QnAs with Charles F. Stevens

Charles F. Stevens applies the methods of theoretical physics, molecular biology, and anatomy to answer fundamental questions about the brain. A professor of neurobiology at the Salk Institute for Biological Studies and a member of the National Academy of Sciences since 1982, Stevens has helped unravel the molecular details of synaptic transmission. Here, Stevens talks to PNAS about his search for the underlying design principles of the vertebrate brain, which achieves a "scalable architecture" that allows it to expand computational power simply by increasing in size.

PNAS: What spurred your interest in neuroscience?

Stevens: I was a psychology major. One of the central problems of psychology at that time was how animals learn. It was believed that you had to understand the synapses better to understand how learning and memory worked, so that was my original motivation.

PNAS: When did you decide to pursue a research style that combined theoretical and experimental approaches?

Stevens: I've always enjoyed doing theory. When I was a graduate student, I studied mostly physics and math; later, I spent a year doing a sabbatical in theoretical physics. Five or six years ago, I started doing theory pretty much full time. I also do some experiments, in collaboration with other people and sometimes in my own laboratory: when the theories make particular predictions, we test them. Or sometimes you have to do experiments to find numbers that you need to form the theory. There is a growing consensus among biologists that there needs to be more. Of course you still always need to do experiments, but I think a lot of people feel that we're getting to the stage where you need theory to guide how you think about the questions you ask.

PNAS: What questions are you trying to answer?

Stevens: I think I'm the only person in the world who is asking my [particular research] question. In order for evolution to work, neural circuits have to have what the computer scientists call a scalable architecture. That means that you have to be able to make the computer more powerful just by making it bigger—you don't have the luxury of redesigning it; and so the question that I'm asking is: What are the design principles that brains use to give their circuits a scalable architecture? So far we have worked out six or seven of these design principles.

Image courtesy of Charles F. Stevens.

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PNAS: Can you give an example of a design principle at work?

Stevens: If you examine the retina of a vertebrate eye, you find about two dozen different kinds of retinal ganglion cells that sense the information about the intensity of light provided by photoreceptors and send that information back to the brain. Each one of those retinal ganglion cell types tiles the retina, with each cell forming a pixel. So you can ask the question: How big should a pixel be? Answering that question identifies a design principle, and there are three possibilities you can consider. For the retina to have the best possible resolution, you pick the smallest pixel size you can make, and when you increase retina size you just add more pixels of that size to produce a retina with the most possible megapixels. Or you might pick a pixel size that gives adequate resolution and keeps the ratio of pixel size to retina size constant for larger retinas; this way the resolution stays constant, but the bigger you make each pixel, the less noise there is because you average over more photoreceptor signals. Or maybe evolution has picked a strategy where it says, "I'm going to maintain a constant ratio between resolution and signal-to-noise ratio so that both improve with larger retinas but neither as much as with the two other strategies." Each of these three possibilities makes a specific prediction about the area sampled by a retinal ganglion cell—the pixel size—and the area of the retina.

PNAS: How do you determine which of these options the brain uses?

Stevens: It's hard to do in mammals. Their retinas are complicated—most of them have a fovea, and all of the pixels aren't the same size across the retina. You can solve that problem very easily by using goldfish or zebrafish. Their retinas are like familiar cameras, with pixels all of the same size. Fish grow throughout their entire lives, and as their eyes get bigger, they generate more cells in the retina. To do the pixel/retina size experiment you just go to the pet store and get some goldfish of all different sizes, measure the sizes of their retinas, stain some retinal ganglion cells, and measure the area over which each cell collects information from the photoreceptors. Then you just plot pixel size vs. retina size. We did this and found a straight line with a slope of 2/3, predicted as a constant ratio between accuracy and resolution. It turns out that this same design principle predicts the 2/3 slope for plots that relate the number of neurons in a brain structure to the structure's volume; and so the design principle is that if you're a bigger animal with a bigger brain, your neurons sample information over a bigger area so that you balance the signal-to-noise ratio and the resolution.

Sandeep Ravindran, *Science Writer*