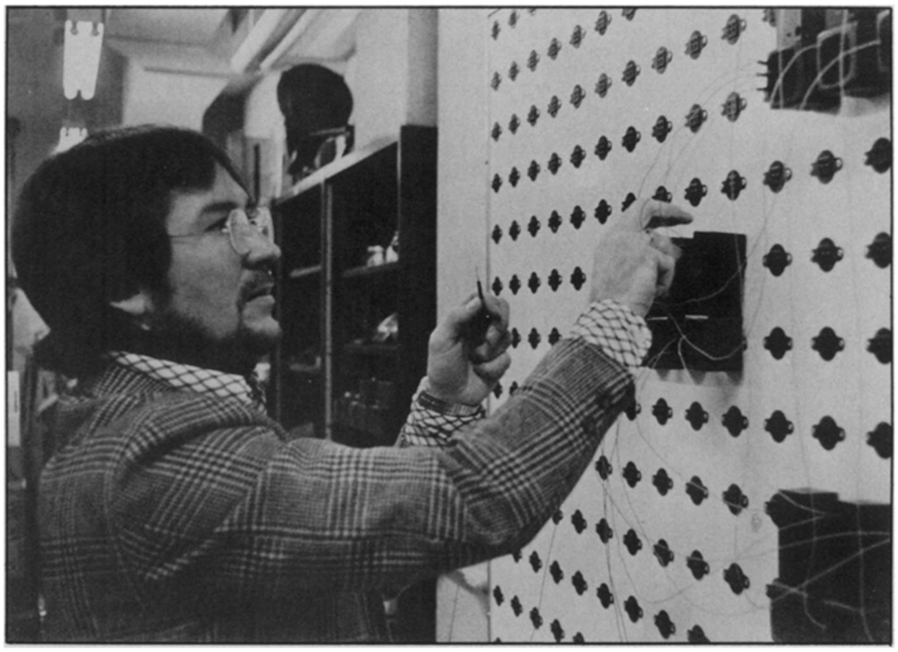
# To Build a Brain



Eitemiller, University of Colorado

*MacGregor hooks up a network of electronic model nerve cells on a power board.*

## An engineer uses electronic components to identify basic interactions of nerve cells

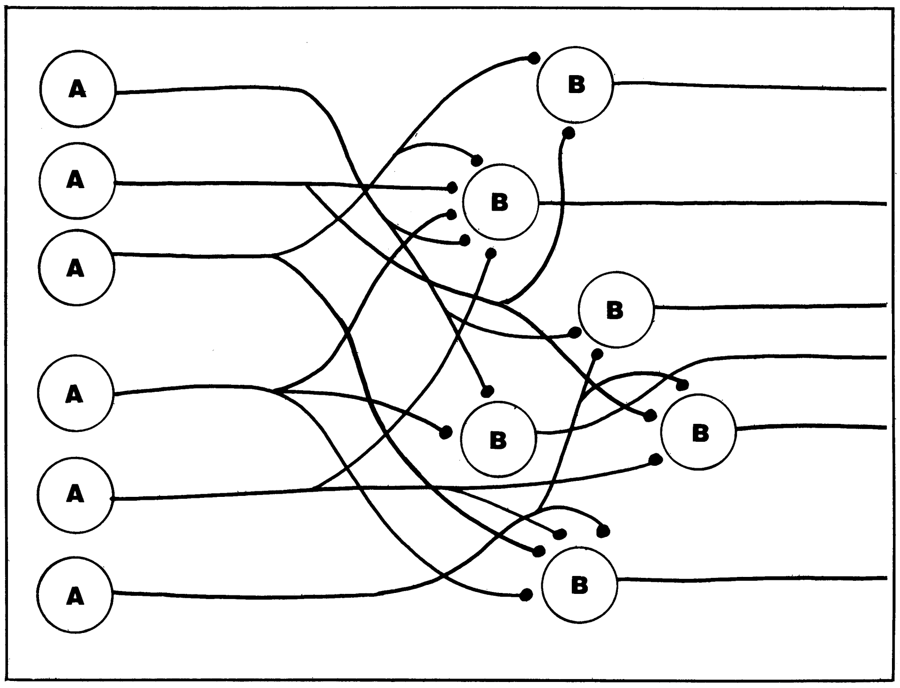
BY JULIE ANN MILLER

The portrait painter looks at his model, then makes a stroke with his brush while watching the canvas to see whether he has produced the likeness he intended. Scientists in a new approach to study of the brain examine the electrical patterns in a rat's brain, then plug and unplug electronic components to mimic the characteristics. Research on the brain has produced many theories, but to make the most of such models one needs to be better able to spell out their dynamic predictions, says Ronald J. MacGregor, an engineer at the University of Colorado.

MacGregor and Robert M. Oliver designed electronic models of nerve cells to investigate how groups of brain cells may function. Each imitation nerve cell contains printed electronic circuit boards, amplifiers and some other gadgets, as MacGregor describes it. The circuits in the model were derived from a set of complex equations relating the input and output of real nerve cells.

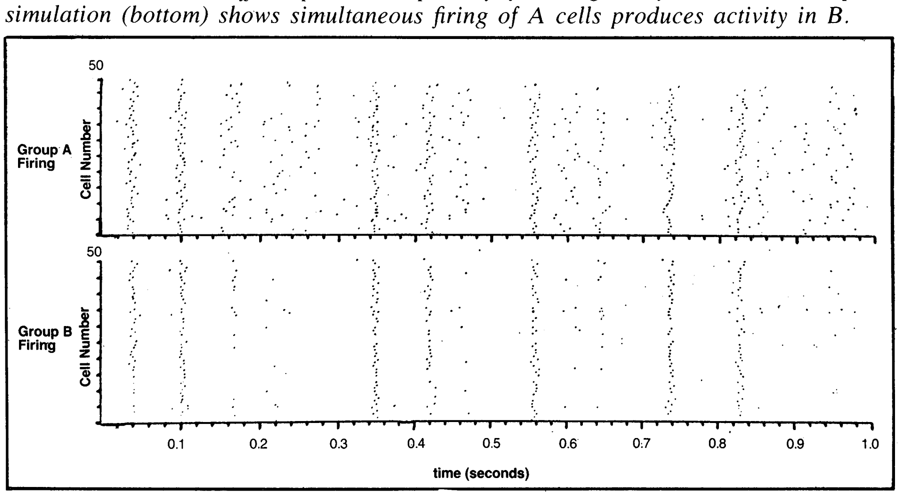
Like nerve cells, the model will produce a signal when its electrical input is above a set threshold; the signal is a series of impulses of fixed amplitude. Another realistic feature is that inputs to the model from some components can be more influential than others in making the model cell fire. The model also requires a refractory period before it can fire for a second time, and can display what biologists call plasticity, a response that is altered by past experience. For example, the model, like many real cells, will respond to continuing stimuli with a burst of activity, but after a while the model cell will shut off.

The electronic models can be adjusted with a screwdriver to vary four parameters, so that different types of nerve cells can be represented. The researchers have set the parameters so that the model cells approximate cells in the reticular formation, the area of the brain they study. With their most sophisticated components, the researchers are able to hook up 100 model cells on a power board.




MacGregor

*Cells connected in diffuse pattern (top) may filter signals from noise. Computer simulation (bottom) shows simultaneous firing of A cells produces activity in B.*



Although more cells can be included in an experimental network if the researchers use a digital computer simulation, they prefer the electronic models. "You take the wires with metal tips and just plug in and pull out. Lights blink and you immediately see how the system operates. You can be part of the system," MacGregor explains. "With digital, you have to wait hours and then evaluate the output."

MacGregor approaches the complexity of the brain, with its more than 10 billion nerve cells and more than 100 trillion interconnections, by assuming that there will be basic patterns of activity. These "canonical systems" will be used in different parts of the brain as basic circuits are repeated in different parts of a television or computer. With his 100 electronic model cells, MacGregor hopes to reproduce and investigate the interactions of the basic patterns.

MacGregor has in the last 12 years explored several elements of brain activity—the rhythmic firing of nerve cells, feedback inhibition and filtering of signals from background noise. These patterns tend to produce a synchronous cluster of nerve cell signals. "Clusters might be the language between parts of the brain," MacGregor says.

MacGregor's investigations begin with real nerve cells. He and his colleagues insert needlelike tungsten and glass electrodes into a specific area of the rat brain. The electrodes are connected to an oscilloscope, which displays electrical signals of the nerve cells as sharp spikes. MacGregor has examined the electrical activity of single cells and small groups of cells.

Many cells fire in a set rhythm, MacGregor and co-workers Wally Miller and Philip M. Groves discovered when they recorded nerve cell activity in the reticular formation. This region is important in arousing the brain to a threatening situation. The reticular cells seem to regulate input and output of the brain and to modulate and monitor other brain processes.

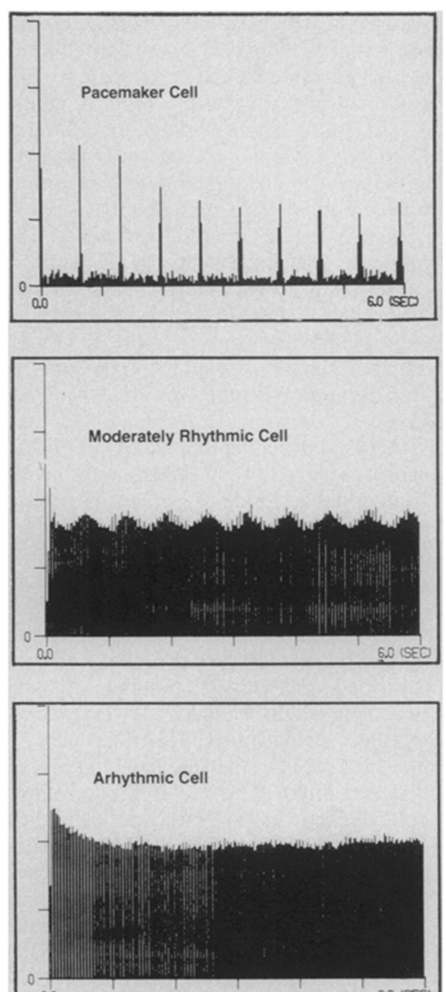
The researchers found that some reticular formation cells, which they call pacemaker cells, fire at intervals of 0.64 seconds. When the electrical activity of these cells was converted into an audible signal, they heard a steady, compelling beat. "We have found that you can dance to it," MacGregor says.

Other cells, the researchers find, have a more subtle rhythm that no dancer, without a computer, could follow. In those cells the rhythm is disguised by background electrical activity. MacGregor used complex mathematical techniques to uncover this moderate rhythmic pattern. "Picture time marked off in clear divisions," MacGregor explains. "Cells with moderate rhythms are more likely to fire at that time than in between. Moderately rhythmic cells have around a 50-percent probability of firing on schedule." Many other cells in the reticular formation appear to have no rhythm at all, but fire randomly. The graphs show the probability that each type of cell will fire at any time given that it fired at the time point marked zero.

Cells with strong, moderate, weak and no firing rhythms were all found in the same cell population. The researchers do not yet know how to predict what the firing pattern of a cell will be. They suspect that the rhythm originates within the nerve cell, but the rhythm may also result from the signals the cell receives.

MacGregor wants to focus not on the individual cell but on patterns of interaction. The researchers have been able to measure simultaneously the firing of pairs of brain cells to detect whether they are communicating with each other. Sometimes a single electrode positioned between cells picked up signals from two or three neighboring nerve cells. The signals from the different cells could be distinguished by their different strengths. In other experiments two separate electrodes were used to record signals from cells hundreds of microns apart.

For most of the cells examined, the researchers found no correlation between the timing of their spikes. Firing in a few cell pairs, however, was strongly correlated, so that the cells were likely to fire simultaneously. These cells probably were stimulated by the same input from other cells. Activity of other pairs of cells had a weaker correlation, which might reflect either a connection between them or a shared input. "Thus, this is not a highly reliable telephone-switchboardlike connection, but rather a line of influence which tends to modulate and play upon the activity of the cells in terms of many other ongoing variables," MacGregor concludes. Correlated firing was more likely between neighboring cells than between distant cells, and cells with strong rhythms were most likely to exhibit correlated firing.




*Graphs reveal rhythm in many brain cells.*

MacGregor et al., Experimental Neurology

Another element of brain activity is feedback inhibition. When one group of nerve cells fires, the impulses not only stimulate other cells to fire, but also loop back along branched fibers to temporarily inhibit further activity by the original group. Per Andersen of the University of Oslo suggested that this mechanism is responsible for the alpha-rhythm of the brain. MacGregor, in this case, used a computer to simulate nerve-cell activity. "We validated the Andersen model and cleared up some details," MacGregor reports.

Studies of brain cells have suggested that some groups of cells act like electronic filters to sort synchronized signals from random noise. MacGregor has suggested that a group of nerve cells, hooked up in a particular way, filters the signals sent by another group. The key is diffuse connections, which are illustrated in the diagram. Each cell of population A sends signals to a large number of cells in B, and each cell in B receives input from many A cells. Cells in B will fire only when they receive several signals simultaneously. Therefore when a single A cell fires, no B cell is adequately stimulated. But if several A cells fire, B cells will fire in turn. "A synchronous cluster of signals in A produces a synchronous cluster of signals in B," MacGregor says. "Ongoing random activity doesn't get through."

MacGregor and co-workers continue to work both on recording the relationships in firing among brain cells and in generating the relevant patterns electronically. "We hope these techniques will be useful in investigating basic principles that will improve our understanding of diseases," MacGregor says. "Take epileptic seizures, for example. There are lots of theories around. If we can use electronic and digital models for spelling them out in detail, we may be able to validate a theory.

"Psychologists tend to study the overall functioning of the brain. Biologists, on the other hand, tend to study detailed mechanisms of electrical signal generation in the cells," MacGregor says. "Between those two poles, engineering emphasis on how systems work may be precisely what is needed." □