

## REVIEW

## PATTERNS AND PAUSES IN PURKINJE CELL SIMPLE SPIKE TRAINS: EXPERIMENTS, MODELING AND THEORY

E. DE SCHUTTER<sup>a,b,\*</sup> AND V. STEUBER<sup>c</sup><sup>a</sup>Computational Neuroscience Unit, Okinawa Institute of Science and Technology, Japan<sup>b</sup>Theoretical Neurobiology, University of Antwerp, Belgium<sup>c</sup>Science and Technology Research Institute, University of Hertfordshire, UK

**Abstract**—We review our recent experimental and modeling results on how cerebellar Purkinje cells encode information in their simple spike trains and present a theory of the function of pauses and regular spiking patterns. The regular spiking patterns were discovered in extracellular recordings of simple spikes in awake and anesthetized rodents, where it was shown that more than half of the spontaneous activity consists of short epochs of regular spiking. These periods of regular spiking are interrupted by pauses, which can be tightly synchronized among nearby Purkinje cells, while the spikes in the regular patterns are not. Interestingly, pauses are affected by long-term depression of the parallel fiber synapses. Both in modeling and slice experiments it was demonstrated that long-term depression causes a decrease in the duration of pauses, leading to an increase of the spike output of the neuron. Based on these results we propose that pauses in the simple spike train form a temporal code which can lead to a rebound burst in the target deep cerebellar nucleus neurons. Conversely, the regular spike patterns may be a rate code, which presets the amplitude of future rebound bursts. © 2009 IBRO. Published by Elsevier Ltd. All rights reserved.

**Key words:** cerebellum, Purkinje cell, deep cerebellar nucleus, neural coding, long-term depression, rebound burst.

Contents	
The DCN rebound burst as a timing signal	817
Regular firing of Purkinje cells	817
Synchronization of pauses and regular spikes in Purkinje cells	819
Learning by PF LTD changes pause duration	820
Mechanisms of regular firing and pauses in Purkinje cells	821
A theory of coding by regular firing and pauses	823
Pauses	823
Regular spiking patterns	824
Conclusion	824
Acknowledgments	824

\*Correspondence to: E. De Schutter, Biomedical Sciences, University of Antwerp, Universiteitsplein 1, 2610 Antwerpen, Belgium. Tel: +32-3-8202616.

E-mail address: erik@oist.jp (E. De Schutter).

**Abbreviations:** CF, climbing fiber; CS, complex spike; CV, coefficients of variation; DCN, deep cerebellar nuclei; ISI, interspike interval; LTD, long-term depression; LTP, long-term potentiation; PF, parallel fiber; SS, simple spike.

0306-4522/09 \$ - see front matter © 2009 IBRO. Published by Elsevier Ltd. All rights reserved.  
doi:10.1016/j.neuroscience.2009.02.040

References

824

In this review we present an interpretation of how Purkinje cells encode information in their simple spike (SS) trains, based on our experimental and modeling studies that were published in recent years. Although many researchers have recorded and analyzed Purkinje cell firing under diverse conditions, few have asked the question of how these cells encode information in the structure of their spike trains. In fact, the standard approach has been to look at changes in mean firing rates, averaged over many trial repetitions. When looking at such studies in more detail, it is noticeable that statistically significant responses correspond to widely varying modulations of the firing rate, from rather modest changes (Goossens et al., 2004; Roitman et al., 2005) to changes beyond 100 spikes/s (Krauzlis and Lisberger, 1994). As the dynamic range of Purkinje cells is large, from 0 to 400 Hz (Monsivais et al., 2005), studies showing small modulations may not have captured the main response features of the recorded neurons. Moreover, if one considers the cerebellar involvement in more complex motor control tasks like limb movement, where the motor plan resides in cerebral cortex and the cerebellum is involved in controlling mainly the timing of muscle contractions (Hikosaka et al., 1999), one wonders whether the single trial behavior is not more important than the average. Because movements show sizable natural variability, their real time control (often called “coordination”) is expected to require signals which vary a lot from trial to trial so as to compensate for the trial by trial deviations from the learned motor plan. Though more difficult to investigate in a setting of restrained animals doing over-trained movements—conditions reducing the natural variability—this observation calls for data analysis methods that study coding principles at the single trial level (see also Medina and Lisberger, 2008). In this context it seems sensible to focus more on the output of the cerebellar cortex, the SSs, than on the presumed learning signal, the complex spikes (CSs). This view is reinforced by the finding that the CS burst signal is not fully transmitted by the Purkinje cell axon, at least in the cerebellar slice condition (Monsivais et al., 2005).

Over the last few years we have started to study SS coding at the single trial level by analyzing spontaneous Purkinje cell spiking activity in awake and anesthetized rodents and stimulus-evoked activity in anesthetized rats (Shin and De Schutter, 2006; Shin et al., 2007). While the

analysis started out with no a priori assumptions about the structure of the Purkinje cell SS trains, it will be easier to describe the significance of the findings if one assumes that SS pauses are an important mechanism to evoke rebound bursts in the deep cerebellar nuclei (DCN). We will therefore first develop the basis of this assumption and relate it to recent literature on rebound bursts. Next we will demonstrate that the Purkinje cell SS train can be subdivided into two components: regular firing at rates beyond 50 Hz, which probably mostly reflects intrinsic excitability, interrupted by irregular longer interspike intervals (ISIs), which we will name pauses. This observation will be extended by a parallel combined modeling-experimental study, which demonstrated that cerebellar learning through long-term depression (LTD) of parallel fiber (PF) synapses may change the duration of SS pauses. We will conclude this review by proposing a data-driven theory on how the two SS components relate to each other, based on pauses evoking DCN rebound bursts.

### THE DCN REBOUND BURST AS A TIMING SIGNAL

The only targets of Purkinje cells outside of cerebellar cortex are neurons in the deep cerebellar and vestibular nuclei, which they inhibit. How does this inhibition affect the firing of DCN neurons? Most cerebellar theories and corresponding models have assumed an effect on the mean firing rates of DCN neurons (Ito, 1984), but these neurons have also the interesting property of responding to disinhibition with a characteristic post-inhibitory rebound burst (Llinás and Muhlethaler, 1988). Such a high frequency burst of spikes following a pause in firing can form a powerful timing signal (Kistler and van Hemmen, 1999; Koekoek et al., 2003; Wetmore et al., 2008), which is potentially useful in controlling the timing of muscle contraction (Hikosaka et al., 1999; Ivry and Spencer, 2004).

The rebound burst has been mainly studied in *in vitro* slices (Fig. 1). Unfortunately, most slice studies have not distinguished between excitatory and inhibitory DCN neurons (with as exception Uusisaari et al., 2007). In the context of motor control, the glutamatergic projection neurons are most relevant. All DCN neurons fire spontaneously (Uusisaari et al., 2007). Several ion currents may contribute to the rebound burst, including low-threshold calcium currents and persistent sodium currents (Jaeger et al., 2005; Molineux et al., 2006; Gauck et al., 2001), and the responses are variable, with not all DCN neurons showing strong rebounds (Uusisaari et al., 2007; Molineux et al., 2006, 2008). The level and duration of the hyperpolarization preceding the rebound burst exert a strong effect on its amplitude (Aizenman and Linden, 1999).

Unfortunately, less information is available about rebound spiking *in vivo*. However, while many DCN neurons show continuous irregular firing in anesthetized rats, others have a more complex rhythm consisting of pauses, most likely caused by PC inhibition, mixed with transient periods of fast bursting that resemble long rebounds observed *in vitro* (Rowland and Jaeger, 2005). A recent study

questioned the role of rebound bursts by reporting that they were only rarely observed in a DCN slice preparation and in anesthetized mice (Alviña et al., 2008). Though this study provides some valuable information about the conditions required to evoke rebound bursts (see below), it cannot be considered conclusive. In all experiments only one stimulation sequence was tested, 10 stimuli at 100 Hz; the dependence of stimulus characteristics on the likelihood of rebound spiking was not investigated. This reduces the generality of the Alviña et al. (2008) study as it has previously been demonstrated that rebound spiking is very sensitive to the duration and frequency of the inhibitory stimulus sequence (Fig. 1B, C) (McKay et al., 2005; Tadayonnejad et al., 2008). In the rest of this review we will therefore assume that rebound spiking can occur under certain conditions *in vivo*.

### REGULAR FIRING OF PURKINJE CELLS

*In vivo*, Purkinje cells were presumed to fire very irregularly, with coefficients of variation (CV) of the SS interspike intervals close to or even higher than 1, the CV of a Poisson process (Goossens et al., 2004; Vos et al., 1999b). This contrasts with the regular firing of Purkinje cells in the *in vitro* slice preparation (Häusser and Clark, 1997; Raman and Bean, 1999). Visual inspection of actual SS trains recorded *in vivo* already suggests that there may be more regularity than predicted by the CV (Fig. 2A), but as the epochs of regular firing are relatively short they are obscured in a CV measure computed over long time intervals.

Therefore a metric is needed which computes variability over shorter time periods. We selected the  $CV_2$  (Holt et al., 1996), which is the CV of two consecutive ISIs. The  $CV_2$  reflects the instantaneous irregularity of spike trains, with a value of zero for perfectly regular firing and large values indicating high irregularity. In both anesthetized and awake rodents we found that the distribution of  $CV_2$  values for spontaneous SS spike trains is strongly skewed towards low values. This is very different from the distributions found in neocortical neurons, which approximate a Poisson process (Shin et al., 2007).

While this indicates that there is a preponderance of consecutive ISIs with very similar lengths in Purkinje cell SS trains, a distribution does not give any indication on the temporal structure of this regular firing. To investigate this we introduced a new analysis of spike trains based on a  $CV_2$  threshold (Fig. 2B) (Shin et al., 2007). This analysis, which can be applied on-line or off-line, compares consecutive ISIs. If the  $CV_2$  is lower than or equal to a threshold (taken to be 0.2 in our study) this is considered the start of a regular spiking pattern. This pattern is extended by following ISIs as long as the  $CV_2$  stays below threshold and the pattern ends after the first ISI of a pair where  $CV_2$  crosses threshold. A regular spiking pattern is therefore a sequence of ISIs for which all  $CV_2$  values are below threshold; in the case of a threshold of 0.2 this corresponds to a maximum variance of 10% of ISI duration.

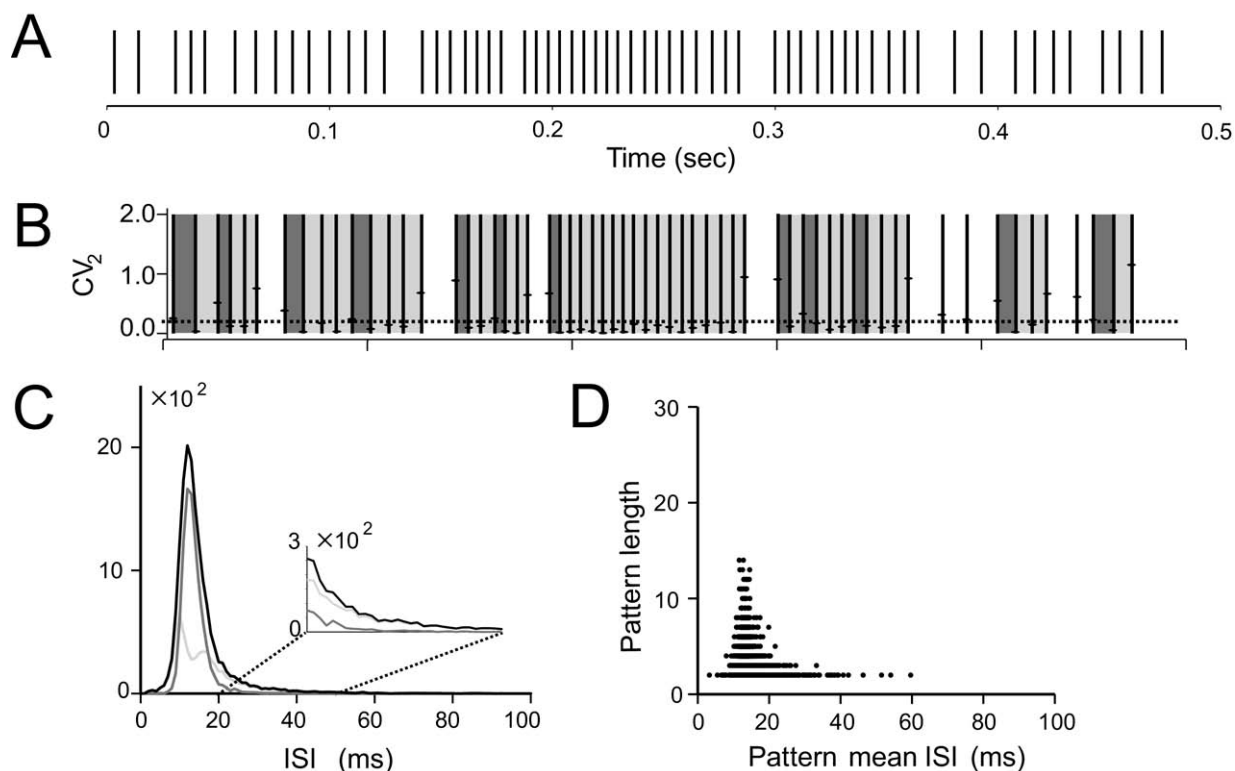
**Fig. 1.** Rebound discharge is dependent on presynaptic input pattern. (A–C) Representative whole-cell recordings of rebound discharge in a DCN transient burst neuron of the interpositus nucleus *in vitro* at 34 °C. The rebound response is shown expanded in insets. (A) The ability to generate a transient rebound burst (142 Hz) is confirmed by a step current pulse. (B, C) Repetitive activation of Purkinje cell inputs at 100 Hz for 10 (B) or 20 stimuli (C) (stimulus duration bracketed by arrows). A stronger transient burst component is reliably evoked after an input train of 20 IPSPs (53 Hz) compared to 10 IPSPs (19 Hz). Stimulus strength in B and C was set to evoke a 270 pA IPSC (70% maximum strength) and stimulus artifacts were truncated. A calculated junction potential of  $-11$  mV was subtracted and  $E_{Cl}$  was calculated as  $-75$  mV. Courtesy of R. Tadayonnejad and R. W. Turner.

Using this measure we could investigate the properties of regular spiking patterns in spontaneous Purkinje cell SS trains. In this review we report the properties recorded extracellularly in awake mice, but the findings were very similar in anesthetized rodents (Shin et al., 2007). Slightly more than half of all ISIs belonged to regular spiking patterns. The lengths of these ISIs were not uniformly distributed, but were concentrated in the peak of the ISI distribution: most regular spiking pattern ISIs were 8–20 ms long for a mean firing rate of the neuron of about 50 Hz (Fig. 2C). Thus, the tail of the ISI distribution, comprising longer ISIs which we will call pauses, rarely contained regular spiking patterns.

While many regular spiking patterns were quite short (two to three ISIs), about 20% contained four or more ISIs with a maximum length of 21 ISIs (Fig. 2D; longer patterns were observed in anesthetized animals).

The preponderance of regular spiking patterns is increased by tactile stimulation in anesthetized rats (Shin et al., 2007) and the properties of the patterns are modulated by oculomotor activity in rhesus monkeys (Guo et al., 2007), suggesting a behavioral relevance of these temporal structures in the SS trains.

We conclude that the SS train can be subdivided into two main components: short ISIs belonging to regular spik-



**Fig. 2.** Regular spiking patterns in Purkinje cell SS trains recorded *in vivo*. (A) Raster plot of a SS train showing epochs of regular firing. (B) The ISIs in this train have been labeled based on the  $CV_2$  threshold method. Marks on each spike show corresponding  $CV_2$  value for the surrounding ISIs. Grey colors indicate regular spiking patterns, with the first ISI of each pattern colored more darkly. Most blank ISIs are pauses. Broken line indicates the  $CV_2$  threshold. (C) ISI histogram for a single Purkinje cell, inset shows magnification of the tail of the distribution. Black: complete distribution, dark grey: ISIs belonging to regular spiking patterns, light grey: all other ISIs. (D) Properties of the regular spiking patterns of the same Purkinje cell: mean ISI versus length of the pattern (number of ISIs). Note that longer patterns are constrained to a narrow range of ISI values. Modified with permission from Shin et al. (2007).

ing patterns of variable lengths and longer ISIs called pauses, which show little regularity. Notice that a small number of ISIs falls into neither category: the short ISIs which are not part of regular spiking patterns (Fig. 2C). These will not be considered further, they may be noise or may have a specific coding function which we have not yet identified.

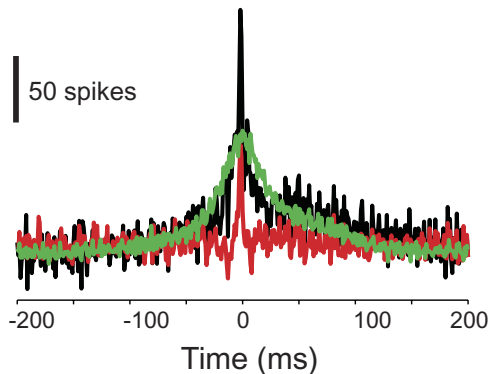
### SYNCHRONIZATION OF PAUSES AND REGULAR SPIKES IN PURKINJE CELLS

Before attributing specific roles to these two components it is useful to consider how this activity is distributed across an assembly of Purkinje cells. Ideally one would like to record from a large number of Purkinje cells simultaneously and study the correlation between different features of the SS train. Unfortunately it is much more difficult to do multi-unit recording in cerebellum than in cortex, with success achieved only for rather long distances between recorded Purkinje cells (Hofmann et al., 2006). As it has previously been demonstrated that SSs do not synchronize over distances of more than 100  $\mu\text{m}$  (Ebner and Bloedel, 1981; Jaeger, 2003), while they do so over shorter distances (Ebner and Bloedel, 1981; Bell and Grimm, 1969; De Zeeuw et al., 1997) we focused our study on the

latter case, using paired recording methods (Vos et al., 1999a).

We recorded from pairs of Purkinje cells, separated by 50–100  $\mu\text{m}$  along the transverse axis, in anesthetized rats (Shin and De Schutter, 2006). In most pairs statistically significant synchronization of SS firing was observed (Fig. 3). This correlation was quite tight with a large, sharp central peak. A noticeable feature was that the sharp peak comprising this precise synchronization was riding on top of a broader peak, as had also been observed in earlier studies (Ebner and Bloedel, 1981; Bell and Grimm, 1969). In cross-correlation studies broad central peaks are usually caused by firing rate co-modulation—if firing rates increase together in both neurons of a pair they will more likely spike closely together and vice versa—and are not indicative of real synchronization (Eggermont and Smith, 1995; Maex et al., 2000).

So it seems that the cross-correlation between nearby Purkinje cells comprises two components: a tight synchronization which may be significant for population coding and a loose synchronization which is not significant. Can these two kinds of synchronization be mapped onto the two components of the SS train? We investigated this by two types of analysis giving identical conclusions: spikes were



**Fig. 3.** Tight synchronization of pauses in Purkinje cell SS trains. Cross-correlogram of SSs in a nearby pair of Purkinje cells in anesthetized rat cerebellum recorded with two separate electrodes. The mean number of spikes has been subtracted. Black: cross-correlogram of all spikes. Red: cross-correlogram of spikes bordering on a pause (here defined as an ISI longer than 12 ms). Green: cross-correlogram of all other spikes. Note that the spikes associated with pauses cause the sharp central peak, while the non-pause spikes cause the broad peak. Modified with permission from Shin and De Schutter (2006).

either classified as bordering pauses or not, based on thresholding the duration of their adjacent ISIs (Fig. 3) (Shin and De Schutter, 2006), or categorized as part of regular spiking patterns or not, based on the CV<sub>2</sub> analysis that was described above (Shin et al., 2007). The precise synchronization observed was exclusively caused by spikes bordering pauses, with about 13% of the pauses occurring spontaneously in SS trains being synchronized (Shin and De Schutter, 2006). Note that, in addition, pauses following CSs (Bell and Grimm, 1969; Latham and Paul, 1971; McDevitt et al., 1982) may also synchronize (Welsh et al., 1995; Kitazawa and Wolpert, 2005), but these were excluded from the study as we wished to focus on SS coding. Conversely, the loose synchronization was caused by spikes belonging to regular spiking patterns and could indeed be shown to be based on firing rate co-modulation (Shin and De Schutter, 2006; Shin et al., 2007). In a subset of pairs we found, however, that the start of regular spiking patterns (their first spike) was significantly correlated while their firing rates were independent of each other (Shin et al., 2007).

The main conclusion was therefore that a significant fraction of SS pauses are synchronized between nearby Purkinje cells, causing the sharp central peak on the cross-correlogram. As a synchronized pause in firing of afferent Purkinje cells will lead to disinhibition of DCN neurons, the conditions for evoking rebound bursts in the DCN occur *in vivo*.

### LEARNING BY PF LTD CHANGES PAUSE DURATION

The existence of synchronized pauses in neighboring Purkinje cells suggests that pauses may play an important role for neural coding in the cerebellum. This raises the question how the duration of pauses could be regulated. A

candidate mechanism for the modulation of pause duration is plasticity at the afferent synapses onto Purkinje cells. Purkinje cells receive excitation from a large number of PFs and from a single climbing fiber (CF), and inhibition from stellate and basket cells. Both types of excitatory synapses and the inhibitory synapses exhibit activity dependent plasticity (Hansel et al., 2001; Jörntell and Hansel, 2006). It has been known for more than 25 years that co-activating PF and CF inputs induces LTD of the PF synapses (Ito et al., 1982). Activation of PFs on their own can lead to long-term potentiation (LTP) of the PF inputs, which can be expressed both presynaptically (Sakurai, 1987; Salin et al., 1996) and postsynaptically (Lev-Ram et al., 2003). Stimulation of the CF can result in LTD of the CF responses (Hansel and Linden, 2000) and when paired with depolarization of Purkinje cells in immature cerebellar slices, also in CF LTP (Bosman et al., 2008). Moreover, the synapses between inhibitory interneurons and Purkinje cells can be depressed by pairing inhibitory synaptic input with CF stimulation (Mittmann and Häusser, 2007), and they can be potentiated by unpaired CF input (Kano et al., 1992).

Out of these different forms of synaptic plasticity, LTD at the PF synapses has received by far the most attention, and is often considered the primary mechanism of motor learning in the cerebellar cortex (Marr, 1969; Albus, 1971; Ito, 1984, 2001). According to classic theories of cerebellar learning, a PF activity pattern is learned by pairing it with CF input to the Purkinje cell, which results in LTD of the active PF synapses. It has been assumed that this leads to a reduced Purkinje cell spike response when the PF pattern is presented again, which in turn could result in decreased Purkinje cell inhibition of DCN neurons and increased output from the cerebellum (Ito, 1984; Mauk et al., 1998; Hansel et al., 2001; Ito, 2001; Boyden et al., 2006). By combining computer simulations with electrophysiological recordings *in vitro* and *in vivo*, we have recently shown that this assumption is too simplified, and that Purkinje cells can use a fundamentally different neural code (Steuber et al., 2007). While the number of spikes fired by the Purkinje cell can reflect the intensity of PF stimulation or the PF synaptic weights in response to weak PF inputs (Walter and Khodakhah, 2006; Mittmann and Häusser, 2007), strong PF inputs predominantly affect the duration of pauses in Purkinje cell spiking that follow the short burst of spikes triggered by the PF stimulus (Steuber et al., 2007). Moreover, when the Purkinje cell learns a number of PF activity patterns by LTD of the active PF synapses, the best criterion to distinguish the responses to these learned patterns from responses to novel patterns is the duration of pauses.

To demonstrate this, we simulated learning by PF LTD in the Purkinje cell model in two steps (Steuber and De Schutter, 2001; Steuber et al., 2007). We initially generated a number of random binary patterns and applied an LTD learning rule to adapt the weights of an artificial neural network. After having learned a large number of patterns, we then transferred the resulting vector of synaptic weights onto AMPA ( $\alpha$ -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate)

receptor conductances in a biologically detailed conductance based Purkinje cell model (De Schutter and Bower, 1994a,b). We compared the responses of the model to learned and novel patterns, and evaluated the pattern recognition performance for different features of the spike response. To reflect the continuous activity of Purkinje cells *in vivo*, the Purkinje cell model fired SSs at varying rates (mean rate 48 Hz, maximum rate 130 Hz). The simulated continuous activity led to a surprising result: by far the best criterion for the recognition of learned patterns was the duration of the pause that followed the pattern presentation, with shorter pauses in response to patterns that had been learned by LTD (Fig. 4B,C). This result was robust against varying Purkinje cell firing rates and channel conductances and was unaffected by the presence of feed-forward inhibition and different kinds of noise in the input patterns.

In collaboration with Wolfgang Mittmann and Michael Häusser, we then went on to confirm our modeling prediction in non-invasive extracellular recordings from Purkinje cells in cerebellar slices. In agreement with previous findings (Bower and Woolston, 1983; Lev-Ram et al., 2003), we found that strong PF stimulation resulted in pauses in Purkinje cell firing. The duration of these pauses increased with increasing stimulus strength, which supported the predictions of our model. Moreover, a standard LTD induction protocol resulted in shortening of the pauses, with other features of the spike train being affected to a much lesser extent (Fig. 4D). Thus, the *in vitro* data supported the prediction that pause duration was the best criterion for detecting PF patterns learned by LTD. To strengthen this prediction further, we analyzed *in vivo* data from awake behaving mice that were provided by Chris De Zeeuw's laboratory. When LTD deficient mice were compared to their wild-type littermates, they showed a significant increase in long ISIs in the range of the pause durations in the simulations and *in vitro*. Moreover, the difference between LTD deficient and wild-type mice was more pronounced during optokinetic stimulation, which indicated a behavioral relevance of the pauses. Taken together, the computer simulations and *in vitro* and *in vivo* data suggest that Purkinje cells can use a neural code that is based on the duration of pauses, and that the pause duration can be changed by PF LTD.

The effect of other types of cerebellar plasticity on the duration of pauses is an interesting subject for future research, but some predictions can be made based on the presumed mechanism of the SS pause. In the model, the pauses are caused by voltage-gated calcium influx, which is evoked by strong PF input and activates K<sup>+</sup> channels (Steuber et al., 2007). As the decreased synaptic response amplitude caused by PF LTD decreases the calcium influx and thereby shortens the pause, one can speculate that PF LTP would trigger the opposite change.

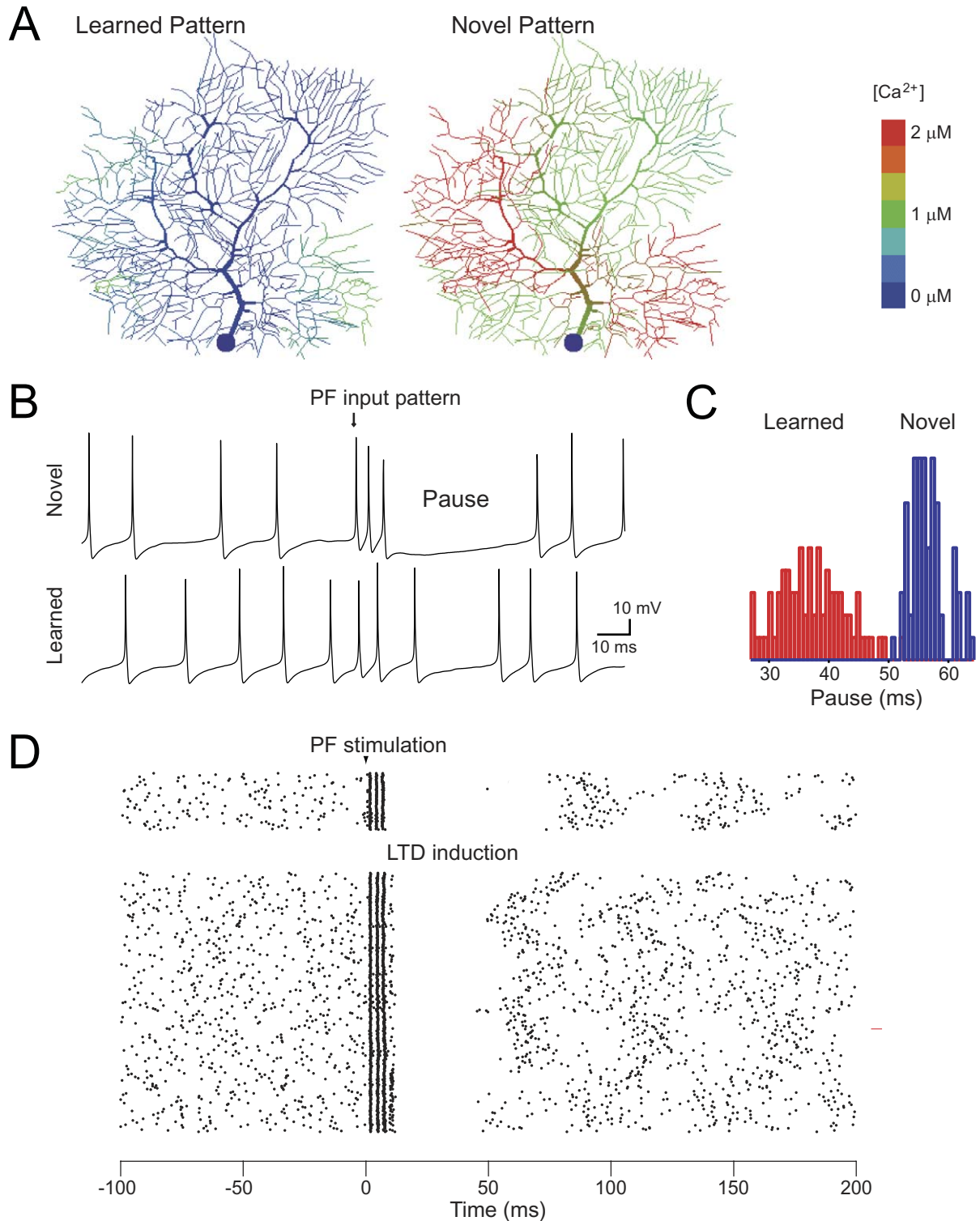
## MECHANISMS OF REGULAR FIRING AND PAUSES IN PURKINJE CELLS

Before proposing a theory of coding by regular spiking patterns and pauses it is useful to consider what may

cause these specific modulations of SS firing. It is important to distinguish these SS properties from Purkinje cell bistability, which has been demonstrated in cerebellar slices (Fernandez et al., 2007; Loewenstein et al., 2005; Williams et al., 2002), but may (Yartsev et al., 2009; Loewenstein et al., 2005) or may not (Schonewille et al., 2006) be causing transitions from up to down states and vice versa *in vivo*. In general the phenomena we describe here are much shorter in duration. We showed that an *in vivo* up state contains several regular spiking patterns (Shin et al., 2007) and the synchronized pauses (Shin and De Schutter, 2006) we measured are much shorter than the down states, which are about 1 s long. In general, it would be useful if the cerebellar community came to an agreement on what can be called a pause. In some contexts down states have also been referred to as pauses (Schonewille et al., 2006; Yartsev et al., 2009), which may cause confusion.

The pauses we describe last tens to hundreds of ms and are probably caused either directly or indirectly by synaptic input. Molecular layer inhibition is a logical candidate and inhibitory basket and stellate cells can provide common input to nearby Purkinje cells (Solinas et al., 2003), evoking a synchronized hyperpolarization. Pauses caused indirectly by synaptic input were described above: strong PF stimulation can trigger a calcium-activated hyperpolarization (Fig. 4A), manifest as a pause in SS firing (Steuber et al., 2007). While it is unclear at present how much each mechanism contributes to the large number of pauses in SS trains, both have the advantage that they can be modulated by cerebellar learning. As described above, PF LTD can change the duration of pauses (Steuber et al., 2007) and several forms of plasticity of inhibitory input have been described (Hansel et al., 2001; Smith and Otis, 2005; Mittmann and Häusser, 2007).

Our extracellular recordings do not provide conclusive evidence on the mechanisms causing regular spiking patterns. However, as Purkinje cells fire regularly in slice preparations when the synaptic inputs are blocked (Häusser and Clark, 1997; Raman and Bean, 1999) and since they show increased irregularity following mutations of their voltage-gated calcium channels (Hoebeek et al., 2005), the intrinsic excitability of Purkinje cells is probably the main drive of regular spiking. If this is the case, synaptic input would play a role mainly in controlling the start and end of a regular spiking pattern, as well as its mean firing rate. Because CSs do not seem to contribute to pattern initiation or completion in anesthetized rats (Shin et al., 2007), it is most likely that PF inputs combined with molecular layer inhibition control the properties of patterns. How PF input interacts with the intrinsic excitability of Purkinje cells *in vivo* is currently poorly understood. While it has been demonstrated repeatedly in cerebellar slices that PF input can activate voltage-gated calcium channels (De Schutter and Bower, 1994c; Eilers et al., 1995; Rancz and Häusser, 2006), it is noticeable that *in vivo* recordings of Purkinje cells show very little synaptic noise (Loewenstein et al., 2005), raising the question of how granule cell inputs affect the membrane potential. Possible explanations like low granule cell firing rates (Chadderton et al., 2004), silent



**Fig. 4.** PF LTD shortens the duration of SS pauses. (A) The Purkinje cell model was presented with a learned pattern and with a novel pattern, and a snapshot of the Ca<sup>2+</sup> concentration in all compartments 10 ms after the pattern presentation is shown. The increase of the Ca<sup>2+</sup> concentration in response to the novel pattern (right) was much greater than that caused by the learned pattern (left), because LTD of PF synapses led to reduced voltage-gated Ca<sup>2+</sup> influx. (B) Spiking response of the Purkinje cell model to the two patterns shown in A. Note the shorter pause for the learned pattern. (C) The distributions of the lengths of SS pauses following presentation of learned and novel patterns in the model are clearly separated. (D) Experimental confirmation in a cerebellar slice preparation. Spike raster shows the spiking pattern of a Purkinje cell in response to PF stimulation before and after an LTD induction protocol consisting of conjunctive PF and CF stimuli (1 Hz for 300 s). Note that while the spike burst hardly changed, the pause following the burst became consistently shorter. Modified with permission from Steuber et al. (2007).

synapses (Isope and Barbour, 2002) and differences between synapses made by the ascending axon versus PF (Grillner et al., 2005) only partially explain the apparent lack of spontaneous EPSPs in dendritic recordings *in vivo*, as these should be visible based on predictions from standard cable modeling (De Schutter, 1998).

## A THEORY OF CODING BY REGULAR FIRING AND PAUSES

In this final section we propose a theory of what the two different components of the Purkinje cell SS train contribute specifically to coding in the cerebellar cortex. This data-driven theory will focus mainly on the output side of the encoding process. By turning observations into a detailed theory (De Schutter, 1995) we hope to promote further research in this fascinating topic within a clearly defined framework. If future observations confirm the theory, large progress will have been made in unraveling how the cerebellum works. But even if all or part of the theory is eventually proven to be false, the process of uncovering this fact will significantly improve our understanding and allow better theories to be formulated.

Our theory can be summarized as follows: the SS train consists of two components that each have a specific role related to evoking rebound bursts in DCN neurons. The rebound bursts are assumed to form an important timing signal in the cerebellar output. The pauses in SS trains may, when sufficiently synchronized between afferent Purkinje cells, evoke the rebound burst. As such the pauses form a temporal code in the Purkinje cell spike train. The other component, the regular spiking patterns, forms a pure rate code. Their function is to determine, in an additive manner across afferent Purkinje cells, the level of DCN inhibition, which then controls both the likelihood and amplitude of any rebound burst that may be triggered by subsequent disinhibition. In addition, regular firing may control the mean firing rate of DCN neurons that cannot generate rebound bursts or in conditions where no timing signal is required.

We will now explore both the quantitative aspects and the supporting evidence of different aspects of the theory in more detail.

## PAUSES

The idea that pauses in Purkinje cell firing would trigger rebound spiking in DCN neurons is not novel (Kistler and van Hemmen, 1999; Wetmore et al., 2008), but previously this has been proposed mainly for the pause following CSs (Aizenman and Linden, 1999). We specifically propose that synchronized SS pauses can play a similar role in evoking a rebound burst. An advantage is that SS pauses occur frequently in the absence of CF input (Shin and De Schutter, 2006) and that they can exert their function independently of the teaching signal attributed to the CF (Marr, 1969; Albus, 1971; Ito, 2001). Two questions need to be addressed: the fraction of Purkinje cells that need to synchronize their SS pauses and the minimal pause duration that is required.

A problem in addressing the first question is that an exact quantification of the synaptic convergence of Purkinje cells onto DCN neurons is lacking, with numbers reported in the literature varying from 100 (De Zeeuw et al., 1994) to 1000 (Chan-Palay, 1977) afferent Purkinje cells. Moreover, nothing is known about the degree of overlap in Purkinje cell input between neighboring DCN neurons and, more importantly, between DCN neurons with different rebound properties (Uusisaari et al., 2007; Molineux et al., 2006, 2008).

It is unlikely that all afferent Purkinje cells need to stop firing to cause effective disinhibition. While miniature inhibitory synaptic currents recorded in DCN neurons in slice are quite large (Uusisaari and Knöpfel, 2008), the inhibitory currents depress very fast (Pedroarena and Schwarz, 2003; Telgkamp and Raman, 2002) so that the steady state inhibition caused by a single active Purkinje cell is small. In the end, the effective disinhibition will be determined by the interplay of many factors, related to both the synaptic input and the intrinsic excitability of DCN neurons, and it is difficult to make exact predictions without quantitative modeling. Nevertheless, we can assume that tens if not hundreds of Purkinje cells need to synchronize their pauses. The experimental data available (Shin and De Schutter, 2006) studied pause synchronization only in pairs of neighboring Purkinje cells, so it is difficult to extend the measured fraction of 13% synchronous pauses to larger populations. If the synchronization of pauses were not coordinated across the afferent population this proportion would rarely result in any effective disinhibition, and learning mechanisms are therefore required to coordinate pause synchronization. A probabilistic framework may be useful to describe how this operates at a population level. Learning could change both the probability and duration of pauses in a single neuron for a specific motor context, thereby affecting their overall probabilities of being synchronized with pauses in other Purkinje cells.

These ideas tie in with the question of the minimal duration of the pause. It is important to realize that it is not necessary that the pauses in all afferent Purkinje cells have the same length or that they overlap perfectly. As long as they coincide over the minimal duration, effective disinhibition can be achieved. Unfortunately this duration has not been studied in slice experiments. Extensive parameter studies have been performed on the required hyperpolarization (Aizenman and Linden, 1999) or inhibition (Tadayonnejad et al., 2008), but these stimuli are then followed by long periods of disinhibition, much longer than the pauses usually recorded *in vitro* (Steuber et al., 2007) or *in vivo* (Shin and De Schutter, 2006; Shin et al., 2007). It should be straightforward to measure in slice experiments the minimal duration of disinhibition needed to evoke DCN rebound bursts under different inhibitory stimulus conditions. An indication of the possible range of values can be derived from the recovery time constant from inactivation of the  $Ca_v3.1$  calcium channel expressed by DCN neurons, which is around 100 ms at body temperature (Iftinca et al., 2006).

## REGULAR SPIKING PATTERNS

Our theory proposes that the regular spiking patterns are close to a perfect rate code, which is a type of code that benefits from regular spiking (Koch, 1999). The regular firing matches very well with the synaptic properties of the Purkinje cell to DCN synapses (Pedroarena and Schwarz, 2003; Telgkamp and Raman, 2002). These synapses show fast, frequency dependent synaptic depression upon repeated activation. This endows them with low-pass filtering properties and makes them rather insensitive to small fluctuations in firing frequency (Abbott and Regehr, 2004). As demonstrated by quantitative modeling, regular firing reduces the fluctuations of synaptic conductance by a factor of two or more compared to completely irregular firing at the same mean rate (Shin et al., 2007). This effect can be seen even for short regular patterns comprising only three ISIs. Moreover, the lack of synchronization of spikes in the regular patterns further diminishes fluctuations at the population level (Shin and De Schutter, 2006; Shin et al., 2007).

The question arises, however, whether the convergence of many Purkinje cell inputs, by itself, could turn many strongly fluctuating synaptic conductances by addition into a stable, less noisy one (Softky and Koch, 1993), and abolish the benefits gained from the regularity of individual input. This will critically depend on the degree of convergence of Purkinje cells to DCN neurons and on what fraction of Purkinje cells is active at any moment of time (Loewenstein et al., 2005). As mentioned before, consistent data on these numbers are lacking at present. For the lower range of reported connectivities (100; De Zeeuw et al., 1994) it seems unlikely that the convergence will be enough to remove the fluctuations, for the higher range (1000; Chan-Palay, 1977) this argument would not hold.

In absence of better anatomical data we therefore propose that the inhibition from a single Purkinje cell during a regular spiking pattern injects a steady conductance, with its amplitude directly, but non-linearly, determined by firing frequency (Pedroarena and Schwarz, 2003). Over the population of afferent Purkinje cells, the inhibition caused by regular firing can therefore be added together when only conductance is considered, resulting in a population rate code. However, the physiological effect of regular Purkinje cell spiking is more complex as inhibitory currents will rapidly saturate due to the small difference between resting membrane potential and chloride reversal potential. This brings us to the effect of the inhibition caused by regular spiking patterns on rebound spiking in DCN neurons. As demonstrated in Fig. 1B and C (see also McKay et al., 2005; Tadayonnejad et al., 2008), the probability that disinhibition evokes a rebound burst compared to just a return to firing depends critically on the pattern of inhibition preceding the disinhibition, being sensitive both to frequency and number of inhibitory pulses. In addition, the depolarization and firing frequency during the transient rebound burst also depend on these factors (Aizenman and Linden, 1999). The exact mechanisms still need to be clarified in detail, but they most likely involve temporal sensitivities of the deinactivation processes governing the

currents underlying the rebound burst (Gauck et al., 2001; Iftinca et al., 2006; Molineux et al., 2008). Based on these physiological effects of inhibition, our theory predicts that regular spiking patterns in the afferent population of Purkinje cells determine both the likelihood and burst frequency of rebound bursts evoked by subsequent coordinated disinhibition. The specific effect of a regular spiking pattern will depend on its interaction with the intrinsic excitability of DCN neurons (Aizenman and Linden, 2000) and with their chloride reversal potential, which can be regulated (Lee et al., 2007).

## CONCLUSION

Based on extensive modeling and experimental work we have proposed a theory which attributes specific roles to two different components of the Purkinje cell SS train. Regular spiking patterns function as a rate code and set the “amplitude”—which can be zero—of subsequent rebound bursts in DCN neurons, while pauses provide a temporal coding signal which, when sufficiently synchronized across afferent Purkinje cells, will evoke a rebound burst at the preset amplitude. This theory provides a specific framework and questions which can be addressed by more experiments and modeling studies on Purkinje cells and DCN neurons.

*Acknowledgments*—We thank R. Tadayonnejad and R.W. Turner for the data shown in figure 1. This work was supported by Antwerp, Fonds Wetenschappelijk Onderzoek (Flanders) and the Human Frontier Science Program.

## REFERENCES

- Abbott LF, Regehr WG (2004) Synaptic computation. *Nature* 431:796–803.
- Aizenman CD, Linden DJ (1999) Regulation of the rebound depolarization and spontaneous firing patterns of deep nuclear neurons in slices of rat cerebellum. *J Neurophysiol* 82:1697–1709.
- Aizenman CD, Linden DJ (2000) Rapid, synaptically driven increases in the intrinsic excitability of cerebellar deep nuclear neurons. *Nat Neurosci* 3:109–111.
- Albus JS (1971) A theory of cerebellar function. *Math Biosci* 10:25–61.
- Alviña K, Walter JT, Kohn A, Ellis-Davies G, Khodakhah K (2008) Questioning the role of rebound firing in the cerebellum. *Nat Neurosci* 11:1256–1258.
- Bell CC, Grimm RJ (1969) Discharge properties of Purkinje cells recorded on single and double microelectrodes. *J Neurophysiol* 32:1044–1055.
- Bosman LW, Takechi H, Hartmann J, Eilers J, Konnerth A (2008) Homosynaptic long-term synaptic potentiation of the “winner” climbing fiber synapse in developing Purkinje cells. *J Neurosci* 28:798–807.
- Bower JM, Woolston DC (1983) Congruence of spatial organization of tactile projections to granule cell and Purkinje cell layers of cerebellar hemispheres of the albino rat: vertical organization of cerebellar cortex. *J Neurophysiol* 49:745–766.
- Boyden ES, Katoh A, Pyle JL, Chatila TA, Tsien RW, Raymond JL (2006) Selective engagement of plasticity mechanisms for motor memory storage. *Neuron* 51:823–834.
- Chadderton P, Margrie TW, Häusser M (2004) Integration of quanta in cerebellar granule cells during sensory processing. *Nature* 428:856–860.

- Chan-Palay V (1977) Cerebellar dentate nucleus. New York: Springer-Verlag.
- De Schutter E (1995) Cerebellar long-term depression might normalize excitation of Purkinje cells: a hypothesis. *Trends Neurosci* 18:291–295.
- De Schutter E (1998) Dendritic voltage and calcium-gated channels amplify the variability of postsynaptic responses in a Purkinje cell model. *J Neurophysiol* 80:504–519.
- De Schutter E, Bower JM (1994a) An active membrane model of the cerebellar Purkinje cell. I. Simulation of current clamps in slice. *J Neurophysiol* 71:375–400.
- De Schutter E, Bower JM (1994b) An active membrane model of the cerebellar Purkinje cell. II. Simulation of synaptic responses. *J Neurophysiol* 71:401–419.
- 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* 91:4736–4740.
- De Zeeuw CI, Koekoek SKE, Wylie DR, Simpson JI (1997) Association between dendritic lamellar bodies and complex spike synchrony in the olivocerebellar system. *J Neurophysiol* 77:1747–1758.
- De Zeeuw CI, Wylie DR, DiGiorgi PL, Simpson JI (1994) Projections of individual Purkinje cells of identified zones in the flocculus to the vestibular and cerebellar nuclei in the rabbit. *J Comp Neurol* 349:428–447.
- Ebner TJ, Bloedel JR (1981) Correlation between activity of Purkinje cells and its modification by natural peripheral stimuli. *J Neurophysiol* 45:948–961.
- Eggermont JJ, Smith GM (1995) Rate covariance dominates spontaneous cortical unit-pair correlograms. *Neuroreport* 6:2125–2128.
- Eilers J, Augustine GJ, Konnerth A (1995) Subthreshold synaptic  $Ca^{2+}$  signaling in fine dendrites and spines of cerebellar Purkinje neurons. *Nature* 373:155–158.
- Fernandez FR, Engbers JDT, Turner RW (2007) Firing dynamics of cerebellar Purkinje cells. *J Neurophysiol* 98:278–294.
- Gauck V, Thomann M, Jaeger D, Borst A (2001) Spatial distribution of low- and high-voltage-activated calcium currents in neurons of the deep cerebellar nuclei. *J Neurosci* 21:RC158.
- Goossens HH, Hoebeek FE, Van Alphen AM, Van Der Steen J, Stahl JS, De Zeeuw CI, Frens MA (2004) Simple spike and complex spike activity of floccular Purkinje cells during the optokinetic reflex in mice lacking cerebellar long-term depression. *Eur J Neurosci* 19:687–697.
- Grillner S, Markram H, De Schutter E, Silberberg G, LeBeau FE (2005) Microcircuits in action—from CPGs to neocortex. *Trends Neurosci* 28:525–533.
- Guo C, Shin S-L, Raymond JL (2007) Precise spike timing in Purkinje cells during oculomotor behavior. *Soc Neurosci Abstr* 409:17.
- Hansel C, Linden DJ (2000) Long-term depression of the cerebellar climbing fiber—Purkinje neuron synapse. *Neuron* 26:473–482.
- 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* 4:467–475.
- Häusser M, Clark BA (1997) Tonic synaptic inhibition modulates neuronal output pattern and spatiotemporal synaptic integration. *Neuron* 19:665–678.
- Hikosaka O, Nakahara H, Rand MK, Sakai K, Lu X, Nakamura K, Miyachi S, Doya K (1999) Parallel neural networks for learning sequential procedures. *Trends Neurosci* 22:464–471.
- Hoebeek FE, Stahl JS, van Alphen AM, Schonewille M, Luo C, Rutteman M, van den Maagdenberg AM, Molenaar PC, Goossens HH, Frens MA, De Zeeuw CI (2005) Increased noise level of Purkinje cell activities minimizes impact of their modulation during sensorimotor control. *Neuron* 45:953–965.
- Hofmann UG, Folkers A, Mosch F, Malina T, Menne KML, Biella G, Fagerstedt P, De Schutter E, Jensen W, Yoshida K, Hoehl D, Thomas U, Kindlundh MG, Norlin P, de Curtis M (2006) A novel high channel-count system for acute multisite neuronal recordings. *IEEE T Biomed Eng* 53:1672–1677.
- Holt GR, Softky WR, Koch C, Douglas J (1996) Comparison of discharge variability in vitro and in vivo in cat visual cortex neurons. *J Neurophysiol* 75:1806–1814.
- Iftinca M, McKay BE, Snutch TP, McRory JE, Turner RW, Zamponi GW (2006) Temperature dependence of T-type calcium channel gating. *Neuroscience* 142:1031–1042.
- Isope P, Barbour B (2002) Properties of unitary granule cell→Purkinje cell synapses in adult rat cerebellar slices. *J Neurosci* 22:9668–9678.
- Ito M (1984) The cerebellum and neural control. New York: Raven Publishing.
- Ito M (2001) Cerebellar long-term depression: characterization, signal transduction, and functional roles. *Physiol Rev* 81:1143–1195.
- Ito M, Sakurai M, Tongroach P (1982) Climbing fiber induced depression of both mossy fibre responsiveness and glutamate sensitivity of cerebellar Purkinje cells. *J Physiol* 324:133–134.
- Ivry RB, Spencer RM (2004) The neural representation of time. *Curr Opin Neurobiol* 14:225–232.
- 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* 14:311–327.
- Jaeger D, De Schutter E, Steuber V (2005) A computational study of rebound responses in a conductance-based model of a deep cerebellar nucleus cell. *Soc Neurosci Abstr* 179:11.
- Jörntell H, Hansel C (2006) Synaptic memories upside down: bidirectional plasticity at cerebellar parallel fiber—Purkinje cell synapses. *Neuron* 52:227–238.
- Kano M, Rexhausen U, Dreessen J, Konnerth A (1992) Synaptic excitation produces a long-lasting rebound potentiation of inhibitory synaptic signals in cerebellar Purkinje cells. *Nature* 356:601–604.
- Kistler WM, Leo van Hemmen J (1999) Delayed reverberation through time windows as a key to cerebellar function. *Biol Cybern* 81:373–380.
- Kitazawa S, Wolpert DM (2005) Rhythmicity, randomness and synchrony in climbing fiber signals. *Trends Neurosci* 28:611–619.
- Koch C (1999) Biophysics of computation: information processing in single neurons. New York: Oxford University Press.
- Koekoek SK, Hulscher HC, Dortland BR, Hensbroek RA, Elgersma Y, Ruigrok TJ, De Zeeuw CI (2003) Cerebellar LTD and learning-dependent timing of conditioned eyelid responses. *Science* 301:1736–1739.
- Krauzlis RJ, Lisberger SG (1994) Simple spike responses of gaze velocity Purkinje cells in the floccular lobe of the monkey during the onset and offset of pursuit eye movements. *J Neurophysiol* 72:2045–2050.
- Latham A, Paul DH (1971) Spontaneous activity of cerebellar Purkinje cells and their responses to impulses in climbing fibres. *J Physiol* 213:135–156.
- Lee HH, Walker JA, Williams JR, Goodier RJ, Payne JA, Moss SJ (2007) Direct protein kinase C-dependent phosphorylation regulates the cell surface stability and activity of the potassium chloride cotransporter KCC2. *J Biol Chem* 282:29777–29784.
- Lev-Ram V, Mehta SB, Kleinfeld D, Tsien RY (2003) Reversing cerebellar long-term depression. *Proc Natl Acad Sci U S A* 100:15989–15993.
- Llinás R, Muhlethaler M (1988) Electrophysiology of guinea-pig cerebellar nuclear cells in the in vitro brain stem-cerebellar preparation. *J Physiol* 404:241–258.
- Loewenstein Y, Mahon S, Chadderton P, Kitamura K, Sompolinsky H, Yarom Y, Häusser M (2005) Bistability of cerebellar Purkinje cells modulated by sensory stimulation. *Nat Neurosci* 8:202–211.
- Maex R, Vos BP, De Schutter E (2000) Weak common parallel fibre synapses explain the loose synchrony observed between rat cerebellar Golgi cells. *J Physiol* 523:175–192.
- Marr DA (1969) A theory of cerebellar cortex. *J Physiol* 202:437–470.
- Mauk MD, Garcia KS, Medina JF, Steele PM (1998) Does cerebellar LTD mediate motor learning? Toward a resolution without a smoking gun. *Neuron* 20:359–362.

- McDevitt CJ, Ebner TJ, Bloedel JR (1982) The changes in Purkinje cell simple spike activity following spontaneous climbing fiber inputs. *Brain Res* 237:484–491.
- McKay BE, Molineux ML, Mehaffey WH, Turner RW (2005) Kv1 K<sup>+</sup> channels control Purkinje cell output to facilitate postsynaptic rebound discharge in deep cerebellar neurons. *J Neurosci* 25:1481–1492.
- Medina JF, Lisberger SG (2008) Links from complex spikes to local plasticity and motor learning in the cerebellum of awake-behaving monkeys. *Nat Neurosci* 11:1185–1192.
- Mittmann W, Häusser M (2007) Linking synaptic plasticity and spike output at excitatory and inhibitory synapses onto cerebellar Purkinje cells. *J Neurosci* 27:5559–5570.
- Molineux ML, McRory JE, McKay BE, Hamid J, Mehaffey WH, Rehak R, Snutch TP, Zamponi GW, Turner RW (2006) Specific T-type calcium channel isoforms are associated with distinct burst phenotypes in deep cerebellar nuclear neurons. *Proc Natl Acad Sci U S A* 103:5555–5560.
- Molineux ML, Mehaffey WH, Tadayonnejad R, Anderson DM, Tennent AF, Turner RW (2008) Ionic factors governing rebound burst phenotype in rat deep cerebellar neurons. *J Neurophysiol* 100:2684–2701.
- Monsivais P, Clark BA, Roth A, Häusser M (2005) Determinants of action potential propagation in cerebellar Purkinje cell axons. *J Neurosci* 25:464–472.
- Pedroarena CM, Schwarz C (2003) Efficacy and short-term plasticity at GABAergic synapses between Purkinje and cerebellar nuclei neurons. *J Neurophysiol* 89:704–715.
- Raman IM, Bean BP (1999) Ionic currents underlying spontaneous action potentials in isolated cerebellar Purkinje neurons. *J Neurosci* 19:1663–1674.
- Rancz EA, Häusser M (2006) Dendritic calcium spikes are tunable triggers of cannabinoid release and short-term synaptic plasticity in cerebellar Purkinje neurons. *J Neurosci* 26:5428–5437.
- Roitman AV, Pasalar S, Johnson MT, Ebner TJ (2005) Position, direction of movement, and speed tuning of cerebellar Purkinje cells during circular manual tracking in monkey. *J Neurosci* 25:9244–9257.
- Rowland NC, Jaeger D (2005) Coding of tactile response properties in the rat deep cerebellar nuclei. *J Neurophysiol* 94:1236–1251.
- Sakurai M (1987) Synaptic modification of parallel fibre-Purkinje cell transmission in in vitro guinea-pig cerebellar slices. *J Physiol* 394:463–480.
- Salin P, Malenka RC, Nicoll RA (1996) Cyclic-AMP mediates a pre-synaptic form of LTP at cerebellar parallel fiber synapses. *Neuron* 16:797–803.
- Schonewille M, Khosrovani S, Winkelmann BH, Hoebeek FE, De Jeu MT, Larsen IM, Van der Burg J, Schmolesky MT, Frens MA, De Zeeuw CI (2006) Purkinje cells in awake behaving animals operate at the upstate membrane potential. *Nat Neurosci* 9:459–461.
- Shin S, de Schutter E (2006) Dynamic synchronization of Purkinje cell simple spikes. *J Neurophysiol* 96:3485–3491.
- Shin S, Hoebeek FE, Schonewille M, de Zeeuw CI, Aersten A, de Schutter E (2007) Regular patterns in cerebellar Purkinje cell simple spike trains. *PLoS ONE* 2:e485.
- Smith SL, Otis TS (2005) Pattern-dependent, simultaneous plasticity differentially transforms the input-output relationship of a feedforward circuit. *Proc Natl Acad Sci U S A* 102:14901–14906.
- Softky WR, Koch C (1993) The highly irregular firing of cortical cells is inconsistent with temporal integration of EPSPs. *J Neurosci* 13:334–350.
- Solinas S, Maex R, De Schutter E (2003) Synchronization of Purkinje cell pairs along the parallel fiber axis: a model. *Neurocomputing* 57:97–102.
- Steuber V, De Schutter E (2001) Long-term depression and recognition of parallel fibre patterns in a multicompartmental model of a cerebellar Purkinje cell. *Neurocomputing* 38:383–388.
- 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* 54:121–136.
- Tadayonnejad R, Mehaffey WH, Turner RW (2008) Deep cerebellar nuclear neurons use different strategies for coding physiological patterns of Purkinje cell activity. *Soc Neurosci Abstr* 471:4.
- Telgkamp P, Raman IM (2002) Depression of inhibitory synaptic transmission between Purkinje cells and neurons of the cerebellar nuclei. *J Neurosci* 22:8447–8457.
- Uusisaari M, Knöpfel T (2008) GABAergic synaptic communication in the GABAergic and non-GABAergic cells in the deep cerebellar nuclei. *Neuroscience* 156:537–549.
- Uusisaari M, Obata K, Knöpfel T (2007) Morphological and electrophysiological properties of GABAergic and non-GABAergic cells in the deep cerebellar nuclei. *J Neurophysiol* 97:901–911.
- Vos BP, Maex R, Volny-Luraghi A, De Schutter E (1999a) Parallel fibers synchronize spontaneous activity in cerebellar Golgi cells. *J Neurosci* 19:RC6.
- Vos BP, Volny-Luraghi A, De Schutter E (1999b) Cerebellar Golgi cells in the rat: receptive fields and timing of responses to facial stimulation. *Eur J Neurosci* 11:2621–2634.
- Walter JT, Khodakhah K (2006) The linear computational algorithm of cerebellar Purkinje cells. *J Neurosci* 26:12861–12872.
- Welsh JP, Lang EJ, Sugihara I, Llinás R (1995) Dynamic organization of motor control within the olivocerebellar system. *Nature* 374:453–457.
- Wetmore DZ, Mukamel EA, Schnitzer MJ (2008) Lock-and-key mechanisms of cerebellar memory recall based on rebound currents. *J Neurophysiol* 100:2328–2347.
- Williams SR, Christensen SR, Stuart GJ, Häusser M (2002) Membrane potential bistability is controlled by the hyperpolarization-activated current I(H) in rat cerebellar Purkinje neurons in vitro. *J Physiol* 539:469–483.
- Yartsev MM, Givon-Mayo R, Maller M, Donchin O (2009) Pausing Purkinje cells in the cerebellum of the awake cat. *Front Syst Neurosci* 3:2.