Mimicking the Brain

Using computers to investigate neurological disorders

By LISA SEACHRIST

Deep within the brain a single neuron fires. That electrical signal triggers a biochemical chain reaction that courses from neuron to neuron, ultimately forming a set of connections that brings alive a scenic vista, a child's touch, or the memory of a long-ago event. Arresting any part of that signal devastates the cognitive activities that appear to make us human.

While the speed and precision of the human brain lead some people to refer to it as the ultimate computer, the brain maintains a distinct advantage over the computer—resilience. When crucial interactions between neurons falter, the brain reroutes signals in an attempt to maintain the ability to think, remember, and perceive. "When you damage just one small part of the computer, the whole thing will collapse," says neurologist and computer scientist James Reggia of the University of Maryland in College Park. "The brain is very different. It is able to adjust its own circuitry."

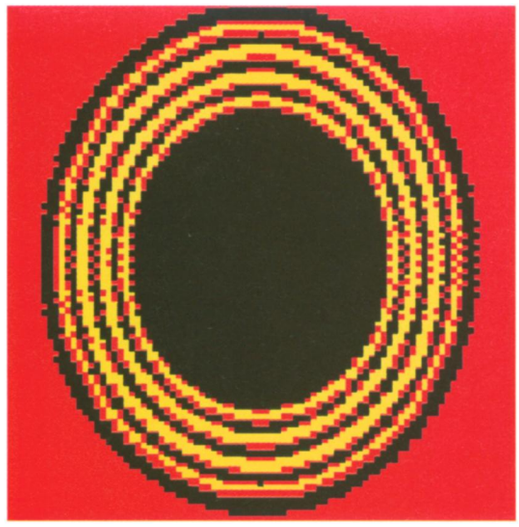
Despite this resilience, the brain has its limitations. Neurological diseases such as Alzheimer's and Parkinson's cause progressive losses of vital cognitive functions that no degree of brain-initiated rewiring can repair.

Scientists do not know why some conditions spur the brain to large-scale reorganization of the synapses, or junctions between neurons, whereas others result in permanent damage. The problem lies in a basic dichotomy in neuroscience: Remarkable gains in elucidating the way neurons communicate with each other on the molecular level simply haven't explained the biology of how we think, sense, and feel.

For the past decade, researchers have employed a controversial tool to decipher this puzzle: computer systems known as neural networks. These networks simulate elementary, but poorly understood, brain functions such as reading and language (SN: 11/26/88, p. 344). Scientists exploring artificial intelligence have also made extensive use of neural networks. Now, some researchers are using them to model disorders of the brain, with an eye to discovering better therapeutic strategies.

Reggia organized a workshop at the University of Maryland in June to explore ways in which computational models of brain disorders ranging from phantom limb pain to stroke to Alzheimer's will enable scientists to test theories of how and why the brain responds to disease and trauma.

"The complexity of the brain makes it necessary that we use computational models to understand how disease affects the brain," says Reggia. Otherwise, "it's almost like trying to understand the climate without using computer models."



Computer simulation of a premigraine visual aura shows a central blind spot with only peripheral vision active.

Psychiatrist-turned-computer-modeler Manfred Spitzer of Heidelberg University in Germany used neural modeling to tackle the enigma of phantom limb pain.

For over a hundred years, physicians have reported that amputees not only continue to feel their amputated limbs, they often suffer cramping, burning, and shooting pains in specific regions of those limbs. Researchers have traced the origin of such pains to reorganization of the brain area that formerly processed sensations in the absent limb. As neurons in that area adapt to some new purpose, their activity manifests itself as phantom pain (SN: 6/10/95, p.357).

Spitzer, however, questioned just how such a reorganization would occur. Paraplegics, like amputees, suffer loss of stimulation from large sections of their bodies, and presumably their brains contain areas that cease activity for want of stimulation and become ripe for reorganization. Yet the paralyzed don't suffer phantom limb pain.

The cortex of the brain creates specific areas that both receive neural impulses from various parts of the body and issue instructions to them. Spitzer and his colleagues developed a neural network that mimics this mapping electronically. When the team deprived the network of a specific input, as might happen after amputation of a limb or loss of stimulation as a result of paralysis, the areas of the network responsible for that input didn't undertake any new functions, says Spitzer.

Unlike a paraplegic, whose spinal cord is severed, an amputee retains neural connections between all parts of his or her body and the brain. Neurons attached to the spinal cord, which used to serve as conduits between the now-severed limb, the spinal cord, and ultimately the brain, still exist. Previous research indicates that these leftover neurons often fire at random.

The German team discovered that adding random firings—or noise—to the neural network indeed forced the network to reorganize, much as the brain does. Spitzer speculates not only that this phenomenon explains the origins of phantom limb pain, but also that "noise drives cortical reorganization."

Neural rewiring may result in pain for amputees, but stroke victims depend on it to regain speech and movement. Stroke occurs when tissue in some areas of the brain is deprived of oxygen and dies. Patients who suffer little damage and whose brains reorganize to compensate for the loss can make remarkable recoveries.

But not all stroke patients do well.

Some appear to stabilize at first, but over the next 8 to 10 hours they decline until the nervous system supports only basic biological functions. To explore this series of events, Reggia and his colleagues focused on a phenomenon that occurs in brain tissue surrounding the stroke-damaged area. The region around the dead tissue, known as the penumbra, loses its ability to transmit and receive electrical impulses because it lacks an adequate blood supply. Many researchers suspect that saving the penumbra is the key to limiting the effects of stroke.

The Maryland group created a computer model that simulated stroke-induced loss of feeling in various areas of the body. The model then tried to recover "sensation," and it often did so, with varying degrees of success. But sometimes the model couldn't recover, getting much worse instead.

"This was particularly surprising," says Reggia. "In certain versions of the model, it mimicked real life and got worse."

Reggia is still investigating what causes such deterioration. He intends to incorporate the neurochemical changes that accompany stroke in an attempt to understand why the penumbra dies.

Meanwhile, Eytan Ruppin, a Tel Aviv University neurologist and computer scientist who is collaborating with Reggia on the penumbra work, has used a neural network to explore what characteristics of stroke lead to cognitive damage, such as stroke-related dementia.

Ruppin's model incorporated data from computed tomography, or CT scans, of the brain. These images show how large an area—or how much structure—of the brain has been affected by a stroke. He also used data from positron emission tomography (PET) and functional magnetic resonance (MR), which measure brain activity and indicate the extent to which function has been impaired.

Ruppin found that the number, rather than the size, of strokes determined how much brain function a person is likely to lose. Moreover, the extent of the functional damage revealed in PET scans proved a much better predictor of cognitive impairment than any measure of structural damage. "However, we are using a very simple model, so we can't relate damage to the model to specific damage to the brain," says Ruppin.

Ruppin's model does offer an explanation for a well-known clinical observation. People with Alzheimer's disease who suffer a stroke usually end up suffering much greater functional damage than other stroke victims. To mimic the loss of neurons that an early-stage Alzheimer's patient experiences, Ruppin eliminated some of the pathways in the model network. The model couldn't compensate for the "stroke" damage. "This could account for the multiplicative effect that Alzheimer's patients show," says Ruppin.

Random firings in a neuron travel across the synapse between amputated limb and spinal cord on their way to the brain.

Apart from the effects of stroke, the complexities of Alzheimer's disease provoke many questions about how the characteristic destruction of neurons leads to dementia. Michael Hasselmo, a neuroscientist at Harvard University, is using a computational model to test a theory that could explain why one of the first symptoms of Alzheimer's disease is loss of short-term memory.

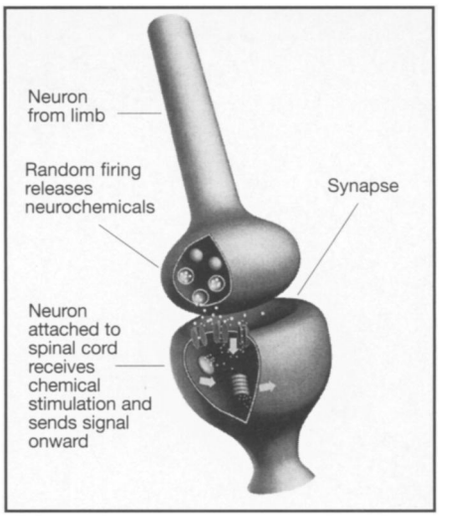
Alzheimer's patients develop characteristic plaques and tangles in their brains. Both structures result from the buildup of certain proteins, and both multiply as the illness progresses.

Tangles first begin to form in the hippocampus, a region of the brain responsible for making new memories. The hippocampus takes in new information and, in a process called synaptic modification, rapidly strengthens the connections among synapses in other areas of the brain needed to store the memory. Because people with early Alzheimer's typically have trouble remembering recent events—where they put their glasses, for example—the Harvard team chose to study the hippocampus.

Hasselmo suggests that a breakdown in the metabolic controls of a single neuron in the hippocampus could result in the activation of many neuronal connections—a process he calls runaway synaptic modification. "What I am proposing is that the pathology is flowing from the hippocampus [to other areas of the brain]," says Hasselmo.

Suppose a person meets someone named Fred. The hippocampus sets to work associating this new face with the name Fred. When this person meets Fred a second time, the hippocampus strengthens the synapses that connect the face with the name. Hasselmo proposes, however, that the situation may be quite different for an Alzheimer's patient. On the second encounter, instead of strengthening the association between the name Fred and that particular face, the hippocampus strengthens all the synapses storing the faces of anyone called Fred that the person has ever come across. "The information just gets mushier," says Hasselmo.

Hasselmo created a network to model this information-storing function of the hippocampus. Then, he damaged a part of the model so that it activated too many neurons. Neuronal stimulation spread through the hippocampus to other areas of the brain. Hasselmo theorizes that regions of the brain which undergo the greatest amount of synaptic modification, like the hippocampus, were the most susceptible to runaway synaptic modification.



"This is just a hypothesis now, but it is a testable one," says Hasselmo. "We can test whether compounds that limit synaptic modification will stop the progression throughout the brain."

Reggia maintains that the potential benefit of computational simulation depends upon creating models that not only mimic biology but also test hypotheses. His group is testing an old theory about migraine headaches.

Many migraine sufferers experience visual hallucinations before the pain of the headache hits them. Some scientists speculate that the visual disturbances result from a wave of electrical and biochemical changes spreading across the cortex.

However, scientists can't test this hypothesis in humans, and animals can't tell researchers what they're seeing. Reggia and his colleagues created a model that maps the wave onto the visual cortex. Early results create patterns similar to those that patients describe. "We need to have a way to test those things that we simply can't do ethically with humans," says Reggia. "Modeling offers us that opportunity."

But computer models, limited by the information that experimentalists obtain, can only approximate the human brain. The new imaging technologies—particularly MR, which explores brain activity as a person performs simple cognitive tasks—hold the promise of strengthening models. "Functional imaging is going to be important in providing a means of linking theories with biology," says Hasselmo, who is beginning his own MR study.

As Reggia and Hasselmo point out, however, understanding brain disorders will require all the tools currently available, whether theoretical or experimental. "We may study Alzheimer's disease at the molecular level forever," says Hasselmo. "But the structure and the function of the tau [tangles-causing] protein is never going to explain why the Alzheimer's patient associates vegetables with tools." □