Complex Spike Wars: a New Hope

Martha L. Streng · Laurentiu S. Popa · Timothy J. Ebner

Published online: 7 July 2018 © The Author(s) 2018

Abstract
The climbing fiber–Purkinje cell circuit is one of the most powerful and highly conserved in the central nervous system. Climbing fibers exert a powerful excitatory action that results in a complex spike in Purkinje cells and normal functioning of the cerebellum depends on the integrity of climbing fiber–Purkinje cell synapse. Over the last 50 years, multiple hypotheses have been put forward on the role of the climbing fibers and complex spikes in cerebellar information processing and motor control. Central to these theories is the nature of the interaction between the low-frequency complex spike discharge and the high-frequency simple spike firing of Purkinje cells. This review examines the major hypotheses surrounding the action of the climbing fiber–Purkinje cell projection, discussing both supporting and conflicting findings. The review describes newer results establishing that climbing fibers and complex spikes provide predictive signals about movement parameters and that climbing fiber input controls the encoding of behavioral information in the simple spike firing of Purkinje cells. Finally, we propose the dynamic encoding hypothesis for complex spike function that strives to integrate established and newer findings.

Keywords Purkinje cell · Complex spike · Climbing fibers · Simple spike · Motor error · Cerebellar cortex

Introduction
The distinctive morphology, cellular actions, and physiological properties of the climbing fiber–Purkinje cell synapse suggest a unique role in the cerebellum and behavior [1–3]. As one of the strongest synapses in the mammalian central nervous system, the action of climbing fibers on Purkinje cells sparked great interest among neuroscientists and continues to be at the center of efforts to understand cerebellar function. Climbing fiber input is essential to the cerebellum’s role in controlling movements, and malfunction of the climbing fiber–Purkinje cell synapse is a central component in the movement disorder characterizing several of the spinocerebellar ataxias [4]. Several major hypotheses have been proposed on the function of the climbing fiber–Purkinje cell synapse in both cerebellar information processing and behavior. This review examines each of these established hypotheses. The review also describes recent results that offer new insights into the action of the climbing fibers in the cerebellum.

Properties of Climbing Fibers and Synaptic Action on Purkinje Cells
Climbing fiber afferents originate solely from the inferior olive, a group of nuclei in the lower medulla, and form the olivocerebellar projection. Being one of the most conserved pathways in the vertebrate nervous system highlights the importance of the olivocerebellar projection [5]. The axons from inferior olivary neurons cross in the midline and travel through the inferior cerebellar peduncle to enter the cerebellum. Climbing fibers provide one of the two main inputs to the cerebellar cortex, the other source being mossy fibers (Fig. 1a). Unique to the climbing fibers is that they monosynaptically innervate Purkinje cells, the sole output neuron of the cerebellar cortex. Therefore, climbing fibers have direct control over the output of the cerebellar cortex.

Through hundreds of glutamatergic synapses along two thirds of the proximal dendritic tree, a Purkinje cell receives input from a single climbing fiber in the adult animal (Fig. 1a). Each climbing fiber synapses on 5–10 Purkinje cells that tend to be located in a parasagittal plane, a prominent feature of the olivocerebellar projection. This parasagittal architecture matches the overall longitudinal zonation of the cerebellum. In this organization, a parasagittal zone or strip of Purkinje cells, as defined by the presence of zebrin II ± bands [6],
receives climbing fiber input from a circumscribed region of the inferior olive, and the same zone of Purkinje cells project to a specific region of the cerebellar nuclei (for review, see [7–9]). The differential expression of numerous molecules on Purkinje cells within these zonal compartments complements the parasagittal anatomy (for review, see [6]).

The climbing fiber–Purkinje cell synapse is one of the most powerful in the CNS and its distinctive properties have stimulated intense interest [10–12]. Firing at low rates (~0.5–2.0/ s), a climbing fiber produces a massive depolarization of the entire Purkinje cell resulting in a complex spike (CS) (Fig. 1b). A CS consists of a large Na⁺ somatic spike and burst of smaller spikelets generated in the initial axon segment. The strong depolarization also opens voltage-gated Ca²⁺ channels that result in Ca²⁺ spikes throughout the entire dendritic tree (Fig. 1c) [13, 14]. Therefore, while separate mechanisms underlie the CS and dendritic Ca²⁺ spikes, both have important roles in understanding climbing fiber action on Purkinje cells. Although traditionally considered an all-or-none response [1], recent work demonstrates that both CSs and dendritic Ca²⁺ responses can be graded via pre- and post-synaptic modulation (for review, see [15]).

In sharp contrast to the monosynaptic climbing fiber–Purkinje cell circuit, mossy fibers act through the highly divergent granule cell-parallel fiber–Purkinje cell circuit and Purkinje cell projection to the cerebellar nuclei. “+” and “−” denote excitatory and inhibitory synapses, respectively (modified with permission from [31]). b Top panel: intracellular recording from a Purkinje cell of both a complex spike (CS) with its initial Na⁺ spike and prolonged depolarization and a spontaneous simple spike SS (modified with permission from [12]). Bottom panel: extracellular recording from a Purkinje cell shows the high-frequency SS firing and low-frequency CS discharge (modified with permission from [61]). c Spatial profile of Ca²⁺ influx evoked by climbing fiber input displaying Ca²⁺ transients at multiple locations along the dendritic tree (modified with permission from [61]).

parallel fiber synapses on several hundred Purkinje neurons but makes only a few en-passant synapses on an individual Purkinje cell [1, 2]. In comparison with climbing fiber input, a parallel fiber produces only a small excitatory response in a Purkinje cell [17].

To complete the circuitry, Purkinje cells project to and inhibit the cerebellar and vestibular nuclei. In turn, a population of excitatory neurons in the cerebellar and vestibular nuclei project to the spinal cord, brainstem, and thalamic nuclei, modulating downstream structures including the cerebral cortex via the cerebello-thalamo-cortical pathway (Fig. 1a) [18]. A separate population of inhibitory neurons in the cerebellar nuclei project to the inferior olive, completing a closed-loop circuit of the cerebellar cortex, cerebellar nuclei, and inferior olive [19–21]. Using this nucleo-olivary circuit, the cerebellar cortex can modulate climbing fiber input to Purkinje cells [22–25].

Event Detection Hypothesis

The low firing frequency of climbing fibers and associated CSs evoked in Purkinje cells prompted the early suggestion that the olivocerebellar system is not capable of encoding information using a conventional rate code. Combining the “phasic” nature of the CS discharge with observations that climbing fibers are highly responsive to small perturbations led to the “event detector” hypothesis [26, 27]. Most of these early experiments were performed in anesthetized or decerebrate preparations. However, during voluntary movements, CS responses to somatosensory stimuli are greatly diminished.
and instead are evoked when a stimulus is not anticipated, leading to the “unexpected event” hypothesis (for reviews, see [11, 28]). Subsequent work in a variety of preparations and behaviors demonstrated that CSs provide considerable information about reflex and voluntary behaviors and do not just signal events (see Beyond Error Signaling: Parametric and Predictive Encoding). Therefore, the event detector hypothesis failed to capture the complete properties of climbing fibers and their action on Purkinje cells.

**Error Hypothesis**

One of the most accepted hypotheses is that CSs signal errors. Initially proposed in the framework of a comparator, Oscarsson postulated that the inferior olive compares command signals from higher centers with feedback from the spinal cord, thereby generating a type of error signal [29]. In support of the comparator hypothesis, the inferior olive integrates both feedforward and feedback information as it receives a variety of excitatory and inhibitory inputs from the spinal cord, nuclei at the mesodiencephalic junction, cerebellar nuclei, and cerebral cortex (for reviews, see [29–31]). However, individual inferior olive neurons generally do not receive both descending and ascending inputs, suggesting that these neurons do not perform the comparison necessary to generate an error signal [30].

The comparator hypothesis quickly evolved into the error hypothesis and was coupled to synaptic plasticity and motor learning (for reviews [32–34]). In the Marr-Albus-Ito hypothesis, motor learning is mediated by long-term depression (LTD) of parallel fiber–Purkinje cell synapses resulting from co-activation of parallel fiber and climbing fiber inputs [35–37]. In this view, CSs are evoked by errors and CSs provide a teaching signal that modifies subsequent SS activity to correct the behavior [37–41]. Although controversial (for reviews, see [34, 42, 43]), for nearly a half century, the error signaling/motor learning hypothesis has dominated the field’s view of climbing fiber function.

Many studies observed CS firing in relation to motor errors. In the floccular complex, CSs are driven by retinal-slip during smooth pursuit and VOR adaptation [44–46]. In the ventral paraflocculus, CSs modulate with the retinal slip during the ocular following response [47], and in the oculomotor vermis, CSs modulate with induced saccade errors [48]. The error hypothesis received further support with the observation of CS modulation in relation to reach end point errors in the monkey (Fig. 2a) [41]. In agreement, several arm movement studies documented that CSs modulate with unexpected loads [38], redirection of a reach [49], and during adaptation to visuomotor transformations [50]. In addition, CS discharge increases with perturbations applied during locomotion [51–53].

However, other studies found limited support for the classical error encoding view. As described above, CS discharge is associated with end point errors during saccades. One method to induce saccade end point errors is by changing the instructed target location while the eyes are in flight (Fig. 2b) [54]. Over time, the subject learns to predict the change in target location and alters the motor command so that the eyes successfully reach the desired end point. During this type of saccadic adaptation, the error encoding hypothesis predicts that CSs would be highly modulated early in adaptation, when errors are maximal. As the animal learns to predict the change in target position and errors are reduced, the CS modulation should also decrease. In the oculomotor vermis, however, the opposite relationship is observed, with CS discharge increasing late in adaptation when errors have decreased greatly (Fig. 2b) [54]. A similar build-up of CS discharge occurs as performance errors decrease during smooth pursuit adaptation [55, 56]. These observations demonstrate that CS error signals are conditional upon the behavioral and experimental context and challenge the assumption that climbing fibers predominately respond to motor errors.

Similarly, perturbations and performance errors during reaching in cats do not evoke responses in inferior olive neurons [57]. During reaching movements in the monkey, CS modulation could not be related to direction or speed errors [58, 59] nor were CSs associated with learning a mechanical perturbation [60]. During pseudo-random tracking, CSs are not associated with error events [61]. Smooth pursuit learning does not drive CS modulation in the oculomotor vermis [62]. Also, in the oculomotor vermis, CS error modulation with saccades may be limited to direction errors, and whether they encode error magnitude is unclear [63, 64]. Even when associated with errors, CSs occur with low probability [41, 50, 61]. Therefore, the precision, specificity, and extent to which CSs encode error information remain unknown.

Motor learning does not depend exclusively on climbing fiber input [60, 65–67] nor does it depend solely on LTD at the parallel fiber–Purkinje cell synapse [34]. Also, SS discharge carries robust error signals, both for eye and arm movements [68–72]. Therefore, error processing in the cerebellum is more multi-faceted than originally proposed, and to paraphrase a wise old man from a galaxy far, far away, “these aren’t the error signals you’re looking for.”

**Rhythmicity and Timing Hypothesis**

One of the intriguing properties of inferior olive neurons is the presence of gap junctions [73, 74]. When combined with a set of voltage-gated calcium and potassium conductances, the electrotonic coupling supports the synchronous [75–78] and rhythmic activity of most inferior olive neurons (with the exception of neurons in the dorsal cap of Kooy). The 1–10-Hz oscillations occur in both the subthreshold membrane potential [79, 80] and
discharge of olivary neurons [81–84]. The timing of the inferior olive neuronal firing is tightly linked to membrane potential phase [85] and the firing waveform reflects the amplitude [86] and synchrony of the subthreshold oscillations [87]. Disruption of the electrotonic coupling in the inferior olive decreases the coherence of muscle activation [88].

The rhythmicity and synchronicity of climbing fibers suggest a role in movement timing independent of their action on SS firing [12, 84, 89]. Rhythmic CS discharge has been argued to underlie physiological tremor [90]. Elegant studies using simultaneous recordings from multiple Purkinje cells documented these oscillatory and coupled discharge properties of CSs in the intact animal [77, 83, 84, 91], including during rhythmic tongue movements [89]. However, the behavioral studies did not disambiguate the source of the rhythmicity, whether driven by the movements or by the inferior olive.

In the awake, behaving animal, evidence for strong CS rhythmicity remains controversial [11, 92, 93]. The lack of rhythmic CS firing has been particularly striking in the non-human primate [60, 69, 94, 95]. However, CS synchronicity is likely an important element of climbing fiber action in the cerebellar cortex and behavior. For example, the synchronous activation of CF microzones could reliably encode sensory inputs [96] or impose encoding changes on a functionally related group of Purkinje cells [69].

Control of Purkinje Cell Excitability, Gain Change, and Bistability Hypotheses

The error and motor learning hypotheses do not readily account for spontaneous CS firing and the observation that removal or stimulation of climbing fiber input results in a dramatic change in the SS firing pattern [97–100]. Lesions or blockade of the inferior olive produces large increases in the SS firing rate and stimulation largely decreases. Climbing fiber stimulation suppresses conditioned eye blink responses, suggesting that on-going CSs directly influence motor behavior [100]. Furthermore, lesions of the inferior olive result in the rapid emergence of a striking cerebellar-like motor disorder [101, 102]. Therefore, climbing fiber input must play a role in on-line cerebellar function and motor control.

Several earlier hypotheses on the CS contribution to real-time motor control emphasize short-term changes in Purkinje cell excitability. The “gain change” hypothesis postulated climbing fiber input controls the responses of Purkinje cell inputs, either increasing or decreasing the responsiveness [103, 104]. In the decerebrate preparation, the magnitude of the SS responses to peripheral inputs depends on the timing relative to CS occurrence. A similar gain was observed in the decerebrate ferret during locomotion and led to the “dynamic selection hypothesis” proposing that climbing fibers act to spatially focus a set of Purkinje cells by emphasizing their responsiveness to parallel fiber input [53, 105]. However, in the awake rabbit, SS responses to vestibular and optokinetic stimulation do not appear to be controlled by climbing fiber input [11]. Therefore, while the gain change hypothesis remains interesting, the concept lacks adequate support in intact, behaving animals.

Subsequently, the “bistability” hypothesis stated that CSs control the responses of a Purkinje cell to parallel fiber inputs by switching between “up” and “down” SS firing states [106–108]. In the context of error signaling, the bistability allows for toggling a Purkinje cell between states for instantaneous correction following an error [106]. Other possible
functions include providing short-term memory capabilities or generation of temporal pattern (for review, see [92]). However, CS-coupled changes in SS firing rates are only prominent in reduced or anesthetized preparations. In the awake mouse, tagging between high and low SS firing was not observed during optokinetic and vestibular reflexes [92, 93]. In the monkey, short-term changes in SS firing following a CS are limited, with the exception of a brief inactivation period [50, 69, 109]. Several explanations have been offered to account for discrepancies across studies, including Purkinje cell heterogeneity, neuromodulators, and level of network activity [92]. However, in the awake animal, climbing fiber input appears to have a very restricted effect on SS firing rate beyond the inactivation period.

Complex Spike-Simple Spike Discharge Reciprocity

The discharge of CSs and SSs is often modulated reciprocally in which an increase in CS firing is accompanied by a decrease in SS firing and vice versa. Reciprocal CS–SS modulation is thought to be a fundamental feature of Purkinje cell physiology and its role in controlling movements [98, 110–112]. This reciprocity has been described in several species, stimulus paradigms, and cerebellar cortical regions. Examples include during optokinetic stimulation in the flocculus and paraflocculus of the rabbit [44, 11] and mouse [112, 113] and during smooth pursuit in the monkey [114]. In the cat, CS–SS modulation reciprocity occurs in the vermis during background firing [110, 115], in lobules V and VI following electrical stimulation of the radial and vagus nerve [116], and during passive wrist movements [117]. However, it should be stressed that many of the above reports of CS–SS reciprocity were in reduced or anesthetized preparations.

Whether the reciprocity is due to climbing fiber input was difficult to test due to the tonic action of CSs on SS firing reviewed above [97–100]. A recent study provided clarification using Ptf1a::cre;Robo3lox/lox mice in which the climbing fibers are selectively re-routed from a contralateral to an ipsilateral projection [112]. Surprisingly, the CS modulation during optokinetic stimulation was reversed as was the SS firing. In addition, climbing fibers acting on inhibitory interneurons likely contribute to the antiphase CS–SS firing pattern, as the interneuron modulation was also inverted.

Reciprocal CS–SS modulation may be less prominent than previously thought. Reciprocity is not present in the dark or during three-dimensional vestibular stimulation [118, 119]. In the oculomotor vermis, reciprocity was not observed for either saccades or smooth pursuit [62]. During pseudorandom tracking, the differences in CS and SS directional tuning are distributed uniformly [61]. A similar diversity in CS and SS tuning occurs in reaching tasks [41, 50, 59]. Therefore, CS and SS discharge reciprocity appears to be conditional rather than deterministic.

Beyond Classical Concepts: Parametric and Predictive Encoding

During various vestibular and oculomotor behaviors, CSs carry parametric information about movements. For example, CS modulation occurs in the flocculus during VOR rotation in the dark when retinal slip is absent [119], carries kinematic information, in addition to retinal slip signals, in the ventral paraflocculus during ocular pursuit [47], and is directionally tuned in the nodulus during three-dimensional vestibular stimulation (Fig. 3a) [118]. Also, CS firing modulates with both reach direction and amplitude [58]. A relationship to motor commands has been suggested based on the increased CS discharge around limb movement onset [58, 109] and climbing fiber modulation with vibrissae and tongue movements [58, 109].

Previous studies typically examined CS modulation during low dimensional, stereotypic movements, including saccades, VOR, and reaching. Therefore, we evaluated CS firing during a pseudo-random, manual tracking task in the monkey [61]. Pseudo-random tracking allows for an examination of the interactions among CS discharge and behavior in which the correlations between parameters are reduced and provides extensive coverage of the work space [68, 120]. The result is a robust data set able to assess the behavioral parameters that modulate climbing fiber input. Using reverse correlation, we constructed both feedforward and feedback two-dimensional probability maps of CS firing with kinematics (hand position, velocity, and acceleration) and with position error, a measure of tracking performance (Fig. 3b).

For Purkinje cells in lobules V and VI, CSs significantly encode all three kinematic parameters and position error in this task (Fig. 3b). The CSs are spatially tuned and provide a linear representation of each parameter. Modulation with acceleration is particularly common. The paradigm also provides a definition of salient events, for example an error event defined as crossing out of the target, as this triggers the need for a timely corrective action. During pseudo-random tracking, climbing fiber modulation was not related to “events”, either for position error or kinematics. Therefore, CSs carry an array of continuous parametric motor signals and support the hypothesis that climbing fiber input has a prominent role in online motor control.

In addition, increasing evidence challenges the concept that climbing fiber input is solely feedback driven. For example, CSs modulate in response to inferred errors related to eye movements [119, 121, 122]. During pseudo-random tracking, feedforward CS modulation is almost three times more common than feedback modulation (Fig. 3b) [61]. Highlighting
the predictive nature of climbing fiber input, CSs precede but rarely respond to errors. Feedforward CS responses occur during eye blink conditioning, with CS increases prior to and predicting the conditioned response (Fig. 3c) [123, 124].

The mechanism underlying predictive CS encoding remains to be determined. As noted above, the inferior olive receives a variety of excitatory and inhibitory inputs from multiple structures that provide both feedforward and feedback information. For the development of predictive CS signals during classical conditioning, recurrent activity within the olivocerebellar network was postulated to play a major role [124]. Other potential sources of feedforward signals are the premotor and motor cortices. Intriguingly, the responses of inferior olivary neurons to glutamatergic inputs from the motor cortex are bi-phasic in a manner that appears to penalize late inputs [125]. This pattern could create a bias toward feedforward motor signals and a mechanism for predictive CS modulation. Taken together, these observations demonstrate that CS discharge contains predictive motor signals about multiple aspects of the upcoming behavior, instead of only reporting errors or providing only sensory feedback.

**Dynamic Encoding Hypothesis**

Error and motor learning roles for climbing fiber action in the cerebellum have dominated the literature since their introduction. This review has highlighted several problems with these views. Clearly, CSs do not simply signal errors, as they fail to respond with errors in many behaviors and instead modulate predictively with multiple parameters of movement. Movements with higher dimensionality reveal the predictive
nature of CS discharge. Therefore, CS modulation with behavior is highly dependent on the experimental paradigm, further raising the need to consider other functions for climbing fiber input.

Two additional features of climbing fiber input and CS discharge lead us to consider other possible functions. First, CSs fire spontaneously and the importance of that background firing to SS firing and cerebellar function implies an ongoing role in cerebellar computations, irrespective of errors or learning. Second, the massive depolarization of the Purkinje cell due to climbing fiber input likely resets the residual effects of prior inputs as well as change how subsequent inputs act on the Purkinje cell (Fig. 1c). Therefore, we hypothesized that climbing fibers change the encoding of the information in the SS firing.

We evaluated this hypothesis during pseudo-random tracking, revealing that climbing fiber discharge dynamically controls the information present in the SS firing, triggering robust and rapid changes in SS encoding of motor signals in Purkinje cells [69]. The changes in encoding consist of increases or decreases in the SS sensitivity to kinematics or position errors. An example of the change in SS encoding is shown in Fig. 4 for a Purkinje cell with SS modulation with hand velocity. Prior to CS occurrence, the encoding of velocity in the SS discharge is weak and markedly increases following CS occurrence (Fig. 4a–c). Furthermore, the changes in encoding are tightly coupled to CS occurrence. In the light of the gain change, bistability, and rhythmicity hypotheses, we investigated and showed that encoding changes are not due to differences in SS firing rates or variability. Nor are the changes in sensitivity due to CS rhythmicity, as there was no evidence for rhythmicity of CS firing during pseudorandom tracking.

In addition, the CS-coupled changes in encoding are not evoked by changes in kinematics or position errors. Instead, CS discharge most often leads alterations in behavior, consistent with our recent report [61]. Nearly all of the CS-coupled changes in SS encoding changes are associated with predictive CS modulation with behavior. Furthermore, at the population level, the changes in sensitivity are consistent with optimizing behavior. Increases in SS encoding of position error are followed by and scale with decreases in error (Fig. 4d). Also, increases in SS encoding of a kinematic parameter are associated with larger changes in that parameter than are decreases in SS encoding. Intriguingly, the CS-coupled changes in encoding for a given Purkinje cell tend to oppose the encoding drift occurring independent of CS firing. For example, a Purkinje cell with a CS-coupled increase in SS encoding of velocity will tend to show a decrease in velocity encoding in the absence of CSs.

An outstanding question is the potential mechanism(s) by which these alterations in SS encoding occur. A number of candidates could explain the changes. First, the number of spikes in a given climbing fiber discharge affects the CS burst pattern, dendritic Ca\(^{2+}\) spikes, and plasticity [86, 126]. Just as the degree of parallel fiber–Purkinje cell synaptic plasticity varies with the duration of the CS discharge [39, 127], short-term changes in firing have been observed. In anesthetized rats, increased SS firing preceding climbing fiber discharge is followed by a higher number of CS spikelets that in turn associate with a subsequent reduction in SS activity [128]. An additional mechanism for CS-coupled changes in SS encoding is via local inhibition by GABAergic interneurons that modifies the conductance changes and Ca\(^{2+}\) fluxes evoked by climbing fiber input [129, 130]. Low amplitude, extended Ca\(^{2+}\) responses inhibit the parallel fiber–Purkinje cell synapse, while high amplitude Ca\(^{2+}\) fluxes could increase the gain, potentially facilitating bidirectional changes in SS encoding [131, 132]. Also, the timing of climbing fiber discharge may differentially modulate parallel fiber input and contribute to the direction of synaptic potentiation [133, 134].

Integrating these new observations with previous results argues for a new hypothesis in which climbing fiber discharge dynamically controls the information present in the SS discharge (Fig. 5). Purkinje cells have the capacity for a large theoretical bandwidth [135], and an array of movement signals is encoded in the SS firing (for review, see [136]). Both climbing fiber input and Purkinje cell output are crucial for continuous, online control of movement as well as motor learning and adaptation. The dynamic encoding hypothesis provides a framework for both spontaneous and evoked climbing fiber discharge. In this view, spontaneous climbing fiber input resets the encoding state of the Purkinje cell to maintain an optimal computational state of the SS firing. In other words, the CS corrects for continuous “drifts” in SS encoding, stabilizing the information conveyed by the Purkinje cell output (Fig. 5). Conversely, behaviorally evoked climbing fiber discharge, either predictive or feedback driven, reallocates the bandwidth of the Purkinje cell to optimize the SS information to the most salient aspects of the task to control behavior (Fig. 5).

A major challenge in determining the function of climbing fiber discharge is interpreting the spectrum of experimental observations regarding spontaneous and evoked CS firing. Importantly, the dynamic encoding hypothesis is compatible with most previous results. The same behavioral parameters linearly modulate both CSs and SSs in the same reference frames [61, 68, 70, 137]. This suggests that these two discharge modes of Purkinje cells function in concert during movements, as opposed to acting independently. In agreement, Purkinje cells are organized according to CS directional tuning such that the SS population response, when based on climbing fiber directional responsiveness, improves the decoding the speed and direction of saccades [138]. Also, the parasagittal organization of the olivocerebellar projection and tendency for synchronous climbing fiber activation will work to reset the SS representations within a microzone resulting in a coordinated change of the information to downstream targets.
Recent studies emphasize that the heterogeneity in the cerebellar circuitry is associated with differential Purkinje cell excitability and firing statistics. For example, the spontaneous SS and CS firing rates are higher in zebrin II− zones than in zebrin II+ zones [139, 139–141]. Zebrin II+ zones also have higher SS variability and longer duration SS suppression following a CS [139]. In addition, Purkinje cells in zebrin II± bands respond differently to PF input [142, 143] and show different SS modulation patterns preceding CS occurrence [144]. In our study, the CS-coupled encoding changes occur in the vast majority of Purkinje cells recorded, arguing that the encoding is not necessarily restricted to specific subpopulations defined by the local heterogeneity of the cerebellar cortex. However, it remains to be determined to what degree local differences in the circuitry modulate the dynamic encoding processes.

For CS signaling events or errors, the evoked climbing fiber discharge reflects the need to change the encoding state of Purkinje cells due to errors. The changes in SS sensitivity evoked by CS are arguably a form of bistability. Given that bistability occurs primarily in reduced or anesthetized preparations in which the physiology of both Purkinje cells and the cerebellar cortical circuitry is altered (for review, see [92]), the information present in SS firing is limited. Therefore, the effect of a CS manifests as an overall change in firing rate as opposed to a change in encoding. Finally, the dynamic encoding hypothesis accounts for the suppressive action of climbing fibers on SS firing. As uncorrected drifts in SS encoding accumulate and firing rates increase, cerebellar representations of motor behavior are corrupted and ataxia develops. Thus, this novel framework provides a unifying view of climbing fiber function, capable of incorporating previous experimental observations.

Importantly, the dynamic encoding concept provides a unifying framework for both spontaneous and evoked CSs. The hypothesis is also compatible with climbing fiber involvement in learning and adaptation [32–34]. For example, spontaneous climbing fiber input has been proposed to perturb movements as a probe for initiating plasticity [145] and CS-evoked changes in SS encoding are consistent with this view. Behaviorally evoked CSs are likely to engage plasticity mechanisms at the parallel fiber–Purkinje cell synapses within a microzone. Together with previous descriptions of bi-directional plasticity mechanisms [133, 134, 146, 147], SS resetting may contribute to the rules governing the direction of plasticity.
Dynamic Encoding Hypothesis

Fig. 5 Illustration of the dynamic encoding hypothesis. The inferior olive integrates behavioral information from the cerebral cortex, sensory system, and computational state of the cerebellar cortex from the cerebellar nuclei. The cerebellar cortex also receives cortical, brainstem (not shown), and sensory information and transforms these inputs into representations of movement kinematics (red arrow) and motor errors (blue arrow) in the simple spike firing of Purkinje cells. The dynamic encoding hypothesis states that climbing fibers, the output of the inferior olive, provide an encoding control signal (red arrow) that resets the sensitivity of the Purkinje cell simple spike firing. Cerebellar cortex output is integrated at level of the cerebellar nuclei. In this example, inferior olive activity drives an increase in simple spike encoding of kinematics as indicated by increased thickness of red lines (similar to Fig. 4 example). Climbing fiber can also drive decreases in kinematic encoding, as well as bidirectional changes in error encoding.

Conclusions

This review examined the various hypotheses on the function of the climbing fiber–Purkinje cell synapse. Each of the traditional hypotheses has merit and has problems. Newer results show that the field needs to move beyond CSs serving as an error feedback signal. Climbing fiber input has spatially rich information about kinematics and performance errors present. We postulate that climbing fiber discharge controls the signals encoded in the SS firing. This dynamic encoding hypothesis is consistent with many of the observations in the literature.

Acknowledgements We wish to thank Kathleen Beterams for help with manuscript preparation.

Funding This study was supported in part by NIH grants: R01 NS18338, T32 GM008471, and F31 NS095408, and NSF grant IGERT DGE-1069104.

Compliance with Ethical Standards

Conflict of Interest Statement There are no current or potential conflicts of interest for the three authors, Martha L. Streng, Laurentiu S. Popa and Timothy J. Ebner.

References

1. Eccles JC, Ito M, Szentagotai J. The cerebellum as a neuronal machine. Berlin: Springer-Verlag; 1967.
2. Ito M. The cerebellum and neural control. New York: Raven Press; 1984.
3. Ito M. The cerebellum: brain for an implicit self. FT Press; 2011.
4. Smeets CJ, Verbeek DS. Climbing fibers in spinocerebellar ataxia: a mechanism for the loss of motor control. Neurobiol Dis. 2016;88:96–106.
5. Ariens-Kappers CU, Huber GC, Crosby EC. The comparative anatomy of the nervous system of vertebrates including man. New York: Macmillan; 1936.
6. Apps R, Hawkes R. Cerebellar cortical organization: a one-map hypothesis. Nat Rev Neurosci. 2009;10:670–81.
7. Sugihara I, Shinoda Y. Molecular, topographic, and functional organization of the cerebellar cortex: a study with combined aldolase C and olivocerebellar labeling. J Neurosci. 2004;24:8771–85.
8. Voogd J, Ruigrok TJ. The organization of the corticonuclear and olivocerebellar climbing fiber projections to the rat cerebellar vermis: the congruence of projection zones and the zebrin pattern. J Neurocytol. 2004;33:5–21.
9. Najac M, Raman M. Integration of Purkinje cell inhibition by cerebellar nucleo-olivary neurons. J Neurosci. 2015;35:544–9.
10. Schmolesky MT, Weber JT, De Zeeuw CI, Hansel C. The making of a complex spike: ionic composition and plasticity. Annu NY Acad Sci. 2002;978:359–90.
11. Simpson JJ, Wylie DR, DeZeeuw CI. On climbing fiber signals and their consequence(s). Behav Brain Sci. 1995;19:385–98.
12. Llinas RR. The olivo-cerebellum: a key to understanding the functional significance of intrinsic oscillatory brain properties. Front Neural Circuits. 2013;7:96.
13. Llinas R, Sugimori M. Electrophysiological properties of in vitro Purkinje cell dendrites in mammalian cerebellar slices. J Physiol. 1980;305:197–213.
14. Davie JT, Clark BA, Hauser M. The origin of the complex spike in cerebellar Purkinje cells. J Neurosci. 2008;28:7599–609.
15. Najafi F, Medina JF. Beyond “all-or-nothing” climbing fibers: graded representation of teaching signals in Purkinje cells. Front Neural Circuits. 2013;7:115.
16. Raman IM, Bean BP. Resurgent sodium current and action potential formation in dissociated cerebellar Purkinje neurons. J Neurosci. 1997;17:4517–26.
17. Barbour B. Synaptic currents evoked in Purkinje cells by stimulating individual granule cells. Neuron. 1993;11:759–69.
18. Allen GI, Tsukahara N. Cerebro-cerebellar communication systems. Physiol Rev. 1974;54:887–1006.
19. Chan-Palay V. Cerebellar Dentate Nucleus. New York: Springer; 1977.
20. Teune TM, Van d BJ, De Zeeuw CI, Voogd J, Ruigrok TJ. Single Purkinje cell can innervate multiple classes of projection neurons in the cerebellar nuclei of the rat: a light microscopic and ultrastructural triple-tracer study in the rat. J Comp Neurol. 1998;392:164–78.

Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.
63. Soetedjo R, Fuchs AF. Complex spike activity of Purkinje cells in the oculomotor vermis during behavioral adaptation of monkey saccades. J Neurosci. 2006;26:7741–55.
64. Soetedjo R, Kojima Y, Fuchs A. Complex spike activity signals the direction and size of dysmetric saccade errors. Prog Brain Res. 2008;171:153–9.
65. Nguyen-Vu TD, Kimpo RR, Rinaldi JM, et al. Cerebellar Purkinje cell activity drives motor learning. Nat Neurosci. 2013;16:1734–6.
66. Ke MC, Guo CC, Raymond JL. Elimination of climbing fiber instructive signals during motor learning. Nat Neurosci. 2009;12:1171–9.
67. Kahlon M, Lisberger SG. Changes in the responses of Purkinje cells in the floccular complex of monkeys after motor learning in smooth pursuit eye movements. J Neurophysiol. 2000;84:2945–60.
68. Popa LS, Hewitt AL, Ebner TJ. Predictive and feedback performance errors are signaled in the simple spike discharge of individual Purkinje cells. J Neurosci. 2012;32:15345–58.
69. Streng ML, Popa LS, Ebner TJ. Climbing fibers control Purkinje cell representations of behavior. J Neurosci. 2017;37:1997–2009.
70. Popa LS, Streng ML, Ebner TJ. Long-term predictive and feedback encoding of motor signals in the simple spike discharge of Purkinje cells. eNeuro 2017;4:ENEURO.0036, ENEU17.2017.
71. Streng ML, Popa LS, Ebner TJ. Modulation of sensory prediction error in Purkinje cells during visual feedback manipulations. Nat Commun. 2018;9:1099.
72. Gomi H, Shidara M, Takemura A, Inoue Y, Kawano K, Kawato M. Temporal firing patterns of Purkinje cells in the cerebellar ventral paraflocculus during ocular following responses in monkeys I. Simple spikes. J Neurophysiol. 1998;80:818–31.
73. Sotelo C, Llinas R, Baker R. Structural study of inferior olivary nucleus of the cat: morphological correlates of electrotonic coupling. J Neurophysiol. 1974;37:541–59.
74. King JS. The synaptic cluster (glomerulus) in the inferior olivary nuclei. J Comp Neurol. 1976;165:387–400.
75. Llinas R, Baker R, Sotelo C. Electrotonic coupling between neurons in cat inferior olive. J Neurophysiol. 1974;37:560–71.
76. Lemik E, Llinas R. Role of gap junctions in synchronized neuronal oscillations in the inferior olive. J Neurophysiol. 2005;94:2447–56.
77. Blenkinopp TA, Lang EJ. Block of inferior olive gap junctional coupling decreases Purkinje cell complex spike synchrony and rhythmicity. J Neurosci. 2006;26:1739–48.
78. Turecek J, Han VZ, Cuzon CV, Grant KA, Welsh JP. Electrical coupling and synchronized subthreshold oscillations in the inferior olive of the rhesus macaque. J Neurosci. 2016;36:6497–502.
79. Bleasel AF, Pettigrew AG. Development and properties of spontaneous oscillations of the membrane potential in inferior olivary neurons in the rat. Brain Res Dev Brain Res. 1992;65:43–50.
80. Chorev E, Yarom Y, Lampl I. Rhythmic episodes of subthreshold membrane potential oscillations in the rat inferior olive nuclei in vivo. J Neurosci. 2007;27:5043–52.
81. Bledel JR, Ebner TJ. Rhythmic discharge of climbing fibre afferents in response to natural peripheral stimuli in the cat. J Physiol. 1984;352:129–46.
82. Sugihara I, Lang EJ, Llinas R. Serotonin modulation of inferior olivary oscillations and synchronicity: a multiple-electrode study in the rat cerebellum. Eur J Neurosci. 1995;7:521–34.
83. Lang EJ, Sugihara I, Llinas R. GABAergic modulation of complex spike activity by the cerebellar nucleocerebellary pathway in rat. J Neurophysiol. 1996;76:255–75.
84. Lang EJ, Sugihara I, Welsh JP, Llinas R. Patterns of spontaneous purkinje cell complex spike activity in the awake rat. J Neurosci. 1999;19:7278–39.
85. van der Giessen RS, Koekkoek SK, van DS, et al. Role of olivary electrical coupling in cerebellar motor learning. Neuron. 2008;58:599–612.
86. Bazzigaluppi P, de G Jr, van der Giessen RS, Khosrovari S, De Zeeuw CI, De Jeu MT. Olivary subthreshold oscillations and burst activity revisited. Front Neural Circuits. 2012;6:91.
87. Lang EJ, Tang T, Suh CY, et al. Modulation of Purkinje cell complex spike waveform by synchrony in levels in the olivocerebellar system. Front Syst Neurosci. 2014;8:210.
88. Placantonakis DG, Bukovsky AA, Zeng XH, Kiem HP, Welsh JP. Fundamental role of inferior olive connexin 36 in muscle coherence during tremor. Proc Natl Acad Sci U S A. 2004;101:7164–9.
89. Welsh JP, Lang EJ, Sugihara I, Llinas R. Dynamic organization of motor control within the olivocerebellar system. Nature. 1995;374:453–7.
90. Llinas R, Volkind RA. The olivo-cerebellar system: functional properties as revealed by harmaline-induced tremor. Exp Brain Res. 1973;18:69–87.
91. Khosrovari S, van der Giessen RS, De Zeeuw CI, De Jeu MT. In vivo mouse inferior olive neurons exhibit heterogeneous subthreshold oscillations and spiking patterns. Proc Natl Acad Sci U S A. 2007;104:15911–6.
92. Engbers JD, Fernandez FR, Turner RW. Bistability in Purkinje neurons: ups and downs in cerebellar research. Neural Netw. 2013;47:18–31.
93. Schonewille M, Khosrovari S, Winkelman BH, et al. Purkinje cells in awake behaving animals operate at the upstate membrane potential. Nat Neurosci. 2006;9:459–61.
94. Keating JG, Thach WT. Nonclock behavior of inferior olive neurons: interspike interval of Purkinje cell complex spike discharge in the awake behaving monkey is random. J Neurophysiol. 1995;73:1329–40.
95. Hakimian S, Norris SA, Greber G, Keating JG, Anderson CH, Thach WT. Time and frequency characteristics of Purkinje cell complex spikes in the awake monkey performing a nonperiodic task. J Neurophysiol. 2008;100:1032–40.
96. Ozden I, Sullivan MR, Lee HM, Wang SS. Reliable coding emerges from coactivation of climbing fibers in microbands of cerebellar Purkinje neurons. J Neurosci. 2009;29:10463–73.
97. Colin F, Manil J, Desclin JC. The olivocerebellar system. I. Delayed and slow inhibitory effects: an overlooked salient feature of cerebellar climbing fibers. Brain Res. 1980;187:3–27.
98. Montarolo PG, Palestini M, Strata P. The inhibitory effect of the olivocerebellar input on the cerebellar Purkinje cells in the rat. J Physiol. 1982;332:187–202.
99. Cerminara NL, Rawson JA. Evidence that climbing fibers control an intrinsic spike generator in cerebellar Purkinje cells. J Neurosci. 2004;24:4510–7.
100. Zucca R, Rasmussen A, Bengtsson F. Climbing fiber regulation of spontaneous Purkinje cell activity and cerebellum-dependent blink responses. eNeuro. 2016;3
101. Llinas R, Walton K, Hillman C, Sotelo C. Inferior olive: its role in motor learning. Science. 1975;190:1230–1.
102. Horn KM, Deep A, Gibson AR. Progressive limb ataxia following inferior olive lesions. J Physiol. 2013;591:5475–89.
103. Ebner TJ, Yu QX, Bledel JR. Increase in Purkinje cell gain associated with naturally activated climbing fiber input. J Neurophysiol. 1983;50:205–19.
104. McDevitt CJ, Ebner TJ, Bledel JR. The changes in Purkinje cell simple spike activity following spontaneous climbing fiber inputs. Brain Res. 1982;237:484–91.
105. Lou JS, Bloedel JR. Responses of sagittally aligned Purkinje cells during perturbed locomotion: relation of climbing fiber activation to simple spike modulation. J Neurophysiol. 1992;68:1820–33.
106. Loewenstein Y, Mahon S, Chadderton P, Kitamura K, Sompolinsky H, Yarom Y, et al. Bistability of cerebellar
107. Yartsev MM, Givon-Mayo R, Maller M, Donchin O. Pausing Purkinje cells in the cerebellum of the awake cat. Front Syst Neurosci. 2009;3:2.

108. McKay BE, Engbers JD, Mehaffey WH, et al. Climbing fiber discharge regulates cerebellar functions by controlling the intrinsic characteristics of Purkinje cell output. J Neurophysiol. 2007;97:2590–604.

109. Mano N, Kanazawa I, Yamamoto K. Complex-spike activity of cerebellar Purkinje cells related to wrist tracking movement in monkey. J Neurophysiol. 1986;56:137–58.

110. Bloedel JR, Roberts WJ. Action of climbing fibers in cerebellar cortex of the cat. J Neurophysiol. 1971;34:17–31.

111. Rawson JA, Tilokskulchai K. Suppression of simple spike discharges of cerebellar Purkinje cells by impulses in climbing fibre afferents. Neurosci Lett. 1981;25:125–30.

112. Badura A, Schonewille M, V oges K, Galliano E, Renier N, Gao Z, et al. Climbing fiber input shapes reciprocity of Purkinje cell firing. J Neurosci. 2010;30:9668–78.

113. Yakhnitsa V, Barmack NH. Antiphasic Purkinje cell responses in response to transparent retinal slip. Neuron. 2001;30:795–803.

114. Stone LS, Lisberger SG. Visual responses of Purkinje cells in the cerebellar cortex as an assembly of non-uniform Purkinje cell modules. J Neurosci. 2011;31:10843–51.

115. Murphy JT, Sahab NH. The inhibitory effect of climbing fiber activation on cerebellar Purkinje cells. Brain Res. 1970;19:486–90.

116. Rubia FJ, Kolb FP. Responses of cerebellar units to a passive movement in the decreebrate cat. Exp Brain Res. 1978;31:387–401.

117. Rubia FJ, Hennemann HE. Discharge patterns of Purkinje cells activated through the climbing fiber system by stimulation of somatic and visceral afferents. Pflugers Arch. 1978;375:125–9.

118. Stone LS, Lisberger SG. Visual responses of Purkinje cells in the cerebellar flocculus during smooth-pursuit eye movements in monkeys. I. Simple spikes. J Neurophysiol. 1990;63:1241–61.

119. Murphy JT, Sahab NH. The inhibitory effect of climbing fiber activation on cerebellar Purkinje cells. Brain Res. 1970;19:486–90.

120. Hewitt A, Popa LS, Pasalar S, Hendrix CM, Ebner TJ. Representation of limb kinematics in Purkinje cell simple spike discharge is conserved across multiple tasks. J Neurophysiol. 2011;106:4232–47.

121. Frens MA, Mathoera AL, van der SJ. Floccular complex spike response to transparent retinal slip. Neuron. 2001;30:795–801.

122. Winkelman BH, Belton T, Suh M, Coesmans M, Morpurgo MM, Simpson JP. Nonvisual complex spike signals in the rabbit cerebellar flocculus. J Neurosci. 2014;34:3218–30.

123. Hewitt A, Popa LS, Pasalar S, Hendrix CM, Ebner TJ. Representation of limb kinematics in Purkinje cell simple spike discharge is conserved across multiple tasks. J Neurophysiol. 2011;106:2232–47.

124. Ten Brinck MM, Boele HJ, Spanke JK, et al. Modulating effects of Pavlovian conditioning: cerebellar cortical dynamics in awake behaving mice. Cell Rep. 2015;13:1977–88.

125. Garden DL, Rinaldi A, Nolan MF. Active integration of glutamatergic input to the inferior olive generates bidirectional postsynaptic potentials. J Physiol. 2017;595:1239–51.

126. Mathy A, Ho SS, Davie JT, Duguid JC, Clark BA, Hauser M. Encoding of oscillations by axonal bursts in inferior olivary neurons. Neuron. 2009;62:388–99.

127. Rasmussen A, Jirenhed DA, Zucca R, Johansson F, Svensson P, Hesslow G. Number of spikes in climbing fibers determines the direction of cerebellar learning. J Neurosci. 2013;33:13436–40.

128. Burroughs A, Wise AK, Xiao J, Houghton C, Tang T, Suh CY, et al. The dynamic relationship between cerebellar Purkinje cell simple spikes and the spikelet number of complex spikes. J Physiol. 2017;595:283–99.

129. Callaway JC, Lasser-Ross N, Ross WN. IPSPs strongly inhibit climbing fiber-activated [Ca2+] increases in the dendrites of cerebellar Purkinje neurons. J Neurosci. 1995;15:2777–87.

130. Kitamura K, Hauser M. Dendritic calcium signaling triggered by spontaneous and sensory-evoked climbing fiber input to cerebellar Purkinje cells in vivo. J Neurosci. 2011;31:10847–58.

131. Bouvier G, Higgins D, Spolidoro M, Carrel D, Mathieu B, Léna C, et al. Burst-dependent bidirectional plasticity in the cerebellum is driven by presynaptic NMDA receptors. Cell Rep. 2016;15:104–16.

132. Jorntell H, Hansel C. Synaptic memories upside down: bidirectional plasticity at cerebellar parallel fiber-Purkinje cell synapses. Neuron. 2006;52:227–38.