MEMS and MICROSYSTEMS DESIGN AND MANUFACTURE

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Module -1

Overview of MEMS and Micro systems: MEMS and Microsystems, Typical MEMS and Microsystem Products, Evolution of Microfabrication, Micro systems and Microelectronics, Multidisciplinary nature of Microsystem design and Manufacture, Microsystems and Miniaturization, Applications of Microsystem in Health-care Industry. (Text 1: 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.8.1)

Bio-MEMS: Fabrication of Bio-MEMS, Structure, The Driving Force behind Biomedical Application, Biocompatibility, Reliability consideration. (Text 2: 1.1, 1.1.1, 1.1.2, 1.2, 1.3, 1.4)

Microsensors: Acoustic wave sensor, Biomedical Sensors and Biosensors, Chemical Sensors, Optical Sensors, Pressure sensors, Thermal sensors.(Text 1: 2.2)

Chapter 1

Overview of MEMS and Microsystems

WHAT IS MEMS?

MEMS = MicroElectroMechanical System

Any engineering system that performs *electrical* and *mechanical* functions with *components* in *micrometers* is a MEMS. (1 μm = 1/10 of human hair)

Available MEMS products include:

- **Micro sensors** (acoustic wave, biomedical, chemical, inertia, optical, pressure, radiation, thermal, etc.)
- **Micro actuators** (valves, pumps and microfluidics;
  electrical and optical relays and switches;
  grippers, tweezers and tongs;
  linear and rotary motors, etc.)
- **Read/write heads** in computer storage systems.
- **Inkjet printer heads**.
- **Micro device components** (e.g., palm-top reconnaissance aircrafts, mini robots and toys, micro surgical and mobile telecom equipment, etc.)

HOW SMALL ARE MEMS DEVICES?

in plain English please!

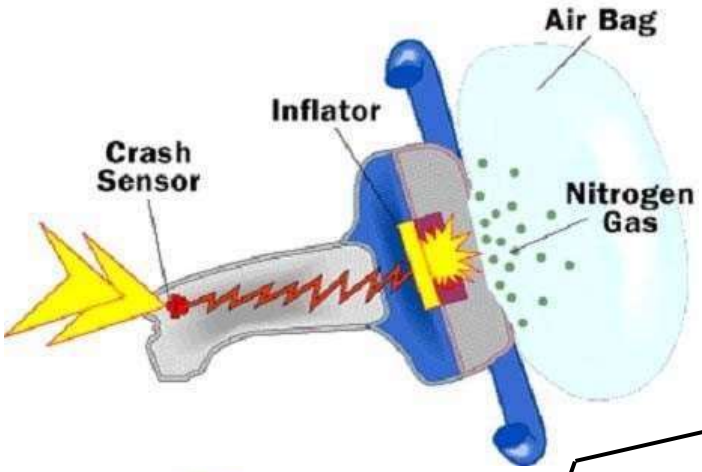
They can be of the size of a rice grain, or smaller!

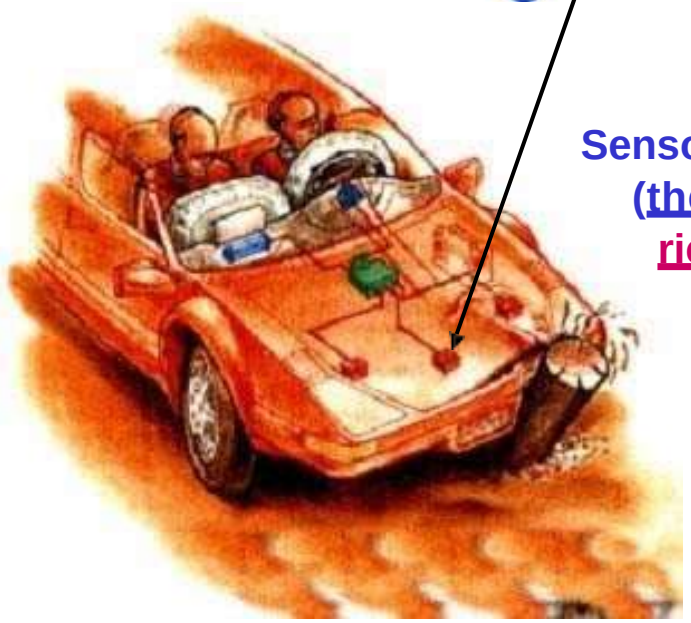
Two examples:

- Inertia sensors for air bag deployment systems in automobiles

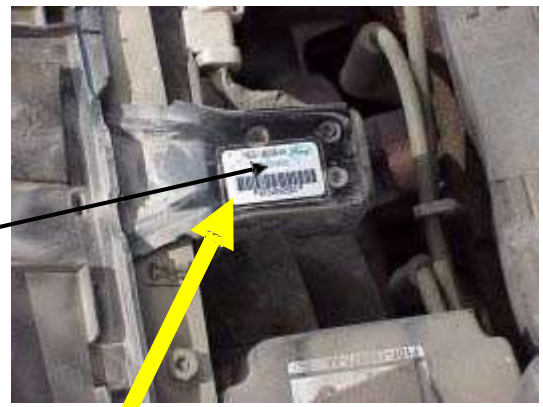
- Microcars

Inertia Sensor for Automobile "Air Bag" Deployment System





Micro inertia sensor (accelerometer) in place:

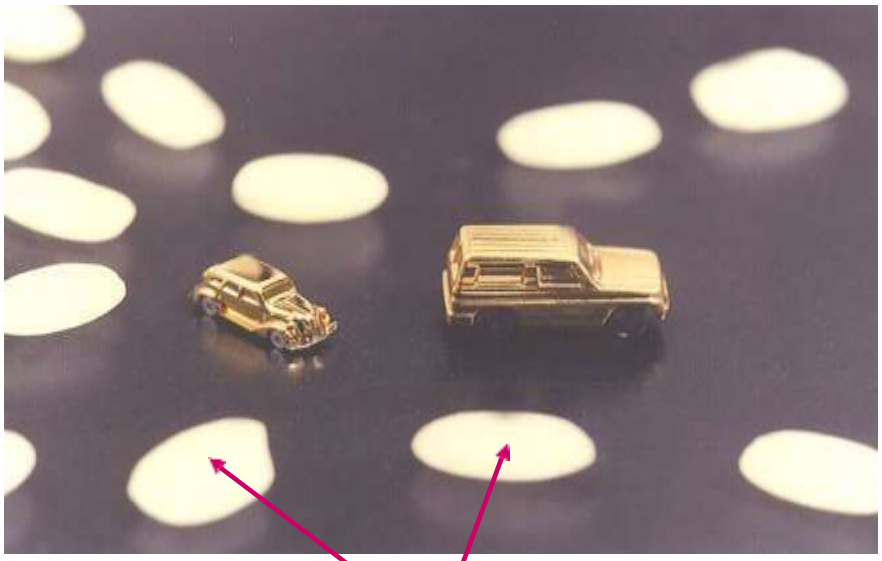


Sensor-on-a-chip:
(the size of a rice grain)

(Courtesy of Analog Devices, Inc)

Micro Cars

(Courtesy of Denso Research Laboratories, Denso Corporation, Aichi, Japan)



Rice grains

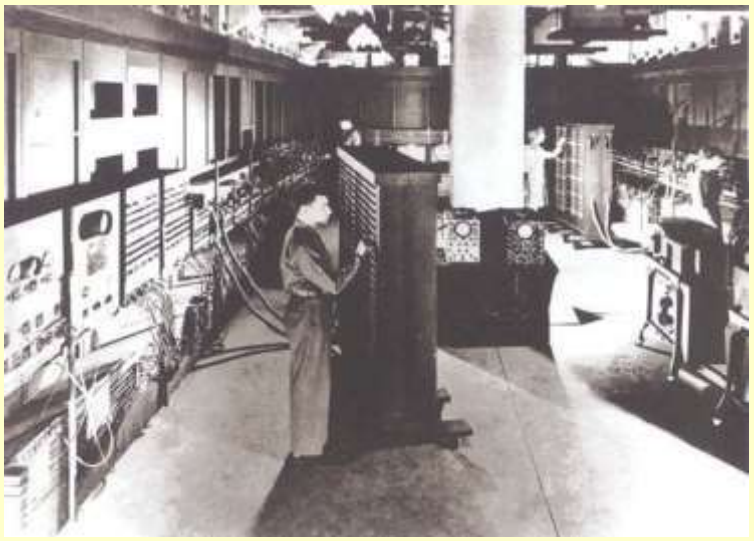
MEMS = a pioneer technology for Miniaturization

A leading technology for the 21st Century, and

an inevitable trend in industrial products and systems development

Miniaturization of Digital Computers

- A remarkable case of miniaturization!



The ENIAC Computer in 1946

Size: 10^6 down
Power: 10^6 up

A “Lap-top” Computer in 1996

Size: 10^8 down
Power: 10^8 up

A “Palm-top” Computer in 2001

This spectacular miniaturization took place in 50 years!!

MINIATURIAZATION – The Principal Driving Force for the 21st Century Industrial Technology

There has been increasing strong market demand for:

"Intelligent,"

"Robust,"

"Multi-functional," and

"Low-cost" industrial products.

Miniaturization is the only viable solution to satisfy such market demand

Market Demand for Intelligent, Robusting, Smaller, Multi-Functional Products - the evolution of cellular phones

Mobil phones 10 Years Ago:

Transceive voice only

Current State-of-the Art:

Size reduction

Palm-top Wireless PC

Transceive voice+ multi-media + others (Video-camera, e-mails, calendar, and access to Internet, GPS and a PC with key pad input)

The only solution is to pack many miniature function components into the device

Miniaturization Makes Engineering Sense!!!

- Small systems tend to move or stop more quickly due to low mechanical inertia. It is thus ideal for *precision movements and for rapid actuation*.
- Miniaturized systems encounter less thermal distortion and mechanical vibration due to low mass.
- Miniaturized devices are particularly suited for biomedical and aerospace applications due to their minute sizes and weight.
- Small systems have *higher dimensional stability at high temperature* due to low thermal expansion.
- Smaller size of the systems means less space requirements. This allows the *packaging of more functional components in a single device.*
- Less material requirements mean low cost of production and transportation.
- Ready *mass production in batches*.

Enabling Technologies for Miniaturization

Microsystems Technology (MST) (1 μm - 1 mm)*

A top-down approach

Initiated in 1947 with the invention of transistors, but the term "Micromachining" was coined in 1982

Miniature devices (1 nm - 1 mm)

Nanotechnology (NT) (0.1 nm – 0. 1 μm)**

A bottom-up approach

Inspired by Richard Feynman in 1959, with active R&D began in around 1995

There is a long way to building nano devices!

* 1 μm = 10^{-6} m ≈ one-tenth of human hair

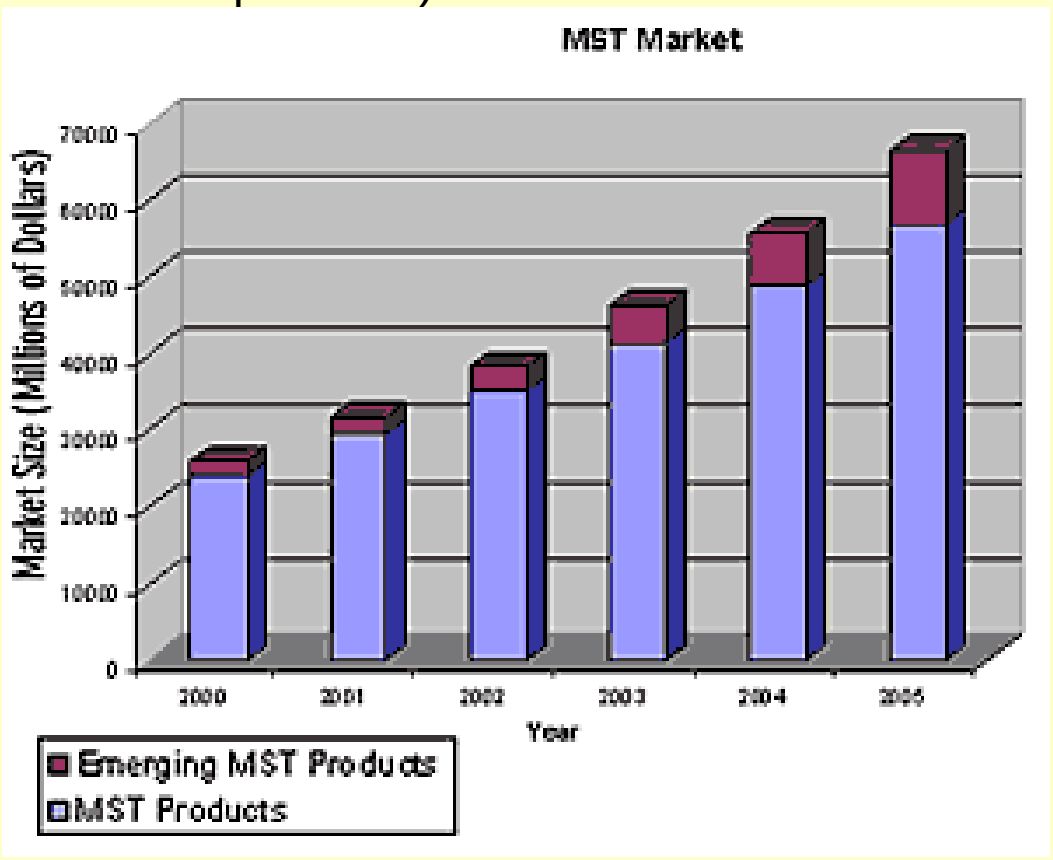
** 1 nm = 10^{-9} m ≈ span of 10 H_2 atoms

The Lucrative Revenue Prospects for Miniaturized Industrial Products

Microsystems technology:

$43 billion - $132 billion* by Year 2005

(*High revenue projection is based on different definitions used for MST products)



Source: NEXUS http://www.smalltimes.com/document_display.cfm?document_id=3424

The Lucrative Revenue Prospects for Miniaturized Industrial Products –Cont'd

Nanotechnology:

$50 million in Year 2001

$26.5 billion in Year 2003

(if include products involving parts produced by nanotechnology)

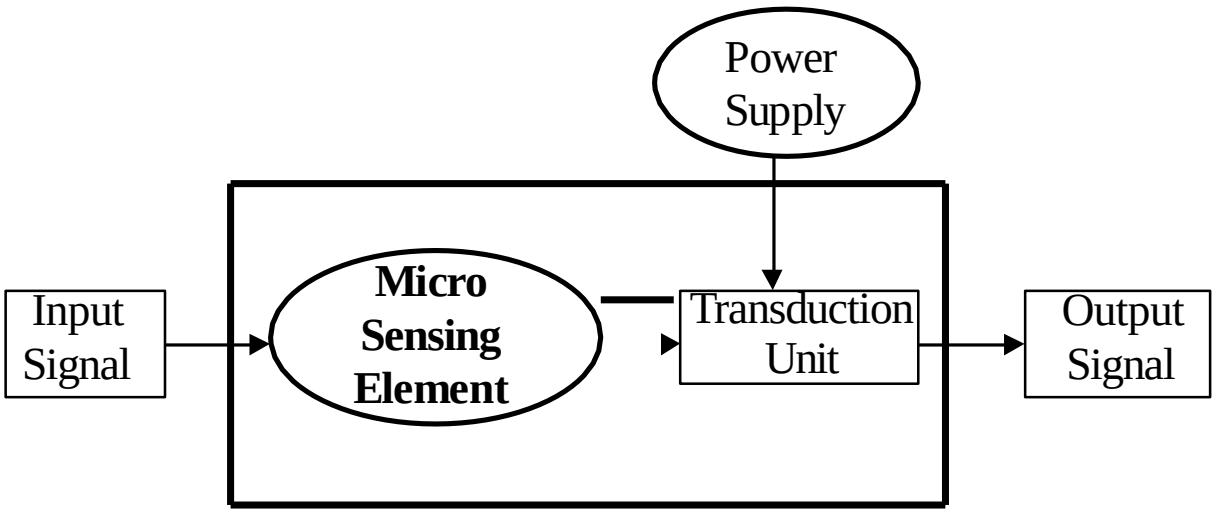
$1 trillion by Year 2015 *(US National Science Foundation)*

An enormous opportunity for manufacturing industry!!

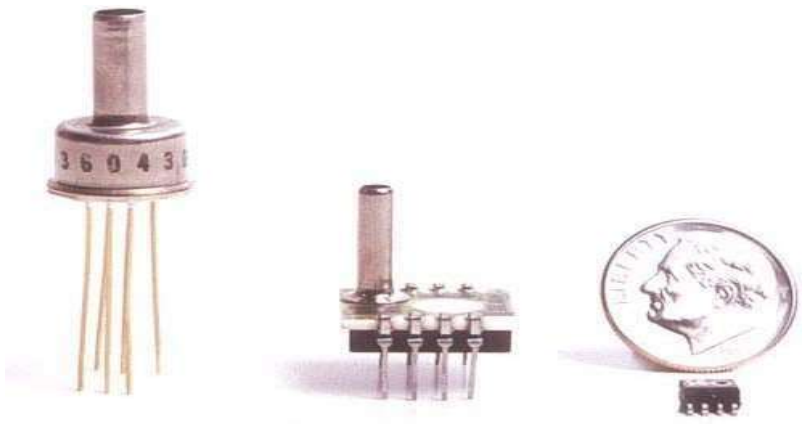
- **There has been colossal amount of research funding to NT by governments of industrialized countries around the world b/c of this enormous potential.**

MEMS Products

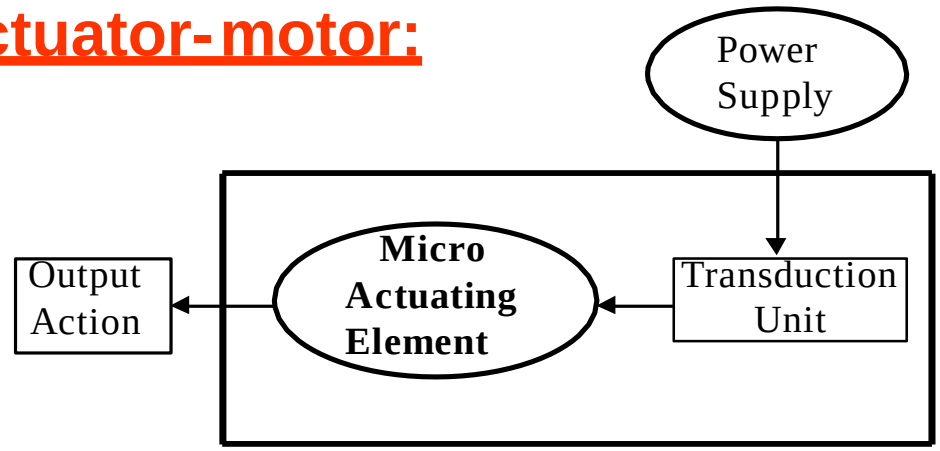
MEMS as a Microsensor:

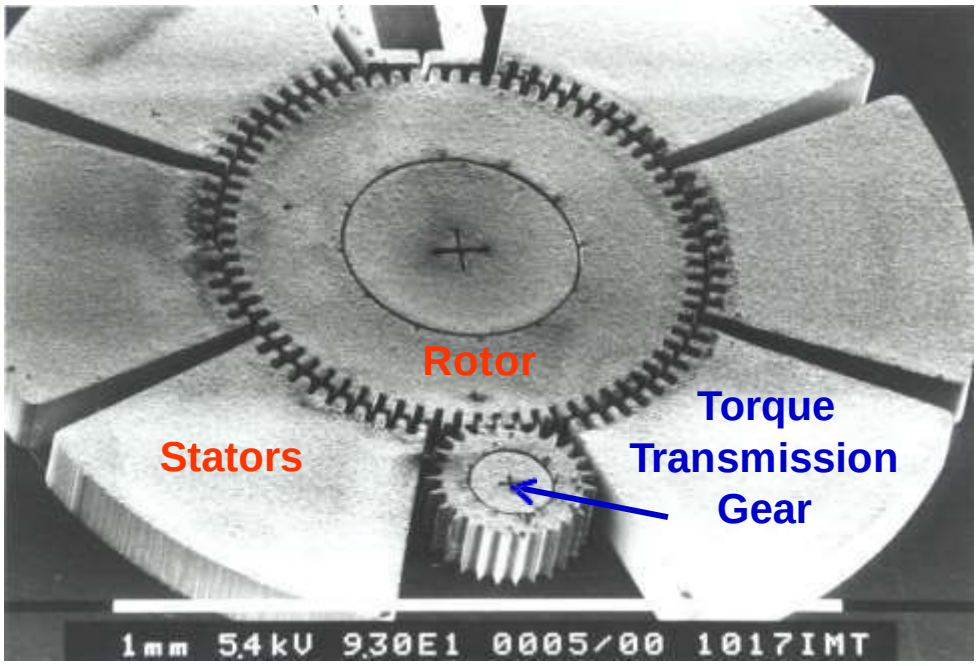


Micro pressure sensors



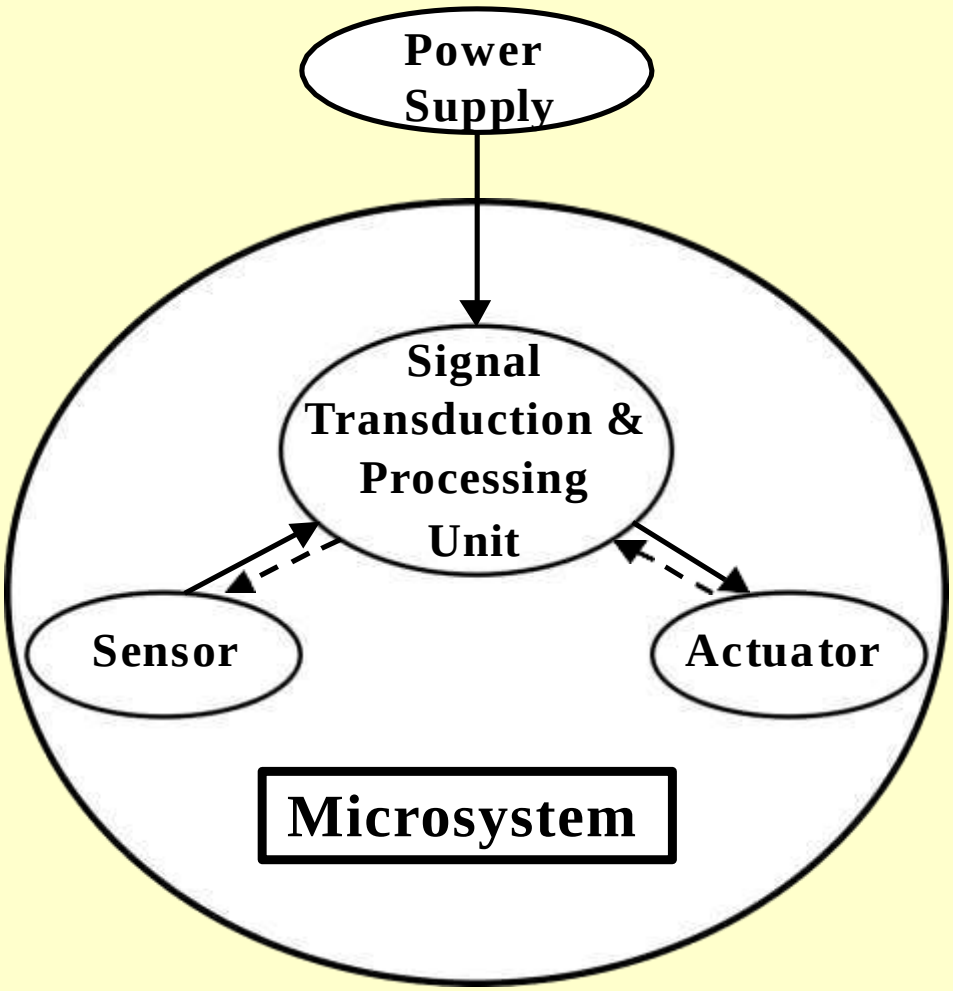
MEMS as a Microactuator-motor:





Micro motor produced by a LIGA Process

Components of Microsystems

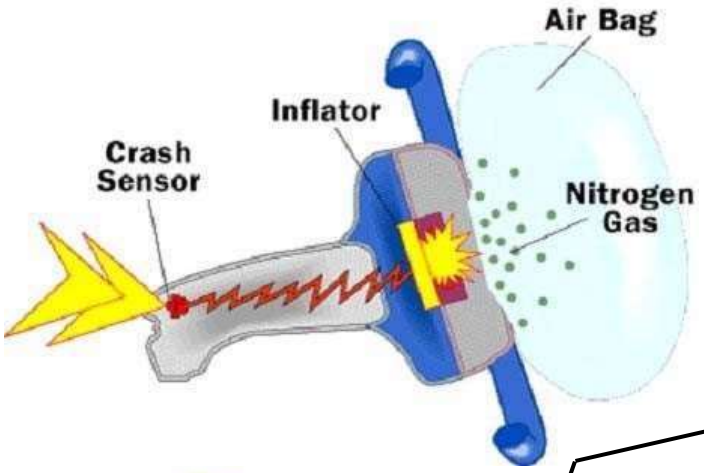


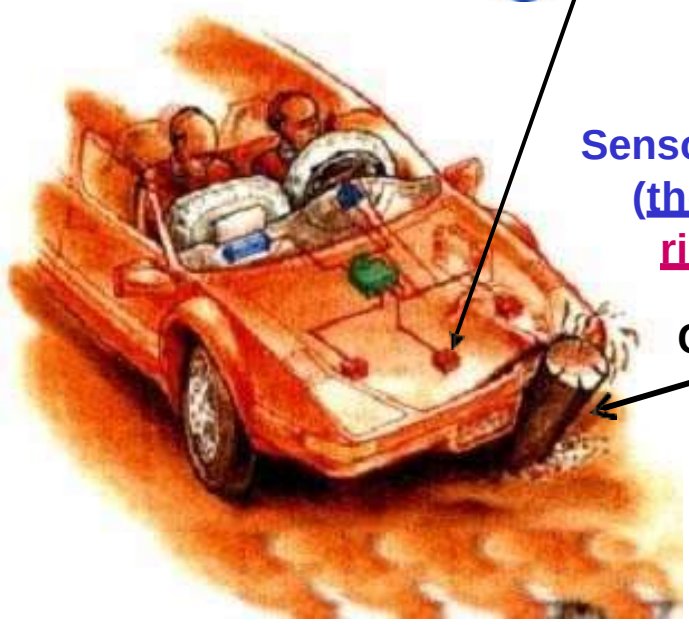
Typical Microsystems Products

Inertia Sensor for “Air Bag” Deployment System

(Courtesy of Analog Devices, Inc.)

Inertia Sensor for Automobile "Air Bag" Deployment System





Collision

Micro inertia sensor (accelerometer) in place:

Sensor-on-a-chip: (the size of a rice grain)

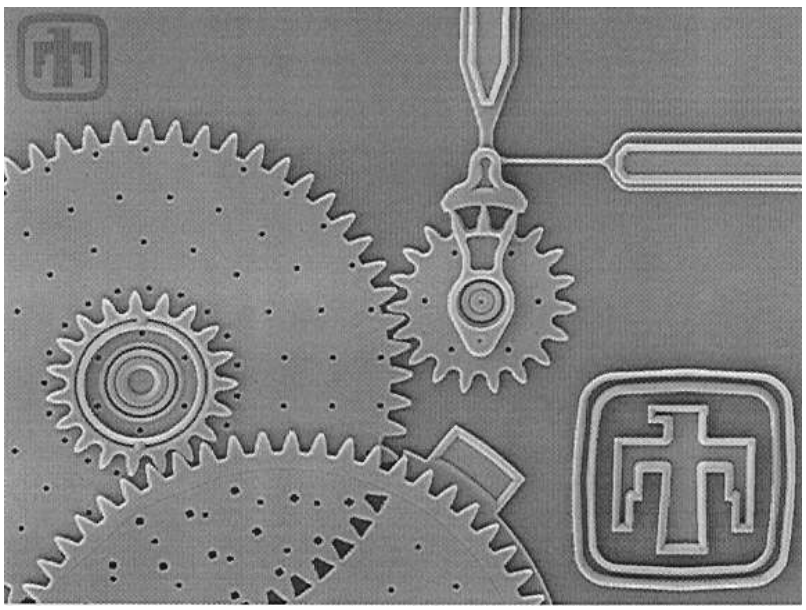
(Courtesy of Analog Devices, Inc)

Unique Features of MEMS and Microsystems

- A great challenge to engineers

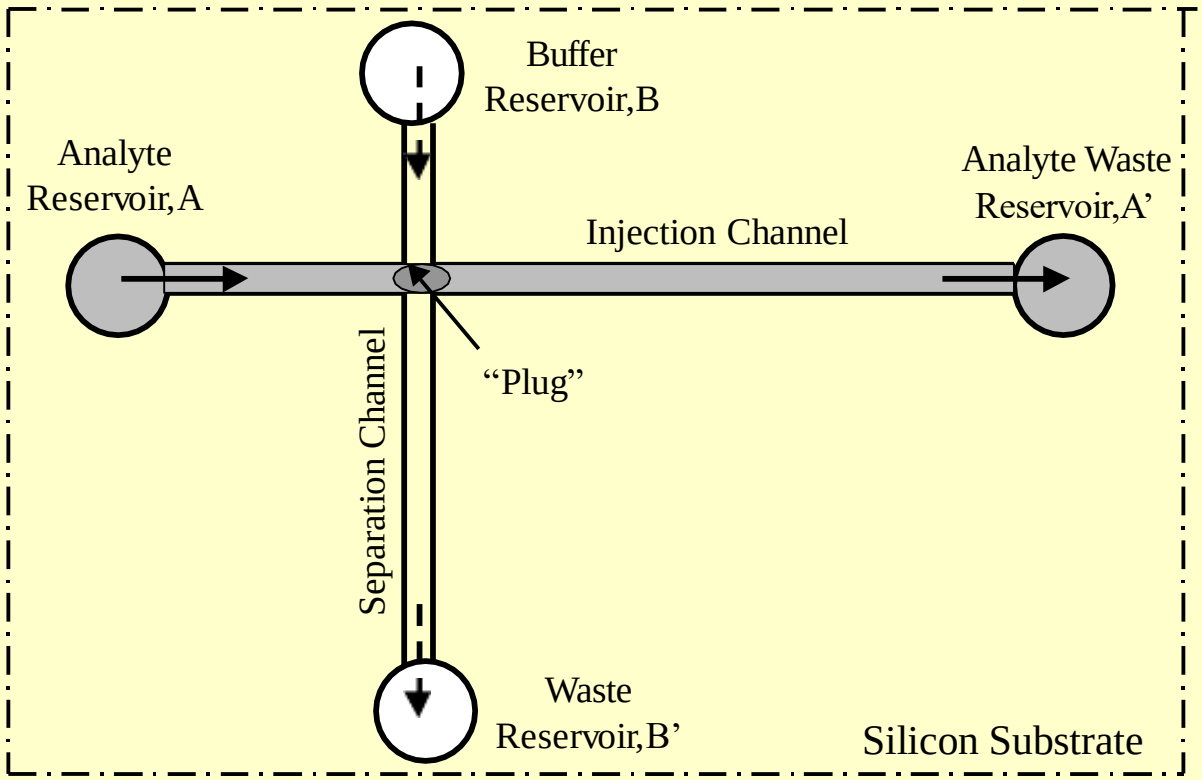
- **Components are in micrometers with complex geometry using silicon, si-compounds and polymers:**

A micro gear-train by
Sandia National Laboratories



Capillary Electrophoresis (CE) Network Systems for Biomedic Analysis

A simple capillary tubular network with cross-sectional area of 20x30 μm is illustrated below:



Work on the principle of driving capillary fluid flow by applying electric voltages at the terminals at the reservoirs.

Commercial MEMS and Microsystems Products

Micro Sensors:

Acoustic wave sensors
Biomedical and biosensors
Chemical sensors
Optical sensors
Pressure sensors
Stress sensors
Thermal sensors

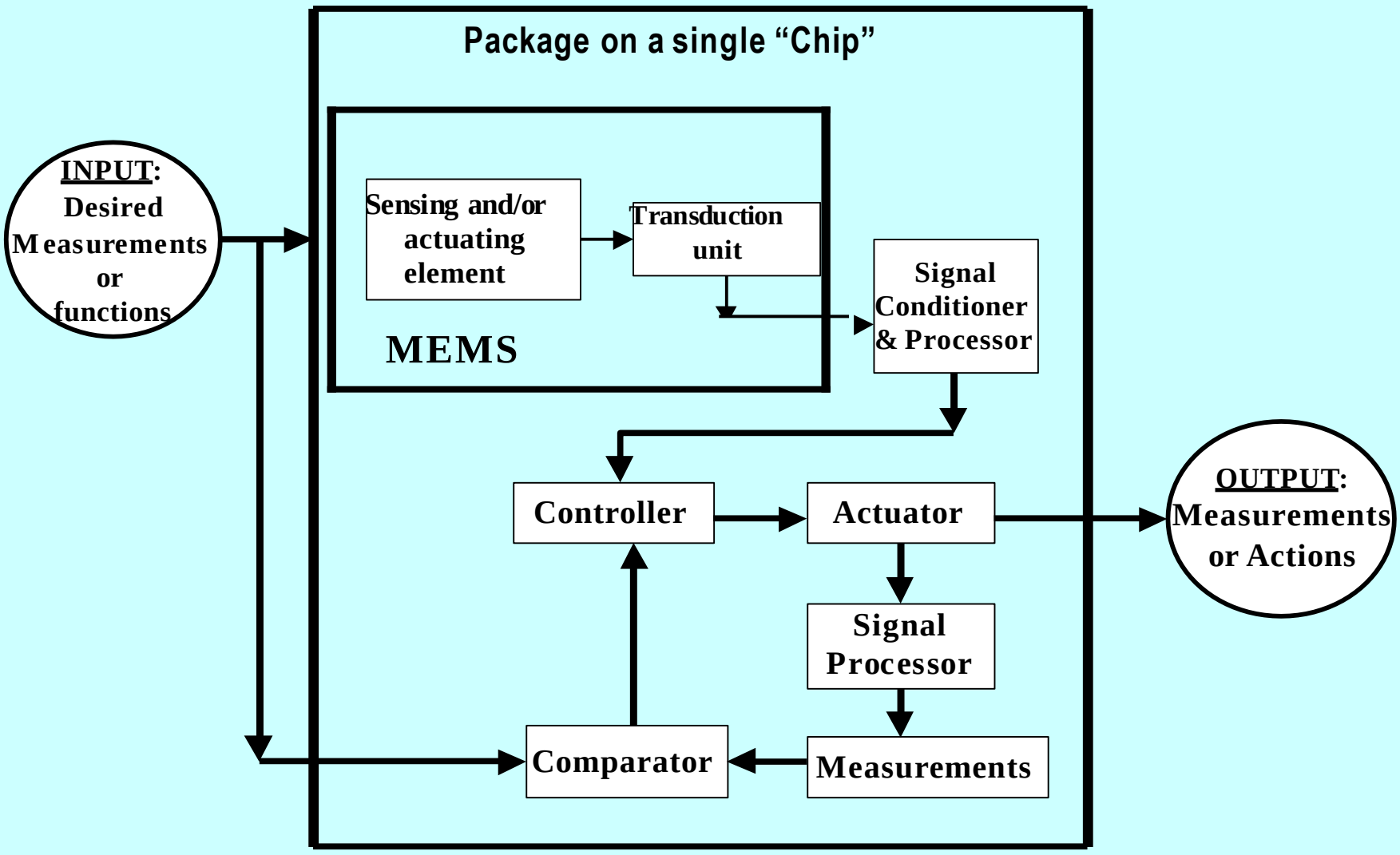
Micro Actuators:

Grippers, tweezers and tongs
Motors - linear and rotary
Relays and switches
Valves and pumps
Optical equipment (switches, lenses & mirrors, shutters, phase modulators, filters, waveguide splitters, latching & fiber alignment mechanisms)

Microsystems = sensors + actuators + signal transduction:

- Microfluidics, e.g. Capillary Electrophoresis (CE)
- Microaccelerometers (inertia sensors)

Intelligent Microsystems - Micromechatronics systems



Evolution of Microfabrication

- There is no machine tool with today's technology can produce any device or MEMS component of the size in the micrometer scale (or in mm sizes).

- The complex geometry of these minute MEMS components can only be produced by various physical-chemical processes – the microfabrication techniques originally developed for producing integrated circuit (IC) components.

Significant technological development towards miniaturization was initiated with the invention of transistors by three Nobel Laureates, W. Schockley, J. Bardeen and W.H. Brattain of Bell Laboratories in 1947.

This crucial invention led to the development of the concept of integrated circuits (IC) in 1955, and the production of the first IC three years later by Jack Kilby of Texas Instruments.

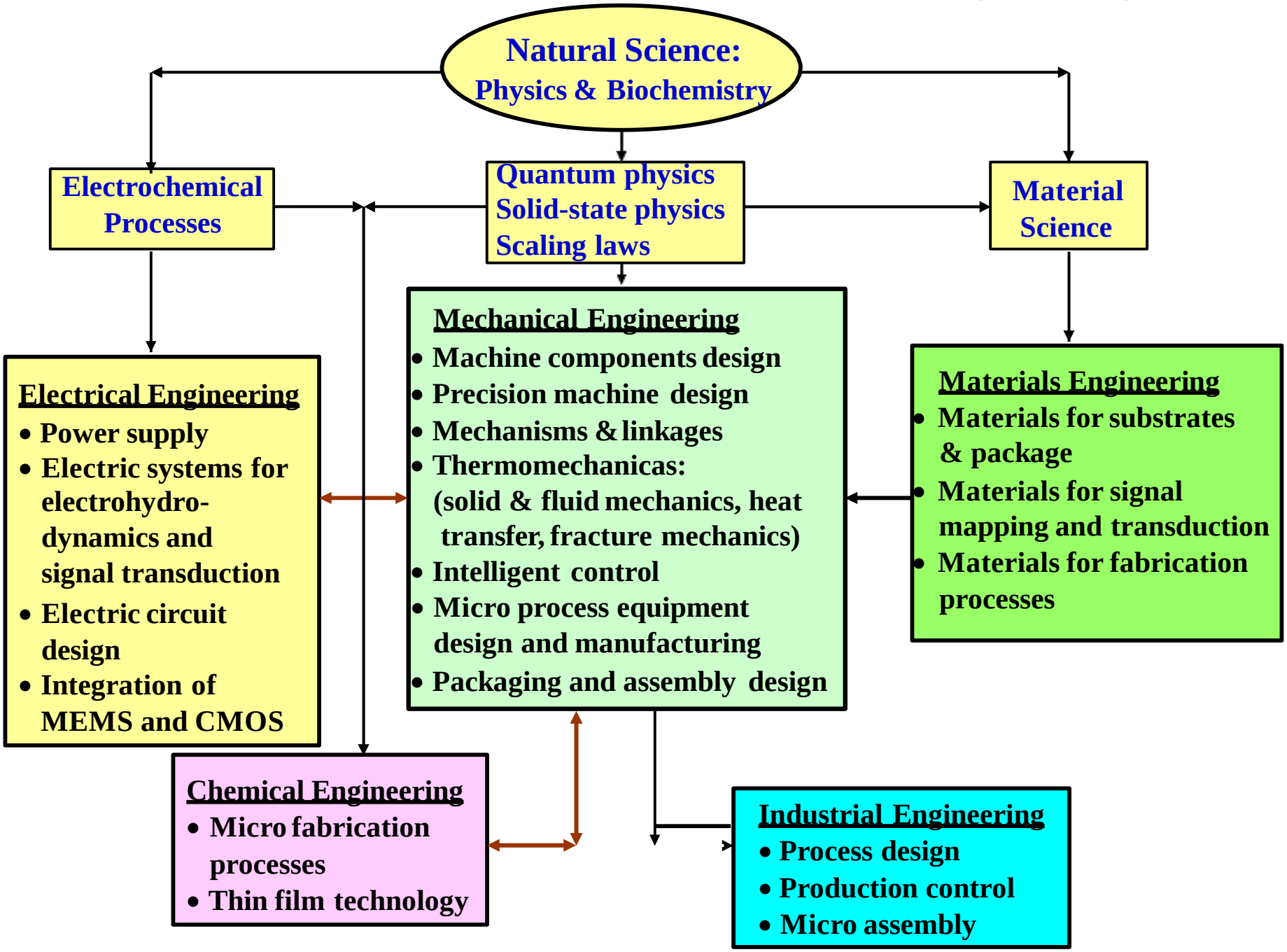
ICs have made possible for miniaturization of many devices and engineering systems in the last 50 years.

The invention of transistors is thus regarded as the beginning of the *3rd Industrial Revolution* in human civilization.

Comparison of Microelectronics and Microsystems

Microelectronics	Microsystems (siliconbased)
Primarily 2-dimensionalstructures	Complex 3-dimensionalstructure
Stationary structures	May involve movingcomponents
Transmit electricity for specific electrical functions	Performa great variety of specific biological, chemical, electromechanical andopticalfunctions
IC die is protectedfromcontactingmedia	Delicate components are interfaced with workingmedia
Use single crystal silicon dies, silicon compounds, ceramics and plastic materials	Use single crystal silicon dies and few other materials, e.g. GaAs, quartz, polymers, ceramicsand metals
Fewercomponentsto beassembled	Manymore components to be assembled
Mature ICdesign methodologies	Lack of engineering design methodologyand standards
Complex patterns with high density of electrical circuitry oversubstrates	Simpler patterns over substrates withsimpler electrical circuitry
Largenumberof electrical feed-throughand leads	Fewer electrical feed-through andleads
Industrial standardsavailable	No industrial standard to follow in design, material selections, fabrication processes andpackaging
Massproduction	Batch production, or on customer-needbasis
Fabricationtechniques are provenand well documented	Manymicrofabricationtechniques areusedfor production,but with no standardprocedures
Manufacturingtechniques are provenand well documented	Distinct manufacturingtechniques
Packagingtechnology is relatively well established	Packagingtechnology is at the infant stage
Primarily involves electrical andchemical engineering	Involves all disciplines of science and engineering

The Multi-disciplinary Nature of Microsystems Engineering



Commercialization of MEMS and Microsystems

Major commercial success:

Pressure sensors and inertia sensors (accelerometers) with worldwide market of:

- **Airbag inertia sensors at 2 billion units per year.**
- **Manifold absolute pressure sensors at 40 million units per year.**
- **Disposable blood pressure sensors at 20 million units per year.**

Recent Market Dynamics

Old MEMS	**New MEMS**
Pressure sensors	**BioMEMS**
Accelerometers	**IT MEMS for Telecommunication:**
Other MEMS	**(OptoMEMS and RF MEMS)**

Application of MEMS and Microsystems in Biomedical Industry

Disposable blood pressure transducers:
Lifetime 24 to 72 hours; annual production 20 million units/year, unit price $10

Catheter tip pressure sensors

Sphygmomanometers

Respirators

Lung capacity meters

Barometric correction instrumentation

Medical process monitoring

Kidney dialysis equipment

Micro bio-analytic systems: bio-chips, capillary electrophoresis, etc.

Chapter 1

Introduction to BioMEMS

1.1 What are BioMEMS?

BioMEMS, or *biomedical microelectromechanical systems*, has emerged as a subset of MEMS devices for applications in biomedical research and medical

microdevices.* Merging traditional MEMS devices with discussion of bioMEMS is essential, because some readers will not have engineering backgrounds or familiarity with MEMS technology. For the purpose of teaching bioMEMS, the following subjects will be covered:

(1) Microfabrication of silicon, glass, and polymer devices
(2) Microfluidics and electrokinetics
(3) Sensors, actuators, and drug-delivery systems
(4) Micro-total-analysis systems (μTAS) and lab-on-a-chip devices (LOC)
(5) Clinical laboratory medicine
(6) Detection and measuring systems
(7) Genomics, proteomics, DNA, and protein microarrays
(8) Emerging applications in medicine, research, and homeland security
(9) Packaging, power systems, data communication, and RF safety
(10) Biocompatibility, FDA, and ISO 10993 biological evaluations

The bioMEMS industry is increasing rapidly with a growth rate of 11.4%, with projected revenues of $850 million in 2003 to over $1 billion in 2006 [Rebello, 2004].

1.1.1 Fabrication

Traditional fabrication techniques previously imported from integrated circuit manufacturing to MEMS devices have undergone yet another transition for bioMEMS devices, with an increased awareness of microfluidic physics and the surface science of silicon, glass, polymers, and ceramics. Modification of surfaces for biomedical assays and biocompatibility has emerged as a complex science, with abundant opportunities for creating novel techniques and applications that can be patented and ultimately brought to market. New techniques are being developed for molding, replication, casting, and bonding that are essential for mass production with reproducibility and functional reliability at low cost, both of which are vital to the medical disposables market. In addition, the 3D construction of bioMEMS devices, not just in shape but in the embodiment of electromechanical, chemical, and biological materials, reaches beyond the basic concepts of cantilevers, inertial masses, and diaphragms of typical MEMS devices.

Fabrication process steps are becoming more complex as integrated electronics, once thought better left to side-by-side devices in the MEMS realm, are now becoming essential as microreactor chambers, and as detection schemes become incorporated into the device itself. In addition, packaging for safety and biocompatibility poses a significant challenge for the bioMEMS engineer.

*In Europe the term *microsystem or microstructure technology* (MST) is used instead of MEMS.

1.1.2 Structure

BioMEMS devices can typically be considered as having at least one feature's dimension in the submicron to micron range (~100 nm–200 μm), and other dimensions of up to several millimeters. On one end of the application scale they may be the platform for nanotechnologies, while on the other end they may be the key component to a much larger device such as a medical imaging machine. They may operate *in vivo* or *in vitro* (inside or outside a living system), and have self-contained or external power sources. They may be *smart systems* with integrated microprocessors, and operate as either an open-ended (sensor or actuator) system or a closed-loop system (autoregulation). They may be all encompassing devices, but more typically they are integrated with other components and perform one or more functions in a chain of operations connected by tubing or other conduits. Implanted devices may be part of a distributed system such as fiber optic sensors that provide continuous information via light from various parts of the body to a central medical device.

Among the advantages of biochip miniaturization are lower manufacturing costs, reproducibility, small sample size, and reagent use. Improved signal-to-noise ratio, improved response time, precise control of mixing, reacting, and discarding of waste products, in-line or embedded detection methods, and high throughput are also advanceges of miniaturized biochips.

1.1.3 Goal of this book

Upon completing this book you will have acquired an understanding of the many necessary skills for conceiving, and designing bioMEMS and medical microdevices, and for applying them to research and medicine. This includes fabrication with silicon, glass, and polymers substrates; covalent and noncovalent surface modifications; self-assembled monolayers (SAMs); transport processes such as laminar flow and electrokinetic phenomena (electro-osmosis, electrophoresis, dielectrophoresis, and electrowetting); and sensor and actuator concepts.

Next you will learn about micro-total-analysis systems (μTAS) and lab-on-a-chip (LOC) devices, and basic genomics and proteomics as a prelude to DNA and protein microarrays. You will also develop an understanding of biocompatibility based on the ISO 10993 Standard, and the options for powering and packaging devices to obtain optimal performance and safety.

Although this book is suitable for a one-semester course at the graduate level, instructors may additionally incorporate a laboratory experience to provide hands-on design and fabrication of a bioMEMS device. Moreover, this book may serve as useful extension for a MEMS engineering class, technology management course, or elective study for anyone in related fields.

1.2 The Driving Force Behind Biomedical Applications

1.2.1 Diagnostics

The acceleration of new biomedical instrumentation in recent years is due in part to the demand for higher-quality medical care, especially in highly developed countries. This includes an emphasis on preventive care, accuracy, and minimally invasive procedures [Dario et al., 2000].

By improving current techniques for sample preparation and assay of blood, urine, cerebral spinal fluid, extracts, cells, cultures, and tissues diagnostic systems can be improved. Additionally, new technologies in microfluidics and lab-on-a-chip design provide new types of studies that were unimaginable ten years ago. This is especially true in genomics. The physics and implementation of these microfluidic devices and the necessary detection schemes are investigated thoroughly in later chapters.

1.2.1.1 Health screening

Screening studies as part of a *preventive medicine examination* for early disease detection has taken on both a social and economic importance as patients desire to remain healthy. An emphasis on *evidence-based medicine* has been occurring, where a specific study or treatment is prescribed because it is supported by the current literature. Unfortunately this method is subject to debate, and some studies and treatments may be unjustly denied by payors who decide themselves what is an appropriate test or procedure. Clearly, in these matters there is a conflict of interest.

Another expression commonly heard is *best medical practices*. From the payors perspective this provides a predictable cost, limit to liability, and an ability to *minimally* meet a patient's needs. There is also the opportunity to reduce adverse outcomes and collectively improve quality of care. From the physician's perspective there may be a disagreement as to what an appropriate test or procedure is, and revisions to the list of acceptable studies and procedures may be incremental (in years) rather than continuous. Analogous to this is the use of incentive payments to medical clinics to perform in a certain manner, occasionally at odds with what is best for the patient, or creating unhealthy competition between centers for bonuses. Data collection and data mining are important as we move forward in understanding diseases and the consequences of the treatments offered. This has the allure to legislators and patients because it appears that healthcare is not *substandard*. This also has an allure to medical centers that by virtue of size, organization, and computer resources are more comfortable with a uniform approach to patient management and data collection.

The irony is that as patients move from one health plan to another as a result of changing employers or retire, there is little economic incentive to consider the long-term benefits of preventive medicine. This is very important to the future of bioMEMS. Although new technologies may ultimately reduce rather than increase the cost of healthcare, they may not be perceived as valuable when the payor is operating on a short economic horizon.

To the engineer this may sound a bit scary. Ideally we strive to identify a problem—usually in concert with the medical community—and try to design, test, and implement a device that will be accurate, useful, safe, and low cost. We avoid the broader economic issues, or hope that someone else will deal with them. However, given the several-year timeline and costs for a new device, all of these factors must be considered in advance.

1.2.1.2 Individualized treatment

"Personalized medicine" or individualization of treatment based on matching the right therapy to the right patient derives from six technologies and approaches [Jain, 2002]: (1) molecular diagnostics, particularly single nucleotide polymorphism (SNP) genotyping; (2) integration of diagnostics with therapy, (3) monitoring of therapy; (4) pharmacogenomics; (5) pharmacogenetics; and (6) pharmacoproteomics.

Genomic medicine uses genotypic analysis to improve medical care by identifying those individuals with a predisposition to a disease, preventive intervention, selection of pharmacotherapy, and individual design of medical care based on genotype. DNA and protein microarray chips offer the ability to screen for numerous genetic traits rapidly and inexpensively, and will be an acceptable part of medical practice during the next decade.

Pharmacogenetics concerns the study of the influence of genetic factors on the action of drugs. This includes study of the drug metabolism and pharmacological effects, predicting genetically determined adverse reactions, and drug discovery and development. *Pharmacogenomics* is the application of genomics to drug discovery and development, and involves the study of mechanisms of drug action on cells as revealed by gene expression patterns. *Pharmacoproteomics* is the application of proteomics to drug discovery and development. Patients subtyped based on protein analysis may help to match a particular target-based therapy to a particular marker in a subgroup of patients.

The two most important technologies relevant to personalized medicine are SNP genotyping and the DNA microarray chip. SNPs are small stretches of DNA that differ by only one base pair and serve to distinguish one individual's genetic material from that of another. Identification of SNPs is important in understanding the genetic basis of common human disease. Potential uses for SNP markers include drug discovery and prediction of adverse effects of drugs [Jain, 2002].

DNA and protein microarray chips in personalized medicine offer (1) storage of a patient's genomic information, (2) SNP genotyping, (3) genetic screening for detection of mutations, (4) gene expression profiling, (5) diagnosis and prognosis of cancer, (6) drug safety for pharmacogenetics, (7) monitoring of pathogens and resistance in infections, and (8) stratification of patients in clinical trials.

The downside to genomic medicine includes knowing more than we may want to know about our future, unnecessary preemptive treatment (when waiting may allow for better therapeutic intervention with newer technology or understanding), loss of privacy as employers and government agencies take note of groups with certain genetic markers, discrimination based on genetic profiling, and insurability as insurers select or rate applicants based on genetic predisposition to certain diseases.

1.2.2 Drug-delivery systems

Micro devices allow precise drug delivery by both implanted and transdermal techniques. There are active devices with powered actuators for dispensing minute quantities of drugs (for example, through microneedles) as opposed to passive devices that rely on diffusion of medication via hydrogels and transdermal patches.

Most devices are simple reservoirs that dispense drugs in response to an external command. New smart systems may offer closed-loop sensing and assaying with onboard interpretation of results and automatic titration of drugs (or hormones). The convenience of these systems, improved response time, and precise regulation of the medical condition (e.g., glucose level in a diabetic patient) will be the driving force behind these technologies.

Having said this, it must also be understood that there are few drug-delivery devices in actual use today, and the technical challenge of producing these systems is enormous.

1.2.3 Tissue engineering

This emerging technology represents a substantial portion of the bioMEMS literature, and applies the principles of biology and engineering to the development of viable substitutes that restore, maintain, or improve the function of human tissue [Dario et al., 2000]. Applications driving this technology include the need for nerve regeneration, organ repair and replacement, and development of a suitable skin grafting material. Tissue-scaffolding devices, various sensor and stimulating electrodes, and electroactive polymers as muscle substitutes are but a few of the new technologies.

1.2.4 Minimally invasive procedures

Endoscopic techniques using fiber optic instruments and small percutaneous operating ports, rather than wide-open excisions have largely replaced traditional methods for minor joint procedures and cholecystectomies (excision of the gallbladder). Reduced operative time, lower risk for infection, less trauma and discomfort, shorter hospital stays, and ultimately lower costs are the driving force behind these technologies.

The challenge for new instrumentation to accomplish minimally invasive procedures exemplifies the need for a close working relationship between the physician and engineer. In addition to providing an alternative to some traditional surgical procedures, minimally invasive procedures offer opportunities for therapies never imagined before. These include targeting specific tumors and other organs for drug delivery; microvisualization and manipulation; and implantation of microsensors and microactuators, and other components of a larger implanted device or external system.

1.3 Biocompatibility

The ISO 10993 Standards define in eighteen subparts criteria to meet for biological evaluation of medical devices (the International Standards Organization is represented in the United States by ANSI, the American National Standards Institute).[†]

The standards (numbered by subpart) include: (1) overview of evaluation and testing; (2) animal welfare requirements; (3) tests for genotoxicity, carcinogenicity, and reproductive toxicity; (4) selection of tests for interaction with blood; (5) test for in-vitro cytotoxicity; (6) tests for local effects after implantation; (7) ethylene-oxide sterilization residuals; (8) selection and quantification of reference materials for biological tests; (9) framework for identification and quantification of potential degradation products; (10) tests for irritation and delayed-type hypersensitivity; (11) tests for systemic toxicity; (12) sample preparation and reference materials; (13) identification and quantification of degradation products from polymeric medical devices; (14) identification and quantification of degradation products from ceramics; (15) identification and quantification of degradation products from metals and alloys; (16) toxicokinetics study design for degradation products and leachables; (17) establishment of allowable limits for leachable substances; (18) chemical characterization of materials; and (19) physicochemical, mechanical, morphological, and topographical characterization of materials.

Packaging of bioMEMS devices is important when considering biocompatibility, and is discussed in Chapter 14, Packaging, Power, Data and RF Safety, followed by Chapter 15, Biocompatibility, FDA and ISO 10993.

1.4 Reliability Considerations

BioMEMS devices must perform safely and reliably to be commercially successful. Reliability issues are introduced now because of the tendency for engineers to postpone such analysis until well into product development.

Reliability is defined by Pan (2004, adopted from others) as "the probability that a component, device, or system will perform its prescribed duty without

[†]www.ansi.org

failure, for a given period of time, when operated correctly in a specified environment." Predictability and reproducibility of devices and their manufacturing processes are essential. Mechanical limits such as fatigue and wear; isolation concerns such as dividing membranes and seals; performance issues such as pump operation, clogging of microfluidic channels or barriers, "biofouling" or interference of function based on biological responses to implanted devices; and accuracy related to sample size and physics of the micro-environment all must be considered. These issues are not confined to surgery, drug delivery, and implantable devices. A clinical laboratory machine that assays biological material or an imaging machine that visualizes internal organs could indirectly inflict significant morbidity and mortality if not operating reliably. Life-and-death decisions are made regularly based on laboratory results and review of x-rays, ultrasounds, and CT and MRI scans. Often decisions are made quickly (e.g., in the Emergency Department) without opportunity for waiting or performing confirming studies.

Implantable devices provide a challenge not unlike designing a satellite for space communication. Implanted devices are exposed to a harsh environment, may have onboard power systems or a means for obtaining power, usually need telemetry systems for communicating data and self-diagnostics, require redundancy systems for critical functions, and must operate and be programmed without physical contact from the outside world.

1.5 Regulatory Considerations

The driving forces behind bioMEMS reliability typically include one or more governing agencies (depending on the country) and product liability. The cost for a product recall, both monetarily and in goodwill, can be enormous.

In the United States, the *Food and Drug Administration* (FDA) impacts bioMEMS development the most. The Clinical Laboratories Amendments (CLIA) and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) indirectly influence bioMEMS development by their monitoring of healthcare delivery. Clinical laboratories must conform to a number of requirements imposed by CLIA and JCAHO.

1.5.1 Food and Drug Administration (FDA)

The Food and Drug Administration (FDA) is part of the U.S. Department of Health and Human Services. The FDA regulates food, drugs, medical devices, biologics (vaccines and blood products), animal feed and drugs, cosmetics (safety and labeling), radiation-emitting products (cell-phones, lasers, and microwaves), and combination products. The FDA participates in the publication of The Federal Register, which contains The Code of Federal Regulations (CFR), a code of general rules established by the Executive departments and agencies of the federal government.

The FDA Center for Devices and Radiological Health (CDRH), and its Offices of Device Evaluation (ODE) and In Vitro Diagnostic Device Evaluation and Safety (OIVD) are responsible for approving new medical devices.

The CDRH is responsible for regulating firms who manufacture, repackage, relabel, and/or import medical devices sold in the United States. In addition, CDRH regulates radiation emitting electronic products (medical and non-medical) such as lasers, x-ray systems, ultrasound equipment, microwave ovens and color televisions.

Medical devices are sorted into Classes I–III, through which regulatory control increases incrementally. The device classification defines the regulatory requirements for a general device type. The basic regulatory requirements that manufacturers of medical devices distributed in the United States must comply with are: (1) premarket notification 510(k), unless exempt, or premarket approval (PMA); (2) establishment registration on form FDA-2891; (3) medical device listing on form FDA-2892; (4) quality system (QS) regulation; (5) labeling requirements; and (6) medical device reporting (MDR).

The FDA is also responsible for the Good Manufacturing Practice (GMP) requirements, which require that domestic or foreign manufacturers have a quality system for the design, manufacture, packaging, labeling, storage, installation, and servicing of finished medical devices intended for commercial distribution in the United States. The regulation requires that various specifications and controls be established for devices; that devices be designed under a quality system to meet these specifications; that devices be manufactured under a quality system; that finished devices meet these specifications; that devices be correctly installed, checked and serviced; that quality data be analyzed to identify and correct quality problems; and that complaints be processed.

The FDA maintains two databases through its CDRH division for collected device experience reports on medical devices that may have malfunctioned or caused a death or serious injury. These are the Medical Device Reporting (MDR) and the Manufacturer and User Facility Device Experience (MAUDE) databases. The MDR files contain reports received under both the mandatory Medical Device Reporting Program (MDRP) from 1984–1996, and voluntary reports up to June 1993. The database currently contains more than 600,000 reports. The MAUDE data consists of all voluntary reports since June 1993, user facility reports since 1991, distributor reports since 1993, and manufacturer reports since August 1996. The database currently contains about 1.2 million reports.[‡]

CDRH has also implemented the FDA's Good Guidance Practices (GGPs). These include the processing, content, and evaluation of regulatory submissions; the design, production, manufacturing, and testing of regulated products; and inspection and enforcement procedures. The guidance documents are updated regularly, and public submission for topics is requested. A list of the current guidance

[‡]www.fda.gov

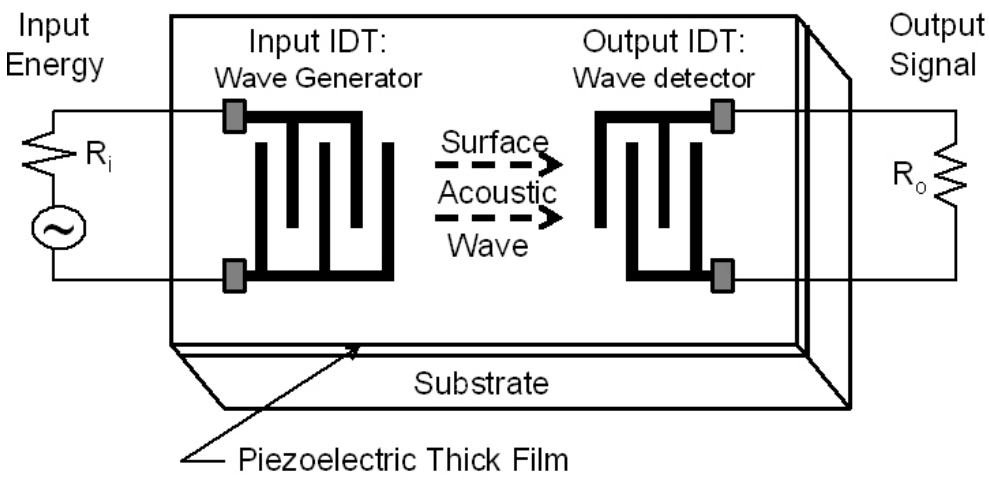
Acoustic Wave Sensors

Acoustic wave sensor does not related to the sensing of acoustic waves transmitted in solids or other media, as the name implies.

Primary application of these sensors is to act like “band filters” in mobile telephones and base stations.

Other applications include:

- Sensing of torques and tire pressures
- Sensing biological and chemical substances
- Sensing vapors, humidity and temperature
- Monitor fluid flow in microfluidics



- 2 sets of “Interdigital Transducers” (IDT) are created on a piezoelectric layer attached to a tiny substrate as shown
- Energize by an AC source to the “Input IDT” will close and open the gaps of the finger electrodes, and thus surface deformation/ stresses transmitting through the piezo-electric material
- The surface deformation/stresses will cause the change of finger electrodes in the “Output IDT”
- Any change of material properties (chemical attacks) or geometry due to torques will alter the I/O between the “Input IDT” and “Output IDT.”
- The sensing of contact environment or pressure can thus be accomplished

BioMEMS

The term "**BioMEMS**" has been a popular terminology in the MEMS industry in recent years due to the many break-through in this technology, which many believe to be a viable lead to mitigate the sky-rocketing costs in healthcare costs in many industrialized countries.

BioMEMS include the following three major areas:

(1) Biosensors for identification and measurement of biological substances,

(2) Bioinstruments and surgical tools, and

(3) Bioanalytical systems for testing and diagnoses.

Major Technical Issues in BioMEMS Products:

(1) Functionality **for the intended biomedical operations.**

(2) Adaptive **to existing instruments and equipment.**

(3) Compatibility **with biological systems of the patients.**

(4) Controllability, mobility, and easy navigation **for operations such as those required in laparoscope's surgery.**

(5) Functions of MEMS structures with high aspect ratio (defined as the ratio of the dimensions in the depth of the structure to the dimensions of the surface)

Note: Almost all bioMEMS products are subjected to the approval for marketing by the FDA (Food and Drug Administration) of the US government.

Biomedical Sensors and Biosensors

These sensors are extensively used in medical diagnosis, environmental protection, drug discovery and delivery, etc.

Biomedcial Sensors

For the measurements of biological substances in the sample and also for medical diagnosis purposes.

Input signal: Biological sample (e.g., blood samples or body fluids typically in minute amount in µL or nL)

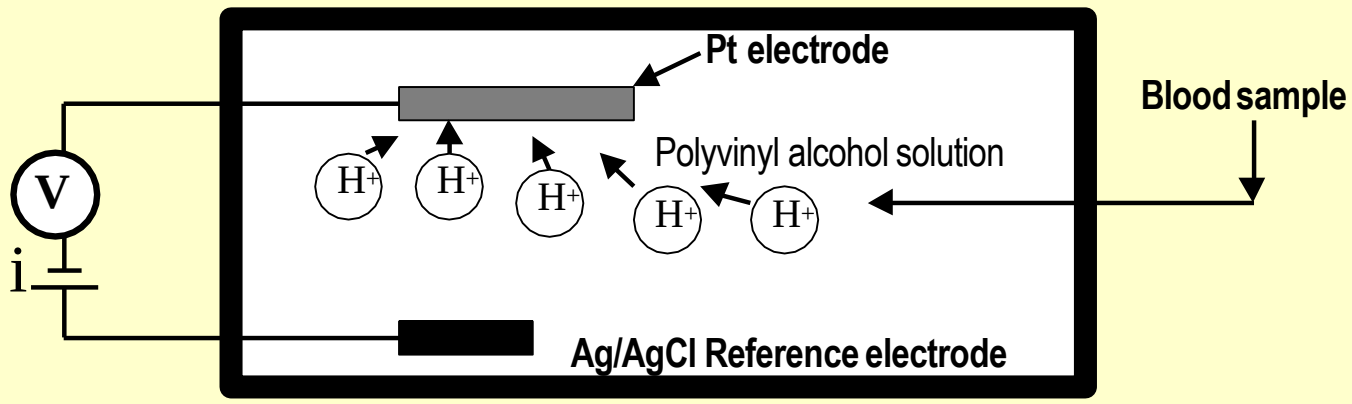
Microsensing element: a chemical that reacts with the sample.

Transduction unit: the product of whatever the chemical reactions between the sample and the chemical in the sensing element will convert itself into electrical signal (e.g. in milli volts, mV).

Output signal: The converted electrical signal usually in mV.

Example of a biomedical sensor:

A sensor for measuring the glucose concentration of a patient.



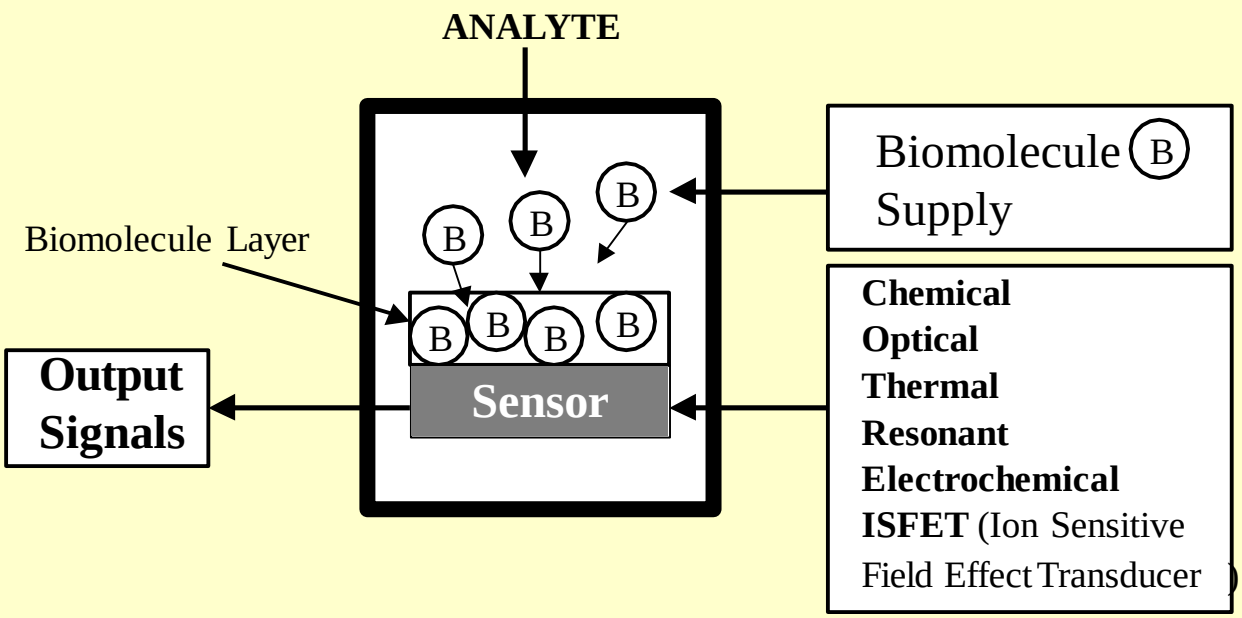
Working principle:

- The glucose in patient's blood sample reacts with the O_2 in the polyvinyl alcohol solution and produces H_2O_2.
- The H_2 in H_2O_2 migrates toward Pt film in a electrolysis process, and builds up layers at that electrode.
- The difference of potential between the two electrodes due to the build-up of H_2 in the Pt electrode relates to the amount of glucose in the blood sample.

Biosensors

These sensors work on the principle of interactions between the biomolecules in the sample and the analyte (usually in solution) in the sensor.

Signal transduction is carried out by the sensing element as shown below:



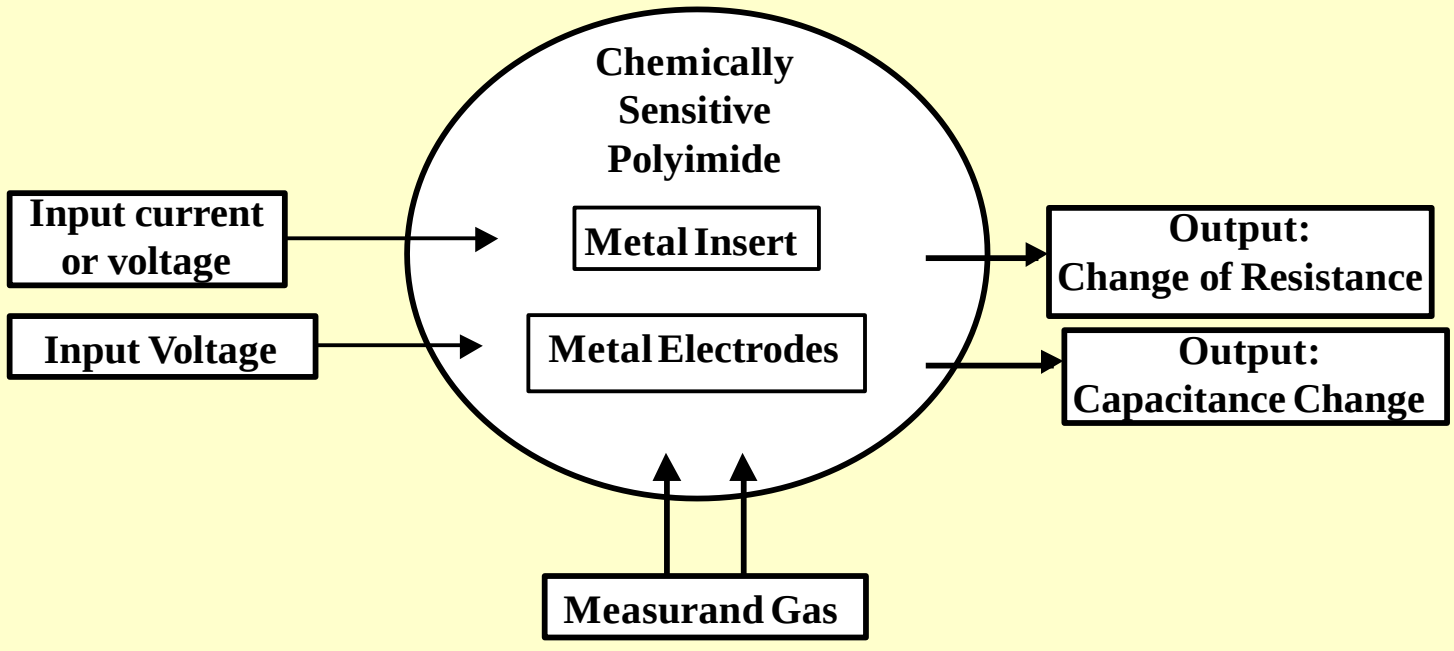
Chemical Sensors

Work on simple principles of chemical reactions between the sample, e.g. ,O_2 and the sensing materials, e.g., a metal.

Signal transduction is the changing of the physical properties of the sensing materials after specific type of chemical reactions.

There are four (4) common types of chemical sensors:

(1) Chemiresistor sensors.
(2) Chemicapacitor sensors.



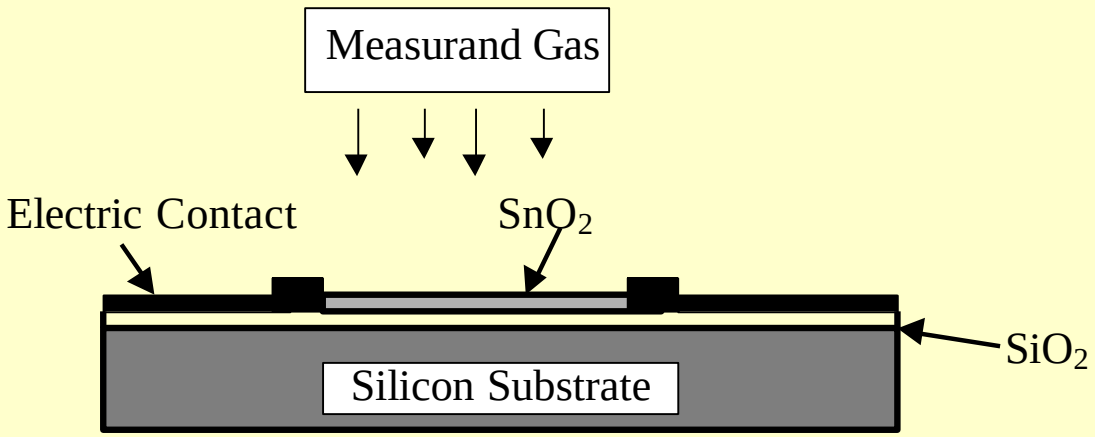
Chemical Sensors-Cont'd

(3) Chemimechanical sensors:

Work on certain materials (e.g. polymers) that change shapes when they are exposed to chemicals. Measuring the change of the shape of the sensing materials determines the presence of the chemical.

(4) Metal oxide gas sensors:

Sensing materials: certain semiconducting materials, e.g., SnO_2 change their electrical resistance when exposed to certain chemicals.



Chemical Sensors-Cont'd

Available metal oxide gas sensors:

Semiconducting Metals	Catalyst Additives	Gas to be Detected
$BaTiO_3/CuO$	La_2O_3, $CaCO_3$	CO_2
SnO_2	Pt + Sb	CO
SnO_2	Pt	Alcohols
SnO_2	Sb_2O_3	H_2, O_2, H_2S
SnO_2	CuO	H_2S
ZnO	V, Mo	Halogenated hydrocarbons
WO_3	Pt	NH_3
Fe_2O_3	Ti-doped + Au	CO
Ga_2O_3	Au	CO
MoO_3	None	NO_2, CO
In_2O_3	None	O_3

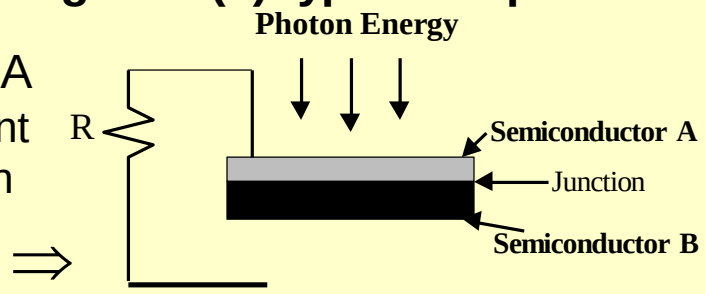
Optical Sensors

- **These sensors are used to detect the intensity of lights.**

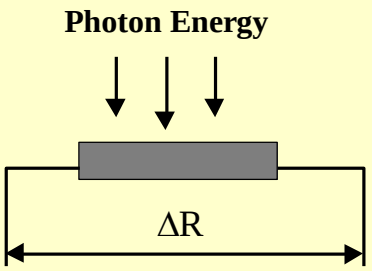
- **It works on the principle of energy conversion between the photons in the incident light beams and the electrons in the sensing materials.**

- **The following four (4) types of optical sensors are available:**

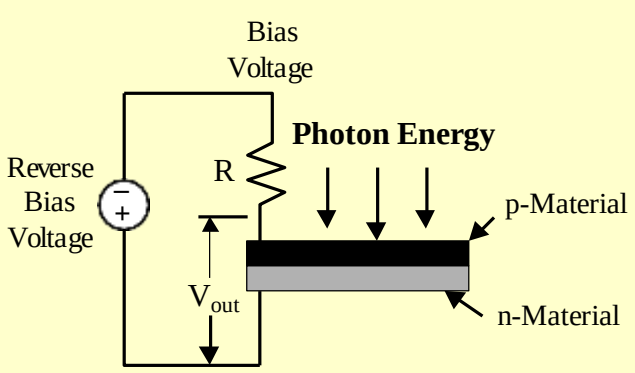
Semiconductor A is more transparent to photon energy in incident light



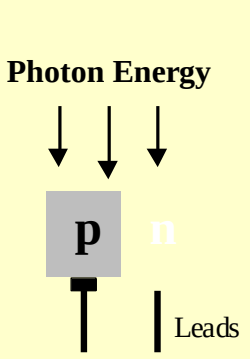
(a) Photovoltaicjunction



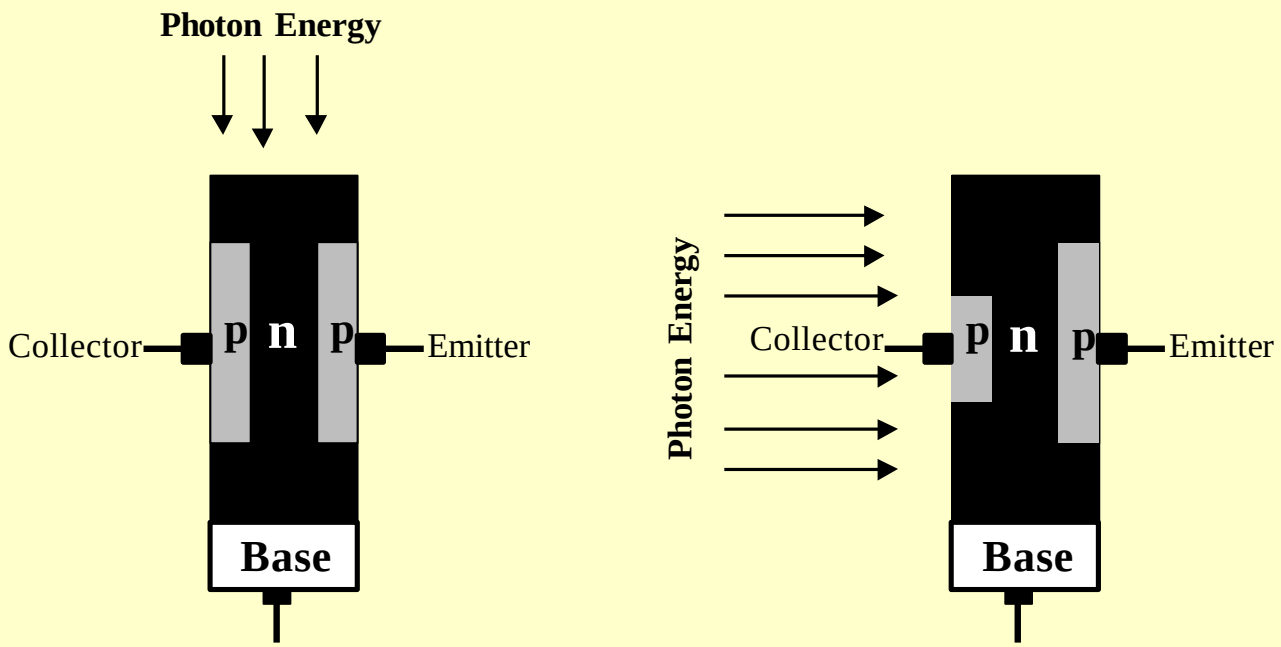
(b) Photoconductive device



(c) Photodiodes



Optical Sensors-Cont'd



(d) Phototransistors

Silicon (Si) and Gallium arsenide (GaAs) are common sensing materials. GaAs has higher electron mobility than Si- thus higher quantum efficiency.

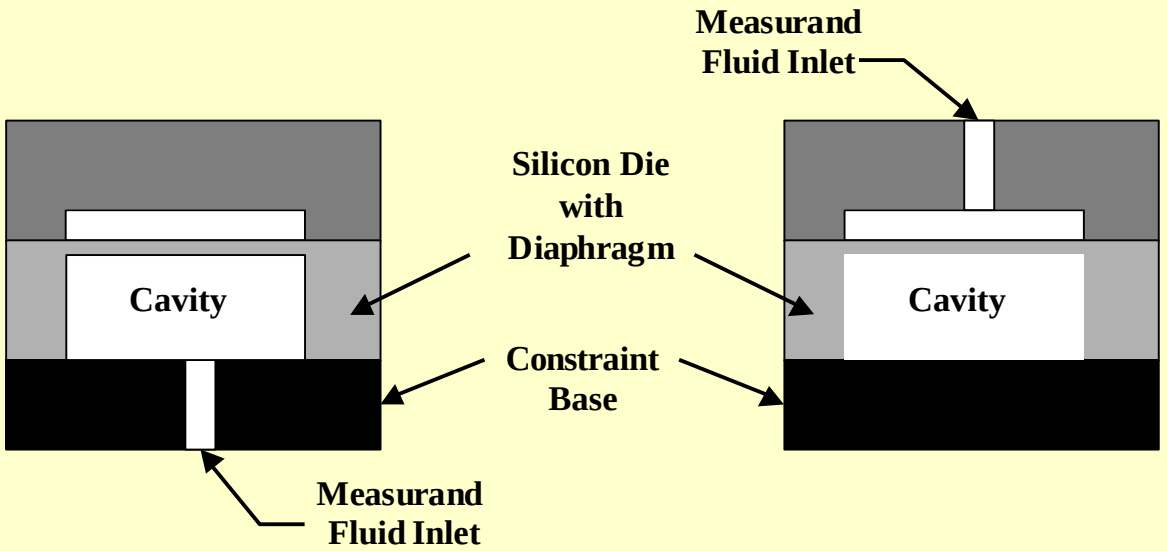
Other materials, e.g. Lithium (Li), Sodium (Na), Potassium (K) and Rubidium (Rb) are used for this purpose.

Pressure Sensors

- Micro pressure sensors are used to monitor and measure minute gas pressure in environments or engineering systems, e.g. automobile intake pressure to the engine.

- They are among the first MEMS devices ever developed and produced for "real world" applications.

- Micro pressure sensors work on the principle of mechanical bending of thin silicon diaphragm by the contact air or gas pressure.

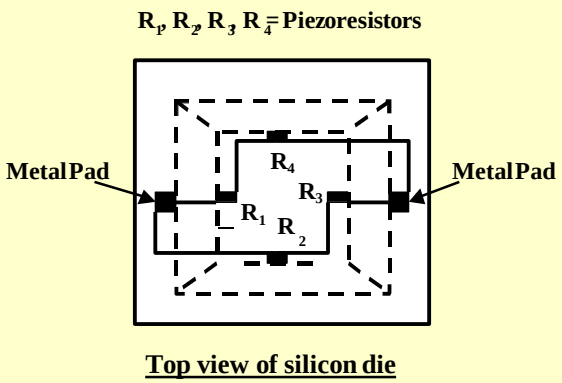


(a) Back side pressurized

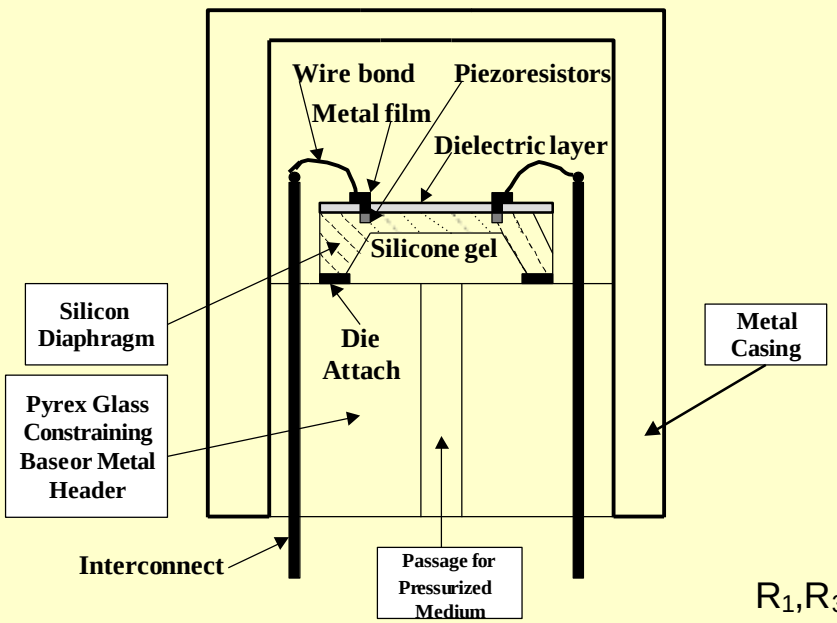
(b) Front side pressurized

Pressure Sensors-Cont'd

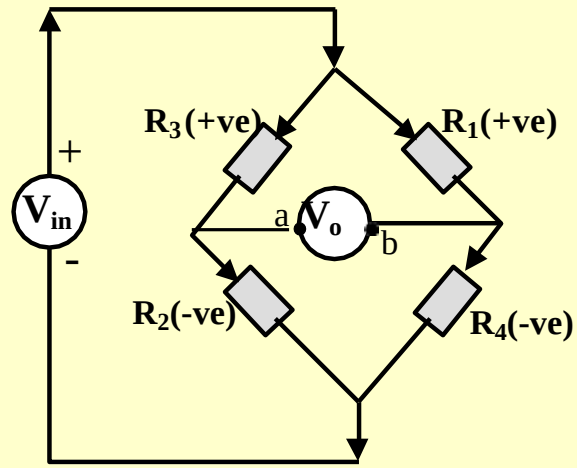
- **The strains associated with the deformation of the diaphragm are measured by tiny "piezoresistors" placed in "strategic locations" on the diaphragm.**



Top view of silicon die



- **These tiny piezoresistors are made from doped silicon. They work on the similar principle as "foil strain gages" with much smaller sizes (in μm), but have much higher sensitivities and resolutions.**



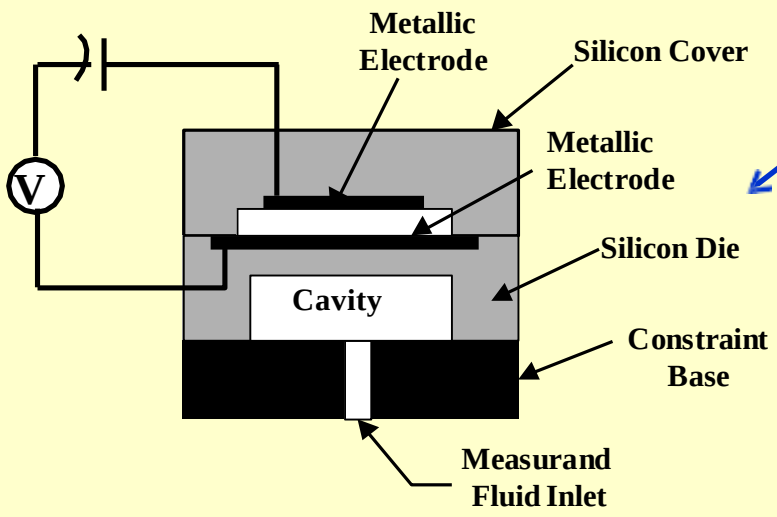
Wheatstone bridge for signal transduction

$$V_o = V_{in}\left(\frac{R_1}{R_1 + R_4} - \frac{R_3}{R_2 + R_3}\right)$$

R_1,R_3 = resistance induced by longitudinal and transverse stresses
R_2,R_4 = reference resistors

Pressure Sensors-Cont'd

- **Other ways of transducing the deformation of the diaphragm to electronic output signals are available, e.g.,**

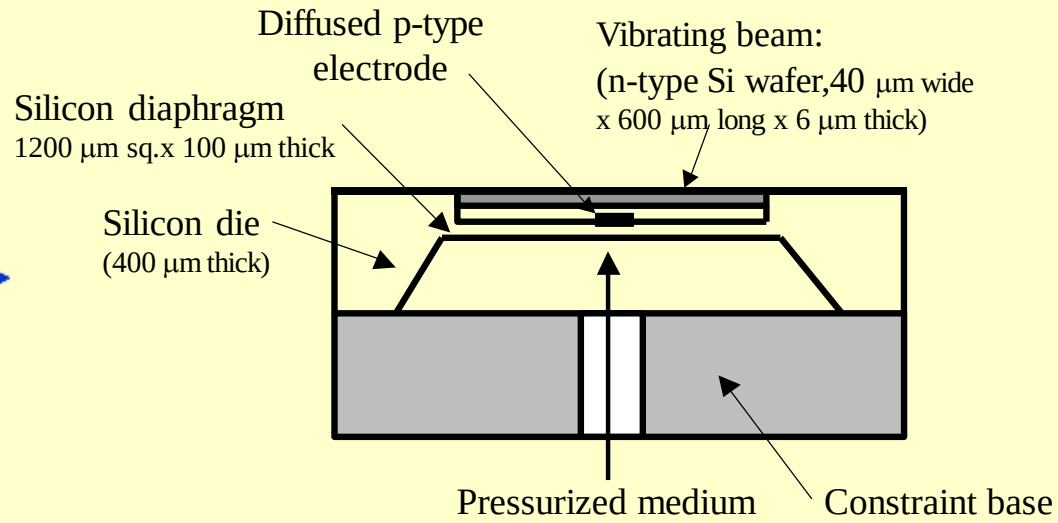


Signal output: capacitance changes
(for higher temperature applications)

$$C = \varepsilon_r \varepsilon_o \frac{A}{d}$$

ε_r= Relative permittivity = 1.0 with air
ε_o= Permittivity in vacuum = 8.85 pF/m
A = Overlap area
D = Gap between plate electrodes

By resonant vibration
(for higher resolutions)
Signal output: Shift of resonance frequencies by change of stresses in lower plate electrode by applied pressure loading



Two Common Types of Micro Pressure Sensors

Sensors using piezoresistors:

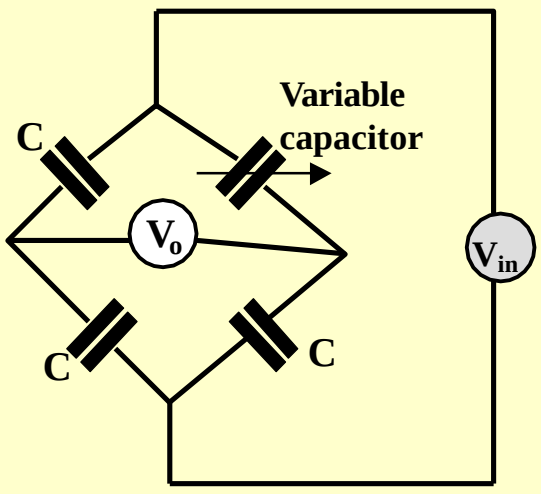
- Small in size
- Linear I/O relation
- Temperature sensitive

Sensors using capacitances:

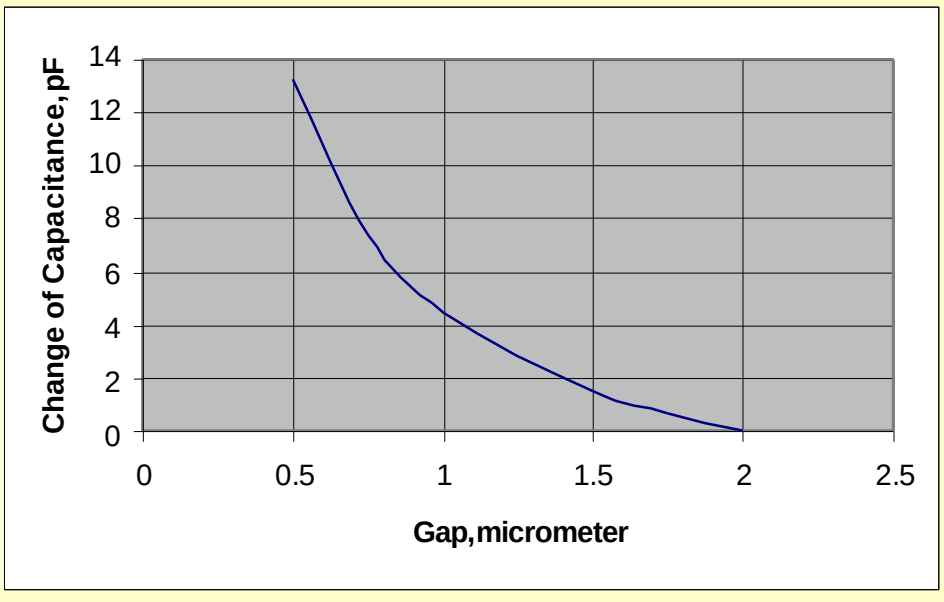
- Tends to be bulky
- Suited for elevated temperature application
- *Nolinear I/O relations*
- Lower cost

Nonlinear I/O with plate pressure sensors using electrodes

Electric circuit bridge for converting capacitance changes to voltage output:



$$V_o = \frac{\Delta C}{2(2C + \Delta C)} V_{in}$$



Pressure Sensors-Cont'd

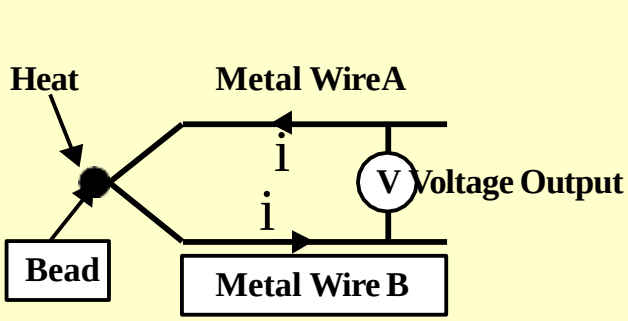
- **Major problems in pressure sensors are in the *system packaging* and *protection of the diaphragm* from the contacting pressurized media, which are often corrosive, erosive, and at high temperatures.**

Thermal Sensors

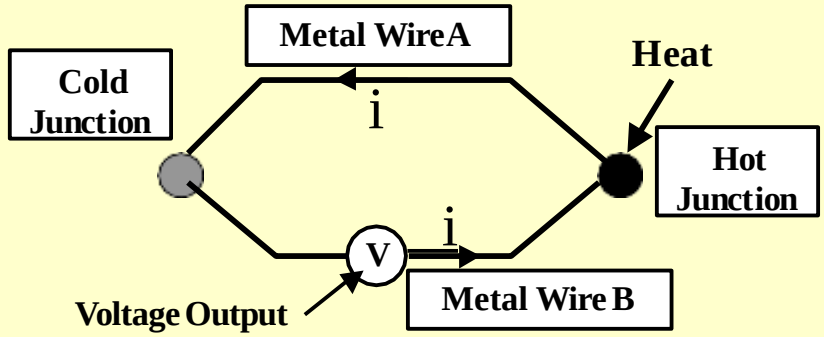
- **Thermal sensors are used to monitor, or measure temperature in an environment or of an engineering systems.**

- **Common thermal sensors involve thermocouples and thermopiles.**

- **Thermal sensors work on the principle of the electromotive forces (emf) generated by heating the junction made by dissimilar materials (beads):**



(a) A thermocouple



(b) A dual junctionthermocouple

The generated voltage (V) by a temperature rise at the bead (ΔT) is:

$$V = \beta \Delta T$$

where β = Seebeck coefficient

Thermal Sensors-Cont'd

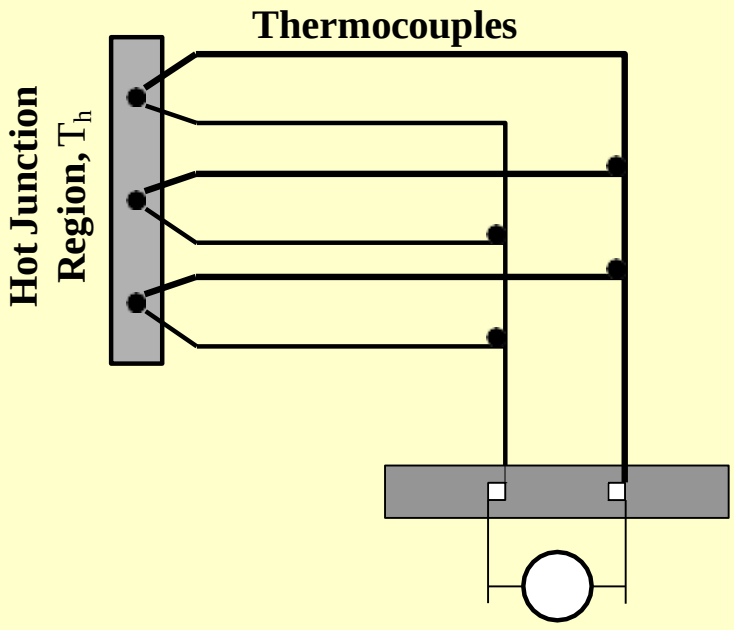
The Seebeck coefficients for various thermocouples are:

Type	Wire Materials	Seebeck Coefficient (μV/°C)	Range (°C)	Range (mV)
E	Chromel/Constantan	58.70 at 0°C	-270 to 1000	-9.84 to 76.36
J	Iron/Constantan	50.37 at 0°C	-210 to 1200	-8.10 to 69.54
K	Chromel/Alumel	39.48 at 0°C	-270 to 1372	-6.55 to 54.87
R	Platinum (10%)-Rh/Pt	10.19 at 600°C	-50 to 1768	-0.24 to 18.70
T	Copper/Constantan	38.74 at 0°C	-270 to 400	-6.26 to 20.87
S	Pt (13%)-Rh/Pt	11.35 at 600°C	-50 to 1768	-0.23 to 21.11

Common thermocouples are of K and T types

Thermal Sensors-Cont'd

Thermopiles are made of connecting a series of thermocouples in parallel:



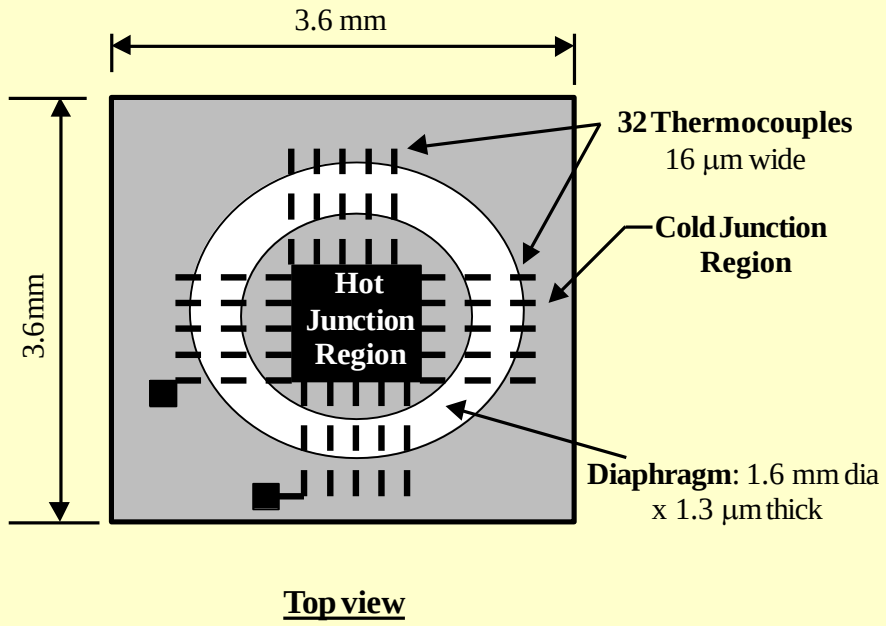
The induced voltage (ΔV) by the temperature change at the hot junction (ΔT) is:

$$\Delta V = N \beta \Delta T$$

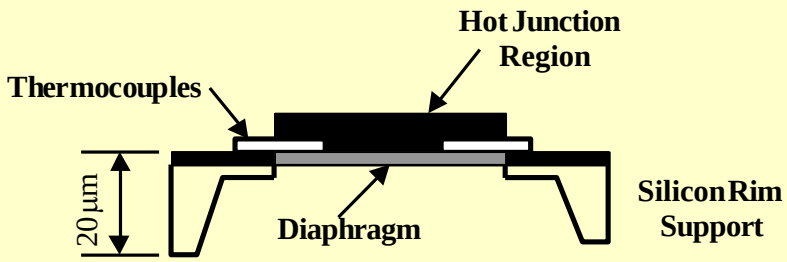
with N = number of thermocouple pairs in the thermopile.

Thermal Sensors-Cont'd

A micro thermal sensor:



Top view



Elevation

- 32 polysilicon-gold thermocouples
- dimension of thermopile is: 3.6 mm x 3.6 mm x 20 µm thick
- Typical output is 100 mV
- Response time is 50 ms