

SENSORS AND PROBES

A 'nano' era for electrophysiology

Researchers in three independent laboratories develop nanoscale devices for network-level electrophysiology.

Imagine that you are standing outside the closed doors of a concert hall, trying to listen to the music being played inside. The sharpness and detail of the sound of the instruments dissolves in surrounding ambient noise, making it impossible to distinguish between the cellos, the violins, the violas and so on; if you walk in, you know you must be as quiet and inconspicuous as possible.

Similarly, if at a different scale, physiologists have been trying to 'listen to the music' generated by ensembles of connected electrical cells in the heart or brain for centuries. Each of these cells—like individual instruments in an orchestra—generates a melody (its electrical activity) that can be recorded by measuring the flow of electrical currents across its plasma membrane. One can 'listen' to the concerted activity of these cells by placing electrodes outside the cells, but the outcome is similar to attending a concert outside a closed door.

The flow of electrical currents in a given cell can also be measured using electrodes placed inside it, but doing this inconspicuously—without harming the cell's membrane or interfering with its activity—is extremely hard. Moreover, at best only one or two such electrodes can be used, so only a minute sample of the cells that are playing the tune can be recorded. "What one needs are new methods that allow us to simultaneously record intracellularly from many neurons over very long periods of time," explains neuroscientist and electrophysiologist Micha Spira, from the Hebrew University of Jerusalem. In three recently published papers researchers show how nanotechnology can help achieve just that.

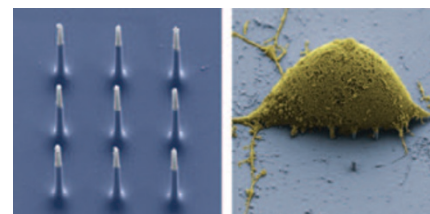
The groups of Hongkun Park at Harvard University and Yi Cui and Bianxiao Cui at Stanford University independently engineered nanoscale versions of microelectrode arrays and used them for intracellular

recordings. Park and co-workers (Robinson *et al.*, 2012) built a vertical array of 150-nanometer-diameter silicon wires capped by a conducting metal tip. They cultured rat neurons on them and both recorded and stimulated intracellular action potentials and mapped synaptic connections in the cultures. The Stanford University group (Xie *et al.*, 2012) also built arrays of similar-sized 'nanopillars' but made of platinum, and they cultured mouse cardiomyocytes and studied changes in the intracellular action potentials induced by drugs.

To get the nanowires efficiently into cells, both groups resorted to membrane electroporation by applying small electrical currents through the nanoelectrodes themselves. Both of these nanostructured arrays allow monitoring intracellular electrical signals from multiple cells simultaneously for hours to days, and given their small size they appear to be less damaging to the cells than conventional micrometer-sized pipettes.

A third group led by Charles Lieber (Duan *et al.*, 2012) also at Harvard University took a different approach to the matter. Instead of nanoelectrodes, Lieber and co-workers used field-effect transistors (FETs) to record intracellular action potentials from cultured cardiomyocytes. Although it is known that FETs are great for making high-resolution electrical recordings, it was hard to engineer a way of introducing them into multiple cells at once. Lieber's group first made vertical FET-based sensors by placing the FET at the base of a silicon nanotube only 55 nanometers in diameter at its tip. To get the tubes into the cells, they coated them with lipids to promote cellular fusion. Once inside the cells, the intracellular fluid entered the hollow nanotubes and came in contact with the FET, enabling electrical recordings to be collected.

The group assembled a few of these 'branched' FETs and made repeated measurements in single cells or simultaneously from groups of cells. This type of device produced higher signal-to-noise



Electron micrographs of a vertical nanowire electrode array (left) and a neuron cultured on top of it (right). Reprinted from *Nature Nanotechnology*.

ratios than nanoelectrodes, and its small size offers the exciting future possibility of performing electrical recordings at the sub-cellular level.

As a neurophysiologist, Spira is very excited about these three papers: "I think we are at a turning point in the development of technologies that allow exciting new possibilities [for the study of neuronal networks]," but several challenges remain. "It will be important to determine if these devices can be used to record excitatory and inhibitory subthreshold synaptic potentials," he explains, and to thoroughly assess the effect of these nanostructures on cells. Down the line, it will also be important to determine whether they can be used to record from cells in slice preparations or *in vivo*.

At this point, however, one can already start to imagine how one can use these methods to, for example, begin to deconstruct the role of individual components in neuronal networks and reveal the orchestral beauty of the brain's electrical tune.

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RESEARCH PAPERS

Duan, X. *et al.* Intracellular recordings of action potentials by an extracellular nanoscale field-effect transistor. *Nat. Nanotechnol.* **7**, 174–179 (2012).

Robinson, J.T. *et al.* Vertical nanowire electrode arrays as a scalable platform for intracellular interfacing to neuronal circuits. *Nat. Nanotechnol.* **7**, 180–184 (2012).

Xie, C. *et al.* Intracellular recording of action potentials by nanopillar electroporation. *Nat. Nanotechnol.* **7**, 185–190 (2012).