BioMEMS Overview
Primary Knowledge (PK)
Instructor Guide

Notes to Instructor

This learning module explains what "BioMEMS" are and how they are used today in different fields. An activity provides the opportunity to reinforce the importance of BioMEMS, where they are used, and the endless possibilities of future BioMEMS devices.
BioMEMS = Bio MicroElectroMechanical Systems

This Primary Knowledge unit provides an overview of biomedical Microelectromechanical Systems (MEMS). Such devices are a sub-set of a broader category referred to as BioMEMS.

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

- **BioMEMS Overview PK** (Reading material)
- BioMEMS Overview Activity
- BioMEMS Overview Assessment

Description and Estimated Time to Complete

This learning module explains what "BioMEMS" are and how they are used in different fields. An activity provides the opportunity to reinforce the importance of BioMEMS, where they are used, and the endless possibilities of future BioMEMS devices.

BioMEMS = Bio MicroElectroMechanical Systems

This unit provides an overview and introductory information on the emergence of bioMEMS and how these devices are used in the medical field. BioMEMS is a subset of MEMS (microelectromechanical systems) that has biological and/or biomedical functions and applications. This unit focuses on the areas for biomedical applications of bioMEMS. It is important to note that bioMEMS is one of the fastest growing fields in microtechnology; therefore, many of the specific devices discussed in this unit may have changed dramatically due to the vast improvements in technologies over the past 5 – 10 years.

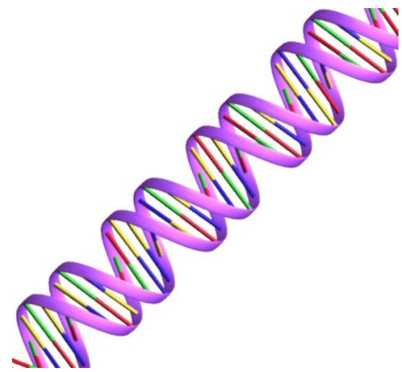
<u>Estimated Time to Complete</u>
Allow approximately 30 minutes.

Introduction

BioMEMS is a subset of microelectromechanical systems (MEMS) and microtechnology. BioMEMS applies to biological systems in general and to human health, in particular. This unit discusses the following subjects:

- BioMEMS definition including the distinction between MEMS devices used for biological procedures (e.g., drug delivery) and those that utilize 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

This unit explores biological applications of microtechnology within biological and medical contexts. This knowledge is important because the use of microtechnology, particularly MEMS, is changing medical applications for areas such as detection, diagnostics, monitoring, and drug delivery. For example, potential heart problems can now be detected early by having the patient wear a non-invasive heart monitor 24/7. Also, the aggressiveness of some cancers can now be determined by analyzing DNA from cancerous and non-cancerous tissue. This aids in the determination of a personalized treatment for each patient.



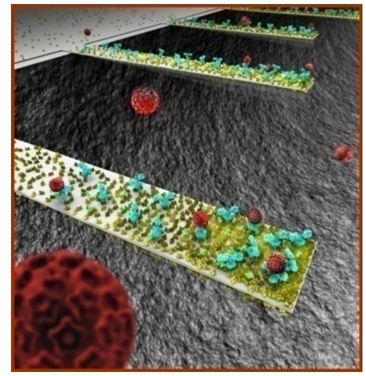
Double-stranded DNA (Deoxyribonucleic acid) molecule.
One of the biological molecules used in bioMEMS applications.

Objectives

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

MEMS vs. BioMEMS

MEMS are microelectromechanical systems that 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. In a pacemaker the MEMS inertial sensor (specifically an accelerometer) is used to sense a patient's activity. When the accelerometer senses acceleration in the patient's activity, its output causes the control circuitry of the MEMS to more quickly stimulate one or more electrodes connected to the heart muscle. This electrode stimulation causes the heart to beat faster. As the patient's activity slows, the MEMS in turn, slows the heart rate.



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.

[Image generated by and courtesy of Seyet LLC].

Both types of MEMS are referred to as bioMEMS. BioMEMS is a general term for any MEMS used in biological applications.

The following is a brief overview of bioMEMS and select applications within the medical field. Review the SCME BioMEMS Applications Overview for a broader view of bioMEMS applications.

BioMEMS Glucose Sensors with Microtransducer

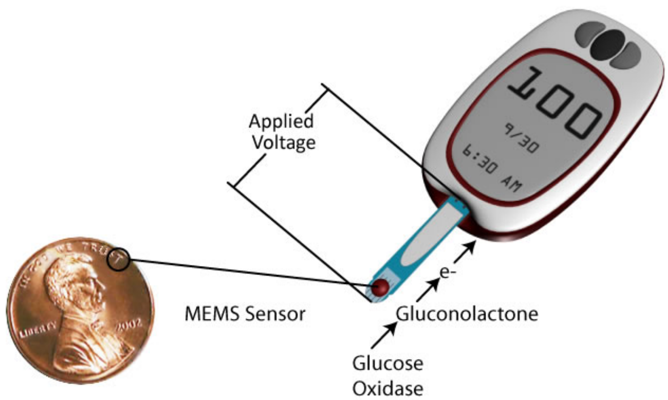
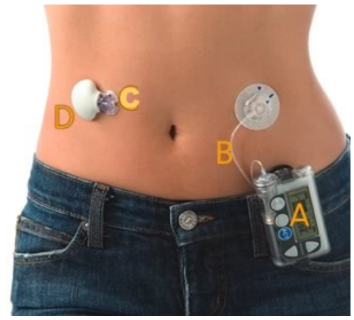


Diagram of a blood glucose monitor utilizing a biochemical transducer located at the very tip of the device. This transducer is about the size of one of the letters on the coin shown.

This blood glucose monitor (shown in the graphic) works on the basis of a glucose oxidase reaction with blood plasma. A transducer is located at the end of the sensor strip. The transducer is about as big as the "T" in the word "TRUST" on a penny (1 mm long by 200 µm wide. Newer glucose sensors use even smaller transducers.) A drop of blood is placed on top of the transducer. The transducer has a thin film coating which starts the glucose oxidase reaction with the glucose in the blood plasma. Part of the output of the reaction is Gluconolactone and an electron. The electronic component of the sensor senses the released electrons as current and uses that as a measurement of the amount of glucose in the blood sample. Microtechnology has revolutionized the area of glucose monitoring by allowing for the production of even smaller transducers and biocompatible transducers that can be implanted allowing for 24/7 monitoring. Following is an example of such a device.

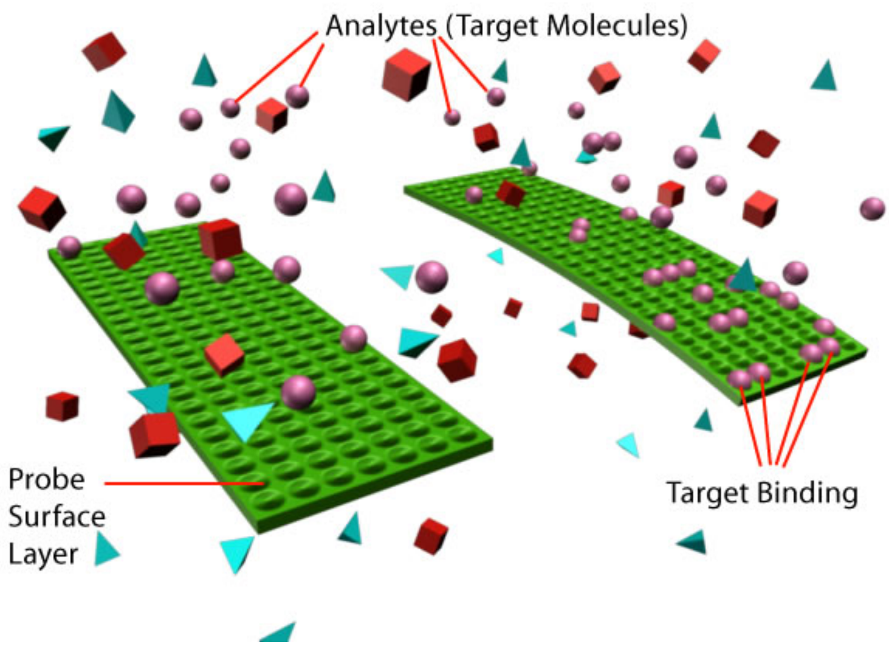
BioMEMS Continuous Glucose Monitoring with Glucose Sensor and Micropump

The figure to the right shows a continuous glucose monitoring and drug delivery system. The glucose is continuously 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).[1] These devices have greatly advanced over the past 10 years leading to a better quality of life for the patients.



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

Microcantilever Sensors



Microcantilever bending due to surface stress
caused by the attachment of analytes to sensor's surface.

The microcantilever biosensor is an example of bioMEMS that incorporates biological molecules as part of its function. In a biosensor, the biological molecules are used to functionalize the sensing capability of the MEMS device. For example, microcantilevers are constructed with a specific probe surface layer used to detect a variety of analytes such as DNA, proteins, and antigens *(see above graphic)*. In the detection of analytes such as a specific antigen, the antigen attaches to the probe molecules on the surface of the microcantilever. The collection of the specific analyte on the cantilever surface induces surface stress causing the cantilever to bend. The amount of bend is measured either electronically, using a piezoresistive film in the cantilever, or optically, using a laser reflected off the cantilever surface and measuring the change in the angle of reflection. This type of microsensor is referred to as a surface stress-based chemical sensor or biosensor.

BioMEMS devices, such as these microcantilevers, are small devices with at least one dimension being in the range of 100 nanometers to 200 micrometers. The coatings themselves may be as thin as a few nanometers or a monolayer (a layer 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)*. Issues such as biocompatibility and biofouling are of great concern for implantable devices. The body presents a harsh environment for the operation of bioMEMS. Implantable devices can be rejected by an inflammatory response due to bio-incompatibility between the host and the device. BioMEMS device functions can also be affected by biofouling, a biological response by the host (measured by the presence of macrophages or foreign body giant cells) that interferes with the functioning of the device.

These issues and other bioMEMS topics are covered in greater detail in other units. (See **Related SCME units**)

Advancing Technologies

The evolution of microtechnologies coupled with the recent advances in the understanding of genomics, proteomics, and biotechnology techniques permit new and exciting opportunities for advancing the applications of bioMEMS devices. These devices will enable new modes of biosensing, molecular identification and monitoring, drug delivery, lab on a chip technology, and futuristic biomedical and biological systems that utilize microtechnology.

Relatively new areas of biotechnology have opened exciting opportunities to refine bio techniques using microtechnology. Such areas include the following:

- DNA sequencing and identification
- Gene mutation identification
- Gene expression profiles
- PCR (Polymerase Chain Reaction) used for DNA amplification
- ELISA (Enzyme Linked Immunosorbent Assay) *(see figure)*
- Cell sorting devices
- Sequencing of the human and other genomes
- New molecular separation techniques
- 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 from BioLOC)

Applications of bioMEMS

Many areas are benefitting from the use of microtechnology to improve health care and serve to enhance the understanding of biological systems. Areas that would benefit from the enhancement of current methods include the following:

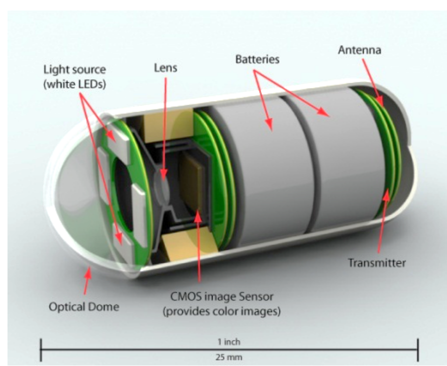
- Sample preparation
- Screening
- Diagnostics
- Monitoring
- Drug delivery
- Individualized treatment
- Less invasive surgical procedures

BioMEMS provides the opportunity to improve upon current methods, develop new ones, and potentially lower the cost of medical care. Examples of bioMEMS devices that are already available include a micro-sized insulin pump for diabetics, DNA microarray chips for multiple analyses of DNA, and various biosensors for detecting a variety of specific analytes simultaneously in samples such as blood, urine and sputum.

Shrinking Technologies

BioMEMS are revolutionizing medical practice and environmental monitoring. The potential for these miniaturized devices provides obvious advantages, whether in vivo or in vitro. Such advantages include reduced manufacturing cost for devices such as µTAS (micro-total-analysis systems) and LOC (lab-on-a-chip) devices, smaller sample size, and smaller amounts of reagents. The physical space savings achieved using microdevices rather than large pieces of lab equipment are also cost effective.

For the diabetic, a small monitoring and insulin delivery device greatly contributes to the ease of disease regulation, leading to a better quality of life. Persons undergoing somewhat invasive tests such colonoscopies or endoscopies appreciate a smaller detection device *(see photo)*. Portability of small test devices makes it possible for testing in remote areas where clinical labs are not available, or onsite such as at an accident scene. From a money-making point of view, the development of disposable devices could also be desirable.



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

There has been much debate about changing existing biomedical practices and using smaller devices. There are concerns about safety and long-term costs. For instance, will in vivo bioMEMS be biocompatible in the long term or will the host body eventual reject the device or will the bioMEMS device cause additional, more serious problems to the host body? However, these concerns are being overshadowed by the new possibilities 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. Whereas microtechnology is an enabling technology for applications in the life sciences (e.g., drug delivery, genetic analysis, proteomics and drug discovery[5]), the new biotechnologies (e.g., genetic engineering, drug production, and gene therapy), are enabling technologies for the applications of bioMEMS.

The Current Market

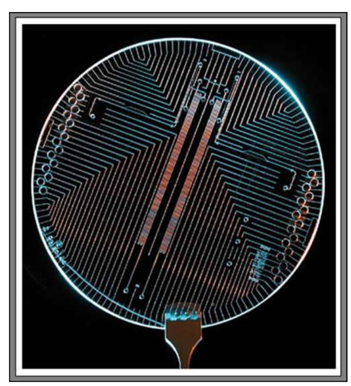
As we explore the possibilities of bioMEMS applications, we can find many bioMEMS devices already on the market (e.g., real-time glucose monitoring, pacemakers, drug delivery, home pregnancy tests). Many more are very promising for commercialization within the next few years. Some are in the research phase with an unknown commercialization date but holding great promise for the future.

Point-of-Care (POC) Devices

BioMEMS technologies have been boosted in part by funding from the US Defense Advanced Research Projects Agency (DARPA) for the development of portable medical diagnostic devices for military applications.[6] 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 and health care benefits for everyone.

Lab-on-a-Chip (LOC)

An example of a POC device is the Lab-on-a-Chip (LOC). In research and clinical laboratories, these are some of the most successful applications for bioMEMS. This figure is an example of an LOC.

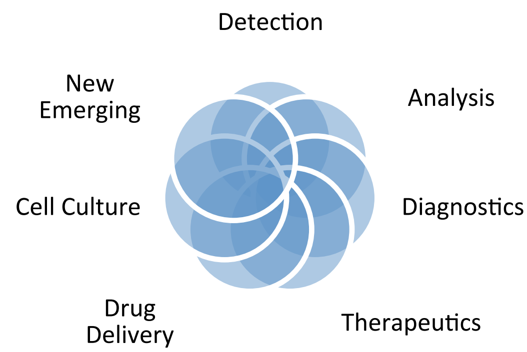


Lab-on-a-Chip (LOC)
LOCs are designed to analyze samples as small as a picoliter. They are also point-of-use devices; in other words, they can be used in the field, at the site of an accident, or in remote areas where medical laboratories are non-existent.
[Printed with permission. From Blazej,R.G.,Kumaresan,P. and Mathies, R.A. PNAS 103,7240-7245 (2006).]

Oh – The Possibilities!

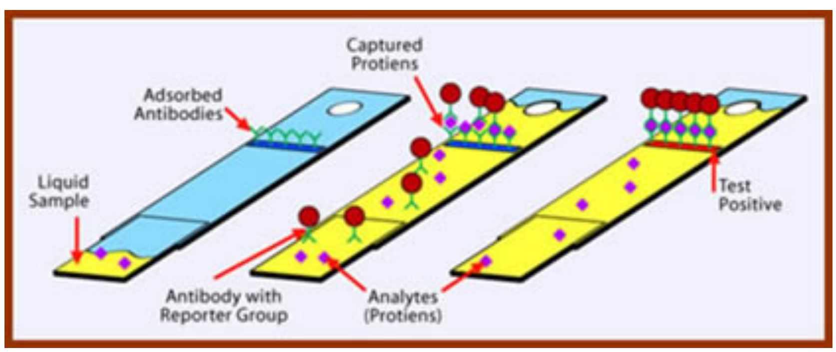
BioMEMS are being researched for possible applications in a variety of areas. For example, biotechnology research involves the manipulation of DNA[8] and the actual use of DNA to direct the synthesis of materials.[9] BioMEMS research has already led to multiple applications in the following medical areas:

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



See **Related SCME Units** at the end of this guide for a list of material that will further clarify the extensive possibilities of using bioMEMS technology.

BioMEMS for Detection

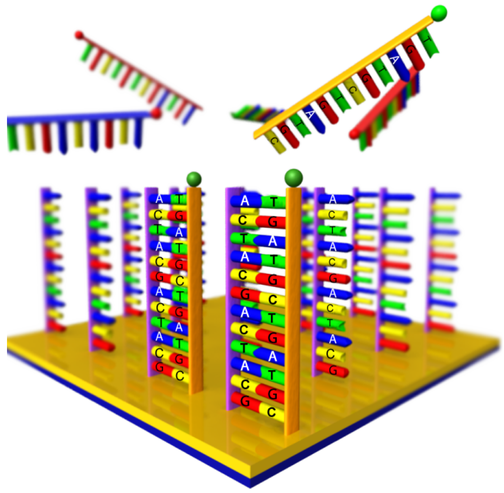


Home Pregnancy Test (Detection of protein in the urine of a pregnant woman)

BioMEMS for detection applications include the following:

- Sensors for chemical detection (e.g., toxins, ions, proteins)
- Bacterial, fungal, and viral detection
- Antibody detection
- Disease detection
- Examination devices (such as endoscopes and catheters)

BioMEMS for Analysis

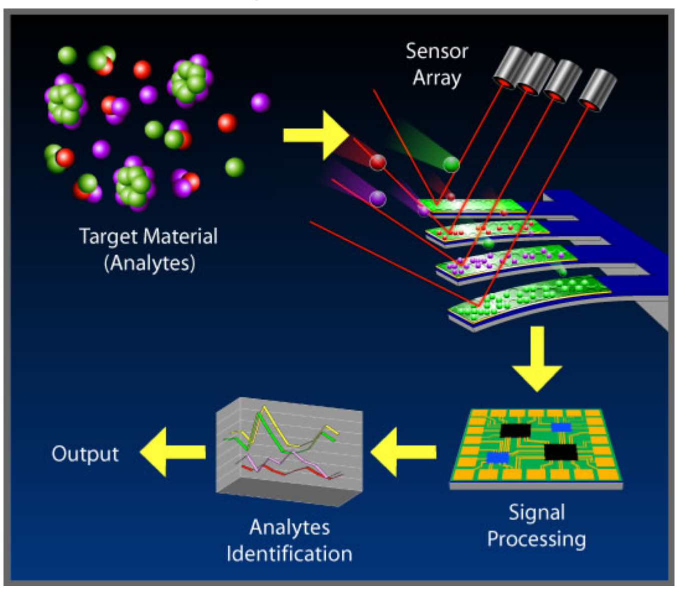


DNA Microarrays identify complementary DNA through the hybridization process. This graphic illustrates what happens in a biochip or DNA microarray: The target DNA single strand (yellow rail) attaches to a complementary capture DNA probe on the substrate. (Notice that the matching base pairs in the sequence.)

BioMEMS that analyze specific analytes in a sample include the following:

- Bacterial identification and antibiotic susceptibility
- Clinical laboratory medicine (clinical chemistry) testing and analysis
- DNA analysis for forensics identification *(see above graphic)*
- DNA analysis for specific genes, gene mutations, and gene activity

BioMEMS for Diagnostics



Chemical Sensor Arrays can detect, identify and determine the amount of an analyte in a sample. [For a detailed discussion of how a chemical sensor array works, review the SCME unit on Chemical Sensor Arrays]

Examples of bioMEMS for diagnostics applications include the following:

- Disease identification (e.g., various cancers and autoimmune diseases)
- Protein isoform identification (used to assist in prescribing appropriate drugs for personalized medicine)
- Antibody identification

BioMEMS for Monitoring

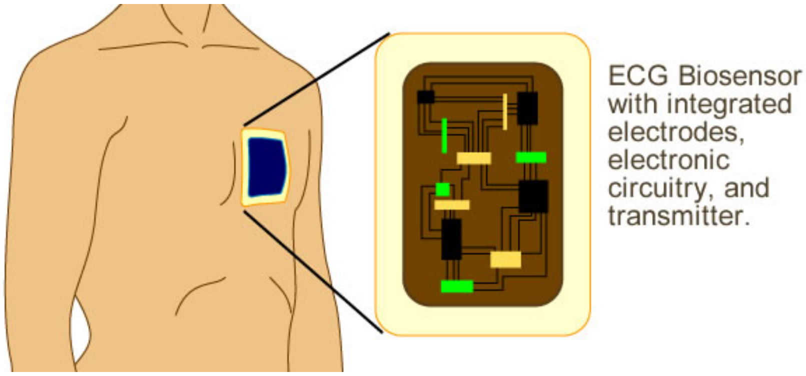
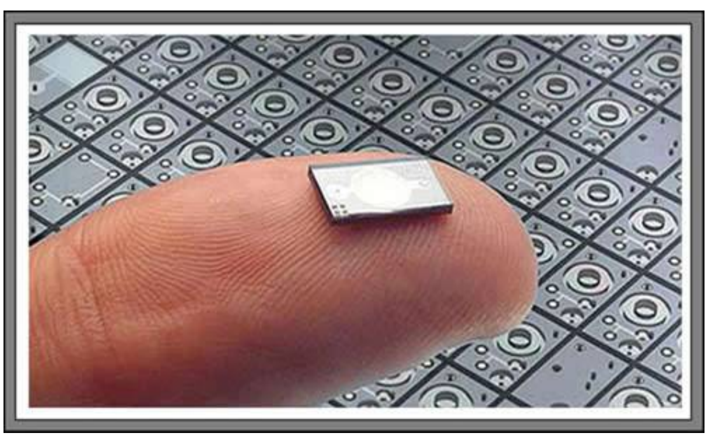


Illustration of a MEMS electrocardiogram (ECG) patch monitor. Such a device is being developed by Belgium's IMEC that " measures up to 3 lead ECG signals, tissue-contact impedance and includes a 3D-accelerometer for physical activity monitoring".[10]

Following are bioMEMS used for continuous as well as specific monitoring applications.

- 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) monitor which "integrates electrodes, a biochip sensor, an accelerometer, a microcontroller unit, and a transmitter in a package the size of a very thin wristwatch. Algorithms running on the patch's processor monitor patients for arrhythmias day and night. The patch can run on a small 200mAh Li-Po battery for up to a month, depending upon what is being measured and transmitted.*[10]*)*

BioMEMS for Drug delivery

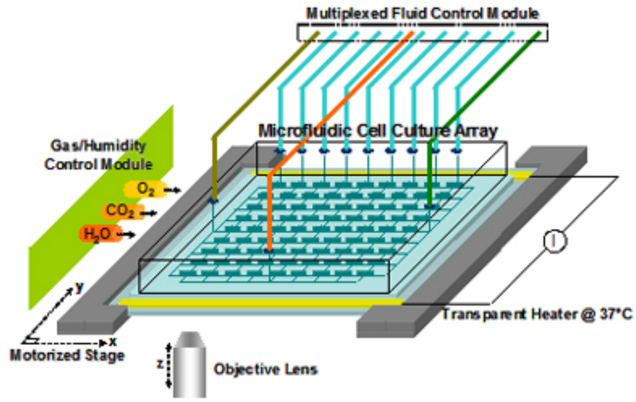


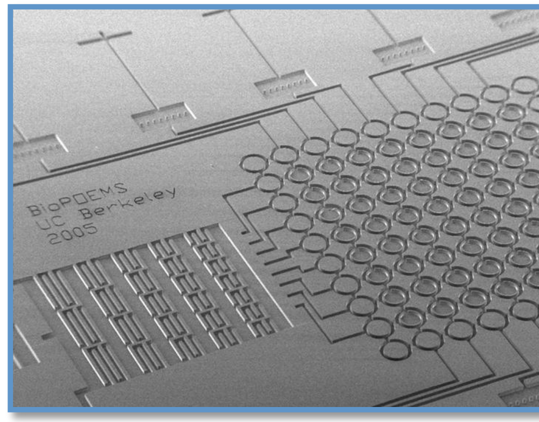
Insulin pump for drug delivery system
[Printed with permission from Debiotech SA.]

BioMEMS enable the delivery of drugs, examples include the following:

- 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 by and courtesy of BioPOETS Lab, UC-Berkeley][12]

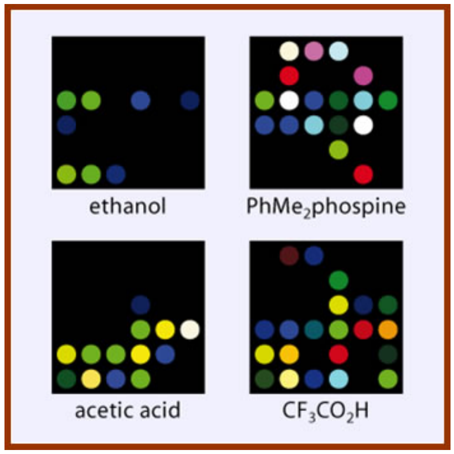
Cultivation of cells in vitro are also enabled by the applications of bioMEMS:

- Cell separation and counting
- Microenvironments for growing cells in vitro and analysis *(see above graphic)*
- Magnetic microbeads used to levitate cells for 3-D cell culture.

Emerging Applications

There are several additional categories that have not mentioned and more being added; however, the previous six areas provide a core from which we can launch a discussion regarding the types of bioMEMS devices currently being used or developed for biological applications. Hopefully, advances in these six areas will encourage further interest in emerging applications of microtechnologies for medicine and life sciences with the purpose to improve the quality of life for all.

Further Miniaturization of Existing Techniques



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.

Key concepts that are covered in greater detail in other units are miniaturization of the following techniques:

PCR, polymerase chain reaction:, A method used to amplify DNA sample commonly 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 within cells.

Gel electrophoresis: Separation of molecules in a gel using an electrical charge to attract molecules based on molecular weight.

Chromatography: Molecular separation based on size, charge, or other properties. *(see figure)*

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

Microarrays: Devices that use small samples with multiple tests being run at the same time.

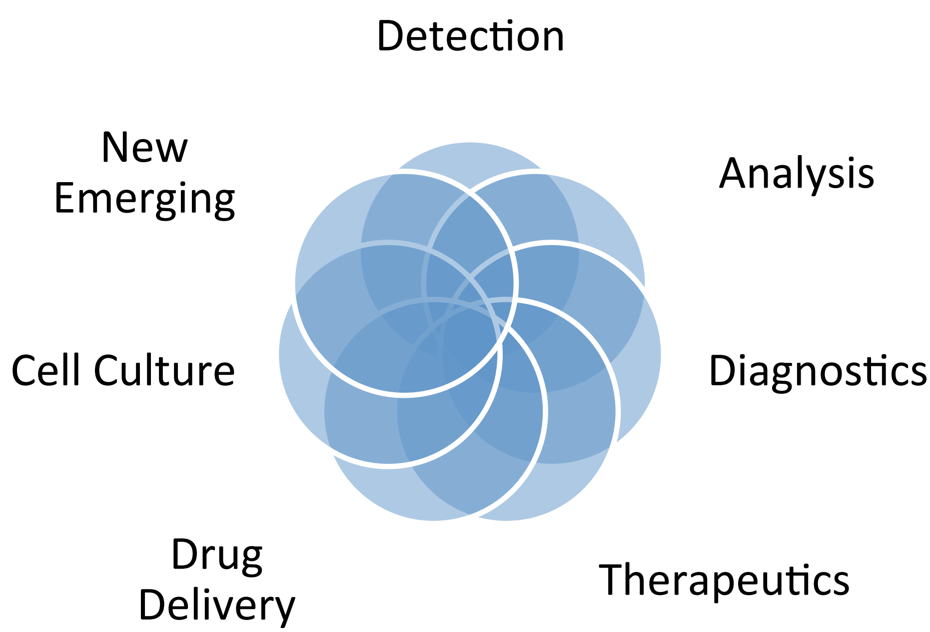
Lab on a Chip Devices: A collection of small scale miniaturized devices that are used to perform laboratory operations.

Microfluidics: Systems designed to rapidly measure characteristics of small amounts of fluids.

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.



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 microtechnologies be used effectively for bioMEMS?
- What concerns need to be addressed in order to make bioMEMS applications successful?

Food for Thought Questions / Answers

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?*

Answer:

Benefits of miniaturizing techniques are

- *Smaller sample size*
- *Reduced cost*
- *Portability*
- *Disposability*
- *Availability for point of care use – immediate test results*
- *Comfort for patients*
- *Better Compliance to regulations*

Concerns:

- *Reliability*
- *Biocompatibility*
- *Biofouling*
- *Accuracy and precision*
- *Durability*
- *Safety*

Glossary

Analysis: The identification or separation of ingredients of a substance. An examination of a complex, its elements, and their relations.

Biocompatibility: The in vivo inflammatory response of the body to and bioMEMS device.

Biofouling**:** Interference of function caused by such things as non-specific affinity of proteins and cells to attach to surfaces.

BioMEMS: MEMS systems with applications for the biological / analytical chemistry market.

Biotechnology: A set of biological techniques developed through basic research and now applied to research and product development. The use of microorganisms, such as bacteria or yeasts, or biological substances, such as enzymes, to perform specific industrial or manufacturing processes.

Detection: Act of detecting, discovery, the laying open of what was concealed or hidden or of what tends to elude observation.

Genomics: The study of all of the nucleotide sequences, including structural genes, regulatory sequences, and noncoding DNA segments, in the chromosomes of an organism.

In vitro: In an artificial environment outside of a living organism.

In vivo: That which takes place inside an organism.

Lab on a Chip: Devices that integrate (multiple) laboratory functions on a single chip of only millimeters to a few square centimeters in size and that are capable of handling extremely small fluid volumes down to less than a few picoliters.

Micro-total-analysis systems (µTAS): Devices that integrate the total sequence of lab processes to perform chemical analysis on a single chip of only millimeters to a few square centimeters in size.

MEMS: MicroElectroMechanical Systems – microscopic devices such as sensors and actuators, typically fabricated on silicon wafers.

Microfluidics: The technology of designing, manufacturing, and formulating devices and processes that deal with the delivery of volumes of fluid on the order of microliters, nanoliters or picoliters.

Proteomics: A complete analysis of all, or most, of the proteins in a particular cell type or organism.

Sensor: A device that responds to a stimulus, such as heat, light, or pressure, and generates a signal that can be measured or interpreted. A sensor typically converts a measured physical property into an electrical signal which can be processed by microelectronics logic systems (computers).

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Related SCME Units

- BioMEMS Applications Overview Learning Module
- Diagnostic Applications Learning Module
- Therapeutic Applications Learning Module
- Mapping Biological Concepts Learning Module
- DNA Overview
- DNA to Protein Overview
- Cells, The Building Blocks of Life
- Applications of Biomolecules in bioMEMS
- Chemical Sensor Arrays (Unit in MEMS Cantilever Learning Module)

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