

Within A Nanometer of Your Life

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Introduction

An inevitable outgrowth of modern technology has been an increasing trend toward the miniaturization of components. We are at the dawn of an era where the forefronts of both biomedical engineering and basic sciences have reached the length scale of nanometers. In areas as diverse as biomechanics, electrical engineering, molecular biology, and ultrasound new tools and approaches have been developed to enable both the fabrication and the study of molecular complexes or even single molecules.

The essence of nanotechnology is the creation and utilization of materials and devices at the level of atoms, molecules, and supramolecular structures, and the exploitation of unique properties and phenomena of matter at 1 – 100 nm scale. Biological Microsystems can provide excellent models and applications for the development of this new nanotechnology. These Microsystems will ultimately incorporate functional components based on nanotechnology.

There are many state of the art nanotechnology applications in the biomedical engineering field, such as biomechanics materials and design related to spine research, ultrasound imaging technologies and the biocomputer chip for the brain. The application of nanotechnology to mimic a brain circuit for Alzheimer's that can perform biologically inspired computations using metal oxide semiconductor field effect transistors and microsensors based stand-ins for brain neurons is one of the latest miracles of the biocomputer chip. In this paper we attempt to provide a recent review of the applications of nanotechnology in medicine. We have organized the devices based on their applications. The broad based headings are Nanomaterials and Biomechanics, Nano Electromechanical Systems (NEMS), Nanobioelectronics, Nanostructures, Optical and Ultrasound Sensing and Nanotherapeutics.

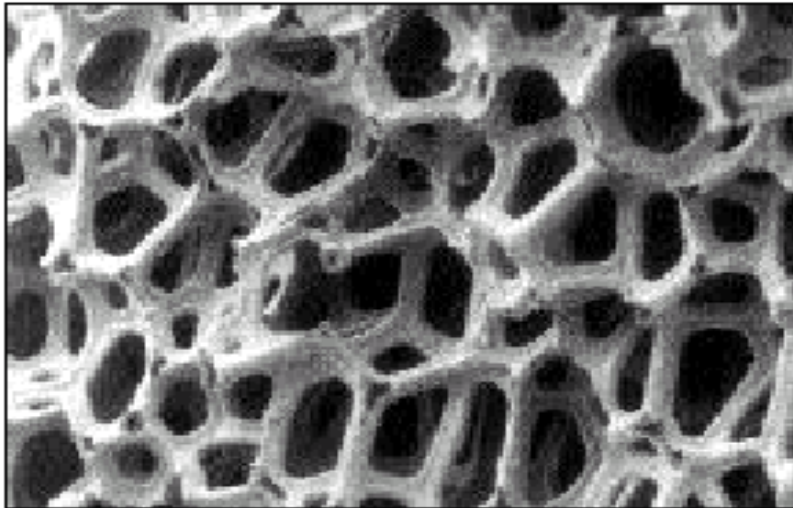
I. Nanomaterials and Biomechanics

Biocompatible surfaces are vital for implantable sensors or drug delivery devices to work effectively within the body. Use of nanomaterials for implantation in the body leads to substrate effects. This leads to applications in bone regeneration and prosthetic bioengineering. Regeneration of severed tendons on textured surfaces leading to the use of textured bandages to accelerate healing for tissues where damage is almost irreparable without the use of textured bandages. The directed growth of cells on micromachined structures has applications in artificial implants or test structures.^[1]

Replacement Discs:

The problems of the aging spine are attributed to loss of soft tissue between the vertebrae. Pain is caused from compressed spinal nerves. Degenerative diseases such as arthritis, spine metastasis caused by cancer and spinal trauma are known to compromise soft tissue. A novel material has been developed for use in replacement discs for the spinal column. The replacement acts as a spacer in support of the vertebral body. The porous natural structure of bone is simulated by the nanomaterial. Bone can gradually infiltrate into the artificial disc just as it would with damaged natural bone. The replacement is screwed in place optionally with a cement accompaniment. Consolidation takes place between the bone and the nanomaterial. They fuse together. The fusion obviates the necessity for the soft tissue disc and the two bony processes grow together reducing the possibility of nerve compression and therefore pain.

The nanomaterial is composed of a carbon foam skeleton that is treated by a chemical vapor deposition (CVD). A continuous thin film of metals such as rhenium or tantalum, or compounds such as silicon carbide are distributed throughout the interior of the construct lending certain thermal or tensile properties to the carbon foam substrate and to the structure as a whole. The resulting product is characterized by low cost, low density, high chemical purity, controlled thermal expansion, and high thermal stability. The nanomaterial can be made resistant to oxidation and can withstand temperatures of up to 6,000° F by design. The high strength and porous structure of the nanomaterial makes it a biocompatible replacement for the vertebral bodies that make up the spinal column. The nanomaterial is a tantalum-coated carbon porous matrix product that mimics the properties of bone and is biocompatible.^[2]



***Figure 1: Nanofabricated Synthetic Cellular Material Compatible With Bone.
Ultramet Corporation.^[2]***

Dendrimers:

Dendrimers are large, spherical polymers with dimensions of about 10 nanometers in diameter. Dendrimers are synthesized by the attachment of branched molecules to an initial core structure. Iterative polymerization of more branched molecules ultimately leads to a globular structure unable to accommodate further branching because of steric hindrance. Dendrimers contain carbon based organic molecules such as polyamidoamines, amino acids, DNA, sugars, organosilicons and organic/inorganic hybrids. The dendrimer is either hydrophilic or hydrophobic by construction. The dendrimer molecule contains holes in the core structure and folded branches of molecules create cages and channels which depending on construction cavities in the dendrimer either accommodate water-soluble or water-insoluble molecules. The exterior of the molecule can be designed with a multitude of accessible, arm-like branches to bind a particular nucleic acid or protein. The exterior can be electrically charged so that the entire dendrimer behaves as a polyelectrolyte. Dendrimers are used in drug delivery and gene therapy. The dendrimers can form the basis of larger supramolecular structures that can be used in replacement therapy.^[3]

II. Nano Electromechanical Systems (NEMS)

Micro Total Analytical Systems:

Most of the chemical and biological processes in living systems take place in liquid environments. Nanofluidic systems have critical dimensions on the order of a few nanometers to a few hundred nanometers, comparable to relevant length scales in fluidic environments including diffusion lengths of nanoparticles and molecules, molecular size and electrostatic screening lengths of ionic conducting fluids. “Lab On A Chip” or u-TAS systems make use of MEMS fabricated fluid systems to transport liquids in channels on the order of ten to hundreds of micrometers. The flow of liquids or the motion of individual molecules is driven or controlled by hydrostatic pressure along with electric fields in ionic conducting fluids. Controlled channel geometry, Surface Charge and applied electrostatic potentials cause electroosmotic flow or electrophoretic motion of charged molecules. Asymmetric diffusion array devices have structure dimensions comparable to diffusion lengths of single-molecule systems. These devices dynamically sort molecules by the rectification of size-dependant Brownian motion of the molecules. Sorting can also be performed by creating structures smaller than the radius of gyration of the molecules. This technique is used in the sorting of DNA. Molecular transport effects imposed by the structure dimensions have a significant impact on these systems.^[4]

Nanoactuators and Nanorobots:

Nanoactuators need to operate in biological environments under liquid flow forming a part of nanofluidic systems described above. A response time on the order of seconds or lower is desired depending on the application. The ability to integrate the nanoactuator with the nanofluidic chip is also greatly desired. The nanoactuators are used to grab small objects whose geometry is suitable for making mechanical contact. This leads to the ability of making electrical contact if the geometry of the object grabbed and

the actuator make proper electrical connection. An example of this technique in application would be grabbing a neuron and recording its electrical response. The actuator may be used as a lid for microvials or in manipulating surfaces by exposing one or the other side of a surface with the microactuator acting like a flap. A nanorobotic arm consisting of an elbow, wrist, hand and fingers has been fabricated. The arm had the capability of picking up, lifting and moving a 100 um glass bead. A potential application could be the transfer of cells in a lab-on-a-chip system. The microactuators function as hinges that open and close plates covering microcavities containing drugs or other chemicals. The devices can be used to study single cells by trapping them in the cavities. The devices are known as cell clinics. The microactuators are used in tapping individual cells to study its response to mechanical stimulus. The microactuators are used in blocking the flow of liquids, valves for nanofluidic systems. The microactuators are compatible with and work well with biological media such as salt solutions, blood plasma, urine and cell culture medium.^[5]

Another theoretical application of a nanorobot would be to provide oxygen in the event of impaired circulation. In the event of poor blood flow, oxygen supply is low and tissue damage can occur. One way to improve the levels of oxygen during poor blood flow would be to provide an artificial red blood cell. Research claims to have designed an artificial red blood cell. The device is called a "respirocyte". The respirocyte is about 1 micron in diameter and floats in the blood stream. It is spherical in shape and consists of 18 billion atoms. The atoms are made from carbon arranged in a diamond lattice. The device acts as a tiny pressure tank that is filled with up to 9 billion oxygen and carbon dioxide molecules. These gases are released from the tank when needed. The surface of the respirocyte consists of about 30,000 molecular rotors that load and unload gases into the tanks. A sensor outside of each device monitors gas concentrations. Doctors will be able to modify each respirocyte's behavior using ultrasound signals.^[6]

A cell sorter is another kind of nanofluidic system. It is a two layer device, the bottom layer is a T-shaped fluidic channel and the top layer contains pneumatic control line for pumps and valves along with cavities to smooth out oscillations. The nanoscale chip cell sorters have the advantage of being able to sort rare cells that are not limited by the valve switching speed in standard systems. Chemical control of nanofluidic devices is being investigated. In one approach hydrogel structures are fabricated in nanofluidic channels. The pH of the solution modifies the shape of the hydrogel structures causing them to swell or shrink. This varying of shape with the pH of the solution is used to regulate flow control. A drawback of these valves is they are much slower than mechanical valves but operate independent of any control circuitry.^[4]

Nanomotors:

In order to power NEMS researchers are looking into biological sources of power such as the motor proteins. A system of nanopropellers is being developed that makes use of ATP synthase that harbors a shaft that spins inside a cylinder. Metal bars are attached to the top of the shaft giving the device the appearance of a helicopter blade. The device is placed in a solution to which ATP(Adenosine Tri Phosphate) is added which causes the

rotor to spin. A further development incorporates the use of ATP generating liposomes which when added to the solution and exposed to light produce ATP which powers the rotor. The nanomotor is attached to a Nickel nanofabricated substrate by synthetic peptide link. This may provide the basis of integration with digital electronics to control the motor.^[7] Another kind of motor has been developed that makes use of carbonyl dichloride in place of ATP. The motor is made up of 78 atoms and works like a ratchet. Carbonyl dichloride is a much simpler molecule than ATP consisting of only 4 atoms compared to ATPs 47 atoms.^[8]

Nanodiagnosics:

A chip has been developed that has the ability to diagnose the presence of pathogens in the bloodstream. Bacteria and viruses vary in size from 10 to 250 nm have specific electrical properties. An electric field causes the particle to move depending on the strength of the applied field and the frequency of oscillation of the particle. Electrodes 1-2 microns across are fabricated using micro-fabrication techniques. The edge of the electrode is well defined to 50 nanometers using electron beam lithography with a spot size of 20 nanometers. This results in a precise electric field geometry. Using the precise electric field the researchers are able to separate cells, viruses and proteins. Each particle moves with a different velocity and direction depending on its electrical properties. Optical waveguide technique is used to detect this motion. In case of viruses such as AIDS, the presence of antibodies is the standard test for the viruses. However the virus may exist in the body for months before antibodies are produced. Thus this novel technology provides a method for early detection of the virus. It is hope that one day this technology will be used to detect and separate various pathogens and components from the blood plasma.^[9]

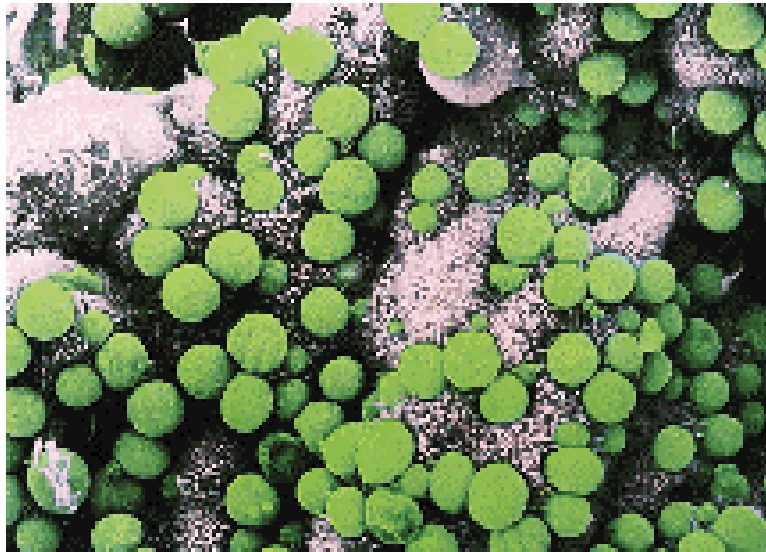


Figure 2: The Glasgow-Bangor microchip detecting “cryptosporidium” bacteria in water supplies. EPSRC United Kingdom^[9]

Nanotweezers:

The scanning probe microscope is an expensive and hard to use piece of equipment. Manipulation using the scanning probe microscope is limited to 2 dimensions. A nanotweezer has been developed that has the ability to manipulate particles 10 nanometers across. The device is fabricated from micropipettes and nanotubes made of fullerene. Two 50 nanometer diameter nanotube bundles are attached to one another and each attached to gold electrodes formed as a layer on the tip of a micropipette. As in an electroscope like charges cause the nanotubes to repel each other and unlike charges causes them to attract each other. This results in the opening and closing of the nanoforceps. The nanotweezers are limited only by the visibility of objects under an optical microscope. The arms of the tweezer are slightly longer than the wavelength of visible light. The tweezer can be used in the manipulation of genes, fabrication of miniature electrical devices and microsurgery.^[10]

Nanoneedle:

The nanoneedle is a 50-nm-diameter silver-coated optical fiber carrying a helium-cadmium laser beam. Monoclonal antibodies that attach and bind to BPT are attached to the tip. The laser light, wavelength 325 nm, excites the antibody-BPT complex at the fiber tip causing the complex to fluoresce. The fluoresced light travels up the fiber to an optical detector. A layer of silver deposited on the fiber wall prevents the laser excitation light and the fluorescence emitted by the antibody-BPT complex from escaping through the fiber. The device using antibodies that target specific chemicals present in cells can be used to study them.^[11]

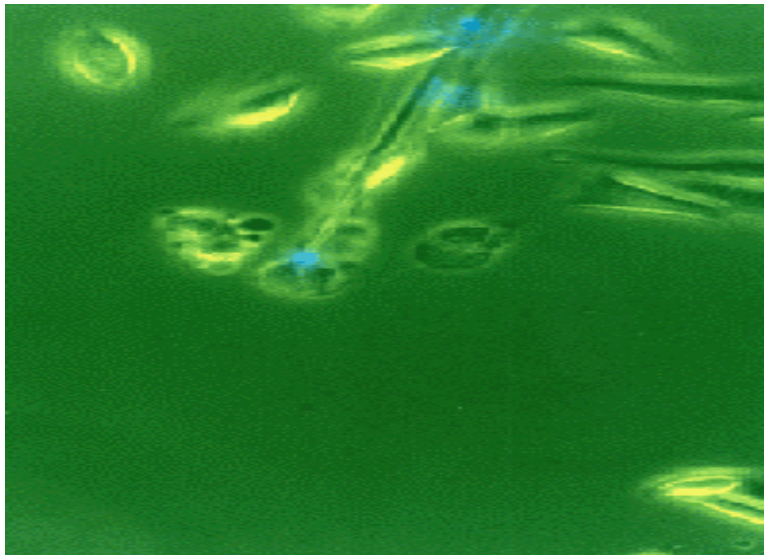


Figure 3: A Nanoneedle carrying a laser beam penetrates a living cell to detect the presence of a product indicating that the cell has been exposed to a cancer-causing substance
ORNL Review^[11]

Nanoactuated Ultrasound Transducers:

Nanofabrication technology is used to steer an ultrasound transducer within a catheter inserted into a blood vessel within the patient's body. An array of 250,000 electrostatic capacitors fabricated into a polyamide membrane (dimensions 3 mm x 10 mm x 2 microns) forms the device. The force generated by the capacitors in the membrane size causes the ultrasound transducer to wobble in a sector scan within the cardiac catheter.^[12]

III. Nanobioelectronics

Neurochip:

The neurochip is basically a neuron silicon junction. A neuron makes contact with an open metal free gate of a metal oxide semiconductor field effect transistor. The ionic transport in the neuron is the source of the membrane potential causes a motion of ions in the electrolyte modulating the source drain current of the transistor. This enables recording of the membrane potential of the neuron. This device is called the neurotransistor. Tracks fabricated in growth medium using microfabrication allow for directed growth of dendrites, extensions of the neuron. A neural network is thus formed when many neurons are grown as described earlier. These neurons are mounted on neurotransistors and thus the neural networks can be manipulated and studied. Current advances in neurotransistor technology allow for the stimulation and recording of neurons mounted on the device. The neural network circuits thus developed may replace damage neural circuits in the brain as in Alzheimer's disease. Sufficient development in this technology could lead to the development of a computer brain interface.^[13]

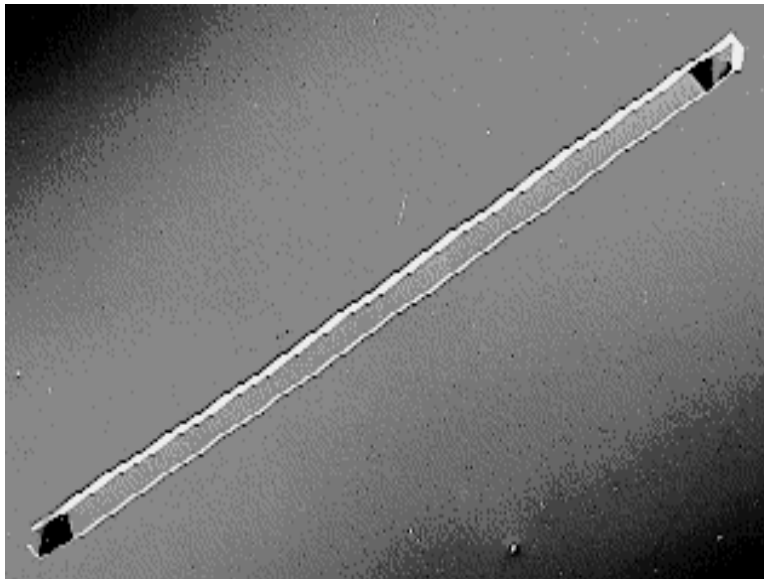


Figure 4: Micromechanically etched and thermally oxidized grooves in a silicon crystal

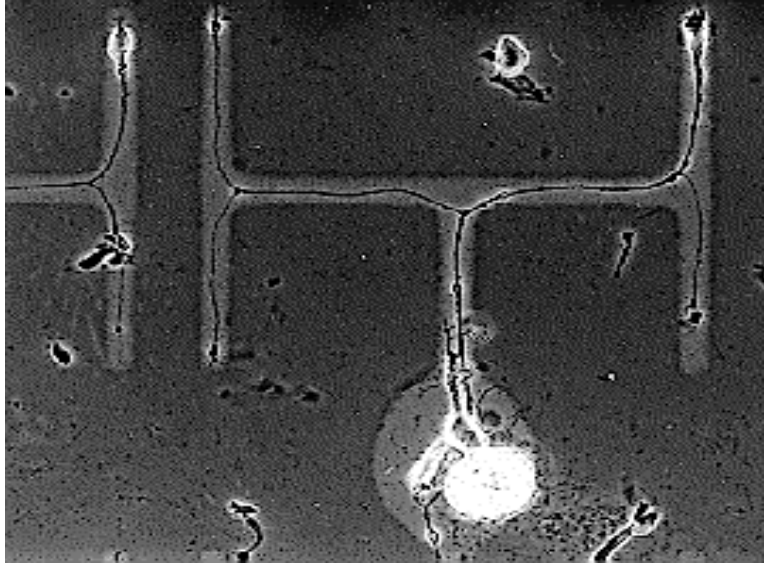


Figure 5: Right-angled branched neuron
Membrane and Neurophysics, Max-Planck Institute Of Biophysics, Martinsried, Germany.^[13]

IV. Nanostructures

Cantilevers:

A cantilever is a simple nanostructure used in probing DNA. It is based on the principle of the Atomic Force Microscope (AFM). The tip of a microscopic cantilever is run across an object under study. Intermolecular forces between the cantilever and the object cause the bending of the cantilever and a laser beam is used to record this motion. The cantilever bending recorded by the reflected laser beam gives an image of the surface of the object. An AFM cantilever a blade of silicon 500 nm long and 100 nm wide is coated with short DNA chains called oligonucleotides. The blade is placed in a solution of oligonucleotides with a complimentary sequence of base pairs as the ones on the cantilever beam. Matching pairs bind and this binding force expands the coating on the cantilever beam bending it downwards. A larger number of matching pairs cause greater bending. Thus the cantilever serves as a sensitive probe in searching for matching DNA sequences. As in the AFM a scanning laser is used to measure the extent of the bending. This technology is used to find particular sequences of DNA that are of interest and is a potential rival to DNA arrays.^[14]

Another use of cantilever technology is the “Smart Gate”. These gates release drugs or other chemicals in response to precise molecular stimuli. A specially tailored molecular adhesive coated on a cantilever beam responds to particular proteins causing the cantilever to bend as in the DNA probes leading to the release of a chemical stored in an area where the cantilever serves as a gate. In case of tumor proteins this would lead to the release of tumor-specific drugs at the site of the tumor itself.^[14]

The cantilever is the main component in a nanomechanical oscillator. The shift in the resonance frequency of the oscillator caused by a change in mass is used to detect change in mass. NEMS are capable of detecting mass changes in the order of 1 picogram. A silicon nitride cantilever beam coated with a layer of bacteria specific antibody with dimensions comparable to those of the bacterium under study. The shift in frequency attributed to the cell is detected with the cantilever vibrating in air. The shift corresponds to a mass of about 1 picogram which is equivalent to the mass of the bacterium.^[15]

Smart Bandage:

About one-third of the operations carried out to repair severed tendons are unsuccessful. This is attributed to the fact that the regenerating tissue sheathing the tendon attaches itself to the tendon making it unable to move. A specially designed bandage with grooves that have been fabricated using lithography and dry etching is wrapped around the tendon. The bandage is made of biodegradable plastic. The macrophages cells 10 microns wide grow into the grooves of similar dimensions and the tendon grows on top of the bandage. The shape of the groove causes the macrophage cells to grow long and thin along their length. The cell undergoes internal changes and the agents that hold the cell together are aligned in the direction of the groove promoting healing. A further development of this technology is the use of 50 nanometer diameter plastic dot mesh bandages used in directed growth of tissue. Thus any pattern of tissue can be grown which will be used in reconstructive surgery.^[16]

V. Optical and Ultrasound Sensing

As with other electrically based sensors, the ability to fabricate and machine components on a nanoscale level is providing an avenue for the realization and commercial development of optical sensors in the areas of biomedical diagnostics, sensing and therapeutics. In the past decade, considerable progress in the areas of biomedical optics has developed through the advancement of technology and research. The reasoning behind the heightened focus and research interests in this area are partly due to the clear and potential advantages optical sensors can offer in comparison to more traditional type of electrical and electrochemical based sensing technologies. One of the main advantages is the ability to sense or measure biological parameters in a noninvasive manner thus requiring no physical contact with the sample. This is made possible because the majority of optical techniques are solely based on observing and quantifying the effect or changes in light as it interacts with the sample. These changes are directly correlated to the parameter of interest. Under the same reasoning, most sensing based techniques that employ light are reagentless, which is another clear advantage in the development of sensors that are to be integral parts of artificial organs or other devices to be implanted in the body over long periods of time.

More specific medical applications of recent focus and interest in the field of optical and bioengineering are in the areas of diabetic glucose sensing, cancer diagnostics and genetic research. Although the number of optical techniques being applied to these

areas is large, some of the more common modalities include optical polarimetry, interferometry, and a number of spectroscopic techniques such as Raman, absorption and fluorescence spectroscopy. Regardless of the optical technique, to date, these methods have already demonstrated the ability or potential to sense physiological glucose levels noninvasively, distinguish between normal and cancerous tissue/cells noninvasively and to provide real-time genetic screening for multiple diseases in a single measurement. Furthermore, this is just a brief summary of the numerous potential applications that have been demonstrated or will be made possible in the near future. The focus in the upcoming decade will be concentrated on realizing this technology in the commercial marketplace. Therefore, the ability to integrate and miniaturize current prototype bench-top optical setups and support electronics into a single unit through advances in nanotechnology will indeed play a crucial role in making devices based on this technology commercially feasible and cost effective.

Ultrasound transducers are the hearts and the central pieces of ultrasound applications in all areas such as sonar, medical imaging and nondestructive evaluation of materials (NDE). In medical applications transducer piezoelectric materials are cut into fine fibers and mixed with soft polymers to form the “composite transducers”. These transducers have low ultrasound impedances and can transmit ultrasound energy into biological soft tissues more easily. With the conventional ultrasound transducer frequencies of 1-10 Mhz, the fiber diameters are in the range of microns. As the frequency is increased, the transducer sizes can be shrunk to allow transducers to be put into blood vessels. Thus, the fiber sizes need to be reduced for high frequency small transducers. Nanotechnology can provide the opportunity to help the development of such tiny fibers, and thus improve the quality of ultrasound microscopes.

Another area of application is 2D arrays (similar to CCD arrays used in camcorders), ultrasound transducers can be produced in millions on a small silicon wafer. The small capacitance transducers on the wafer can be used in both transmission of ultrasound energy into the human body and reception of ultrasound echo signals. The signal received can be processed by the electronics integrated on the silicon chip. As more transducer elements are built into the chip, smaller elements are required. Thus nanotechnology provides an opportunity to further reduce the size of transducer elements.

Biochemical assays generate optical energy. This creates the need to efficiently couple light into and out of nanofluidic chips. A method of achieving this coupling is the inclusion of optics near the flow channels. Various optical elements such as beam splitters, lenses etc can be easily fabricated into the nanostructure. ^[17]

Nanodyes:

Crystals of semiconductors with dimensions in the 2- to 20-nm range are called nanocrystals or quantum dots. Nanocrystals have an indium arsenide core coated with shell of cadmium sulphide. These crystals have different optical properties from the bulk material. The properties of the crystal vary as an increasing number of atoms are added

approaching bulk values. The bandgap is found to increase with size. This property is attributed to the large surface to volume ratio of nanoscale crystals.

Semiconductor materials such as silicon, indium arsenide and cadmium sulfide fluoresce. The variance of the semiconductor's bandgap with crystal dimensions allows the relation of the fluorescence wavelengths with crystal dimension. The quantum yield of the fluorescence is sensitive to surface conditions. In order to increase stability cadmium selenide is added to protect the crystal core.

Nanocrystals are prepared by epitaxy or vapor deposition. Nanocrystals find applications as fluorescent tags in biological systems. A nanocrystal is attached to a protein which transports the tag to a specific cell structure. This technique makes it possible to use different sizes of inorganic nanocrystals which fluoresce different colors for different structures in a cell instead of using a single colored dye for a specific cell structure. Nanocrystals replace organic dyes.^[18]

VI. Therapeutic Nanotechnology

Nanofabricated chips containing stem cells, cells that promote the growth of specific cells are used in treating damaged cardiac tissue. The devices are implanted in the hearts of the subject using robotic arms. The chips implanted in the damaged areas release stem cells for repair as well as drugs for therapeutic purposes. A typical human cell such as a red blood cell is about five micrometers in diameter. DNA is less than three nanometers in diameter about a 100 times smaller than the cell. Many common proteins are only a few nanometers across.^[19]

Biomedical research in the nanoscale is relatively new. Current semiconductor manufacturing technology is able to fabricate features on silicon chips only a few hundred nanometers across. This technique is used to fabricate nanoscale silicon capsules that can hold healthy cells that can replace dysfunctional ones. An example of this technique would be implantation of capsules containing replacement cells beneath a diabetic patient's skin. The implanted cells take over the function of the patient's dysfunctional pancreatic cells. Cell implantation using nanotechnology provides a valuable way to treat diseases caused by enzyme or hormone deficiencies. However immune reactions pose a major problem. Implanted replacement cells are foreign to the body and are attacked by the body's immune system, with detrimental results.^[20]

Using nanotechnology a novel technique has been devised to counter the effect of the immune system. A foreign organism in the body triggers an immune system response releasing antibodies to attack the foreign organism. An artificial barrier is fabricated which prevents the immune system from reaching the transplanted cells. A silicon capsule with a membrane barrier is fabricated with pores of diameters small enough to block out antibodies and large enough to let desirable molecules flow in and out. Antibodies have the capability of penetrating any orifice larger than about 18 nanometers (the exact size is still unknown). State of the art photolithography techniques for

integrated circuits are good for features small as a few hundred nanometers. Modifying the technology used in the semiconductor industry researchers have been able to create holes only a few nanometers wide.

In diabetes mellitus, the cells in the pancreas that produce insulin called the islets of Langerhans malfunction. A possible cure would be to implant fresh copies of the cells into the body. These would replace the malfunctioning pancreatic cells and restore the body's feedback loop. The replacement tissue is harvested from compatible nonhuman species such as pig islet cells. Earlier replacement therapy required that the patient take drugs to suppress the immune response. The strategy leaves a patient dangerously susceptible to infections.

The solution is to house replacement cells in a container made with a nanoporous membrane material. The smaller glucose molecules can stream easily through the nanopores into the capsule to activate the cells and the insulin trickles out controlling the blood chemistry. A similar approach is being researched for use in treating diseases such as Alzheimer's. Patients with Alzheimer's have dysfunctional neurons which do not release neurotransmitters. Nanopore fabrication technology is used to make microcapsules for implanting neurons in the brain. Once the capsules are implanted the neurons are electrically stimulated to release neurotransmitters. Disorders where basic neurosecretory-cells are missing or damaged can be treated using Nanopore technology.

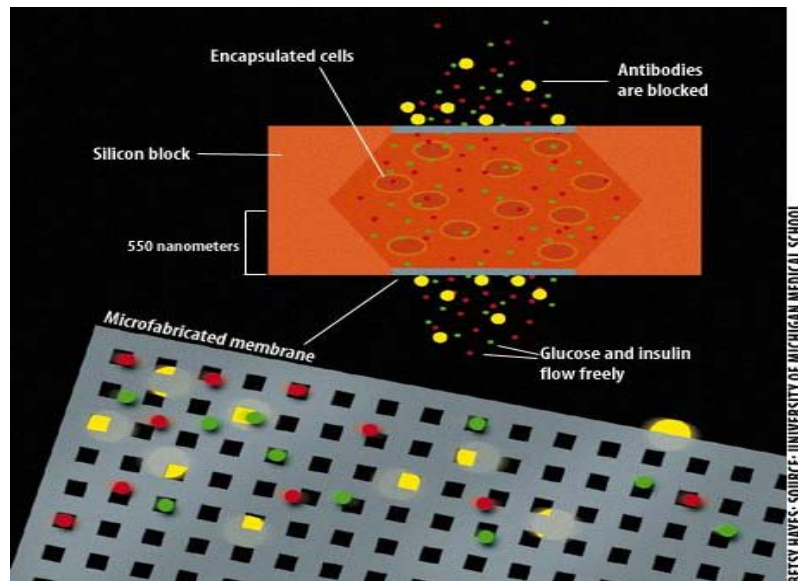


Figure 6: Transplanted pancreatic cells are shielded in a silicon block with nanometer holes large enough to let glucose and insulin flow freely, but too small to allow antibodies to enter and attack the foreign cells
University Of Michigan Medical School^[20]

Nanobioreactors:

Nanofabrication techniques such as photolithography, soft lithography and electrochemical etching techniques have been used to fabricate structures that

house cells extracorporeally, outside the body. These structures are being used to house hepatic tissue in a kind of bioreactor setup. The liver cells are housed in micro-fabricated silicon pores. A real advantage of this setup is that the cells can be studied in 3 dimensions over 2 dimensional techniques involved in earlier research. This technique leads to the development of an artificial liver that can be housed outside the body and assume the livers functions without putting the patient through the risk of a liver transplant.^[21]

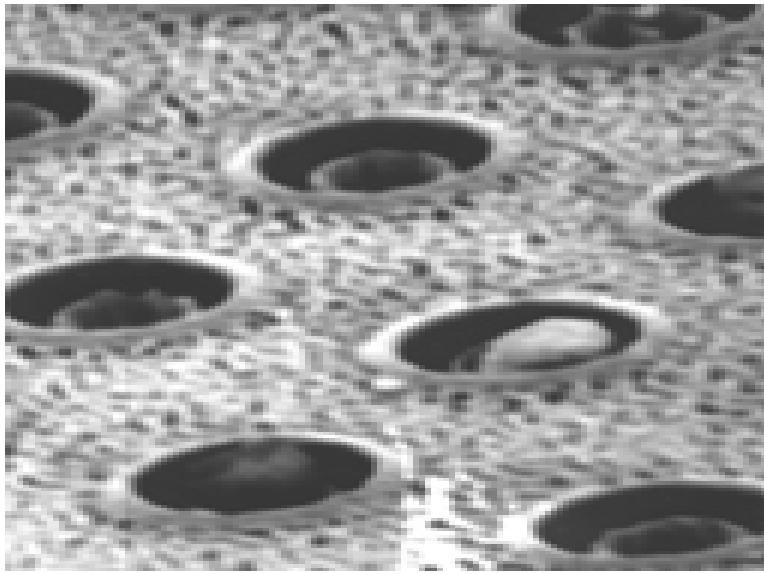


Figure 7: Biomimetic Porous Silicon with "Trapped" Hepatocyte MTEL University Of California San Diego^[21]

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