Chapter 7

Bioreceptors

GABRIEL GOMES DE OLIVEIRA, VENKATESAN RAJINIKANTH, YUZO IANO, RANGEL ARTHUR, AND NAVID RAZMJOOY

A biosensor consists of a biological recognition site, a transducer, and an electronic system that has a signal amplifier, a processor, and a display. Transducers and electronics are combined CMOS microsensor systems [1, 2, 3]. The biological recognition component, called a bioreceptor, uses biomolecules from organisms or receptors modeled after biological systems to interact with the analyte of interest. This interaction is measured by a transducer, which returns an output signal proportional to the presence of the target analyte in the sample. The general objective in the development of a biosensor is enabling a quick test in some place or some sample obtained [4, 5, 6].

7.1 Concepts

In a biosensor, a bioreceptor is designed to interact with a specific analyte of interest, producing an effect that can be measured by the transducer. High selectivity for a given analyte present in a matrix with other chemical or biological compounds is a key requirement of a bioreceptor. The types of biomolecules that can be used are wide, and biosensors can be classified according to the type of interactions that occur with the bioreceptor: antibody/antigen [7, 8, 9], enzymes/ligands, nucleic acids/DNA, cell structures/cells, or biomimetic materials [10, 11, 12].

7.1.1 Antibody/Antigen Interactions

An immunosensor utilizes the high specificity binding capacity of antibodies for a particular compound or antigen. The specific nature of antibody-antigen interactions is analogous to the lock-key idea, i.e., the antigen will only bind to the antibody if its conformation is correct. The binding processes result in physico-chemical changes that, in combination with a marker such as fluorescent molecules, enzymes, or radioisotopes, can generate a response signal.

When using antibodies as sensors, some limitations arise:

- The binding capacity of the antibody strongly depends on the conditions of the medium in which it is inserted;
- Antibody-antigen interactions are irreversible. it can only be broken by chaotropic reagents, organic solvents, or even by ultrasonic radiation [13].

7.1.2 Artificial Proteins

The use of antibodies as a recognition element has several drawbacks. They have high molecular weight and limited stability, contain disulfide bonds, and are costly to produce. To overcome these limitations, fragments of recombinant ligands (Fab, Fv, or scFv) or domains (VH, VHH) of antibodies were designed [13, 14, 15, 16, 17, 18]. In other approaches, small protein structures with favorable biophysical properties have been developed to generate artificial families of antigens or antigen-binding proteins (agBP), capable of forming a specific binding with different target proteins while maintaining the properties of the parent molecules. Family members that specifically bind to a given target antigen are selected by in vitro display techniques: phage, ribosome, yeast, or mRNA. These binding proteins are very small compared to antibodies (usually less than 100 amino acid residues), have strong stability, lack disulfide bonds, and can be expressed in low-yield cell media such as bacterial cytoplasm, in contrast to antibodies and their derivatives [19, 20, 21]. These proteins are therefore more suitable for creating biosensors [22, 23, 24].

7.1.3 Enzymatic Interactions

The high binding specificity and their catalytic activity have made the enzymes popular receptors [25, 26, 27]. Its ability to recognize the analyte can be done by several mechanisms:

- The conversion of the enzyme into the analyte to produce something detectable by the sensor;
- Detecting enzyme inhibition or activation in the analyte;
- Monitoring of changes in enzymatic properties with the analyte.

The main reasons for using enzymes as a biosensor are the ability to catalyze a wide range of reactions, the potential to detect several types of analyte groups (substrate, product, inhibitors, and modulators of catalytic activity), and suitability with various transduction methods for analyte detection.

Since enzymes are not consumed in reactions, the biosensor can be used more than once. Furthermore, the catalytic activity of the enzymes allows for low detection thresholds compared to other detection techniques. However, the useful life of the sensor is limited by the stability of the enzyme.

7.1.4 Epigenetics

There is a approach proposal that would use optical resonators to detect epigenetic modifications (e.g., DNA methylation or post-translational modifications of histones) in body fluids of patients affected by cancer or other diseases [28, 29, 30]. Photonic biosensors with ultrasensitivity are currently being developed to facilitate the detection of cancer cells in the urine of patients. Different research projects aim to develop new portable devices that use disposable, cheap, and ecological cartridges, in addition to providing simple handling, without the need for additional processing, such as washing or manipulation by specialized technicians [31, 29, 30, 32, 33].

7.1.5 Organelles

Organelles form separate compartments inside cells and function independently. Different types of organelles have different metabolic pathways and contain various enzymes to assist in these functions. The most commonly used organelles are lysosomes, chloroplasts, and mitochondria. The space-time pattern of calcium is closed concerning signaling pathways. Mitochondria effectively participate in the metabolism of calcium ions to control the function of modulating calcium-related pathway signals. Experiments have proven that mitochondria can respond to the high concentrations of calcium generated nearby, opening the calcium channel [34, 35, 36]. In this way, mitochondria can be used to detect calcium concentrations in any medium with a high degree of sensitivity. Another application of mitochondria is for the detection of water pollution, as the toxicity of detergent compounds damage cell and subcellular structure, including mitochondria. Detergents cause a swelling effect which can be measured by a change in absorbance. Some experimental data show that the rate of this change is proportional to the detergent concentration, providing a high standard of detection and high accuracy [37, 38, 39].

7.1.6 Cells

Cells can be used as receptors due to their high sensitivity to the surrounding environment and can respond to different types of stimulants. Cells tend to be attached to the surface so that they can be easily immobilized. Compared to organelles, cells are active for a longer period and their ability to reproduce makes them reusable. they are commonly used to detect global parameters such as stress conditions, toxicity, and organic derivatives. in addition, the cells can be used to monitor the effect of some drug treatments. In aquatic environments, the cells can be used to detect contaminants such as herbicides[40, 41, 42]. For this, microalgae are trapped in quartz microfiber and the fluorescence of chlorophyll (modified) by herbicides is collected at the tip of a bundle of optical fibers and transmitted to a fluorimeter. Algae are continuously produced and cultivated for this measurement purpose. Results show a limit of detection at sub-ppb levels. Other cells can be used for microbial corrosion detection [43, 44, 45], where *Pseudomonas sp.* are isolated from the surface of the corroded material and immobilized on an acetylcellulose membrane. Thus, the respiratory activity determined by oxygen consumption has a linear relationship with the concentration of sulfuric acid.

7.1.7 Tissue

Tissues are used as biosensors for the great abundance of enzymes that exist. The advantages of using these biosensors include [46, 47, 48]:

- Ease of immobilization compared to cells and organelles;
- The great activity and stability keep the enzymes in a natural environment;
- Great viability and low price;
- No need to carry out the work of extraction, centrifugation, and purification of enzymes;
- There are cofactors necessary for enzyme function
- Diversity provides a wide range of options for different purposes.

There are also some disadvantages in using tissues, such as the lack of specificity due to the interference of other enzymes and a longer response time due to the transport barrier.

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