A physical answer to Peters quadrant mystery: a modeling study

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Abstract
In the development of oligodendrocytes in the central nervous systems, the inner and outer tongue of the myelin sheath tend to be located within the same quadrant, which was named as Peters quadrant mystery. In this study, we conduct in silico investigations to explore the possible mechanisms underlying the Peters quadrant mystery. A biophysically detailed model of oligodendrocytes was used to simulate the effect of the actional potential-induced electric field across the myelin sheath. Our simulation suggests that the outer tongue of the oligodendrocyte connecting with its soma breaks the central symmetry of the myelin sheath, causing the more concentrated electric field near the outer tongue and directly inducing the same quadrant phenomenon. This model also sheds light on how the electrical activity of oligodendrocytes affects the myelin growth.
Introduction

Since the pioneering electron microscope (SE) observations of the spiral structure of myelin sheath were conducted between 1950s and 1980s \(^{[1-2]}\), the ultrastructure and function of the myelin sheath have been paid more attention in neuroscience \(^{[3][4]}\). The myelin sheath was initially reported as a pure eclectic insulator, enabling a "saltatory" impulse propagation \(^{[5]}\). However, this hypothesis cannot explain many experimental observations in myelin ultrastructures. For example, myelin in the superficial layers of the cortex has diversified longitudinal distribution \(^{[6]}\); myelin sheaths in the peripheral nervous system (PNS) spiral oppositely and the same to its neighbor on the same \(^{[7][8]}\) and adjacent axon, respectively \(^{[9]}\); and in particular, Peters quadrant mystery \(^{[10,11,14-19]}\) has been observed in many myelin sheaths. These non-trivial ultrastructures imply that the function of the myelin is more than an insulating layer.

An anatomically accurate and biophysically detailed model can improve our understanding of myelin ultrastructures and functions. For example, a coil inductor model of the spiraling structure was used to understand the unique spiraling directions between adjacent myelin sheaths. \(^{[12]}\) To achieve a positive mutual inductance, the neighboring myelin on the same axon shall have opposite spiraling directions, while the neighboring myelin on the adjacent axons shall have the same spiraling direction. This simulation has been confirmed by EM observations \(^{[11]}\).

This study follows the same research paradigm to explore the possible mechanisms underlying the Peters quadrant mystery. In particular, the myelin sheath is modeled as a distributed parameter circuit \(^{[13]}\), and the electric field (E-field) distribution induced by neural electric activities is investigated \textit{in silico}. The simulated E-field was used to explain why the inner tongue and outer tongue of the myelin sheath tend to locate in the same quadrant, a repeatedly observed intriguing phenomenon \(^{[10,11,14-19]}\). The new knowledge gained in this study provides new insights into the relationships between neural electrical activity and myelin growth.

Peters quadrant mystery

During axon growth, the myelin wraps around it as a spiral "bandage". However, there is an interesting tendency for this spiral's initial and end points to occur close together, as if the myelin were insisting on running only complete laps of the arena \(^{[14][15]}\). This is analogous to winding rope into a film spool until the rope spills at the angle where the initial "lump" occurs. Initial and end points will tend to occur within the same "quadrant" (Figure1(a)). Peters first observed this phenomenon in the optic nerves of rodent models in 1964, then further confirmed by multiple studies in visual callosal \(^{[11]}\), dorsal and anterior root axon \(^{[16][17]}\) and sural nerves \(^{[18][19]}\). Interestingly, Schwann cell myelination in PNS demonstrated quadrant tendency diminishing gradually with the thickening of myelin \(^{[17]}\). In contrast, myelination of oligodendrocytes in the CNS exhibits a stronger tendency with the thickening of myelin \(^{[10]}\).
Peter's quadrant mystery indicates that the growth of the inner terminal is inhibited when it is located at the same quadrant of the outer tongue. The mechanism underlying this radial-angle-modulated growth rate is still an open question \cite{15}. In this study, to verify the hypothesis that the neural electrical activities modulate the myelin growth rate, a distributed parameter circuit is built to analyze the E-field on the cross-section of the myelin sheath.

**Method**

The action potential propagation will induce an electric potential across the axon (equivalent to the current source connecting the inside and outside terminals of the axon in Figure 1(c)). The E-field on the cross-section of myelin sheath can be simulated by the distributed circuit (Figure 1(c)). In particular, the transmembrane parts are modeled as an RC circuit. The non-transmembrane parts are modeled as resistors. The outer tongue possesses a larger cell-membrane area, and cell fluid cytoplasm has lower resistance and higher capacitance \cite{25-27}. Since the inner tongue is the growing terminal, we mainly focus on the E-field on the inner tongue. That is the voltage on the transmembrane capacitance of the inner tongue in Figure 1(d). The more detailed modeling approach can be found in Supplementary S1.

**Result**

1. **The E-field distribution is stronger at the outer tongue zone.**

The current of each transmembrane capacitor (Figure 1(c)) is re-distributed into a round shape analogous to the circle of the myelin sheath (overlapped with actual myelin spirals for a clear illustration). As shown in Figure 2(a), the current is preferentially concentrated at the outer tongue zone, regardless of the position of the inner tongue. A robust test is shown in Figure 2(b) by changing the value of capacitance and resistance applied in the simulation, suggesting the consistently high-current zone near the outer tongue in all conditions. All model details and parameter values are described in the Table 1 in Supplementary S1.

2. **The radial angle influences the electric voltage on the inner tongue**

Since the outer tongue zone demonstrates a stronger E-field, the voltage on the inner tongue will have a periodical maximum when it passes through this area in each growth circle (Figure 2(c)). In particular, the voltage on the inner tongue will have a polarity reverse when it passes the same quadrant area, causing a sudden change from positive maxima to negative maxima (Figure 2(c)). This periodic amplitude and polarity change of the transmembrane voltage of the inner tongue directly leads to the same quadrant phenomenon.

**Discussion**

1. **The voltage polarity**

A typical waveform of the action potential is shown in Figure 3. Since we only consider the absolute voltage change (start from 0 mV rather than -70 mV), the action potential is very similar to a positive monophasic voltage waveform (take the inside terminal of the axon as the reference point in Figure 3). Therefore, the E-field across the myelin
has a dominant positive component, which is equivalent to a current from the inside to the outside. This E-field direction is quite critical for the myelin growth and play a key role in the same quadrant phenomenon.

2. **The explanation to Peter quadrant mystery**

The relationship between the transmembrane voltage of the inner tongue and its radial position is illustrated in Figure 4. When the inner tongue locates in position 1 (entering the outer tongue zone), the transmembrane E-field of the inner tongue reaches the maximum outward value. In Peters's observations, position 1 showed the lowest occurrence frequency \[^{10}\], indicating the fastest growth rate. With further growth, the inner tongue will reach position 2 (leaving the outer tongue zone). The transmembrane E-field of the inner tongue reaches the maximum inward value. The occurrence frequency at this position is the highest, indicating the slowest growth rate. Therefore, we can conclude that the growth rate is correlated with the polarity (direction) and amplitude of the transmembrane E-field. An outward E-field can facilitate growth, while an inward E-field can inhibit growth. In other words, an extracellular negative E-field can facilitate myelin growth by inducing an outward transmembrane E-field.

All our simulations suggested that the outer tongue breaks the central symmetrical structure of the myelin sheath, resulting in a focused current concentration at the outer tongue zone. Therefore, the inner tongue will experience a periodical voltage change as shown in Figure 4. The E-field facilitates the growth at the left half circle and inhibits the growth at the right half circle, leading to the observed "same quadrant mystery." Interestingly, this phenomenon does not only appear in Oligodendrocytes\[^{10}\][\(^{11}\]) but also exists in the early stage of the myelination by Schwann cells in PNS\[^{17}\]. However, the nucleus and soma of Schwann cells are also wrapped around the axons, which is different from that of Oligodendrocytes. As the number of myelin sheaths increases, the central symmetrical structure will gradually recover. Therefore, the same quadrant tendency will diminish gradually with the thickening of myelin (Figure 5)\[^{20}\].

3. **A possible explanation for g-ratio**

The g-ratio is the ratio of the inner axonal diameter to the total outer diameter including the myelin sheath\[^{21}\]. The g-ratio ranged from 0.72 to 0.81 in CNS, and 0.46 to 0.8 in PNS. The increase of the g-ratio the increasing of axon’s diameter, and the increase of g-ratio is sharper with the smaller axonal diameter. However, if the axon diameter is less than 0.4 μm, it will fail to form the myelin sheath\[^{22}\], indicating the key role of the axonal physical properties in terminating the growth of myelin. Although there are still controversies\[^{22}\][\(^{23}\]), earlier studies suggested the contribution of g-ratio in modulating conduction velocity\[^{24}\]. However, this theory fails to build the connection between the signal propagation and the inner tongue, which is the growth terminal of the myelin. In this study, the modelled E-field generated from the action potential, tends to decrease by increasing the size of myelin layers. Thus, when the E-field is lower than a certain threshold, the growth of the inner tongue will be automatically terminated. Since this driven force is action potential, whose amplitude is proportional to the axonal diameter,
the maximum myelin layer shall be correlated with the axonal diameter. Thus, this theory indicates the potential correlation between the g-ratio and the E-field on the inner tongue.

**Conclusion**

The physical origin of the same quadrant mystery is the preferential E-field distribution on the cross-section of the myelin. Since actional potentials induce E-field, it explains the relation between neural electric activity and the ultrastructure of myelin. Furthermore, the preferential E-field distribution resulted from the breaking of the central symmetry by the outer tongue, which explains the difference of the "same quadrant" observation between Oligodendrocytes in CNS and Schwann cells in PNS. Meanwhile, this study also reveals the physical factor to facilitate or inhibit myelin growth: extracellular negative or positive E-field can facilitate or inhibit the myelin growth, respectively. Finally, the computational approach can probe neuronal ultrastructures at a resolution far beyond the current state-of-the-art biological experiments, providing a promising tool to explore neuroscience from a physical perspective.

**Acknowledgments**

This work was supported by the grant from Guangdong Research Program (2019A1515110843), Shenzhen Research Program (JCYJ20170818152810899, GJHZ20200731095206018) and Chinese Academy of Sciences Research Program (2011DP173015,172644KYSB20190077).

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Figure 1. (a) The illustration of the Peters quadrant mystery in Oligodendrocytes: there is a relative angle $\beta$ between the inner and outer tongue. When $\beta$ is lower than 50º, the inner and outer tongues are considered in the same quadrant. (b) The frequency of $\beta$ within each 45º octant (Reproduced from Peters observation [10]). (c) The equivalently distributed circuit network model of the cross-section of a myelinated axon. Two kinds of circuit components representing different local electrical properties of the myelin sheath are showed. (d) The transmembrane capacitance of the growth terminal of the inner tongue.
Figure 2. (a) The E-field distribution of on the cross-section of the myelinated axon. (i) The actual myelin spirals are overlapped for a clearer illustration; (ii-iv) The Robustness test results of the distributed circuit network by different electrical parameters, the test results show a similar electric field distribution. (b) Simulation results of transmembrane voltage on the growth terminal of inner tongue in the 2nd, 3rd, 4th, 5th layers of myelin. The voltage on the inner tongue has a periodical maxima and polarity reverse when it passes through the outer tongue zone in each growth circle.
Figure 3. A typical waveform of the action potential and current path between the node of Ranvier and internode of myelin.

Figure 4. The relationship between the transmembrane voltage of the inner tongue and its radial position. The growth rate is correlated with the polarity (direction) and amplitude of the transmembrane E-field.
Figure 5. The change in centrosymmetric structure between immature and mature myelin formed by Schwann Cells and oligodendrocytes.