WEARABLE PHYSIOLOGICAL SENSORS AND BIOSENSORS

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Introduction

- Wearable sensors have diagnostic, as well as monitoring applications.
- Their current capabilities include physiological and biochemical sensing, as well as motion sensing.
- Physiological monitoring could help in both diagnosis and ongoing treatment of a vast number of individuals with neurological, cardiovascular and pulmonary diseases such as seizures, hypertension, dysrthymias, and asthma.
- Recent advances in sensor technology, microelectronics, telecommunication, and data analysis techniques have enabled the development and deployment of wearable systems for patients' remote monitoring.

Patel *et al.*, *Journal of NeuroEngineering and Rehabilitation,* 2012

Remote Monitoring Systems

Georga *et al.*, *IFMBE MobiHealth Inter. Conf.*, 2014

Remote Monitoring Systems

Sensors to monitor vital signs (e.g. respiratory rate) would be deployed when monitoring patients with congestive heart failure or patients with chronic obstructive pulmonary disease undergoing clinical intervention.

Sensors for movement data capturing would be deployed in applications such as monitoring the effectiveness of home-based rehabilitation interventions in stroke survivors or the use of mobility assistive devices in older adults.

Wireless communication is relied upon to transmit patient's data to an access point (e.g. smart phone) and relay the information to a remote center via the Internet.

Critical situations (e.g. falls) are detected via data processing implemented throughout the system and an alarm message is sent to the corresponding service.

Patel *et al.*, *Journal of NeuroEngineering and Rehabilitation*, 2012

Remote Monitoring Systems

Despite the potential advantages of a remote monitoring system relying on wearable sensors, there are significant challenges ahead before such a system can be utilized on a large scale.

- Technological barriers: e.g. limitations of currently available battery technology, too obtrusive hardware to be suitable for long-term health monitoring applications
- Cultural barriers: e.g. the association of a stigma with the use of medical devices for home-based clinical monitoring

Patel *et al.*, *Journal of NeuroEngineering and Rehabilitation,* 2012

WEARABLE PHYSIOLOGICAL SENSORS

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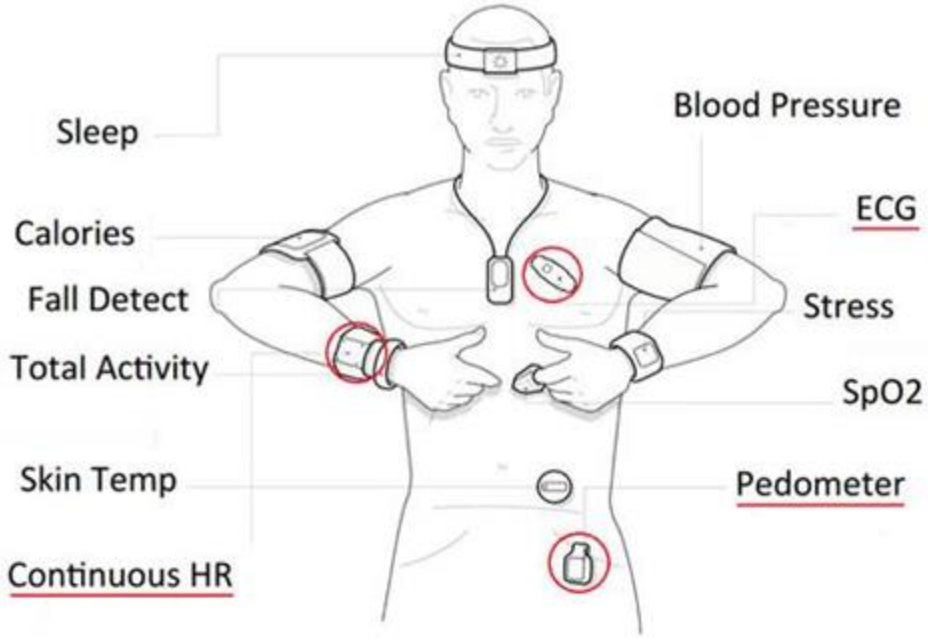
Wearable Physiological Sensors

- Health monitoring applications of wearable systems most often employ multiple sensors that are typically integrated into a **sensor network** either limited to **body worn sensors** or integrating body-worn sensors and ambient sensors.

Patel *et al.*, *Journal of NeuroEngineering and Rehabilitation,* 2012

Physiological Sensors

- Physiological sensors enable continuous monitoring of a variety of human vital signs and other physiological parameters:
  - heart rate
  - blood oxygen saturation (SpO_2)
  - respiration rate
  - blood pressure
  - body temperature
  - electrocardiogram (ECG)
  - body posture and activity



- Parameters extracted from such measures can provide indicators of health status and have tremendous diagnostic value.
- Integrating physiological monitoring in a wearable system often requires ingenious designs and novel sensor locations.

Pantelopoulos *et al.*, *IEEE Transactions on Systems, Man and Cybernetics*, 2010
http://www.eetimes.com/document.asp?doc_id=1320045

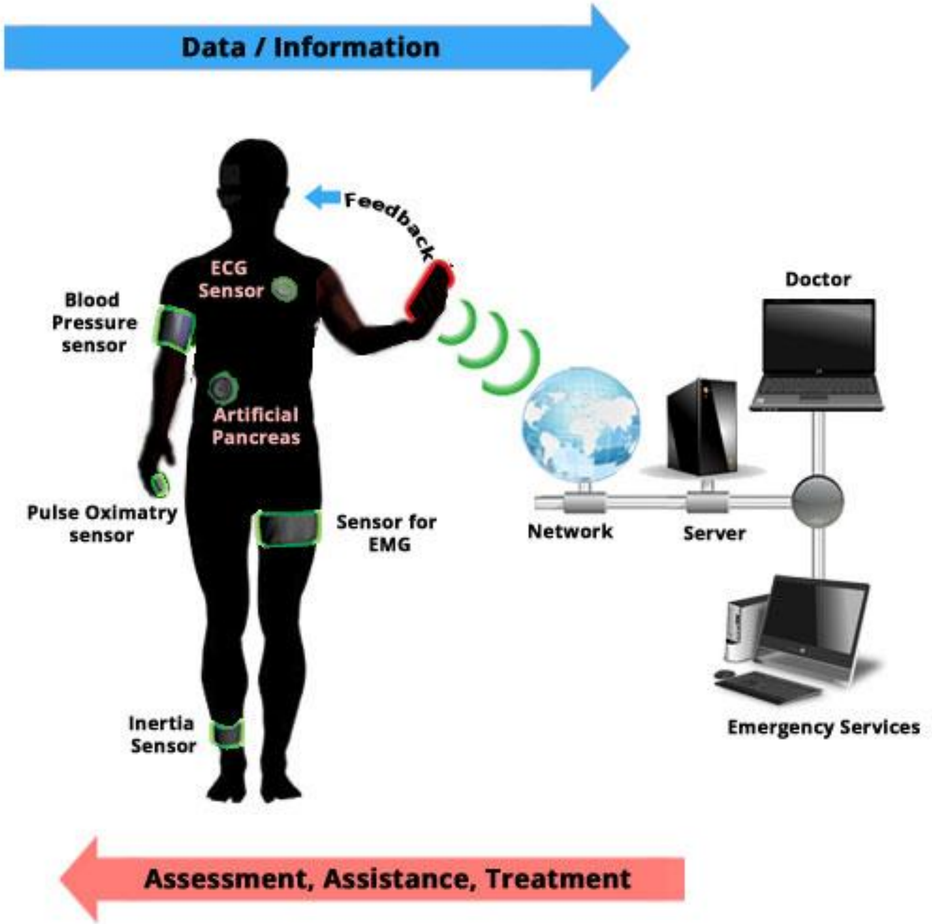
Physiological Sensors

Type of Biosignal	Type of Sensor	Description of Measured Data
Electroencephalogram (EEG)	Scalp-placed electrodes	Measurement of electrical spontaneous brain activity and other brain potentials
Electrocardiogram (ECG)	Skin/Chest electrodes	Electrical activity of the heart (continuous waveform showing the contraction and relaxation phases of the cardiac cycles)
Electromyogram (EMG)	Skin electrodes	Electrical activity of the skeletal muscles (characterizes the neuromuscular system)
Heart rate	Pulse oximeter / skin electrodes	Frequency of the cardiac cycle
Blood pressure	Arm cuff-based monitor	Refers to the force exerted by circulating blood on the walls of blood vessels, especially the arteries
Respiration rate	Piezoelectric/piezoresistive sensor	Number of movements indicative of inspiration and expiration per unit time (breathing rate)
Oxygen saturation	Pulse oximeter	Indicates the oxygenation of the amount of oxygen that is being carried in an individual’s blood
Perspiration or skin conductivity	Galvanic skin response	Electrical conductance of the skin is associated with the activity of the sweat glands
Body and/or skin temperature	Temperature probe or skin patch	A measure of the body’s ability to generate and get rid of heat
Body movements	Accelerometer	Measurement of acceleration forces in the 3D space

Pantelopoulos *et al.*, *IEEE Transactions on Systems, Man and Cybernetics*, 2010

Wearable Health Monitoring System

- A wearable health monitoring system may encompass a wide variety of components:
  - sensors
  - wireless communication modules
  - control and processing units
  - graphical user interface
  - advanced algorithms
- The obtained measurements are communicated to a central node, e.g. a smartphone, which displays, processes, or transmits the aggregated vital signs.



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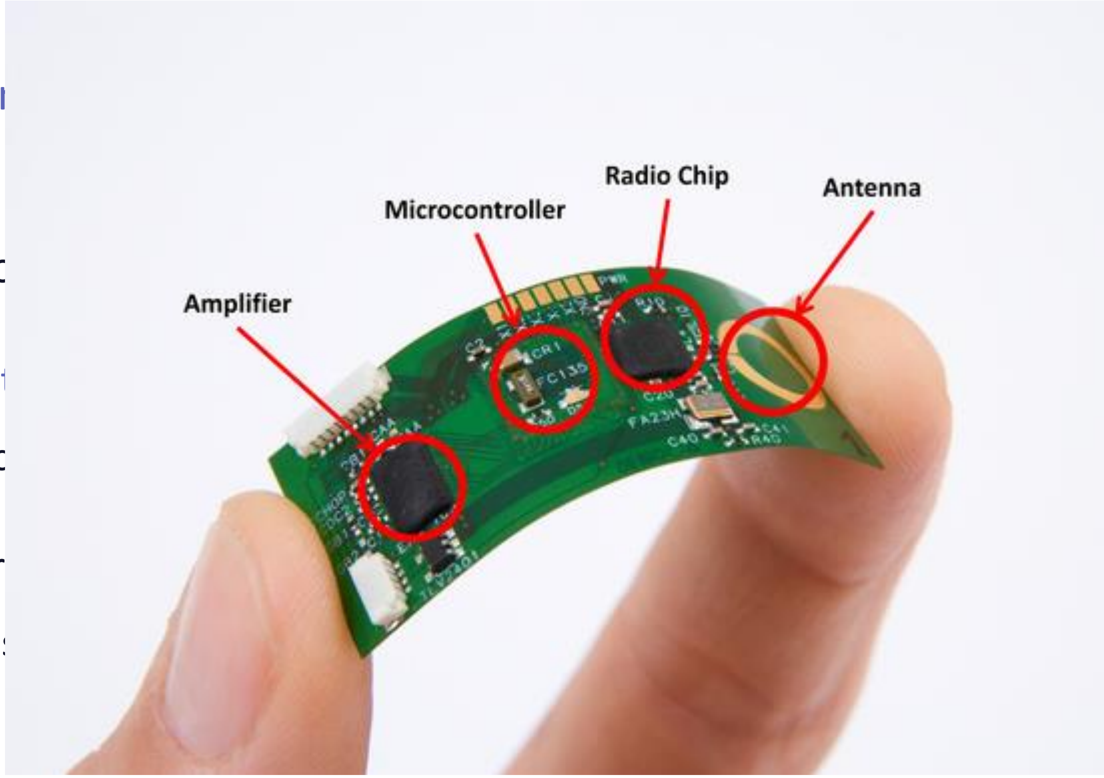
Pantelopoulos *et al.*, *IEEE Transactions on Systems, Man and Cybernetics*, 2010
https://www.mepits.com/tutorial/180/Latest-Technologies/Wearable-Biosensors

Key Enabling Technologies

- Recent developments in the field of microelectronics have allowed researchers to develop miniature circuits entailing sensing capability, front-end amplification, microcontroller functions, and radio transmission.

- Microelectron ent of miniaturized d other health status monito
  - By using ba ost of sensors has been ac
  - Microelectr such as microproce circuit thus resulting in



Flexible wireless ECG sensor with a fully functional microcontroller by IMEC.

Patel *et al.*, *Journal of NeuroEngineering and Rehabilitation,* 2012

Key Enabling Technologies

- Advances in material science have enabled the development of e-textile based systems that integrate sensing capability into garments.
- Rapid advances in this field promise to deliver technology that will soon allow one to print a full circuit board on fabric.

Patel *et al.*, *Journal of NeuroEngineering and Rehabilitation,* 2012

Key Enabling Technologies

- The Institute for Integrated Circuits IIS of the Fraunhofer research organization is working on a sport shirt that monitors health and fitness and syncs wirelessly with a smartphone.
- The FitnessSHIRT includes textile electrodes – conductive portions of fabric – that pick up electrical activity from the cardiac muscle, as well as an elastic band around the chest that measures breathing.
- The shirt tracks both medical and performance measures, including heart rate, respiratory activity, arterial oxygen saturation, posture and movement.
- An electronic unit snaps into the shirt for monitoring and removes easily for washing. The unit houses the battery, stores data and provides for wireless transmission.

http://www.fraunhofer.de/en/press/research-news/2013/november/intelligent-training.html

Key Enabling Technologies

- Recently developed wearable systems integrate individual sensors into the sensor network by relying on modern wireless communication technology.
  - With the development of IEEE 802.15.4/ZigBee and Bluetooth, tethered systems have become obsolete.
  - The recently developed IEEE 802.15.4a standard based on Ultra-wide-band (UWB) impulse radio allows for low-power, low-cost but high data rate sensor network applications with the possibility of highly accurate location estimation.

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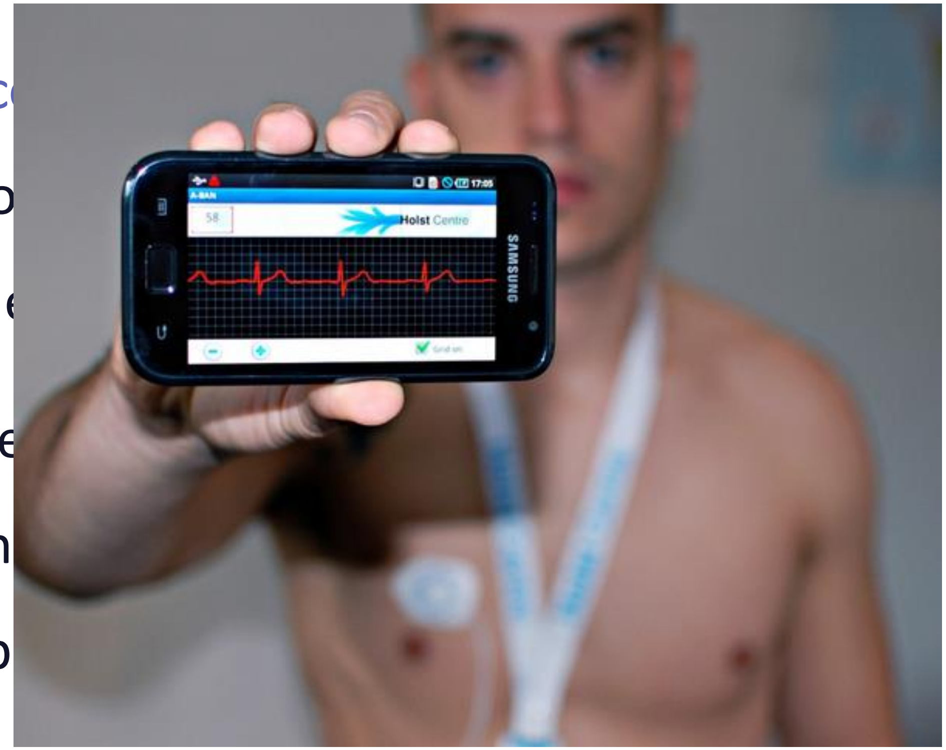
Patel *et al.*, *Journal of NeuroEngineering and Rehabilitation,* 2012

Key Enabling Technologies

With increasing computational and storage capacity and ubiquitous connectivity, smart phones are expected to truly enable continuous health monitoring.



Smart phone based ECG monitoring system by IMEC. The Android based mobile application allows low power ECG sensors to communicate wirelessly with the phone.

- As storage and computation be… health monitoring systems can… independent, rapidly deployab…
- Smart phone technology has had a major impact on the development of remote monitoring systems based on wearable sensors.

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Patel *et al.*, *Journal of NeuroEngineering and Rehabilitation,* 2012

Key Enabling Technologies

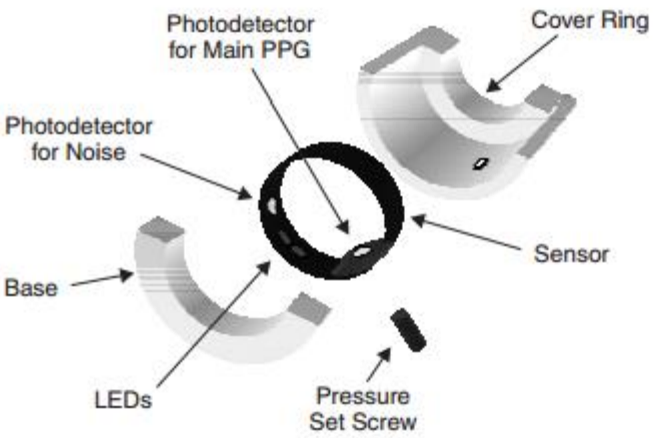
- The massive amount of data that one can gather using wearable systems for patient's status monitoring has to be managed and processed to derive clinically relevant information.
    - Signal processing, pattern recognition, data mining and other artificial intelligence-based methodologies

Data processing and analysis techniques are an integral part of the design and development of remote monitoring systems based on wearable technology.

Patel *et al.*, *Journal of NeuroEngineering and Rehabilitation,* 2012

Wearable Sensors – Heart Rate, SpO_2

- Asada *et al.* presented a ring sensor capable of reliably monitoring a patient's heart rate and blood oxygen saturation (SpO_2).
- The ring sensor combines miniaturized data acquisition features with advanced ***photoplethysmographic (PPG) techniques*** to acquire data related to the patient's cardiovascular state.
- Technical issues, including motion artifact, interference with blood circulation, and battery power issues were effectively addressed.



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Patel *et al.*, *Journal of NeuroEngineering and Rehabilitation,* 2012

Wearable Sensors – Blood Pressure

- A self-contained wearable **cuff-less photoplethysmographic (PPG)** based blood pressure monitor was subsequently developed by the same research group.

The sensor integrated a novel height sensor based on two MEMS accelerometers for measuring the hydrostatic pressure offset of the PPG sensor relative to the heart.

→

The mean arterial blood pressure was derived from the PPG sensor output amplitude by taking into account the height of the sensor relative to the heart.

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Patel *et al.*, *Journal of NeuroEngineering and Rehabilitation*, 2012

Wearable Sensors – Respiratory Rate

- Another example of ingenious design is the system developed by Corbishley *et al.* to measure respiratory rate using a miniaturized wearable **acoustic sensor (i.e. microphone)**.

The microphone was placed on the neck to record acoustic signals associated with breathing, which were band-pass filtered to obtain the signal modulation envelope.

→

By developing techniques to filter out environmental noise and other artifacts, the authors managed to achieve accuracy greater than 90% in the measurement of breathing rate.

- The authors also presented an algorithm for the detection of apneas based on the above-described sensing technology.

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Patel *et al.*, *Journal of NeuroEngineering and Rehabilitation,* 2012

Wearable Sensors – Motion

- Remote monitoring applications have largely relied upon inertial sensors for movement detection and tracking.
- Inertial sensors include accelerometers and gyroscopes.
  - Often, magnetometers are used in conjunction with them to improve motion tracking.
- Today, movement sensors are inexpensive, small and require very little power, making them highly attractive for patient monitoring applications.

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Patel *et al.*, *Journal of NeuroEngineering and Rehabilitation*, 2012

Wearable Sensors – Motion Artifacts

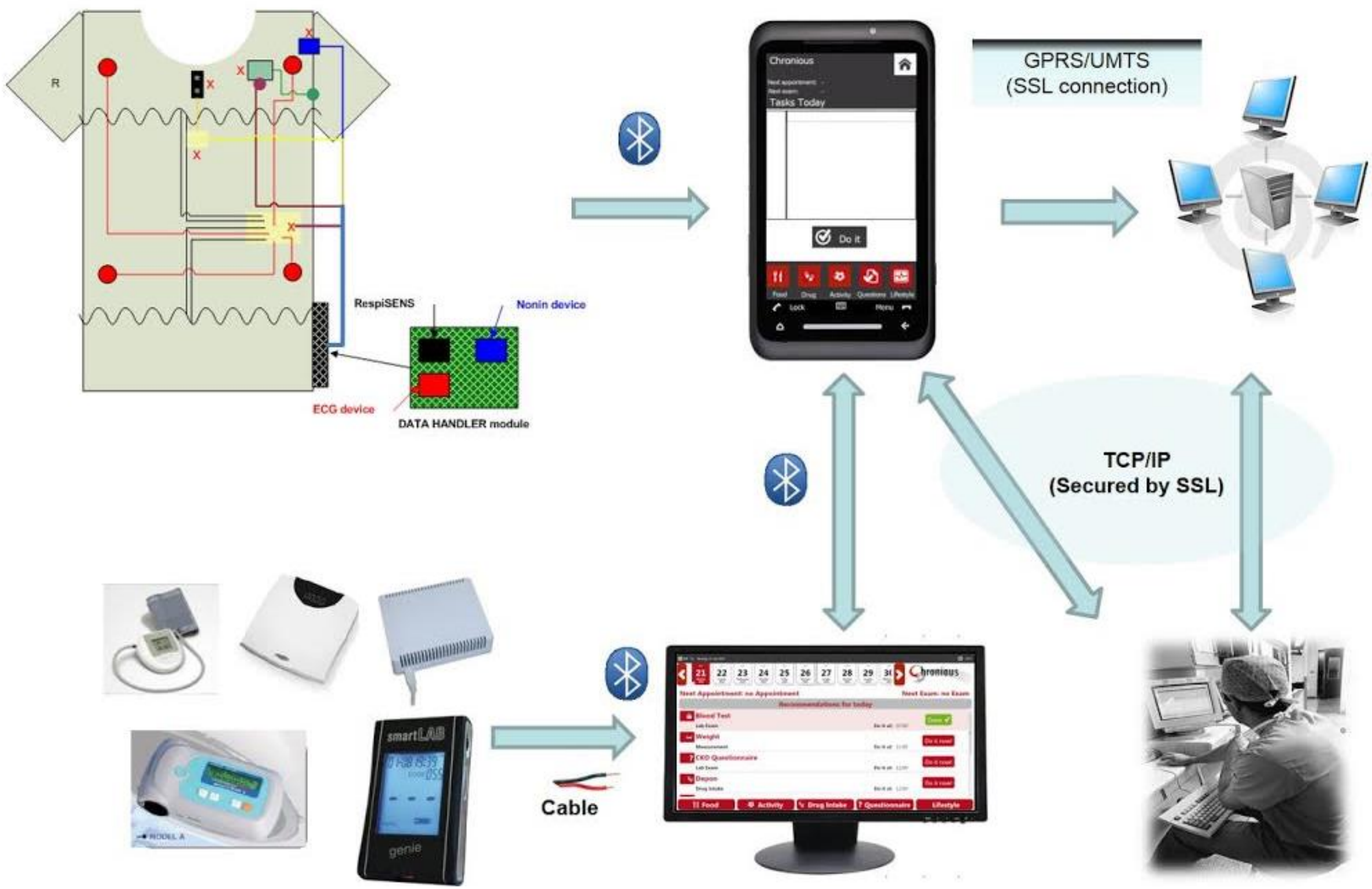
- Proper **attenuation of motion artifacts** is essential to the deployment of wearable sensors.
- Some of the problems due to motion artifacts could be minimized by integrating sensors into tight fitting garments.
- A comparative analysis of different wearable systems for monitoring respiratory function was presented by *Lanata et al.*
  - The analysis showed that piezoelectric pneumography performs better than spirometry.
- Nonetheless, further advances in signal processing techniques to mitigate motion artifacts are needed.

Patel *et al.*, *Journal of NeuroEngineering and Rehabilitation,* 2012

Wearable Systems – The Chronious Project

- A light-weight smart T-shirt is equipped with wearable heart, respiratory and activity monitoring sensors.
- The system relies on additional information gathered by the external devices such as a digital weight scale, glucometer, blood pressure monitor, spirometer and air quality sensor.
- Data collected by these sensors is sent to a mobile device such as a smartphone, which relay the data to their care provider where it is analyzed with intelligent data processing software.
- The system is open and modular, thus enabling a flexible approach where different types of sensors can be used according to the monitored condition.

Wearable Systems – The Chronious Project



www.chronious.eu

Commercial Devices – BodyMedia SenseWear Armband

- The SenseWear System is an affordable way to collect and analyze continuous and accurate physiological and lifestyle data.
- The system is comprised of 3 components:
  - the SenseWear Armband,
  - the optional SenseWear Display, and
  - the SenseWear Software.

- The hardware and software are highly accurate, easy-to-use, and cost efficient alternatives for continuously monitoring energy expenditure, sleep, and other physiological data for basic and applied medical research.

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http://sensewear.bodymedia.com/

Commercial Devices – BodyMedia SenseWear Armband

The Hardware

- Memory capacity: about 28 days under steady use
- Battery power: about 5-7 days under steady use
- Allows for specific events to be time stamped and annotated
- Collects physiological data at a rate of 32 times/second

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http://sensewear.bodymedia.com/

Commercial Devices – BodyMedia SenseWear Armband

SenseWear Software

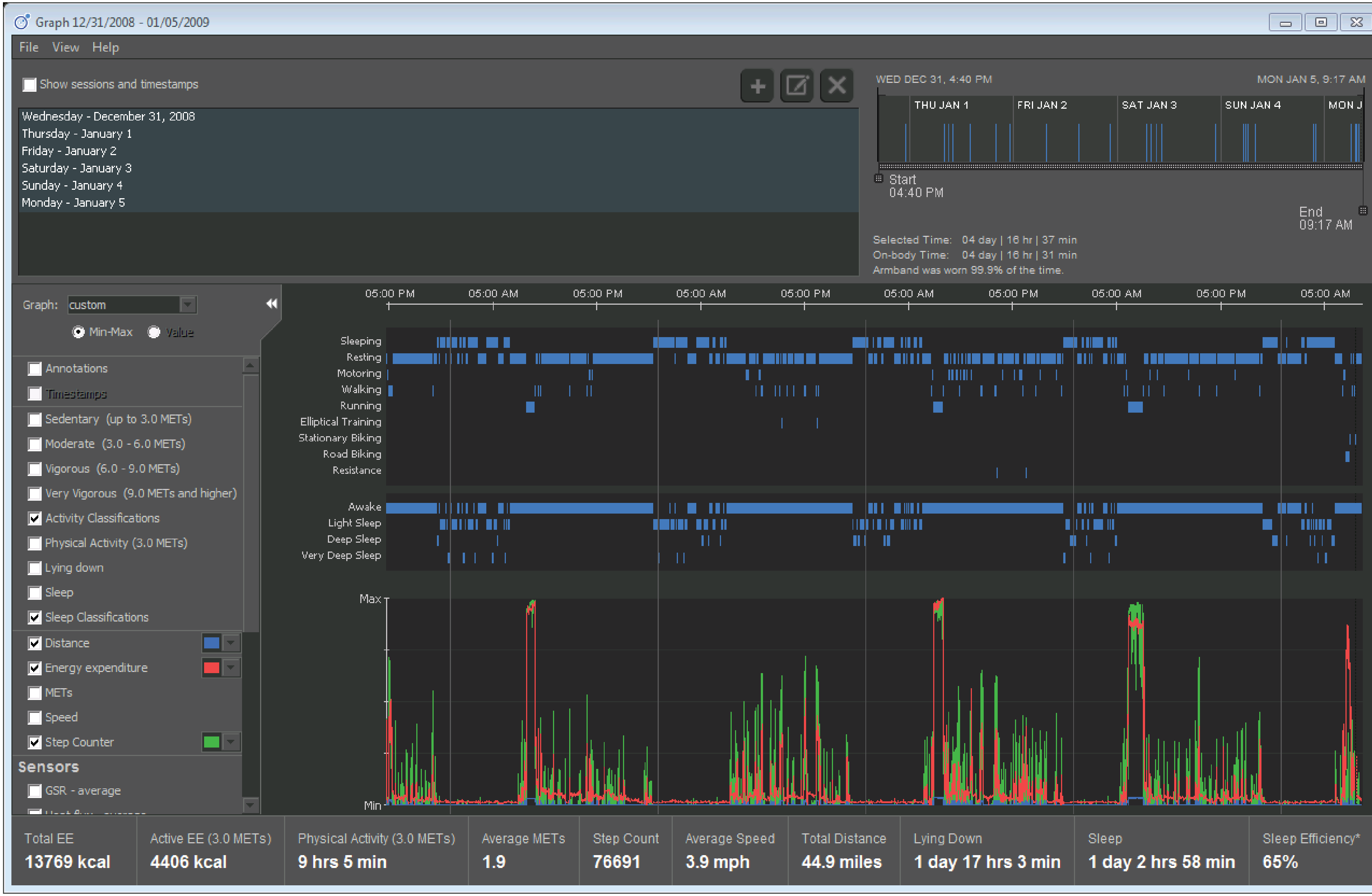
- PC based software application
- Easily upload, annotate, analyze and share data recorded from the SenseWear Armband
- Print or view reports in pdf
- Review user event markers via the Time Stamp feature

Clinically Validated
Used by clinical and research groups, the SenseWear System is scientifically validated and featured in over a hundred of peered reviewed papers.

SenseWear Professional Software

- Graph the raw data for specified time periods, including speed and distance.
- **Activity Classifications for time spent: Sleeping, Resting, Motoring, Walking, Running, Elliptical Training, Stationary, Biking, Road Biking, and Resistance Training**
- Export data in XLS or CSV format
- Customize the collection rate of each sensor channel
- **Specify activity levels and set their thresholds (sedentary, light, moderate, vigorous, very vigorous)**

http://sensewear.bodymedia.com/



http://sensewear.bodymedia.com/

Commercial Devices – Withings Pulse Activity Tracker

During the day	It captures steps taken, distance travelled, elevation climbed, calories burned and run (distance and duration).
At night	It tracks sleep duration, sleep quality, light vs. deep sleep and sleep interruptions.
On demand	It measures the instant heart rate and blood oxygen level.
Sync seamlessly	The Pulse O_2 automatically syncs to the smartphone all throughout the day thanks to its embedded Bluetooth Low Energy technology.

http://www.withings.com/

Commercial Devices – Withings Pulse Activity Tracker

The Hardware

- **Memory capacity:** 30 days
- **Battery power:** 2 week average use between charges
- **Heart rate & SpO_2 sensors**
  - Optoelectronics sensor
- **Day & Night motion sensor**
  - High precision MEMS 3-axis accelerometer

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http://www.withings.com/

Commercial Devices – Fitbit Flex Activity Tracker

During the day	It captures steps taken, distance travelled, calories burned and active minutes.
At night	It tracks sleep duration, sleep quality and sleep interruptions.
On demand	Flex uses five white LED indicator lights to show daily progress against personal goals. Each light represents 20% of a user's goal.
Sync seamlessly	Flex automatically syncs to user's PC and smartphone thanks to its embedded Bluetooth Low Energy technology.

https://www.fitbit.com/

Commercial Devices – Fitbit Flex Activity Tracker

The Hardware

- **Memory capacity:** 30 days
- **Battery power:** Flex battery lasts approximately five days when fully charged.
- **Day & Night motion sensor**
  - High precision MEMS 3-axis accelerometer
- Flex also contains a vibration motor, which allows it to vibrate when alarms are set to go off.

http://www.withings.com/

Commercial Devices - iHealth

- Wireless Pulse Oximeter
  - The iHealth Pulse Oximeter (PO3) measures the amount of oxygen in blood and the pulse rate. The oximeter works by shining two light beams into the small blood vessels or capillaries of the finger, reflecting the amount of oxygen in the blood and displaying the measurement on the oximeter's screen. The oxygen saturation (SpO2) is measured as a percentage of full capacity.

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http://www.ihealthlabs.com/

Commercial Devices - iHealth

- Ambulatory Blood Pressure Monitor
  - The monitor connects to a user's mobile devices via Bluetooth, or to a PC via USB, and is meant to be worn inside a vest. Users can choose how often it delivers blood pressure readings, with an option of 15-, 30-, 45-, 60-, or 120-minute intervals.

http://www.ihealthlabs.com/

Commercial Devices - iHealth

- Wireless ambulatory ECG
  - The company's new device features built-in electrodes and a monitor that were ergonomically designed to be lightweight and fit under normal clothing, and to attach directly to a user's chest. The data gathered by the device is delivered wirelessly to the user's mobile phone, which then automatically sends it to the cloud.

http://www.ihealthlabs.com/

Commercial Devices – CARDIO CORE

- QardioCore is a revolutionary, smart, connected EKG/ECG monitor, designed to improve detection of cardiac conditions while fitting with ease into daily

QardioCore will begin selling in the US after receiving US Food and Drug Administration clearance.

http://www.getqardio.com/

Commercial Devices – CARDIO CORE

- EKG/ECG
  - Medical-grade wireless electrocardiogram monitoring without the hassle of gels and patches.
- HEART RATE
  - Measure beat-by-beat heart rate on the go as well the resting rate.
- BODY TEMPERATURE
  - Continuous reading of body temperature with notifications and historical data. Galvanic skin response provides an indication of stress levels over time.
- ACTIVITY TRACKING
  - Daily tracking of steps, distance, calories.

http://www.getqardio.com/

BIOSENSORS

Definition

*"A **biosensor** is an analytical device incorporating a biological or biologically derived sensing element either intimately associated with or integrated within a physicochemical transducer**.** The usual aim is to produce a digital electronic signal which is proportional to the concentration of a chemical or set of chemicals."*

- "*Biosensors* usually yield a digital electronic signal which is proportional to the concentration of a specific analyte or group of analytes. While the signal may in principle be continuous, devices can be configured to yield single measurements to meet specific market requirements." (One-shot biosensors)

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Turner et al., *Biosensors: Fundamentals and Applications*. Oxford University Press, 1987

Biosensors

- The field of biosensors may be viewed as comprising essentially two broad categories of instrumentation:
  a. sophisticated, high-throughput laboratory machines capable of rapid, accurate and convenient measurement of complex biological interactions and components
  b. easy-to-use, portable devices for use by non-specialists for de-centralised, in situ or home analysis
- The former are expensive and the latter are mass produced and inexpensive.

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Turner, *Chemical Society Reviews*, 2013

Biosensors

- Biosensors find application in
  - medicine,
  - drug discovery,
  - food and process control,
  - environmental monitoring,
  - defense and security,

  but most of the market of over US$13 billion is driven by medical diagnostics and, in particular, glucose sensors for people with diabetes.
- The most significant trend likely to impact on biosensors is the emergence of personalized medicine.

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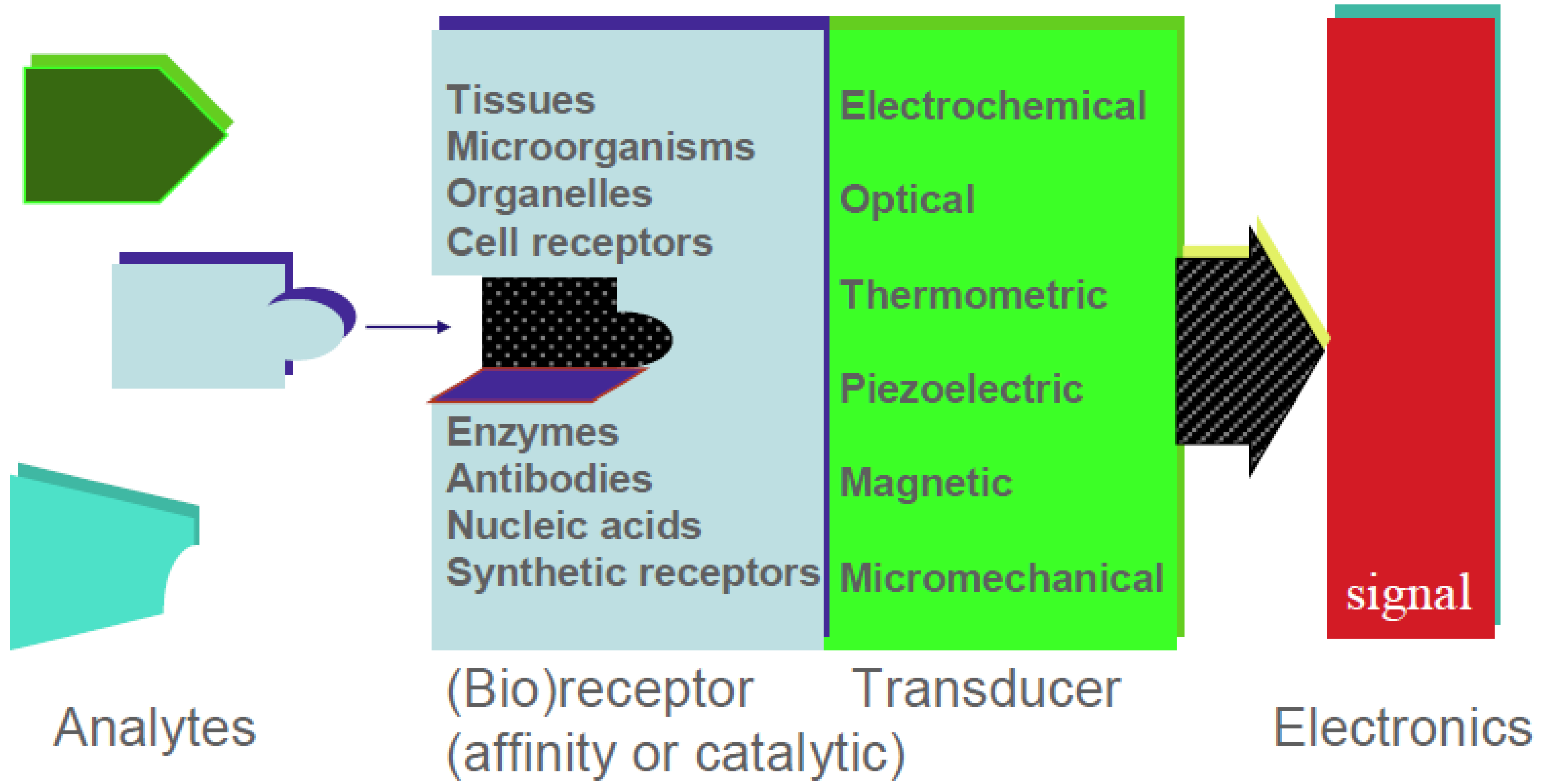
Turner, *Chemical Society Reviews*, 2013

Type of Biosensors

- Affinity based (molecular recognition)
  - Antigen – antibody
  - Receptor – ligand (drugs, neurotransmitters,…)
  - DND, RNA – complementary strands
- Reaction based
  - Enzymes
  - Whole cells

Turner, *Chemical Society Reviews*, 2013

The Biosensor



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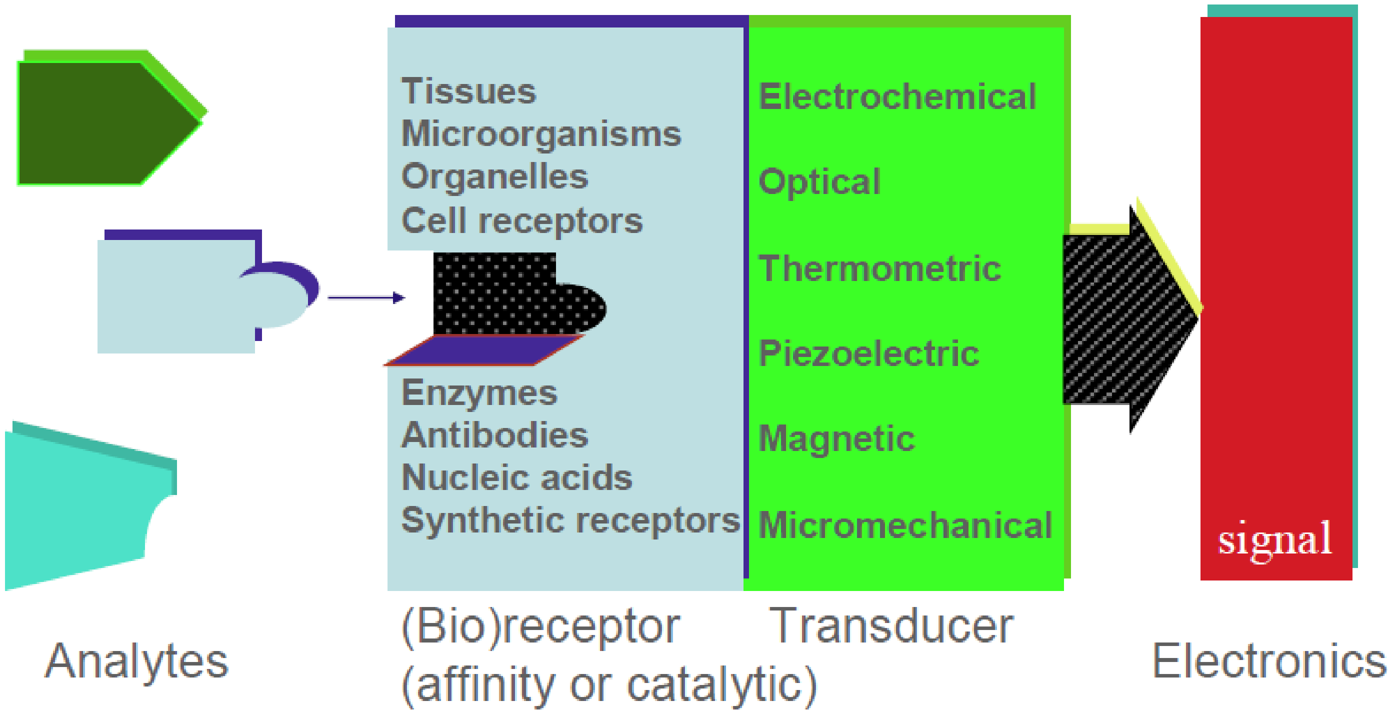
Turner, *Chemical Society Reviews*, 2013

The Biosensor

- A specific “bio” element (e.g. enzyme) recognizes a specific analyte and the “sensor” element transduces the change in the biomolecule into an electrical signal.



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Turner, *Chemical Society Reviews*, 2013

The Biosensor – Working Principle

The analyte diffuses from the solution to the surface of the biosensor.

↓

The analyte reacts specifically and efficiently with the biological component of the biosensor.

↓

This reaction changes the physicochemical properties of the transducer surface.

↓

This leads to a change in the optical/electronic properties of the transducer surface.

↓

The change in the optical/electronic properties is measured/converted into electrical signal, which is detected.

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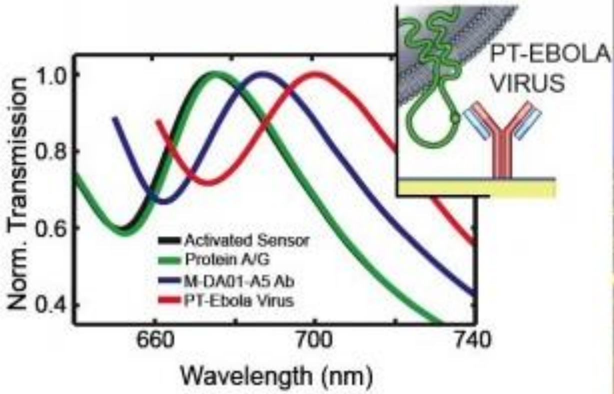
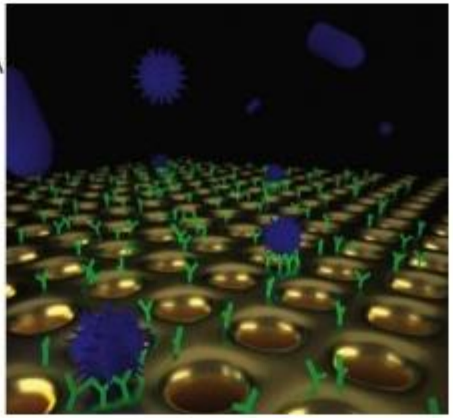
Mohanty *et al.*, *IEEE Potentials*, 2006

The Analyte

- The substance to be measured is also referred to as the **analyte** or **substrate**.
- In principle, any substance that is consumed or produced in a biochemical process:
  - Anorganic: Gases, ions , heavy metals
  - Organic: Aminoacids, proteins, glucose, urea, paracetamol and DNA
- More generally, any unit, (part of) which is involved in a biochemical process:
  - Microorganisms
  - Microbial cells
  - Antibodies
  - Antigens





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Munnikes, *Lecture notes in Nanobiotechnology and Biosensors,*2006
Mohanty *et al.*, *IEEE Potentials*, 2006

Receptors for Biosensors - Biomeaterials

Enzymes

Antibodies

Nucleic Acids

Chemoreceptors

- Chemoreceptors are proteins inside a cell membrane that can recognize either neurotransmitters or hormones.
- The binding of the analyte to the chemoreceptor activates a physiological response, such as ion channel opening, a second messenger system or the activation of enzymes.
- Thus they can be seen as natural biosensors, regulating the electrical signals in our nerves.
- It is difficult to isolate them, but whole nerve cells can be used as well, for instance to determine the presence of drugs.

Mohanty *et al.*, *IEEE Potentials*, 2006

Receptors for Biosensors

Any biological substance that can attach itself to a particular analyte.

Biological materials

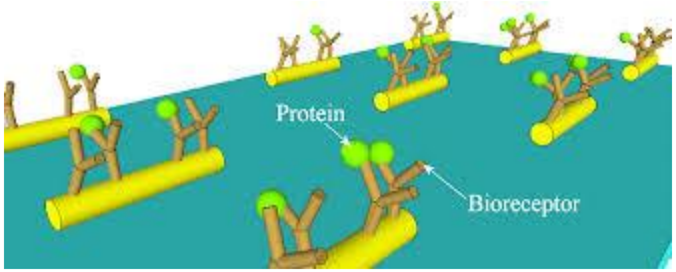
- tissue, microorganisms, organelles, cell receptors, enzymes, antibodies, nucleic acids, natural products etc.

Biologically derived materials

- recombinant antibodies, engineered proteins, aptamers etc.

Biomimics

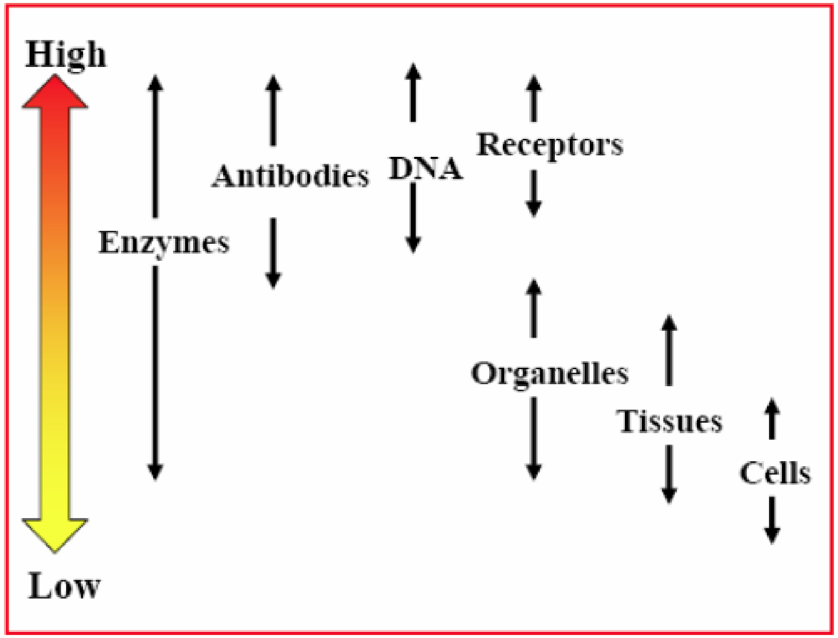
- synthetic receptors, bimimetic catalysts, combinatorial ligands, imprinted polymers etc.



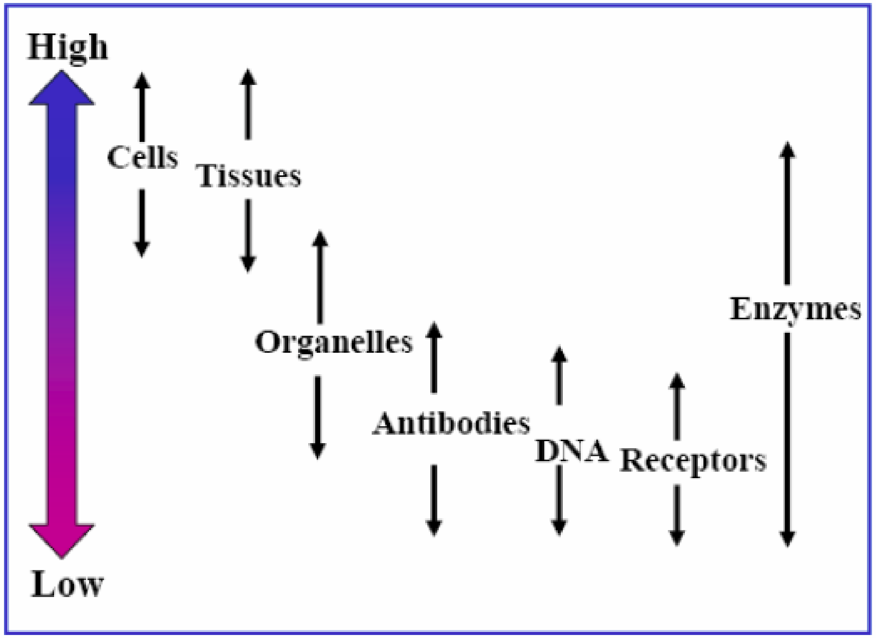
Munnikes, *Lecture notes in Nanobiotechnology and Biosensors*,2006
Mohanty *et al.*, *IEEE Potentials*, 2006

Receptors: Specificity vs. Stability

Specificity



Stability



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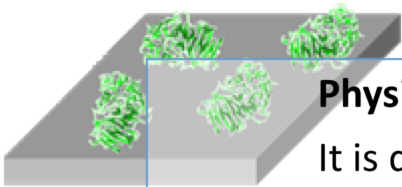
Munnikes, *Lecture notes in Nanobiotechnology and Biosensors,*2006
Mohanty *et al.*, *IEEE Potentials*, 2006

Immobilization

The process of attaching the biological component to the transducer.

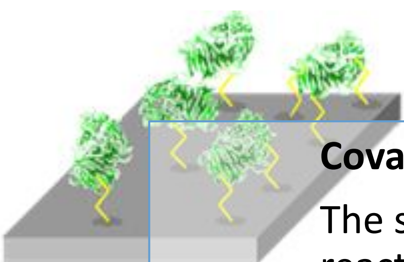


Physical Adsorption

It 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.

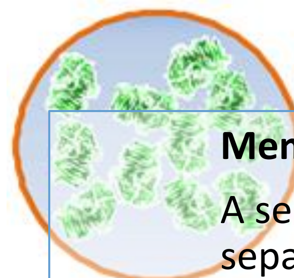
Matrix Entrapment

It is based on forming a porous encapsulation matrix around the biological material that helps in binding it to the sensor.



Covalent Bonding

The sensor surface is treated as a reactive group to which the biological materials can bind.



Membrane Entrapment

A semi permeable membrane separates the analyte and the bioelement, and the sensor is attached to the bioelement.

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Munnikes, *Lecture notes in Nanobiotechnology and Biosensors,*2006
Mohanty *et al.*, *IEEE Potentials*, 2006

Transducers for Biosensors

Electrochemical

- conductimetric, amperometric, potentiometric, impedimetric

Optical

- surface plasmon resonance (SPR), fluorescence, interferometric, holographic

Thermometric

- enzyme thermistor, thremal enzyme-linked immunosorbent assay

Piezoelectric

- quartz crystal microbalance (QCM), surface acoustic wave devices (SAW) (mass changes)

Magnetic

- magneto resistive devices, paramagnetic labels

Micromechanical

- resonating beam structures (mass changes)

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Munnikes, *Lecture notes in Nanobiotechnology and Biosensors*,2006
Mohanty *et al.*,*IEEE Potentials*, 2006

Electrochemical Transducers

- Electrochemical biosensors are mainly used for the detection of hybridized DNA, DNA-binding drugs, glucose concentration, etc.

Underlying principle

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.

- Electrochemical biosensors can be classified based on the measuring electrical parameters as:
    - Conductimetric, amperometric and potentiometric.

Munnikes, *Lecture notes in Nanobiotechnology and Biosensors,*2006
Mohanty *et al.*, *IEEE Potentials*, 2006

Electrochemical Transducers

Conductimetric

Amperometric

Potentiometric

- The measured parameter is oxidation or reduction potential of an electrochemical reaction.
- The working principle relies on the fact that when a ramp voltage is applied to an electrode in solution, a current flow occurs because of electrochemical reactions.
- The voltage at which these reactions occur indicates a particular reaction and particular species.

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Munnikes, *Lecture notes in Nanobiotechnology and Biosensors*,2006
Mohanty *et al.*, *IEEE Potentials*, 2006

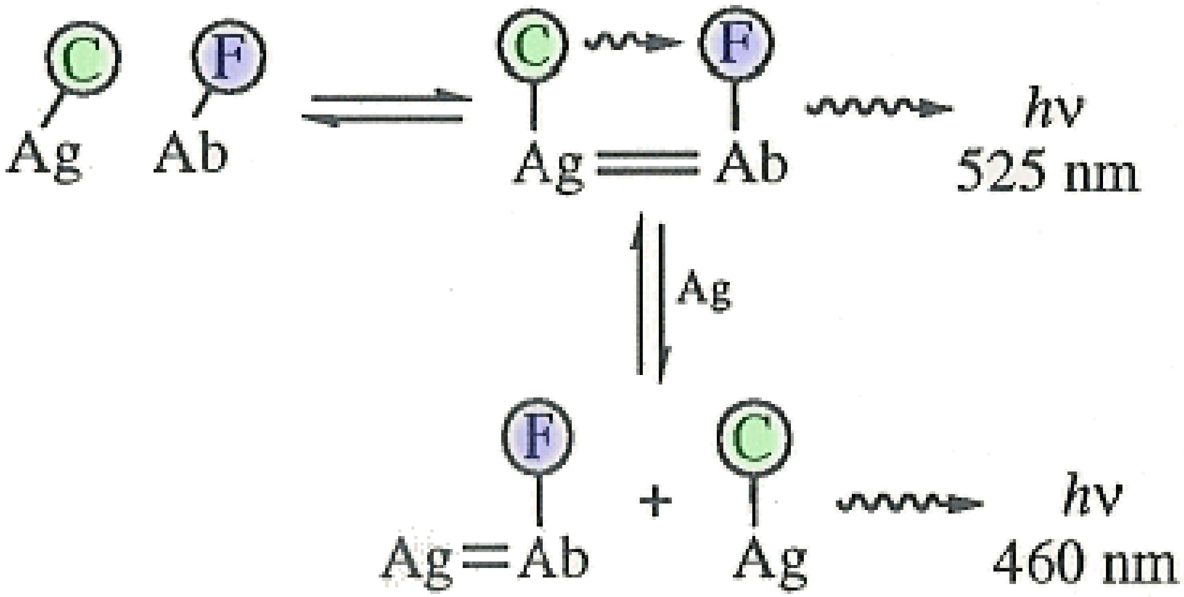
Optical Transducers

- Optical methods have become increasingly popular due to the development of optical fibres.
- A change in optical properties can be achieved by using :
  - Ultraviolet-visible absorption
  - Luminescence
  - Internal Reflection Spectroscopy
    - Surface Plasmon Resonance (SPR)
  - Laser light scattering

Munnikes, *Lecture notes in Nanobiotechnology and Biosensors*,2006
Mohanty *et al.*, *IEEE Potentials*, 2006

Optical Transducers

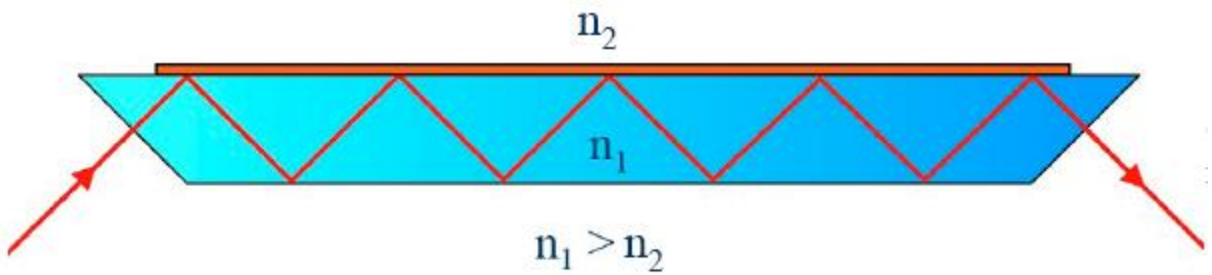
Example of a luminescence-based method: Combining chemiluminescence and fluorescence in a competitive immunoassay.



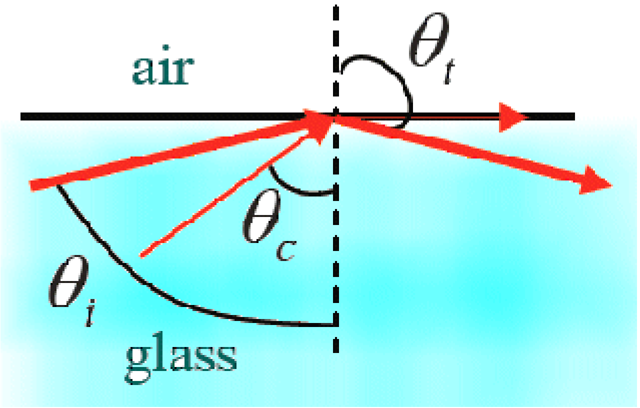
Munnikes, *Lecture notes in Nanobiotechnology and Biosensors*,2006

Optical Transducers – Total Internal Reflection

- Total Internal Reflection (TIR) methods are based on the complete reflection of a ray of light that hits a less dense medium.



Snell's law: $n_1 * \sin\theta_1 = n_2 * \sin\theta_2$
$\Longrightarrow \theta_c = sin^{-1}(n_2/n_1)$



- The transmitted light beam vanishes for angles larger than the critical angle θ_c.
- According to quantum mechanics, there is a finite probability for a photon, which should be reflected, to reach into the classically forbidden medium.

Munnikes, *Lecture notes in Nanobiotechnology and Biosensors*,2006

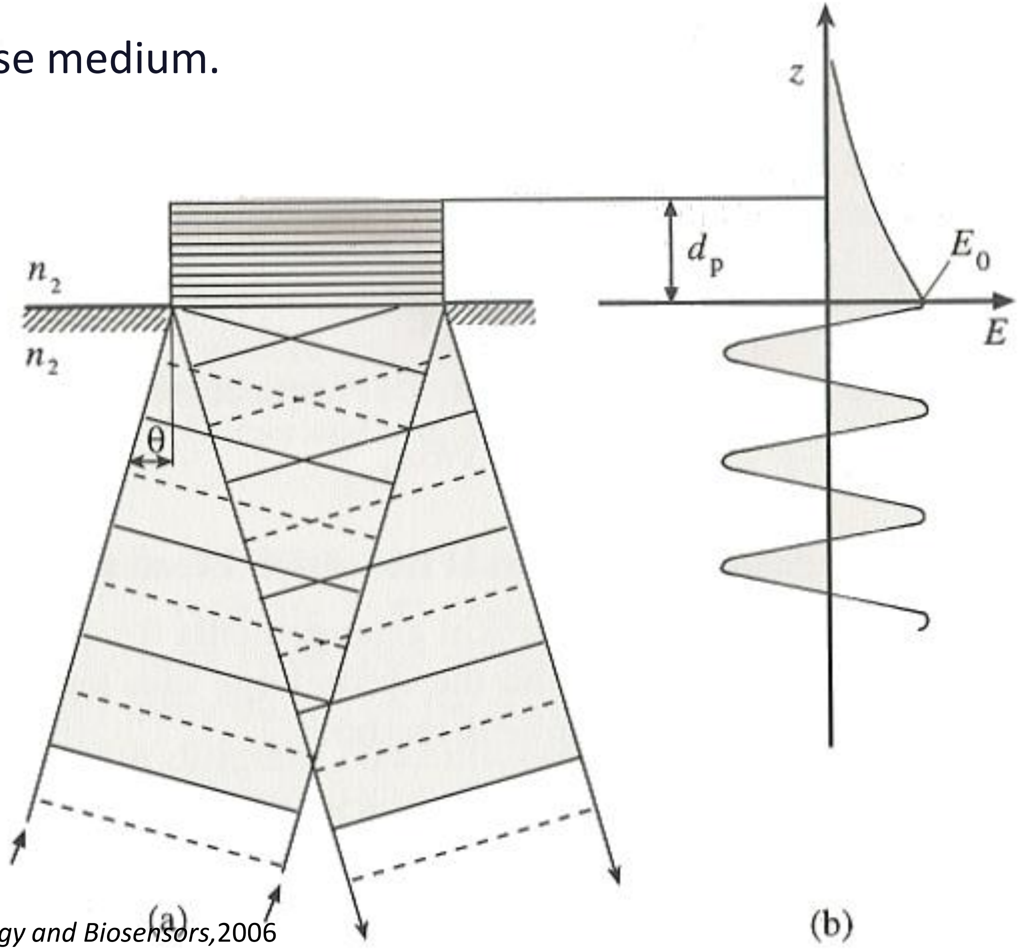
Optical Transducers – Total Internal Reflection

- Thus, there is an **exponentially decaying (=evanescent) wave** on the other side.
- This evanescent wave can be used for in an immunoassay, where the antigens are located at the surface in the less dense medium.

$$E_z = E_0 e^{\left(-z/d_p\right)}$$

$$d_p = \frac{\lambda}{2\pi n_1 \left[sin^2\theta - \left(\frac{n_2}{n_1}\right)\right]^{1/2}}$$

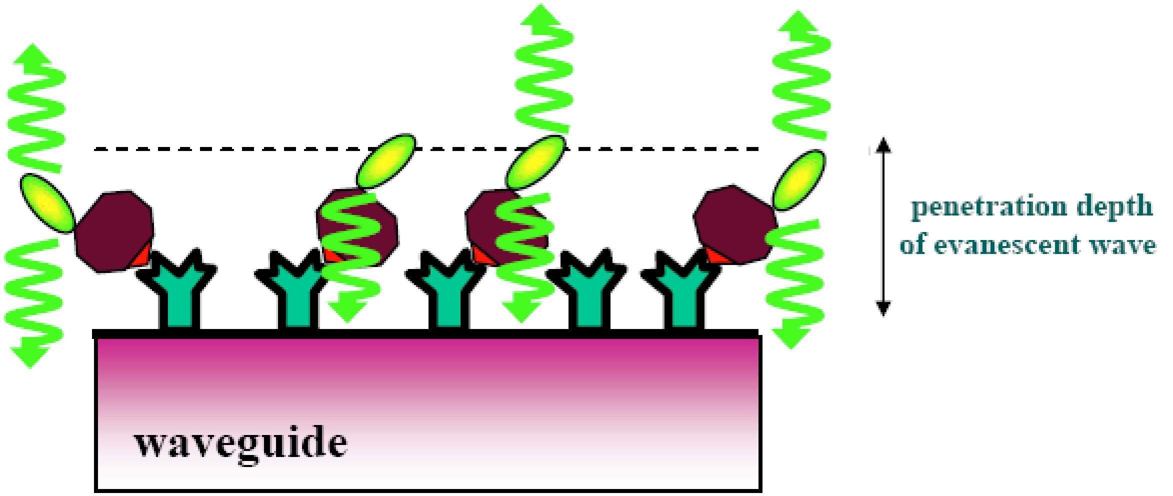
.



Munnikes, *Lecture notes in Nanobiotechnology and Biosensors*,2006

Optical Transducers – Total Internal Reflection

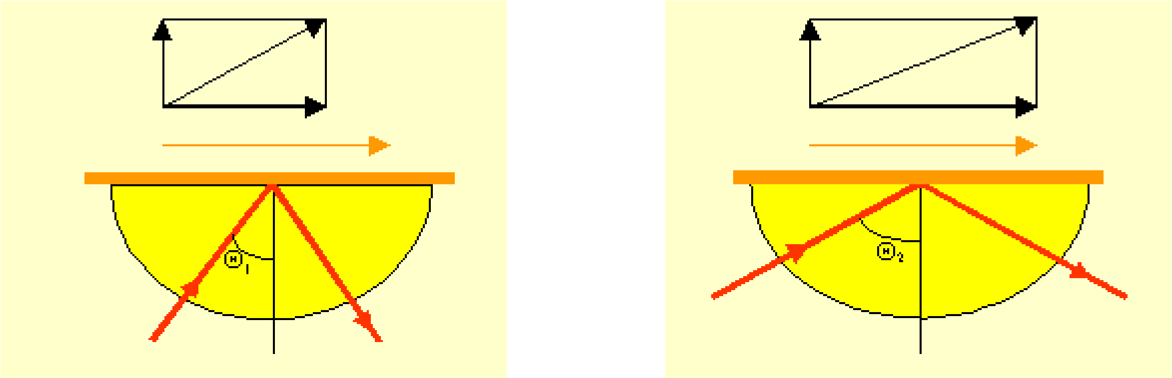
- Part of the corresponding antibodies can be labelled with **fluorescent** particles.
- When the antibodies bind themselves to the antigens, the fluorescent particles can absorb the energy of the evanescent wave and re-emit it into the dark medium, which can be detected.



Munnikes, *Lecture notes in Nanobiotechnology and Biosensors*,2006

Optical transducers – Plasmon & TIR

- Another way to use the evanescent wave in a biosensor is by using Surface Plasmon Resonance (SPR).
- A plasmon is a quasiparticle, belonging to a collective oscillation of the free electron gas in (semi)conductors.

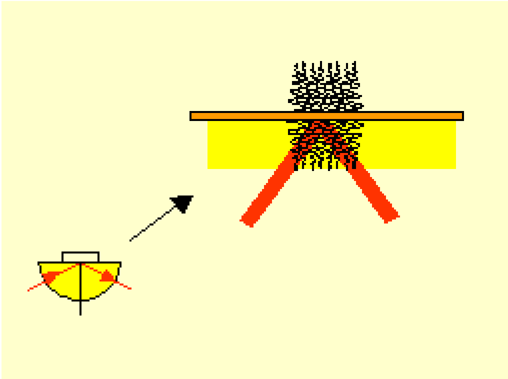


- An evanescent wave at a dielectric/conducting medium interface can excite surface plasmons.

Munnikes, *Lecture notes in Nanobiotechnology and Biosensors*,2006

Optical transducers – Plasmon & TIR

- A surface plasmon can be excited by an evanescent wave, if the quantum energy of the photons is equal to the energy of plasmons in that material.
- This so-called resonance leaves a gap in the reflected light intensity at one particular frequency.



- How to involve biomaterial in this?
  - Thin conducting layer with biomaterial on the other side. A small change in refractive index of the biomaterial causes a large shift of θ.

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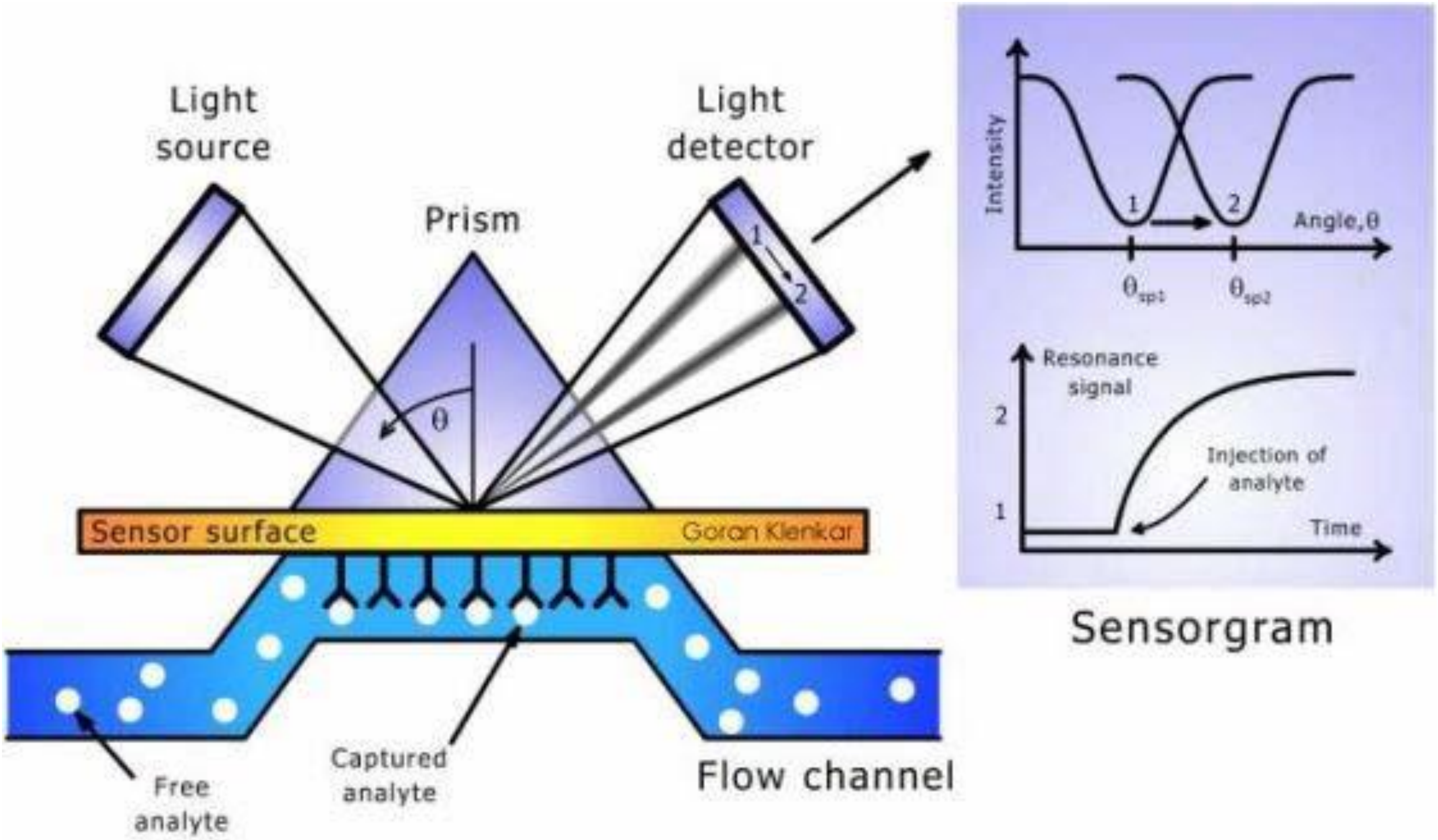
Munnikes, *Lecture notes in Nanobiotechnology and Biosensors*,2006

Optical Transducers – Surface Plasmon Resonance



Munnikes, *Lecture notes in Nanobiotechnology and Biosensors*,2006

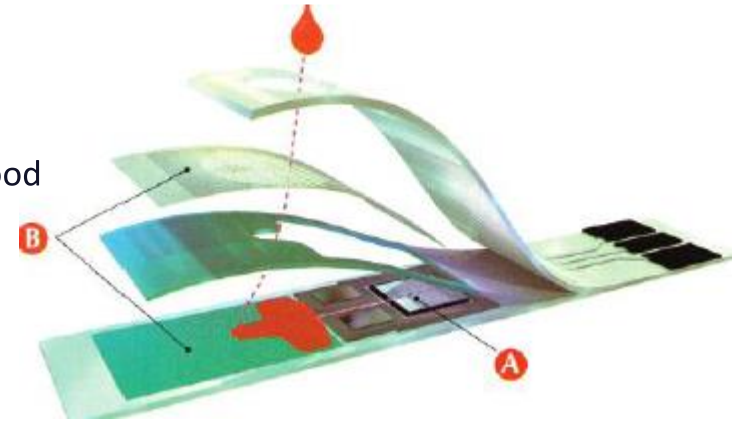
Biosensors

- Electrochemical biosensors currently dominate the field, but are focused mainly on metabolite monitoring, while bioaffinity monitoring is carried out principally using optical techniques.
- However, both transducers find utility across the whole field, along with piezoelectric, thermometric, magnetic and micromechanical transducers.
- The emergence of semi-synthetic and synthetic receptors is yielding more robust, versatile and widely applicable sensors.
- Nanomaterials are facilitating highly sensitive and convenient transduction of the resulting binding and catalytic events.

Turner, *Chemical Society Reviews*, 2013
Wang, *Electroanalysis*, 2013

Biosensors for Diabetes: Blood Glucose Meters

- Electrochemical biosensors are well suited for addressing the needs of personal (home) blood glucose monitoring in diabetes disease.
  - Since blood glucose home testing devices are used daily to diagnose potentially life-threatening events they must be of extremely high quality.
- The majority of personal blood glucose monitors rely on disposable screen-printed enzyme electrode test strips.



Cross section of a commercial strip for self-monitoring of blood glucose (based on the Precision biosensor manufactured by Abbott Inc.):

A. electrode system
B. hydrophobic layer (drawing the blood)

Georga, *Health and Technology*, 2014
Wang, *Chemical Reviews*, 2008

Biosensors for Diabetes: Blood Glucose Meters

- The screen-printing technology involves printing patterns of conductors and insulators onto the surface of planar solid (plastic or ceramic) substrates based on pressing the corresponding inks through a patterned mask.
- Each strip contains the printed working and reference electrodes, with the working one coated with the necessary reagents (i.e., enzyme, mediator, stabilizer, surfactant, linking, and binding agents) and membranes.
- The reagents are commonly dispensed by an ink-jet printing technology and deposited in the dry form.
- A counter electrode and an additional (‘baseline’) working electrode may also be included.
- Various membranes (mesh, filter) are often incorporated into the test strips and along with surfactants are used to provide a uniform sample coverage and separate the blood cells.

Georga, *Health and Technology*, 2014
Wang, *Chemical Reviews*, 2008

Biosensors for Diabetes: Blood Glucose Meters

Such single-use devices eliminate problems of carry over, cross contamination, or drift. Overall, despite their low cost and mass production such sensor strips are based on a high degree of sophistication essential for ensuring high clinical accuracy.

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Georga, *Health and Technology*, 2014
Wang, *Chemical Reviews*, 2008

Biosensors for Diabetes: Blood Glucose Meters

- The control meter is typically small (pocket-size), light, and battery operated.
- It relies on a potential-step (chrono-amperometric) operation in connection with a short incubation (reaction) step.
- In 1987 Medisense Inc. (in the United Kingdom) launched the first product of this type, the pen-style Exactech device, based on the use of a ferrocene-derivative mediator.
- Since then, over 40 different commercial strips and pocket-sized monitors have been introduced for self-testing of blood glucose.
- However, over 90% of the market consists of products manufactured by four major companies, including Life Scan, Roche Diagnostics, Abbott, and Bayer.
- Most of these meters rely on a ferricyanide mediator, except for the Abbott devices that employ a ferrocene derivative or an osmium-based redox polymer.

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Georga, *Health and Technology*, 2014
Wang, *Chemical Reviews*, 2008

Biosensors for Diabetes: Blood Glucose Meters

- In all cases, the diabetic patient pricks the finger, places the small blood droplet on the sensor strip, and obtains the blood glucose concentration (on a LC display) within 5-30 s.
- Some of the new meters allow sampling of sub-microliter blood samples from the forearm, thus reducing the pain and discomfort associated with piercing the skin.
- For example, the FreeStyle monitor of Abbott relies on coulometric strips with a 50 μm gap thin-layer cell for assays of 300 nL blood samples.
- Widespread use of such alternative sampling sites requires that the collected samples properly reflect the blood glucose values (especially when these levels change rapidly).
- In addition to fast response and small size, modern personal glucose meters have features such as extended memory capacity and computer downloading capabilities.

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Georga, *Health and Technology*, 2014
Wang, *Chemical Reviews*, 2008

Biosensors for Diabetes: Blood Glucose Meters

- Despite these remarkable technological advances, home testing of blood glucose often suffers from low and irregular testing frequency (related to the inconvenience and discomfort), inadequate interpretation of the results by the patient, or liability issues and requires compliance by patients.
- More integrated devices, offering multifunctional capability, enhanced interface with the physician's work, and convenient tracking of changes in the glucose level, are expected in the near future.

Georga, *Health and Technology*, 2014
Wang, *Chemical Reviews*, 2008

All Printed Biosensing System

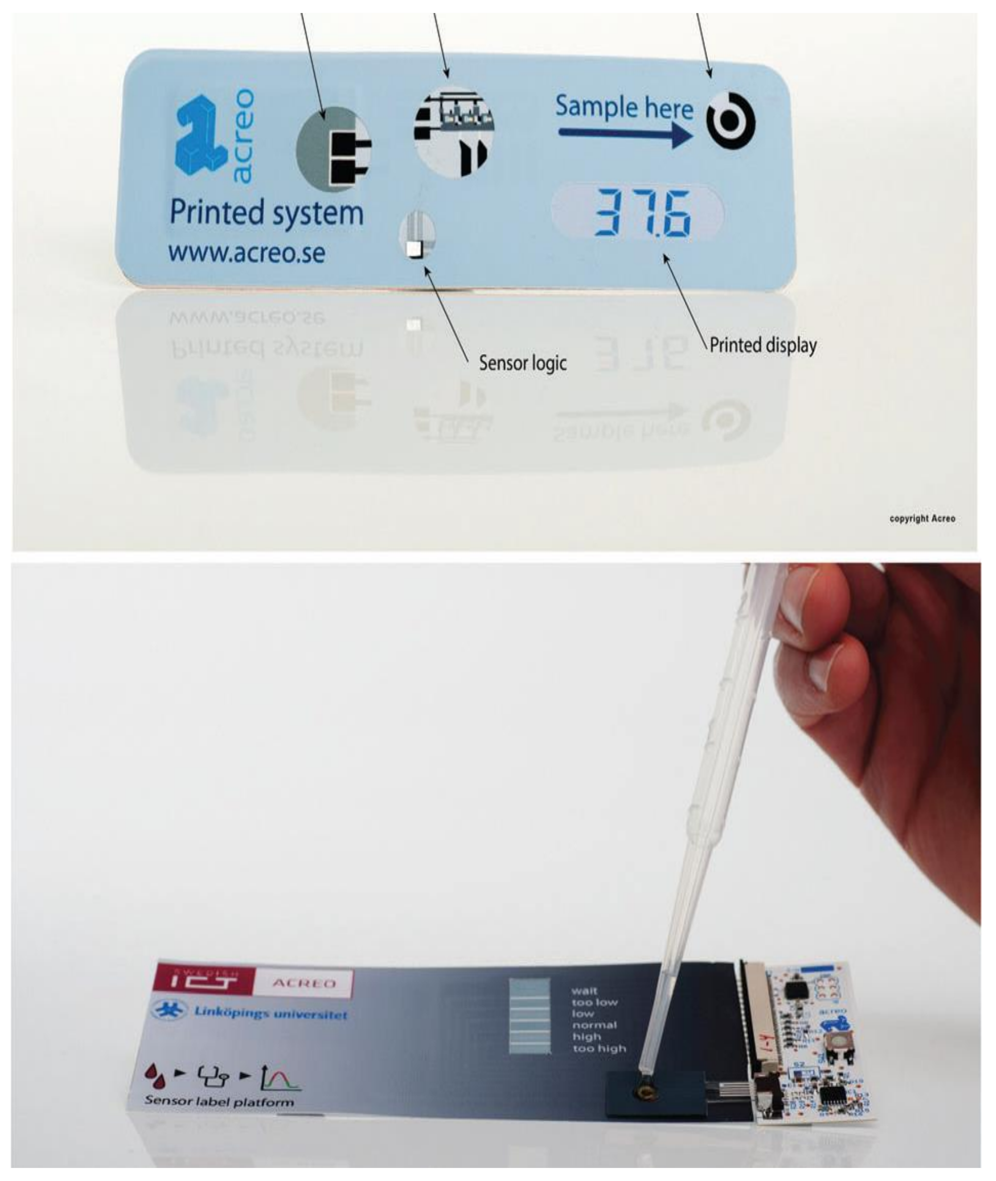
Top: shows the concept of an all-printed biosensing system, where not only is the amperometric sensor printed, but all the associated elements such as battery, display and circuitry are printed on a single sheet of PET and then laminated in an appropriate casing.

Below: shows the reality to date, a prototype functioning system resulting from collaboration between Acreo AB and Linkoping University.

Glucose concentration can be measured in a few seconds and observed via the printed display using this device, powered by a printed battery.

Rudimentary silicon circuitry can be seen to the right of the picture, but this could be readily integrated into a tiny inexpensive silicon chip.

This device is being used as a concept demonstrator to develop a range of new products, principally for medical diagnostics.



Georga, *Health and Technology*, 2014
Turner, *Chemical Society Reviews*, 2013

Biosensors for Diabetes: Continuous Glucose Monitoring

- Self-monitoring of blood glucose (SMBG) as an intermittent procedure cannot capture the temporal variations in 24-h glucose levels especially during the night when blood glucose is seldom measured.
- On the other hand, the temporal resolution of continuous glucose monitoring (CGM) offers the potential to gain a deeper insight into 24-h glucose dynamics.
- Towards this direction, the American Diabetes Association recognizes the usefulness of CGM in type 1 diabetes and recommends that "CGM may be a supplemental tool to SMBG in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes" .

Georga, *Health and Technology*, 2014
Wang, *Chemical Reviews*, 2008

Biosensors for Diabetes: Continuous Glucose Monitoring

- Most of the recent attention regarding real-time in-vivo monitoring has been given to the development of subcutaneously implantable needle-type electrodes.
- Such devices track blood glucose levels by measuring the glucose concentration in the interstitial fluid of the subcutaneous tissue (assuming the ratio of the blood/tissue levels is constant).
- Subcutaneously implantable devices are commonly designed to operate for a few days, after which they are replaced by the patient.
- They are commonly inserted into the subcutaneous tissue in the abdomen or upper arm.

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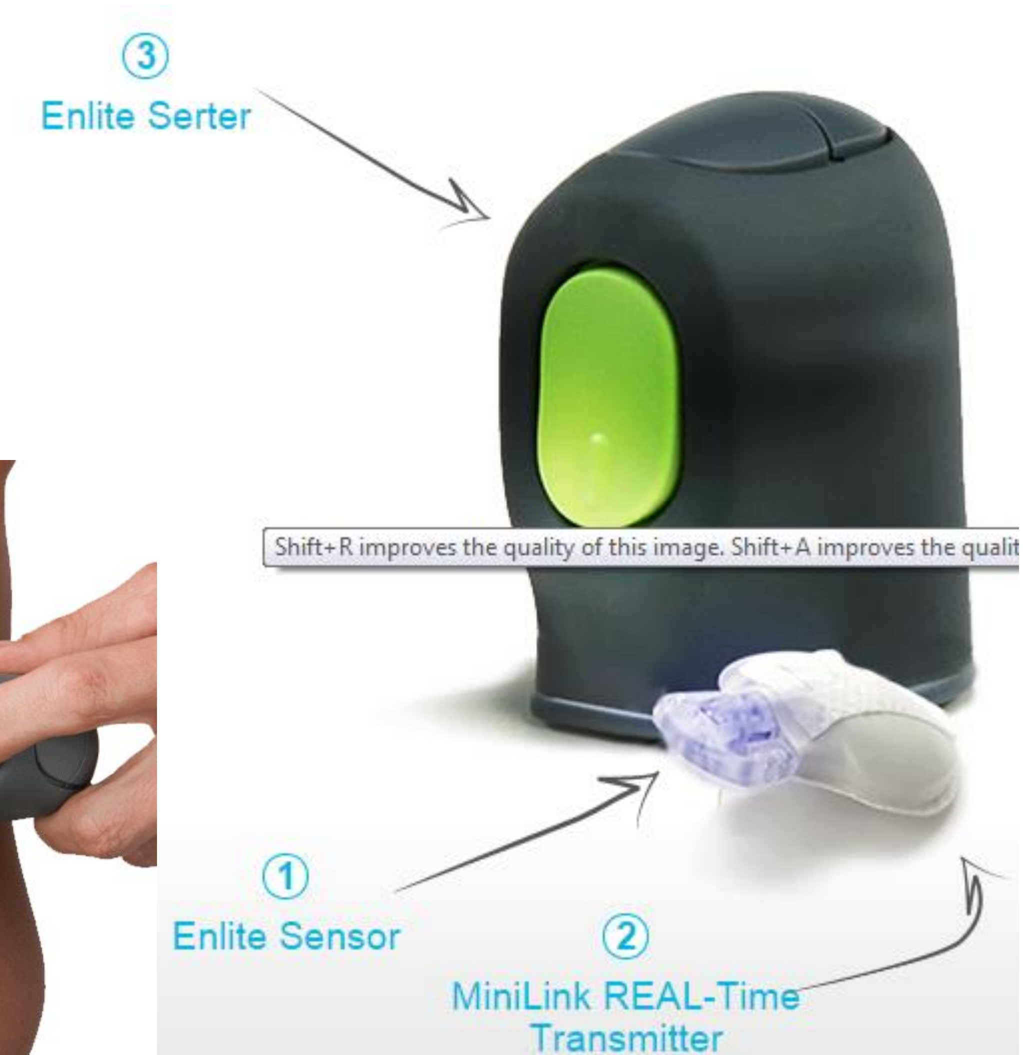
Georga, *Health and Technology*, 2014
Wang, *Chemical Reviews*, 2008

Medtronic Enlite Sensor

The CGMS unit of Medtronic Minimed Inc. offers a 72 h period of subcutaneous monitoring with measurement of tissue glucose every 5 min.

Calibration is required 3–4 times a day for optimal sensor accuracy.



http://www.medtronicdiabetes.net/

Medtronic Guardian® REAL-Time CGM System

The Guardian REAL-Time inform patients in real-time on their sub-cutaneous glucose levels, trends and rate of change enabling real-time decisions to be taken by patients themselves.

http://www.medtronicdiabetes.net/

Biosensors for Diabetes: Continuous Glucose Monitoring

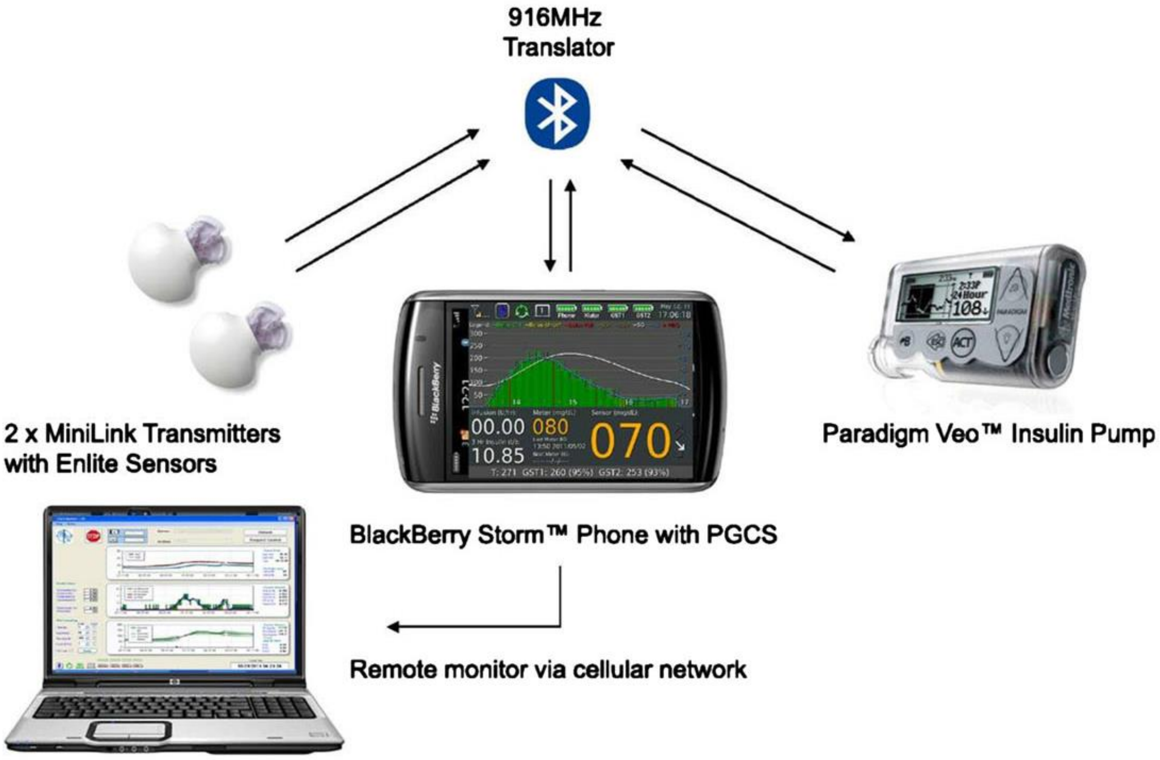
- Success in this direction has reached the level of short-term human implantation; continuously functioning devices, possessing adequate (>1 week) stability, are expected in the very near future.
- Such devices would enable a swift and appropriate corrective action through use of a closed-loop insulin delivery system, i.e., artificial pancreas.
- A closed-loop artificial pancreas should ideally provide 24-h automatic control of insulin delivery with the aim of achieving tight glucose control and minimizing the risk of hypoglycemia.
    - The realization of that idea is predictably gradual with overnight closed-loop delivery being at its infancy.

Georga, *Health and Technology*, 2014
Wang, *Chemical Reviews*, 2008

Modern Approaches to Closed-Loop Systems

The generic architecture of such systems includes a CGM system, an insulin pump, a mobile phone with the insulin controller embedded, and a remote web-based application.

The Medtronic Portable Glucose Control System utilizes two glucose sensors for more safe decisions.



Georga, *Health and Technology*, 2014

Biosensors for Diabetes: Toward Noninvasive Glucose Monitoring

- Noninvasive methods are preferable to invasive techniques, provided that they do not compromise the clinical accuracy.
- Such ability to measure glucose noninvasively will thus revolutionize the treatment of diabetes.
- This approach has been directed toward glucose measurements in saliva, tears, or sweat.
- Other routes for “collecting” the glucose through the skin and for noninvasive glucose testing are currently being examined by various groups and companies.
    - Most of these approaches rely on optical detection.

Wang, *Chemical Reviews*, 2008

Biosensors for Diabetes: GlucoWise

- GlucoWise™ technology enables the blood glucose concentration to be measured at the capillary level.
- The glucose levels are extracted by a non-invasive technique which transmits low-power radio waves through a section of the human body, such as the area between the thumb and forefinger or the earlobe.
- These areas have adequate blood supply and are thin enough for waves to pass through the tissue.
- These signals are then received by a sensor on the opposite side of the GlucoWise device, where the data about the characteristics of the blood within the flesh are collected and analyzed.
- GlucoWise™ is currently in development and will be available to purchase once clinical trials are completed (in late 2016).

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http://www.gluco-wise.com/

Biosensors for Diabetes

- The enormous activity in the field of glucose biosensors is a reflection of the major clinical importance of the topic.
- Such huge demands for effective management of diabetes have made the disease a model in developing novel approaches for biosensors.
- The success of blood glucose meters has stimulated considerable interest in in-vitro and in-vivo devices for monitoring other physiologically important compounds.
- Similarly, new materials (membranes, mediators, electrocatalysts, etc.) and concepts, developed originally for enhancing glucose biosensors, now benefit a wide range of sensing applications.

Wang, *Chemical Reviews*, 2008

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