

BioMEMS Applications Overview

Primary Knowledge (PK)

Instructor Guide

Note to Instructor

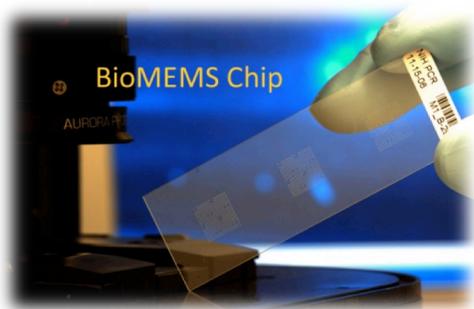
This Primary Knowledge (PK) unit provides an overview of the biomedical applications of MicroElectroMechanical Systems (MEMS). Such devices are referred to as bioMEMS.

This primary knowledge unit is part of the *BioMEMS Applications Overview Learning Module*.

- BioMEMS Applications Knowledge Probe (PK – pretest)
- **BioMEMS Applications Overview PK**
- BioMEMS Applications Overview Activity: Nanomachines
- BioMEMS Applications Overview Activity: ELISA
- BioMEMS Applications Overview Activity: DNA Hybridization
- BioMEMS Applications Overview Assessment

Description and Estimated Time to Complete

This learning module is an overview of some of the major biomedical developments and applications of BioMEMS. There are three activities that provide further exploration into some of these applications, how they are used and how they work.



*Biochip slide for testing protein arrays
[Image courtesy of Argonne National
Laboratories]*

This unit provides an overview of Microelectromechanical Systems (MEMS) applications in the biomedical field. Such devices are referred to as bioMEMS. The size of the medical industry and the number of applications that could benefit from MEMS devices, make the medical industry an ideal market to take advantage of the MEMS already on the market and those in research and development.

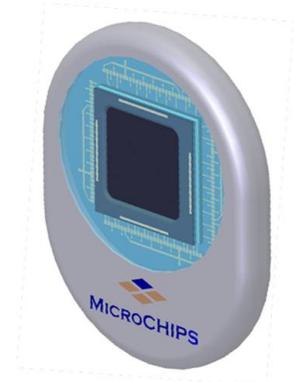
Estimated Time to Complete

Allow approximately 30 minutes.

Introduction

Imagine a device that restores sight when implanted on the retina of the eye, or a "skin patch" chip capable of detecting an invading microorganism before symptoms develop. A type of retinal implant was recently approved (Feb 2011) for commercialization by both Europe and the U.S. "Skin patch chips" are being developed and tested for a variety of applications which include diagnostics as well as therapeutics.

One company, MicroCHIPS, is developing both active and passive drug delivery systems based on its proprietary reservoir arrays. The figure shows one of MicroCHIPS' implantable active drug delivery systems. This product contains a reservoir, microprocessor, and sensor feedback system which allows for a controlled release of a drug.¹ In 2011, a more advanced version of MicroCHIPS's drug delivery system shown here went to clinical trial. Continue reading to learn more.



MicroCHIPS Subcutaneous Active Drug Delivery System [Printed with permission of MicroCHIPS, Inc.]

Other bioMEMS products include DNA and protein analysis chips, lab-on-a-chip (LOC) devices, miniaturized sensors for smart catheters, chemical and biological sensors, and optical devices for medical imaging.

The market for bioMEMS devices has been growing rapidly for many years. According to "The Global BIO-MEMS Devices Market forecast, 2012-2018", the bioMEMS market is expected to grow "from \$2.3 Billion in 2013 to \$6.6 Billion by 2018, at a CAGR (compound annual growth rate) of around 23% for the given period." This report analyzed "the market of devices by products such as DNA-Chips, Lab-on-chips, Drug delivery systems, Biosensors, Microfluidic Devices, Biomems implants, Silicon Microphones, Accelerometers, Gyroscopes, and microactuators."² This increase is being partially driven by the increase in the patient pool, new diagnostic and therapeutic devices, and advanced treatments for cardiology, neurology, and oncology.

This unit will answer the questions

- Where might you encounter bioMEMS devices?
- How will bioMEMS impact your life?

Objectives

- Summarize at least three (3) areas of applications for bioMEMS devices.
- Describe specific examples within at least three (3) areas of applications for bioMEMS devices.
- Analyze advantages and possible disadvantages of bioMEMS devices.

Key Terms (See Glossary at the end of this unit for definitions)

Antibody
Biochips
ELISA
Enzyme
Gas Chromatography
Microarrays
Microspheres
Piezoelectric effect
Pyroelectricity
Reporter group
Substrate (bioMEMS)
Thermistor

The State of bioMEMS

Applications for bioMEMS devices exist in clinical medicine, environmental, biological and chemical analysis. Applications from one area often overlap with other areas. Applications can be broadly placed into the categories of

- clinical diagnostics and therapeutics,
- environmental applications including Homeland Security,
- food safety, and
- bioprocessing.

In addition, there are basic research applications that inform and drive applications in other areas.

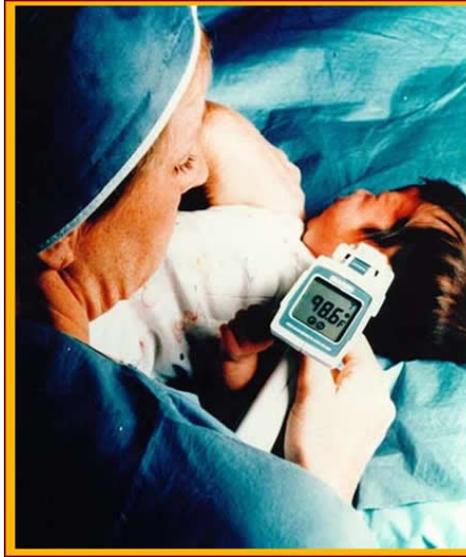
BioMEMS are revolutionizing the field of medicine. Clinical applications of bioMEMS include both diagnostic (e.g., utilizing micro sensors and transducers), and therapeutics applications (e.g., drug delivery actuators, disease monitors).

BioMEMS Sensors Placement

BioMEMS sensor placement depends on the device and its application. A sensor can be

- topical (applied to skin or placed in the mouth)
- externally connected (*in vitro* or external with *in vivo* or internal device)
- implanted devices (totally *in vivo*)

Topical Sensors



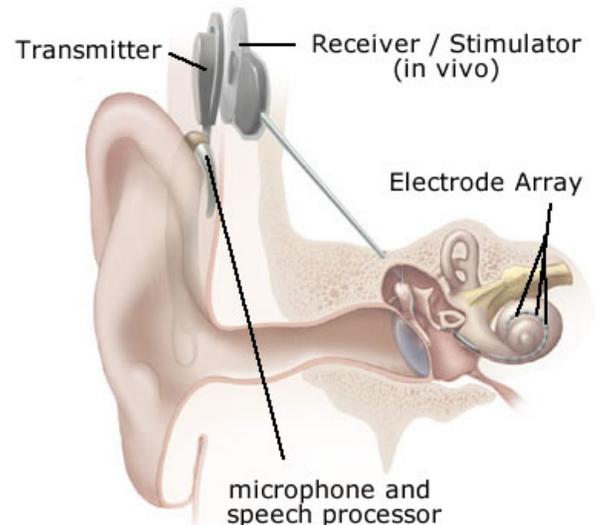
Infrared ear thermometer

[Image courtesy of NASA Jet Propulsion Laboratory]

Topical sensors are those that are applied to skin or placed in the mouth. One familiar device is the thermometer used for measuring body temperature. Thick-film disposable thermistors and infrared ear thermometers have largely replaced the mercury thermometer.

Externally Connected Sensors

Externally connected sensors are devices that can contain both an *in vivo* part and an external part. An example of such a device is the cochlear implant shown in this figure. These devices contain a microphone, a speech processor, a transmitter and receiver/stimulator, and an electrode array. The microphone picks up sounds and selects and arranges the sounds for the transmitter. Once received from the transmitter, the receiver/stimulator converts these signals to electric impulses which are used to stimulate the array. The array then stimulates different regions of the auditory nerve.



The implant does not restore normal hearing, but it does give a deaf person a useful representation of his environment and helps him understand speech. To see an animation, go to the following link: <https://youtu.be/zeg4qTnYOpw> (How a Cochlear Implant Works by Advanced Bionics)

The Cochlear Implant image is modified from image courtesy of National Institute of Health

Another Externally Connected bioMEMS



MiniMed Paradigm[R] 522 insulin pump, with MiniLink™ transmitter and infusion set. [Printed with permission from Medtronic Diabetes]

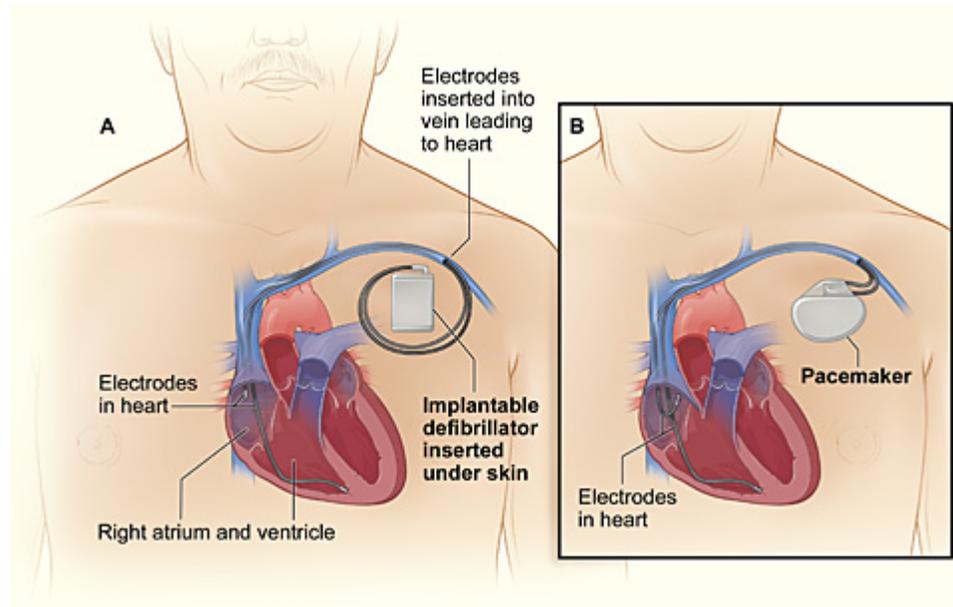
Another externally connected bioMEMS is the glucometer. These devices have an implanted glucose sensor that communicates with external components, such as a computer and micropump. Glucometers with implanted sensors that are currently available include the following:

- MiniMed Paradigm [R] 522
- One Touch© Ping™
- GlucoDay® S (Menarini Diagnostics)

The MiniMed system (*Paradigm 522 shown in the figure*) uses an in vivo glucose sensor that transmits its results to a micropump that delivers insulin continuously to the body. (*See the following "Glucometer" section for a discussion of how this device works.*) The One Touch© Ping™ uses skin sensors to measure blood sugar without a poke or a prick. GlucoDay® S consists of a micro-pump and a microfiber biosensor inserted under the skin. (This device is discussed in more detail later on in this unit.)

Implanted Devices

The third category of sensor is the fully implanted device. This area of bioMEMS has numerous possibilities, but few of these devices have made it to market. Implantable bioMEMS that have been on the market for years are defibrillators and pacemakers (*see graphics below*).



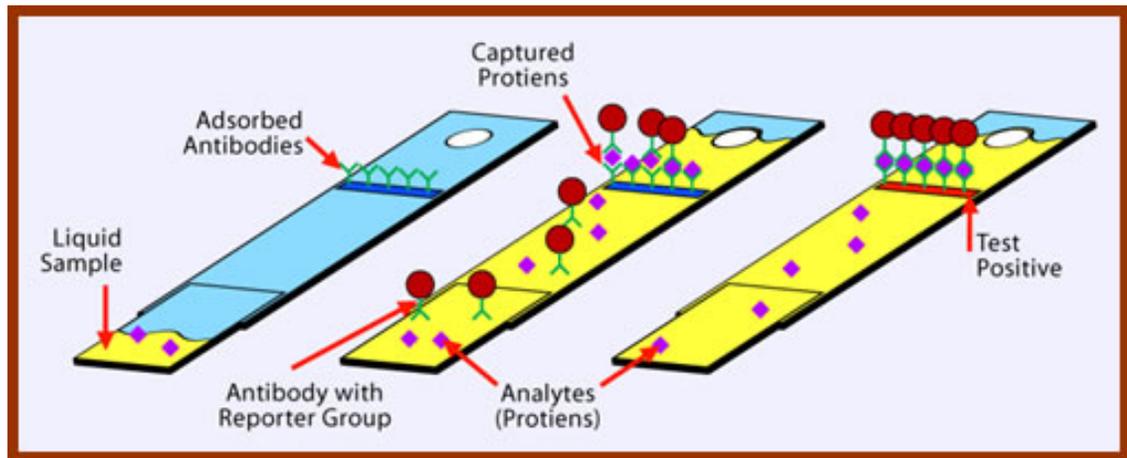
*(Left) Implantable Defibrillator (used to control dangerous irregular heartbeats)
(Right) Implantable Pacemaker (used to control less-dangerous irregular heartbeats or to beat the heart in cases of second and third-degree heart block)
[Courtesy of National Heart Lung and Blood Institute – National Institute of Health]*

Other emerging applications for implantable devices include neural implants and spinal cord stimulators to treat intractable pain and spasticity. The implantable microelectrodes for neural applications are based on thin-film polymer foils with embedded microelectrodes for both recording and stimulation.⁴ Implantable pressure sensors are being tested that can be used in cardiovascular monitoring, glaucoma monitoring, and monitoring of intracranial pressure.⁵

It may take years for more of these devices to get FDA approval due to the regulations for proof of concept to prototype to FDA approval. During this time there is the on-going challenge of keeping a project's funding.⁵ A device may show technical promise, but the process to get to commercialization is cumbersome, costly and time-consuming.

Following are several discussions of bioMEMS that have already made it to the market or that are in the final stages of testing.

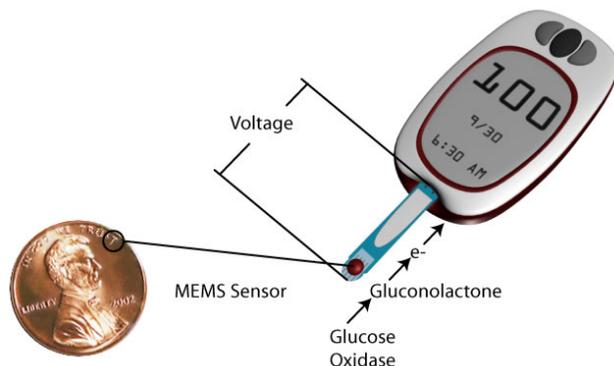
Biological Molecule Sensors



Home Pregnancy Test

Biological molecules have the ability to detect and recognize other biomolecules. This characteristic of biomolecules has provided the science that has enabled the development of biosensors that detect, capture and analyze specific analytes (i.e. target particles or molecules). One example is the home pregnancy test kit that employs antibodies as biosensors. The antibodies have a reporter group attached, which detects a small protein produced during pregnancy and present in the urine.

Glucometers

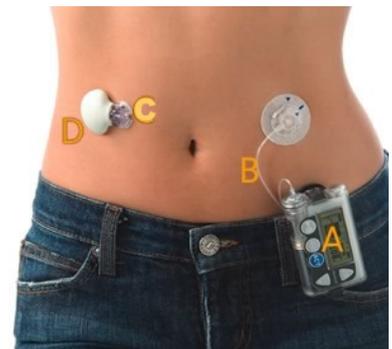


This is an external glucometer that requires the patient to place a droplet of blood on the MEMS sensor. To get the blood sample, the patient must prick a finger.

The glucose in the blood reacts with the enzymes on the coating of the biosensor. Gluconolactone is produced releasing an electron.

Another very successful biosensor is the glucometer which monitors blood glucose levels of diabetics. The glucometer unit contains a strip impregnated with enzymes that react with glucose, and an electrode which tracks chemical changes through fluctuations in current (moving electrons). Glucometers provide a sensitive measurement of blood glucose levels from a single droplet of blood. The glucometer is strictly a diagnostics sensor.

However, implantable devices may cross the boundary between diagnostics into therapeutics by not only utilizing a sensor but also incorporating an actuator or micropump that administers the necessary drug, such as insulin. The glucometer shown in the picture monitors the glucose (C), using a chemical transducer, and delivers insulin on an as-needed basis using a micropump (A/B). D is the transmitter that relays the information from the glucose sensor (C), to the computer (A).⁶

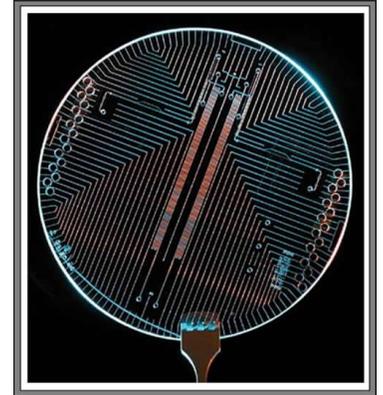


*MiniMed Paradigm[R] REAL-Time System from Medtronic Diabetes
[Printed with permission from Medtronic Diabetes]*

Both of these devices have become smaller, more accurate and more efficient over the past five years due to the continuous developments in microtechnology. Visit the Medtronic website (<https://www.medtronicdiabetes.com/home>) to see the latest and greatest in glucose monitoring.

Microfluidics

Another MEMS platform used in diagnostic bioMEMS makes use of microfluidic components. Integrated fluidic microchips allow separations, chemical reactions, and calibration-free analytical measurements to be directly performed in very small quantities of complex samples such as whole blood and contaminated environmental samples. This technology lends itself to applications such as clinical diagnostics (including tumor marker screening) and environmental sensing in remote locations. Lab-on-a-Chip (LOC) systems (*see LOC*) enable sample handling, mixing, dilution, electrophoresis and chromatographic separation, staining and detection on single, micro-integrated systems.⁷



Lab-on-a-chip (LOC)

[Printed with permission. From Blazej, R.G., Kumaresan, P. and Mathies, R.A. PNAS 103, 7240-7245 (2006).]

Here's a good read about LOCs: "Introduction to Lab-On-A-Chip 2015: Review, History and Future." Elveflow Plug & Play Microfluidics. <http://bit.ly/1PVjW1k>

One company, BioLOC, developed a lab on a disk to perform ELISAs (Enzyme-linked Immunosorbent Assays) on a polymeric compact disk (*shown in the figure*). ELISAs use antibodies as biosensors and is one of the most common immunoassays. They have been widely used for detection and quantification of biological agents (antigens, mainly proteins and polypeptides) and chemical agents. An ELISA's high selectivity and sensitivity has made it an important device in clinical, food safety, and environmental applications.⁸



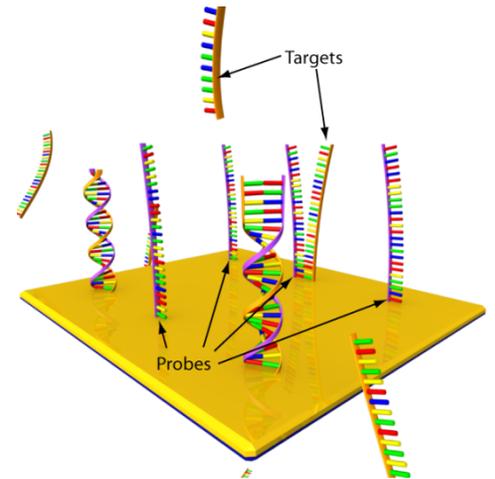
BioLOC's CD-ELISA™

[Printed with permission of BioLOC LLC]

DNA (Deoxyribonucleic acid) and BioMEMS

The Human Genome Project introduced an era in which individualized approaches to medicine are possible through an analysis of a person's DNA. The 1997 movie "GATTACA", considered a world in which genetic engineering allowed parents to determine the complete genetic makeup of their children. With genetically perfect offspring, the film proposed a new brand of discrimination, one based on "science."

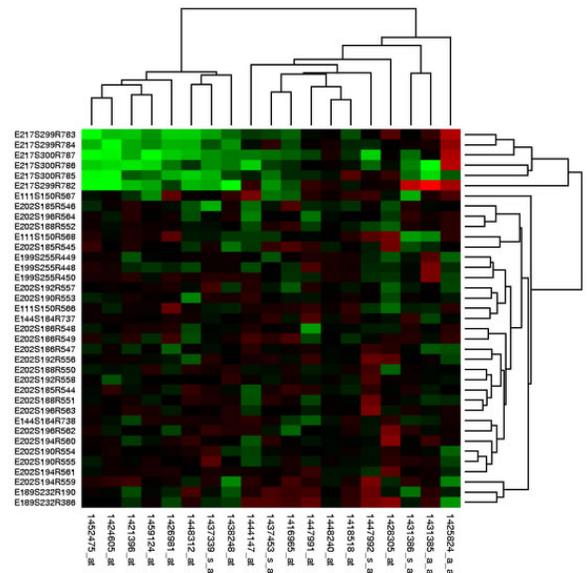
In 2007 the concept introduced in "GATTACA" became a possibility with the development and availability of DNA Lab-on-a-chip devices. These devices are used not only for basic research, but also in the field of forensics and disease prediction. The DNA microarray in the graphic uses single-stranded DNA probes to bond with complementary single-stranded target DNA in the sample thus enabling the DNA microarray to identify the target DNA.



Identifying target DNA through the hybridization process (Graphic illustrates what happens in a DNA Microarray: The target single strand DNA bonds with a matching complementary capture DNA probe.)

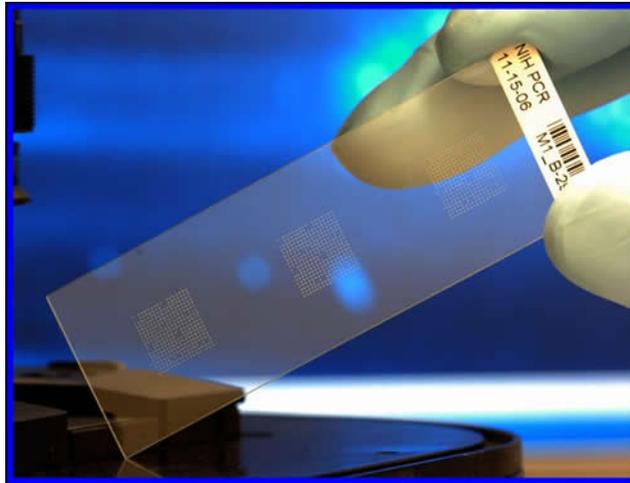
DNA microarrays are tools used to identify specific genes and gene mutations as well as analyze and measure the activity of genes. Researchers can use microarrays and other methods to measure changes in gene expression (activity) and thereby learn how cells respond to a disease or to some other challenge.⁹ Gene expression microarrays (*image right*) measure tens of thousands of genes on a single microarray and provide scientists the data to understand regulatory processes at the cellular level.

Gene expression values from microarray experiments can be represented as heat maps or optical maps to visualize the results of data analysis. The green represents gene expression or activity with DNA in a control sample. The red represents activity with DNA in a target sample. Black indicates no activity with DNA in either sample – control or target. [Image is public domain. Image source: Wikipedia: Gene Expression Profiling]



Protein and BioMEMS

Like DNA microarrays, protein microarrays allow for the simultaneous analysis of thousands of proteins within a single experiment. Protein microarrays provide a means for high throughput study of protein abundance and function. Protein microarray technology allows for the creation of antigen microarrays for vaccine development and the diagnosis of infectious diseases. Microarrays spotted with tumor proteins provide a mechanism for tumor antigen profiling, thus enabling improved treatment for the patient.¹⁰

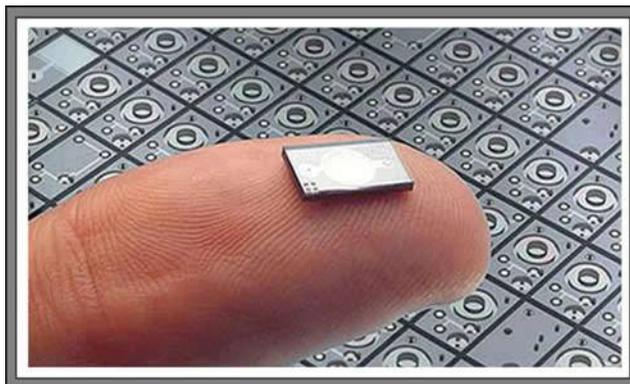


*Biochip slide for testing protein arrays
[Image courtesy of Argonne National Laboratories]*

The picture shows a biochip slide developed at Argonne National Laboratories. Each biochip has hundreds to thousands of gel drops on a glass, plastic or membrane support. The biochip system can identify infectious disease strains in less than 15 minutes when testing protein arrays and in less than two hours when testing nucleic acid arrays.¹¹

For more information on microarrays, be sure to review the SCME BioMEMS learning module - *DNA Microarray Learning Module*. (<http://bit.ly/2uuJiNs>)

Drug Delivery Systems



*Insulin pump for drug delivery system
[Printed with permission from Debiotech SA¹²]*

In 2014 Debiotech introduced its JewelPUMP Insulin delivery platform with smartphone remote control for diabetic patients. The JewelPUMP is a patch containing a reservoir that holds a week's worth of insulin, a MEMS pump-chip, cannula and nano-sized needle. The patch is worn on the arm of the patient. The Debiotech designed smartphone contains a blood glucose monitor that can be used by the patient to test blood glucose levels. If test results show that the patient is in need of insulin, the smartphone signals the pump to deliver a precise amount of insulin.²⁶

Drug delivery systems are a therapeutic application of bioMEMS. Pumps delivering insulin in implantable devices are examples of a drug delivery system (See above figure of insulin pump). Other examples include the Medtronic SynchroMed Pump that administers morphine within the spine, and piezoelectrically activated pumping devices used for drug delivery applications.

Researchers are also examining long-term integration of living cells with inorganic materials creating a sensing and delivery platform both in vitro and in vivo. The in vivo application creates a novel immune-isolation environment for the cells. This system could provide a means of avoiding host immune rejection responses with transplants. It could also allow the transplanting of cells from donor to host for purposes of obtaining secretory products for the host.

Microchips are being developed that contain arrays of micro-reservoirs each of which can contain combinations of drugs, biosensors, or reagents/chemicals. Such an example is the MicroCHIPS active drug delivery system in the figure. "This technology is unique in its use of wireless signaling, its system of reservoirs allowing precise, efficient delivery of solids, liquids or gels, and its small size. It is not expected to replace all pills or other forms of drug delivery. Rather, it will deliver proteins, small molecules and other drugs that are highly potent, have limited stability, and must be delivered in precise doses at specific times."¹³

MicroCHIPS Subcutaneous Active Drug Delivery System [Printed with permission of MicroCHIPS, Inc.]



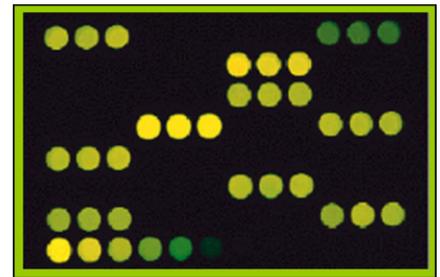
In 2011 a clinical trial implanted MicroCHIPS drug delivery in eight post-menopausal women suffering from severe osteoporosis. At the time, the women had to administer daily injections subcutaneously to prevent bone loss and to improve bone density. The implanted MicroCHIPS system contained several reservoirs each holding a single dose of an osteoporosis drug. When needed, an external wireless signal would open a reservoir allowing the drug to enter the patient's system. The results of this trial, published in February 2012, showed that the implanted MicroCHIPS drug delivery systems were qualitatively and quantitatively similar to the results of the daily injections. None of the implanted devices were rejected and the patients indicated that the implant did not affect their quality of life.²⁵

Another type of drug delivery system being researched and exploited is the use of microspheres or microbeads as drug carriers. Some microspheres have been being designed to stay at the delivery site for prolonged periods of time, providing slow release of the drug. Currently, microspheres are being added to the blood stream to provide a controlled release of drugs such as antibiotics for treatment of Kaposi's sarcoma.

Environmental Applications

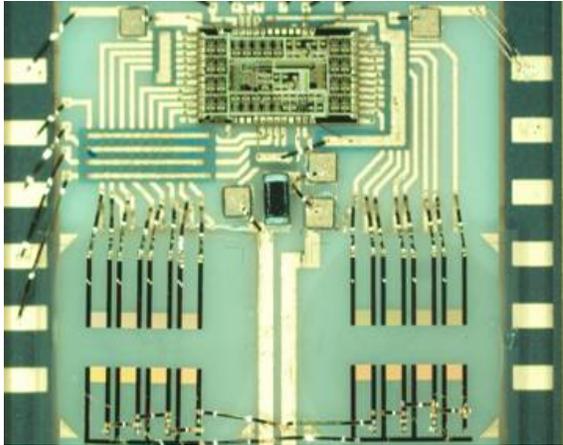
Environmental applications are a growing part of the bioMEMS field. In one example, a gene from a firefly is added to mammalian cells so that the cells glow when exposed to the toxin dioxin. As the amount of dioxin increases, the cells glow more brightly. This assay provides a quick and simple test for dioxin. The figure shows how the firefly luciferase reporter gene luminesces to test for the presence of dioxin in environmental samples.¹⁴

Another application uses cultured mammalian cells to predict lethal toxicity of chemicals in humans. The initial application used a micropipette tip to hold the cells.¹⁷ This assay can be adapted to a MEMS device.

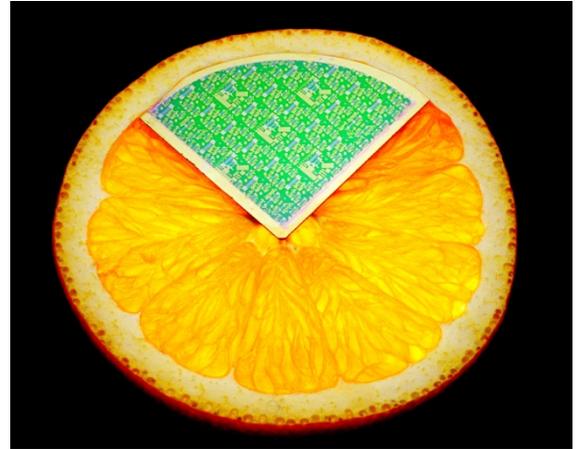


*Firefly luciferase reporter gene
[National Institute of Environmental
Health Sciences, NIH,
Photo credit: Michael Denison
Printed with permission]*

Both environmental scientists and homeland security personnel are interested in the rapid detection and identification of bacteria and pathogens. Researchers have developed microsystems which concentrate components specific to certain pathogens, then release these to a micro gas chromatography unit so that the components can be separated. The separate components are passed to a surface acoustic wave sensor array (SAW) for component identification. A working example of such a system was developed by Sandia National Labs (*See below*). This device will provide portable, rapid detection and early warning of the presence of pathogens in air or water.^{15,16}

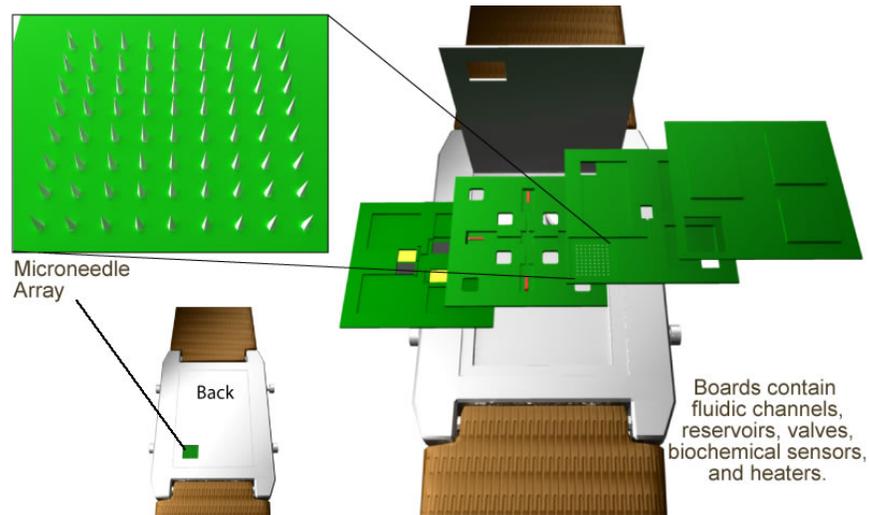


*“The eight-sensor MicroChemLab surface acoustic wave (SAW) based sensor system-on-a-chip is capable of near simultaneous detection of a wide variety of chemical compounds. It is about the size of dime”.¹⁰
[Image courtesy of Sandia National Laboratories]*



*“ORANGE YOU TINY? -- Some 30 individual chips with acoustic wave sensors make up this quarter of a wafer, which fits nicely on an orange slice”.¹¹
[Image courtesy of Sandia National Laboratories]*

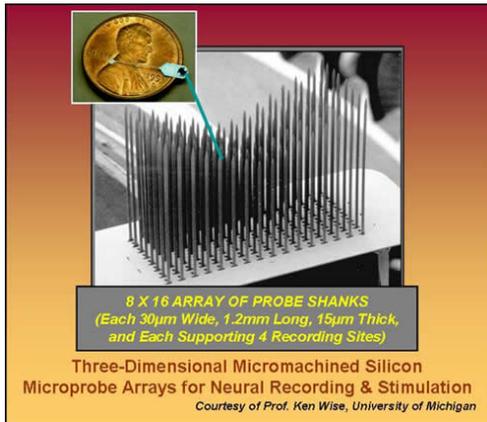
DARPA



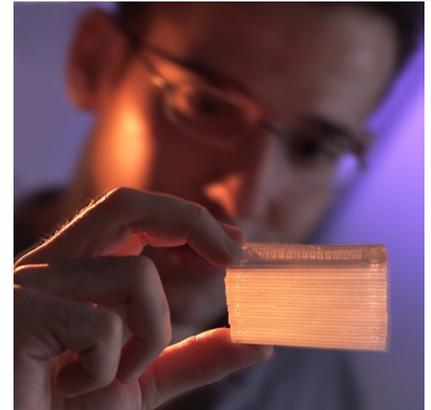
The biofluidic chips in the figure are chips that integrate diagnostics, rapid detection and potential treatment in a single chip. This illustration is loosely based on the BioFLIPS being developing by CFD Research Corporation as part of the DARPA BioFLIPS program.

The Defense Advanced Research Projects Agency's (DARPA) Bio-Fluidic Chips (BioFlips) represent another application of BioMEMS. The goal of BioFlips is the presymptomatic diagnostics of infected soldiers through "lab-on-a-chip" detectors (wristwatch size). These bio-fluidic chips will integrate diagnostics, rapid detection and potential treatment in a single chip. Commercial applications include the continuous monitoring of high-risk (e.g., post-surgery) and chronically ill patients as well as individuals in potentially dangerous environments. When fully developed, BioFlips will advance the state-of-the-art technologies to merge *in vitro* diagnostics with *in vivo* sample acquisition and drug delivery.^{17,18}

Additional Applications



*Artificial Kidney Tissue
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Neural Probe Array

Other bioMEMS applications are constantly emerging:

- Minimally invasive surgery with haptic feedback
- Point-of-care (POC) clinical diagnosis
- Magnetic microbeads in sample preparations for clinical testing
- Neural probes (*left image above*)
- Nerve regeneration
- Retinal implants
- Miniaturized dermabrasion tools
- Cell-based biosensors
- Olfactory sensors
- Minimally invasive devices endoscopy/colonoscopy techniques
- Tissue engineering (*picture right*)

Summary

Based on the numerous applications and application possibilities, it seems safe to say that bioMEMS devices will impact every aspect of our lives, from medical devices to food and environmental screening. Ultimately these systems promise to significantly improve medical care on a global scale.

Food For Thought

What are disadvantages to the current glucometer system? Provide a rationale for the development of the fully implantable devices described in the unit.

What are some of the envisioned applications of bioMEMS devices for the neurosciences?

Why do biological molecules provide an approach to the development of specific biosensors?

What are examples of drug delivery systems?

Food For Thought / Answers

What are disadvantages to the current glucometer system? Provide a rationale for the development of the fully implantable devices described in the unit.

Answer: The individual must prick him/herself at regular intervals to use the glucometer, and then must inject insulin as needed. The fully implantable devices eliminate the need for needlesticks, provide a continuous monitoring of blood glucose, and are "on site".

What are some of the envisioned applications of bioMEMS devices for the neurosciences?

Answer: Neural probes and nerve regeneration are emerging applications of BioMEMS devices in the neurosciences.

Why do biological molecules provide an approach to the development of specific biosensors?

Answer: Many biological molecules are designed to detect and recognize small molecules. For example, antibodies react with antigens, enzymes react with specific substrates, and DNA binds to complementary sequences of DNA. These molecules can be adapted to the field of bioMEMS and used in diagnostic applications.

What are examples of drug delivery systems?

Answer: Pumps and pumping devices, the integration of cells with inorganic materials, and coupling drugs to microspheres are all examples of drug delivery systems.

Glossary of Key Terms

Antibody: a protein used by the immune system to identify and neutralize foreign substances (e.g. virus, bacteria). Each antibody is highly specific to the substance that elicited the immune response.

Biochips: a generic term that includes the lab-on-a-chip devices and microarray devices.

Cannula: A flexible tube which when inserted into the body is used either to withdraw fluid or insert medication.

ELISA: a sensitive immunoassay that uses an enzyme linked to an antibody or antigen as a marker for the detection of a specific protein, especially an antigen or antibody.

Enzyme: a molecule (protein, RNA) that functions as a biological catalyst.

Gas Chromatography: a type of chromatography in which the mobile phase is a carrier gas, usually an inert gas such as helium, nitrogen or hydrogen and the stationary phase is a microscopic layer of liquid or polymer on an inert solid support, inside glass or metal tubing, called a column.

Infrared ear thermometer: a device that measures body temperature by measuring the infrared energy emitted from an individual's eardrum in a calibrated length of time. The infrared energy falls on a thin pyroelectric crystal that develops a charge proportional to the collected energy.

Luciferase: An enzyme that aids the oxidation of luciferin in the cells of organisms that emit light.

Microarrays: a tool used for the study of DNA, proteins, and genomes. Typically, a 2-D array prepared on glass, filter, or silicon wafer.

Microspheres: a sphere sized from about 0.5 to 100 micrometers and made of any material.

Piezoelectric effect: the ability of crystals and certain ceramic materials to generate a voltage in response to applied mechanical stress.

Pyroelectricity: the ability of certain materials to generate an electrical potential when they are heated or cooled. As a result of change in temperature, the material becomes polarized and an electrical potential is established.

Reporter group: Usually enzymes (e.g. alkaline phosphatase, β -D-galactosidase) or fluorescent dyes used to provide a visual signal for a reaction.

Spasticity: A disorder of the body's motor system in which certain muscles are continuously contracted.

Substrate (BioMEMS): the substance acted upon by an enzyme.

Thermistor: A variable resistor comprised of semiconductors that varies rapidly and predictably with heat. A change in temperature causes a change in resistance. Thermistor is a combination of the words thermal and resistor.

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