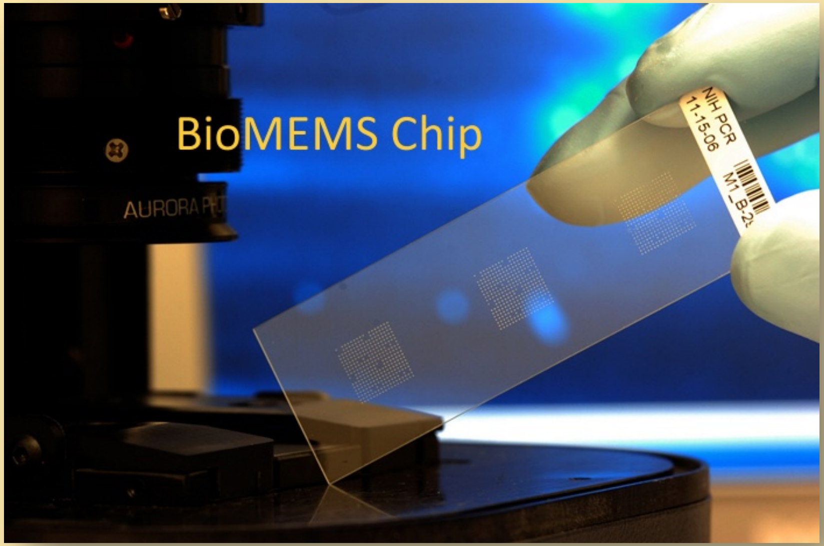
BIOMEMS APPLICATIONS OVERVIEW



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

Unit Overview

Imagine a device that restores sight when implanted on the retina of the eye, or a "skin patch" capable of detecting an invading microorganism before symptoms develop.

These are two possible future applications of bioMEMS devices.

This unit explores several current and future applications of bioMEMS.

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.

BioMEMS Market

BioMEMS products include

- DNA and protein analysis chips (microarrays)
- Lab-on-a-chip (LOC) devices
- Miniaturized sensors for smart catheters
- Chemical and biological sensors
- Optical devices for medical imaging

"..over the past few years, bioMEMS devices have become the largest and most diverse applications of MEMS devices." *(R&D Magazine)*

MicroCHIPS Subcutaneous Activie Drug Delivery System contains a reservoir, microprocessor, and sensor feedback system allowing for a controlled release of a drug. [Figure reproduced by permission of MicroCHIPS, Inc.]

What You Will Learn?

This unit answers the questions

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

The State of bioMEMS

Applications for bioMEMS devices exist in clinical medicine and environmental, biological, and chemical analysis.

Applications can be

- 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 is expected to revolutionize the field of medicine.

BioMEMS Sensor Placement

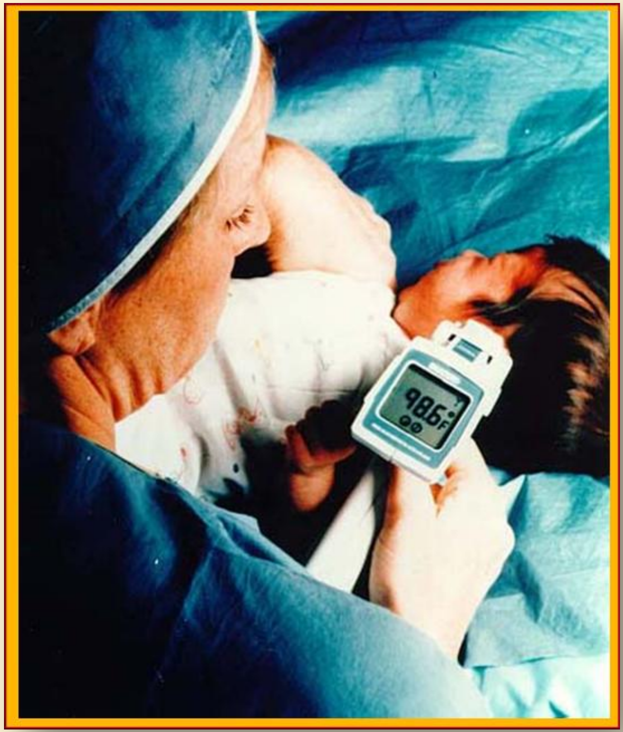
BioMEMS sensor placement depends on the device and its application.

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

- 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.



Infrared Ear Thermometer [Image courtesy of NASA Jet Propulsion Laboratory)

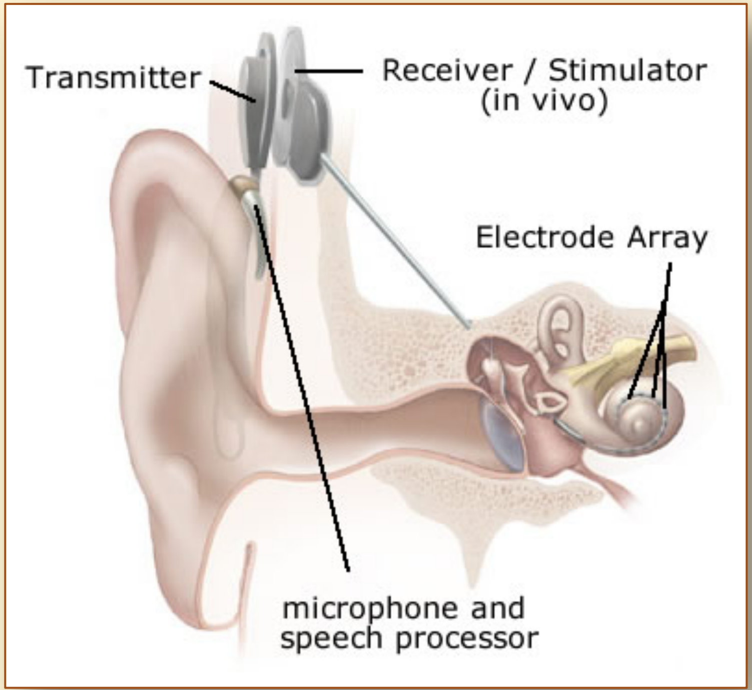
Externally Connected bioMEMS

Externally connected sensors are devices that contain both an in vivo part and an external part.

An example of such a device is the cochlear implant *(see figure)*.

These devices contain a microphone, a speech processor, a transmitter and receiver/stimulator, and an electrode array.

The implant gives a deaf person a useful representation of his environment.



Cochlear Implant
[Modified from image courtesy of National Institute of Health]

Other Externally Connected bioMEMS

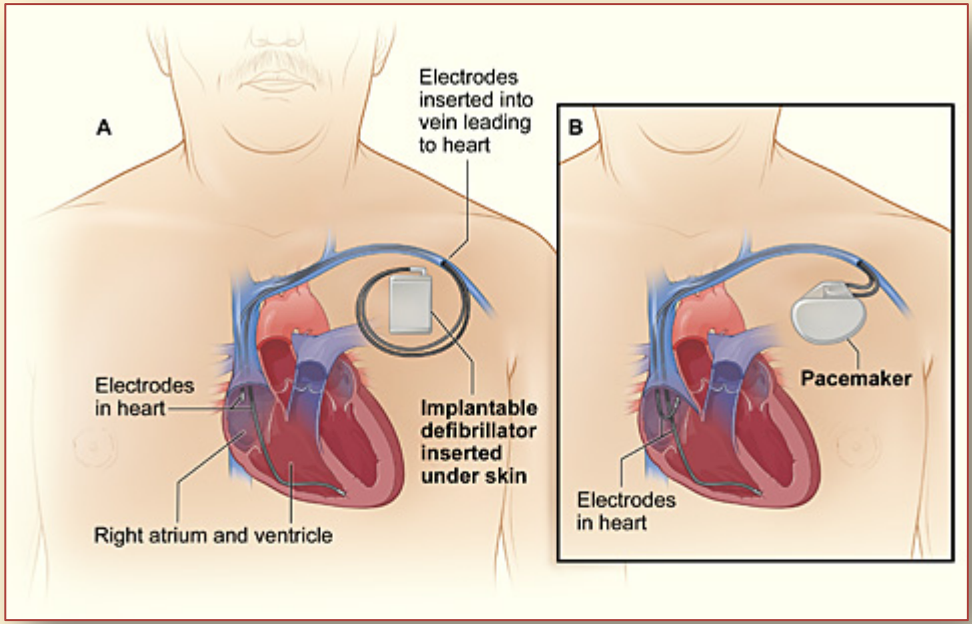
Glucometers and Drug Delivery Systems

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

- The MiniMed system *(shown above)* uses an in vivo glucose sensor that transmits its results to a micropump that delivers insulin continuously to the body
- 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.

Implantable bioMEMS

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]

Implantable bioMEMS

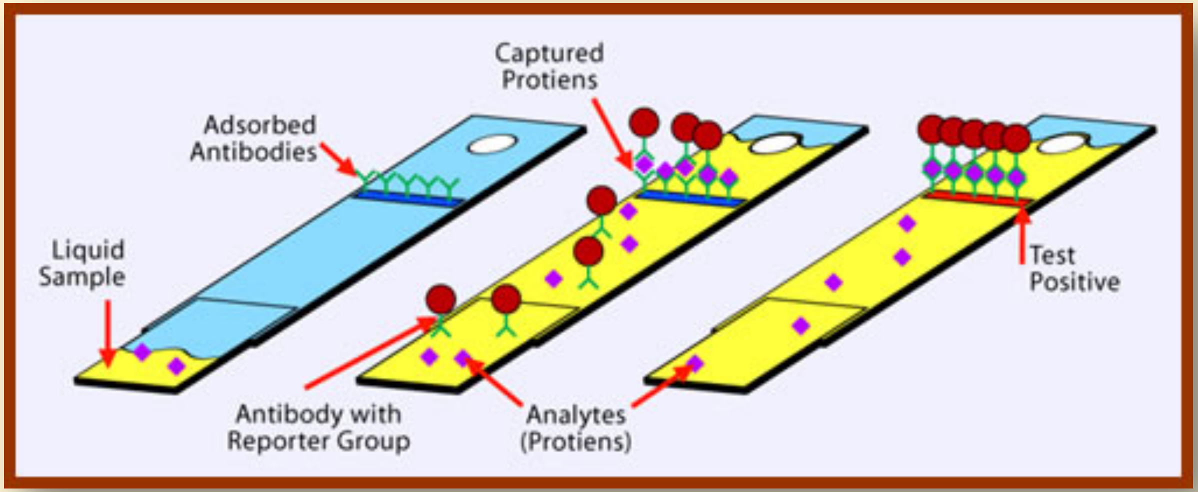
Other emerging applications for implantable devices include the following:

- ❖ Neural implants
- ❖ Spinal cord stimulators to treat intractable pain and spasticity.
- ❖ Pressure sensors for cardiovascular monitoring, glaucoma monitoring, and monitoring of intracranial pressure

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.

Biological Molecules Sensors

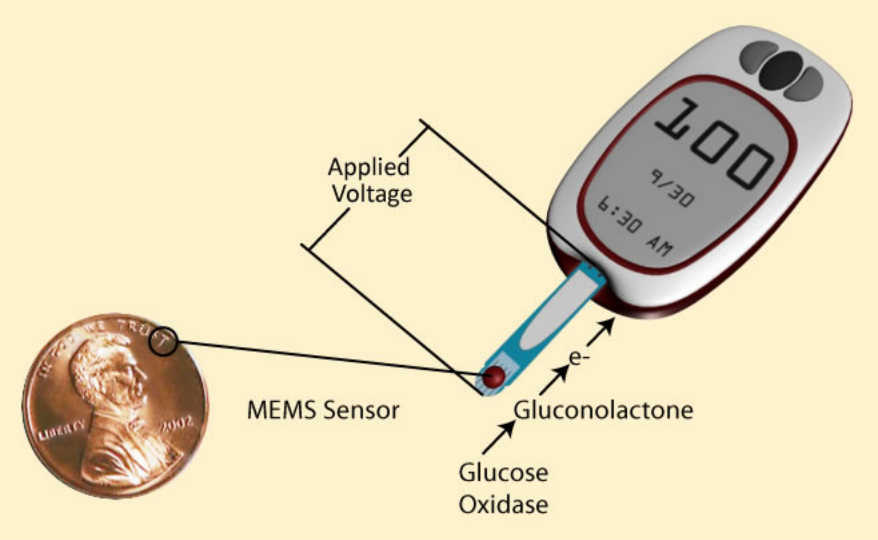
Home Pregnancy Test



Biological molecules have the ability to detect and recognize other biomolecules. This characteristic has enabled the development of biosensors that detect, capture and analyze specific analytes.

An example - The home pregnancy test kit that employs antibodies as biosensors. The antibodies have an attached reporter group which detects a protein produced during pregnancy and present in the urine.

Glucometer



This is an external glucometer that requires the patient to place a drop 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.

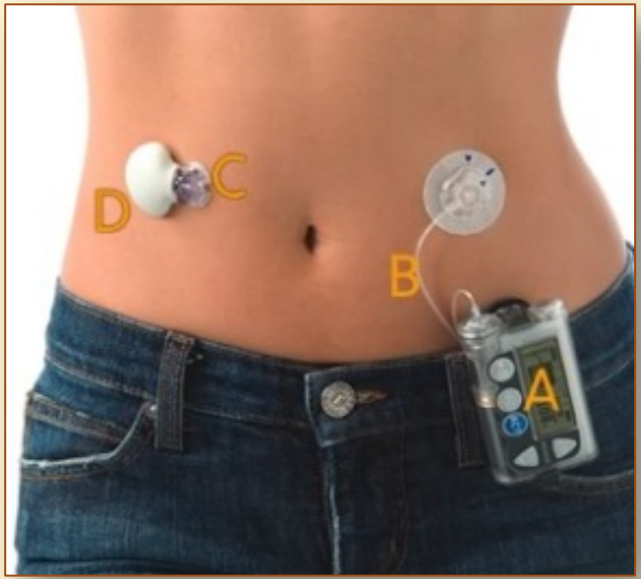
The glucometer is a diagnostic biosensor that monitors blood glucose levels of diabetics from a single drop of blood.

It contains a strip impregnated with enzymes that react with glucose, and an electrode which tracks chemical changes through fluctuations in current.

Implantable Glucometer

Implantable devices cross the boundary into therapeutics and contain an actuator or micropump that administers the necessary glucose. The implantable glucometer (C) shown in the picture

- monitors the glucose (C) and
- delivers insulin on an as-needed basis using a micropump (A) and cannula (B).
- D is the transmitter that relays the information from the glucose sensor (C) to the computer (A).



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

BioMEMS Microfluidics

- Microfluidics are integrated microchips that allow separations, chemical reactions, and calibration-free measurements to be directly performed with minute quantities of complex samples (blood, environmental gases).
- Microfluidics applications are used in remote locations for clinical diagnostics and environmental sensing.
- Lab-on-a-Chip (LOC) systems enable the design of small, portable, rugged, low-cost, easy to use, yet extremely versatile and capable diagnostic instruments.

Lab-on-a-chip (LOC)
[Printed with permission from Blazej,R.G.,Kumaresan,P. and Mathies, R.A. PNAS 103,7240-7245 (2006)]

ELISA

BioLOC developed a LOC to perform ELISAs (Enzyme-linked Immunosorbent Assays) on a polymeric compact disk *(shown in the figure)*.

ELISAs use antibodies as biosensors for applications such as

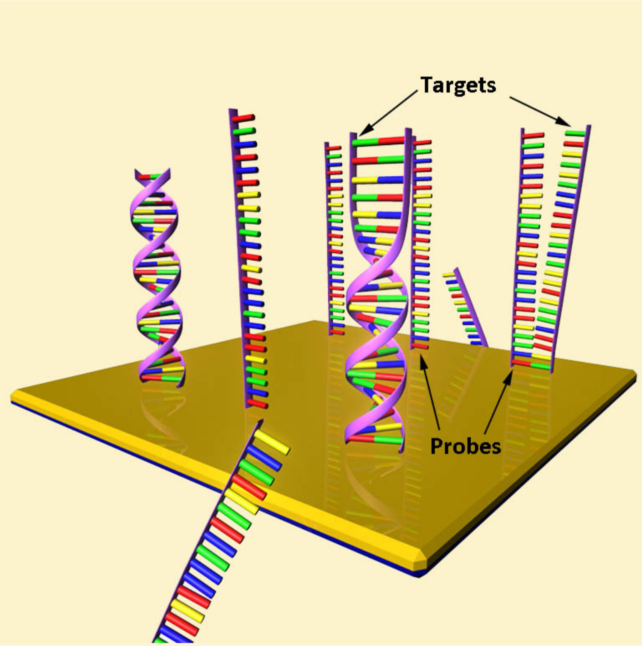
- medical diagnostics and research
- drug screening
- food safety
- environmental monitoring

BioLOC's CD-ELISA™ [Printed with permission of BioLOC LLC]

DNA and bioMEMS

DNA microarrays are tools used to analyze and measure the activity of genes as well as detect and identify specific genes and gene mutations.

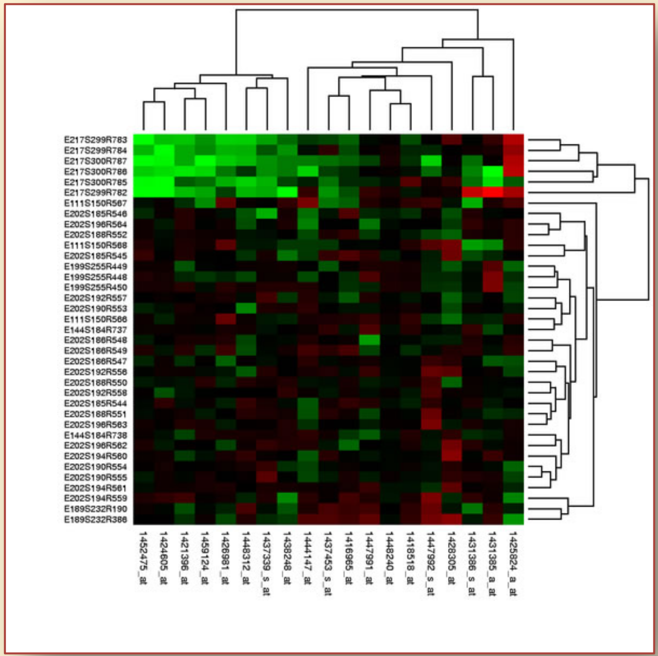
The DNA microarray in the graphic uses single-stranded DNA probes to identify the target DNA in a sample.



Identifying specific DNA through the hybridization process (Graphic illustrates what happens in a DNA microarray: The target single strand DNA in the test samples bond with a complementary DNA probe on the substrate creating a hybrid and enabling the identification of the target DNA as well as its quantity and/or activity in the sample.)

DNA and bioMEMS

- Microarrays measure changes in gene expression (activity) and thereby identify how cells respond to a disease, a drug or drug dosage, or another stimuli.
- Gene expression microarrays measure tens of thousands of genes on a single array and provide scientists the data to understand regulatory processes at the cellular level.

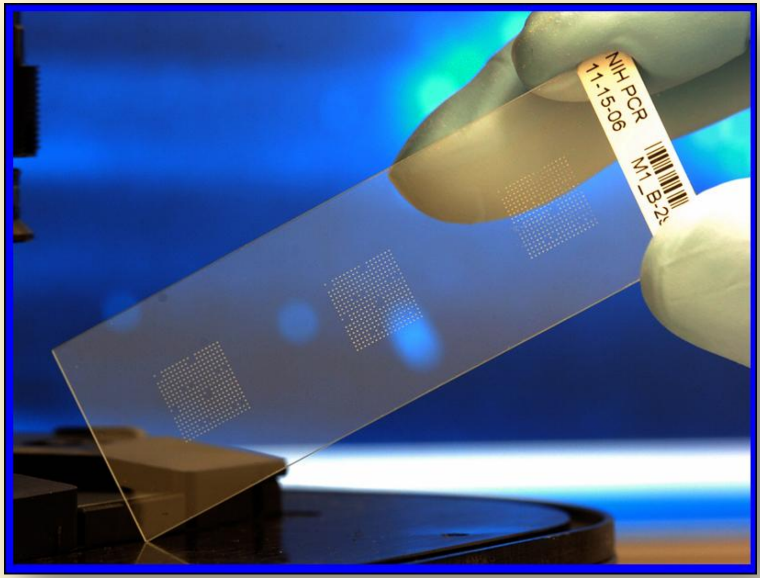


Gene expression values from microarray experiments can be represented as heat maps or optical maps to visualize the results of data analysis. The green represents activity between probe DNA on the array and target DNA in the control sample. Red represents activity between probe DNA and DNA in the test sample. The black areas represent no activity with either the control or test sample.
[This 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
- provide a high throughput study of protein abundance and function
- allow for the creation of antigen microarrays for vaccine development and the diagnosis of infectious diseases.



Biochip slide for testing protein arrays

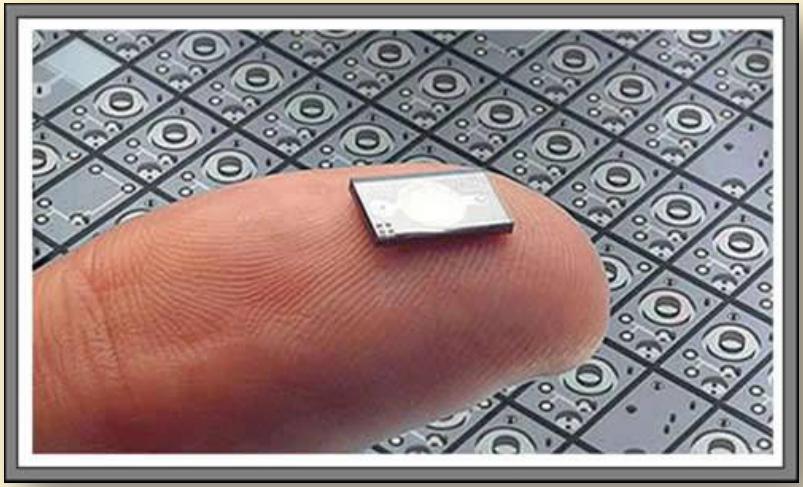
[Image courtesy of Argonne National Laboratories]

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.

Therapeutics: Drug Delivery Systems

Pumps delivering insulin in implantable devices are examples of a drug delivery system *(see figure)*.

Other examples include the Medtronic SynchroMed Pump that administers morphine within the spine, and piezoelectrically activated pumping devices used for various drug delivery applications.



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

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, canula and nano-sized needle.

Microchips

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 drug delivery system in the figure.
- ❖ Microspheres or beads are also being exploited in drug delivery systems where they function as carriers of drugs.
- ❖ Microspheres can stay in the bloodstream or at the site for prolonged periods of time, providing slow release of the drug. *(Some of these devices are still in development as of 2014.)*

MicroCHIPS Subcutaneous Active Drug Delivery System

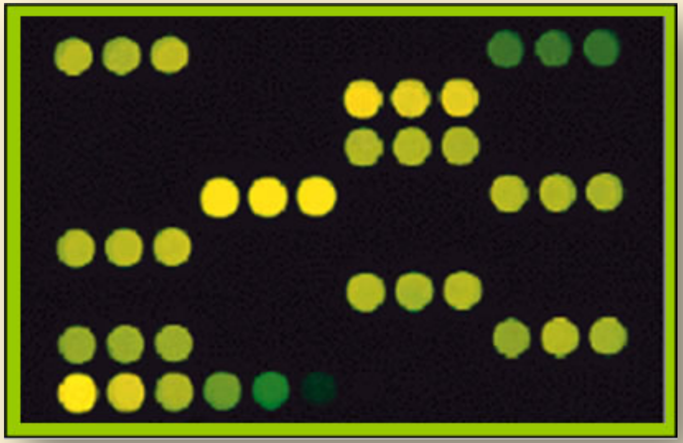
This technology is unique in its use of wireless signaling, its system of reservoirs allowing precise, efficient delivery of solids, liquids or gels, and its small size. [Figure reproduced by permission of MicroCHIPS, Inc.]

Environmental Applications

Environmental applications are a growing part of the bioMEMS field.

One example adds a gene from a firefly to mammalian cells so that the cells glow when exposed to the toxin dioxin *(see figure).*

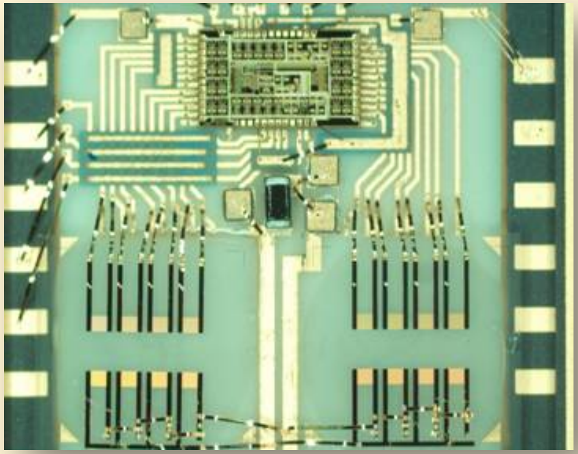
- As the amount of dioxin increases, the cells glow more brightly.
- This assay provides a quick and simple test for dioxin.
- The figure shows how the firefly luciferase reporter gene luminesces to test for the presence of dioxin in environmental samples.



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

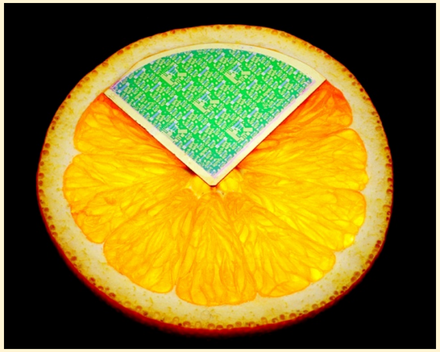
Environmental Applications

Rapid detection and identification of bacteria and other pathogens.



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. [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. [Image courtesy of Sandia National Laboratories]

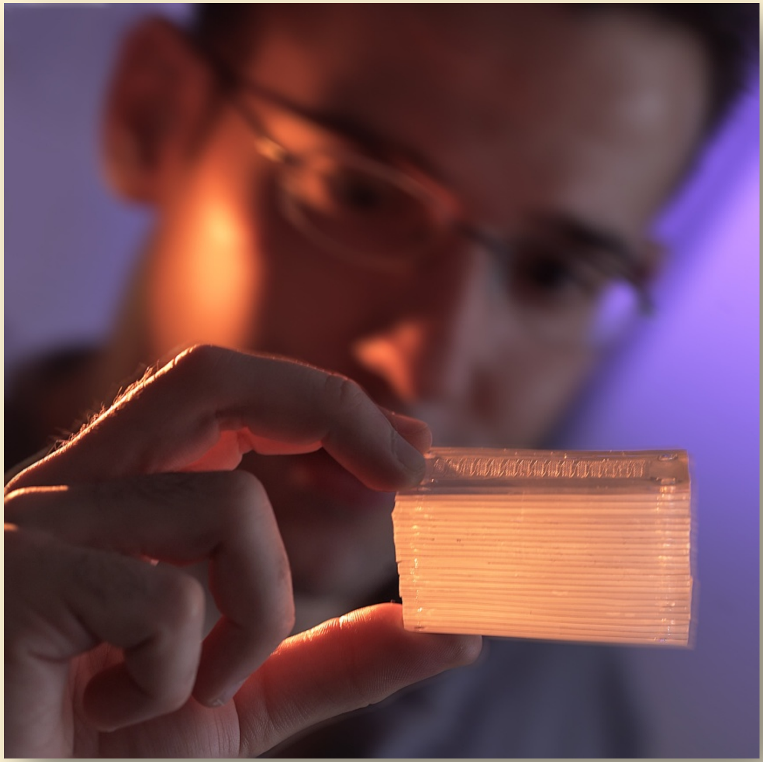


Researchers are working on microdevices for detecting pathogens in a sample concentration. A working example is the surface acoustic wave (SAW) sensor array developed by Sandia National Labs. This device provides portable, rapid detection and early warning of the presence of pathogens in air or water.

Additional Applications

Many other bioMEMS applications have been developed and are emerging:

- point-of-care clinical diagnosis
- neural probes
- nerve regeneration
- retinal implants
- tissue engineering *(see figure)*
- olfactory sensors



Artificial Kidney Tissue
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What Do You Think?

- *Why do biological molecules provide an approach to the development of specific biosensors?*
- *What are some examples of bioMEMS that have been approved for commercialization during the past 5 years?*
- *How have bioMEMS impacted your life?*

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.

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