Overview, history & types of biosensors

Introductory Week

Faculty: Dr. Javed H. Niazi KM
Faculty of Engineering & Natural Sciences
Sabanci University
Topics that will be covered in the course

- History of biosensor development, applications and requirements of biosensors and classification
- Principles of molecular recognition and transduction signal acquisition
  - Sources of Biological Recognition elements – enzymes/proteins, ssDNAs, antibody and Others
  - Design considerations for use of recognition elements in biosensors
  - Modeling of reactions for various biosensor applications- electrochemical, optical, piezoelectric, colorimetric, fluorometric and others.
- Modification of sensor surfaces and immobilization techniques
  - Covalent modification of surfaces using surface chemistry
  - Self Assembled Monolayers (SAM) and adsorptions
  - Other ways to immobilize biological macromolecules on various solid surfaces
- Detection methods and Physical Sensors
  - Electrodes/transducers – electrochemical (amperometric, potentiometric, and conductimetric transductions)
  - Other sensors - for e.g., optical sensors (colorimetric/fluorimetric/luminometric sensors), Surface Plasmon Resonance (SPR) sensors, and piezoelectric resonators.
- Fabrication of biosensors
  - Miniaturization-application of nano-materials, nanoparticles, carbon nanotubes (CNTs) and others
  - Biocompatibility – stability, reproducibility and repeatability of biomolecules on transducer surfaces
- Data acquisition, statistical and error analysis
  - Inter and Intra-assays and Coefficient of variation (CV)
  - Signal to noise ratio
  - Normalization/optimization and signal retrieval
- Examples of commercial biosensors
Biosensors - combines multiple disciplines

- **Chemistry**
  - Synthetic bioreceptor
  - Electrode material
  - Polymers
  - Disposable
  - Membranes
  - Immobilization

- **Physics**
  - Optics
  - Semiconductor

- **Biology**
  - Biorecognition molecule
  - Protein engineering
  - Receptor technology
  - DNA

- **Electronics**
  - Opto electronics
  - Silicon technology
  - Data processing
  - Control

- **Instrumentation**
  - Portable
  - Microinstrumentation

- **Market opportunity**
  - On-line
  - In-vivo implantable

- **Molecular electronics**
  - Bioelectronic?
  - Molecular electronic device

**Bio-Chem** | **Bio-Electronics** | **Micro-Electronics**
**Biosensing**

**Bio-recognition elements**
- Biomolecules on sensor surface

**Transducers**
- Capacitance/Voltage controlled oscillator

**Sensor surface**
- Electrode
  - Interdigitated array chip
  - Metal surface - gold, platinum
  - Glass
  - Silicon &/or dioxide
  - Whole cells

**Detection System**
- Electrochemical - amperometric, potentiometric, conductimetric
- Optical - SPR, fibre-optic, interferometric
- Colorimetric/Fluorimetric - Color change, fluorescence, luminos
- Piezoelectric
- Microbalance - QCM, cantilevers
- Capacitive/impedance spectroscopy

**Apply Pretreated Sample**

**Signal Output**

- Antibodies/antigens (immunosensors)
- Enzymes/receptors (any other protein)
- Whole microbial/animal cells
- Small organic molecules
- Nanoparticles
- Unlimited types of other molecules

- Electrodes (metal-Au, Ag, Pt, Ni, Cu)
- Device that measure light intensity/RI
- Spectrophotometric
- Digital read out - current change
- Photomultiplier tubes, CMOS, CCDs etc.
History of biosensors

Clarks electrode - glucose biosensor

The first and the most widely used commercial biosensor: the blood glucose biosensor - Developed by Leland C. Clark in 1962

Examine solution

Glucose + O₂ → Gluconic Acid + H₂O₂

PT

H₂O₂ * 0.6 V vs. SHE → 2H⁺ + O₂ + 2 e⁻

Substrates:
- Ethanol
- Glucose
- Glycerol

Products:
- Acetaldehyde
- Gluconic acid
- Dihydroxyacetone

Enzymes:
- ox₁
- red₂
- PQQ-ADH
- PQQ-GDH
- PQQ-GlyDH

Graphite electrode

Biocatalytic film of the redox polymer with immobilized enzymes

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

Leland Clark Jr.

Number of articles published
## History of biosensors

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Year</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1916</td>
<td>First report on the immobilization of proteins: adsorption of invertase on activated charcoal -Nelson and Griffin</td>
</tr>
<tr>
<td>2</td>
<td>1922</td>
<td>First glass pH electrode</td>
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<tr>
<td>3</td>
<td>1956</td>
<td>Invention of the oxygen electrode (Clark)</td>
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<td>4</td>
<td>1962</td>
<td>First description of a biosensor: an amperometric enzyme electrode for glucose (Clark)</td>
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<tr>
<td>5</td>
<td>1969</td>
<td>First potentiometric biosensor: urease immobilized on an ammonia electrode to detect urea</td>
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<tr>
<td>6</td>
<td>1970</td>
<td>Invention of the Ion-Selective Field-Effect Transistor (ISFET) (Bergveld)</td>
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<tr>
<td>7</td>
<td>1972/5</td>
<td>First commercial biosensor: Yellow Springs Instruments glucose biosensor (pen shaped single use electrode)</td>
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<tr>
<td>8</td>
<td>1975</td>
<td>First microbe-based biosensor</td>
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<td></td>
<td></td>
<td>First immunosensor: ovalbumin on a platinum wire</td>
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<td></td>
<td>Invention of the pO2/pCO2 optode (fluorescence signal &amp; gas permeable membrane usage)</td>
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<td>9</td>
<td>1976</td>
<td>First bedside artificial pancreas (Miles)</td>
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<td>10</td>
<td>1980</td>
<td>First fibre optic pH sensor for in vivo blood gases (Peterson)</td>
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<tr>
<td>11</td>
<td>1982</td>
<td>First fibre optic-based biosensor for glucose</td>
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<tr>
<td>12</td>
<td>1983</td>
<td>First surface plasmon resonance (SPR) immunosensor</td>
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<tr>
<td>13</td>
<td>1984</td>
<td>First mediated amperometric biosensor: ferrocene used with glucose oxidase for the detection of glucose</td>
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<tr>
<td>14</td>
<td>1987</td>
<td>Launch of the MediSense ExacTech™ blood glucose biosensor (strips/pen model and disposable)</td>
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<td>15</td>
<td>1990</td>
<td>Launch of the Pharmacia BIACore SPR-based biosensor system</td>
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<tr>
<td>16</td>
<td>1992</td>
<td>i-STAT launches hand-held blood analyser</td>
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<tr>
<td>17</td>
<td>1996</td>
<td>Glucocard launched</td>
</tr>
<tr>
<td>18</td>
<td>1996</td>
<td>Abbott acquires MediSense for $867 million</td>
</tr>
<tr>
<td>19</td>
<td>1998</td>
<td>Launch of LifeScan FastTake blood glucose biosensor</td>
</tr>
<tr>
<td>20</td>
<td>1998</td>
<td>Merger of Roche and Boehringer Mannheim to form Roche Diagnostics</td>
</tr>
<tr>
<td>21</td>
<td>2001</td>
<td>LifeScan purchases Inverness Medical's glucose testing business for $1.3billion</td>
</tr>
<tr>
<td>22</td>
<td>1999 to now</td>
<td>BioNMES, Quantum dots, Nanoparticles, Nanocantilever, Nanowire and Nanotube</td>
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</tbody>
</table>
Status of merging interdisciplinary areas toward miniaturization
Bioreceptors

Transducer

Amplifier

Microelectronics

Interfering molecules

Sample analyte

Immobilized enzymes, receptors, immunoagents, DNA, whole cells

Electrochemical:
- Potentiometric
- Amperometric
- Conductimetric

Optical:
- Adsorption
- Fluorescence
- Reflection
- Luminoscence
- Piezoelectric

Signal

Data processing

Working principle of biosensors

Generalized scheme of biosensors

CO₂

CO₂

NO₂

PER

glucose,

Species to be detected

Filter

Recognition level (Sensor)

Transducer

Electronics

Electrical Signal
Classification scheme for different types of sensors

- SENSORS
  - PHYSICAL SENSORS
  - INTERFACE
  - CHEMICAL SENSORS
  - BIOSENSORS
An overview of a biosensor components

**Bioreceptor**
- Caltalytic (steady state)
- Enzyme
- Whole cells
- Affinity (equilibrium)
- Antigen/antibody
- DNA
- Others

**Transducers**
- Electrochemical
  - Amperometric
  - Potentiometric
  - Conductometric
  - Others
- Piezoelectric
- Thermometric
- Optical
  - Fluorescence
  - SPR
  - Colorimetric
  - Others

**Immobilization**
- Chemical - covalent, crosslinking
- Physical - adsorption, entrappment, confining, encapsulation

**Biosensor**

**User end**
- Medical & health - disease risk
- Food contaminants
- Toxins - water, food
- Pharmaceuticals
- Environment
- Others
Biosensors

Based on mode/transducers

Electrochemical
- Amperometry
- Potentiometry
- Voltammetry
- Conductometry
- Field-effect transistors (surface charge)

Optical
- Colorimetric (NP, QDs)
- Fluorimetric (fluorescent chemicals)
- Luminometric (chemo/bio)
- RI (SPR, interferometer, resonant mirror)
- Fibre-optic

Piezoelectric
- QCM
- Cantilever
- Ultrasonic
- Acoustic emission
- Other actuators

Biocatalytic - enzyme, cells, tissues
Biocomplexing - Ag/Ab - immunosensor
Receptor/antagonist

Nanobiosensors

QD's
- Nanoparticles
- Nanotubes (CNTs)
- Nanowires
- Porous silicon

Classification
Electrochemical Biosensor

Electrochemistry

Where there is oxidation, there is reduction

Substance oxidized loses electron(s)
Substance reduced gains electron(s)

Conventional current flow is opposite to electron flow

to be continued...
### Table 2. Mass sensitive sensor formats

<table>
<thead>
<tr>
<th>Method</th>
<th>Schematic representation</th>
<th>Signal output</th>
<th>Principle</th>
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<tbody>
<tr>
<td>Mass sensitive aptasensors</td>
<td><img src="image" alt="Diagram A" /></td>
<td><img src="image" alt="Diagram B" /></td>
<td>A: Surface Plasmon Resonance based aptasensors — capable of registering mass changes by the associated change in refractive index at the surface.</td>
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<tr>
<td></td>
<td><img src="image" alt="Diagram B" /></td>
<td><img src="image" alt="Diagram C" /></td>
<td>B: Quartz crystal microbalance (QCM)-based aptasensors — The frequency of the quartz crystal is controlled by changes in the mass associated with the crystal, thus the association of a target onto aptamer-modified crystals increases the mass on the transducer, resulting in a decrease in the resonance frequency of the crystal.</td>
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<tr>
<td></td>
<td><img src="image" alt="Diagram C" /></td>
<td><img src="image" alt="Diagram D" /></td>
<td>C: Surface acoustic wave (SAW)-based aptasensors — When mass is loaded onto the surface of these sensors, the propagation velocity of acoustic waves decreases, resulting in a reduction of resonance frequency or in alteration of the phase shift between output and input signals.</td>
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<tr>
<td></td>
<td><img src="image" alt="Diagram D" /></td>
<td></td>
<td>D: Micromechanical cantilever-based aptasensors — binding of target to aptamer immobilized cantilever induces a change in surface stress that causes a differential cantilever bending in the range 3–32 nm, depending on aptamer concentration.</td>
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