com, accessed July 12, 2025, https://www.britannica.com/science/node-of-Ranvier#:~:text=However%2C%20nodes%20of%20Ranvier%20interrupt,process%20known%20as%20saltatory%20

conduction.&text=Nodes%20of%20Ranvier%20are%20approximately,membrane%20to%20the%20external%20environment.
32. Node of Ranvier | Myelin sheath, Schwann cells, Neurotransmission | Britannica, accessed July 12, 2025, https://www.britannica.com/science/node-of-Ranvier
33. Node of Ranvier - Wikipedia, accessed July 12, 2025, https://en.wikipedia.org/wiki/Node_of_Ranvier
34. Neuroanatomy, Nodes of Ranvier - StatPearls - NCBI Bookshelf, accessed July 12, 2025, https://www.ncbi.nlm.nih.gov/books/NBK537273/
35. Nodes of Ranvier: structure and function - Kenhub, accessed July 12, 2025, https://www.kenhub.com/en/library/physiology/nodes-of-ranvier
36. Myelin And Axon Diameter Effect On Action Potential Conduction Velocity (Schwann Cells), accessed July 12, 2025, https://www.youtube.com/watch?v=5WNWFyvUA5w
37. Full article: G-Ratio Commentary—Why You've Been Doing It Wrong, accessed July 12, 2025, https://www.tandfonline.com/doi/full/10.1080/17590914.2025.2486962
38. pmc.ncbi.nlm.nih.gov, accessed July 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC2771903/#:~:text=The%20ratio%20of%20the%20inner,ratio%20of%200.6%20%5B1%5D.
39. What Is the Optimal Value of the g-Ratio for Myelinated Fibers in the Rat CNS? A Theoretical Approach - PubMed Central, accessed July 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC2771903/
40. What is the optimal value of the g-ratio for myelinated fibers in the rat CNS? A theoretical approach - PubMed, accessed July 12, 2025, https://pubmed.ncbi.nlm.nih.gov/19915661/
41. Functional Trade-Offs in White Matter Axonal Scaling | Journal of Neuroscience, accessed July 12, 2025, https://www.jneurosci.org/content/28/15/4047
42. What Is the Optimal Value of the g-Ratio for Myelinated Fibers in the Rat CNS? A Theoretical Approach - PLOS, accessed July 12, 2025, https://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0007754&type=printable
43. What Is the Optimal Value of the g-Ratio for Myelinated Fibers in the ..., accessed July 12, 2025, https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0007754
44. What Is the Optimal Value of the g-Ratio for Myelinated Fibers in the Rat CNS? A Theoretical Approach - ResearchGate, accessed July 12, 2025, https://www.researchgate.net/publication/38091579_What_Is_the_Optimal_Value_of_the_g-Ratio_for_Myelinated_Fibers_in_the_Rat_CNS_A_Theoretical_Approach
45. Distribution and function of voltage-gated sodium channels in the nervous system - PMC, accessed July 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC5786190/
46. Neurological perspectives on voltage-gated sodium channels | Brain - Oxford Academic, accessed July 12, 2025, https://academic.oup.com/brain/article/135/9/2585/330191
47. Voltage-Gated Sodium Channel Dysfunctions in Neurological Disorders - MDPI,

accessed July 12, 2025, https://www.mdpi.com/2075-1729/13/5/1191
48. Severe deficiency of voltage-gated sodium channel NaV1.2 elevates neuronal excitability in adult mice | bioRxiv, accessed July 12, 2025, https://www.biorxiv.org/content/10.1101/2021.02.02.429384v1.full
49. The Segregated Expression of Voltage-Gated Potassium and Sodium Channels in Neuronal Membranes: Functional Implications and Regulatory Mechanisms - Frontiers, accessed July 12, 2025, https://www.frontiersin.org/journals/cellular-neuroscience/articles/10.3389/fncel.2017.00115/full
50. Mechanisms of Neurodegeneration and Axonal Dysfunction in Progressive Multiple Sclerosis - MDPI, accessed July 12, 2025, https://www.mdpi.com/2227-9059/7/1/14
51. Neuronal voltage-gated sodium channel subtypes: Key roles in inflammatory and neuropathic pain - UQ eSpace - The University of Queensland, accessed July 12, 2025, https://espace.library.uq.edu.au/view/UQ:80415/UQ_AV_80415.pdf
52. Voltage-Gated Ion Channels - Neuroscience - NCBI Bookshelf, accessed July 12, 2025, https://www.ncbi.nlm.nih.gov/books/NBK10883/
53. Potassium Channels - Sigma-Aldrich, accessed July 12, 2025, https://www.sigmaaldrich.com/US/en/technical-documents/technical-article/protein-biology/protein-expression/potassium-channels
54. Voltage-gated potassium channels (K v): Introduction, accessed July 12, 2025, https://www.guidetopharmacology.org/GRAC/FamilyIntroductionForward?familyId=81
55. Going native: voltage-gated potassium channels controlling neuronal excitability - PMC, accessed July 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC2976014/
56. Use-Dependent Activation of Neuronal Kv1.2 Channel Complexes, accessed July 12, 2025, https://www.jneurosci.org/content/35/8/3515
57. Expression of Kv1 Potassium Channels in Mouse Hippocampal Primary Cultures: Development and Activity-Dependent Regulation - PubMed Central, accessed July 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC6772941/
58. VOLTAGE-GATED POTASSIUM CHANNELS AT THE CROSSROADS OF NEURONAL FUNCTION, ISCHEMIC TOLERANCE, AND NEURODEGENERATION - PMC - PubMed Central, accessed July 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC3946373/
59. Voltage-gated potassium channels as a potential therapeutic target for the treatment of neurological and psychiatric disorders - Frontiers, accessed July 12, 2025, https://www.frontiersin.org/journals/cellular-neuroscience/articles/10.3389/fncel.2024.1449151/full
60. Kv3 Channels: Enablers of Rapid Firing, Neurotransmitter Release, and Neuronal Endurance | Physiological Reviews, accessed July 12, 2025, https://journals.physiology.org/doi/10.1152/physrev.00002.2017
61. Function of Specific K+ Channels in Sustained High-Frequency Firing of Fast-Spiking Neocortical Interneurons | Journal of Neurophysiology | American

Physiological Society, accessed July 12, 2025, https://journals.physiology.org/doi/10.1152/jn.1999.82.5.2476
62. Roles of specific Kv channel types in repolarization of the action potential in genetically identified subclasses of pyramidal neurons in mouse neocortex - PubMed Central, accessed July 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC4922457/
63. A-Type KV Channels in Dorsal Root Ganglion Neurons: Diversity, Function, and Dysfunction - Frontiers, accessed July 12, 2025, https://www.frontiersin.org/journals/molecular-neuroscience/articles/10.3389/fnmol.2018.00253/full
64. Myelin Loss and Axonal Ion Channel Adaptations Associated with ..., accessed July 12, 2025, https://www.jneurosci.org/content/35/18/7272
65. Saltatory conduction in normally myelinated and demyelinated axons. (A)... | Download Scientific Diagram - ResearchGate, accessed July 12, 2025, https://www.researchgate.net/figure/Saltatory-conduction-in-normally-myelinated-and-demyelinated-axons-A-At-the-active_fig5_272520576
66. Block AP: Page 3 - Case Western Reserve University, accessed July 12, 2025, https://case.edu/groups/ANCL/pages/01/01_03.htm
67. Effect of Skin Temperature on Nerve Conduction Velocity and Reliability of Temperature Correction Formula in Indian Females, accessed July 12, 2025, http://www.efha.in/wp-content/uploads/2015/01/JESP-5-24.pdf
68. The Temperature-Induced Changes in Membrane Potential - ResearchGate, accessed July 12, 2025, https://www.researchgate.net/publication/41030333_The_Temperature-Induced_Changes_in_Membrane_Potential
69. academic.oup.com, accessed July 12, 2025, https://academic.oup.com/brain/article/124/4/816/354723#:~:text=The%20conduction%20velocity%20increases%20by,al.%2C%201981%3B%20Lang%20and
70. Effects of temperature on the excitability properties of human motor ..., accessed July 12, 2025, https://academic.oup.com/brain/article/124/4/816/354723
71. Study of Effect of Temperature on Motor Nerve Conduction Velocity in Normal Healthy Young Adults - IOSR Journal, accessed July 12, 2025, https://www.iosrjournals.org/iosr-jdms/papers/Vol19-issue2/Series-9/D1902092527.pdf
72. Warm Body Temperature Facilitates Energy Efficient Cortical Action Potentials - PLOS, accessed July 12, 2025, https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1002456
73. A delta and C fibres, which transmit pain - THE BRAIN FROM TOP TO BOTTOM, accessed July 12, 2025, https://thebrain.mcgill.ca/flash/d/d_03/d_03_cl/d_03_cl_dou/d_03_cl_dou.html
74. Nerve conduction velocity - Wikipedia, accessed July 12, 2025, https://en.wikipedia.org/wiki/Nerve_conduction_velocity
75. Physiology, Nociception - StatPearls - NCBI Bookshelf, accessed July 12, 2025, https://www.ncbi.nlm.nih.gov/books/NBK551562/
76. Corticospinal Tract - Physiopedia, accessed July 12, 2025,

https://www.physio-pedia.com/Corticospinal_Tract
77. Sensory and motor pathways | Clinical Gate, accessed July 12, 2025, https://clinicalgate.com/sensory-and-motor-pathways/
78. Pain and Nociception – Introduction to Neuroscience, accessed July 12, 2025, https://openbooks.lib.msu.edu/introneuroscience1/chapter/pain/
79. Spinothalamic tract: Anatomy and function - Kenhub, accessed July 12, 2025, https://www.kenhub.com/en/library/anatomy/spinothalamic-tract
80. Chemical Vs Electrical Synapse - Simply Psychology, accessed July 12, 2025, https://www.simplypsychology.org/chemical-vs-electrical-synapse.html
81. The synapse (article) | Human biology - Khan Academy, accessed July 12, 2025, https://www.khanacademy.org/science/biology/human-biology/neuron-nervous-system/a/the-synapse
82. Electrical synapse - Wikipedia, accessed July 12, 2025, https://en.wikipedia.org/wiki/Electrical_synapse
83. Chemical vs Electrical synapses - YouTube, accessed July 12, 2025, https://www.youtube.com/watch?v=YhG_wUx627c&pp=0gcJCfwAo7VqN5tD
84. Understanding electrical and chemical transmission in the brain - Frontiers, accessed July 12, 2025, https://www.frontiersin.org/journals/cellular-neuroscience/articles/10.3389/fncel.2024.1398862/pdf
85. Multiple sclerosis - Symptoms and causes - Mayo Clinic, accessed July 12, 2025, https://www.mayoclinic.org/diseases-conditions/multiple-sclerosis/symptoms-causes/syc-20350269
86. Multiple sclerosis - Wikipedia, accessed July 12, 2025, https://en.wikipedia.org/wiki/Multiple_sclerosis
87. Multiple sclerosis pathophysiology (video) - Khan Academy, accessed July 12, 2025, https://www.khanacademy.org/science/health-and-medicine/nervous-system-and-sensory-infor/multiple-sclerosis/v/multiple-sclerosis-pathophysiology
88. The Molecular Basis for Remyelination Failure in Multiple Sclerosis - ResearchGate, accessed July 12, 2025, https://www.researchgate.net/publication/334966681_The_Molecular_Basis_for_Remyelination_Failure_in_Multiple_Sclerosis
89. 3.3 Demyelinating diseases with an emphasis on Multiple Sclerosis – Neuroscience: Canadian 3rd Edition - eCampusOntario Pressbooks, accessed July 12, 2025, https://ecampusontario.pressbooks.pub/neurosciencecdn3/chapter/2-4-demyelinating-diseases-with-an-emphasis-on-multiple-sclerosis/
90. Mechanisms of Neuronal Dysfunction and Degeneration in Multiple Sclerosis - PMC - PubMed Central, accessed July 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC3030928/
91. Conduction in Myelinated, Unmyelinated, and Demyelinated Fibers - Portal de Periódicos da CAPES, accessed July 12, 2025, https://www.periodicos.capes.gov.br/index.php/acervo/buscador.html?task=detalhes&id=W1991601479

92. Conduction in Segmentally Demyelinated Mammalian Central Axons - PMC, accessed July 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC6573430/
93. Loss of Saltation and Presynaptic Action Potential Failure in Demyelinated Axons - Frontiers, accessed July 12, 2025, https://www.frontiersin.org/journals/cellular-neuroscience/articles/10.3389/fncel.2017.00045/full
94. Altered Expression of Ion Channels in White Matter Lesions of Progressive Multiple Sclerosis: What Do We Know About Their Function? - Frontiers, accessed July 12, 2025, https://www.frontiersin.org/journals/cellular-neuroscience/articles/10.3389/fncel.2021.685703/full
95. Mechanisms of Neurodegeneration and Axonal Dysfunction in Progressive Multiple Sclerosis - PMC - PubMed Central, accessed July 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC6466454/