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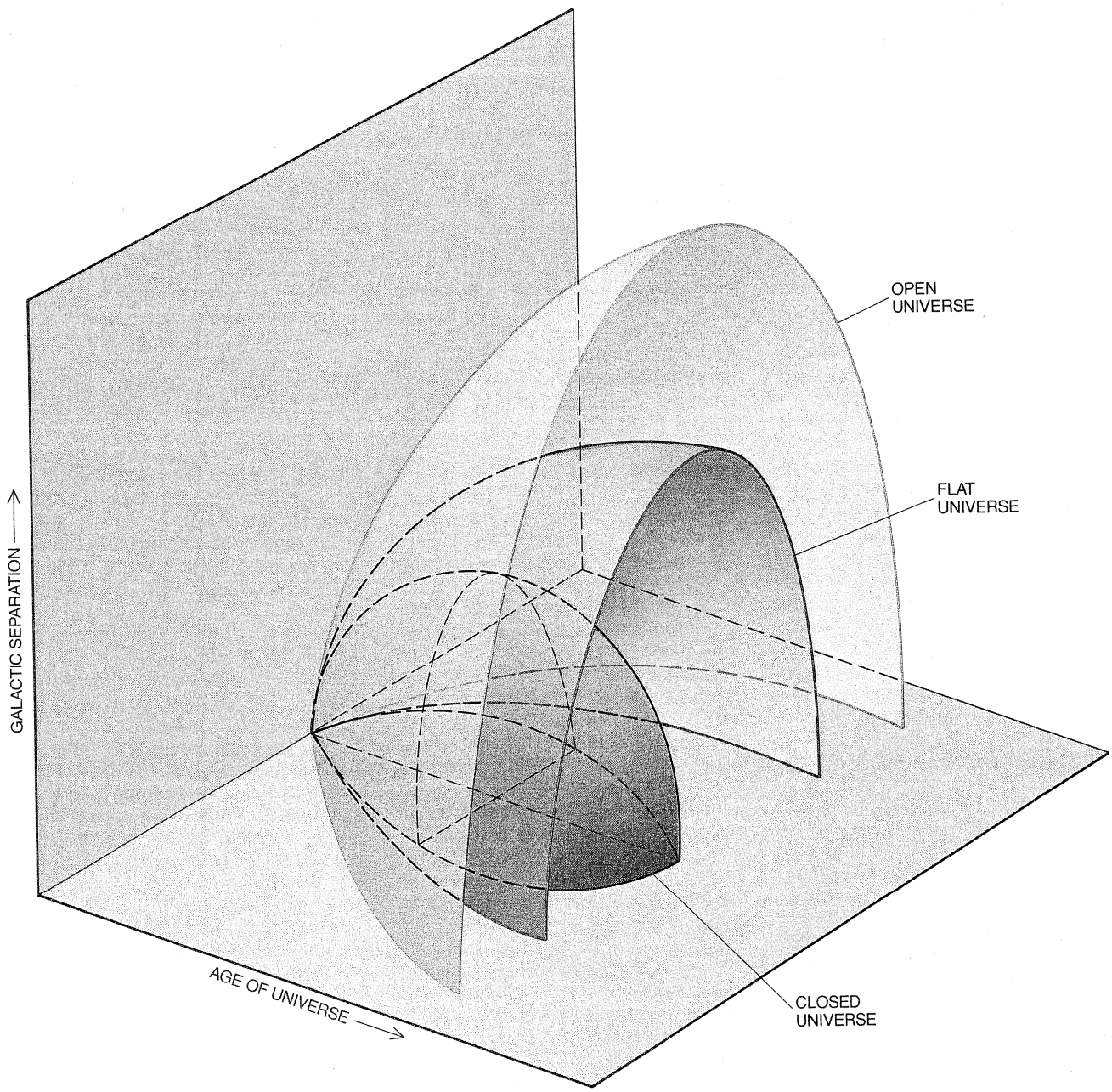
the matter must be something other than baryons. Numerous candidates have been proposed [see "Dark Matter in the Universe," by Lawrence M. Krauss; SCIENTIFIC AMERICAN, December, 1986].

Nevertheless, the possibility still remains that the dark matter, if it exists, could consist of baryons. One of us (Mathews) and co-workers at the Livermore Laboratory and investigators at a number of institutions have recently begun exploring in detail the possibility that such dark matter could have been formed if the baryon density of the universe were inhomogeneous during the big bang. The baryonic dark matter would now reside in regions that have collapsed into invisible remnants, such as black holes. The scenario could still be consistent with the big-bang nucleosynthesis of the light elements.

Although the variety of theories emphasizes the fact that the question of whether the universe is open or closed cannot be conclusively resolved as yet, the preliminary results point the way for studies that may eventually yield an answer. Moreover, the origin of the three peculiar elements lithium, beryllium and boron provides a wealth of clues about the origin and nature of the universe. From the cryptic messages being delivered by the cosmic radiation that continuously bombards the earth to the ever unfolding puzzle of the birth of the cosmos, it appears that the three elements were probably in some way a part of every high-energy event in the universe.



FATE OF THE UNIVERSE depends on its present mass density. The universe is now expanding. If the mass density is less than that for which the gravitational force would be sufficient to halt the expansion, the universe is open: it will expand forever. If the mass density is so large that the gravitational potential energy exceeds the energy in expansion, the universe is closed: it will stop expanding and ultimately collapse into a hot, dense fireball of fundamental particles. If the mass density produces gravitational potential energy that exactly equals the energy in expansion, the universe is said to be flat. The data pertaining to lithium 7 suggest that the universe is open, but the question is still far from being resolved; prevailing theory suggests that the universe is flat.

Synapses That Compute Motion

How do nerve cells process the information they receive from the environment? Studies of cells in the eye that interpret movement may define a mechanism involved in many other neural operations

by Tomaso Poggio and Christof Koch

The brain is the most sophisticated and powerful computing machine on earth, and its components are far more perplexing than those of the present-day computer. The computational capabilities of the tiny silicon chips that make up computer hardware are familiar and explicable, since they are built by human hands. Not so the functional subunits of the brain. What elementary mechanisms does this complex piece of "wetware" use to process information? What operations do they perform? Are there biological equivalents of transistors and diodes inside the skull?

The neuron, or nerve cell, is the basic information-processing unit of the brain. Early in this century scientists realized that neurons could process information by generating an electrical impulse called an action potential. In 1943 Warren S. McCulloch and Walter H. Pitts of the Massachusetts Institute of Technology proposed a formal model for neuronal activity. In their view the neuron adds together the excitatory and inhibitory signals sent by neighboring cells, then produces an action potential if the electrical sum exceeds a certain threshold. Otherwise it is silent. It was easy to show—as McCulloch and Pitts did—that circuits consisting of such units could perform all logical operations, and that these idealized neurons could in principle be the building blocks for the most complex digital computer.

In spite of its utility, this model is in need of replacement. For many years it has been clear that nerve cells are much more complicated than McCulloch and Pitts suggested. Nerve cells exhibit a variety of information-processing mechanisms; the nerve-cell membrane produces and propagates many different types of electrical signals and can alter its electrical properties to adapt to long-lasting stimuli. Many neurons do not generate classical action potentials at all. Although the generation and propagation of the action potential undoubtedly plays a major role in neuronal information processing, there are many other processing mechanisms operating in and among cell membranes whose roles are still a mystery.

In order to explore one of the processing operations, we are studying the means by which the eye detects motion, or the direction of a moving stimulus. We want to illuminate the underlying biophysical mechanism of motion detection and define the limitations of this operation as it is implemented in the brain. Already our work has focused on a novel processing mechanism that could be involved in many other kinds of neural operations. We hope the answers to our simple questions will ultimately lead to an understanding of higher processes such as perception, thought and the transformation from sensory input to motor output that takes place in all nervous systems.

The structure of the brain reflects its functional complexity. It is made up of about 1,000 billion neurons, and most neurons receive and send signals to thousands of other cells. A typical neuron has a cell body, which harbors the metabolic machinery that sustains it, a number of threadlike branches known as dendrites and one somewhat thicker branch called the axon. Usually the dendrites receive incoming signals and the axon provides the pathway by which the nerve cell sends signals to other nerve cells. Inside the neuron these signals can be chemical or electrical; they are communicated between cells by special chemicals secreted at a junction called the synapse [*see illustration on page 48*].

The retina, a sheet of cells lining the back of the eye, detects and transmits to the brain information about the visual environment. It is not much thicker than the edge of a razor and consists of a small number of cell layers. The cells we study, called ganglion cells, are the farthest from the photoreceptor cells, which convert light into electrical signals. In between are cell layers that feed signals from the photoreceptors to the ganglion cells. Axons from the ganglion cells make up the optic nerve, which links the eye to the brain.

Most organisms that can see are sensitive to the direction of motion of a visual stimulus. The neurons in the retina that distinguish direction, called direction-selective neurons, are specialized to recognize movement in just one direction. Motion in that preferred direction elicits a vigorous response, whereas the cell does not respond to movement in the opposite, or "null," direction.

Attempts to quantify this behavior date to the 1960's, when Horace B. Barlow and William R. Levick found direction-selective ganglion cells in the retina of the rabbit. They stimulated the cells by illuminating two slits in sequences that mimicked motion, then measured the responses by monitoring electrical activity close to, but outside, the ganglion cell body. First they illuminated each slit separately and recorded the neuronal response to each illumination. Then they simulated motion by flashing the pair of slits from left to right and from right to left and measured the responses [*see top illustration on page 49*].

Barlow and Levick found that motion in the preferred direction elicited action potentials and motion in the null direction did not. They also found that apparent motion in the null direction prompted a smaller response from the ganglion cell than the illumination of a single slit did. This observation was puzzling because twice as much light struck the photoreceptors during sequential illumination. The null-direction response was much weaker than expected.

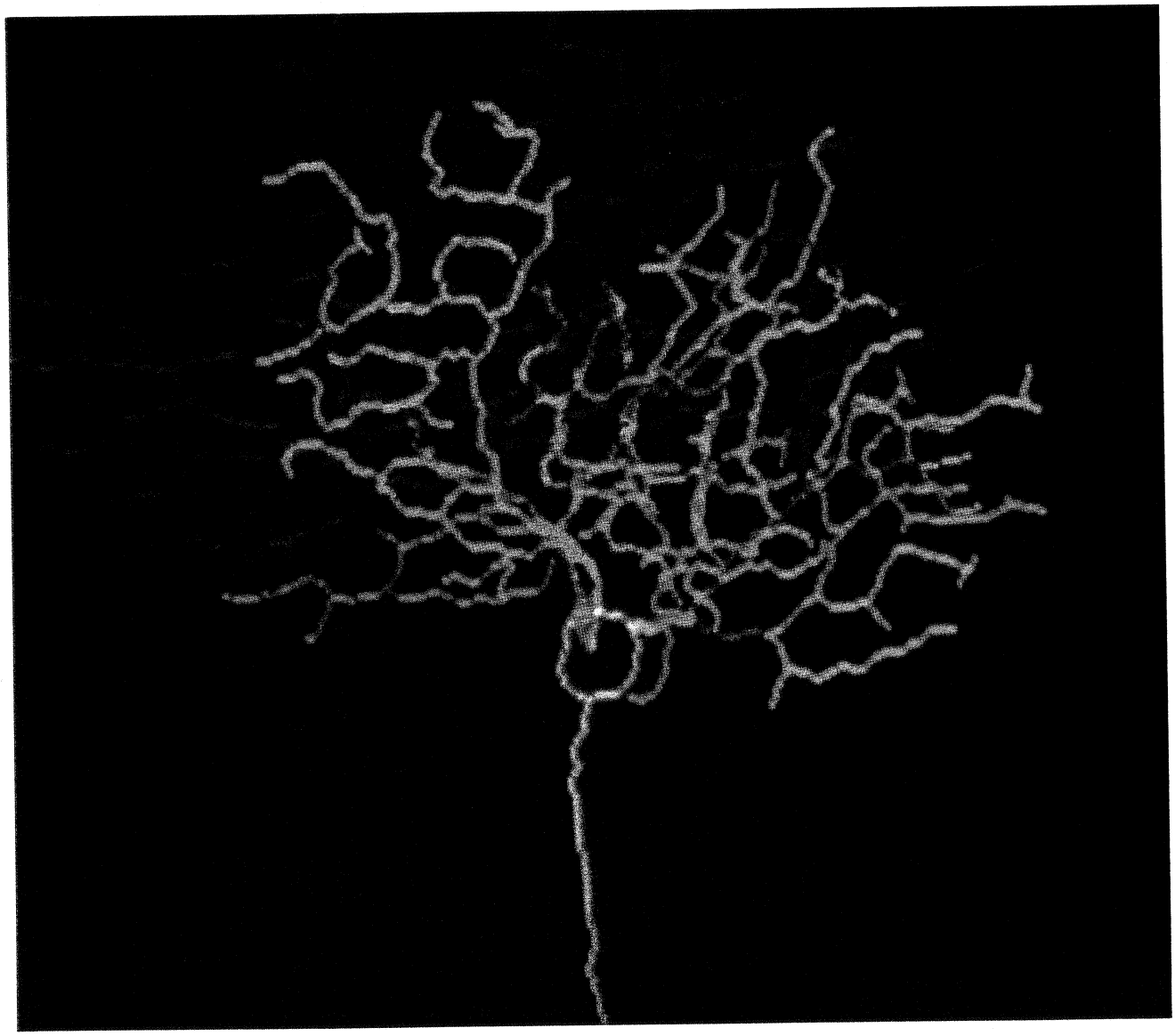
The investigators concluded that the

cells must achieve directional sensitivity by some kind of veto operation; that is, the weak response to motion in the null direction indicated not just a lack of sensitivity but an active damping, or veto, of an excitatory response. Neuroscientists of the day knew that nerve cells send two types of signals: excitatory signals, which promote the action potential, and inhibitory signals, which prevent it. The notion that excitation could be muffled by inhibition was not unusual. But how was inhibition triggered so selectively? After all, sequential illumination in either direction activates the same inhibitory and excitatory photoreceptors; the difference is just a matter of timing.

To explain their observations, Barlow and Levick put together a broad scheme for retinal reaction to motion; their model was built on the one proposed by the West German scientists Werner E. Reichardt and Bernhard Hassenstein in the 1950's to explain motion analysis in the visual system of insects. The theory advanced by Barlow and Levick specifies that photoreceptors connected to direction-selective cells are arranged so that a stimulus moving in the preferred direction activates excitatory cells before it reaches inhibitory cells. Hence motion in the preferred direction leaves inhibitory pulses trailing behind the excitatory pulses. This time lag is compounded, Barlow and Levick suggested, because inhibitory signals move more slowly than excitatory signals.

Therefore, when they are activated by movement in the preferred direction, excitatory signals easily outdistance inhibitory ones. They race through layers of retinal nerve cells to the ganglion cell body, where they spark action potentials. Because of the delay, the inhibitory signals arrive too late to veto the excitatory ones. If, on the other hand, motion is in the null direction, the inhibitory receptors are activated first, but the excitatory signals overtake the slower inhibitory signals. When they intercept one another, they cancel one another.

Barlow and Levick's model explains why stationary light, which activates excitatory and inhibitory receptors simultaneously, results in more excitation than light moving in the null direction, which gives inhibitory signals a head start. Furthermore, because the ganglion cell responds differentially to very small displacements of the slit in

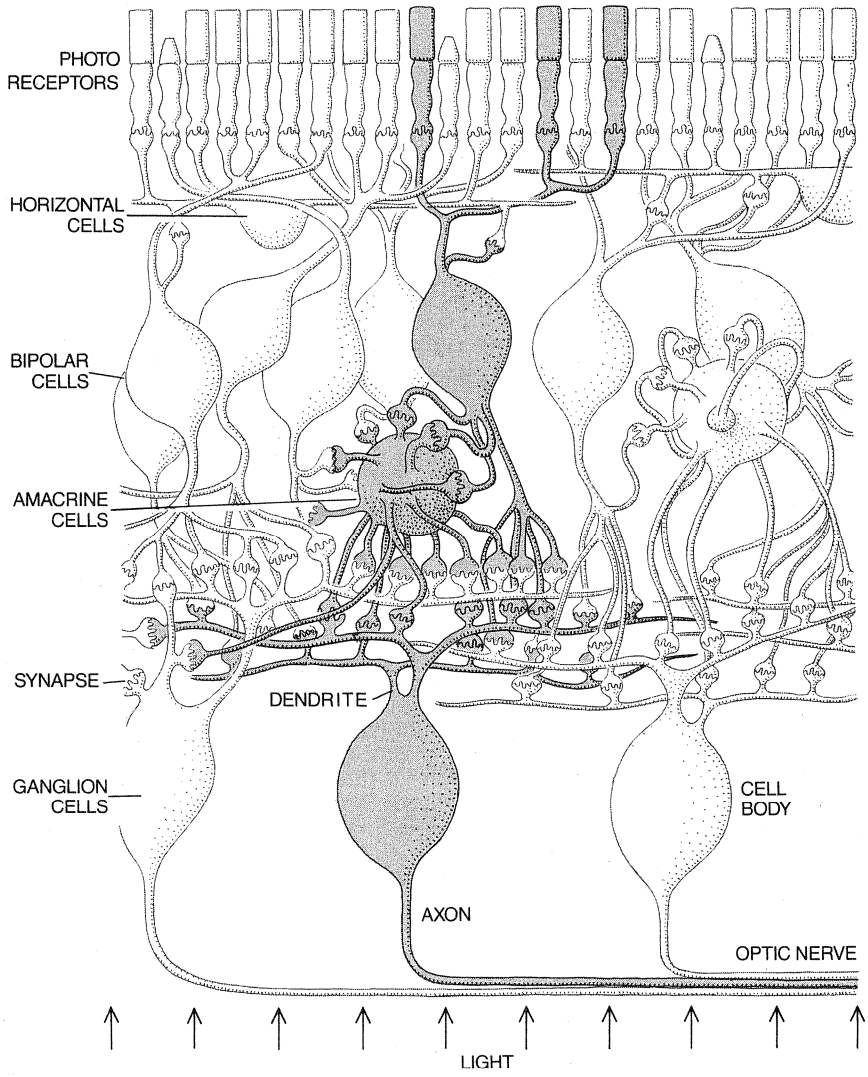


GANGLION CELL, part of the retina of the eye, can sense the direction in which an object in the field of vision is moving. Each ganglion cell responds to movement in one direction by sending electrical impulses to the brain. It ignores motion in the opposite direction. Frank R. Amthor and his colleagues at the University of Alabama identified and stained this cell, which was isolated from the retina of a rabbit. The colors distinguish different layers of cell branches. The cell has been enlarged about 5,000 diameters.

both the null and the preferred direction throughout its receptive field, it seemed that this veto operation must occur at many different places in the retinal nerve cells. Yet one question remained: What biophysical process could be responsible for the unusual veto interaction?

Understanding the generation of electrical signals in neurons requires some understanding of the events that precede them. As we have said, each branching dendrite of a neuron carries many hundreds of synapses receiving signals from "presynaptic" cells. When the action potential of a presynaptic cell arrives at the synapse, it triggers the release of a chemical messenger into the synapse. This messenger, called a neurotransmitter, diffuses across the small space between cells and binds to specialized receptors in the "postsynaptic" dendritic membrane. Neurotransmitter binding induces the opening of specialized channels in the cell membrane. The open channels allow ions, molecules or atoms that bear an electric charge, to enter and leave the nerve cell.

This opening and shutting of ion channels in the neuron membrane governs the electrical status of the cell. The most important ions taking part in this process are sodium, potassium and chloride. Pumps in the cell membrane increase the concentrations of certain ions and expel others; hence there is more potassium inside a cell than there is outside, and more sodium and chloride in the fluid surrounding the cell. The differences in concentration constitute what is called a concentration gradient for each ion.



THREE RETINAL LAYERS process visual stimuli and relay sensory information to the brain. Photoreceptors, which line the back of the retina, transform light energy into chemical and electrical signals that pass through the horizontal, bipolar and amacrine cells to the ganglion cells. Ganglion-cell axons form the optic nerve linking eye and brain.

As a consequence of ion distribution and the contributions of other charged molecules in the cell, the inside of a neuron is more negative than the outside by about 60 to 90 millivolts. (A millivolt is equal to one-thousandth of a volt; a 1.5-volt battery will power a flashlight.) This voltage is known as the resting potential because it is present when the cell is not conducting an impulse. The difference in voltage between the inside and the outside of the cell creates what is known as the potential gradient.

When synaptic stimulation opens up ion channels near the synapse, ions enter and leave the cell and the resting potential in this localized area is disturbed. The cell is said to be depolarized if this potential becomes more positive and hyperpolarized if it becomes more negative. This newly generated potential travels toward the cell body, decaying as it propagates, in a manner similar to electrical signal propagation in an underwater cable. If the final depolarization at the cell body is pronounced enough, it will induce an action potential. Therefore depolarizing stimulation is excitatory; the change in voltage is called the excitatory postsynaptic potential (EPSP). Inhibitory stimulation, which is most often hyperpolarizing, generates an inhibitory postsynaptic potential (IPSP).

Some synapses transmit excitation and some transmit inhibition, depending on which ion channels they regulate. When ion channels are open, the direction in which each ion moves is determined by the forces exerted by concentration and potential gradients. Hence sodium, a positively charged ion, diffuses into the cell through open sodium channels because both its concentration gradient and its potential gradient favor that direction. The influx of positive sodium ions causes depolarization of the nerve cell; therefore synapses that control sodium channels are excitatory.

By the same principle, potassium, which also bears a positive charge, leaves the cell when potassium channels are open. The concentration gradient encourages potassium's exit; in fact, it is so strong that it overcomes the force of the potential gradient, which works to draw positive charges into the interior of the cell. The departure of positive potassium ions hyperpolarizes the cell. Synapses that control potassium channels are therefore inhibitory.

A single nerve cell can experience many excitatory and inhibitory signals simultaneously. EPSP's and IPSP's propagate toward the cell body and can be measured as positive and negative contributions to the cellular potential.

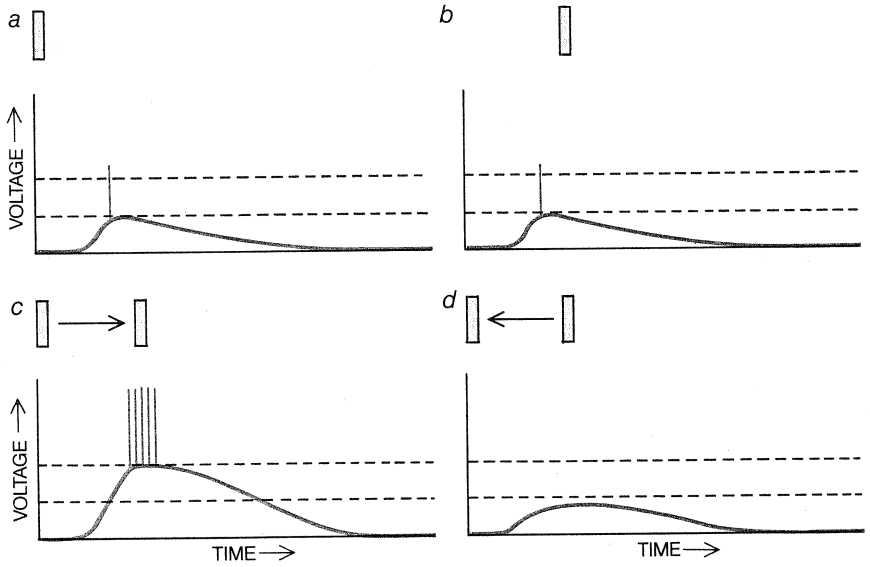
So far this view of neuronal activity does not stray from the one embodied by McCulloch and Pitts's formal neurons, and many neural functions appear to reflect this mode of operation.

In the late 1970's, however, several lines of evidence made it apparent that the ordinary interaction of excitation and inhibition could not account for the veto operation observed in motion detection. For instance, experiments that measured electrical activity inside rather than outside ganglion cells revealed the inner workings and interactions of EPSP's and IPSP's that control the generation of action potentials. They showed that when ordinary inhibition meets excitation, the net effect is usually hyperpolarization [*see bottom illustration at right*]. Intracellular recordings in turtle retinas, however, done by Piero L. Marchiafava at Italy's National Research Council in Pisa, showed that the interaction of excitation and inhibition that occurs during motion detection always results in mild depolarization rather than hyperpolarization. Indeed, hyperpolarization is never detected.

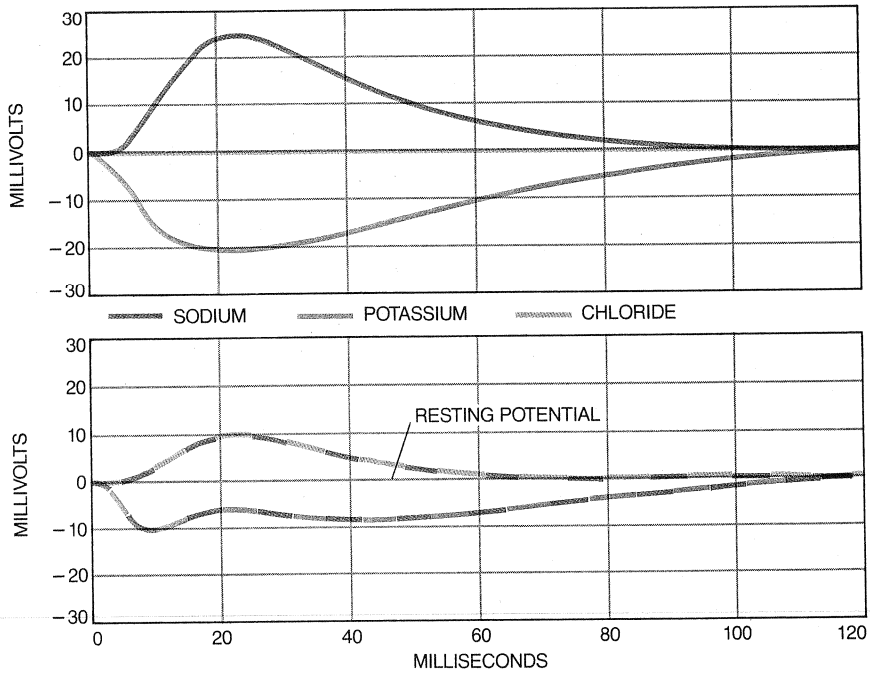
In 1978 Vincent Torre of the University of Genoa and one of us (Poggio, who was then at the Max Planck Institute for Biological Cybernetics in Tübingen) suggested a third type of synaptic mechanism that could be responsible for the veto effect observed in the detection of motion. The mechanism involves another type of inhibition called silent inhibition, which had been recognized in the 1950's; it is sometimes called shunting inhibition. We can use chloride to illustrate the basic principle, even though some experiments hint that chloride may not be the only ion involved.

Like sodium, chloride is present in a greater concentration outside the cell than it is inside; unlike sodium, chloride is negatively charged, and the potential gradient discourages the negative ions from entering the negative cell interior at rest. The concentration gradient and the potential gradient balance each other, so that when a silent inhibitory synapse signals chloride channels to open, nothing happens. Virtually no net redistribution of chloride occurs and there is almost no change in the resting potential.

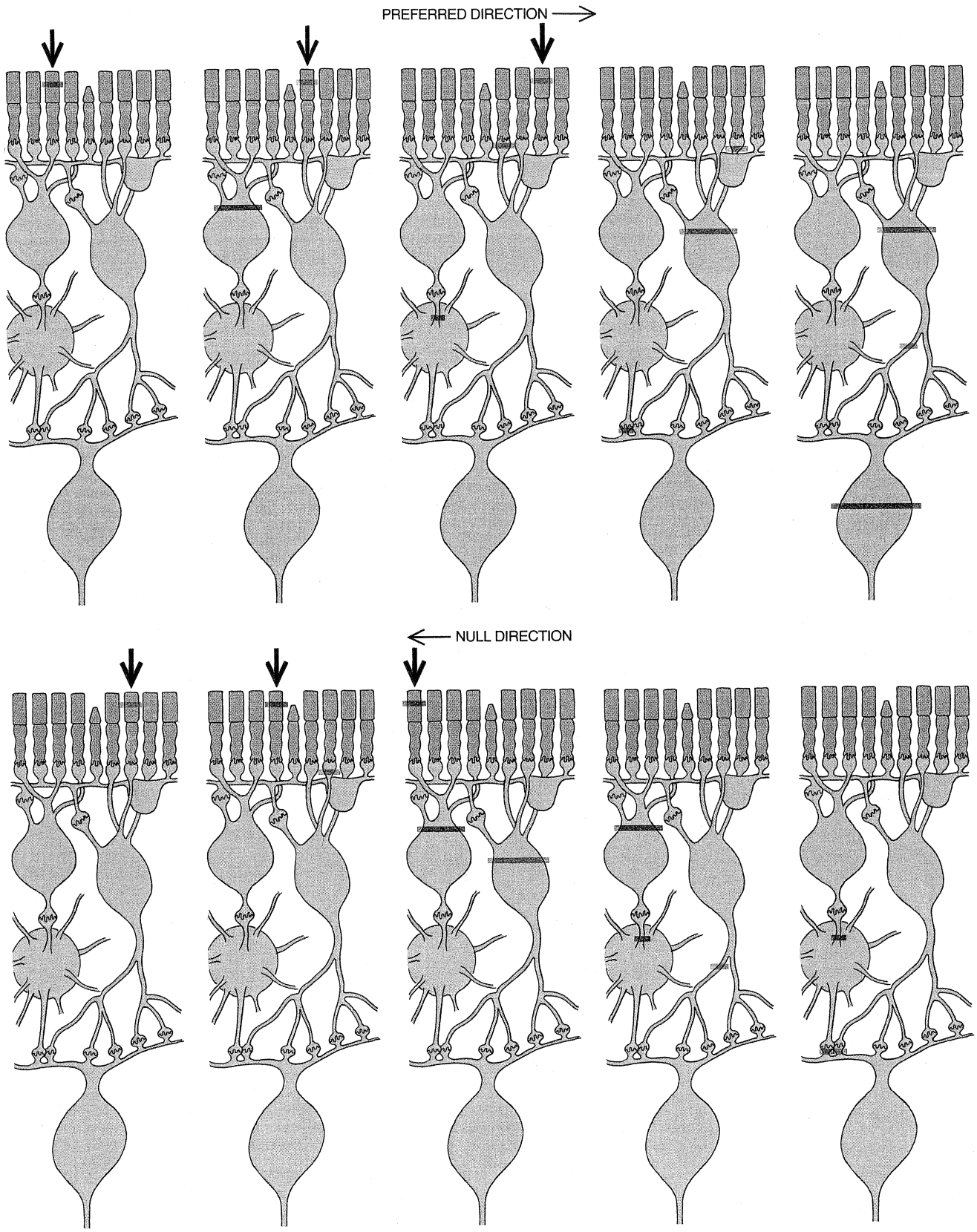
On the other hand, if a silent inhibitory synapse is activated at the same time as an excitatory synapse, the sudden influx of sodium depolarizes the cell and upsets the balance between the two gradients. The repelling effect of the potential gradient decreases and the concentration gradient overcomes it, drawing in chloride ions. The net effect of the interaction is a mild depo-



ELECTRICAL ACTIVITY OF GANGLION CELLS gave early clues to the mechanism underlying motion detection. In the 1960's Horace B. Barlow and William R. Levick of the University of California at Berkeley exposed rabbit retinas to light through two slits that could be illuminated singly (*top*) or, to mimic motion, sequentially (*bottom*). Illuminating either slit individually gave rise to an action potential, an electrical spike that propagates to other nerve cells (*a, b*). Apparent motion in one direction (the "preferred" direction) generated many action potentials (*c*), whereas motion in the opposite direction (the "null" direction) usually prompted a much smaller response (*d*). From these results, shown schematically, Barlow and Levick concluded that some kind of biophysical "veto" operation was selectively blocking the excitation caused by motion in the null direction.



NERVE POTENTIALS result from changes in ion concentrations inside the cell. An excitatory postsynaptic potential, or EPSP (*red line*), is sparked by the influx of positive sodium ions that occurs when an excitatory stimulus opens sodium channels in the nerve-cell membrane. When an inhibitory stimulus opens potassium channels, positive potassium ions escape from the cell, generating an inhibitory postsynaptic potential, or IPSP (*blue*). No movement of chloride ions occurs when only chloride gates are open (*green*). If chloride channels and sodium channels open simultaneously, however, chloride ions will enter the cell and dampen the EPSP; this effect is called silent inhibition (*red and green line*). Note that ordinary inhibition can make the cell more negative as it interacts with excitation (*red and blue line*), whereas silent inhibition has a positive influence.



RACE BETWEEN NERVE POTENTIALS has different outcomes at the ganglion cell depending on whether motion is in the preferred direction (*top*) or the null direction (*bottom*). In this model the photoreceptors for each ganglion cell are arranged so that a stimulus (*heavy arrow*) moving in the preferred direction activates excitatory receptors (*red*) before inhibitory receptors (*blue*). The model also assumes that inhibitory signals (*blue bars*) are delayed in time with respect to excitatory signals (*red bars*). When motion is in the preferred direction, inhibitory pulses never catch excitatory impulses, which generate action potentials at the ganglion cell body. For movement in the null direction, however, the inhibitory signal arrives at the ganglion cell at the same time as the excitatory signal and prevents the generation of an action potential. The authors suggest that the mechanism by which the two signals negate each other, implementing the veto operation proposed by Barlow and Levick, might involve silent inhibition.

larization like those Marchiafava observed in the retina of turtles.

Unless the inhibitory signal coincides with an excitatory signal, it cannot be detected through monitoring of the nerve potential; hence the name "silent" inhibition. Silent inhibition depends on excitation to activate it and, as Barlow and Levick's model predicts, excitatory and inhibitory signals coincide only when they are stimulated by motion in the null direction. For movement in the preferred direction, the inhibitory delay prevents the vetoing of excitation and the cell responds vigorously. Thus our concept of silent inhibition represents a viable implementation of the abstract models advanced by Reichardt and Hassenstein and by Barlow and Levick.

The silent-inhibition mechanism is attractive for application to direction selectivity for another reason. Our model implies that the best placement for a silent inhibitory synapse is either at the same location as an excitatory synapse or somewhere between the excitatory synapse and the ganglion cell body. The model therefore needs just a few synapses and a patch of dendritic membrane to operate. The two signals interact before they reach the cell body, thereby satisfying the observation that the veto probably occurs at many different locations in the retinal neurons.

We were still unsure, however, that the physiological features our model requires were realistic. What kind of proximity did inhibitory and excitatory synapses need to influence one another's potential? What were the optimal locations for synapses and the optimal configurations of dendrites? We turned to the computer for answers.

The theory we used to describe the spread of the electric potential in a nerve cell is a descendant of the theory developed by Lord Kelvin in the 19th century to analyze current flow in transatlantic telephone transmission lines. Wilfrid Rall of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases first applied Kelvin's analysis to the spread of potential in dendritic trees. The actual computation began at the Max Planck Institute; later we turned to a circuit-simulation program called SPICE, which was developed more than 10 years ago at the University of California at Berkeley.

We began developing our particular version about three years ago with the help of Patrick A. O'Donnell of the Artificial Intelligence Laboratory at M.I.T. From anatomical descriptions of the shape of a neuron, the length and diameter of its branches and so on our version of SPICE constructs an appropriate cable model and then assigns electrical properties to the computer-generated dendritic tree. It can plot in color the course of the nerve potential in response to the synaptic input that we dictate.

Such simulations have shown that our proposed mechanism is credible: it generates patterns of electrical activity that account for direction selectivity. Our simulations also confirmed our hunch that silent inhibition must be a very localized phenomenon, dependent for its efficacy on the relative positions of excitation and inhibition in the dendritic tree. In order to block the propagation of an EPSP, silent inhibition must occur on the direct path between the excitatory synapse and the cell body. Although these simulations assume that the dendritic membrane does not amplify excitatory signals, these limitations would still hold true if it did. Hence our simulation has enabled us to demonstrate that the veto operation takes place at many different locations within the dendritic tree and before the signals reach the cell body.

In recent years additional information has accumulated from recordings of the electrical events on the inside of direction-selective cells. How well does our theoretical model fare in view of new experimental evidence? Recordings from ganglion cells in the retina of turtles and bullfrogs support the scheme of synaptic interactions represented in our model. Furthermore, Marchiafava's more recent intracellular recordings have revealed the workings of silent inhibition that are usually invisible when inhibitory synapses are activated alone. By injecting a positive current into a cell through a recording electrode, Marchiafava managed to make the cell's resting potential more positive; then the isolated action of silent inhibitory signals appeared as hyperpolarization of the elevated resting potential.

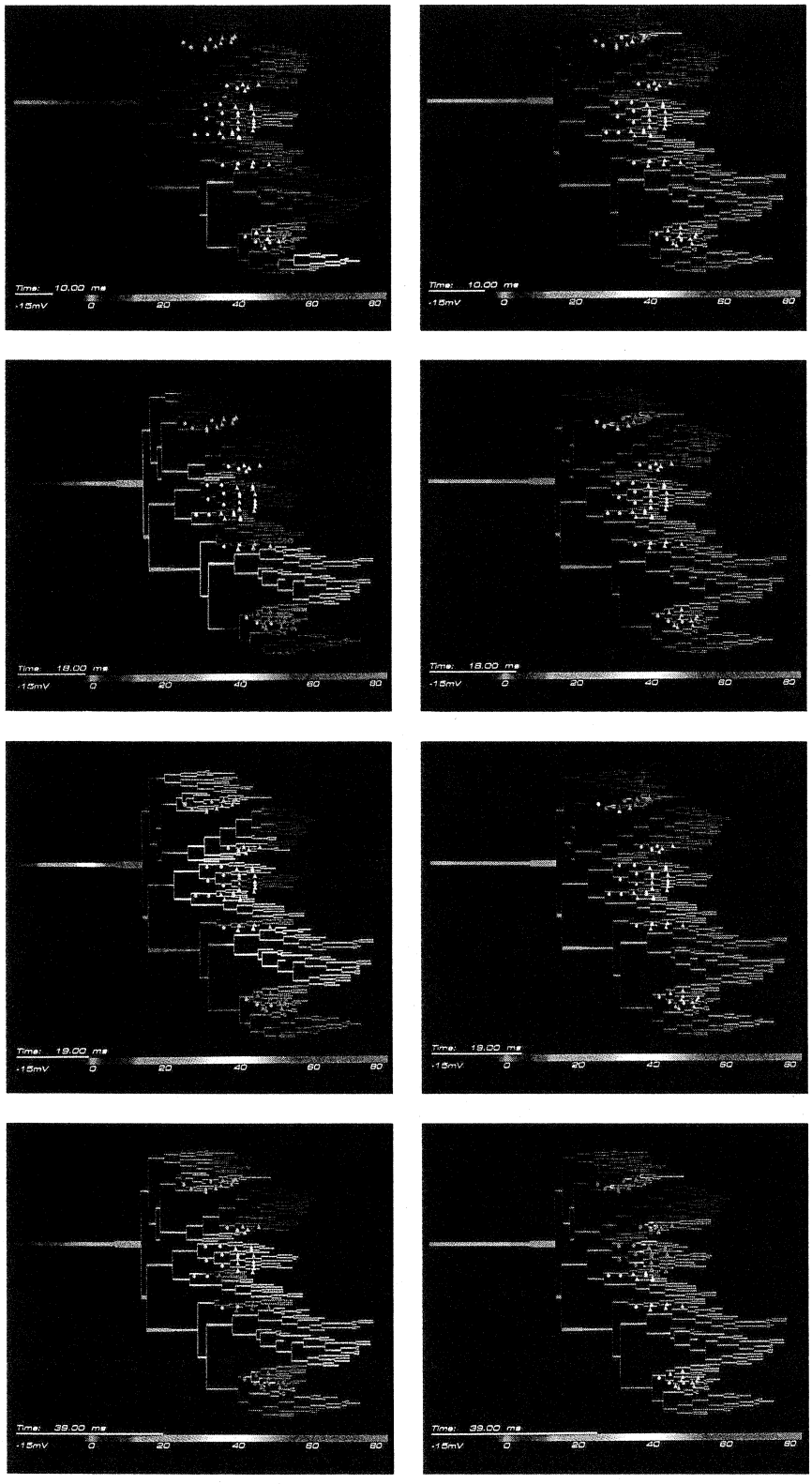
Other investigations have disclosed the anatomy of the direction-selective cells. By injecting fluorescent dyes into the cells, Frank R. Amthor, Clyde W. Oyster and Ellen S. Takahashi of the University of Alabama obtained a clear image of the rabbit retinal cells Barlow and Levick had explored 20 years earlier. Ralph J. Jensen and Robert DeVoe, then at the Johns Hopkins University School of Medicine, carried out the same procedure on turtle ganglion cells with equal success. The cells have highly branched dendrites with extremely fine extensions, maximizing the number of sites where synaptic interactions can operate. This configuration matches our notion of silent inhibition as a distinctly localized phenomenon.

One prediction that remains to be tested is the relative location of excitatory and inhibitory synapses in the dendritic tree of the direction-selective cell. The recent discovery of the neurotransmitters that mediate the EPSP and IPSP will aid this investigation. The amino acid gamma-amino-butyric acid (GABA), a common inhibitory neurotransmitter in the central nervous system, also plays the inhibitory role in direction selectivity: direction-selective ganglion cells treated with drugs that block GABA action respond equally to motion in the null and preferred directions. With experiments of similar design Richard H. Masland of the Massachusetts General Hospital and Michael Ariel and Alan R. Adolph of the Eye Research Institute in Boston have shown that acetylcholine (ACh) acts as the excitatory neurotransmitter for motion discrimination in the retina of turtles and rabbits.

Because ACh and GABA can be labeled, it may now be possible to identify the excitatory and inhibitory synapses on stained direction-selective ganglion cells. Such work is currently in progress in the laboratory of John E. Dowling at Harvard University. We expect that the results of this experiment will be critical in confirming or refuting our model.

Our model is sufficient to account for current empirical evidence, but other models for direction selectivity have not been ruled out. For instance, it is conceivable that excitation and silent inhibition interact before reaching the ganglion cell, on the dendrites of another retinal neuron. One possible host for such interaction is the starburst amacrine cell described by Masland [see "The Functional Architecture of the Retina," by Richard H. Masland; SCIENTIFIC AMERICAN, December, 1986]. The amacrine cells lie in the intermediate layer of the retina that carries signals from the photoreceptors to the ganglion cells.

Amacrine cells are the only cells in the retina that synthesize and secrete ACh; thus they are the likeliest to provide the excitatory input to direction-selective ganglion cells. The release of transmitter from the cell might already reflect the influence of inhibition, however. Furthermore, DeVoe and his collaborators have found the first evidence for direction-selective properties in turtle amacrine and bipolar cells, which also reside in the cell layer between the photoreceptors and the ganglion cells. Their finding raises the possibility that motion may be



COMPUTER SIMULATIONS re-create the morphology and electrical properties of the ganglion cell on page 47. "Hot" colors, such as red, orange and yellow, indicate excitation; "cool" colors indicate inhibition. The activity of excitatory synapses (*triangles*) and inhibitory synapses (*circles*) is similarly depicted. In the left-hand sequence a stimulus moves from the bottom to the top of the frame and inhibitory responses are delayed by 20 milliseconds to model motion in the preferred direction, whereas there is no delay on the inhibitory signals in the right-hand sequence, which models null-direction stimulation. Excitatory signals reach the cell body and generate an action potential at 19 milliseconds in the left-hand sequence. The model, which was programmed by Patrick A. O'Donnell of the Massachusetts Institute of Technology, showed that excitatory and inhibitory synapses must be quite close together in order to achieve the veto effect of silent inhibition.

computed in other retinal locations instead of in the ganglion cells or in addition to them.

A combination of theory, modeling and experimentation is therefore on the verge of elucidating the mechanism underlying detection of motion in the animal retina. Why is this operation so interesting? As an important function in the first stage of vision, direction sensitivity is a worthy subject by itself. Much more important would be the understanding of an elementary information-processing mechanism that could turn up in other computational tasks. A number of researchers using different animals have proposed that the same mechanism is involved in the computation of binocular depth, visual motion discontinuities and tactile motion across the body surface.

As a computational element the synaptic veto model is attractive because of its localized action and its flexibility, particularly in contrast to action-potential generation. Because it operates on such a small scale, the mechanism could be replicated hundreds of times in the dendritic branches, establishing more or less independent subunits in a single neuron. One can think of the McCulloch and Pitts model as equating a neuron with a single transistor, whereas our model suggests that neurons are more like computer chips with hundreds of transistors each.

We call our genre of investigation the biophysics of computation; it is the study of the involvement of the various biophysical mechanisms underlying information processing by the nervous system. Of course, the biophysics of computation is not confined to the generation of the action potential and the interactions among synaptic inputs. There are many biophysical phenomena capable of processing, propagating and storing information. We have examined a variety of biophysical mechanisms; they implement operations such as filtering the signals that occur at a particular frequency, modifying the strength of connections between nerve cells and controlling with slow-acting chemicals the output of nerve cells.

Both experimentalists and theoreticians are engaged in identifying these phenomena and characterizing their roles in information processing. It may someday be possible to infer from the cellular morphology of any given neuronal circuit the operations it can perform. Thus probing the intricate secrets of the central nervous system may eventually unite the sophisticated processing of the human brain with the depth of understanding that created computers.