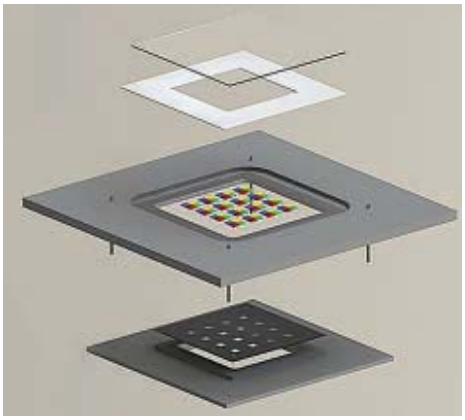
Carbon nanotubes are considered to have great potential in biology and medicine, thanks to their desirable properties.

MAKING THE SMALLEST MEDICAL DEVICES

AS ENGINEERS SEEK TO MANUFACTURE NANOSCALE PRODUCTS FOR MEDICAL APPLICATIONS, SEVERAL PATHS LOOK PROMISING.

BY YUNUS ALAPAN, ISMAIL SAYIN, AND UMUT ATAKAN GURKAN

THERE IS A POTENTIAL MEDICAL REVOLUTION AWAITING US if we can master the fabrication of medical devices that are smaller than the eye can see—products with feature sizes measured in nanometers, or billionths of a meter. Nanoscale fabrication can create devices that can work on individual cells and provide treatments that would be impossible if we were trying to issue them in bulk throughout the body.



One microfabrication system uses photolithographic techniques such as optical masks and photoresists to build complex tissue structures.

IT'S EASY TO HEAR SUCH PREDICTIONS AND TUNE THEM OUT. When many people hear the term "nanoscale fabrication," they shelve everything that comes after as science fiction. But it is no exaggeration to say that advances in micro- and nano-scale manufacturing technologies already have led to a veritable revolution. Semiconductor manufacturing, which entails incorporating millions to billions of transistors into tiny devices known as integrated circuits, is a $250 billion industry today, and it's likely impossible to list all the parts of society and the economy that have been impacted by digital technology.

Optical lithography or photolithography has been the workhorse of semiconductor nanofabrication, which uses light, optics, and photosensitive materials to produce minuscule patterns on a surface; repeated deposition and etching away of thin layers of that photosensitive material result in the fabrication of devices with nanoscale features. Current state-of-the-art in photolithography can produce features as small as 24 nm and pack as many as 1.7 billion transistors per square centimeter. This level of fabrication performance and control are generally reserved for advanced integrated circuits, especially for high performance processors and computers.

Fabricating sub-micrometer features has been a challenging task for many engineers and researchers. Will this difficulty limit their use in biological and medical applications, where they may have as profound an effect as in digital technology?

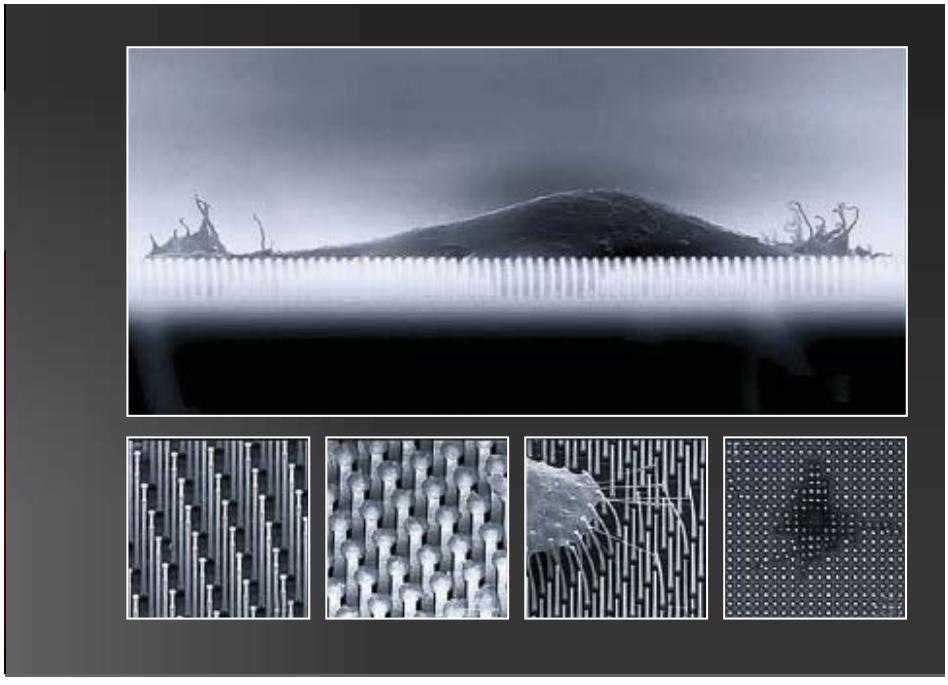
Perhaps not. Most biomedical applications which relate to cellular and tissue level organization do not require the high resolution and precision of integrated circuits. Cells in the body are generally in the order of 10 micrometers in size, which means that devices that involve manipulation of cells or interaction with them can be made at this scale.

For instance, a photolithography-based fabrication technology developed back in the 1970s recently has been adapted to manufacture intricate 3-D brain tissue in a Petri dish. This new method is a simplified version of multilayer photolithography used by the semiconductor industry, and it is a significantly low-cost way of creating fabrication precision using overhead transparencies, thin aluminum plates, and steel alignment pins. With this method, thousands of 3-D tissue constructs can be built quickly with a precision of 10 micrometers, one tenth of the average thickness of human hair, or the typical size of a single cell body.

On the other hand, pathogens and biological molecules are much smaller than cells, typically 1 nm to 1 μm in size. Products designed to interact with such tiny biological entities require much higher resolution and precision in fabrication. In order to achieve feature sizes that cannot be obtained through conventional photolithography, nano-bioengineers have reached for advanced manufacturing techniques, everything from x-ray lithography, deep reactive-ion etching, and electron-beam lithography to scanning-probe lithography, two-photon polymerization, pulsed laser deposition, and focused ion beam lithography.

Already, nanofabrication methods comparable to those in the modern semiconductor industry have been used for complex biomedical products with nanoscale features. These include microfluidics, micro- and nanostructures for drug delivery, and nanoparticles for medical imaging.

Photolithography is but one example of a top-down approach to manufacturing. Top-down methods involve extracting material from the bulk until all that remains is the desired device. Even though photolithography has been the



Reseachers used top-down fabrication methods to build an array of nanostructures. Stem cells cultured on the array (center) followed the grid pattern as they grew. Credit: Bucaro, et al. (2012)

dominant and most commonly used method in micro- and nanofabrication, it is not always the best choice for all applications due to its restrictions in building non-planar surfaces and structures. What's more, this manufacturing method has limitations in facilitating specific chemical functionalities and it is only applicable to a limited selection of light-sensitive materials, known as photoresists, for patterning.

Bottom-up manufacturing is also possible. Bottom-up approaches are based on fabricating the higher level structures from smaller building blocks; at the macro-scale, additive manufacturing—also known as 3-D printing—is an example of this, with nanoliter droplets or units deposited layer by layer to form the final product.

Non-photolithographic manufacturing technologies, cumulatively called soft lithography, were developed in the 1990s. Using materials known as elastomers, soft lithography methods include variations and subcategories such as microcontact printing, micromolding, cast molding, and embossing with resolutions down to the nanometer scale.

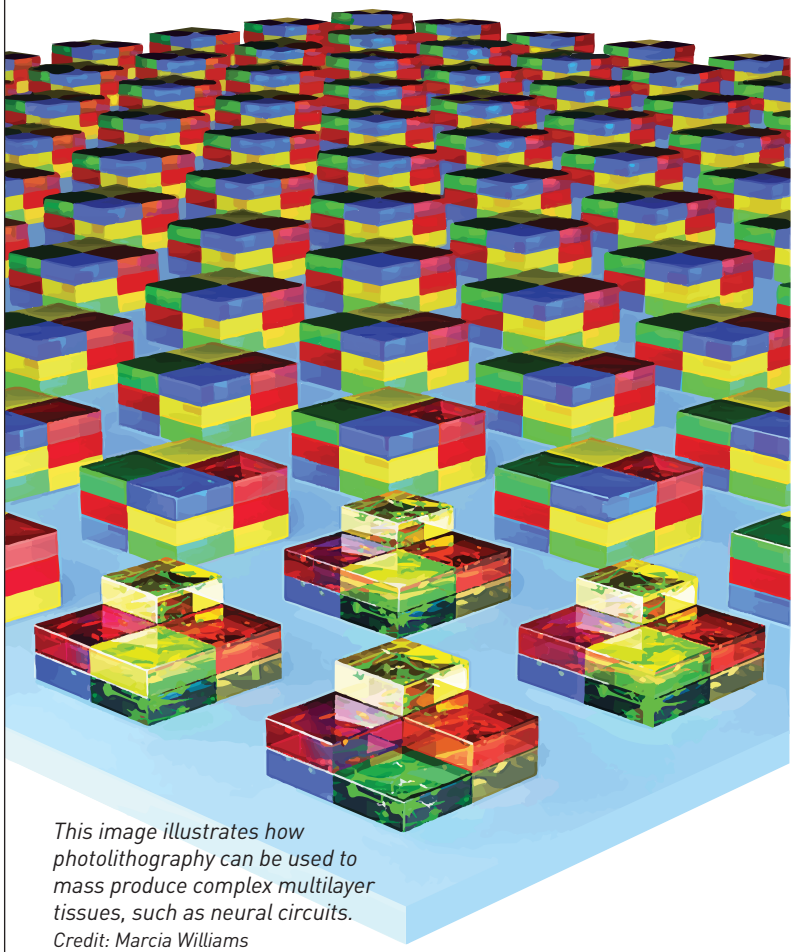
Soft lithography has given rise to the field of microfluidics and lab-on-a-chip systems, which have revolutionized the way we handle small volumes of fluids in channels with micro- and nanoscale dimensions and features. Microfluidic systems have enabled biomedical technologies through such devices as biosensors, point-of-care diagnostic assays, microchips that can sequence the human genome, and tissue-mimicking organ-on-a-chip devices.

Micro- and nanoscale structures have given us capabilities to interact with cells and pathogens at their level as never before and helped us understand how they live, grow, multiply, differentiate, and die.

CARBON NANOTUBES AND OTHER KINDS OF NANOPARTICLES are most closely identified in the public imagination as "nanotechnology." These tiny nano-products have unique optical, electrical, chemical, and physical properties, which make them indispensable in advanced biomedical applications. Already, those nanoscale particles have found significant uses in biomedicine with applications in imaging, drug delivery, and drug targeting.

One example of a nano product is the quantum dot, which is a crystal made of semiconductors just 2 to 100 nm in size. Quantum dots robustly fluoresce when exposed to light—a handy feature in medical and biological imaging. Quantum dots have been commissioned as imaging probes due to their extraordinary photostability, in combination with the smallest functional biological entities, antibody proteins and DNA. Quantum dots are already important to the study of individual cells and biological phenomena such as embryogenesis, cancer cell metastasis, and stem cell function.

Nanoparticles can be fabricated using both top-down and bottom-up fabrication methods. In the top-down method, nanoparticles are carved from the bulk materials using techniques such as electron-beam lithography, reactive ion etching, and wet etching. Top-down nanofabrication must be done with particular care to avoid the incorporation of impurities and structural imperfections during manufacturing.



This image illustrates how photolithography can be used to mass produce complex multilayer tissues, such as neural circuits. *Credit: Marcia Williams*

Bottom-up nanofabrication methods are broadly subdivided into self-assembly, chemical synthesis, and vapor phase deposition methods. Self-assembly, a fundamental method found in Nature, is a process in which spontaneous organization of the components and building blocks are ordered, and functional superstructures can be achieved without any outside intervention. The chemical synthesis methods—which include techniques such as sol-gel, microemulsion, and hot solution decomposition processes—form particles via nucleation, followed by controlled limited growth. In vapor phase deposition, the layers of the nanoparticles are formed atom by atom, which can be considered the ultimate bottom-up fabrication process.

Carbon nanotubes are a macromolecular form of carbon; while their diameters are suitably nanoscale, ranging from 0.4 nm to 100 nm, they can be as much as several thousand nanometers long. CNTs are known for having very desirable properties, including low weight, high electrical conductivity, high chemical stability, high thermal conductivity, large surface area, high mechanical strength, flexibility, and easy integration with functional groups.

Thanks to these properties, nanotubes are considered to have great potential in biology and medicine. Some notable biomedical applications of these tiny carbon macromolecules are reinforcements in biomaterials, drug and gene delivery vehicles for cancer therapy, and ultra-sensitive biosensors.

Carbon nanotubes are currently fabricated using a variety of methods, including arc discharge, laser ablation, and chemical vapor deposition. CVD-based methods are the prevalent CNT fabrication techniques for biomedical applications, due to their

high-throughput, controllable, versatile, simple and low-cost nature.

Advanced manufacturing research has been focused for years on improving nano- and microstructures: reducing the minimum feature size, increasing the spatial density, and optimizing the aspect ratio of features. Complex methods, such as the stepper photolithography and deep reactive ion etching, also known as the Bosch process, have helped researchers achieve some of these goals. For instance, researchers at Harvard recently used top-down methods to build extremely high-spatial-density, high-aspect-ratio nanostructures on the order of 100 nm to study stem cells using well-defined nanostructures mimicking natural cell microenvironments.

Though such methods pushed the limits of top-down fabrication technologies, they point to inherent difficulties in those approaches due to their complex nature. One promising alternative is the introduction of hybrid nanofabrication technologies. Hybrid methods promise to integrate bottom-up and top-down nanofabrication in new and innovative ways by leveraging the strengths and unique features of both approaches.

For instance, nanoparticle lithography and nano-molding can be used to fabricate nanostructures smaller than 100 nm with a simple method. In this novel approach, a research team in Taipei grew nanoparticles on silicon substrates via spin coating, followed by deposition of a metal layer through an electron beam evaporator. When those nanoparticles were removed, they produced nanopatterns with high precision, effectively controlled by the initially deposited nanoparticle size and shape.

These nanopattern arrays were used as stamps for nanocontact printing to create fibronectin nanoarrays, which were used to study the size dependent formation of focal adhesion in cells.

That example among many others demonstrates the benefits of hybrid methods. Such methods integrate already developed and well characterized top-down and bottom-up nanofabrication approaches to achieve enhanced precision and control without compromising fabrication complexity and cost.

Throughput, speed, scalability, user friendliness, and cost of nanofabrication methods still have plenty of room for improvement, which have rightfully been the research focus of many scientists and engineers for many years now. It is certain that we will continue to be amazed with the advancements and the pioneering and lifesaving possibilities offered by this field. **ME**

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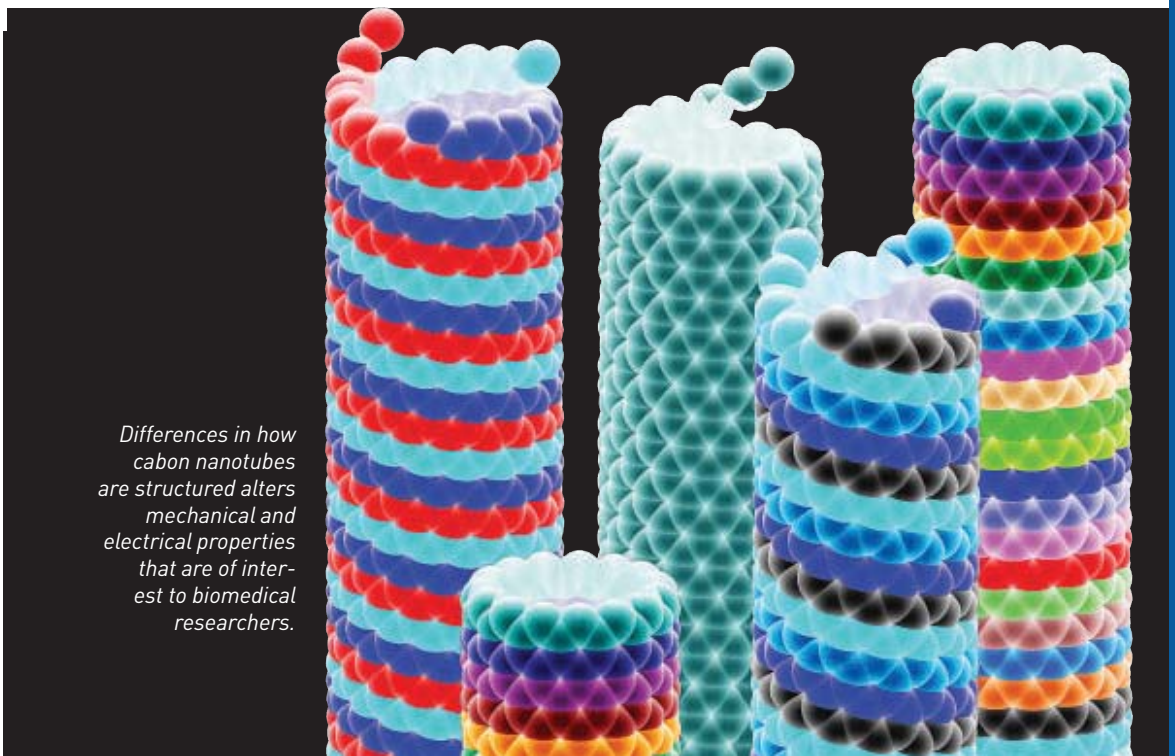

Differences in how cabon nanotubes are structured alters mechanical and electrical properties that are of interest to biomedical researchers.

TO LEARN MORE

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