Biosensors : A Survey Report

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Abstract

A biosensor is a sensing device made up of a combination of a specific biological element and a transducer. The "specific biological element" recognizes a specific analyte and the changes in the biomolecule are usually converted into electrical signal (which is in turn calibrated to a certain scale) by a transducer. Aim of this survey work is to discuss the various biosensors available for different biosensing applications. Initially, the survey focuses on the basics of biosensing devices which can serve as introductory tutorial for the readers who are new to this field. Later, the survey highlights the technicalities of few biosensors in great detail. The survey ends with brief discussion on the major difficulties the biosensor research communities normally encounter.

1 Introduction

The history of biosensors started in the year 1962 with the development of enzyme electrodes by the scientist Leland C. Clark. Since then the research communities from various fields like VLSI, physics, chemistry, material science, and so on, have come together to develop more sophisticated, reliable and matured biosensing devices for applications in the fields of medicine, agriculture, and biotechnology, etc.

What is a biosensor ? Various definitions and terminologies are used depending on the field of applications. Depending on the field of applications biosensors are known as : *immunosensors*, *optrodes*, *chemical canaries*, *resonant mirrors*, *glucometers*, *biochips*, *biocomputers*, and so on. Two generalized definitions of biosensors can be found in [2, 4]. Authors in [2] define it as : "a biosensor is a chemical sensing device in which a biologically derived recognition entity is coupled to a transducer, to allow the quantitative development of some complex biochemical parameter". According to the authors [4] : "a biosensor is a analytical device incorporating a deliberate and intimate combination of a specific biological element (that creates a recognition event) and a physical element (that transduces the recognition event)".

The name "biosensor" signifies that the device is a combination of two parts :

- bio-element
- sensor-element.

The *bio*-element may be an enzyme, antibody, antigen, living cells, tissues, etc. The large variety of *sensor*-elements includes electric current, elec-

tric potential, intensity and phase of electromagnetic radiations, mass, conductance, impedance, temperature, viscosity, and so on. The basic concepts of biosensor can be illustrated by the help of Fig. 1. A specific "bio" element (say, enzyme) recognizes a specific analyte and the "sensor" element transduces the change in the biomolecule into electrical signal. The bio element is very specific to the analyte to which it is sensitive. It does not recognizes other analytes.

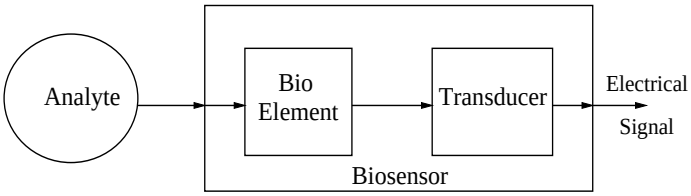


Figure 1: Basic Concepts of Biosensor

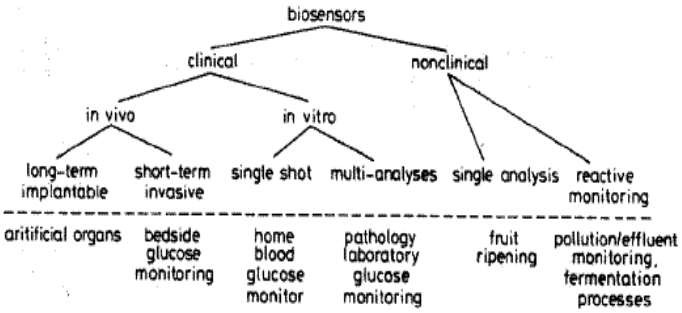


Figure 2: Potential Applications of Biosensors, Source : [2]

Depending on the transducing mechanism used the biosensors can be of many types such as :

- Resonant biosensors
- Optical-Detection biosensors
- Thermal-Detection biosensors
- Ion-Sensitive FETs (ISFETs) biosensors
- Electrochemical biosensors

Details of all these different types will be discussed in this survey work. The electrochemical biosensors based on the parameter measured can be further classified as [1]:

- conductimetric
- amperometric
- potentiometric

The biosensors can have variety of biomedical and industry applications. Some of the possible applications are shown in Fig. 2. The major application so far is in blood glucose sensing because of abundant market potential. But, biosensors have tremendous opportunity for commercialization in other fields of application as well. Fig.3 shows a needle-type glucose biosensor implanted in subcutaneous fatty tissue. Some commercially available glucose biosensors products from Medisense are shown in Fig. 4 and Fig. 5. A handheld biodetector developed by G. Kovacs [19] is shown in Fig. 6. Even though biosensors have got very good application potential it has not been highly commercialised because of several difficulties, for example, due to the presence of biomolecules alongwith semiconductor materials the biosensor contamination is a major issue [2, 6].

This survey paper is organized as follows. Section 2 discusses the fundamental mechanisms of biosensors. Different types of biosensors are detailed in Section 3. Section 4 discusses details of a biosensor that can be used to monitor cell morphology in tissue culture environment. A biosensor based on using hologram to detect pancreatic disorders is discussed in section 5. Section 6 discuses DNA detection-on-a-chip. Various glucose biosensors are discussed in section 7.

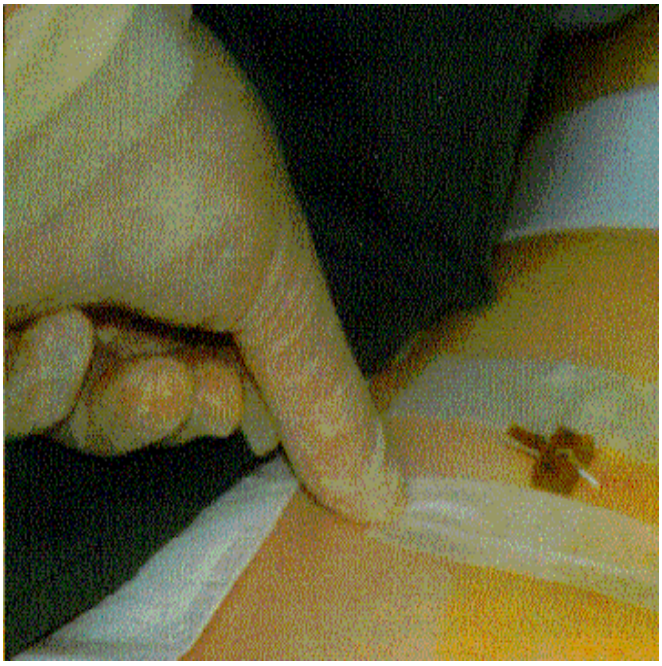


Figure 3: A needle-type glucose biosensor implanted in subcutaneous fatty tissue

Figure 4: Medisense glucose biosensor Pen, Source: http://www.medisense.com

Figure 5: Medisense glucose biosensor with Big Digital Display, Source: http://www.medisense.com

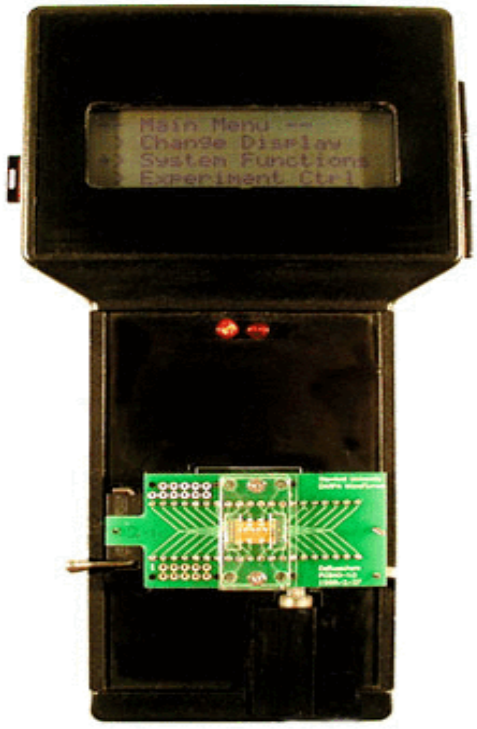


Figure 6: A handheld biodetector developed by G. Kovacs, Source: [20]

2 Basic Concepts of Biosensors

We have already seen that a biosensor consists of a bio-element and a sensor-element. The bio-element of the may be an enzyme, antibody, living cells, tissue, etc., and the sensing element may be electric current, electric potential, and so on. A detailed list of different possible bio-elements and sensor-elements is in Fig. 7.

The ”bio” and the ”sensor” elements can be coupled together in one of the four possible ways listed below [19] (refer Fig. 8).

- Membrane Entrapment
- Physical Adsorption
- Matrix Entrapment
- Covalent Bonding

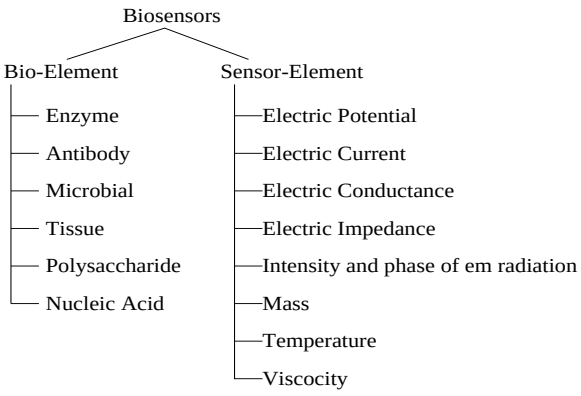


Figure 7: Elements of a Biosensor

In the membrane entrapment scheme, a semipermeable membrane separates the analyte and the bioelement, and the sensor is attached to the bioelement. The physical adsorption scheme is dependent on a combination of van der Waals forces, hydrophobic forces, hydrogen bonds, and ionic forces to attach the biomaterial to the surface of the sensor. The porous entrapment scheme is based on forming a porous encapsulation matrix around the biological material that helps in binding it to the sensor. In the case of the covalent bonding the sensor surface is treated as a reactive groups to which the biological materials can bind.

A typically used bioelement is an enzyme. These are large protein molecules that act as catalysts in chemical reactions, but remain unchanged at the end of reaction. Fig. 9 shows the working principle of enzymes. The enzymes are extremely specific in their action. Meaning, an enzyme X will change a specific substance A (not C) to another specific substance B (not D). This is illustrated in the Fig. 10. *This extremely specificity action of the enzymes is the basis of biosensors*.

3 Types of biosensors

In this section we will discuss the various types of possible biosensors. We will analyze the working mechanism of each one of them.

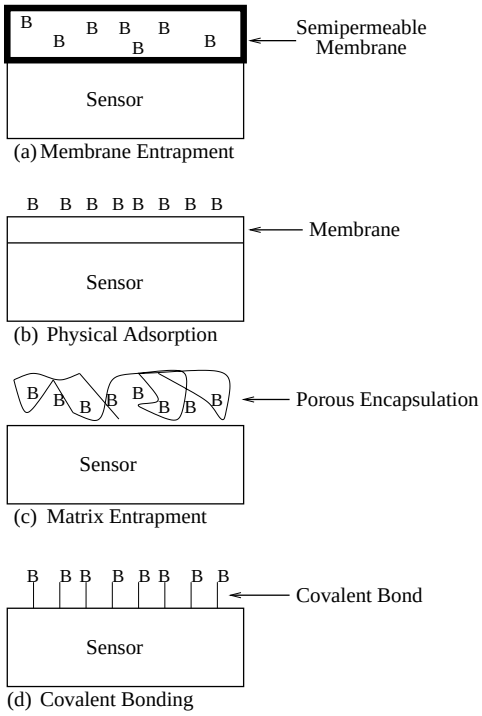


Figure 8: Coupling of Bio-Material with the Sensor, Source : [19]

3.1 Resonant biosensors

In this type of biosensors an acoustic wave transducer is coupled with antibody (bio-element). When the analyte molecules (antigen) get attached to the membrane, the membrane mass changes, resulting in a subsequent change in the resonant frequency of the transducer. This frequency change is measured out [19].

3.2 Optical-detection biosensors

The output transduced signal that is measured is light signal for this type of biosensors. The biosensors can be made based on optical diffraction or electrochemilluminence. In optical diffraction based devices, a silicon wafer is coated with a protein via covalent bonds. The wafer is exposed to UV light through a photomask and the antibodies made inactivated in the exposed regions. The diced wafer chips when incubated in analyte

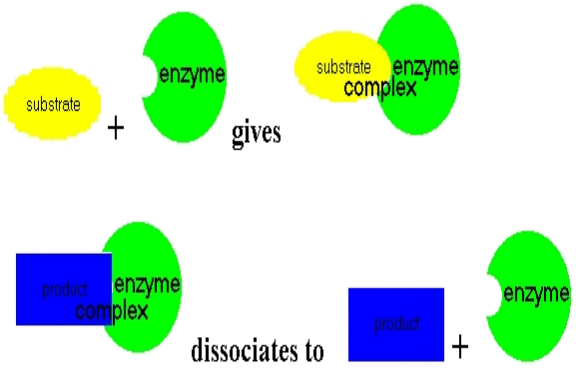


Figure 9: Working Principle of Enzymes, Source : [5]

antigen-antibody binding is formed in active regions, thus creating diffraction grating. This grating produces diffraction signal when illuminated with a light source such as laser. This signal can be measured or can be further amplified before measuring for improving sensitivity [19].

3.3 Thermal-detection biosensors

This type of biosensors are constructed combining enzymes with temperature sensors. When the analyte comes in contact with the enzyme, the heat reaction of the enzyme is measured and is calibrated against the analyte concentration [19].

3.4 Ion-Sensitive biosensors

These are basically semiconductor FETs having ion-sensitive surface [7, 19]. The surface electrical potential changes when the ions and the semiconductor interact. This potential change can be measured. The Ion Sensitive Field Effect Transistor (ISFET) can be constructed by covering the sensor electrode with a polymer layer. This polymer layer is selectively permeable to analyte ions. The ions diffuse through the polymer layer and in turn cause a change in the FET surface potential. Fig. 11 shows an ISFET having enzyme enzyme layer

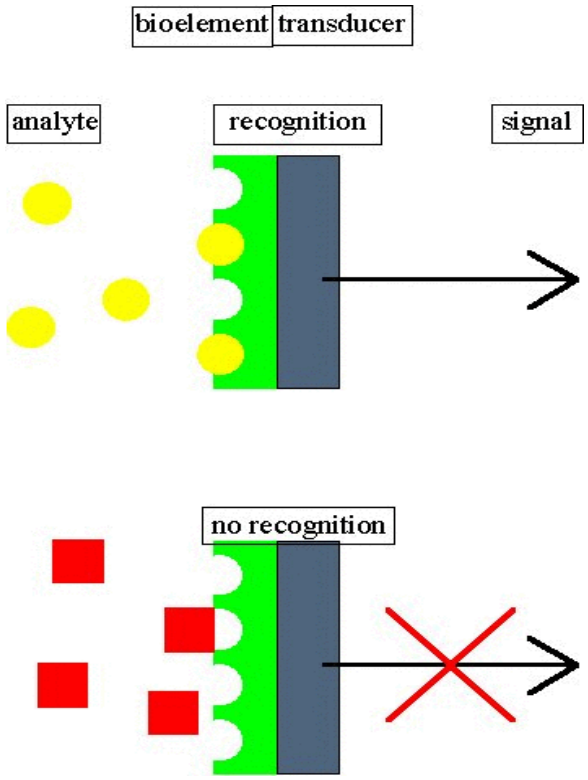


Figure 10: Specificity of Enzymes, Source : [5]

placed on it; also called ENFET (Enzyme Field Effect Transistor) [7]. This type of biosensor are primarily used for pH detection.

3.5 Electrochemical biosensors

Electrochemical biosensors are mainly used for detection of hybridised DNA, DNA-binding drugs, glucose concentration, etc. The underlying principle for this class of biosensors is that many chemical reactions produce or consume ions or electrons which in turn cause some change in the electrical properties of the solution which can be sensed out and used as measuring parameter [1, 19]. The electrochemical biosensors can be classified based on the measuring electrical parameters as : (1) conductimetric, (2) amperometric and (3) potentiometric [1]. A comparative discussion of these three types is give in Table 1.

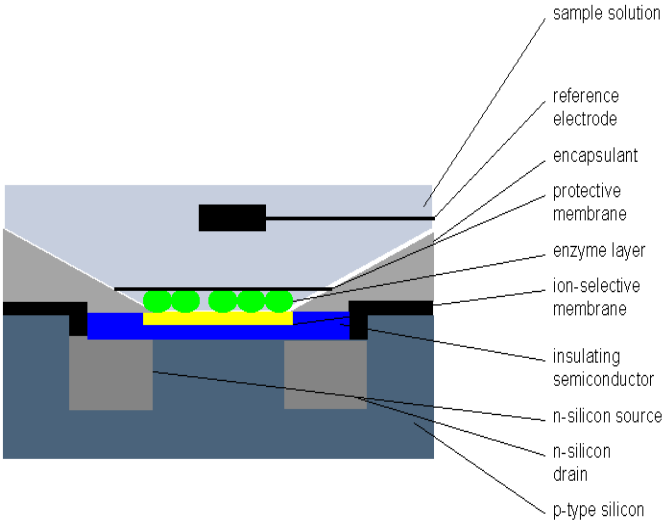


Figure 11: Enzyme Field Effect Transistor (ENFET), Source : [7]

3.5.1 Conductimetric biosensors

The measured parameter is the electrical conductance/resistance of the solution. When electrochemical reactions produce ions or electrons the overall conductivity/resistivity of the solution changes. This change is measured and calibrated to a proper scale. Conductance measurement has relatively low sensitivity. The electric field generated using sinusoidal voltage (AC) which helps in minimizing undesirable effects such as Faradaic process, double layer charging and concentration polarization [1].

3.5.2 Amperometric biosensors

This high sensitivity biosensor cab detect elctroactive species present in biological test samples. Since the biological test samples may not be intrinsically electro-active, enzymes needed to catalyze production of radio-active species. In this case, the measured parameter is current [1].

Characteristics	Electrochemical Sensing		
	Conductimetric	Amperometric	Potentiometric
Measured Parameter	Conductance/ Resistance	Current	Potential/ Voltage
Applied Voltage	Sinusoidal (AC)	Constant Potential (DC)	Ramp Voltage
Sensitivity	Low	High	
Governing Equation	Incremental Resistance	Cottrell Eqn.	Nesrt Eqn.
Fabrication	FET+Enzyme	FET+Enzyme 2 elctrodes	FET+Enzyme oxide electrode

Table 1: Different Electrochemical Sensing

3.5.3 Potentiometric biosensors

In this type of sensors the measured parameter is oxidation/reduction potential (of an electrochemical reaction). The working principle of that when a ramp voltage is applied to an electrode in solution the current flow occurs because of electrochemical reaction. The voltage at which these reactions occurs indicate a particular reaction and particular species [1].

4 A biosensor to monitor cell morphology

Keese and Giaever [3] have designed a biosensor that can be used to monitor cell morphology in tissue culture environment. The sensing principle used is known as Electric Cell-substrate Impedance Sensing (ECIS). In this process, a small gold electrode is immersed in tissue culture medium. When cells get attached and spread on the electrodes, the impedance measured across the electrodes change. This changing impedance can be used for understanding cell behavior in culture medium. This is the key theme behind the proposed biosensor which is well projected by the help of Fig. 12.

The *attachment* and *spreading* behavior of the cells are important factors for this biosensor. The cancerous cells usually can grow and reproduce

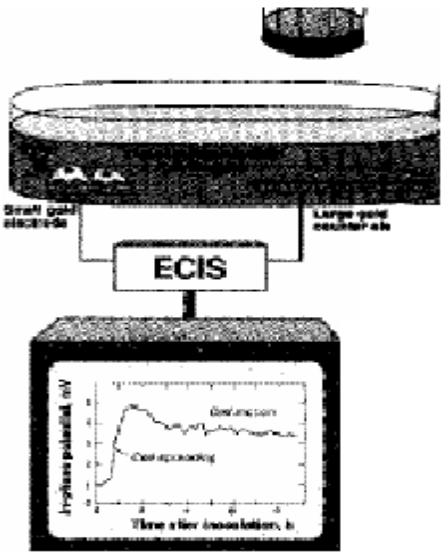


Figure 12: Electric Cell-substrate Impedance Sensing (ECIS), Source : [3]

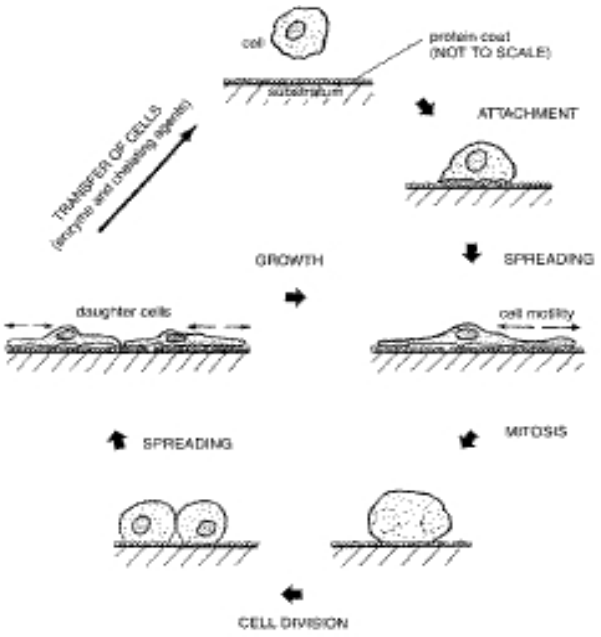


Figure 13: A cell in tissue culture medium, Source : [3]

(*mitosis*) freely in a medium without being attached to any substrate/surface. But, normal cells need to be attached to a surface before they grow. After attachment the shape of the cells becomes flat and no longer remains spherical shaped. Fig. 13 demonstrates this cell behavior in a tissue culture medium.

The principle of measurement is schematically represented by the help of Fig. 14. The cells are grown on gold electrodes. The electrodes are immersed in tissue culture medium which works as electrolyte. The applied voltage is $1V, 4kHz$. The voltage is applied through a $1M\Omega$ resistance. To measure magnitude and phase of the voltage the lock-in-amplifier is used. Since, the current is constant, the measured magnitude and phase can be assumed as proportional to impedance (resistance and capacitance). Fig. 15 shows capacitance and resistance measurements over a time period. After some time it is found that the R, C values fluctuate very often. This happens when cells are alive and moving.

The electrodes used above is fabricated by the following process steps:

- a thin gold film is sputtered on a polycarbonate substrate
- film is patterned and insulated by lithography techniques.

The small electrode made is of $250\mu m$ diameter. A complete six well unit with ECIS electrodes is shown in Fig. 16.

The advantages of this biosensor are :

- The biosensor is less time consuming compared to the conventional methods.
- It is possible to automate and quantify cell morphology measurement.
- The fluctuating pattern can be used as signature for a cell.

The possible disadvantages of this biosensor may be :

- The accuracy of the biosensor is doubtful, it may happen two cells can have almost similar pattern.

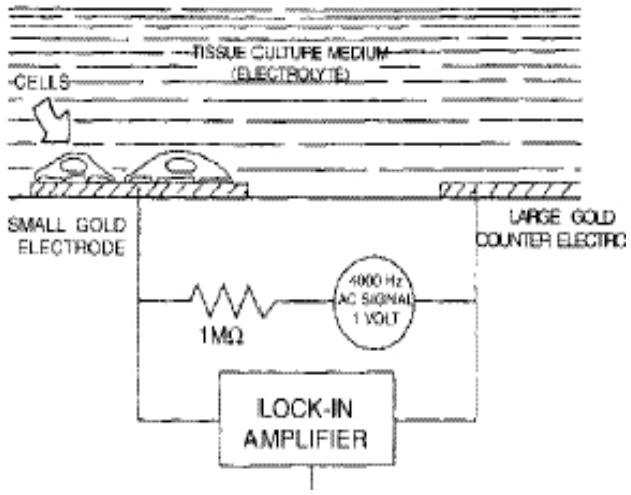


Figure 14: ECIS schematic diagram, Source : [3]

- If the average impedance is to be taken as a measure then it is possible that two entirely different patterns can have same average value.
- It is not clear if the biosensor is useful for nonmammalian cells and plant cells.

5 A holographic biosensor for screening pancreatic disorders

Holograms are photographs of 3D impressions on the surface of light. To make a hologram one needs to photograph light waves. When an object wave meets a reference wave, a standing wave pattern of interference is created which can be photographed; thus creating a hologram. A hologram is generally recorded on silver hallide film. The film consists of a base material of glass or plastic. Then there is a photoactive layer called *emulsion*. This emulsion layer is made up of gelatin (a colorless / yellowish protein). Silver and hallide materials float in the gelatin layer. They chemically react to form silver hallide molecule. When light energy goes into the gelatin it is transfered to the sil-

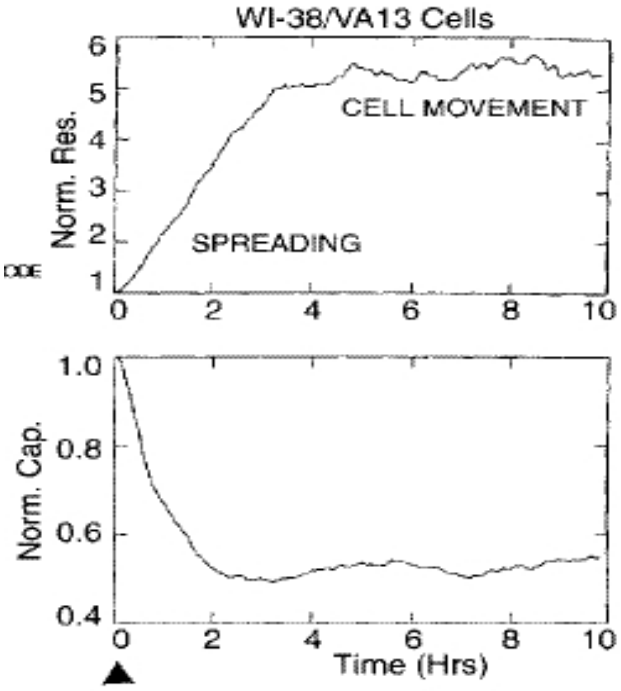
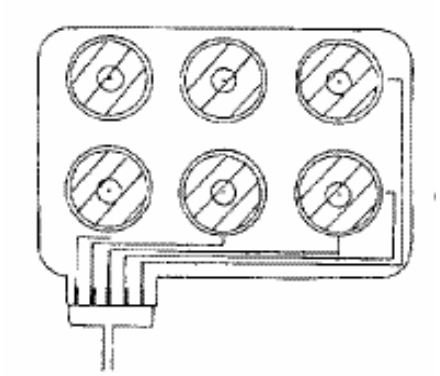
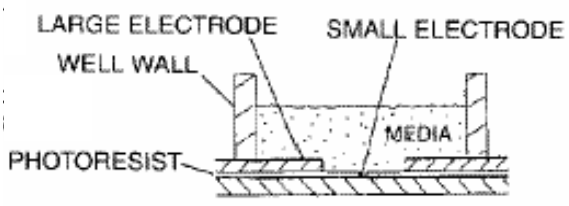


Figure 15: Resistance and capacitance measurement over time, Source : [3]



(a) Six electrode array



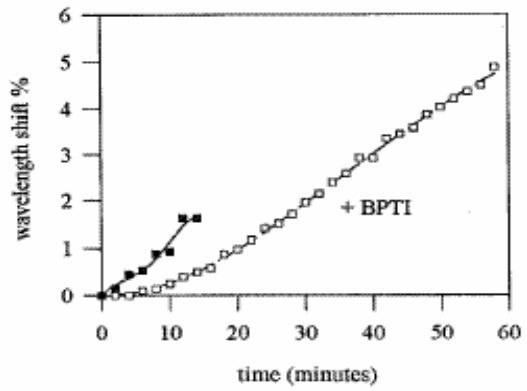
(b) Cross section of one electrode

Figure 16: Electrode structure, Source : [3]

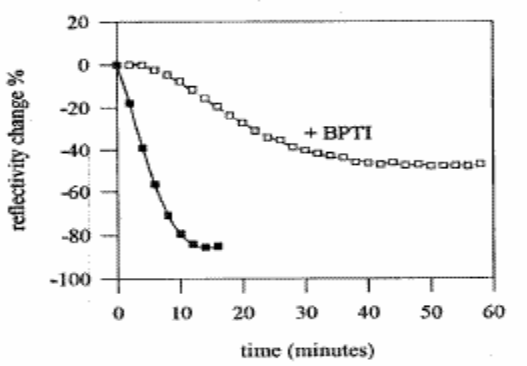
ver hallide molecule. For more details of holography readers are recommended to visit the URL : http://www.holography.ru/ .

Millington, et al. [8] have developed a biosensor which uses hologram as sensing element. This biosensor can have potential applications in screening pancreatic disorders at lower price. The bioelement used is *bovine pancreatic trypsin inhibitor* (BPTI) which is an enzyme. To screen pancreatic disorders *trypsin* needs to be detected in duodeneal fluid or stool sample. By proper use of BPTI trypsin detection can be made possible.

When the hologram is illuminated by white light constructive interference gives a characteristic spectrum having spectral peak and wavelength peak described by "Bragg equation". The characteristic spectrum is dependent on the gelatin matrix of the hologram. If gelatin molecules of hologram film are protease degraded the characteristic spectrum changes. This changes is specific to the type of degradation. The authors studied the spectrum after degrading the gelatin with trypsin and BPTI. The reflected light from the hologram was detected by spectrograph and CCD detector at intervals of 1 or 2 minutes and were analyzed for peak wavelength and reflectivity change with time. Fig. 17 shows the peak wavelength and reflectivity response. The major advantage of this biosensor is that very small trypsin levels can be detected within 60 minutes period.



(a) Peak wavelength response

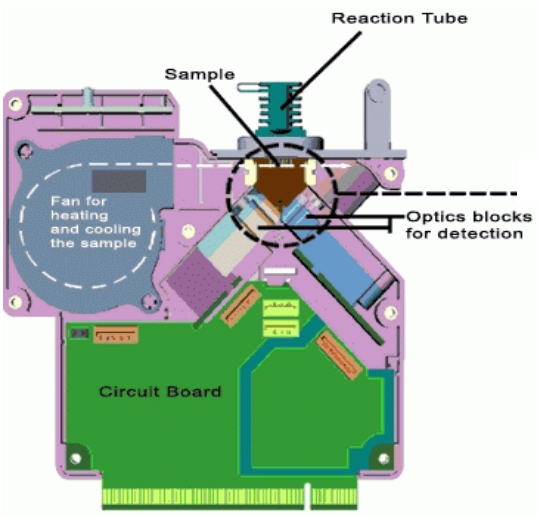


(b) Peak reflectivity response

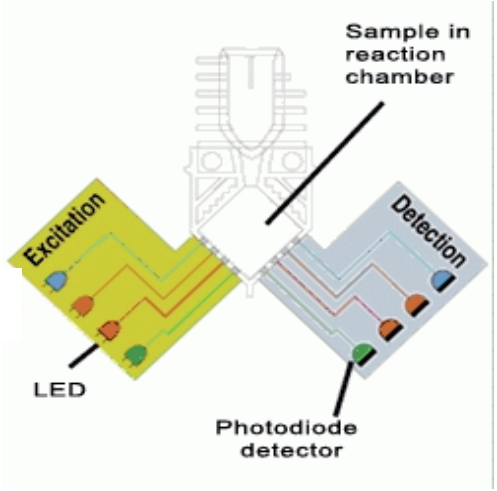
Figure 17: Peak wavelength and reflectivity response, Source : [8]

6 DNA detection-on-a-chip (Lab-on-a-chip system)

The category of biosensors used for DNA detection are also known as *biodetectors*. The biodetectors are used to identify a small concentration of DNA (of microorganism like virus or bacteria) is large sample. This relies on comparing sample DNA with DNA of known microorganism (probe DNA). Since the sample solution may contain only a small number of biorganism molecules, multiple copies of the sample DNA needs to be created for proper analysis. This is achieved by the help of *polymerase chain reaction* (PCR). PCR starts by splitting sample's of double-helix DNA into two parts by heating it about 95^oC. If the reagents contain proper growth enzymes, then each of these strands will grow the complementary missing part and form double-helix structure again. This happens when temperature is lowered. This in one heating/cooling cycle the amount of sample DNA is doubled (one cycle time is one about minute). Thus, for n cycles 2^n copies are made. Typically, 25-40 cycles are needed to produce approximately a billion copies. This amount is sufficient enough to be detected optically. While the PCR is busy in copying DNA identification also could be made



(a) Peterson's microfluidic device



(b) Magnified view of chamber unit

Figure 18: Biodetector developed by K. Peterson, Source : [20]

possible using fluorescent DNA probes.

In general, PCR is very very power consuming because of heating/cooling cycle which takes about 30 minutes. So it was previously not possible to fabricate portable battery operated biodetectors which can do PCR. But, using MEMS such kind biodectors which are basically lab-on-a-chip systems have been developed. In these MEMS based devices the amount of reagent used is scaled down. Fig. 18 shows a microfludic device developed by K. Peterson [13, 20]. This lab-on-a-chip system contains channels, valves and chambers as shown in the figure. To detect microorganism DNA steps followed are :

- Some milliliters of sample solution are pumped into the chamber.
- The sample is concentrated to a volume of a microliter.
- Sample DNA are now extracted from sample solution.
- PCR is performed. A small thin-film heater heats the DNA and fan helps in cooling. The cycle time is 25 seconds.
- Flouroscence probe DNAs bind the sample DNA.
- When the LEDs cause the probe DNAs to fluorescent the glow is captured by photodiode and hence can be detected.

In [20] another biodetector has been discussed. This biodetector uses magnetic field instead of optics or flouresence. This biodetector with the help of magnetic sensors and microbeads is able to detect presence and concentrate of bioagents. Fig. 19 shows a magnetic biodetector developed by Naval Research Laboratory (NRL). The magnetic sensor or group of sensors is coated with single-stranded (i.e. one part of double-helix) DNA probes specific for a bioagent or sample DNA. Once a single-strand of DNA probe and a single-strand of sample DNA combine they form a double stranded (double-helix) structure. The resulting double-helix structure binds a single magnetic microbead. When a magnetic bead is present above a sensor, the sensor's resistance decreases which is the detectable entity. The magnetic beads are of-the-shelf products of diameter $2.8\mu m$ which are commonly used for biochemical separation. The more beads, larger is the decrease in resistance.

The MEMS based microreactor developed by Northrup, et al. [10] have cycle times as short as

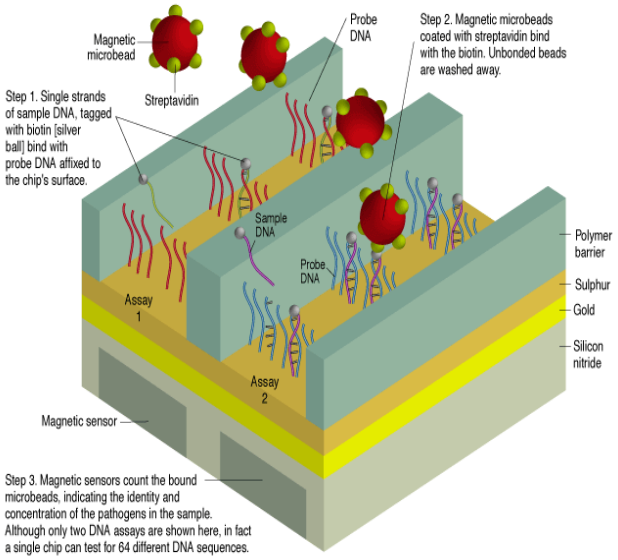


Figure 19: Magnetic biodetector developed by NRL, Source : [20]

several seconds and 35 cycles (for full amplification of DNAs) takes several minutes. The advantages of this biosensor are :

- $5-10$ times faster than conventional PCRs
- 30% more efficient in number of DNA copies produced
- easily designed to use small volumes
- economical.

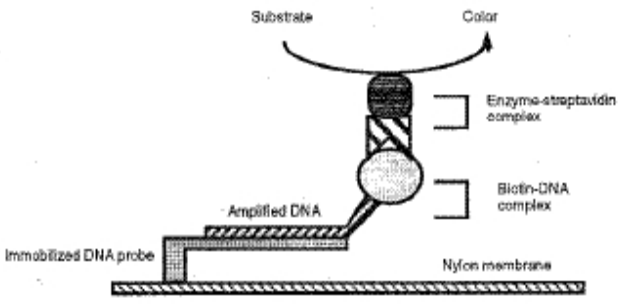


Figure 20: Biodetector developed by Northrup et al., Source : [10]

Fig. 20 illustrates the schematic detection process after the PCR-amplification being completed in a reaction chamber. The nylon based test strip contains the specific DNA probe. The sample (amplified) DNA is put into a reagent. If the two types of DNAs bind each-other then the DNA-biotin-steptavidin-enzyme complex will change color, thus detecting the sample DNA. The PCR reaction chamber can be designed of several different sizes. The cross-section of a reaction chamber is shown in Fig. 21. The IC-fabrication steps used to develop this PCR are listed below.

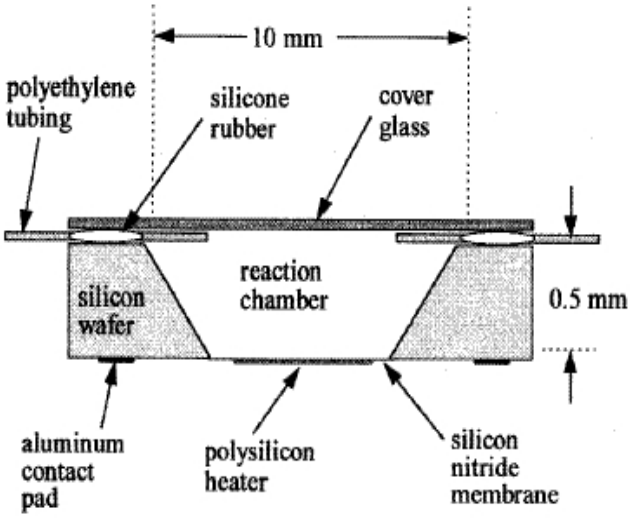


Figure 21: PCR cross-section developed by Northrup et al., Source : [13]

- A $3in$ diameter, $0.5mm$ thick single crystal silicon wafer is taken.
- Silicon nitride (of thickness $1-2\mu m$) is deposited on to entire wafer by LPCVD.
- Photolithographic pattern is done for reaction chamber.
- Silicon nitride is etched by RIE process over the chamber area.
- Silicon is etched to silicon nitride backside defining the chamber volume.

- The wafer is patterned and etched depending upon reaction chamber design.
- Silicon nitride alongwith polysilicon deposited by LPCVD.
- Polysilicon is doped with boron up to resistivity of $50 - 200\Omega/square$.
- Aluminum contact deposited that defines the heater geometry.
- Polyethylene input and output tubes are constructed.
- Glass cover sealing is done.

7 Glucose biosensors

The most successful commercial biosensors are amperometric glucose biosensors. These biosensors have been made available in the market in various shapes and forms such as glucose pens, glucose big display, and so on as discussed in section 1. The aim of this section is to do an detailed study of some glucose biosensors.

The first historic experiment that served as origin of glucose biosensors was carried out by Leland C. Clark [5]. He used platinum (Pt) electrodes to detect oxygen. The enzyme *glucose oxidase* (GOD) was placed very close to the surface of platinum by physically trapping it against the electrodes by a piece of dialysis membrane. The enzyme activity changes depending on the surrounding oxygen concentration. Fig. 22 shows the reaction catalysed by GOD. Glucose reacts with glucose oxidase (GOD) to form gluconic acid. At the same time producing two electrons and two protons, thus reducing GOD. This reduced GOD, surrounding oxygen, electrons and protons (produced above) react to form hydrogen peroxide (H_2O_2) and oxidized GOD (the original form). This GOD can again react with more glucose. More the glucose content, more the oxygen consumption and hence less is the detection. On the other hand, more the glucose, more the H_2O_2 production. Hence, either the consumption of O_2 or the production of H_2O_2 can be detected by the help of platinum electrodes which can serve as measures for glucose concentration.

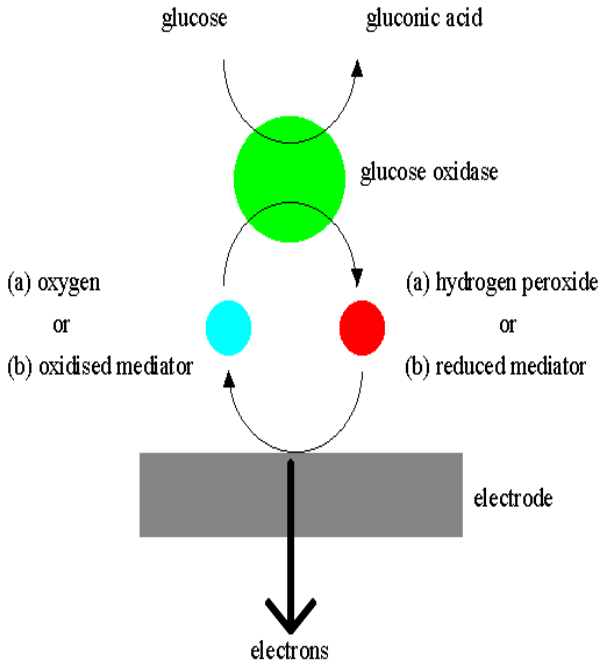
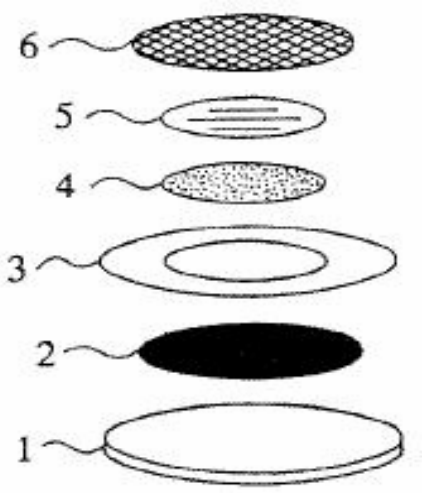


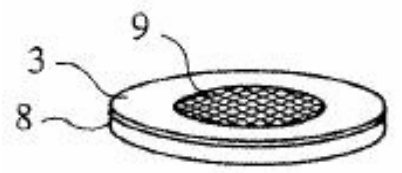
Figure 22: Clark's Experiment, Source : [5]

P. Yu and S. Dong [9] have developed a disposable amperometric biosensor for detection of glucose. The biosensor is button-shaped having overall diameter of $8mm$ and thickness of $0.88mm$. Fig. 23 shows the construction of the biosensor. The disposable sensor consists of following layers :

- layer1 : metallic substrate
- layer2 : graphite layer
- layer3 : isolating layer
- layer4 : mediator modified membrane
- layer5 : immobilized enzyme membrane (GOD)
- layer6 : cellulose acetate membrane



(a) Construction Layers



(b) Botton-shaped biosensor

Figure 23: Details of a disposable glucose biosensor, Source : [9]

This biosensor uses graphite electrode instead of platinum electrode (used in case of Clark). The isolating layer is placed on the graphite electrodes that can filter out certain interfering substances (ascorbic acid, uric acid) while allowing passage of H_2O_2 and O_2. The mediator modified membrane helps in keeping the GOD membrane attached with the graphite electrode when electrochemical reaction takes place at applied potential $(). 35V$). The cellulose acetate outer layer placed over the GOD membrane also provides barrier for interfering substances. The amperometric reading of the biosensor (current Vs glucose concentration) is shown in Fig. 24. The relationship is linear upto glucose concentration of $25mMol/liter$.

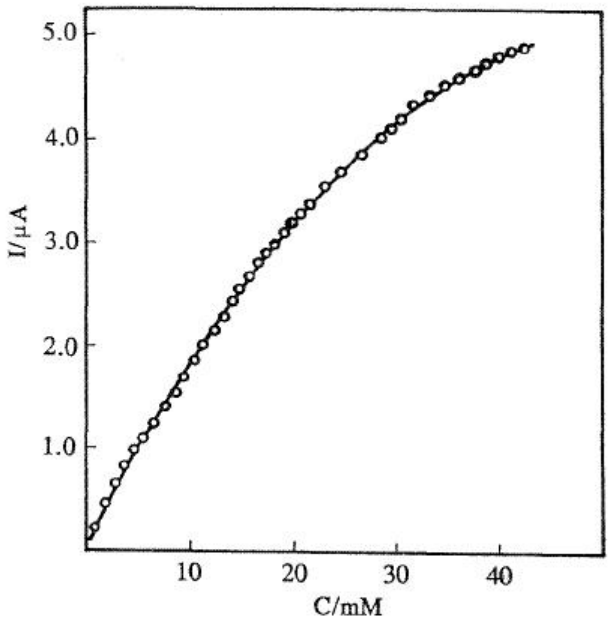


Figure 24: Calibration curve of a disposable glucose biosensor, Source : [9]

8 Conclusions

In this survey report we have discussed various biosensor in detail. The survey initially, briefly introduces the basic concepts on the biosensor. Highl-evel view of different types of biosensors also given. Working principles, constructions, advantages and disadvantages of many biosensors given. The author would like to mention that there are various difficulties for which some solutions exist, but still more research efforts need to be given to find better alternatives. Few of them mentioned below :

- **contamination** : bioelements and chemicals used in the biosensors need to be prevented from leaking out of the biosensor over time (serious issue for nondisposable ones).
- **immobilisation of biomolecules** : to avoid contamination, biomolecules are attached to the transducer as strongly as possible, but the problem with this is that the behavior of enzymes when absorbed on surface is less un-

derstood (reaction of enzymes in free solution is better uderstood.

- **sterilization** : if a sterilized probe is used some sensor's biomolecules may be destroyed whereas if non-sterile probes used some compromises needed.
- **uniformity of biomolecule preparation** : fabrication of biosensors that can reproduce results need such uniformity.
- **selectivity and detection range** : should be more selective and more detection range should be large.
- **cost** :research should be focussed for development of low-cost biosensors.

At present, when people talk about **bioterrorism**, the development of faster, reliable, accurate, portable and low-cost biosensors has become more important than ever.

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Disclaimers

Some of the figures used in this paper are borrowed from other sources and used here only for academics purpose and the author doesn't claim any originality for the same.

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