



Models of the Cortico-cerebellar System 121

M. Negrello and E. De Schutter

Contents

Introduction	3506
A Plethora of Models	3508
Forward and Inverse Models	3508
Functional Models	3509
Marr-Albus Type Models	3509
Extensions of MAI Model: Adaptive Filter Model and Distributed Synaptic Plasticity	3511
Information Encoding and Channel Capacity	3511
Successes and Failures of the MAI Model	3511
Dynamical Models	3513
The Cerebellum Implements Spatiotemporal Transformations	3513
Mathematical Properties of the Circuit (Tidal Waves)	3513
Reverberating Loops and Golgi Gating	3514
Single Cell Models of the Granular Layer	3516
Inferior Olivary Models	3516
Coupled Oscillators and Electrotonic Coupling	3516
Phase Resets and Synchronous Groups	3518
Cerebellar Nucleus	3519
Conclusion	3519
Consilience: Meeting in the Middle	3519
References	3520

M. Negrello (✉)
Erasmus Medical Center, Rotterdam, The Netherlands
e-mail: mnegrello@gmail.com

E. De Schutter
Computational Neuroscience Unit, Okinawa Institute of Science and Technology, Kunigam,
Okinawa, Japan
e-mail: erik@oist.jp

Abstract

Without the cerebellum, organisms are challenged in the learning and execution of accurate and coordinated actions. It has a central position in the nervous system receiving and projecting to the spinal cord, midbrain, and cerebral cortex, implying convergence of sensory and motor streams. Its highly conserved neuroarchitecture would imply it is very good at what it does and that what it does is very general. Here we review theoretical, modeling, and computational work that has attempted to capture the dynamics and/or function of the cerebellum.

Keywords

Adaptive filter model · Bottom-up models · Cerebellar nucleus · Coupled oscillators · Dynamic models · Golgi gating · Granule cell models · Reverberating loops model · Spatiotemporal patterns in cerebellum · Tidal wave · Echo-state machine · Forward and inverse models · Functional models · Golgi gating · Granule cell models · Inferior olivary models · Coupled oscillators · Echo-state machine · Phase resets · Synchronous groups · Marr-Albus type models · Adaptive filter model and distributed synaptic plasticity · **Information encoding and channel capacity** · Purkinje neuron single cell modeling · Successes and failures · Pellionisz and Llinas's model · Purkinje neuron single cell modeling · Reverberating loops model · Synchronous groups · Tidal wave hypothesis

Introduction

Without the cerebellum, organisms are challenged in the learning and execution of accurate and coordinated actions. It has a central position in the nervous system, and it both receives and projects to the spinal cord and midbrain, implying convergence of sensory and motor streams, and in mammals also sends and receives from the cerebral cortex. Its highly conserved neuroarchitecture would imply it is very good at what it does and that what it does is very general.

A clue to its basal function is readily available from comparative neuroanatomy. The cerebellum first appears in gnathostomata fish, the jawed vertebrates, which underlie 99% of all vertebrates. In its most primitive instantiations, the cerebellum arises with the horizontal canal of the vestibular system, and thus the compensatory vestibular reflexes are among the first functions performed by the early cerebellum. Vestibular reflexes are implemented essentially by a feedback system, where visual and vestibular information are transformed into compensatory motor action. Further down the evolutionary road, the cerebellum retains that functionality (flocculus) and expands on it, by applying this compensatory function to a vast class of problems, exemplified in paradigms that study cerebellar function such as learning of timed reflexes as in eye blink conditioning (Brinke et al. 2015; Mauk et al. 1986;

Ohyama et al. 2003; Rasmussen et al. 2013), visuomotor feedback and adaptation (Optican and Robinson 1980; Thier et al. 2000), force-field adaptation (Donchin et al. 2012), sequence learning (Spencer and Ivry 2009), postural corrections (Angelaki et al. 2009; Clark 1939), and rhythmic finger tapping (Del Olmo et al. 2007) to name a few. In addition to these, the cerebellum of mammals seems to be concerned with the learning and acquisition of novel motor behaviors, in association with the basal ganglia, thalamus, and the cerebral cortex. In humans, the cerebellum has been implicated in cognitive function (Schmahmann and Caplan 2006).

The million-dollar question in cerebellar modeling is how does the cerebellar structure enable these functions.

The cerebellum is one component of a tripartite system involving the inferior olive (IO) and the cerebellar nucleus (figure elsewhere). While early models have focused on the most conspicuous elements of the cerebellar circuitry, particularly the interaction between parallel fibers and Purkinje cells, the field has broadened its scope to include various models of the inferior olive and cerebellar nucleus. Given how tightly these three systems interact, all these models are included in the chapter.

There have been multiple forays at modeling the cerebellum, attempting to capture the abstract nature of cerebellar transformations (Albus 1971; Braitenberg 1987; Braitenberg et al. 1997; Marr 1969). David Marr recognized in the large arbor of the Purkinje neuron the potential for pattern recognition, in analogy to the McCulloch-Pitts neuron (McCulloch and Pitts 1943), and Rosenblatt's perceptron learning rule (Rosenblatt 1958). Eccles suggested that the cerebellum exhibited spatiotemporal transformations without being explicit about what they would be. Valentino Braitenberg saw in the orthogonal arrangement between parallel fibers and Purkinje cells temporal summation and coincidence detection (Braitenberg et al. 1997). Llinás saw in the oscillations in the inferior olive a form of binding different actions together through synchrony (Kazantsev et al. 2003). All these traditions have seen data that corroborates or questions their assumptions.

In a first approximation, computational models of the brain can be categorized as functional models and dynamical models, depending on assumptions and emphasis. Functional models, also called top-down, assume a set of functions and attempt to interpret the components of the architecture as realizing that function (such as finding the weights of a network that performs a certain transformation). Bottom-up models focus on the dynamical implications of selected aspects of anatomy and physiology. In one case, data on anatomy and physiology takes precedence, on the other, the focus is on enabling the assumed function with neural components with varying degrees of plausibility (Houk and Fagg 2014; Medina 2010; Medina and Lisberger 2008).

This chapter represents the multiplicity of the literature on cerebellar modeling. We survey multiple proposals and their perspectives, from those emphasizing physiological plausibility, through those that interpret the circuits in terms of their mathematical/physical properties (e.g., summation along delay lines – tidal waves/ decorrelation – sparsity/transients – echo states/granular layer resonances), to those that predict physiological properties (Golgi network oscillations/resonance with cerebellar nucleus) to those that have been embodied in robots, as well as

conceptual-mathematical models (forward and inverse models). The inferior olive has also received modeling attention, and we add a section devoted to it, as it is an essential element to the cerebellar system.

The chapter begins with introducing the concepts of forward and inverse models, which appear relevant to multiple aspects of the subsequent discussion. After that, we look into more detail into models in the literature, in a gradient from functional (top-down) to dynamic-physiological-anatomical models (bottom-up). Single cell models are briefly introduced in the proper context.

A Plethora of Models

Forward and Inverse Models

Without any knowledge about how the brain works, it is possible to perform a correct movement – a movement where the *plan* is identical to the *execution*. The brain is faced with the *inverse problem* of finding a sequence of muscle activations, to a given desired state. That is, knowing how to move is the same as knowing how to transform the desire to reach a state into the sequence that will bring it about. This is the definition of an inverse model.

How do we know that the movement is correct? When by the end of the movement, all looks as expected. For instance, the visual outcome of the action should match the desired/predicted movement. Expectations are not exclusively visual and can have any sensory feedback. And thus, to know whether a motor action was correct, we also have to know what we expect in terms of sensory feedback. This knowledge of how the outcome of an action *should feel like* is a “forward model.”

Forward and inverse models dissociate two aspects of motor function, planning and execution. This separation between forward and inverse is effectively a linearization of the tasks of the motor system. Wolpert and Kawato (1998) have proposed that motor control is in effect a collection of such forward and inverse models in “modules.” They propose a method to learn multiple paired forward-inverse models, and a context switcher – a responsibility estimator. The search for the counterparts of forward-inverse modules in the brain is a current field of research. As the theory is somewhat reticent about the actual neural implementation of said models, the identification of the cortical substrates is not obvious.

Nevertheless, modern discussions of cerebellar function have often attributed the role of forward model to the cerebellum (Wolpert and Kawato 1998), calculating sensorimotor expectations of a given action, a fact which has found confirmation in related brain regions (Han et al. 2000). The critical question in designing an inverse model is the encoding of “goal” or “end-state” as well as the form of the “sensory prediction” that inverse models need for training. For example, in a paradigm such as saccadic adaptation, in what form comes the information about the vector error (saccadic mismatch)? If we presume, as many do, that complex spikes encode error, they are burdened with a very specific signal to encode in very few spikes. Given the

anatomy and the physiology of the Inferior Olive, specific encoding such as required by feedback theories seems contentious.

Functional Models

What is the function of the cerebellum? Attributing a specific function to a brain region is a notorious fallacy (Edelman and Gally 2001). Functional models are not bogged down by this remark, as the function is assumed – based on clinical observations (intention tremor in ataxias and cerebellar lesions), comparative neuroanatomy (compensatory movements), lesions, and a variety of experiments. The task for functional models is to enable the assumed function with selected neural components. For instance, one of the earliest functional models of the cerebellum, due to Marr (1969) and Albus (1971), imagines the Purkinje cell as analogous to a perceptron (Rosenblatt 1958), which is a mathematical function that linearly sums weighted inputs and applies a threshold, performing linear pattern separation. Though Purkinje cell physiology is not so simple, models of the cerebellum based on simple perceptrons have been able to perform a variety of functions attributed to the cerebellum (Casellato et al. 2014; Houk and Fagg 2014; Medina 2010), and some assumptions of early models remain valid today, if with interesting caveats.

Marr-Albus Type Models

It is illustrative to trace the evolution of Marr-Albus models to their historical assumptions and how they were updated over time.

In Marr-Albus type models, cerebellar function is essentially pattern recognition performed by the Purkinje neuron, in analogy with a perceptron rule. Inputs are weighted by parallel fiber synapses and the Purkinje neuron performs a hard threshold function. The Purkinje neuron is trained to recognize spatial patterns of parallel fibers carrying sensorimotor and other brain signals through a teaching signal, provided by the climbing fiber, which provides a “supervision” signal (Doya 2002). In Marr’s original suggestion, this would increase the efficiency of the synapses encoding the input pattern. Albus later suggested a decrease, which has been experimentally corroborated by Ito, as long-term depression (LTD) of the parallel fiber synapse (Ito 1989; Ito and Kano 1982).

According to Marr, a cerebellum made of pattern recognizers is able to perform two functions, learned movements and learned conditional reflexes. In the original formulation, the *cerebrum* produces a motor plan that activates inferior olivary cells in a sequence such as to produce the desired movement. As the desired movement is performed stepwise by the brain, the sensorimotor context (muscle and sensor activations converging into Purkinje cells) is learned in the parallel fiber to Purkinje cell synapses, upon the IO teaching signal. IO cells representing elemental movement would fire in the sequence determined by the cerebral cortex.

In this theory, the cerebrum outsources movements to the cerebellum by having the Purkinje neuron recognizing (through parallel fiber synapses) the context of motion. After learning, the Purkinje neuron would be able to recognize input from parallel fibers, thereafter performing automated sequences on recognizing a sensorimotor context.

In this theory, the only role of the climbing fibers, and indeed, of the IO cells, is to copy the cerebral signals into single Purkinje neurons, carrying the sequence of activated motor outputs. Essentially, this model links the output of the Purkinje neuron to a motor command that activates the IO cell innervating the Purkinje neuron.

Marr and Albus conducted a very meticulous analysis of all the cerebellar components in association with the primary role of the neurons. Marr has calculated combinatorial properties of recognizable patterns, effectively computing the channel capacity and information encoding properties of the assumed pattern separation. More recently, there have been elaborations on those quantifications that incorporated new phenomena. Particularly, on the basis of the *in vitro* finding that a majority of parallel fiber Purkinje neuron synapses appear to be silent (*in vitro* only 1% generate synaptic current) (Barbour 1993), the information capacity of the Purkinje cell has been quantified (Barbour et al. 2007). Anatomical observations in the granular layer have also led to quantifications of pattern separation and have led to the statement that the granule layer would perform lossless encoding (Billings et al. 2014), a statement already present in Marr's seminal paper.

Relationship with Reality: Are Purkinje Neurons Perceptrons?

The Purkinje neuron is a constantly active neuron, with tonic firing rates of "simple" spikes in the range between 20 and 200 Hz, providing a fairly graded output signal. As a teaching signal, the climbing fibers provide at most an imperfect feedback signal. The complex spike rate is low and highly variable, has very broad receptive fields, and unreliable spikes in a variety of event-triggered measurements (Frens et al. 2001; Herzfeld et al. 2015; Hoogland et al. 2015; Sauerbrei et al. 2015; Soetedjo et al. 2008). Because the complex spikes respond to a large array of stimuli, the mutual information for specific stimuli has a low upper bound. Moreover, the climbing fiber signal does more than change the recently active synapses (Medina and Lisberger 2008), as it is often accompanied by a postcomplex pause (Bloedel and Roberts 1971; Eccles et al. 1972), caused by a large calcium influx and the activation of calcium activated potassium channels (De Schutter and Steuber 2009). Reflecting on the graded nature of a calcium influx, the alterations of synapses can also be a graded phenomenon (Coemans et al. 2004). In fact, systematic changes of Purkinje cell responses to complex spike with different spike counts have been recorded (Rasmussen et al. 2013). Modeling has shown that the number of spikelets in the olivary spike is related to the calcium influx in the olivary cell (De Gruij 2012), though the extra spikes in the climbing fiber do not directly reflect on the number of spikelets in the Purkinje neuron (Mathy et al. 2009). Amidst these complications, and albeit the successes of MAI model, the physiology and dynamics of the cerebellum have cast doubt on its validity.

Extensions of MAI Model: Adaptive Filter Model and Distributed Synaptic Plasticity

One of the most conspicuous mismatches between prediction and reality in Marr's model has been the strict assumption that the only locus of plasticity in the cerebellum is the Purkinje cell parallel fiber synapse. Recent research has shown that virtually every cerebellar synapse that has been tested for plasticity has shown long-term changes upon paired stimulations (Gao et al. 2012b).

In order to salvage the original model, many sites of plasticity have been grafted onto the original trunk of the MAI (Clopath et al. 2014; Hansel et al. 2001; Houk and Fagg 2014; Porrill and Dean 2007). These extensions have been able to reproduce some learning phenomena in simplified paradigms of cerebellar function, and particularly, in some cases reproduced learning rates observed in experiments (Clopath et al. 2014).

Information Encoding and Channel Capacity

If the Purkinje neuron is viewed as a binary pattern recognition, i.e., a McCulloch-Pitts unit, one may ask what is its information capacity, in bits. This question has been addressed by Barbour and colleagues on the basis of the observation that most parallel fiber-Purkinje synapses are silent (Barbour et al. 2007). It has also been addressed by Clopath under the assumption of correlated inputs (Clopath et al. 2012). Within a MAI formalism, the capacity of channels can be computed for mostly all elements of the circuit. Silver has recently suggested that the convergence of mossy fibers onto granule cell synapse (4–6) promotes lossless encoding of the mossy fiber input (Billings et al. 2014) (see also Heck and Sultan 2002). Marr himself has made a similar prediction on the basis of the ability of Purkinje neurons to decode “codons.” Though an interesting exercise, the meaning of the quantification of information channels is not immediately evident in motor control.

Successes and Failures of the MAI Model

MAI type models still face substantial criticism, reflected in the ongoing debates about the interpretation of the climbing fiber signal.

When the first models of the cerebellum were proposed, most of the information available was anatomical, which is reflected on the emphasis of early models from Marr, or Braitenberg. Alongside with developments of experimental science, models systematically incorporated more plausible physiological assumptions. Now there is a rich set of electrophysiological and molecular data that have complexified the picture and sharply contrasts the attractive simplicity of initial models. Some of the physiological phenomena could have broad implications for cerebellar function and modeling. Long-term potentiation of parallel fiber synapses is behaviorally quite important (Schonewille et al. 2010), climbing fibers do more than modify the

synapses, as in calcium related pauses in Purkinje neurons (De Schutter and Steuber 2009), complex spike spikelets (De Gruijl et al. 2012; Jirenhed et al. 2007; Mathy et al. 2009; Rasmussen et al. 2013), and the suggestion that they can be graded error signals (De Gruijl 2012). Zebrin bands, i.e., distinct subdivisions of the cerebellum, which are related to different IO nuclei, have substantial physiological differences (Zhou et al. 2014). Anatomy has also shown that there are inhibitory feedbacks to the cerebellar cortex (Uusisaari and Knöpfel 2012; Wulff et al. 2009). Electrophysiology has shown the importance of inhibition in behavioral learning under the form of sharp ephaptic inhibition of Purkinje neurons by basket cells (Blot and Barbour 2013, 2014). The relationship between parallel fiber input and Purkinje cell output has become unclear, with increasing evidence that Purkinje cell spiking is largely driven by intrinsic mechanisms (Shin et al. 2007) and a possible pronounced role of the ascending branch of the parallel fiber (Bower 2010). It is an interesting question whether the functional simplicity of early models is compatible with these physiological observations.

Purkinje Neuron Single Cell Modeling

The Purkinje neuron is one of the neurons most frequently modeled in physiological detail, with compartmental models dating back to 1977, with a 62 compartmental model based on the Hodgkin Huxley formalism, with three ionic sorts, sodium, potassium, and a leak current (Pellionisz et al. 1977).

Later models increased the level of morphological detail, along with differential distributions of more ion channels over the dendrite and simulation of calcium dynamics (De Schutter and Bower 1994a, b) (Fig. 1b). This model has predicted parallel fiber mediated calcium influx (De Schutter and Bower 1994c) and that LTD of parallel fiber synapses causes decreased calcium influx, leading to shorter pauses in simple spike firing (Steuber et al. 2007). This is a counterintuitive result, as this would mean that Purkinje cell would increase its firing rate after LTD.

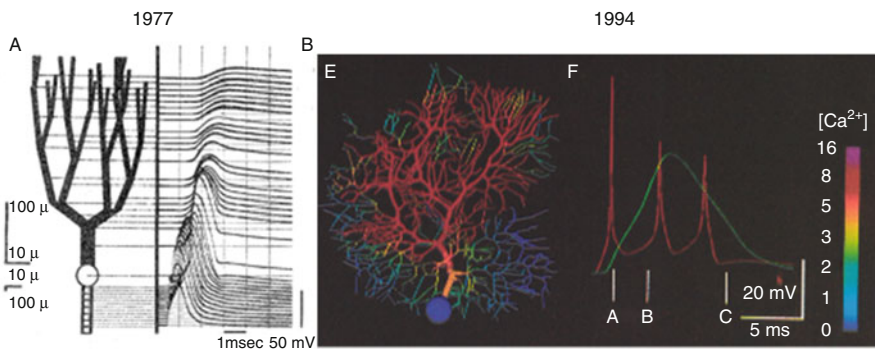


Fig. 1 (a) Pellionisz and Llinas's model, showing the propagation of the action potential in a compartmental model of the Purkinje neuron. (b) Calcium concentrations during an action potential in the arbor of the Purkinje neuron (*left panel*), and the dendritic spikes created by the calcium transient (*right panel*) from De Schutter and Bower (1994a)

This prediction has been confirmed *in vitro*, but not yet *in vivo* under physiological conditions. There has been little progress in modeling the complete Purkinje cell since, but extensive voltage clamp measurements of channels in isolated Purkinje cell somata have led to a detailed model of somatic spike initiation (Khaliq and Raman 2006) that is used extensively (de Solages et al. 2008; Ostojic et al. 2015; Phoka et al. 2010).

Increasing the level of magnification further, Purkinje cell models also focused on single dendritic branches and even on complex biochemical expression networks in single dendritic spines (Anwar et al. 2012, 2013). Using reaction diffusion formalisms, it has been shown that the stochastic gating of calcium-activated K^+ channels causes the large variability of dendritic calcium spikes that may have large implications for plasticity mechanisms, which depend on the calcium concentration in the spine probabilistically (Antunes and De Schutter 2012).

Dynamical Models

The Cerebellum Implements Spatiotemporal Transformations

As early as 1958, Braitenberg has proposed that the lattice structure of the cerebellum causes transformations of spatial patterns into temporal patterns and vice versa (Braitenberg and Atwood 1958). A similar suggestion appears in “Cerebellum as a Computer” from Eccles et al. (1967), where the authors mention spatiotemporal patterns but do not elaborate past that suggestion. As spatiotemporal patterns are very general, the burden is to be explicit about the sensorimotor patterns and what are their entailments.

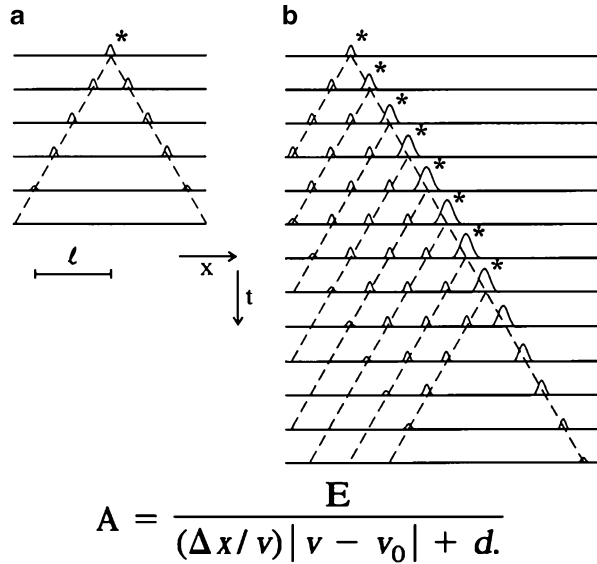
Spatiotemporal patterns in the cerebellum may have a great variety of origins – in the delay line properties of parallel fibers, in the oscillatory resonances of the Golgi-granule cell network (Maex and De Schutter 1998; Solinas et al. 2010; Vervaeke et al. 2012), in the coupled oscillations of the inferior olive (Llinas and Yarom 1981), in the longitudinal distribution of climbing fiber afferents, in the organization of cerebellar Zebrin stripes (Marshall and Lang 2004; Shinoda et al. 2000; Sugihara et al. 2001), in the loops between the cerebellar modules in the cortex, deep cerebellar nuclei (DCN), and IO (reviewed from a functional perspective in Glickstein et al. 2011).

The models above, in one way or another, imply spatiotemporal transformations although it is not immediately obvious how the spatiotemporal patterns would map into behavior. The interpretation of cerebellar output is a responsibility of its targets, and it is not clear what is the general principle that unifies all cerebellar output.

Mathematical Properties of the Circuit (Tidal Waves)

One of the earliest proposals interpreting the cerebellum in terms of its anatomical features was the timing hypothesis, which observed that granule cell “activity will

Fig. 2 Summation of synaptic potentials along parallel fiber bundles, according to Braitenberg (1967, 1983)



reach different Purkinje cell arbors at different times” (Braitenberg and Atwood 1958). The next instantiation of this idea specified that parallel fiber propagation times would directly reflect the order of muscle activations (Braitenberg 1965). The proponent himself later deemed this unlikely, given that even if the parallel fibers are very long axons with very slow conduction velocities (~ 0.5 m/s), the propagation is of the order of 10 ms, much shorter than the 50 plus ms necessary for even the shortest of movements. This led to the “Tidal wave” hypothesis (Braitenberg 1983, 1987), which shifted the emphasis from the propagation delays of individual parallel fibers into temporal summation along the parallel fiber bundles in the folia (Fig. 2).

Against empirical tests, the proposal met with conflicting results. While some did observe sequential activity between Purkinje neurons arranged along a parallel fiber (Ebner and Bloedel 1981; Eccles et al. 1966), others did not encounter them, unless inhibitory interneuron influence on Purkinje neurons was blocked. A parsimonious conclusion is that temporal summation along parallel fiber bundles indeed exists, albeit gated by inhibitory interneuron intervention (Bower 2010).

Reverberating Loops and Golgi Gating

Due to anatomically closed loops, components of the extended olivocerebellar circuit influence themselves, with delays (Apps and Hawkes 2009; Ekerot et al. 1987; Jörntell et al. 2010; Voogd et al. 2003, 2010). For example, a pause in Purkinje cell spiking, whether from an inhibitory interneuron or from the complex spike, feeds back on itself through two routes (mesodiencephalic junction as well as the cerebellar nuclei) which re-converge onto the same inferior olivary nucleus, which

ultimately projects back to Purkinje neurons in the same microzone (Apps and Hawkes 2009). The activity of the cerebellar cortex thus influences itself in a time-delayed fashion. This observation has been spelled out with attention to detail in Kistler's "reverberating loops" model (De Zeeuw et al. 2000; Kistler and van Hemmen 1999), which identifies two reverberating loops within the cerebellar system, one due to rebound firing of the cerebellar nuclear cells (B. D. Armstrong and Harvey 1966; De Gruijl et al. 2013; Ruigrok and Voogd 1995) creating delayed responses on the IO and the other due to Golgi cell oscillatory gating of granule cell activity.

Golgi cell's low frequency of oscillation, broad receptive fields (Prsa et al. 2009; Vos et al. 1999), gap junctioned network (Dieudonne 1998; Dugué et al. 2009), and relatively limited dynamic range in response to input have led many to propose its role as an oscillatory gating of the granule cells (Kistler and van Hemmen 1999; Maex and De Schutter 1998; Solinas et al. 2010; Vervaeke et al. 2012). Kistler has further proposed that this oscillatory gating would generate reverberatory loops in the cerebellar system within the 100 ms scale, and this discretization step would be essential to production of motor sequences. An abrupt signal into the granule layer would lead Golgi cells to transiently and synchronously oscillate, gating their own input by inhibiting surrounding granule cells. Glutamate spillover depression of inhibition most likely promotes a winner takes all scenario that is compatible with all the theories mentioned here (Hull and Regehr 2012; Mitchell and Silver 2000).

Though sought for, the predicted ability of Golgi cells to create gated oscillations has not been conclusively confirmed. Nevertheless, some corroboration for the assumption may be derived from the frequency spectrum of the local field potential of the granular layer, which has been observed to correlate with the predicted bands.

The spatial properties of the putative Golgi gating spatial extent has been investigated in the model by Solinas (Solinas et al. 2007, 2010), which produces "center-surround" inhibition properties. It is worth noting that the shape of the center surround in this model is determined by the range and shape of the Golgi cell axonal arbor, which is a crucial assumption of the model. This overlooks, for instance, the fact that the axonal arbor is not round or cylindrical, rather flat and constrained by zebrin bands (Hawkes et al. 2008).

The second reverberating loop was proposed by Kistler and involves the delayed reverberation from the cerebellar nucleus. In this idea, a complex spike on the Purkinje neuron lifts inhibition from the cerebellar nucleus, which produces a set of rebound spikes (D. M. Armstrong and Harvey 1968; Witter et al. 2013), which in turn reset oscillations on the IO, and 100 ms later, rebound IO spikes, subsequently translated to complex spikes in the cerebellum, potentially closing the loop. This is an attractive idea because it implies temporal binding of cerebellar actions on the motor system, within a plausible window for motor control. Several caveats should be mentioned. The complex spike pause is highly variable in duration and comprises only a small fraction of the pauses in Purkinje neuron spiking (Warnaar et al. 2015); these other pauses can also be synchronized among Purkinje neurons (Shin and De Schutter 2006). Moreover the presence of rebound spikes in DCN neurons is specific to certain classes of neurons (Najac and Raman 2015), though other forms of

phase-locking between Purkinje neuron and DCN neuron activity have been described recently (Person and Raman 2012). The latter, together with recent optogenetic studies confirming the functioning of the Purkinje neuron–DCN–IO loop (Chaumont et al. 2013), suggests the possible presence of more complex forms of reverberating loops. The existence of multiple loops in the olivocerebellar system would seem essential, although it has not so far been tied with a necessary correlate.

Single Cell Models of the Granular Layer

The dynamical behavior of network models evidently depends on the dynamics of the component cells. The two main players in the granule cell layer have seen devoted modeling efforts. Network oscillations are often an emergent property of single cell oscillations. Golgi cell models have reproduced the single cell oscillations on the basis of a persistent sodium current and a slow potassium current (Solinas et al. 2007). Golgi cell model produces robust oscillations upon both phasic and tonic depolarizing input, which implies that synaptic input to Golgi cells inhibits those cells that excite it, effectively gating the granule cells to particular windows (Table 1).

Granule cell models have shown high reliability of mossy fiber signal transmission. A full-fledged compartmental model of the turtle granule cell with differential ion channel expressions shows dynamic models: a linear relationship between mossy fiber activity and granule cell firing (Gabbiani et al. 1994). A later model based on measurements from rodent cells emphasized resonant properties of this neuron (D'Angelo et al. 2001) and was extended by showing that the active sodium conductance sharpens the action potential being propagated in the ascending axon to an almost instantaneous signal transmission (<200 us) (Diwakar et al. 2009).

Inferior Olivary Models

Coupled Oscillators and Electrotonic Coupling

Weakly coupled oscillators are able to maintain phase differences. Moreover, they can often be reset, which can be regarded as a short-term memory mechanism. The inferior olivary physiology supports these assumptions in spades, as IO cells have been shown to robustly oscillate (due to an interplay between calcium low threshold channels and calcium activated potassium channels) (Llinas and Yarom 1981; Manor et al. 1997). Crucially, these cells are robustly coupled electrotonically (De Zeeuw et al. 1997; Llinas et al. 1974), causing phase shifts in neighboring cells. Finally, both inhibitory and excitatory stimuli to the IO cells produces phase resets, according to phase of the oscillation (van der Giessen 2007). These three facts stand as compelling evidence that the IO acts as a network of coupled oscillators. Multiple models have examined these properties and their consequences in the

Table 1 Summary of network models discussed in this chapter

Model	Circuit	Neural model	Prediction	Emphasis	Mechanism (?)	References (e.g.,)
Marr (1970)	Cer + DCN (IO assumed)	McCulloch-Pitts	No other modifiable synapses Complex spikes carry semantic information	Functional	Supervised learning	(Marr 1969)
Albus	Olivocerebellar system	IAF	LTD learning	Functional	Supervised learning	(Albus 1971)
Tidal wave	Cerebellar cortex	Conceptual	Summation over time	Functional	Synaptic summation	(Braitenberg 1987)
Adaptive filter	Olivocerebellar system	Integrate and fire	Nonlinear filter function	Functional	Supervised learning	(Dean 2011)
Lossless granules	Granule layer	Multicompartment HH	Optimal convergence ratio MF:GR 4:1	Dynamical	Sparse encoding	(Marr 1969, Billings et al. 2014)
Golgi gating	Cerebellar cortex	Multicompartment HH	Reverberation window	Dynamical	Refractory periods	(Solinas et al. 2010, Maex and De Schutter 1998)
Silent synapses and information	Cerebellar cortex and Purkinje neuron	McCulloch-Pitts	N/A	Functional	Pattern recognition	(Clopath et al. 2014, Barbour et al. 2007)
Passage of time	Olivocerebellar system	IAF	N/A	Dynamical	Echo-state property	(Yamazaki and Tanaka 2007)
VOR and OKR learning	Olivocerebellar system	IAF	N/A	Functional	Supervised learning	(Clopath et al. 2014)
Robotic model	Olivocerebellar system	IAF	Kinematics of motion under lesion	Functional	Supervised learning	(Clopath et al. 2014)
Two joint limb	Olivocerebellar system	Multicompartment HH	Kinematics of motion under lesion	Functional	Supervised learning	(Houk and Fagg 2014, Neymotin et al. 2011)
Reverberating loops (Kistler)	Olivocerebellar system	Multicompartment H.H.	Long transients	Dynamical	Golgi gating through oscillations DCN reverberatory delay	(De Zeeuw et al. 2000)

network (Kazantsev et al. 2004; Latorre et al. 2013; Lefler et al. 2013; Schweighofer et al. 1999; Torben-Nielsen et al. 2012).

Not all olivary cells maintain robust oscillations, however (Bazzigaluppi and Bazzigali 2013; Bazzigaluppi et al. 2012). Intracellular recordings in vivo (but under anesthesia) have verified that around one third of cells robustly oscillate, with another third exhibiting transient oscillations, and a third of nonoscillating cells. This proportion varies considerably from subnucleus to subnucleus of the olive, indicating that robust oscillations may not be necessary for all olivary function. Interestingly, modeling has shown that even nonoscillating cells, when coupled, may engage a group of coupled cells in oscillations (Torben-Nielsen et al. 2012), suggesting that the combination of physiological properties of the cells in a group determines the group behavior.

Phase Resets and Synchronous Groups

Upon perturbations, olivary cells may produce a spike and reset, as a function of perturbation phase, sign, and intensity. This endows a group of coupled oscillators with the ability of maintaining phase differences, as a function of their correlated input (Jacobson et al. 2009; Kazantsev et al. 2004; Latorre et al. 2013; Torben-Nielsen et al. 2012). It is natural to interpret this property as underlying the temporal organization of muscle synergies. Synchronous groups have indeed been observed experimentally (Lang et al. 2006; Welsh et al. 1995), as and correlate with different phases of the activation of muscle ensembles. This could imply that simultaneous groups of Purkinje neurons would be activated in functional sequences, rather than exclusively synchronously.

Early oscillatory models of cerebellar function attribute to the complex spike a direct effect on the outcome of movements, rather than a teaching/error signal. This seems consistent with the outcome of experiments, which observe stark motor deficits from pharmacological, lesion, and genetic model experiments (Gao et al. 2012a; Llinas et al. 1975; Schonewille et al. 2011). Nevertheless, the complex spike has been shown to modify the response properties of Purkinje neuron simple spikes (Medina and Lisberger 2008), and so, it does not seem improbable that the two functions may coexist. And indeed, even features of the complex spike shape have also been shown to correlate with particular alterations of the Purkinje neuron simple spike responses (Rasmussen et al. 2013; Warnaar et al. 2015), such as the number of spikelets. The number of spikelets has been studied in a small network setting (De Gruijl 2012), from which the authors concluded that phase relationships and synchronicity between cells could explain the number of spikelets.

Echo State Machines

Still in the topic of dynamical models of the cerebellum, it has been suggested that the architecture of the cerebellum supports the encoding of transients, as in an echo-state

machine (Jaeger 2003). Interestingly, this model has suggested that the cerebellar architecture may be interpreted as encoding the passage of time (Yamazaki and Tanaka 2007).

Cerebellar Nucleus

Most models that feature a cerebellar nucleus often assume a very simplified version of its fairly intricate architecture and physiology. Until recently, the cerebellar nuclei did not receive extensive attention (Uusisaari and De Schutter 2011). Detailed anatomical and physiological work has shown that the cerebellar nucleus has a nonnegligible set of cell types, about five, and that these cells differ in their innervation schemes from the cerebellar cortex (some receiving somatic inhibition from Purkinje neurons, some distal dendritic input), anatomical properties (cell sizes), response properties (some with fast responses and rebounds), while some have much broader responses. A further complication of the overall picture of the olivocerebellar system is that some of the cells send feedback projection to the cerebellar cortex (Ankri et al. 2015), effectively dispelling the assumption that the cerebellum is exclusively a feed-forward system.

From the perspective of cerebellar nuclei output, two cells are of particular interest. The nucleo-olivary gabaergic projection cells and the glutamatergic projection cells have substantially different projection schemes and physiological responses (Houck and Person 2014; Kalmbach et al. 2011; Najac and Raman 2015; Uusisaari and Knöpfel 2012), the latter being fast firing and producing rebounds and the former being a slowly modulating cell. Most models of the cerebellar nucleus tend to include only the former, although it was often assumed that the output was of the fast/rebounding type. And as there are differences in the projection cells, it is likely that circuit dynamics of the DCN still reserve discoveries in the interactions of the poorly described interneurons (Table 2).

Conclusion

Consilience: Meeting in the Middle

Our exposition focuses on cerebellar modeling from two perspectives, functional and dynamical, which should be ultimately complementary. Nevertheless, the interfaces between functional models and dynamical necessities of the circuit are not always evident. Though many layers of biophysical phenomena appear exquisitely adapted, the functional relevance of biological mechanisms is not always apparent. Physiologically accurate modeling does not assume we know what the cerebellum does, but it does assume that things exist for a reason, unless there are compelling reasons to think otherwise. Functional modeling produces meaningful motor behavior, at the expense of biological accuracy. Although all models are fated to exclude something, both types of models are effective testbeds for assumptions both biological and functional.

Table 2 Single neuron models mentioned in this chapter

Single cell model	Animal model	Phenomenon of interest	Type	Notes	References (e.g.,)
Purkinje	Turtle	Simple spikes	Hodgkin Huxley (original)	Multicompartment	(Pellionisz and Llinas 1977)
Purkinje	Cat, rat, mouse	Simple and Complex spikes	Hodgkin Huxley	Calcium dynamics	(de Schutter and Bower 1994b)
Purkinje	Mixed	Spike initiation	Hodgkin Huxley – soma only	1 compartment	(Khaliq et al. 2003)
Golgi	Rat	Gap junctions	Hodgkin Huxley	Reconstructed morphology	(Vervaeke et al. 2010)
Golgi	Mixed	Pacemaking	Hodgkin Huxley multicompartment		(Solinas et al. 2007)
DCN	Mouse	Rebound	Hodgkin Huxley single compartment	Glutamatergic projection neuron (see Najac and Raman 2015)	(Steuber et al. 2010)
Inferior olivary neurons	N/A	Oscillations	Fitzh-Hugh Nagumo and Van Der Pol oscillators	Simplified model	(Velarde et al. 2002)
Inferior olivary neurons	Rat	Oscillations	Two compartments	Calcium low threshold and calcium activated potassium	(Manor et al. 1997)
Inferior olivary neurons	Rat	Oscillations	Two compartments	Information transmission	(Schweighofer et al. 2004)

References

- Albus JS (1971) A theory of cerebellar function. *Math Biosci* 10(1/2):25–61. doi:10.1016/j.gaitpost.2012.10.015
- Angelaki DE, Klier EM, Snyder LH (2009) A vestibular sensation: probabilistic approaches to spatial perception. *Neuron* 64(4):448–461. <https://doi.org/10.1016/j.neuron.2009.11.010>
- Ankri L, Husson Z, Pietrajtis K, Proville R, Léna C, Yarom Y et al (2015) A novel inhibitory nucleo-cortical circuit controls cerebellar Golgi cell activity. *eLife* 4. doi:10.7554/eLife.06262
- Antunes G, De Schutter E (2012) A stochastic signaling network mediates the probabilistic induction of cerebellar long-term depression. *J Neurosci* 32(27):9288–9300. <https://doi.org/10.1523/JNEUROSCI.5976-11.2012>
- Anwar H, Hong S, De Schutter E (2012) Controlling Ca²⁺-activated K⁺ channels with models of Ca²⁺ buffering in Purkinje cells. *Cerebellum (London, UK)* 11(3):681–693. <https://doi.org/10.1007/s12311-010-0224-3>
- Anwar H, Hepburn I, Nedelescu H, Chen W, De Schutter E (2013) Stochastic calcium mechanisms cause dendritic calcium spike variability. *J Neurosci* 33(40):15848–15867. <https://doi.org/10.1523/JNEUROSCI.1722-13.2013>
- Apps R, Hawkes R (2009) Cerebellar cortical organization: a one-map hypothesis. *Nat Rev Neurosci* 10(9):670–681. <https://doi.org/10.1038/nrn2698>
- Armstrong BD, Harvey RJ (1966) Responses in the inferior olive to stimulation of the cerebellar and cerebral cortices in the cat. *J Physiol* 187(3):553–574

- Armstrong DM, Harvey RJ (1968) Responses to a spino-olivo-cerebellar pathway in the cat. *J Physiol* 194(1):147–168
- Barbour B (1993) Synaptic currents evoked in Purkinje cells by stimulating individual granule cells. *Neuron* 11(4):759–769
- Barbour B, Brunel N, Hakim V, Nadal J-P (2007) What can we learn from synaptic weight distributions? *Trends Neurosci* 30(12):622–629. <https://doi.org/10.1016/j.tins.2007.09.005>
- Bazzigaluppi P, Bazzigali (2013) The inferior olive: coupling, oscillations and bursting activity. Erasmus MC, Rotterdam
- Bazzigaluppi P, Ruigrok TJ, Saisan P, de Jeu MTG, De Zeeuw CI (2012) Properties of the nucleo-olivary pathway: an *in vivo* whole-cell patch clamp study. *PLoS One* 7(9):e46360. <https://doi.org/10.1371/journal.pone.0046360.t003>
- Billings G, Piasini E, Lorincz A, Nusser Z, Silver RA (2014) Network structure within the cerebellar input layer enables lossless sparse encoding. *Neuron* 83(4):960–974. <https://doi.org/10.1016/j.neuron.2014.07.020>
- Bloedel JR, Roberts WJ (1971) Action of climbing fibers in cerebellar cortex of the cat. *J Neurophysiol* 34(1):17–31
- Blot A, Barbour B (2013) Analysis of the study of the cerebellar pinceau by Korn and Axelrad. *Biorxiv preprint server* <http://doi.org/10.1101/001123>
- Blot A, Barbour B (2014) Ultra-rapid axon-axon ephaptic inhibition of cerebellar Purkinje cells by the pinceau. *Nat Neurosci* 17(2):289–295. <https://doi.org/10.1038/nn.3624>
- Bower J (2010) Model-founded explorations of the roles of molecular layer inhibition in regulating Purkinje cell responses in cerebellar cortex: more trouble for the beam hypothesis. *Front Neurosci* 4:1–37
- Braitenberg V (1965) A note on the control of voluntary movements. In: *Proceedings from cybernetics of neural processes*, Napoli, pp 1–8
- Braitenberg V (1967) Is the cerebellar cortex a biological clock in the millisecond range? *Prog Brain Res*, 1–15
- Braitenberg V (1983) The cerebellum revisited. *J Theoret Neurobiol* 2:237–241
- Braitenberg V (1987) The cerebellum and the physics of movement: some speculations. In: *Cerebellum and neuronal plasticity*. Plenum Press, New York, pp 193–208
- Braitenberg V, Atwood R (1958) Morphological observations on the cerebellar cortex. *J Comp Neurol* 109(1):1
- Braitenberg V, Heck D, Sultan F (1997) The detection and generation of sequences as a key to cerebellar function: experiments and theory. *Behav Brain Sci* 20(2):229–245; discussion 245–277
- Casellato C, Antonietti A, Garrido JA, Carrillo RR, Luque NR, Ros E et al (2014) Adaptive robotic control driven by a versatile spiking cerebellar network. *PLoS One* 9(11):e112265. <https://doi.org/10.1371/journal.pone.0112265>
- Chaumont J, Guyon N, Valera AM, Dugué GP, Popa D, Marcaggi P et al (2013) Clusters of cerebellar Purkinje cells control their afferent climbing fiber discharge. *Proc Natl Acad Sci* 110(40):16223–16228. <https://doi.org/10.1073/pnas.1302310110>
- Clark SL (1939) Responses following electrical stimulation of the cerebellar cortex in the normal cat. *J Neurosci* 2(1):19–35
- Clopath C, Nadal J-P, Brunel N (2012) Storage of correlated patterns in standard and bistable Purkinje cell models. *PLoS Comput Biol* 8(4):e1002448. <https://doi.org/10.1371/journal.pcbi.1002448.g005>
- Clopath C, Badura A, De Zeeuw CI, Brunel N (2014) A cerebellar learning model of vestibulo-ocular reflex adaptation in wild-type and mutant mice. *J Neurosci* 34(21):7203–7215. <https://doi.org/10.1523/JNEUROSCI.2791-13.2014>
- Coesmans M, Weber JT, De Zeeuw CI, Hansel C (2004) Bidirectional parallel fiber plasticity in the cerebellum under climbing fiber control. *Neuron* 44(4):691–700. <https://doi.org/10.1016/j.neuron.2004.10.031>

- D'Angelo E, Nieuw T, Maffei A, Armano S, Rossi P, Taglietti V et al (2001) Theta-frequency bursting and resonance in cerebellar granule cells: experimental evidence and modeling of a slow k^+ -dependent mechanism. *J Neurosci* 21(3):759–770
- De Gruijl JR (2012) Timing and graded signals in the inferior olive. Erasmus MC, Rotterdam
- De Gruijl JR, Bazzigaluppi P, de Jeu MTG, De Zeeuw CI (2012) Climbing fiber burst size and olivary sub-threshold oscillations in a network setting. *PLoS Comput Biol* 8(12):e1002814. <https://doi.org/10.1371/journal.pcbi.1002814>
- De Gruijl JR, Bosman LWJ, De Zeeuw CI, de Jeu MTG (2013) Inferior olive: all ins and outs. In: *Handbook of the cerebellum and cerebellar disorders*. Springer Netherlands, Dordrecht, pp 1013–1058. https://doi.org/10.1007/978-94-007-1333-8_43
- De Schutter E, Bower JM (1994a) An active membrane model of the cerebellar Purkinje cell II. Simulation of synaptic responses. *J Neurophysiol* 71(1):401–419
- De Schutter E, Bower JM (1994b) An active membrane model of the cerebellar Purkinje cell. I. Simulation of current clamps in slice. *J Neurophysiol* 71(1):375–400
- De Schutter E, Bower JM (1994c) Simulated responses of cerebellar Purkinje cells are independent of the dendritic location of granule cell synaptic inputs. *Proc Natl Acad Sci U S A* 91(11):4736–4740
- De Schutter E, Steuber V (2009) Patterns and pauses in Purkinje cell simple spike trains: experiments, modeling and theory. *Neuroscience* 162(3):816–826. <https://doi.org/10.1016/j.neuroscience.2009.02.040>
- de Solages C, Szapiro G, Brunel N, Hakim V, Isope P, Buisseret P et al (2008) High-frequency organization and synchrony of activity in the Purkinje cell layer of the cerebellum. *Neuron* 58(5):775–788. <https://doi.org/10.1016/j.neuron.2008.05.008>
- De Zeeuw CI, Koekkoek SK, Wylie DR, Simpson JI (1997) Association between dendritic lamellar bodies and complex spike synchrony in the olivocerebellar system. *J Neurophysiol* 77(4):1747–1758
- De Zeeuw CI, van Hemmen L, Kistler WM (2000) Time window control: a model for cerebellar function based on synchronization, reverberation, and time slicing. *Prog Brain Res* 124:275–297
- Del Olmo MF, Cheeran B, Koch G, Rothwell JC (2007) Role of the cerebellum in externally paced rhythmic finger movements. *J Neurophysiol* 98(1):145–152. <https://doi.org/10.1152/jn.01088.2006>
- Dieudonne S (1998) Submillisecond kinetics and low efficacy of parallel fibre-Golgi cell synaptic currents in the rat cerebellum. *J Physiol* 510(Pt 3):845–866
- Diwakar S, Magistretti J, Goldfarb M, Naldi G, D'Angelo E (2009) Axonal Na^+ channels ensure fast spike activation and back-propagation in cerebellar granule cells. *J Neurophysiol* 101(2):519–532. <https://doi.org/10.1152/jn.90382.2008>
- Donchin O, Rabe K, Diedrichsen J, Lally N, Schoch B, Gizewski ER, Timmann D (2012) Cerebellar regions involved in adaptation to force field and visuomotor perturbation. *J Neurophysiol* 107(1):134–147. <https://doi.org/10.1152/jn.00007.2011>
- Doya K (2002) Metalearning and neuromodulation. *Neural Netw* 15(4–6):495–506
- Dugué GP, Brunel N, Hakim V, Schwartz E, Chat M, Lévesque M et al (2009) Electrical coupling mediates tunable low-frequency oscillations and resonance in the cerebellar Golgi cell network. *Neuron* 61(1):126–139. <https://doi.org/10.1016/j.neuron.2008.11.028>
- Ebner TJ, Bloedel JR (1981) Temporal patterning in simple spike discharge of Purkinje cells and its relationship to climbing fiber activity. *J Neurophysiol* 45(5):933–947
- Eccles JC, Llinas RR, Sasaki K (1966) Parallel fibre stimulation and the responses induced thereby in the Purkinje cells of the cerebellum. *Exp Brain Res (Experimentelle Hirnforschung Expérimentation Cérébrale)* 1(1):17–39. <https://doi.org/10.1007/BF00235207>
- Eccles JC, Ito M, Szentágothai J (1967) The cerebellum as a neuronal machine. Springer, Berlin
- Eccles JC, Sabah NH, Schmidt RF, Táboriková H (1972) Cutaneous mechanoreceptors influencing impulse discharges in cerebellar cortex. II. In Purkinje cells by mossy fiber input. *Experimental Brain Research Experimentelle Hirnforschung Expérimentation Cérébrale* 15(3):261–277

- Edelman GM, Gally JA (2001) Degeneracy and complexity in biological systems. *Proc Natl Acad Sci U S A* 98(24):13763–13768. <https://doi.org/10.1073/pnas.231499798>
- Ekerot CF, Gustavsson P, Oscarsson O, Schouenborg J (1987) Climbing fibres projecting to cat cerebellar anterior lobe activated by cutaneous A and C fibres. *J Physiol* 386:529–538
- Fagg AH, Sitko N, Barto AG, Houk J (1997) A computational model of cerebellar learning for limb control. *Mh. In: Neural Computation Meeting proceedings, NCM 1997*
- Frens MA, Mathoera AL, van der Steen J (2001) Floccular complex spike response to transparent retinal slip. *Neuron* 30(3):795–801
- Gabbiani F, Midtgaard J, Knöpfel T (1994) Synaptic integration in a model of cerebellar granule cells. *J Neurophysiol* 72(2):999–1009
- Gao Z, Todorov B, Barrett CF, van Dorp S, Ferrari MD, van den Maagdenberg AMJM et al (2012a) Cerebellar ataxia by enhanced CaV2.1 currents is alleviated by Ca²⁺-dependent K⁺-channel activators in Cacna1aS218L mutant mice. *J Neurosci* 32(44):15533–15546. <https://doi.org/10.1523/JNEUROSCI.2454-12.2012>
- Gao Z, van Beugen BJ, De Zeeuw CI (2012b) Distributed synergistic plasticity and cerebellar learning. *Nat Neurosci* 13:619–635. doi:10.1038/nrn3312
- Glickstein M, Sultan F, Voogd J (2011) Functional localization in the cerebellum. *Cortex* 47(1): 59–80. <https://doi.org/10.1016/j.cortex.2009.09.001>
- Han VZ, Grant K, Bell CC (2000) Reversible associative depression and nonassociative potentiation at a parallel fiber synapse. *Neuron* 27(3):611–622
- Hansel C, Linden DJ, D'angelo E (2001) Beyond parallel fiber LTD: the diversity of synaptic and non-synaptic plasticity in the cerebellum. *Nat Neurosci* 4(5):467–475. <https://doi.org/10.1038/87419>
- Hawkes R, Sillitoe RV, Chung SH, Fritschy JM, Hoy M (2008) Golgi cell dendrites are restricted by Purkinje cell stripe boundaries in the adult mouse cerebellar cortex. *J Neurosci* 28(11): 2820–2826. <https://doi.org/10.1523/JNEUROSCI.4145-07.2008>
- Heck D, Sultan F (2002) Cerebellar structure and function: making sense of parallel fibers. *Hum Mov Sci* 21(3):411–421
- Herzfeld DJ, Kojima Y, Soetedjo R, Shadmehr R (2015) Encoding of action by the Purkinje cells of the cerebellum. *Nature* 526(7573):439–442. <https://doi.org/10.1038/nature15693>
- Hoogland TM, De Griijl JR, Witter L, Canto CB, De Zeeuw CI (2015) Role of synchronous activation of cerebellar Purkinje cell ensembles in multi-joint movement control. *Curr Biol* 25(9):1–10. <https://doi.org/10.1016/j.cub.2015.03.009>
- Houck BD, Person AL (2014) Cerebellar loops: a review of the nucleocortical pathway. *Cerebellum* 13(3):378–385. <https://doi.org/10.1007/s12311-013-0543-2>
- Houk J, Fagg A (2014) A computational model for cerebellar learning for limb control. 1–16
- Hull C, Regehr WG (2012) Identification of an inhibitory circuit that regulates cerebellar Golgi cell activity. *Neuron* 73(1):149–158. <https://doi.org/10.1016/j.neuron.2011.10.030>
- Ito M (1989) Long-term depression. *Annu Rev Neurosci* 12:85–102
- Ito M, Kano M (1982) Long-lasting depression of parallel fiber-purkinje cell transmission induced by conjunctive stimulation of parallel fibers and climbing fibers in the cerebellar cortex. *Neurosci Lett* 33:253–258
- Jacobson GA, Lev I, Yarom Y, Cohen D (2009) Invariant phase structure of olivo-cerebellar oscillations and its putative role in temporal pattern generation. *Proc Natl Acad Sci* 106(9): 3579–3584. <https://doi.org/10.1073/pnas.0806661106>
- Jaeger D (2003) No parallel fiber volleys in the cerebellar cortex: evidence from cross-correlation analysis between Purkinje cells in a computer model and in recordings from anesthetized rats. *J Comput Neurosci* 14(3):311–327
- Jirenhed DA, Hesslow G, Bengtsson F (2007) Acquisition, extinction, and reacquisition of a cerebellar cortical memory trace. *J Neurosci* 27(10):2493–2502. <https://doi.org/10.1523/JNEUROSCI.4202-06.2007>
- Jörntell H, Bengtsson F, Schonewille M, De Zeeuw CI (2010) Cerebellar molecular layer interneurons – computational properties and roles in learning. *Trends Neurosci* 33(11):524–532. <https://doi.org/10.1016/j.tins.2010.08.004>

- Kalmbach BE, Voicu H, Ohyama T, Mauk MD (2011) A subtraction mechanism of temporal coding in cerebellar cortex. *J Neurosci* 31(6):2025–2034. doi:10.1523/JNEUROSCI.4212-10.2011
- Kazantsev VB, Nekorkin VI, Makarenko VI, Llinas RR (2003) Olivo-cerebellar cluster-based universal control system. *Proc Natl Acad Sci U S A* 100(22):13064–13068. <https://doi.org/10.1073/pnas.1635110100>
- Kazantsev VB, Nekorkin VI, Makarenko VI, Llinas RR (2004) Self-referential phase reset based on inferior olive oscillator dynamics. *Proc Natl Acad Sci U S A* 101(52):18183–18188. <https://doi.org/10.1073/pnas.0407900101>
- Khaliq ZM, Raman IM (2006) Relative contributions of axonal and somatic Na channels to action potential initiation in cerebellar Purkinje neurons. *J Neurosci* 26(7):1935–1944. <https://doi.org/10.1523/JNEUROSCI.4664-05.2006>
- Khaliq ZM, Gouwens NW, Raman IM (2003) The contribution of resurgent sodium current to high-frequency firing in Purkinje neurons: an experimental and modeling study. *J Neurosci* 23(12):4899–4912
- Kistler WM, van Hemmen L (1999) Delayed reverberation through time windows as a key to cerebellar function. *Biol Cybern* 81(5–6):373–380
- Lang EJ, Llinas RR, Sugihara I (2006) Isochrony in the olivocerebellar system underlies complex spike synchrony. *J Physiol* 573(Pt 1):277–9– author reply 281–2. <https://doi.org/10.1113/jphysiol.2006.571101>
- Latorre R, Aguirre C, Rabinowitch M, Varona P (2013) Transient dynamics and rhythm coordination of inferior olive spatio-temporal patterns. *Front Neural Circuits* 1–18. <https://doi.org/10.3389/fncir.2013.00138/abstract>
- Lefler Y, Torben-Nielsen B, Yarom Y (2013) Oscillatory activity, phase differences, and phase resetting in the inferior olivary nucleus. *Front Syst Neurosci* 1–9. <https://doi.org/10.3389/fnsys.2013.00022/abstract>
- Llinas RR, Yarom Y (1981) Properties and distribution of ionic conductances generating electro-responsiveness of mammalian inferior olivary neurones in vitro. *J Physiol* 315:569–584
- Llinas RR, BAKER R, Sotelo C (1974) Electrotonic coupling between neurons in cat inferior olive. *J Neurophysiol* 37(3):560–571
- Llinas RR, Walton K, Hillman DE, Sotelo C (1975) Inferior olive: its role in motor learning. *Science* (New York, NY) 190(4220):1230–1231. <https://doi.org/10.1126/science.128123>
- Maex R, De Schutter E (1998) Synchronization of golgi and granule cell firing in a detailed network model of the cerebellar granule cell layer. *J Neurophysiol* 80(5):2521–2537
- Manor Y, Rinzel J, Segev I (1997) Low-amplitude oscillations in the inferior olive: a model based on electrical coupling of neurons with heterogeneous channel densities. *J Neurophysiol* 77:2736
- Marr D (1969) A theory of cerebellar cortex. *J Physiol* 202(2):437–470
- Marshall SP, Lang EJ (2004) Inferior olive oscillations gate transmission of motor cortical activity to the cerebellum. *J Neurosci* 24(50):11356–11367. <https://doi.org/10.1523/JNEUROSCI.3907-04.2004>
- Mathy A, Ho SSN, Davie JT, Duguid IC, Clark BA, Häusser M (2009) Encoding of oscillations by axonal bursts in inferior olive neurons. *Neuron* 62(3):388–399. <https://doi.org/10.1016/j.neuron.2009.03.023>
- Mauk MD, Steinmetz JE, Thompson RF (1986) Classical conditioning using stimulation of the inferior olive as the unconditioned stimulus. *Proc Natl Acad Sci U S A* 83(14):5349–5353
- McCulloch WS, Pitts W (1943) A logical calculus of the ideas immanent in nervous activity. *Bull Math Biophys*
- Medina JF (2010) A recipe for bidirectional motor learning: using inhibition to cook plasticity in the vestibular nuclei. *Neuron* 68(4):607–609. <https://doi.org/10.1016/j.neuron.2010.11.011>
- Medina JF, Lisberger SG (2008) Links from complex spikes to local plasticity and motor learning in the cerebellum of awake-behaving monkeys. *Nat Neurosci* 11(10):1185–1192. <https://doi.org/10.1038/nn.2197>
- Mitchell SJ, Silver RA (2000) Glutamate spillover suppresses inhibition by activating presynaptic mGluRs. *Nature* 404(6777):498–502. <https://doi.org/10.1038/35006649>

- Najac M, Raman IM (2015) Integration of Purkinje cell inhibition by cerebellar nucleo-olivary neurons. *J Neurosci* 35(2):544–549. <https://doi.org/10.1523/JNEUROSCI.3583-14.2015>
- Neymotin SA, Lee H, Park E, Fenton AA, Lytton WW (2011) Emergence of physiological oscillation frequencies in a computer model of neocortex. *Front Comput Neurosci* 5:19. <https://doi.org/10.3389/fncom.2011.00019>
- Ohyama T, Nores WL, Murphy M, Mauk MD (2003) What the cerebellum computes. *Trends Neurosci* 26(4):222–227
- Optican LM, Robinson DA (1980) Cerebellar-dependent adaptive control of primate saccadic system. *J Neurophysiol* 44(6):1058–1076
- Ostojic S, Szapiro G, Schwartz E, Barbour B, Brunel N, Hakim V (2015) Neuronal morphology generates high-frequency firing resonance. *J Neurosci* 35(18):7056–7068. <https://doi.org/10.1523/JNEUROSCI.3924-14.2015>
- Pellionisz A, Llinas RR (1977) A computer model of cerebellar Purkinje cells. *Neuroscience* 2(1):37–48
- Pellionisz A, Llinas RR, Perkel DH (1977) A computer model of the cerebellar cortex of the frog. *Neuroscience* 2(1):19–35
- Person AL, Raman IM (2012) Purkinje neuron synchrony elicits time-locked spiking in the cerebellar nuclei. *Nature* 481(7382):502–505. <https://doi.org/10.1038/nature10732>
- Phoka E, Cuntz H, Roth A, Häusser M (2010) A new approach for determining phase response curves reveals that Purkinje cells can act as perfect integrators. *PLoS Comput Biol* 6(4):e1000768. <https://doi.org/10.1371/journal.pcbi.1000768>
- Porrill J, Dean P (2007) Cerebellar motor learning: when is cortical plasticity not enough? *PLoS Comput Biol* 3(10):e197. <https://doi.org/10.1371/journal.pcbi.0030197>
- Prsa M, Dash S, Catz N, Dicke PW, Thier P (2009) Characteristics of responses of Golgi cells and mossy fibers to eye saccades and saccadic adaptation recorded from the posterior vermis of the cerebellum. *J Neurosci* 29(1):250–262. <https://doi.org/10.1523/JNEUROSCI.4791-08.2009>
- Rasmussen A, Jirenhed DA, Zucca R, Johansson F, Svensson P, Hesslow G (2013) Number of spikes in climbing fibers determines the direction of cerebellar learning. *J Neurosci* 33(33):13436–13440. <https://doi.org/10.1523/JNEUROSCI.1527-13.2013>
- Rosenblatt F (1957) The perceptron – a perceiving and recognizing automaton. Report 85-460-1. Cornell Aeronautical Laboratory
- Rosenblatt F (1958) The Perceptron—a perceiving and recognizing automaton. Cornell Aeronautical Laboratory, Report 85-460-1
- Ruigrok TJ, Voogd J (1995) Cerebellar influence on olivary excitability in the cat. *Eur J Neurosci* 7(4):679–693
- Sauerbrei BA, Lubenov EV, Siapas AG (2015) Structured variability in Purkinje cell activity during locomotion. *Neuron* 87(4):840–852. <https://doi.org/10.1016/j.neuron.2015.08.003>
- Schmahmann J, Caplan D (2006) Cognition, emotion and the cerebellum. *Brain* 129(Pt 2):290–292. <https://doi.org/10.1093/brain/awh729>
- Schonewille M, Hoebeek FE, Belmeguenai A, Koekkoek SK, Houtman SH, Boele HJ et al (2010) Purkinje cell-specific knockout of the protein phosphatase PP2B impairs potentiation and cerebellar motor learning. *Neuron* 67(4):618–628. <https://doi.org/10.1016/j.neuron.2010.07.009>
- Schonewille M, Gao Z, Boele H-J, Vinuela Veloz MF, Amerika WE, Šimek AAM et al (2011) Reevaluating the role of LTD in cerebellar motor learning. *Neuron* 70(1):43–50. <https://doi.org/10.1016/j.neuron.2011.02.044>
- Schweighofer N, Doya K, Kawato M (1999) Electrophysiological properties of inferior olive neurons: a compartmental model. *J Neurophysiol* 82(2):804–817
- Schweighofer N, Doya K, Fukai H, Chiron JV, Furukawa T, Kawato M (2004) Chaos may enhance information transmission in the inferior olive. *Proc Natl Acad Sci U S A* 101(13):4655–4660. <https://doi.org/10.1073/pnas.0305966101>
- Shin SL, De Schutter E (2006) Dynamic synchronization of Purkinje cell simple spikes. *J Neurophysiol* 96(6):3485–3491. <https://doi.org/10.1152/jn.00570.2006>

- Shin SL, Hoebeek FE, Schonewille M, De Zeeuw CI, Aertsen A, De Schutter E (2007) Regular patterns in cerebellar Purkinje cell simple spike trains. *PLoS One* 2(5):e485
- Shinoda Y, Sugihara I, Wu HS, Sugiuchi Y (2000) The entire trajectory of single climbing and mossy fibers in the cerebellar nuclei and cortex. *Prog Brain Res* 124:173–186. [https://doi.org/10.1016/S0079-6123\(00\)24015-6](https://doi.org/10.1016/S0079-6123(00)24015-6). Elsevier
- Soetedjo R, Kojima Y, Fuchs AF (2008) Complex spike activity in the oculomotor vermis of the cerebellum: a vectorial error signal for saccade motor learning? *J Neurophysiol* 100(4): 1949–1966. <https://doi.org/10.1152/jn.90526.2008>
- Solinas S, Forti L, Cesana E, Mapelli J, De Schutter E, D'Angelo E (2007) Computational reconstruction of pacemaking and intrinsic electroresponsiveness in cerebellar Golgi cells. *Front Cell Neurosci* 1:2. <https://doi.org/10.3389/neuro.03.002.2007>
- Solinas S, Nieuwenhuis T, D'Angelo E (2010) A realistic large-scale model of the cerebellum granular layer predicts circuit spatio-temporal filtering properties. *Front Cell Neurosci* 4:12. <https://doi.org/10.3389/fncel.2010.00012>
- Spencer RMC, Ivry RB (2009) Sequence learning is preserved in individuals with cerebellar degeneration when the movements are directly cued. *J Cogn Neurosci* 21(7):1302–1310. <https://doi.org/10.1162/jocn.2009.21102>
- Steuber V, Mittmann W, Hoebeek FE, Silver RA, De Zeeuw CI, Häusser M, de Schutter E (2007) Cerebellar LTD and pattern recognition by Purkinje cells. *Neuron* 54(1):121–136. <https://doi.org/10.1016/j.neuron.2007.03.015>
- Steuber V, Schultheiss NW, Silver RA, Schutter E, Jaeger D (2010) Determinants of synaptic integration and heterogeneity in rebound firing explored with data-driven models of deep cerebellar nucleus cells. *J Comput Neurosci* 30(3):633–658. <https://doi.org/10.1007/s10827-010-0282-z>
- Sugihara I, Wu HS, Shinoda Y (2001) The entire trajectories of single olivocerebellar axons in the cerebellar cortex and their contribution to cerebellar compartmentalization. *J Neurosci* 21(19): 7715–7723
- Ten Brinke MM, Boele H-J, Spanke JK, Potters JW, Kornysheva K, Wulff P et al (2015) Evolving models of Pavlovian conditioning: cerebellar cortical dynamics in awake behaving mice. *CellReports* 13(9):1977–1988
- Thier P, Dicke PW, Haas R, Barash S (2000) Encoding of movement time by populations of cerebellar Purkinje cells. *Nature* 405(6782):72–76. <https://doi.org/10.1038/35011062>
- Torben-Nielsen B, Segev I, Yarom Y (2012) The generation of phase differences in a network model of the inferior olive subthreshold oscillations. *PLoS Comput Biol* 1–10. <https://doi.org/10.1371/journal.pcbi.1002580>
- Uusisaari M, De Schutter E (2011) The mysterious microcircuitry of the cerebellar nuclei. *J Physiol* 589(14):3441–3457. <https://doi.org/10.1113/jphysiol.2010.201582>
- Uusisaari MY, Knöpfel T (2012) Diversity of neuronal elements and circuitry in the cerebellar nuclei. *Cerebellum* (London, England) 11(2):420–421. <https://doi.org/10.1007/s12311-011-0350-6>
- van der Giessen RS (2007) Role of electrotonic coupling in the olivocerebellar system. Erasmus MC, Rotterdam
- Velarde MG, Nekorkin VI, Kazantsev VB, Makarenko VI, Llinas RR (2002) Modeling inferior olive neuron dynamics. *Neural Netw* 15(1):5–10
- Vervaeke K, Nusser Z, Silver RA (2010) Rapid desynchronization of an electrically coupled interneuron network with sparse excitatory synaptic input. *Neuron* 67(3):435–451. <https://doi.org/10.1016/j.neuron.2010.06.028>
- Vervaeke K, Lorincz A, Nusser Z, Silver RA (2012) Gap junctions compensate for sublinear dendritic integration in an inhibitory network. *Science* (New York, NY) 335(6076): 1624–1628. <https://doi.org/10.1126/science.1215101>
- Voogd J, Pardoe J, Ruigrok TJ, Apps R (2003) The distribution of climbing and mossy fiber collateral branches from the copula pyramidis and the paramedian lobule: congruence of climbing fiber cortical zones and the pattern of zebrin banding within the rat cerebellum. *J Neurosci* 23(11):4645–4656

- Voogd J, De Zeeuw CI, Schraa-Tam CKL, Geest JN (2010) Visuomotor cerebellum in human and nonhuman primates. *Cerebellum* (London, England) 11(2):392–410. <https://doi.org/10.1007/s12311-010-0204-7>
- Vos BP, Volny-Luraghi A, De Schutter E (1999) Cerebellar Golgi cells in the rat: receptive fields and timing of responses to facial stimulation. *Eur J Neurosci* 11(8):2621–2634
- Wamaar P, Couto J, Negrello M, Junker M, Smilgin A, Ignashchenkova A et al (2015) Duration of Purkinje cell complex spikes increases with their firing frequency. *Front Cell Neurosci* 9:1–30. <https://doi.org/10.3389/fncel.2015.00122>
- Welsh JP, Lang EJ, Sugihara I, Llinas RR (1995) Dynamic organization of motor control within the olivocerebellar system. *Nature* 374(6521):453–457. <https://doi.org/10.1038/374453a0>
- Witter L, Canto CB, Hoogland TM, De Gruijl JR, De Zeeuw CI (2013) Strength and timing of motor responses mediated by rebound firing in the cerebellar nuclei after Purkinje cell activation. *Front Neural Circuits* 7:133. <https://doi.org/10.3389/fncir.2013.00133>
- Wolpert DM, Kawato M (1998) Multiple paired forward and inverse models for motor control. *Neural Netw* 11(7–8):1317–1329
- Wulff P, Schonewille M, Renzi M, Viltono L, Sassoè-Pognetto M, Badura A et al (2009) Synaptic inhibition of Purkinje cells mediates consolidation of vestibulo-cerebellar motor learning. *Nat Neurosci* 12(8):1042–1049. <https://doi.org/10.1038/nn.2348>
- Yamazaki T, Tanaka S (2007) The cerebellum as a liquid state machine. *Neural Netw* 20(3):290–297. <https://doi.org/10.1016/j.neunet.2007.04.004>
- Zhou H, Lin Z, Voges K, Ju C, Gao Z, Bosman LW et al (2014) Cerebellar modules operate at different frequencies. *eLife* 3:e02536. <https://doi.org/10.7554/eLife.02536>