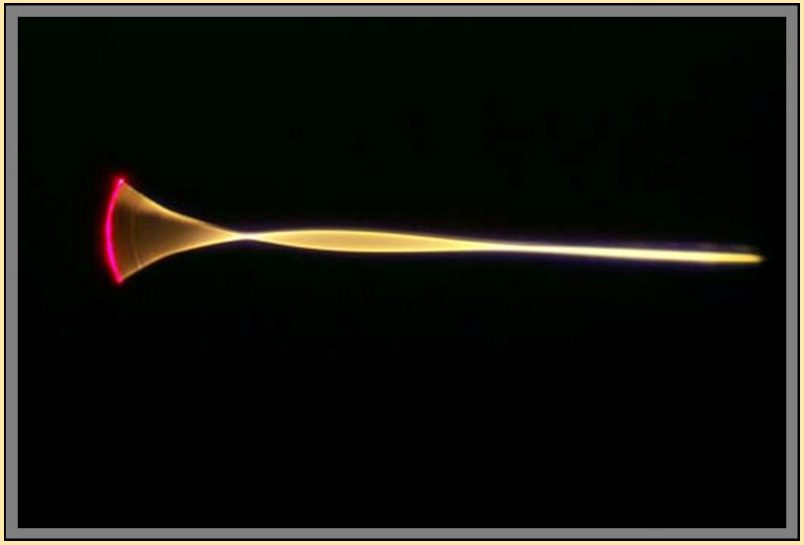
DIAGNOSTICS BIOMEMS



Microscope image of the Micro-optical fiber scanner used in endoscope systems. [Image Courtesy of Eric Seibel and Mark Fauver]

Unit Overview

This unit explores the areas in diagnostic medicine that are being or will be impacted by the introduction of bioMEMS.

This unit discusses the advantages and disadvantages of adapting existing diagnostic laboratory tests and materials to MEMS, the areas in medicine that will be impacted and how, and examples that are already being tested.

Objectives

- Discuss examples of at least two diagnostic bioMEMS medical devices currently in use.
- Describe three main areas in medical diagnostics which have been impacted by bioMEMS technology.

Introduction

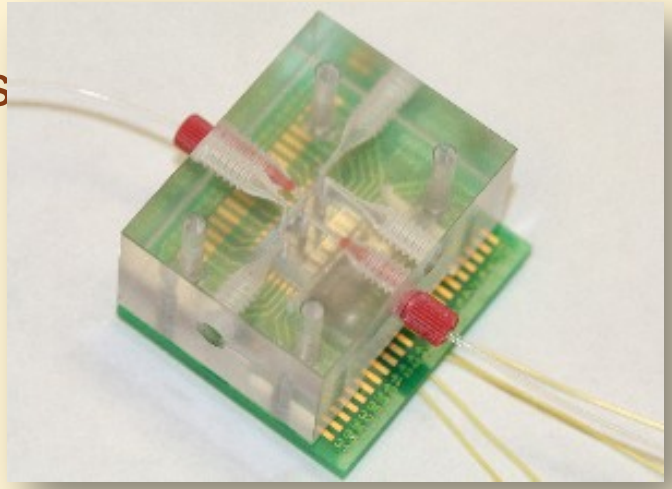
Wouldn't it be nice to have a medical device that could identify clues within our bodies to tell us what our ailments might be?

If you have ever watched Star Trek, you can imagine what such a device would be like – a handheld optical or x-ray scanner used externally to "see" what is happening inside. The possibility of such a device is becoming closer to reality.

Lab-on-a-Chip

A miniaturized, portable version of a blood-count machine used by astronauts in the space station to test blood samples.

The portable clinical blood analyzer (PCBA) is about the size of a smart phone, requires a tiny drop of blood (as small as a 65 microliter sample), and provides results in 120 seconds. Blood analysis includes glucose level, pH, potassium, sodium and more.



The Lab-on-a-chip initially test at the International Space Station [Photo courtesy of Y. Tai, California Institute of Technology]

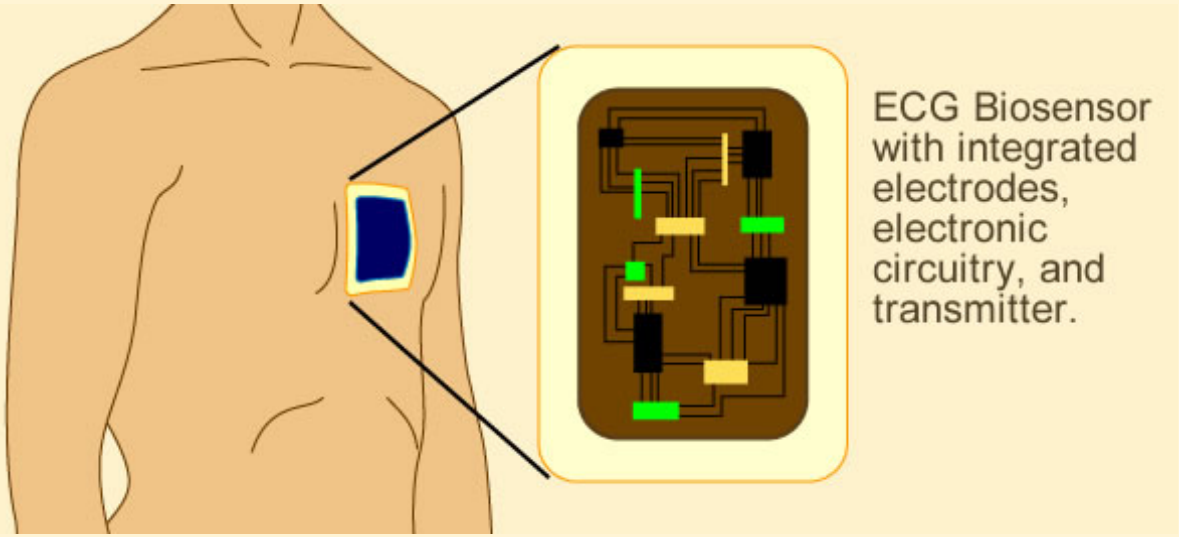
Why do we need Diagnostic bioMEMS?

…In order to diagnose particular diseases or conditions by identifying specific biological markers (e.g., antibodies, proteins, genes).

Scientists are still in the process of deciphering the biomarker landscape associated with specific disease states; however, as biomarkers are identified, bioMEMS diagnostic devices that isolate these biomarkers are being developed.

BioMEMS Diagnostics

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. Patients that are high risk for cardiac events can wear this devices 24/7.



BioMEMS Diagnostic devices can be

- cost effective,
- easier to administer, and can be
- used for in vivo (internal) or in vitro (external) monitoring.

Areas being impacted

- Clinical Laboratory testing
- Patient examinations and monitoring
- Medical Imaging
- Therapeutics

BioMEMS in these areas are having a positive impact, particularly in underdeveloped countries that presently do not have the expensive diagnostic medical technology of developed countries.

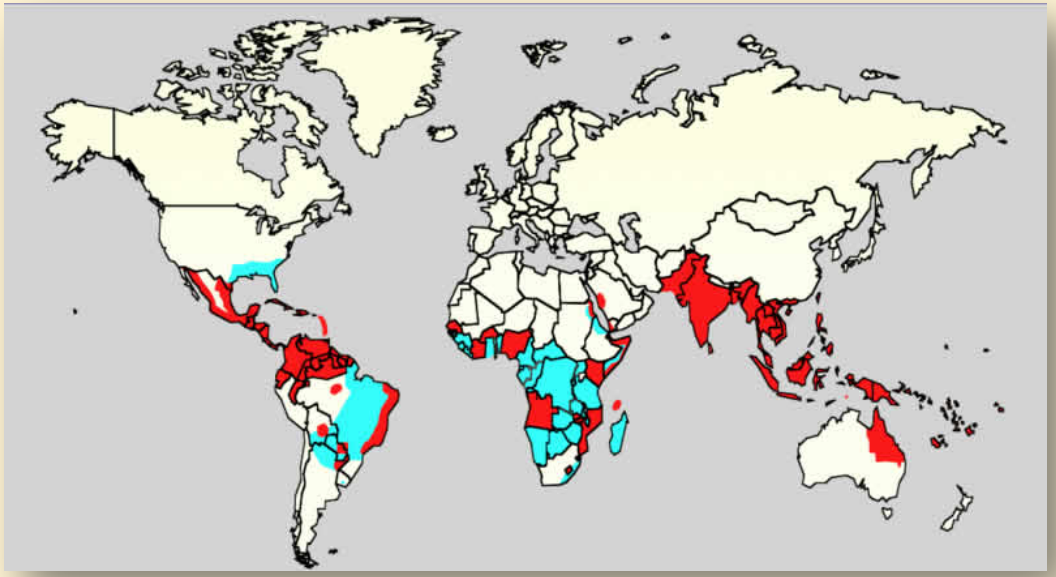
The versatility and portability of bioMEMS allows for the presence of medical devices in places where none have gone before.

Diagnosing Dengue Fever

An example of a bioMEMS currently in use is a microchip assay that detects Dengue Fever, an acute illness that causes fever, rash, headaches, and muscle and joint pains.

In 2015 there were over 3.5 million reported cases in the Americas, SE Asia, ad Western Pacific. This map shows 2006 current (cyan) and recent (red) cases.

The first 11 weeks of 2017 showed a reduction of reported cases compared to this time mark of previous years.



Distribution of Dengue Fever in the world as of 2006. [Map produced by and courtesy of the Agricultural Research Service of the US Department of Agriculture]

Dengue Fever

There are several problems associated with the diagnosis and treatment of Dengue Fever.

- Early diagnosis is very difficult.
- Once diagnosed, there are no good drugs for treatment, especially if the disease has progressed.
- The mortality rate is high.
- If someone is immune to one type (virus) of Dengue Fever, he/she is not immune to the other three types of Dengue Fever.
- Programs to eradicate the mosquito responsible for transmitting the virus have not been effective (e.g., Governments spray the outside areas but the mosquito is found inside buildings).

In theory, early diagnosis and treatment would decrease the mortality rate.

BioMEMS Diagnostics for Dengue Fever

- In 2014 the results of a study were published that showed positive results of using a colorimetric ELISA (Enzyme-Linked Immunosorbent Assay) for a point-of-care (POC) dengue detection system on a LOC compact disc.
- This ELISA was found to have “clinical sensitivity of 95.2% and specificity of 100%”.
- The POC has an integrated platform that allows minimal input from the user while being able to display results via a smartphone application, making the results easy to read and interpret.

Advantages of Diagnostics BioMEMS

- Due to smaller volumes, quicker reaction concentrations and temperatures, resulting in a faster test result are achieved
- More sensitive and specific (the detector is the size of the target).
- Smaller tests volumes resulting in a decreased cost of reagents.
- Amenable to point-of-care, either in vitro or in vivo.
- Allows for miniaturization and portability.
- A safer platform for chemical, radioactive, or biological studies (large integration of functionality and low stored fluid volumes).
- Compactness allows for multiplexing and massive parallelization.
- The possibility of lower fabrication costs, allowing for cost-effective disposable chips, fabricated in mass production.

Disadvantages of Diagnostic BioMEMS

- MEMS technology for biomedical applications is still relatively new technology and has been slow to develop to the point of current diagnostics technologies, especially when human interface or device implantation is required. Although…it's looking up!
- Detection principles may not scale down well, leading to low signal to noise ratios.
- Physical and chemical effects, like quantum or capillary forces, can create problems at the molecular level as a result of the small size becoming a dominant force.

Clinical Chemistry

- Developments with microfluidic devices have enable point-of-care (POC) devices such as the microfluidic-based micro-total-analysis systems (μTAS) and Lab-on-a-chip (LOC).
- μTAS are usually hybrids of many biochips, integrated electronics, and external supports for chemical analysis that perform all or part of a chemical analysis.
- A LOC device refers more specifically to a microfluidic chip or other device that performs a well defined task or a series of tasks on a single chip.
- Clinical chemistry and molecular diagnostics have been the largest users of these first generation bioMEMS devices.

Lab-on-a-chip (LOC)

"The photo *(right)* shows a "lab on a chip" that is designed to sequence large genomes quickly and cost-effectively. Researchers say this work ultimately could provide important medical benefits, allowing preventative and therapeutic care tailored to each patient's genome."
"The beauty of the pursuit of knowledge as seen in this "lab on a chip"." UC Berkeley News. January 2, 2007.

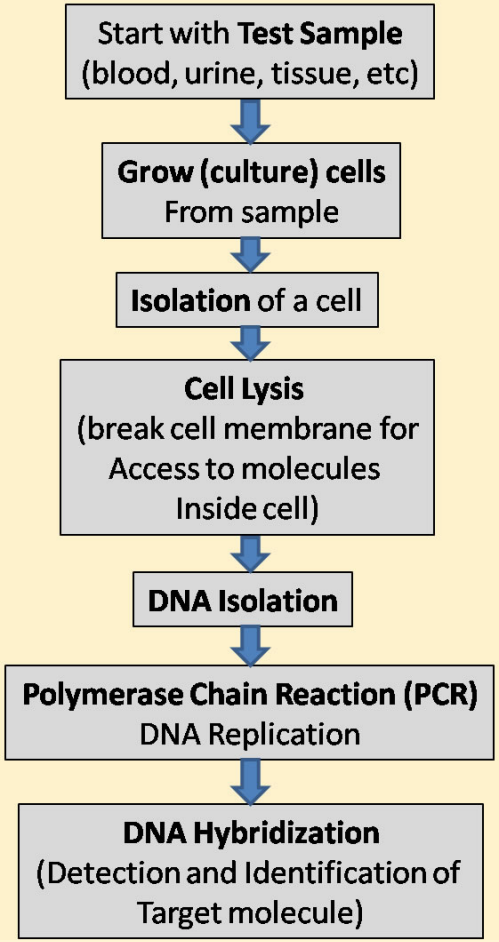
In general, biochips include LOC devices and microarray devices. Microarray devices are mainly being used commercially for drug discovery and development.

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

μTAS Diagnostic Testing

The panel of reactions shown in the flowchart is a basic design for a μTAS device that could be used to detect genetic diseases, pathogens in the blood such as the HIV virus, or genetically determine what drugs a person should take for cancer treatment (i.e., pharmacogenetics).

How would this test work?



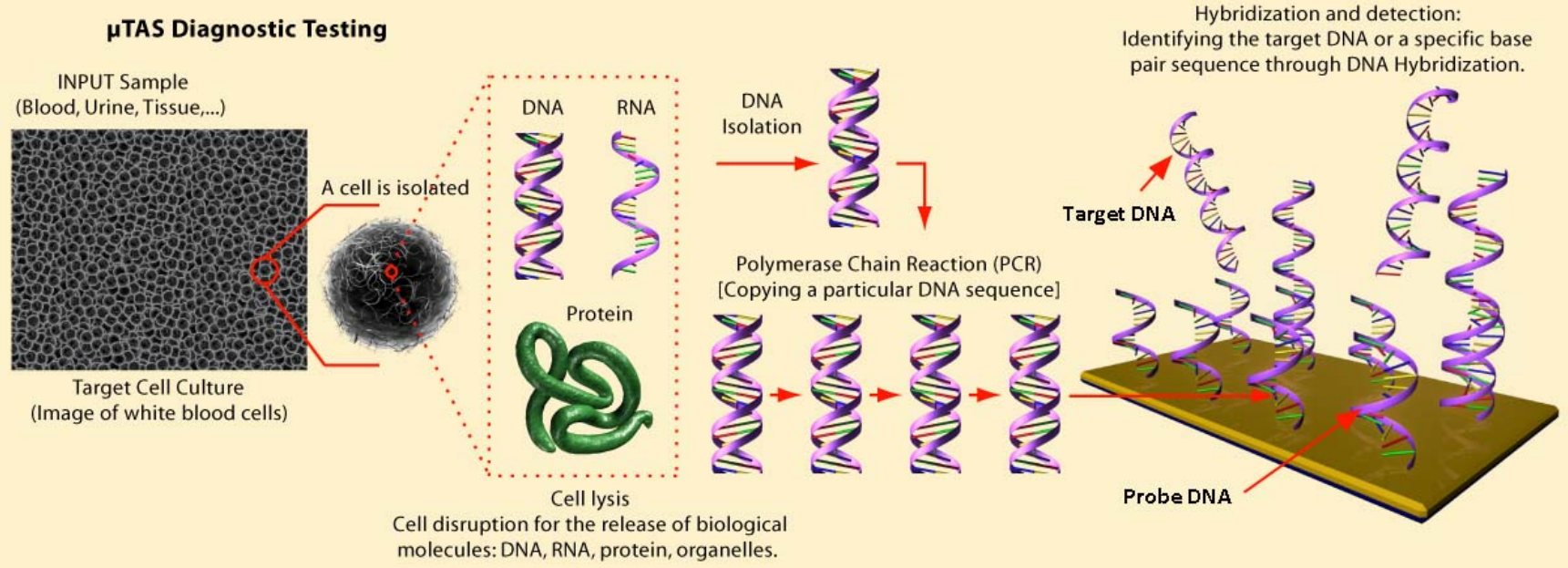
Scenario for μTAS Diagnostic Testing

Let's take for example a woman who has developed blood clots after taking estrogen for two months for menopausal symptoms.

- It is suspected that she has a genetic defect known as Factor V Leiden.
- This defect increases a person's tendency to develop blood clots and is the most common hereditary blood coagulation disorder in the United States.
- It is present in 2-7% of the Caucasian population and 1.25% of the African American population.
- This genetic defect is caused by a single base change in the DNA making the coagulation Factor V more resistant to activated protein C.
- This increases the predisposition to blood clot formation.

µTAS Diagnostic Testing Flowchart

For the µTAS test, a blood sample drawn from the woman could be injected right into the device. The following is an example of a diagnostic flow for the µTAS test.



Polymerase Chain Reaction (PCR)

- A lab-on-a-chip performs the Polymerase Chain Reaction (the amplification of DNA) step in the μTAS diagnostic.
- All of the steps described before and after PCR are normally done by the lab tech; however, MEMS technology has now enabled the development of cell culture devices as well as biochips for DNA hybridization.
- The highly complex systems found in present day clinical labs, including molecular diagnostics, are excellent candidates for μTAS devices.

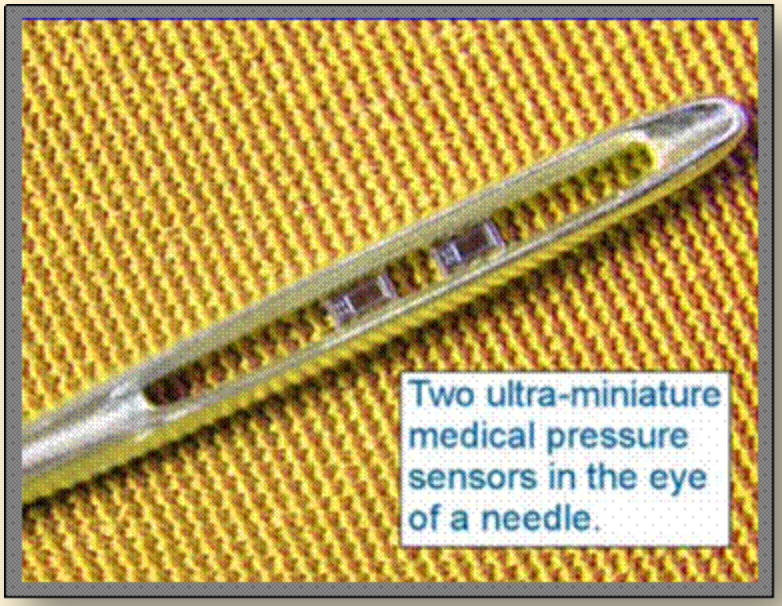
Patients Examinations and Monitoring

Several bioMEMS have been developed and proven to be effective for the following sensing and/or measurement applications:

- Pressure in arteries
- Spinal fluid
- Brain cavity
- Body temperature
- Force generated by muscles
- Skin tension
- DNA factors and biomarkers (i.e. if and when validated)
- Glucose
- Ions
- Gases (i.e. oxygen and carbon dioxide)

Patients Examinations and Monitoring

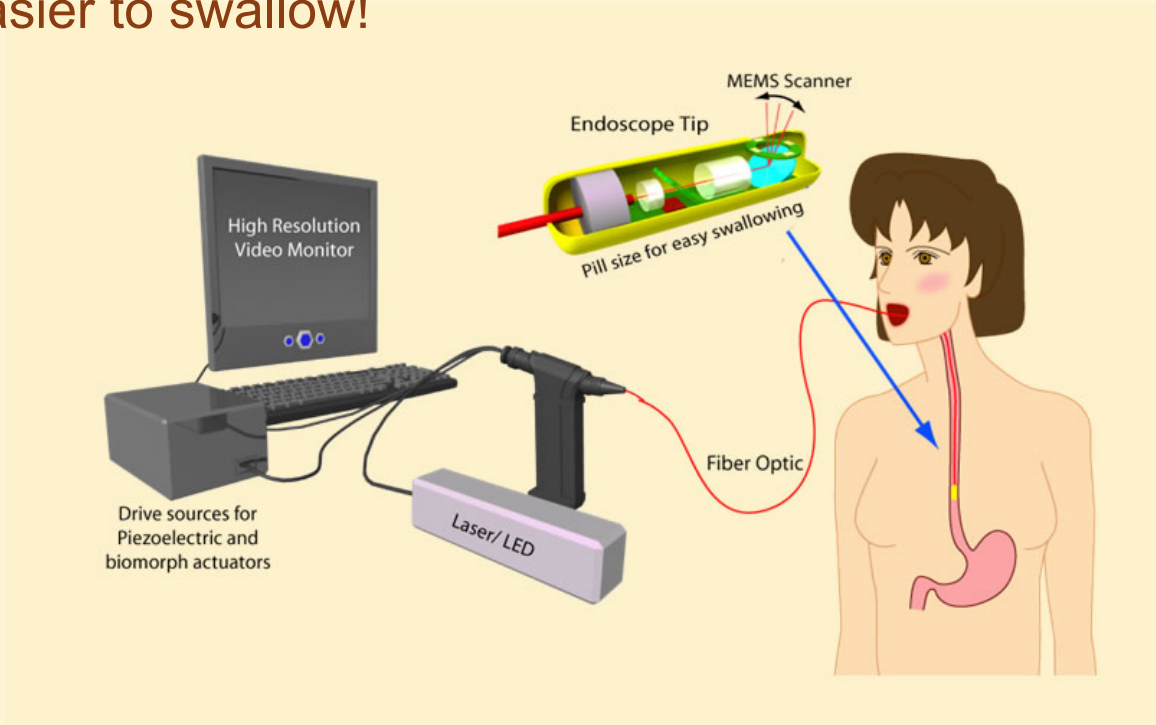
- The figure shows a couple of the first Integrated Sensing Systems (ISSYS) implantable sensors.
- These sensors are implantable, wireless and self powered.
- ISSYS has received patents for implantable sensors to monitor biological parameters to analysis chronic disease such as congestive heart failure.
- CardioMEMS is marketing such a device for monitoring pulmonary artery pressures in cardiac patients.



Integrated Sensing Systems Sensors
[Image courtesy of ISSYS]

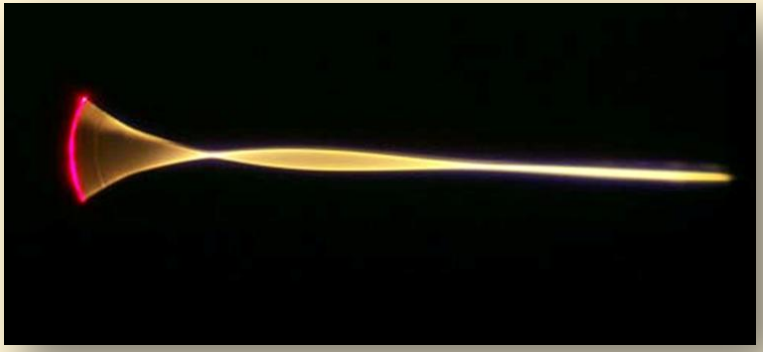
Medical Imaging

MEMS technology in the area of medical imaging includes the use of optical measurement devices such as a micro-optical scanner. A diagram illustrating such a scanner is shown in the figure. Notice that the endoscopy imaging device is a small pill-sized device connected to a fiber optic cable. For patients undergoing an endoscopy, this little pill is much easier to swallow!



Micro-Optical Scanner

The scanner is an optical fiber and a MEMS device placed inside the 1 mm diameter tip of a flexible endoscope. The fiber scanner is driven in one dimension with a piezoelectric actuator, producing a line scan. The microscope image of the micro-optical fiber scanner and its one dimensional scan is shown below. By knowing and controlling the fiber position and acquiring backscattered intensity with a photodetector, an image is acquired.



Microscope image of the Micro-optical fiber scanner. The diameter of the fiber tip, where red laser light is exiting, is approx. 10 microns. [Image Courtesy of Eric Seibel and Mark Fauver]

Micro-optically Scanned Image

A sample image formed with the macro-sized version of the fiber optic scanner is seen to the right. A single micro-machined optical fiber, optimized for its dynamic properties to maximize scan frequency, tip displacement, and field of view is responsible for this picture.

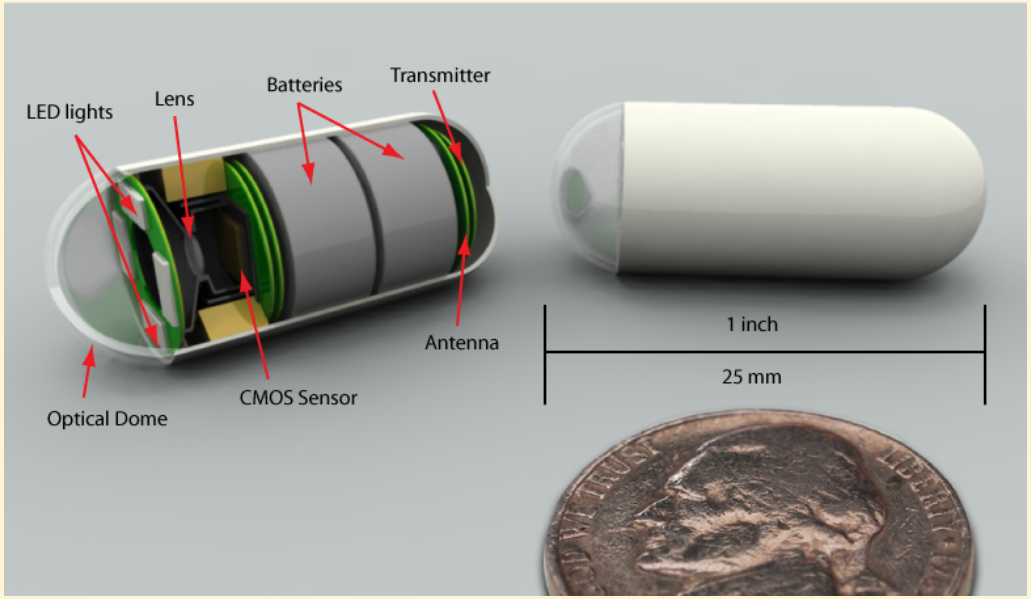
The letters in this image are 2.5 mm high and the field of view is 5.9 mm x 4.4 mm. *[Image courtesy of Eric Seibel, PhD]*

Pill Cam for Endoscopies/Colonoscopies

Further advancements in imaging has resulted in the pill cam. A nickel sized "pill" that can be swallowed and, as it travels through the gastrointestinal tract, records images and transmits those images to a receiver worn by the patient. Images are later downloaded and evaluated by the doctor.

Pill cam contains:

- Battery
- LED lights
- Lens
- CMOS Sensor
- Transmitter
- Antenna



Enabling Biomedical Principles

Several biomedical principles used for diagnostic purposes have enabled the development of bioMEMS diagnostic devices. For example, each of the following produces a biological molecule (biomarker) or physical change that can be detected:

- Pathogenic agents such as bacteria and viruses produce detectable chemicals.
- Certain medical conditions produce specific antibodies or proteins (e.g., Pregnancy produces a protein that can be detected in the urine).
- DNA replication produces mRNA and proteins.
- Cancer, infections and injuries can create physical changes in cells or tissues that can be seen and measured.

Let's Review

What are four of the main areas in medical diagnostics impacted by bioMEMS Technology? Describe some bioMEMS that have contributed to this impact.

Why is the development and implementation of diagnostic bioMEMS important to developing countries?

What are some areas of diagnostic medicine that could benefit from diagnostic MEMS?

Summary

Diagnostics bioMEMS already exist in many areas:

- A PCR is being used to detect the genetic defect, Factor V Leiden.
- Dengue Fever or HIV can be detected using a LOC.
- Cancerous cells or tissues in the colon can be visualized (i.e., endoscopy) using a micro-optical imaging.
- Cells and tissues infected with viruses and bacteria, such as in the sinuses, can be visually identified using the same micro-optical scanner.
- Implantable sensors can measure biological parameters in the heart as well as intracranial pressure in hydrocephalus patients.
- New diagnostics bioMEMS are being realized with each advancement of micro and nano-technologies.

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