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Cerebellar supervised learning revisited: biophysical modeling and degrees-of-freedom control

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The biophysical models of spike-timing-dependent plasticity have explored dynamics with molecular basis for such computational concepts as coincidence detection, synaptic eligibility trace, and Hebbian learning. They overall support different learning algorithms in different brain areas, especially supervised learning in the cerebellum. Because a single spine is physically very small, chemical reactions at it are essentially stochastic, and thus sensitivity–longevity dilemma exists in the synaptic memory. Here, the cascade of excitable and bistable dynamics is proposed to overcome this difficulty. All kinds of learning algorithms in different brain regions confront with difficult generalization problems. For resolution of this issue, the control of the degrees-of-freedom can be realized by changing synchronicity of neural firing. Especially, for cerebellar supervised learning, the triangle closed-loop circuit consisting of Purkinje cells, the inferior olive nucleus, and the cerebellar nucleus is proposed as a circuit to optimally control synchronous firing and degrees-of-freedom in learning.

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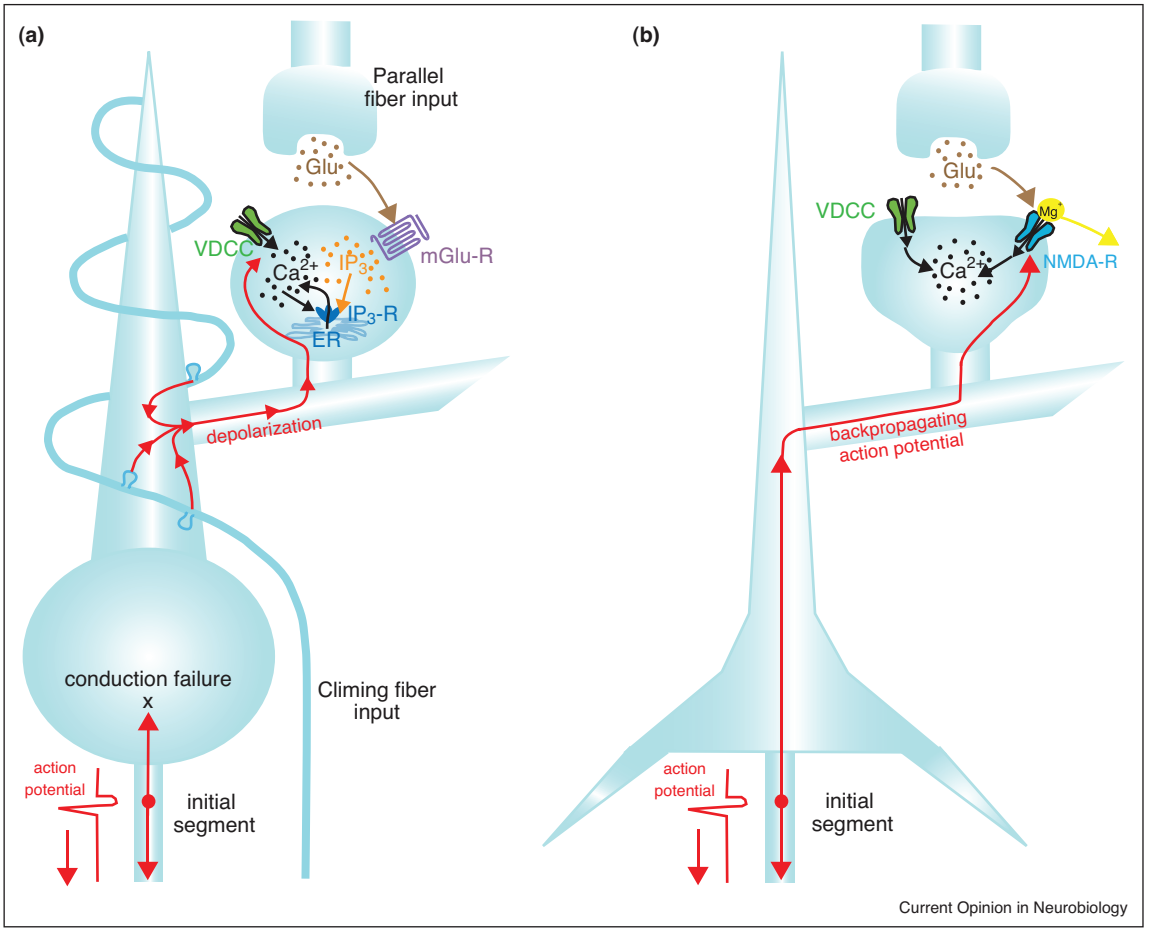
Introduction

The most influential computational model of cerebellar function is the learning theory [1–3]. The authors postulated that the climbing fiber input to Purkinje cells carry error signals so that the internal models of motor apparatus, the environments, and other agents can be learned in the cerebellum, mainly dependent on the synaptic plasticity of parallel-fiber-Purkinje-cell synapses [4,5]. Recently, several good reviews are available on computational and system-level studies of mossy-fiber and parallel-fiber input systems and the inhibitory interneurons in the cerebellar cortex [6,7]. Thus, to complement them, we here concentrate on biophysical models of synaptic plasticity and climbing-fiber input system. About ten years ago, Kenji Doya proposed that the cerebellum, cerebral cortex, and the basal ganglia implement supervised, unsupervised, and reinforcement learning algorithms, respectively, mainly based on system-level data and previous computational models [8]. The theory is also supported by biophysical models of synaptic plasticity, which demonstrate distinct features in the three brain regions as illustrated in Figure 1 and Table 1. We then review recent studies pointing to a new hypothesis that the triangle closed circuit, which consists of inferior olive, Purkinje cells, and the cerebellar nucleus, provides a neural mechanism that automatically regulates the synchronous firing and degrees-of-freedom in cerebellar learning.

Biophysical models of synaptic plasticity and suggested learning rules for different brain regions

Large calcium increase in dendritic spines induces long-term decrease of synaptic efficacy in the cerebellum (long-term depression; LTD) while it induces long-term increase of synaptic efficacy in the cerebral cortex (long-term potentiation; LTP). By contrast, small calcium increase induces LTD in the cerebral cortex, while it alone does not induce LTP in the cerebellum. Figure 1a depicts schematically the early phase of LTD of parallel-fiber-Purkinje-cell synapses up to large calcium increase [9,10•,11,12•]. Glutamate released from parallel fibers binds to metabotropic glutamate receptors (mGluRs) inducing a slow increase of inositol 1,4,5-triphosphate (IP_3) with 100 ms-order time to peak, via G-proteins (Gq) and phospholipase Cβ (PLCβ) [10•]. On the contrary, climbing fiber inputs, which lagged about 100 ms to parallel fiber inputs, induce large depolarization in dendrites through multiple strong excitatory synapses and open voltage-dependent calcium channels on the spine and induce calcium influx [9,10•]. Because the latter electrical event is much faster than the former biochemical event, IP_3 and Ca^{2+} concentrations increase simultaneously in the spine. This triggers a regenerative Ca^{2+} increase via Ca^{2+}-induced Ca^{2+} release (CICR) via IP_3 – bound IP_3 receptors (IP_3Rs). IP_3Rs are IP_3-gated Ca^{2+} channels on the endoplasmic reticulum (ER), which is the intracellular Ca^{2+} store. CICR results in a supralinear Ca^{2+} surge with several micro-molar peaks [10•,13•]. The Ca^{2+} surge induces the subsequent reactions shown in Figure 2 and consolidates LTD [12•].

Figure 1



Comparison of biophysical mechanisms included in coincidence detection mechanisms of synaptic plasticity in cerebellum **(a)** and cerebral cortex **(b)**. Biophysical models for early phase of long-term depression in cerebellum and long-term potentiation in cerebral cortex up to large calcium increase are shown.

Thus, IP_3Rs and IP_3-dependent CICR act as coincidence detectors of the parallel fiber and climbing fiber inputs.

By contrast, in cerebral pyramidal neurons, as shown in Figure 1b, NMDA receptors (*N*-methyl D-aspartate receptor, NMDAR) are coincidence detectors of glutamate released from presynaptic terminals and the backpropagating action potential from the axon initial segment [14,15]. Glutamate, released from presynaptic terminal, binds to NMDAR, and backpropagating action potential increases the postsynaptic voltage and consequently releases a Mg^{2+}-block of glutamate-bound NMDAR, resulting in full activation of NMDAR [14–16]. This leads to large Ca^{2+} influx via NMDAR and induces subsequent reactions and consolidates LTP.

Because the large Ca^{2+} surge in Purkinje cells is CICR from IP_3Rs and is mainly triggered by calcium influx caused by climbing fiber inputs, supervised learning guided by error signals is suggested for the cerebellum [5]. Note that action potentials in Purkinje cells do not backpropagate because of excessive electrical load by extensive branching [17] and low density of sodium channels on dendrites [18,19]. By contrast, since the release of NMDAR from the Mg^{2+}-block by backpropagating action potential is the decisive event that leads to large calcium influx [14,16], Hebbian and unsupervised statistical learning is suggested for the cerebrum (Table 1, bottom two rows). In the striatal medium spiny neurons, while Ca^{2+} influx depends on the NMDAR activation by backpropagating action potentials similarly to the cerebrum, synaptic plasticity also depends on the activation of dopamine receptors [20,21]. In D1 receptor expressing neurons, activation of the positive feedback loop composed of PKA, PP2A and DARPP-32 serves as the coincidence detector of Ca^{2+} influx and dopamine input [22•,23,24]; thus reinforcement learning rule is supported [20]. Because D1 receptors and DARPP-32 are expressed in prefrontal cortex but with much less amount, the positive feedback loop cannot probably possess bistability