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## Synapses May Fire Neurotransmitters Like a Shotgun

Researchers have constructed a new detailed map of the three-dimensional terrain of a synapse—the junction between neurons which are critical for communication in the brain and nervous system. The “nano-map,” which shows the tiny spines and valleys resolved at nanometer scale, or one-billionth of a meter, has already proven its worth in changing scientists' views of the synaptic landscape.

Using the map as a guide, the research team, led by Howard Hughes Medical Institute investigator Terrence Sejnowski, has developed a biologically accurate computer simulation of synaptic function. The simulation combines 3-D electron microscope maps with computer simulation and physiological measurements from real neurons. Their *in silico* modeling indicates that the synapse may behave more like a shotgun than a rifle when it comes to firing the neurotransmitters involved in neuronal communication.

The textbook view of the synapse describes it as a place where rifle-like volleys of neurotransmitter are launched from one defined region of the sending neuron to another defined target on the receiving neuron. In contrast, the new data suggest that synapse can act like a shotgun, firing buckshot-like bursts of neurotransmitter to reach receptors arrayed beyond the known receiving sites. The researchers say that right now they have little idea of how the synaptic shotgun functions.

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- Terrence J. Sejnowski

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The research was published in the July 15, 2005, issue of the journal *Science*. Sejnowski, who is at The Salk Institute, and colleagues Darwin Berg and

Mark Ellisman, both of the University of California, San Diego, led the research team, which also included co-authors from Carnegie Mellon University and the University of Pittsburgh.

In the collaborative studies, Ellisman and his colleagues first used electron microscopic tomography—the microscopist's equivalent of a CAT scan—to create a detailed 3-D map of the synapse of a chick ciliary ganglion. This ganglion is a cluster of neurons that connect the brain to the iris of the eye. It launches the neurotransmitter acetylcholine from sac-like vesicles across the synapse to two types of receptors, called alpha 7 and alpha 3.

Sejnowski and his colleagues transformed their map into a functional computer model by incorporating the physiological details of neurotransmitter release sites and receptors. The researchers then compared the behavior of the model under different scenarios with the electrophysiological behavior of actual ganglia measured in Berg's laboratory.

The results, said Sejnowski, provide evidence for a different concept of the synapse. “The image of this ganglion is not one of a simple synapse with a single release site, but multiple release sites. And it shows alpha 3 receptors within the postsynaptic region, but alpha 7 receptors outside this region. Our model showed that if we assumed that neurotransmitter is released only from vesicles in active zones, where everybody thinks it is released, we get a very bad match to actual properties of the neuron. But if we model broader neurotransmitter release, where these alpha 7 receptors are located, we can match the actual properties of the synapse very accurately.” This type of broader neurotransmitter distribution is called ectopic release.

“We can only be sure of data on this one type of neuron, the ciliary ganglion,” said Sejnowski. “But we are confident that this evidence points to ectopic release, and this means that you can't really trust the traditional textbook view—in which all the vesicles are released at the active zone—that's taken for granted now.”

The function of shotgun neurotransmitter release is unknown, said Sejnowski. “There's just nothing solid on our radar screen right now,” he said. “There is speculation that ectopic release represents some sort of spillover that neurons use under certain circumstances. Or, it may be an alternative mode of neurotransmission that neurons use at different points in their life cycle.” Sejnowski and his colleagues have initiated further studies using their simulation technique to confirm the ectopic release mechanism and explore its possible functions.

“Although we are convinced that ectopic release exists, any time you question an accepted concept, there will be doubt and resistance,” said Sejnowski. “So, we will continue to develop this new picture of the synapse to convince doubters, because this is such a different way of looking at how

the synapse functions.” Sejnowski said that he and his collaborators will extend their study to other types of synapses that are more complex and difficult to study.

More broadly, said Sejnowski, the new 3-D modeling technique could offer a powerful tool for understanding neurological disease, such as myasthenia gravis, a common disorder in which a defect in nerve impulse transmission results in muscle weakness. In this and other neurological diseases, “there may be an anomaly at the receptor level, but it is impossible to pinpoint the problem with existing techniques. With our modeling technique, we can explore the detailed geometry of the damaged tissue and ask how much of that anomaly is caused by the geometry itself,” he said.

"Once we have pinned down where the real problem is, we can use the model as a fantastic tool for drug discovery. We can tell drug developers precisely where the anomaly is and where they should focus drug discovery efforts."