MASAO ITO

THE CEREBELLUM

Brain for an Implicit Self

Contents

1

Neuronal Circuitry: The Key to Unlocking the Brain

1-1 Introduction

The central nervous system (CNS) of vertebrates contains an enormous number of neurons, each having elaborate electrical and chemical signaling mechanisms. These neurons are interconnected via synapses to form intricate neuronal circuits. While such a circuit is composed of molecules within cells, it also processes information and generates a multitude of functions. Much effort has been and continues to be devoted to bridging these two properties of neuronal circuits to explore still largely unknown mechanisms of the CNS. The circuits of the cerebellum have been on the forefront of this endeavor. This chapter addresses the methodologies and fundamental concepts that are currently being used in the study of generic complex neuronal circuits before focusing in succeeding chapters on the cerebellum.

1-2 Decomposition and Reconstruction

At a far earlier time, René Descartes (1596–1650) discussed the search for complex mechanisms of the universe and life by using the clock as a metaphor. During his time, this machine was considered the most complex of all the world's man-made structures. Following Descartes (1649), it can be argued, as is prevalent today, that if one can dismantle a clock into its pieces and then successfully reconstruct them into the same functional machine, the precise nature of the clock is revealed. This methodology is still widely applicable when examining an object of unknown nature. It is dissected into simpler pieces, which can be understood, and then an attempt is made to reconstruct a model composed of all the pieces. If this model exhibits all the properties of the original object, it is indeed understood.

The CNS includes the brain (contained within the skull), which weighs 1.3–1.4 kg in humans, and also the spinal cord, which extends into the vertebral canal. On the basis of conventional anatomy, the brain is grossly divided into the brainstem, cerebellum, and cerebrum. The cerebrum is further divided into the basal ganglia, limbic system, and neocortex (Figure 1). The cortex of the cerebral hemisphere is further subdivided to 52 areas (Brodmann, 1909; Garey, 1994) (Figure 2). The cerebellar cortex is also subdivided into nearly a hundred areas (see below and Color Plate II). Currently, we know that each of these divisions is composed of characteristic neuronal circuits that consist of numerous neurons of diverse types interconnected with each other via synapses. Moreover, there are even more numerous glial cells and finely branch blood vessels that support and nourish the neurons. The neuronal circuits in each subdivision constitute local networks, which are further integrated to form global neural systems across subdivisions or divisions. Current neuroscience is based on the belief that these networks and systems operate through specific mechanisms and play specific functional roles in the living body.

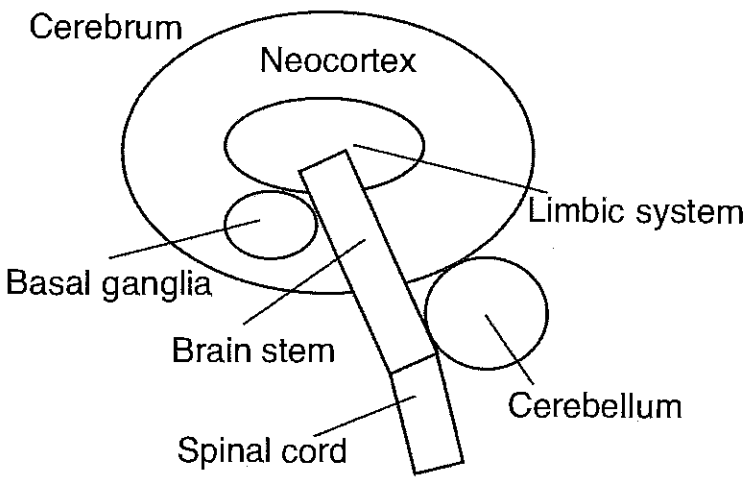

Figure 1 A sketch of major divisions of the CNS.

How can we unveil such mechanisms and the functional roles of neuronal circuits? The initial approach was to dissect the brain into experimentally manageable parts. This was the strategy adopted a century ago by Sherrington (1857–1952) and his group. They severed a segment of the cat spinal cord from its upper (and sometimes lower) segments (Figure 3A). Freed from the effects of other structures, the

severed segments exhibited reflexes with stable, straightforward input-output relationships via the dorsal and ventral roots, which could be subjected to precise scientific investigation.

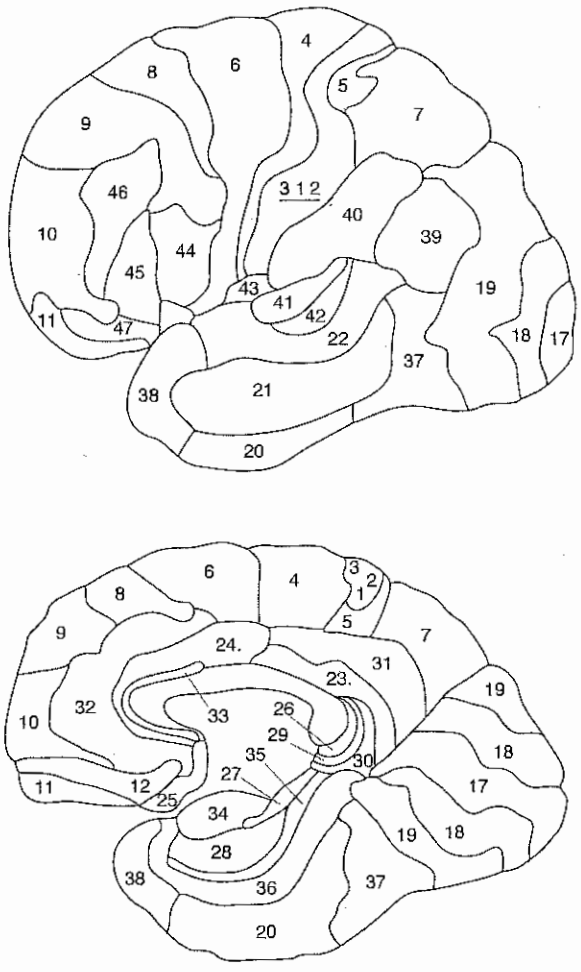

Figure 2 Brodmann's cerebral cortical areas.

The original dotted map published by Brodmann (1909) is converted here to outlined areas. (The original color version was provided by courtesy of Mark Dubin: http://spot.colorado.edu/~dubin/talks/brodmann/brodmann.html.)

When a neuronal circuit is defined in terms of its gross structure and function, it can then be decomposed into its individual neurons and their dendrites, axons, and synapses, using the currently available technologies of neuroscience. Thereafter, one may try to reconstruct a model of the initial reflex circuit by using the

properties of all its constituent parts. In the process of reconstruction, the mechanistic principle(s) operating in the neuronal circuit may well be revealed.

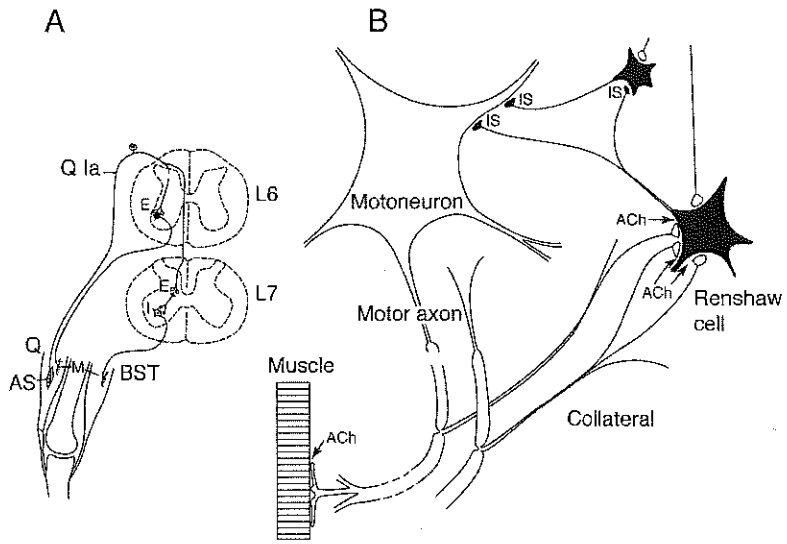

Figure 3 Sketch of some spinal reflex circuitry.

(A) Schematic of some spinal reflex pathways (modified from Eccles et al., 1954). (B) Spinal circuitry drawn by Eccles as based on his group's intracellular recording data on the recurrent Renshaw cell pathway (Eccles, 1963). In this and subsequent figures, sketches of a single cell and fiber (axon) usually represent groups of such units. A includes muscle spindles and their Ia afferents, two spinal cord segments, spinal motoneurons, Ia inhibitory interneurons, and two opposing muscles. B includes motoneurons and their axons supplying parts of muscle fibers, recurrent motor axon collaterals, Renshaw cells, and other spinal inhibitory interneurons. Abbreviations: ACh, acetylcholine; AS, annulospiral endings; BST, biceps and semitendinosus muscles; E, excitatory synapses: I/IS, inhibitory synapses; L6-L7, lumbar spinal segments; Q, quadriceps muscle; Qla, spindle Ia afferents supplying Q spindles. Symbols: black-filled neurons and their endings, inhibitory; open neurons and their endings, excitatory. This figure is dedicated to a 1963 Nobel Laureate, John Carew Eccles (1903–1997), who was my postdoctoral mentor in Canberra, Australia, from 1959 to 1962. (See Ito, 1997a, 2000; Stuart and Pierce, 2006.)

Sherrington's group assumed that peripheral stimuli induced excitatory and inhibitory "states" in the spinal centers for various reflex circuits. John Eccles (1903–1997) and his colleagues (e.g., Brock et al., 1952) later identified these as formed by the membrane depolarization and hyperpolarization of spinal motoneurons via excitatory and inhibitory synapses (Figure 3B). Hubel and Wiesel (1960) discovered the unique responsiveness of individual neurons to line stimuli in the

visual cortex. They proposed a model of a neuronal circuit to explain how the characteristic responsiveness of "simple" and "complex" cells are formed, using input from concentric receptive fields of the lateral geniculate neurons. These early discoveries marked the start of modern neuroscience.

Neuroscience is now dominated by the effort to decompose neuronal circuits into their cellular and molecular components. Many would argue, however, that reconstructing models of such circuits is equally important in our attempt to comprehend their functional principles (e.g., van Hemmen and Sejnowski, 2006; Stuart, 2007; for biology as a whole, see Noble, 2006). In the reconstruction process, it is possible to uncover novel principles operating in the original neuronal circuits. Analogies to man-made systems such as computers, control devices, and communication networks have also been helpful, as emphasized in the field of cybernetics by Nobert Wiener (1894–1964).

The circular approach through decomposition and reconstruction provides a general method of fundamental research that features close interactions between experiments and theory (Figure 4). Initially, a factual observation of a complex subject may suggest a crude conceptual model, which serves to generate a prediction for a more focused experimental observation. If the prediction turns out to be correct, it supports the crude model, which is then refined to a more accurate conceptual model. This, in turn, can be converted into a substantial computational model, which is reproducible on a computer. Such an advanced model enables us to make further predictions, which can again be tested in even more precise experiments. In this iterative, cyclic development using observation-inspired models, model-based predictions, and experimental testing of the predictions, a model is continuously refined until it accurately simulates the complex subject.

A well-known and unique difficulty in research on the CNS arises from its highly hierarchical structure. Comprehension of our current understanding of the brain requires knowledge integrated across several hierarchical levels including molecules, cells, circuits, systems, and behaviors. It seems that ever since organic molecules appeared on earth, these hierarchical levels gradually accumulated through evolution until the human CNS evolved. The above-mentioned decomposition-reconstruction approach can be applied to any two successive levels of the overall hierarchy. For example, a simple neuronal circuit set can be reduced to its component neurons having somata, axons, dendrites, and synapses (Figure 5). In turn, these component neurons can be combined to reconstruct a model of the circuit at its original hierarchical level. Next, the component neurons can be further reduced to the lower level of ion channels, receptors, first and second messengers, and various organelles, whose combined properties can provide models of

electrical and chemical signaling processes in neurons. Ion channels, receptors, and messenger molecules can be further reduced to an even lower level of proteins and their genes. The latter's properties can be incorporated into models of the original ion channels and signaling molecules. By this method, the initial simple neural circuit can be linked step by step (not by jumps) to the molecular mechanisms subserving neuronal functions.

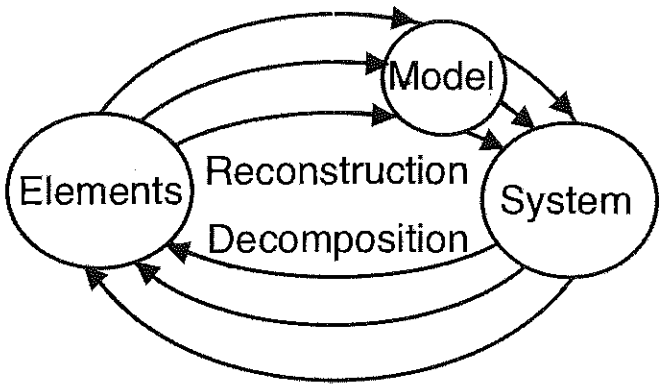

Figure 4 A decomposition/reconstruction cycle.

Research on the CNS starts usually with the experimental dissection of a relatively complex system into its simpler elements. To this end, a system is defined as a CNS unit (e.g., a spinal segment, the pineal body, oculomotor system) while it is undertaking a specific operation. In some cases the system can include peripheral effectors (i.e., glands, muscles). The dissected elements are assorted to construct models of the original system by means of theories and simulations. This circular approach may be based on observation-inspired models, model-based predictions, or experimental testing of a prediction. The model is continuously refined until it accurately simulates the complex system, as symbolized by three trajectories, which represent the first cycle (outer trajectory), an intermediate (middle) cycle, and the most refined (inner) cycle.

These processes can be considered as a long chain of decomposition-reconstruction events. By successively linking hierarchical levels, neuroscience research can trace the long pathway of evolution, from organic molecules to the cells of multicellular organisms, and eventually to the differentiated and diversified neurons that constitute simple neuronal circuits. In addition, evolutionary processes starting from simple neuronal circuits gradually led to the development of increasingly complex circuits and finally the human CNS. The fields of many subdisciplines of neuroscience are found at specific levels of the hierarchy. For one to understand the mechanisms and roles of neuronal circuits in the CNS, consistent and sustained effort is required to link coherently all levels of the hierarchy centering

around neuronal circuits that extend to cells and molecules on one hand, and to complex networks and systems on the other. In later chapters, we will see how far the cerebellum has been decomposed and reconstructed using these general methodologies.

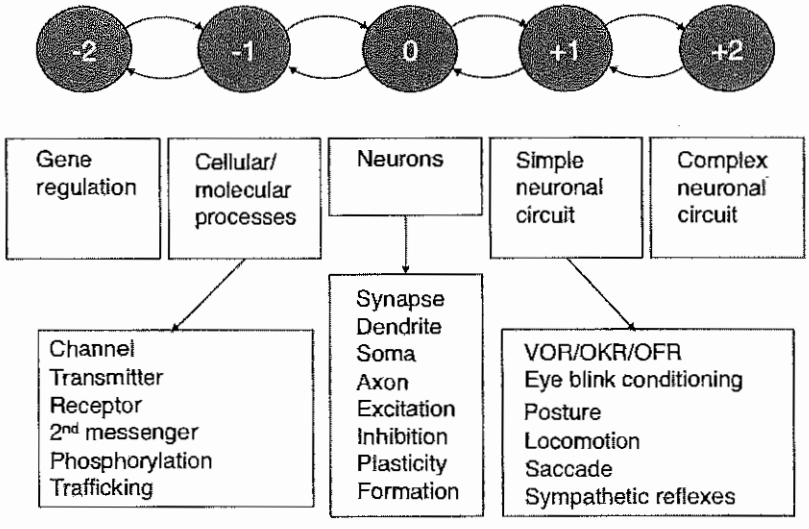

Figure 5 The progression of decomposition/reconstruction cycles.

Shown are levels of analysis that extend from gene regulation (-2) to the cellular/molecular- (-1), neuronal- (0), simple circuit- (+1), and finally, complex circuit (+2) level of analysis. Major themes at levels -1 to +1 are also shown.

1-3 Neurons and Synapses

The concept of the "neuron" was established over a century ago as the unitary component of neuronal circuits. Ramón y Cajal (1852–1934), hereafter shortened to "Cajal," presented clear evidence for this in 1888, when referring to the relationship between Purkinje and basket cells in the cerebellum (see below and Color Plate IV) (Lopez-Munoz et al., 2006). Heinrich von Waldeyer-Hartz (1836–1921) formally proposed the neuron theory in 1891. Also, near the end of the nineteenth century, Sherrington and Michael Foster (1836–1907) coined the term "synapse" and spotlighted it as a key structure of the CNS. Since then, neurons and synapses have been the major targets of neuroscience investigations. All neurons commonly have somata extruding axons and dendrites (except for dorsal root ganglion cells, which have no dendrites). Dendrites not only expand the membrane area to accommodate many hundreds of synapses, but they also have finely

compartmentalized functions (Hausser and Mel, 2003). On the other hand, different types of neurons are distinguished by their characteristic morphology, spike activities, synaptic actions (excitatory or inhibitory), and synaptic receptiveness (chemical or electrical). Subcellular structures such as postsynaptic density (PSD), cytoskeleton, endoplasmic reticulum, Golgi organ, and mitochondrion support these neuronal functions. Signal transduction involves various transmitters, modulators, receptors (ionotropic or metabotropic, or both), and second messengers. For these molecular mechanisms of neurons, numerous proteins, glycoproteins, and lipids, and their genes play essential roles.

1-4 Neural Networks

Numerous neurons in the CNS assemble to form a structure called a "nucleus." In certain areas of the brain and spinal cord (e.g., the superior colliculus, cerebellar cortex, hippocampal cortex, cerebral neocortex), different types of neurons regularly assemble to form a multilayered network. Donald Hebb (1904–1985) proposed the concept of "neuron assembly," that is, a collation of neurons interconnected by synapses, in which the connectivity is modifiable according to experienced activities (Hebb, 1949). A famous proposal by Hebb is that the connection between two neurons firing synchronously is strengthened. Because of this "Hebbian" type of synaptic plasticity; a neuronal assembly can change its circuitry structure (corresponding to memory) and consequently modify its input-output relationships (corresponding to learning), as dependent on experienced activities.

In an effort to verify Hebb's concept of neuron assembly, Frank Rosenblatt (1928–1971) constructed a model network named a "simple perceptron." It consisted of three layers of neurons connected in one direction, from the sensory cell layer to the association cell layer, to the response cell layer (Figure 6). Connections from the first to the second layer were fixed, whereas those from the second to the third layer were modifiable according to the instruction of an outside "teacher." The teacher increased the weight of connection at all junctions transmitting signals from the second to the third layer when the simple perceptron responded correctly to sensory stimuli. The teacher decreased the weight at all second-to-third layer connections transmitting signals when the response was incorrect. When this training process was repeated, the simple perceptron improved its performance toward a success rate of 100%. This was the first man-made machine capable of learning. Ten years later, a counterpart of the simple perceptron was found in the cerebellum (see Chapters 3 and 9). The simple perceptron exemplified the success of the constructive approach (i.e., to understand by construction) for clarifying the operation of neuronal networks in the CNS.

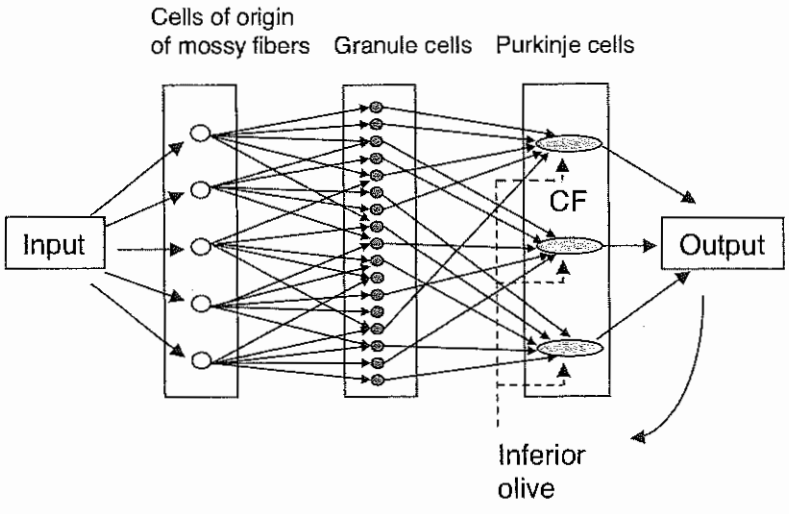

Figure 6 The simple perceptron model of the cerebellum.

This figure is self-explanatory. See the text for further details on the operation of a simple perceptron. Abbreviation: CF, climbing fiber.

Twenty-four years after the construction of the simple perceptron, another form of multilayered neuronal assembly was proposed. It is usually called a "neurocomputer" (Rumelhart et al., 1986), in which errors were estimated by comparing the output of the third layer with a preset goal and were back propagated to the third-layer neurons. The errors acted on the junctions on the third-layer neurons formed with second-layer (hidden layer) neurons, and modified the efficacy of transmission from second-layer to third-layer neurons. The neurocomputer is often applied to model information processing in hippocampal and neocortical networks.

1-5 Systems Control Mechanisms in the CNS

Local networks are interconnected globally throughout the CNS to form neural "systems." A major type of such a system has the general form of a "control system," which consists of a "controller (g)" acting on a "controlled object (G)" (Figure 7A). The controller receives input instruction that provides information about the nature of the required output (e.g., the goal, the trajectory of a movement). In turn, the controller generates command signals that drive the controlled object to respond appropriately. The controller may receive information about the performance of the controlled object (Figure 7A, feedback control), or it may operate without peripheral information (Figure 7B, feedforward control). The goal

of a control system is to generate output responses identical to the input instruction. This can be achieved in a feedback control system if g is sufficiently larger than G, but in a feedforward control system, g needs to equal 1/G (Figure 7B). As emphasized by Baev (1999), this basic control system concept applies to various levels of organization within the CNS: in this monograph from reflexes to isolated voluntary movements and finally to coordinated motor actions. In addition, the concept is applied formalistically to cognitive functions.

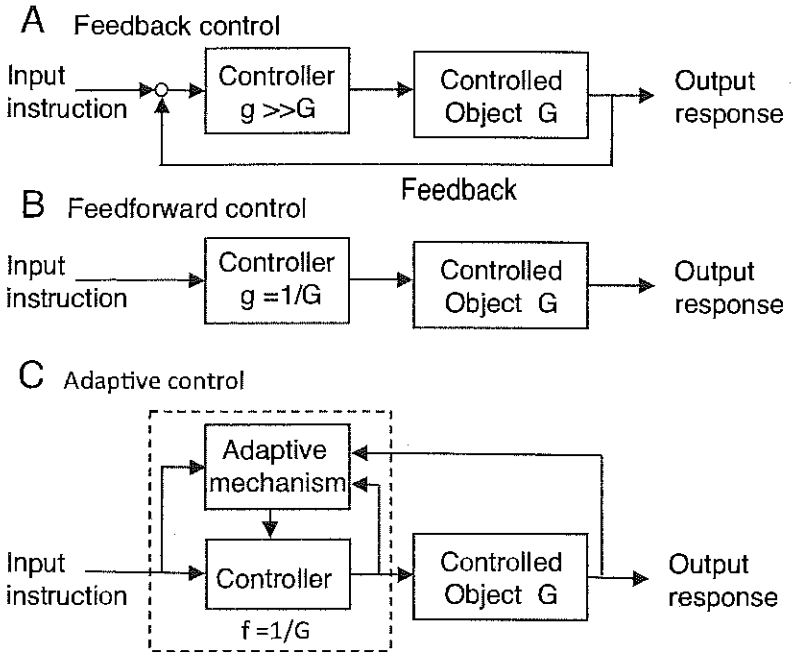

Figure 7 The fundamental structures of a control system.

(A) A basic feedback control system. (B) A basic feedforward control system. (C) An adaptive control system equipped with an adaptive mechanism. This schematic applies to the cerebellar control of reflexes.

In recent years, modern control theory studies have opened the new fields of "adaptive control" and "model-based control." In adaptive control, the controller is equipped with an adaptive mechanism to constitute an adaptive controller, which learns how to perform effectively in a given situation by altering its performance to match ever-changing environments. When a mechanism is attached to a feedforward controller, their overall input-output relationship f should be adjusted to 1/G (Figure 7C). On the other hand, model-based control was developed for robotic

arm control (An et al., 1988), and it has opened a new field of computational neuroscience for research on the cerebellum (Kawato et al., 1987).

In the model-based control, a feedforward control system (Figure 7B) is attached with one of the two types of internal models, "forward" and "inverse" (Figure 8A, B). An internal forward model simulates the kinematics of a controlled object, whereas an internal inverse model simulates the dynamics or kinetics of them (for a definition, see Chapter 15, "Internal Models for Voluntary Motor Control"). Internal forward models support the controller by predicting the state of the system during actual actions. On the other hand, internal inverse models map the relationship between intended actions (or goals) and the motor command to bring about the action. An internal inverse model uses the desired position of the body as inputs to estimate the necessary motor commands, which would transform the current position into the desired one. An adaptive mechanism is involved to secure close simulation by these models. Such models may be formed in various parts of the CNS including, in particular, the elaborate neuronal networks of the cerebellar and cerebral cortices. Hereafter, models formed in the cerebellum and cerebral cortex will be called "cerebellar internal models" and "cerebral cortical models," respectively.

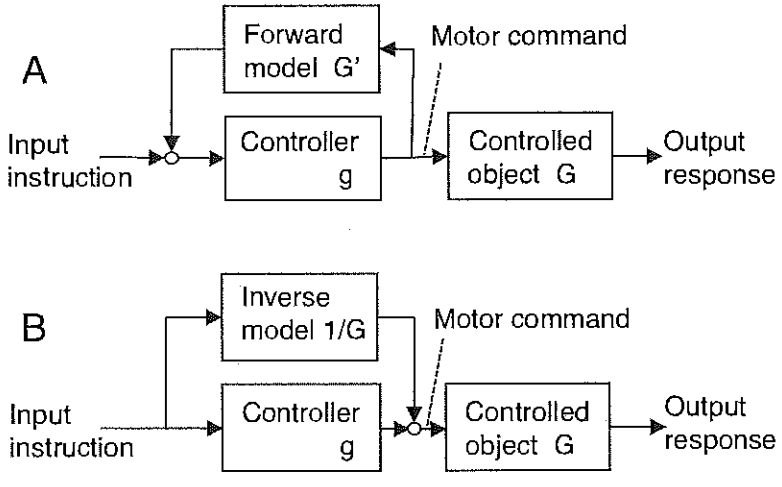

Figure 8 General forms of model-based control systems.

(A) Internal forward model (G') simulates the input-output relationship of the controlled object (G) and is inserted between the output and input of the controller (g). (B) Internal inverse model (1/G) simulates the output-input relationship of the controlled object (G) and is inserted between the input instruction and output response of the controller (g).

1-6 Reflexes and Voluntary Movements

The most fundamental control system structure in the CNS is an individual reflex operating via the spinal cord or brainstem. A reflex is performed by sequential activities in a neuronal circuit that connects serially sensory receptor cells, an afferent path, a reflex center, an efferent path, and an effector (a muscle, set of muscles, or a secretory gland or glands). This is typically exemplified by the stretch reflex, in which motoneurons maintain the length of a muscle constant by using feedback from muscle spindles (Chapter 11, "Somatic and Autonomic Reflexes"). In this case, a group of motoneurons and associated segmental interneurons constitute a controller, whereas the motor apparatus composed of the muscle(s) and a joint provides the controlled object. Numerous reflexes of various types operate in the spinal cord and brainstem to control simple somatic and visceral functions of a living body. The operation of reflexes is usually automatic—that is, it does not reach the level of conscious awareness—but in ever-changing environments it is indeed modifiable by use of adaptive mechanisms of the cerebellum (Chapters 10–12).

We traditionally consider voluntary movements as a much higher order of movements than reflexes in the sense that they are controlled by "free will" and can be performed both automatically and at the level of conscious awareness, whereas reflexes are driven by peripheral stimuli and executed solely by automatic means. However, as our understanding advances for neuronal mechanisms underlying volnntary movements, distinctions between such movements and reflexes become blnrred because many of the same neuronal circuits are employed for both types of movement (Prochazka et al., 2000; Hultborn, 2001). Practically speaking, however, we may still distinguish voluntary movements as initiated from the cerebral cortex, whereas reflexes operate largely within the spinal cord and brainstem. Typically, two cortical areas, the primary motor cortex and the frontal eye field, are involved in voluntary movements of the limbs and eyes, respectively (Chapters 13 and 14). In the systems control parlance emphasized in this volume, reflexes and voluntary movements may share neuronal circuits for their controller and controlled object structures, but they are separated from each other by the nature of the instruction signals that drive the controller. Instructions for reflexes arise from periphery, whereas voluntary movements are driven by "top down" instruction signals generated in higher centers of the cerebral cortex, including but not limited to the supplementary motor cortex and the anterior cingulate gyrus (see Chapter 13, "Voluntary Motor Control").

An interesting idea has been put forward to suggest that a central instruction causes a voluntary movement by an imitation or replacement of the peripheral stimulus that induces a reflex (the imitation hypothesis; Berkinblit et al., 1986). For instance, the CNS can voluntarily elicit a saccadic eye movement by means of the

imitation of the visual signals that could elicit the saccadic movement reflexively. In this sense, the central instruction may imply an "afference copy" of the peripheral stimulus. Such a capability of imitating a peripheral stimulus might emerge during evolution to develop a neuronal mechanism of voluntary motor control. Neuronal mechanisms underlying the postulated capability of imitation are unknown, but one may suppose that a group of neurons memorize those signals of peripheral stimuli that evoke a motor behavior reflexively and reproduce the same signals whenever a similar motor behavior is to be generated voluntarily. Here, one may recall the "mirror" neurons, which are present in certain cerebral cortical areas and are activated during both observed and performed hand actions, as discussed below (Section 8 and also in Chapter 16, "Motor Actions and Tool Use," Section 5). These neurons appear to memorize perceptive signals representing certain successful motor actions performed by another individual and reproduce them as central instructions for their own body's motor actions. Admittedly, however, the neuronal sites and mechanisms underlying free will in the high cerebral centers are still an enigma (Wegner, 2002).

1-7 Integration of reflexes

One of the major ideas that Sherrington outlined in his 1906 book "The Integrative Action of the Nervous System" was that complex actions of the nervous system could be composed of a collation of reflexes, somewhat like building a house by piling up bricks. From the control systems perspective, there now appear to be at least eight ways to integrate reflexes into the overall control of movement. First, many that are driven by different sensory inputs may share the same controller and controlled object (Figure 9A). For example, three types of relatively slow ocular reflexes are driven individually by vestibular or visual stimuli, as will be seen later in Chapter 10, "Ocular Reflexes." Nonetheless, they commonly share vestibular nuclear neurons as the controller, and eyeballs and the associated oculomotor system, as the controlled object. By this means, such a group of reflexes can achieve the common purpose of securing visual stability and acuity under natural behavioral conditions. In other words, these individual ocular reflexes are combined together to form a "multi-input" control system. Second, several individual reflexes may have different controllers (Figure 9B, Reflex 1, 2, 3 controllers), but they may share the same controlled object. For example, a slow ocular reflex can be integrated with a brisk saccade only in the form of half-fused control because these eye movements require controllers having substantially different properties for generating slow and brisk eye movements, respectively (Chapter 10). Third, reflexes may also be combined with a voluntary motor control system in a hybrid way (Figure

9C) because of the similarity of control system structures for reflexes and voluntary movements (see Section 6). Design problems in such hybrid systems will be discussed later (Chapter 15).

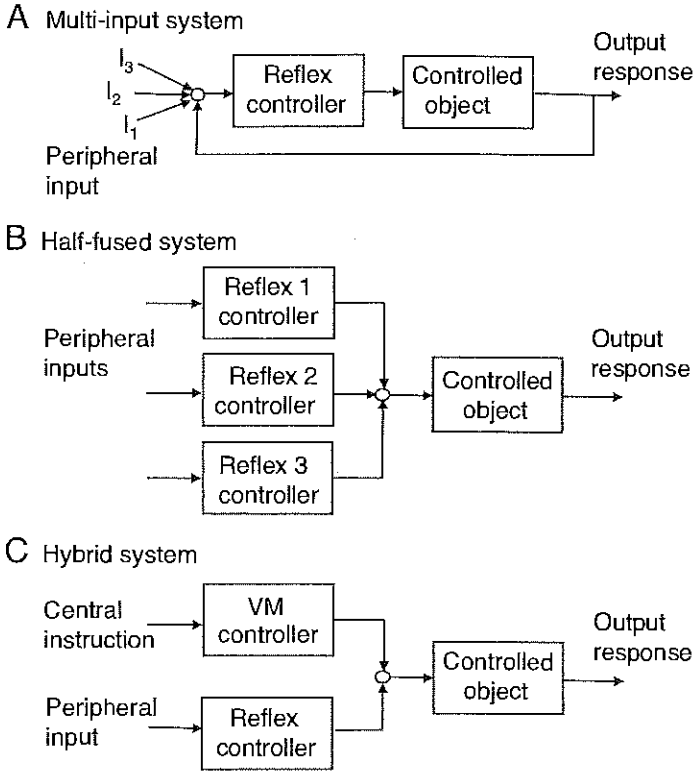

Figure 9 Schematics of types of integrated reflex control.

(A) A multi-input reflex. (B) Half-fused system. (C) Hybrid control of a reflex and a voluntary movement. For further explanation, see the text. Abbreviations: $I_{1,2,3}$, three sensory inputs of different modality; VM, voluntary movement.

The spinal cord and brainstem contain a collation of reflexes to elaborate compound movements such as when assuming a posture, or when walking, swimming, and flying. Hence, a fourth way of integration is for some reflexes to be combined by mutual interaction (Figure 10A, Reflexes 1 and 2). For example, when one explores the visible world, a saccade and a head movement, the latter inducing the vestibuoocular reflex, occur in combination. This eye-head coordination involves an inhibitory cross talk between the independent eye and head controllers (Kardamakis and Moschovakis, 2009). A fifth way is for reflexes to be compounded when signals in a descending tract activate some combinations of reflexes to express behaviorally meaningful compound reflexes (Figure 10B, for review, see

Lemon, 2008). Anders Lundberg (1920–2009) and his colleagues found a good example in the cervical segments of the spinal cord. In the C3–C4 propriospinal system of the cat, interneurons were shown to receive extensive convergence from different primary sensory afferents and supraspinal centers (Lundberg, 1999; Alstermark et al., 2007). Through excitation or inhibition of relevant interneurons in this system, signals of each descending tract could produce compound reflexes to provide desired movement patterns, such as target reaching by the hand (Chapter 13). Operation of segmental spinal circuits sometimes involves a type of function generator (FG in Figure 10B, b). Locomotion is a good example of this type of compounding reflex. It involves flexion reflexes, crossed extension reflexes, interlimb coordination, and, in addition, a central pattern generator (CPG) mechanism for rhythm generation (Grillner et al., 1991, 2007; Grillner and Jessel, 2009) (see Chapter 11).

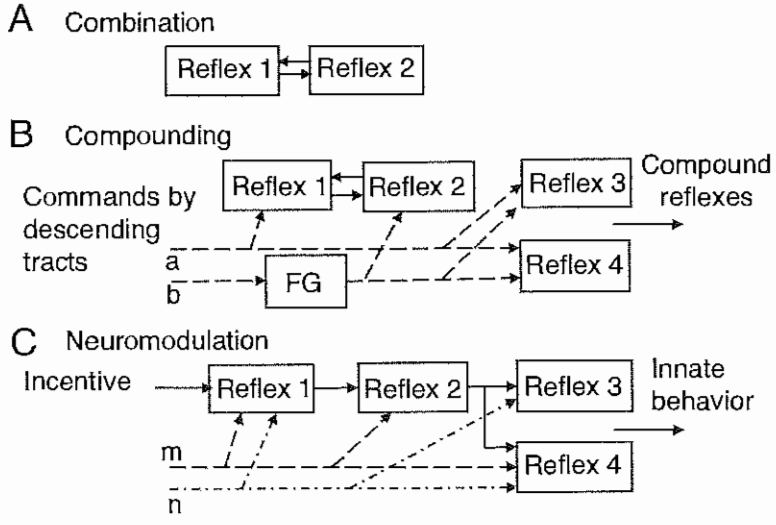

Figure 10 Schematics of the mutual interaction, compounding, and neuromodulation of reflexes.

Arrows denote synaptic actions, either excitatory or inhibitory. A shows how reflexes are combined by mutual interactions (Reflexes 1 and 2). In B, the compounding of reflexes 1, 3, and 4 is brought about by commands from descending tracts (a). Alternatively, reflexes 2, 3, and 4 can be coactivated by descending tracts (b) via FG, a function-generator. C shows how reflexes are modulated by aminergic and/or peptidergic innervation (represented by m and n) to exhibit a specific pattern of combination for behavior (m to reflexes 1, 2, and 4 and n to reflexes 1, 3, and 4). "Incentive" means a stimulus that leads to a specific behavior.

The sixth way to integrate reflexes is by "neuromodulation." As demonstrated in the crustacean stomatogastric nervous system (Marder et al., 1986; Selverston 1995), a small amount of a single peptide or amine may instantaneously rewire a neuronal circuit and switch behavior expression of the system. This mechanism may apply to the hypothalamus located in the most rostral and ventral part of the brainstem, which regulates innate behaviors including food intake, drinking, and reproduction; they are evoked by incentives such as the need for food, water, and reproductive activity, respectively. These behaviors involve a series of complex movements in order to approach and acquire the incentives. On the other hand, noxious stimuli such as drinking stale water or the figure of an enemy induce aversion, aggression, or defense reactions. An innate behavior involves a combination of reflexes and compound movements. For example, food intake involves locomotion to approach the food, rhythmic mastication, and the swallowing reflex. The hypothalamus contains a number of innate behavioral centers, each of which produces a specific pattern of behavior by secreting a neuromodulator substance through their widely distributed axons in the brainstem and spinal cord. The secreted neuromodulator substance may activate or inhibit a number of component reflexes and compounded movements (Figure 10C); hence, one circuit can be configured to perform a variety of different behaviors by activating neurons via certain types of neuromodulator receptors.

The seventh way to use reflexes, and probably the most important in regard to the cerebellum, is by "nesting" (as in "matryoshka"), which has been used to explain perceptual organization (Leyton, 1987) and even the entire hierarchical organization of the CNS (Baev, 1999). The nesting idea is that a reflex composed of a controller and controlled object at the lowest level can be regarded as a controlled object at the next higher level. For example, a stretch reflex is a control system at the segmental level (Figure 11A), but at a brainstem level, it acts as the controlled object of the vestibulospinal descending tract neurons, which act as the controller (Figure 11B). In a similar vein, the primary motor cortex acts as a controller of the spinal segmental circuits, which are the controlled objects (Figure 12A, B). Furthermore, the entire corticospinal system constitutes a controlled object for the premotor cortex, which serves as its controller (Figure 12C). Through use of this nesting principle, collective reflexes integrated in the previous six ways constitute a controlled object for a higher-level controller, which can thereby exert control over many reflexes in various combinations.

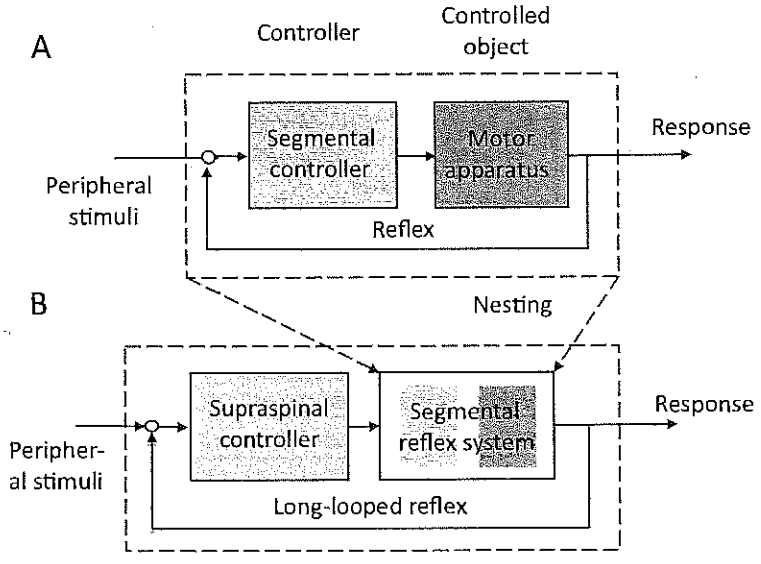

Figure 11 The one-step nesting of a reflex within a supraspinal controller.

(A) The control system structure of a segmental reflex. (B) A being nested within the controlled object of a supraspinal controller. For further details, see the text.

Finally, the imitation hypothesis discussed in Section 6 provides the eighth strategy used by the CNS to evolve voluntary motor control systems utilizing the reflex control systems formed in the brain stem and spinal cord as a basement structure.

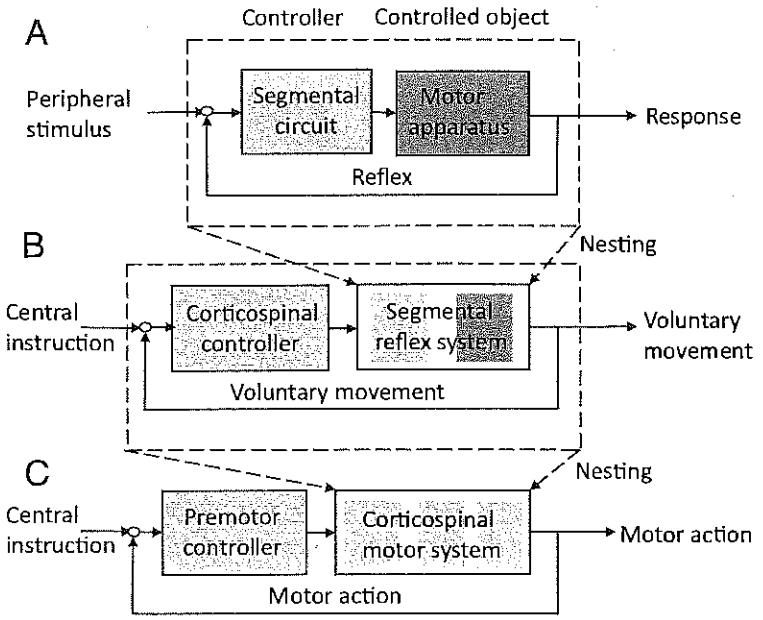

Figure 12 The two-step nesting of a reflex within the premotor cortical control of a motor action.

(A) and (B) are similar to those in Figure 11. (C) shows a further nesting for control at a cortical level.

1-8 Motor Actions

In the study of voluntary movements, the convention is to begin with analysis of a simple movement such as flexion of an elbow. However, voluntary movements that we perform daily are parts of "motor actions" that involve the participation of many body parts and even use of a tool to attain a purposeful goal. Moreover, motor actions also involve perceptual and conceptual activities, for example, in piano playing and dancing. It has been suggested that an "action schema" representing and coding motor actions is expressed in the posterior parietal and premotor (Broadmann's area 6, see Figure 2) cortices (Jeannerod, 1994). For the present purposes, an action schema can be considered to be a cerebral cortical model.

In primates, the premotor cortex expands rostrally from the primary motor cortex. It is generally assumed that the premotor cortex, in particular its dorsal part, plays a major role in computing and controlling complex motor actions (Wise et al., 1997). Moreover, the premotor cortex includes "mirror neurons," which discharge similarly during a motor action performed by the self or by another individual, as discovered by Rizzolatti and his colleagues (Rizzolatti and Craighero,

2004). Based on these and other lines of evidence presented in Chapter 16, we assume that the premotor cortex acts as the controller of motor actions. The premotor controllers act on controlled objects, which nest the primary motor cortex and lower motor systems (see Figure 12C). The postulated action schema is assumed to reside in the temporoparietal cortex and provide a cerebral cortical model to the premotor cortex. The same control system structure may apply to tool use if a tool is represented in an action schema together with body parts (Chapter 15).

Action schema may include two related concepts (actually CNS properties) that are prominent in psychology: the "body schema," which possesses a continually updating map of the self's body shape and postures; and the "motor schema," the self's long-term memory structure capable of being retrieved as a whole, and then controlling the elaboration of motor skills composed of complex actions and movements. Both schemata are acquired or at least further refined by learning (Arbib, 2005; Stamenov, 2005). Along with the model-based control concepts discussed above (Section 5), these body/motor schemata can be considered as components of cerebral cortical models representing the forward and inverse models of the controlled object (Figure 8). These cerebral cortical models are presumably acquired during the initial learning of motor actions. As learning advances, the acquired body schema and motor schemata are transferred to cerebellar internal models (Chapter 15).

1-9 Thought as a Control Mechanism

The various forms of control systems discussed above operate in the physical domain. Our CNS moves various body parts daily by contracting or relaxing muscles to make a purposeful movement. Analogously, we manipulate daily a thought in the mental domain. For example, we use languages, make evaluations, and come to decisions, these being major components of human intelligence. Formalistically, as a controlled object, an idea or concept in the mental domain is analogous to a body limb in the physical domain. At present, however, there is as yet no experimental or computational way to bridge the physical and mental domains that operate in the CNS. Hence, any postulated thought control mechanism has no unequivocal representation in neuroscience.

Nevertheless, we find some concepts in the field of psychology that mediate physical and mental domains. For example, there is the term "mental model," which Craik (1943) and Johnson-Laird (1983) defined as a psychological substrate for a mental representation of real or imaginary situations. It is defined as a small-scale model of reality that the mind constructs and uses to reason, underlie

explanations, and anticipate a future event. More concretely, mental models in psychology are representations of images, concepts, and ideas. One may also recall another term in psychology called "schema," which Jean Piaget (1896–1980) defined as being formed in a growing child learning to interpret and understand the surrounding world (Piaget, 1951). Piaget's schema includes both a category of knowledge and the process of obtaining that knowledge.

Currently, the above two concepts are not mechanistic, and they lack a computational basis. Hence, the examples presented below in Chapter 17, "Cognitive Functions," are largely hypothetical. Nevertheless, I believe that once neural correlates of a mental model and Piaget's schema have been established, the present well-accepted control system models that exist in the physical domain will be shown to also apply to the mental domain, and thereby help understand various cognitive mechanisms.

1-10 Beyond Movements

Figure 8, which shows model-based control system designs, may be referred to for considering a mental model as a controlled object. For the present, computer simulation cannot reproduce this model because it lacks a computational basis. This difficulty is like the one that arose in the field of artificial intelligence. More than 50 years ago, a group of computer scientists proposed a study that would "... proceed on the basis of the conjecture that every aspect of learning or any other feature of intelligence can in principle be so precisely described that a machine can be made to simulate it." These scientists were eager to make "... an attempt to find how to make computers that use language, form abstractions and concepts, solve kinds of problems now reserved for humans, and improve themselves" (McCarthy et al., 1955). This tempting approach in artificial intelligence, however, remains unsuccessful because it lacks the clarification provided by neural network mechanisms that can encode a concept or a specific piece of knowledge.

Another profound question is how the operation of a neuronal circuit can be undertaken with conscious awareness. Sigmund Freud (1856–1939) and many more recent researchers have emphasized that only a few of the activities of the CNS are executed consciously. For example, one cannot bring to conscious awareness the thought processes involved in improving motor skills (e.g., skiing) by training (non-declarative memory). In contrast, one can readily recall cognitive experiences (declarative memory) (Squire, 2009). In other words, the neuronal circuits implicated in non-declarative memory are remote from the mechanisms of conscious awareness, whereas those involved in declarative memory are closely connected to conscious awareness. On the other hand, it has been shown that

electric or transcranial magnetic stimulation (TMS) of the neocortex usually evokes vivid sensations or perceptions (Penfield and Perot, 1963; Coway and Welsh 2001), whereas stimulation of the cerebellum (Riklan et al., 1976; Koch et al., 2006) and basal ganglia (Chen et al., 2006) has no impact on conscious awareness. Conventionally, intelligence has been considered to require consciously activated cortical functions, but a substantial part of it is probably exerted subcortically and consequently unconsciously. In fact, intuitive thought is an important part of intelligence, but it is exerted uuconsciously without obvious reasoning (Chapter 17).

Neuroscience has reached a level of sophistication that is on the verge of addressing neural mechanisms underlying intelligence and conscious awareness. It seems likely that research on the cerebellum will be on the forefront of this endeavor.

1-11 Scope of This Monograph

In the chapters that follow, the neuronal circuits of the cerebellum are decomposed and reconstructed as explained in this chapter. Early and recent historical material is presented in Chapters 2 and 3, and Chapters 4–9 update uuderstanding of the cerebellum as an elaborate neuronal and molecular machine. Next, recent progress is presented about how this machine provides an advanced type of systems control for reflexes (Chapters 10–12) and voluntary movements (Chapters 13–15). The material covered in Chapters 10–15 reviews findings that came mainly after my 1984 book, *The Cerebellum and Neural Control*, and Barlow's 2002 monograph, *The Cerebellum and Adaptive Control*. Chapters 16 and 17 examine the new possibility that the involvement of the cerebellum goes beyond movements to the higher-level functions of motor actions and cognition. The last Chapter 18, "Concluding Thoughts," includes a summary of points made in preceding chapters about structural-functional relationships in neuronal circuit structures of the cerebellum as developed step by step in evolution.

1-12 Summary

The decomposition-reconstruction method provides a logical and effective approach to studying the structure-function relationships of neuronal circuits. They are composed of local multilayered networks that interconnect globally to form neural control systems. Reflexes are the most fundamental units of neuronal circuits. Multi-input, half-fused, hybridized, mutually interacting, compounding, neuromodulating, nesting, and imitating are the eight ways to integrate reflexes into complex movements, voluntary movements, and innate behavior. A further integrated control is needed for both motor actions and, as yet to be determined, the mechanisms of cognitive thought.

2

Traditional Views of the Cerebellum

2-1 Introduction

The cerebellum is a regular part of the CNS in vertebrate animals. It is recognized in lampreys, fish, amphibians, reptiles, birds, and mammals, up to humans. Among nonvertebrate animals, a cerebellum-like structure has been reported in octopus ganglia (Hochner et al., 2006), but its presence in other nonvertebrate species is unclear. The unique morphology of the cerebellum has been studied thoroughly for over a century. This led to the establishment of a map commonly applicable to various animals. Characteristically, the map initially involved the cerebellum's connections with the vestibular nuclei in the medulla oblongata and with the spinal cord. The map then expanded in parallel with the further evolutionary development of the cerebral cortex. Distinctive involvement of the cerebellum in the acquisition of motor skills has also been uncovered on the basis of a large amount of data accumulated from lesion studies on animals and clinical investigations in humans. Furthermore, the cerebellum has been examined extensively by microscopy, revealing the presence of Purkinje cells and other cells of unique morphology. In this chapter, we trace the history of how these traditional views of the cerebellum have been formulated.

2-2 Morphological Map

Erasistratus (304–250 BC) of Greece distinguished the cerebrum from the cerebellum (Malomo et al., 2006). Anatomical descriptions of the brain were almost complete during the Renaissance period, as we see in fine sketches of human brains drawn at that time. In the middle of the twentieth century, the characteristic morphology of the cerebellum was rigorously analyzed, and the data were compiled in two monumental volumes (Jansen and Brodal, 1954; Larsell, 1970).

When viewed from above, the mammalian cerebellum appears like a butterfly (Color Plate I). The middle part lying along the anterior-posterior axis is called the vermis because of its wormlike appearance. From the vermis, the hemispheres expand to the right and left like wings. Deep grooves divide the wings into three parts; the primary fissure separates the anterior and posterior lobes, and the posterolateral fissure separates the flocculonodular lobe from the posterior lobe. These divisions are further subdivided by transversely running grooves into individually named lobules (Color Plate II). Each lobule contains shallow folds, i.e., folia. The cerebellum is subject to a greater range of species variations than any other parts of the brain, but after much effort for over a century, anatomists reached a fundamental design of the cerebellum common to various vertebrate species (Larsell, 1970). It consists of ten divisions (lobules I–X) anteroposteriorly laid along the vermis and their transverse expansion into the hemispheres (lobules HI–HX). These divisions are shown schematically in an unfolded surface of the cerebellum (Color Plate II).

Comparison of cerebella in various vertebrate species reveals the evolutionary origin of the lobal and lobular structures of the cerebellum. The flocculonodular lobe is phylogenetically the oldest (thus called the archicerebellum) and closely associated with the vestibular organ (thus called the vestibulocerebellum). The vermis is also old (paleocerebellum), and it is closely associated with the spinal cord (spinocerebellum). The cerebellar hemispheres are "new," being expanded in mammals and primates in association with the development of the cerebral neocortex (neocerebellum or cerebrocerebellum). Particularly notable are the large paraflocculus in the porpoise and whale, the wide ansoparamedian lobule in the monkey, and the width of the entire hemisphere in the human.

In addition to the right-left transversal lobular structure, the cerebellum is also divided into a number of longitudinal zones by various landmarks (Voogd, 1964; Groenewegen and Voogd, 1977; Groenewegen et al., 1979). First, the connections from the cerebellar cortex to the cerebellar nuclei by Purkinje cell axons are organized in three parts. The vermis is connected to the medial (fastigial) nucleus, the intermediate part of the hemispheres to the interpositus nucleus (in humans, emboliform and globose nuclei), and the lateral part of the hemispheres to the lateral nucleus (dentate nucleus in primates) (Color Plate III). In addition, a part of the vermis and the flocculonodular lobe are connected directly to the vestibular and other nuclei in the medulla oblongata. Second, in the afferent projection from the inferior olive (IO) to the cerebellar cortex, each small area of the IO projects to an anteroposteriorly extended longitudinal zone of the cerebellar cortex (Color Plate III). In this projection, seven major zones (A, B, C_1, C_2, C_3, D_1, and D_2) are distinguished. The A and B zones are in the vermis, whereas the C_1, C_2, and C_3

zones cover the intermediate part of the hemispheres. The D_1 and D_2 zones are in the lateral part of the hemispheres. Third, a peptide, zebrin, distributes unevenly in the cerebellar cortex and marks the seven zones (Leclerc et al., 1992). A number of marker molecules are now available to label the longitudinal bands. Additional zones such as A_2-, X-, Y-, and D_0- zones have been defined (see Apps and Hawkes, 2005); they are not shown in Color Plates II and III. An interesting finding used intraventricular injection of adenovirus-carried markers, which labeled neuronal progenitor cells in a birth date-specific manner. Such injection in embryonic mice revealed that a cohort of Purkinje cells generated by mitosis on the same day formed a specific set of longitudinal bands, whereas Purkinje cells born one day earlier or later formed different sets of such bands (Hashimoto and Mikoshiba, 2004).

The horizontal lobules and longitudinal bands form a latticed map that divides the cerebellar surface into nearly a hundred small areas (Color Plate II)). This lattice provides a guide map for exploration of the cerebellum. Earlier, Bolk (1906) noticed in the giraffe that the lobule simplex (lobule VI) was extraordinarily large. In view of the giraffe's long neck, he pointed out the possibility that this cerebellar area was for the precise control of the long neck by powerful shoulder muscles (Glickstein and Voogd, 1955). Bolk's idea of a single somatotopical map in the cerebellum does not hold for the entire cerebellum, but it pointed to the presence of functional localization in the cerebellar cortex (Manni and Petrosini, 2004). The elephant with a long trunk that is used like a human hand has an extraordinarily large cerebellum (18.6% of the total brain, as contrasted to 10% to 11% in humans), but no regional expansion has been described yet as specifically related to this animal's nose (Shoshani et al., 2006).

Another interesting and long-standing question concerns the prominent difference in the maps of the cerebellum of whales versus primates. In human and nonhuman primates, the cerebellum expands laterally, particularly in crus I and crus II (part of lobule HVII). The large cerebellum in whales (20% to 25% of the total brain), however, is due to an expansion of the paraflocculus, which occupies about three-fourths of the cerebellar surface (Oelschläger, 2008; Oelschläger and Oelschläger, 2009). It has been suggested that the whale's large paraflocculus is a result of its adaptation to aquatic life, in which echolocation and acoustic communication are essential for survival and a meaningful social life (Oelschläger, 2000). In this regard, it is interesting that in the rat, the auditory cortex projects to the paraflocculus via the pontine nucleus (Azizi et al., 1985). In bats, which possess supersonic echolocation, the paraflocculus neurons respond to acoustic stimuli, specifically to their first harmonics (Horikawa aud Suga, 1986). Hence, it is

probable that the paraflocculus is involved in echolocation and acoustic communication. The question of how the cerebellum contributes to such sonar systems will be discussed later in connection with its role in "sensory cancellation" (i.e., cancelling sensory perturbations evoked by self-initiated movements; Chapters 15 and 18). A large expansion of the ventral paraflocculus has been recognized in the endocast of a Cretaceous multituberculate, a mouse-sized mammal that appeared 130 million years ago and became extinct 90 million years later (Kielan-Jaworowska, 1986). It is interesting to speculate that this mammalian species also developed a sonar system for communication in the dark with the aid of the paraflocculus.

Another unique development is observed in the cerebellar valvula of mormyrid fish. This is basically a rostral protrusion of the cerebellum in the midbrain ventricle and much enlarged and folded over the brainstem and the telencephalon (Shi et al., 2008). The valvula is characterized by the prominent pattern of ridges on its dorsal surface. The valvula has been called a gigantocerebellum and intensively studied by neuroanatomists (Nieuwenhuys and Nicholson, 1967). It shares the general and basic organizational features with all other cerebella and cerebellar subdivisions but has in addition a number of unique features. For example, the efferent cells (corresponding to cerebellar nuclear neurons in Chapter 6, "Pre- and Post-Cerebellar Cortex Neurons") are located close to Purkinje cells, and there are numerous deep stellate cells supplying specific inhibitory projections to efferent cells (Meek et al., 2008). This does not occur in usual cerebella (see Chapter 5, "Inhibitory Interneurons and Glial Cells in the Cerebellar Cortex"). Because the valvula receives much of its input from the electrosensory system, its role in electrosensation is probable (Finger et al., 1981).

The latticed areas have common homogenous microscopic structures, as will be examined later. In functional terms, they play diverse roles in connection with other divisions of the brain and spinal cord. It appears that numerous small "computers" of uniform structure and function are utilized individually for diverse purposes. The still remaining large blank in the mosaic map of the cerebellum implies that many more concrete roles of the cerebellum are yet to be identified.

2-3 Motor Skills

In addition to the comparative anatomy mentioned previously, valuable strategy used widely in neuroscience research is to place a lesion in a brain and test for subsequent dysfunctions. Cutting, ablating, coagulating, and injecting certain toxic amino acids into brain tissues have been used to make lesions. Clinical cases with discrete cerebellar lesions also provide similarly useful data. Dow and Moruzzi

(1958) compiled such data from lesion studies collected up to the middle of the twentieth century. Transient blockade of functions by applying various pharmacological inhibitors or antagonists is a further development, and most recently, genetic manipulation has become a powerful tool to form a lesion in a specific element of neuronal circuits. Elaborate test paradigms for detecting lesion-induced behavioral disorders have also been developed recently.

It is interesting that in phrenology, as initiated by Franz Joseph Gall (1758–1828), the occipital part of the cranium that overlies the cerebellum was assigned as the center of love. This assertion was groundless, but it apparently stimulated pioneers of the nineteenth century. Luigi Rolando (1773–1831) removed the cerebellum in various animals and found subsequent motor disturbances. Jean Pierre Flourens (1794–1867) ablated the cock cerebellum, but seeing the cock still seeming to be attracted to a hen, he discarded the phrenological hypothesis (Glickstein et al., 2009). Flourens (1822) also observed that animals with a lesioned cerebellum still moved spontaneously, but only clumsily. He concluded that the cerebellum was responsible for movement coordination, in contrast to the cerebrum, which initiated movements via the spinal cord. This was amazing insight for a nineteenth century scientist!

In the early twentieth century, clinical neurology revealed that cerebellar dysfunction in humans was characterized by the loss of smooth, precise movements. Babinsky (1857–1932) defined dysmetria as a characteristic symptom of cerebellar dysfunction. A simple clinical test for dysmetria is a patient's failure, with the eyes closed, to quickly and accurately touch the nose with an index finger (Chapter 15, "Internal Models for Voluntary Motor Control"). During World War I, Gordon Holmes (1876–1965) examined soldiers with a discrete gunshot wound in the cerebellum. He found that they exhibited a significantly slower onset of arm retraction on the damaged side. The cerebellum thus appeared to be required for a movement that was too quick to be influenced by sensory feedback. Intention tremor is another symptom frequently observed in cerebellar patients. It is characterized by coarse trembling of a forelimb, which is accentuated by the execution of purposeful voluntary movements such as reaching by the hand. It may expand to involve the head, eyes, and the upper half of the body. Intention tremor has been reproduced in monkeys by cooling the dentate and interpositus nuclei (Flament and Hore, 1988). It thus appears that the cerebellum normally prevents intrinsic potential oscillations to ensure smooth movements.

Early on, such subtle control of movements suggested the need for a form of motor learning in the cerebellum. In fact, there were classic observations that suggested the learning capabilities of the cerebellum. Flourens (1842) removed the

superior half of the cerebellum in a young cock and observed 15 days later that equilibrium was totally reestablished. However, when he removed the entire cerebellum from a hen, it did not recover its equilibrium even four months after the operation. Luciani (1891) reported a notable observation in 1891. He made a partial lesion in the cerebellum of a dog. After the animal's full recovery, he placed a second lesion adjacent to the original one. A severe motor disturbance ensued as if to suggest that the first and second lesions were made at the same time. This was interpreted to mean that the second lesioned area was involved in recovery from the first lesion. Moruzzi (1910–1986) and his group postulated that cerebellar circuits either have a learning capability in and of themselves, or they are required for recalling a memory stored somewhere else in the CNS (Batini et al., 1976). They apparently considered that the cerebral cortex was a possible memory site, because of the observation that a later cerebral lesion cancelled motor recovery after cerebellar ablation.

The capability of cerebellar circuits to recover from and compensate for a functional deficit, as demonstrated in animals, argues against a perplexing question we sometimes face: why does a human who lacks a cerebellum, as is sometimes reported, exhibit no obvious dysfunction? Glickstein (1994) examined a number of such individuals and reported that the cerebellum was still present, albeit severely atrophied. He also emphasized that individuals with such an atrophied cerebellum definitely exhibited certain abnormal motor behavior. It seems likely that the viable portion of the cerebellum may compensate for deficits produced by its damaged portions. Possibly, the cerebral cortex provides additional compensation.

Experimental lesion studies and clinical observations have certainly highlighted the involvement of the cerebellum in the control of movement. As a result, the popular idea that the cerebellum is solely a motor center has tended to prevail. However, Moruzzi (1940) recognized several decades ago that the cerebellum contributed to both cardiovascular and respiratory regulation. The involvement of the cerebellum in mental activities has been suggested, albeit only occasionally and mainly on the basis of clinical observations that focused until recently on disturbances in expression using spoken words and gestures (Chapter 17, "Cognitive Functions").

2-4 Microscopic Features

In 1837, Jan E. Purkinje (1787–1869) observed cerebellar tissues under a microscope and found oval objects. These were the first individual neurons observed in the literature, and they are now called "Purkinje cells." In the early twentieth century, using the amazing silver staining method, Cajal observed and drew intricate

neuronal network structures that he found throughout the brain (Ramón y Cajal, 1911; Sotelo, 2003). In the cerebellum, he depicted the characteristic morphology of Purkinje cells, Golgi cells, basket cells, stellate cells, and granule cells (Color Plate IV). He also identified mossy fiber and climbing fiber terminals. His drawings even indicated the possible directions of neuronal signals conducted and transmitted from one cell to another. These elements are arranged in three layers (molecular layer, Purkinje cell layer, and granular layer). The structure is homogenous throughout the cerebellar cortex except for some regional differences. The tradition of Cajal's fine microscopic anatomy was continued by a number of distinguished anatomists, aud in the 1960s it was further advanced by the widespread contributions of electron microscopists.

As a harbinger of the coming breakthrough in the 1960s, some important findings were reported in the 1950s. Ragner Granit (1900–1991) and Charles Phillips (1916–1994) used microelectrode recording to demonstrate the antidromic spikes of Purkinje cells and the so-called D potentials. The latter corresponded to intracellularly recorded climbing fiber responses (Granit and Phillips, 1956). Janos Szentágothai (1912–1994) and coworkers identified the origin of climbing fibers in the IO. They surmised from the pattern of connections among granule cells, Purkinje cells, and basket cells that basket cells were iuhibitory neurons (Szentágothai and Palkovits, 1959; Szentágothai, 1963).

2-5 Summary

Morphological studies revealed evolution-related structural-functional maps of the cerebellum, and lesion studies established the specific involvement of the cerebellum in the learning of precise movements. These studies laid a firm foundation for the modern approach to the cerebellum, which focuses on neuronal circuits that are discussed in later chapters.

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 nniformly 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 nenrons. At that time, there were the beliefs that (1) large nenrons 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 nenrons 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*.

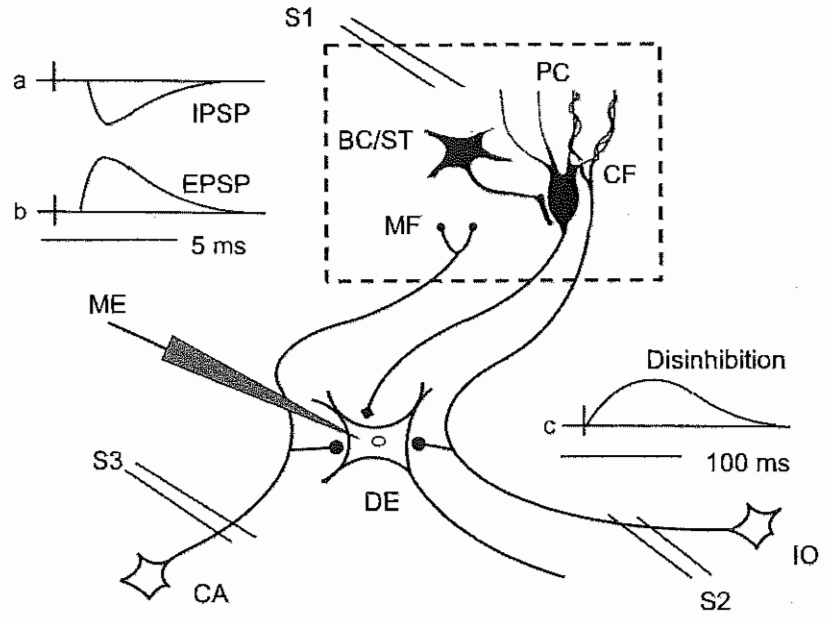

Figure 13 Schematic neuronal circuit showing how electrical stimulation of the cerebellar cortex induces three major effects in Deiters neurons.

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 disibhibitory 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

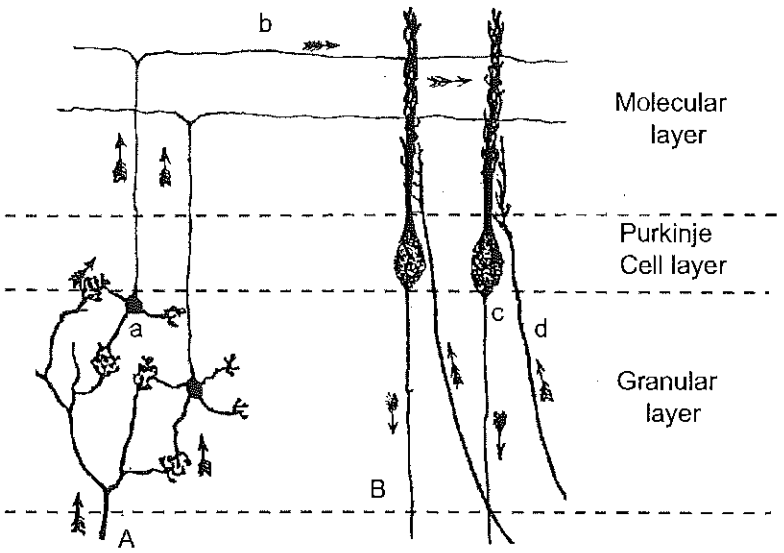

Figure 14 Convergence of climbing and parallel fibers onto Purkinje cells.

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.

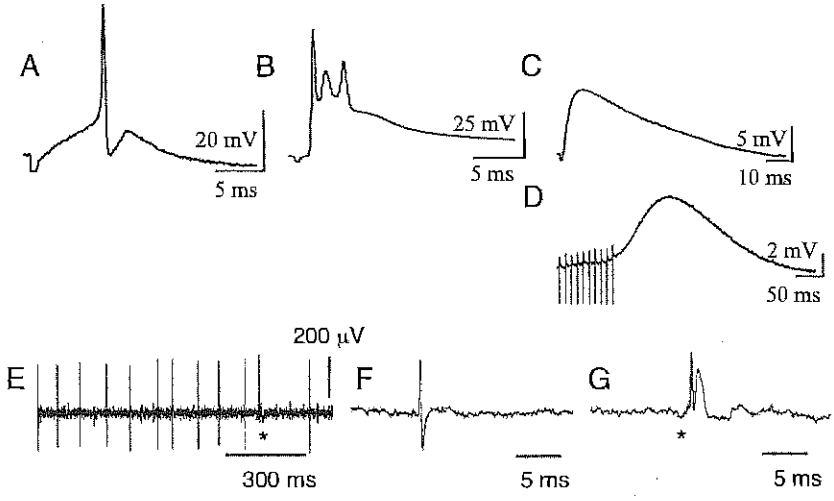

Figure 15 Bioelectric potentials of Purkinje cells.

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) mGluR-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").

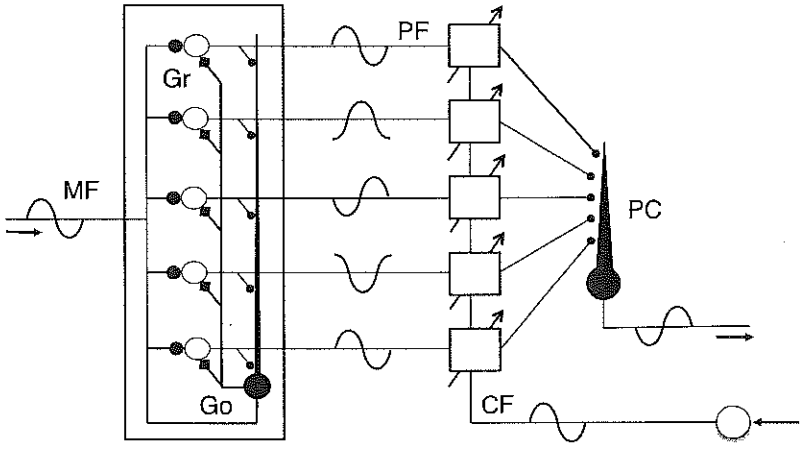

Figure 16 Adaptive filter model of the cerebellum.

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* snch 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.

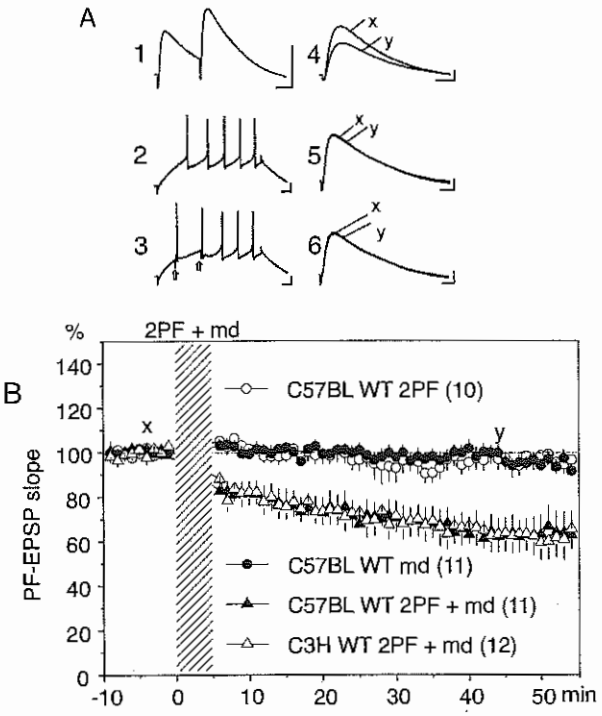

Figure 17 Induction of LTD in a slice of the cerebellum.

(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 au 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 exterual 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, aud 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").

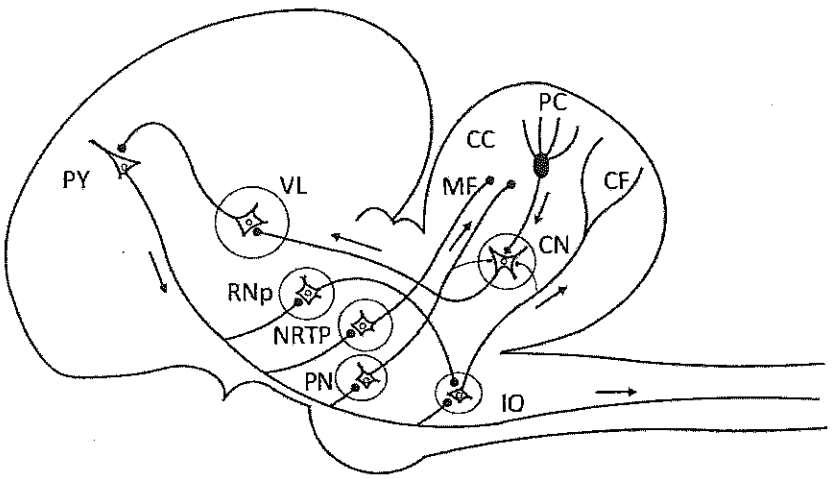

Figure 18 The cerebrocerebellar loops.

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 amplitnde 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 beeu 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 ueurons in the cerebellum, extendiug magnificent planar deudrites 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 spiues 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 Purkiuje 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.