BME3570.01 BIOSENSORS
SYLLABUS

Date: October 6, 2020

Semester : 2020 Fall
Course : BME3570.01, Biosensors
Level of Course : Undergraduate
Year of Study : 3
Type of Course : BME
Language of Instruction : English

Instructor : Assist. Prof. Dr. Sakip ONDER

Instructor's office hours : Thursday, 10:00-11:00
Instructor's phone no/e-mail address : (0212) 3836303, sonder@yildiz.edu.tr

Class hours : BME3570.01 / Tuesday 14:00-17:00/online
Prerequisite :
Corequisite :

Course description

Fundamentals of biosensor systems. Types of biosensors, such as catalytic, affinity, enzyme, DNA etc. Transducers. Methods used in the attachment of biosensing element. Membrane proteins as biosensing element. Label-free biosensors, such as SPR, QCM. Production and usage of biochips in medical field. Effect of nanotechnology on biosensor technology. Examples for current applications of biosensors.

Recommended Textbook (s) :

1.) Label-Free Biosensors: Techniques and Applications/ edited by Matthew A. Cooper, Cambridge University Press, Cambridge, UK, 2009
(2.) Nanomedicine: Design and Applications of Magnetic Nanomaterials, Nanosensors and Nanosystems/ by Vijay K. Varadan, LinFeng Chen, Jining Xie, Wiley, West Sussex, UK, 2008
(3.) Biosensors and Modern Biospecific Analytical Techniques / edited by L. Gorton; Elsevier, Amsterdam, 2005
(4.) Biochips : Technology and Applications/ Wan-Li Xing, Jing Cheng, eds; Springer, Berlin- NY, 2003
(5.) Protein Arrays, Biochips, and Proteomics/ by Joanna S. Albala, Marcel Dekker, NY, 2003 (6.) Biosensors: an Introduction/ Eggins, Brian R.; Wiley-Teubner, Chichester, 1996

Tentative Schedule

Weeks	Topics
1	Course Introduction
2	Catalytic vs affinity sensors
3	Classical biosensing elements: Enzyme and DNA sensors
4	New trends in biosensing elements: Carbohydrate, lipids, natural and synthetic receptors and aptamer sensors
5	Membrane proteins as biosensing element: Their importance in drug and toxic compound screening
6	Transducers
7	Label-free biosensors: Surface Plasmon Resonance and Quartz Crystal Microbalance sensors. Methods used in the attachment of biosensing element
8	Midterm I
9	Biochips: Production methods, their advantages and limitations
10	Biochips: Their use in genetic studies and medical field
11	Effect of nanotechnology on biosensor technology (nanotubes, nanoparticles, nanocantilevers, etc)
12	Micro and nano-elecromechanic systems (MEMS/NEMS) and Bio-NEMS
13	Examples for current applications (Student presentations)
14	Examples for current applications (Student presentations)

Attendance Policy:
%70 classroom attendance is mandatory. Regular attendance to the lectures is strongly recommended to be successful in this course. Therefore, please try to attend to each lecture.

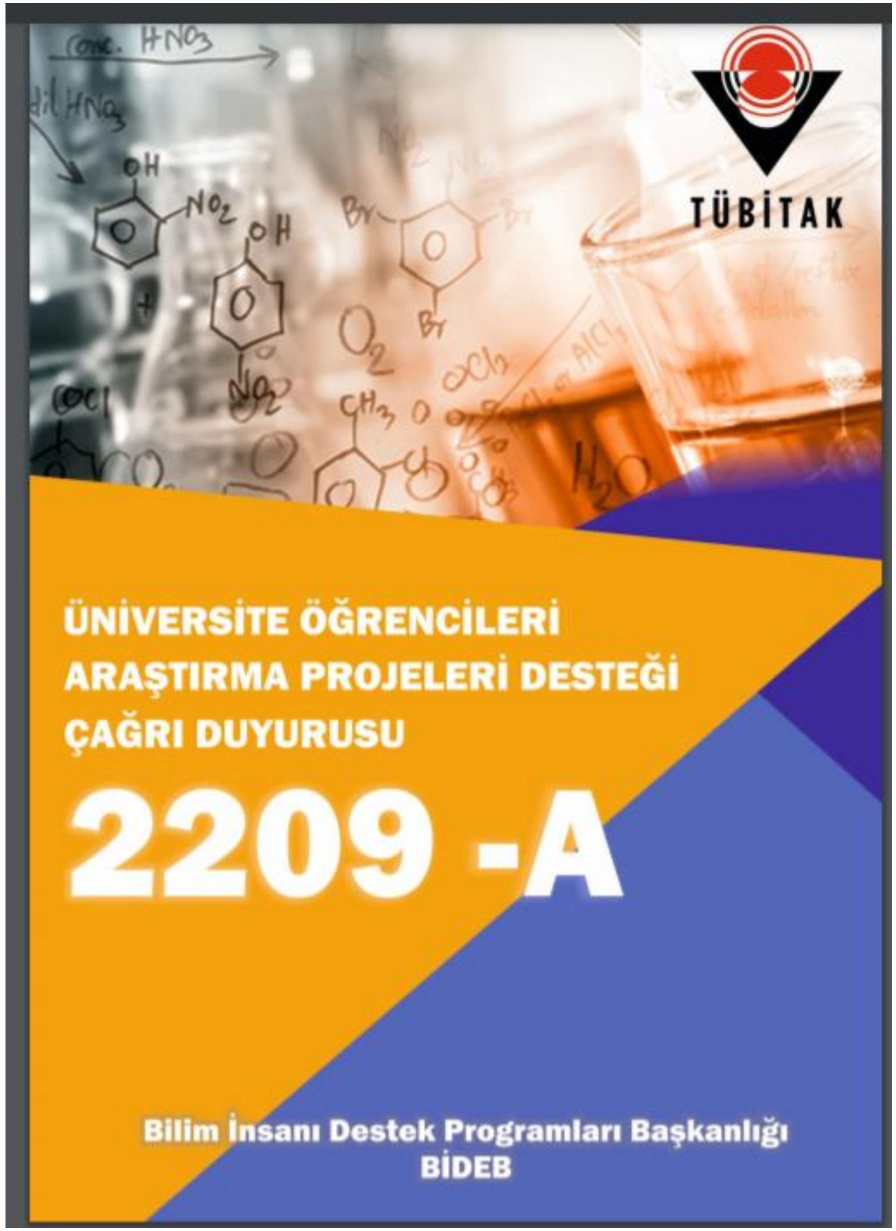
Make-up Policy:
Make-up examinations will only be given to students who miss examinations as a result of excused absences according to applicable current university policy.

Grading Policy:
Final course grades will be computed according to the following:

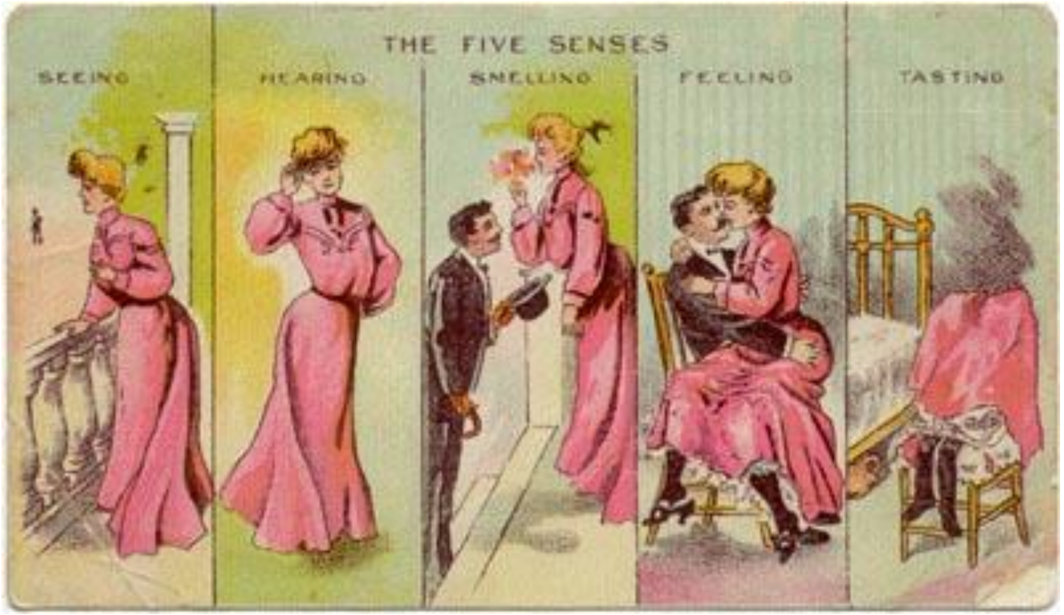
Midterm I	25%
Student presentations	35%
Final	40%

The avesis will be the main source of information for the course. Homework and announcements will be posted. It is the student’s responsibility to download and print the necessary documents needed in the course.

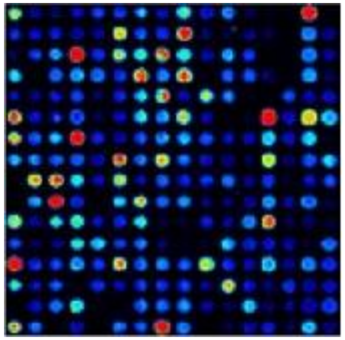
The topic for the presentation must be decided until midterm week.

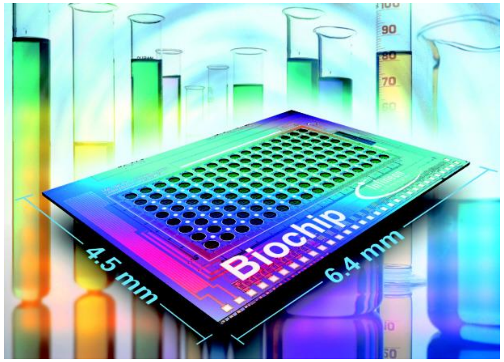


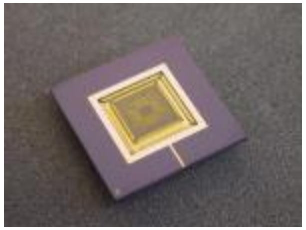
https://www.tubitak.gov.tr/sites/default/files/4000/2209a_2020_cagri_duyurusu.pdf



Biosensing & Biosensors



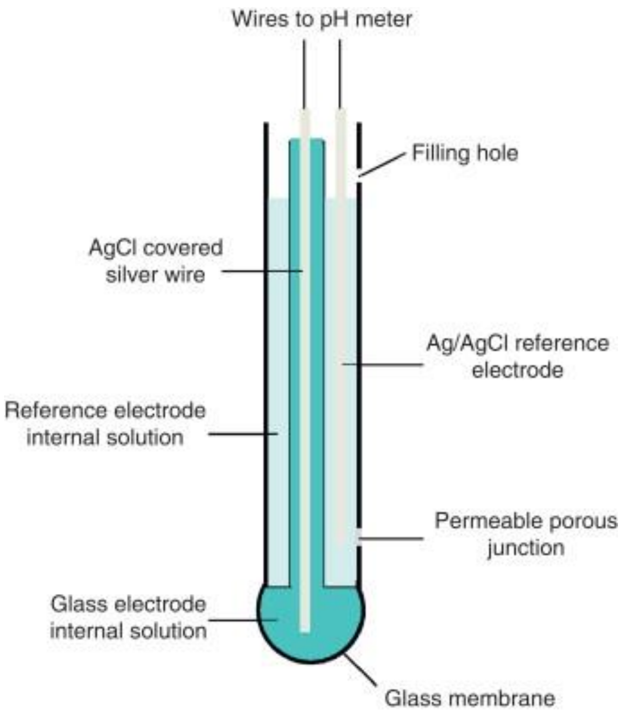




Chemical Sensors vs Biosensors

Chemical Sensors:
"A chemical sensor is a device that transforms chemcial information, ranging from the concentration of a specific sample component to total composition analysis, into an analytically useful signal" – IUPAC

IUPAC- ***International Union of Pure and Applied Chemistry***



The first (and also best known) chemical sensor is the glass electrode (a type of ion-selective electrode) for pH determination, which indicates the activity of the hydrogen ion in a solution.

Chemical Sensors vs Biosensors

Biosensors are chemical sensors in which the recognition system is based on biochemical or biological mechanisms

IUPAC* definition

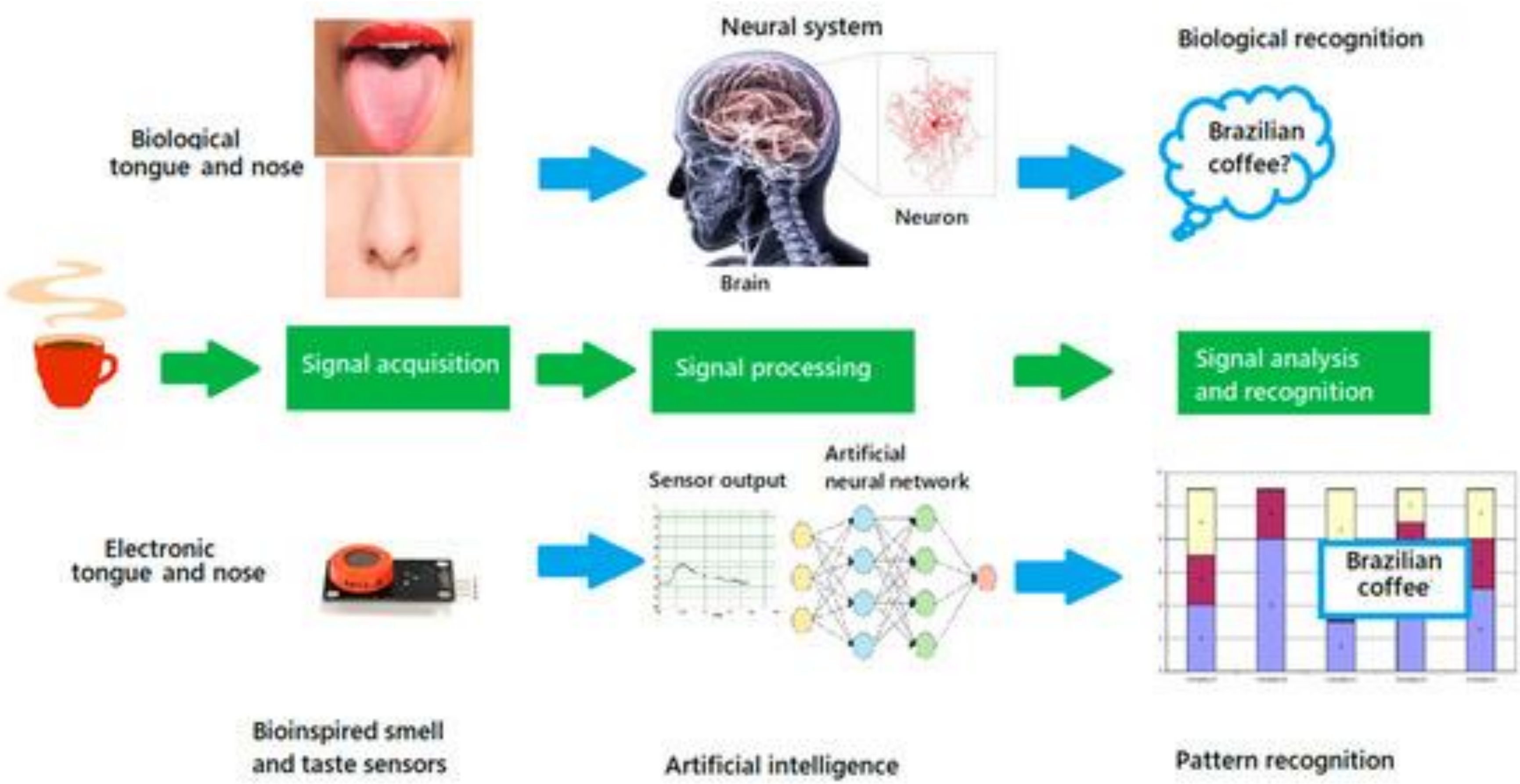
‘A device that uses specific biochemical reactions mediated by isolated enzymes, immunosystems, tissues, organelles or whole cells to detect chemical compounds usually by electrical, thermal or optical signals’

***** *International Union of Pure and Applied Chemistry***

Biosensor is a compact analytical device incorporating a biological sensing element with a transducer

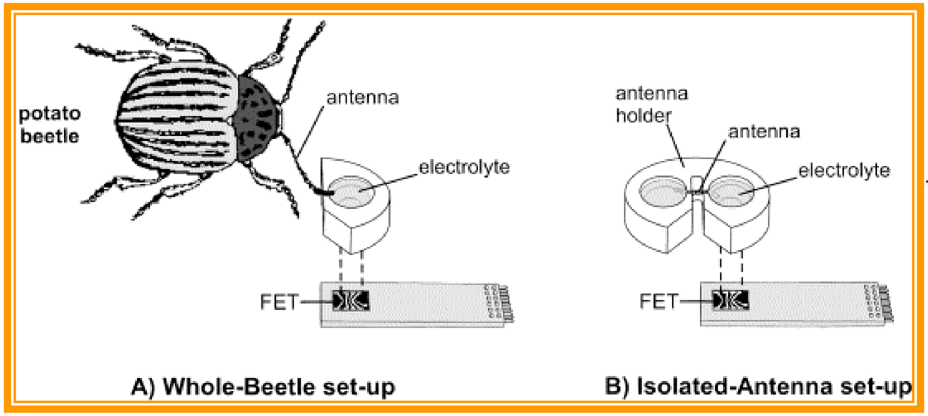
Inspired by Nature: Our Biosensors

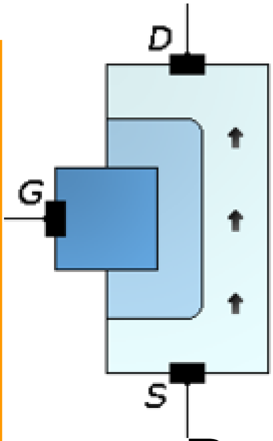
Human nose/tongue vs electronic nose/tongue



Inspired by Nature: Beetle/Chip Sensor

Schroth P. et al., *Sensors and Actuators B*, 78: 1-5, 2001

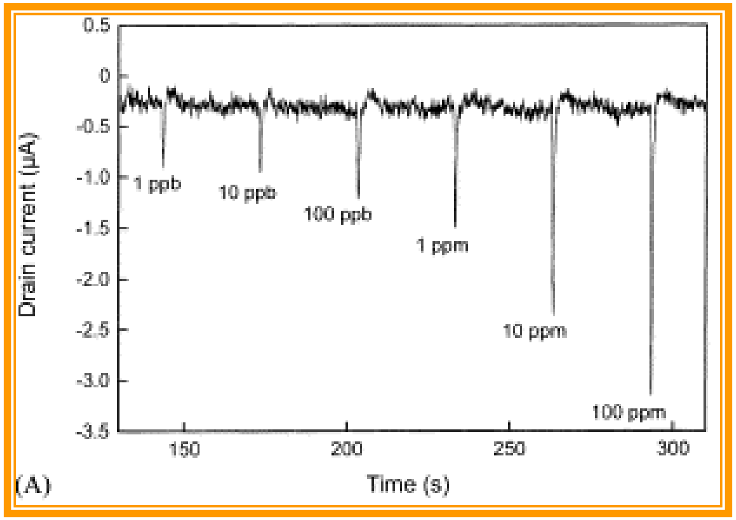




Whole-beetle

Antenna

Receptor Molecules



Detection of a single, damaged potato plant within a field of a thousand undamaged plant …

Inspired by Nature-1

Oh et al, Biomimetic virus-based colourimetric sensors, Nature Communications, 2014

- A group of scientists at the University of California, Berkeley, has created a color-changing biosensor that can detect the explosive agent TNT using a design inspired by a turkey's wattle.
- Wattle structure: bundles of collagen enriched with lots of blood vessels*****.
- In a relaxed turkey, the collagen bundles are small and transparent, and the blood vessels show through the skin, creating a bright red wattle. But when a turkey gets excited, the collagen bundles expand, become opaque and scatter light. With the blood vessels obscured, the turkey's wattle goes from red to white, or even blue.

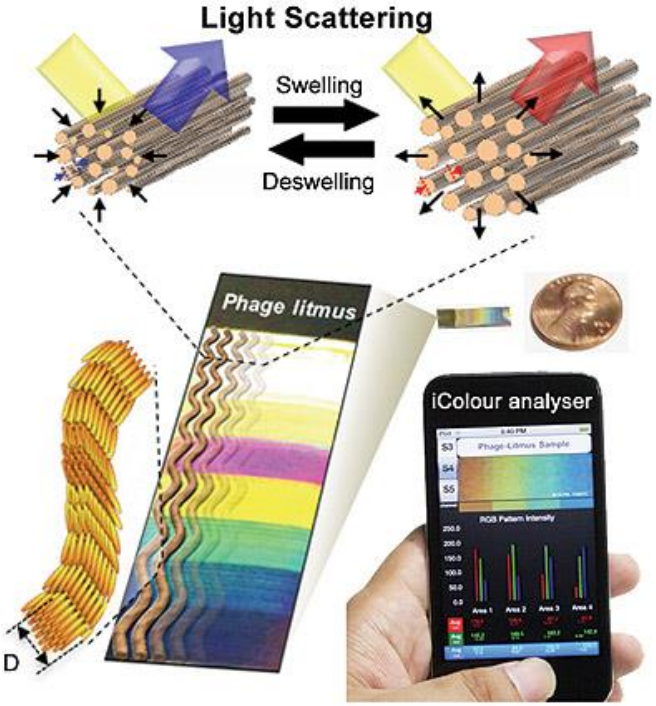
***FACT:** These long, thin proteins can form into bundles arranged in different patterns. In one pattern, collagen makes up the lens of our eyes. Arranged another way, it forms tendons and scars. In a third formation, it helps our kidneys filter waste.*

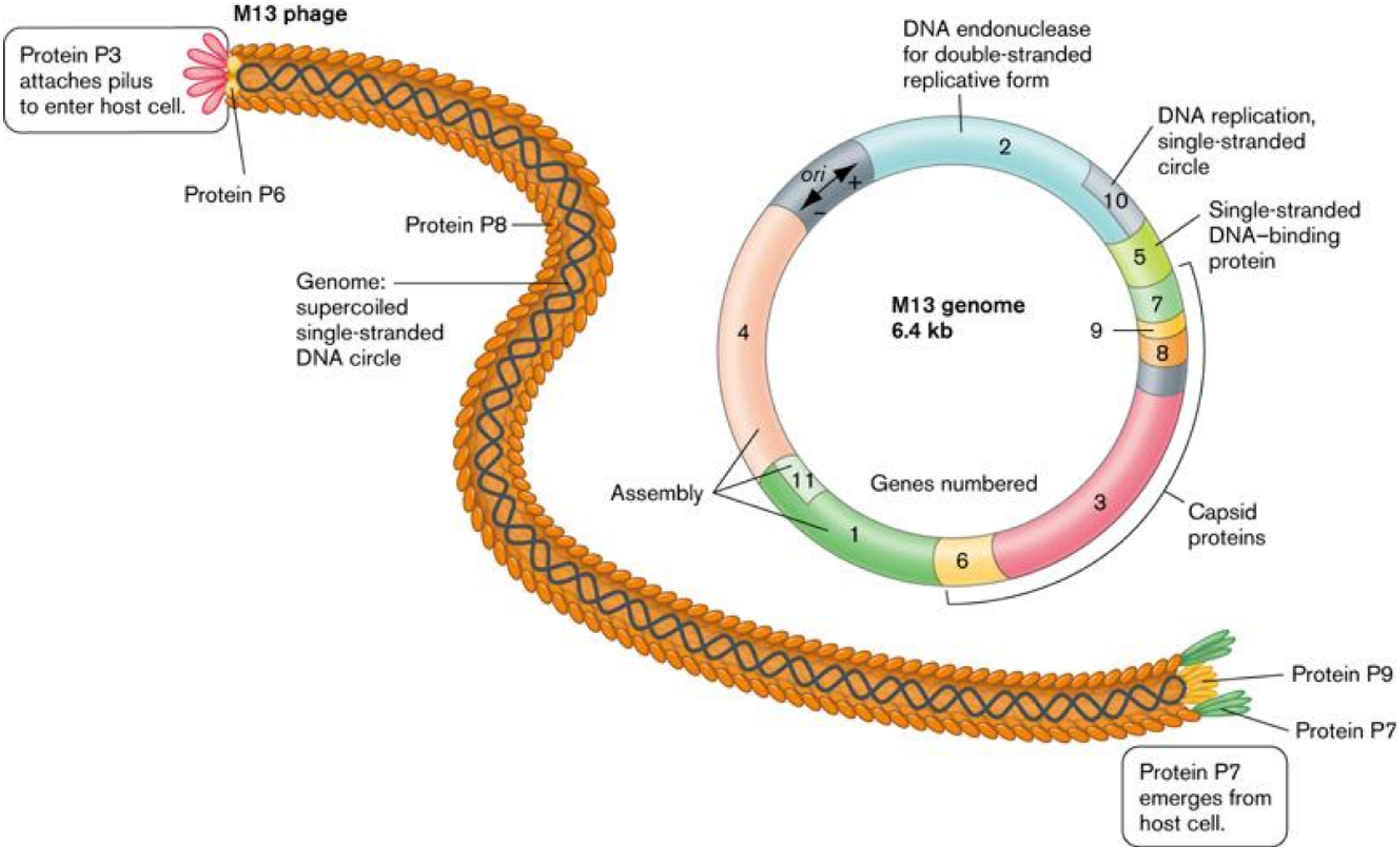
Inspired by Nature-2

Oh et al, Biomimetic virus-based colourimetric sensors, Nature Communications, 2014

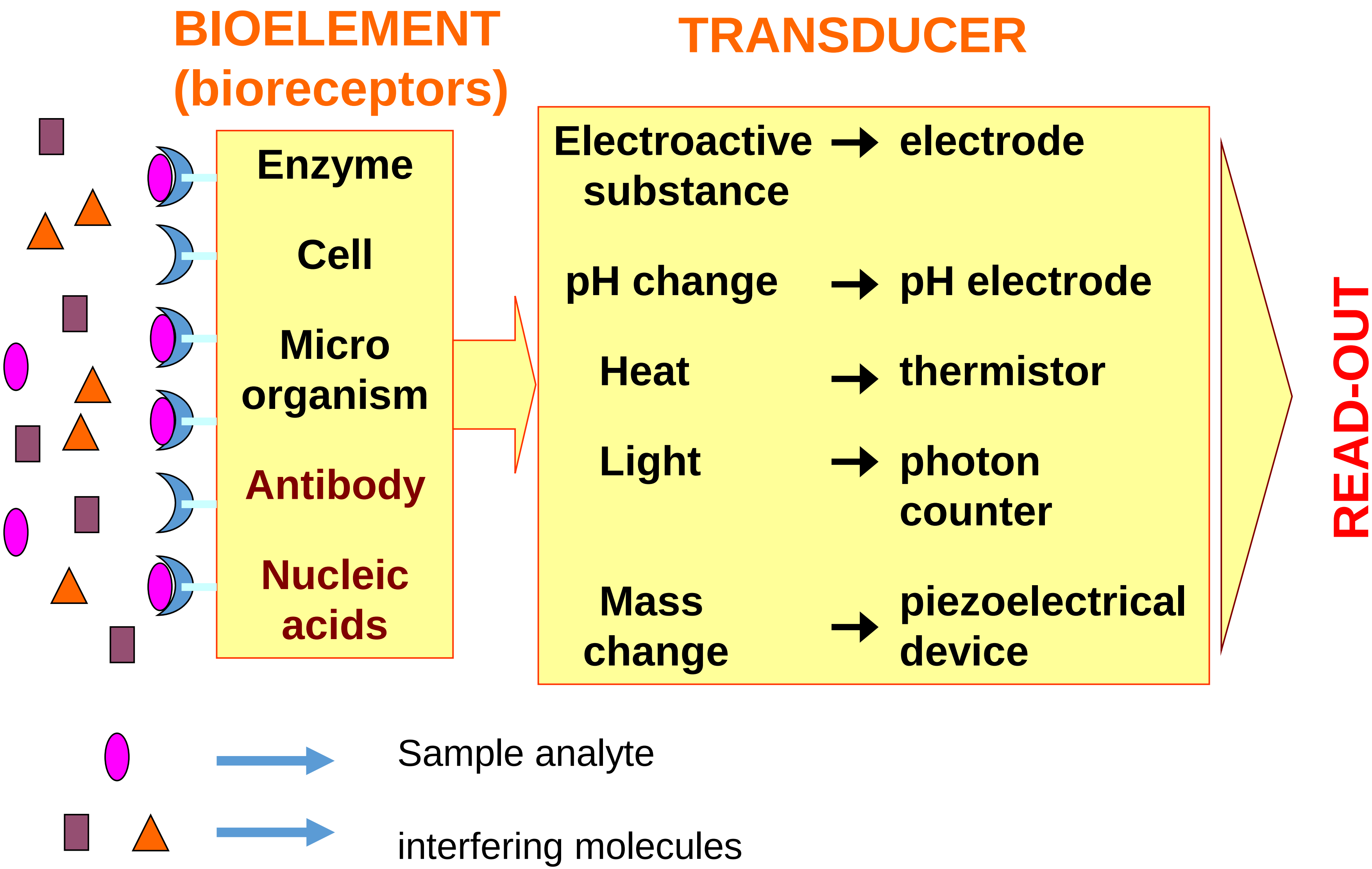
- Instead of collagen bundles→ self-assembly of genetically engineered viruses (M13 phage) into target-specific, colourimetric biosensors.
- The sensors are composed of phage-bundle nanostructures and exhibit viewing-angle independent colour, similar to collagen structures in turkey skin.

- On exposure to various volatile organic chemicals, the structures rapidly swell and undergo distinct colour changes.
- Trinitrotoluene (TNT)-binding peptide motifs identified from a phage display selectively distinguish TNT down to 300 ppb over similarly structured chemicals.




M13 phage
Protein P3 attaches pilus to enter host cell.
Protein P6
Protein P8
Genome: supercoiled single-stranded DNA circle
DNA endonuclease for double-stranded replicative form
DNA replication, single-stranded circle
Single-stranded DNA–binding protein
ori
+
−
2
10
5
7
9
8
4
3
6
1
11
M13 genome 6.4 kb
Genes numbered
Assembly
Capsid proteins
Protein P9
Protein P7
Protein P7 emerges from host cell.

Working Principle of Biosensors



Applications of Biosensors

- **Health care and life sciences research applications**
  - **Glucose and urea sensors**
  - **Proteomics**
  - **Genomics**
  - **Toxicology**
  - **Oncology**
  - **Drug discovery**

- **Food and drink**
  - **Contaminant/Pathogen Detection**
  - **Process/Quality Control**
  - **Detection of Genetically Modified Organisms in Food**

- **Environmental monitoring**
  - **Pesticide**

- **Defence and security**
  - **Military; Nerve gases and explosives**
  - **Forensics; DNA identification**

Pregnancy test

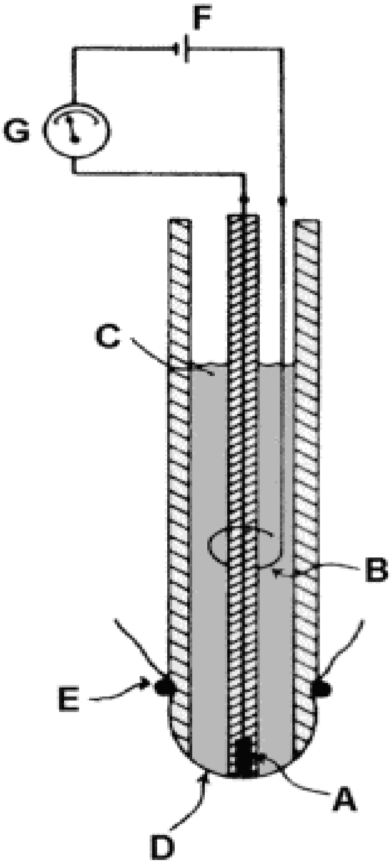
Detects the hCG protein in urine.

Glucose monitoring device (for diabetes patients)

Monitors the glucose level in the blood.

History

Professor Leland C Clark (1918–2005)



- **Mid 1950's - Leland C Clark "Father of Biosensors"** invents an electrode that measures dissolved oxygen in the blood of patients undergoing surgery.

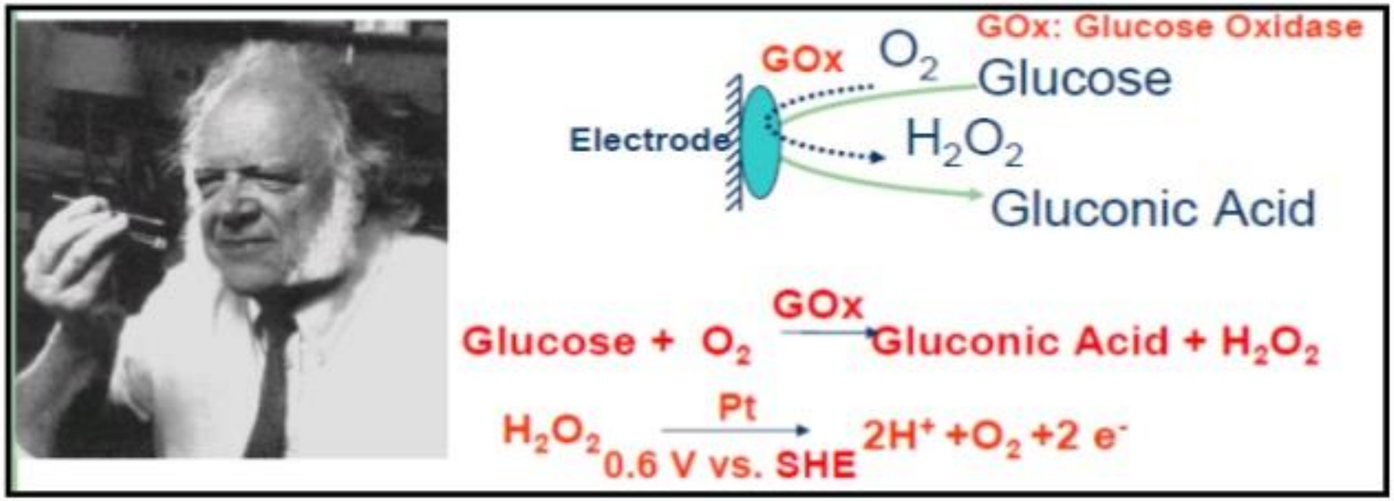
- The **Clark electrode** is an electrode that measures oxygen on a catalytic platinum surface using the net reaction:

$$O_2 + 4\,e^- + 2\,H_2O \rightarrow 4\,OH^-$$

The voltage differential measured between the two electrodes, gave the rate at which the oxygen was being diffused.

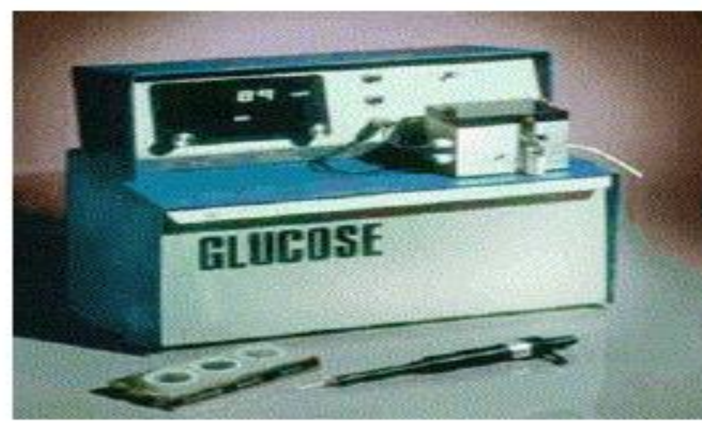
(A) Pt- electrode
(B) Ag/AgCl-electrode
(C) KCl electrolyte
(D) Teflon membrane (permeable to gases)
(E) rubber ring
(F) voltage supply
(G) galvanometer

Clarks electrode-glucose biosensor



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

İnvented by Clark in 1962
Commercialized in 1974
World market in 2004
$5 billion



First commercial glucose biosensor

History

Date	Event
1916	First report on the immobilization of proteins: adsorption of invertase on activated charcoal
1922	First glass pH electrode
1956	Invention of the oxygen electrode
1962	First description of a biosensor: an amperometric enzyme electrode for glucose
1969	First potentiometric biosensor: urease immobilized on an ammonia electrode to detect urea
1970	Invention of the ion-selective field-effect transistor (ISFET)
1972–75	First commercial biosensor: Yellow Springs Instruments glucose biosensor
1975	First microbe-based biosensor
	First immunosensor: ovalbumin on a platinum wire
	Invention of the pO_2/pCO_2 optode
1976	First bedside artificial pancreas (Miles)
1980	First fiber optic pH sensor for in vivo blood gases
1982	First fiber optic-based biosensor for glucose
1983	First surface plasmon resonance (SPR) immunosensor
1984	First mediated amperometric biosensor: ferrocene used with glucose oxidase for the detection of glucose
1987	Launch of the MediSense ExacTech blood glucose biosensor
1990	Launch of the Pharmacia BIACore SPR-based biosensor system
1992	i-STAT launches hand-held blood analyzer
1996	Glucocard launched
1996	Abbott acquires MediSense for $867 million
1998	Launch of LifeScan FastTake blood glucose biosensor
1998	Merger of Roche and Boehringer Mannheim to form Roche Diagnostics
2001	LifeScan purchases Inverness Medical's glucose testing business for $1.3 billion
2003	i-STAT acquired by Abbott for $392 million
2004	Abbott acquires Therasense for $1.2 billion

1999-Current BioMEMS,Quantum dots, nanoparticles, nanowire, nanotube, etc

i-STAT Hand Held Blood Analyzer

Product Specifications

McKesson #	984885
Manufacturer #	03P7506
Brand	i-STAT® 1 Wireless
Manufacturer	Abbott Point of Care
Country of Origin	Singapore
Application	Handheld Blood Analyzer
Contents1	Analyzer
Power Source	Battery Operated
Readout Type	Digital and Printout
Sample Type	Whole Blood Sample
Test Name	Blood Gases, Electrolytes, Chemistries, Coagulation, Hematology, Cardiac Markers
Time to Results	2 Minute Results
UNSPSC Code	41115807

https://mms.mckesson.com/product/984885/Abbott-Point-of-Care-03P7506

PERFORMANCE FACTORS

Selectivity: Selectivity means that sensor detects a certain analyte and does not react with added mixtures and contaminants.

Precision: is the degree to which repeated measurements under unchanged conditions show the same results**.**

Signal stability : signal drift under constant conditions, which causes an error in measured concentration.

Sensitivity (detection limit): the minimal amount (or concentration) of analyte that can be detected.

Working range : range of analyte concentrations in which the sensor can operate.

Regeneration time : time required to return the sensor to working state after interaction with the sample.

Response time : this usually much longer (30 s or more) with biosensors than with chemical sensors.

Life time : is usually determined by the stability of the selective material for biological materials this can be a short as a few days, although it is often several months or more.

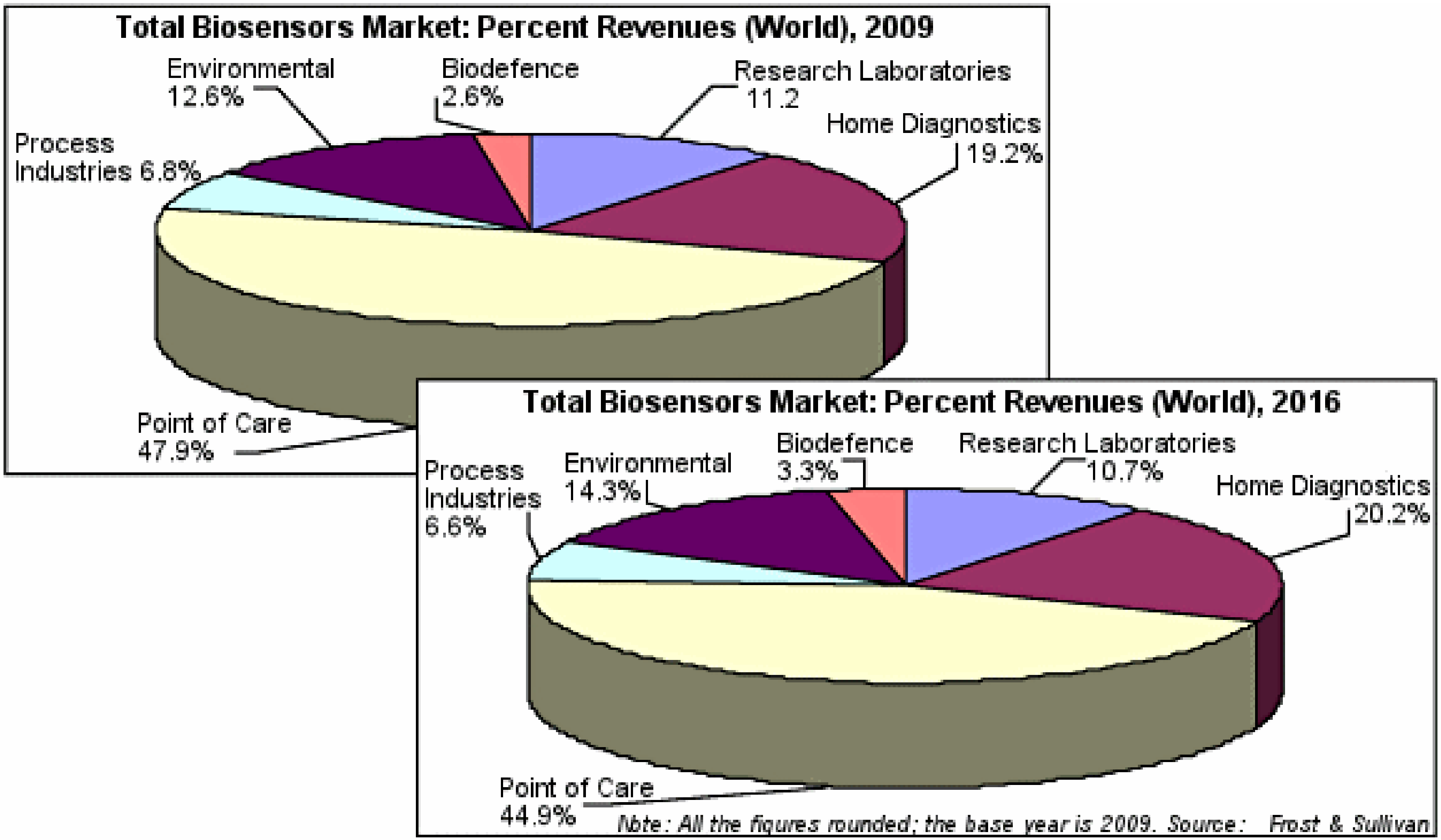
The biosensor should be cheap, small, portable and capable of being used by semi-skilled operators

Trends

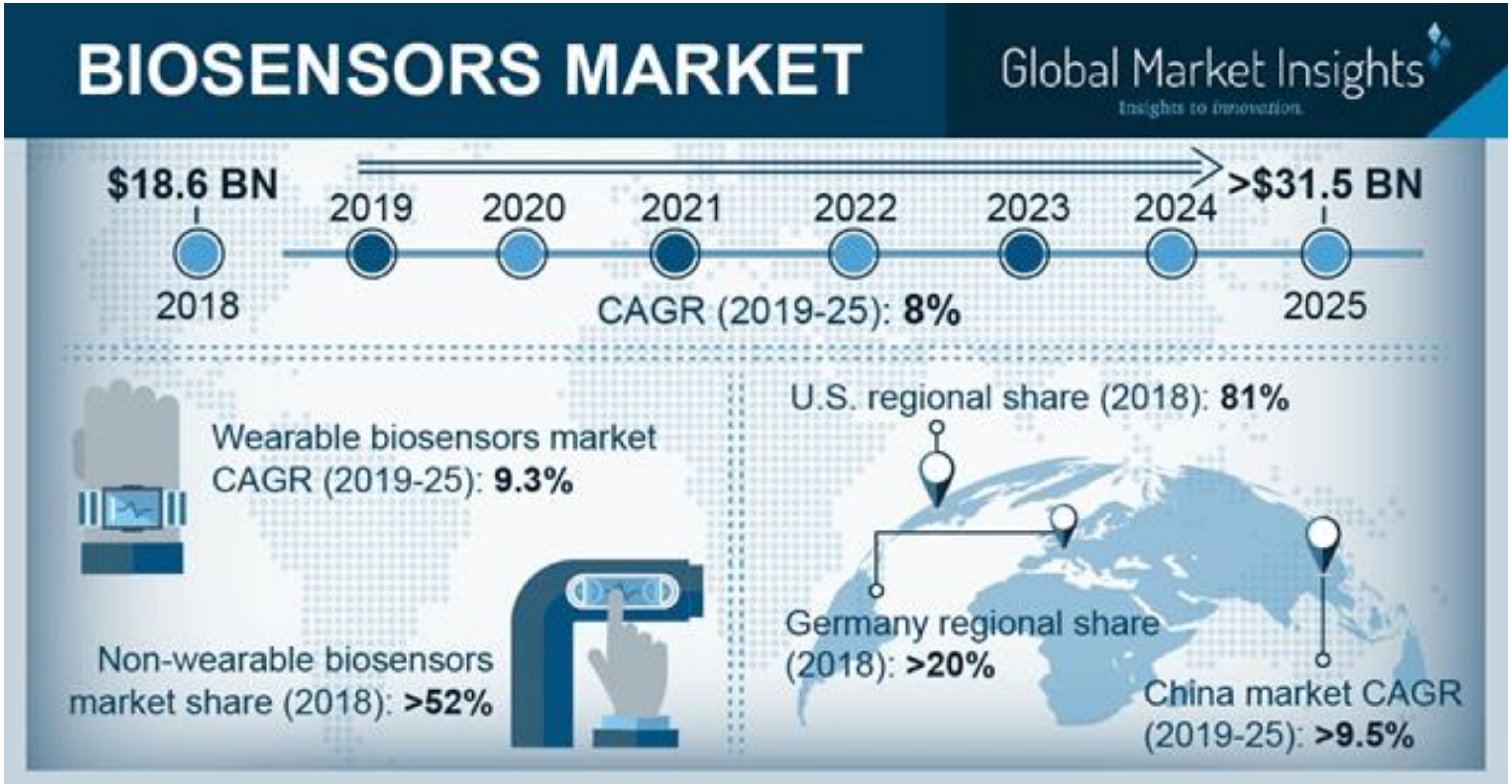
Properties	**Recognition Element**	**Integration & Miniaturisation**
Robust	Senthetic receptors	Multiple analytes
Specific	Aptamers	Smaller integrated systems (micro to nano; lab-on-a-chip)
Cheap	Membrane Proteins	Mass production
Portable	…	Cheaper components
…		Integration of nanotechnology

Strong Growth Predicted for Biosensors Market

2010; By: Dr. Rajender Thusu, PhD, Frost & Sullivan



Biosensors Market



Biosensors Market size was valued over USD 18.6 billion in 2018 and is expected to witness growth of around 8.0% Compound annual growth rate (**CAGR**) from 2019 to 2025 *.

* https://www.gminsights.com/industry-analysis/biosensors-market

Biosensors Market Report Coverage*

Report Coverage	Details		
Base Year:	2018	**Market Size in 2018:**	18.6 Billion (USD)
Historical Data for:	2014 to 2018	**Forecast Period:**	2019 to 2025
Forecast Period 2019 to 2025 CAGR:	8%	**2025 Value Projection:**	31.5 Billion (USD)
Pages:	203	**Tables, Charts & Figures:**	240
Geographies covered (16):	U.S., Canada, Germany, UK, France, Spain, Italy, Russia, Switzerland, China, India, Japan, Brazil, Mexico, South Africa, Saudi Arabia		
Segments covered:	Type, Technology, Medical Application, End-use and Region		
Companies covered (15):	Abbott Laboratories, Bio-Rad International, Biosensors International, DowDuPont Inc., Ercon, Inc., Gwent Group, Johnson & Johnson, Molecular Devices Corp., Pinnacle Technology, QTL Biosystems, Roche Diagnostics, SDIX, LLC, Siemens Healthineers, TE Connectivity Corporation, Thermo-Fisher Scientific		
Growth Drivers:	•Growing applications of biosensors in the medical field •Rising prevalence of diabetes globally •High demand for portable biosensors in Asia Pacific and Europe •Technological advancements		
Pitfalls & Challenges:	•Stringent regulatory scenario •High cost of product development		

* https://www.gminsights.com/industry-analysis/biosensors-market

Technological Challenges

In spite of product and technology innovations and improvements, the growth of the biosensors market is still restricted. Most biosensors are patented and their market penetration is limited by the resources of the patenting company.

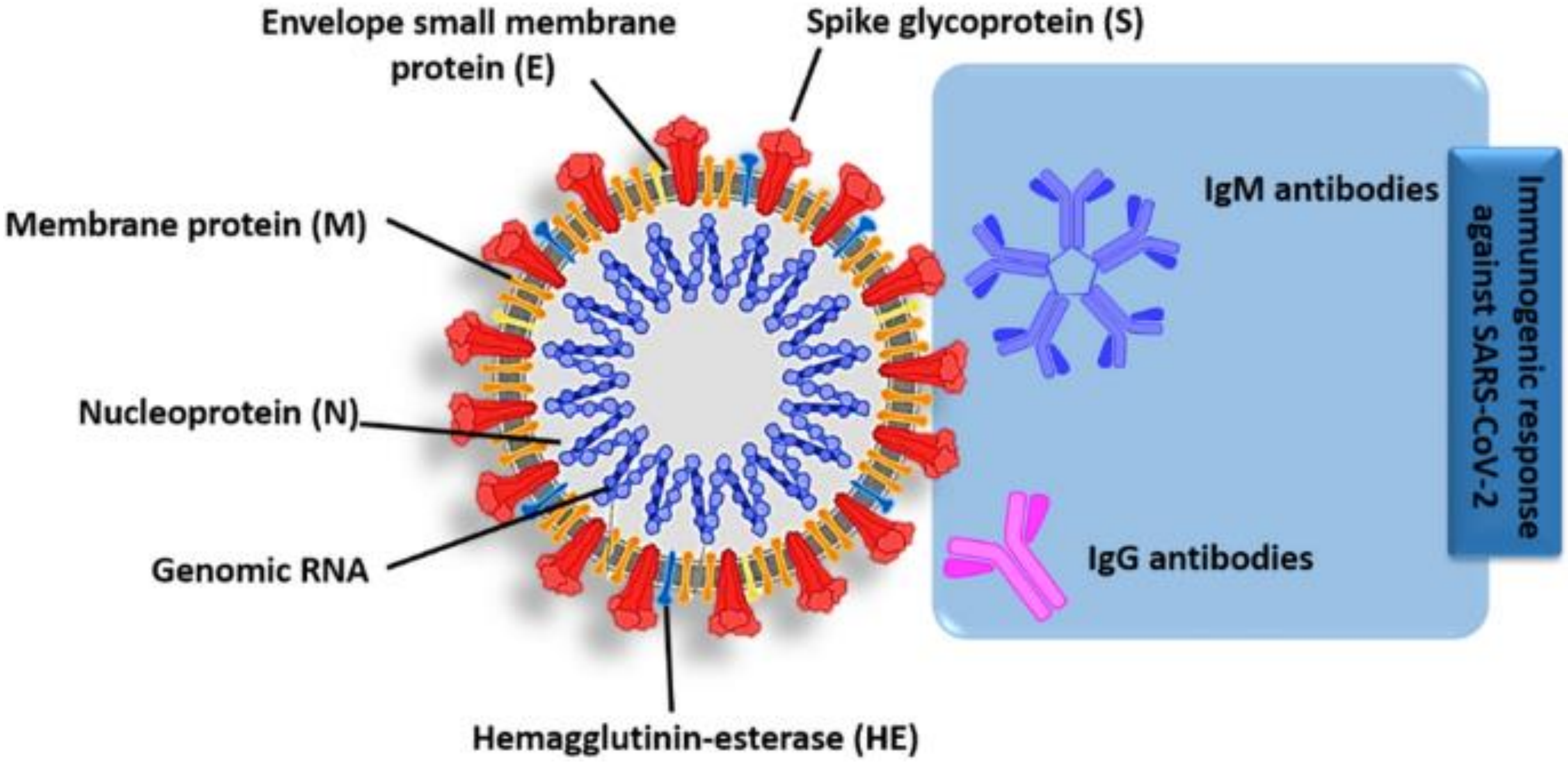
Biosensor awareness and use is limited by a number of factors such as:

- Sensitivity in a biosensor refers to real-time detection and measurement of the reaction of the target analyte, and conversion of this measurement into a usable signal.Readout times that vary greatly from one biosensor to another. In some biosensors, readout times are very long, in certain cases >20 s.
- The life span of a biomolecule is limited.
- In certain cases, biosensors require a special pre-treatment prior to each use.
- Miniaturization in sensors poses technical challenges.
- Some biosensors are too expensive for commercial production.
- Some biosensors are not sufficiently robust for their intended applications.


- Rapid methods for the detection of viruses
- Bioelectronics (including biocomputing, bio-fuel and photovoltaic cells, and electronic noses)
- Commercial biosensors, manufacturing and markets
- DNA- and nucleic acid-based sensors and aptasensors
- Enzyme-based biosensors
- Immunosensors
- Lab-on-a-chip and multiplexed sensors
- Microfluidics and immobilisation technology
- Smartphone diagnostics, wearable biosensors and mobile health
- Nanobiosensors, nanomaterials & nanoanalytical systems
- Natural & synthetic receptors (including MIPs)
- Organism-, whole cell- and organ-based biosensors
- Printed biosensors and microfabrication
- Novel transducers
- Single molecule detection
- Theranostics, implantable and ingestible sensors

Schematic structure of SARS-Cov-2 and its possible targets for diagnosing

Biosensors: frontiers in rapid detection of COVID-19 (2020)
Rachel Samson, Govinda R. Navale & Mahesh S. Dharne



Future perspectives of biosensors for the detection of SARS-CoV-2

Biosensors: frontiers in rapid detection of COVID-19 (2020)

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