Another Train Paradox

May the myelin be with you!

Bernard Delalande
Hirohisa Tamagawa
Vladimir Matveev

> Simplicity is the ultimate sophistication
>
> *Leonardo da Vinci*

Abstract For more than 70 years, biologists and biophysicists have been trying to unravel the mystery that exists regarding the saltatory conduction of so-called myelinated neurons. Albert Einstein used the train metaphor to explain the theory of relativity. It is possible to use a similar metaphor to better understand this transient functioning of the neuron: the action potential. We will, once again, use a train to demonstrate unequivocally that the action potential does not jump from node of Ranvier to node of Ranvier (noR) as we thought it would. It is possible to describe that the neuron uses an elegant method to increase the speed of transmission of the neural message. It is also important to conclude that this increase in speed, contrary to the common idea, has a certain energy cost that is proportional to speed and in accordance with thermodynamics.

Keywords axon · neuron · saltatory conduction · action potential · impulse propagation · HH model

Bernard Delalande
280, avenue de la Pierre Dourdant, 38290 La Verpilliere, France
E-mail: bernard@somasimple.com

Hirohisa Tamagawa
Department of Mechanical Engineering, Faculty of Engineering, Gifu University, 1-1 Yanagido, Gifu, Gifu, 501-1193 Japan
E-mail: tmgwhrhs@gifu-u.ac.jp

Vladimir Matveev
Laboratory of Cell Physiology, Institute of Cytology, Russian Academy of Sciences, Tikhoretsky Ave 4, St. Petersburg 194064, Russia
E-mail: vladimir.matveev@gmail.com

1 Introduction

For centuries, scientists have been fascinated by the nervous system and the manner in which messages pass through it. This animal electricity has been and remains the scene of intense research and theories. It is even possible to say that the mechanism of nerve transmission remains mysterious and that several contradictory hypotheses are still in the spotlight, even today.

"This nerve impulse spreads electrically" is a common notion for most of the physioloigsts [1,2], while some proposed that it is a mechanical soliton [3]. Finally, some try to link all the theories to unify them while others [4] return to more plausible bases.

In the meantime, biologists have separated neurons into two categories: so-called myelinated neurons and those that would not be myelinated. Of course, neuro-cytologists do not agree with this last distinction [5], which would suggest that some axons are naked.

Biologists and biophysicists have relaunched a debate related to this anatomical distinction: is the action potential propagation, for myelinated neurons, saltatory or not?

Table 1 Symbols used in the text

Symbols	Definition
t_0	start of the AP spike
t_1	end of the AP spike and begin of recovery period
t_2	end of recovery period
d_{AP}	action potential duration
d_{spike}	spike duration
l_{myel}	length of the spike
l_{inoR}	internode length
l_{noR}	node length $= l_{myel}$
l_{unmyel}	length of the spike
v_{myel}	conduction velocity for myelinated axon
v_{unmyel}	conduction velocity for unmyelinated axon
d_t	distance covered by the AP at t time
noR_t	noR reached at t time

2 A little physics in a short time

An observer, Albert, sees a train passing by at a known speed v. He can see it for a duration t. The length of the train is

$$l = v \cdot t. \qquad (1)$$

Namely, the train has covered a distance l during this period t

3 Let's uncover the action potential

We will examine the different common and particular properties that make it possible to differentiate neurons.

3.1 Common properties for all neurons

Considering the electrical component of the action potential (see fig 2): it has a duration that depends on the type of neuron being considered.

$$d_{AP} = t_2 - t_0 \tag{2}$$

The duration of the *effective* signal of the action potential, the spike, is almost constant regardless of the type of neuron considered.

$$d_{spike} = t_1 - t_0 \tag{3}$$

There is only one spike at any given time t and at a location x on the axon. This uniqueness suggests that its purely electrical nature may be already questionable. This is particularly true since it is constantly stated that a tiny fraction of the locally available ions are used. What is the phenomenon that prevents most of the unused ions from reacting and neutralizing the action potential at this place?

On the other hand, it is possible to have several action potentials on the same axon and at the same time but of course located at different locations. This primordial and undeniable concept, which has been observed time and again, is not in favor of an electrical propagation.

Each AP is electrically independent of the others that may be present on the axon. Even when there is a pulse train, electrical *interference* only occurs during the refractory period. The AP moves (usually) along the axon in only one direction. Its speed of displacement or conduction velocity v depends on the nature of the surrounding myelin.

The conduction velocity is always higher for myelinated neurons. The exception concerning giant axons is very controversial: Most would be a fusion of several hundred of axons, which suggests a very different functioning that may involve neurons selection.

$$v_{unmyel} < v_{myel} \tag{4}$$

The electrical component of the action potential is incompletely recorded. It does not reflect in any way its spatial dimension related to its geometry. He is also unable to give us back a major notion, his conduction velocity.

Because it has a duration d_{spike} and also because it has a velocity (v_{myel} or v_{unmyel}), it is possible to say that the spike has a length. The spike occupies a finite surface on the axon. It can therefore be said that it has a rather cylindrical shape that has a length l_{myel} or l_{unmyel}. It should be noted, however, that while the length appears to be proportional to the conduction velocity
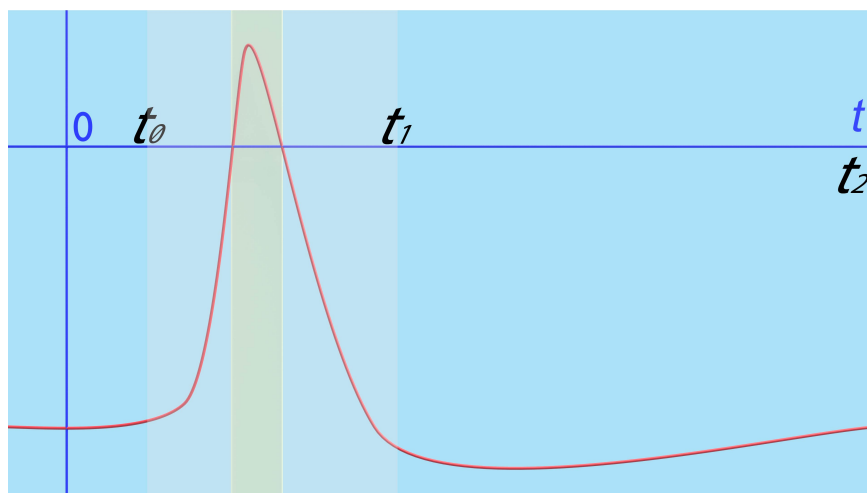
Fig. 1 Graphic representation of the electrical component of an action potential.

for unmyelinated fibres, the spike length appears to be fixed for myelinated axons. This raises more questions about the *electrical* nature of the AP, a second time.

$$l_{myel} = Const. \tag{5}$$

$$l_{unmyel} = v_{unmyel} \cdot d_{spike} \tag{6}$$

All axons are myelinated [6]. They are all surrounded by specialized cells that produce a myelin barrier that may or may not be compact [7]. It is interesting to ask the question of the existence of so-called unmyelinated fibers since neuro-cytology dispels this myth through anatomical evidence [8,5].

The worst example is the giant squid axon [9] used as a model in the HH model: It is surrounded by the thickest (0.7 *to* 1.3 μm) myelin layer in the animal kingdom and yet we are taught that it is not myelinated and it is a fusion of multiple axons [10]...

Most of the electrical component of the AP is negative. It is only at the moment of the peak that the voltage becomes very transiently positive before returning to negative again.

3.2 Unique properties of the unmyelinated neuron

The propagation of the action potential on the unmyelinated axon is continuously observable. it is therefore possible to know the position at a time t of the AP by simple computation, with x_0 the position of the AP at a time t_0:

$$d_t = v_{unmyel} \cdot t + x_0 \tag{7}$$
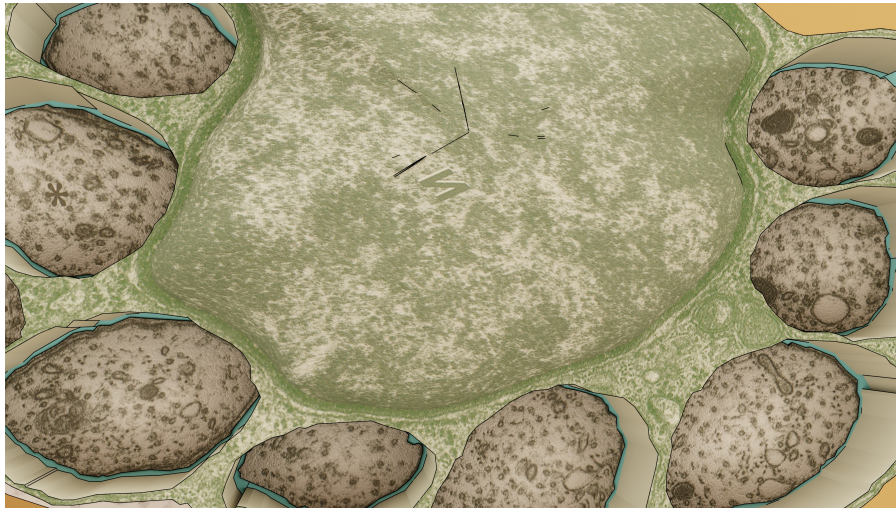
Fig. 2 Eight unmyelinated axons surrounnded by myelin (in light green). The Schwann nucleus takes the major area. 3D reconstruction from an microscopy by courtesy of Ennio Pannese.

We have seen that for unmyelinated fibers, the action potential has a physical length on the axon. The usual cylindrical shape of the neuron extension allows us to conclude that the AP occupies a surface proportional to the speed.

$$s = 2\pi \cdot r_{unmyel} \cdot (v_{unmyel} \cdot d_{spike}) \tag{8}$$

$$s \propto v_{unmyel} \tag{9}$$

It is therefore also possible to assume that energy consumption is proportional to speed. It is also likely that the ionic quantities and their counterparts, the ion channels involved, will become too large to ensure any propagation. It is also perfectly understandable that this operating mode for signal transmission, robust for low speeds, becomes a candidate for failure because it is exposed to possible mechanical obstacles. The speeds normally observed for this type of neurons are between 0.2 and 3 $m\ s^{-1}$. The spike has a more or less constant duration, this length varies between $2 \cdot 10^{-4}$ and $3 \cdot 10^{-3}\ m$.

3.3 Special properties of the myelinised neuron

In myelinated neurons, conduction is called saltatory although this statement is not yet clear-cut [11–14]. It is stated, without irrefutable evidence, that the action potential seems to jump from noR to the next one [15,16]. The process would of course be linked to the presence of myelin, which would improve electrical conduction while reducing energy costs [17].

It can be said that it is not possible to increase the transmission speed of a signal without increasing the energy expenditure. This goes beyond the thermodynamic principles and all the theories we apply and therefore successfully test every day on electrical signals.

We will demonstrate this without any uncertainty or ambiguity.

As mentioned above, the action potential, for myelinated fibers, is observed over a constant length related to the anatomy of the myelin surrounding the axon. This is the size of the noR which is about 1.0 μm. The small surface area suggests a better robustness.

However, the AP is continuously observable, in time, at this same noR.

On the other hand, the surface area occupied on the axon is greatly reduced and it could therefore be assumed that there is a reduction in the energy and physical resources (ion channels) involved.

This configuration contradicts any possible electrical propagation.

If we know the internode length, it is perfectly possible to know both the distance covered since the instant t_0 but also the number of jumped nodes noR_t. In the same way, we calculate the distance covered, which will then be divided by the length of the internode and the length of the node itself. Let us not neglect any length because all of them seem to be more crucial than they appear [18–20].

$$d_t = v_{myel} \cdot t \tag{10}$$

$$noR_t = \frac{d_t}{l_{inoR} + l_{noR}} \tag{11}$$

This gives us with a l_{inoR} value of 10^{-3} and l_{noR} of 10^{-6} m and a speed between 4 and 150 m s^{-1}: This gives already extraordinary numbers for our neurons of 4,000 and 149,850 noR *jumped* in only 1 second.

It is also perfectly possible to state without any doubt with eq. 10 and eq. 11 that the number of noRs traversed is both proportional to the duration t and the conduction speed v_{myel}.

4 Let's take the train

It is possible to solve the mystery of saltatory conduction by using trains instead of APs. A single but important distinction is that unlike a real train, the AP does not travel but is rebuilt from place to place.

4.1 The train metaphor

Our trains have a length determined by their speed and type. They are more or less long as described above for unmyelinated neurons. A train, on the opposite, appears relatively compressed (it should be even more so) and reflects the length of the AP at a noR (see fig. 3). The axons will look like rails, of course.

We add tunnels to represent, as it should be, the compact myelin because in fact much of the riddle lies in the darkness of their understanding.
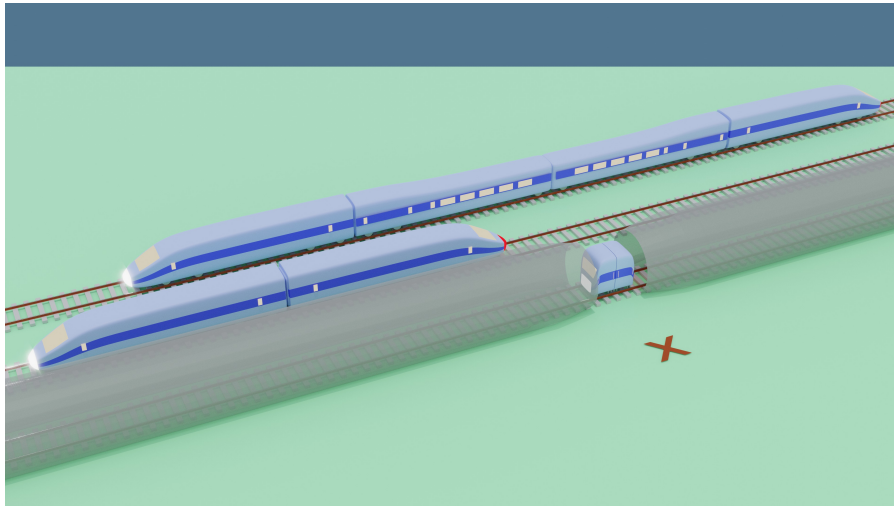
Fig. 3 3 action potentials: Axons are shown as rails. 2 APs on unmyelinated fibers at the top, the fastest is the longer one but its duration is similar. The tunnels are like compact myelin. The AP at noR seems compressed and looks quite stationary. its duration is the same as the others.

4.2 An observer looking at his watch

Our observer is asked to position himself at location X and start his stopwatch as soon as he sees the headlights of a train and stop it when he sees the taillights. He is certain: the transit time was almost identical for all 3 trains.

He noted that the farthest train seemed to go the fastest. Anyway, faster than the one on the central line.

He has a doubt about the last one: it seems that he appeared directly between the two tunnels and disappeared in the same way.He even had the impression that the train was running well in front of him but more like a movie than a real train, weird.

4.3 Trains don't jump

Let's twist the neck once and for all to this saltatory conduction. We have been led to believe for too long that the action potential jumps from noR to noR and that is what explains its increased speed [11,21]. Let's place a second observer at the exit of the first tunnel and ask him to perform the same measurements at the same time as the first one.

The second observer must see the train's headlights while the first observer must see the rear lights: there would then be an unequivocal saltatory conduction (see fig.4). That is not what is being witnessed [22]!

Otherwise, the observation time should necessarily decrease as the speed increases.
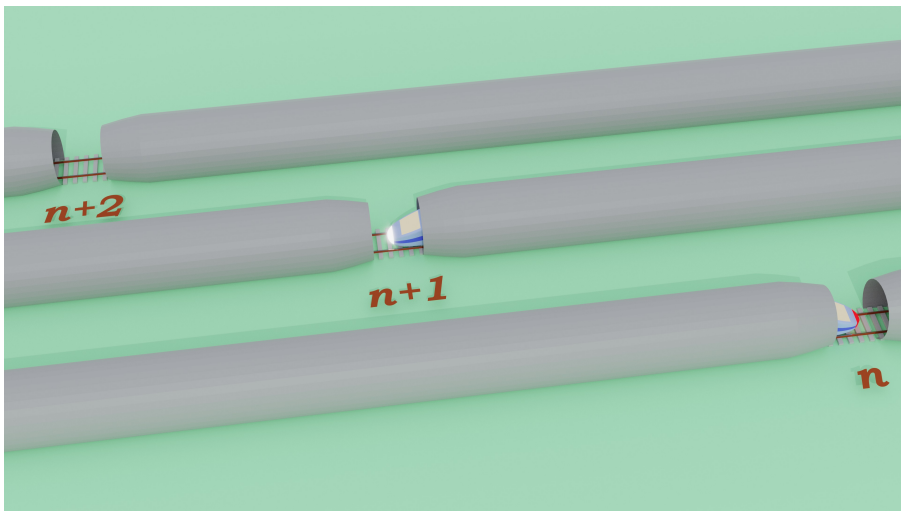
Fig. 4 Conventional saltatory conduction: the train jumps at the next node when it ends at the current one.
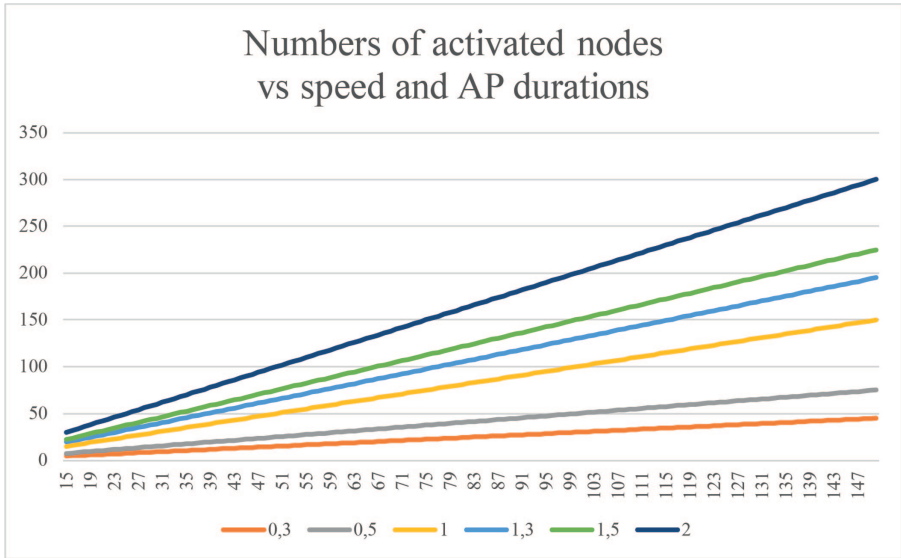
Fig. 5 Numbers of noRs activated vs conduction velocity (4 to 150 $m\ s^{-1}$) and internode length, and AP duration (0.3 to 2 ms). The energetic cost is higher with myelinated neurons.

That is not what is being witnessed!

There is only one solution that can satisfy our observation: There are two trains. It can be said that the number of APs existing on the axon is proportional to the conduction speed (see fig. 5). We already knew this truth from the beginning of this article with the equations 1, 10 and 11. Some of us cannot of course be convinced by this evidence. It doesn't matter because

mathematics is always uncompromising. Let us take an easy and uncontroversial example to satisfy potential critics. A myelinated fiber with an internode length of $2 \cdot 10^{-3}$ m, an AP (spike) of $5 \cdot 10^{-4}$ s and an average velocity of 40 m s^{-1}.

If it is true that it is only at the end of the action potential that the signal jumps to the next noR then we should be able to confirm by computation the speed of 40 m s^{-1}.

$$\frac{1}{d_{spike}} \cdot l_{inoR} = \frac{1}{5 \cdot 10^{-4}} \cdot 2 \cdot 10^{-3} = 4.0 \ m \ s^{-1} \ll 40 \ m \ s^{-1}$$

Or by the opposite method of calculation;

$$v_{myel} \cdot d_{spike} = 40 \cdot 5 \cdot 10^{-4} = 2.0 \cdot 10^{-2} \ m \gg 2 \cdot 10^{-3} \ m$$

It is also possible to check that the system reaches its low operating limit of 4.0 ms^{-1} which is well over the length of the internode.

$$v_{myel} \cdot d_{spike} = 4.0 \cdot 5 \cdot 10^{-4} = 2.0 \cdot 10^{-3} \ m$$

The system therefore only works when;

$$v_{myel} \cdot d_{spike} \geq l_{inoR} \tag{12}$$

It is only logical that it is the front of the train that triggers the departure of the next train. It is unlikely that the rear would be able to trigger an event that would be in front of the head of the train.

Saltatory conduction is not verified but we then have a major new problem: If there are several APs on the axon how, on arrival, there is only one left?

4.4 Electric trains without catenary cables

It is undeniable that the cells contain ions. It is also not disputed that the movement of these ions creates an electric field and also a potential difference. It is perfectly possible to elicit an AP with an *electrical* stimulus, but where is the generator of this impulse in the neuron? A few ions that have changed places, nothing more but nothing less.

Nevertheless, in the absence of an electrical circuit, these movements remain governed by the laws of electrostatics.

Of course, we must try to prove it, whereas an abundance of articles use, for example, an "electric" neuron model, the Hodgkin and Huxley model. It's a kind of reference, but is it accurate?

While it is true, and why contest it, that the action potential is closely linked to the presence of ion channels, it is also perfectly proven that myelin damage, compact or not (as in multiple sclerosis) leads to a slower conduction rate for all types of fibres. The action potential is even eliminated when the compact myelin disappears consecutively over a tiny length of the axon [23].

It is therefore also perfectly possible to state that conduction can only be carried out correctly when ion channels are present (which is why unmyelinated fibres are less affected in MS). And, it is undeniably known that the internodal zone has an area where ion channels are completely absent. If the conduction stops then it cannot be electric in the sense that we mean it.

We will explain why the para-nodal zone, on the other hand, has totally essential ion channels.

4.5 You shall not pass!

It is accepted that the axon membrane undergoes a slight vertical deformation in unmyelinated fibers. We also know that there is no doubt that the membrane undergoes a phase transition during the AP. Nor can we dispute the essential presence of ion channels. There are also many references [24–29] showing that the compression of axons, myelinated or not, leads to a slowing down and then the disappearance of APs. As it is also known that the optimal conduction rate depends on the quality of the myelin.

We have enough evidence to understand that the basic propagation system is based on a vertical force associated with horizontal translation (see fig.6). This process is repeated throughout the axon, which obviously wastes time and energy. If we accept that increased speed is linked to an improvement in the basic system, then we must admit that by reducing the presence of action potential at noR, it leads to a summation of the forces we have described. We have a larger but slower vertical and horizontal component. The solution being of course to transform this large quantity gathered at the noR into a faster horizontal component than usual.

The best way to change the speed of a system that is too slow is to replace it with a faster one.

If the neuron membrane is prevented from deforming by surrounding it with a sufficiently rigid envelope made of layers, reinforced by tight junctions, the mechanical wave is then sent to the next node in a liquid medium without much loss.

And it works: We use this kind of device every day in the industry. It is quite easy to verify because the available speed can go up to more than $1,500 \ ms^{-1}$.

We need to lift our last problem. The AP that activates the next noR is not transmitted because the ion channels under the myelin activate as soon as the "liquid" wave passes. These firm locks provide better strength and pressure transmission and limit ionic movements at the noR (see fig.6).

It becomes clear that the minimal functional unit of the nervous system is not, and has never been, the neuron alone.

It is always associated with myelin and cannot function without it.
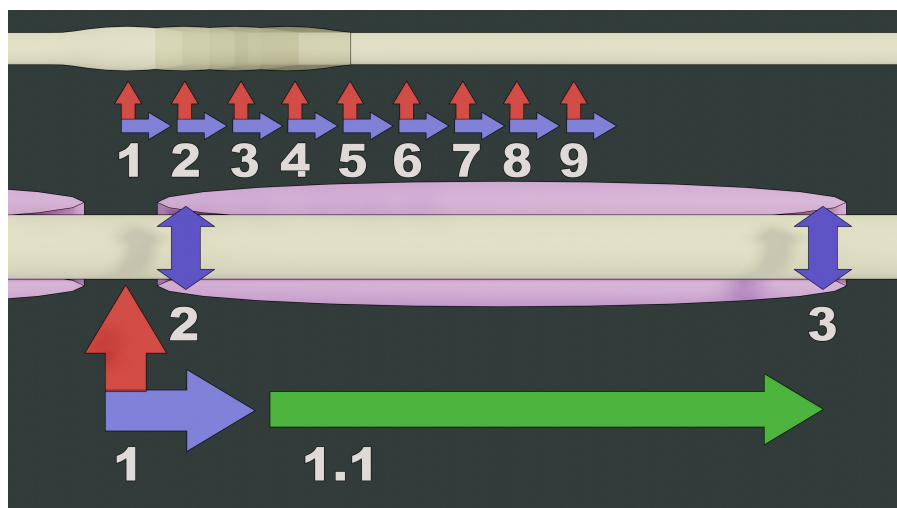
Fig. 6 Propagation methods of APs in unmyelinated vs myelinated neurons.

5 Conclusion

We have shown that conduction is not saltatory as some people thought. We provide mathematical evidence that can be verified but is not questionable and confirm our theory, which sheds new light on events that seemed obscure and complex.

This does not detract from the precursors who have tried to give a "truth" but which is too incomplete, limited to a single aspect but pleasant.

We provide an elegant and straightforward solution that better explains the facts observed.

This vision, which is based on scientific observations, restores the nobility of this essential couple of the nervous system: the neuron and its companion, the myelin.

References

1. A. L. Hodgkin. Evidence for electrical transmission in nerve: Part I. *The Journal of Physiology*, 90(2):183–210, July 1937.
2. A. L. Hodgkin. Evidence for electrical transmission in nerve: Part II. *The Journal of Physiology*, 90(2):211–232, July 1937.
3. Thomas Heimburg and Andrew D. Jackson. On soliton propagation in biomembranes and nerves. *Proceedings of the National Academy of Sciences of the United States of America*, 102(28):9790–9795, July 2005.
4. Tetsuya Akaishi. Saltatory Conduction as an Electrostatic Compressional Wave in the Axoplasm. *The Tohoku Journal of Experimental Medicine*, 244(2):151–161, 2018.
5. Ennio Pannese. *Neurocytology: fine structure of neurons, nerve processes, and neuroglial cells*. G. Thieme Verlag ; Thieme Medical Publishers, Stuttgart ; New York : New York, 1994.
6. Maurizio De Pittà. Myelin and saltatory conduction. *arXiv:1708.00534 [q-bio]*, August 2017.

7. Richard S. Bear, Francis O. Schmitt, and John Z. Young. The Sheath Components of the Giant Nerve Fibres of the Squid. *Proceedings of the Royal Society of London. Series B, Biological Sciences*, 123(833):496–504, 1937.

8. J. P. Fraher and A. W. O'Sullivan. Interspecies variation in axon-myelin relationships. *Cells, Tissues, Organs*, 167(2-3):206–213, 2000.

9. E. R. Brown and N. J. Abbott. Ultrastructure and permeability of the Schwann cell layer surrounding the giant axon of the squid. *Journal of Neurocytology*, 22(4):283–298, April 1993.

10. R. Martin. On the structure and embryonic development of the giant fibre system of the squid Loligo vulgaris. *Zeitschrift Fur Zellforschung Und Mikroskopische Anatomie (Vienna, Austria: 1948)*, 67(1):77–85, July 1965.

11. R. Fitzhugh. Computation of impulse initiation and saltatory conduction in a myelinated nerve fiber. *Biophysical Journal*, 2:11–21, January 1962.

12. Mauricio J. Giuliodori and Stephen E. DiCarlo. MYELINATED VS. UNMYELINATED NERVE CONDUCTION: A NOVEL WAY OF UNDERSTANDING THE MECHANISMS. *Advances in Physiology Education*, 28(2):80–81, June 2004.

13. Y. Laporte. Continuous conduction of impulses in peripheral myelinated nerve fibers. *The Journal of General Physiology*, 35(2):343–360, November 1951.

14. M. Rasminsky and T. A. Sears. Internodal conduction in undissected demyelinated nerve fibres. *The Journal of Physiology*, 227(2):323–350, December 1972.

15. A. F. Huxley and R. Stampfli. Effect of potassium and sodium on resting and action potentials of single myelinated nerve fibers. *The Journal of Physiology*, 112(3-4):496–508, February 1951.

16. A. F. Huxley and R. Stämpfli. Evidence for saltatory conduction in peripheral myelinated nerve fibres. *The Journal of Physiology*, 108(3):315–339, May 1949.

17. Thomas Sangrey and William B Levy. Conduction velocity costs energy. *Neurocomputing*, 65-66:907–913, June 2005.

18. Marc C. Ford, Olga Alexandrova, Lee Cossell, Annette Stange-Marten, James Sinclair, Conny Kopp-Scheinpflug, Michael Pecka, David Attwell, and Benedikt Grothe. Tuning of Ranvier node and internode properties in myelinated axons to adjust action potential timing. *Nature Communications*, 6(1):8073, November 2015.

19. A. Foust, M. Popovic, D. Zecevic, and D. A. McCormick. Action Potentials Initiate in the Axon Initial Segment and Propagate through Axon Collaterals Reliably in Cerebellar Purkinje Neurons. *Journal of Neuroscience*, 30(20):6891–6902, May 2010.

20. Amanda J. Foust, Yuguo Yu, Marko Popovic, Dejan Zecevic, and David A. McCormick. Somatic membrane potential and Kv1 channels control spike repolarization in cortical axon collaterals and presynaptic boutons. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 31(43):15490–15498, October 2011.

21. Barbara E. Goodman and Steven B. Waller. Propagation of action potentials in myelinated vs. unmyelinated neurons. *Advances in Physiology Education*, 26(1-4):223, December 2002.

22. Dominique Debanne, Emilie Campanac, Andrzej Bialowas, Edmond Carlier, and Gisèle Alcaraz. Axon Physiology. *Physiological Reviews*, 91(2):555–602, April 2011.

23. Marion Baraban, Sigrid Mensch, and David A. Lyons. Adaptive myelination from fish to man. *Brain Research*, 1641(Pt A):149–161, 2016.

24. Felipe A. Court, Diane L. Sherman, Thomas Pratt, Emer M. Garry, Richard R. Ribchester, David F. Cottrell, Susan M. Fleetwood-Walker, and Peter J. Brophy. Restricted growth of Schwann cells lacking Cajal bands slows conduction in myelinated nerves. *Nature*, 431(7005):191–195, September 2004.

25. R. Fern and P. J. Harrison. The relationship between ischaemic conduction failure and conduction velocity in cat myelinated axons. *Experimental Physiology*, 79(4):571–581, July 1994.

26. Charles ffrench Constant, Holly Colognato, and Robin J. M. Franklin. Neuroscience. The mysteries of myelin unwrapped. *Science (New York, N.Y.)*, 304(5671):688–689, April 2004.

27. Marina Grandis, Massimo Leandri, Tiziana Vigo, Michele Cilli, Michael W. Sereda, Gianfranco Gherardi, Luana Benedetti, Gianluigi Mancardi, Michele Abbruzzese, Klaus-Armin Nave, Lucilla Nobbio, and Angelo Schenone. Early abnormalities in sciatic nerve

function and structure in a rat model of Charcot-Marie-Tooth type 1a disease. *Experimental Neurology*, 190(1):213–223, November 2004.

28. R. Padrón and L. Mateu. Repetitive propagation of action potentials destabilizes the structure of the myelin sheath. A dynamic x-ray diffraction study. *Biophysical Journal*, 39(2):183–188, August 1982.

29. Anna C. Williams and Peter J. Brophy. The function of the Periaxin gene during nerve repair in a model of CMT4f. *Journal of Anatomy*, 200(4):323–330, April 2002.