IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A REVIEW OF BIOSENSORS AND THEIR MEDICAL APPLICATIONS

M. Vishnu Vardhan[1], Dr. P. Thimmaiah[2] and S. Khaja Hussain[3]
[1]Research Scholar, [2]Asst.Professor and [3]Research Scholar,
[1]Dept. of Electronics,
[1]S.K. University, Ananthapuramu, A.P. India

Abstract: This paper presents a concise overview of biosensors, their components, characteristics, supporting Bio sensing technologies, and mechanisms of biological recognition elements. It discusses advancements in electrochemical, optical, piezoelectric, and calorimetric-based biosensors, highlighting their principles, recent developments, and medical applications.

***Index Terms*:** Biosensors, optical biosensors Sensors, piezoelectric biosensors and Calorimetric-based biosensors etc.

1. Introduction

Biosensors are analytical devices that convert biological responses into electrical signals. They are used in applications in multiple fields, including healthcare, environmental monitoring, food safety, and biotechnology [1].

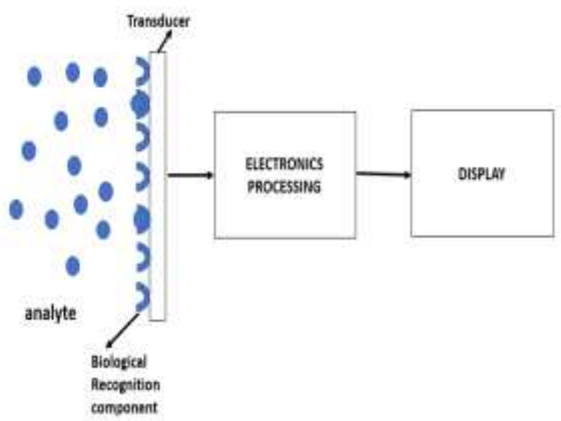

Figure 1: Block diagram & Schematic representation of a Biosensor

Biosensors typically consist of three main components:

1. **Analyte:** The substance of interest requiring detection (e.g., glucose).
2. **Biological recognition element:** A molecule recognizing the analyte, such as enzymes, cells, DNA, or antibodies.
3. **Transducer:** Converts the bio-recognition event into a measurable signal (usually optical or electrical).

The biosensor also includes electronics for signal processing, involving amplification and conversion to digital form. The processed signals are then displayed, often in a user-friendly format, using hardware and software, such as a liquid crystal display, generating numeric, graphic, tabular, or image outputs.

Materials, transducing devices, and immobilization methods fall into three categories: biocatalytic (enzymes), bio affinity (antibodies and nucleic acids), and microbe-based (microorganisms) [2].

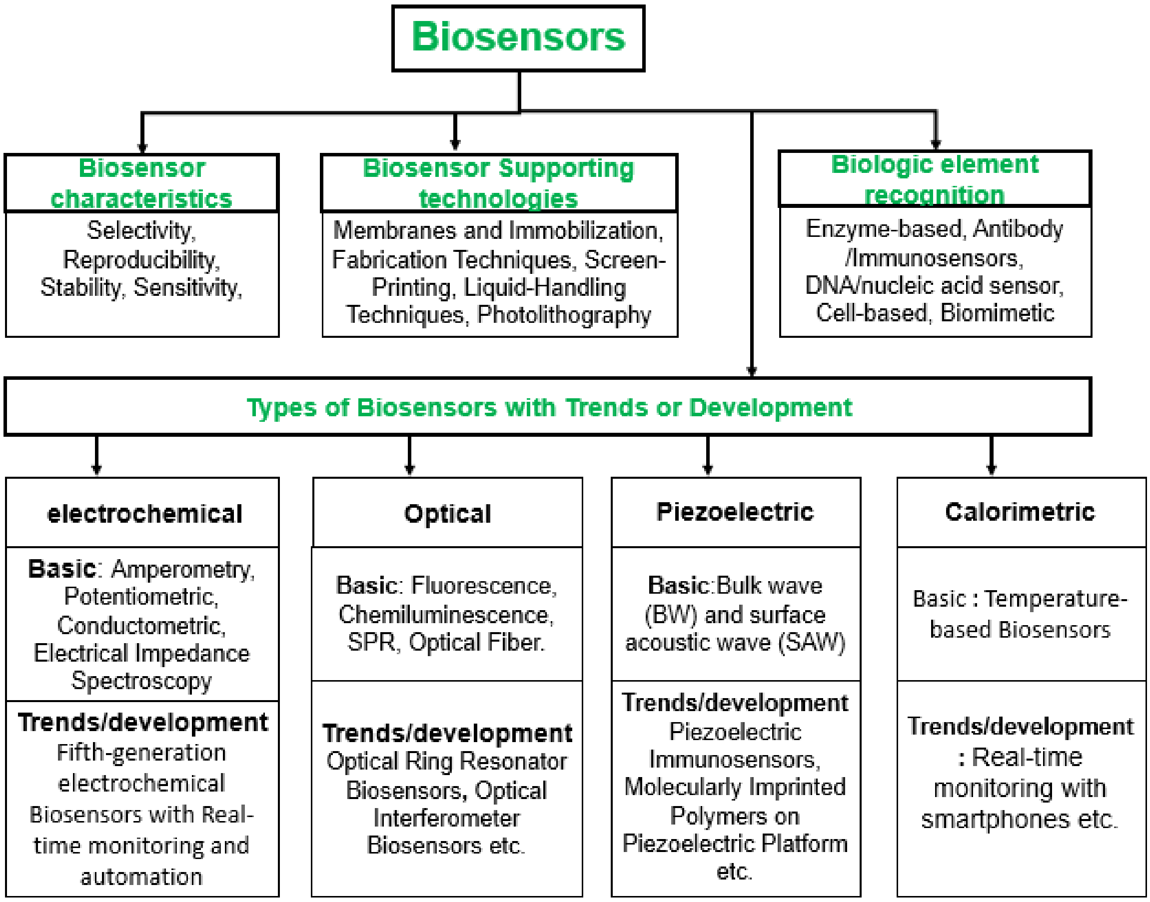

Figure 2: Different types of Biosensors with characteristics, bio recognition and supported technologies

2. Biosensor Characteristics

The following are the main characteristics of biosensors.

- **Selectivity**: The ability of a biosensor's bio receptor to specifically detect an analyte amid diverse contaminants, crucial for optimal performance.
- **Reproducibility**: The biosensor's capacity to consistently produce identical responses in duplicated experimental setups is determined by precision and accuracy.
- **Stability**: The degree to which a biosensor is resistant to ambient disturbances, essential for maintaining accuracy over time, especially in prolonged or continuous monitored applications.
- **Sensitivity**: The minimum detectable amount of analyte, defining the biosensor's limit of detection (LOD), is crucial in applications requiring the identification of trace concentrations.
- **Linearity:** The biosensor's accuracy in generating responses, is mathematically represented as $y = mc$, where y is the output signal, c is the analyte concentration, and m is sensitivity. Linearity is associated with resolution and the range of analyte concentrations under test.

3. Biosensors supporting technologies

The supporting technologies are crucial for Biosensors development and function:

- Membranes and Immobilization: Biosensors depend on interactions between a target molecule (analyte) and a receptor immobilized on a surface. Membranes allow the target to reach the receptor while blocking unwanted interferents. Immobilization techniques like covalent bonding or physical entrapment keep receptors fixed for continuous and reliable detection.

- Fabrication Technologies: Methods like thin-film deposition, etching, and micromachining are used to construct the biosensor platform, enabling miniaturized and integrated devices.
- Screen Printing: A cost-effective technique for mass-producing biosensors, screen printing deposits patterned layers of ink or conductive material onto a substrate, ideal for simple electrode designs.
- Liquid Handling: Precise fluid manipulation is essential. Microfluidic systems with microchannels and micropumps deliver small sample volumes to the sensor surface, promoting efficient and automated analysis.
- Photolithography: Using light-sensitive materials to create high-resolution patterns on a substrate, photolithography is crucial in microfabrication, allowing for intricate features on biosensor chips, such as microelectrodes and microfluidic channels.

These technologies are vital for developing advanced biosensors with improved sensitivity, specificity, and miniaturization for healthcare, environmental monitoring, and food safety applications.

4. Biological recognition element mechanism

Biological recognition elements are crucial components of biosensors [3]:

- Enzyme-based Biosensors: These devices incorporate enzymes, efficient biocatalysts with specific recognition capabilities, into a sensing layer coupled with a transducer. They rely on catalytic action and binding for specific analyte detection, making them effective in various analytical devices.
- Antibody/Immunosensors: Utilizing the specificity of antibodies, immunosensors bind corresponding antigens, with common detection methods including optical and electrochemical techniques. Antibodies, forming Y-shaped immunoglobulin structures, are integral to this recognition mechanism.
- DNA/Nucleic Acid Sensors: Leveraging the specific binding reaction between single-stranded DNA (ssDNA) chains to form double-stranded DNA (dsDNA), these sensors use nucleic acids as the recognition element. This approach advances DNA-based sensing from traditional, costly methods to more efficient ones.
- Cell-based Sensors: Employing living cells as biospecific sensing elements, these sensors detect intracellular and extracellular conditions, responding to stimuli through interactions between the cell and its environment. Microorganisms and proteins serve as biosensors for detecting specific molecules or environmental states.
- Biomimetic Biosensors: Designed to mimic natural biosensor functionality, these artificial sensors include aptasensor which use aptamers as the biocomponent. Aptamers, artificial nucleic acid ligands, offer specificity akin to natural recognition elements.

5. Types of Biosensors with Trends

5.1 Electrochemical biosensors

Electrochemical biosensors use an electrode as the transduction element and a biochemical receptor for biological recognition. They measure current generated from oxidation and reduction reactions, with the signal proportional to analyte concentration [4].

Transduction Methods:

- **Amperometry:** Measures current changes from electroactive species' oxidation and reduction at a constant potential using three electrodes: working (gold, carbon, platinum), reference (silver/silver chloride), and counter. Commonly used in clinical diagnostics, though interference can cause false readings, mitigated by sample dilution or electrode coatings.
- **Potentiometry:** Uses ion-selective electrodes and ion-sensitive field-effect transistors to measure potential changes during recognition, governed by the Nernst equation, with high-impedance voltammetry.
- **Conductometry:** Measures changes in electrical conductivity due to enzymatic reactions between two electrodes. It is cost-effective and suitable for miniaturization, with recent improvements enhancing sensitivity.
- **Electrochemical Impedance Spectroscopy**: Measures resistance to electrical current flow using AC potential, suitable for high-frequency electron transfer and low-frequency mass transfer analysis, typically at an open circuit potential during reactions

5.1.1 Development in electrochemical biosensors

The development of the Electrochemical Biosensors in Generations wise are explained in the table.

Table 1: Development in electrochemical biosensors

First Generation	Used trapped glucose oxidase (GOx) for glucose detection. Weaknesses included deep enzyme sites, slow electron transport, and interference from electro-active compounds.
Second Generation	Introduced mediators to regenerate FAD (Flavin Adenine Dinucleotide), improving sensor performance. Overcame issues of the first generation with synthetic mediators and reduced interference.
Third Generation	Immobilized mediators on the electrode surface for direct electron transfer, improving efficiency. Achieved in vivo monitoring and eliminated background interference
Fourth Generation	Integrated nanomaterials for enhanced sensor performance. Example: MXene-polymer nanocomposites for NH_3 detection.
Fifth Generation	Focus on real-time monitoring, autonomous control, and precise detection. Integration of AI and IoT technologies for continuous healthcare monitoring and cloud-connected diagnostics

5.1.2 Medical applications of Electrochemical sensors

Electrochemical biosensors are transforming medicine by offering innovative methods for diagnosing diseases, monitoring health, and improving patient care [5]. Key applications include:

- **Diabetes Management:** Glucose meters use enzymes to detect blood sugar levels, allowing diabetic patients to monitor their condition effectively.
- **Monitoring Biomarkers:** These sensors detect various molecules in bodily fluids, aiding in the management of conditions like Parkinson's disease by monitoring drugs such as L-Dopa.
- **Early Disease Detection:** They identify specific biomarkers at early stages, aiding in the diagnosis of diseases like cancer.
- **Continuous Health Monitoring:** Integrated into wearable devices, these sensors enable real-time monitoring, crucial for conditions like heart disease.

Advancements in materials science and AI are enhancing the sensitivity and functionality of these sensors, making them a promising technology for future medical diagnostics.

The different disease detection with electrochemical Biomarkers [6] are given in the table.

Table 2: Some medical applications of electrochemical biosensors

Electrochemical Biomarker	Disease
Glucose	Diabetes
Neuron-specific enolase	Small cell lung cancer
α-fetoprotein	Liver cancer
Cancer antigen 72–4	Gastric cancer
Leukemia cancer cells	Acute lymphoblastic leukemia

5.2 Optical biosensors

Optical biosensors use a bio recognition element and an optical transducer to detect analyte concentration in real-time without labels. They involve enzymes, antibodies, aptamers, cells, and tissues, causing changes in absorption, transmission, or reflection. Types include fluorescence-based, chemiluminescence-based, SPR-based, and optical fiber-based biosensors [7].

Types of Optical Biosensors:

- **Fluorescence-based:** Utilize fluorescence with dyes and proteins, employing techniques like quenching and FRET, which are highly sensitive and useful in clinical applications.
- **Chemiluminescence-based:** Generate light through chemical reactions, offering simplicity, low detection limits, and cost-effectiveness. Nanomaterials like graphene oxide enhance sensitivity, achieving detection limits as low as 34 pM.
- **SPR-based:** Detect refractive index changes on metal surfaces using the SPR phenomenon, including localized surface plasmon resonance (LSPR), applicable in disease diagnosis and environmental monitoring with detection limits down to 1.0 nM.
- **Optical Fiber-based:** Use optical fibers and evanescent field sensing to detect biological species, useful in measuring refractive index, absorption, fluorescence, and SPR variations. Examples include sensors for cholesterol and glucose with detection ranges of 25–250 mg/dL and 50–700 mg/dL, respectively.

5.2.1 Development in optical Biosensors

The development of optical biosensors with different Mechanisms [8] are given in the table.

Table 3: Development in Optical Biosensors

Optical Biosensor Type	Description
Optical Fiber Biosensors	Optical fiber biosensors leverage total internal reflection for analyte detection, employing elements like enzymes and antibodies immobilized on the fiber core. Widely applicable, they have been employed for protein, DNA, and bacteria detection. Notable examples include low-cost plastic optical fiber biosensors for lard adulterant detection and fiber-optic Fabry–Perot interferometers for glucose and hemoglobin measurement.
Optical Ring Resonator Biosensors	Comprising closed loop waveguides, optical ring resonators utilize changes in light behavior to detect analytes. Their applications range from label-free breast cancer detection using opto-fluidic ring resonators to the integration with microfluidic environments for enhanced testing. Nano-ring resonators and highly sensitive micro-ring resonators have been developed for various biomolecular detections.
Optical Interferometer Biosensors	Interferometers, such as Mach–Zehnder and Fabry–Perot, rely on the differences sensed by two light beams. Examples include silicon Mach–Zehnder interferometers for high-sensitivity optical biosensing and Sagnac-interferometers for streptavidin detection. Additionally, microcavity In-Line Mach Zehnder and Long-Period Gratings have been explored for bacterial sensing.
Optical Waveguide Biosensors	Comprising sensitive layers, cladding, and waveguide layers, optical waveguide biosensors utilize evanescent wave scattering for detection. They find successful applications in clinical diagnosis, therapy, and imaging. Examples include TiO2/Ag film-based optical waveguide biosensors for mycotoxin detection and silicon nitride Y-branch optical waveguide biosensors for high sensitivity.
Optical Photonic Crystals Biosensors	Photonic crystal biosensors leverage modifications in refractive index and periodicity for sensing. While facing challenges related to sensitivity, they offer smaller sizes and high sensitivity. Recent developments include 2D photonic crystal biosensors and SPR-dual-polarized spiral photonic crystal fiber biosensors

5.2.2 Some medical applications with Optical Biosensors

Optical biosensors offer unique advantages in the medical field with applications including:

- **Disease Diagnosis and Biomarker Detection:** They detect biomolecules with high sensitivity, aiding in accurate disease diagnosis, such as using SPR biosensors for cancer biomarkers.
- **Drug Screening and Development:** Ideal for drug screening due to their label-free, real-time detection capabilities.
- **Point-of-Care Diagnostics:** Miniaturized sensors enable rapid diagnosis in remote or resource-limited settings.
- **Continuous Monitoring of Physiological Parameters:** They non-invasively monitor vital signs, benefiting patients with chronic conditions or in critical care.

Advancements in material science and nanotechnology, along with smartphone integration, enhance their sensitivity, specificity, and user-friendliness.

The different disease detection with electrochemical Biomarkers [9] are given in the table.

Table 4: Some medical applications of Optical biosensors

Optical Biosensors	**Disease Detection**
Surface Plasmon Resonance	Ebola, Dengue, HIV, H5N1 - Avian influenza
Fluorescence	alkaptonuria disease, H1N1 influenza, tau protein-Alzheimer's disease, H9N2- Avian influenza, HIV, Dengue
Interferometric and optical fiber	Staphylococcus aureus, Breast cancer, Cancer
Chemiluminescence-based Optical Biosensors	Heart related

5.3 Piezoelectric Biosensors

Piezoelectric biosensors, which are mass-to-frequency transducers, have significant applications in analytical chemistry. They detect changes in mass, density, or viscosity on their surface via the piezoelectric effect induced by pressure, generating mechanical and electrical forces, often as acoustic waves. There are two main types: bulk wave (BW) devices and surface acoustic wave (SAW) devices, with SAW devices offering lower detection limits and greater promise for biosensor development.

5.3.1 Development in Piezoelectric Biosensors

Some development mechanisms of piezoelectric biosensors are Piezoelectric immunosensors, Molecularly Imprinted Polymers on Piezoelectric Platform and other types of Piezoelectric Biosensors [10].

Table 5: Development in piezoelectric biosensors

Piezoelectric Biosensor Type	Description
Piezoelectric Immunosensors	Piezoelectric immunosensors detect macromolecular compounds and microorganisms using antibodies for recognition. They rely on high specificity and can be configured with immobilized antibodies or antigens. While effective for high-molecular-weight analytes, they face challenges in directly detecting low-molecular-weight analytes.
Molecularly Imprinted Polymers on Piezoelectric Platform	Molecularly Imprinted Polymers (MIPs) are synthetic materials designed for biosensors, replacing antibodies or antigens. They are synthesized with a target molecule (template) and various materials like acrylates, acrylamides, sol-gels, chitosan, dextrin, and organo-metallic composites.In piezoelectric biosensors, MIPs function similarly to piezoelectric immunosensors, directly reacting with analytes through affinity reactions. A decrease in oscillation frequency indicates analyte presence. Specific reagents are often unnecessary, but sensitivity relies on analyte molecular weight.
Other Types of Piezoelectric Biosensors	Alternative proposals have been explored alongside conventional piezoelectric biosensors. Lectins, carbohydrate-rich proteins with sugar affinity, can substitute antibodies in immunoassays. For instance, the D-mannose-binding lectin from jackfruit was used in a biosensor detecting N-glycosylated receptors on leukemia-associated hematopoietic cells. Peptides like cysteinylglycine, glutathione, and specific sequences were tested as biorecognition elements for biosensors detecting volatile compounds. Immobilized on a 20 MHz QCM for gas detection, these peptides show potential for real gas detectors capable of identifying various volatile chemical compounds.

5.3.2 Medical Applications of Piezoelectric Biosensors

Piezoelectric biosensors convert pressure changes from biomolecular interactions into electrical signals, with key medical applications including:

- **Early Disease Detection and Biomarker Monitoring:** Detecting mass changes from biomolecule binding, aiding in early disease detection.
- **Monitoring Cellular Activity and Function:** Monitoring cellular activities crucial for drug discovery and understanding diseases.
- **Drug Screening Platforms:** Ideal for drug screening due to their label-free, real-time monitoring capabilities.
- **Point-of-Care Diagnostics:** Miniaturized sensors hold potential for portable, rapid disease diagnosis in remote settings. Further research is needed to enhance their sensitivity and specificity, with integration with microfluidic technologies improving their functionality.
- **COVID-19 detection with piezoelectric mechanism:** Micro cantilever biosensors detect mass changes during analyte adsorption on their functionalized surface, causing deflection due to antibody-antigen interactions. These sensors, fixed at one end and free at the other, offer adjustable selectivity through surface functionalization, making them ideal for fast COVID-19 detection. They operate in both liquids and air, using piezoelectric signalling to generate an electrical response from mechanical stress. In this study, a multilayer piezoelectric micro cantilever, with an elastic bottom layer and a piezoelectric top layer, detects adsorption-induced surface stress. This stress causes tip deflection,

producing mechanical force and strain on the piezoelectric layer, which generates voltage from charge accumulation [11].

5.4 Calorimetric-based biosensors

Calorimetric biosensors, inspired by the first enzyme-based biosensors by Clark and Lyons in 1962, measure temperature changes from biochemical reactions, correlating them to reactant consumption or product formation. Initially for enzyme-based sensors, they now also apply to cell and immunosensors.

The enzyme thermistor (ET) is widely researched for its stability, sensitivity, and miniaturization potential. Calorimetric biosensors, easily miniaturized and integrated with microfluidics, measure heat changes using a thermistor (metal oxide) or thermopile (ceramic semiconductor). This label-free method is effective for rapid biomolecule interaction screening, including DNA hybridization, with applications in the food industry and environmental monitoring .

5.4.1 Some medical applications with Calorimetric-based biosensors

Calorimetric biosensors detect biomolecular interactions through heat exchange, with potential applications including:

- **Drug Discovery and Affinity Studies:** Measuring heat released or absorbed during drug-target interactions to determine binding affinity and efficacy.
- **Microbial Detection and Monitoring:** Detecting heat signatures of microbial growth, useful in food safety testing and water supply monitoring.
- **Enzyme Activity Assays:** Monitoring enzymatic activity for studying enzyme functions, screening inhibitors, and diagnosing diseases.

Challenges remain in enhancing their sensitivity and specificity, with miniaturization and integration with other biosensing platforms necessary for broader medical use.

6. Conclusion

In conclusion, biosensors represent a transformative force in modern healthcare, each type offering unique advantages in detecting analytes with high sensitivity and specificity. Electrochemical biosensors leverage oxidation-reduction reactions for precise detection, enabling applications from diabetes management to early disease diagnosis. Optical biosensors utilize light-based detection methods, enhancing sensitivity and expanding capabilities in disease diagnostics and drug screening. Piezoelectric biosensors detect mechanical changes, promising advancements in rapid and selective disease detection. Calorimetric biosensors monitor temperature changes, offering label-free detection for diverse medical and environmental applications.

Despite their advancements, ongoing research focuses on improving sensitivity, specificity, and integration with digital technologies to realize their full potential in personalized medicine and healthcare delivery worldwide. Each biosensor type continues to evolve, driven by innovations in materials science, nanotechnology, and artificial intelligence, paving the way for more accurate diagnostics and enhanced patient care in the future.

References

[1] Bhalla, N., Jolly, P., Formisano, N., & Estrela, P. (2016). Introduction to biosensors. *Essays in Biochemistry*, *60*(1), 1–8.

[2] Chandra Mouli Pandey, B. D. M. (n.d.). *Biosensors _ fundamentals and applications*.

[3] Perumal, V., & Hashim, U. (2014). Advances in biosensors: Principle, architecture and applications. In *Journal of Applied Biomedicine* (Vol. 12, Issue 1, pp. 1–15). University of South Bohemia.

[4] Sumitha, M. S., & Xavier, T. S. (2023). Recent advances in electrochemical biosensors – A brief review. *Hybrid Advances*, *2*, 100023.

[5] Haleem, A., Javaid, M., Singh, R. P., Suman, R., & Rab, S. (2021). Biosensors applications in medical field: A brief review. In Sensors International (Vol. 2). KeAi Communications Co. https://doi.org/10.1016/j.sintl.2021.100100.

[6] Kim, J. H., Suh, Y. J., Park, D., Yim, H., Kim, H., Kim, H. J., Yoon, D. S., & Hwang, K. S. (2021). Technological advances in electrochemical biosensors for the detection of disease biomarkers. In *Biomedical Engineering Letters* (Vol. 11, Issue 4, pp. 309–334). Springer Verlag.

[7] Naresh, V., & Lee, N. (2021). A review on biosensors and recent development of nanostructured materials-enabled biosensors. In *Sensors (Switzerland)* (Vol. 21, Issue 4, pp. 1–35). MDPI AG.

[8] Singh, A. K., Mittal, S., Das, M., Saharia, A., & Tiwari, M. (2023). Optical biosensors: a decade in review. In *Alexandria Engineering Journal* (Vol. 67, pp. 673–691). Elsevier B.V

[9] Tannenberg, R., Paul, M., Röder, B., Gande, S. L., Sreeramulu, S., Saxena, K., Richter, C., Schwalbe, H., Swart, C., & Weller, M. G. (2023). Chemiluminescence Biosensor for the Determination of Cardiac Troponin I (cTnI). *Biosensors*, *13*(4).

[10] Pohanka, M. (2018). Overview of piezoelectric biosensors, immunosensors and DNA sensors and their applications. In *Materials* (Vol. 11, Issue 3). MDPI AG.

[11] Kabir, H., Merati, M., & Abdekhodaie, M. J. (2021). Design of an effective piezoelectric microcantilever biosensor for rapid detection of COVID-19. Journal of Medical Engineering and Technology, 45(6), 423–433.