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ABSTRACT: The cerebellum is that part of the brain which coordinates motor reflex behavior. To perform effectively, it must learn to generate specific motor commands at the proper times. We propose a fundamental circuit, called the MicroCircuit, which is the minimal ensemble of neurons both necessary and sufficient to learn timing. We describe how learning takes place in the MicroCircuit which then explains the global behavior of the cerebellum as coordinated MicroCircuit activity.

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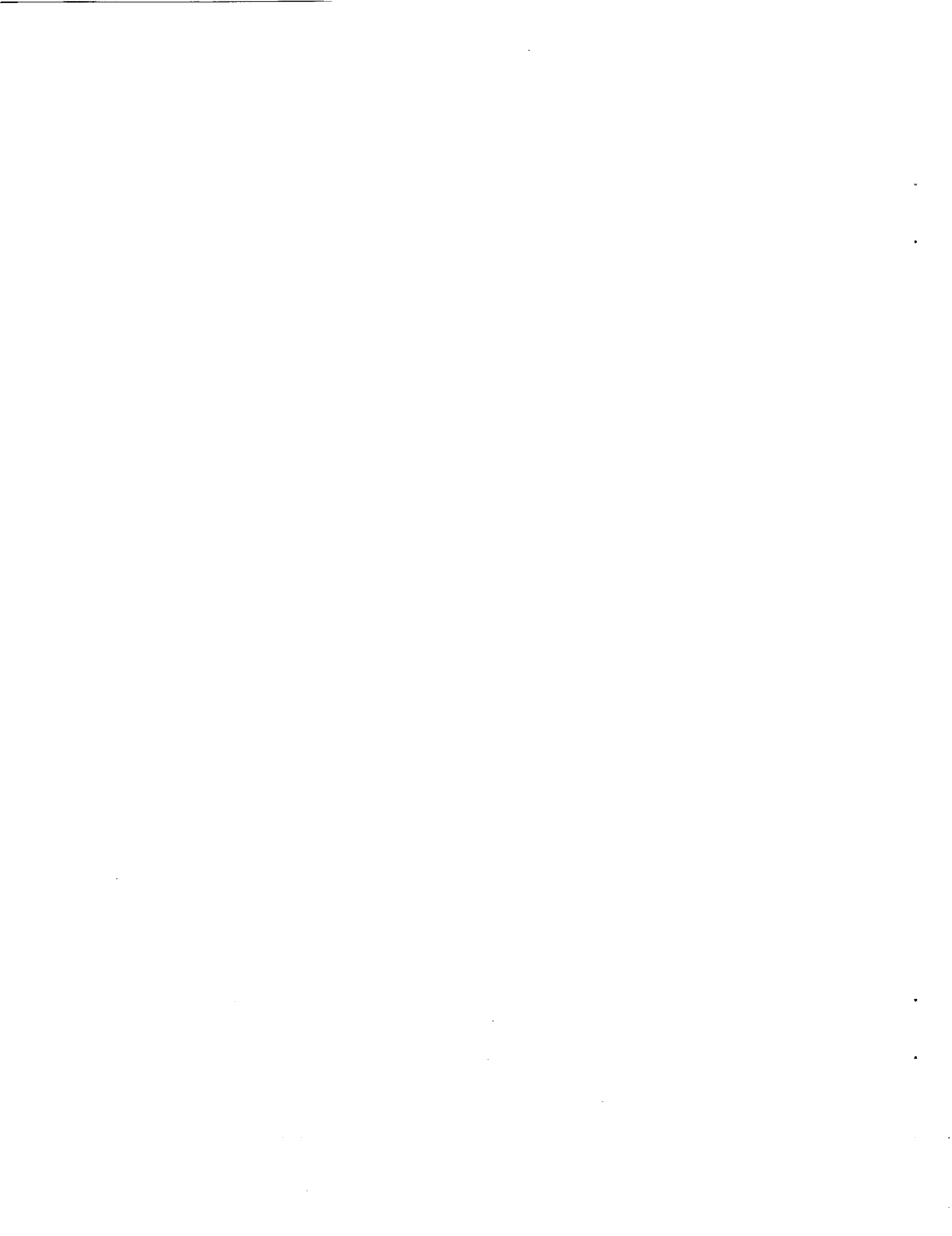NASA Ames Research Center - MS: 244-4
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ABSTRACT

The cerebellum is that part of the brain which coordinates motor reflex behavior. To perform effectively, it must learn to generate specific motor commands *at the proper times*. We propose a fundamental circuit, called the *MicroCircuit*, which is the minimal ensemble of neurons both necessary and sufficient to learn timing. We describe how learning takes place in the MicroCircuit which then explains the global behavior of the cerebellum as coordinated MicroCircuit activity.

Introduction

The cerebellum plays a key role in the control of complex motor movements (Ito, 1984). A recent analysis of the cerebellum's functional characteristics by Loebner (1989) places it at the focal point of a complex network whose primary purpose is to orchestrate reflex actions. As currently viewed, the cerebellum does not initiate motor movement, but rather integrates incoming sensory information to carry out the desired motion smoothly and efficiently. To accomplish this orchestration, the cerebellum must be able to adjust not only the motor responses needed to coordinate reflexes, but also *time* the responses to ensure each action occurs at the proper moment. Current models of the cerebellum, e.g. those of Marr (1969), Albus (1971), and Kanerva (1984), propose mechanisms for learning the motor responses but do not account for the equally fundamental need to learn timing.

There is an ongoing debate among scientists as to whether learning occurs in the cerebellar cortex. A basic assumption of this work is that it does. While some researchers argue against this (Krauzlis & Lisberger, 1989; Lisberger, 1988; Lisberger & Pavelko, 1988) we are convinced by the work of Thompson (1986,1988), Thompson and Donegan (1986), Steinmetz et al. (1986a,1986b,1987), and Gluck et al. (1990) that the necessary and sufficient neural pathways for reflex learning exist within the cerebellar cortex. Additionally, Anderson et al. (1989), Greenough et al. (1989), and Black et al. (1990) have shown that motor learning activities cause synaptic growth in the cerebellar cortex.

In this paper we introduce the MicroCircuit model of the cerebellum. This is a functional (information processing) model which incorporates both the spatial *and temporal* aspects of motor reflex behavior. The MicroCircuit refers to an ensemble of interconnected Purkinje cells, basket cells, and climbing fibers and is responsible for the ability of the cerebellum to learn timing.

Experimental Paradigm

We will describe our model of the cerebellum using, as a framework, the eyeblink (nicititating membrane) training procedure in rabbits. See Figure 1. At time t_0 the rabbit is exposed to a neutral, non-threatening, event known as the conditioned stimulus (CS). At time t_1 an aversive event, known as the unconditioned stimulus (US), is presented. In the classic eyeblink training procedure, the CS is an audible tone and the US a puff of air to the rabbit's cornea. The important aspect of a US is that it provoke a motor response, such as the closure of the rabbit's eyelid. The time between CS and US onset is fixed and known as the interstimulus interval (ISI). Over time the pairing of CS and US stimuli trains the rabbit to give the US-invoked response to CS presentation alone. The learned reaction is called the conditioned response (CR). After training, the tone alone is sufficient to elicit an eyeblink response from the rabbit; maximal eyelid closure occurs at the expected time of the air-puff (Coleman & Gormezano, 1971). Training allows the rabbit to *predict* when an aversive event (US) is going to occur and preempt its effect by generating an avoidance reflex (CR).
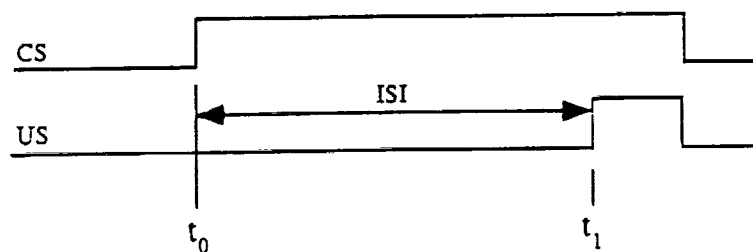

Figure 1: Eyeblink Conditioning Timing Diagram. In the simplest form of Pavlovian conditioning a nonaversive conditioned stimulus (CS) is presented at time t_0. After a fixed interstimulus interval (ISI) the unconditioned stimulus (US) is presented. Initially the CS does not generate a motor response, whereas the US does. After many presentations, the subject learns to associate the CS with the upcoming aversive US event, causing the proper avoidance reflex to occur at the proper time.

We believe any successful model of the cerebellum must answer the following three questions:

1. *What* is the desired output of the cortex?

2. *Which* cells participate in learning?

3. *How* does the cerebellum generate its output at the appropriate time?

We will show how the MicroCircuit model answers these questions, and explains much of the complex experimental data gathered concerning the eyeblink training procedure.

What Is The Desired Output Of The Cortex?

Thompson (1986, 1988), Thompson and Donegan (1986), Mauk et al. (1986), and McCormick et al. (1984) have shown that the inferior olive (IO) and its climbing fiber (CF) projections to the cerebellar cortex are essential for learning the eyeblink reflex. The CF projections, conveying US information, excite a set of Purkinje cells and a set of Purkinje associated basket cells. The basket cells inhibit some of their neighboring Purkinje cells. Purkinje cells provide input to deep cerebellar nuclear neurons which then issue output to motor neuron centers, effecting the desired physiological response. However, the climbing fiber system lacks the modal specificity to provide the cortex with sensory detail (Murphy & Sabah, 1971, reference 32). Instead, IO cells act as *event detectors*, where an *event* is defined as the onset of an unanticipated sensory experience or the absence of an expected action (King, 1976; Gellman et al., 1985; Lou & Bloedel, 1986; Mano et al., 1986; Kim et al., 1987, 1988; Houk, 1986; MacKay, 1988). This allows an IO cell's overall frequency to be low while providing for the rapid recognition of novel or unexpected occurrences. Examples of events include the unexpected touch of the skin, a puff of air to the eye, or the onset of an audible tone.

Some patterns of CF firing cause no motor responses. For example, the CF pattern invoked by the onset of a tone causes no reflex. Other patterns of CF firing do cause a motor reflex to occur. For example, the CF pattern invoked by a puff of air to the eye causes an eyeblink response. The cortical output caused by the unconditioned stimulus climbing fiber input (CF_{us}) defines *what* output is needed to effect the desired conditioned response: an *excitation* of Purkinje cells directly touched by CF_{us}, and an *inhibition* of Purkinje cells touched by CF_{us}-stimulated basket cells. See Figure 2.

In addition to CF-induced output, commonly referred to as *complex-spikes*, Purkinje cells generate streams of *simple-spikes*; these are thought to result from parallel fiber excitation of a Purkinje cell's dendrites. Since CF activity diminishes as learning progresses (Gluck et al., 1990), learning must involve changes in the simple-spike behavior of Purkinje cells. Experiments by Mano and Yamamoto (1980) and Mano et al. (1986) describe Purkinje cell simple-spike activity following climbing fiber activation in monkeys. They found that in Purkinje cells showing synchronized activity to a learned wrist tracking motion, roughly half increased and half decreased their simple-spike firing rates following climbing fiber activation. In similar work McDevitt et al. (1982) reports that, following spontaneous climbing fiber activity in awake cats, 14% returned their firing rates to background levels, 68% increased and 17% decreased their simple-spike firing rates.[1]
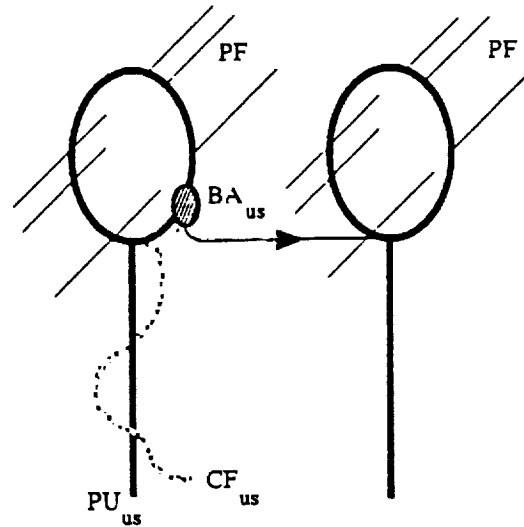
Figure 2: Climbing Fiber Induced Activity Patterns. Unconditioned stimulus induced climbing fiber (CF_{us}) activity defines the desired cortical output. Purkinje cells touched directly by CF_{us} should learn to increase their activity. Cells touched by CF_{us} stimulated basket cells should learn to decrease their activity.

Which Cells Participate In Learning?

In the previous section we proposed that the cortical output generated by the US is what the system needs to learn. After learning, this output must be triggered by the CS alone. Thus, the cells that participate in learning must have access to both CS and US information. The Marr-Albus-Kanerva model proposes that the CS information is carried by the parallel fibers (PF_{cs}) and the US information by the climbing fibers (CF_{us}); learning occurs at parallel fiber/Purkinje cell synapses (Marr, 1969; Albus, 1971; Kanerva, 1984).

Experiments by Steinmetz et al. (1989) using direct electrical stimulation of the IO for the US and of the pontine nucleus (the ultimate source of parallel fiber information) for the CS, the rabbit did learn the eyeblink response, but blinked at the wrong time. This contrasts with earlier reports that showed rabbits trained with an externally-applied CS, such as a tone, learned to synchronize their responses with the expected time of US onset (Coleman & Gormezano, 1971). *We conclude that CS onset provides information, in addition to parallel fiber activity, which is necessary for the cerebellum to learn the timing characteristics of the eyeblink reflex. Further, we postulate that this information is carried to the cortex via conditioned stimulus climbing fibers (CF_{cs}).*

In our model, for the cerebellum to learn to generate the proper output at the proper time, it needs to have access to three sources of information: CF_{us}, to provide the output pattern; PF_{cs}, for details about the CS event; and CF_{cs}, for information about the onset of the CS. After learning, PF_{cs} and CF_{cs} are sufficient to effect the proper output at the proper time. Cells which participate in

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1. It is not clear whether the differences in reported Purkinje cell behavior between McDevitt and Mano are due to the different species being studied (cat versus monkey), or due to methodology-based differences having more to do with recording techniques and experimental sample size.

learning must have access to both CF_{cs} and CF_{us} information in order to learn timing. We propose a fundamental circuit, called the *MicroCircuit*, which is the minimal ensemble of neurons both necessary and sufficient to learn timing. See Figure 3.
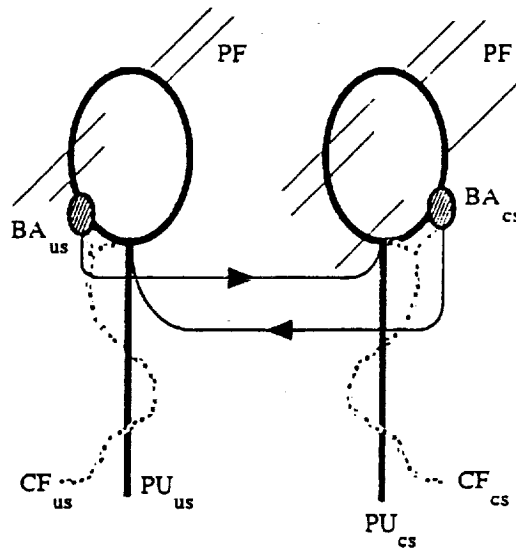

Figure 3: MICROCIRCUIT. Basket cells receiving CS and US climbing fiber information establish interconnection patterns between a pair of Purkinje cells. Called a MicroCircuit, this construct allows neighboring Purkinje cells to share event information making it possible for them to learn the interstimulus interval. PU_{cs} and BA_{cs} refer to CS climbing fiber related Purkinje and basket cells. PU_{us} and BA_{us} refer to US climbing fiber related Purkinje and basket cells.

The MicroCircuit structure allows each Purkinje cell access to the event information needed to determine the interstimulus interval (ISI) -- using basket cell axon collaterals to establish a two-way communication path between pairs of Purkinje cells (Palkovits et al., 1971; Eccles et al., 1967; Hamori and Szentagothai, 1966). When the CS event occurs, CF_{cs} fires, which in turn fires basket cell BA_{cs}. Subsequently, US onset fires CF_{us} causing basket cell BA_{us} to fire. Each Purkinje cell has now received two signals: a climbing fiber excitation and a basket cell inhibition. The time gap between these signals is the ISI.

We return to the question: Which cells participate in learning? The CS and US each define a set of climbing fibers, $\{CF_{cs}\}$ and $\{CF_{us}\}$. A MicroCircuit must have one Purkinje cell in $\{CF_{cs}\}$ and the other Purkinje cell in $\{CF_{us}\}$ to participate in learning the desired reflex behavior. Thus, the Purkinje cells eligible for learning are precisely those that are members of such a MicroCircuit.

How Does The Cerebellum Generate Its Output At The Appropriate Time?

Most current models of the cerebellum propose that learning occurs via modification of parallel fiber/Purkinje cell synapses. We agree this is likely, as a Purkinje cell should use the detailed information available on conditioned stimulus parallel fibers to determine whether it should respond to the CS. However, this form of learning is not sufficient to account for the Purkinje cell's learning of the ISI.

To learn timing, the Purkinje cell must be able to realize large variations in its simple-spike output frequency independent of changes in its parallel fiber input. We propose a Purkinje cell must recognize event onset (via climbing fiber and basket cell input), effect a delay in modulating its output to reflect the experimental ISI, and then modulate its quiescent simple-spike firing rate. This modulation can be manifest as either a decrease or an increase in simple-spike firing rate. Such dramatic simple-spike modulation has been observed by Mano and Yamamoto (1980), Mano et al. (1986), McDevitt et al. (1982), and Kim et al. (1988). However, work by Pellionisz and Szentagothai (1973) suggest that the granule-Golgi cell interface is capable of stabilizing parallel fiber activity over a large range of mossy fiber input; thus, parallel fiber activity alone can not account for the observed simple-spike frequency swings.

These results can be explained by postulating that Purkinje cell simple-spike modulation is governed by an internal delay accumulator mechanism. At event onset the accumulator is cleared. Thereafter, the Purkinje cell computes a running sum of the cell's afferent parallel fiber activity. When the accumulator reaches a threshold value, the Purkinje cell modulates its simple-spike firing rate. The interstimulus interval is reflected in the threshold setting of the delay accumulator.

Using this hypothesis of the Purkinje cell's behavior, we can describe how learning takes place in the MicroCircuit which, in turn, allows us to explain the global behavior of the cerebellum as coordinated MicroCircuit activity.

How Does The MicroCircuit Learn?

Consider the paired presentation of a tone conditioned stimulus (CS) and a corneal air puff unconditioned stimulus (US). Before learning has taken place, the following actions occur at CS onset:

1. CS climbing fiber (CF_{cs}) activation excites CS Purkinje (PU_{cs}) and basket (BA_{cs}) cells; BA_{cs} collaterals deliver an inhibitory input pulse to Purkinje cell PU_{us}.

2. CS parallel fiber (PF_{cs}) information begins to pass through the cortex; both Purkinje cells, PU_{cs} and PU_{us}, mark these recently-activated parallel fibers for future reference.

Subsequently, the following actions occur at US onset:

1. US climbing fiber (CF_{us}) activation excites US Purkinje (PU_{us}) and basket (BA_{us}) cells; BA_{us} collaterals deliver an inhibitory input pulse to Purkinje cell PU_{cs}.

2. Coincident to US presentation, Purkinje cells PU_{cs} and PU_{us} receive a learning signal which facilitates increasing the efficacy of their previously marked PF_{cs} synapses[2].

3. PU_{cs} and PU_{us} reset their modulation delays to reflect the ISI. (For PU_{cs}, this is the interval between receipt of CF_{cs} and BA_{us} signals. For PU_{us}, this is the interval between receipt of BA_{cs} and CF_{us} signals).

Once training has been effected, the MicroCircuit can generate the proper output at the proper time given only the conditioned stimulus. (The desired output is PU_{cs} decreasing its simple-spike

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2. One possible source is norepinephrine, a widely dispersed chemical agent to the molecular layer. Norepinephrine is released by the locus coeruleus in response to noxious events (Rasmussen et al., 1986; Rasmussen & Jacobs, 1986; Jacobs, 1987). Keeler et al. (1989), Waterhouse et al. (1988), and Moises et al. (1983) describe the action of norepinephrine as a signal-to-noise improvement agent, enhancing the cerebellum's ability to modify specific parallel fiber synaptic junctions.

frequency, and PU_{us} increasing its simple-spike frequency). At CS onset, the following actions occur:

1. CS climbing fiber (CF_{cs}) activation excites CS Purkinje (PU_{cs}) and basket (BA_{cs}) cells; this resets the delay accumulator in PU_{cs}. BA_{cs} collaterals deliver an inhibitory input pulse to Purkinje cell PU_{us}; this resets the delay accumulator in PU_{us}.

2. CS parallel fiber (PF_{cs}) information begins to pass through the cortex; both PU_{cs} and PU_{us} are highly stimulated by the previously-learned PF_{cs} patterns which, in turn, advance the Purkinje cell's delay accumulators toward their thresholds.

3. When their accumulator thresholds are reached, the Purkinje cells begin to modulate their simple-spike firing frequency. If the accumulator was reset by a climbing fiber activation the cell modulates downward; if it was reset by basket cell input the cell modulates upward.

With this procedure, the MicroCircuit accounts for the major functionality needed to learn motor reflex responses. It can learn the proper output; it can recognize the appropriate input needed to effect the output; and most importantly, it can learn the ISI needed to generate the proper output at the proper time.

How Does The Cerebellar Cortex Learn?

The MicroCircuit model shows how a pair of Purkinje cells can learn to give the proper output at the proper time. However, work by McDevitt (1985) demonstrates that single Purkinje cells have little effect in modifying the output of cerebellar nuclear neurons. This implies that large numbers of Purkinje cells (in many MicroCircuits) must change their output in concert to affect nuclear output. It is the mass action of many MicroCircuits that cause the desired output to occur. This mass action allows the cerebellar system to use low-resolution Purkinje cells to generate a high-resolution output -- the hyperacuity effect (Gluck et al., 1990).

Since the learned reflex is distributed over many Purkinje cells, it is resilient: later acquired reflexes may overwrite some of the component Purkinje cells, but unless either their CS or US are identical, most of the Purkinje cells will remain unaffected. Similarly, the learned reflex is tolerant to the dysfunction of individual Purkinje cells.

Conclusion

Most models of the cerebellum focus on its ability to learn and generate motor commands. An equally important task is to generate commands at the proper time. For example, after training the rabbit with a tone CS and an air-puff US, the learned eyeblink is timed so that maximal eyelid closure occurs at the expected time of the air-puff. Thus, while it is important for the cerebellum to learn *what* to output, it is equally important to learn *when* to perform the reflex: the proper reflex at the improper time serves little purpose.

To learn reflex timing, a neural circuit must have access to both CS and US information. To accomplish this we propose the MicroCircuit: a pair of Purkinje cells, one receiving a CS-activated climbing fiber, and one receiving a US-activated climbing fiber, interconnected by a pair of basket cells. The existence of this circuit would explain the failure of the cerebellum to learn timing when direct pontine stimulation is used for the CS (Steinmetz et al., 1989). We postulate learning

of timing can only occur when both the conditioned and unconditioned stimuli cause climbing fiber activation. The MicroCircuit is the site where CS and US information converge and where timing is learned. The ability of the cerebellum to learn timing results from the mass action of many MicroCircuits.

Work by Mano (1980, 1986) and others demonstrates dramatic modulation of Purkinje cell simple-spike frequency following climbing fiber stimulation; we propose a delay preceding the modulation is learned by the Purkinje cell and reflects the experimental interstimulus interval. The desired output is represented by the pattern of increased, or decreased, Purkinje cell simple-spike modulations over the cerebellar cortex.

The MicroCircuit model of cerebellar activity thus explains how both action and timing are learned and how the proper reflex is generated after learning. It accounts for the previously unexplained failure of the cerebellum to learn timing when direct pontine stimulation is used for the CS. It explains the role of bidirectional modulation of simple-spike activity first seen by Mano. Most importantly, this model incorporates the *timing* of motor commands, a feature we consider essential for any complete description of cerebellar activity.

Dedication

To Egon Loebner (1924-1989), a grand scientist and a good friend.

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