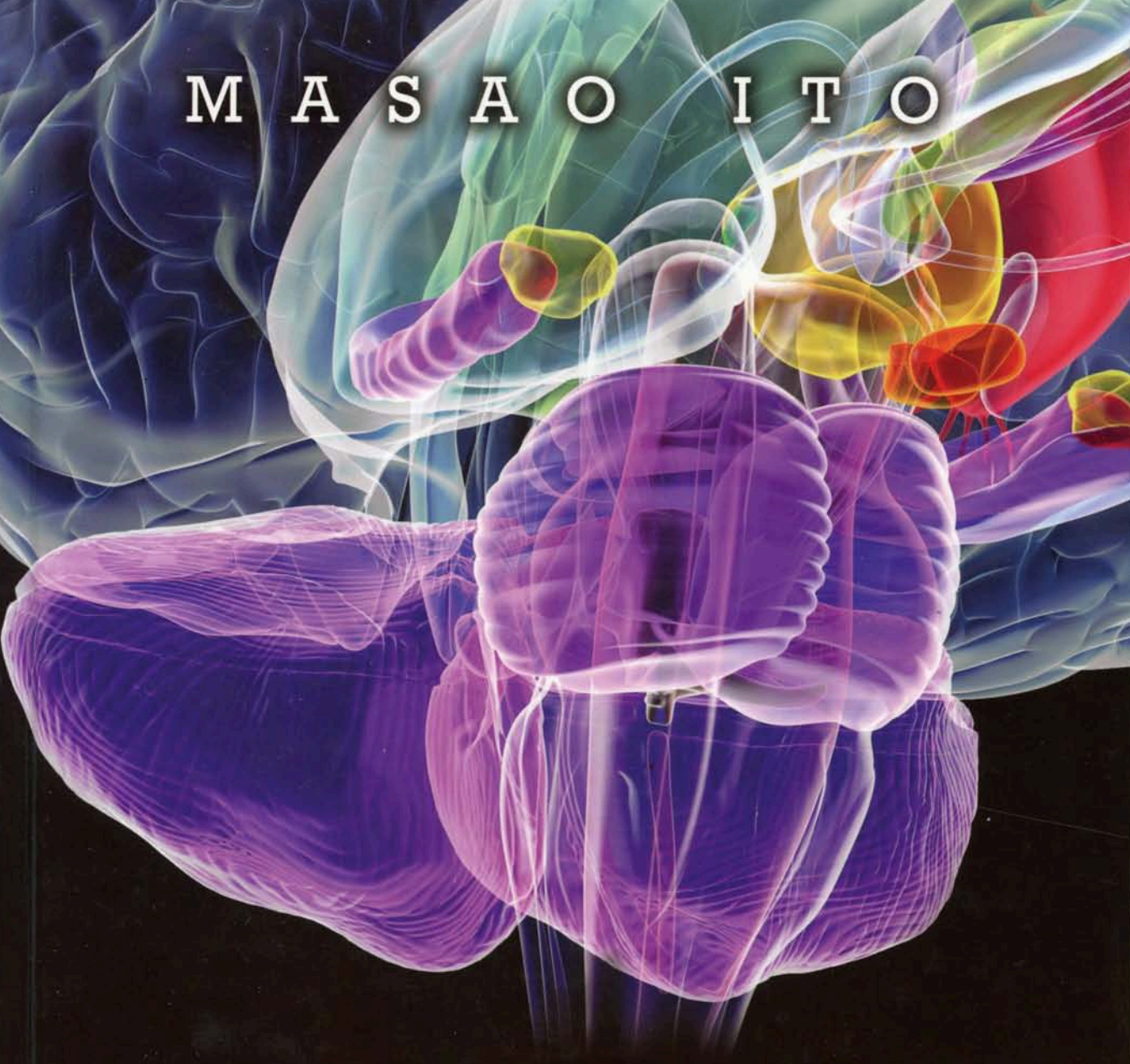
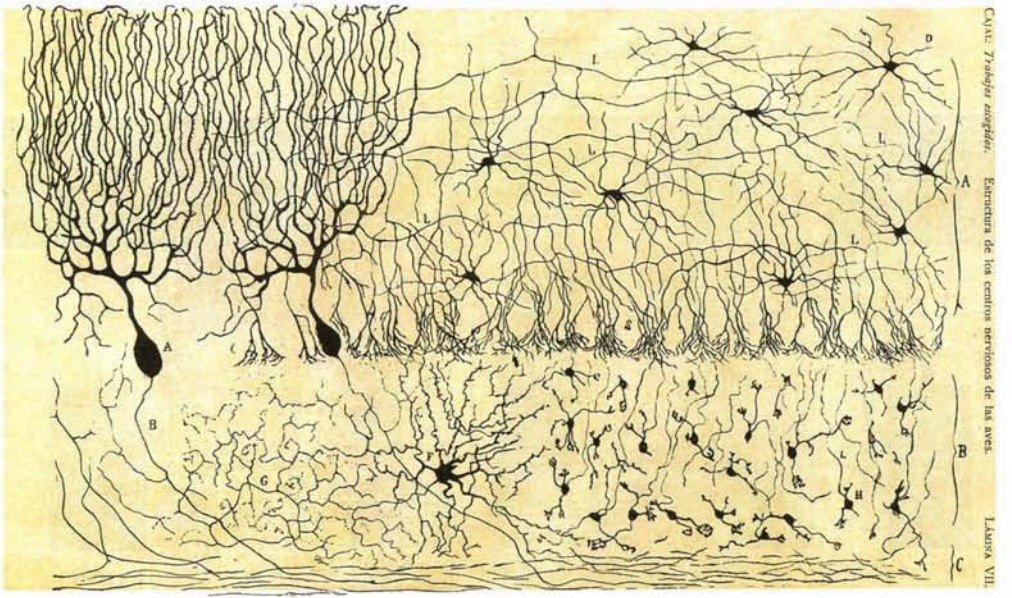


MASAO ITO

THE CEREBELLUM

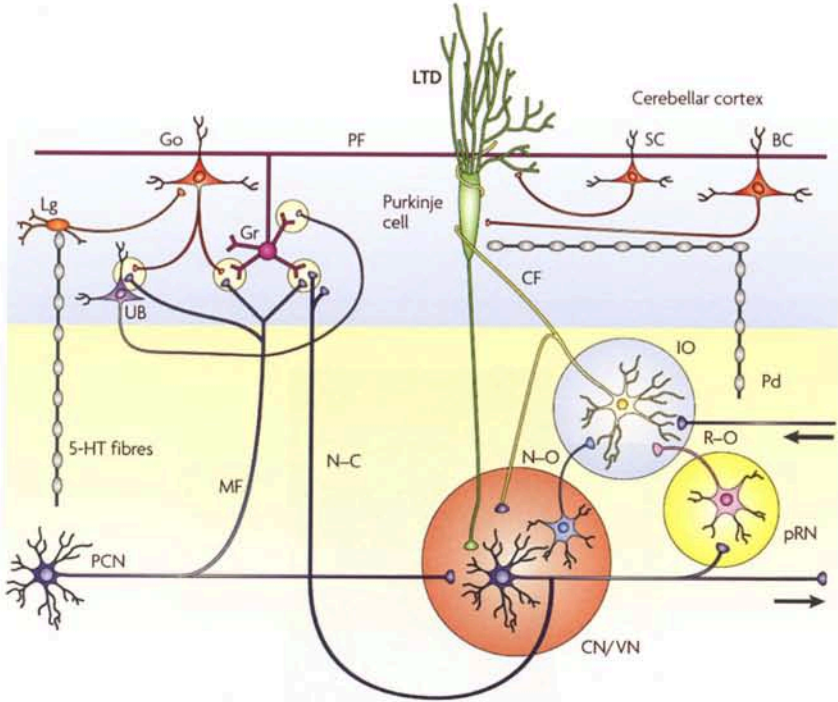
Brain for an Implicit Self



Color Plate IV

A classic Ramón y Cajal drawing of cerebellar cells.

Shown are Purkinje (A, B), stellate (D), Golgi (F), and granule (H) cells in the cerebellum. Also note the basket-cell axons (S) terminating freely around the Purkinje cell bodies. (Courtesy of the Instituto de Neurobiología "Ramón y Cajal," Madrid, Spain.)



Color Plate V

Sketch of neuronal circuits in the cerebellum.

Long-term depression of Purkinje cells is induced by the conjunctive activation of parallel fibers and climbing fibers. (From Ito, 2009.)

3

The Cerebellum as a Neuronal Machine

3-1 Introduction

In the 1960s, the cerebellum was considered to be an elaborate neuronal machine composed of intricate neuronal circuits with geometrical refinement. It was thought to process information that was critical for the acquisition of motor skills. During the five subsequent decades, research on the cerebellum has been devoted largely to addressing questions about how its neuronal circuits are constructed and function, and what specific roles they play. The principles of modern systems control, particularly adaptive and model-based control, have been introduced. Furthermore, the role of the cerebellum in the manifestation of intelligence is now under consideration. This progress is summarized in the following sections, including some of my personal experiences and impressions throughout this 50-year period.

3-2 The 1960s

In the 1960s, Professor John Eccles, who had discovered inhibitory synapses in the spinal cord (Brock et al., 1952), turned to the study of the cerebellum with his talented colleagues in Canberra, Australia. It was a remarkable time when electrophysiology with glass microelectrodes enabled intracellular recording in individual neurons. Using this technology, Eccles distinguished two types of neurons, excitatory and inhibitory, in the cat spinal cord (Figure 3A, B). Excitatory neurons were shown to supply solely excitatory synapses and induce excitatory postsynaptic potentials (EPSPs) or currents (EPSCs) in their target neurons. In contrast, inhibitory neurons were shown to supply inhibitory synapses that induced inhibitory postsynaptic potentials (IPSPs) or currents (IPSCs) in their targets. Using the same technology and taking advantage of the geometrical arrangement in cerebellar circuits, Eccles and his associates quickly identified basket cells, stellate cells, and Golgi cells as inhibitory neurons, and granule cells, mossy fibers, and climbing fibers as excitatory elements (Chapters 4 and 5).

Here, let me recall my first experience with the cerebellum. In 1962, I returned to Tokyo from Eccles' laboratory where I had studied spinal motoneurons for three years. On my return I worked with several colleagues on two types of giant neurons in the brainstem. These were Otto Deiters' (1834–1863) giant neurons (Deiters, 1865; see Mazzarello, 1999) and magnocellular red nucleus neurons. I was familiar with these neurons from the earlier anatomy lectures of Professor Teizo Ogawa (1901–1984), which I had heard while a medical student. We equipped one laboratory exclusively with hand-made electronic instruments. It was shared by two subgroups: the late Nakakira Tsukahara (1933–1985) and Kesiuke Toyama for the red nucleus and the late Mitsuo Yoshida (1933–1998) and me for Deiters neurons. In November 1963, we were successful in recording intracellularly in a Deiters neuron of an anesthetized cat. When we applied an electric shock to needle electrodes inserted into the cerebellum, it caused a large swing of green spots on the screen of a cathode ray oscilloscope. This was an IPSP induced via long axons of Purkinje cells (Figure 13) (Ito and Yoshida, 1964). We then recorded from cerebellar nuclear neurons and confirmed the consistent occurrence of inhibition, thereby enabling our conclusion that Purkinje cells were uniformly inhibitory neurons (Ito et al., 1964). Moreover, when Kunihiko Obata joined us a short time later, we found that iontophoretic application of gamma-amino-butyric acid (GABA) to Deiters neurons induced a membrane hyperpolarization like IPSPs (Obata et al., 1967). This evidence showed that Purkinje cells were GABA-releasing inhibitory neurons. At that time, there were the beliefs that (1) large neurons with long axons were excitatory, whereas small neurons with short axons were inhibitory; and (2) excitatory neurons were major "players" in the brain, whereas inhibitory neurons acted as "local commutators." Indeed, the inhibitory neurons identified by Eccles and his colleagues in the spinal cord, hippocampus, and cerebellar cortex were all short-axoned, relatively small neurons. Our Purkinje cell finding was also at variance with the then-conventional thought that the cerebellum was involved in both excitatory and inhibitory functions because its stimulation induced either contraction or relaxation of limb muscles, as dependent on the stimulation conditions. We showed, however, that target neurons for Purkinje cell inhibition receive excitation via axon collaterals of mossy fiber and climbing fiber afferents (Figure 13) (Ito et al., 1969). Morphological details of such axon collaterals were revealed later (Shinoda et al., 1992; Sugihara et al., 1996). We found also that stimulation of the cerebellum often facilitated Deiters neurons via inhibition of Purkinje cell inhibition—that is, disinhibition (Ito et al., 1968). When these controversies subsided, Eccles generously offered me the opportunity to co-write with Szentágothai and him the 1967 monograph, *The Cerebellum as a Neuronal Machine*.

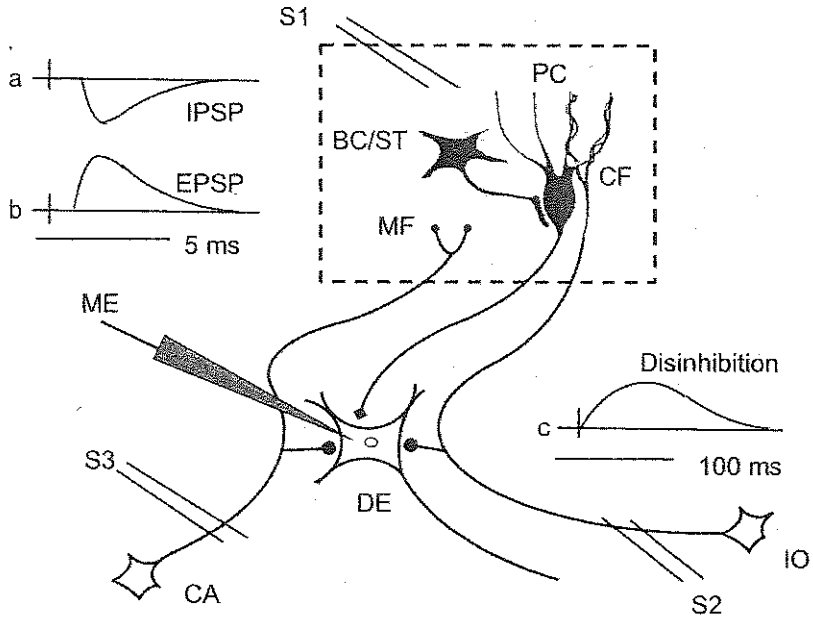


Figure 13 Schematic neuronal circuit showing how electrical stimulation of the cerebellar cortex induces three major effects in Deiters neurons.

When recorded intracellularly in a Deiters giant neuron (DE), electrical stimulation of Purkinje cells induces inhibitory postsynaptic potentials (IPSPs)(a). However, excitatory postsynaptic potentials (EPSPs) are also induced by activation of mossy fibers and climbing fibers via their axon collaterals (b). If basket cells are stimulated, they inhibit Purkinje cells so that Deiters neurons are disinhibited and generate slow disinhibitory depolarization (c). Part of the neuronal circuit located in the cerebellar cortex is enboxed by broken lines. Abbreviations: CA, cells of origin of mossy fibers (MF); IO, inferior olive that issues climbing fibers (CF); ME, microelectrode; PC, Purkinje cells. Note that both CF and MF project collaterals to the Deiters cells. (Based on the data of Ito and Yoshida, 1966, Ito et al., 1968, 1969.)

We wrote this book at a time when computers were beginning to be used widely in neuroscience and artificial intelligence seemed of particular promise. After Wiener popularized cybernetics in his 1948 book, modern control theories had appeared to be a promising approach for advancing understanding of the mechanisms of the CNS. For example, Arbib (1971) applied cybernetic concepts to brain theories. Our 1967 monograph emphasized wiring diagrams of the cerebellum, and we encouraged computational scientists to collaborate with biological researchers to determine their significance. At the end of the book, we stated confidently that the enlightened discourse between such theorists on the one hand and neurobiologists on the other will lead to the development of revolutionary hypotheses of the way in which the cerebellum functions as a neuronal

machine and predicted that these hypotheses will lead to revolutionary developments of experimental investigation (Eccles et al., 1967).

Several international symposia were held with a focus on this theme. The most impressive one for me was held in 1967 at Salishan Lodge near Gleneden Beach on the Oregon coastline, USA, as organized by Francis Schmitt (1903–1995) and Eccles. Donald MacKay (1922–1987) led discussions among theorists, computer experts, and bioengineers. There was no immediate outcome from this and other such meetings, however. Despite the impressive beauty of its wiring diagrams (Color Plate V), the "neuronal machine" concept of the cerebellum remained vaguely defined as "a relatively simple machine devoted to some essential information processing." I was frustrated enough at the Salishan meeting to ask what else experimentalists would need to uncover before we would be able to understand the meaning of these wiring diagrams. Someone equally frustrated replied that the available diagrams were too simple to construct even a primitive radio, so more information was urgently needed before any meaningful model could be conceived. However, an important clue had already been with us for a long time—that is, the presence of climbing fibers in the cerebellum, as described by Cajal (1911) (Figure 14). The contrasting connectivity of each Purkinje cell with only one

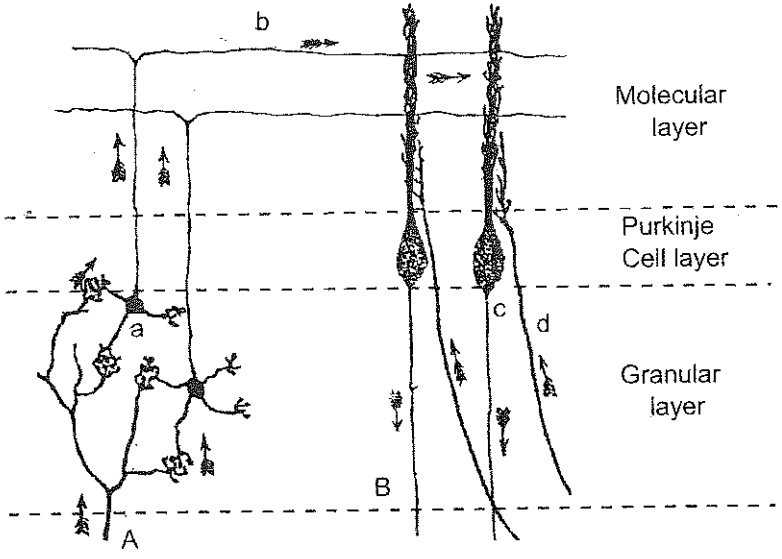


Figure 14 Convergence of climbing and parallel fibers onto Purkinje cells.

A part of Figure 104 of Cajal (1911) is shown with the right, left axis reversed to match Color Plate V. A, mossy fiber; B, Purkinje cell axon; a, granule cell; b, parallel fiber; c, Purkinje cell; d, climbing fiber. Arrows indicate the supposed directions of signal flow.

climbing fiber and numerous parallel fibers had been interpreted only as unique cases of convergence and divergence. Characteristic electrical events induced in a Purkinje cell by impulses of parallel fibers and climbing fibers (as exemplified in Figure 15) had been revealed by Eccles et al (1966a, b) and Thach (1967), but no one thought of its implication for synaptic plasticity except Brindley (1964) who pointed out this possibility.

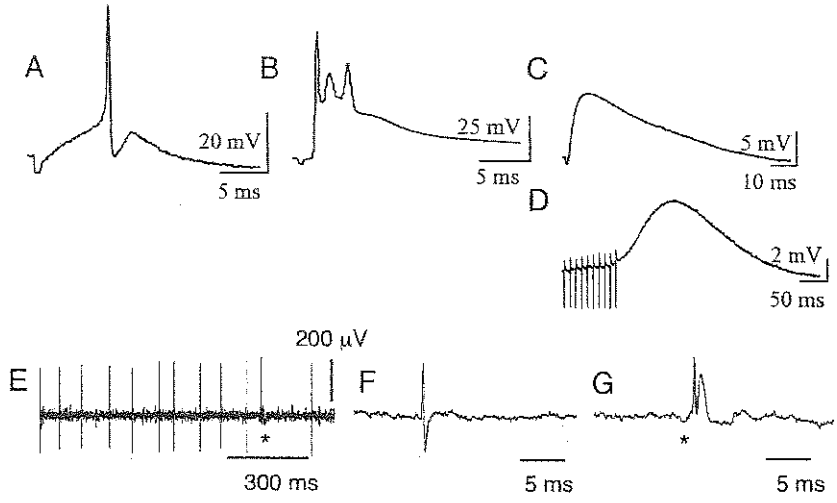


Figure 15 Bioelectric potentials of Purkinje cells.

Both intracellular recordings in slices (A–D) and extracellular recordings in vivo (E–G) are shown. (A) Simple spikes induced by stimulation of parallel fibers (PFs) on the pial surface of a cerebellar folium. (B) Complex spikes evoked by stimulation of climbing fibers in the white matter. The complex potentials so evoked are composed of an EPSP and Na^+ and Ca^{2+} spikes. (C) An AMPA-EPSP evoked by stimulation of parallel fibers. (D) mGlůR-EPSPs evoked by repetitive stimulation of parallel fibers in the presence of an AMPA antagonist. (E) Spontaneous discharge from a Purkinje cell. (F) A simple spike in an expanded time scale. (G) A complex spike similarly shown. In A–D, five consecutive sweeps repeated at 0.2 Hz were averaged. (From unpublished data of Le and Ito.)

3-3 The Marr-Albus Model

In the aforementioned climate, David Marr (1945–1980), James Albus, and a few other theorists proposed theoretical models of the cerebellar neuronal machine (e.g., Marr, 1969; Albus, 1971). This was an eagerly awaited breakthrough for computational neuroscience. I remember its great impact on me after reading Marr's 1969 article. I felt that his theory converted our wiring diagrams of the cerebellum into a meaningful blueprint.

The crucial assumption adopted in Marr's theory was the use of synaptic plasticity as a memory element in neuronal circuits. At that time this was but a theoretical possibility and totally lacking in supportive experimental evidence. As mentioned in Chapter 1, "Neuronal Circuitry: The Key to Unlocking the Brain," Hebb (1949) had already proposed the concept of Hebbian synapses, whose transmission efficacy increased when the presynaptic and postsynaptic neurons fired in synchrony. Brindley (1964) pointed out the possibility that the convergence of parallel fibers and climbing fibers onto Purkinje cells implied the presence of Hebbian synapses, since climbing fiber signals are so powerful that these inevitably excited Purkinje cells. Thus, if both parallel fibers and climbing fibers were activated synchronously, parallel fiber-Purkinje cell synapses were activated both presynaptically and postsynaptically, that is, the type of condition that induced a Hebbian form of plasticity. In Marr's (1969) model, as based on Brindley's suggestion, learning actions were considered to occur as follows. Each climbing fiber conveyed a cerebral instruction for an elemental movement, and the receiving Purkinje cell was also exposed via the mossy fiber input to information about the context in which the climbing fiber fired. During rehearsal of an action, each Purkinje cell could learn to recognize such contexts, and later, after the action had been learned, the occurrence of the context alone was enough to fire the Purkinje cell, which then caused the next elemental movement.

Albus' model (1971) was a close analogy to the simple perceptron, assuming that climbing fibers played the role of the outside teacher as a supervisor (recall Figure 6). When a successful performance of the cerebellum was recognized, relevant climbing fibers sent signals that potentiated concurrently activated parallel-fiber synapses on Purkinje cells (i.e., potentiation of the synapses that brought about success). On the other hand, when the performance was unsuccessful, relevant climbing fibers sent signals to depress concurrently activated, parallel-fiber synapses on Purkinje cells (i.e., depression of the synapses involved in failure). However, it is impossible to use the same climbing fiber for both potentiation and depression in real synapses. This meant that one of them had to be chosen. Albus (1971) selected depression for several technical reasons, whereas Marr used potentiation after success. Theoretically speaking, learning was possible using either model. Thus, these models raised alternative possibilities to be selected on an experimental basis.

It is to be noted that the simple perceptron is primarily designed for discrimination of spatial patterns and has no capability of discriminating temporal patterns. A decade after Marr's and Albus' models, Fujita (1982a) proposed an adaptive filter model of the cerebellum able to discriminate temporal patterns by assuming that the neuronal circuit involving mossy fibers, granule cells, parallel fibers, and Golgi cells constitutes a phase converter, which generates a set of multiphase

versions of a mossy fiber input. Figure 16 shows schematically the early idea of the operation of Fujita's adaptive filter model of the cerebellum when the input signal is sinusoidal. Fujita (1982b) incorporated successfully this phase converter concept into a model of VOR adaptation and reproduced successfully the adaptation of the VOR (Chapter 10, "Ocular Reflexes"). The importance of the granule cell-Golgi-cell-granule cell pathway as a clock in the cerebellum has now been well recognized (Chapter 9, "Network Models").

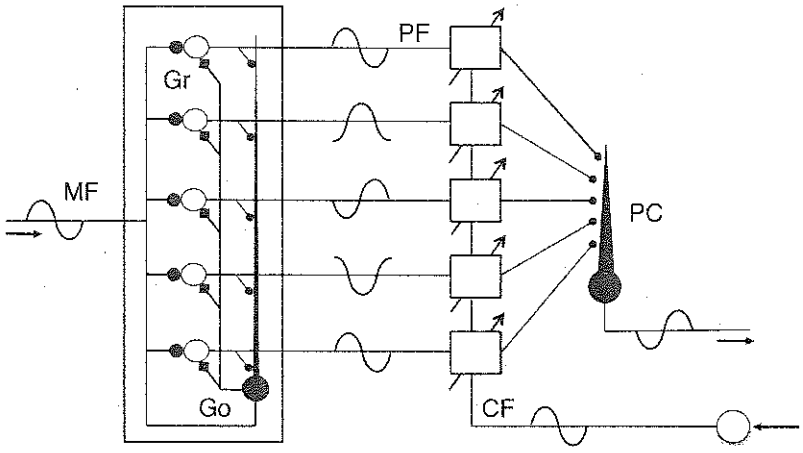


Figure 16 Adaptive filter model of the cerebellum.

This model explains how the cerebellar network recognizes temporally encoded signals. It is assumed that a phase-converter consisting of the mossy fiber (MF)-granule cell (Gr open circle)-Golgi cell (Go filled circle) circuit generates a set of multiphase versions of mossy fiber (MF) input (represented by sinusoidal discharge). When Purkinje cells (PC) use conjunctive LTD in their learning, a certain phase-shifted version of the input, which is out of phase to the climbing fiber error signals, is selected by Purkinje cells. On the other hand, granule cell to Purkinje cell transmission in phase with the climbing fiber (CF) input (indicated by a left-directed arrow) will be depressed. (Explanation based on Fujita's [1982a] model; see also Dean et al., 2010 for another explanation of the model.)

3-4 Long-Term Depression

In the late 1960s and early 1970s, many laboratories apparently tried to reveal such synaptic plasticity, but in vain. It is widely known that Eccles invited Marr to sit in front of a cathode ray oscilloscope with him while they tested the effects of conjunctive stimulation of climbing fibers and parallel fibers using stimulus parameters chosen by Marr. No sign of synaptic plasticity was then observed, however. At that time, experiments were conducted *in vivo* such that stable intracellular

recording was not possible for a period sufficiently long to detect synaptic plasticity. Accordingly, transmission across parallel fiber-Purkinje cell synapses was examined only by extracellular recording of field potentials. However, as compared to field potentials recorded in the hippocampus to reveal long-term potentiation (Bliss and Lomo, 1973), those in the cerebellar cortex were ten times smaller. This meant that before the availability of high-performance electronic averagers, any potential long-term modification of synaptic transmission could not be detected. The observation was further impeded because several factors in *in vivo* experiments were later shown to interfere with the occurrence of the synaptic plasticity: postsynaptic inhibition caused by basket/stellate cells (Ekerot and Kano, 1985), local bleeding resulting in the release of hemoglobin that absorbs nitric oxide (Nagao and Ito, 1991), and general anesthesia (Vigot et al., 2002).

Despite the preceding evidence to the contrary, I agreed with the two theorists, Marr and Albus, because, as shown below, the flocculus hypothesis of the vestibuloocular reflex (VOR) that I was proposing at that time matched very well with their models. In 1979, I visited Professor David Hubel at Harvard Medical School to present a seminar. When it ended, Marr approached me, this being our first and only interaction. He mentioned his interest in my flocculus hypothesis for the VOR and asked me to send him any related publications. He also said that he would soon leave for the U.K. for leukemia treatment but would possibly visit Japan the following year to receive a prize from an artificial intelligence group. I told him that I had been waiting to meet him for ten years and that I was continuing my research on synaptic plasticity. Upon returning home, I received a letter from Marr, in which he mentioned gracefully that he, too, had been waiting ten years to meet me. Sad to say, Marr did not come to Japan, and I regretted that I could not tell him person to person about the new positive evidence of synaptic plasticity, which I reported at the XXVII Congress of the International Physiological Union (IUPS), which was held in Budapest in June 1980 (Ito et al., 1981). Béla Julesz (1928–2003) consoled me to some extent, however, when he informed me that he had written to Marr, who was by then quite ill in bed in Cambridge, Massachusetts, to tell him about my Budapest report. Sadly, Marr died in late 1980.

The new evidence presented in Budapest (Ito et al., 1981) was a result of my change in strategy from using field potentials to test for parallel fiber-Purkinje cell transmission to measuring the rate of Purkinje cell discharge in response to half-maximum parallel fiber stimulation ("firing index"). While recording from a Purkinje cell in the flocculus, Masaki Sakurai, Pavich Tongroach, and I witnessed that conjunctive stimulation of vestibular mossy fibers and climbing fibers decreased unfailingly the firing index (Ito et al., 1982). Even though we were stimulating vestibular mossy fibers, field potentials in the vestibular nuclei and flocculus

granule layer were confirmed not to reveal any related changes. We also recorded from putative basket cells, in which conjunction induced no depression like that observed in Purkinje cells. Because Purkinje cells and basket cells share the mossy fiber-parallel fiber pathway, we reasoned that the depression specific to Purkinje cells must have taken place in the Purkinje cells, themselves. Moreover, we demonstrated that the sensitivity of Purkinje cells to iontophoretically-applied glutamate (the transmitter released from parallel fibers), but not to aspartate or N-methyl aspartate (not a transmitter for parallel fibers), was depressed for a considerable duration after combining climbing fiber stimulation and glutamate application. Shortly thereafter, we received a grant to purchase a high-performance electronic averaging instrument. Its use enabled Masanobu Kano and me to record the field potentials representing monosynaptic activation of Purkinje cells by parallel fiber impulses and to demonstrate that conjunction induced long-lasting depression of these potentials, this being definite evidence of the manifestation of LTD (Ito and Kano, 1982). Next in my laboratory, Karl-Frederic Ekerot and Kano used direct stimulation of parallel fibers combined with Purkinje cell firing indices to reveal the occurrence of LTD (Ekerot and Kano, 1985). Later, the successful recording of LTD in cerebellar slices (Sakurai, 1987) prompted many more studies of LTD, which were undertaken worldwide. By 1990, LTD was established as a unique type of synaptic plasticity (Ito, 1989). Nowadays, conjunctive LTD can be observed routinely in tissue cultured Purkinje cell preparations developed by Linden's group and in the cerebellar slice preparations used in other laboratories, including my own (Figure 17).

In the 1990s, signal transduction processes underlying LTD became a subject of extensive investigation in many laboratories (see Daniel et al., 1998). I recall that when I moved to RIKEN (Institute of Physical and Chemical Research) in 1990, little was known about this subject. Now, however, a complex flow chart is available. It shows chemical signals involving more than 30 different molecules (for review, see Ito, 2001, 2002). While I was concentrating on the mechanism of signal transduction for LTD, there were notable research developments in several directions on the nature of cerebellar synaptic plasticity. Postsynaptic LTP as the counterpart of conjunctive LTD had long been missing, but Lev-Ram et al. (2002, 2003) finally found it. The involvement of cerebellar/vestibular nuclear neurons in learning, in addition to LTD in the cerebellar cortex, was suggested early on (Miles and Lisberger, 1981; Lisberger and Sejnowski, 1992; Raymond et al., 1996). It has now been shown quite clearly (Kassardjian et al., 2005; Shutoh et al., 2006; McElvain et al., 2010). Moreover, a wide variety of synapses in the cerebellar cortex have been shown to be activity-dependent and subject to plastic modification (see Hansel et al., 2001). These advances are reviewed in later chapters.

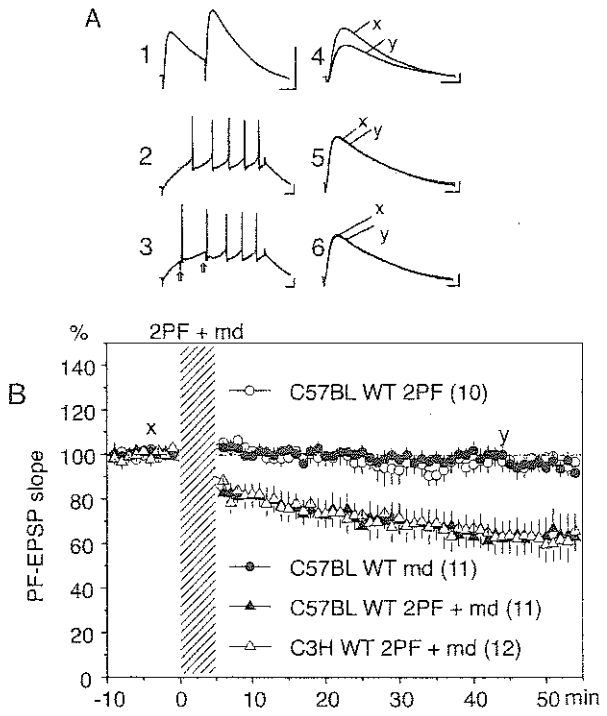


Figure 1.7 Induction of LTD in a slice of the cerebellum.

(A) Intracellular recording from a Purkinje cell in a slice of the mouse cerebellum. 1, EPSPs evoked by double shock stimulation of parallel fibers (2PF). 2, Five Ca^{2+}-spikes induced by application of a membrane depolarizing current pulse (md). 3, Similar to 2, but initial two Ca^{2+}-spikes were driven by 2PF (at upward arrows) superimposed on an md. 4, An averaged single shock-evoked parallel fiber EPSP recorded before (x) and after (y) conjunction of PF stimulation and an md at 1 pulse/second for 5 minutes to bring on LTD (x minus y). 5, A record similar to that in 4 except for the stimulation being restricted to before and after 2PF. 6, A record similar to 5 except for the stimulation being restricted to before and after an md. (B) Time course of LTD in two mouse strains (C57BL WT and C3H WT). Abscissa, time in minutes (min) relative to onset of stimulation. Ordinate, relative rising rate of Purkinje cell EPSP responses to PF stimulation. For both mouse strains, plots are shown for control 2PF and md stimulation versus conjunction of these stimuli. x and y, time for recording of the traces x and y in A4. In brackets, number of tested cells for each stimulating condition. (From Le and Ito, unpublished material.)

3-5 Adaptive Control

In the 1970s, functional roles of the cerebellum were under intense discussion. Even though the role of the cerebellum in the control of body equilibrium, the finger-nose test, and arm retraction had been proposed in classic studies, mechanisms underlying these roles seemed too complex to analyze experimentally. Jun Fukuda,

Stephen Highstein, and I searched for a simple system to analyze. We found that the vestibuloocular reflex (VOR) was an appropriate experimental model. In response to a head movement sensed by the vestibular organ, the VOR produces an eye movement to maintain stable retinal images during head movement. We first showed that the VOR was inhibited directly by Purkinje cells located in the flocculus, that is, in the phylogenetically oldest part of the cerebellum (Fukuda et al., 1972; Kawaguchi, 1985). This finding was the beginning of our flocculus hypothesis for VOR adaptation (Ito, 1972, 1974, 1982) and continuing debate about its mechanism, as will be introduced in Chapters 10 and 12.

Importantly, VOR is a feedforward control system that has no feedback from output to input; that is, there is no way to inform the vestibular system directly about eye movement (Ito, 1974). In engineering systems, feedforward control alone is undesirable because without feedback, the control cannot be precise. However, in biological systems, feedback may not always be available. In such cases, another CNS pathway (or pathways) is needed to replace the traditional feedback loop. We reasoned that this could be the flocculus. Our assertion was supported by the observation that the vestibulospinal reflex held head position constant by using direct feedback from the neck's position to the vestibular organ but using no cerebellar inhibition. For the VOR to obtain precise compensatory eye movements without feedback, there had to be a visual pathway to the flocculus that informed about errors in the operation of the reflex (Ito, 1970). To test this prediction, the late Kyoji Maekawa (1929–1990) and John Simpson (Maekawa and Simpson, 1973) indeed discovered in my laboratory a powerful climbing fiber projection from the retina to the flocculus. Input to the flocculus from the vestibular organ via mossy fibers had already been shown in the cat (Brodal, 1972). In summary, our VOR model incorporated a set of three elements of the Marr-Albus model: mossy fiber-parallel fiber input, climbing fiber input, and Purkinje cell output. Also, the VOR was testable in a behaving animal!

The XXVth Congress of the IUPS was held in Munich in 1971. It was an unforgettable experience for me. I reported about the direct inhibition of VOR relay neurons by flocculus Purkinje cells and proposed that the flocculus plays a key role in the feedforward control of the VOR. To my great surprise in this same session, Geoffrey Melvill Jones reported that when a human subject wore Dove-prism goggles, which reversed the right-left relationship in the visual field for one month, the result was a clear-cut depression and final reversal of the VOR (Gonshor and Melvill Jones, 1974). David Robinson, a world-renowned oculomotor physiologist/bioengineer, was leading discussions in this session. After the Congress, he attached Dove-prism goggles to a kitten and showed that the VOR was substantially depressed

(Robinson, 1976). Moreover, he showed that the depression did not occur when the flocculus had been lesioned bilaterally. I learned the "double rotation" technique (use of vestibular and visual stimuli in various combinations) from an otologist, who was working on vestibular functions in race-car drivers, and applied it to rabbits. We oscillated them sinusoidally on a horizontal turntable and also moved a surrounding screen horizontally (Ito et al., 1974). When the screen was rotated in the direction opposite to the turntable rotation, the VOR was gradually enhanced (i.e., to catch up with the increased relative movement of the screen). Likewise, while the screen was rotated in the same direction as the turntable, the VOR was gradually depressed. These adaptive changes in the VOR were abolished when the flocculus was ablated bilaterally (Batini et al., 1979) or when climbing fibers were lesioned bilaterally (Ito and Miyashita, 1975). We then proceeded to record from flocculus Purkinje cells during VOR adaptation (Ghelarducci et al., 1975; Dufosse et al., 1978). Since that time, numerous such studies have been carried out in many laboratories, but nonetheless, VOR adaptation remains a valuable system for investigating mechanisms of cerebellar motor control and such work still generates new issues in cerebellar research (Chapter 10).

A frequently discussed question in the late 1960s and early 1970s was what signals climbing fibers conveyed as a set of unique afferents to the cerebellum. Marr (1969) assumed that they provided instruction signals from the cerebral cortex, whereas Albus (1971) thought that climbing fiber input implied errors in the simple perceptron-like operation of a cerebellar network. Miller and Oscarsson (1970) proposed that the inferior olive acted as a comparator between command signals from higher centers and the activity these signals evoked at lower levels. I proposed that climbing fibers monitored "control errors" for the VOR (Ito, 1970). Amat (1983) observed in the frog cerebellum that climbing fibers responded to a shift in the position of a forelimb and suggested that these responses represented a deviation of the forelimbs from a predetermined position. Since then, the signal contents of climbing fiber discharges have been investigated extensively. It seems to be a general principle that climbing fiber signals encode errors of some sort; not always an error occurring as a consequence of a movement, but also an error generated intrinsically within a neuronal circuit (Chapter 13, "Voluntary Motor Control"). When climbing fibers convey error signals, LTD would be induced in those parallel fiber-Purkinje cell synapses that are involved in erroneous performance. Learning would then occur to reduce such incorrect behavior (i.e., "error learning"). This notion has been expanded to motor learning in general, and it is sometimes called Marr-Albus-Ito hypothesis.

3-6 Cerebellar Internal Models

Also about 40 years ago, I speculated about the function of a then well-known anatomical structure of the cerebellum, the cerebrocerebellar loop that links the primary motor cortex and the intermediate part of the cerebellar hemisphere (Figure 18). Initially, I failed to relate this loop to the circuit structure I had proposed for VOR adaptation. Therefore, I then introduced the idea that the cerebellum provided an internal model that helped the cortical controllers. The idea was as follows. In performing unskilled voluntary movements, the initial instruction arising from an association area of the cerebral cortex would be transferred to the primary motor cortex and then through the pyramidal tract down to the spinal motor centers. The final outcome would be checked through sensory pathways by the association cortex, there being a large negative feedback loop formed through the external world. In this case, the cerebral cortex had to be continuously aware of what was being performed and had to be available for adjusting the performance from time to time. As experience was gained in the performance of these movements, they would become refined to the level of being skilled voluntary movements. As the learning process progressed, it was suggested that the large loop through the external world would be effectively replaced by an internal loop passing through the cerebellum, such that it would serve as a model simulating the combination of the spinal control system, the external world, and the sensory pathways. In this gestalt, the original negative feedback system would be converted by learning into a feedforward system that needed no straightforward negative feedback from the output to the input. I submitted an invited manuscript on this idea of an internal model to the 4th Symposium of the Fulton Society on the Cerebellum, which was held in New York City in 1969. Unfortunately, an illness prevented me from attending the meeting, but the manuscript was nonetheless circulated among the participants and eventually published in a journal that collected publications concerning that meeting (Ito, 1970). I also presented the idea in my 1984 monograph, *The Cerebellum and Neural Control.*

In the 1980s, movements of multijoint robotic fingers, arms, and hands became a challenging control task because such movements have a large number of degrees of freedom (Chapter 13). Hollerbach (1982) and An et al. (1988) introduced a clever way of controlling a robot's arm using feedforward control via an inverse model of the arm. In 1987, Mitsuo Kawato and his colleagues proposed an ingenious two-degrees-of-freedom control, in which the feedback control by the primary motor cortex was combined with feedforward control by the cerebellum (Figure 8B). If the cerebellum represented the output-input relationship of the controlled object, this inverse model could play the role of a feedforward

controller. For this system, Kawato et al. (1987) incorporated an ingenious way of learning, that is, "feedback error learning" that derived errors from the primary motor cortex performing its feedback control. The Kawato model seemed to be an effective way to explain the learning process in voluntary motor control. Initially, the primary motor cortex would exert feedback control to perform accurate movements. Meanwhile, the cerebellar inverse model would gradually be modified by error signals to provide precise feedforward control. Then the feedback control by the primary motor cortex would be replaced by feedforward control from the cerebellum unless the latter happened to be inaccurate. It could be reasoned that the initial feedback control was performed consciously, whereas the later feedforward control by the cerebellum is performed unconsciously, this idea being in good general agreement with our daily experiences. Moreover, a combination of forward and inverse models was applied successfully to the creation of a robot that was able to learn movement skills (Wolpert and Kawato, 1989). A major advantage of Kawato's control system model was its computational expression, such that it could be installed in a robot that was capable of learning complex movements. The biological validity of the forward and inverse models is now being tested in an ever-increasing number of experimental studies on Purkinje cell discharges during various movement paradigms (Chapter 15, "Internal Models for Voluntary Motor Control").

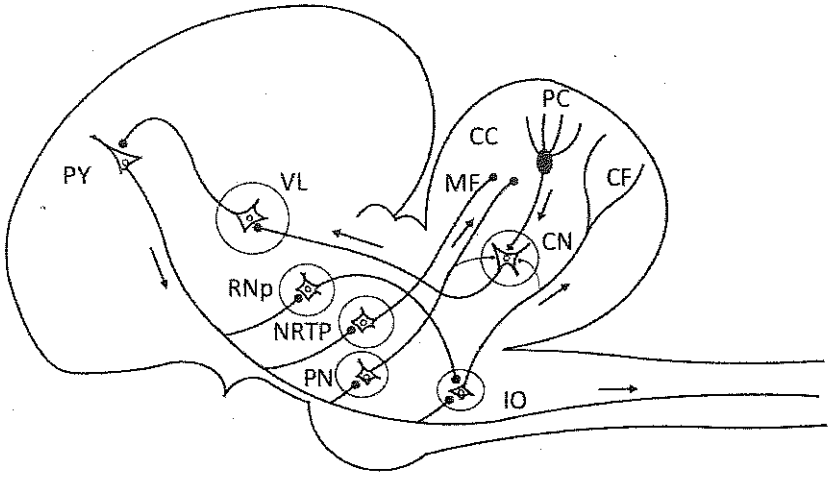


Figure 18 The cerebrocerebellar loops.

This figure schematizes the loop connections between the cerebral cortex and the cerebellum. Abbreviations: CC. cerebellar cortex; CF, climbing fiber; CN, cerebellar nucleus; IO, inferior olive; MF, mossy fiber; NRTP, nucleus reticularis tegmenti pontis; PC, Purkinje cell; PN, pontine nucleus; Py, pyramidal cell in the cerebral cortex; RNp. parvocelluir red nucleus; VL, ventrolatertal thalamic nucleus.

3-7 Cognitive Functions of the Cerebellum

A major new development in cerebellar research toward cognitive functions began in the early 1990s. A role for the cerebellum was postulated for cognitive functions, such as language acquisition, on the basis of the considerable expansion of the most lateral part of the cerebellar hemispheres in humans (Leiner et al., 1993). Clinical observations had also shown by then that lesions in the cerebellum often accompanied mental and affective disorders with characteristic symptoms, which Schmahmann (1991) called mental dysmetria. In spite of these important developments, the general line of thought at that time was rather negative (e.g., Leiner, 2010).

At an earlier time, the late Robert Dow (1908–1995) asked me to write an article on the cerebellum for a special issue of Trends in Neuroscience in 1993. I reflected on how cerebellar neuronal circuits might process information not only for body movements in the physical domain but also for conceptual functions in the cognitive domain. I was inspired with the idea that in the control systems gestalt, the control of a body part is analogous to manipulation of a mental model, like those proposed by Craik (1943) and Johnson-Laird (1983), and even by Piaget's (1951) schema (Chapter 1).

I presented this view in the Pontifical Academy of Sciences Symposium organized by John Eccles and the late Otto Detlev Creutzfeldt (1927-1992) at the Vatican in 1988. The overall reaction to my talk (Ito, 1990a) was that the hypothesis was interesting, but had no supportive data. Decety encouraged me, however, by showing a PET image of the cerebellum of a tennis player playing the game in his mind without making any movement (i.e., an image training paradigm) (Decety et al., 1990). In the following years, I developed the view that the cerebellum controls movements and thoughts with the same overall neuronal circuit mechanisms (Ito, 1993a, 1997b). I further speculated that a presumed mental model is initially formed in the temporoparietal cortex, and as learning proceeds, it is copied in cerebellar internal models (Ito, 2005).

Early in the 2000's, Strick's group undertook precise anatomical remapping of the cerebrocerebellar communication loops (Kelly and Strick, 2003; Dum and Strick, 2003). One of the two loops so defined is attached to the cortical motor areas, whereas the other is attached to areas 46 and 9 of the cerebral prefrontal cortex (Figures 42 and 53). Ramnani (2006) reviewed anatomical data about these loops and pointed out that, whereas in macaque brains, fibers from the cortical motor system occupied the largest proportion of the cerebral peduncle, a comparatively small proportion was occupied by fibers from the prefrontal cortex. Importantly, he also pointed out that in the human brain, the largest contribution came

not from the cortical motor areas but from the prefrontal cortex, suggesting that in humans the cerebellum has a more important role than in macaques in processing information from the prefrontal cortex. This is probably information at a more abstract level than that processed in the motor cortex. To explain such a non-motor role of the cerebellum, Ramnani (2006) adopted (as did I) the formalistic analogy between motor and cognitive systems as internal model-based control systems. Thus, we may conceive that a provisional thought system includes the prefrontal cortex as a controller, which is assisted by an internal model formed in the cerebellar hemisphere (Ito, 2008). Supportive evidence for such a thought system is available in the wealth of ever-increasing brain imaging data, and in the brain lesion and disease data that had accumulated over many years (see Chapter 17, "Cognitive Functions").

3-8 Summary

The history of research on the cerebellum is certainly replete with excitement and thrilling experimental possibilities. Over the past five decades, in particular, basic concepts of synaptic plasticity, error learning, adaptive control, and model-based control have been formulated and substantiated experimentally. This has changed the once widely held belief that the function of the cerebellum was strictly for a relatively simple form of motor control to the current idea that it is an elaborate neuronal machine equipped with learning capabilities and devoted to far-more-advanced forms of systems control for posture and movement and probably also for participation in the control of complex motor actions and cognitive functions.

4

Input and Output Pathways in the Cerebellar Cortex

4-1 Introduction

We are now ready to begin decomposing neuronal circuits in the cerebellar cortex into component neurons and examining them one by one. This exercise provides the basis for considering principles operating in these circuits and also for testing the validity of thus-far-derived hypotheses, which are discussed in later chapters. The focus in this chapter is on the neuronal elements that comprise the input and output interactions with the cerebellar cortex via mossy fibers, granule cells, and Purkinje cells. Unipolar brush cells and beaded fibers are also considered.

4-2 Mossy Fibers

Mossy fibers are the most numerous afferent fibers that reach the cerebellar cortex through the white matter and terminate in the cerebellum's granular layer, forming a mosslike structure (Figure 14). Some mossy fibers originate as sensory peripheral nerves, but most mossy fibers arise from neurons located within the spinal cord and brainstem. They also arise from unipolar brush cells in the granular layer (see below) and from cerebellar nuclei (Chapter 6, "Pre- and Post-Cerebellar Cortex Neurons"). Mossy fibers terminate within a glomerulus, which forms a characteristic rosette structure. Within a glomerulus, granule cell dendrites receive α-amino-3-hydroxy-5-methyl-4-isoxazolone propionic acid (AMPA)-mediated excitatory synapses from a mossy fiber terminal. Granule cells receive also inhibitory synapses supplied by a Golgi cell axon terminal. Descending dendrites of mostly deep Golgi cells also receive excitatory synapses directly from a mossy fiber terminal.

Most mossy fibers release glutamate as a transmitter, but some in the vestibulocerebellum release acetylcholine (Barmack et al., 1992a,b; Jaarsma et al., 1997).

Both AMPA and N-methyl-D-aspartate (NMDA) receptors mediate mossy fiber-granule cell synapses in glomeruli (Traynelis et al., 1993). Within a glomerulus, NMDA receptor subunits (NR1, NR2A, and NR2C) are co-located between the centrally positioned rosette structure and the peripherally positioned, tiny Golgi cell axon terminals at the postsynaptic junction with granule cell dendrites (Yamada et al., 2001).

A marked "spillover" phenomenon has been reported to occur in both glutamate released from a mossy fiber terminal and gamma-amino-butyric acid (GABA) released from Golgi cells. Single AMPA-receptor-mediated excitatory postsynaptic currents (EPSCs) or potentials (EPSPs) at the mossy fiber-granule cell connection are mediated by both the direct release of glutamate and the rapid diffusion of glutamate from neighboring synapses. Spillover currents contribute about one-half of the synaptic charge and improve transmission efficacy by increasing both the amplitude and duration of EPSPs (DiGregorio et al., 2002). Fluctuation analysis indicates that these indirect release sites are at least fourfold more numerous than those directly connected to the postsynaptic cell. As a result, spillover is predicted to improve the reliability and reduce the variability of transmission at this glomerular synapse. The unique firing behavior of granule cells may also be relevant; a single impulse in a mossy fiber tends to induce bursting spikes in a granule cell (Chadderton et al., 2004).

4-3 Granule Cells

Granule cells are individually the smallest (soma diameter, 5–8 micrometers (μm)) and the most numerous neurons in the CNS (Braitenberg and Atwood, 1958; Zagon et al., 1977). A large divergence and a small convergence characterize the mossy fiber-granule cell pathway. Each granule cell receives mossy fiber terminals via only four to five excitatory synapses (Eccles et al., 1967; Chadderton et al., 2004). The functional significance of this small convergence number will be considered later in Chapter 8, "Multiplicity and Persistency of Synaptic Plasticity." In contrast, one mossy fiber supplies excitatory synapses to 400–600 granule cells in a folium and probably more when the branches of a mossy fiber reach two or more folia. The efficacy of synaptic transmission from a mossy fiber to granule cells may vary probabilistically from glomerulus to glomerulus. Such relative efficacy may also be affected by the following three factors: activity-dependent induction of long-term potentiation (LTP) (Chapter 8), enhancement of intrinsic excitability (Armano et al., 2000), and Golgi cell inhibition (Chadderton et al., 2004; see also below).

Parallel fiber axons of granule cells run along the folia of the cerebellar surface after ascending vertically from the granular layer to the molecular layer and then

bifurcating into two parallel fiber collaterals. The formation of parallel fibers is controlled genetically. This is known because in Pax6 mutant rats, granule cells in the external germinal layer fail to form parallel fiber axons (Yamasaki et al., 2001). In normal animals, the length of a parallel fiber from terminal to terminal across its T-junctions has been reestimated to be as long as 4–6 mm (Mugnaini, 1983; Harvey and Napper, 1988; Pichitpornchal et al., 1994). Optical recording in mice shows that the local stimulation of a parallel fiber bundle excites Purkinje cells along the bundle over a distance of more than 3 mm (Coutinho et al., 2004). This extent of excitation was also observed by optical recording in neonatal rats on postnatal day 5, although it reduced to 1.5–2 mm at postnatal days 6–7 (Arata and Ito, 2004).

Ascending segments of granule cell axons form synapses with spines, which are located exclusively on the smallest diameter distal regions of Purkinje cell dendrites (Gundappa-Sulur et al., 1999; Lu et al., 2009). This contrasts to parallel fibers, which form synapses on the intermediate or large diameter regions of spiny branchlets, as well as the smallest diameter distal regions. The ascending segments form about 20% of the granule cell-Purkinje cell synapses. A differential stimulation of parallel fibers and ascending segments of granule cell axons in cerebellar slices revealed substantial differences in the properties of EPSCs generated in Purkinje cell dendrites (Sims and Hartell, 2005). Ascending segment synapses release a transmitter with a higher mean release probability and larger mean quantal amplitude than parallel fiber synapses, and they do not exhibit LTD (Chapter 7, "Conjunctive Long-Term Depression (LTD)"). These different properties of parallel fiber versus ascending segment synapses suggest that they have different roles in Purkinje cell function.

4-4 Unipolar Brush Cells

Unipolar brush cells of unique morphology are located primarily in the granular layer of the vestibulocerebellum. This portion of the cerebellum, which corresponds roughly to the flocculonodular lobe, receives primary vestibular afferents in the form of mossy fibers. These cells receive excitatory synapses on their dendritic "brush" from a single mossy fiber terminal (Color Plate VI). This connection has the form of a giant glutamate-mediated synapse (Diño et al., 1999). The unipolar brush cell's axon forms branches within the granular layer, which give rise to large terminals that synapse with both granule cell and unipolar brush cell dendrites. This arrangement is within glomeruli that resemble those formed by extrinsic mossy fibers. Hence, unipolar brush cells are an intracortical source of mossy fibers.

Unipolar brush cells receive inputs from glutamate-mediated primary vestibular fibers and choline-acetyltransferase-positive mossy fibers. Some of the latter

originate from the medial and descending vestibular nuclei (Diño et al., 2001). An excitatory effect of muscarine, but not nicotine, was detected in ~15% of granule cells tested in the vestibulocerebellum (Takayasu et al., 2003). Evidence suggests that this effect is caused by the inhibition of an intrinsic outward K^+ current via the activation of muscarinic M3 receptors. Two subtypes of unipolar brush cells have been distinguished: one expresses calretinin, and the other expresses metabotropic glutamate receptor type 1a (mGluR1a) (Nunzi et al., 2002). Both subtypes express glutamate receptor subunit 2 (GluR2) (Sekerková et al., 2004). Tbr2/Eomes, a T-domain transcription factor (Tbr2), has been considered to be a specific marker of both subtypes of unipolar brush cells in the adult and developing cerebellum (England et al., 2006) (Color Plate VII). Unipolar brush cells express NMDA, kainite, and AMPA receptors in the synaptic membrane. They also express metabotropic glutamate receptors (mGluR1 and mGluR2/3) on the perisynaptic and extrasynaptic parts of the spiny appendages of dendrites (Jaarsma et al., 1995, 1998; Billups et al., 2002). Mossy fiber impulses induce an AMPA-mediated fast EPSC and a predominantly NMDA-mediated slow EPSC in unipolar brush cells (Rossi et al., 1995). It has been suggested that unipolar brush cells may amplify mossy fiber inputs in the vestibulocerebellum (Kalinichenko and Okhotin, 2005; Barmack and Yakhnitsa, 2008).

4-5 Purkinje Cells

Purkinje cells are the largest neurons in the cerebellum, extending magnificent planar dendrites to receive numerous synaptic inputs (Color Plate VII). Purkinje cells mediate the sole outputs of the cerebellar cortex, which are exclusively inhibitory in action upon their target neurons. Parallel fibers form excitatory synapses on dendritic spines of Purkinje cells. The synaptic membrane, lined with postsynaptic density (PSD), is located on the side (but not top) of a spine head and is therefore located at an optimal distance from the endoplasmic reticulum that protrudes to the spine head (Launey et al., 2004) (Color Plate VIII). A large divergence and an enormous convergence characterize the parallel fiber-Purkinje cell connection. While a single parallel fiber extends for ~3 mm (i.e., ~1.5 mm on each side of the T-junction), it passes through the dendrites of ~450 Purkinje cells and thereby forms synaptic contacts with the dendritic spines of at least 300 Purkinje cells (Eccles et al., 1967). On the other hand, the number of parallel fibers making synaptic contacts with the dendritic arborization of a Purkinje cell can be as large as 180,000 in the human (Fox and Bernard, 1957) or either ~60,000–80,000 (Palay and Chan-Palay, 1974) or ~175,000 (Napper and Harvey, 1988a,b) in the rat. Note that parallel fibers form synaptic contacts with only ~54% of the Purkinje cells through whose dendritic arborization they pass. Simultaneous whole-cell recording

from synaptically connected granule and Purkinje cells in cerebellar slices revealed that an impulse from a single granule cell evoked a fast EPSC of 2–60 pA in a Purkinje cell (Barbour, 1993). This suggests that ~50 simultaneously active granule cells are sufficient to excite a single Purkinje cell.

Parallel fiber impulses release glutamate as a transmitter, which evokes two pharmacologically distinct types of synaptic potential in Purkinje cells. One is mediated by AMPA receptors, and the other by mGluR1. AMPA-mediated EPSPs are fast and evoked individually by each granule cell's impulses (Figure 15C), whereas mGluR1-EPSPs are slow and observed only after a brief tetanus of parallel fibers (8 pulses at 50 Hz) in the presence of an AMPA receptor antagonist (Batchelor and Garthwaite, 1993) (Figure 15D). Slow EPSPs are accompanied by an increase in intradendritic sodium concentration, but the mechanism underlying this excitation remains unclear. The above two types of EPSP have different frequency characteristics. For example, following a single-shock stimulation of parallel fibers, fast EPSPs predominate, whereas in a burst stimulation of parallel fibers, slow EPSPs are facilitated. When a parallel fiber bundle is repetitively stimulated with 10 pulses at 100 Hz, the mGluR1- and AMPA receptor-mediated activations of Purkinje cells are equally potent (Coutinho et al., 2004). Metabotropic $GABA_B$ receptors are expressed in the extra-postsynaptic sites of parallel fiber-Purkinje cell synapses. The activation of $GABA_B$ receptors leads to the augmentation of mGluR1-mediated parallel fiber-Purkinje cell transmission (Hirono et al., 2001). This is an interesting case of interaction between two types of metabotropic receptor.

Purkinje cell outputs from the cerebellar cortex inhibit their target neurons with GABA as the transmitter. Because Purkinje cells provide ~73% of the total synapses of cerebellar nuclear neurons, including almost all of the somatic synapses of cerebellar nuclear neurons (Palkovits et al., 1977; De Zeeuw and Berrebi, 1995), the question arises as to how such inhibitory inputs accurately control spiking in the latter neurons. To answer this question, Gauck and Jaeger (2000) applied the dynamic clamp method, in which they injected a conductance waveform that simulated the synaptic input of several hundred GABA A-type inputs to a cerebellar nuclear neuron in *in vitro* slices. They found that the time of inducing individual spikes was controlled precisely by brief decreases in inhibitory conductance, these being the consequence of the synchronization of many inputs. They also showed that spike rate was controlled linearly by the discharge rate of inhibitory inputs.

Purkinje cells project recurrent axon collaterals and thereby inhibit each other. These collaterals extend to neighboring Purkinje cells within ~300 micrometers of the parent cell (Hawkes and Leclerc, 1989; O'Donoghue and Bishop, 1990). Axon

collaterals of Purkinje cells also inhibit basket cells, which, in turn, inhibit Purkinje cells. Therefore, Purkinje cells may be involved in a mixed reciprocally inhibitory network containing both Purkinje cells and basket cells.

4-6 Climbing Fibers

Climbing fibers are a unique structure of the cerebellum with no homolog elsewhere in the CNS (Color Plate IX A–B). The major transmitter of climbing fibers is glutamate. Each Purkinje cell is innervated by one climbing fiber. This is a consequence of the postnatal elimination of multiple innervation, which, after birth in rats and mice, attains its maximum in one week and fades out in two weeks via its interaction with developing parallel fiber-Purkinje cell synapses (Mariani and Changeux, 1981; Hashimoto and Kano, 2003; Scelfo and Strata, 2005; Hashimoto et al., 2009). Each climbing fiber forms numerous synaptic contacts with the dendrites of a single Purkinje cell [~1,300 in proximal dendrites of rat Purkinje cells (Strata, 2002), but a much larger number,~26,000, is derived from the density ratio of climbing fiber to parallel fiber synapses (Nieto-Bona et al., 1997)].

The above arrangements for climbing fibers result in a particularly large EPSP in Purkinje cells superimposed with Ca^{2+} spikes (Llinas and Sugimori, 1980a,b). Extracellular recording has revealed that Purkinje cells spontaneously generate two different types of spike: simple spikes (Figure 15E, F) and complex spikes (E, G). In intracellular recording, stimulation of parallel fibers cells elicits simple spikes (Figure 15A), whereas climbing fiber stimulation evokes complex spikes (Figure 15B). Simple spikes are actually Na^{2+} spikes generated in the somatic region that spread passively into the dendrites, whereas complex spikes involve Ca^{2+} spikes generated in dendrites. In *in vivo* conditions, simple spikes discharge spontaneously at a rate of 50–100 Hz, whereas complex spikes discharge at an irregular, low rate of ~1 Hz (Thach, 1967).

The unique role of climbing fibers in inducing synaptic plasticity in Purkinje cells is dealt with in Chapter 7. Because of the powerful depolarizing action accompanying Ca^{2+} entry, it has been suggested that climbing fiber responses also play a critical role in cellular function. Indeed, in rat cerebellar slices, climbing fiber discharges occurring at physiological frequencies (0.4–10 Hz) substantially modified the frequency and pattern of simple spike discharges (McKay et al., 2007). Repetitive climbing fiber discharges converted a spontaneous pattern of simple spike discharges into a more natural nonbursting pattern that consisted of simple spike trains interrupted by short climbing fiber-evoked pauses or longer pauses associated with state transitions. These effects were reproduced by injecting currents simulating complex spike depolarizations in the presence of synaptic blockers.

Hence, these appeared to occur intrinsically—for example, by activation of Ca^{2+}-dependent K^+ channels.

In regard to the function of climbing fibers in cerebellar circuits, recent studies have revealed unexpectedly that climbing fibers also excite interneurons in the cerebellar cortex via atypical transmission mechanisms, as explained in Chapter 5, "Inhibitory Interneurons and Glial Cells in the Cerebellar Cortex." In brief, such transmission might be mediated by a spillover of glutamate released from climbing fiber terminals (Szapiro and Barbour, 2007), which may then spread to interneurons via volume transmission (Agnati et al., 1995). An alternative mechanism would be for climbing fibers to activate synaptically NG2+ glial cells, which could, in turn, excite interneurons (Lin et al., 2005).

4-7 Beaded Fibers

The cerebellar cortex receives not only mossy fibers and climbing fibers, but also beaded fibers, which contain various amines, such as serotonin, norepinephrine, or histamine, or neuropeptides, such as angiotensin II or orexin (Haines and Dietrichs, 1984; Haines et al., 1984; Airaksinen and Panula, 1988; King et al., 1992; Onat and Cavdar, 2003; Zhu et al., 2006; Ito, 2009). The beaded fibers extend fine varicose axonal fibers sparsely throughout the granular and molecular layers to form direct contacts with Purkinje cells and other cerebellar neurons. These axonal fibers are often called the third type of cerebellar afferent. On the basis of their diffuse extensions, it is considered that this third type of afferent does not convey specific information to the cerebellar cortex. Rather, its role could be modulatory. Akin to stomatogastric ganglia (Marder et al., 1986), such neuromodulation would set the activity level or switch the operational mode of a cerebellar microcomplex (Chapter 9, "Network Models") to match a behavioral demand (Schweighofer et al., 2004) (for further description, see Chapter 6).

4-8 Summary

The mossy fiber-granule cell-Purkinje cell pathway provides the core of cerebellar cortical neuronal circuits. Unipolar brush cells appear to amplify the mossy fiber-to-granule cell transmission, but their special need in the vestibulocerebellum is unclear. This pathway, together with climbing fiber and beaded fiber afferents, forms the skeleton of the cerebellar neuronal circuits. Other types of neurons and glial cells put flesh on this skeleton to achieve the elaborate functional mechanisms of the cerebellum.