بسم الله الرحمن الرحیم

Sensor and biosensors in medical sciences

By:

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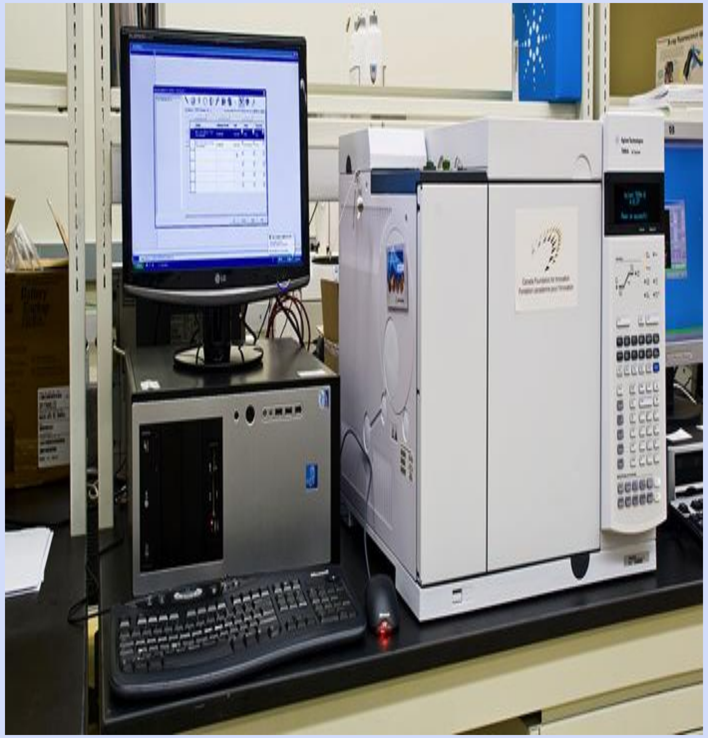
Contents

Introduction

Classical (traditional) customary analytical methods

HPLC



GC

ELISA

Comparision between classic analytical methods and (bio)sensors

Classical methods

Advantages

- Possibility to measure several analytes
- Commercial availability
- Sensitive
- Specific

Limitations

- Time-concuming
- Expensive
- laborious and long sample preparation
- Need to skilled user
- High organic solvent consumption

(Bio)sensors

Advantages

- Fast, real-time measurement
- Easy, affrodable
- Simple device
- Sensitive and ultra-sensitive
- Reusability
- Low organic solvents consumption
- Portable (on-site measurement)

Limitations

- Commercial availability restrictions
- Single Analyte detection

Historical background

The history of biosensors dates back to as early as 1906 when M. Cremer demonstrated that the concentration of an acid in a liquid is proportional to the electric potential that arises between parts of the fluid located on opposite sides of a glass membrane.

Between 1909 and 1922, Griffin and Nelson first demonstrated immobilisation of the enzyme invertase on aluminium hydroxide and charcoal.

The first *'true'* biosensor was developed by Leland C. Clark, Jr in 1956 for oxygen detection. He is known as the *'father* of *biosensors'*

The demonstration of an amperometric enzyme electrode for the detection of glucose by Leland Clark in 1962 was followed by the discovery of the first potentiometric biosensor to detect urea in 1969 by Guilbault and Montalvo, Jr .

Eventually in 1975 the first commercial biosensor was developed by Yellow Spring Instruments (YSI)

Sensors

Sensors are devices that detect physical, chemical, and biological signals and provide a way for those signals to be measured and recorded.

1. Simultaneous detection of pH value and glucose concentrations for wound monitoring applications.

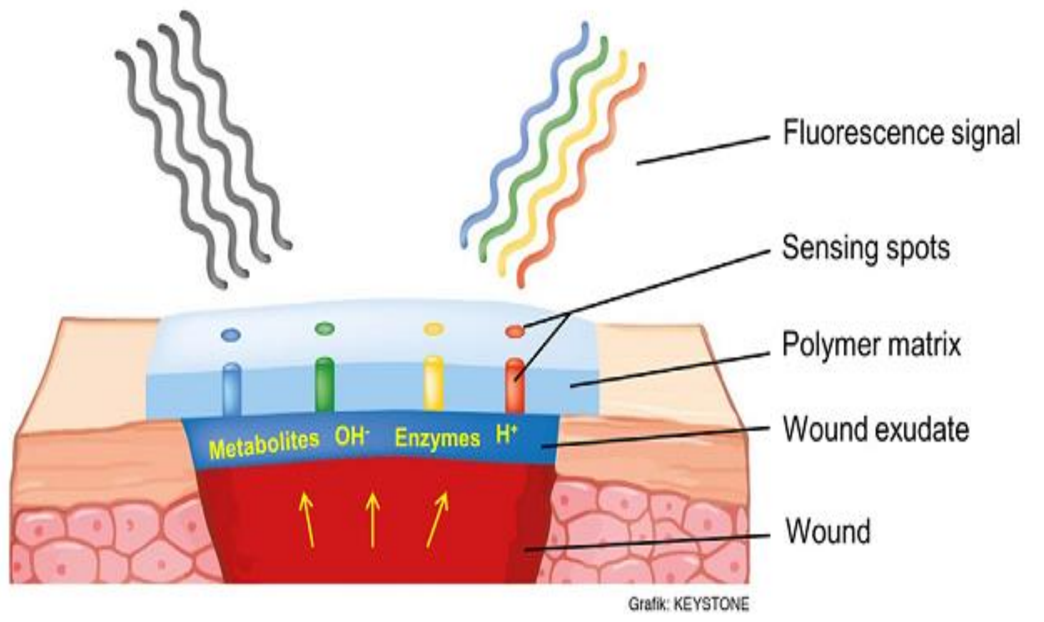
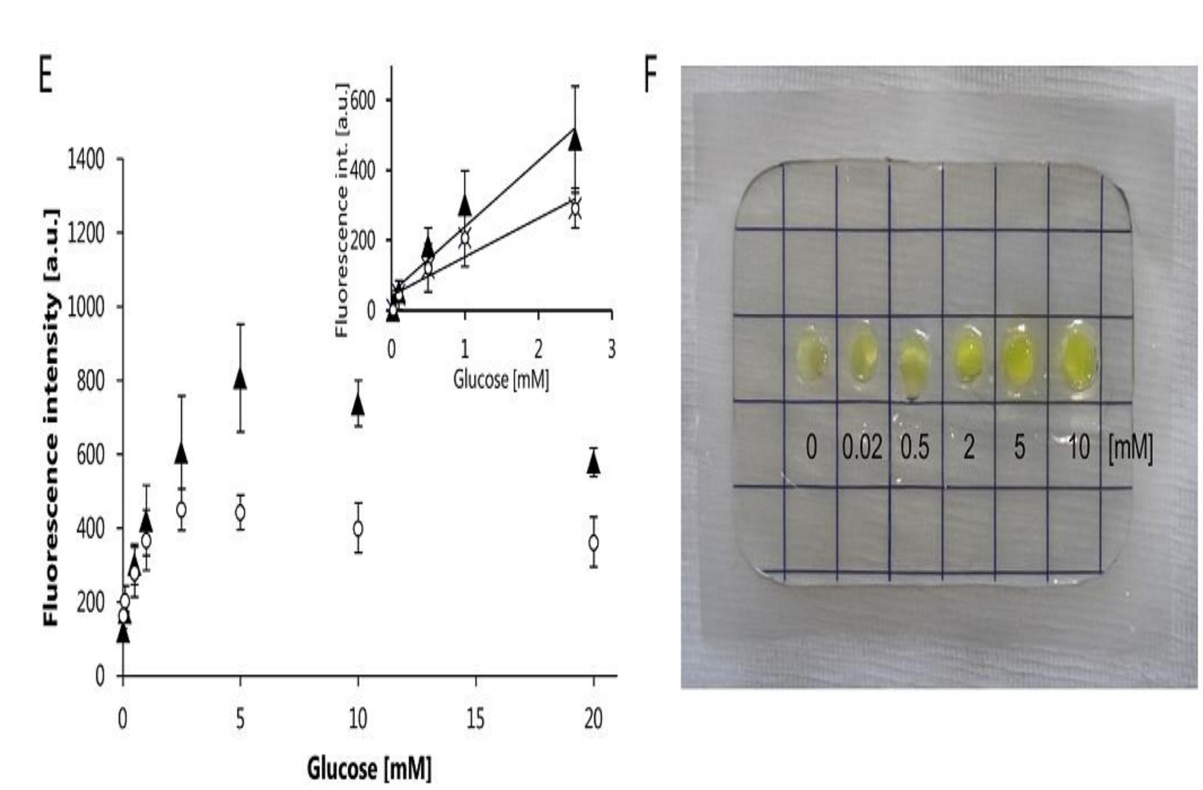


Fig. 1. Scheme of the sensing principle for non-invasive wound monitoring based on the detection of pH-values and glucose concentrations.



2. Temperture and pH sensors based on graphenic materials

P. Salvo et al. *Biosensors and Bioelectronics 91 (2017) 870–877*

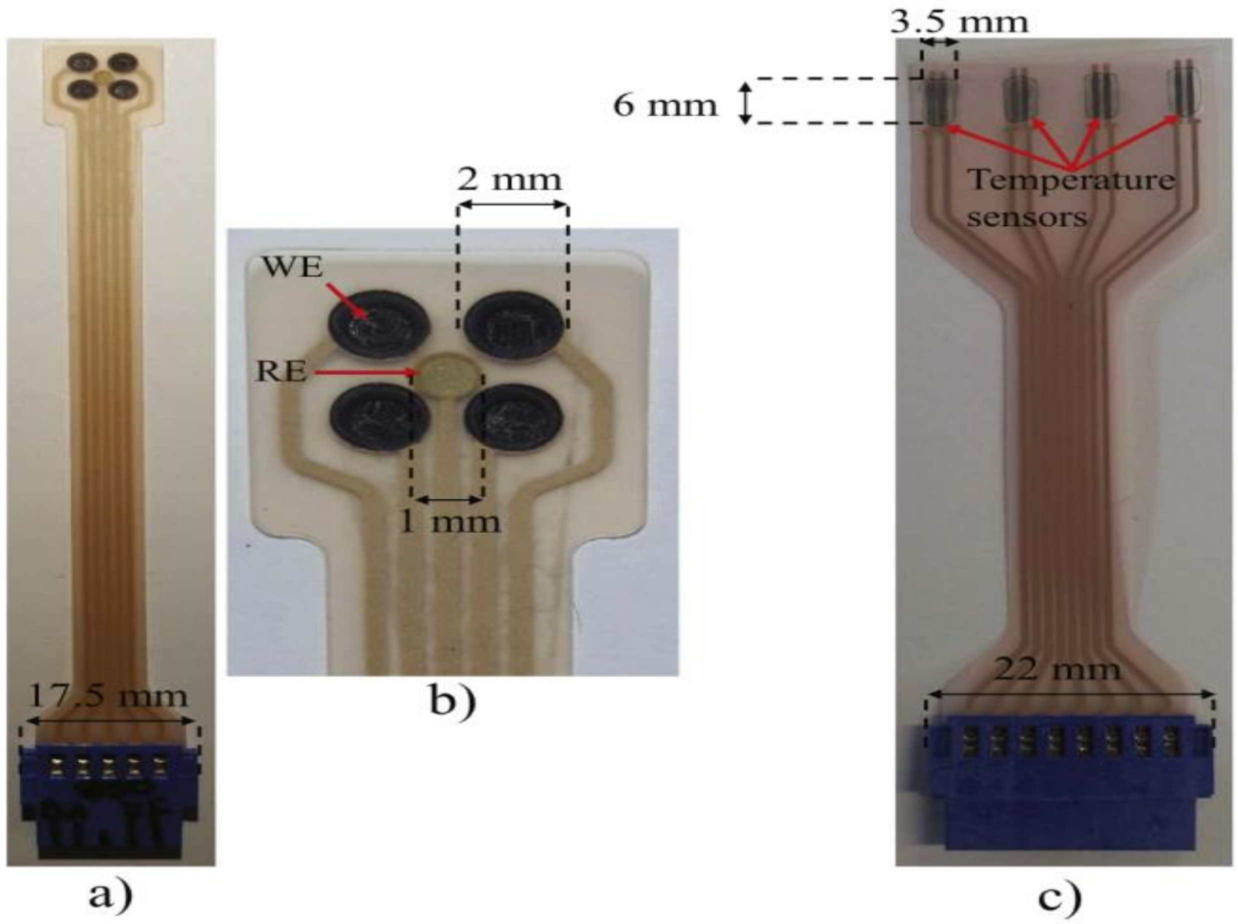
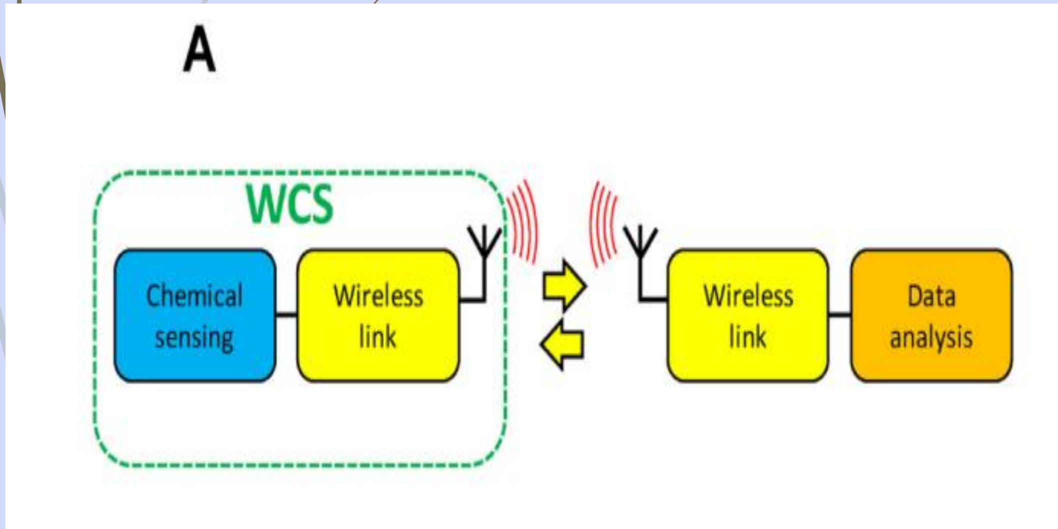


Fig. 1. a) A flexible PET screen printed board used for measuring pH. Boards with different lengths and number of sensors can be used according to wound dimensions. b) Detail of the pH sensor board. Each working electrode (WE, diameter 2 mm) is coated with a GO film. The reference electrode (RE, diameter 1 mm) is Ag/AgCl. c) A flexible PET screen printed board used for measuring temperature. The active area is 6 mm×3.5 mm and electrodes (600 µm wide – 500 µm spaced) are connected to the readout electronics by silver tracks. The sensitive layer consists of reduced graphene oxide. Boards with different lengths can be used according to wound dimensions.

3. Wireless chemical sensors and biosensors

Wireless chemical sensors (WCSs) are hybrid devices that collect (bio)chemical data from their local environment and then process and transmit this chemical analytical information to a remote device, or devices, by wireless technology, most usually by radio communications,



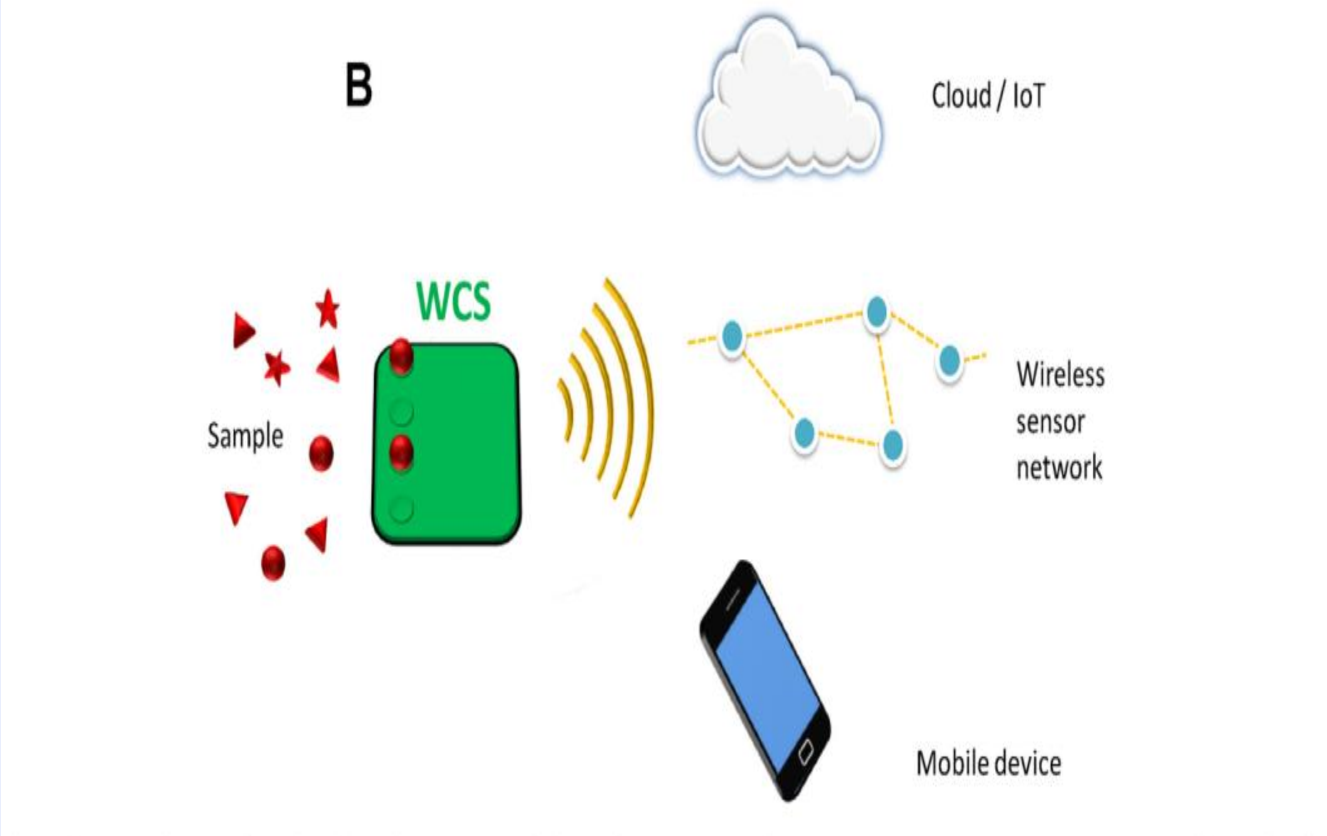


Fig. 1. (a) Generic schematic of a wireless chemical sensor system. The data analysis output can inform a user, or initiate an appropriate system response. (b) Examples of communications with WCSs include single point-to-point reading (e.g. to a personal mobile device), and distributed systems where the WCS forms part of a wider network. In either case, data can be aggregated to cloud-hosted databases, as necessary.

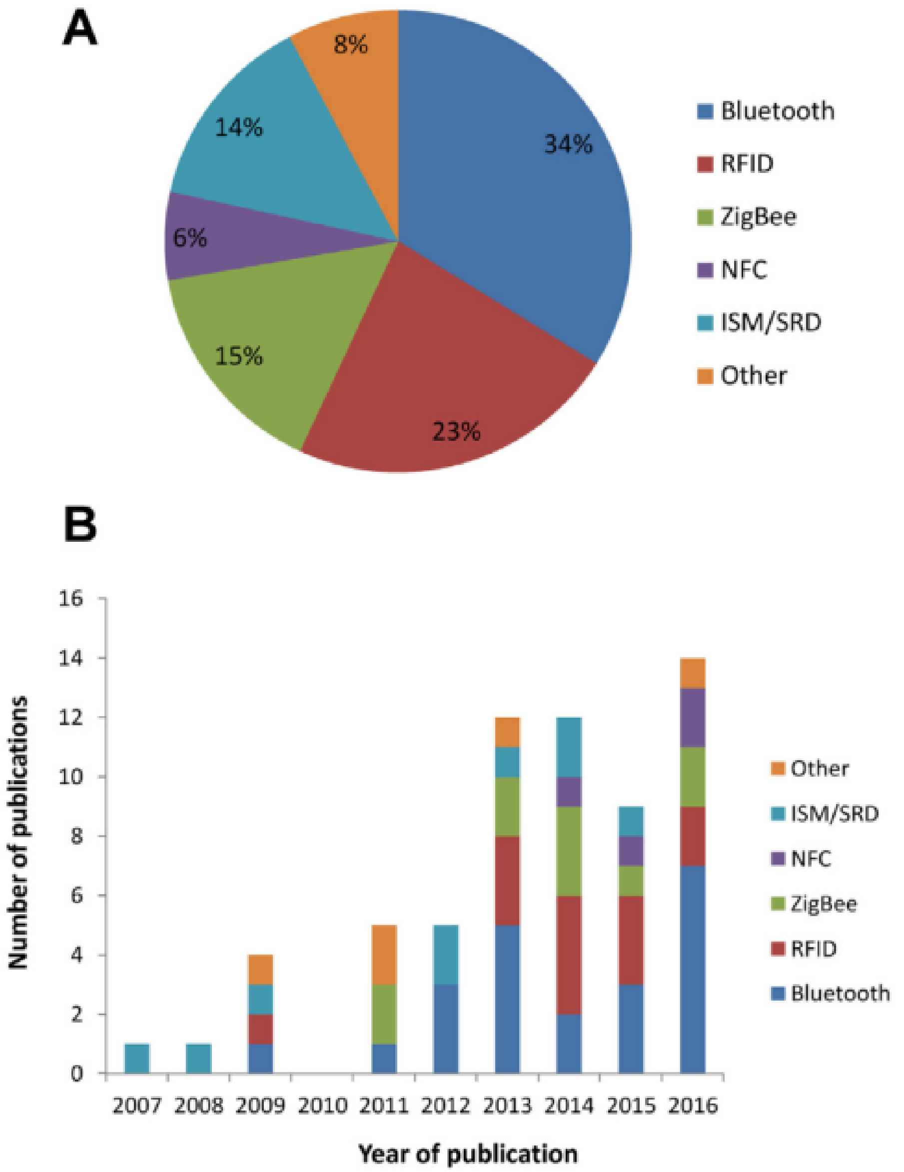


Fig. 2. (a) Wireless communication protocols deployed in wireless chemical sensors, and (b) incidence of the different protocols by year of journal publication, 2007–2016.

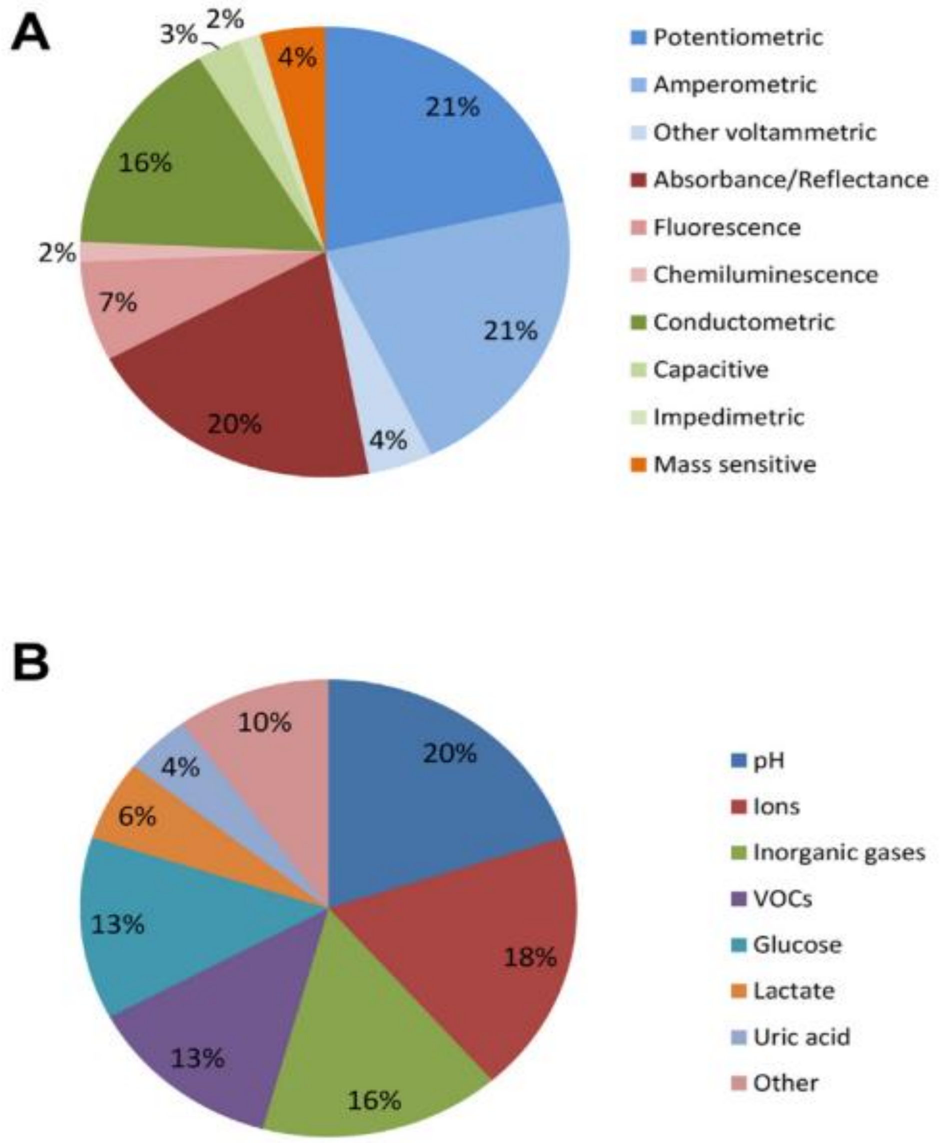
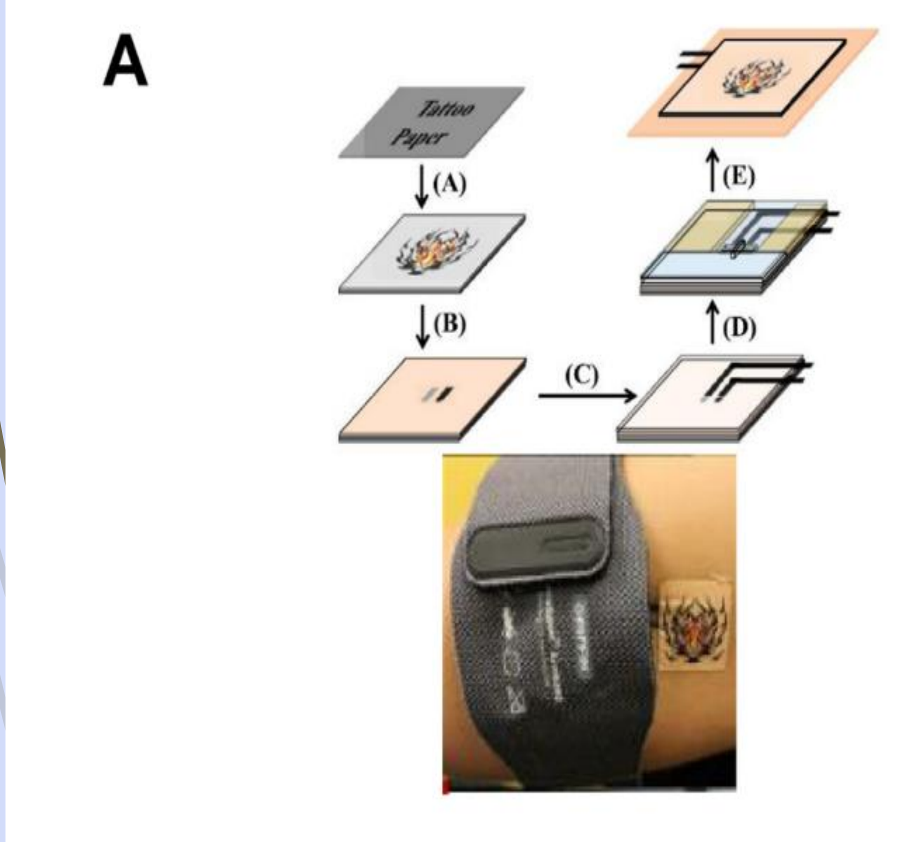


Fig. 3. (a) Transduction mechanisms deployed in wireless chemical sensors (blue – electrochemical, red – optical, green – electrical, orange – mass sensitive). (b) Distribution of WCS publications by target analyte. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. A wearable sensor for determining sodium in sweat during exercise



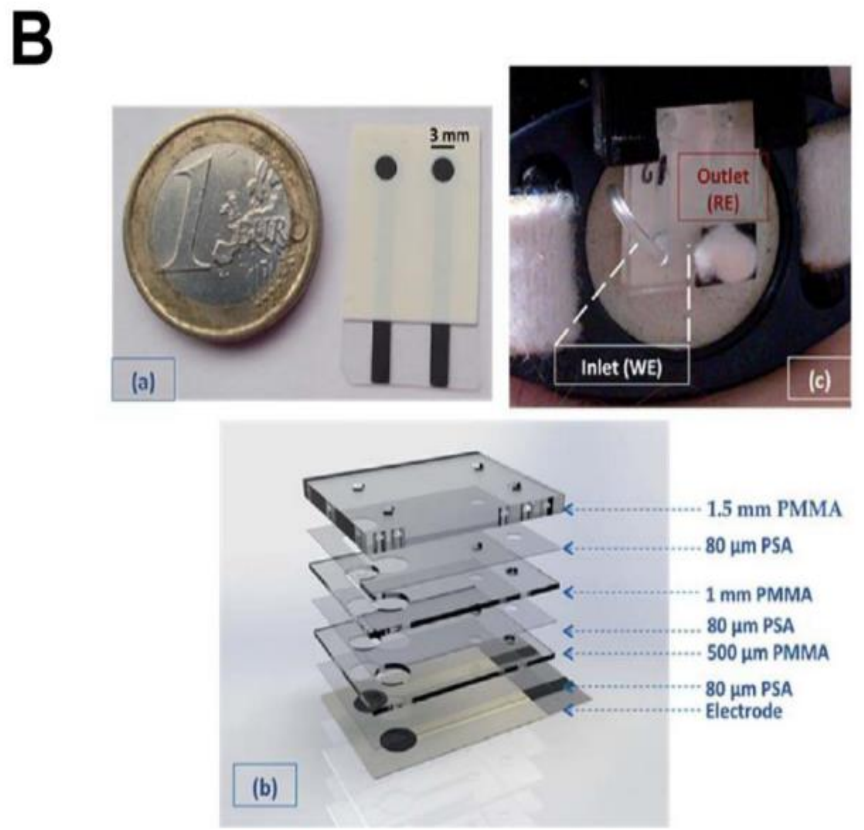


Fig. 4. Wearable wireless potentiometric sensors for determining sodium in sweat: (a) Fabrication and transfer process of the Bluetooth-based tattoo sensor, Reprinted from Biosensors & Bioelectronics, 54, A.J. Bandodkar et al., Epidermal tattoo potentiometric sodium sensors with wireless signal transduction for continuous non-invasive sweat monitoring, 603-9, Copyright (2014), with permission from Elsevier [58]; (b) ZigBee-based system incorporating microfluidic chip, adapted from Ref [59] with permission of The Royal Society of Chemistry (https://doi.org/10.1039/C5AY02254A).

5. Design and operation of the wireless smart bandage for uric acid

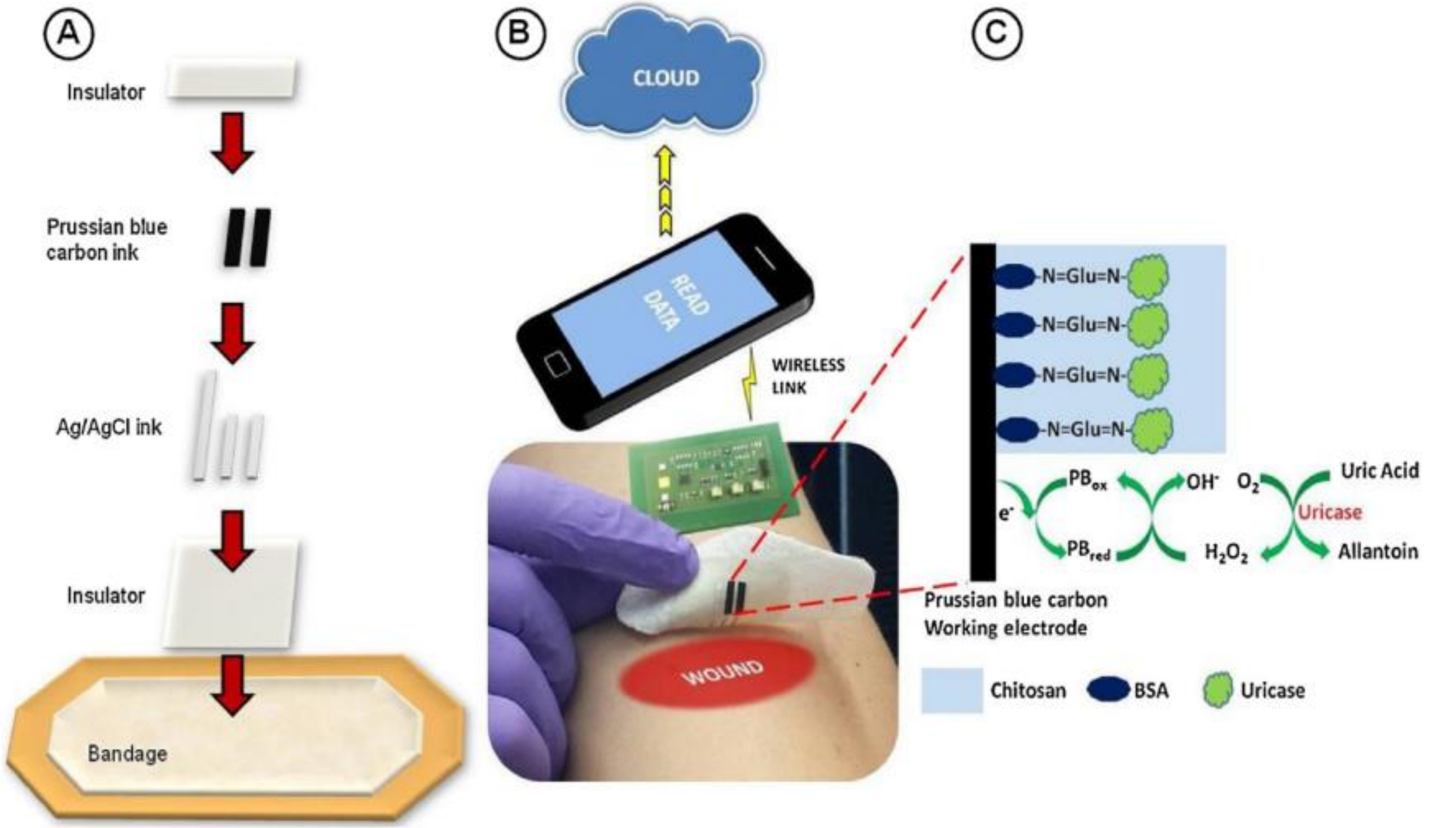


Fig. 5. Design and operation of the wireless smart bandage for uric acid determination, reprinted from Electrochemistry Communications, 56, P. Kassal et al., Smart bandage with wireless connectivity for uric acid biosensing as an indicator of wound status, 6–10, Copyright (2015), with permission from Elsevier [28].

Immobilised urate oxidase, paired with a printed catalytic Prussian blue transducer, facilitates chronoamperometric detection of uric acid at a low working potential.

Table 3
Wireless electrical chemical sensors.

Analyte	Recognition element	Transduction mechanism	Wireless system	Application	Ref.
CO, CO_2, SO_x, NO_x, O_2	MOx	Conductometric	ZigBee	Environmental, pollution	Kumar et al. [80]
H_2, CH_4	Fe_2O_3	Conductometric	ZigBee	Security	Song et al. [81]
ethanol	PEDOT:PSS	Conductometric	RFID	General	Steinberg et al. [82]
methanol	CNT	Conductometric	Bluetooth	General	Jang et al. [83]
NO_2	Oxygen plasma modified MWCNT	Conductometric	RFID	General	Clement et al. [29]
DNT	DNA-modified SWCNT	Conductometric	ZigBee	Security	Liu et al. [84]
pH	poly(1-amino anthracene) with SWCNT	Conductometric	RFID	General	Gou et al. [85]
sevoflurane	MWCNT-loaded Polypyrrole	Conductometric	ISM/SRD	General	Chavali et al. [86]
VOCs	MWCNT/polymer composites	Conductometric	ZigBee	Environmental Wearable	Lorwongtragool et al. [26]
NH_3 Humidity	Polyaniline/carbon nanocomposite	Conductometric Capacitive	RFID	Environmental	Quintero et al. [87]
VOCs (EtOH, EtOAc, humidity)	PDMS, PBMA, PHEMA	Capacitive	Zigbee	Environmental (industrial workplace)	Oikonomou et al. [88]
VOCs	ZnO-graphene modified eelctrodes	Impedimetric	Bluetooth	Sports (acetone), other	Liu et al. [89]

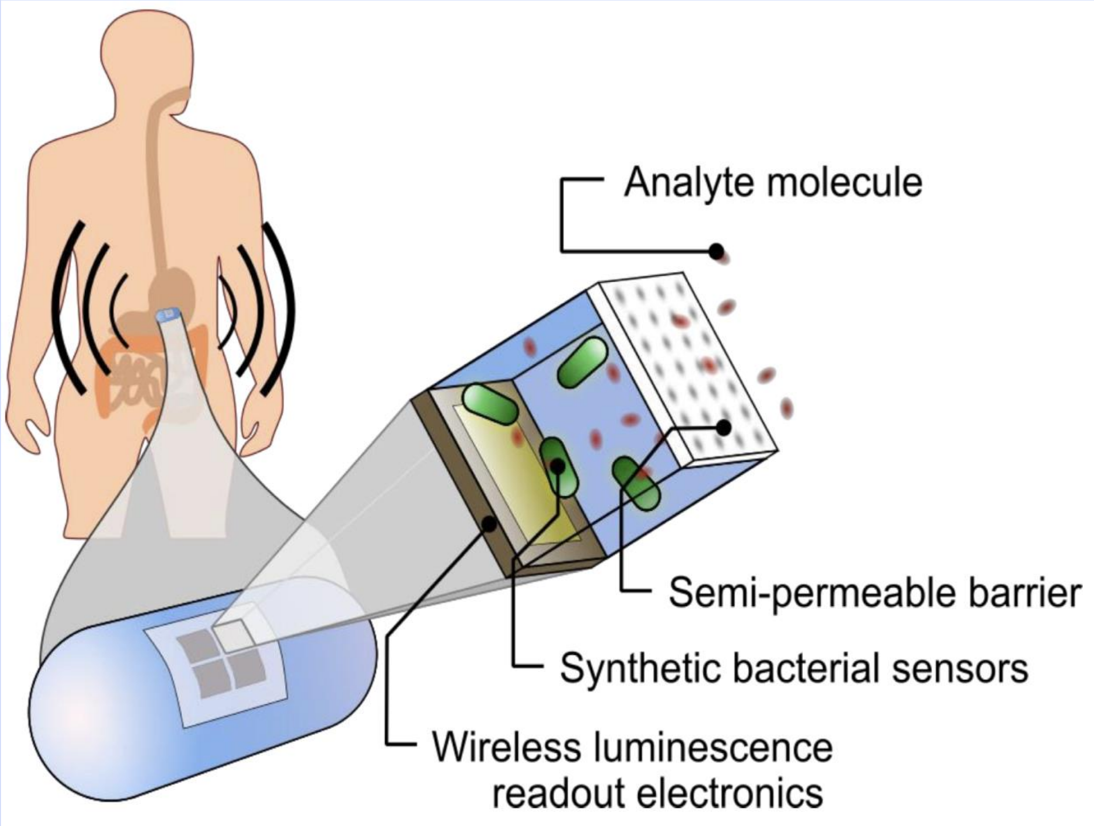
Table 4
Optical wireless chemical sensors.

Analyte	Recognition element	Transduction mechanism	Wireless system	Application	Ref.
pH	Bromocresol green	Reflectance	RFID	General	Steinberg et al. [92]
Model dye, K^+	Valinomycin, N—Octadecanoyl-Nile blue	Absorbance	RFID	General	Steinberg et al. [93]
Acetic acid vapour	Bromophenol blue	Absorbance	ISM/SRD	Environmental, gas	Shepherd et al. [94]
NH_3 vapour	3′-3″-dichlorophenolsulfonephthalein	Absorbance	ZigBee	Environmental, Cultural Heritage conservation	Llorente-Alonso et al. [27]
NO_2	diazo coupling reagents	Absorbance	ISM/SRD	Environmental, air quality	Maruo et al. [34]
Humidity	Direct absorbance	IR Absorbance	ZigBee	General	Cao et al. [95]
$KMnO_4$ (model)	$KMnO_4$ (model)	Absorbance	Bluetooth	General	Camarillo-Escobedo et al. [96]
pH	Bromocresol purple	Absorbance	Bluetooth	Environmental, water quality	Czugala et al. [97]
pH	Bromocresol purple	Reflectance	ISM/SRD	Sports, sweat monitoring	Morris et al. [98]
pH	Bromocresol purple	Absorbance	Bluetooth	Sports, sweat monitoring	Curto et al. [99]
pH	7-Hydroxyphenoxazone	Reflectance	Bluetooth	Sports, sweat monitoring	Caldara et al. [25]
pH	Bromophenol blue	Absorbance	Bluetooth	Wearable, wound monitoring	Schyrr et al. [100]
pH	GJM 534	Reflectance	RFID	Wearable, wound monitoring	Kassal et al. [101]
O_2	Pt octaethylporphyrin	Fluorescence	RFID	Food quality	Martinez-Olmos et al. [30]
CO_2, NH_3, humidity, O_2	α-naphtholphthalein, bromophenol blue, crystal violet, PdTFPP	Absorbance, Fluorescence	NFC	Food quality	Escobedo et al. [102]
Glucose	Bis-boronic acid fluorescent indicator	Fluorescence	NFC	Implantable, glucose monitoring	Mortellaro et al. [32]
Glucose	Fluorescent labelled analyte binding protein	Fluorescence	ISM/SRD	Implantable, glucose monitoring	Valdastri et al. [103]
Fluorescein (marker)	Direct fluorimetry	Fluorescence	Zigbee	Swallowable, Gastrointestinal bleeding	Nemiroski et al. [104]
Thyroid-stimulating hormone TSH	Antibody (sandwich immunoassay)	Chemiluminescence	RFID	Healthcare, POC diagnostics	Yazawa et al. [105]

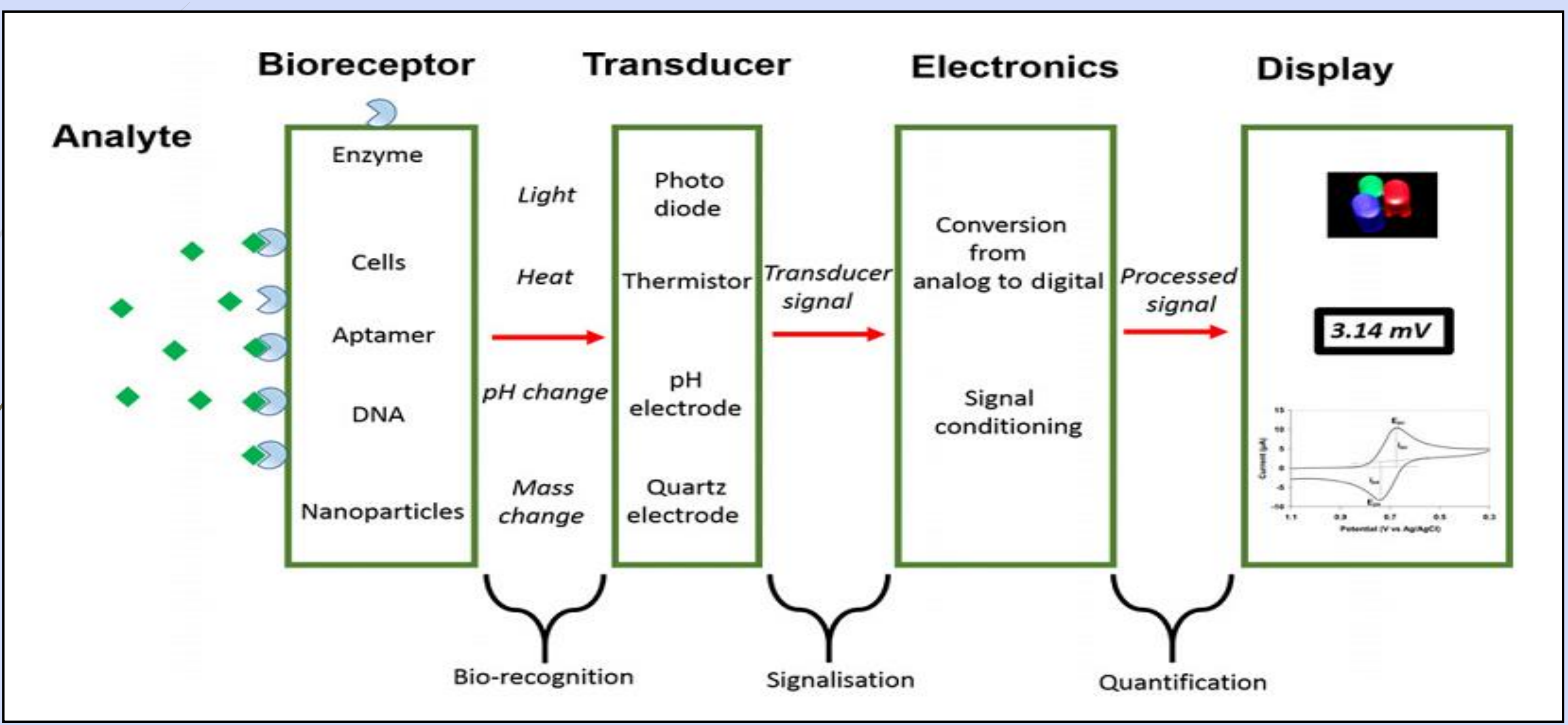
Biosensor

A biosensor is an analytical device. The sensor which integrates the biological elements with the physiochemical transducer to produce an electronic signal is proportional to a single analyte.

The sensitive biological element (e.g. tissue, microorganisms, cell receptors, enzymes, aptamers, antibodies, nucleic acids, etd.) is a biologically derived material or biomimetic component that interacts (binds or recognizes) with the analyte under study.



Representation of a biosensor



Characteristics of a biosensor

Selectivity

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

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.

Reproducibility

Reproducibility is the ability of the biosensor to generate identical responses for a duplicated experimental set-up.

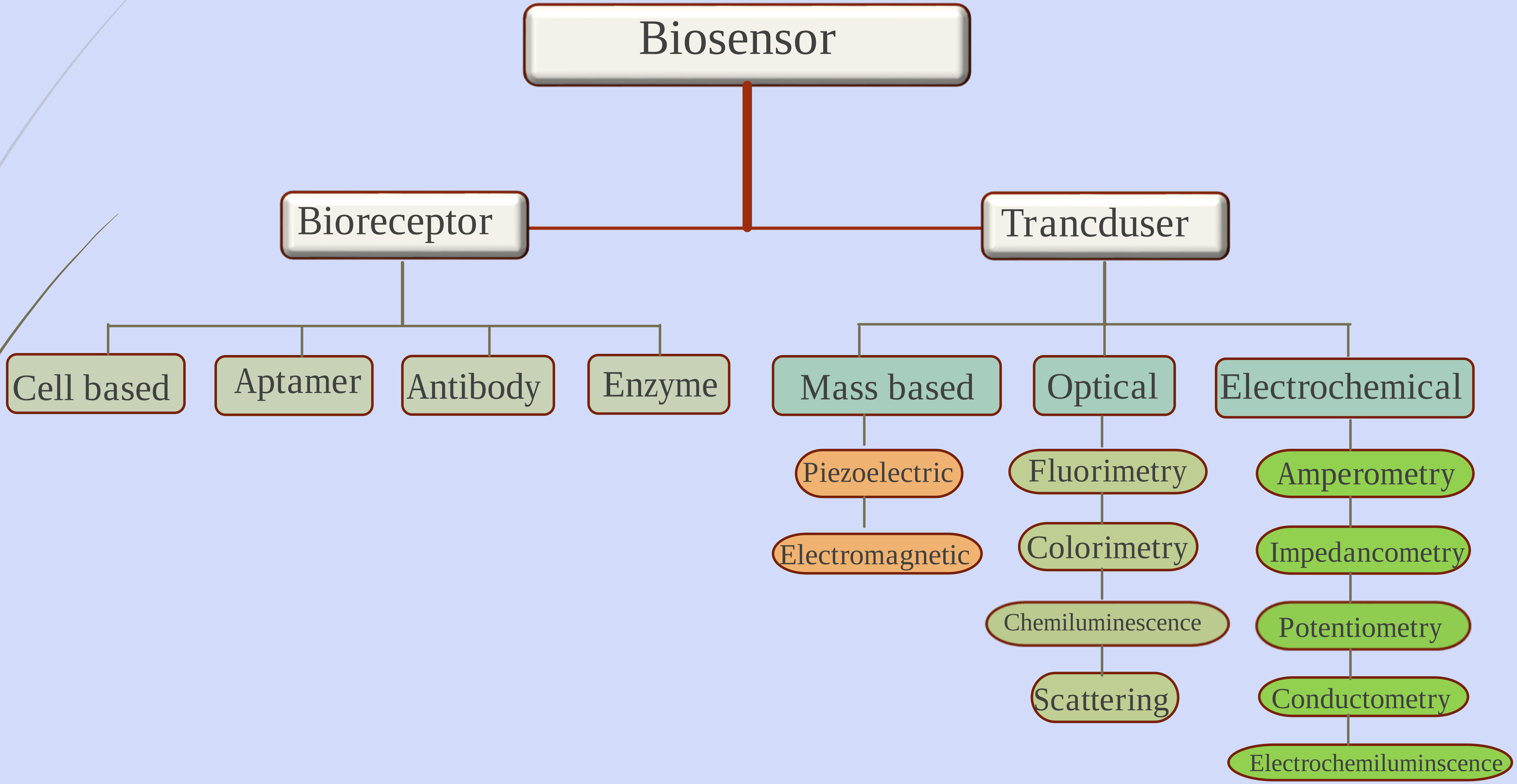
Stability

Stability is the degree of susceptibility to ambient disturbances in and around the biosensing system. These disturbances can cause a drift in the output signals of a biosensor under measurement.

Sensitivity

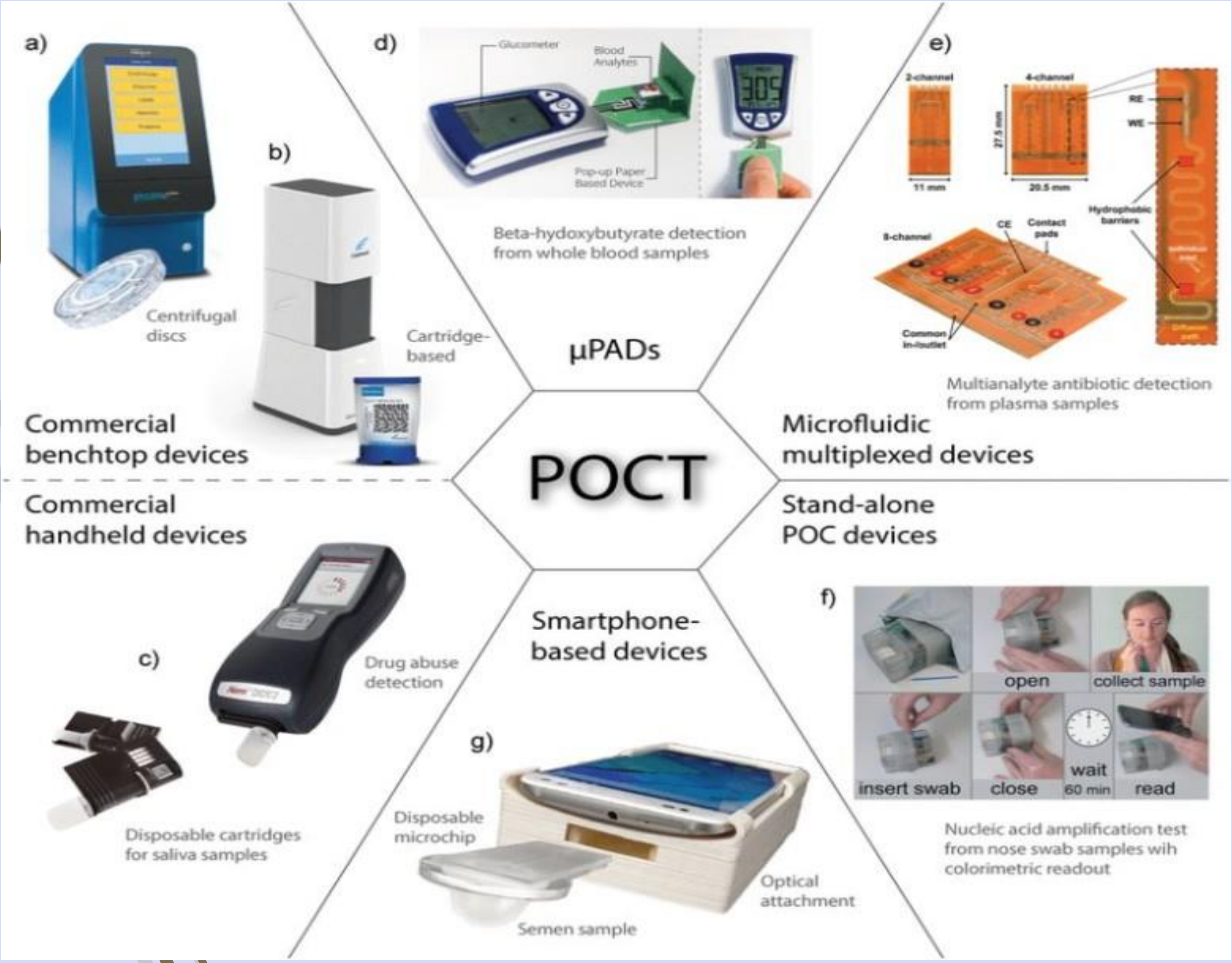
The minimum amount of analyte that can be detected by a biosensor defines its limit of detection (LOD) or sensitivity.

Types of biosensors based on the various transducer mechanisms (sensor devices) and biological materials

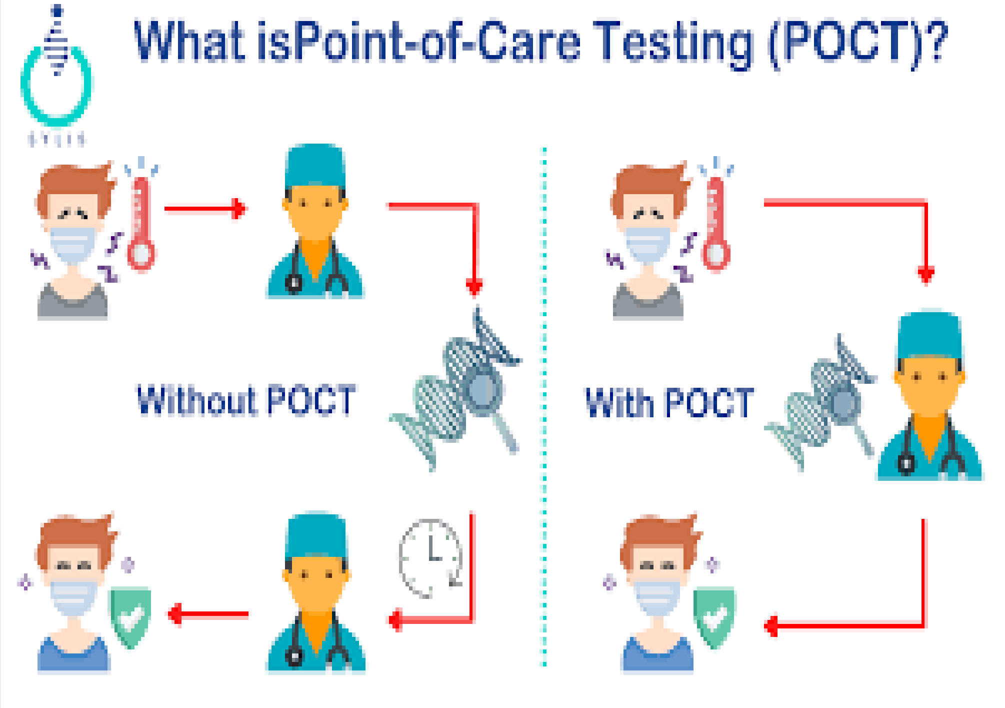


Major areas of applications for biosensors

- Medical diagnosis (both clinical and labroatory use)
- Study of biomolecules and their interaction
- Point-of-care testing
- Drug Development
- Crime detection
- Agriculture and food industry
- Environmental field monitoring
- Quality control
- Industrial Process Control
- Detection systems for biological warfare agents



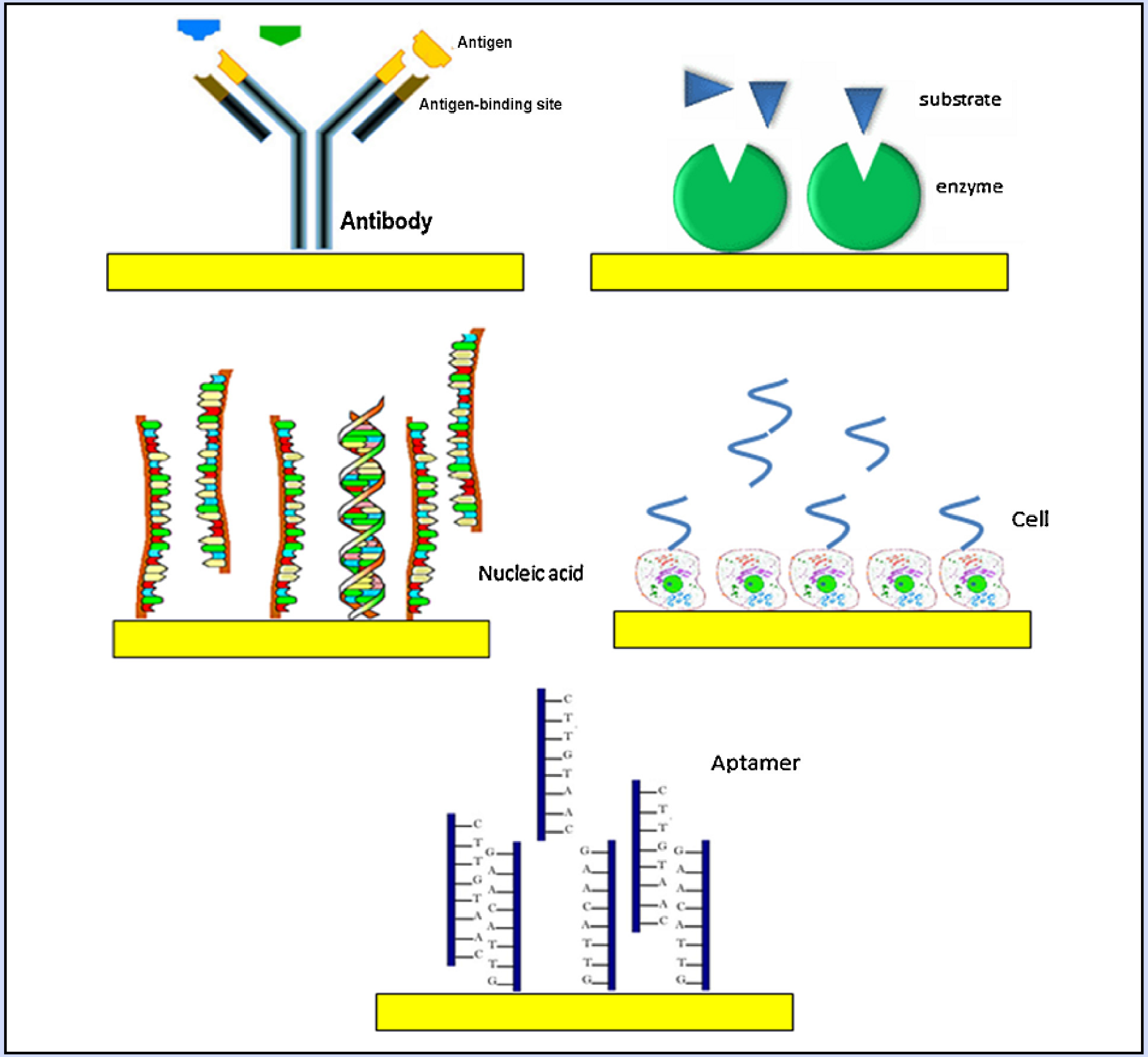
POCT
a)
Centrifugal discs
b)
Cartridge-based
Commercial benchtop devices
d)
Beta-hydoxybutyrate detection from whole blood samples
μPADs
e)
Multianalyte antibiotic detection from plasma samples
Microfluidic multiplexed devices
Commercial handheld devices
c)
Drug abuse detection
Disposable cartridges for saliva samples
Stand-alone POC devices
f)
open
collect sample
insert swab
close
wait
60 min
read
Nucleic acid amplification test from nose swab samples wih colorimetric readout
Smartphone-based devices
g)
Disposable microchip
Optical attachment
Semen sample



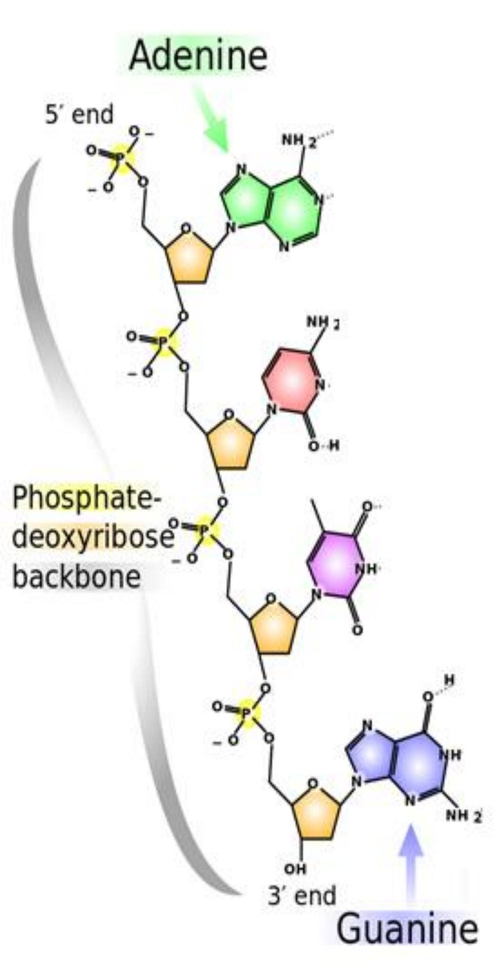
What isPoint-of-Care Testing (POCT)?
Without POCT
With POCT

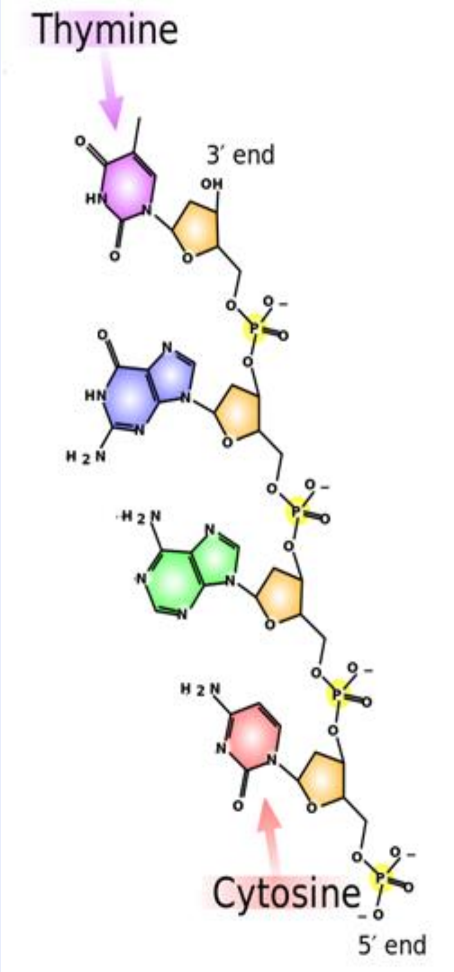
Methods of biosensing with various biological signal mechanism:

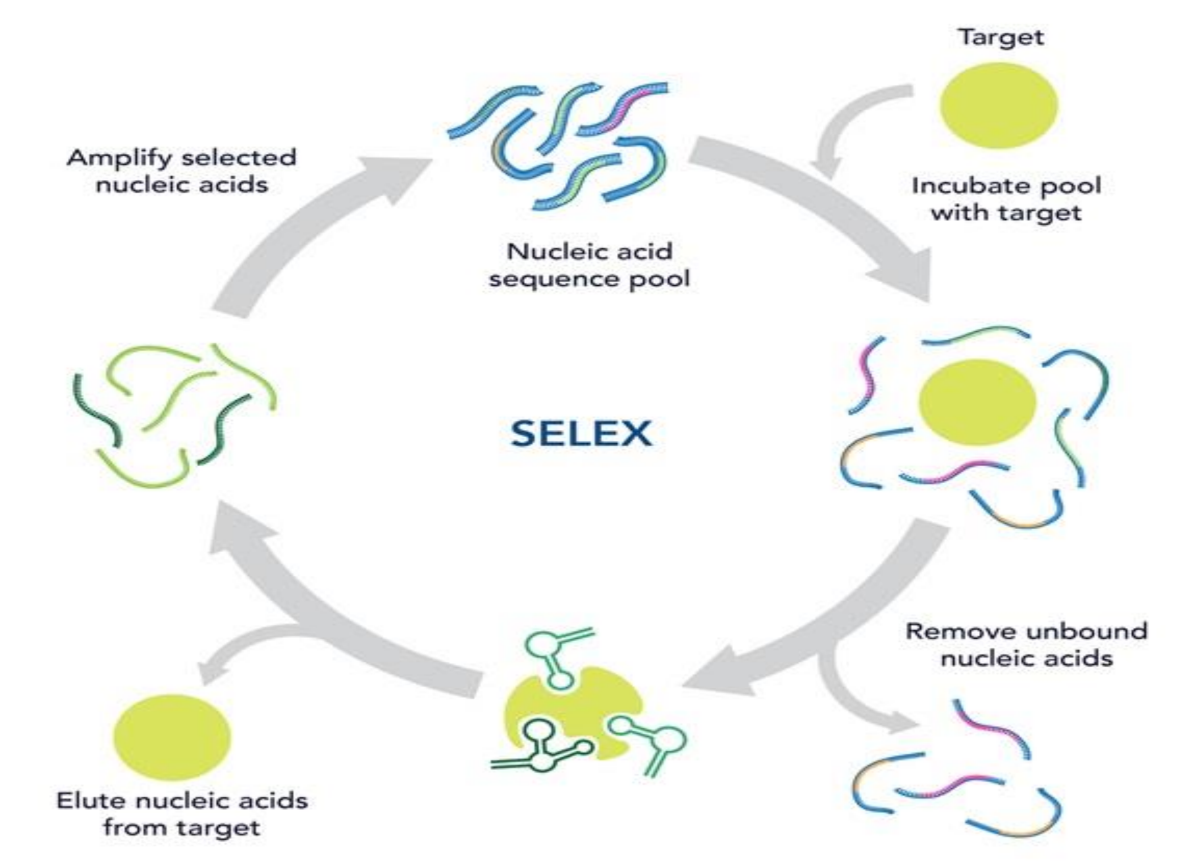
(a) Antibody/antigen
(b) Enzyme catalyze
(c) Nucleic acid
(d) Cell-based
(e) Aptamer



Aptamers







SELEX (Systematic evolution of ligands by exponential enrichment)

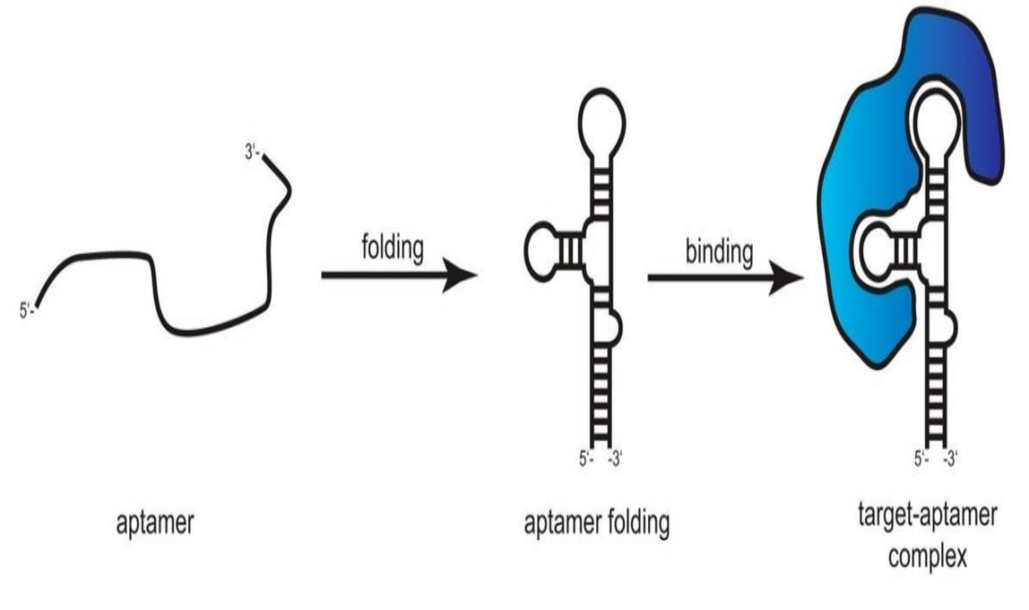
Features of an ideal diagnostic component (bioreceptor)

- high sensitivity
- Acceptable selectivity
- Quick response
- The ability to respond to a wide range of analytes

Aptamar's superiority to antibody

- Ability to detect non-immunogenic target analytes
- lower price
- Chemical synthesis
- Longer shelf life and storage capability for later use
- The ability to detect a wide range of molecules including small metal ions, small organic molecules, proteins, even cells and bacteria and ...
- Suitable flexibility for attaching types of labels such as fluorophore , electrochemical detectors and nanoparticles

Molecular interaction between aptamer and its target



Mechanism of recognized a target analyte by Aptamar

- Hydrogen bonding
- Electrostatic interactions
- Stacking of aromatic rings
- Van der Waals interaction

Optical aptamer-based biosensors (aptasensors)

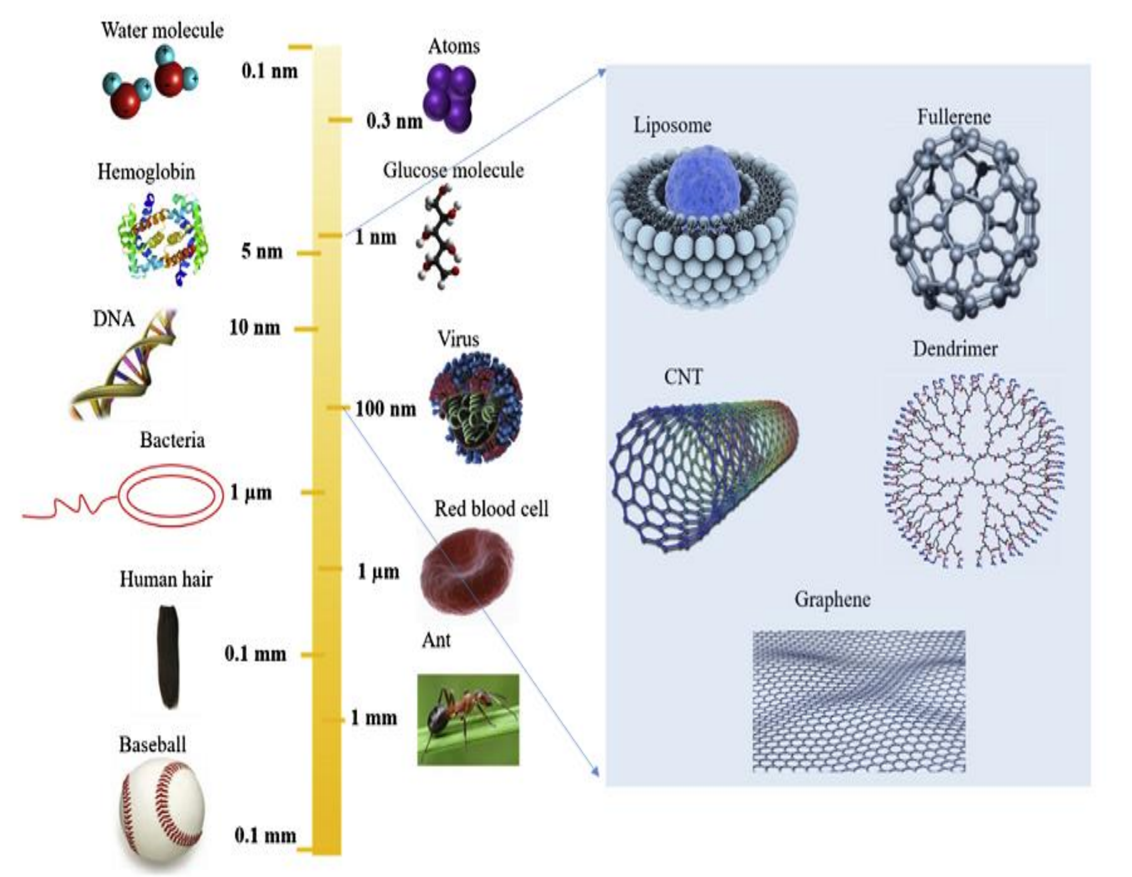
1. Colorimetric-based aptasensors →
   - Simplest strategy
   - Easily distinguish of analyte by naked eye
   - Presence of UV- VIS spectrophotometer in most labs

2. Fluorescence-based aptasensors →
   - High sensitivity (low LOD)
   - Ease of detection procedure

3. Chemiluminescence-based aptasensor →
   - Simple instrumentation
   - Wide calibration ranges
   - Suitability for miniaturization in analytical chemistry

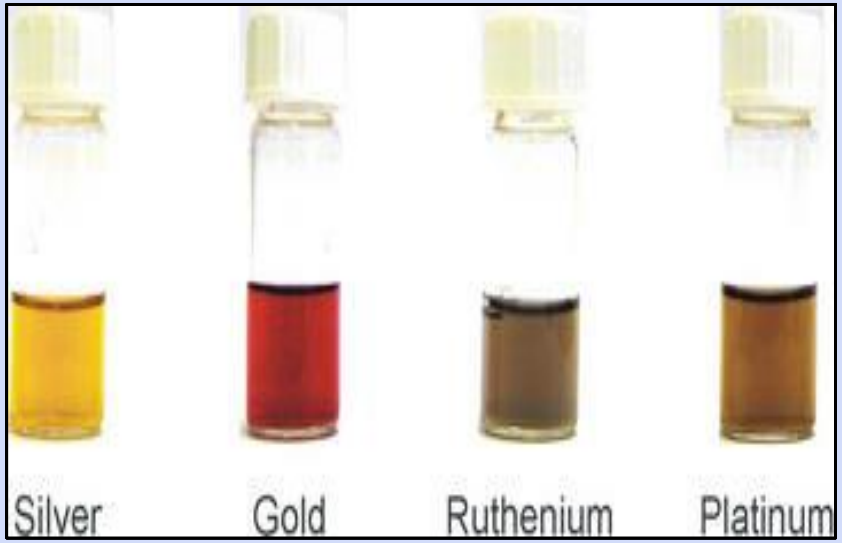
Nanotechnology

1. Reducing the size of the biosensor to the micro- or nano-scale can result in a better signal-to-noise ratio as well as the possibility of using smaller sample volumes, which means lower assay costs.
2. Increase sensivity, decrease response time, biocompatible for in-vivo bioassay
3. Ability to conjugate to variety of biological detection elements
4. The same particle size and optical properties associated with size and shape, high surface energy and high surface-to-volume ratio and adjustable surface properties
5. Reduced non-specific binding and increased binding efficiency towards the target molecule



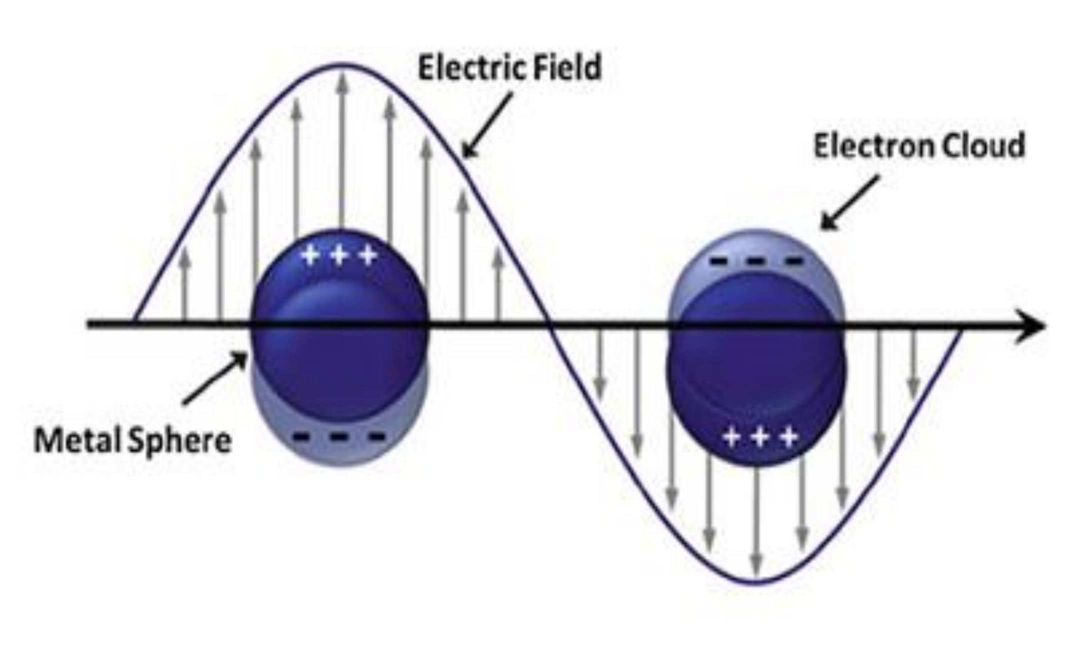
Metallic nanoparticles

1. Easy to modified with simple chemistry
2. The high surface-to-volume ratio with special spectral and optical properties
3. Their high compatibility with biomolecules (specialy Au and Ag nanoparticles)
4. Their excellent optical performance(specialy Au and Ag nanoparticles)
5. Ability to control the process of making them
6. AuNPs catalytic activity

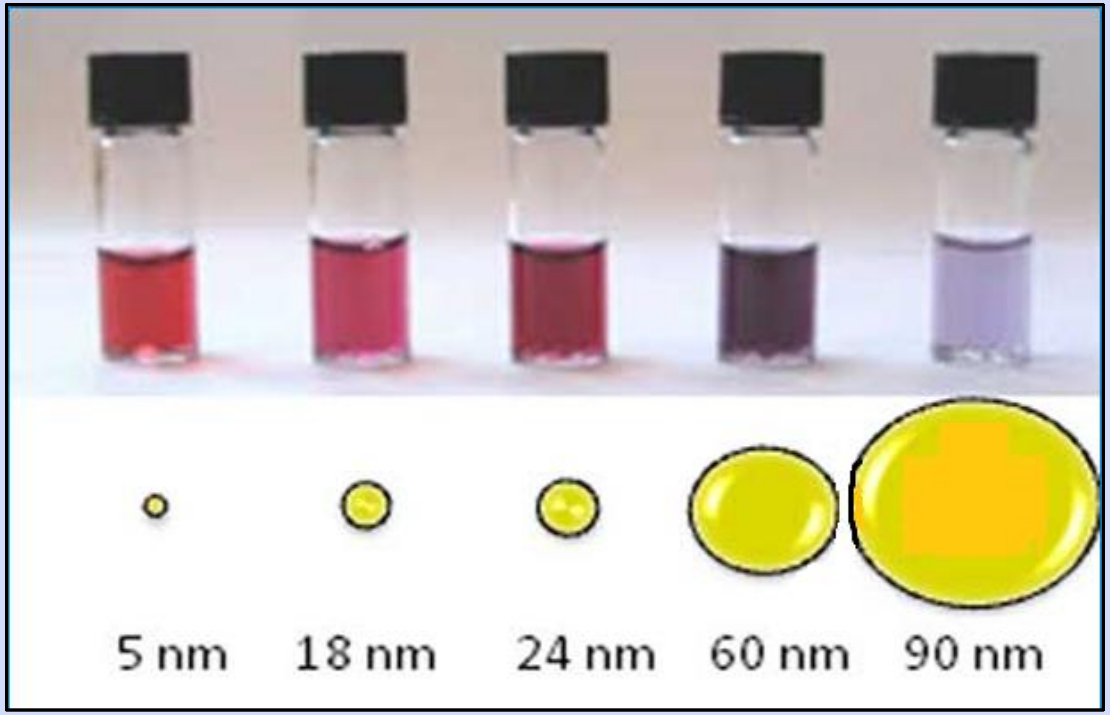


Biosensing using Metal Nanoparticles

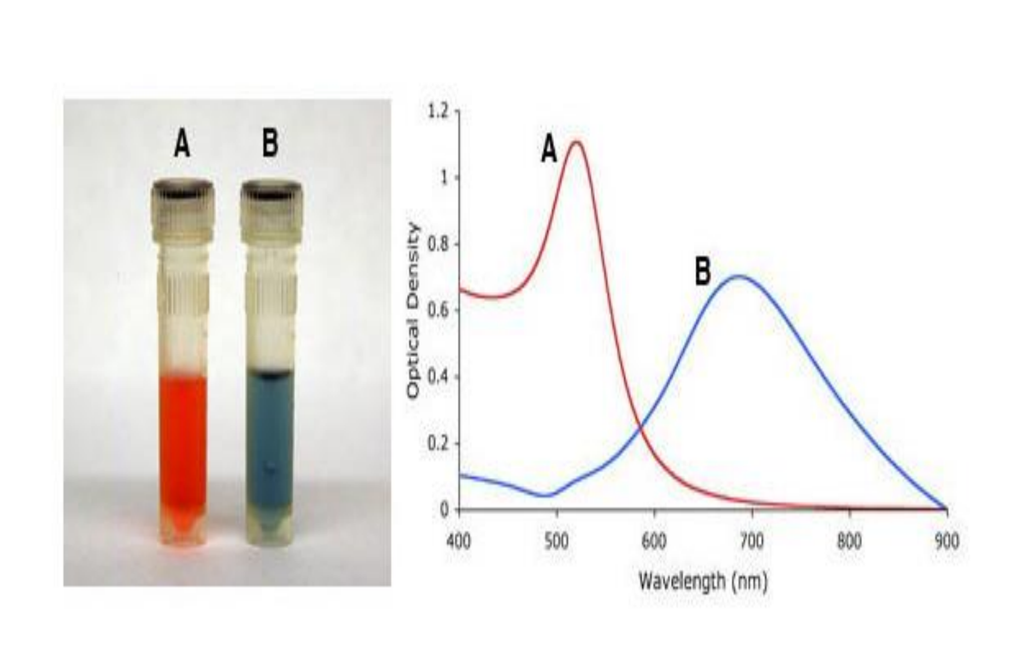
The unique optical and electromagnetic properties of metal nanoparticles can be utilized in several areas including biosensing.

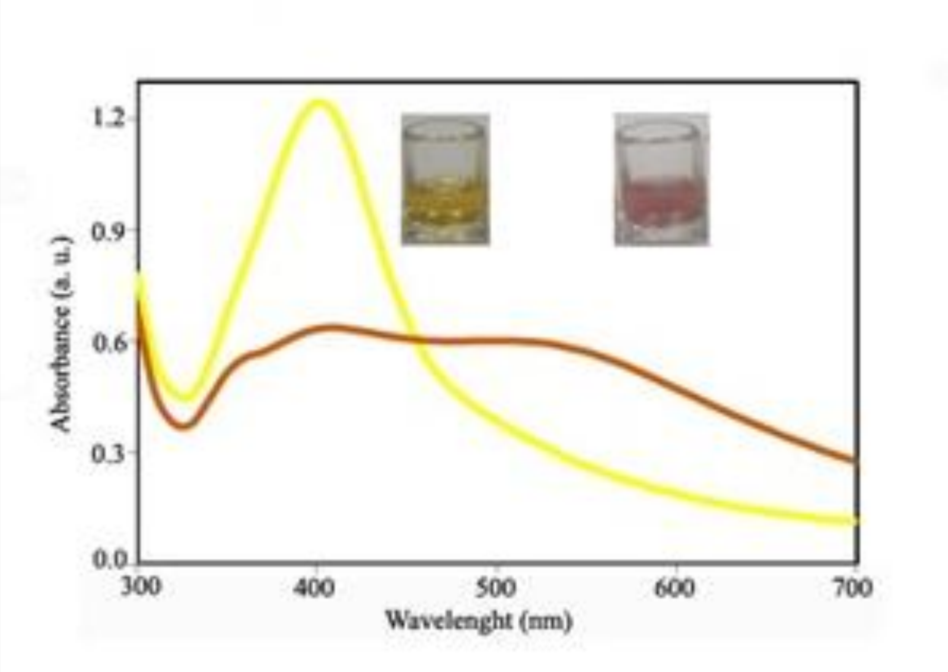


Schematic representation of localized surface plasmon resonance phenomenon (LSPR)



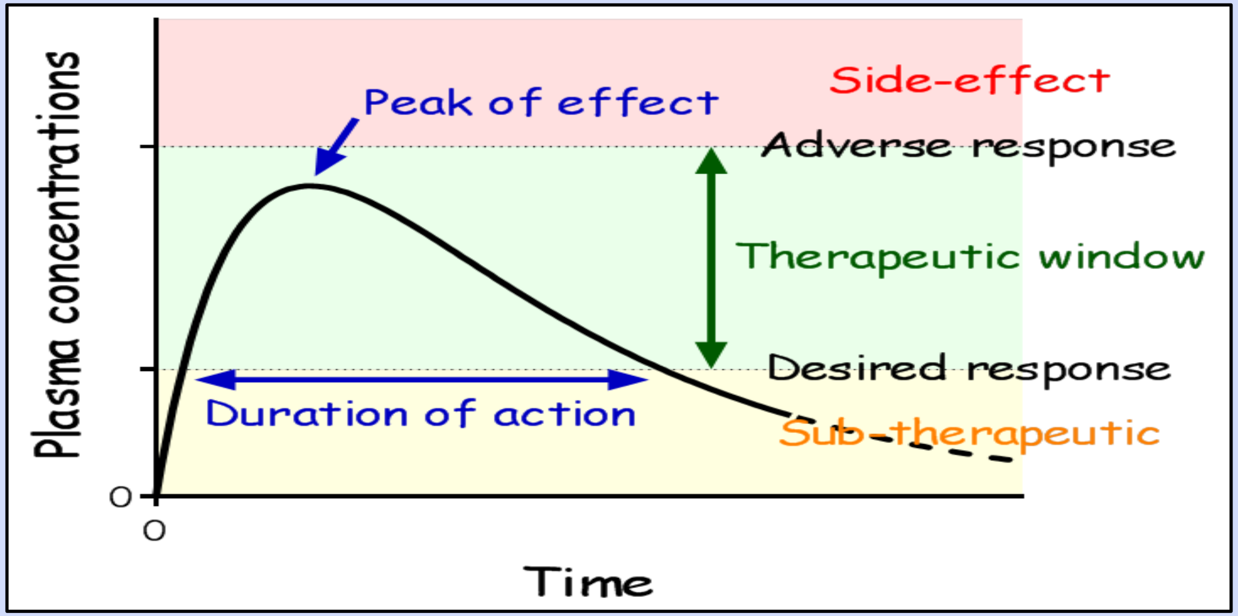
The plasmonic resonance created in metal nanoparticles is extremely sensitive for changes in their surroundings, making them suitable elements for sensing applications.





Narrow Therapeutic Index Drugs (NTIDs)

Drugs with a narrow TI (NTIDs) have a narrow window between their effective doses and those at which they produce adverse toxic effects.



Clinical Pharmacokinetic of (NTIDs)

Cancer

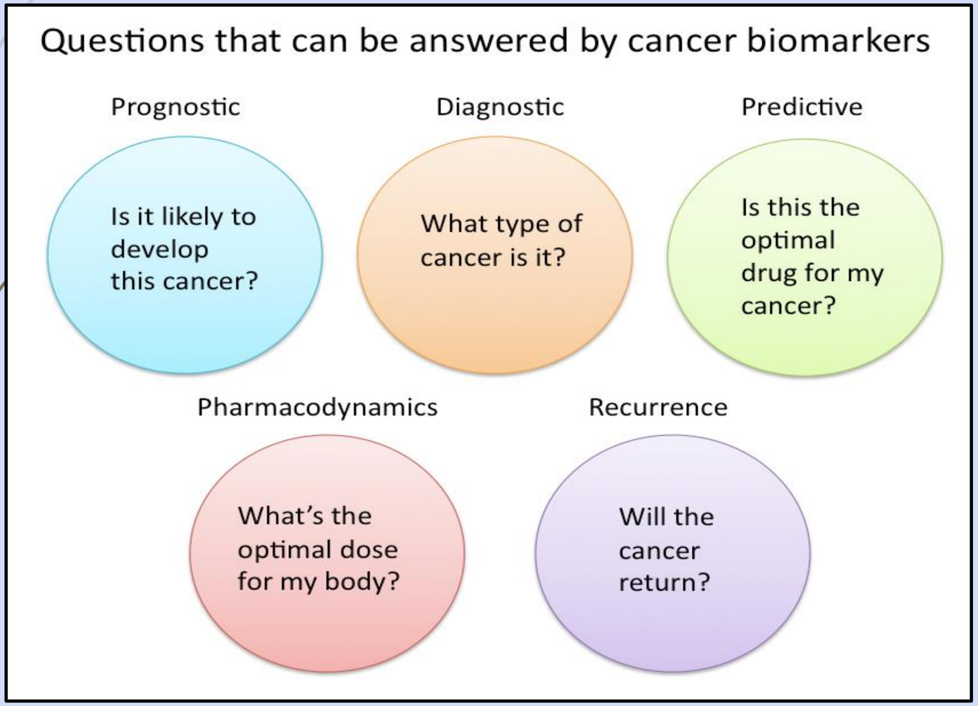
The Importance of early detection of Cancer

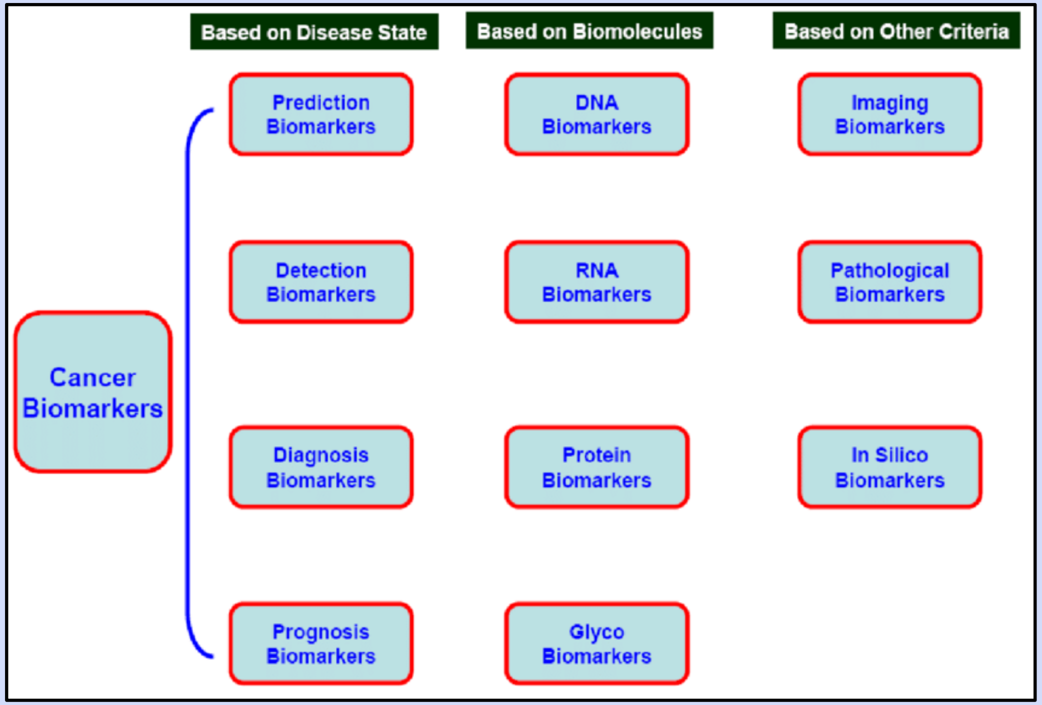
Techniques used to detect cancer and their limitations

Technique	Limitations
Mammography	Detects only 70% of breast cancers Low sensitivity and specificity Sensitivity decreases as breast tissue density increases Fails to detect tumor in dense and small tissue at early stage Frequent false positive results Low energy X- rays may cause mutations in tissue Disintegration of tumor tissue during analysis may cause metastasis
Biopsy	May miss tumor cells Unnecessary surgery May lead to metastasis of tumor Need skilled expertize Performed for confirmation in later stages Expensive
MRI	Unable to detect all types of cancers such as ductal and lobular carcinoma Expensive
Sonography	Less sensitive and relatively expensive Need experienced expertize to analyse real time examination
FISH (Fluorescence in situ hybridization)	Provide semi-quantitative results Separate patients in biomarker positive or negative groups
ELISA	Time consuming Expensive Insensitive to low level markers Intrinsic color of analytes may lead to false results Require trained personal to carry out analysis
RIA	Radioactivity risk Complex procedure Time consuming Require trained personal to carry out analysis
IHC	Complicated technique Time consuming Require trained personal to carry out analysis

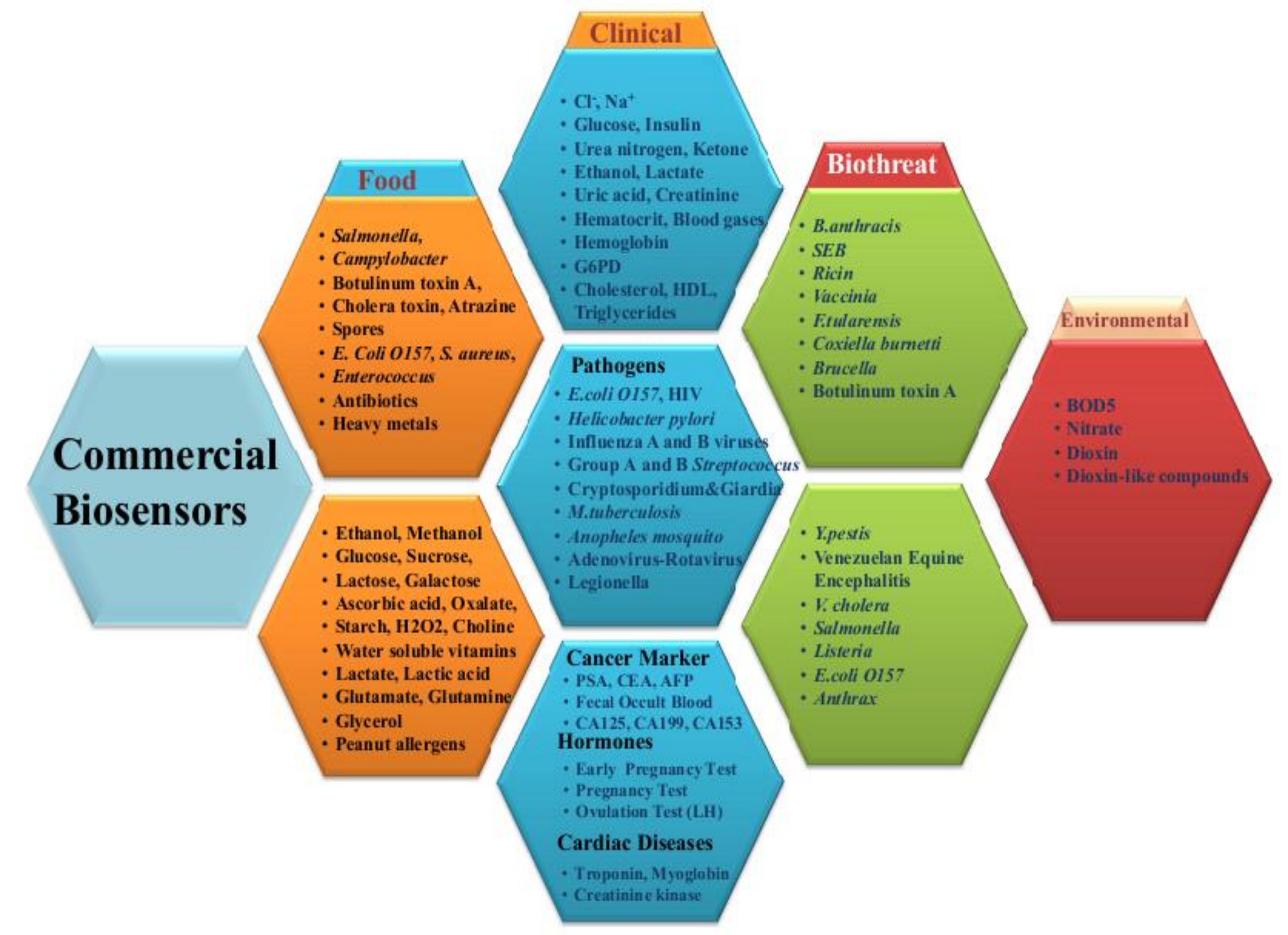
Cancer biomarkers

Cancer biomarkers (CB) are biomolecules produced either by the tumor cells or by other cells of the body in response to the tumor.





Commercial biosensors



Commercial biosensors in clinical analysis

Biosensors have many advantages such as low cost, high sensitivity, fast response, and easy operation for analyte detection.

Commercial glucose biosensors

$$\text{glucose} + O_2 \rightarrow \text{gluconolactone} + H_2O_2$$

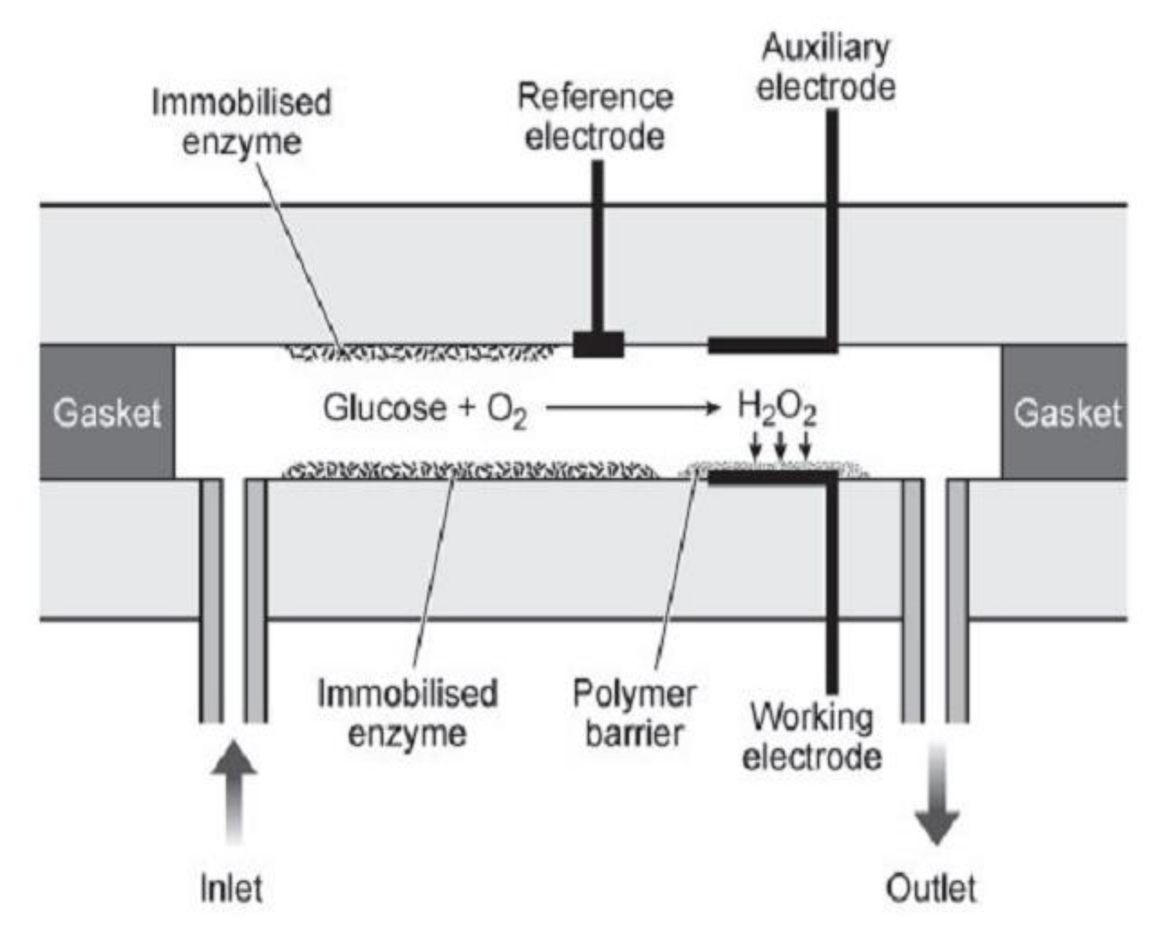


Table 1
Commercially available clinical biosensors and their characteristics [9–33].

Company	Model	Analyte	Measuring range (mM)	Stability
Yellow Springs Instruments	23A 13L 27	Glucose Lactate Ethanol	1–45 0–15 0–60	300
Zentrum für Wissenschaftlichen Geratebau, Berlin, Germany	Glucometer	Glucose Uric acid	0.5–50 0.1–1.2	>1000 samples; 10 days
Fuji Electric, Tokyo, Japan	Gluco 20	Glucose α-amylase	0–27	>500 samples
Pulsatum Health Care Ltd, India	Glucometer	Glucose	0–600 mg/dl	6 months
Abbott, USA	FreeStyle Life FreeStyle Freedom FreeStyle InsuLinx Precision Xtra Overview	Glucose Glucose Glucose, insulin Glucose, ketone	20–500 mg/dl 20–500 mg/dl 20–500 mg/dl, – –, –	– – –, – –, –
EKF Industrie-Elektronik GmbH	Biosens 040	Glucose	–	–
Daiichi, Kyoto, Japan	Autostat GA-1120	Glucose	1–40	–
Roche, Basel, Switzerland	LA 640 Accu-chek Aviva Plus Accu-chek Nano Smart Accutrend Plus System	Lactate Glucose Glucose Glucose, cholesterol	0.5–12 – – 20–600 mg/dl, 150–300 mg/dl	40 days – – –, –
Eppendorf, Germany	ADM 300 ECA 20 (ESAT 6660) ACC	Glucose Glucose, lactate Uric acid, lactate	1–100 0.6–60, 1–30 0.1–1.2, 1.2–18.7	>2000 samples; 10 days 14 days 10 days
Accusport lactate analyzer (ACC)	–	Total cholesterol, alcohol	–, 0.1%	
Lifestream cholesterol monitor Alcosan saliva alcohol dipstick	i-STAT PCA HHxx series	Glucose Urea nitrogen, Cl^-, K^-, Na^+, hematocrit blood gases Water, urine, blood	 0–25000 ± 6.1 PA	

Table 1 (*continued*)

Company	Model	Analyte	Measuring range (mM)	Stability
Prodigy Diabetes Care, Charlotte, NC, USA	Prodigy AutoCode	Glucose	20–600 mg/dl	–
	Prodigy Pocket	Glucose	20–600 mg/dl	–
	Prodigy Voice	Glucose	20–600 mg/dl	–
Nova Diabetes, USA	Nova Max Plus	Glucose, ketone	–	–
	Nova Max Link	Glucose	–	–
Gediabetes, Taiwan	GE 100	Glucose	20–600 mg/dl	–
Aga Matrix, USA	Wavesense Presto	Glucose	50–400 mg/dl	–
EPS Bio Technology Corp, Taiwan	MDT2	Glucose	20–630 mg/dl	–
	EME	Glucose	20–630 mg/dl	–
	EMM	Glucose	20–630 mg/dl	–
	EMV2	Glucose	20–630 mg/dl	–
	MasterDriver	Glucose	20–630 mg/dl	–
	R13 N	Glucose	20–630 mg/dl	–
American Screening Corp., USA	Q. STEPS G/C ADMS	Glucose, cholesterol	100–400 mg/dl	–
Omnis Health, USA	Embrace Meter	Glucose	–	–
	Embrace Evo	Glucose	–	–
	Embrace Pro	Glucose	–	–
Simple Diagnostics, USA	Clever Choice Voice HD	Glucose	20–600 mg/dl	–
	Clever Choice HD	Glucose	20–600 mg/dl	–
	Clever Choice Mini	Glucose	20–600 mg/dl	–
	Clever Choice Pro	Glucose	20–600 mg/dl	–
Medline, USA	EvenCore G3	Glucose	20–600 mg/dl	96 weeks
	EvenCore G2	Glucose	20–600 mg/dl	96 weeks
Bionime, Taiwan	GM 700	Glucose	100–600 mg/dl	–
	GM 720		100–600 mg/dl	–
	GM 700S		100–600 mg/dl	–
	GM 260		100–600 mg/dl	–

Challenges in (bio)sensing research

Except lateral flow pregnancy tests and electrochemical glucose biosensors, very few biosensors have achieved global commercial success at the retail level.

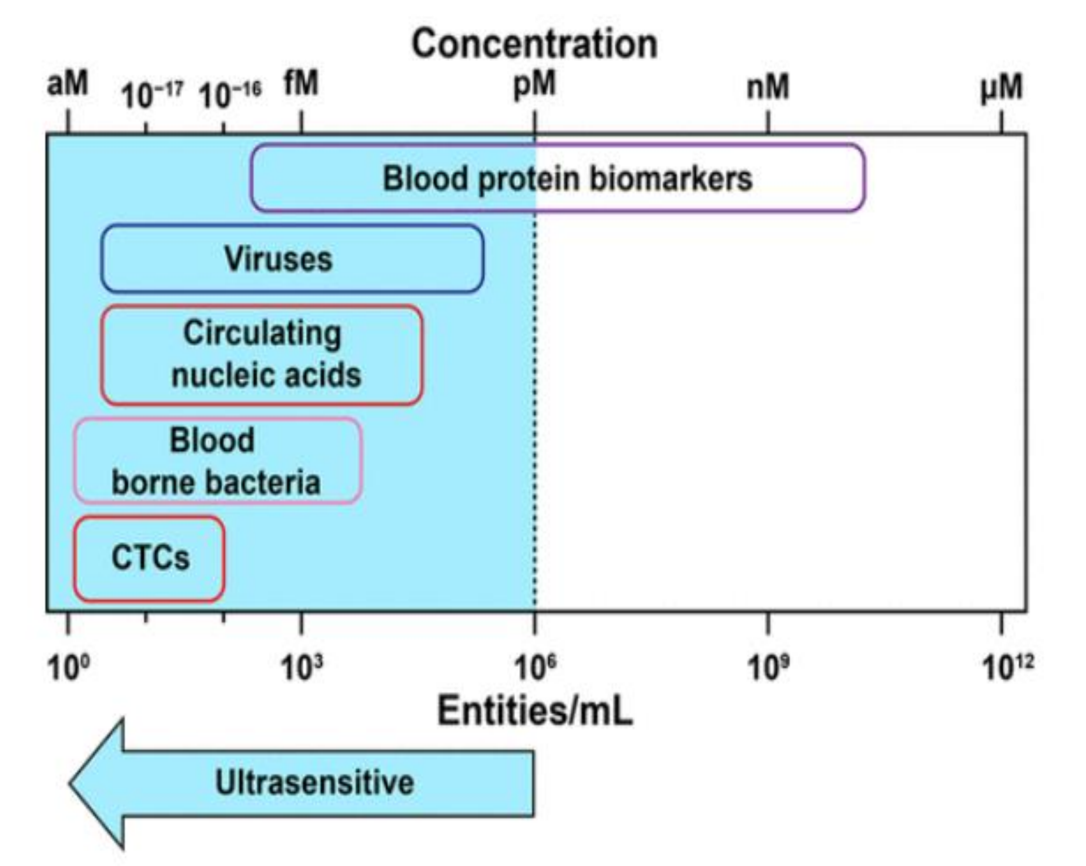
1. Difficulties in translating academic research into commercially viable prototypes by industry.

2. Complex regulatory issues in clinical applications

3. It is difficult to engage researchers from different disciplines of science and engineering to work together.

4. Stability, costs and ease of manufacturing each component of the biosensor.

5. Increase of selectivity and sensivity, decrease of detection limit and time of analyze.




Thanks for
attention