BIOMEMS OVERVIEW

BioLOC's CD-Enzyme Linked Immunosorbent Assay (ELISA™)
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Unit Overview

This unit provides an overview and introductory information on the emergence of bioMEMS into MEMS (Microelectromechanical Systems) technologies.

As a subset of MEMS (microelectromechanical systems), bioMEMS have biological and/or biomedical functions and applications.

This unit focuses on the areas for biomedical applications of bioMEMS.

Objectives

- Provide an operational definition of bioMEMS.
- Describe five basic categories of bioMEMS.
- List at least five applications of bioMEMS devices.

What You Will Learn

- A bioMEMS definition including the distinction between micro-devices used for biological procedures (e.g., drug delivery) and those that use biological molecules in their operation (e.g., virus detection).
- The importance of bioMEMS in advancing global health and applications necessary for understanding biological systems.
- Broad applications for bioMEMS technology and still growing.
- Advancements in bioMEMS have come quickly over the past 10 years due to the growth of microtechnology.

Why You Need to Learn It

This knowledge is important because the use of microelectronics, particularly MEMS, is changing the medical fields of

- detection,
- diagnostics,
- monitoring,
- drug delivery,
- analysis,
- therapeutics and
- others.

MEMS vs. bioMEMS

MEMS use micro-sized components such as sensors, transducers, actuators, and electronic devices.

Many of the MEMS used in the medical field perform the same tasks as those used in other applications such as environmental, aerospace and consumer products.

For example, the MEMS inertial sensor found in airbag deployment mechanisms is also found in a pacemaker.

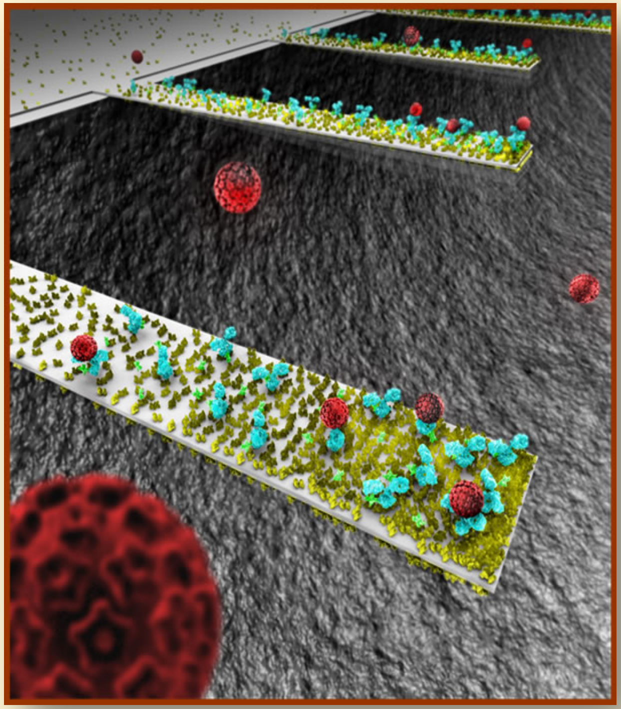
Any research into bioMEMS would yield an ever changing and growing market.

MEMS vs. bioMEMS

Another category of MEMS used in the medical field incorporates biological molecules as an integral part of the device.

For example, a microcantilever transducer *(graphic right)* may be coated with antibodies (green spheres) that capture a virus (red sphere) in a blood sample while ignoring the other components in the sample.

Therefore, bioMEMS are MEMS that have biological and/or biomedical functions or applications.

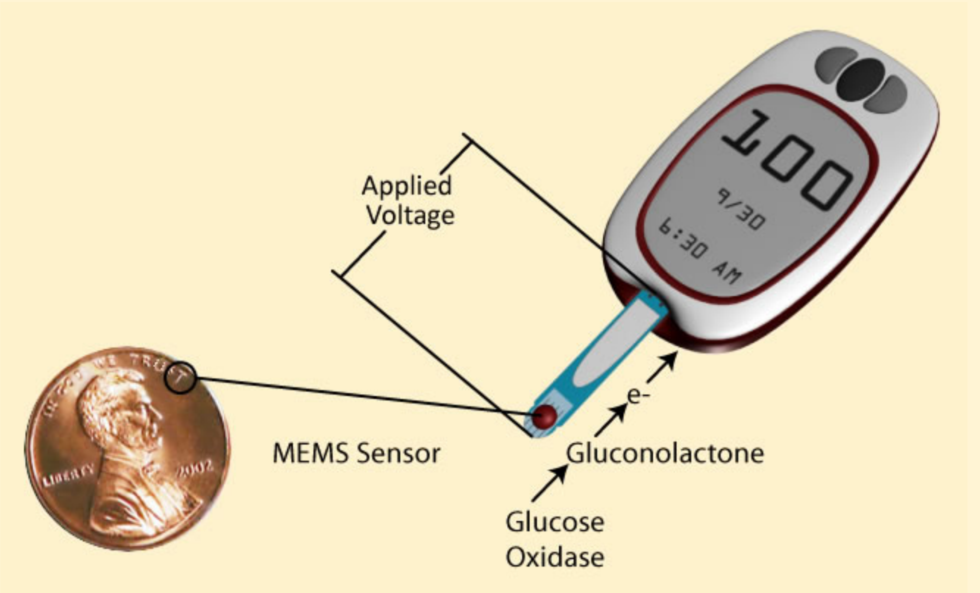


Micro and nano-sized cantilevers used to identify a virus (red sphere) in a sample. The capture biomolecules are specific antibodies (green particles) [Image generated by and courtesy of Seyet, LLC].

Glucose Monitor with Microtransducer

MEMS used for medical applications include devices to detect disease, monitor chemicals, and deliver drugs.

An example is the glucose sensor *(see figure).* This blood glucose sensor works on the basis of a glucose oxidize reaction with blood plasma.

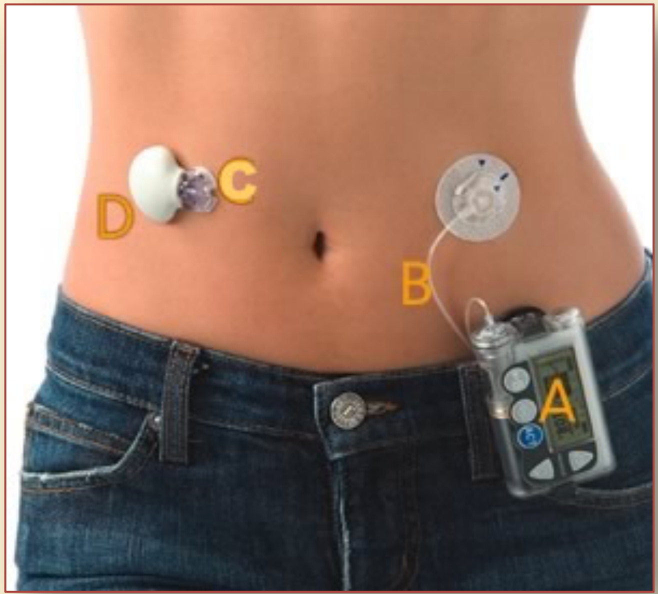


Blood Glucose Monitor
[The MEMS transducer is at the end of the sensor. A droplet of blood is placed on top of the transducer, voltage is applied and a chemical reaction takes places. The current produced by the chemical reaction is measured indicating the amount of glucose in the blood sample.

MEMS Glucose Monitor and Micropump

The figure to the right shows a complete glucose monitoring and drug delivery system.

- The glucose is constantly monitored using an in vivo (implanted) chemical transducer (C).
- A micropump in (A) delivers insulin via a cannula (B) on an as-needed basis .
- D is the transmitter that relays the information from the glucose sensor (C) to the computer (A).



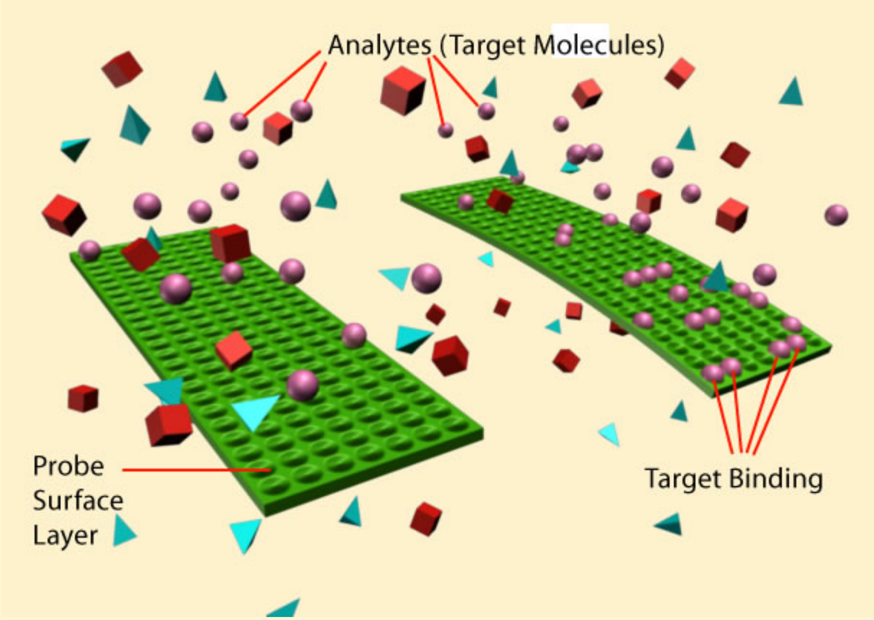
MiniMed Paradigm[R] REAL-Time System from Medtronic Diabetes [Printed with permission from Medtronic Diabetes]
Check the Medtronics website to see new advancements in this technology.

Microcantilever Sensors

BioMEMS can use the properties of biological molecules to actuate a small machine.

For example, microcantilevers are used to detect a variety of analytes such as DNA, proteins, and antigens *(see graphic).*

The analytes attach to a probe surface layer of biomolecules. This load induces surface stress causing the cantilever to bend.



Biomolecules are produced by living cells. All known forms of life are comprised solely of biomolecules. These microcantilevers are designed to use biomolecules to detect and capture other specific biomolecules. This is accomplished with a functionalized cantilever surface. In this case a probe surface layer of biomolecules whose function is to capture the target molecules is deposited on the cantilever's surface. This probe layer can be as thin as a monolayer (one molecule thick).

In Vivo Devices

Another distinction of bioMEMS is between implantable devices (in vivo) and devices used outside of the body (in vitro).

Biocompatibility and *biofouling* are of great concern for implantable devices.

The body presents a harsh environment which can cause implantable devices to be rejected due to an inflammatory response. This response indicates *bio-incompatibility* between the host and the device.

BioMEMS device functions can also be affected by *biofouling*, a biological response by the host that interferes with the functioning of the device.

The Evolution of bioMEMS

The evolution of MEMS technologies coupled with advances in the understanding of genomics, proteomics, and biotechnology techniques permit new opportunities for advancing the applications of bioMEMS devices.

BioMEMS will enable new modes of biosensing, molecular identification and monitoring, and futuristic biomedical and biological systems that use MEMS technology.

Advancing Technologies

New areas of biotechnology have provided opportunities to refine bio techniques using MEMS technology.

- DNA sequencing
- ELISA (Enzyme Linked Immunosorbent Assay) *(see figure)*
- Sequencing of the human and other genomes
- New advancers in drug discovery and delivery
- Increased emphasis on homeland security
- Environmental monitoring

BioLOC's CD-Enzyme Linked Immunosorbent Assay (ELISA™) [Printed with permission]

Applications of bioMEMS

Areas that would benefit from the development of bioMEMS to enhance current methods include the following:

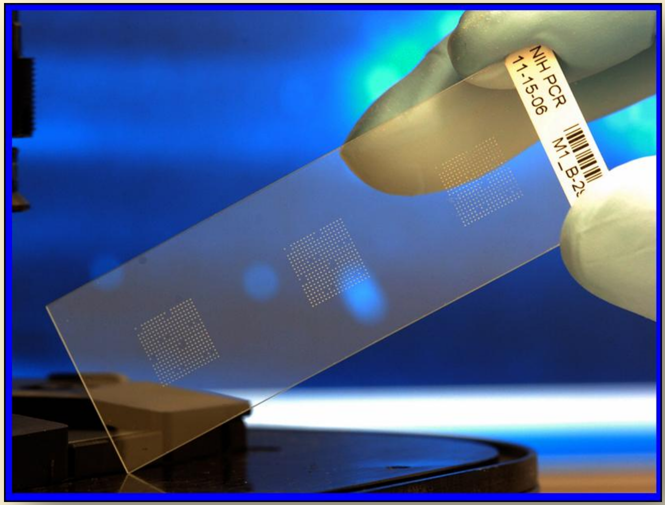
- Sample preparation
- Screening
- Diagnostics
- Monitoring
- Drug delivery
- Individualized treatment
- Less invasive surgical procedures

What's Out There Now?

BioMEMS provide the opportunity to improve upon current methods, develop new ones, and potentially lower the cost of medical care.

Examples of bioMEMS devices already available include a

- ❖ tiny insulin pump for diabetics,
- ❖ DNA microarray and protein array chips *(see figure), and*
- ❖ various biosensors.



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

Shrinking Technologies

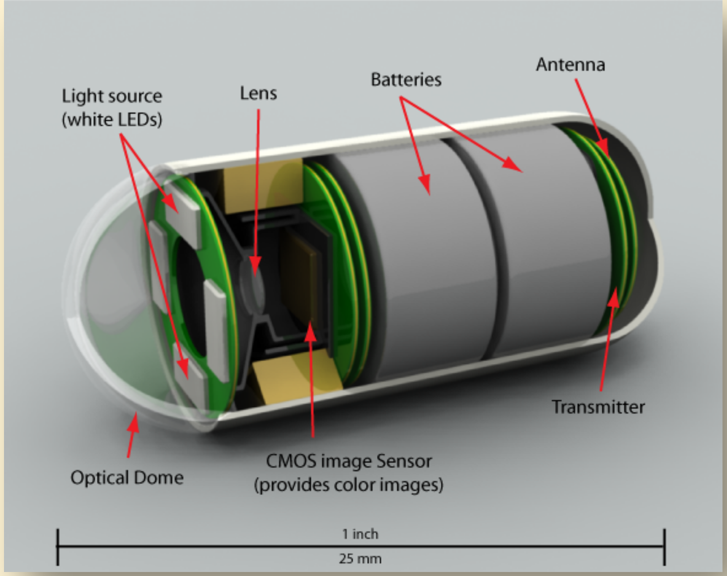
The potential for miniaturized devices provides obvious advantages, whether in vivo or in vitro.

Such advantages include reduced manufacturing cost, smaller sample size, and small amount of reagents.

The physical space savings of using microdevices rather than large pieces of lab equipment is also cost effective.

Improving the Quality of Life

- For the diabetic, a small monitoring (C/D) and insulin delivery (A/B) device greatly contributes to the ease of disease regulation
- Persons undergoing invasive tests such colonoscopies or endoscopies appreciate a smaller detection device. *(see figure)*
- Portability of small test devices makes testing in remote areas where clinical labs are not available possible.



Gastrointestinal Diagnostics
This "pill" that is used to look at the entire gastrointestinal (GI) tract, including the small intestine. The patient swallows the pill and as the pill travels through the GI track, it transmits high resolution video to an external receiver.
The pill is later discharged naturally.

Enabling Technologies

MEMS is an enabling technology for applications in the life sciences. New biotechnologies are enabling technologies for the applications of MEMS.

New possibilities are created by merging our knowledge of biological systems into existing research tools.

These possibilities could lead to providing better health care, identifying key molecules, delivering targeted therapy, and creating possibilities for small point of care tools.

The Current Market

There are already many bioMEMS devices commercially available to the industry as well as for in-home use.

There are also some very promising bioMEMS for commercialization within the next five years.

There are a growing number in the research phase with an unknown commercialization date, but holding great promise for the future of bioMEMS applications.

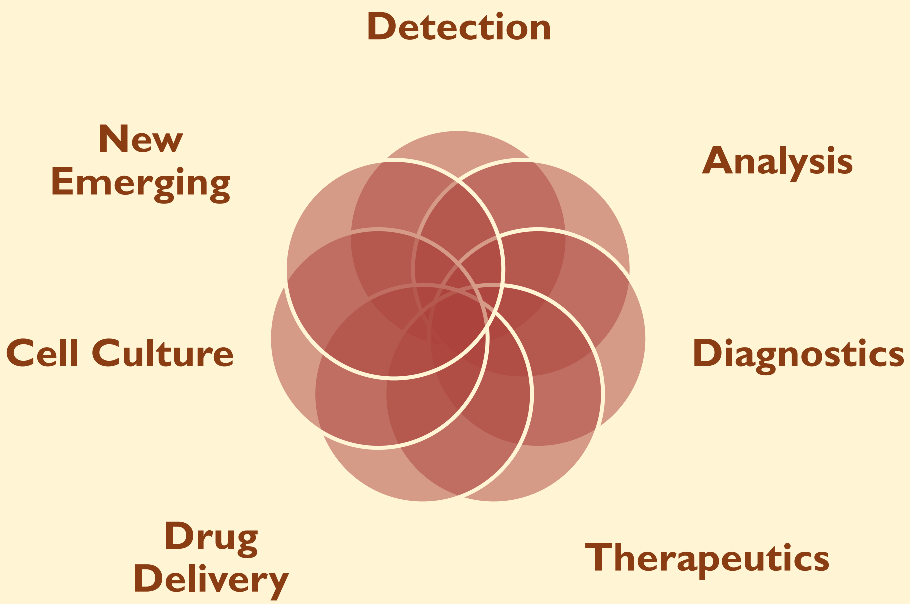
Point of Care Devices

- Rugged small diagnostic microfluidic devices that can withstand harsh conditions present attractive alternatives to current laboratory tests.
- Such medical diagnostic systems hold promise for portable point-of-care (POC) testing in the developing countries where sophisticated laboratories do not exist.
- The development of inexpensive, accurate, and durable diagnostic tools that do not require highly trained medical technicians and that can be used on-site, have cost-saving benefits for everyone.

Oh - The Possibilities!

BioMEMS are being researched for possible applications in a variety of areas, but have already led to multiple applications in the following areas:

- Detection
- Analysis
- Diagnosis
- Therapeutics
- Drug delivery
- Cell culture



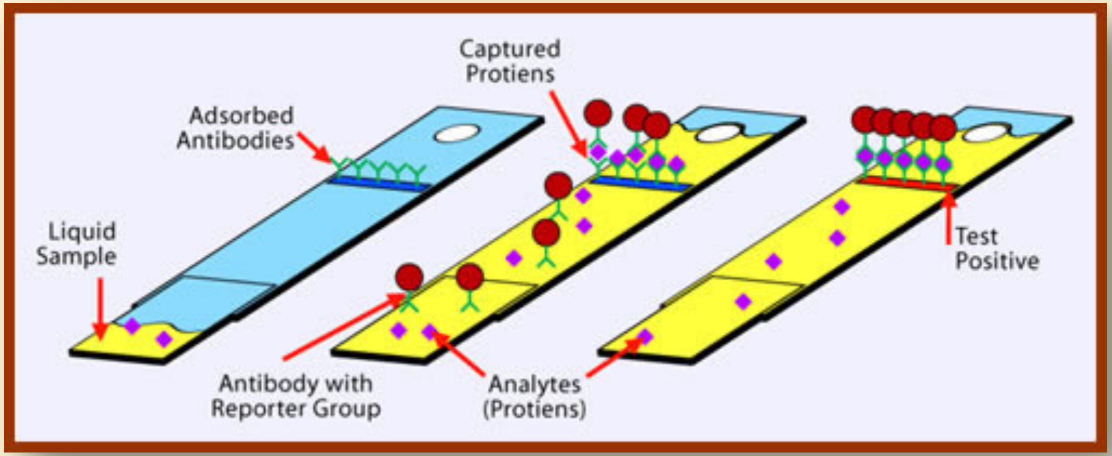
Lab-on-a-Chip (LOC)

In research and clinical laboratories, the µTAS (micro-total-analysis systems) and LOC (lab-on-a-chip) devices are the most successful applications for bioMEMS. LOCs are designed to analyze samples as small as a picoliter. They are also point-of-use devices; in other words, they can be used in the field, at the site of an accident, or in remote areas where medical laboratories are non-existent.

The figure is an example of an LOC.

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

BioMEMS for Detection

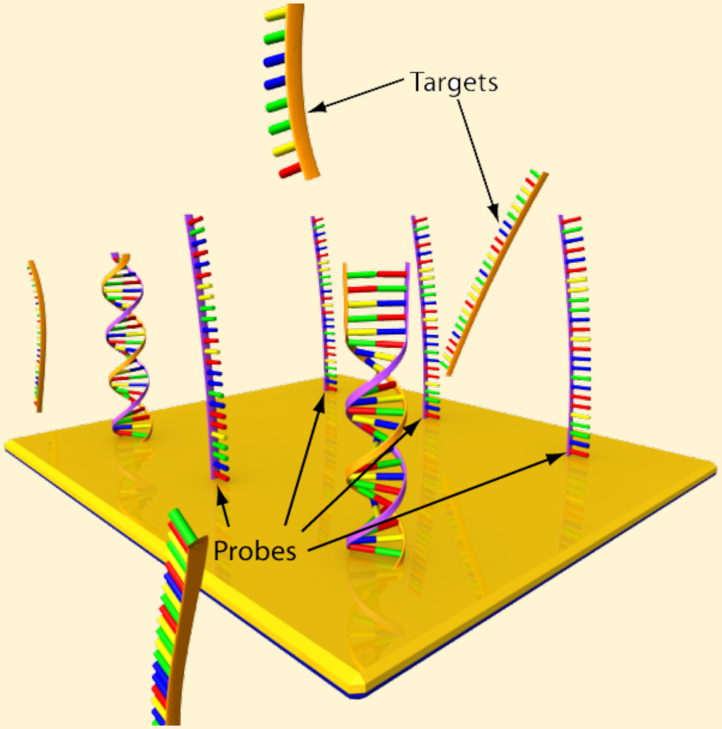


Home Pregnancy Test
(Detection of protein
in the urine of a pregnant woman)

- Sensors for chemical detection
- Bacterial, fungal, and viral detection
- Antibody detection
- Disease detection
- Examination devices (such as endoscopes and catheters)

BioMEMS for Analysis

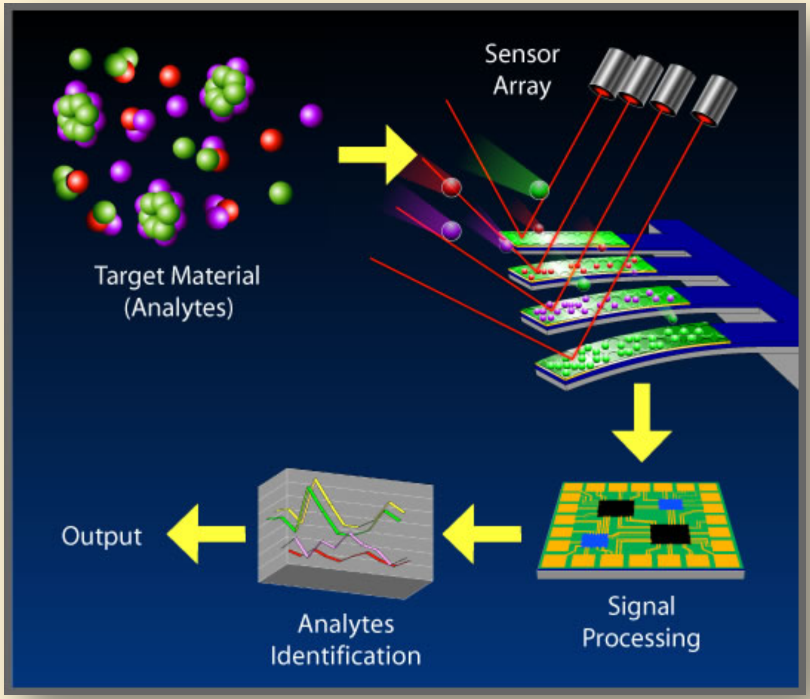
- Bacterial identification and antibiotic susceptibility
- Clinical laboratory medicine (clinical chemistry)
- DNA analysis for forensics identification *(See graphic)*



Identifying complementary DNA through the hybridization process
Graphic illustrates what happens in DNA Microarray:
The target single-strand DNA attaches to a complementary capture probe or a matching DNA single strand.

BioMEMS for Diagnostics

- Disease identification
- Protein isoform identification (used to assist in prescribing appropriate drugs for personalized medicine)
- Antibody identification using MEMS chemical transducers and sensors *(See graphic)*



Chemical Sensor Arrays
(Can detect, identify and determine the amount of an analyte in solution for the purpose of diagnosis)

BioMEMS for Monitoring

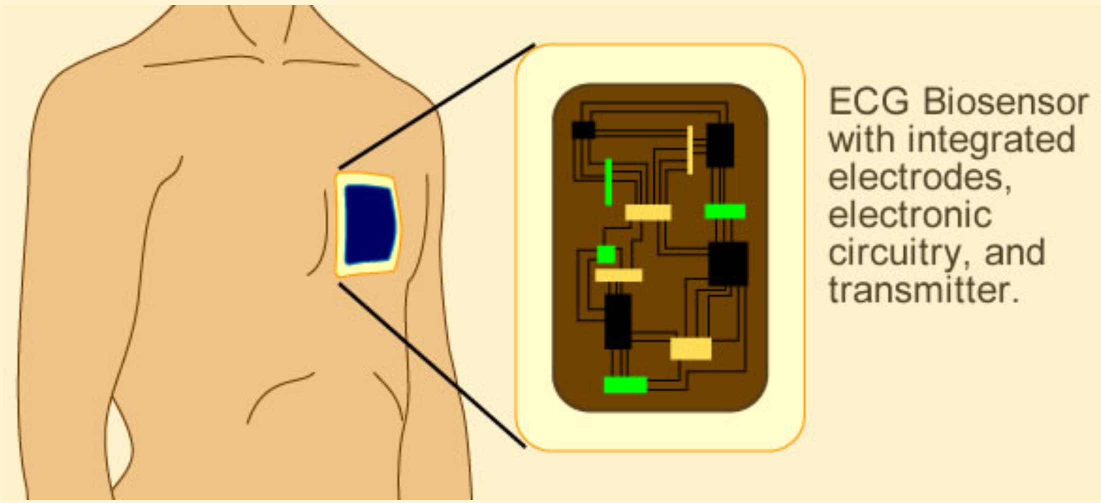
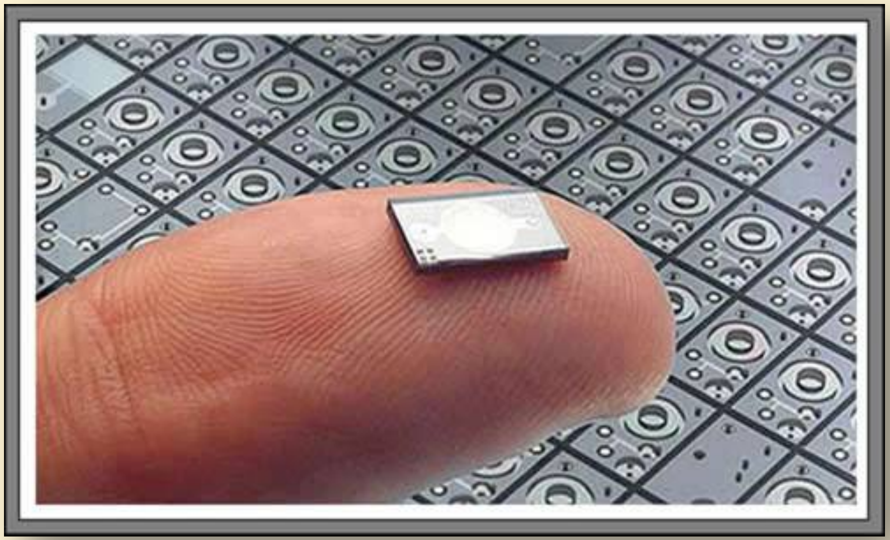


Illustration of a MEMS electrocardiogram (ECG) patch monitor. Such a device is being developed by Belgium's IMEC for monitoring a patient's arrhythmias all day and night.

- Blood glucose level for diabetics
- Antibody level monitoring for HIV patients
- Blood cell concentrations for patients undergoing chemotherapy
- Continuous monitoring of high-risk patients *(The graphic illustrates an electrocardiogram (ECG) patch which monitors patients for arrhythmias day and night.)*

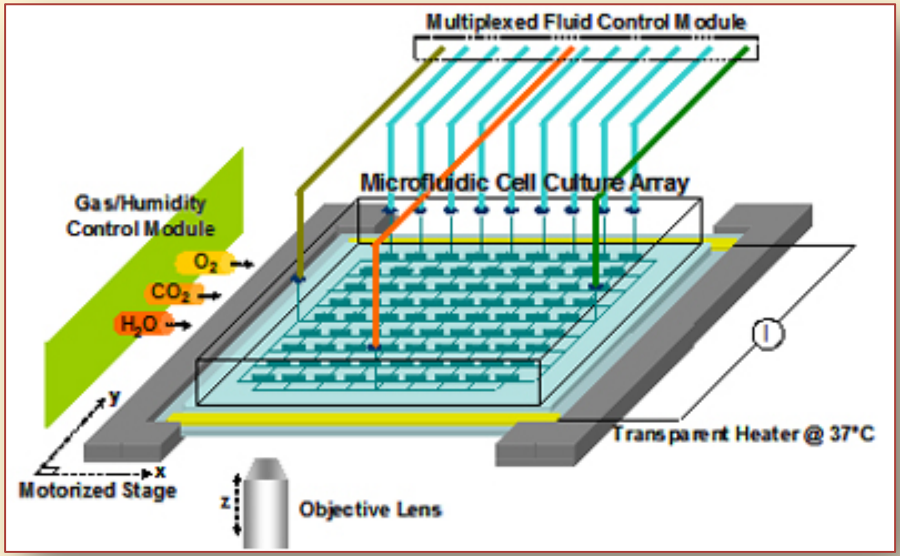
BioMEMS for Drug Delivery

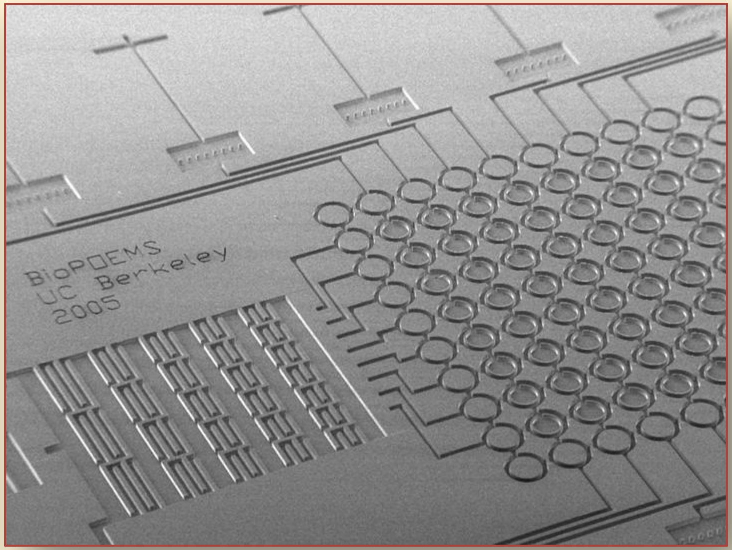


Insulin pump for drug delivery system
[Printed with permission from Debiotech SA]

- Antibiotic administration
- Intravenous nutritional supplementation
- Pain medication

BioMEMS for Cell Culture





MEMS Cell Culture Array. This array creates a microenvironment for growing cells in vitro and in parallel, allowing for the analysis of multiple cell growth conditions. A diagram of how it works is on the left. The constructed array is shown with a SEM image on the right.
[Developed at and courtesy of BioPOETS, UC-Berkeley.]

- Cell separation and counting
- Microenvironments for growing cells in vitro and analysis *(see above graphics)*

Emerging Applications

There are additional categories but these six areas provide a core from which we can launch a discussion about the types of MEMS devices and how they are currently being used or developed for bioMEMS.

Hopefully, advances in these six areas will encourage further interest in emerging applications of MEMS technologies for medicine and life sciences.

Miniaturization

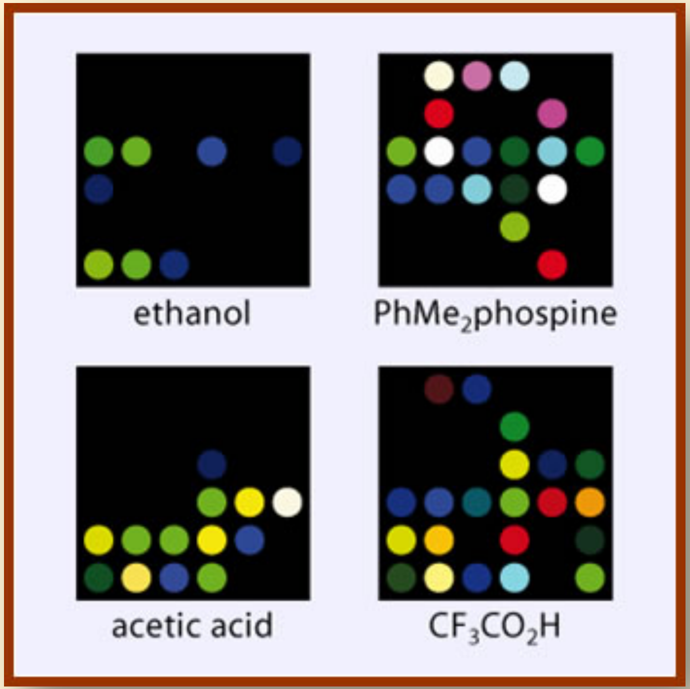
Processes that have been miniaturized:

PCR, polymerase chain reaction: A method used to amplify DNA samples used in forensics and other applications.

DNA sequencing: A process for identifying the order of the molecular components of the DNA molecules that contain the genetic blueprint for heredity.

Chromatography: Molecular separation based on size, charge, or other properties.

ELISA, enzyme-linked immunosorbent assay: Used in common tests such as HIV and pregnancy tests.



Partial output of a Colorimetric Sensor Array used to analyze the makeup of a gas mixture. This array can detect up to 15 pathogens in a sample concentration.

Food For Thought

The relatively new areas of bioMEMS technology have opened exciting opportunities to refine bio-technology applications. In discovering the possibilities of bioMEMS applications think about answers to the following questions.

What are the benefits of miniaturizing existing techniques?

How could MEMS technologies be used effectively for bioMEMS?

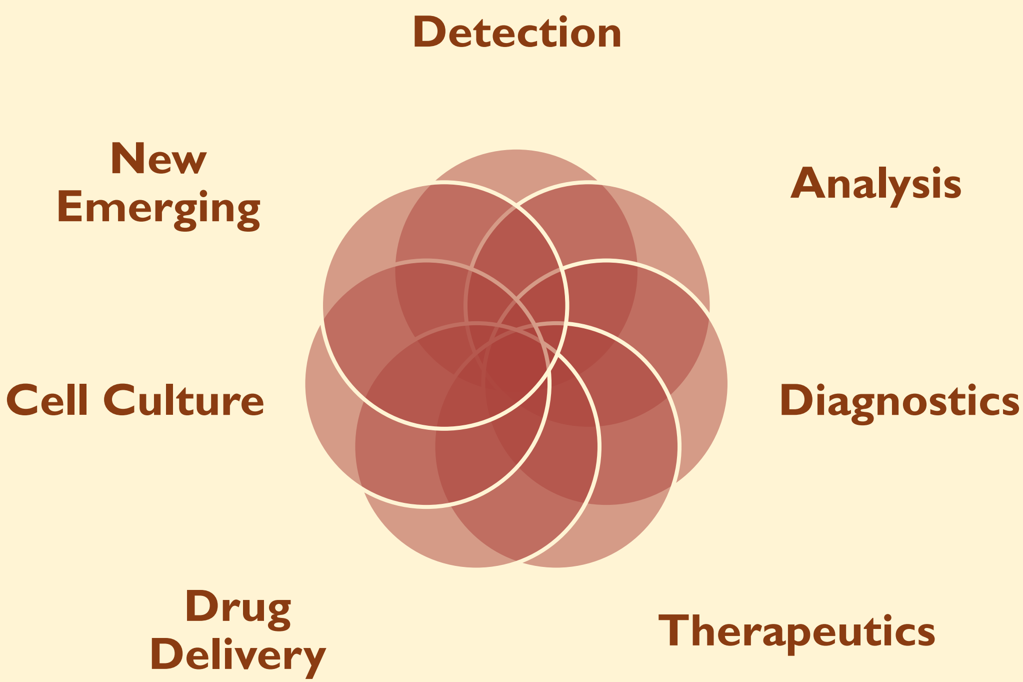
What concerns need to be addressed in order to make bioMEMS applications successful?

Summary

BioMEMS is a subset of MEMS (microelectromechanical systems). It refers to any MEMS used in a biological application. BioMEMS utilize micro-sensors, transducers, actuators, and electronic components. Some bioMEMS incorporate biomolecules as an integral part of the device.

BioMEMS are being researched and developed for possible applications in a variety of medical areas. Much of this research has already lead to the commercialization of many devices in the following medical areas. *(See next slide)*

Areas of bioMEMS Applications



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