3

Challenging Marr's theory of the cerebellum

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Introduction to motor learning theory

There have been successive attempts to understand the relationships between the structure, function, and dynamics in neuronal circuits (Arbib et al., 1998) in the hope of explaining behavior. At different times these attempts have been based on the available experimental data and conceptual tools and have been synthesized into various theories and models. One of the most famous is Marr's theory of the cerebellum, the so-called motor learning theory (MLT; Marr, 1969), which was developed in the late 1960s and has since then dominated the view of how the cerebellum might function. To be fair we must say that the MLT was extended by Albus two years later (Albus, 1971) and then further developed by Ito in the subsequent decades (Ito, 1972; Ito, 1984; Ito, 1993, 2006, 2008). Thus, it is appropriate to consider it as the Marr–Albus–Ito theory. The MLT was based purely on statistical connectivity rules, so that, unavoidably, it did not take into account the myriad biological parameters that are now considered critical to guarantee cerebellar network functioning. Therefore, over the years Marr's theory has been repeatedly challenged by new experimental findings and concepts. In this chapter, I analyze the major aspects of the MLT, how it has been challenged experimentally, and how it has contributed to our understanding of the structure–function relationship of the cerebellar circuit and the adaptive behaviors that are dependent on the cerebellum.

The foundations of Marr's theory of cerebellum

The MLT was based on two series of anatomical observations: the number of neurons of a given species and the divergence/convergence ratios between these neurons. In addition, the excitatory or inhibitory nature of neuronal connections was known, largely based on the work of Eccles and collaborators (summarized in Eccles et al. (1967)). This made it possible to set up a statistical model of connectivity and to draw a general picture of the presumed role of neurons in the circuit. A critical element in the theory was that the weight of specific parallel fiber–Purkinje cell connections could be tuned depending on error signals coming from the inferior olive through the climbing fibers.

In the MLT, the granular layer performed an operation of expansion recoding of contextual information and the molecular layer an operation of learning of this information depending on climbing fiber activity. As a whole, the cerebellar cortex appeared as a perceptron-like structure, with Purkinje cells operating like integrators and regulating the output through the deep cerebellar nuclei. The sign of learning was predicted to be long-term potentiation (LTP), although in the Albus version this was converted into long-term depression (LTD).

The MLT was attractive because the cerebellum, embedded in the sensorimotor control system, could exploit the massive mossy fiber input to extract the contextual information it needs to produce accurate movements from high-level motor commands.

> It is reasonably certain that patterns of activity on mossy fibers represent to the cerebellum the position, velocity, tension, and so on of the muscles, tendons, and joints. This is feedback information that is required to control precise or sequential movements, or both. This information must modulate signals to the muscles to achieve precise movement under varying load conditions. (Albus, 1971, p.59)

Moreover, if the teaching signal conveyed through climbing fibers was a motor error, then the cerebellum could implement motor adaptation depending on the precision

of movement execution. Recast in modern terms, the MLT predicts that the cerebellum could implement the long-sought forward controller operation needed to regulate movement in a predictive manner. The MLT has been later generalized from motor execution to motor planning and cognitive control (Ito, 1993, 2008), implying that the cerebellum could play a role in higher brain functions.

The MLT principles have been included into models of signal processing (e.g., Tyrrell and Willshaw, (1992)). In the Adaptive Filter Model (AFM) (Fujita, 1982), the consequences of MLT have been especially developed in mathematical form (Dean and Porrill, 2010, 2011; Dean et al., 2010). The MLT principles have also been implemented in robotic models (Kawato and Gomi, 1992; Schweighofer et al., 1998a, 1998b; Wolpert et al., 1998; Imamizu et al., 2000; Kawato et al., 2003; Imamizu and Kawato, 2009, 2012; Kawato et al., 2011). These illustrate the variety of ways in which the MLT scheme might be used in adaptive control. The evolution of these concepts is explained in the following sections of this chapter.

Critical experimental evidence from cellular neurophysiology

Recent experimental studies in cellular neurophysiology have provided results which confronted the MLT, since they could either provide proofs in favor or undermine the foundations of the theory itself. The most critical advances have been done in three fields —neuronal dynamics, local network connectivity, synaptic plasticity. These provide new clues on microcircuit functions and raise specific issues for the Marr theory that can be summarized as follows:

- The cerebellar granular layer does not simply perform pattern discrimination (see Chapter 2), expansion recoding (see Chapter 4) and gain regulation of mossy fiber inputs.
- There are different coding schemes: spike-timing versus spike-rate coding.
- There are microcircuit structures that go beyond simple statistical rules.
- The olivo-cerebellar loop performs complex timing operations.
- The Purkinje cell and other cerebellar neurons are not simple linear integrators.
- Learning in the circuit is not solely related to parallel fiber LTD under climbing fiber control.
- Oscillation and resonance, together with nonlinear neuronal and synaptic time-dependent properties, could design dynamic spatiotemporal geometries in the circuit.

The extended function of the granular layer

Marr noticed that, since granule cells are much more numerous than mossy fibers, incoming signals should diverge over many more lines than in the input, allowing decorrelation of common components. The main role envisaged by Marr for the Golgi cells was that of controlling the transmission gain along these lines. There is now evidence that the cerebellar granular layer does not simply perform a combinatorial decorrelation of the inputs but rather it may perform complex nonlinear spatiotemporal transformations under the guidance of local synaptic plasticity.

The mossy fibers were shown to activate independent synapses on granule cell dendrites (D'Angelo et al., 1995) and this was also subsequently shown for Golgi cell inhibitory synapses (Mapelli L et al., 2009) providing evidence in favor of the decorrelation hypothesis. Moreover, the convergence/divergence ratio at the mossy fiber–granule cell relay was shown to enable efficient lossless sparse encoding (Billings et al., 2014). These concepts are consistent with MLT predictions. Nonetheless, at least 50% of the information carried through the mossy fiber–granule cell relay is carried by

first-spike timing and the rest by as few as another 1–3 spikes (Arleo et al., 2010). Other experiments have shown that several forms of plasticity can change transmission at the mossy fiber–granule cell relay (D'Angelo et al., 1999; Armano et al., 2000; Nieus et al., 2006). Therefore, signal transfer through the granular layer is probably only partly explained by the anatomical circuit arrangement and can be modified by intrinsic neuronal responsiveness and synaptic plasticity (see "Numerous forms of synaptic plasticity in addition to parallel fiber LTD").

A tonic component of synaptic inhibition in the cerebellar glomerulus was shown to regulate mossy fiber–granule cell gain (Mitchell and Silver, 2003). This result attracted considerable interest as it supported Marr's prediction. However, the impact of dynamic inhibitory transmission was neglected, although this is several times more potent than tonic inhibition and plays a critical role in controlling the information transmitted through the mossy fiber–granule cell relay during impulsive signaling. The dynamic role of inhibition in controlling granule cell spike patterning was demonstrated about 10 years later (Nieus et al., 2014). These observations therefore indicate that Marr's predictions on gain control have a biological underpinning but also indicate that this latter is much more complex than predicted by the MLT. Actually, gain control turned out to be highly non-linear and input pattern-dependent (Mapelli et al., 2010).

Another relevant observation was that most granule cells in vivo are inactive at rest (Chadderton et al., 2004). This result was used to support the concept of sparseness: that is, that only a minor proportion of granule cells have to be active at a time in order to allow efficient input pattern decorrelation. However, since no activity patterns were actually conveyed through the circuit, the concept of sparseness in those experiments appears hard to evaluate. In a more effective assessment obtained in response to punctuate stimulation, granule cells were activated in dense clusters with an estimated spike generation probability of about 10% (Diwakar et al., 2011). This result was deemed to support the sparseness hypothesis in relation to inputs activating local signal processing. In no case, however, has the sparseness hypothesis ever been tested during effective behaviors in alert animals.

Finally, the signals transferred through the granular layer were shown to follow complex spatiotemporal rearrangements leading to combinatorial operations and frequency-dependent gain control (Mapelli and D'Angelo, 2007; Mapelli et al., 2010a, 2010b). These results showed that the concept of expansion recoding could be interpreted in terms of local signal processing depending on molecular properties of ionic channels and synaptic receptors and the local geometry of circuit connections.

Spike patterns in time and space

Marr's theory of the cerebellum is characterized by the absence of explicit representation of time and geometrical organization. The statistical nature of model connectivity generates a topological map and the coding scheme that seems to best approximate Marr's idea is that of rate-coding, i.e. of a continuously modulated spike discharge flowing through the various network elements.

Early in the 1980s, the nature of mossy fiber discharges was demonstrated during eye movements: some fibers carry on–off spike burst while others carry protracted frequency-modulated spike discharges (Kase et al., 1980; van Kan et al., 1993). These patterns have more recently been supported by whole-cell recordings in vivo showing that granule cells respond to mossy fiber activity by generating spike bursts following punctuate sensory stimulation (Chadderton et al., 2004; Rancz et al., 2007) and by generating protracted discharges during head rotation in a vestibulo-ocular reflex (VOR) protocol (Arenz et al., 2008). Therefore, the two modalities coexist and the cerebellum is able to process both spike patterns simultaneously.

The implications of spike-burst coding are broad and go beyond Marr's intuition, introducing unpredicted consequences for signal processing. By virtue of Golgi cell lateral inhibition, the granular layer response to mossy fiber bursts becomes spatially organized in a center–surround pattern with a radius of about 50 m, in which excitation prevails in the center and inhibition in the surround (Mapelli and D'Angelo, 2007). By virtue of Golgi cell feedforward inhibition, the granular layer generates a time-window

effect limiting the duration and intensity of the output (Nieus et al., 2006; D'Angelo and De Zeeuw, 2009). The molecular properties at granular layer synapses add further complexity. In response to specific burst patterns, NMDA and GABA receptors control the induction of long-term synaptic plasticity at the mossy fiber–granule cell synapse. Since induction is regulated by synaptic inhibition (which controls membrane depolarization and therefore the level of NMDA channel unblocking and calcium influx), LTP dominates in the center and LTD in the surround of the response fields, consolidating specific geometries of activity. In these structures, the NMDA and GABA receptors generate a high-pass filter allowing bursts over 50 Hz to be optimally transmitted (Mapelli et al., 2010a, 2010b; Gandolfi et al., 2014).

As a whole, the granular layer appears to transform incoming signals by making use of specific cellular mechanisms translating incoming spike patterns into local responses (Farrant and Nusser, 2005; D'Angelo, 2008; D'Angelo et al., 2013; Mapelli et al., 2014). The emerging view is that the granular layer network behaves as a complex set of filters operating in the space and time domains, and that this filter can be adapted through long-term synaptic plasticity (Garrido et al., 2013a; Nieus et al., 2014), Thus, the original idea of input decorrelation should be extended to the spatiotemporal dynamics of circuit activity, an aspect that deserves specific future investigations. A way to test this would require independent measurement of multiple neurons in active clusters at high temporal resolution, for example applying multiphoton recording techniques in vivo (Gandolfi et al., 2014).

Microcircuit structure beyond statistical connectivity rules

Since Marr's theory is based on statistics rather than the geometry of connectivity, it is challenged by discoveries revealing critical spatial structures in the circuit. There is indeed a fundamental property that needs to be revisited. The parallel fibers, after dividing into two opposite branches originating from the ascending axon of granule cells, travel transversly for millimeters, contacting numerous Purkinje cells. This fact has inspired the idea that signals generated by granule cells activate beams of Purkinje cells (Eccles et al., 1967; Eccles, 1973; Braitenberg et al., 1997). In Marr's theory, this is translated into the idea that Purkinje cells operate as perceptrons, homogeneously receiving the sparse signal representation generated by granule cells. Actually, beam activation can be easily demonstrated by direct parallel fiber stimulation (e.g. Vranesic et al., 1994; Baginskas et al., 2009; Reinert et al., 2011). However, when cerebellar activation is elicited by natural stimuli, the activation of parallel fiber beams is less evident and spots of activity are more likely to be observed (Cohen and Yarom, 1998, 1999). This is possibly in relation to the center–surround organization of granular layer responses to high-frequency mossy fiber bursts (Gandolfi et al., 2014) and the low-pass filtering exerted by the molecular layer interneuron network. This allows only low frequencies to be transmitted along the parallel fibers; Mapelli et al., (2010a)), although further experiments are needed to confirm this hypothesis.

As seen earlier, activation of granule cells by punctate sensory stimulation occurs in dense clusters, reflecting activity of mossy fiber bundles in the afferent trigemino-cerebellar sensory pathway and in the associated thalamo-cortico-ponto-cerebellar channel (Diwakar et al., 2011). As indicated by experiments in vitro, this effect would correspond to the formation of center–surround structures in the granular layer (Mapelli and D'Angelo, 2007; Mapelli et al., 2010a, 2010b; Gandolfi et al., 2014) with the effect that signals are focused and contrasted before being retransmitted to the molecular layer. Recently, another discovery has lent support to this geometrical organization: the Golgi cells receive over 50% of their connections from neighboring granule cells (Cesana et al., 2013; D'Angelo et al., 2013), suggesting that their inhibition is closely related to local activity clusters. There are indications that a similar effect could also occur in Purkinje cells (Llinas and Sugimori, 1980a, 1980b).

Actually, punctate sensory stimulation in vivo causes a prominent "vertical" pattern of cerebellar cortex activation, in which Purkinje cells overlying the active granular layer clusters are organized in spots rather than beams. The formation of these spots could be reinforced in the molecular layer by various mechanisms including higher

synaptic density, lower activation times, higher spike frequency transmission, and lower synaptic inhibition in the spot than in the associated parallel fiber beam (Bower and Woolston, 1983; Cohen and Yarom, 1998; Hartmann and Bower, 1998; Lu et al., 2005; Rokni et al., 2007; Santamaria et al., 2007; Bower, 2010). Moreover, although the synapses formed by granule cell ascending axon and parallel fibers on Purkinje cells were shown to be functionally equivalent (Isope and Barbour, 2002; Walter et al., 2009), differences in terms of long-term synaptic plasticity have been reported (Sims and Hartell, 2005, 2006).

Another relevant case concerns the olivo-cerebellar loop, in which inhibitory connections have been reported between the deep cerebellar nuclei and the inferior olive, an issue that is considered in the next section. Thus, there is a conspicuous body of experiments supporting a specific geometrical organization that could involve formation of multiple vertical columns of active cells communicating though the parallel fibers, a concept resembling the organization of the cerebral cortex. Computation may then be reflected in the geometry of neuronal activation rather than statistics of neuronal connectivity.

Timing in the olivo-cerebellar loop

A critical issue in Marr's theory is the role attributed to climbing fibers. Marr's intuition was that climbing fibers had to be functional to instruct the cerebellar cortex on the need to generate long-term synaptic plasticity at the parallel fiber–Purkinje cell synapses and, as a consequence, for motor learning. However, some investigations have challenged the teaching role of climbing fibers and some remarkable aspects of microcircuit spatiotemporal organization have emerged that could be important in explaining the function of the olivo-cerebellar loop.

The olivo-cerebellar loop was reported to perform complex timing operations by dynamically wiring groups of Purkinje cells (Llinas, 1988; Welsh et al., 1995). This observation led to the hypothesis that the olivo-cerebellar loop operates as a generator of temporal patterns encoded by complex spikes (Yarom and Cohen, 2002; Jacobson et al., 2008, 2009) and was proposed as an alternative to the teaching role of climbing fibers. The basis of this hypothesis is that inferior olivary neurons form a network of electrically coupled cells and this coupling is modulated by inhibitory inputs from the deep cerebellar nuclei.

It has been proposed that, when Purkinje cells inhibit the deep cerebellar nuclei neurons, these latter modify the oscillatory state of inferior olive neuronal clusters, which in turn can recruit different groups of Purkinje cells. Thus, a "request" for specific patterns delivered via the mossy fiber system could be translated into patterns of inferior olive activity, which could in turn reorganize activity in specific sections of the cerebellar cortex by sending climbing fiber signals to Purkinje cells organized in sagittal bands (Yarom and Cohen, 2002). Although attractive, this hypothesis lacks experimental validation at present and its relationship to cerebellar learning remains unknown.

The most conservative conclusion is that, while the intuition of parallel fiber plasticity remains, it should be coupled to the dynamic assembly of spatiotemporal geometries in the inferior olive and to the concept that the the inferior olive, deep cerebellar nuclei, and Purkinje cell neurons form a dynamics subcircuit. These concepts are further expanded in the next section.

Complex dynamics in Purkinje cells and other cerebellar neurons

On the basis of the histological observation that Purkinje cells receive the signals generated by about 200 000 granule cells, Marr hypothesized that these neurons operate as perceptrons through a linear integration process of parallel fiber inputs. Actually, a more recent investigation has proved that Purkinje cells can optimally store information through changes in their parallel fiber synapses, supporting their perceptron capabilities (Brunel et al., 2004). The simplest implementation of the cerebellar perceptron would be that Purkinje cells operate as linear integrators (Dean and Porrill, 2011). However, computational modeling suggests that Purkinje cells, by generating local regenerative currents at the level of dendritic spines, could express properties going beyond those of a

linear integrator (De Schutter and Bower, 1994a, 1994b; Masoli et al., 2015).

Purkinje cells have a large dendritic tree receiving synaptic inputs and a somato-axonal section (including the initial segment and first Ranvier nodes) responsible for action potential generation (Llinas and Sugimori, 1980a, 1980b; Churchland, 1998). While synaptic potentials, generated by both parallel and climbing fibers, can easily reach the soma, spikes cannot travel efficiently into the dendritic tree. Moreover, these neurons have a complex set of ionic channels distributed unequally over the compartments, generating a rich repertoire of electroresponsive properties including, bursting, rebounds, and pauses. The Purkinje cells generate simple and complex spikes in response to parallel fiber and climbing fiber inputs. These synaptically driven events modulate a basal activity state generating bursts and pauses.

Moreover, recent observations have raised the possibility that Purkinje cells operate as bistable elements (Loewenstein et al., 2005), although the occurrence of this observation in vitro as well as in vivo is still under debate (Schonewille et al., 2006; Yartsev et al., 2009) as it could be related to the level of anesthesia and the action of certain drugs (Zhou et al., 2015). The membrane potential could switch between two stable levels, partially (but not strictly) under the control of simple and complex spikes. Current injections as well as synaptic inputs (either excitatory from parallel and climbing fibers or inhibitory from molecular layer interneurons) can bidirectionally shift the Purkinje cell states (Rokni et al., 2009).

Hence, the current view is that spontaneous firing of Purkinje cells sets the baseline activity of deep cerebellar nuclear neurons and that this activity is modulated by accelerating and decelerating firing frequency (burst–pause behavior) under control of synaptic inputs. Therefore, the existence of complex Purkinje cell firing dynamics surpasses the concepts of continuous spike frequency modulation and simple linear integrator envisaged by Marr. The concept of spike timing, i.e. that the precise relative positioning of a spike is important to generate the neural code (Rieke et al., 1997), is also applicable to other neurons like granule cells (Nieus et al., 2006; Diwakar et al., 2009; D'Angelo and Solinas, 2011), Golgi cells (Solinas et al., 2007a; Solinas et al., 2007b), unipolar brush cells (Subramaniyam et al., 2014), inferior olive cells (De Gruijl et al., 2012), and deep cerebellar nuclei cells (Steuber et al., 2011), which all take part in reshaping the spike discharge in the cerebellar circuit.

Numerous forms of synaptic plasticity in addition to parallel fiber LTD

One major prediction of the MLT was that cerebellar learning should occur through some forms of plasticity between parallel fibers and Purkinje cells under climbing fiber control. The climbing fibers originating from the inferior olive were assumed to play a teaching role, instructing the cerebellar cortex to modify its connectivity in order to cope with new motor demands. Parallel fiber–Purkinje cell LTP was predicted by Marr and reversed into LTD by Albus: LTD was in fact discovered more than a decade later by Ito (Ito et al., 1982). The resonance of this discovery can be compared to that of LTP in the hippocampus (Bliss and Lomo, 1973), which followed Hebb's postulate on brain plasticity (Hebb, 1949). In 1984, the Nobel prizewinner J.C. Eccles said:

> For me the most significant property of the cerebellar circuitry would be its plastic ability, whereby it can participate in motor learning, that is the acquisition of skills. This immense neuronal machine with the double innervation of Purkinje cells begins to make sense if it plays a key role in motor learning … it could be optimistically predicted that the manner of operation of the cerebellum in movement and posture would soon be known in principle (from the foreword to Ito, 1984).

For more than a decade after this, the dominant idea was that LTD was not just the most important but also probably the only relevant form of plasticity in the cerebellum. However, LTP was subsequently induced by parallel fiber stimulation without the need for climbing fiber activity (Sakurai, 1987) and a solitary role for LTD was also challenged computationally since supervised learning schemes require both LTD and LTP (Doya (1999)).

Following these fundamental discoveries, the physiological relevance of LTP and LTD at the parallel fiber–climbing fiber synapse has been evaluated experimentally, leading to contrasting conclusions. Some authors simply dismissed the relevance of parallel fiber–climbing fiber LTD for behavioral learning (De Schutter, 1995; Raymond et al., 1996; Coesmans et al., 2004; De Zeeuw and Yeo, 2005) while others concluded that learning had to occur in deeper structures, like the deep cerebellar nuclei and vestibular nuclei (Raymond et al., 1996). At the same time, several novel forms of plasticity have been demonstrated (for review see Hansel et al., 2001; De Zeeuw et al., 2011; Gao et al., 2012; D'Angelo, 2014; Galliano and De Zeeuw, 2014). Various forms of LTP and LTD have been demonstrated at the mossy fiber–granule cell synapses, at synapses between both mossy fiber and Purkinje cells to deep cerebellar nuclei, and at molecular layer interneuron synapses. Moreover, plasticity of intrinsic excitability has been shown in granule cells, Purkinje cells, and deep cerebellar nuclei cells. It should also be noted that several forms of plasticity exist at parallel fiber synapses, some of which are bidirectional and depend solely on parallel fiber (but not climbing fiber) activity.

Thus, the cerebellar network is plastic in a much more extended sense than originally envisaged. The functional meaning of this extended plasticity in computational terms remains largely to be assessed, although critical experimental and modeling investigations have been carried out (see "The final challenges"). The plasticity issue requires further comments. Just because a synapse is shown to express forms of plasticity does not necessarily mean that it is involved in "learning" in the classical sense. It is likely that at some level, all synapses in the brain are plastic; the question is for what functional purpose. For example, the classical parallel fiber–Purkinje cell LTD is Hebbian and supervised in nature, while the aforementioned mossy fiber–granule cell LTP and LTD are Hebbian but unsupervised with a fundamentally different impact on learning and behavior. In fact, as far as we can understand, plasticity in the granular layer could tune the response timing of specific granule cells and therefore the activation patterns of Purkinje cells rather than implementing "motor learning" directly. In general, multiple forms of plasticity may be needed to operate in concert in order to generate biological learning properties (D'Angelo, 2014).

Oscillation and resonance could design a functional geometry

As noted, the MLT copes with a homogeneous cerebellar structure with prewired anatomical circuits. However, recent experimental evidence suggests that oscillatory and resonant properties in cerebellar neurons could help setting up coherent patterns of activity.

The inferior olivary neurons are electrically coupled (Sotelo and Llinas, 1972), and can generate rhythmic activities propagating to the cerebellar cortex through climbing fiber connections to Purkinje cells and to the deep cerebellar nuclei (reviewed in De Zeeuw et al., 2008; D'Angelo et al., 2009). A similar architecture made up of oscillatory neurons coupled through gap junctions has been recognized in Golgi cells in the granular layer (Dieudonne, 1998; Forti et al., 2006; Dugue et al., 2009; Vervaeke et al., 2010) and in stellate cells in the molecular layer (Mann-Metzer and Yarom, 2000). These oscillations therefore pervade the whole cerebrocerebellar system. The cerebellum has also been involved in large-scale low-frequency oscillation (Gross et al., 2005; Schnitzler et al., 2006) spreading through cerebrocerebellar loops involving various cerebral cortical areas (prefrontal cortex, premotor cortex, primary sensorimotor cortex and posterior parietal cortex) (Schnitzler et al., 2009).

Therefore, some circuit elements of the cerebrocerebellar loops can intrinsically generate and sustain the rhythm, while others are probably entrained by circuit activity. These two mechanisms, entraining and being entrained, are probably not disjoined because large-scale brain oscillations are collective processes, in which coalitions of neurons transiently reinforce their reciprocal interaction (Buzsaki, 2006). Voluntary movement causes oscillatory activity in the prefrontal areas, which propagates to the premotor, motor, and posterior parietal areas and is then relayed to the cerebellum through the pontine nuclei. The cerebellum may therefore initially be entrained and then

participate to reinforce theta-band oscillations in the cerebrocerebellar loop. Both the granular and molecular layers can be entrained into theta-frequency cycles driven by the cerebral cortex (Courtemanche et al., 2009; Ros et al., 2009); the granular layer is resonant at the theta frequency and this may help the entrainment of the cerebellum into such rhythms (Gandolfi et al., 2013).

The double oscillatory system in the granular layer and in the inferior olive could provide the necessary coherence for multiple inputs occurring in different regions of the cerebellum. This involves an extension of the concepts of congruence of climbing and mossy fiber signals (Brown and Bower, 2002; Kistler and De Zeeuw, 2003). The result is also to generate functional assemblies of neurons with variable spatiotemporal geometry (D'Angelo et al., 2009; D'Angelo, 2011).

The final challenges

As we have seen, the main challenge for Marr's MLT is provided by circuit spatiotemporal dynamics. Will Marr's now venerable model suvive or not after dynamic behaviors of the cerebellar circuit are taken into consideration?

The cerebellar circuit has now been modeled in detail using biophysically precise models of neurons and synapses and reproducing several aspects of spatiotemporal circuit processing (Maex and De Schutter, 1998; Medina and Mauk, 1999, 2000; Medina et al., 2000; Solinas et al., 2010; D'Angelo and Solinas, 2011; Jaeger, 2011; De Gruijl et al., 2012). A recent attempt has seemed to provide a favorable answer by incorporating realistic neuronal and synaptic dynamics, previously developed in a highly detailed granular layer model (Solinas et al., 2010), into the AFM (Rossert et al., 2014). The realistic granular layer, once incorporated into the AFM, still performed linear signal transduction under sustained frequency-modulated mossy fiber inputs, supporting Marr's hypothesis. Moreover, synaptic strength at mossy fiber–granule cell synapses exerted a remarkable regulation of transmission gain and phase. Therefore, Marr's hypothesis for the granular layer still holds in the presence of complex nonlinear neuronal and synaptic properties. The best guess to explain the evolutionary relevance of these last properties is that they are required to process complex spatiotemporal sequences when the input is organized in spike bursts.

Another series of observations directly supports the central tenet that supervised learning has to occur at the parallel fiber–Purkinje cell synapse under climbing fiber control. It has been recently possible to incorporate a spiking cerebellar network, endowed with reversible forms of long-term synaptic plasticity at three synaptic sites (parallel fiber–Purkinje cell, Purkinje cell–deep cerebellar nuclei, mossy fiber–deep cerebellar nuclei) into the control system of a robot (Casellato et al., 2012, 2013; Garrido et al., 2013b; Casellato et al., 2014; Luque et al., 2014). Importantly, the presence of the supervised parallel fiber–Purkinje cell plasticity under climbing fiber control remained critical in order to exploit granular layer expansion recoding and to bind learning to sensorimotor errors. The Purkinje cell–deep cerebellar nuclei and mossy fiber–deep cerebellar nuclei plasticities made it possible to generate learning on multiple timescales, to prevent saturation and to determine rescaling and generalization. Therefore, the critical intuition on parallel fiber LTD/LTP remains viable though additional forms of plasticity seem to be required to build up the remaining biological aspects of learning.

Conclusion

Although almost half a century has passed since its formulation, Marr's MLT is still fascinating for its conceptual elegance and remains a fundamental basis for research on the functions of the cerebellum and of the whole brain. Considering that cerebellar computations are based on geometry and timing, the validity of the MLT may have to be confined to homogeneous cerebellar substructures during limited time-periods dominated by modulated firing frequency. In order to understand how the cerebellar network operates, in view of recent discoveries, Marr's MLT is not sufficient in itself. A new comprehensive theory will require extensive experimental research and computational modeling integrated with closed-loop robotic simulations. At present, this is far from achieved.

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