

Biosensors

A biosensor is defined by IUPAC (1997) as:

“A device that uses specific biochemical reactions mediated by isolated enzymes, immunosystems, tissues, organelles or whole cells to detect chemical compounds usually by electrical, thermal or optical signals”.

Almost all biosensors are based on a three-component system: a **support**, a biological recognition element (**ligand**) that facilitates specific binding or biochemical reaction of a target, and a signal conversion unit (**transducer**).

- Biosensors thus have a wide range of applications including:
 - Clinical diagnostics
 - Drug development
 - Environmental monitoring (air, water, and soil)
 - Food quality control

A biosensor in general utilizes a biological recognition element that senses the presence of an analyte (the species to be detected) and creates a physical or chemical response that is converted by a transducer into a signal.

The important components of a biosensor are:

- (i) a sampling unit that introduces an analyte into the detector and can be as simple as a circulator;**
 - (ii) a recognition element that binds or reacts with a specific analyte, providing biodetection specificity (enzymes, antibodies, or even cells, such as yeast or bacteria, have been used as biorecognition elements)**
 - (iii) stimulation that, in general, can be provided by optical, electric, magnetic, or other kinds of force fields that extract a response as a result of biorecognition; and**
 - (iv) a transduction process that transforms the physical or chemical response of the biorecognition in the presence of an external stimulation, into an optical, electrical, or magnetic signal that is detected by the detection unit. The detection unit may include pattern recognition for identification of the analyte**
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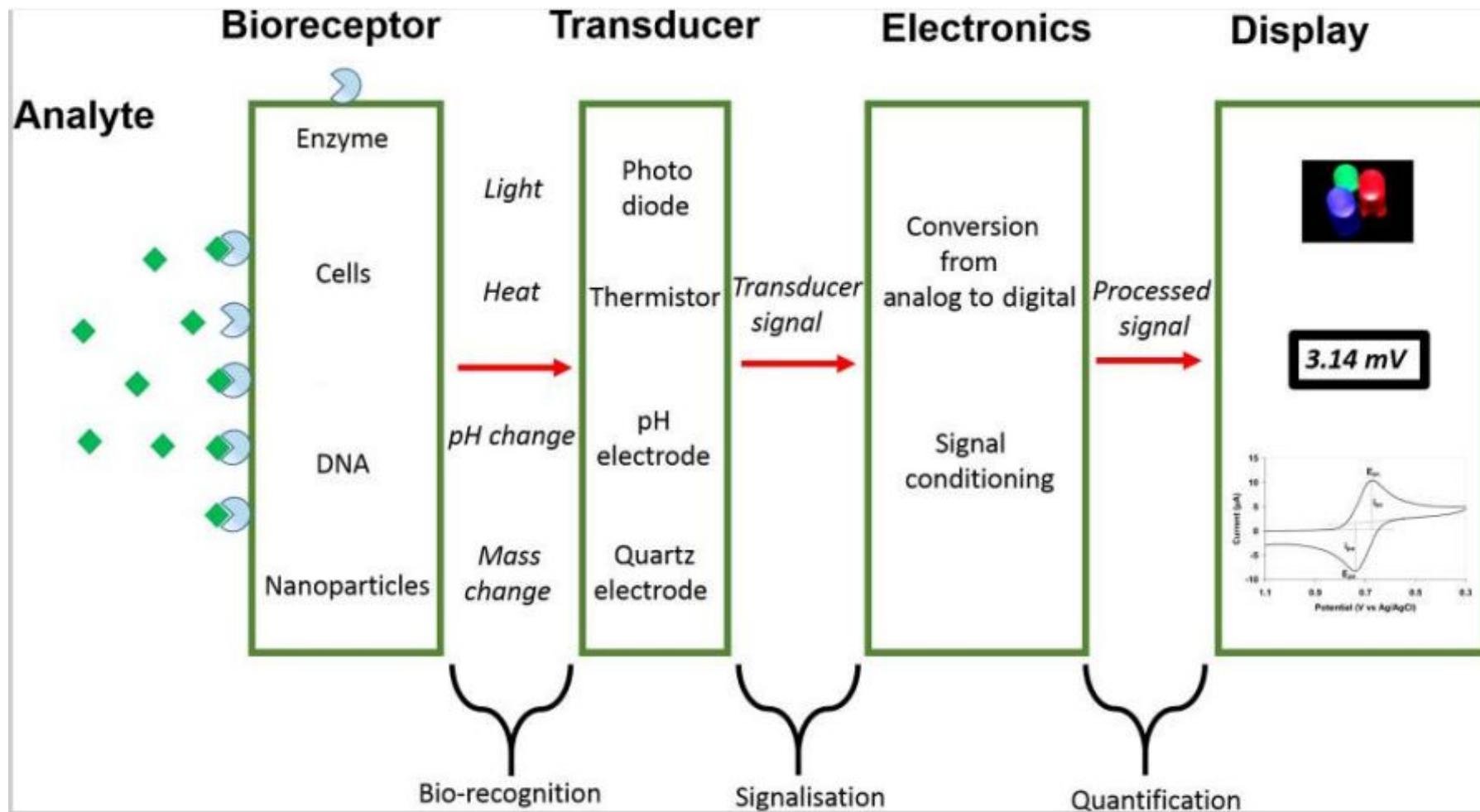
BIORECEPTORS

Bioreceptors can generally be classified into five different major categories

- 1) Antibody/ Antigen,**
- 2) Enzymes,**
- 3) Nucleic acids/DNA,**
- 4) Cellular structures/cells**
- 5) Biomimetic**

Bioreceptors are the key to specificity for biosensor technologies.

They are responsible for binding the analyte of interest to the sensor for the measurement.



Selectivity

Selectivity is perhaps the most important feature of a biosensor.

Selectivity is the ability of a bioreceptor to detect a specific analyte in a sample containing other admixtures and contaminants.

The best example of selectivity is depicted by the interaction of an antigen with the antibody. Classically, antibodies act as bioreceptors and are immobilised on the surface of the transducer. A solution (usually a buffer containing salts) containing the antigen is then exposed to the transducer where antibodies interact only with the antigens.

Biosensor = bioreceptor + transducer. A biosensor consists of two components: a bioreceptor and a transducer. The bioreceptor is a biomolecule that recognizes the target analyte, and the transducer converts the recognition event into a measurable signal. The uniqueness of a biosensor is that the two components are integrated into one single sensor (Figure 6.1.1). This combination enables one to measure the target analyte without using reagents (Davis et al, 1995). For example, the glucose concentration in a blood sample can be measured directly by a biosensor made specifically for glucose measurement, by simply dipping the sensor in the sample. This is in contrast to the commonly performed assays, in which many sample preparation steps are necessary and each step may require a reagent to treat the sample. The simplicity and the speed of measurements that require no specialized laboratory skills are the main advantages of a biosensor.

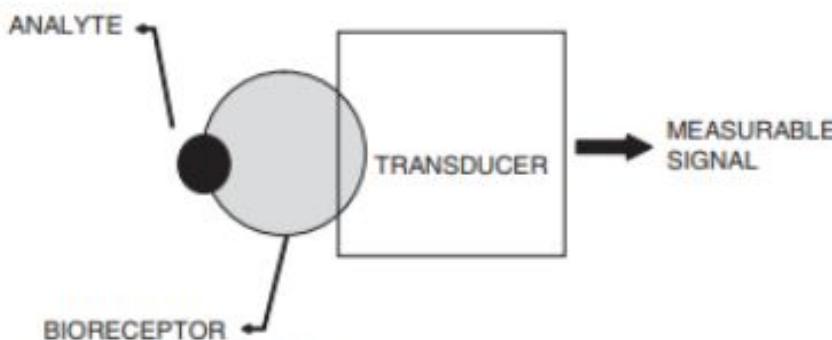


Figure 6.1.1: Biosensor configuration.

Enzyme is a Bioreceptor. When we eat food such as hamburgers and french fries, it is broken down into small molecules in our body via many reaction steps (these breakdown reactions are called *catabolism*). These small molecules are then used to make the building blocks of our body, such as proteins (these synthesis reactions are called *anabolism*). Each of these catabolism and anabolism reactions (the combination is called *metabolism*) are catalyzed by a specific enzyme. Therefore, **an enzyme is capable of recognizing a specific target molecule** (Figure 6.1.2). This biorecognition capability of the enzyme is used in biosensors. Other biorecognizing molecules (= bioreceptors) include antibodies, nucleic acids, and receptors.

Immobilization of Bioreceptor. One major requirement for a biosensor is that the bioreceptor be immobilized in the vicinity of the transducer. The immobilization is done either by physical entrapment or chemical attachment. Chemical attachment often involves covalent bonding to transducer surface by suitable reagents. A comprehensive treatment of immobilization is available in Hermanson (1996). It is to be noted that only minute quantities of bioreceptor molecules are needed, and they are used repeatedly for measurements.

Transducer. A transducer should be capable of converting the biorecognition event into a measurable signal (Figure 6.1.3). Typically, this is done by measuring the change that occurs in the bioreceptor reaction. For example, the enzyme glucose oxidase is used as a bioreceptor in a glucose biosensor that catalyzes the following reaction:



To measure the glucose in aqueous solutions, three different transducers can be used:

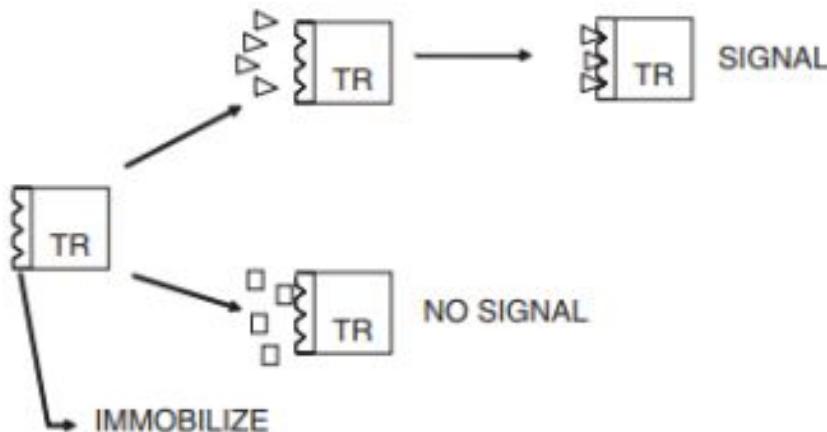
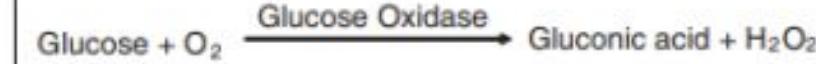
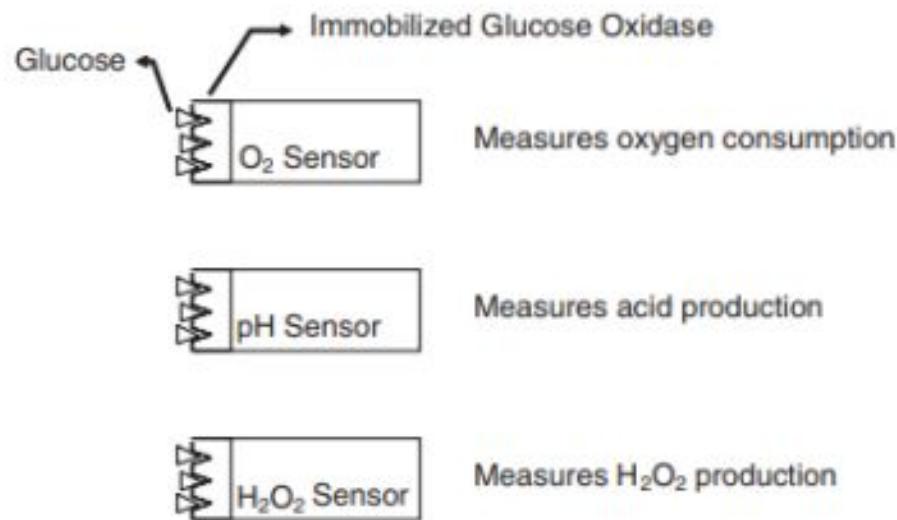


Figure 6.1.2: Specificity of biosensor (TR: transducer).



1. An oxygen sensor that measures oxygen concentration, a result of glucose reaction
2. A pH sensor that measures the acid (gluconic acid), a reaction product of glucose
3. A peroxidase sensor that measures H_2O_2 concentration, a result of glucose reaction



Note that an oxygen sensor is a transducer that converts oxygen concentration into electrical current. A pH sensor is a transducer that converts pH change into voltage change. Similarly, a peroxidase sensor is a transducer that converts peroxidase concentration into an electrical current. An excellent review of glucose sensing technologies was reported by Wilkins and Atansov (1996).

Figure 6.1.3: Three possible transducers for glucose measurement.

Biosensor Characteristics. Biosensors are characterized by eight parameters. These are: (1) *Sensitivity* is the response of the sensor to per unit change in analyte concentration. (2) *Selectivity* is the ability of the sensor to respond only to the target analyte. That is, lack of response to other interfering chemicals is the desired feature. (3) *Range* is the concentration range over which the sensitivity of the sensor is good. Sometimes this is called dynamic range or linearity. (4) *Response time* is the time required for the sensor to indicate 63% of its final response due to a step change in analyte concentration. (5) *Reproducibility* is the accuracy with which the sensor's output can be obtained. (6) *Detection limit* is the lowest concentration of the analyte to which there is a measurable response. (7) *Life time* is the time period over which the sensor can be used without significant deterioration in performance characteristics. (8) *Stability* characterizes the change in its baseline or sensitivity over a fixed period of time.

Considerations in Biosensor Development. Once a target analyte has been identified, the major tasks in developing a biosensor involve:

1. Selection of a suitable bioreceptor or a recognition molecule
2. Selection of a suitable immobilization method
3. Selection and design of a transducer that translates binding reaction into measurable signal
4. Design of biosensor considering measurement range, linearity, and minimization of interference, and enhancement of sensitivity
5. Packaging of the biosensor into a complete device

The first item above requires knowledge in biochemistry and biology, the second and third require knowledge in chemistry, electrochemistry and physics, and the fourth requires knowledge of kinetics and mass transfer. Once a biosensor has been designed, it must be packaged for convenient manufacturing and use. The current trend is miniaturization and mass production. Modern IC (integrated circuit) fabrication technology and micromachining technology are used increasingly in fabricating biosensors, as they reduce manufacturing costs. Therefore, an interdisciplinary research team, consisting of the various disciplines identified above, is essential for successful development of a biosensor.

Transduction principles

6.5 Transduction Mechanisms in Biosensors

Conventional Transducers. The majority of biosensors in use today use three types of transducers for converting the action of the bioreceptor molecule into a measurable signal. These are: amperometry based on H_2O_2 or O_2 measurement; potentiometry based on pH or pI_{on} measurement; and photometry utilizing optical fibers. Biorecognition reactions often generate chemical species that can be measured by electrochemical methods. In these, typically the reaction product is H_2O_2 (or the reactant is O_2) which can be measured by a pair of electrodes. When a suitable voltage is impressed on one of the electrodes against a reference electrode (typically Ag/AgCl or Calomel), the target species (H_2O_2 or O_2) is reduced at the electrode and this generates electrical current (hence the name *amperometry*). In potentiometry, a glass membrane or a polymeric membrane electrode is used for measuring the membrane potential (hence the name *potentiometry*) resulting from the difference in the concentrations of H^+ or other positive ions across the membrane. In photometry, the light

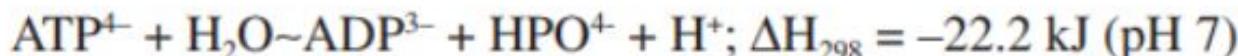
from an indicator molecule is the measured signal. In this method, one of the reactants or products of the biorecognition reaction results in colorimetric, fluorescent or luminescent changes that are measured using photodetectors. Usually, an optical fiber is used for guiding the light signals from the source to the detector. Adaptation and exploitation of these three routes, (**amperometric, potentiometric and photometric**), where user acceptability is already established, has been an obvious approach to the development of reagentless biosensor devices.

Piezoelectric Transducers. The transducer of a biosensor is not restricted to the three described above. In principle, any variable that is affected by the biorecognition reaction can be used to generate the transduced signal. The **piezoelectric materials** and surface acoustic wave devices offer a surface that is sensitive to **changes in mass**. These transducers have been used where the biorecognition reaction causes a change in mass. For example, piezoelectric silicon crystals—called quartz crystal microbalance (QCM)—have been used to measure very small mass changes in the order of picograms. For example see Bunde et al., (1998). QCM with immobilized antibody to pathogens have been successfully used to measure the presence of pathogens in aqueous samples. Piezoelectrically driven cantilevers have also been used to measure adsorption of very minute quantities of biochemicals (Raiteri et al., 2001).

Conductimetric Transducers. Monitoring **solution conductance** was originally applied as a method of determining reaction rates. The technique involves the measurement of changes in conductance due to the migration of ions. Many enzyme-linked reactions result in a change in total ion concentration and this would imply that they are suitable for conductimetric biosensors.

Electrical Capacitance as Transducer. When the biorecognition reaction causes a **change in the dielectric measurement constant** of the medium in the vicinity of the bioreceptor, the capacitance measurement method can be used as a transducer. Antigen-antibody reaction is a good example. Suppose antibody molecules are immobilized between two metal electrodes of known area. When antigen is added and binds with the antibody, the dielectric constant of the medium between the two electrodes is expected to change significantly. This change translates into a change in capacitance.

Thermometric Transducer. All chemical reactions are accompanied by the absorption (endothermic) or evolution (exothermic) of heat. Measurements of ΔH , the enthalpy of reaction at different temperatures, allows one to calculate ΔS (entropy) and ΔG (Gibbs free energy) for a reaction and therefore collect basic thermodynamic data. The hydrolysis of ATP for example is exothermic:



or the immunoreaction between anti-HSA and its antigen HSA yields -30.5 kJ/mol . For this latter reaction, the total increase in temperature for 1 mmol of antibody is of the order of 10^{-5} K , but many enzyme-catalyzed reactions have greater ΔH , and produce more easily measurable changes in temperature.

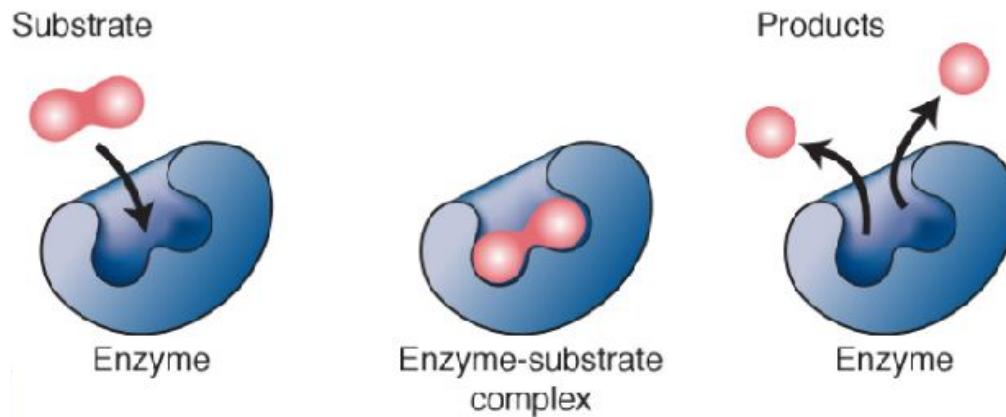
Enzyme Thermistor. For a biosensor device, the biorecognition compound must be immobilized on a temperature-sensing element capable of detecting very small temperature changes. The major initiative in this area has come from the Mosbach group at the University of Lund. Initially, they immobilized glucose oxidase or penicillinase in a small column, so that temperature changes in the column effluent were monitored by thermistors to give an *enzyme thermistor* sensitive to glucose and penicillin, respectively. They have also applied the technique to other substrates and to immunoassay using an enzyme-labeled antigen.

FET as a Transducer. As advances are made in biosensors, a need has developed for miniaturization and mass production. Field effect transistors (FET) used extensively in the semiconductor industry in memory chips and logic chips respond to changes in electric field (in front of the “gate” of the FET). An FET is thus capable of detecting changes in ion concentration when the gate is exposed to a solution that contains ions. Therefore, pH and ion concentration can be measured with an FET. The advantage of this transducer is that it can be incorporated directly into the electronic signal processing circuitry. In fact, a pen-size FET-based pH sensor is being marketed commercially.

Immobilization of biological elements

An enzyme is a biological catalyst and is almost always a protein. It speeds up the rate of a specific chemical reaction in the cell. The enzyme is not destroyed during the reaction and is used over and over. A cell contains thousands of different types of enzyme molecules, each specific to a particular chemical reaction.

Mechanism of enzyme activity



In most of the processes, enzymes are mixed with substrates in the reaction vessel and cannot be economically recovered after the reaction and are generally wasted. Enzymes can catalyze reactions in different states such as

1. individual molecules in solution
2. in aggregates with other entities,

and 3. as attached to surfaces. The attached—or “immobilized” - state has been of particular interest to the researchers to exploit enzymes for technical purposes. The term “immobilized enzymes” refers to “enzymes physically confined or localized in a certain defined region of space with retention of their catalytic activities, and which can be used repeatedly and continuously”.

Benefits of Immobilizing an Enzyme

There are a number of advantages in attaching enzymes to a solid support and a few of the major reasons are listed below:

- ❑ Multiple or repetitive use of a single batch of enzymes (catalyzing the same reaction many times)
- ❑ Immobilized enzymes are usually more stable and less likely to denature (lose their shape)
- ❑ The ability to stop the reaction rapidly by removing the enzyme from the reaction solution (or vice versa)
- ❑ Product is not contaminated with the enzyme (especially useful in the food and pharmaceutical industries)
- ❑ In addition, there will be no enzyme left in the product at the end, therefore, purification is not necessary or we can say easy separation of the enzyme from the product
- ❑ Allows development of a multi enzyme reaction system

There are however, certain disadvantages also associated with immobilization.

1. The possibility of loss of biological activity of an enzyme during immobilization or while it is in use.
2. Immobilization is an expensive affair often requiring sophisticated equipment.
3. Some enzymes become unstable after immobilisation.
4. Sometimes enzymes become inactivated by the heat generated by the system.

Components of immobilization

The major components of an immobilized enzyme system are the enzyme, the matrix, and the mode of attachment of the enzyme to the matrix.

Choice of Supports

The characteristics of the matrix are of paramount importance in determining the performance of the immobilized enzyme system. In order to fully retain the biological activity, enzymes should be attached onto surfaces without affecting their conformational and functional properties. The choice of a suitable immobilization strategy is determined by the physico-chemical properties of both supporting surface and the enzyme of interest.

Ideal support properties include:

- i. Physical resistance to compression,
 - ii. hydrophilicity,
 - iii. inertness toward enzymes,
 - iv. stability,
 - v. Regenerability after the useful lifetime of the immobilized enzyme,
 - vi. Enhancement of enzyme specificity,
 - vii. ease of derivatisation,
 - viii. biocompatibility,
 - ix. reduction in microbial contamination and nonspecific adsorption,
 - x. availability at low cost.
- The form, shape, density, porosity, pore size distribution, operational stability and particle size distribution of the supporting matrix will influence the reaction rate
 - The support should be cheap, inert, physically strong and stable
 - Ideally, it should:
 - increase the enzyme specificity (k_{cat}/K_m)
 - shift the pH optimum to the desired value for the process
 - discourage microbial growth and non-specific adsorption

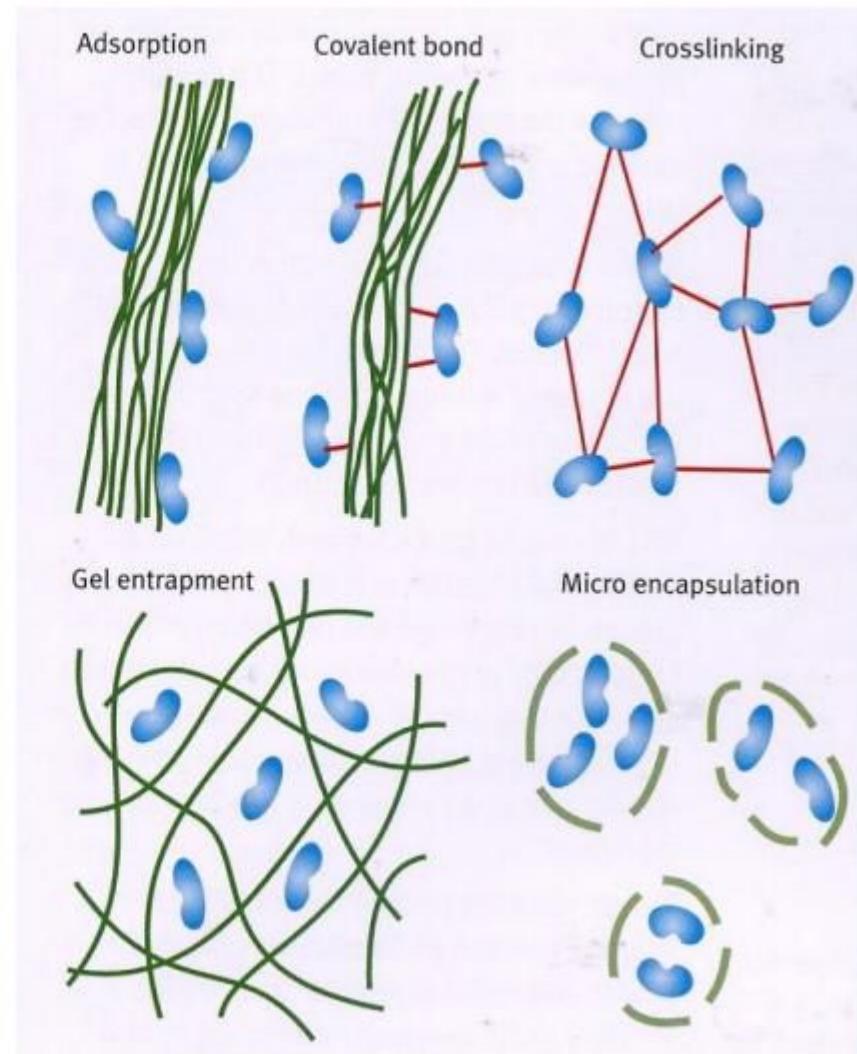
Supports can be classified as inorganic and organic according to their chemical composition. In spite of the many advantages of inorganic carriers (e.g., high stability against physical, chemical, and microbial degradation), most of the industrial applications are performed with organic matrices.

The organic supports can be further subdivided into natural and synthetic polymers. The physical characteristics of the matrices (such as mean particle diameter, swelling behavior, mechanical strength, and compression behavior) will be of major importance for the performance of the immobilized systems and will determine the type of reactor used under technical conditions (i.e., stirred tank, fluidized, fixed beds).

The concept of irreversible immobilization means that once the biocatalyst is attached to the support it cannot be detached without destroying either the biological activity of the enzyme or the support. The most common procedures of irreversible enzyme immobilization are covalent coupling, entrapment or micro-encapsulation, and cross-linking.

Immobilisation methods

- Adsorption
- Covalent bond
- Crosslinking
- Entrapment
- Encapsulation



Receptors immobilisation

Optimal orientation of receptors (antibodies) results in:

- **Greater affinity** of the antigen
- **Increased sensitivity** of the affinity biosensors
- **High reproducibility** of the immobilisation



Adsorption

Adsorption is simply due to interactions between the bioreceptor and its support. If the latter is not charged, low energy bonds (hydrogen bonds, van der Waals forces, or hydrophobic effects) are established between bioreceptor and support. If it is charged, ionic bonds will also occur.

However, bioreceptors immobilised in this way can easily desorb through a change in pH or ionic strength, and this method is not widely used for bioreceptors.

Inclusion

The idea here is to incorporate the bioreceptor in a polymer which is usually in the form of a gel.

The bioreceptor is not therefore directly bound to the substrate.

This technique, also easy to implement, allows a homogeneous distribution of the bioreceptor throughout the gel, but it may cause damage to biological structures, which may be affected by the reagents used in the polymerisation process.

Inclusion is mainly used to immobilise whole cells or subcellular fractions

Confinement

In the confinement technique, the bioreceptor remains in solution inside a compartment bounded by a semi-permeable membrane which only allows through small molecules. The bioreceptor thus remains in solution within a micro compartment of volume in the μL range or less, bounded by the membrane.

Crosslinking

The use of bifunctional agents such as glutaraldehyde $\text{CHO}-(\text{CH}_2)_3-\text{CHO}$ provides a way of crosslinking enzyme molecules one to another or co-crosslinking them in the presence of an inactive protein . Crosslinking is also used to increase the stability of enzyme–substrate complexes obtained by adsorption or inclusion.

Covalent Bonding on an Activated Substrate

The covalent bonding of bioreceptors, mainly proteins, on activated substrates is achieved by setting up covalent bonds between functional groups of the substrate and functional groups of the bioreceptor that are not involved in the molecular recognition process.

The most widespread methods use $-\text{COOH}$, $-\text{NH}_2$, $-\text{OH}$, and $-\text{SH}$ groups on the substrate. These groups are chemically rather inactive and they must first be transformed into activated functions in order to be able to react under mild conditions with the functional groups of the bioreceptor.

Immobilisation method	Substrate
Adsorption	Agarose, alumina, starch, carbon, cellulose, collagen, collodion, silica gel, ion exchange resins, porous glass, polyamide, polystyrene, polyurethane
Inclusion	Gels (alginate, starch, carrageenan, gelatine, polyacrylamide, polysiloxane, polystyrene, polyvinyl alcohol, silica)
Confinement	Dialysis and ultrafiltration membranes
Covalent coupling	Polyamino acids and proteins (polyglutamic acid, L-alanine and L-glutamic acid copolymer, collagen, fibroin) Polysaccharides (polygalacturonic acid, agarose, starch, cellulose, chitin, dextrose) Synthetic polymers (polyacrylamide, polyamide, polymethacrylate, polystyrene, polyvinyl alcohol) Inorganic substrates (silica gel, gold, quartz, porous glass)

Simple

Less stable

Table 1. Immobilization procedures for enzymes		
Method	Advantages	Disadvantages
<u>Adsorption</u> on insoluble matrices (e.g. by van der Waals forces, ionic binding or hydrophobic forces)	Simple, mild conditions, less disruptive to enzyme protein	Enzyme linkages are highly dependent on pH, solvent and temperature; insensitive
<u>Entrapment</u> in a gel (eventually behind a semipermeable membrane)	Universal for any enzyme, mild procedure	Large diffusional barriers, loss of enzyme activity by leakage, possible denaturation of the enzyme molecules as a result of free radicals
<u>Crosslinking</u> by a multifunctional reagent (such as glutaraldehyde bis-isocyanate derivatives or bis-diazobenzidine)	Simple procedure, strong chemical binding of the biomolecules; widely used in stabilizing physically adsorbed enzymes or proteins that are covalently bound onto a support	Difficult to control the reaction, requires a large amount of enzyme, the protein layer has a gelatinous nature (lack of rigidity), relatively low enzyme activity
<u>Covalent bonding</u> onto a membrane, insoluble supports	Stable enzyme-support complex, leakage of the biomolecule is very unlikely, ideal for mass production and commercialization	Complicated and time-consuming; possibility of activity losses due to the reaction involving groups essential for the biological activity (can be minimized by immobilization in the presence of the substrate or inhibitor of the enzyme)

Complex

More stable

BLOOD GLUCOSE BIOSENSOR

Glucose sensors are biosensors designed to detect glucose levels, which is vital to managing diabetes. But do you know how the technology actually works?

Whether in the form of a test strip for a blood glucose meter or a sensor for a continuous glucose monitor, the detection and measurement of glucose levels are similar processes.

The first and the most commonly used commercial biosensor: the blood glucose biosensor – developed by *Leland C. Clark* in 1962

For a glucose biosensor, the following components are used:

Analyte: A substance with chemical constituents that are being identified and measured. In this instance, glucose is the analyte that the biosensor is designed to detect.

Bioreceptor: This is a molecule that specifically recognizes the analyte. For the detection of glucose, specific enzymes are used, which are proteins that facilitate a chemical reaction. For example, the test strip for a blood glucose test contains the enzyme that interacts with the analyte in the drop of blood.

Transducer: This part of the biosensor converts one form of energy into another. Specifically, it converts the recognition of the bioreceptor into a measurable signal. Most modern-day glucose meters and continuous glucose monitors measure electrical signals, although earlier generations of glucose meters used a colorimetric process (color change) that was measured optically.

Electronics and display: These components process the transduced signal and prepare it for display. The processed signals are then quantified and shown on either the glucose meter's display or the receiver for a continuous glucose monitor (or compatible app).

Generally, glucose measurements are based on interactions with one of three enzymes:
hexokinase,
glucose oxidase (GOx) or
glucose-1-dehydrogenase (GDH)

The hexokinase assay is the reference method for measuring glucose using spectrophotometry in many clinical laboratories .

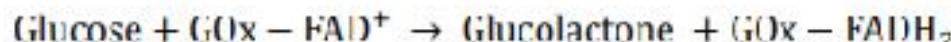
Glucose biosensors for SMBG are usually based on the two enzyme families, GOx and GDH.

These enzymes differ in redox potentials, cofactors, turnover rate and selectivity for glucose .

GOx is the standard enzyme for biosensors; it has a relatively higher selectivity for glucose.

GOx is easy to obtain, cheap, and can withstand greater extremes of pH, ionic strength, and temperature than many other enzymes, thus allowing less stringent conditions during the manufacturing process and relatively relaxed storage norms for use by lay biosensor users.

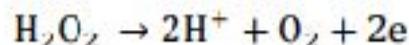
The basic concept of the glucose biosensor is based on the fact that the immobilized GOx catalyzes the oxidation of β-D-glucose by molecular oxygen producing gluconic acid and hydrogen peroxide [35]. In order to work as a catalyst, GOx requires a redox cofactor—flavin adenine dinucleotide (FAD). FAD works as the initial electron acceptor and is reduced to FADH₂.



The cofactor is regenerated by reacting with oxygen, leading to the formation of hydrogen peroxides.

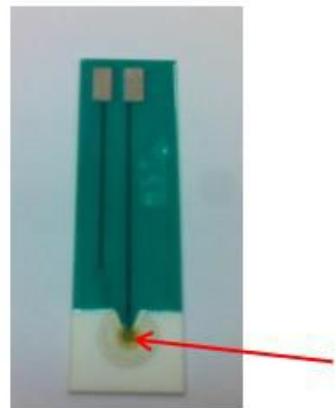


Hydrogen peroxide is oxidized at a catalytic, classically platinum (Pt) anode. The electrode easily recognizes the number of electron transfers, and this electron flow is proportional to the number of glucose molecules present in blood [36].



Three general strategies are used for the electrochemical sensing of glucose; by measuring oxygen consumption, by measuring the amount of hydrogen peroxide produced by the enzyme reaction or by using a diffusible or immobilized mediator to transfer the electrons from the GOx to the electrode. The number and types of GDH-based amperometric biosensors have been increasing recently. The GDH

These devices use enzyme-coated test strips that are manufactured with a precise amount of specific enzymes that can only react to one blood sample. Because of this, test strips are intended for single use and cannot be reused. When inserted into the blood glucose meter and after receiving a blood sample, the test strip communicates with the glucose meter which calculates the amount of glucose in the blood and displays the result on the meter's screen.



Immobilized enzyme onto electrode surface (gel entrapment)

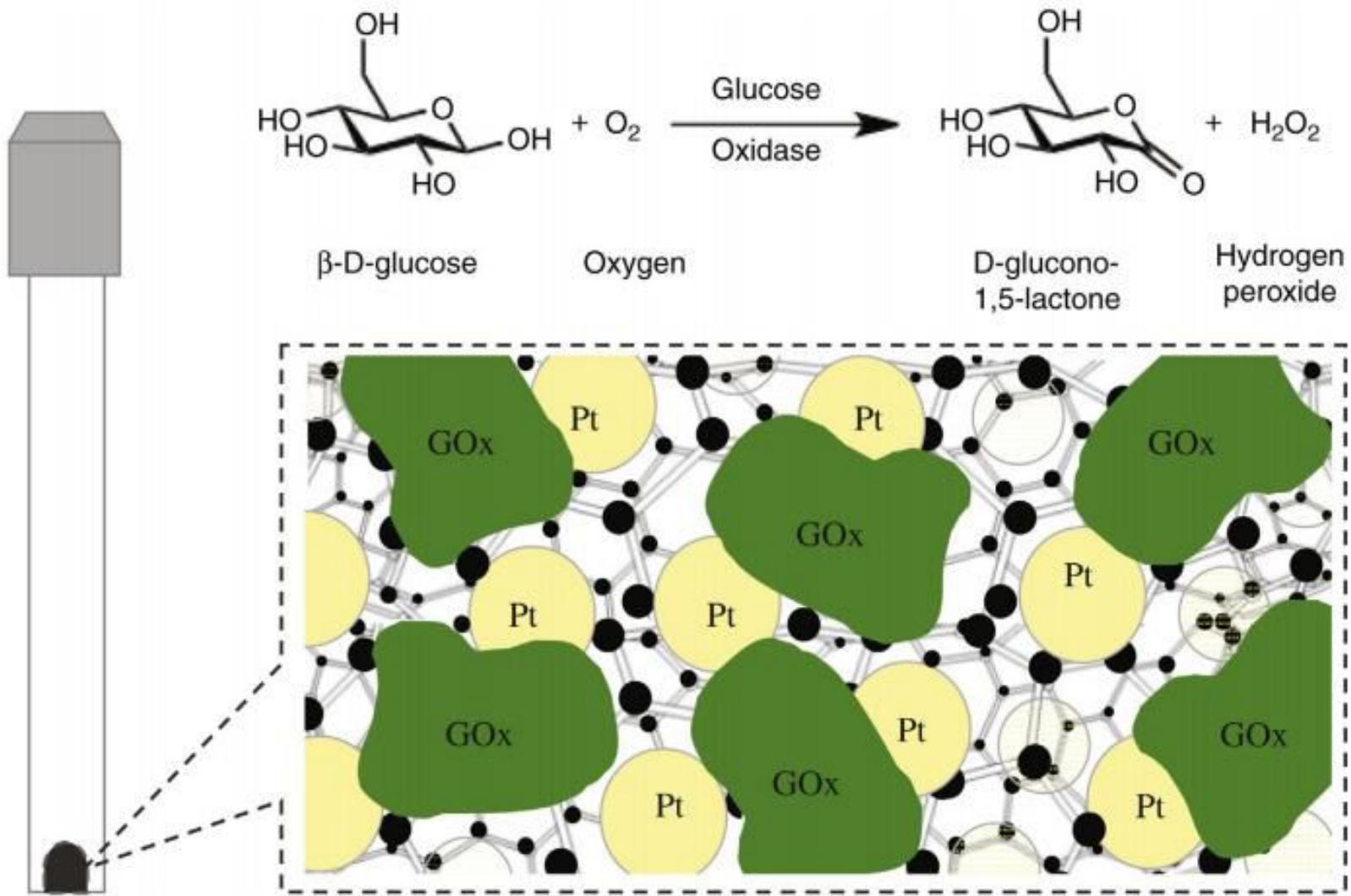


Figure 2.2. Schematic representation of glucose oxidase (GOx) immobilized on a platinum nanoparticle functionalized semi graphitic carbon support. The GOx/Pt/C electrocatalyst was packed into a glassy carbon electrode cavity.

What is blood pressure?

Blood pressure (BP) is a measure of the force that the circulating blood exerted against the arterial walls

Blood Pressure is expressed as the ratio of the systolic pressure over diastolic pressure.

Systolic pressure?

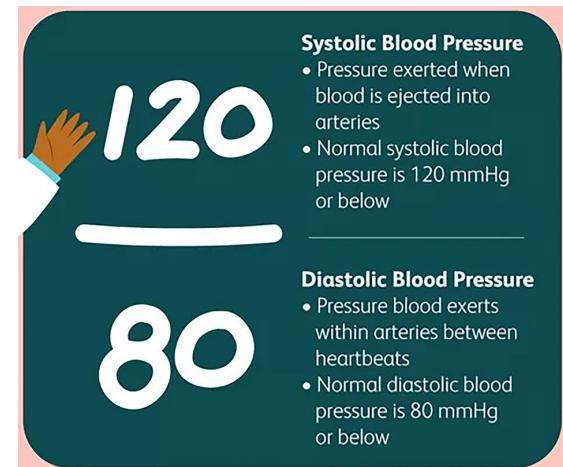
This is the maximum pressure exerted by the blood against the arterial walls

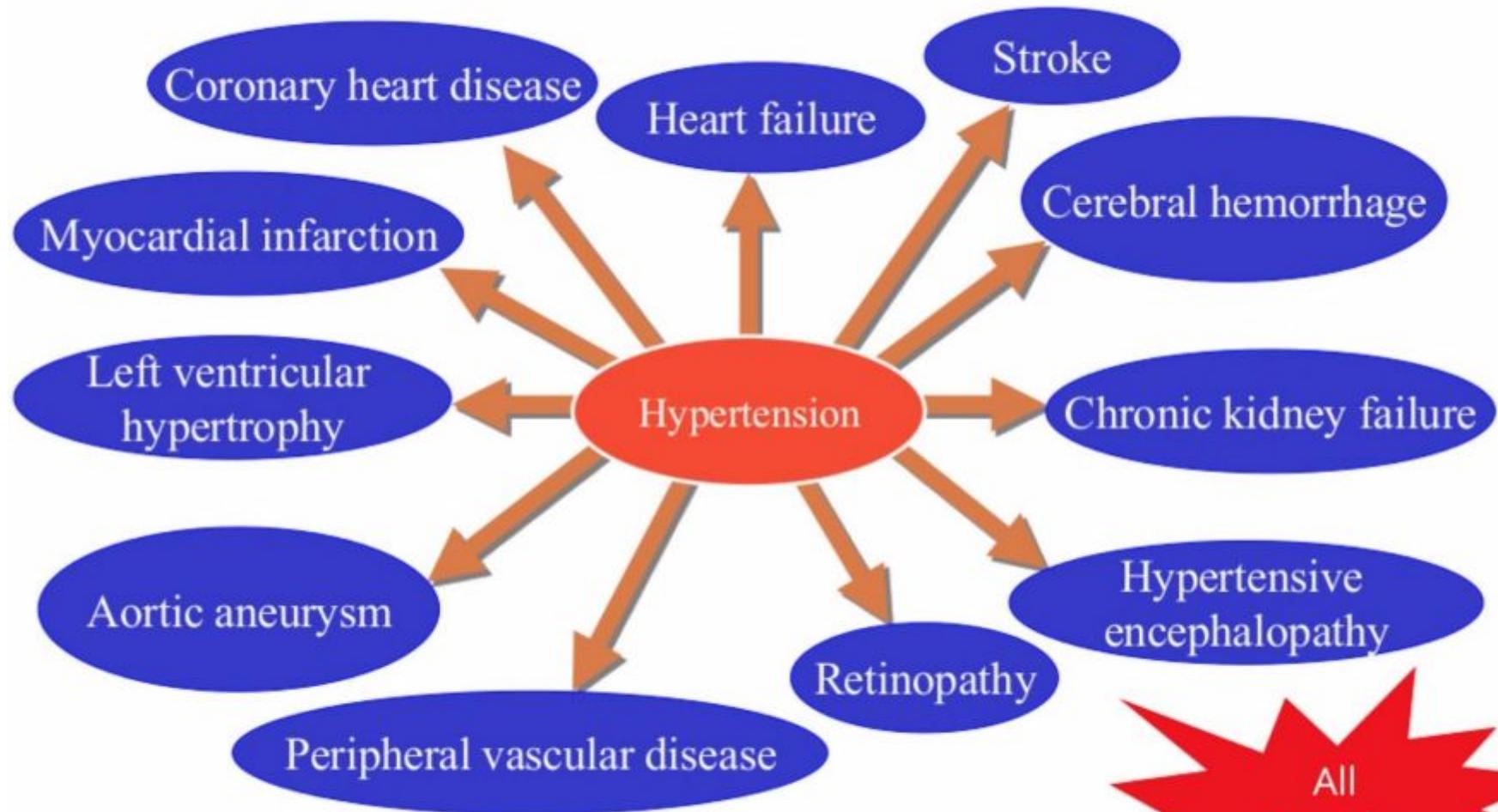
It results when the ventricles contract (systole)

Diastolic pressure?

This is the lowest pressure n the artery

It results when the ventricles relaxed (diastole)





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BP monitoring

Mercury sphygmomanometer is being used for measuring blood pressure. In this, the height of the column of mercury is considered for measuring the blood pressure.

The oscillometric method is used for automated blood pressure measurements since 1981.

Devices:

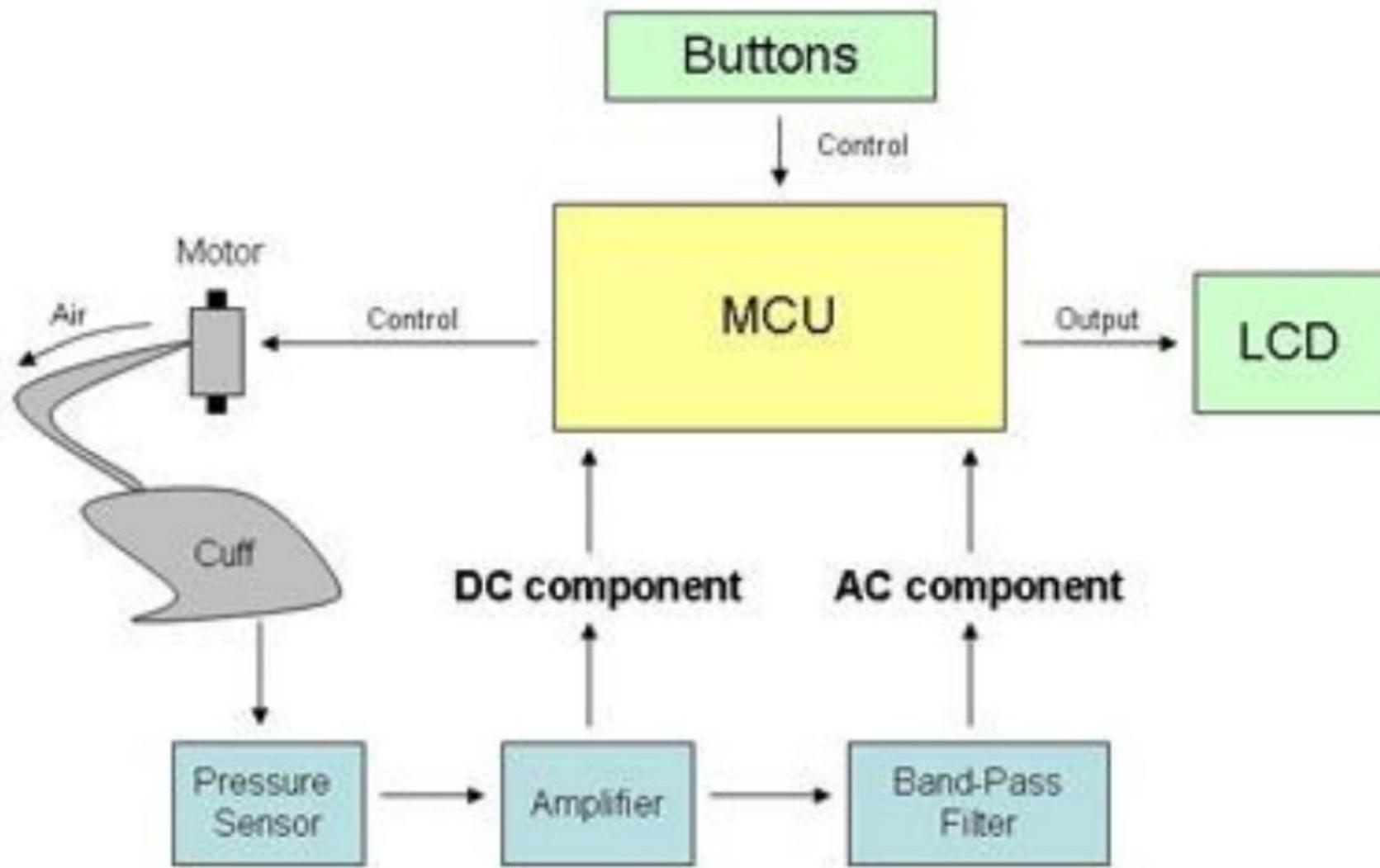
Aneroid. Mercury. Electronic.



What is a Blood Pressure Sensor?

Blood Pressure can be measured both by invasive and non-invasive methods. In the non-invasive method, no piercing is required and is easy to use. Blood Pressure Sensor is used to measure the blood pressure using the non-invasive method. It is similar to sphygmomanometer but instead of the mercury column, a pressure sensor is used to detect the blood pressure

Typical Micro BP sensor circuit diagram



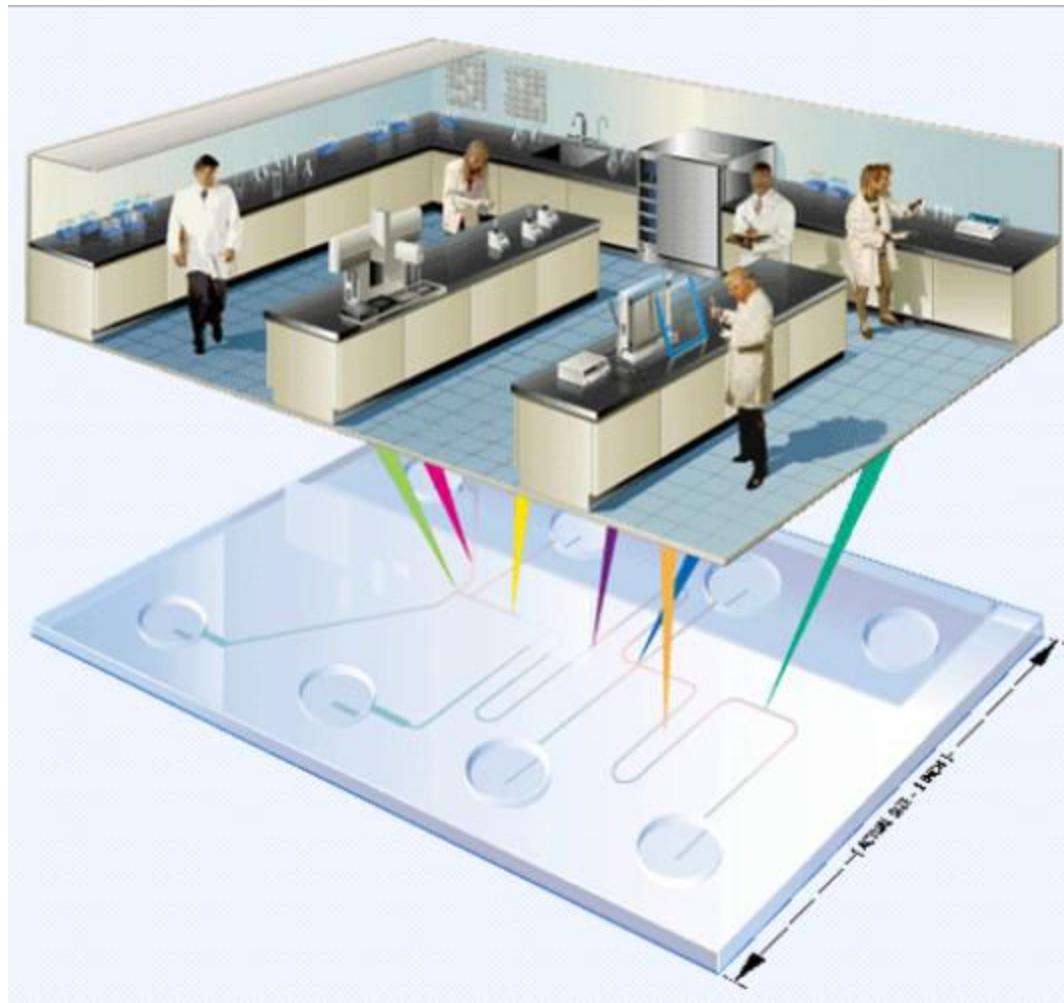
Working,

In automatic Blood Pressure measurement system, instead of mercury a pressure sensor is used to detect the pressure in the artery and give output. This digital output is displayed on the monitor. This monitor has an onboard processor to process the output given by pressure sensor, record results and display them on the digital read-out screen.

Advantages,

- Being non-invasive, this Sensor is safe to use. It is easier to use and can be monitored by any individual. Instead of watching the mercury levels and calculating pressure, this sensor makes the task easier by giving results automatically.
- This system is portable. It is easy to carry and operate and highly useful in remote areas where medical facilities are not available.

LAB-ON-CHIP SENSORS



Lab-on-Chip technology implies those techniques that perform various laboratory operations on a miniaturized scale such as chemical synthesis and analysis on a single chip leading to a handheld and portable device. In other words, LoC is a device which is capable of scaling the single or multiple laboratory functions down to chip-format. The size of this chip ranges from millimeters to a few square centimeters.

Samples analysis can occur on location, where the samples are generated, rather than being carried to an extensive laboratory facility. Fluids' behaviour at this scale makes it easier to control the movement and interaction of samples, causing reactions to be much more potent, and minimizing chemical waste. It also allows reduces exposure to dangerous chemicals.

A lab-on-a-chip (LOC) is an automated miniaturized laboratory system used for different clinical applications inside and outside the hospital.

LoC is basically the integration of fluidics, electronics, optics and biosensors. LoCs prove to be useful for finding the methods for the early stage diagnosis of deadly and chronic diseases

Examples of applications include Measurements of blood gases, blood glucose, and cholesterol or counting the number of HIV cells

LOC-based applications are developing rapidly and that their number will increase in the near future.

Advantages compared to the current test methods.

Fast diagnostics at the location where diagnosis is needed (point of care) and

**Small amounts of samples
and**

Materials required to perform tests

Quality management aspects regarding calibration and maintenance of the device, and training and education of the user is necessary. This way, the benefits of LOC applications will not compromise quality of health care and patient safety

The technology used in LOC applications, microfluidics. This technology provides the possibility to manipulate and handle fluids on microscale.

Microfluidics is both the science which studies the behaviour of fluids through micro-channels, and the technology of manufacturing microminiaturized devices containing chambers and tunnels through which fluids flow or are confined. Microfluidics deal with very small volumes of fluids, down to femtoliters (fL) which is a quadrillionth of a liter. Fluids behave very differently on the micrometric scale than they do in everyday life: these unique features are the key for new scientific experiments and innovations.

Devices incorporating the functionality of sample taking, sample preparation , sensing, and detection on a single microfluidic chip are commonly termed lab-on-a-chip or miniaturized total analysis systems (μ TAS),

Microfluidics is a broader term that describes also mechanical flow control devices like pumps and valves or sensors like flowmeters and viscometers.

At present, there is no system on the market that completely integrates the full scope of these tasks. However, lab-on-a-chip systems have been developed that partially use macro periphery to perform crucial steps, for example, sample preparation and detection

LOC Device materials

The main issues in the manufacturing techniques for microfluidic LOC devices usually lie in the area of forming microfluidic channels which are micro/nanostructures. Various materials are used for the manufacture of microfluidic channels.

1. **Silicon:** microfluidic channels were patterned directly into silicon. In general, the advantages of using silicon as a structural material include its good mechanical properties, excellent chemical resistance, well-characterised processing techniques and the capability of integrating control/sensing circuitry.
2. **Glass:** Glass substrate is also used due to its excellent optical transparency and ease of electro-osmotic flow. One of the most successful examples in the capillary electrophoresis chip, which is manufactured using glass etching and fusion bonding techniques.
3. **Polymers:** Nowadays polymers are plastics have become popular materials due to their low cost, ease of manufacture, and favorable biochemical reliability and capability. Polymers are promising materials in LOC applications, because they can be used for mass production using casting, hot embossing, injection modeling and soft lithography techniques.
4. **Paper:** Recently, the manufacturing of paper based LOCs has been introduced, allowing an even cheaper and more simplified method for manufacturing LOC devices. Paper based LOC devices, commonly referred to as microfluidic paper based analytical devices often have the ability to analyze a single liquid sample for multiple analytes

Each dedicated microfluidic platform also contains sets of microfluidic elements, performing basic fluidic unit operations.

These **basic operations have to be able to transport fluids, storage of reagents and preparation of the sample.**

Microfluidic unit operations can be combined in different microfluidic platforms, such as lateral flow tests, linear actuated devices and surface acoustic waves. LOC can be used for the detection of proteins, nucleic acids, cells, pathogens, metabolites and other small molecules.

The largest LOC market segment clinical diagnostics, can be divided between point-of-care (POC) testing (i.e., a diagnostic test performed near the patients without needing a clinical laboratory) and central laboratory-based testing (i.e., diagnostic laboratory in a hospital).

Clinical diagnostics ranges from relatively simple immunochromatographic strips, similar to pregnancy tests, to highly complex systems requiring external machinery and expert training for their handling. Clinical diagnostic applications also include detecting nucleotides and peptides that are considered early indicators of disease. In many ways, the features of LOC devices fulfil the requirements for a POC diagnostic device: low consumption of reagents and sample, miniaturization of device and fast turn-around time for analysis.

It is a versatile technology that enables the miniaturization of complex fluid handling and integrated detection.

Microfluidic unit operations

Similar to the platforms in the application-specific integrated circuit industry in microelectronics, which provide elements and processes to make electronic circuitries, a **dedicated microfluidic platform comprises a set of microfluidic elements**. These elements have to be able to perform the basic fluidic unit operations

Pumping and valving

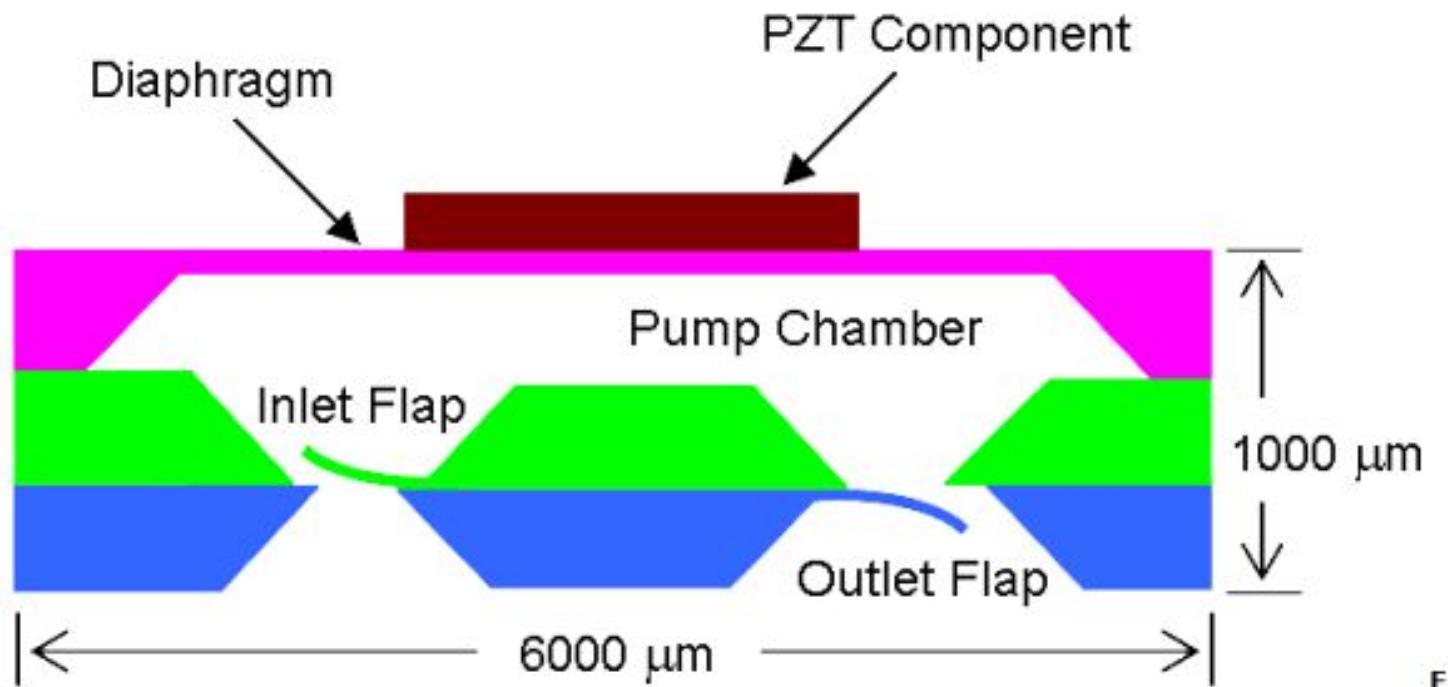
Microfluidic analytical systems require micropumps and microvalves **enabling precise control of sample, buffer, and reagent flow and delivery**

Pumping and valving

Several mechanisms have been used for transporting the fluids in microfluidic systems and they can be categorised in displacement and dynamic pumping.

Displacement pumps exert pressure forces on the fluid through one or more moving boundaries.

Micropumps can be based on reciprocating or rotary actuations or may have piezoelectric, (thermo)pneumatic, electrostatic and electromagnetic moving units to displace fluids



Sketch of micropump cross-section. Alternating voltage causes the PZT component to expand and contract along the horizontal direction. This induces a bending stress on the diaphragm, which in turn pumps the fluid through the chamber.

MIXING

Sample dilution, resuspension of dried reagents, and reaction of multiple reagents in LOC devices often require rapid and efficient mixing.

However, mixing in microfluidic platforms is difficult because flow is laminar and mixing is dominated by diffusion unless special measures are taken. Efficient micro-mixing can be achieved through a number of active and passive mixing mechanisms.

In active mixing, external driving forces such as acoustic waves, magnetic beads coupled with moving permanent magnets, or actuated air bubbles enhance the mixing of samples. In passive mixing, liquids are driven through microstructures designed to increase the contact area between different streams and to speed up diffusive or induce chaotic mixing.

SEPARATION

The beginning of modern microfluidic and LOC devices is closely linked to **separations of (bio)chemical** substances, in particular using electrophoresis.

Separation is important for LOC devices because it increases the target purity by removing interfering agents prior to detection.

Separation methods include capillary electrophoresis, dielectrophoresis, isoelectric focusing, liquid (electro)chromatography, size-based filtration, magnetic fields, acoustic waves, optical tweezers, and various combinations of flow, diffusion, and sedimentation based phenomena.

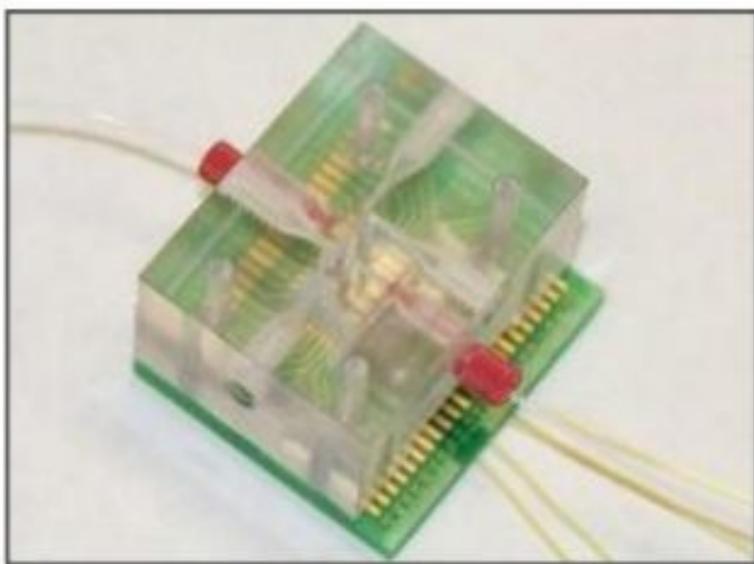
Reagent storage

For practical LOC devices, it is necessary to store reagents for extended periods on or in the device. Reagent, e.g. enzymes or antibodies, can be stored in a wet or dry state. The latter is often preferred in those cases where drying does not cause total and unrecoverable loss of activity, because reagents that are successfully dried typically exhibit improved stability relative to those stored wet

Sample preparation

Sample preparation, a necessary analytical step, is important in achieving adequate sensitivity and specificity in any detection platform. This is especially important in the case of complex matrices, such as blood, saliva, and interstitial fluid. Sample preparation encompasses sample concentration, diffusion, filtration, purification and fractionation of analytes from analytically noisy background matrices. Although large numbers of LOC devices accommodate unprocessed blood samples, the range of assays that can be performed is limited by the lack of well-developed on-chip sample preparation methodologies

Below is a miniaturized, portable version of a blood-count machine that was tested by astronauts. On long missions, astronauts will need the ability to analyze blood samples in real-time to diagnose infection, allergies, anemia or deficiencies in the immune system. This device, about the size of a cell phone, is being designed to accomplish this task



Lab-on-a-chip – Blood Analysis [Photo courtesy of Y. Tai, California Institute of Technology]

Company	Country	Name of device/chip/system	M/D ¹	Application
Abaxis Inc	USA	Piccolo® Xpress	M	blood analysis
Abbott Diabetes Care Inc	USA	FreeStyle Lite®	M	blood glucose
Abbott Diabetes Care Inc	USA	FreeStyle Freedom Lite®	M	blood glucose
Abbott Diabetes Care Inc	USA	FreeStyle InsuLinx	M	blood glucose
Abbott Diabetes Care Inc	USA	Precision Xtra®	M	blood glucose and ketone
Abbott Diabetes Care Inc	USA	Precision Xceed Pro	M	blood glucose and beta-ketone (hospital setting)
Abbott Point of Care Inc	USA	i-STAT®	M	cardiac markers, blood gases, electrolyte analyses, lactate, coagulation, haematology
Abbott Point of Care Inc	USA	i-STAT® 1 Wireless	M	cardiac markers, blood gases, electrolyte analyses, lactate, coagulation, haematology
Achira Labs Pvt Ltd	India	ACHIRA 2000	M	thyroid disorders, infertility
Advanced Liquid Logic	USA	-	D	HIV diagnostics / CD4 count
Agilent Technologies Inc	USA	2100 Bioanalyzer	M	nucleic acids, proteins and cells
Akronni Biosystems Inc	USA	TruDiagnosis®	M	DNA, RNA, and antibody-based testing
Alere Inc	USA	Alere Pima™ CD4 Analyser	M	HIV diagnostics / CD4 count
Alere Inc	USA	NAT System	D	HIV diagnostics / CD4 count
Alere Inc	USA	Alere Cholestech LDX® System	M	cholesterol, blood glucose, liver enzymes
Alere Inc	USA	Alere™ Heart Check System	M	B-type natriuretic peptide
Alere Inc	USA	Alere Triage® MeterPro	M	BNP, CK-MB, D-dimer, myoglobin, NGAL, troponin I, PLGF
Alere Inc	USA	Alere™ INRatio® / INRatio® 2 PT / INR Monitor	M	Anticoagulation
Arkray Global Business Inc	Japan	GLUCOCARD 01	M	blood glucose
Arkray Global Business Inc	Japan	GLUCOCARD 01-mini	M	blood glucose
Arkray Global Business Inc	Japan	GLUCOCARD 01-mini plus	M	blood glucose
Arkray Global Business Inc	Japan	GLUCOCARD X-METER GT-1910	M	blood glucose
Arkray Global Business Inc	Japan	GLUCOCARD X-mini	M	blood glucose
Arkray Global Business Inc	Japan	GLUCOCARD X-mini plus	M	blood glucose
Arkray Global Business Inc	Japan	GLUCOCARD Σ	M	blood glucose
Arkray Global Business Inc	Japan	GLUCOCARD Σ-mini	M	blood glucose
Atonomics A/S	Denmark	Atolyzer	D	cardiovascular disease, prostate cancer
Axis-Shield plc	UK	Afineon	M	CRP, HbA1c, ACR, lipid
Axis-Shield plc	UK	NyoCard	M	CRP, HbA1c, D-dimer, U-albumine

Application of Lab-on-Chip Technology

- ¶ The increased demand of LoC devices in many areas is due to the various technological advantages of LoC technology such as portability, automated sample handling, re-configurability etc.
- ¶ Immunoassay LoC for bacteria detection, Real time PCR detection chips, DNA chip, Gene Chip, Cellular Analysis chip, Flow Cytometer LoC (for HIV) etc. are some of the applications of LoC technology in the biomedical field.
- ¶ LoC to be used for meeting the requirements and improving the efficiency of Point-of-Care diagnostic systems.
- ¶ Since the required functional modules and working principles generally depend on target analytes, so the applications of POCT systems are categorized according to the type of analyte such as cells, proteins, metabolites and nucleic acids. POCT systems have the ability to detect specific biomarkers from these analytes.
- ¶ A Lab-on-Chip device is proposed that uses acoustic streaming technique for promoting the pumping and mixing of microfluids inside microchannels so as to improve the microfluidic device performance.
- ¶ To generate this acoustic streaming, a transducer is used which is based on a piezoelectric material like β -PVDF (polyvinylidene fluoride prepared in its β phase). This polymer is processed to be functionally graded for being able to maintain the heating and to control the movement of fluids in conjunction with the input signal that is applied to the transducer.

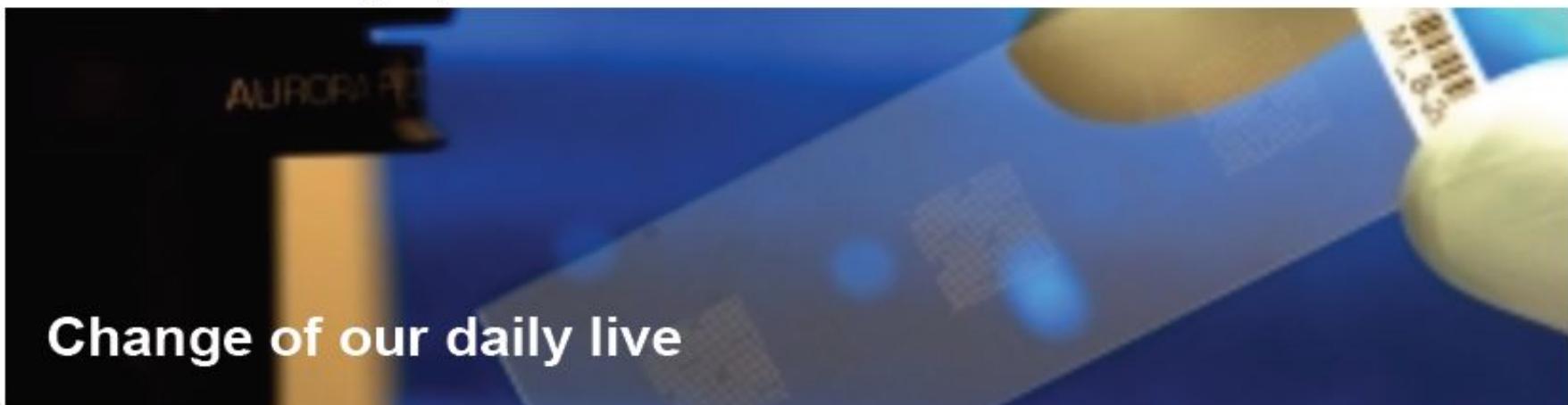
Limitations and Challenges of lab-on-a chip

- signal/noise ratio from miniaturization
- need of external system to work

- current challenges:
 - industrialization for commercialization (fabrication processes, design of specific surface treatments, flow control system...)
 - increase of maximum number of biological operations integrated on the same chip

LOC outlook

- already commercialized: glucose monitoring or HIV detection and heart attack diagnostics
- near future: LOC widely used in hospitals
- later: real time monitoring of health at home
- in developing countries LOC enables diagnostics for wider population



34 <http://nanob2a.cin2.es/publication/articles/integrated-optical-devices-for-lab-on-a-chip-biosensing-applications>, Marielle Bonenberger
downloaded 14.04.16

Integrated sensors: system organization and function

In a simple control system, the sensor is only one of three items required to implement a control strategy. The sensor provides an input to a controller with the desired strategy in its memory, and the controller drives an output stage to modify or maintain the status of a load, such as a light, a motor, a solenoid, or a display. As shown in Figure 1.4, a signal conditioning interface typically exists between the sensor(s) and the controller and between the controller

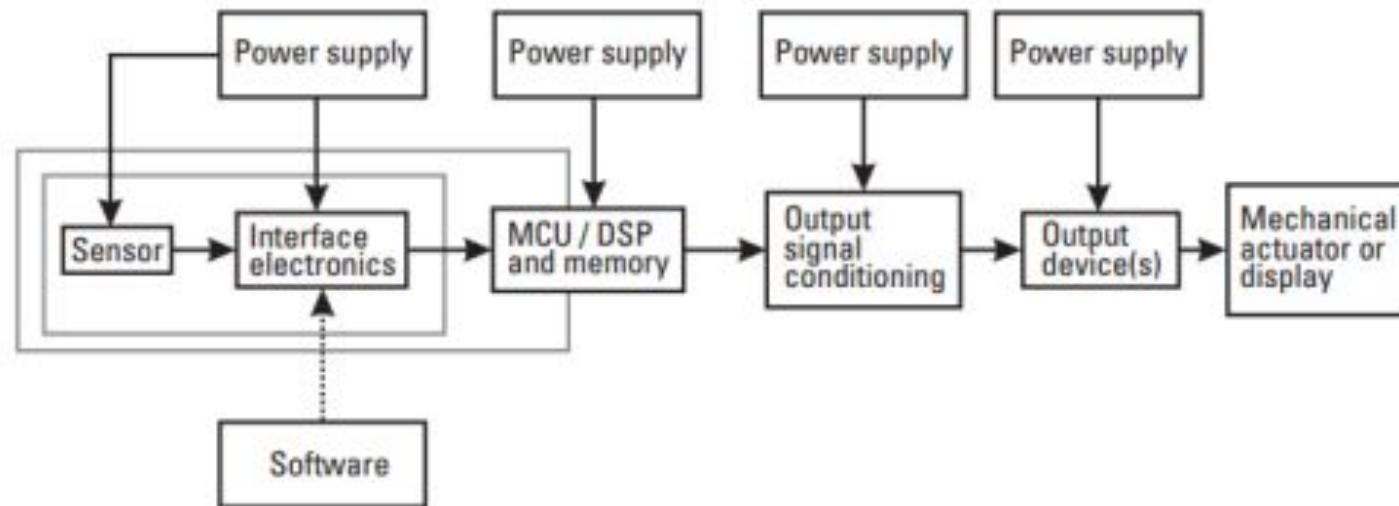


Figure 1.4 Generic control system.

and the output device. Smart sensing includes a portion of the controller's functions in the sensor portion of the system. That means software will play an increasingly important role in smart sensors. The power supply requirements for the electronics and the sensor represent an additional consideration that is becoming more important as MCU voltages are decreased and more sensors are used in battery power or portable applications. The number of supplies in Figure 1.4 may not be required for a particular application, but they serve as a reminder for considering the available voltage for the sensor and the interface versus the rest of the system.

As shown in Figure 1.5, in addition to the sensing element and its associated amplification and signal conditioning, an A/D converter, memory of some type, and logic (control) capability are

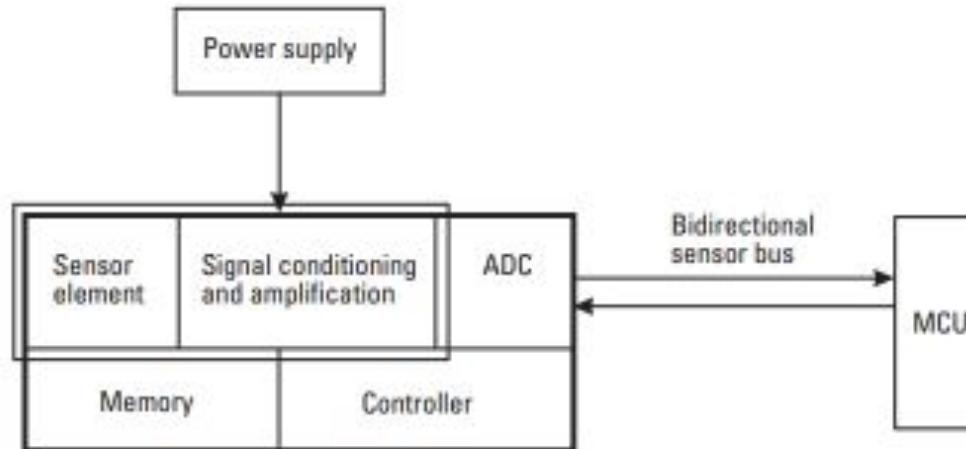


Figure 1.5 Smart sensor model.

included in the smart sensor. Once the signal is in digital format, it can be communicated by several communication protocols. The regulated power supply also required for the system and its effect on system accuracy must be taken into account. That is becoming more of an issue as power management issues are addressed in system design and different supply voltages proliferate.

Reducing the number of discrete elements in a smart sensor (or any system) is desirable to reduce the number of components, form factor, interconnections, assembly cost, and frequently component cost as well. The choices for how that integration occurs are often a function of the original expertise of the integrator. For example, as shown in Figure 1.6, a sensor manufacturer that already uses semiconductor, that is, bipolar or metal oxide semiconductor (MOS), technology for the sensing element may expand the capability and increase the value (and intelligence) of the sensing unit it produces by combining the signal conditioning in the same package or in a sensor module. Through integration, the signal conditioning can also be combined at the same time the sensor is fabricated or manufactured.

While the process of integration is more complex, the integrated sensor can be manufactured with the sensor and signal conditioning optimized for a particular application. Conversely, an MCU manufacturer using a complementary metal oxide semiconductor (CMOS) process typically integrates memory, A/D, and additional signal conditioning to reduce the number of components in the system. A variety of combinations are indicated in Figure 1.6. Processing technology is a key factor. However, manufacturers not only must be willing to integrate additional system components, they also must achieve a cost-effective solution. Combinations of hybrid (package level) and monolithic integration are discussed frequently in the remainder of this book. Different design philosophies and the necessity to partition the sensor/system at different points can determine whether a smart sensor is purchased or, alternatively, designed using a sensor signal processor or other components necessary to meet the desired performance of the end product.

The integration path can have a significant effect on the ultimate level of component reduction. As shown in Figure 1.7 [8], the input (demonstrated by a pressure sensor), computing (high-density CMOS [HCMOS] microcontroller), and output side (power MOS) are all increasing the level of monolithic integration. The choice of sensor technology, such as bipolar, can have a limiting effect on how far the integration can progress. For example, a bipolar sensor can increase integration level by adding signal conditioning and progress to a monolithic level III sensor. Through package-level integration, a two-chip sensor controller can be achieved by combining the sensor with an HCMOS microcontroller. However, the highest level of monolithic integration, level V, will be realized only by pursuing MOS-compatible sensing and power-control technologies. Realizing the full potential of those new sensors will require a new approach to identify sensor applications

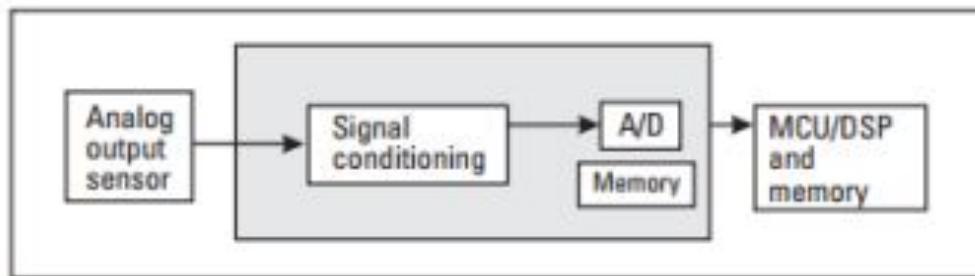
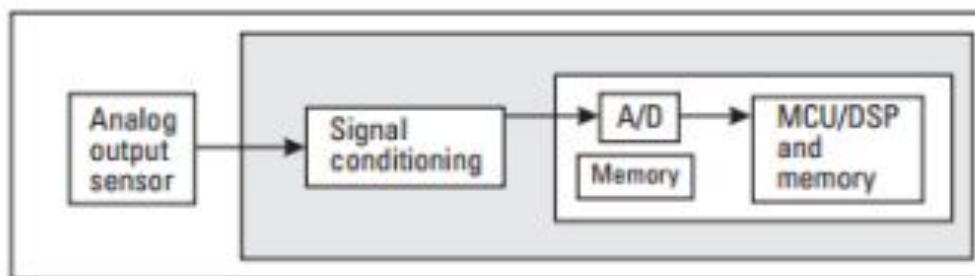
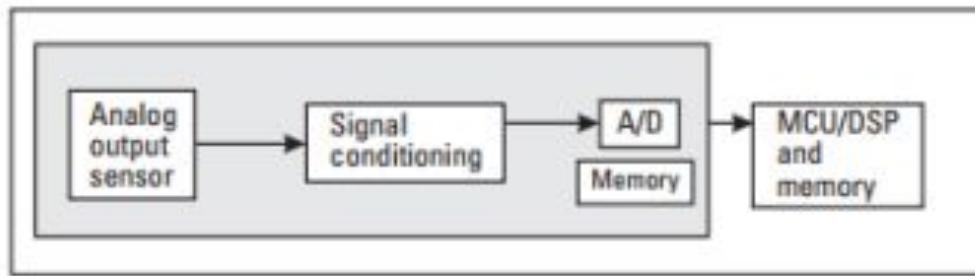
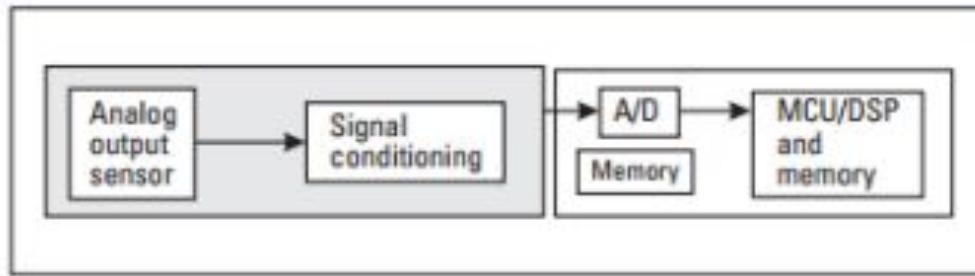


figure 1.6 Partitioning and integration possibilities.

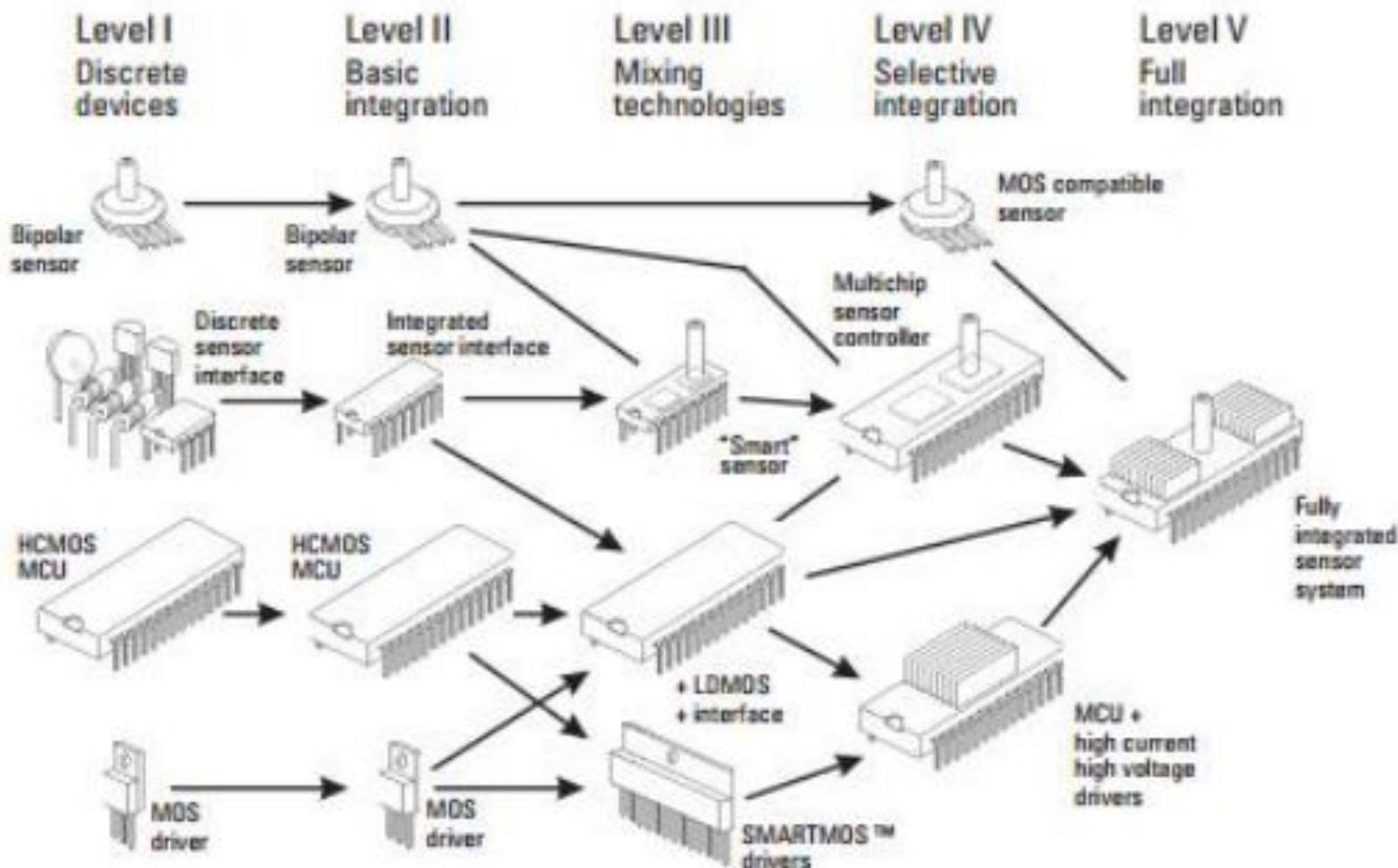


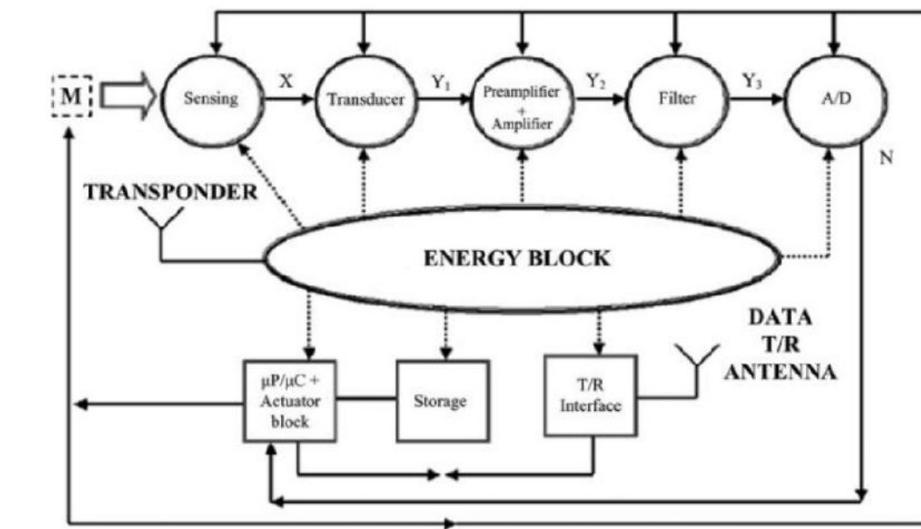
Figure 1.7 Sensor technology migration path.

SENSOR INTERFACING

The concept of interfacing sensors is giving input from sensors to microcontroller or input systems in a way which they can understand and act accordingly. Most of the sensors give output in analog form but the microcontroller or microprocessor needs input as digital so now comparators act as interfacing sensors where they convert analog signals to digital signals.

Interfacing differs by the type of sensor and by the type of system you're interfacing to.

For example, a gas-sensing microsystem typically consists of an array of gas-sensors, a temperature control circuit, an electronic readout block and a data processor. In order to develop a really portable device, the system has to be stand-alone, i.e. has to be able to operate without the aid of any laboratory instrument, while sensors, implemented with silicon based technologies, can detect different physical and chemical quantities with acceptable selectivity, sensitivity and resolution.



Block scheme of a smart sensor system

The sensor response (i.e., the output signal of the sensor) is typically analog and this is why it is said that “the real world is analog”. However, sometimes it can be also convenient to process the information in the digital electrical domain. In this case, a digital electronic system is required for converting the analog sensor response into a suitable digital electrical signal. **This is what electronic interfaces perform:**

they are circuits that convert the sensor responses into proper electric signals easy to be processed. If these interfaces are particularly “intelligent”, including special functions such as auto-calibration, sensor biasing, working temperature control, etc., they can be considered “smart”.

A smart system (if miniaturized, named microsystem) requires, all together, sensors (if miniaturized, named microsensors), actuators and suitable electronic interfaces.

More specifically, the sensor interface is an electronic circuit which allows to read-out the information coming from the signal generated by a sensor, providing a suitable output signal simple to display or to elaborate.

Signal Conditioning Circuits and Interface Devices

In order to get information from a sensor into a computer, the signal from the sensor must first be sent to an interface device of some form and from there to the computer. However, in order to be useful to the interface device, the signal from the sensor must often undergo some form of conditioning. Almost all interface devices designed to allow interfacing of sensors to computers are designed to accept a voltage signal in the range of 0 to 5 volts and to digitize this.

This means that the aim of the signal conditioning circuit is to take whatever output is available from the sensor, whether voltage or resistance, and convert it to a 0 to 5 volt signal. This process generally involves a combination of one or more simple processes: converting a resistance to a voltage, dividing a voltage, amplifying a voltage and shifting a voltage.

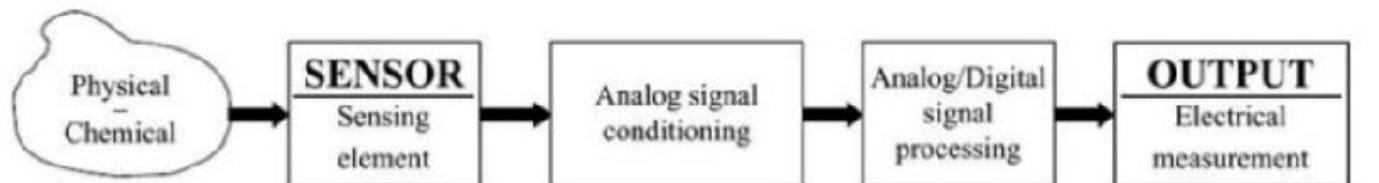
For example, thermocouple signals have very small voltage levels that must be amplified before they can be digitized. Other sensors, such as resistance temperature detectors (RTDs), accelerometers, and strain gauges require excitation to operate. All of these preparation technologies are forms of signal conditioning.

Signal conditioning is one of the fundamental building blocks of modern data acquisition (aka DAS or DAQ system). The basic purpose of a data acquisition system is to make physical measurements. They are comprised of the following basic components:

Basic Sensor Interfacing Techniques: Introduction to Signal Conditioning:

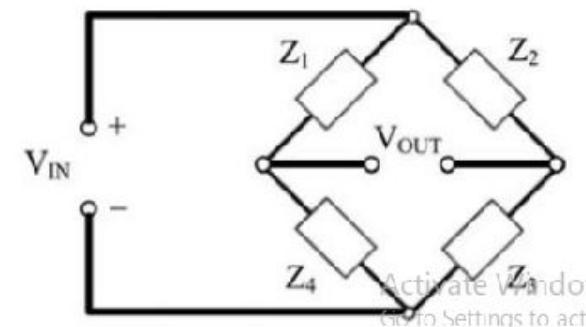
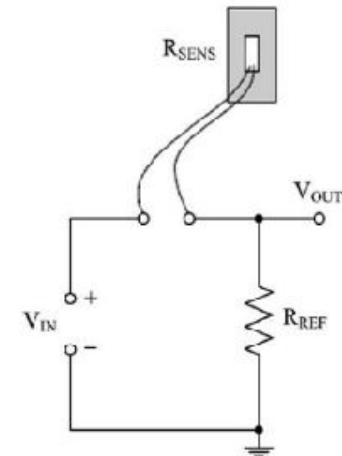
A signal conditioning system (or, in other words, electronic interface, read-out circuit, front-end, etc.) takes the output from a sensing element and converts it into a more suitable form for further processing (e.g., amplification, analog-digital conversion, frequency-voltage conversion, etc.), as described in Fig

Fig. 1



Block scheme of a complete signal conditioning system

The simpler interface circuits, often utilized, for example, as basic signal conditioning stages in resistive sensors, are the voltage divider, shown in Fig. 1, and its differential version, the Wheatstone bridge where V_{IN} is the supply voltage and one (or more) of the bridge elements (impedances) are the sensors. These simple basic solutions are able to perform, more in general, a conversion from an impedance (e.g., a resistance) variation into a voltage one



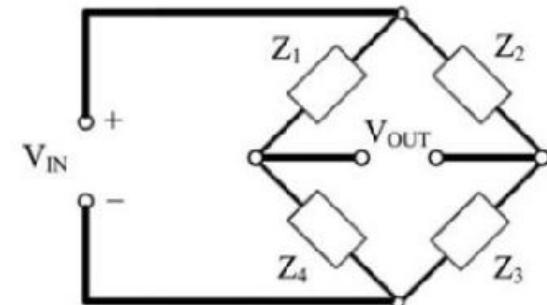
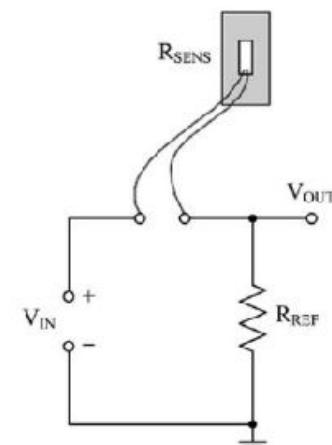
Resistive Sensors Basic Interfacing

When the sensor electrical parameter can be modelled by a resistance that, in particular, varies into a reduced range, not more than two to three decades, a resistive voltage divider circuit, operating a Resistance-to-Voltage (R-V) conversion (as yet shown in Fig.1), can be utilized as simple resistive sensor interface circuit. Typically, it applies a constant voltage so to measure the change of conductivity of the resistive sensing element

Another very simple interfacing circuit for resistive sensors, varying into a reduced range, can be implemented by the well-known Wheatstone bridge which operates also an R-V conversion.

This circuit configuration represents the “fully-differential” version of the basic voltage divider and shows its same sensitivity. In this case, one of the four resistances is the resistive sensor whose sensing element varies when an external physical or chemical phenomenon occurs. The main drawback of this kind of resistive sensor interface is in its unsettable and low sensitivity, only dependent on the total supply voltage.

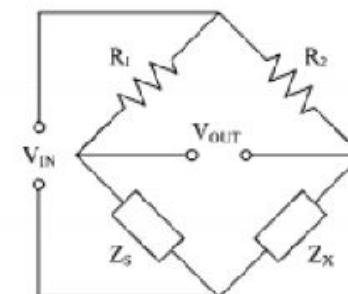
Fig.1



if larger variations of sensor resistive values happen, we can employ a Resistance-to-Time (R-T) conversion, which can be also considered as a Resistance-to-frequency (R-f) conversion when the “time” (period) is related to a periodic waveform. The R-T based interfaces exploit the easiness of measuring time intervals over a wide range of variation. As a consequence, no more scaling factor systems are needed. Typically, an R-T basic scheme is based on an oscillator architecture which exploits the sensor to be excited by a switched voltage (the AC excitation voltage). In this case, the simpler electronic interface which operates An R-T (or R-f) conversion can be implemented by an OA in an astable multivibrator configuration.

Capacitive Sensors Basic Interfacing

The typical simplest way to measure a capacitance is to convert it (or its variation) into a suitable voltage level, performing the so-called Capacitance-to-Voltage (C-V) conversion. This can be simply done by one of the bridge configurations shown in Figure, once that all the other passive components are known or can be accurately measured.



Comparison with series constants

Measures L or C

Balance equations:

$$R_x = R_s \frac{R_2}{R_1}$$

If inductive:

$$L_x = L_s \frac{R_2}{R_1}$$

If capacitive:

$$C_x = C_s \frac{R_1}{R_2}$$

Nevertheless, the main problem related to all these interface solutions concerns the detection of either very low capacitance values or its small variations. In this sense, the proper design of a suitable read-out circuit, which has to be able to provide the smallest parasitic capacitances at its terminals, is another important task, while a special consideration for shielding to still reduce parasitic capacitances of the electronic front-end, which is essential to have suitable performances, has to be also done avoiding the need for large connectors. Therefore, the key aspect of the problem is related to the sensing system, where the sensitivity to parasitic elements, interconnection wires and noise has to be the lowest possible.

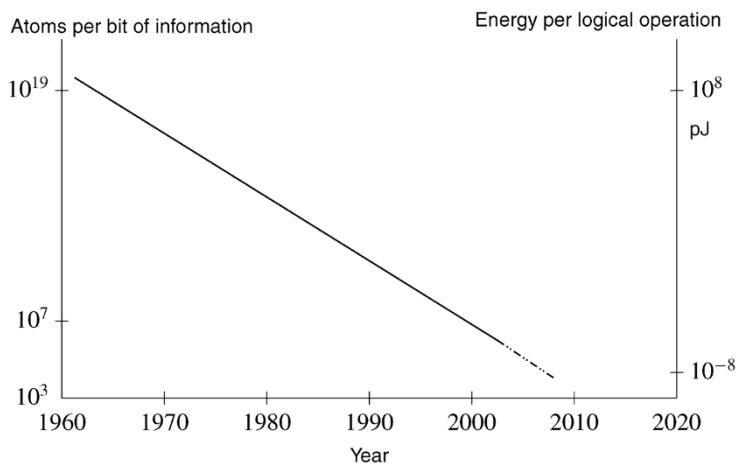
Microsystems Integration (MI)

Definition of MI:

The Microsystems fabrication process to create a device is known as Microsystems Integration (MI). This integration involves combining all the individual silicon processing steps with the appropriate masks and equipment settings to create a functioning device.

Basics of MST:

- ❖ The progress in Microsystems is indicated by the integration level over the last decades of development. Figure 1 shows a curve that J. Meind forecasted in 1980. Gordon Moore, one of the founders of Intel, proposed this representation. The Moore Plot shows that the integration level is doubling every 18 months. Figure 1 shows two tendencies, both are too reserved about the real development, so the curves must be corrected to higher values. Today we have the vision of memory chips made of silicon with a capacity of 160Gbit (4 Gbit can store a whole movie). Such trend curves of Microsystems show the essential characteristics of the devices, systems, or other parameters and can be extrapolated for future predictions. These "laws" are not laws of physics, they are mainly based on the laws of business management. They are valid because many people are working under the same economic conditions and technical prerequisites, and under the same social stability. Under these conditions progress is continuous.



- ❖ In addition, the above-mentioned is only valid under the precondition that the scientific laws allow such a progress. Since the invention of integrated circuits, their characteristics have been changed in the orders of magnitude. If we regard the number of atoms that are necessary for storing or operating 1 bit then we can see the breath-taking development:

- In 1960, one transistor consisted of 1020 atoms in a volume of 0.1 cm^3 , in the year 2000 these numbers were reduced to 107 atoms in 0.01 cm^3 .
- In the same way the energy for storing or operating 1 bit decreased, since the energy for charging and discharging capacities was lowered by the facts that one reduces the area of the capacitors from 1 cm^2 to 0.01 cm^2 and the voltages from 10 V to 1 V.

- The change of 12 orders of magnitude was the prerequisite that Microsystems could have such high integration levels without running into the problems of power dissipation and thermal heating.
 - The increase of the integration level was possible first by reducing the feature size of the devices and in the second place by enlarging the chip area and by functional integration. It is assumed that the silicon technology has its limits for further miniaturization to approximately 0.1 nm in 2040. To overcome this restriction, functional integration and three-dimensional integration are possible solutions. An alternative approach is nanoelectronics.
- ❖ A radical change in the entire field of electronics began in 1947 when the transistor was invented; 11 years later in 1958 the first integrated semiconductor circuit was built. Ever since, electronics has turned almost completely into semiconductor electronics. Microsystems manufacturing methods make it possible simultaneously to produce large numbers of similar components with dimensions that are much too small for precision mechanics.
- ❖ The discovery of the piezoresistive effect in 1953 created the precondition for also applying semiconductor materials and Microsystems production methods to non-electronic components. The first description of how to use a silicon membrane with integrated piezoresistors as mechanical deformation body dates to 1962.
- ❖ The experience of the past shows that throughout constant technology improvement electronics has become more reliable, faster, more powerful, and less expensive by reducing the dimensions of integrated circuits. These advantages are the driver for the development of modern Microsystems. The long-term goal of this development will lead to nanoelectronics. The first Microsystems components and systems were quite expensive and therefore only an adequate solution for space travel.
- ❖ Nowadays integrated circuits as key components are utilized in a broad range of applications. The semiconductor silicon is the most important material in the production of Microsystems circuits. Actually the limit of silicon technology is set by the manufacturing processes and not by silicon itself or the laws of physics.
- ❖ In the beginning of Microsystems in 1960 the way of its development was not clear. It was not obvious that the circuits must be integrated into silicon, however, it was obvious to use solid state switches. The invention of the bipolar transistor (Bardeen, Brittain, and Shockley in 1948) was only possible through extensive studies in the field of solid-state materials some decades before. This pioneering work was awarded the Nobel prize.
- ❖ It was crucial that both the Bell Telephone Company and the inventors shared their knowledge with the public and the further development was not restricted by patents. The invention of the integrated circuit by Kilby and Noice in 1959 was also spectacular, however, it was obvious to integrate both transistors and resistors on a single chip. For this work Kilby was awarded the 2000 Nobel prize. As we know today his idea was the right approach for the development of Microsystems circuits. Other ideas were less spectacular; however, they also influenced the spread of Microsystems. Some examples of these ideas are the planar technology, the microprocessor concept (Hoff 1971 with the Intel 4004), the scaling of MOS circuits (Dennard 1973) and the technology invariant interface of the design rules (Mead and Conway 1980).
- ❖ The significance of Microsystems as a basic technology was hesitatingly accepted by the market. Nowadays we recognize Microsystems as an important key technology for present

and future information systems. In particular, the growing demands of information technology for more powerful Microsystems circuits will enforce the transition to nanoelectronics in the future.

- ❖ The miniaturization advantages of MEMS can be realized only if they can be efficiently integrated with Microsystems. At first glance, it may seem that the most desirable approach to integration of MEMS and Microsystems would be to create a single or monolithic fabrication process capable of supporting both Microsystems and MEMS. This, however, is a difficult undertaking.
- ❖ For example, the removal of all oxide layers in a polysilicon surface micromachining process does not allow monolithic integration with CMOS VLSI circuits. Additionally, the high temperature anneal of MEMS devices to relieve internal stress can be harmful to the carefully controlled diffusion budgets of Microsystems circuits.
- ❖ However, some custom processes, such as Sandia's Modular, Monolithic Micro-Electro-Mechanical Systems (M3EMS) process, have been realized to allow monolithic integration of simple surface micromachined MEMS and electronics by fabricating the MEMS before the Microsystems.
- ❖ Although several custom monolithic fabrication processes of MEMS and Microsystems have been demonstrated, the requirement to remove sacrificial layers in micromachining presents a set of unique problems. For example, the choice of sacrificial material for the MEMS device may be incompatible with the CMOS devices or Microsystems packaging
- ❖ In CMOS, silicon dioxide is critical for the transistor gate insulation and for circuit passivation; but many MEMS processes use silicon dioxide as the sacrificial layer. Thus, the selection of structural and sacrificial materials in the MEMS devices impacts the integration with CMOS electronics.
- ❖ Moreover, some etchants for surface or bulk micromachining are not compatible with Microsystems materials or wiring. For example, KOH is often used in bulk micromachining, but it dissolves aluminum, which is commonly used in IC metallizations. Another bulk micromachining etchant, EDP, is not as aggressive in attacking aluminum but still requires masking the aluminum to preserve the integrated circuits or the package.
- ❖ Other important integration issues include the material properties of the films used (e.g. gate polysilicon may not be the best choice of mechanical polysilicon), the thickness of the thin films and thermal budget restrictions. As a result, the integration of MEMS with electronics usually requires additional processing steps and materials to protect the CMOS circuits and the package during the final MEMS release.
- ❖ Furthermore, electrical and environmental conditions also hamper monolithic integration of CMOS and MEMS. Many MEMS are designed to operate electrostatically with high voltages, which are challenging to implement with digital CMOS technologies. Other MEMS are designed to operate inside living organisms or are exposed to temperatures, radiation or chemicals that would be destructive to the CMOS integrated circuits.
- ❖ All these factors provide challenges for integration of MEMS and CMOS technology. Building monolithically integrated MEMS and electronic circuits in the same process may not always be cost-effective or realizable. However, it may be possible to use multichip module (MCM) technology to gain the benefits of MEMS and CMOS integration with minimum extra cost or additional technical challenges. MCMs offer an attractive integration approach because of the ability to support a variety of die types in a common substrate without requiring changes or compromises to either the MEMS or electronics fabrication processes. Furthermore,

- ❖ MCMs offer packaging alternatives for applications for which it is cost or time prohibitive to develop a monolithic integration solution. One of the main benefits of MCM packaging for MEMS and IC integration is the ability to combine die from incompatible processes in a common substrate. Other benefits of MCM technology are the electrical, size and weight performance improvement over conventional packaging techniques. The two common characteristics for MCM classification are the type of substrate used and the means of interconnecting signals between the dies. The three dominant MCM substrate technologies are MCM-laminate, MCM-ceramic and MCM-deposited, but other substrate alternatives exist.
- ❖ Of particular interest to wafer-scale integration of MEMS may be the MCM-silicon (MCM-Si) or ‘silicon on silicon’ technology. In MCM-Si, IC fabrication processes are used to deposit the interconnect and dielectric layers on a silicon substrate. MCM-Si has the highest signal interconnect density of any substrate choice and its coefficient of thermal expansion is an excellent match for any silicon die.
- ❖ The primary disadvantage of MCM-Si is that silicon is not a good base for the MCM package assembly because it is relatively fragile and consequently the MCM-Si substrate must be repackaged, causing additional cost. An advantage of MCM-Si technology, however, is that bulk micromachining techniques can be used to pattern the silicon substrate. The substrate can be patterned using silicon bulk etchants and wafer bonding to form useful features such as embedded components or microchannels. Microchannels may be used to align optical fibres or carry fluids to and from MEMS mounted in the module. In addition, these microchannels can provide an efficient way to cool the MCM.