Review



# Understanding Cerebellar Input Stage through Computational and Plasticity Rules

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*Review*

# Understanding Cerebellar Input Stage through Computational and Plasticity Rules

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**Simple Summary:** One of the main theories regarding how the brain functions is that plasticity modifies the effectiveness of synaptic transmission to control the signals transfer function. It has been demonstrated that the granular layer in the cerebellum regulates the gain of signals that travel via the mossy fiber channel. Up until now, the influence of plasticity on incoming activity patterns was examined through a combination of computational modeling and electrophysiological recordings in cerebellar slices. This approach revealed a wide range of distinct types of synaptic plasticity in the granular layer, frequently in conjunction with changes in intrinsic excitability. Here, we try to give a quick summary of the most common types of plasticity observed at excitatory synapses formed by mossy fibers onto principal neurons in the granular layer. Next, we will emphasize our current understanding of the mechanisms behind synaptic and intrinsic plasticity and how they affect function, offering important new perspectives on how information is interpreted and rearranged at the cerebellar input stage.

**Abstract:** A central hypothesis on brain functioning is that plasticity regulates the signals transfer function by modifying the efficacy of synaptic transmission. In the cerebellum, granular layer has been shown to control the gain of signals transmitted through the mossy fiber pathway. Until now, the impact of plasticity on incoming activity patterns was analyzed by combining electrophysiological recordings in acute cerebellar slices and computational modeling, unraveling a broad spectrum of different forms of synaptic plasticity in the granular layer, often along with forms of intrinsic excitability changes. Here, we attempt to provide a brief overview of the most prominent forms of plasticity at excitatory synapses formed by mossy fibers onto principal neurons (granule cells, Golgi cells and unipolar brush cells) in the granular layer. Specifically, we will highlight current understanding of the mechanisms and their functional implications of the synaptic and intrinsic plasticity, providing valuable insights into how inputs are processed and reconfigured at the cerebellar input stage.

**Keywords:** cerebellum; plasticity; granule cells; Golgi cells; unipolar brush cells

Long-lasting changes in synaptic connectivity within neural networks are key to shape the activity of neuronal populations [1,2]. Despite being overlooked in classical cerebellar theories [3,4], empirical studies and computational modeling have unraveled a broad spectrum of synaptic and intrinsic plasticity mechanisms in the granular layer, providing valuable insights into how inputs are processed and reconfigured at the cerebellar input stage.

## 1. Plasticity in Granule Cells

A multitude of inputs from various brain regions are conveyed via mossy fibers into the granular layer [5–7]. Within this layer, mossy fibers branch out across different folia, creating multiple ramifications. Each branch then gives rise to numerous rosettes, which are central components of the

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cerebellar glomeruli [7,8]. These rosettes consist of presynaptic elements characterized by multilobed grooves, where dendrites from tens of granule cells establish contact. Completing the cerebellar glomerulus are the axons of Golgi cells and their basal dendrites, which receive input from mossy fibers and ascending axons of granule cells [9]. Over the past decades, studies have revealed that prolonged high-frequency discharges of mossy fibers, extending beyond a specific duration, induce long-term potentiation (LTP) at the mossy fiber-granule cell synapse [10–12]. The induction of mossy fiber-granule cell LTP hinges on intricate changes in intracellular calcium concentrations, orchestrated by a complex interplay of key factors. First, NMDA receptors (NMDARs) serve as the primary conduits for $Ca^{2+}$ influx, together with metabotropic glutamate receptors 1 (mGluR1s) that enhance this process via the inositol trisphosphate ($IP_3$) intracellular pathway [11,13–15]. Secondly, activation of voltage-dependent calcium channels (VDCCs) prompts membrane depolarization and the generation of repetitive spike discharges, significantly contributing to LTP induction [10]. Thirdly, intracellular $Ca^{2+}$ signal modulation through $Ca^{2+}$-induced $Ca^{2+}$ release (CICR) contributes to long-term plasticity by amplifying and prolonging calcium signals [16–18]. At different synapses, LTP controls numerous functional aspects of the synapse, including neurotransmitter release, spillover, and postsynaptic receptor gating and expression [19–21]. Based on patch-clamp recordings and mathematical modeling, mossy fiber-granule cell LTP is manifested by an increased probability of neurotransmitter release [22,23]. However, advancing from the discovery of LTP at the mossy fiber-granule cell synapse, our understanding of plasticity mechanisms in cerebellar granule cells has evolved, uncovering a new layer of complexity (Figure 1).

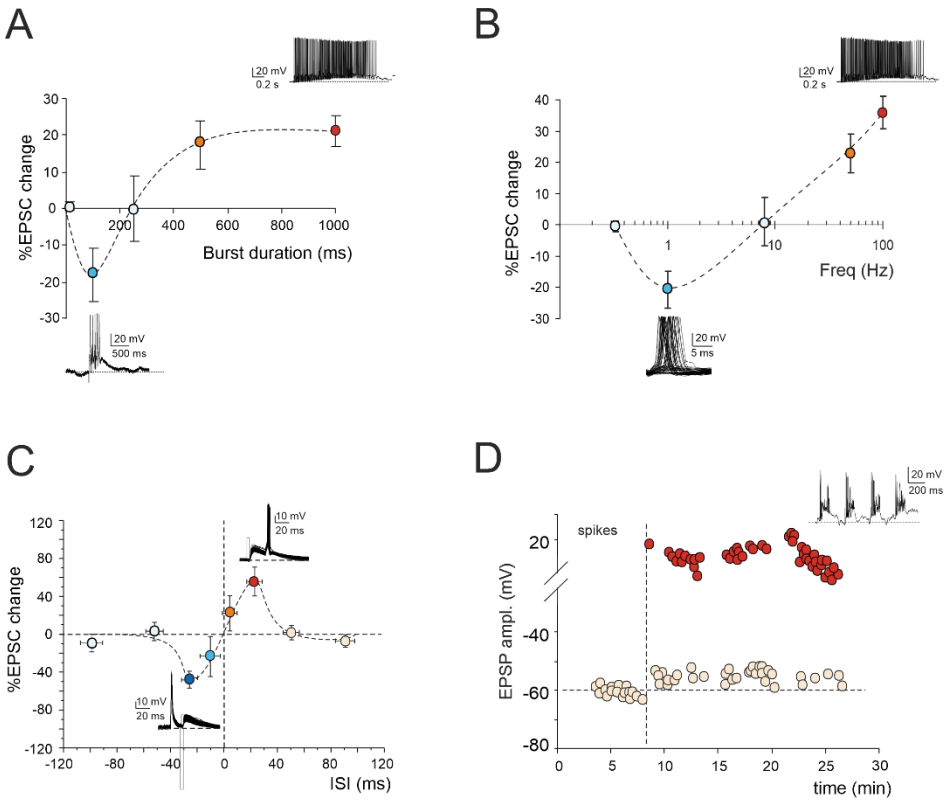


**Figure 1. Multiple forms of long-term plasticity at mossy fiber-granule cell synapse.** (A) Application of 1-100 continuous mossy fiber stimuli at 100 Hz revealed a net LTD at 100 ms bursts, a neutral point at 250 ms, and an LTP at 500 ms. LTP tends to plateau with trains lasting >500 ms. The bottom (LTD) and top (LTP) traces show granule cell response during 100 ms and 1000 ms burst duration, respectively. Data are reported as mean ± SEM (adapted from [30]). (B) LTP or LTD were differentially induced by using the same number of impulses (100) at different frequencies. The probability of obtaining LTD is high at 1 Hz, while that of obtaining LTP is high at 50 Hz, with a neutral point around 8 Hz. The bottom (LTD) and top (LTP) traces show granule cell response during 100 stimuli at the frequencies of 1 Hz and 100 Hz, respectively. Data are reported as mean ± SEM

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(adapted from [28]). (C) Spike timing-dependent plasticity (STDP) was induced pairing an EPSP evoked by mossy fiber stimulation with a spike elicited by current injection into the granule cell. The spike followed or preceded the onset of the EPSP by Δt = ±5, ±25, ±50, and ±100 ms. Pairings was repeated 60 times at 6 Hz. Average plot represents EPSC amplitude changes for different Δt. Note the striking transition from maximal LTP to maximal LTD over the narrow time window ~0 ms. The bottom (LTD) and top (LTP) traces show granule cell response during STDP induction protocol at Δt = -25 ms and Δt = +25 ms, respectively. Data are reported as mean ± SEM (adapted from [45]). (D) Effect of TBS delivered from holding potential of −50 mV. Exemplar recording showing that LTP is manifest as an EPSP increase leading to spike generation in granule cells. The graph shows the time course of EPSP amplitude changes and transition to EPSP–spike complexes. The top trace shows the granule cell membrane depolarization elicited by TBS.

### *1.1. LTP/LTD Balance at Mossy Fiber-Granule Cell Synapse*

According to the Hebb postulate [20] and its extension in the Bienenstock–Cooper–Munro model (BCM; [25], both LTP and LTD can characterize a specific synapse, with their induction contingent upon varying levels of postsynaptic $[Ca^{2+}]_i$ increase, via the activation of distinct biochemical pathways [26,27]. Ex vivo and in vivo studies on cerebellar plasticity have elucidated a bidirectional modulation involving both LTP and LTD at the mossy fiber-granule cell relay [28–31]. The balance between LTP and LTD is crucial for supporting computation and learning in the granular layer, and its regulation relies on diverse mechanisms. Intracellular postsynaptic calcium levels can be regulated by burst patterns of mossy fiber discharge. The extent of $[Ca^{2+}]_i$ increase correlates with the duration of mossy fiber bursts, resembling a BCM-like relationship ([25]. Short, isolated bursts with minor $[Ca^{2+}]_i$ fluctuations induce LTD, whilst prolonged or repeated bursts leading to significant $[Ca^{2+}]_i$ increase result in LTP (Figure 1A). Bidirectional long-term synaptic plasticity can also be influenced by the frequency-coded pattern of mossy fiber stimulation, resulting in different levels of postsynaptic elevations in $[Ca^{2+}]_i$ (Figure 1B). Interestingly, this relationship between plasticity and $[Ca^{2+}]_i$ levels mirrors that induced by high-frequency bursts of varying durations, except that, in this case, low-frequency LTD necessitates the involvement of mGluRs rather than NMDARs. This indicates that receptor pathways activated by diverse afferent patterns via calcium concentration changes shared plastic mechanisms to promote the reconfiguration of inputs within the granular layer [28,30]. However, the balance between LTP and LTD at the mossy fiber-granule cell synapse is not only orchestrated by specific input patterns but also by molecular factors and neuromodulators. Nitric oxide (NO) is released in the granular layer upon high-frequency mossy fiber stimulation via NMDAR-dependent and NOS-dependent mechanisms. Acting as a retrograde messenger, NO favors presynaptic release probability, thus promoting LTP over LTD [32]. Furthermore, the activation of $\alpha 7$ nicotinic acetylcholine receptors ($\alpha 7$nAchRs) on both mossy fiber terminals and granule cell dendrites amplifies the influx of $Ca^{2+}$ at postsynaptic sites. This intensified $Ca^{2+}$ influx has the potential to shift LTD towards LTP, sustaining this plasticity for prolonged durations [33]. The balance between LTP and LTD at the mossy fiber-granule cell synapse is regulated not only by specific input patterns but also by molecular factors and neuromodulators. NO is released in the granular layer upon high-frequency mossy fiber stimulation through NMDAR-dependent and NOS-dependent mechanisms. Functioning as a retrograde messenger, NO enhances presynaptic release probability, thereby favoring LTP over LTD. Additionally, activation of $\alpha 7$ nicotinic acetylcholine receptors ($\alpha 7$nAchRs) on both mossy fiber terminals and granule cell dendrites amplifies $Ca^{2+}$ influx at postsynaptic sites. Additionally, a recent in vivo study has proposed that the 20 Hz facial stimulation triggers $Ca^{2+}$ influx through NMDA receptors, leading to activation of calcium-sensitive proteins and enzymes such as calmodulin and NOS, resulting in increased NO levels, contributing to mossy fiber-granule cell LTP in the mouse cerebellar cortex. Interestingly, this facial stimulation-induced LTP of mossy fiber-granule cell synaptic transmission is abolished inhibiting NO of NOS abolishes, regardless of the absence or presence of nicotine. This suggests that NOS activation is not only required for the induction of facial stimulation-induced MF-granule cell LTP under control conditions but also necessary for the nicotine-induced enhancement of mossy fiber-granule cell synaptic transmission LTP [34].

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*1.2. Spike-Timing Dependent Plasticity at Mossy Fiber-Granule Cell Synapse*

Expanding upon the BCM theory, spike-timing-dependent plasticity (STDP) represents a unique form of synaptic plasticity where the temporal sequence of presynaptic and postsynaptic spikes dictates the $[Ca^{2+}]_i$ levels, determining whether a synapse is strengthened or weakened [35–44]. A recent finding has revealed that the interplay between synaptic response (excitatory postsynaptic potential, EPSP) and spikes can drive STDP at the mossy fiber-granule cell synapse [45] (Figure 1C). Additionally, the activation of $GABA_A$ receptors has been shown to reverse the phase dependence of this STDP, exhibiting an anti-Hebbian effect. Although the molecular mechanisms underlying GABAergic regulation remain elusive, this phenomenon offers a potent mechanism for diversifying the array of possible STDP configurations at mossy fiber–granule cell synapses. Furthermore, mossy fiber-granule cell STDP has been found to be tuned to the theta band (6 Hz) at which Golgi cells and granule cells show oscillations [46]. Therefore, mossy fiber-granule cell STDP may play a crucial role in linking cerebellar learning with low-frequency oscillations observed in thalamocortical and hippocampal circuits, facilitating the coordination of learning and memory processes during different functional states such as voluntary movement, resting attentiveness, and sleep [47–51].

*1.3. Granule Cell Intrinsic Plasticity*

The regulation of information processing in the brain also encompasses persistent adjustments in ionic conductance within specialized neuronal regions, influencing the long-term propagation of neuronal information [52,53]. Following high-frequency activation of the mossy fiber-granule cell relay, LTP triggers a sustained enhancement in granule cell electroresponsiveness, intensifying their firing (Figure 1D). This enhancement involves an increase in granule cell input resistance and a reduction in spike threshold, possibly due to changes in persistent sodium and potassium currents [10,23]. Moreover, similar to synaptic LTP, intrinsic plasticity in granule cells relies on NMDAR activation, ensuring a specific rise in intracellular calcium concentration and subsequent activation of calcium-dependent intracellular pathways. Intrinsic plasticity can restore granule cell excitability levels when synaptic excitation is weak [10]. Through this plastic mechanism, low background firing rates of granule cells, resulting from tonic inhibition by Golgi cells, can thus be reinstated by precise mossy fiber activation, inducing bursting in granule cells [10,54,55]. Therefore, this mechanism ensures high reliability in transmitting specific mossy fiber input patterns to Purkinje cells, thereby regulating input processing and phase learning in the cerebellum. Additionally, when local groups of mossy fibers are active, the pattern of granule cell firing in a region will be determined by the strength of the mossy fiber connections, synchronized quantal release, and improved reliability of excitatory drive, increasing the fraction of active granule cells. This may allow temporal correlations across multiple local mossy fibers to be transmitted through the granular layer as intense patches of synchronized activity, while allowing rate-coded signals to be mediated by lower intensity, uncorrelated granule cell activity [56].

**2. Plasticity in Golgi Cells**

In recent decades, extensive research has shed light on the vital role played by Golgi cells in orchestrating the activity of granule cells [51–56]. Functioning as the primary source of inhibition for granule cells, Golgi cells establish two essential inhibitory circuits: feedforward and feedback inhibition. Feedforward inhibition begins when mossy fibers activate Golgi cells in the glomerulus, leading to subsequent inhibition of granule cells via their axons. This inhibition operates through two mechanisms: phasic and tonic inhibition [55–57]. Phasic inhibition, mediated by synaptic $GABA_A$ receptors, enhances the precision of granule cell spike-timing by narrowing the time window for synaptic integration (time window effect, see [58]). Tonic inhibition, mediated by extrasynaptic $GABA_A$ receptors, establishes the baseline level of granule cell excitability, allowing the neuron to discern significant information from background noise. Feedback inhibition further modulates granule cell activity by engaging Golgi cells, which subsequently inhibit nearby granule cells [55]. Through these two inhibitory loops, Golgi cells regulate the balance between excitation and

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inhibition, with high E/I ratios promoting LTP, intermediate ratios inducing LTD, and very low ratios preventing plastic changes, thereby serving as a primary regulator of long-term synaptic plasticity within the granular layer circuit [58]. Moreover, Golgi cells, with their extensive axonal plexus, establish lateral inhibition, resulting in a center-surround (C/S) organization of granule cell activity. Under prolonged high-frequency activation of the mossy fiber bundle, the granular layer network exhibits specific spatial organization, where high excitation levels in the core permit the passage of high-frequency discharges, while inhibition in the surround filters out low-frequency discharges. This facilitates the transmission of high-frequency bursts along channels formed by the ascending axons of granule cells heading towards the molecular layer. As a result, LTP and LTD are organized in C/S structures, with more active centers favoring LTP and less active surrounds preferentially inducing LTD, thus accelerating (LTP) or delaying (LTD) granule cell responses to mossy fiber bursts. Overall, Golgi cells play a crucial role in controlling the information flow to Purkinje cells by shaping granule cell activity: feed-forward inhibition introduces a time-windowing effect, lateral inhibition establishes a center-surround organization of GCL responses, and local control of GrC excitatory-inhibitory balance determines inhibition-controlled plasticity. Furthermore, feedback GrC inhibition, combined with the broad pf convergence over numerous GoCs, forms the substrate for generating regular synchronous oscillations over large GCL fields [51–54]. While the role of Golgi cells in the inhibition-controlled plasticity of granule cells has been well-characterized, exploration of synaptic and intrinsic plasticity within Golgi cells remains largely unexplored. However, recent investigations and mathematical models of cerebellar Golgi cells have uncovered critical plastic mechanisms that could serve as potent regulatory mechanisms of granular layer plasticity (Figure 2).

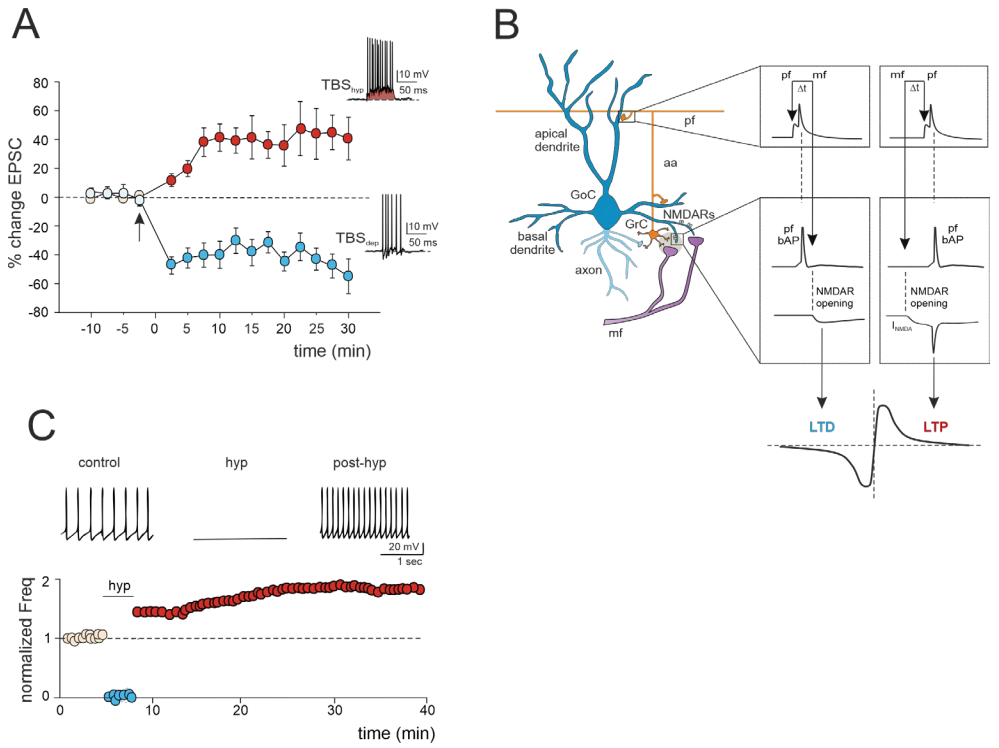


**Figure 2. Multiple forms of long-term plasticity at mossy fiber-Golgi cell synapse.** (A) Bidirectional plasticity at Golgi cell excitatory synapses: dependence on membrane potential. LTP or LTD were induced by delivering TBS from different Golgi cell membrane potentials ($TBS_{hyp}$ and $TBS_{dep}$). The graph shows the average time course of EPSC amplitude changes during LTP and LTD. The arrow indicates the induction time, and each point is the average of 15 contiguous EPSC amplitudes. Data are reported as mean ± SEM. The bottom (LTD) and top (LTP) traces show Golgi cell response during $TBS_{hyp}$ and $TBS_{dep}$ (adapted from [59]). Note the stronger depolarization and spike generation in $TBS_{hyp}$ (red area) than $TBS_{dep}$. (B) STDP at mossy fiber inputs. Backpropagating spikes are elicited by parallel fiber stimulation either ~10 ms before or ~10 ms after a single synapse activation in the mossy fibers. The NMDA receptor-dependent current (INMDA) generated at the mossy fiber synapse is

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shown in the two cases. The bottom plot shows a theoretical STDP curve (adapted from [60]) showing modest INMDA changes leading into the LTD region and large INMDA changes leading into the LTP region. (C) Transient hyperpolarization induces a long-term increase in Golgi cell spontaneous firing. Top, example experiment showing that a 3 min negative current injection of -50 pA hyperpolarizes the Golgi cell membrane to -65 mV and suppresses firing activity. An increase in Golgi cell spiking occurred after hyperpolarization. Bottom, Golgi cell show a long-term increase in spontaneous activity after being hyperpolarized (adapted from [62]).

### *2.1. LTP/LTD Balance at the Mossy Fiber-Golgi Cell Synapse*

A recent study has unveiled bidirectional plasticity at mossy fiber-Golgi cell synapses, marking the first observation of such phenomena in cerebellar Golgi cells [59]. This synaptic plasticity demonstrates a unique voltage dependence, with the direction of plasticity (LTD or LTP) determined by the membrane potential of Golgi cells during theta-burst stimulation (TBS) induction. Specifically, LTP is favored when TBS occurs at depolarized Golgi cell potentials, while LTD is favored at hyperpolarized potentials (Figure 2A). The mechanisms underlying this voltage-dependent plasticity involve the activation of distinct calcium channels: LTP requires the activation of T-type $Ca^{2+}$ channels alongside NMDARs, whereas LTD uniquely relies on L-type $Ca^{2+}$ channels [59]. Notably, this voltage-dependent plasticity differs from the purely NMDAR-dependent plasticity observed at neighboring mossy fiber-granule cell synapses, suggesting that mossy fiber presynaptic terminals engage diverse induction mechanisms depending on the target cell. Furthermore, considering that multiple long-term regulatory mechanisms may coexist, dictating the balance of plasticity at the mossy fiber-Golgi cell synapse, a recent realistic model of Golgi cells predicted that temporally correlated mossy fiber-parallel fiber inputs can induce spike-timing-dependent plasticity (STDP) at the mossy fiber-Golgi cell synapse, when NMDAR is activated [60] (Figure 2B). Specifically, the integration of multimodal information from parallel fibers by apical dendrites could control the coincidence of spikes with specific mossy fiber inputs arriving on basal dendrites, thereby driving the shift between LTD and LTP at the mossy fiber-Golgi cell relay. Therefore, with their electrogenic architecture, Golgi cells may act as cortical detectors, finely regulating information flow through the granular layer under parallel fiber with high temporal precision. Considering that spike timing has been demonstrated to control the LTP/LTD balance at neighboring mossy fiber-granule cell synapses [45], the STDP phenomenon might extend to the entire granular layer, supporting the cerebellar capacity to sustain input integration and network functioning. According to a theoretical model [61], the granular layer circuit may indeed operate within a learning framework. In this scheme, incoming mossy fiber information could initially be stored in the oscillatory network of Golgi cells, subsequently driving STDP at neighboring mossy fiber-granule cell synapses, thus orchestrating spatiotemporal input processing and plasticity within the granular layer.

### *2.2. Golgi Cell Intrinsic Plasticity*

Golgi cell activity can also be affected by other mechanisms that can alter inhibitory transmission and its impact on granule cell plasticity. Temporary hyperpolarization of Golgi cells leads to a significant, long-term increase in their spontaneous firing rate, a phenomenon known as firing rate potentiation (FRP) (Figure 2C). FRP in Golgi cells depends on electrical couplings that regulate the timing and extent of both spontaneous and sensory-evoked correlated activities. This regulation involves cooperative effects related to shared synaptic depolarization, spikelet transmission, and plasticity mechanisms. Furthermore, this process is mediated by calcium-calmodulin-dependent kinase II (CaMKII) and BK-type calcium-activated potassium channels [62]. Golgi cell inhibitory activity is also regulated by gap junctions ([63–65]. Within this electrically coupled network of Golgi cells, action potential synchronization occurs in the absence of correlated input, while transient desynchronization occurs with sparse excitatory synaptic input [64,66]. The amplification of gap junction signals, attributed to sodium currents, implies that electrical synapses are not merely passive intercellular channels but rather dynamic forms of interneuronal communication [65]. Therefore, like chemical synapses, the electrical ones can also exhibit plasticity and be modifiable [67,68]. This

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introduces new perspectives on the concept of gap junction plasticity, a homeostatic mechanism recently explored in various brain regions [69–72]. A computational model, investigating this type of plasticity within a recurrent cortical network [70], simulated that it can regulate the balance between synchronous and asynchronous patterns of activity in the network. Strong electrical coupling between neurons tends to induce oscillatory activities characterized by synchronized bursting mediated by inhibitory neurons. These bursts trigger depression of the gap junctions, allowing the network to transition away from the oscillatory regime and spike asynchronously. Conversely, in the asynchronous regime, neuronal firing is sparse contributing to the potentiation of gap junctions. Consequently, the irregular regime tends to strengthen the connections between neurons via gap junctions. This suggests a direct functional role for gap junction plasticity in information transmission within neuronal assemblies [69–72]. However, despite evidence of modifiable electrical synapses and oscillations in Golgi cells, gap junction plasticity remains unexplored and warrants further investigation.

## 3. Plasticity in Unipolar Brush Cells

Unipolar brush cells (UBCs) are glutamatergic interneurons primarily located in the granular layer of the vestibulocerebellum [73–75]. Unlike granule cells, which typically possess 4–5 dendrites innervated by various mossy fibers, UBCs have a single short dendrite with a brush-like appearance, typically receiving inputs from a single mossy fiber terminal [75]. Additionally, they possess axonal branches constituting a noncanonical, cortex-intrinsic subset of mossy fibers that form synapses with both granule cells and other UBCs [74–78]. Consequently, while neurotransmitters generally have a short lifespan in the synaptic cleft due to rapid diffusion, the specialized three-dimensional arrangement of mossy fiber-UBC synapses promotes a persistent presence of glutamate in the cleft [79,80]. This leads to prolonged and repetitive activation of postsynaptic receptors in UBCs. As a result, in response to mossy fiber input, UBCs display a unique dual-component response: a rapid initial AMPA receptor-mediated current, followed by a sustained tail of inward current lasting seconds (i.e., steady-state current) [77,79,81–84]. Phasic excitation can induce robust action potential bursts and transiently elevated firing rates, whilst persistent inward currents in UBCs facilitate periods of tonic action potential firing. Short-term plasticity mechanisms further refine and modulate both transient and prolonged synaptic currents in UBCs. Fast AMPA and kainate receptor-mediated responses exhibit depression at short inter-stimulus intervals, characterized by a prolonged reduction in the amplitude of fast EPSCs evoked by a secondary mossy fiber stimulus [79–81]. This short-term depression reflects increased availability of unbound AMPA receptors over time, resulting in a smaller response to the second stimulus. Conversely, responses of the slower steady-state current can be either facilitated or depressed, depending on the inter-stimulus interval duration. Specifically, at short intervals (50–400 ms), the initial steady-state current exhibits a positive undershoot, reversing between 400 and 600 ms, and gradually recovering to negative values after several seconds [79]. The characteristics of postsynaptic receptors, combined with limitations on the diffusion of glutamate caused by synaptic ultrastructure and glutamate transporters, thus shape the time course of the resulting steady-state current. This, in turn, advances a sustained series of action potentials in UBCs in response to individual presynaptic stimuli.

### *3.1. The Impact of UBC on Temporal Dynamics in the Granular Layer Network*

The cerebellar ability to learn complex input-output relationships across various time scales relies on establishing a diverse temporal framework [85–89]. Consequently, mossy fiber inputs undergo intricate transformations within the granular layer, giving rise to highly complex spatial-temporal activity patterns in granule cells. Central to this process are UBCs, which play essential roles in shaping the activity dynamics of the granule cell population. UBCs extend axonal branches within the granular layer, likely innervating a group of granule cells [77,80]. A single action potential in UBCs may thus initiate a cascade of excitatory postsynaptic currents (EPSCs) across a large ensemble of granule cells, profoundly impacting their activity. Consequently, UBCs ensures an amplification of mossy fiber signals in a feed-forward manner, enabling intricate temporal adjustments of incoming

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mossy fiber signals [81,84,90–92]. As evidence of the presence of UBCs as presynaptic elements in the granular layer circuitry, granule cells exhibit spontaneous events resembling bursts of action potentials characteristic of UBC activity in whole-cell recordings (Figure 3A). Additionally, fast EPSPs can be observed in a granule cell in response to bursts of action potentials in UBCs following activation of the mossy fiber-UBC synapse (Figure 3B). Furthermore, individual intermediary UBCs have the capacity to modulate the firing phase of their postsynaptic granule cells, with their response to glutamatergic input ranging from partial inhibition (e.g., OFF UBC) to complete excitation (e.g., ON UBC) [90,93,94]. Spiking responses in postsynaptic UBCs evoked by mossy fiber stimulation at 100 Hz demonstrated that high-frequency stimulation could produce a burst of spikes that outlasted the stimulus (ON-UBC) or induce a pause in spontaneous action potential firing (OFF-UBC) (Figure 3C).

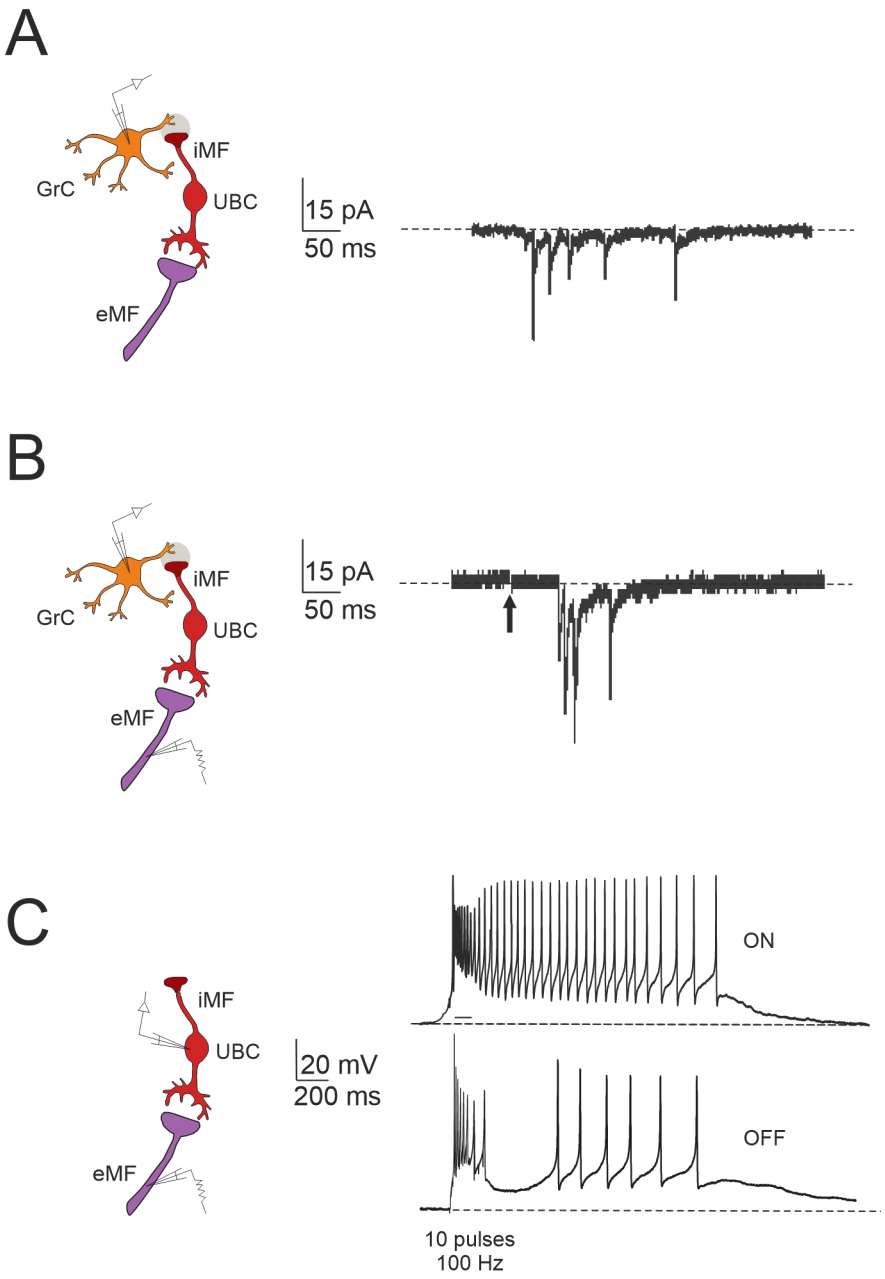


**Figure 3. Forward signaling by UBCs in the vestibulocerebellar granular layer.** (A) Example of whole-cell recordings from a granule cell, displaying spontaneous events reminiscent of UBC discharges [81]. (B) Burst of EPSCs in a granule cell in response to presynaptic stimulation, with a first peak delay [81]. (C) Spiking responses in postsynaptic UBC evoked by mossy fiber stimulation (100 Hz): Note that high-frequency stimulation can produce a burst of spikes that outlasted the stimulus (ON-UBC) or generate a pause in spontaneous action potential firing (OFF-UBC; adapted from [82]).

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Thus, UBCs, classified as ON and OFF cells based on their response to glutamatergic input, may offer distinct parallel processing of multisensory input to their targets [90,93,95]. Delays introduced by intermediary UBCs are attributed to the slow decay of excitatory or inhibitory synaptic currents from presynaptic inputs. Therefore, synaptic pathways involving multiple UBCs may contribute to long pauses and delays crucial for adaptive learning across a range of time scales, as observed in cerebellar-like circuits of electric fish [96]. Even in the absence of plasticity, UBCs enable the granular layer to induce delays in changes of firing rate for periods extending from hundreds to thousands of milliseconds, significantly enhancing the diversity of coding, especially in the temporal domain [91]. While UBCs are distributed across the cerebellum, their prevalence is particularly notable in regions governing eye movement and vestibular processing. The UBC network represents a mechanism that may prolong granule cell firing and contribute to the maintenance of sensory signals underlying motor learning with delayed sensory feedback [81,92,97]. A computational model has explored the implications of the varied phase shifts in UBC responses to sinusoidal vestibular inputs (Figure 4). In the absence of UBCs, granule cells fire in synchrony with extrinsic mossy fiber inputs from the vestibular system, aligning with preferred phases of movement (Figure 4A). However, when UBCs are integrated into the network, the response of granule cells exhibits significantly more diverse phase shifts (Figure 4B).

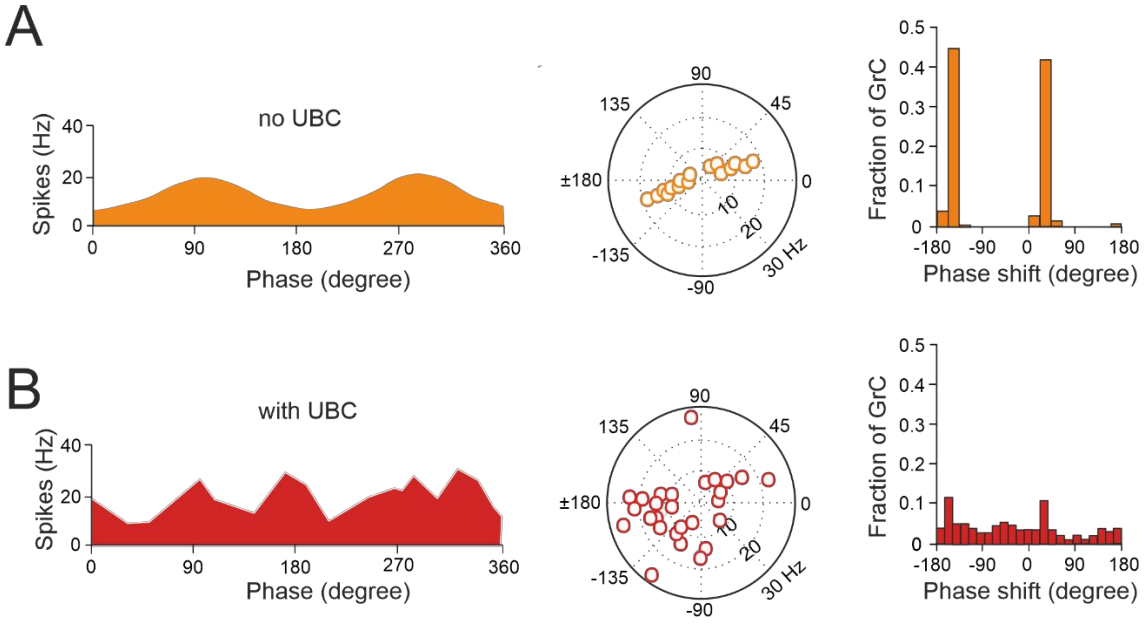


**Figure 4. UBCs increase the phase diversity of granule cell responses.** (A) Simulation of granular circuit without UBCs. The dynamics of the granular layer model (4500 granule cells receiving inputs from 500 mossy fibers) in response to sinusoidal mossy fiber stimulation, in the presence and absence of UBCs, were simulated. (A) Without UBCs, granule cells fire in phase with mossy fiber inputs. Right, average firing rate curve of 30 random selected granule cells in one input period are shown. Left, polar plot and histogram represent the amplitude of modulation and phase shift from the fitted GC firing rate curves, respectively. (B) Same as (A), but for sample granular cell outputs with UBCs in the circuit (adapted from [91]).

This diversity in UBC phase shifts results in a range of phase shifts in granule cells. Consequently, this temporal diversity enables the identification of granule cell firing at any phase of a sinusoidal head movement, aligning with adaptive filter models [98–103], and in vivo observations [104]. However, the presence of UBCs in the dorsal vermis and cerebellar hemispheres of higher mammals, including humans [75,105–107], underscores their potential role beyond vestibular sensory processing. This suggests new perspectives on UBC involvement in modulating granule cell activity to support complex motor and cognitive tasks as well.

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## 4. Granular Layer Plasticity: Insights from Computational Models

The granular layer of the cerebellum exhibits a highly organized arrangement, facilitating the rapid processing of mossy fiber signals within a millisecond timeframe. This intricate architecture gives rise to a diverse spectrum of spatio-temporal patterns through a combination of inhibitory mechanisms and learning processes [85,86,88]. Golgi cells, extending their inhibitory influence across numerous granule cells, establish a brief 5-millisecond window for signal processing (i.e., time window effect, see [88], optimizing the transmission of spikes to Purkinje cells [108,109]. Furthermore, bidirectional plasticity at the mossy fiber–granule cell synapse finely regulates spike timing and number, shaping the window-matching effect due to Golgi cell inhibition [110]. Initial efforts to simulate the impact of granular layer plasticity employed a firing rate model, where synaptic weights were modulated to optimize information transfer through the granular layer [111]. This model highlighted the need of balancing the strength of mossy fiber synapses with that of Golgi cell synapses, complemented by alterations in intrinsic excitability. Moreover, it proposed gating of mossy fiber–granule cell plasticity to address the absence of teaching lines in this section of the cerebellar circuitry. This model anticipated subsequent findings regarding plastic changes in intrinsic excitability [10], the role of acetylcholine in plasticity gating [33] and the role of inhibitory plasticity between Golgi cells and granule cells [57]. Subsequently, recent computational models have simulated the impact of distributed synaptic weights in the cerebellar granular layer network [61,112]. These models elucidated the crucial role of synaptic weights at various connections in regulating spike number and positioning in granule cells in response to mossy fiber bursts. Specifically, synaptic weights at mossy fiber to granule cell synapses regulated the delay of the first spike, while those at mossy fiber and parallel fiber to Golgi cell synapses controlled the duration of the time window for spike emission. Additionally, weights of synapses governing Golgi cell activation modulated granule cell inhibition intensity, thereby influencing spike emission. Through these mathematical models, it was demonstrated that different combinations of synaptic weights optimize either spike timing precision or spike number, effectively governing transmission and filtering properties along the mossy fiber pathway [113]. Furthermore, these models discerned distinct roles for various components of inhibition, with lateral inhibition dictating the center-surround effect, feed-forward inhibition influencing the time-windowing effect, and feedback inhibition regulating coherent oscillations [88,112]. Mathematical modeling has significantly influenced research in the field over the past three decades, revealing that various forms of synaptic and intrinsic plasticity at different sites act conjunctively to enable the cerebellar granular layer to function as an adaptive spatio-temporal filter [99,100,113–116]. In this way, synaptic modifications distributed across the network endow the granular layer with the capability to sustain sensorimotor integration and learning, ultimately orchestrating complex motor and cognitive tasks [116–119].

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