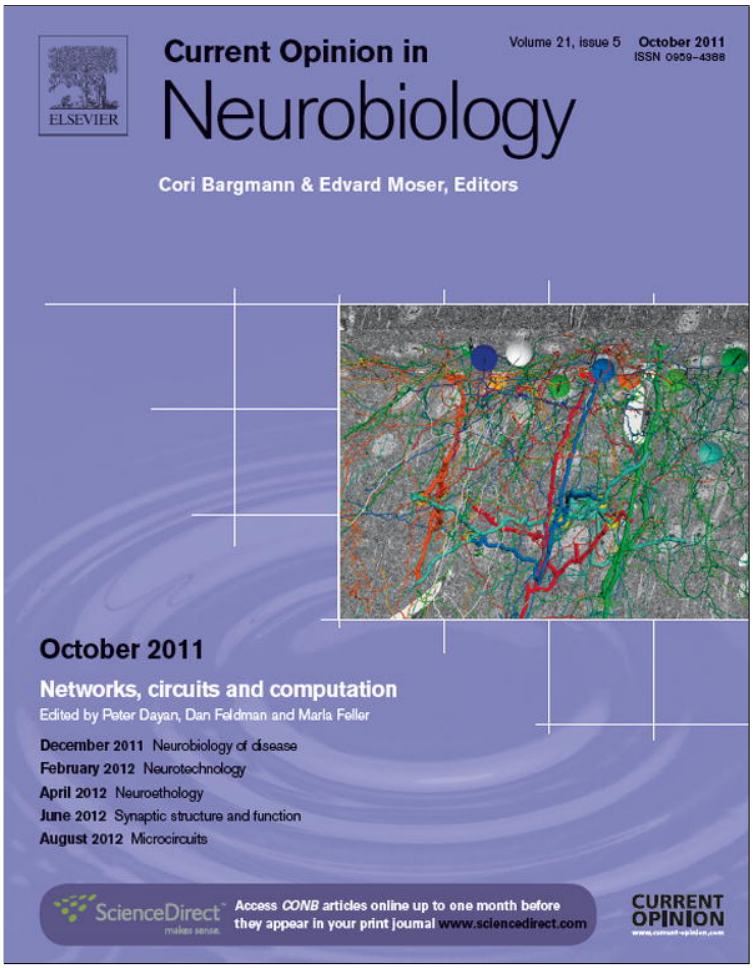

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Cerebellar supervised learning revisited: biophysical modeling and degrees-of-freedom control

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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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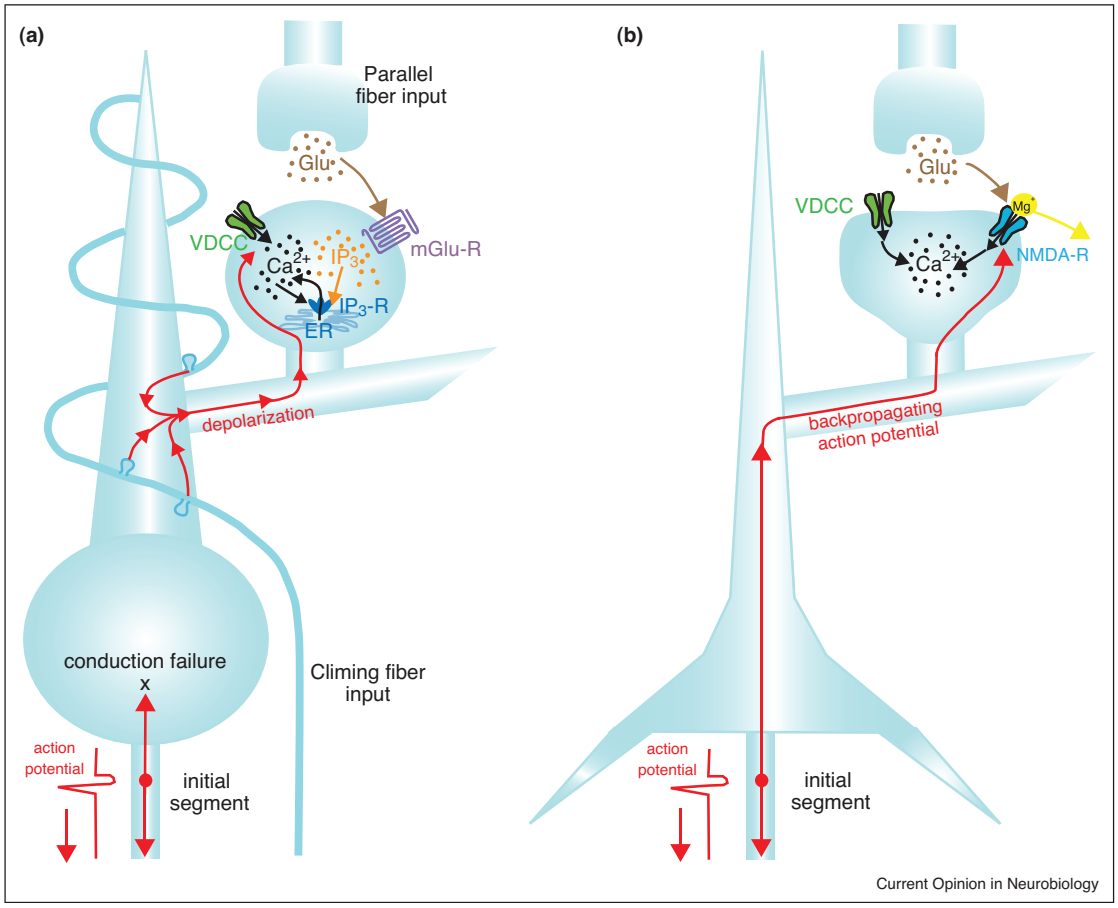
Introduction

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

Table 1

Characteristics of biophysical models of spike-timing-dependent plasticity for three brain regions, cerebellum, cerebrum and basal ganglia. Although in cerebral pyramidal cells NMDAR detects simultaneous pre and postsynaptic activities, adult Purkinje cells lack functional NMDAR for parallel fiber synapses, also suggesting non-Hebbian learning in the cerebellum [81,82]

	Cerebellar Cortex Purkinje cell	Cerebral Cortex Pyramidal cell	Basal Ganglia Medium spiny neuron
Backpropagation of action potential	No	Yes	Yes
Hebbian?	No	Yes	Yes (dopamine dependent)
Functional NMDA receptor in adult	No	Yes	Yes
Coincidence detection	IP_3 and Ca^{2+} increase at IP_3 receptor	glutamate and backpropagating action potential at NMDAR	glutamate and backpropagating action potential for Ca^{2+} increase; Ca^{2+} and dopamine by PKA–PP2A–DARPP-32 positive feedback loop
Substrate for eligibility trace	IP_3 increase by metabotropic GluR activation	glutamate activation of NMDAR	glutamate activation of NMDAR (and IP_3 increase by metabotropic GluR activation)
STDP time difference	100 ms order	10 ms order	10 ms order for glutamate; 100 ms order for dopamine
Major cause of Ca^{2+} increase	Climbing fiber inputs and CICR through IP_3R	NMDAR activation	NMDAR activation
Type of learning	Supervised	Unsupervised	Reinforcement

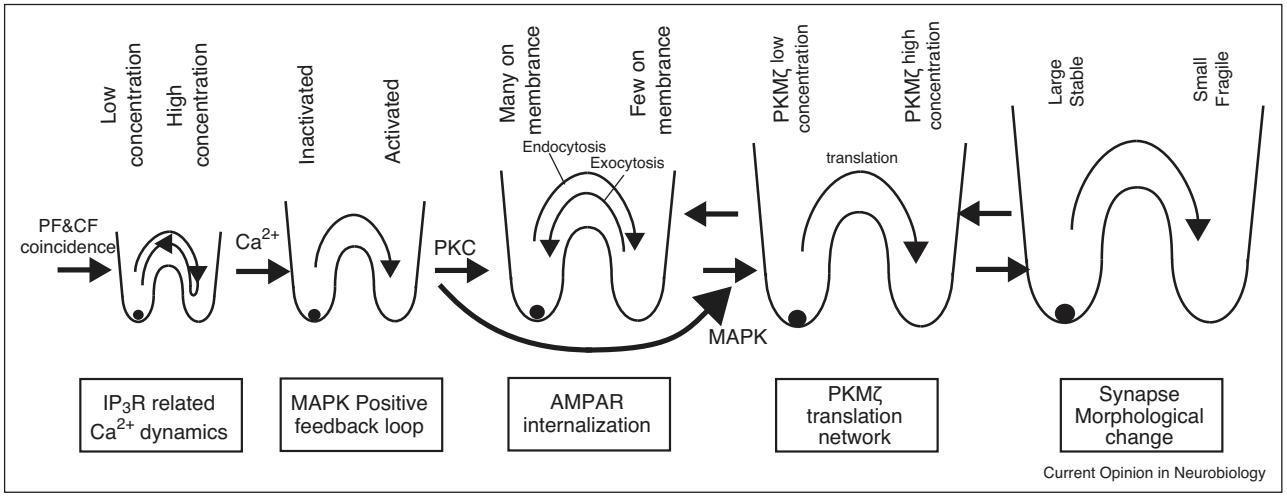
thus cannot implement the reinforcement learning rules such as in the basal ganglia.

The synaptic eligibility trace is a record of the synapse's recent activities to mark it, which is eligible to change and become distinct from other synapses [25]. The synaptic eligibility trace for Purkinje cells is slow rising IP_3 [10•,26], and thus the temporal window of spike-timing-dependent plasticity is 100 ms order in the cerebellum [10•]. By contrast, the NMDAR dynamics is the synaptic eligibility trace for pyramidal neurons, and it determines the time window of 10 ms order (Table 1, rows 5 and 6) [27]. While the late phases of LTD and LTP in different brain regions seem to possess common signal transduction mechanisms as explained in the next section, the early phases are distinctly different as explained above, and partly explain different learning algorithms at a micro level such as dendritic spines.

Sensitivity–longevity dilemma of synaptic plasticity

If synaptic plasticity is the elementary cellular process of learning and memory, it should be sensitive in the sense that a small number of pre and postsynaptic spikes can induce it, and it should also possess a long life since some memories are maintained for dozens of years without being recalled. If synaptic plasticity is merely realized by the production of some substances, it cannot possess longevity because of the continuous turnovers of proteins [28–30]. Thus, the bistability of biochemical reactions, such as MAP kinase and protein kinase C (PKC) positive feedback loop [12•,31] is a very attractive computational machinery with longevity. However, this bistability mechanism for memory suffers from the dilemma between sensitivity and longevity because a single synapse and a spine are physically very small and only a small number of molecules exist. For example, only about a few dozen AMPA receptors exist in a single spine of Purkinje cells [32,33], and the number of free calcium ions in the basal state was estimated to be smaller than a few [10•]. Under such conditions, chemical reactions only occur stochastically, acting as if thermal noise fluctuates the state even over the threshold (barrier) of the double energy wells in Figure 2. Then the dynamical state spontaneously returns to the inactivated stable equilibrium from the activated equilibrium across the barrier and memory is lost within a finite time. To increase this mean transition's time or to secure memory longevity, the following should be increased: number of involved molecules, the threshold (barrier), and the energy required for transition; however, sensitivity is lost in compensation [34]. Thus, the sensitivity–longevity dilemma for synaptic plasticity inevitably appears in a bistable system under a limited numbers of molecules. This sensitivity–longevity dilemma at a single synapse level is conceptually related to stability–plasticity dilemma at a network level proposed by Stephen Grossberg.

Figure 2



Cascade model of five excitable and bistable dynamics for resolution of sensitivity–longevity dilemma in Purkinje cell LTD. Energy double well is shown as an analogy to either excitable or bistable dynamics without implying that each dynamics rigorously possesses a potential. In this analogical interpretation, the energy barrier between the two wells corresponds to a threshold or a stable manifold to a saddle point (watershed), and the two wells correspond to two stable equilibrium points. The left well is the basal equilibrium, and the right well is the activated LTD equilibrium. The black ball represents the state of each dynamics. Larger wells and larger balls imply a larger number of molecules, higher thresholds (energy barriers), longer time constants, and heavier dynamics.

Here, we propose a cascade of five layers of excitable and bistable dynamics (Figure 2) with gradual increases in time constants and thresholds for resolving the sensitivity–longevity dilemma in Purkinje cell LTD. The left side dynamics, which include fewer molecules, possesses a shorter time constant, a lower threshold, and smaller energy, are situated closer to the neural firing inputs. By contrast, the right side dynamics, which includes a larger number of molecules, possesses a longer time constant, a higher threshold, and larger energy, is situated closer to the final morphological change. The output of one dynamics feeds into the next right dynamics as its input. In this sense, this model is a cascade of sequential dynamics from left to right.

The leftmost, lightest, and fastest dynamics in Figure 2 is the CICR dynamics, which is an excitable dynamics, and possesses the threshold for Ca^{2+} concentration and a time constant of 100-ms order (Figure 1a) [10•,13•]. The second left bistable dynamics is the MAP kinase positive feedback loop (MAPK-PFL) [12•,35•], which leakily integrates the Ca^{2+} increase from the CICR dynamics and possesses a longer time constant of several tens minutes and a higher threshold [36••]. If the integrated Ca^{2+} input crosses the threshold, the state of this dynamics jumps from the inactivated equilibrium point to the activated equilibrium point, which yields PKC and MAPK as outputs. MAPK-PFL has been extensively studied experimentally and theoretically [12•,35•,36••,37,38]. The third and middle dynamics are the AMPA-Rs internalization dynamics [39]. PKC, the output from MAPK-PFL, phosphorylates AMPA-Rs on spine membrane, which is responsible for a majority of postsynaptic currents and phosphorylated AMPA-Rs are internalized by endocytosis [40]. Thus, the internalization of AMPA-Rs decreases the number of AMPA-Rs on the membrane and of the synaptic efficacy, which is LTD. We here postulate that this dynamics also possesses bistability under the influence of MAPK-PFL. Alternatively, the recycling of AMPAR phosphorylation and dephosphorylation itself may serve as a bistable system [41]. The fourth bistable dynamics is the PKMξ translation network. Because PKMξ [42] induces its local synthesis with parallel ultrasensitive pathways, its translation network forms a positive feedback loop (PKMξ-PFL) and can exhibit bistable dynamics [37,43]. MAPK, the output from the second bistable dynamics of MAPK-PFL, triggers PKMξ expression and thus is viewed as the input to the fourth dynamics [37]. If MAPK-PFL stays in the activated LTD state long enough, MAPK continues to stimulate PKMξ-PFL so that it crosses its threshold. Then the state of the PKMξ-PFL transits to the activated state with a high concentration of PKMξ, which then induces endocytosis of AMPA-Rs and also shifts the fifth bistable dynamics of the spine morphology toward the small size, which is fragile. Some *in vitro* data [44,45] are against the fifth dynamics, but the *in vivo* data [46] supports it, and further experimental studies are necessary. The glutamate receptor δ2 seems mainly involved in the fifth morphology dynamics [47••]. The parallel connection from the second to the fourth dynamics while bypassing the AMPAR-internalization dynamics may

explain the recent enigmatic experimental data demonstrating that cerebellar motor learning is not impaired by blocking the AMPAR internalization [48•]. Electrophysiologically, LTD is detected by the state of the third dynamics in Figure 2 model. However, behaviorally cerebellar motor learning might be expressed by the combination of the third, fourth and fifth dynamics in Figure 2 model. Thus, the cascade model of Figure 2 introduces rather complex and flexible relationships between LTD and cerebellar motor learning.

Among the five layers of the proposed bistable systems, PKC and MAPK-PFL were most extensively investigated by experiments. The photolysis of the caged Ca^{2+} experimentally confirmed the leaky integration of Ca^{2+} [36••]. Pharmacological perturbation revealed that PKC and MAPK activities are mutually dependent for LTD induction [35•]. Furthermore, based on a MAPK-PFL biophysical model, qualitatively different calcium dose response curves can be reproduced for LTD under normal and PFL cut conditions [36••], which together strongly suggest that LTD is an all-or-none event on a single spine and on a single synapse level. Artificial noise addition was necessary to simulate the calcium-LTD dose response curve [36••], but the artificial noise was interpreted to come in reality from the stochastic nature of the biochemical reactions owing to a small number of molecules [37]. Recently De Schutter and Antunes [49] reproduced the dose response curve utilizing a stochastic version of a MAPK-PFL and AMPA-Rs internalization model using software called STEPS [50].

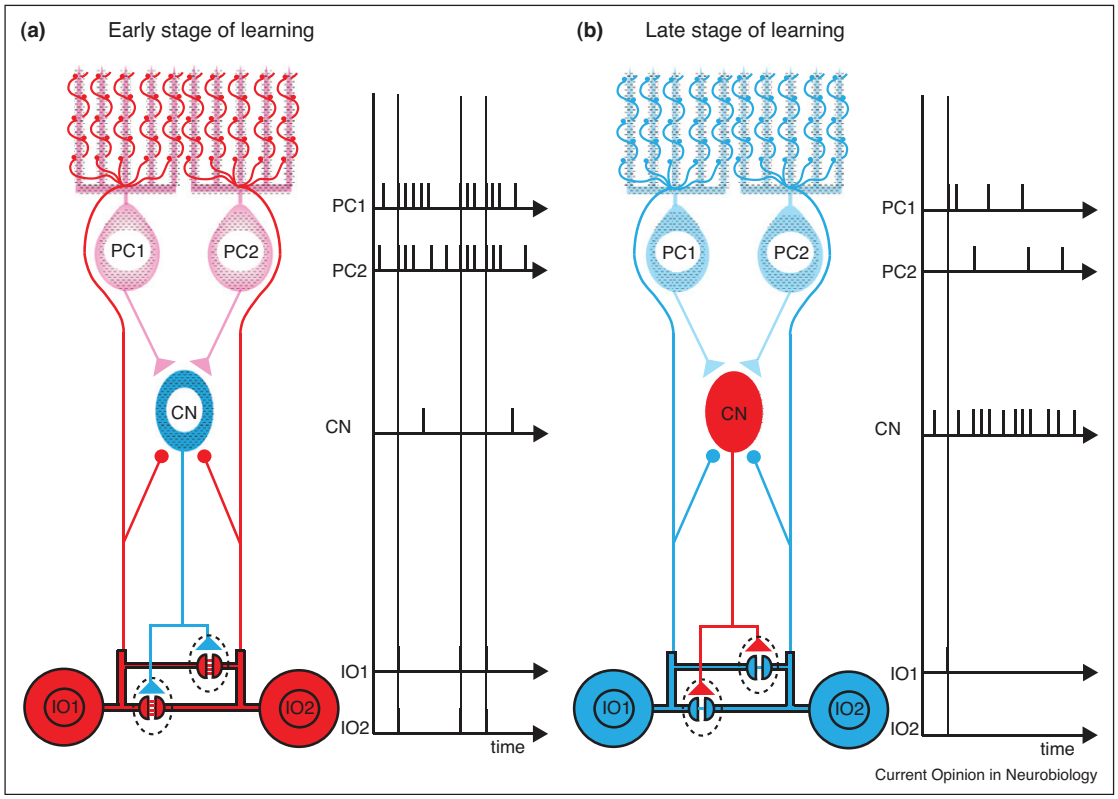
Ogasawara and Kawato simulated the abstract, simplified cascade of only two dynamics models that serves as a prototype of the Figure 2 model [51]. A bistable stochastic dynamics with a shorter time constant and a lower threshold was connected to another stochastic bistable dynamics with a longer time constant and a higher threshold. The smaller dynamics can be excited even with a weak input, but it tends to spontaneously return to the basal state within a relatively short time because of stochasticity. Thus, it has sensitivity but not longevity. The larger dynamics receives and leakily integrates the output from the smaller dynamics and can cross its threshold if the smaller dynamics can maintain its activated state for long enough in one specific run. However, even when the smaller dynamics transits to the activated state, if the state spontaneously returns to the basal state prematurely, the larger dynamics is not excited. The longer time constant of the larger dynamics filters the thermal fluctuation noise, which often appears in a high-frequency, and the larger threshold of the larger dynamics enables robustness against fluctuation or noise. Because of the higher threshold and the longer time constant, the larger dynamics can maintain the activated state for a longer period; thus it possesses longevity. Although the larger dynamics itself does not possess sensitivity [34] the cascade of smaller and larger dynamics possesses both sensitivity and longevity. The cascade of excitable and bistable dynamics with different sizes can also explain the phenomenological stochasticity of LTD/LTP; identical synaptic inputs sometimes induce LTD/LTP but sometimes not. The cascade structure of bistable dynamics shown in Figure 2 may be ubiquitous and even some bistable dynamics such as PKMξ-PFL is probably common for different brain regions. This view is partially supported by a related abstract model [52].

Inferior olive-Purkinje cell-cerebellar nucleus circuit for controlling degrees-of-freedom in cerebellar learning

In the previous two sections, we reviewed cellular and subcellular level evidence for cerebellar supervised learning. They suggest that climbing fiber inputs are most crucial in initiating LTD. If this view catches some truth, we should find sophisticated mechanisms also at the neural-circuit level for controlling climbing fiber inputs. In the cerebellar-learning hypothesis [2–4], the main function of the inferior olive (IO) is postulated to carry error signals to the Purkinje cells (PCs) via its axons, the climbing fibers ([53–55] but also see [56•]). By contrast, in the rhythm and synchronization hypothesis [57], the IO neurons and their innervated PCs fire synchronously and rhythmically for online motor control because of gap junctions whose densities are the highest among mammalian brains. In integrating these two hypotheses, Schweighofer *et al.* demonstrated that coupled IO cells do not necessarily synchronize in their firing and might show anti-phase or even chaotic firings for the intermediate strength of gap junction conductance [58,59]. Chaotic firing, which is beneficial for conveying much information even with the very low firing frequency of IO cells, was recently demonstrated to accelerate motor learning for multi-joint arm models [60]. Recent experimental data support such a link between the degree of IO coupling and motor learning. Mice [61•] and presumably humans [62] with reduced or no IO coupling exhibit no general motor deficits but show motor learning impairments. Additionally, oculopalatal tremor may be due to the removal of inhibition near the electronic gap junctions in the inferior olive, and such patients show slower motor learning [63]. This could be explained by the fact that only poorer error information can be transmitted when IO cells are strongly coupled and oscillate in-phase [58].

However, these previous theories failed to explain the possible functions of the closed triangle circuit consisting of an IO–PC–cerebellar nucleus (CN), especially the inhibitory synapses on the dendrites of IO cells close to their gap junctions within glomeruli (Figure 3 [64,65]). The slow, sustained inhibition provided by DCN to IO glomeruli appears well suited to provide stable decoupling of IO neurons [66]. Furthermore, because the connections between the IO and the cerebellum are

Figure 3



Schematic diagram illustrating possible functions of closed triangle circuit consisting of inferior olive nucleus, Purkinje cells, and cerebellar nucleus. PCs inhibit CN cells. Inhibitory CN cells innervate dendrites of IO cells within glomeruli very close to gap junctions. Circuit diagram does not include mossy-fiber inputs and their target granule cells, parallel-fiber inputs, and inhibitory interneurons, and excitatory cerebellar nucleus neurons. Excitatory inputs to IO cells are not shown either. Blue neurons are not excited, and red are excited. Excitatory synapses are shown by circles, and inhibitory synapses are shown by triangles. Horizontal lines show electrical gap junctions.

precisely, mutually, and spatially aligned, each cerebellar cortical region can control the coupling strength of its own IO inputs [67•]. Here, we hypothesize that the triangle circuit and the inhibitory synapses in the IO glomeruli are the neural mechanisms to optimally tune the degrees-of-freedom of the cerebellar learning system.

PCs inhibit CN cells. Inhibitory CN cells innervate the dendrites of IO cells within glomeruli very close to the gap junctions. Under simplifying assumptions, effective coupling conductance between connected IO cells is computed from gap junction conductance and conductance of inhibitory synapses and from spine neck conductance as follows [68,69]:

$$g_{effective} \doteq (g_{junction} \cdot g_{spine})/(2g_{junction} + g_{spine} + g_{inhibitory})$$

Thus, if the inhibitory synaptic conductance is large, the effective coupling conductance decreases because of shunting inhibition. When CN cells are excited, the IO cells are not only inhibited but their electrical couplings become weaker.

Figure 3a and b illustrate the schematic functions of the IO–PC–CN closed circuit in the early and late phases of cerebellar learning, respectively. In the beginning of motor learning, since the executed trajectories are perturbed, clumsy, and far from the desired behaviors, plans and motor commands must be highly modulated, and the error signals are large. Thus, both mossy-fiber and climbing-fiber inputs are strong. Hence, both PC and IO cells fire vigorously and the CN cells are suppressed. Here, we assume that the increased PC inhibition overlies the increased excitation from the IO and mossy fibers. The inhibitory synapses are inactive within the IO glomeruli, and the IO cells are strongly electrically coupled. Consequently, IO cells and the innervated PCs are strongly and synchronously excited, as shown in the right raster plot.

By contrast, in the late phase of learning, since the movement trajectories are smooth and resemble those

desired, both mossy-fiber and climbing-fiber inputs are weak. Hence, both PC and IO cells fire sporadically and CN cells fire vigorously because of the disinhibition from PC. The LTD of the parallel-fiber-PC synapses and the LTP of the inhibitory synapses on PC may further enhance this contrast with the early phase of learning. Inhibitory synapses are active within the IO glomeruli, and the IO cells are only weakly electrically coupled. IO cells and innervated PCs sporadically and asynchronously fire, as shown in the right raster plot. Those firings might be chaotic, as suggested in [58]. Recent studies that reproduce IO firing data under several experimental conditions from simplified and biophysical IO neuron models support the above hypothesis [68,69,70•].

In statistics, artificial neural networks, and machine learning fields, a long history of studies has addressed how to control the degrees-of-freedom in learning systems dependent on the quantity of training data available for learning. As proposed in Akaike's information criterion [71] and the automatic relevance determination [72], it is better to decrease the degrees-of-freedom when the data are small to avoid overfitting, variance, and poor generalization. On the contrary, if the training data are large, large degrees-of-freedom are preferable to avoid modeling error or bias [73]. These techniques are widely utilized in estimating brain activities, brain decoding, and brain machine interfaces [74–76].

The human brain is an enormous system with at least 10 to the 14th degrees-of-freedom even if we only count the number of synapses. At the beginning of any kind of learning, the available data are small considering how much time is devoted to each learning epoch. Thus, the brain needs to actively reduce its degrees-of-freedom, and synchronous firing is one obvious way. If 100 IO cells perfectly synchronize their firing, the IO region containing 500 IO cells is equivalent to containing only five free neurons: that is, five degrees-of-freedom. However, fixed and reduced degrees-of-freedom are not apparently desirable because they waste neural resources. Depending on different phases of learning, the degrees-of-freedom should be actively and optimally controlled. In the early learning phase, strong synchronization is useful while weak or no synchronization might be beneficial in the late learning phase.

The IO–PC–CN circuit can enhance IO and PC synchronization and reduce the degrees-of-freedom in the early phase of learning. According to the micro-complex hypothesis of Masao Ito that IO–PC–CN loop is topographically organized so that a group of PCs within a micro-complex innervate the downstream premotor network controlling the same group of muscles and/or motor synergy. Thus, degrees-of-freedom control is mainly to reduce the number of independently firing PCs and thus tuned parallel fiber inputs. If many PCs fire synchronously and change their firings guided by almost the same error signals, the learning should be very fast for the early phase, since avoiding failures, pain, and damage makes good sense. Relatedly, IO cells can generate a burst of several spikes that result in an LTD of PCs whose size increases with the number of spikes in the bursts [77••]. Thus large initial error inputs might increase the learning speed both across and within PCs. On the contrary, the same IO–PC–CN circuit can reduce synchronization and even induce chaotic firings of IO and PC and might exhibit full degrees-of-freedom that are identical as the number of neurons or synapses. Because a huge amount of training data has been already accumulated as changes in synaptic weights through LTD/LTP and is in a sense available to the cerebellar learning system, sophisticated learning is realized with small bias.

In motor learning of arm reaching under novel force fields, changes in motor commands are huge for the first few trials, much more than the level of trajectory errors [78]. These behavioral and physiological studies [61•,79], may be consistent with the above hypothesis. Because the brain is a learning machine, degrees-of-freedom control in learning may be ubiquitous, and controlling the firing synchronization seems quite natural. Chemical synapses, which are close to the gap junctions and/or presynaptic inhibitions on mutual excitatory connections, in addition to the possible glomerulus-specific modulation of gap junctions [80], might be general neural mechanisms to control the degrees of synchronization and thus the degrees-of-freedom in learning for all brain regions.

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