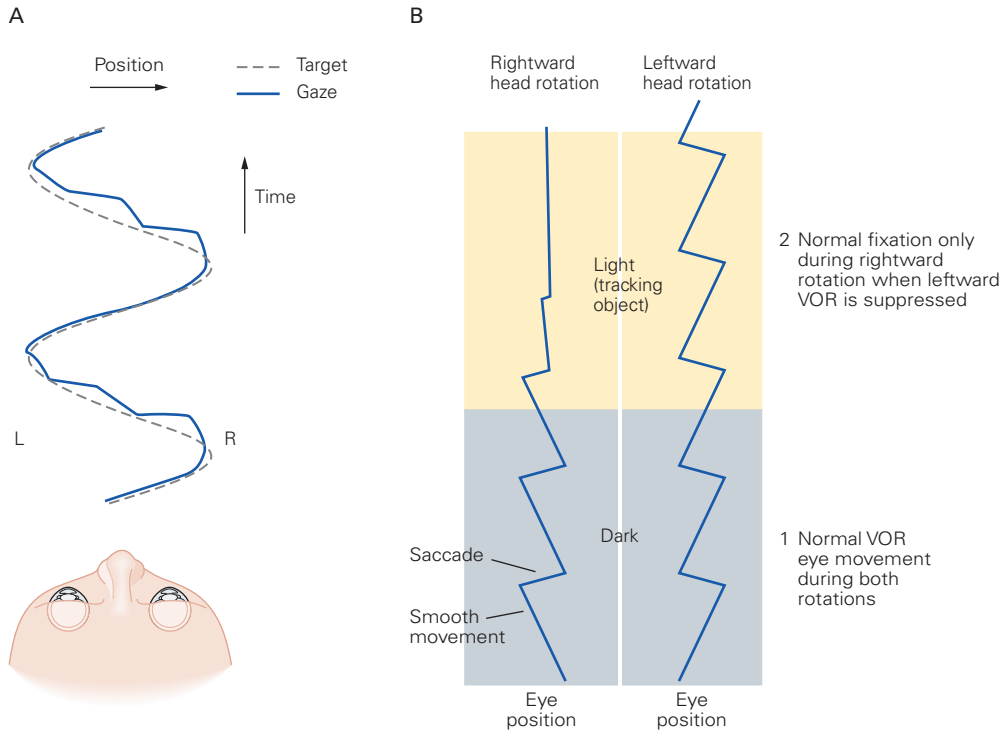

Figure 37–6 Lesions in the vestibulocerebellum have large effects on smooth-pursuit eye movements.

A. Sinusoidal target motion is tracked with smooth-pursuit eye movements as the target moves from left (**L**) to right (**R**). With a lesion of the left vestibulocerebellum, smooth pursuit is punctuated by saccades when the target moves from right to left.

B. In the same patient, responses to vestibular stimulation are normal, whereas object fixation is disrupted during leftward rotation. The traces on the left and right show the eye movements evoked by rightward and leftward head rotation experienced in separate sessions. In each session the patient sat in a chair that rotated continuously in one direction, first in the dark then in the light while fixating on a target that moves along with him. (**1**) In the dark, the eyes show a normal vestibulo-ocular reflex (**VOR**) during rotation in both directions: The eyes move smoothly in the direction opposite to the head's rotation, then reset with saccades in the direction of head rotation. (**2**) In the light, the eye position during rightward head rotation is normal: Fixation on the target is excellent and the vestibulo-ocular reflex is suppressed. During leftward head rotation, however, the subject is unable to fixate on the object and the vestibulo-ocular reflex cannot be suppressed.

vestibulocerebellum is compressed by an acoustic neuroma, a benign tumor that grows on the eighth cranial nerve as it courses directly beneath the lateral vestibulocerebellum.

The *spinocerebellum* is composed of the vermis and intermediate parts of the cerebellar hemispheres (Figure 37–4). It is so named because it receives extensive input from the spinal cord via the dorsal and ventral spinocerebellar tracts. These pathways convey information about touch, pressure, and limb position as well as the spiking activity of spinal interneurons. Thus, these inputs provide the cerebellum with varied information about the changing state of the organism and its environment.

The vermis receives visual, auditory, and vestibular input as well as somatic sensory input from the head and proximal parts of the body. It projects by way of the fastigial nucleus to cortical and brain stem regions that give rise to the medial descending systems controlling proximal muscles of the body and limbs (Figure 37–5A). The vermis governs posture and locomotion as well as eye movements. For example, lesions of the oculomotor region of the vermis cause saccadic eye movements that overshoot their target, much as patients with cerebellar damage make arm movements that overshoot their target.

The adjacent intermediate parts of the hemispheres also receive somatosensory input from the limbs. Neurons here project to the interposed nucleus, which provides inputs to lateral corticospinal and rubrospinal systems on the contralateral side of the brain and controls the more distal muscles of the limbs and digits (Figure 37–5B). Because corticospinal and rubrospinal systems cross the midline as they descend to the spinal cord, cerebellar lesions disrupt ipsilateral limb movements.

The *cerebrocerebellum* comprises the lateral parts of the hemispheres (Figure 37–4). These areas are phylogenetically the most recent and are much larger relative to the rest of the cerebellum in humans and apes than in monkeys and cats. Almost all of the inputs to and outputs from this region involve connections with the cerebral cortex. The output is transmitted through the dentate nucleus, which projects via the thalamus to contralateral motor, premotor, parietal, and prefrontal cortices. The dentate nucleus also projects to the contralateral red nucleus. The lateral hemispheres have many functions but seem to participate most extensively in planning and executing movement. They also have a role in cognitive functions unconnected with motor planning, such as visuospatial and language processes. There is now some correlative evidence implicating the cerebellar hemispheres in aspects of schizophrenia (Chapter 60), dystonia (Chapter 38), and autism (Chapter 62).

Two important principles of cerebellar function have emerged from recordings of the action potentials of single neurons in the cerebellar cortex and deep cerebellar nuclei during arm movements, along with controlled, temporary inactivation of specific cerebellar regions.

First, neurons in these areas discharge vigorously in relation to voluntary movements. Cerebellar output is related to the direction and speed of movement. The deep nuclei are organized into somatotopic maps of different limbs and joints, as in the motor cortex, although the organization of the cerebellar cortex has been characterized as "fractured somatotopy" with multiple disconnected and partial maps. Moreover, the interval between the onset of modulation of the firing of cerebellar neurons and movement is remarkably similar to that for neurons in the motor cortex. This result emphasizes the cerebellum's participation in recurrent circuits that operate synchronously with the cerebral cortex.

Second, the cerebellum provides feedforward control of muscle contractions to regulate the timing of movements. Rather than awaiting sensory feedback, cerebellar output anticipates the muscular contractions that will be needed to bring a movement smoothly, accurately, and quickly to its desired endpoint. Failure of these mechanisms causes the intention tremor of cerebellar disorders. For example, a rapid single-joint movement is initiated by the contraction of an agonist muscle and terminated by an appropriately timed contraction of the antagonist. The contraction of the antagonist starts early in the movement, well before there has been time for sensory feedback to reach the brain, and therefore must be programmed as part of the movement. When the dentate and interposed nuclei are experimentally inactivated, however, contraction of the antagonist muscle is delayed until the limb has overshot its target. The programmed anticipatory contraction of the antagonist in normal movements is replaced by a correction driven by sensory feedback. This correction is itself dysmetric and results in another error, necessitating a new adjustment (Figure 37–7).

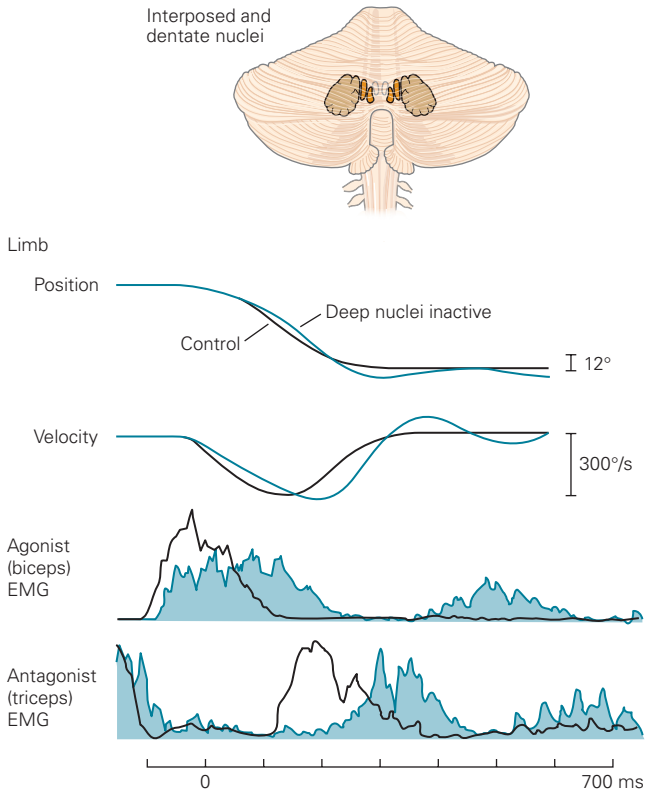

Figure 37–7 **The interposed and dentate nuclei are involved in the precise timing of agonist and antagonist activation during rapid movements.** The interposed (medial) and dentate (lateral) nuclei are highlighted in the drawing of the cerebellum. The records of limb movement show how a monkey normally makes a rapid elbow flexion limb movement and attempts to make the same movement when the interposed and dentate nuclei are inactivated by cooling. The electromyographic (EMG) traces show limb position and velocity and EMG responses of the biceps and triceps muscles. When the deep nuclei are inactivated, activation of the agonist (biceps) becomes slower and more prolonged. Activation of the antagonist (triceps), which is needed to stop the movement at the correct location, is likewise delayed and protracted so that the initial movement overshoots its appropriate extent. Delays in successive phases of the movement produce oscillations similar to the terminal tremor seen in patients with cerebellar damage.

The Cerebellar Cortex Comprises Repeating Functional Units Having the Same Basic Microcircuit

The cellular organization of the microcircuit in the cerebellar cortex is striking, and one of the premises of cerebellar research has been that the details of the microcircuit are an important clue to how the cerebellum works. In this section, we describe three major features of the microcircuit.

The Cerebellar Cortex Is Organized Into Three Functionally Specialized Layers

The three layers of the cerebellar cortex contain distinct kinds of neurons and are functionally specialized (Figure 37–8).

The deepest, or *granular layer*, is the input layer. It contains a vast number of granule cells, estimated at 100 billion, which appear in histological sections as small, densely packed, darkly stained nuclei. The granular layer also contains a few larger Golgi cells and, in some cerebellar regions, a smattering of other neurons such as cells of Lugaro, unipolar brush cells, and chandelier cells. The mossy fibers, one of the two principal afferent inputs to the cerebellum, terminate in this layer. The bulbous terminals of the mossy fibers excite granule cells and Golgi neurons in synaptic complexes called *cerebellar glomeruli* (Figure 37–8). As we will see later when discussing recurrent circuits in the cerebellum, Golgi cells inhibit granule cells.

The middle or *Purkinje cell layer* is the output layer of the cerebellar cortex. This layer consists of a single sheet of Purkinje cell bodies, each 50 to 80 μm in diameter. The fan-like dendritic trees of Purkinje cells extend upward into the molecular layer where they receive inputs from the second major type of afferent to the cerebellum, the climbing fibers, as well as from granule cells and inhibitory interneurons. Purkinje cell axons conduct the entire output of the cerebellar cortex, projecting to the deep nuclei in the underlying white matter or to the vestibular nuclei in the brain stem, where they release the inhibitory transmitter GABA (γ-aminobutyric acid).

The outermost or *molecular layer* contains the spatially polarized dendrites of Purkinje cells, which extend approximately 1 to 3 mm in the anterior-posterior direction but occupy only a very narrow territory in the medial-lateral direction. The molecular layer contains the cell bodies and dendrites of two types of "molecular layer interneurons," the stellate and basket cells, both of which inhibit Purkinje cells. It also contains the axons of the granule cells, called the *parallel fibers* because they run parallel to the long axis of the folia (Figure 37–8). Parallel fibers run perpendicular to the dendritic trees of the Purkinje cells and thus have the potential to form a few synapses with each of a large number of Purkinje cells.

The Climbing-Fiber and Mossy-Fiber Afferent Systems Encode and Process Information Differently

The two main types of afferent fibers in the cerebellum, the mossy fibers and climbing fibers, probably mediate different functions. Both form excitatory synapses with neurons in the deep cerebellar nuclei and in the cerebellar cortex. However, they terminate in different layers of the cerebellar cortex, affect Purkinje cells through very different patterns of synaptic convergence and divergence, and produce different electrical events in the Purkinje cells.

Climbing fibers originate in the inferior olivary nucleus in the brain stem and convey sensory information to the cerebellum from both the periphery and the cerebral cortex. The climbing fiber is so named because each one wraps around the proximal dendrites of a Purkinje neuron like a vine on a tree, making numerous synaptic contacts (Figure 37–9). Each Purkinje neuron receives synaptic input from only a single climbing fiber, but each climbing fiber contacts 1 to 10 Purkinje cells that are arranged topographically along a parasagittal strip in the cerebellar cortex. Indeed, the axons from clusters of related olivary neurons terminate in thin parasagittal strips that extend across several folia, and the Purkinje cells from one strip converge on a common group of neurons in the deep nuclei.

Climbing fibers have an unusually powerful influence on the electrical activity of Purkinje cells. Each action potential in a climbing fiber generates a protracted, voltage-gated Ca^{2+} conductance in the soma and dendrites of the postsynaptic Purkinje cell. This results in prolonged depolarization that produces an electrical event called a "complex spike": an initial large-amplitude action potential followed by a high-frequency burst of smaller-amplitude action potentials (Figure 37–9). Whether these smaller spikes are transmitted down the Purkinje cell's axon is not clear. In awake animals, complex spikes occur spontaneously at low rates, usually around one per second. Specific sensory or motor events cause one or two complex spikes that occur at precise times in relation to those events.

Mossy fibers originate from cell bodies in the spinal cord and brain stem. They carry sensory information from the periphery as well as both sensory information and corollary discharges that report the current movement command (Chapter 30) from the cerebral cortex

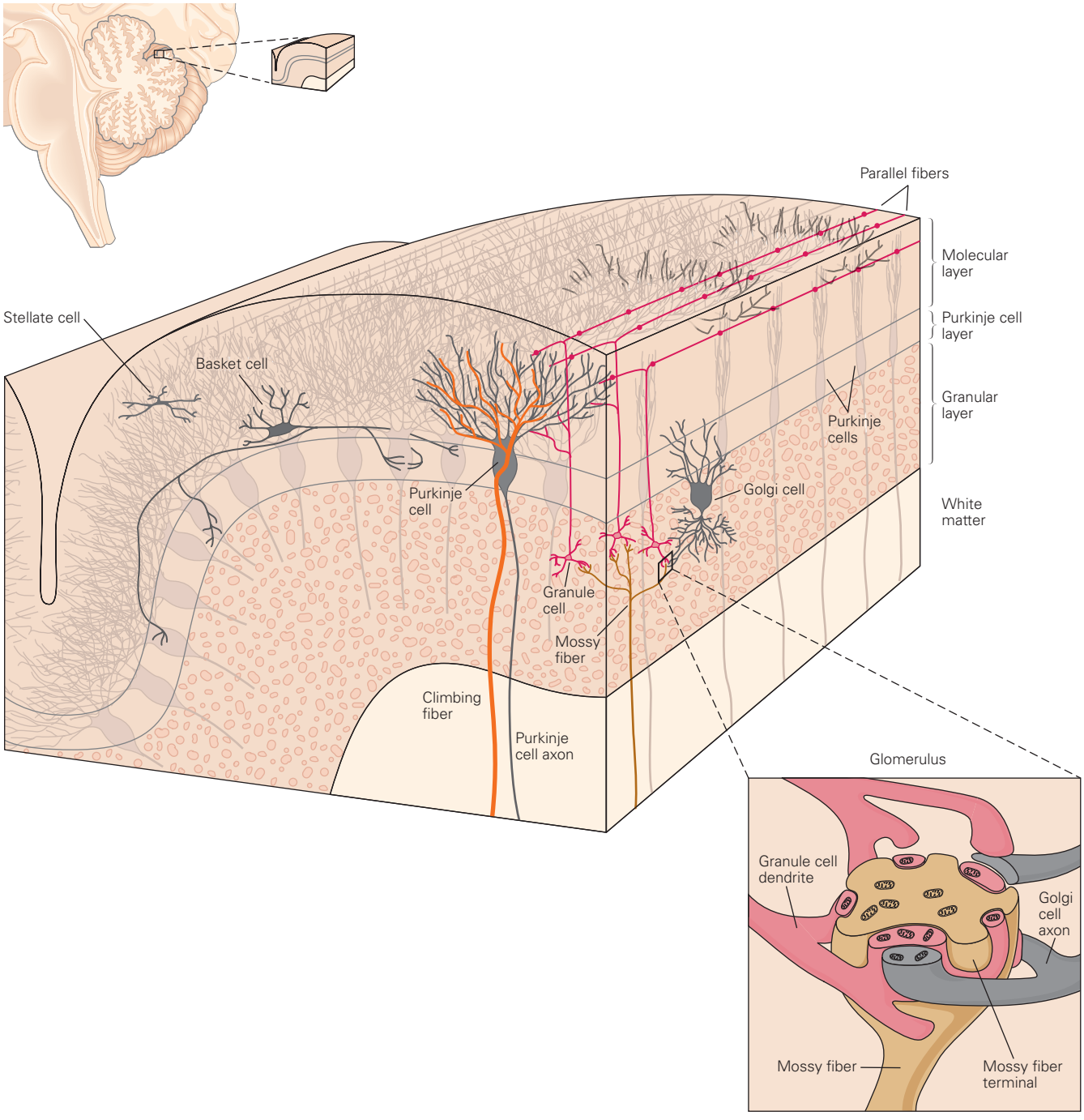

Figure 37–8 The cerebellar cortex contains five main types of neurons organized into three layers. A vertical section of a single cerebellar folium illustrates the general organization of the cerebellar cortex. The detail of a cerebellar glomerulus in the granular layer is also shown. A glomerulus is the synaptic complex formed by the bulbous axon terminal of a mossy fiber and the dendrites of several Golgi and granule cells. Mitochondria are present in all of the structures in the glomerulus, consistent with their high metabolic activity.

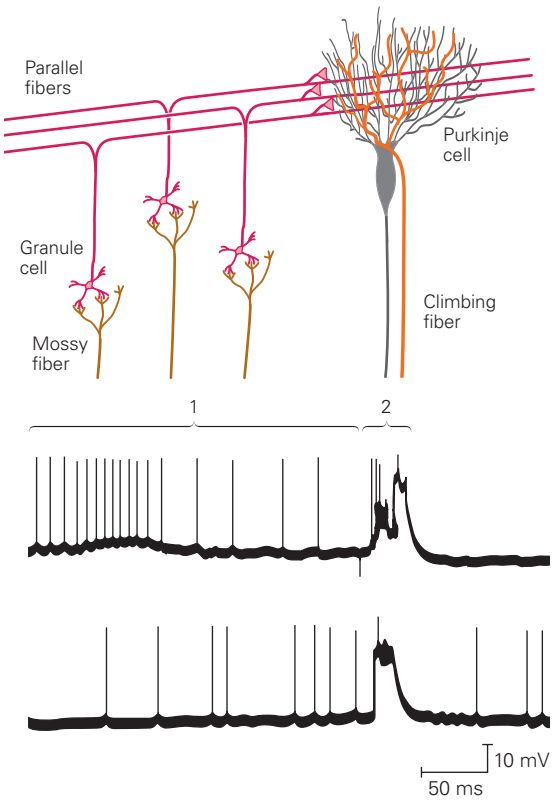

Figure 37–9 Simple and complex spikes recorded intracellularly from a cerebellar Purkinje cell. Simple spikes are produced by mossy-fiber input (**1**), whereas complex spikes are evoked by climbing-fiber synapses (**2**). (Reproduced, with permission, from Martinez, Crill, and Kennedy 1971.)

via the pontine nuclei. Mossy fibers affect Purkinje cells via multisynaptic pathways that have intriguing patterns of convergence and divergence. Individual mossy fibers, acting through granule cells and parallel fibers, have a tiny influence on Purkinje cell output, but collectively, the whole population of mossy fibers has massive effects on cerebellar output.

Mossy fibers form excitatory synapses on the dendrites of granule cells in the granular layer (Figure 37–8). Each granule cell has three to five short dendrites, and each dendrite receives contacts from a single mossy fiber. Due to this paucity of inputs, the spatial integration by a granule cell of its different mossy fiber synapses is not extensive; however, the cell can be the site of convergence of mossy fibers from multiple sensory modalities and motor corollary discharge. The next synaptic relay, between the granule cell axons and Purkinje cells, distributes information with very wide divergence and convergence. The parallel fibers allow each mossy fiber to influence a large number of Purkinje cells, and each Purkinje cell is contacted potentially by axons from somewhere between 200,000 and 1 million granule cells. Importantly, in response to changing conditions there seems to be tremendous potential for adaptation of cerebellar output at the synapses between parallel fibers and Purkinje cells. It appears that only a small fraction of these synapses are active at any given time.

Parallel fibers produce brief, small excitatory potentials in Purkinje cells (Figure 37–9). These potentials converge in the cell body and spread to the initial segment of the axon where they generate conventional action potentials called "simple spikes" that propagate down the axon. In awake animals, Purkinje cells emit a steady stream of simple spikes, with spontaneous firing rates as high as 100 per second even when an animal is sitting quietly. Purkinje cells fire at rates as high as several hundred spikes per second during active eye, arm, and face movements.

The climbing-fiber and mossy-fiber/parallel-fiber systems seem to be specialized for transmission of different kinds of information. Climbing fibers cause complex spikes that seem specialized for event detection. Although complex spikes occur only infrequently, synchronous firing in multiple climbing fibers enables them to signal important events. Synchrony seems to arise partly because signaling between many neurons in the inferior olivary nucleus occurs electrotonically (at gap-junction channels). In contrast, the high firing rates of the simple spikes in Purkinje cells can be modulated up or down in a graded way by mossy-fiber inputs, and thereby encode the magnitude and duration of peripheral stimuli or centrally generated behaviors.

The Cerebellar Microcircuit Architecture Suggests a Canonical Computation

The cerebellar microcircuit is replicated many times across the surface of the cerebellar cortex. This repeating architecture and pattern of convergence and divergence has led to the suggestion that since every such module has the same architecture and pattern of convergence and divergence, the cerebellar cortex performs the same basic "canonical" computation on all of its inputs, and that it potentially transforms cerebellar inputs in a similar way for all cerebellar output systems. Inspection of a diagram of the cerebellar microcircuit (Figure 37–10) reveals a number of different computational components. One general feature is the existence of parallel excitatory and inhibitory pathways to the Purkinje cells or deep cerebellar nuclei. The other general feature is the prevalence of recurrent loops.

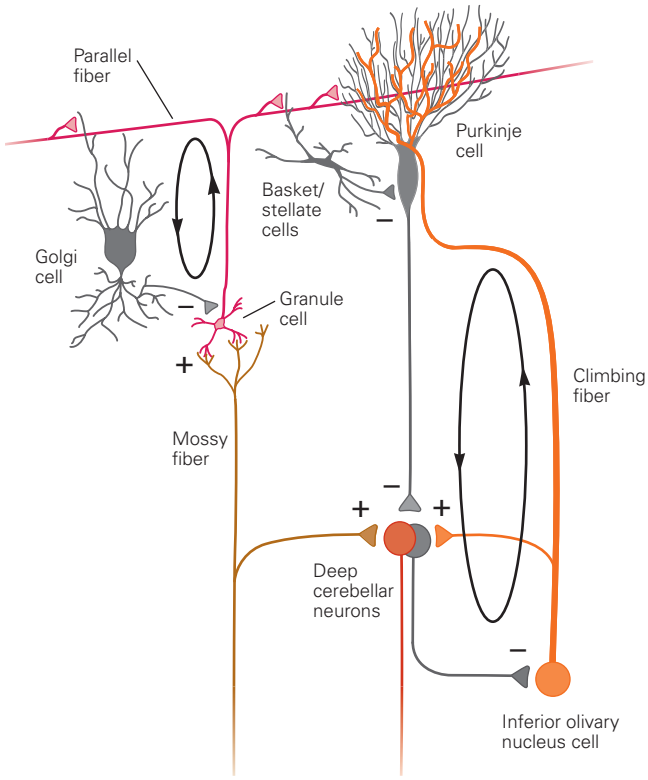

Figure 37–10 Synaptic organization of the cerebellar microcircuit. Excitation and inhibition converge both in the cerebellar cortex and in the deep nuclei. Recurrent loops involve Golgi cells within the cerebellar cortex and the inferior olive outside the cerebellum. (Adapted, with permission, from Raymond, Lisberger, and Mauk 1996. Copyright © 1996 AAAS.)

Parallel Feedforward Excitatory and Inhibitory Pathways

The excitatory inputs relayed from mossy fibers to granule cells to Purkinje cells work in parallel with feedforward inhibitory inputs through the two molecular layer interneurons, the stellate and basket cells. Both of these interneurons receive inputs from parallel fibers and inhibit Purkinje cells, but they have quite different architectures.

The short axons of stellate cells contact the nearby dendrites of Purkinje cells. Thus, a stellate cell acts locally in the sense that it and the Purkinje cell it inhibits are excited by the same parallel fibers. In contrast, a basket cell acts more widely. Its axon runs perpendicular to the parallel fibers (Figure 37–8) and creates flanks of inhibition on Purkinje cells that receive input from parallel fibers other than those that excite the basket cell. Stellate cells affect Purkinje cells via synapses that are on distal dendrites, whereas basket cells make powerful synapses on the cell body of Purkinje cells and seem to be positioned for a powerful influence on Purkinje cell simple spiking. Remarkably, even 60 years after the architecture of the cerebellar microcircuit was described, the functional role of molecular layer interneurons remains a mystery.

Convergence of excitatory and inhibitory pathways is a predominant feature also in the deep cerebellar nuclei. Here, inhibitory inputs from Purkinje cells converge with excitatory inputs from axon collaterals of mossy and climbing fibers (Figure 37–10). Thus, a mossy fiber affects target neurons in the deep nuclei in two ways: directly by excitatory synapses and indirectly by pathways through the cerebellar cortex and the inhibitory Purkinje cells. Neurons of the deep cerebellar nuclei are active spontaneously even in the absence of synaptic inputs, so the inhibitory output of the Purkinje cells both modulates this intrinsic activity and sculpts the excitatory signals transmitted from mossy fibers to the deep nuclei. In almost all parts of the cerebellum, collaterals from climbing fibers to the deep cerebellar nuclei create the opportunity for a similar interaction of excitatory and inhibitory inputs.

Recurrent Loops

An important recurrent loop is contained entirely within the cerebellar cortex and employs Golgi cells to sculpt the activity of the granule cells, the input elements in the cerebellar cortex. Golgi cells receive a few large excitatory inputs from mossy fibers, many smaller excitatory inputs from parallel fibers, and inhibitory inputs from neighboring Golgi cells. The GABAergic terminals from Golgi cells inhibit granule cells (Figure 37–10) and thereby regulate the activity of granule cells and the signals conveyed by the parallel fibers. This loop is evidence that important processing may occur within the granular layer. It may shorten the duration of bursts in granule cells, limiting the magnitude of the excitatory response of granule cells to their mossy fiber inputs, or could ensure that the granule cells respond only when a certain number of their mossy fiber inputs are active.

A second recurrent loop provides Purkinje cells with a way to regulate their own climbing fiber inputs (Figure 37–10). Purkinje cells inhibit GABAergic inhibitory neurons in the deep cerebellar nuclei that project to the inferior olive. When the simple-spike firing of a group of Purkinje cells decreases, the activity of these inhibitory interneurons increases, leading to decreases in the excitability of neurons in the inferior olive. The decreased excitability of the inferior olive reduces both the probability of action potentials in climbing fibers that project to the original group of Purkinje cells and the duration of each burst of climbing fiber action

potentials. In the section on cerebellar learning, we will see how this recurrent loop could allow the cerebellar cortex to control the inputs that cause adaptive changes in the synapses on its Purkinje cells.

The Cerebellum Is Hypothesized to Perform Several General Computational Functions

We know that the cerebellum is important for motor control and some nonmotor functions. Even though we do not yet know how the cerebellar circuit controls these functions, we are able to identity aspects of the control that seem to be particularly "cerebellar." These include reliable feedforward control, internal control of timing, integration of sensory inputs with corollary discharge, and state estimation through internal models.

The Cerebellum Contributes to Feedforward Sensorimotor Control

Sensory feedback is by its nature delayed. Therefore, when a movement is initiated there is a period of time before any useful sensory feedback is received about the movement. We saw earlier that cerebellar damage causes movement disorders that appear to result from out-of-date sensory feedback. If so, it is reasonable to assume that the cerebellum regulates and coordinates movement by preprogramming and coordinating commands for muscular contraction prior to the arrival of useful sensory feedback. The cerebellar output anticipates the muscular contractions that will be needed to bring a movement smoothly, accurately, and quickly to the desired endpoint, and uses sensory feedback mainly to monitor and improve its own performance.

Like neurons in the motor cortex, cerebellar neurons are activated before movement. Still, lesion studies and the symptoms in human motor disorders imply that the cerebellum and motor cortex play very different roles in movement. Lesions of the cerebellum disrupt the accuracy and coordination of voluntary movement, while lesions of the cerebral cortex largely prevent movement.

In addition, the pattern of cerebellar activity, not simply the rate of activity, conveys information for movement control. This is illustrated in mouse models of cerebellar disease. Deletion of certain ion channels produces excessive variability of Purkinje cell simple-spike firing patterns, which seems to lead to ataxia. This suggests that the regularity of cerebellar activity must be closely regulated to achieve normal movement.

The Cerebellum Incorporates an Internal Model of the Motor Apparatus

To program the correct muscle contractions for a smooth, accurate arm movement, the cerebellum needs to have some information about the physical configuration of the arm. Thus, it needs to create and maintain what are called "internal models" of the motor apparatus (Chapter 30). Internal models allow the cerebellum to perform a computation that helps the brain make good estimates of the exact muscle forces needed to move an arm in a desired manner.

An accurate *inverse dynamic* model of the arm, for example, can process sensory data about the current posture of the arm and automatically generate a sequence of properly timed and scaled commands to move the hand to a new desired position. An accurate *forward dynamic* model does the opposite: It processes a copy of a motor command and makes a prediction about the upcoming kinematics (ie, position and speed) of the arm movement. Recordings of the output of the cerebellum have provided evidence compatible with the idea that the cerebellum contains both types of models and that they are used to program both arm and eye movements.

One reason that the cerebellum may need these types of models for motor control is because of the complexities associated with moving linked segments of the body. Consider the mechanics of making a simple arm movement. Because of the mechanics of the arm and the momentum it develops when moving, movement of the forearm alone causes inertial forces that passively move the upper arm. If a subject wants to flex or extend the elbow without simultaneously moving the shoulder, then muscles acting at the shoulder must contract to prevent its movement. These stabilizing contractions of the shoulder joint occur almost perfectly in healthy subjects but not in patients with cerebellar damage, who experience difficulty controlling the inertial interactions among multiple segments of a limb (Figure 37–1B). As a result, patients exhibit greater inaccuracy of multi-joint versus single-joint movements.

In conclusion, the cerebellum uses internal models to allow it to preprogram a sequence of muscle contractions that will generate smooth, accurate movement. It also anticipates the forces that result from the mechanical properties of a moving limb. We do not yet know what these internal models look like in terms of the activity of cerebellar neurons, the circuits that operate as internal models, or how the cerebellar output is transformed into muscle forces. However, given that the properties of the limbs change throughout life, we can be confident that the cerebellum's learning capabilities

are involved in adapting these internal models to help generate the most proficient movements.

The Cerebellum Integrates Sensory Inputs and Corollary Discharge

Sensory signals converge in the cerebellum with motor signals that are called a corollary discharge (or efference copy) because they report commands that are being sent to motor nerves at the same time. For example, some neurons in the dorsal spinocerebellar tract relay inputs from sensory afferents in the spinal cord and transmit sensory signals to the cerebellum. In contrast, the neurons in the spinal cord that give rise to the axons in the ventral spinocerebellar tract receive the same afferent and descending inputs as do spinal motor neurons, and they transmit the final motor command back to the cerebellum. The interaction of sensory signals and corollary discharge allows comparison of the plans for a movement with the sensory consequences. This comparison occurs to some degree at Purkinje cells, but we now know that at least some granule cells receive converging sensory and corollary discharge inputs and could perform the comparison.

Internal models and corollary discharge together provide one possible explanation of the role of the cerebellum in movement. To be able to program accurate movements the cerebellum must be able to estimate the state of the motor system through sensory feedback and knowledge of prior motor activity. Next, it must combine information on the state of the motor system with the goals of the next movement and use internal models of the effector to help create commands for muscle forces that will generate an accurate and efficient movement. During the movement, the cerebellum must monitor movement performance through sensory feedback. Current thinking is that much of this is done by an internal model that converts corollary discharge into predictions of the sensory feedback. The cerebellum then compares real and predicted sensory feedback to determine a sensory prediction error and uses the sensory prediction error to guide corrective movements and learning.

Using a paradigm that required monkeys to ignore the sensory signals caused by their own movement, Kathy Cullen and colleagues have identified a neural correlate of a sensory prediction error in the deep cerebellar nuclei. Specifically, they studied the vestibular sensory signals that result from an animal's active head movements. They showed that the brain attenuates or even eliminates the vestibular sensory signals caused by one's own active head movement in order to better detect unpredictable vestibular signals due to the environment. However, when the head is effectively made heavier by adding resistance via a mechanical device, the vestibular sensory signals no longer match the predicted sensory signals that normally would attenuate the vestibular input. They showed that the cerebellum adjusts its predictions of the vestibular input to account for the changes in head movement caused by resistance due to the mechanical device. After some practice, the predicted and actual self-generated sensory inputs again match, and neurons in the deep cerebellar nucleus return to being unresponsive to vestibular inputs. Cerebellum-dependent learning is described in detail later in this chapter.

The Cerebellum Contributes to Timing Control

The cerebellum seems to have a role in movement timing that goes well beyond its role in regulating the timing of contractions in different muscles (Figure 37–7). When patients with cerebellar lesions attempt to make regular tapping movements with their hands or fingers, the rhythm is irregular and the motions vary in duration and force.

Based on a theoretical model of how tapping movements are generated, Richard Ivry and Steven Keele inferred that medial cerebellar lesions interfere only with accurate execution of the response, whereas lateral cerebellar lesions interfere with the timing of serial events. Such timing defects are not limited to motor events. They also affect the patient's ability to judge elapsed time in purely mental or cognitive tasks, as in the ability to distinguish whether one tone is longer or shorter than another or whether the speed of one moving object is greater or less than that of another. We will see in our discussion of motor learning that the cerebellum is critical for learning the timing of motor acts.

The Cerebellum Participates in Motor Skill Learning

In the early 1970s, on the basis of mathematical modeling of cerebellar function and the cerebellar microcircuit, David Marr and James Albus independently suggested that the cerebellum might be involved in learning motor skills. Along with Masao Ito, they proposed that the climbing-fiber input to Purkinje cells causes changes at the synapses that relay mossy fiber input signals from parallel fibers to Purkinje cells. According to their theory, the synaptic plasticity would lead to changes in simple-spike firing, and these changes would cause behavioral learning. Subsequent experimental evidence has supported and extended this theory of cerebellar motor learning.

Climbing-Fiber Activity Changes the Synaptic Efficacy of Parallel Fibers

Climbing fibers can selectively induce *long-term depression* in the synapses between parallel fibers and Purkinje cells that are activated concurrently with the climbing fibers. Many studies in brain slices and cultured Purkinje cells have found that concurrent stimulation of climbing fibers and parallel fibers depresses the Purkinje cell responses to subsequent stimulation of the same parallel fibers. The depression is selective for the parallel fibers that were activated in conjunction with the climbing-fiber input and does not appear in synapses from parallel fibers that had not been stimulated along with climbing fibers (Figure 37–11A). The resulting depression can last for minutes to hours.

Many studies in a variety of motor learning systems have recorded activity in Purkinje cells that is consistent with the predictions of the cerebellar learning theory. For example, if an unexpected resistance is applied to a well-practiced arm movement, extra muscle tension will be required to move. Climbing fiber activity can signal error until the unexpected resistance is learned. They presumably depress the synaptic

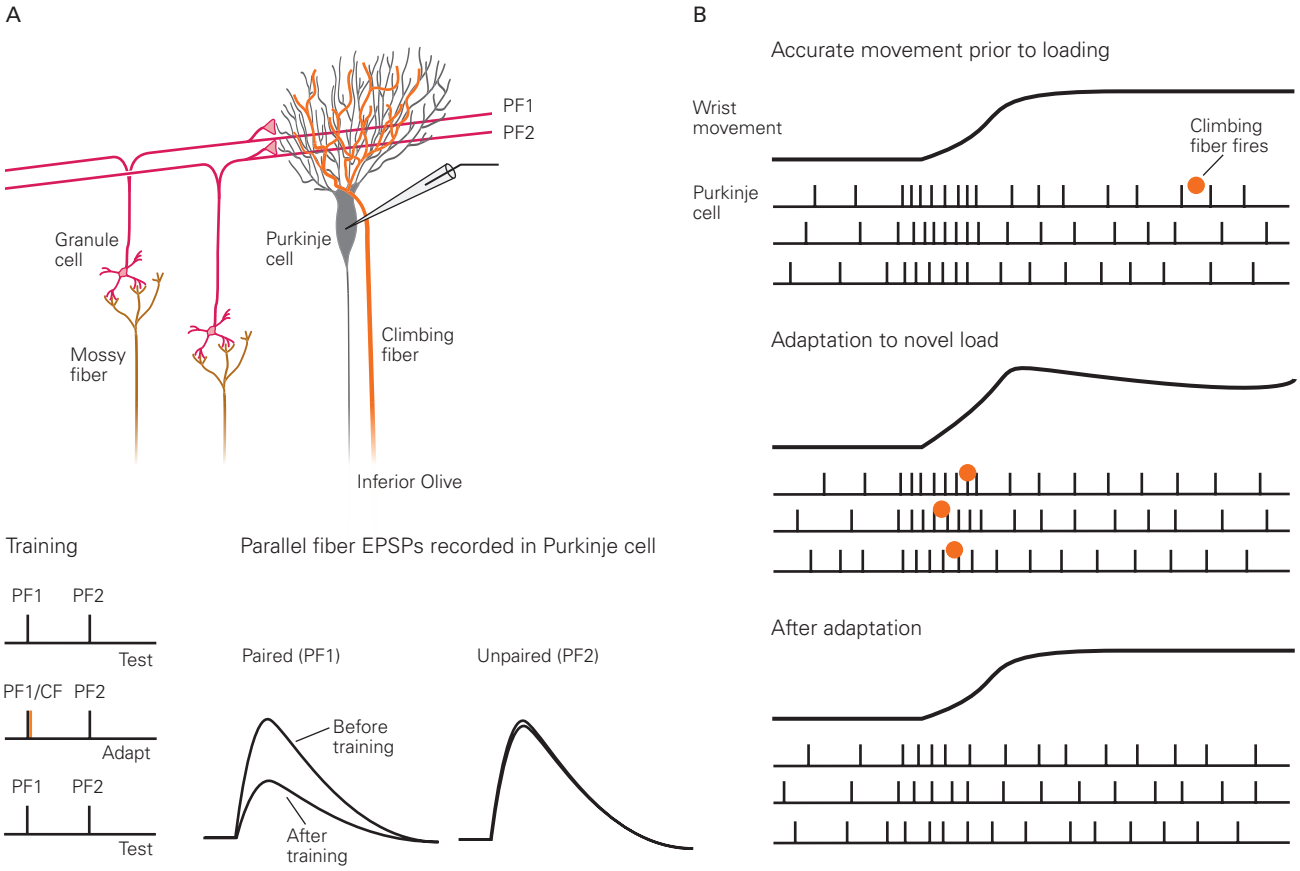

Figure 37–11 Long-term depression of the synaptic input from parallel fibers to Purkinje cells is one plausible mechanism for cerebellar learning.

A. Two different groups of parallel fibers and the presynaptic climbing fibers are electrically stimulated in vitro. Repeated stimulation of one set of parallel fibers (**PF1**) at the same time as the climbing fibers produces a long-term reduction in the responses of those parallel fibers to later stimulation. The responses of a second set of parallel fibers (**PF2**) are not depressed because they are not stimulated simultaneously with the presynaptic climbing fibers. (Abbreviations: **CF**, climbing fiber; **EPSP**, excitatory postsynaptic potential.) (Adapted from Ito et al. 1982.)

B. Top: An accurate wrist movement by a monkey is accompanied by a burst of simple spikes in a Purkinje cell, followed later by discharge of a single climbing fiber in one trial. **Middle:** When the monkey must make the same movement against a novel resistance (adaptation), climbing-fiber activity occurs during movement in every trial and the movement itself overshoots the target. **Bottom:** After adaptation, the frequency of simple spikes during movement is quite attenuated, and the climbing fiber is not active during movement or later. This is the sequence of events expected if long-term depression in the cerebellar cortex plays a role in learning. Climbing fiber activity is usually low (1/s) but increases during adaptation to a novel load. (Adapted, with permission, from Gilbert and Thach 1977.)