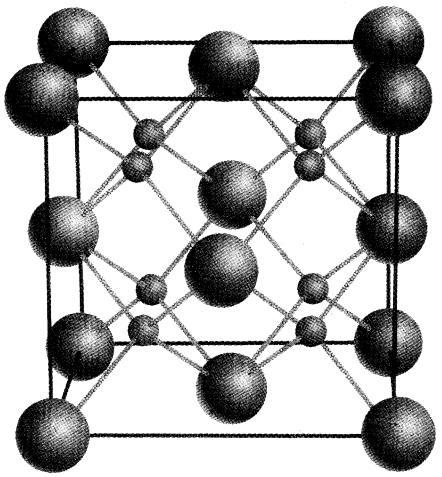

Face-centered-cubic (fcc) crystal structure of PuO_2 (Pu atoms in green, O atoms in red). The lattice constant is 4.3975 Å. PuO_{2+x} has the same structure, with a very similar lattice constant. This is one of the reasons why this compound was not identified prior to the study by Haschke *et al.* (*1*).

more than 50 years that PuO_2 is the highest plutonium oxide that can be prepared. This oxide, which crystallizes in the face-centered-cubic structure (fcc) (see the figure), was believed to be stable over a wide temperature range (from ambient to more than 2000°C). PuO_2 was therefore considered suitable as a component of nuclear reactor fuels, running either with fast or slow neutrons, for electricity production. To prepare these plutonium fuels, PuO_2 is mixed with depleted uranium dioxide, UO_2. The resulting solid solution $(U,Pu)O_2$ is then used to prepare mixed oxide (MOx) fuels. This plutonium recycling strategy has been an industrial reality in Western Europe and in Russia for many years and will also soon be implemented in Japan, where the first water-cooled nuclear reactor will be loaded with MOx fuel. Recycling of plutonium into MOx fuels requires reprocessing of uranium oxide–spent fuels. This is done industrially, for example, at Cogéma's La Hague plants (France) and British Nuclear Fuel Limited's Sellafield THORP plant (UK). Plutonium recovered from these spent fuels is converted into the semifinal product PuO_2. Plutonium recycling is not used in the United States, but PuO_2 is considered a very important compound for the long-term storage of plutonium from dismantled nuclear weapons.

For both civilian and military applications, the stability of PuO_2 was a key factor underlying the industrial strategy. The discovery by Haschke *et al.* that water and humid oxygen can slowly oxidize PuO_2 to PuO_{2+x}, accompanied by generation of hydrogen gas, calls for new evaluations of different aspects of the industrial operations involving PuO_2. Haschke *et al.* show that PuO_2 is metastable under oxidizing conditions and that it can be converted into PuO_{2+x} with x as high as 0.27, in which more than one-fourth of the plutonium atoms are oxidized from their initial oxidation state +IV into the oxidation state +VI. Surprisingly, water vapor was found to be a more efficient oxidizing agent than oxygen itself for the conversion of PuO_2 into PuO_{2+x}.

Future safety evaluations must take into account the temperature range of PuO_{2+x} stability (ambient to 350°C) and also the increased mobility of its Pu(VI) content in various transfer mechanisms. The new results will also have great consequences for the underground disposal of nuclear wastes. Until now, it was assumed that plutonium would not be very mobile in the underground geological environment because of the insolubility of Pu(IV) compounds. But Haschke *et al.* demonstrate that water can oxidize PuO_2 into PuO_{2+x}, in which more than 25% of the plutonium ions exist as Pu(VI), an ion that is far more water soluble, and thus mobile, than Pu(IV). This new property will have important implications for the long-term storage of plutonium.

The report by Haschke *et al.* will stimulate numerous future studies addressing fundamental questions related, for example, to the structure of the new PuO_{2+x} oxide, its thermodynamics properties, and the fascinating oxidizing property of water toward PuO_2.

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PERSPECTIVES: NEUROBIOLOGY

Diversity in Inhibition

Richard Miles

Yin and yang—inhibition and excitation. In the harmonious brain, excitatory and inhibitory synaptic signals coexist in a purposeful balance. But, whereas the neurons that the brain uses to transmit excitatory signals often have rather stereotyped properties, the cells that signal inhibition in the cortex and hippocampus are highly diverse and strikingly different from their excitable cousins. Inhibitory cells (also called interneurons because their effects are often short-range) signal to other neurons by liberating an inhibitory neurotransmitter from synaptic sites. Two articles in this week's issue add to a flood of new data on interneurons and their importance in brain function. In the first, Martina *et al.* (*1*) show on page 295 how the expression of Na^+ channels in neuronal dendritic branches endows one group of inhibitory neurons with an enhanced excitability and an increased speed of electrical signal transmission. In the second, Gupta *et al.* (*2*) present on page 273 an elegant attempt to classify cortical inhibitory cells by their synaptic effects on target neurons.

Cortical inhibitory neurons differ in many ways from their excitatory pyramidal cell partners. They have an entirely different calcium economy (*3*) and, perhaps consequently, it is difficult to induce long-term potentiation at the synapses that excite them (*4*). More importantly, inhibitory cells and circuits are built for speed. Interneuron action potentials are traditionally faster than those of pyramidal cells. This speed may result from the selective expression of specific K^+ channels that repolarize neurons after each action potential (*5*). Furthermore, the kinetics of synaptic events that excite inhibitory cells are faster than those that excite pyramidal cells (*6*). Rapid excitation probably depends on a distinct form of the postsynaptic AMPA receptor that mediates signaling at excitatory junctions with interneurons (*7*). The functional result is that pyramidal cell action potentials can induce interneuron firing with remarkably

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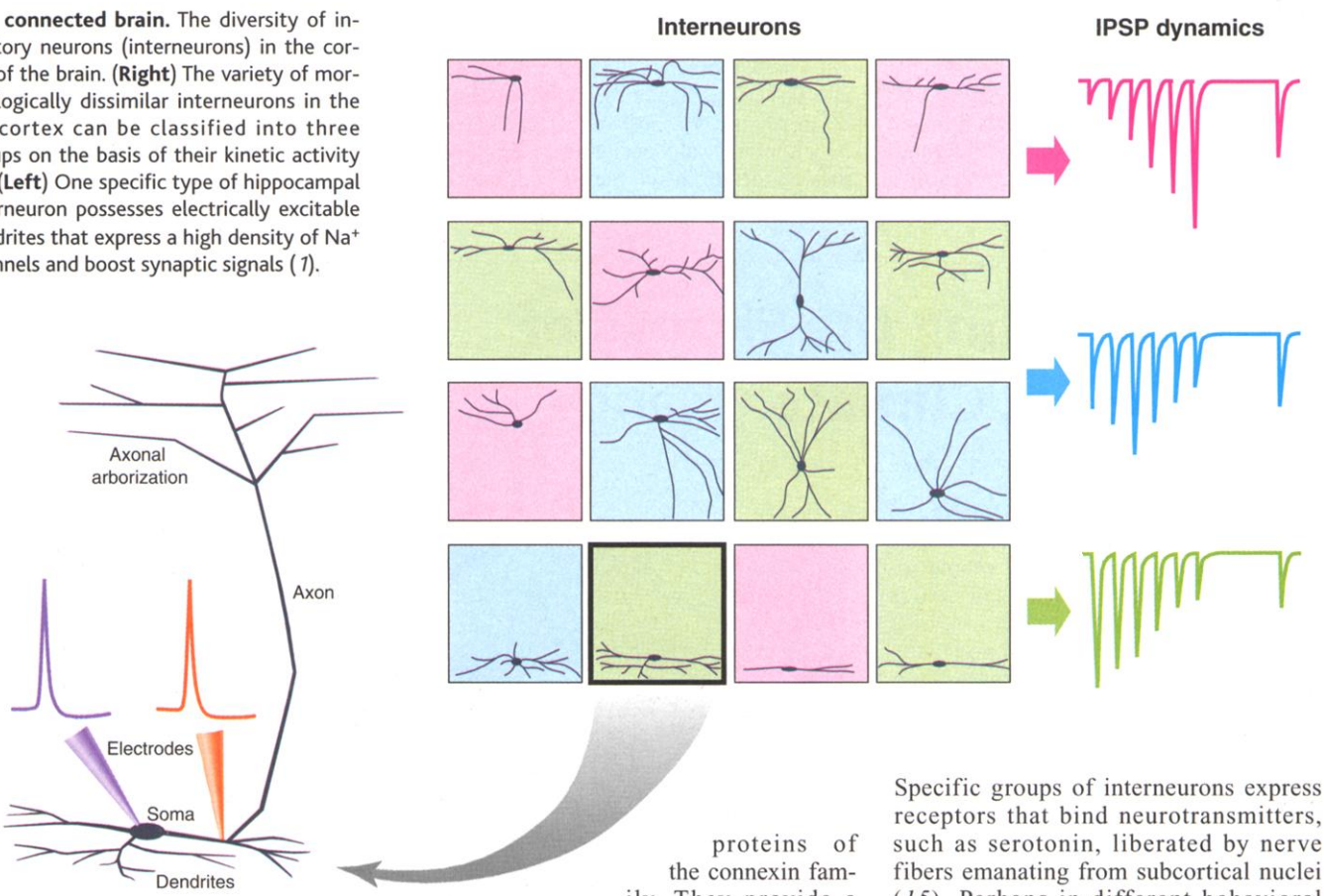
short and fixed latencies of 2 to 3 milliseconds (see the figure, below).

The new study by Martina *et al.* (*1*) reveals another inhibitory cell property that enhances the speed of electrical signal transmission. The axons of the inhibitory cells that they examined emerge not from the cell body (soma), but rather from a dendritic branch (*9*). The density of Na^+ channels is significantly higher—both in the axon-bearing dendrite and in other dendritic branches—than it is in neighboring pyramidal cells. So, fully formed action potentials may be initiated in interneuron dendrites and then may spread rather rapidly to or from the soma. Repetitive discharges propagate with little decrement, and impulse initiation can switch between the soma and the axon-bearing dendrite. However, the most important role of active dendrites of interneurons may be to boost excitatory synaptic events, as predicted theoretically (*10*), and so increase the reliability with which they induce firing.

Why should the excitation of inhibitory cells be so reliable and rapid? Possibly, a precisely timed, feedback inhibition gates information arriving in specific excitatory pathways (*11*). More generally, interneurons play a decisive role in the generation of brain rhythms. Rhythmic, synchronous activities provide the associative firing needed to trigger changes in synaptic strength both during development and in the adult. Recent modeling and experimental studies suggest that highly divergent inhibitory synaptic connections can dictate rhythmic discharges to large populations of pyramidal cells (*12*). However, for a clear rhythm to be transmitted to the larger network, interneurons must fire simultaneously. Two papers recently published in *Nature* (*13*) provide another mechanism through which inhibitory cell discharges might be synchronized. Gap junctions exist when membranes of two cells are connected by proteins of the connexin family. They provide a low-resistance pathway that couples the two cells electrically and acts as an excitatory synapse but without the need to liberate a chemical messenger. One or two (depending on the study) networks of cortical interneurons are connected by gap junctions. Action potentials are transmitted rather effectively between cells to synchronize interneuron firing with millisecond precision.

But perhaps the reader supposes that cortical inhibitory cells form a monolithic and unified cell population. Nothing could be further from the case. Inhibitory cells seem to be so diverse as perhaps to endanger the notion of cell types in the central nervous system. The first premonitions of inhibitory cell diversity may be found in the fantastic drawings of neuronal architecture made by Santiago Ramón y Cajal using the "reazione nera" cell staining technique of Camillo Golgi. More recent work has shown that distinct interneurons inhibit different and precise regions of the pyramidal cell membrane (*14*). Inhibitory cells that contact pyramidal cells selectively on the soma or the initial part of the axon control action potential initiation, whereas other interneurons may regulate dendritic excitability and the efficacy of excitatory inputs.



The connected brain. The diversity of inhibitory neurons (interneurons) in the cortex of the brain. (**Right**) The variety of morphologically dissimilar interneurons in the neocortex can be classified into three groups on the basis of their kinetic activity (*2*). (**Left**) One specific type of hippocampal interneuron possesses electrically excitable dendrites that express a high density of Na^+ channels and boost synaptic signals (*1*).

Specific groups of interneurons express receptors that bind neurotransmitters, such as serotonin, liberated by nerve fibers emanating from subcortical nuclei (*15*). Perhaps in different behavioral states, including various sleep phases, distinct modulators turn specific groups of inhibitory cells on or off and so reconfigure cortical networks. However, the simple hypothesis—that each member of a subset of inhibitory cells expresses receptors for a single modulating neurotransmitter—seems to be doomed. Interneurons are excited or inhibited by a confusing number of combinations of different modulators (*16*). This raises the question of how cell groups should be defined and particularly how many prop-

erties must differ before two neurons are assigned to distinct cell classes. Perhaps cell groups are more useful to neurobiologists than they are to the brains that they study.

Gupta *et al.* (*2*) provide a striking resolution of this apparent impasse. They group cortical interneurons in three different ways. First, according to their discharge pattern, which determines the temporal pattern of inhibitory synaptic events impinging simultaneously onto several hundred target neurons. A second classification based on the axonal tree of interneurons defines the number and spatial distribution of these target cells. The third, functional classification derives from an impressive number of simultaneous recordings from inhibitory cells and multiple postsynaptic targets. When inhibitory cells discharge repetitively, the efficacy of their synapses with pyramidal cells changes in one of three kinetic patterns (see the figure). Although the first two groupings fragment cortical interneurons into 14 different classes, the third sorting maps perfectly onto these classes and reunites interneurons into three functional groups.

So where does the field go from here? Molecular approaches may resolve the question of inhibitory cell diversity. We will eventually be able to measure the entire complement of proteins that a single interneuron expresses and determine how this complement is regulated by cascades of transcription factors and by external signals. The use of gene targeting to kill subsets of interneurons may also help us understand their functions. An impressive study demonstrating motor deficits emerging after selective ablation of cerebellar Golgi cells (*17*) has shown the way, although the adaptive mechanisms initiated by the loss of these interneurons urge caution with this approach. Nonetheless, the current cooperation between anatomists, physiologists, and modelers is increasing our knowledge of inhibitory cell function at a fast pace. Maybe the next step should be to reunite yin and yang and examine how inhibitory and excitatory synaptic signals cooperate in the purposeful and harmonious brain.

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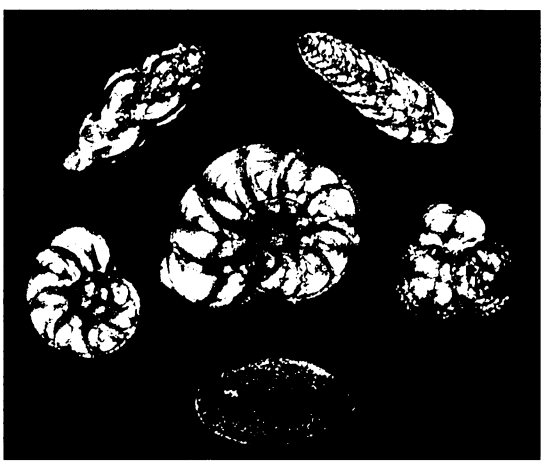
18. I thank A. Gulyas for the neuron morphology scheme in the figure.

PERSPECTIVES: GEOSCIENCE

Unraveling the Signals of Global Climate Change

Gary S. Dwyer

Over the past 50 million years, Earth's climate has been on a wobbly but persistent march toward cooler conditions. A telltale sign is the dramatic overall increase in global ice volume and decrease in deep-sea temperature. One of the best measures of this trend has been the oxygen isotopic composition ($\delta^{18}O$) of shells of ocean-floor microfossils extracted from deep-sea sediment cores. These $\delta^{18}O$ records, which simultaneously capture information regarding global ice volume and deep-sea temperature, are acquired in the vast majority of studies of past deep-sea conditions and have provided Earth scientists with critical paleoceanographic and paleoclimatic insight. Nevertheless, since the pioneering application of this technique in the 1950s and 1960s by Cesare Emiliani and Nicholas Shackleton (*1*), and regardless of the past period of interest, this basic and essential paleoclimatic tool has been plagued by the nagging question of the relative influence of water temperature and ice volume. On page 269 of this issue, Lear *et al.* (*2*) make an important step toward solving this problem for the past 50 million years of Earth's history by combining a recently developed deep ocean paleotemperature proxy—the ratio of magnesium to calcium concentrations in microfossil shells—with the $\delta^{18}O$ record.



Paleothermometers. A variety of shells of foraminifera, whose composition can provide insights into past climatic conditions.

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The Mg/Ca-based reconstruction of deep-sea temperature obtained by Lear *et al.* is remarkable in its similarity to the benthic $\delta^{18}O$ record (*3*). This is critical independent confirmation that a substantial portion of the long-term increase in the benthic $\delta^{18}O$ signal over the past 50 million years is indeed related to cooling of the deep ocean of around 12°C. In turn, it substantiates the hypothesis that this period is characterized by a shift to a global oceanic deep-water system much like the present one, which is driven by high-latitude sinking of cooled surface waters, and, further, that closing of tropical ocean gateways and opening of subpolar ocean gateways likely triggered the deep-water reorganization.

The residual benthic $\delta^{18}O$ record, after removal of the temperature effect by means of the Mg/Ca data, thus provides a record of the $\delta^{18}O$ of seawater for the past 50 million years, which is largely a function of global ice volume (see the figure on the following page). (With the major reorganization in deep-water production and circulation implied by the temperature record, the $\delta^{18}O$ of seawater was likely af-

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