Optical Biosensors: State of the Art and Emerging Bioanalytical Tools

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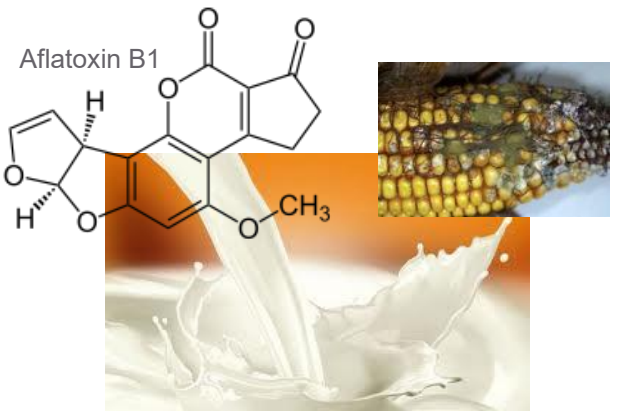
Content

- Analysis of biomarkers, harmful compounds.
- Motivation and evolvement of implementations, from laboratory desktop devices to implanted sensors.
- Definition and types of biosensors
- Sensor schemes in close contact with human body.

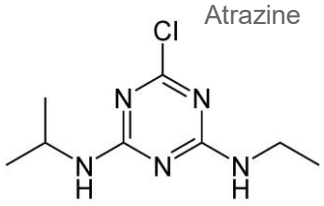
Application Areas

Food control (toxins, bacterial pathogens…)



Medical Diagnostics (biomarkers for cancer, cardiac, inflammation…)

Environmental Monitoring (pollutants in water and soil…)



Homeland Security, **Forensics**….

Established Bioanalytical Technologies

Common Practice

Common practice: Analysis of collected samples (e.g. blood, urine) in central laboratories which is time consuming, require trained personnel and is costly (ELISA, mass spectrometry, HPLC…), centralized laboratories.

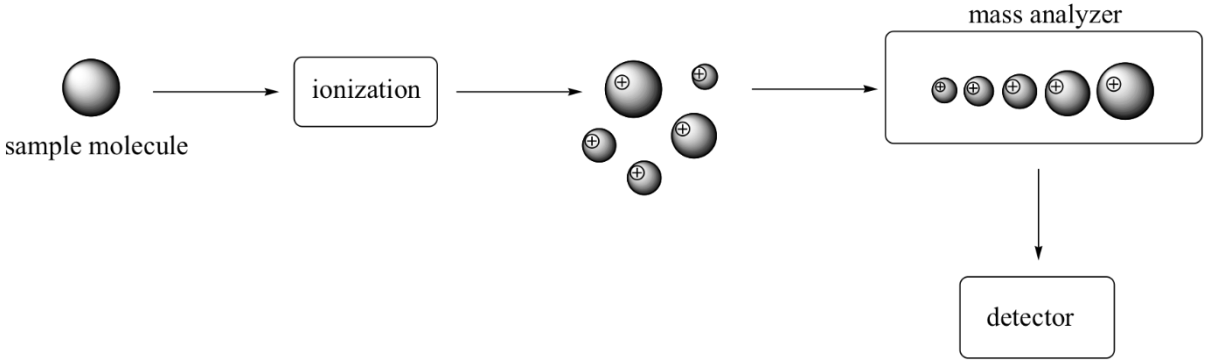
Tecan, Infinite® F50

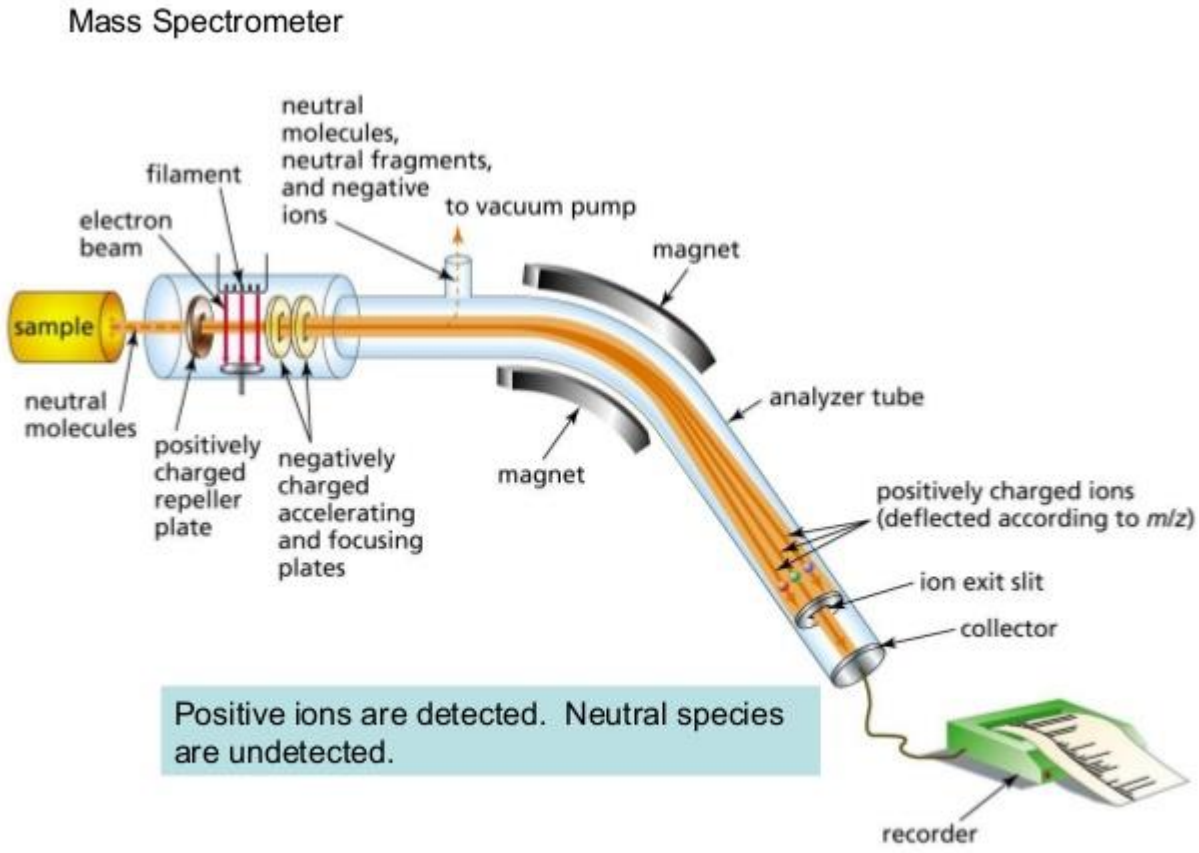
Strip tests

Quantitative, accurate, laborious

Simpler, qualitative

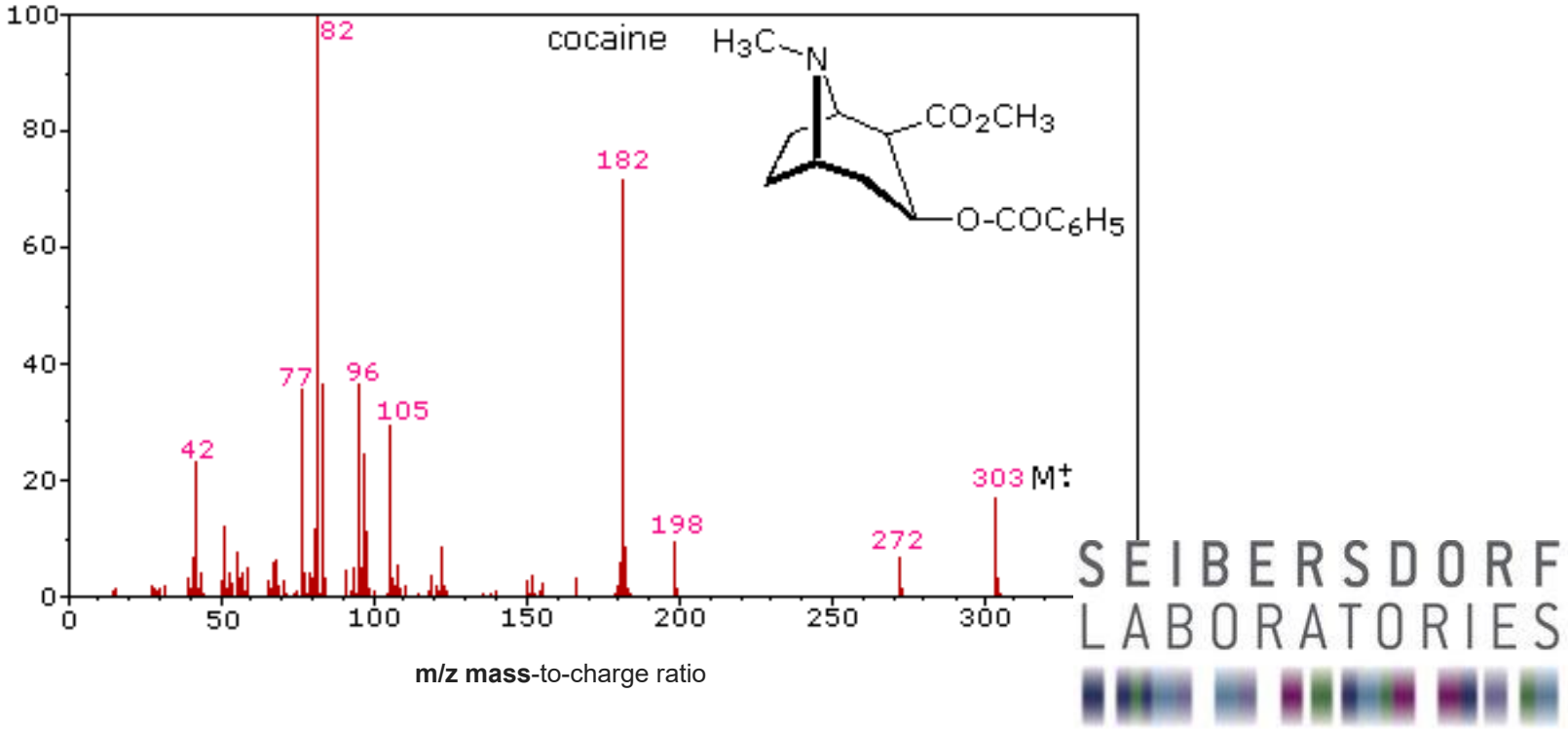
Mass Spectrometry





https://chem.libretexts.org/Courses/SUNY_Oneonta/Chem_221%3A_Organic_Chemistry_I_(Bennett)/1%3ALecture_Textbook/04%3A_Structure_Determination_I-_UV-Vis_and_Infrared_Spectroscopy_Mass_Spectrometry/4.03%3A_Mass_Spectrometry

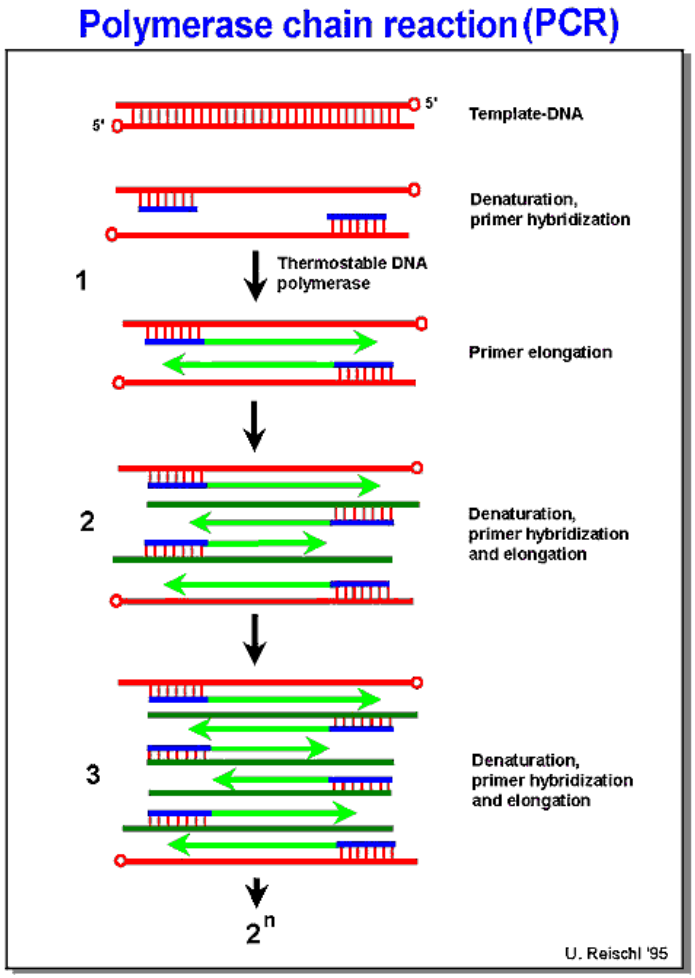
Mass Spectrometry



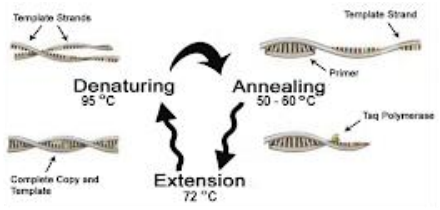
World-Anti-Doping-Agency (WADA).

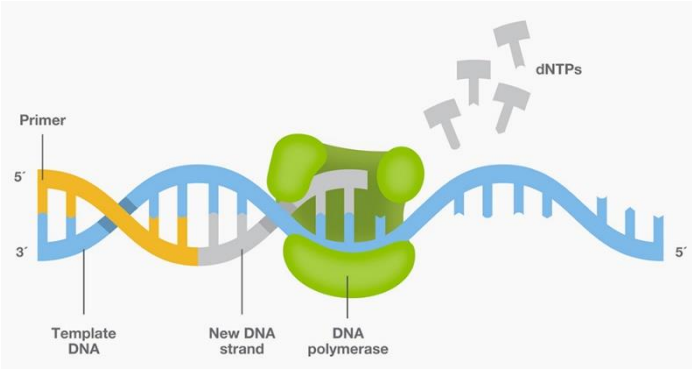
Used also in e.g. doping control and analysis of banned narcotics and stimulants. Legally assumed as a direct method that can be used at court.

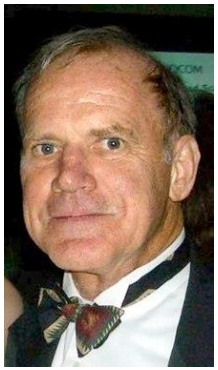
Polymerase Chain Reaction - PCR



Thermocycling

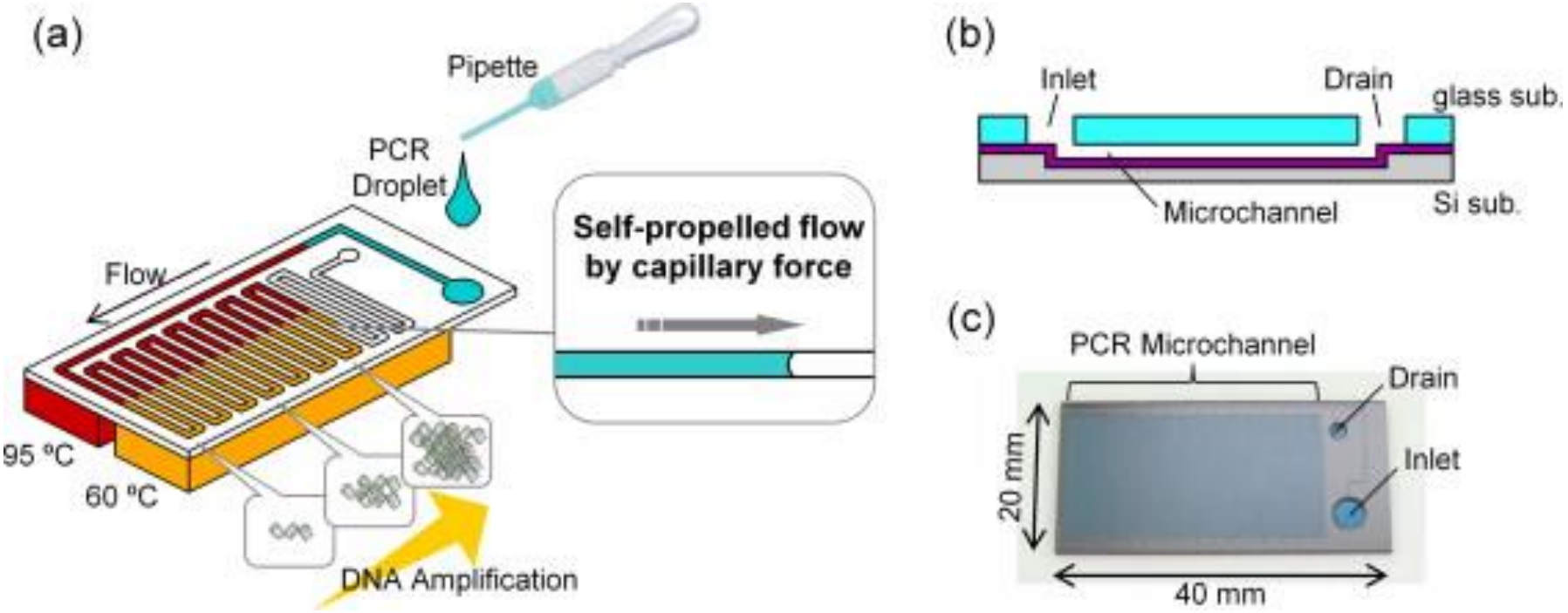






Karry Mullis was awarded the Nobel Prize in Chemistry in 1993 for inventing PCR

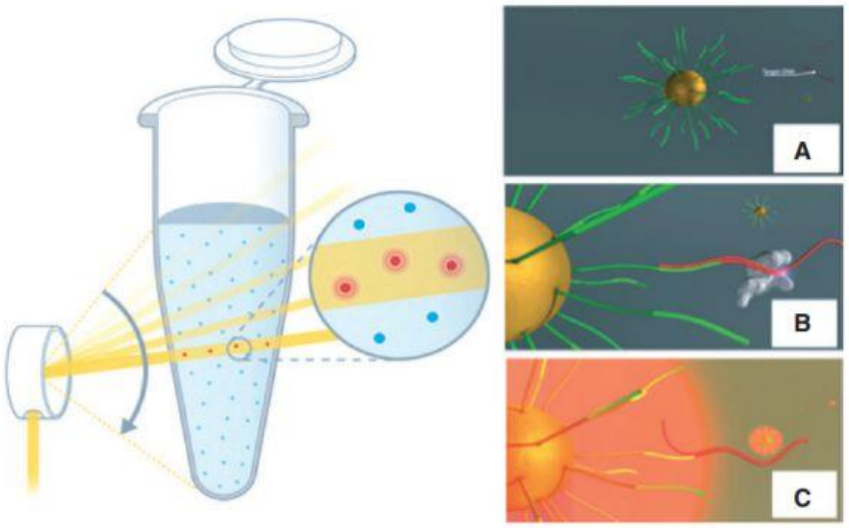
Polymerase Chain Reaction

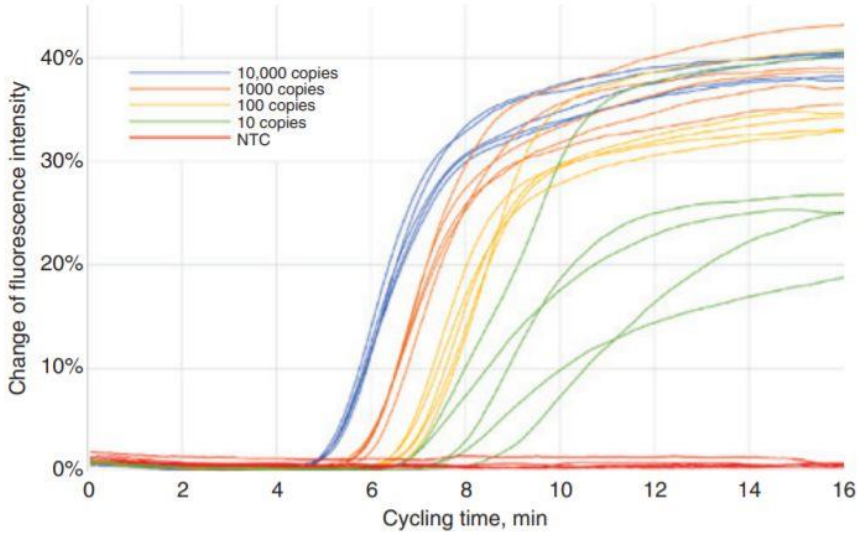


https://doi.org/10.1016/j.snb.2014.09.004

Thermocycling is typically rather slow limiting the speed of PCR.
Possible solution provides microfluidics dealing with small volumes.

Laser Polymerase Chain Reaction



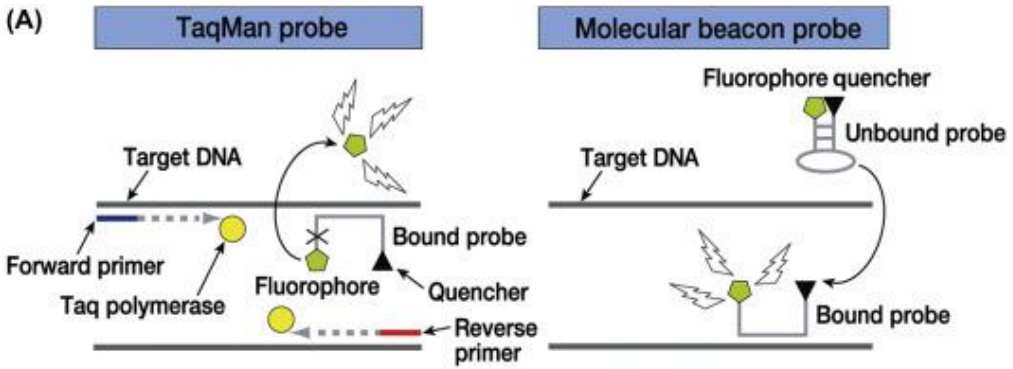


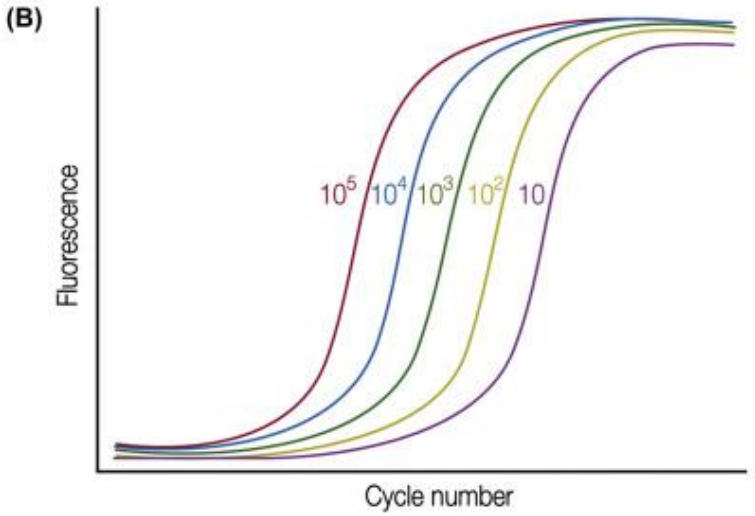
https://doi.org/10.1515/labmed-2017-0093

https://www.gna-bio.com/solutions/

Plasmonic nanoparticles may serve as miniature heat sources to rapidly modulate temperature in extremely low sample volumes.

Real Time - Polymerase Chain Reaction

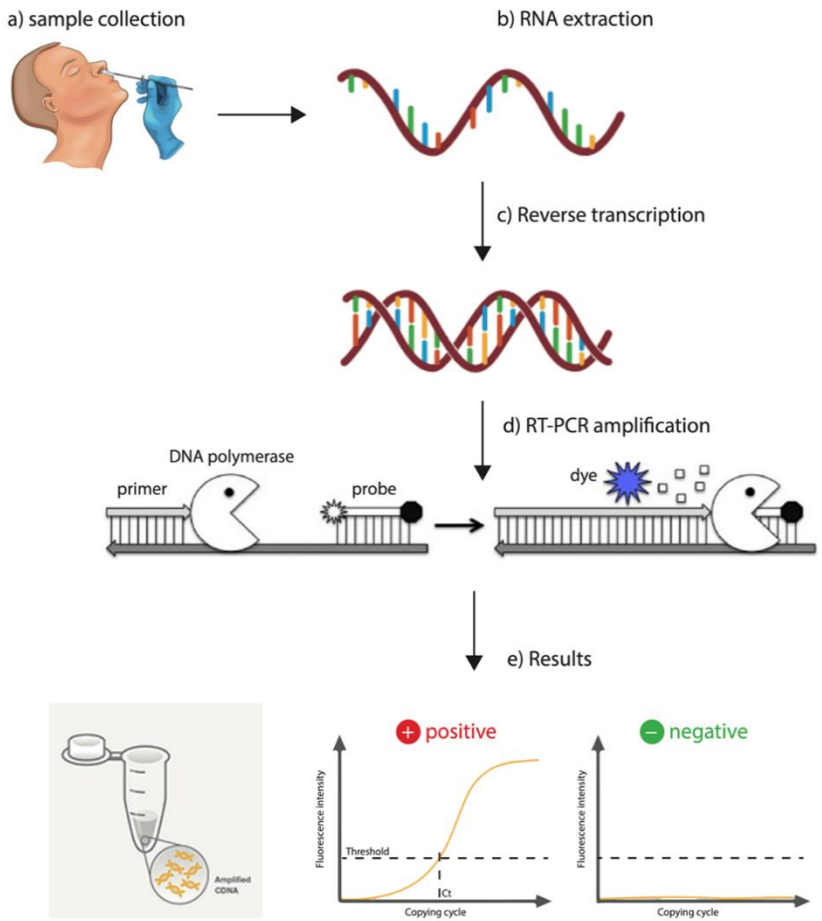




https://doi.org/10.1016/B978-0-12-800838-6.00004-7

- Fluorescence is typically employed for the readout of the presence of the amplified oligonucleotide chains.
- In RT-PCT the FRET or quenching of fluorophores allows for reporting on the presence of selected amplified strands.
- Many other versions – digital PCR, RCA, LAMP…

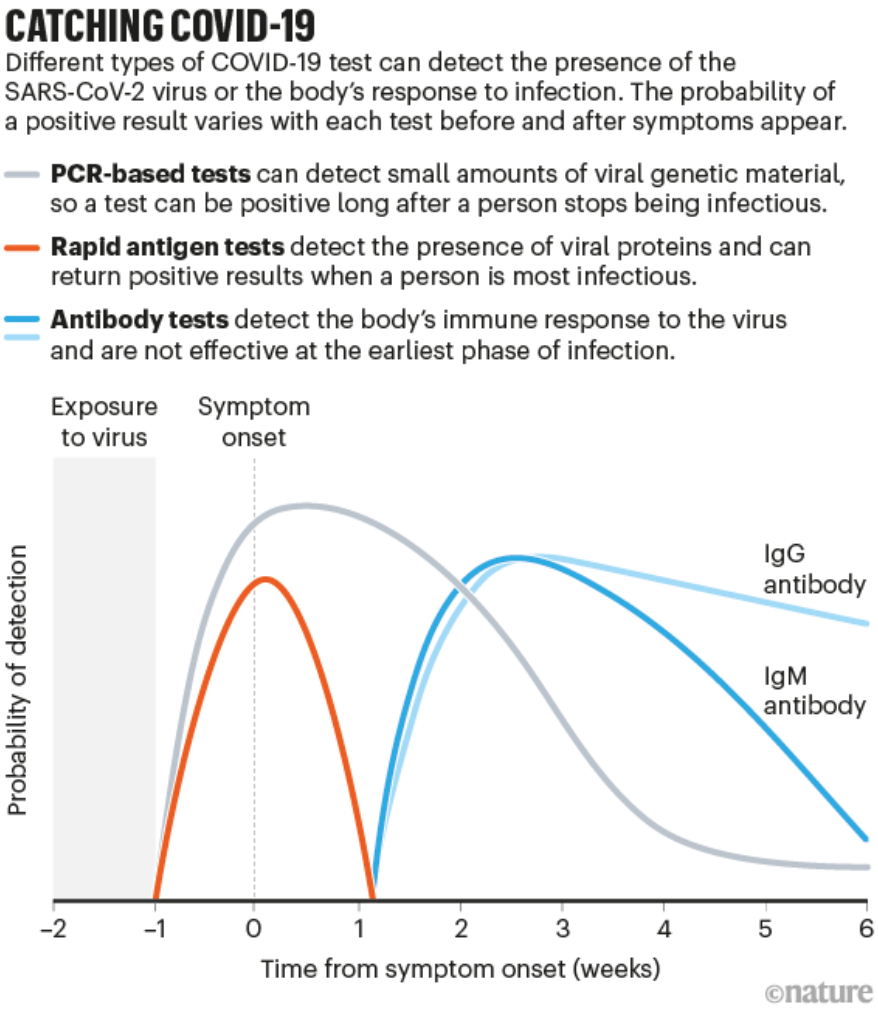
PCR – Covid 19



https://www.globalbiotechinsights.com/articles/20247/the-worldwide-test-for-covid-19

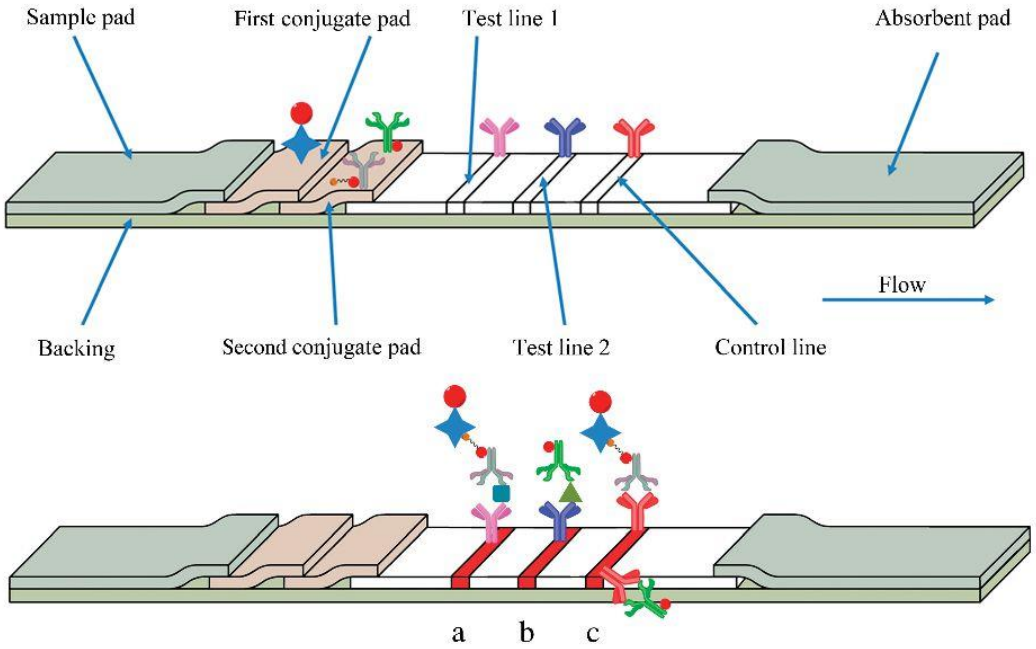
- Reverse Transcription Polymerase Chain Reaction (RT-PCR)
- Whole process takes hours
- Not quatitative, gives either positive or negative result.
- In principle PCR is sensitive technique that can detect several copies of target species in a sample

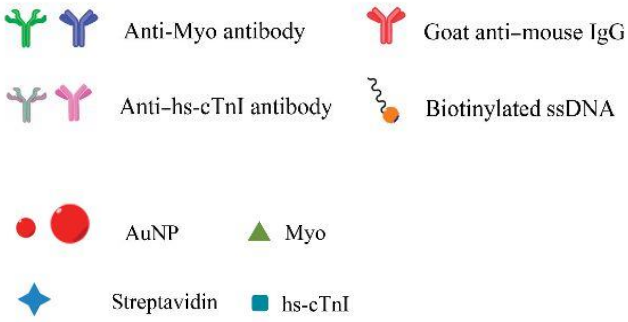
Tracking Covid Infections



https://www.nature.com/articles/d41586-020-02661-2

Strip Immunoassays – Concept of Lateral Flow Assay

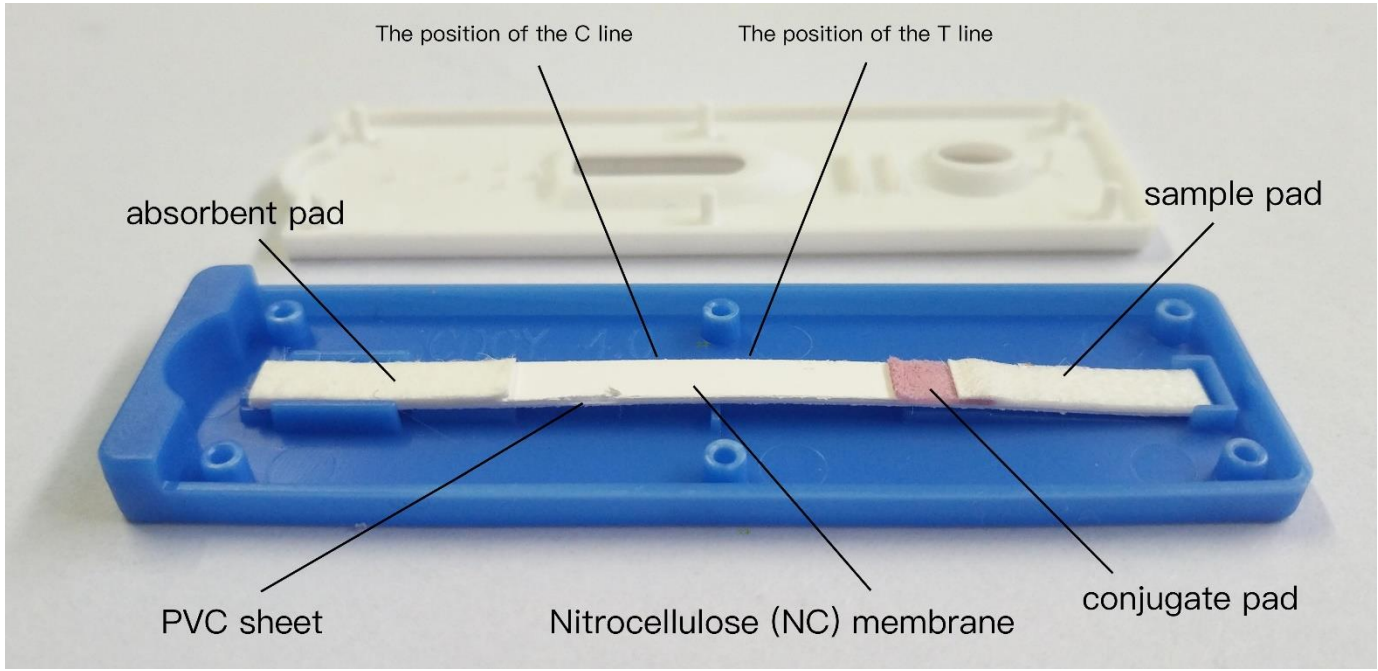




10.1373/clinchem.2011.171694

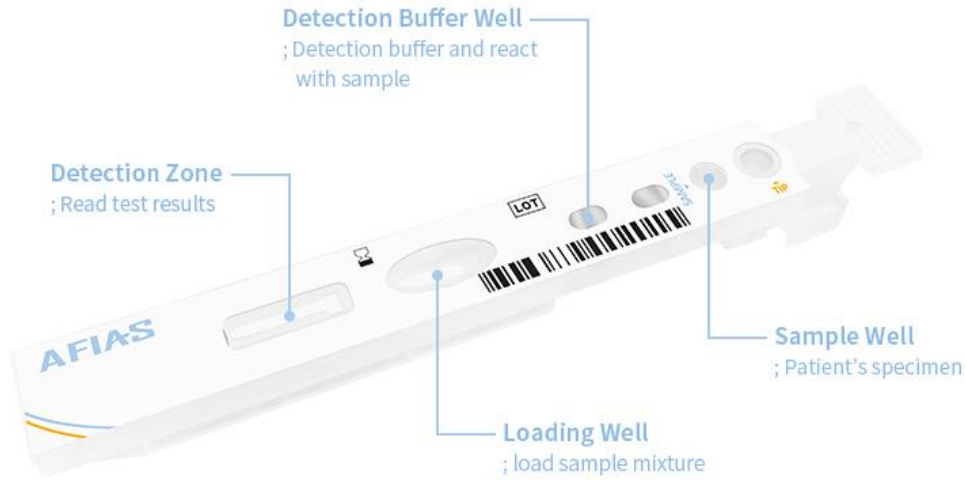
In order to visualize the specific and conteol stripes, originally enzymatic reactions were used. Nowadays increasingly using plasmonic nanoparticle labels offering bright colors.

Lateral Flow Assay - Implementation



https://doi.org/10.3389/fmicb.2018.00953

Rapid Protein Tests



http://www.boditech.co.kr/

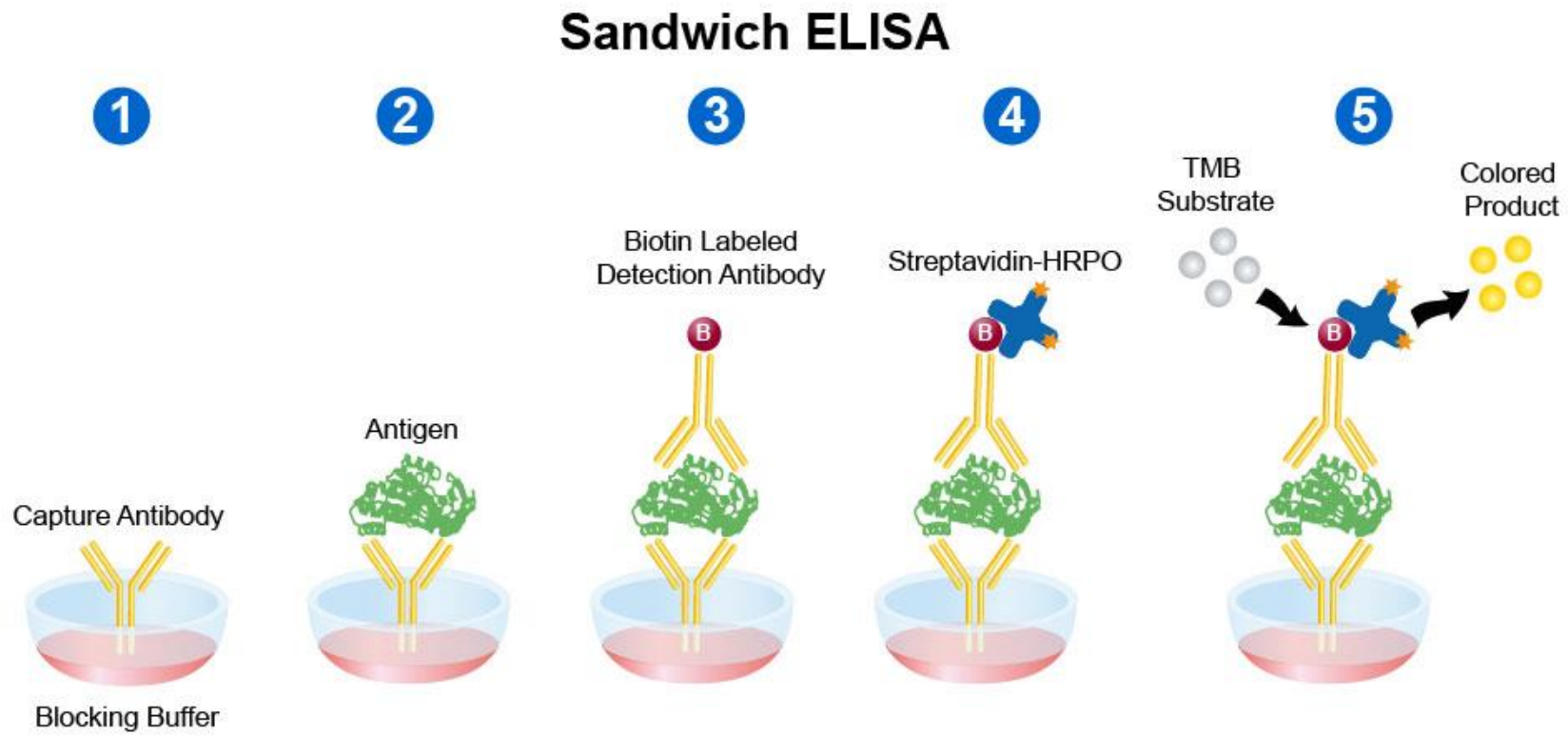
Recently, more advanced cartridges are derived from the strips, allowing for quantiative (concentration) and rapid (15 min) detection in rather automatized manner.

Rapid Protein Covid Tests

Category	Item	Platform					
		ichroma™	iCHROMA II	AFIAS-1	AFIAS-6	iCHROMA-50	iCHROMA M2
Cardiac	Tn-I	●	●				
	Tn-I Plus		●	●	●		
	CK-MB	●	●	●	●		
	D-Dimer	●	●	●	●		
	NT-proBNP		●	●	●		
	Myoglobin	●	●	●	●		
	hsCRP	●	●				
	ST2		*	*	*		
Cancer	PSA	●	●	●	●		
	AFP	●	●	●	●		
	CEA	●	●	●	●		
	iFOB Neo	●	●			●	
Diabetes	HbA1c	●	●	●	●		
	Microalbumin	●	●	●	●		
	Cystatin C	●	●				
Hormone	TSH	●	●	●	●		
	TSH Plus		●	●	●		
	T3	●	●	●	●		
	T4	●	●	●	●		
	FSH	●	●	●	●		
	FSH Plus			*	*		
	Progesterone	●	●				
	β-hCG	●	●	●	●		
	β-hCG Plus		●	●	●		
	LH	●	●	●	●		
	PRL	●	●	●	●		
	Testosterone	●	●	●	●		
	Cortisol	●	●	●	●		
	AMH			●	●		

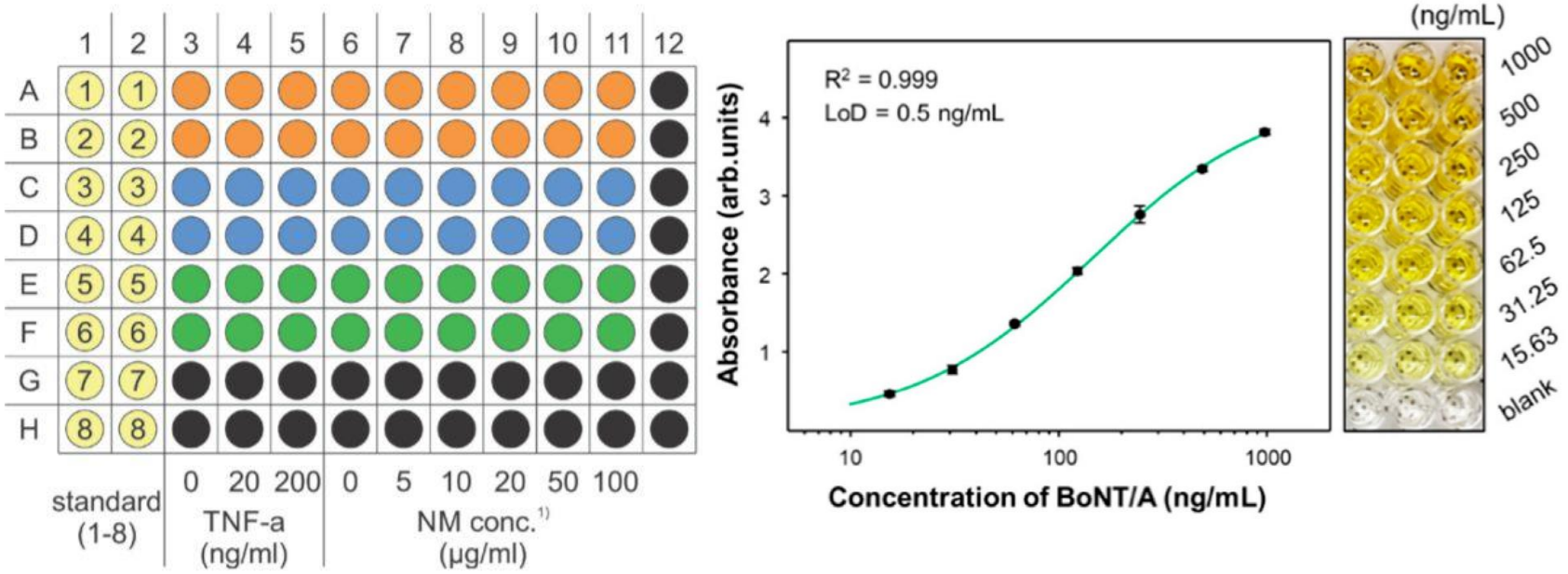
Detection with strip-like catridges is not done only colorimetrically, but also via fluorescence gaining sensitivity and making possible analysis of e.g. cardiac markers present at pM concentrations.

Enzyme-Linked Immunosorbent Assays



https://www.leinco.com/sandwich-elisa-protocol/

Enzyme-linker Immunosorbent Assays



https://www.nanopartikel.info/files/methodik/VIGO/I_ELISA_A549.pdf

https://doi.org/10.3390/s19194081

ELISA replaced radio-immunoassays in 1970ties, still routinely used and other enzymatic reactions exploited for faster and more sensitive readout.

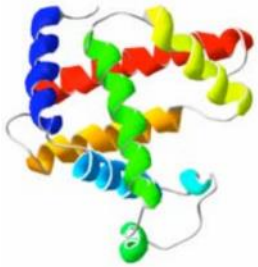
Biosensors

Biosensor

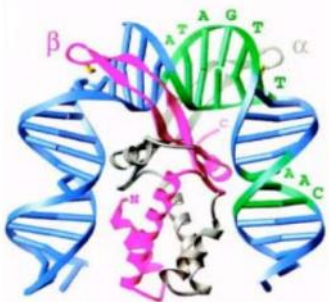
… is self-contained integrated device that is capable of providing specific quantitative or semi-quantitative analytical information using a biological recognition element which is in direct spatial contact with a transduction element (IUPAC 1996).

DNA/DNA

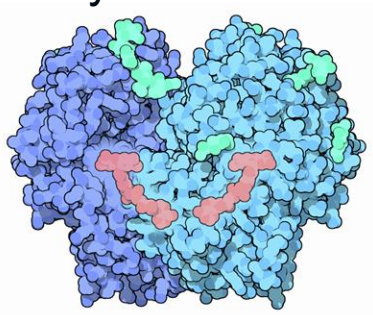
Protein/Protein

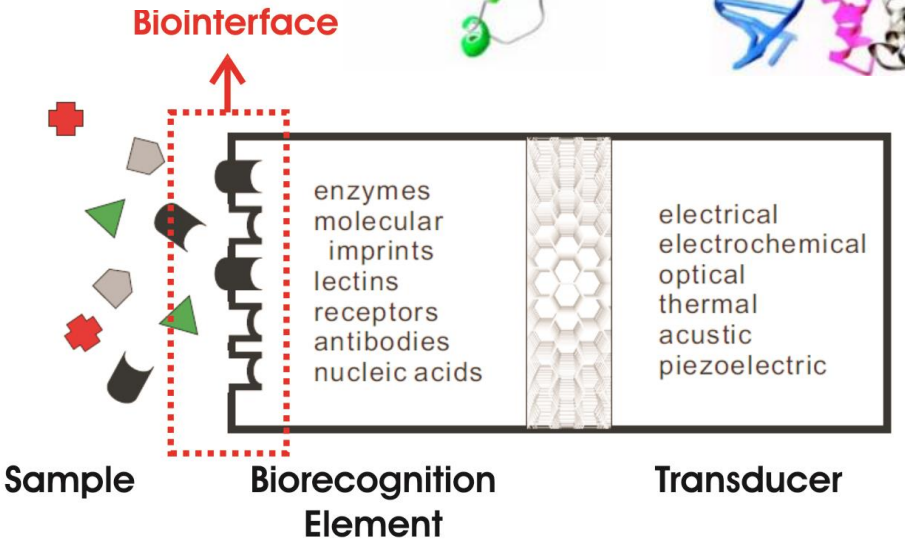


Protein/DNA



Enzyme





Physico-Chemical Transducers

Transducer converts molecular binding events to measurable (physical) signal. Those can be based on various physical quantities:

Mass (quartz crystal microbalance…)

Conductivity (amperometry, voltametry…)

Heat release or absorption (calorimetry)

Refractive index (surface plasmon resonance)

Absorption (colorimetric detection)

Non-linear optical interaction with matter (fluorescence, SERS)

…

Envisioned quite some time ago…

Vision of a device that can “analyze everything at once…”.

Tricorder were used for sensor scanning, data analysis, and recording data

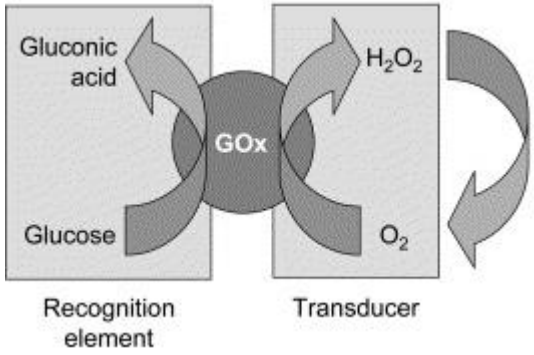
http://www.rounds.com/blog/star-trek-predicted/

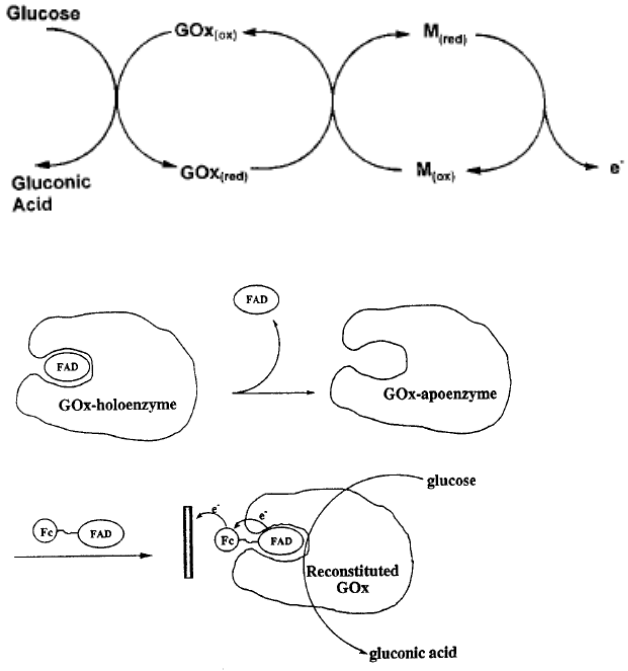
Historical Examples

1962	Invention of a biosensor: an amperometric enzyme electrode for glucose (Clark).
1975	Commercial glucose biosensor (Yellow Springs Instruments)
1980	First fiber optic pH sensor for in vivo blood gases (Peterson)
1983	First surface plasmon resonance (SPR) immunosensor (Liedberg, Nylander, and Lundstrom)
1990	Commercial SPR based biosensor by Pharmacia BIACore
….	

Electro-Chemical Biosensor

Amperometric detection of glucose by using glucose oxidase (GOx) is prominent example of electrochemical biosensor.





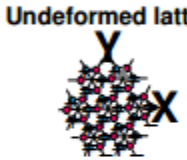
Original Clark concept – detection of depletion of O_2

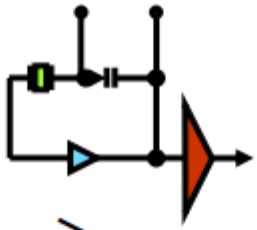
Challenges to compensate to other effects (e.g. O_2 fluctuations). Amperometric detection of $H_2O_2 \rightarrow O_2 + 2H^+ + 2e^-$ and its replacement by mediators to eliminate effect of other electroactive species.

Wang, Glucose Biosensors: 40 years of advances and challenges, Electroanalysis (2001), 13, No.12

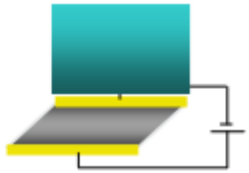
Quartz Crystal Microbalance

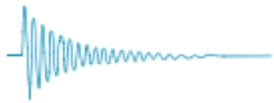
QCM – technique based on piezoelectric effect, coupled mechanical stress with charge





$$\Delta m = -C\frac{1}{n}\Delta f$$





Curie brothers discover piezoelectricity

First quartz crystal controlled oscillator

Sauerbrey relates frequency and mass

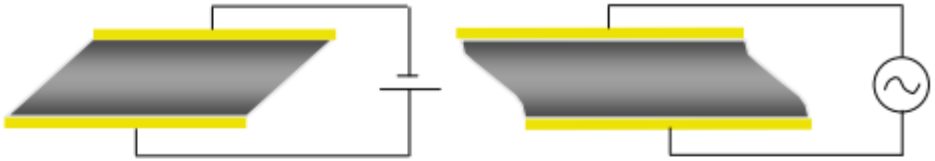
First QCM operating in liquid

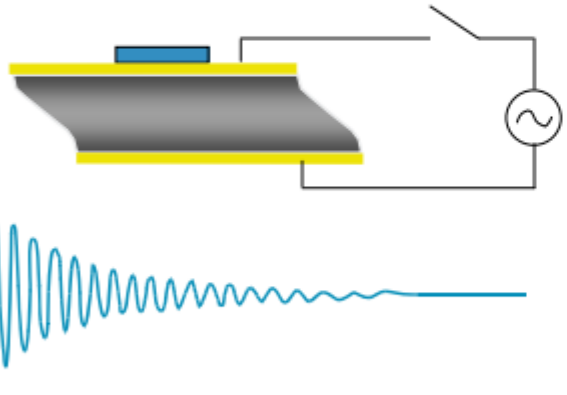
QCM-D Patent filed

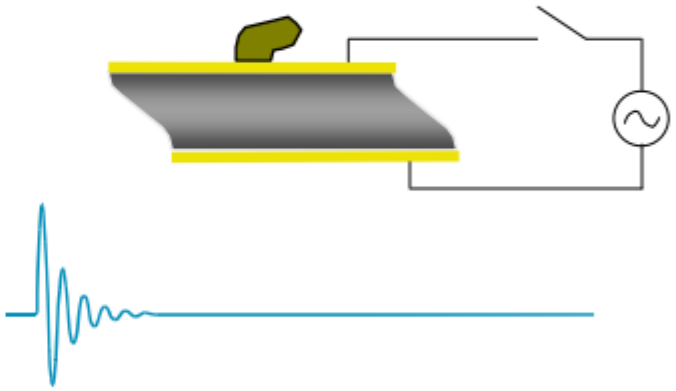
1880 1921 1959 1980 1996

Taken from Q-Sense

Quartz Crystal Microbalance





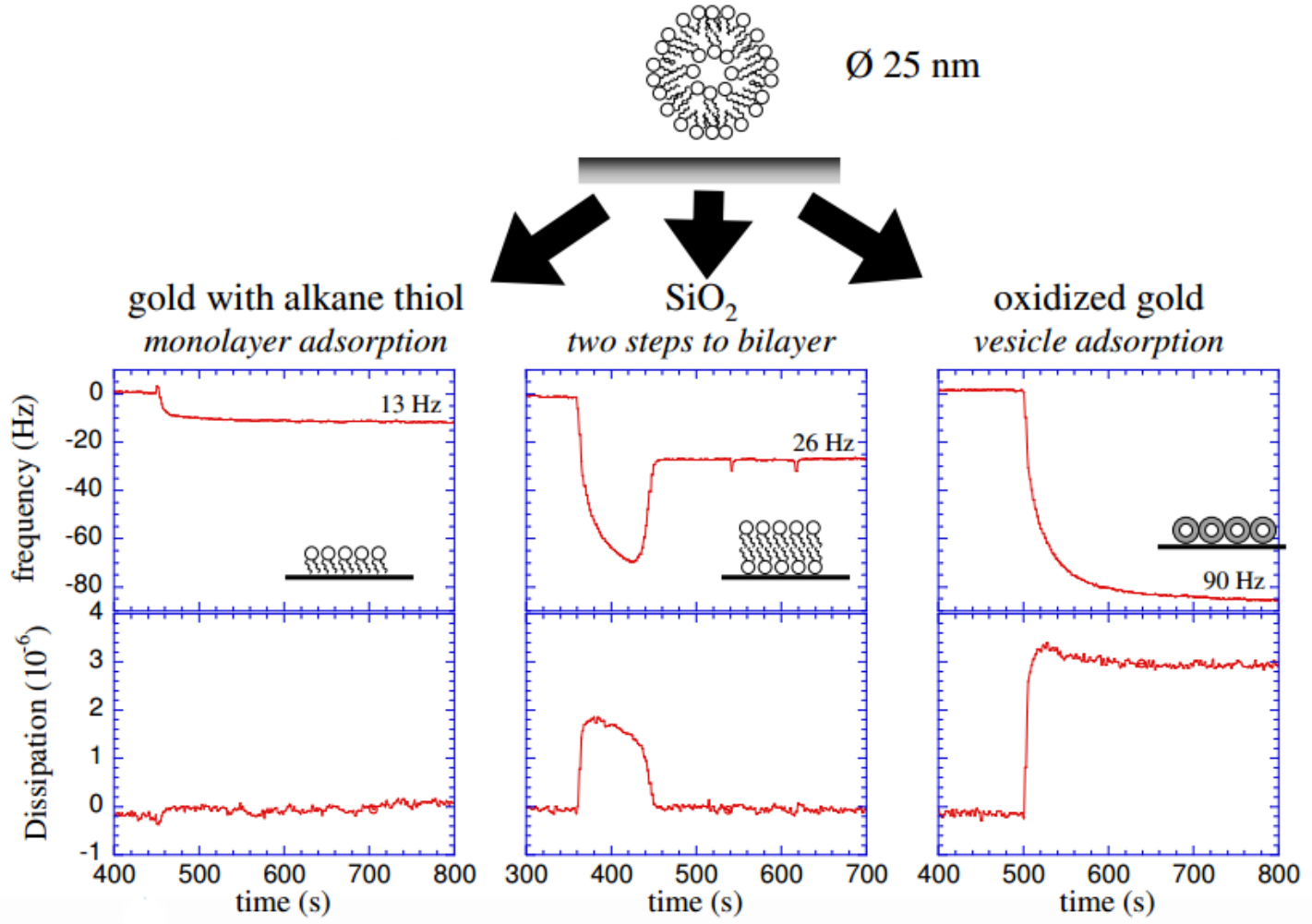


Δf **is related to the mass of the attached film (Sauerbrey relation)**

ΔD **is related to the viscoelasticity**

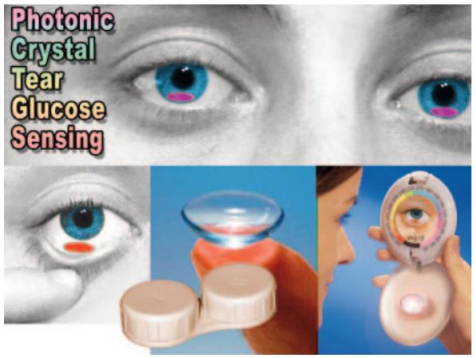
Taken from Q-Sense

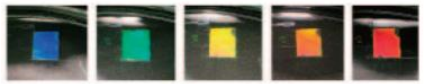
Quartz Crystal Microbalance

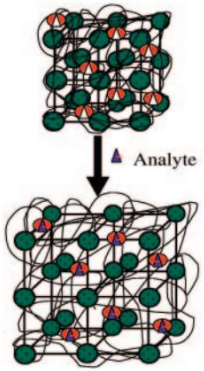


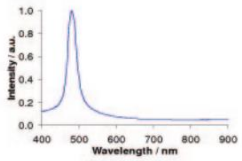
C.A. Keller and B. Kasemo, Biophysical J. 75 (1998) 1397.

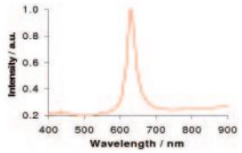
Contact Lens - Tear Fluid Analysis



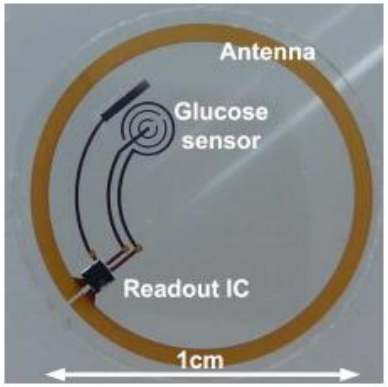


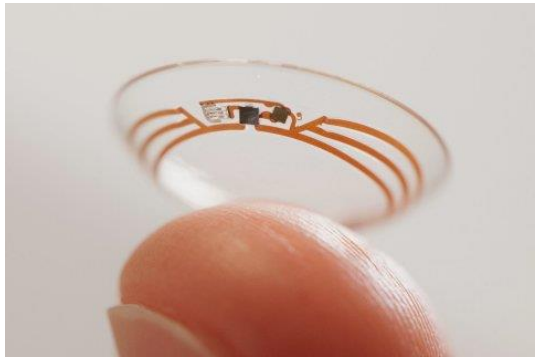






Photonic Crystal Glucose-Sensing Material for Noninvasive Monitoring of Glucose in Tear Fluid," V. Alexeev, S. Das, D.N. Finegold and S.A. Asher, Clinical Chemistry, 50, 2353 - 2360 (2004)

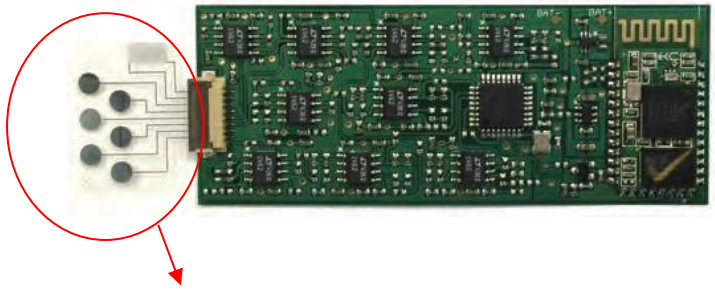




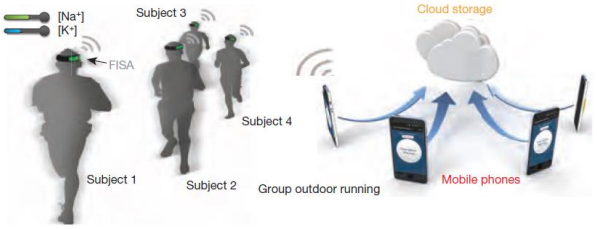
Liao Y-T, Yao H, Lingley A, Parviz B, Otis BP. A 3-uW CMOS glucose sensor for wireless contact-lens tear glucose monitoring. IEEE JSSC 2012;47:335Y44

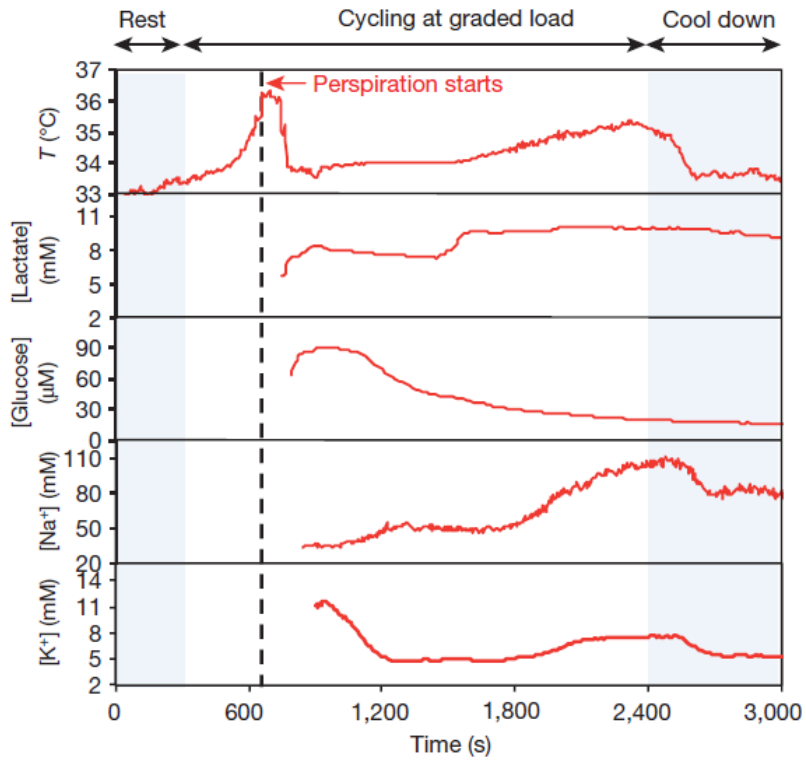
http://noviosense.com/

Wearable Sensors – Sweat Analysis



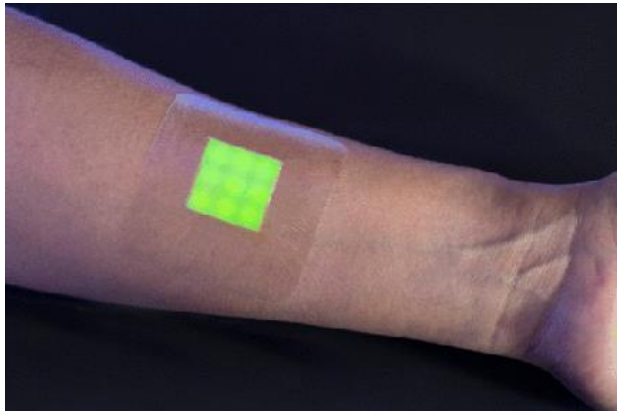
Electrochemical analysis of sweat at molecular level by arrays of sensors in close contact with skin.



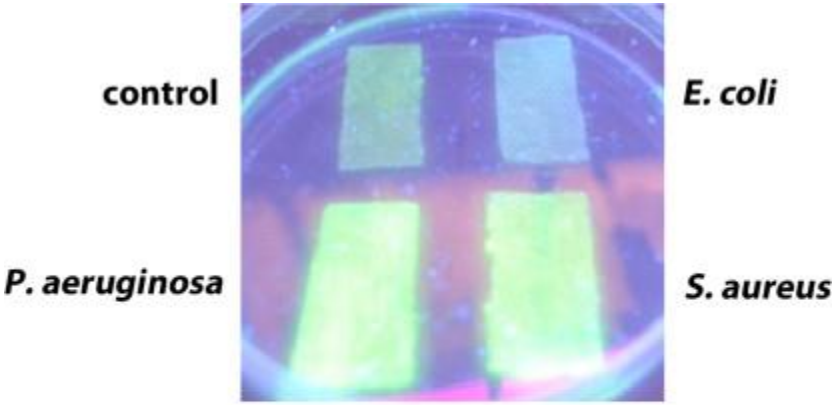


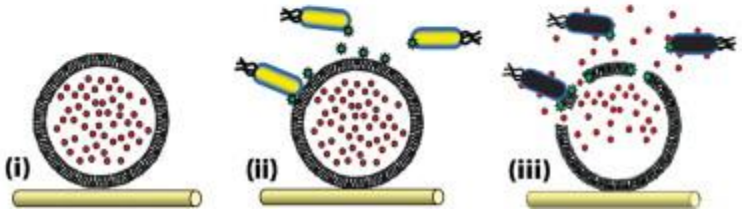
Nature 529(7587):509-514 · January 2016
DOI: 10.1038/nature16521

Smart Wound Dressing



Biosensors embedded in wound dressings to monitor bacterial infections. Possible incorporation of triggered release of a drug.





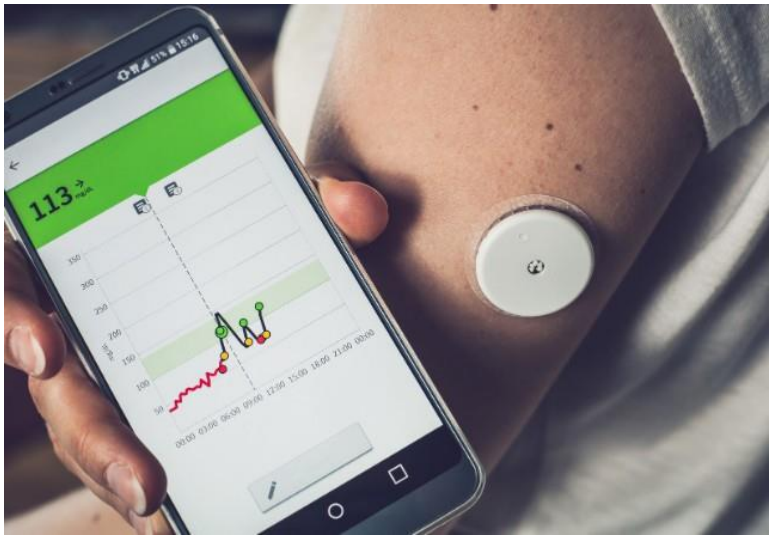
Dye self quenched

Dye bright

Fluorescent dye loaded to lipid vesicle, toxic bacteria destroy the lipid bilayer wall and leaches the dye reporter.

Toby Jenkins laboratory - 10.1021/acsami.5b07372

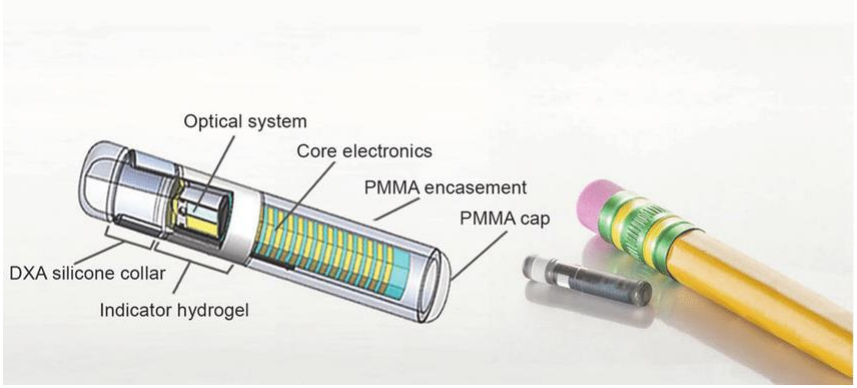
Implanted Glucose Sensing

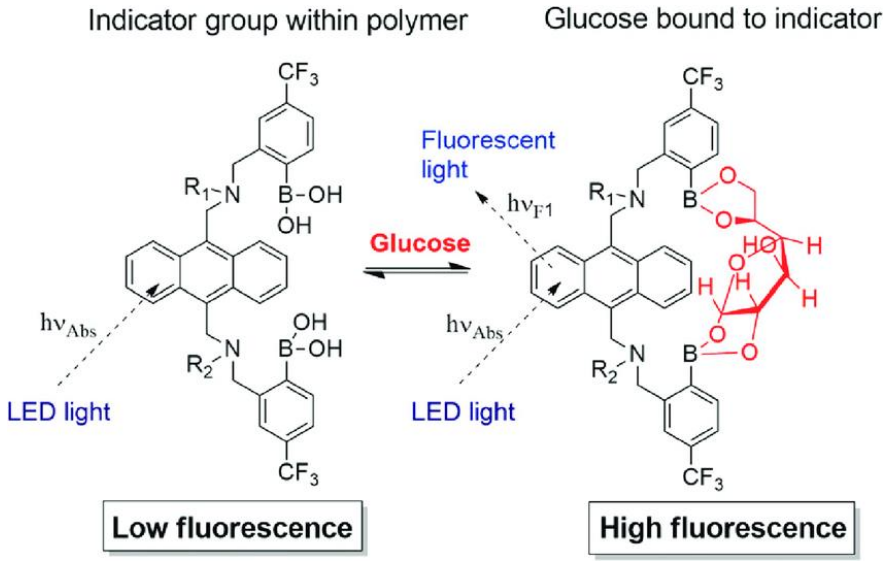


Eversense provides continuous blood glucose monitoring for up to 90 days via an under-the-skin sensor, a removable and rechargeable smart transmitter, and a convenient app for real-time diabetes monitoring and management.

https://www.eversensediabetes.com/sensor

Implanted Glucose Sensing

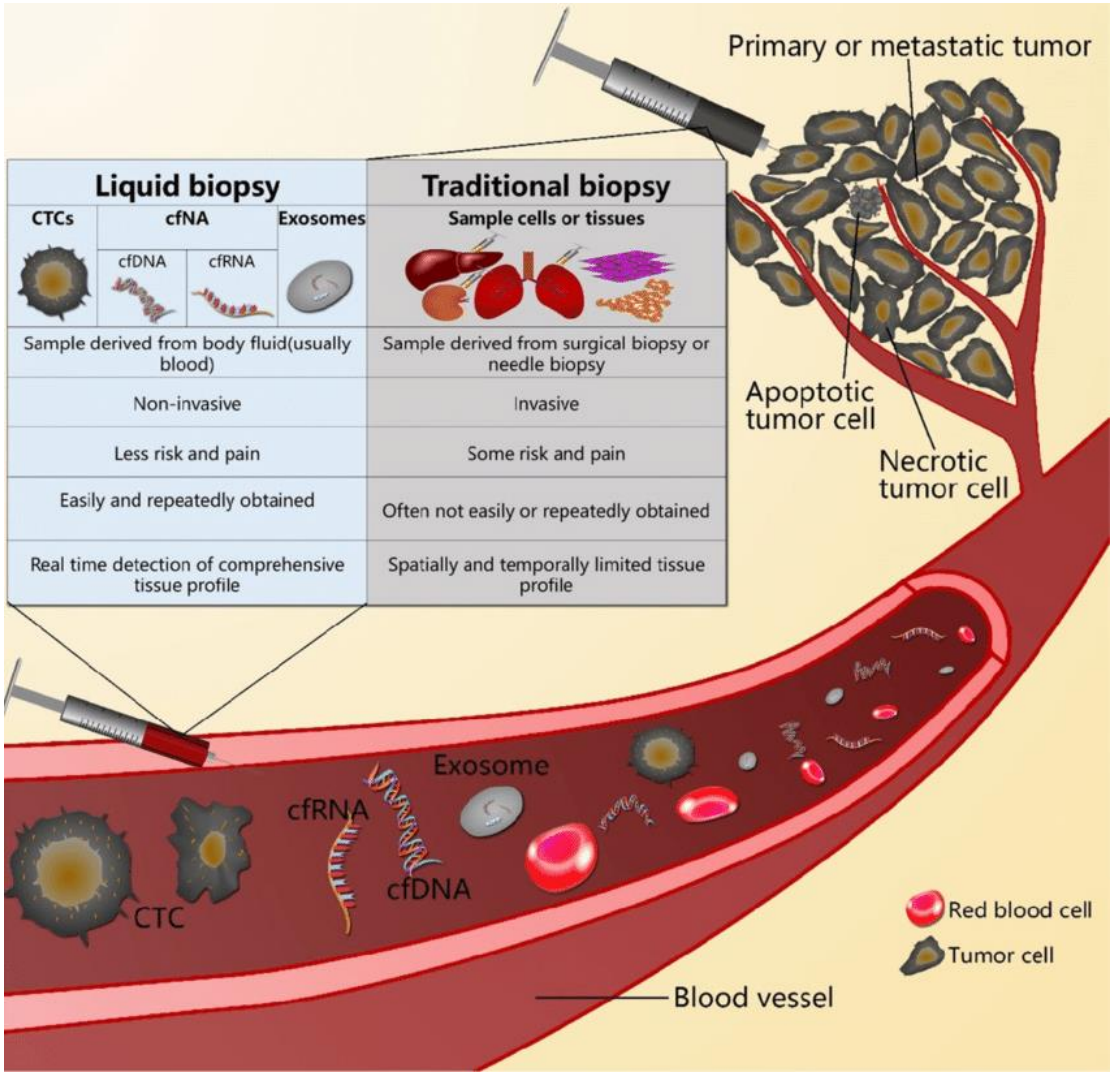




It uses a patented **fluorescent** glucose-indicating polymer technology to measure glucose in the **interstitial fluid** (a thin layer of fluid that surrounds the body's .

https://www.eversensediabetes.com/sensor

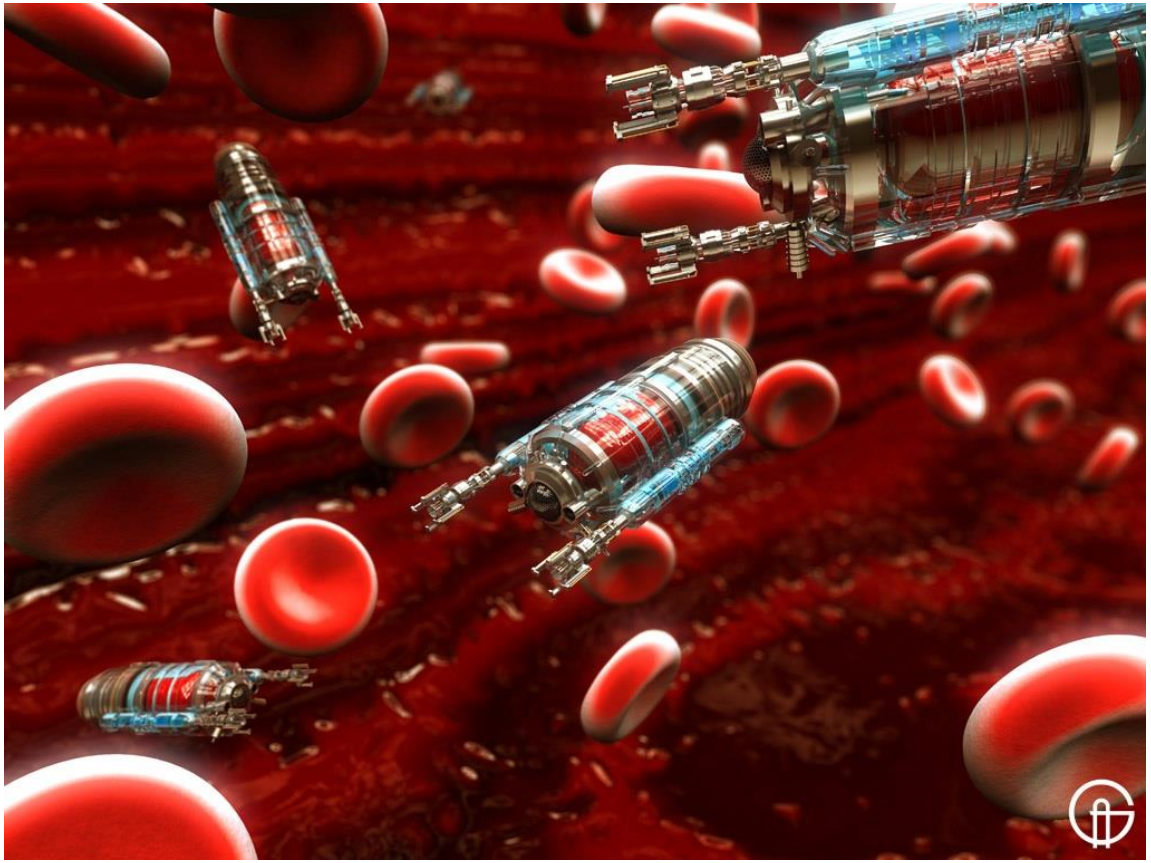
Liquid Biopsy



Liquid biopsy			Traditional biopsy
CTCs	cfNA (cfDNA, cfRNA)	Exosomes	Sample cells or tissues
Sample derived from body fluid(usually blood)			Sample derived from surgical biopsy or needle biopsy
Non-invasive			Invasive
Less risk and pain			Some risk and pain
Easily and repeatedly obtained			Often not easily or repeatedly obtained
Real time detection of comprehensive tissue profile			Spatially and temporally limited tissue profile

•10.7150/jca.24591

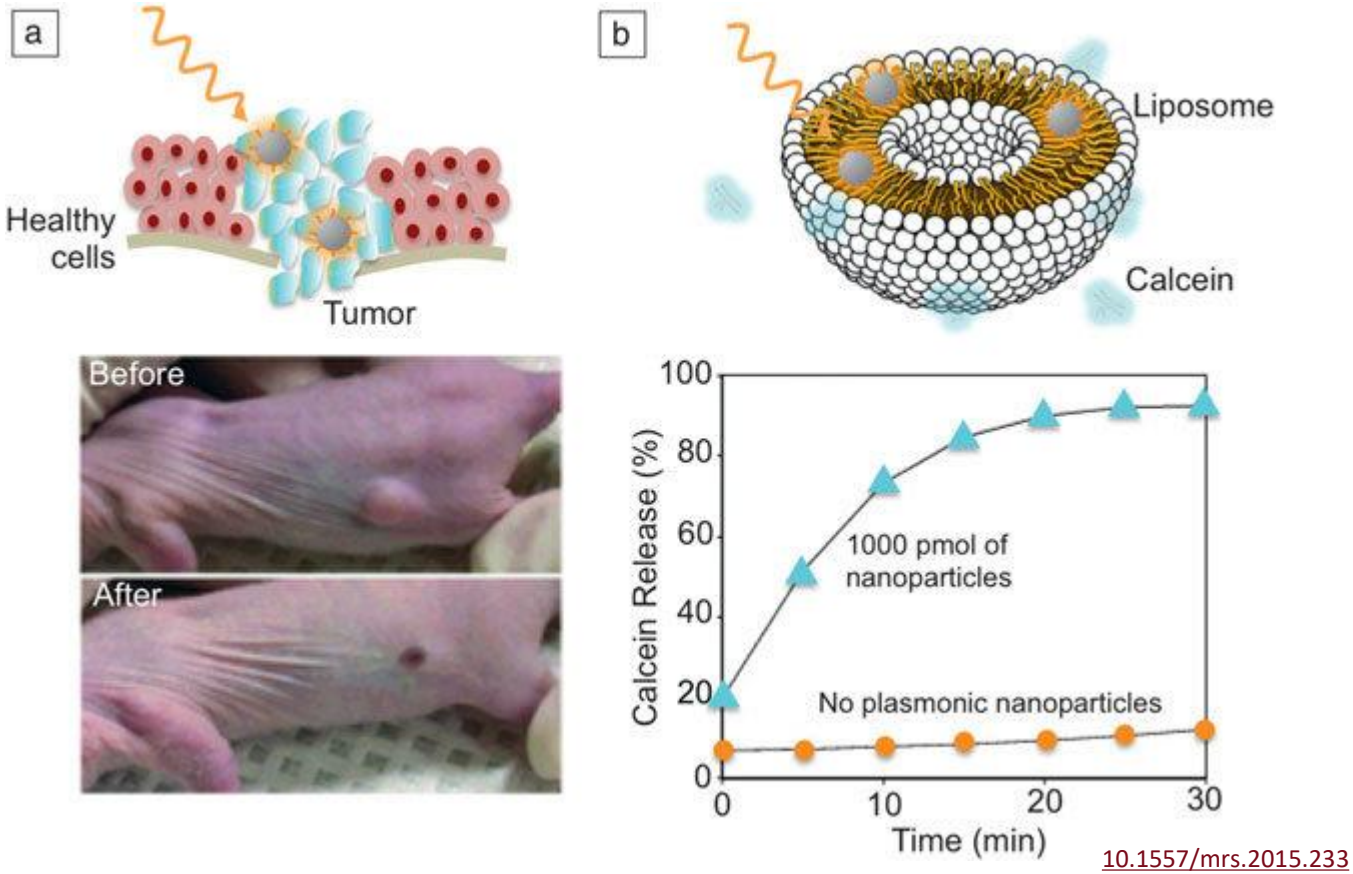
Swallowed Surgeon



1966 movie, *Fantastic Voyage* explored shrinking a medical team to microscopic size in order to save a renowned scientist's life. The Argonauts travel through the bloodstream into the brain where the crew uses a laser gun to blast away a blood clot.

http://internetmedicine.com/2016/11/06/52871/

Thera(g)nostic



10.1557/mrs.2015.233

Thera(g)nostics is a patient management strategy in precision medicine. Aims ay molecular targeting and kills cancer cells whilst sparing healthy tissue.