ELECTRONICS Design Division

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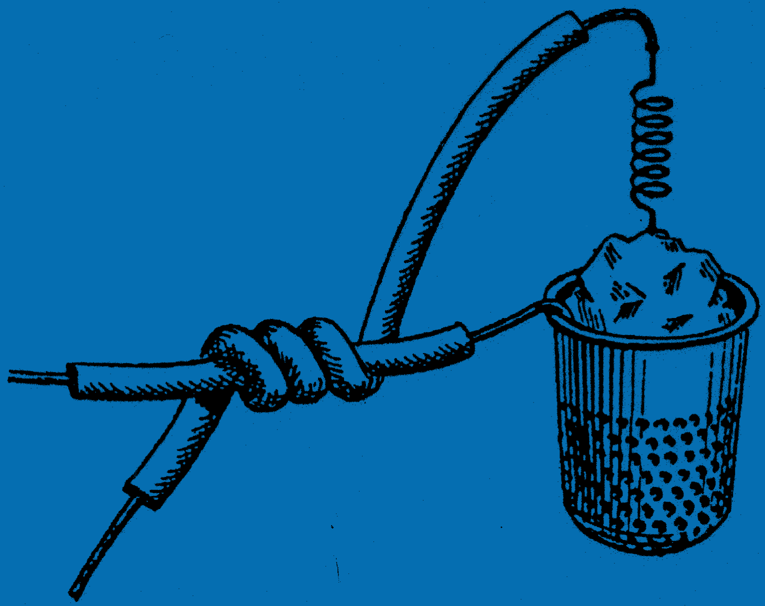
Sensor devices

Biosensors



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Outline

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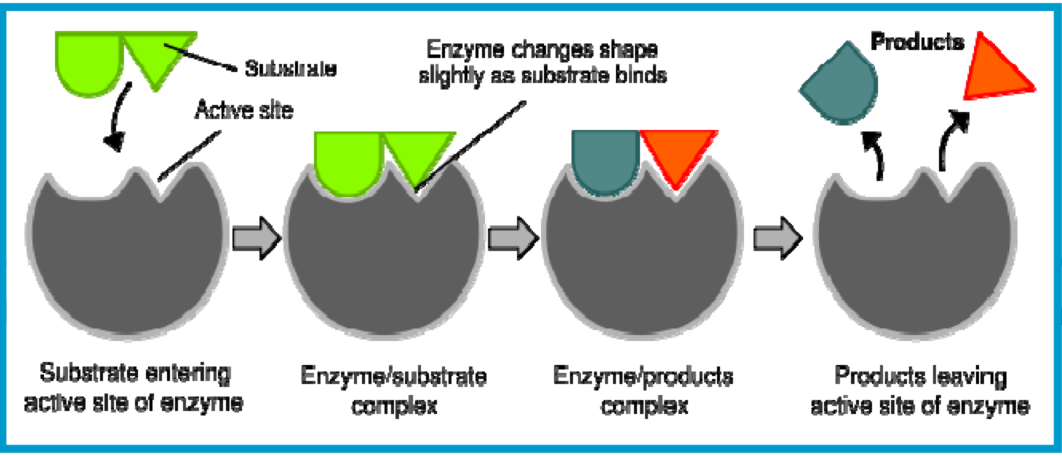
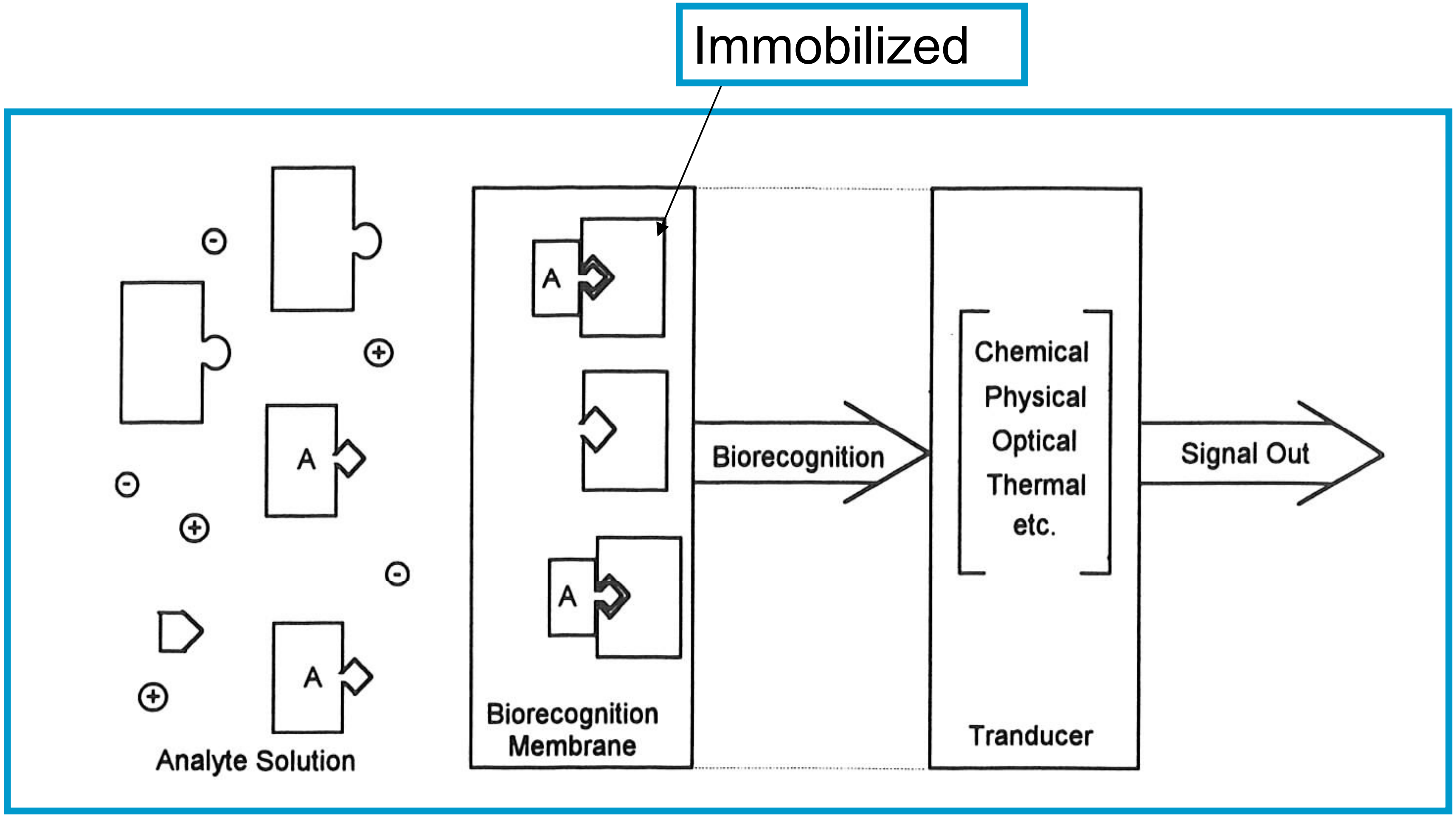
- 9 Biosensors
  - Introduction
  - Immobilization of biological elements
  - Mass transport in Biosensor
  - Transduction Principles
  - Some examples
- 10 Integrated Sensors

Introduction

- Biosensors are a special class of chemical sensors that take advantage of the high selectivity and sensitivity of biologically active materials
- Bio-affinity, strong binding, transducer must detect receptor-analyte pair
- Bio-metabolic, analyte and co-reactant form a product molecules, which the transducer must detect, resulting in a change in concentrations of the products or co-reactant



Introduction



Introduction

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TABLE 1 Classes of Recognizable Biological Chemicals and Some Examples

Analyte	Examples
Metabolic chemicals	Oxygen, methane, ethanol, other nutrients
Enzyme substrates	Glucose, penicillin, urea
Ligands	Neurotransmitters, hormones, pheromones, toxins
Antigens and antibodies	Human Ig, anti-human Ig
Nucleic acids	DNA, RNA

Introduction

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TABLE 2 Biosensor Components

Biological Elements	Transducer Type	Transcucer Example
Organisms	Electrochemical:	
Tissues	a. Potentiometric	Ion selective field-effect transistors and micro-electrodes
Cells		
Organelles	b. Amperometric	Micro-electrodes
Membranes	c. Impedometric	Micro-electrodes
Enzymes	Optical	Fiber optodes and luminescence
Receptors	Calorimetry (thermal)	Thermistors and thermocouples
Antibodies	Acoustic (mass)	Surface acoustic wave delay-lines and bulk acoustic wave microbalances
Nucleic Acids		

A biosensor consists of a biological sensing element (column one) plus a transducer (column two). Examples of specific transducers are given in column three next to the transduction principle.

Introduction

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- Recognition elements
  - Whole organism down to molecules
  - For organic material like cells, organelles and tissues, the problem is to keep them alive
  - Enzyme are proteins, which catalyst the reaction i.e. lower the activation energy
  - Enzymes catalytic activity are strongly depended of the environment condition. For example the pH-level

Introduction

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- Biomimetic structures
  - Artificial structures that are built up to mimic the processes that occur in the cell membranes
  - Receptor can recognise molecules end then change the permeability in the membrane.

Immobilization of biological elements

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- The immobilization process should:
  - Confine the biologically active material on the transducer
  - Allow contact to the analyte solution
  - Reaction products to diffuse out from the immobilization layer
  - Not denature the biologically active material
    - **Mechanical damage**
    - **Heat or freezing**
    - **Chemical toxin**
    - **etc**

Immobilization of biological elements

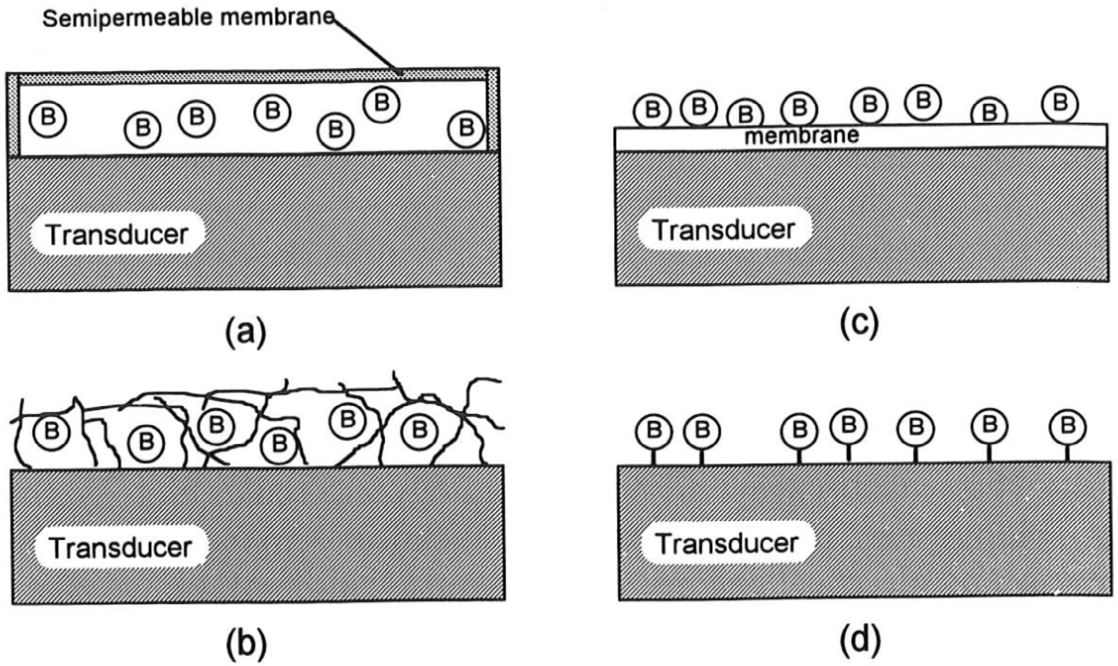

Fig. 5 The four different immobilization schemes: (a) membrane confinement, (b) matrix entrapment, (c) physical adsorption and (d) covalent bonding. "B" stands for the biologically active material, which can include antibodies, enzymes, receptors, organelles, cells, tissues, and organisms.

Mass transport in Biosensor

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- Analyte transport into the membrane
- Transport of reaction products to the transducer
- Transport of products out of membrane
- Similar theory as for diffusion in semiconductor
- Concentration profile for a species can be described by:

$$C(x,t) = C_{\text{bulk}} \operatorname{erf}\left(\frac{x}{2\sqrt{Dt}}\right).$$

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Transduction Principles

- Electrochemical
  - Potentiometric
    - Measuring a potential (voltage) across an electrochemical cell “battery!” containing biological sensing element
  - Amperiometric
    - Measuring a current from an electrochemical cell, the current oxidise or reduce the analyte
  - Impediometric
    - Measuring impedance frequency response

Transduction Principles

- Optical
  - Optical absorption or emission of a molecule or molecules
  - Absorption in infrared to ultraviolet
  - Emission, Fluorescence by x-ray spectroscopy
  - Direct method
    - » **Optical absorption when analyte binds to the receptor**
  - Indirect method
    - » **Two competing reaction**
    - » **1. analyte binds to receptor**
    - » **2. "analog" binds to receptor which emits photons after excitations**

Transduction Principles

- Thermal
  - Measuring the enthalpy of the detected reaction
    - – **TRANSDUCER**
      - » **Thermistor**
      - » **Thermocouples**
      - » **Change in temperatures down to 0.0001 C can be detected**
- Mass
  - Analyte molecules are adsorbed on mechanical resonator. The change in mass result in change of resonance frequency (lower picture)

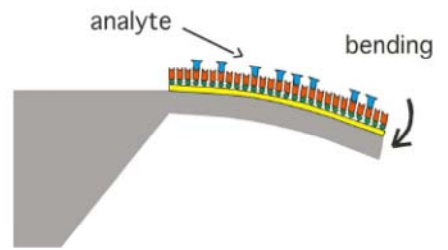

Figure 1: Bending of a static microcantilever due to analyte binding

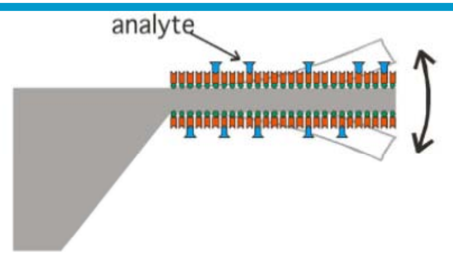

Figure 2: Resonant operation of the microcantilever

Transduction Principles, SAW

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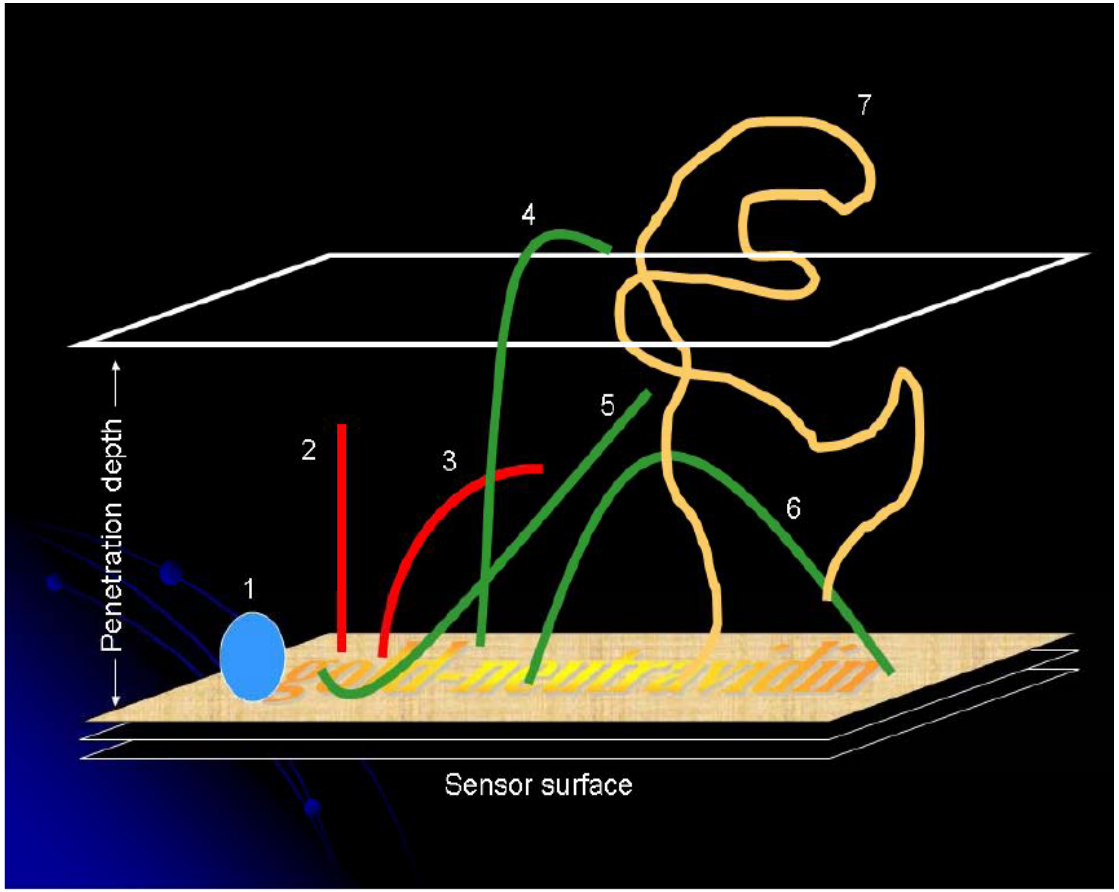

Shape of adsorbed bio-molecule have a large influence on change in surface velocity of an SAW transducer

Some examples

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Bacterial luciferase (Lux): Luciferase is a generic name for an enzyme that catalyzes a light-emitting reaction. Luciferases can be found in bacteria, algae, fungi, jellyfish, insects, shrimp, and squid, and the resulting light that these organisms produce is termed bioluminescence. In bacteria, the genes responsible for the light-emitting reaction (the *lux* genes) have been isolated and used extensively in the construction of bioreporters that emit a blue-green light with a maximum intensity at 490 nm (Figure 2)[2]. Three variants of *lux* are available, one that functions at < 30ºC, another at < 37ºC, and a third at < 45ºC. The *lux* genetic system consists of five genes, *luxA*, *luxB*, *luxC*, *luxD*, and *luxE*. Depending on the combination of these genes used, several different types of bioluminescent bioreporters can be constructed.

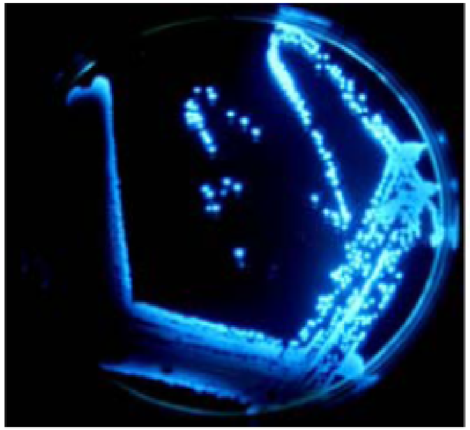
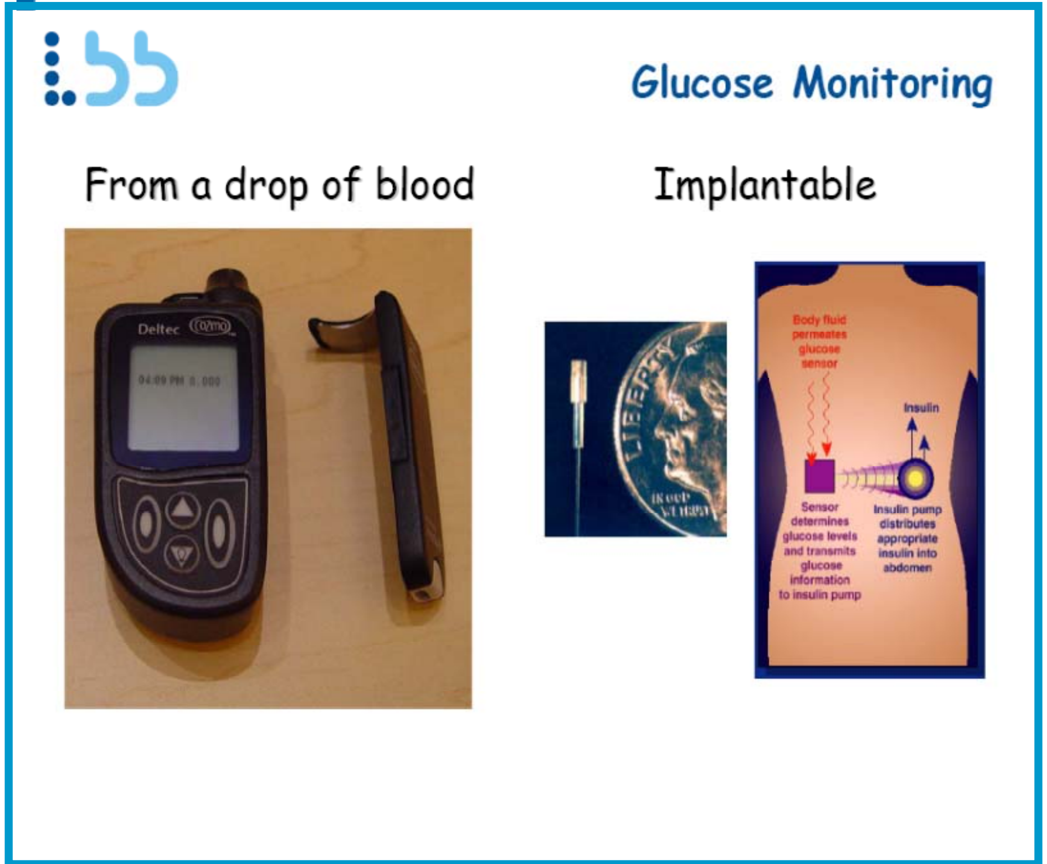


Figure 2. Bioluminescence emitted from individual colonies of microbial cells containing the genes for bacterial luciferase.

Some examples



$$\text{Glucose} + O_2 + H_2O \xrightarrow{\text{Enzyme}} \text{Gluconic acid} + H_2O_2$$

measurement routes:

1. pH change (acid production)
2. O_2 consumption (fluorophore monitor)
3. H_2O_2 production (electrochemical)

Integrated Sensors

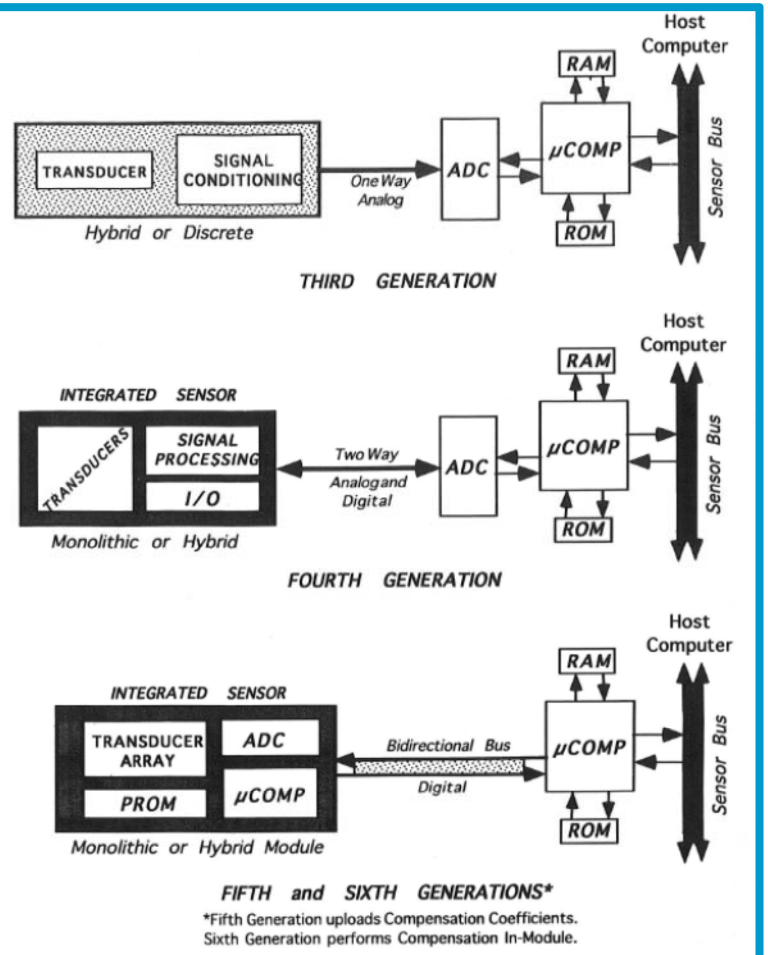


Fig. 2 Evolution of sensor interface from third to sixth generations. (After Refs. 6, 9)

Solid State Sensor Evolution

1. Gen. No electronics in sensor
2. Gen. Amplification and temperature comp.
3. Gen. Amplification and buffering as discrete or hybride
4. Gen. Higher level of integration, some of the electronics integrated on the sensor chip
5. Gen. ADC is performed at the sensor.
6. Gen. Compensation is done in the integrated sensor

Integrated Sensors

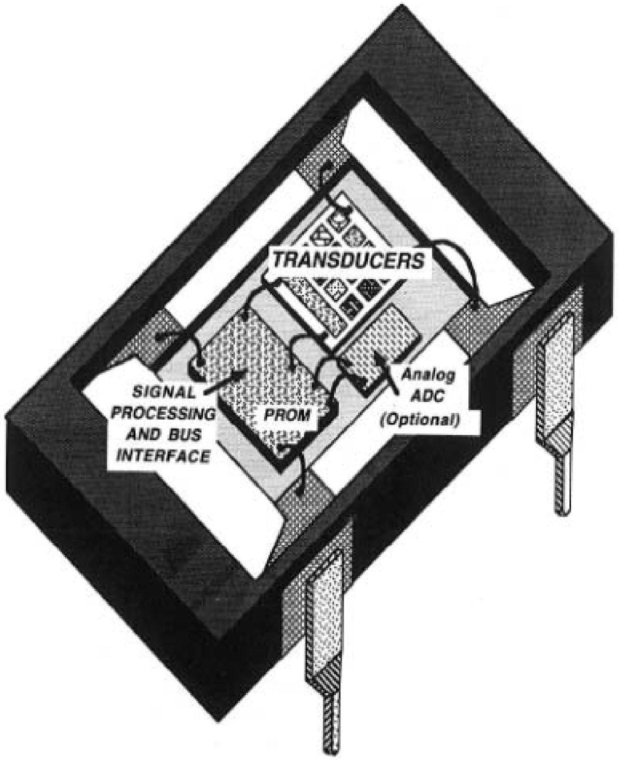
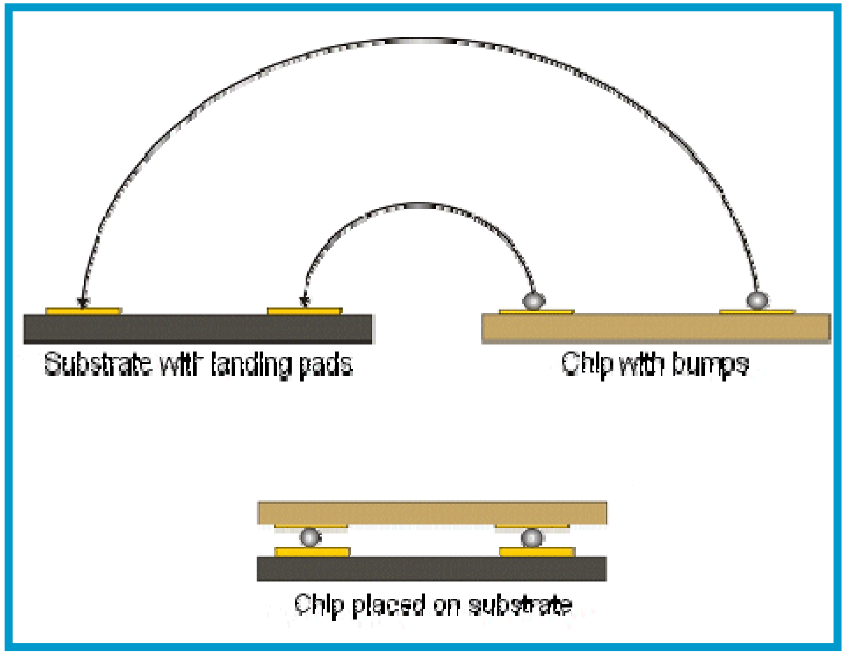


Fig. 6 Schematic representation of a "fifth-generation" hybrid sensing node. (After Refs. 6, 9)

Hybride mounting of a sensor, using wire bondning

Integrated Sensors



Flip chip bonding, sensor chip and electronic chip connected using metallic bumps

Integrated Sensors

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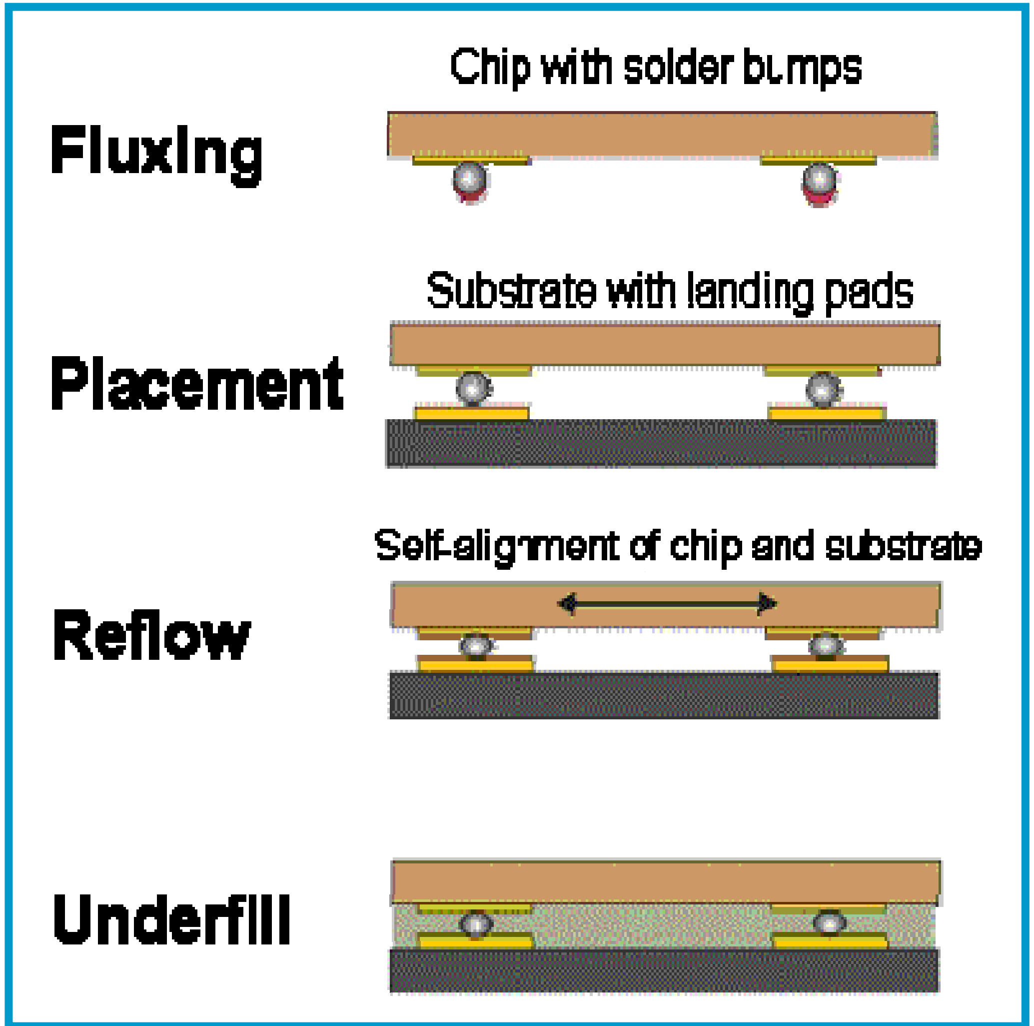

Flip chip boning procedure

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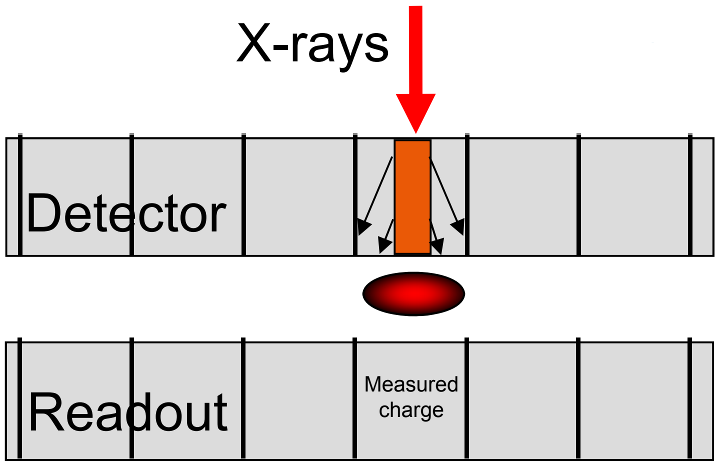
Medipix

A pixellated photon counting readout chip

- One readout circuit per pixel

A pixellated X-ray sensor diode array

Detector matrix bump bonded to the readout chip



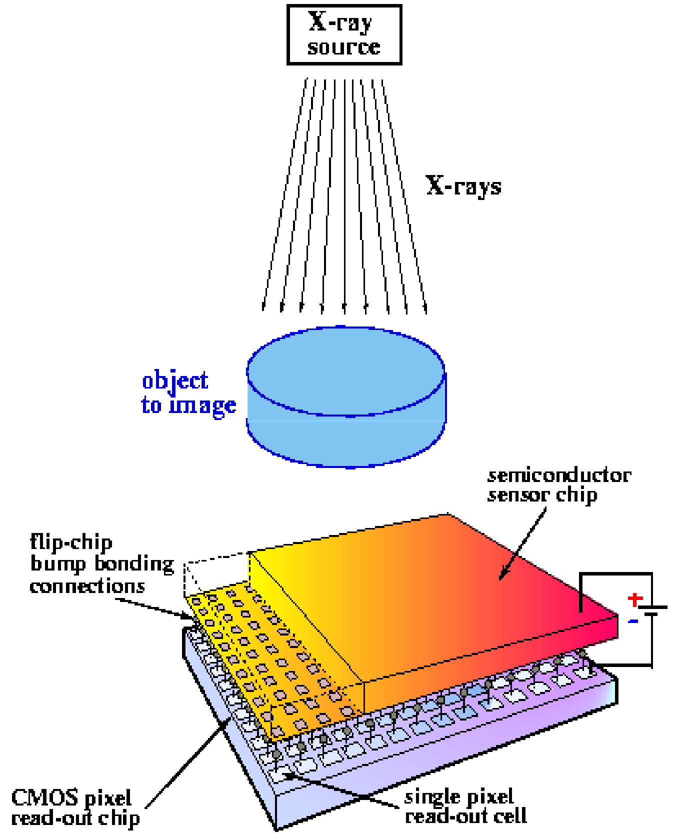


Illustration from http://medipix.web.cern.ch/MEDIPIX/

Medipix

Readout in 55x55 µm size

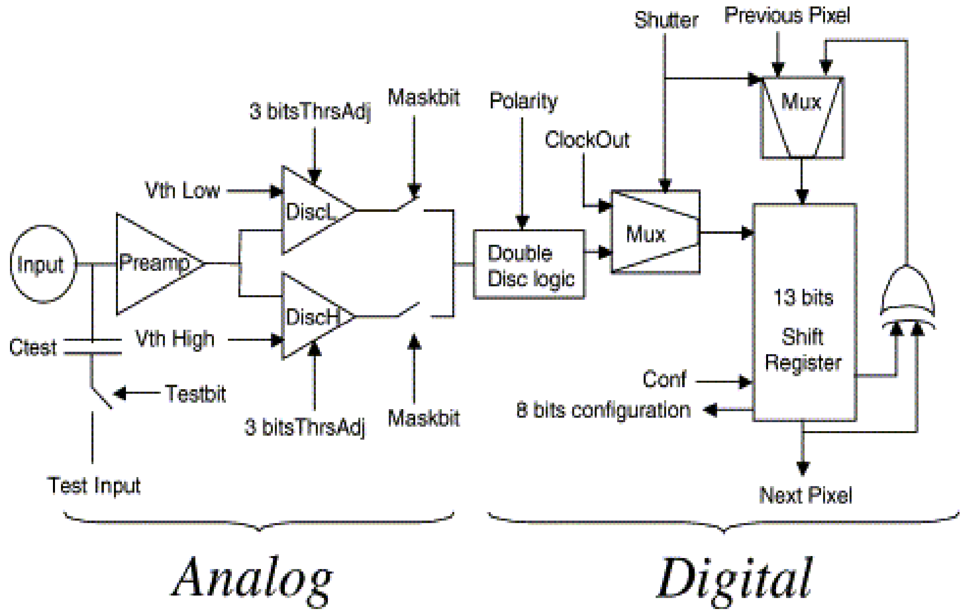
- 0.25 µm CMOS technology for Medipix 2
- 0.13 µm for Medipix 3

– A low and a high threshold is set

– If the charge is between the threshold values the counter is increased one value

– A picture matrix with the number of “correct energy” photons for each pixel is achieved

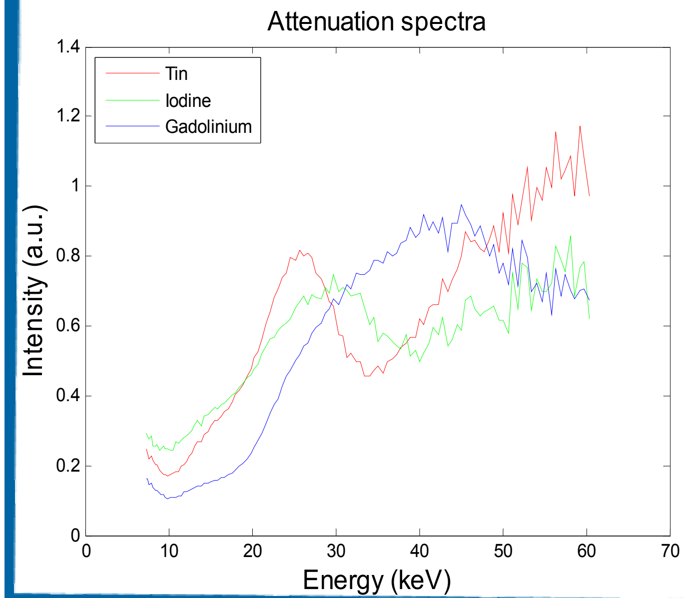
– In this way energy resolved X-ray images are created

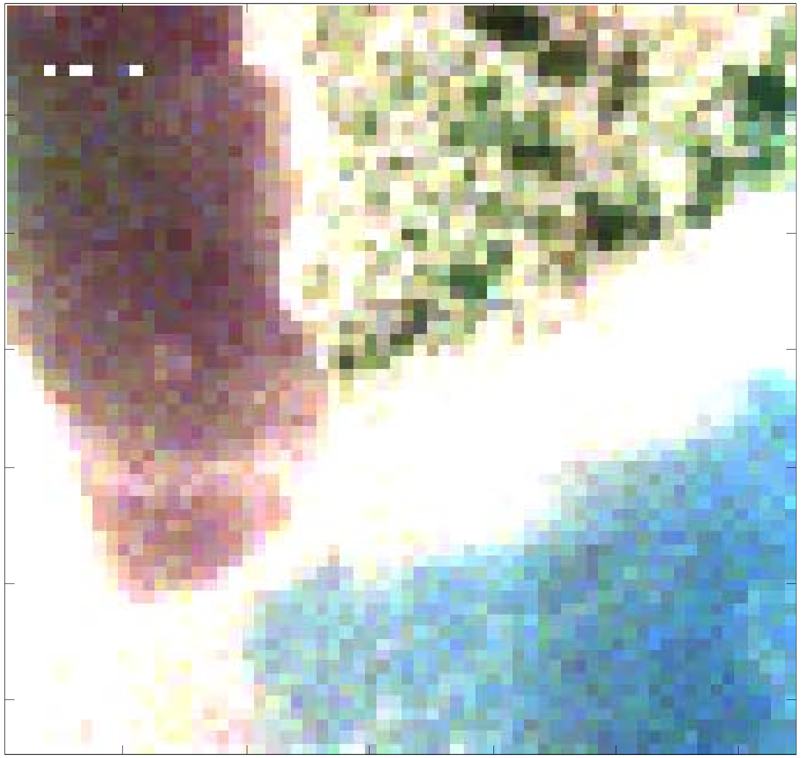


Medipix 2 readout scheme

Medipix

- Energy resolved X-ray image
  - Samples of Tin, Iodine and Gadolinium
  - Medical tracer applications etc.





Test sample	K-edge	Transmission	Energy range
Tin	29.2	Red	21 -28
Iodine	33.2	Green	28 -37
Gadolinium	50.2	Blue	37 -45