

# Reading the Clock: How Purkinje Cells Decode the Phase of Olivary Oscillations

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DOI 10.1016/j.neuron.2009.04.020

Climbing fiber responses in cerebellar Purkinje cells are described as being invariant. In this issue of *Neuron*, Mathy et al. show that the complex spike waveform changes with the number of spikes in a climbing fiber burst, which depends on the phase of olivary oscillations. In turn, different complex spike profiles affect synaptic plasticity at parallel fiber synapses. Thus, information on inferior olive oscillation states is reflected in both the complex spike waveform and the parallel fiber input gain.

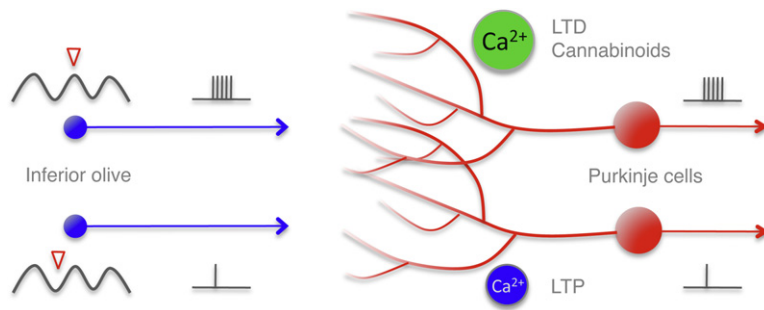
The notion of the “invariant” climbing fiber (CF) response results from early observations of the all-or-none character of CF-evoked complex spikes (Eccles et al., 1966) and the stereotyped calcium transient that CF activity evokes in Purkinje cell dendrites (Ross and Werman, 1987). CFs arise from neurons in the inferior olive, which are characterized by a high degree of electrotonic coupling and, depending on the neuronal subtype, by prominent subthreshold oscillations that occur at low frequencies up to 10 Hz (Khosrovani et al., 2007). Based on this oscillatory behavior, it was suggested that the inferior olive provides a “motor clock” function in the initiation and timing of movements (Welsh et al., 1995). A challenge to this hypothesis has been the observation that both suprathreshold discharges of olivary neurons and complex spike firing in Purkinje cells are at best weakly periodic; hence, it remains unclear how Purkinje cells obtain information on the timing of inferior olive oscillations (for discussion see Keating and Thach, 1995; Welsh et al., 1995; Chorev et al., 2007).

In this issue of *Neuron*, Mathy et al. present an unexpected solution to this problem (Mathy et al., 2009). Olivary axons transmit high-frequency bursts (Maruta et al., 2007). In their new paper, Mathy et al. use cell-attached or whole-cell axonal recordings, paired with whole-cell recordings from rat inferior olive neurons or Purkinje cells, respectively, to examine the relationship between axonal bursts and olivary output on the one hand and Purkinje cell responses on the other. In short, they find that the number of spikes in an axonal burst provides a read-out of

the phase of olivary oscillations. At the level of Purkinje cells, this read-out is reflected in the complex spike waveform, as there is a linear relationship between the number of spikes transmitted in a CF burst and the number of spikelets in a somatically recorded complex spike. It has previously been shown that the complex spike waveform can be modulated as part of a long-term depression at the CF input (Hansel and Linden, 2000). However, in this paper, Mathy et al. take the notion that the CF response is anything but invariant one step further by showing that the complex spike is constantly changing depending on the activity state of the inferior olive and that it actually reflects this activity state quite reliably. As a result, the state of subthreshold olivary oscillations directly affects the output of cerebellar cortex activity.

Activation of olivary principal neurons results in a characteristic compound response, which actually resembles Purkinje cell complex spikes, such that an initial spike is followed by a series of spikelets riding on top of a depolarization plateau. As shown in this paper by Michael Häusser and his colleagues, each spikelet is reflected by an individual action potential that can be recorded in the olivary axon. These action potentials are initiated in the axon as indicated by a delay at which the somatically recorded spikelets occur relative to the axonal spikes. A key finding of the paper is that the axonal spike pattern differs depending on the timing of stimulation (by EPSPs or current injection) relative to the phase of the olivary oscillation: while stimulation at the peak of the depolarizing phase triggers several axonal spikes, acti-

vation outside this optimal timing window elicits fewer spikes or fails to evoke axonal spiking entirely. This read-out of olivary oscillation states is subsequently conveyed to Purkinje cells. The authors report a linear relationship between the number of CF spikes and the number of spikelets in somatically recorded complex spikes, which they predict to result in a “one in, one out” relationship between CF and Purkinje cell axonal spikes (see Khaliq and Raman, 2005; Monsivais et al., 2005). This finding is highly important, but remains somewhat puzzling, as dendritic spike activity is only weakly related to spike patterns in the CF on the one hand and the Purkinje cell soma on the other (Davie et al., 2008; this paper). Nevertheless, a higher number of spikes in a CF burst enhance the probability for eliciting additional dendritic calcium spikes. This finding helps to explain another key observation: pairing of parallel fiber (PF) stimuli with a climbing fiber burst induces PF long-term depression (LTD), whereas pairing with a single climbing fiber stimulus triggers long-term potentiation (LTP). A likely explanation is that a CF burst evokes a larger dendritic calcium signal than a single CF stimulus and thus provides sufficient calcium to reach the LTD induction threshold (Coemans et al., 2004). In addition, Mathy et al. show that the number of CF spikes translates into the strength of short-term inhibition of PF synapses. This form of short-term plasticity is mediated by retrograde endocannabinoid signaling, which is regulated by CF-evoked calcium transients (Brenowitz and Regehr, 2005). CF burst firing might therefore also affect a presynaptic form of PF-LTP that is



**Figure 1. Schematic Drawing of the Purkinje Cell Read-Out of Olivary Oscillations**  
 The number of CF spikes depends on the timing of synaptic input (arrow head) relative to the phase of olivary oscillations. Purkinje cell axonal spiking roughly corresponds to the CF spike pattern. CF bursts cause larger calcium transients, resulting in PF-LTD induction and cannabinoid release, whereas isolated CF spikes cause lower calcium transients and LTP.

suppressed by CB1 receptor activation (Van Beugen et al., 2006).

What is the significance of all these findings? For starters, the notion of the “invariant” climbing fiber response is history. Mathy et al. convincingly make the case that the complex spike waveform is not static and that the number of spikelets provides a read-out of the phase of olivary oscillations. The authors claim that their findings reconcile the learning and timing theories of olivocerebellar function. This might be an exaggeration, but it is certainly true that the study shows for the first time that timing information encoded in subthreshold oscillatory activity in the inferior olive governs cerebellar synaptic plasticity (Figure 1). It is presumably fair to say that with regard to the timing hypothesis the key finding of this paper is that temporal information encoded by inferior olive neurons can be read-out by individual Purkinje cells. An update of the

timing hypothesis would, however, additionally require a better understanding of the type of information encoded. Are subthreshold oscillations in the inferior olive stable, or do they show episodic on- and off-states (see Chorev et al., 2007; Khosrovani et al., 2007)? How does sensory input affect the occurrence, amplitude, and frequency of these oscillations? Addressing these questions will be necessary to evaluate whether the inferior olive can act as a “motor clock.” The data presented by Mathy et al. take “olivary timing” one step further. The precise temporal encoding mechanism described here might allow electrically coupled inferior olive neurons to enforce coherence of complex spike patterns, calcium transients, and axonal output of entire arrays of Purkinje cells aligned in the parasagittal plane. In this scenario, subthreshold olivary oscillations could contribute to a “motor binding” mechanism involved in

both motor coordination and motor learning.

**REFERENCES**

Brenowitz, S.D., and Regehr, W.G. (2005). *Neuron* 45, 419–431.

Chorev, E., Yarom, Y., and Lampl, I. (2007). *J. Neurosci.* 27, 5043–5052.

Coesmans, M., Weber, J.T., De Zeeuw, C.I., and Hansel, C. (2004). *Neuron* 44, 691–700.

Davie, J.T., Clark, B.A., and Häusser, M. (2008). *J. Neurosci.* 28, 7599–7609.

Eccles, J.C., Llinas, R., and Sasaki, K. (1966). *J. Physiol.* 182, 268–296.

Hansel, C., and Linden, D.J. (2000). *Neuron* 26, 473–482.

Keating, J.G., and Thach, W.T. (1995). *J. Neurophysiol.* 73, 1329–1340.

Khaliq, Z.M., and Raman, I.M. (2005). *J. Neurosci.* 25, 454–463.

Khosrovani, S., Van der Giessen, R.S., De Zeeuw, C.I., and De Jeu, M.T.G. (2007). *Proc. Natl. Acad. Sci. USA* 104, 15911–15916.

Maruta, J., Hensbroek, R.A., and Simpson, J.I. (2007). *J. Neurosci.* 27, 11263–11270.

Mathy, A., Ho, S.S.N., Davie, J.T., Duguid, I.C., Clark, B.A., and Häusser, M. (2009). *Neuron* 62, this issue, 388–399.

Monsivais, P., Clark, B.A., Roth, A., and Häusser, M. (2005). *J. Neurosci.* 25, 464–472.

Ross, W.N., and Werman, R. (1987). *J. Physiol.* 389, 319–336.

Van Beugen, B.J., Nagaraja, R.Y., and Hansel, C. (2006). *J. Neurosci.* 26, 8289–8294.

Welsh, J.P., Lang, E.J., Sugihara, I., and Llinas, R. (1995). *Nature* 374, 453–457.