Dual Major

Focused on mechanics as well as theory, Charles Stevens is of a mind to find out how the brain works.

Outside Charles F. Stevens's window at the Salk Institute for Biological Studies in La Jolla, California, the broad expanse of the Pacific Ocean beckons brightly. But the sun, sand, and surf don't often distract the HHMI investigator from his intellectual passion—the organization and biochemical workings of the brain.

At the same time, Stevens's focus on his work doesn't preclude him from taking a big-picture view. As a researcher, he maintains a respected presence in two different but mutually supportive domains—the experimental and the theoretical. "I really enjoy detailed mechanisms," he says, "but I also enjoy some of the bigger questions that are related to what I started out with in psychology."

Two recent papers are cases in point. In June 2003, he and a colleague published findings in *Nature* on what might be considered the very essence of the brain: the delivery of a packet of information across the junction between two neurons. Later that same month, he and another colleague published a theoretical paper in the *Proceedings of the National Academy of Sciences* on why the location and connectivity of one brain region relative to another never vary even though particular regions among individuals may differ greatly in size.

Gary Yellen, a Harvard Medical School neurobiologist who was a graduate student with Stevens in the 1980s, says that two of the things that set him apart from many other scientists are Stevens's capacity to "approach a problem in a very fresh way by, in essence, rethinking it from scratch" and his fruitful deployment of "very impressive mathematical abilities."

Stevens began his education at Harvard University, confident that he would become a practicing physician. But then he read Sigmund Freud for the first time. "I became enormously excited about Freud's ideas, which I was quite naive about," he says. Those ideas led him to pursue experimental psychology.

Later, in medical school at Yale University, Stevens got so caught up in brain research that he had to choose between clinical medicine and research. "I figured I just couldn't do both well enough," he says. After obtaining his M.D., he pursued further graduate studies in mathematics and physics at the Rockefeller University. "Throughout my career," he says, "I have oscillated between things that are biophysical or molecular biological—very mechanistic—on the one extreme, and more theoretical" on the other.

Whether practical or theoretical, Stevens's research has been influential. His work in the 1970s on the conductance of ion channels in cells, for example, paved the way for the development of "patch clamping"—use of electrodes to measure the conductance of single ion channels—for which Bert Sakmann and Erwin Neher shared the 1991 Nobel Prize.

In some of his most recent research, Stevens has studied neural packets, or vesicles, whose chemical cargo—neurotransmitters—relay information from one brain cell to another. In particular, he has focused on how the vesicles get their payload from one side of the cell membrane to the other and on how cells recycle old vesicles.

In one set of experiments, Stevens and Salk colleague Sunil P. Gandhi used a fluorescent dye to make individual vesicles glow when they popped open. This technique gave them a more direct picture than ever before of how individual vesicles open up to the environment outside the cell, release their cargo in the cell synapse, and get reabsorbed into the cell and reloaded with another batch of neurotransmitter.

Stevens and Gandhi found that vesicles use three modes of communication with the synapse, or cell junction. Some vesicles open completely, like a mail carrier dumping a sack of mail into a bin. Others use a small pore that opens and closes rapidly, like a mail carrier shoving a batch of letters into a slot that opens and then quickly slams shut again. Finally, some vesicles get stranded on the surface of the cell after they release their packet, only being drawn into the cell when another nerve impulse arrives.

The first mode, called "classical," takes a minimum of eight seconds. The second, called "kiss and run," is much quicker (less than a second). What Stevens finds intriguing is that different types of synapses preferentially use different modes. Bigger synapses tend to use the classical mode, and smaller synapses generally use kiss and run. "It may be that if you're a small synapse and you have a small number of vesicles," he says, "then in order to transmit information at a high rate, you have to use each vesicle more frequently in order to keep up."

Moreover, he notes that the detailed mechanisms he has unearthed at the synaptic level hint at broader issues. "They may be related to a fundamental limitation on how much information per second a particular synapse can transmit," Stevens says. "So there is a bigger question here about how the brain is designed to be an efficient information processor."

Charles Stevens studies synaptic transmission.

MARC L. LIEBERMAN, THE SALK MULTIMEDIA RESOURCES DEPARTMENT

To find more time and space for thinking theoretically, Stevens spends most summers at the Aspen Center for Physics, in Colorado, and occasionally at the Santa Fe Institute in New Mexico. "I love my lab, the people there, and working with them," he says. "It's very exciting. But I also like to get away and work on some projects just by myself."

Even in Aspen, though, Stevens rarely heeds the call of the great outdoors. He admits that he gets so caught up in his work that in 10 years, he has never been more than a mile and a half outside of town. "I plan on going hiking," Stevens says, laughing, "but I never quite get around to it." **—DIANA STEELE**