Association Learning with Myelin Plasticity

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Abstract

Myelin wraps axons, resulting in increased conduction speed. For a long time, myelin patterns were thought to be established in development, after which they remained static. However, over the past decade, evidence has accumulated demonstrating that myelination changes throughout life, is activity dependent, and that myelin plasticity plays a role in various forms of learning, ultimately shaping behavior. Crucially, blocking the formation of new myelin leads to impaired learning in various domains. Despite the experimental evidence, there has been relatively little computational work exploring myelin plasticity, with no plausible account to how low-level changes in myelin can lead to high-level changes in behavior. Here, we take a step towards such an account. Specifically, we demonstrate that a model of spiking neurons, employing established cortical motifs, and using a simple and biologically grounded myelin learning rule, can learn associations – a cognitive building block that underlies more complex capacities such as motor sequencing and predictive processing. Crucially, synaptic weights are all equal and remain static throughout our simulations; the functional changes we observe arise solely from changes in conduction delays. Our work provides a proof of principle as to how myelin plasticity may shape neural circuits to qualitatively change behavior.

Introduction

Myelin is a fatty substance that ensheaths axons - increasing their conduction speed. It is formed by oligodendrocytes (OL's), which differentiate from oligodendrocyte precursor cells (OPC's), the largest population of proliferating cells in the adult brain (Dawson et al., 2003). It has been generally believed that myelin is established as part of a developmental program to set up circuits, after which it remains largely static. However, in the past decade, evidence has accumulated that challenges this dogma.

Recent research has shown that myelin plasticity continues into adulthood, is modulated in an activity dependent manner, and is implicated in various forms of learning (for a comprehensive review, see Bonetto et al., 2021). Chemogenetic and optogenetic stimulation causes increases in myelination (Gibson et al., 2014; Mitew et al., 2018), whereas sensory and social deprivation results in myelin deficits in specific brain regions (Liu et al., 2012; Xin et al., 2024). Moreover, neurons that are more active tend to be preferentially myelinated (Hines et al., 2015). Further, myelin patterns in the cortex are not all or none, but rather, individual axons exhibit patchy myelination (Tomassy et al., 2014; Hughes et al., 2018), raising the possibility that conduction delays can be adjusted along a broad continuum. Recent studies have demonstrated that various forms of learning, for instance, motor skill learning (Mckenzie et al., 2014; Xiao et al., 2016), and memory consolidation (Steadman et al., 2020) are accompanied by changes in myelin in relevant circuits. Crucially, blocking the differentiation of new OL's (restricting the formation of new myelin) via the deletion of a transcription factor, myrf, is followed by impairments in the acquisition of new skills, while sparing those that have already been learned (Mckenzie et al., 2014; Xiao et al., 2016; Steadman et al., 2020). The body of experimental evidence that has accrued indicates that activity dependent myelin plasticity plays a role in learning-related behavioral change.

Despite the growing body of experimental findings, there has been comparatively little computational work investigating the consequences of myelin plasticity. The few computational studies within this domain have explored how myelin changes can affect aspects of circuit dynamics such as changes in synchrony or correlation structure, often relying on representing the activity of an entire population of neurons as an oscillator, or utilizing complex learning rules (Pajevic et al., 2014; Noori et al., 2020; Talidou et al., 2022; Pajevic et al., 2023). However, these studies have not offered a plausible account to how changing conduction speed can bring about behavioral changes.

Here, we demonstrate that a biologically grounded model of spiking neurons, along with a simple myelin learning rule, can reliably learn associations – a fundamental cognitive function that underlies capacities such as motor sequencing and predictive processing. Our model draws on several established cortical motifs: recurrence, delayed inhibition with long lasting IPSC's (Packer & Yuste, 2011), and clustered neural connectivity (Perin et al., 2011).

Results

Our model consists of 2 layers of recurrently connected leaky integrate and fire neurons (FIg 1A) with randomly sampled conduction delays and biophysically realistic parameters. Each

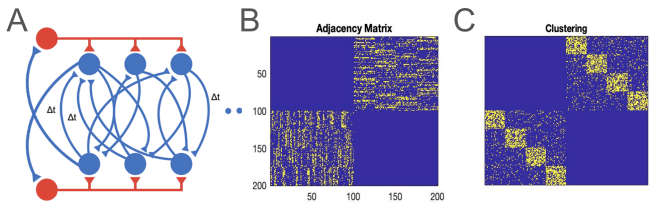

Figure 1: (A) Schematic of the model. (B) Adjacency matrix (C) Clustering revealed by sorting of adjacency matrix.

layer consists of 100 excitatory neurons with each neuron synapsing onto 20 neurons in the opposite layer. Based on cortical connectivity patterns (Perin et al., 2011), we constrain the network connectivity to promote clustering (Fig 1B and C). Additionally, the neurons in each layer synapse on a single inhibitory neuron that provides delayed inhibition to every neuron in the opposite layer, with the decay rate of IPSC's being longer than that of EPSC's. This is modeled after the connectivity patterns and biophysical properties of local inhibitory neurons, for instance, PV+ interneurons (Packer & Yuste, 2011). Along with intrinsic circuit dynamics, we also add noise to each neuron, sampled from a gamma distribution, to mimic spontaneous neural activity. Crucially, synaptic weights are all equal and remain static through our simulations, with the functional changes in our network being brought about solely through changes in delays.

We start by showing that before learning, stimulating (bringing closer to threshold) a subset of neurons, A, in layer 1, results in diffuse activity in layer 2. In the learning stage, we pair stimulation of A with stimulation of a subset, B, in layer 2. We use a simple learning rule – if the firing rate of a neuron over a 200ms sliding window exceeds a threshold, we decrease its delay by a small, fixed amount. The high firing rate requirement is inspired by observations that neural activity can trigger calcium transients in OL processes which in turn are correlated with myelin changes (e.g. Krasnow et al., 2018). After 50 paired stimulation trials, we test the network again with the newly learned delays. After learning, stimulating A results in only neurons in B being activated (Fig 2A). Next, we repeat the process, utilizing the same initial conditions, this time pairing A with a different subset of neurons, C. In this case an association between A and C is formed (Fig 2B)

We provide some intuition as to why the model works. Delayed inhibition produces competitive interactions such that earlier spike arrivals are favored, and later arrivals are ineffective at activating their targets. Initially, stimulating

Figure 2: (A) Learning an association between A and B. (B) Learning an association between A and C.

A results in the arrival of impulses to each layer 2 neuron with roughly equal delays (equal means, but some variance). Thus, there is little bias as to which cluster of neurons in layer 2 will be activated. By pairing A with simultaneous stimulation of B, neurons that are highly connected between A and B will experience positive feedback, and reverberate, leading to higher frequency firing than the stimulation of A or B alone. The reverberation-induced high firing rate puts these neurons over the threshold of the myelin learning rule – decreasing their delays. The result is that the highly connected set of neurons between A and B end up with shorter delays on average than other neurons. Thus, subsequent activation of A will induce earlier activation of neurons in B and competitive inhibition will suppress the rest of the population from firing, reflecting the formed association.

Conclusion

We present a proof of principle as to how myelin plasticity in a network of neurons with established cortical motifs can perform behaviorally relevant computation – forming associations. Association learning is a computational building block for a variety of cognitive functions, from linking together motor sequences, to learning predictive relationships in modalities such as vision and language. In ongoing work, we are exploring sequence learning and representation learning based on the ideas introduced in our model.

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