NANOWIRES MINISCULE DEVICES with LARGE IMPLICATIONS

It has often been said that the "whole is greater than the sum of its parts." However, to fully understand the operations of the 'whole' one must know the functioning of even the smallest parts. To understand the microscopic aspects of biology, scientists have turned to the field of nanotechnology. Charles Lieber, a professor at Harvard University, and his research group now utilize this technology to study some of the minutest biological systems. By researching at the interface between nanosystems and biosystems, they seek to produce breakthroughs in understanding 'whole' systems, such as the human brain.

Currently, some of the most interesting research by this group utilizes silicon nanowires. These tiny wires enable scientists to study the most detailed activities of neurons, including how they communicate with one another. Similarly, nanowires can be used as biosensors to detect the presence of proteins, viruses, and other biological molecules.

Nanowire Manufacturing

In a dimly lit laboratory, a technician dressed in a specialized jumpsuit handles a small disc of silicon. The lights are low and have a yellow tint as to not interfere with the light sensitive chemicals; the technician is dressed in the lint free jumpsuit to prevent any dust from falling onto the silicon. Compared to the size of the structures being made on the silicon, even a single piece of dust is a mountain on the chip. With a flash of purple UV light, the first step towards making the chip is complete. In a few hours, this piece of silicon will be transformed into a remarkable research tool.

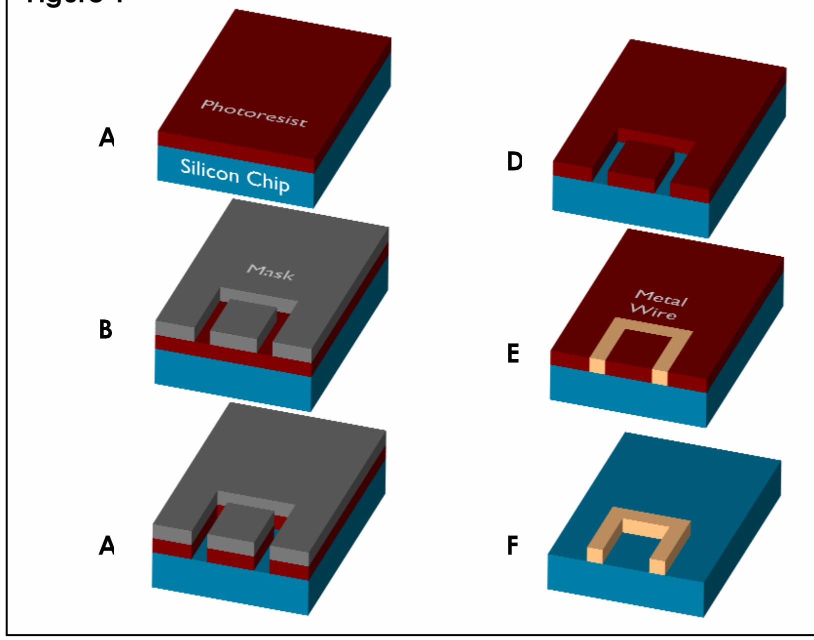
Nanowire devices show great promise in many fields of research, and part of the motivation behind finding applications for these wires is that they can be manufactured cheaply and easily. The production of nanowire devices utilizes existing technologies, which means that labs already set up for researching traditional silicon devices, such as computer chips, can be used for nanowire research. Another useful feature of nanowires is that the size and electrical properties of the wires are easy to keep consistent between batches.

The basic process for creating a nanowire device starts with the creation of the wires themselves. Crystals of gold are first sprinkled onto a plate. By controlling the size of the initial crystals, the diameter and the growth pattern of the nanowires can be precisely regulated because the properties of silicon atoms only allow them to bond in a certain predictable way. The plate is then placed into a specialized furnace where the crystals are formed.

Present in the furnace is a gas called silane, which is formed when silicon is vaporized. When the silane gas comes into contact with the gold nanoparticles, the crystal structure of the nanowire begins to form. The wires form in the same way rock candy is made from sugar water. Additional gasses can be added to control the electrical properties of the nanowires. Contingent on the gasses present in the oven, the nanowires can be either p-type (positively charged), or n-type (negatively charged). Depending on the intended use, scientists will either make p- or n-type, and in some applications both types are used in the same device.

Once the nanowire structures have been formed, they are removed from the plate and suspended in liquid while a microchip is made using traditional manufacturing technology. To make the microchip, a piece of silicon is covered with a chemical called a photoresist (Figure 1a). When ultraviolet light is shone on selected regions of photoresist, the photoresist becomes soluble and is easily rinsed away (Figures 1b to 1e). This process, known as photolithography, is similar to developing photographs in a darkroom. Once the soluble photoresist is cleared away, metal is deposited on the silicon (Figure 1f). It only sticks where the photoresist was removed, which creates metal wires and contacts on the chip. After the remaining resist is removed, only the metal wires remain (Figure 1g). The process is then repeated, but instead of putting down metal, the solution of nanowires is placed on the silicon. The nanowires then only stick where the resist was removed, and the excess is washed away. The device is inspected using high-magnification microscopes to make sure that

Figure 1



nanowires are connected to the larger metal wires in the proper places. After the device is checked for defects, it is ready to be further processed to make either a biosensor or a neuron nanowire device.

Neuronal Communication

The human brain is made up of billions of cells called neurons. Communication between neurons is crucial for being aware of the presence of your professor in the classroom, learning to concentrate on the exercise problems instead of your friend's text messages, and making the resolution to never fall asleep again during the lecture. To keep track of all kinds of complicated messages being sent around the brain, the information is converted to simple electrical signals – a language that the neurons can understand and communicate with one another. In order for the information to get from one side of the brain to the other side, neurons have to fire an "action potential", or a rapid voltage change, to drive the flow of information. During the process, signals flow from a neuron's incoming branch, called the axons, through the cell body to the outgoing branch, called the dendrites (Figure 2). Upon reaching the end of the current neuron, the signal jumps to the neighboring neuron by a process called synaptic transmission. The flow of the signal then continues through the next neuron. The entire neuron communication process is similar to a game called "telephone" in which children line up and whisper information from one person to the next. In the case of neurons, however, each neuron often has thousands of other neurons that it can communicate with (Neuroscience, p 5).

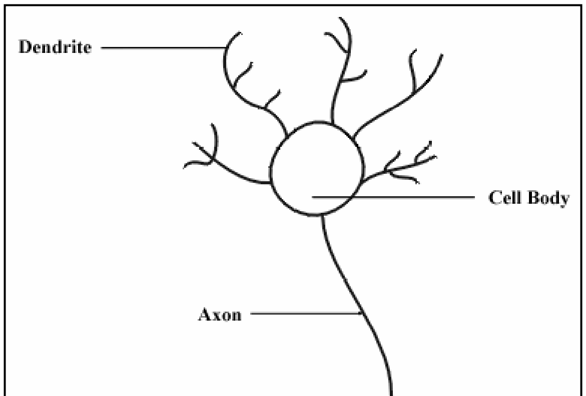


Figure 2

People are therefore always interested in disclosing the mysterious details of the communication game in the brain. What exactly is every neuron saying to its neighbors? Which neuron is the fastest in finishing up its job and which neuron is the slowest? If the information has ever gotten lost or misinterpreted during the process, where does the problem occur? In reality, because of the small size of the neurons and the complexity of the neuron networks, our understanding of our own brain is far less than that of quantum mechanics. In 2006, the Lieber's research group successfully applied nanowires to listen to neuron signaling and helped to expand our knowledge on the subject.

To assemble a neuron-nanowire device, silicon nanowires are glued to rat neurons using an adhesion chemical. Because the growth conditions of the neurons are harsh for the wires, extra care has to be paid to make sure the neuron and the wire can coexist. Throughout the entire process, Lieber's group can create as many as 50 nanowire-neuron junctions within a single neuron (Figure 3). More impressive is that they can control the spatial separations between the junctions as they wish. The cross-sectional area of the neuron-wire contact surfaces can be as small as 20 nm in diameter, which is about 200 times smaller than the diameter of a human hair (Science, Vol 313, p 1100). In contrast, existing devices can only be inserted to the neuron at one or two locations due to their larger size.

In order to study the neural signal flow, action potentials are applied at the junctions between the wire and the axon of a neuron. The corresponding

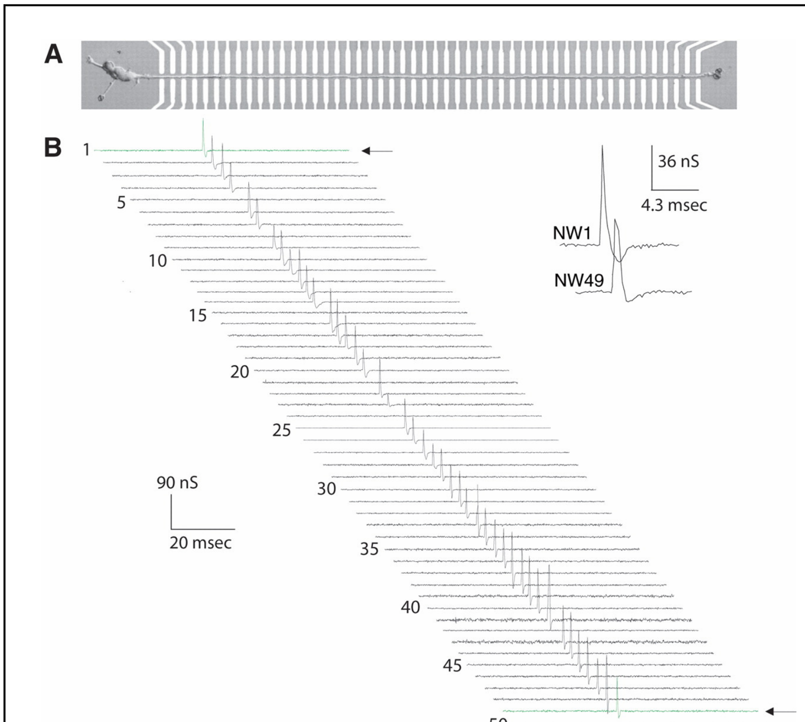


Figure 3

conductance of the neuron can be detected at the junctions. The neuron-wire device therefore allows you to simultaneously send inputs to a neuron and sense how the neuron responds. In addition, the wire-neuron device can be used to simulate long periods of action potential pulses without damaging neurons. Since the signals produced by the wires are similar to those sent by neurons, it is possible to use the wire-neuron device as an alternative pulse generator in the brain. This discovery suggests new treatments for neuron disorders caused by failure of neuronal action potential excitation.

When the wires are connected to the axon and dendrites of a neuron, the device can read neural signaling in the absence of input signals from the cell body. Both forward and backward signals are detected when action potentials are generated from the axon. This finding dispels the popular view that neuron signals can only travel in a single direction (Encyclopedia Britannica, March 11, 2007), which implies the importance of the cell body in guiding the direction of signal transmission in neurons. In addition, when the wires and neurons are arranged in linear order, researchers can simultaneously study signal transmission in both axons and dendrites. Obtaining such high-resolution data is impossible using classical microelectrodes. The calculated rates of signal transmission in both dendrites and axons provide valuable information to people who are interested in building an artificial brain.

Aside from detecting and simulating neuronal signals, the nanowire-neuron device can regulate the neural communication process. By varying the electrical input levels on neurons, both the signal transmission speed and the potential spike amplitude can be controlled. This regulation process is similar to the natural inhibition of signal transmission in the brain. For neurons, failure to inhibit unnecessary neuronal signals may lead to overexcitement and eventual death. This is a common phenomenon observed in brain damage during stroke and Alzheimer's disease (Journal of Experimental Medicine, March 09, 2006). Nanowires therefore offer new hope to patients who are suffering from various kinds of neural disorders with a solution of complete remote-controlled regulation of neuron excitement level in the brain.

The "telephone game" of the neurons is difficult to study, particularly because the signals travel across neurons by rapid swings in the cell's voltage from positive to negative and back within a few milliseconds. The nanowire-neuron device allows detailed investigation of signal flows by collecting data at many places along a neuron. This would be impossible using traditional micro-electrodes, since the signals they pick are likely affected by neighboring neurons. Lieber's work is a great leap forward in nanotechnology. "It shows that work in this field can become revolutionary and important in other fields such as biology", says Zhong Lin Wang, director of the Center for Nanostructure Characterization at Georgia Tech (Technology Review, August 8, 2006).

There is no doubt that the nanowires have provided valuable input to for neuroscience research. A clearer picture of our brain and some of its finest characteristics is now emerging, and it could provide valuable insight into the underpinnings of learning and memory. Patients who are suffering from diseases such as Alzheimer's and Parkinson's may one day utilize a sophisticated nanowire machine that can interface with the brain and regulate all kinds of neural disorders.

However, a lot of work remains before these devices can be implanted in humans. The long term effects of injecting stimuli into the brain must be studied further, and there still exists potential for creating more damage than the device fixes. Questions remain including, will silicon react with the brain in adverse ways? And, what happens if a nanowire were to break? Silicon reacts with many different elements, including many common ones in the human body. If the silicon nanowires were to degrade over time from chemical reactions, complications could arise, and pieces of the wire may even break off. Loose pieces of silicon nanowires are tiny compared to neurons; however, even a tiny fragment may cause irreparable damage. While nanowire devices show great promise, further testing has to be done before they are ready to be deployed in humans.

Biosensors

Imagine that you are sitting in a doctor's office. The doctor just told you that your symptoms could be explained by an unusual virus. Instead of taking a blood sample and sending it out to a lab, he asks if he can prick your finger. A drop of blood falls onto a small silicon chip, which he places in a device sitting on the counter. Within minutes, the device recognizes the specific virus in your blood; the doctor can begin treatment immediately.

This scenario shows yet another revolutionary effect that nanowire-based devices, in this case biosensors, could have on medicine. Biosensors are tools used to detect the presence of specific molecules in a solution. They will be especially important in diagnosis, where some kind of molecular marker—a protein, DNA sequence, or virus—indicates the presence of a disease. The Lieber Group has successfully employed nanowire field-effect sensors to accurately and consistently measure molecular markers.

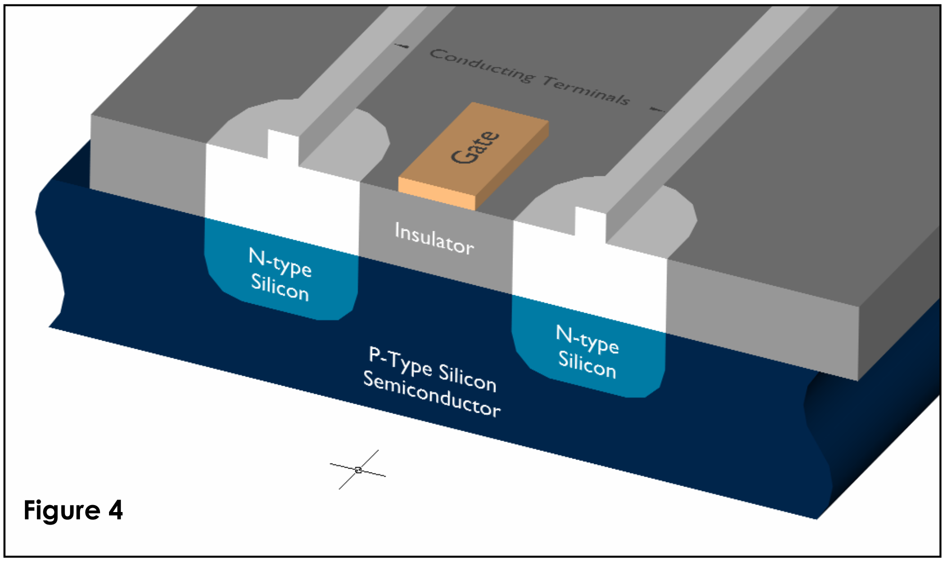


Figure 4

Scientists use computers to measure these changes in conductivity. Unfortunately, the connecting bridge is a wide, flat surface—small molecules can only minimally affect the conductance of the large FET.

Nanowire field-effect sensors operate by the same principle as field-effect-transistors (FETs), the building blocks of computers. FETs consist of two conducting terminals bridged by a silicon semiconductor (Figure 4). The FET acts like a switch—it is either fully insulating or fully conducting, depending on the electric field that is applied to the center of the semi-conducting bridge, called the gate. Because the electric fields of nearby molecules alter the conductivity between the terminals, FETs have been considered for use as biosensors.

Nanowire field-effect sensors (FESs) address this problem by replacing the flat silicon semi-conducting bridge with a nanowire composed of silicon or similar material (Figure 5). The thin structure and small mass of the nanowire means that a nearby molecule will affect the conductance of the wire's entire cross-section. Researchers attach specific receptor molecules to the nanowires so that they become conductive only when the target molecule binds to the receptor. Receptor molecules are the key to

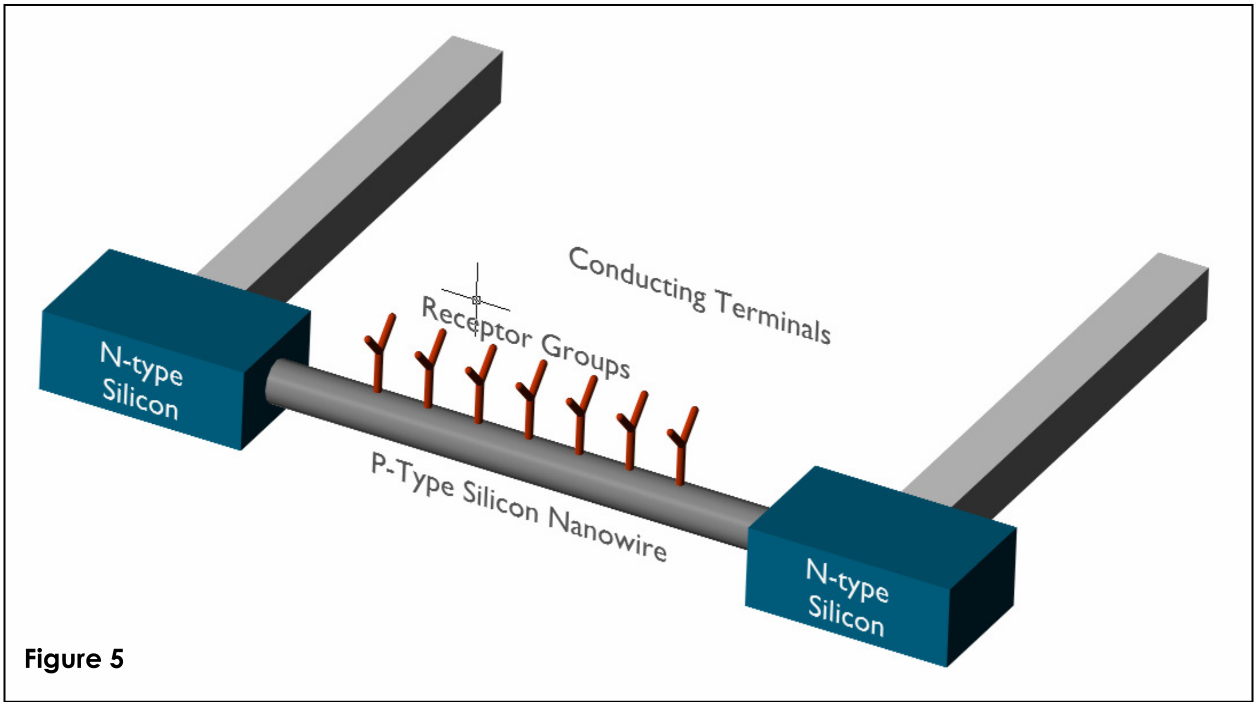


Figure 5

useful nanowire biosensors. They allow precise molecule recognition and make it possible for one chip of nanowire FESs to detect a whole range of target molecules.

Nanowire biosensors will be useful in everything from medical diagnosis to bioweapon detection. In an especially promising study last year, the Lieber Group created a nanowire device that could measure multiple proteins at once. It consists of a single silicon chip holding a series of nanowire FESs with a number of different receptors. Eventually, tools such as these will allow doctors to identify complex diseases, such as cancer, which have a number of characteristic protein markers. The Lieber group has also successfully sensed strands of DNA with a specific sequence by using receptor molecules with a complementary sequence. This technology hints at a time when genetic diseases could be diagnosed immediately. The ability to use different receptor molecules makes Nanowire biosensors an attractive technology, especially in situations where speed or portability are an issue.

Conclusion

Nanowires create abilities that previously lived in the world of science fiction—the power to peer into the minute and mysterious activities of the brain, to detect single viruses, and to diagnose cancer as easily as strep throat. Even though this seems like the product of imagination, nanowires are easy and cheap to manufacture and small enough to accomplish the seemingly impossible. Having created great leaps in research concerning neuron dynamics, they will one day serve as the best interface with the brain. At the same time, nanowire field effect transistors already provide an effortless method of detecting proteins and have a future as the cornerstone of medical diagnoses. Nanowires promise to revolutionize the way we practice medicine.

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