Emerging Trends In Computational Biosensors: Challenges And Future Directions

Abhishek Futane[1], Vigneswaran Narayanamurthy[2,3]*, Vigneswara Rao Gannapathy[2], Pramod Jadhav[4], Kok Swee Leong[5]

[1]Fakulti Kejuruteraan Elektronik dan Kejuruteraan Komputer , Universiti Teknikal Malaysia Melaka, Hang Tuah Jaya, 76100 Durian Tunggal, Melaka, Malaysia
[2]Advance Sensors and Embedded Systems (ASECs), Centre for Telecommunication Research & Innovation, Fakulti Teknologi Kejuruteraan Elektrik Dan Elektronik, Universiti Teknikal Malaysia Melaka, Hang Tuah Jaya, 76100 Durian Tunggal, Melaka, Malaysia
[2,3*]Department of Biotechnology, Saveetha School of Engineering, Saveetha Institute of Medical and Technical Sciences, Chennai, India
[4]Faculty of Civil Engineering Technology, Universiti Malaysia Pahang (UMP) Lebuhraya Tun Razak, 26300 Gambang, Kuantan, Pahang, Malaysia
[5]Advance Sensors and Embedded Systems (ASECs), Centre for Telecommunication Research & Innovation, Fakulti Kejuruteraan Elektronik dan Kejuruteraan Komputer , Universiti Teknikal Malaysia Melaka, Hang Tuah Jaya, 76100 Durian Tunggal, Melaka, Malaysia

***Corresponding Author:** Vigneswaran Narayanamurthy
[*]Department of Biotechnology, Saveetha School of Engineering, Saveetha Institute of Medical and Technical Sciences, Chennai, India, Email: vigneswaran@utem.edu.my

Abstract
Biosensors are powerful analytical devices that detect and quantify target analytes in a sample. Due to their high selectivity and sensitivity, enzymes, proteins, antibodies, peptides, and whole cells are commonly used as sensing elements in biosensors. However, the design and optimization of biosensors can be challenging due to the complexity of these biomolecules and their interactions with target analytes. In recent years, computational methods have emerged as powerful tools for designing and optimizing biosensors, enabling researchers to predict the behavior of biomolecules and their interactions with target analytes. Computational fluid mechanics can aid in the design of microfluidic systems for biosensing applications. In contrast, molecular dynamic simulation, molecular docking, quantum mechanics, and virtual screening methods can be used to predict the behavior of biomolecules at the atomic level and study the binding kinetics and thermodynamics of interactions. This paper critically discusses the use of computational methods in biosensors, focusing on enzyme-based, protein-based, antibody-based, peptide-based, and whole-cell-based biosensors. We also review using computational fluid mechanics, molecular dynamic simulation, molecular docking, quantum mechanics, and virtual screening methods in biosensor design and optimization. Additionally, we discuss the applications of these computational methods and biosensors in healthcare, environmental monitoring, food safety, biodefense, and security. Combining computational biosensors and computational methods offers tremendous potential for developing advanced biosensors with enhanced sensitivity, specificity, and accuracy. However, challenges remain, such as the need for more accurate models and the integration of experimental and computational approaches. We conclude by discussing the prospects and challenges of computational biosensors and methods, highlighting the need for further research to drive innovation and improve human health and well-being.

Keywords: Computational biosensors, Computational methods, Target analytes

1.0 Introduction

Biosensors are analytical devices that detect and quantify the presence of target analytes in a sample by exploiting biological recognition events (1). Due to their high selectivity and sensitivity towards target analytes, enzymes, antibodies, peptides, and whole cells are commonly used as sensing elements in biosensors (2). However, the design and optimization of biosensors can be challenging due to the complexity of these biomolecules and their interactions with target analytes. The capacity to detect and discriminate nucleic acid sequences is essential for a wide range of applications, such as high throughput screening, mutation tracking for disease emergence, monitoring genetically modified organisms (GMOs), molecular computing, biometrics fingerprinting, and various genotype-associated studies (3). Traditional sensor systems are multistep platforms that frequently rely heavily on post-processing performed off-platform to determine the success of detection or categorize the biomolecule discovered. Modern high-throughput systems interpret molecular recognition events using conventional or silicon-based computing (4). De-noising and processing sensor output signals are tasks that sophisticated bioinformatics algorithms perform (5). For portable, lab-on-chip systems, this method can be error-prone and difficult to integrate into emerging microsystem technologies (6). Portable computational biosensor systems would

be especially helpful for monitoring and diagnostic purposes in resource-constrained environments or circumstances, such as those found in developing countries and in military medical support applications (7).

Recently, research scientists and medical organizations have switched to adopting affordable biosensors to control human biological processes and to evaluate accurate health diagnoses. To conduct their research, scientists and medical professionals require cost-effective, safe methods to ensure public safety and provide patients with personalized health alternatives. The use of biosensors is one simple way to implement such a solution. Biomedical studies of diagnosis are becoming more important in the modern medical field (8). It is now possible to identify diseases and monitor the body's response to treatment due to advancements in biosensor technology. Modern medical gadgets are capable of a wide range of low-cost and improved feasible factors in emerging sensor technology (9)

Computational methods have emerged as powerful tools for designing and optimizing biosensors, enabling researchers to predict the behavior of biomolecules and their interactions with target analytes (10). Computational fluid mechanics can aid in the design of microfluidic systems for biosensing applications (11). In contrast, molecular dynamic simulation, molecular docking, quantum mechanics, and virtual screening methods can be used to predict the behavior of biomolecules at the atomic level and study the binding kinetics and thermodynamics of interactions (12). This combination of computational biosensors and computational methods offers tremendous potential for developing advanced biosensors with enhanced sensitivity, specificity, and accuracy. In this context, We highlight their applications in the design and optimization of biosensors, focusing on enzyme-based, protein-based, antibody-based, peptide-based, and whole-cell-based biosensors with computer methods used in biosensor improvement.

2.0 Computational biosensors

The roots of computational biosensors can be found in the young discipline of biocomputing (3). Significant improvements in chemical and biochemical information processing have been made because of increased biocomputing research; this success is partly attributable to the inherent high specificity and selectivity of biological molecules. Additionally, the general compatibility of biomolecules permits the close assembly of various biomolecules within cascading networks that can carry out a variety of reactions (13). Bioreceptor, transducers, and signal processing systems are the three fundamental parts of a biosensor (14). Enzymes, proteins, peptides, antibodies, nucleic acids, and aptamers are receptors binding to their specified objective (4). Biochemical signals from the target interaction with its bioreceptor are converted to a detectable electrical signal using transducers. A signal processing system then measures the amplified electrical signal and converts the measurable signal. (15) Perhaps the most promising application of biocomputing with analytical systems is in the field of biomedicine (16,17). A new class of computationally intelligent biosensors that can accept input signals and systematically compute and analyze them could be produced using biocomputing and logic operations. For the system to sense and respond, the biosensors' signal output can also be coupled to signal-responsive components or procedures (18). Such "intelligent" biosensors would have several advantages over conventional biosensors, which typically only accept a single input and output a signal that needs further processing and analyzing by a skilled operator to yield meaningful results. Significant and exciting developments in intelligent computational biosensors have resulted from successfully integrating biocomputing principles with biosensing. A thorough review involves multiple target analyses using computational biosensors

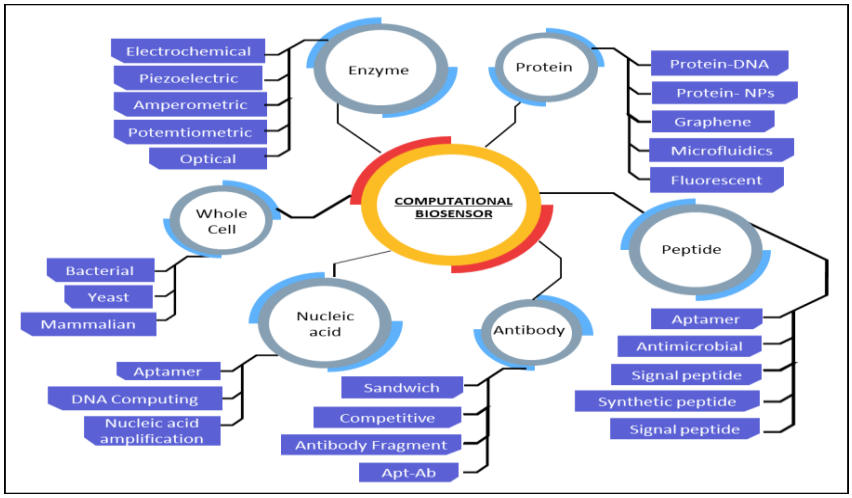

Fig 1 Computations biosensors

2.1 Enzymes-based computational biosensor

Enzymes are very beneficial in constructing POC biosensing platforms because enzymes are highly stable and simple to control (19). Enzyme-based computational biosensors are a type of biosensor that uses enzymes as the sensing element and integrate computational methods to analyze and interpret the data generated by the biosensor. Enzymes can catalyze specific reactions that produce a measurable signal, and computational methods can analyze this signal to provide

quantitative measurements of the target analyte. There are several examples of enzyme-based computational biosensors, including the use of machine learning algorithms to analyze data from glucose biosensors for the monitoring of diabetes and the use of neural networks to analyze data from lactate biosensors for the monitoring of athletes (20).

Amperometric biosensors use enzymes to catalyze reactions that produce an electrical current, which can be measured to provide quantitative measurements of the target analyte (21). For enzyme-based biosensors, electrochemical transducers are most frequently employed. Glucose and urea biosensors are the most popular enzyme-based biosensors. For in vitro real-time monitoring of glucose in the brain, Cordeiro et al. developed and characterized W-Au-based amperometric enzyme-based glucose biosensors. Their research showed that an advanced W-Au-based sensor could track changes in brain glucose in response to pertinent pharmacological tests. Computational methods can be used to analyze the data and improve the accuracy and sensitivity of the biosensor (4). Lactate biosensors are used to measure lactate levels in biological samples, such as blood or sweat, which can be an important parameter for monitoring exercise performance, assessing tissue oxygenation, or diagnosing certain medical conditions (22,23).

Alcohol biosensors are used to measure alcohol concentration in breath, blood, or other biological samples, which is important for monitoring blood alcohol content (BAC) in forensic and law enforcement settings (24),16). Phenol biosensors monitor phenol and phenolic compounds in environmental, industrial, and clinical samples (26). Glutamate biosensors are used for measuring glutamate levels in biological samples. The resulting current can be measured and analyzed using a computer-based system to provide real-time monitoring of glutamate levels in neuroscience research or clinical diagnostics (27). Potentiometric biosensors use enzymes to catalyze reactions that produce a change in voltage, which can be measured to provide quantitative measurements of the target analyte. Glucose biosensors are used to monitor blood glucose levels in diabetic patients, while cholinesterase biosensors are used to detect organophosphate pesticides and nerve agents (28). Urea biosensors measure urea levels in biological fluids, which are important indicators of renal function and metabolic disorders (29). Nanoparticles were used by Uygun et al. to create a highly stable potentiometric urea biosensor. Their developed sensor had a 30 s response time and a 0.77 M detection limit, respectively (30). Enzyme-based computational potentiometric biosensors offer high specificity and sensitivity for target analytes. It can provide real-time monitoring and quantitative analysis of various biomolecules and analytes when integrated with computational methods.

Optical biosensors use enzymes to catalyze reactions that produce a change in fluorescence, absorbance, or reflectance, which can be measured to provide quantitative measurements of the target analyte. Horseradish peroxidase (HRP)-based optical biosensors are used to detect hydrogen peroxide, -galactosidase, glucose oxidase (GOx), and alkaline phosphatase. HRP is an enzyme that catalyzes the oxidation of substrates using hydrogen peroxide (H2O2) (31). β-galactosidase is an enzyme that catalyzes the hydrolysis of β-galactosides, such as lactose, to produce galactose and glucose(32). GOx is an enzyme that catalyzes the oxidation of glucose to produce gluconic acid and hydrogen peroxide (H2O2) (33). Alkaline phosphatase is an enzyme that catalyzes the hydrolysis of phosphate groups from a wide range of substrates (34). The resulting signal can be detected and quantified using an optical detector and analyzed using a computer-based system.

Piezoelectric biosensors use the piezoelectric effect to generate an electrical signal in response to mechanical stress or pressure. Enzymes can be immobilized on the piezoelectric surface, where they catalyze the conversion of the target analyte, leading to a change in mass or surface stress, which is then detected as a change in the piezoelectric signal. Lipase-based biosensors for detecting triglycerides in food and biological samples (35), protease-based biosensors for detecting proteolytic activity in food and environmental samples(36), choline oxidase-based biosensors for detecting choline in biological samples(37), lactate oxidase-based biosensors for detecting lactate in blood and other biological fluids(22). These biosensors offer high sensitivity and specificity, fast response time, and can be used for a wide range of applications in healthcare, environmental monitoring, food safety, and more. The biosensor design and performance may vary depending on the specific analyte and enzyme used and the overall biosensor configuration. Enzyme-based computational biosensors offer a powerful tool for detecting and analyzing specific biomolecules with high accuracy and reliability and have the potential to revolutionize many areas of research and industry, including medicine, biotechnology, and environmental science.

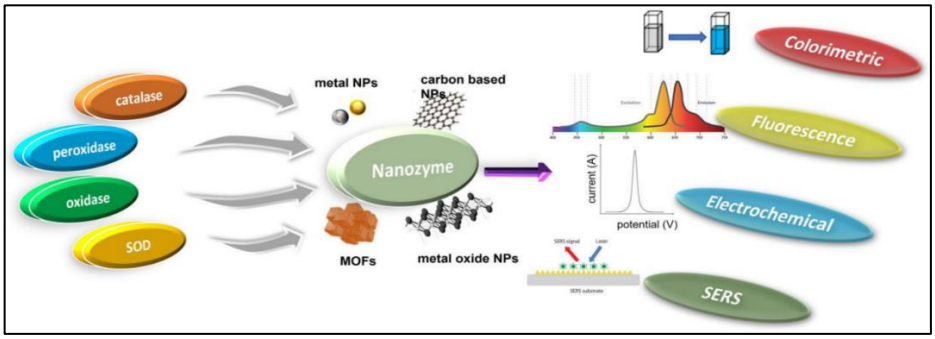

Fig 2 Enzymes-based computational biosensor (38)

2.2 Protein-based computational biosensor

Protein-based computational biosensors use proteins as the sensing element and integrate computational methods to analyze and interpret the data generated by the biosensor (39). These biosensors combine the high sensitivity and specificity of protein-based biosensors with the computational power of modern computing to produce highly accurate and reliable measurements. In a protein-based computational biosensor, the protein sensing element is immobilized on a transducer surface and interacts with the target analyte to produce a measurable signal (40). The signal is then processed using computational methods, such as machine learning algorithms, to analyze the data and provide quantitative measurements of the target analyte. Protein-based computational biosensors have several advantages over traditional biosensors, including improved accuracy, reduced noise, and the ability to detect multiple analytes simultaneously. There are several types of protein-based computational biosensors.

Protein-DNA interactions play a crucial role in various biological processes. Computational methods are employed to study the binding kinetics, thermodynamics, and stability of protein-DNA complexes. Protein-DNA biosensors leverage these interactions to detect and quantify target analytes, such as DNA sequences or DNA-binding proteins (41).. Nanomaterials such as Au nanoparticles, graphene based assemblies, carbon nanotubes and magnetic nanoparticles are the most widely used nanomaterials for biosensing. Preparation mechanisms and surface engineering are the driving forces for a biosensing suitability of these entities (42). Protein nanoparticle-based materials provide increased sensitivity and specificity for electrochemical and other biosensor configurations (43). Computational methods assist in the design and optimization of protein-nanoparticle hybrid biosensors. These biosensors utilize the unique properties of nanoparticles, such as enhanced sensitivity and signal amplification, in combination with protein receptors to detect and quantify target analytes. Machine learning-based biosensors use machine learning algorithms to analyze data from protein-based biosensors and provide quantitative measurements of the target analyte. Machine learning algorithms can identify patterns and trends in the data, improving the accuracy and reliability of the biosensor (39). Neural networks can model complex relationships between the data and the target analyte, improving the sensitivity and specificity of the biosensor. Neural network-based biosensors use neural networks to analyze data from protein-based biosensors and provide quantitative measurements of the target analyte (44). Graphene-based biosensors use graphene as the transducer surface and proteins as the sensing element to detect and measure specific biomolecules. The high conductivity and sensitivity of graphene, combined with the specificity of proteins, make graphene-based biosensors highly sensitive and accurate (45). Microfluidic biosensors use microfluidic devices to manipulate and analyze samples, allowing for highly accurate and precise measurements of specific biomolecules. Proteins can be immobilized on the microfluidic channels to act as the sensing element, and computational methods can be used to analyze the data generated by the biosensor (46). The fluorescence intensity can be measured using computational methods to provide quantitative measurements of the target analyte. Fluorescent biosensors use fluorescent proteins as the sensing element to detect and measure specific biomolecules (47).

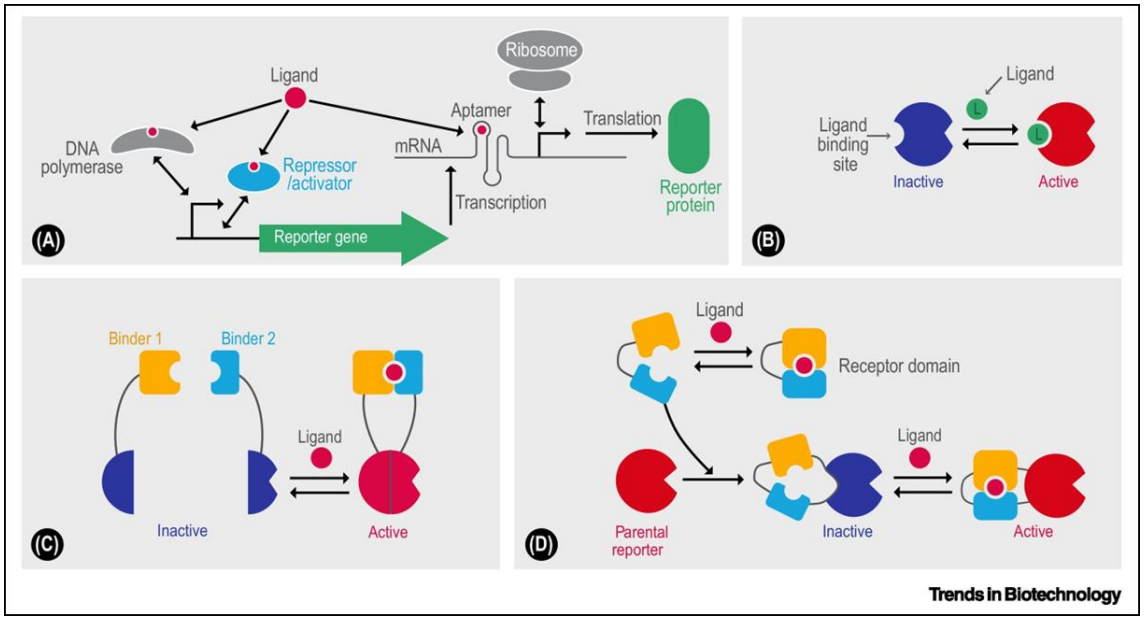

Fig 3. Protein-based biosensor (48)

2.3 Peptide-based computational biosensor

Peptide-based computational biosensors use peptides as the sensing element and integrate computational methods to analyze and interpret the data generated by the biosensor (49). Peptides are short chains of amino acids that can bind to specific target molecules with high affinity and specificity, making them ideal for sensing elements in biosensors (50). There are several examples of peptide-based computational biosensors, including using peptide aptamers to detect small molecules and using peptides to detect proteins and viruses. Aptamer-based biosensors use peptides, or peptide aptamers,

as the sensing element to detect target analytes such as small molecules, proteins, and viruses (51). The peptides are designed to bind specifically to the target analyte, and computational methods can be used to optimize the design of the peptides for maximum binding affinity and specificity (52). The peptides are designed to bind specifically to the surface of the microorganisms, and computational methods can be used to optimize the design of the peptides for maximum binding affinity and specificity. The effectiveness of antimicrobial peptides (AMPs) as potential new therapeutic agents against pathogenic microorganisms has been emphasized (53). AMPs are a part of the immune systems of many different types of organisms, including bacteria (54), mammals (55), plants (56), and insects (57). In 2009, Zampa and colleagues (58) conducted the first study demonstrating the label-free detection of microbial cells by a biosensor using AMPs. Dermaseptin-01 AMPs immobilized in electroactive nanostructured layered films allowed for detecting the *Leishmania chagasi* parasite at a detection limit of 103 cells mL-1. Cyclic voltammetry measurements were made, demonstrating the viability of using unlabelled AMPs in biosensors. Such a strategy has a number of advantages because it typically makes the detection process simpler (59).

Successful peptide-based sensing platforms must carefully choose, synthesise, and characterize the bioreceptor to maximize target interaction and surface coverage and ensure high-affinity, selective, and repeatable recognition. Proteases serve as indicators for numerous other uses. For example, proteases made by bacteria can be used to detect their presence. That particular (synthetic) peptide sequences may be used as recognition receptors in quantitative/qualitatively detecting and monitoring various bacteria. Therefore, peptide-based biosensors might represent a quick and affordable system for defense against pathogenic bacteria. In light of this, Eissa and Zourob (60) developed a method for the multiplexed detection of Listeria monocytogenes (LOD of 9 CFU/mL) and Staphylococcus aureus (LOD of 3 CFU/mL) by utilizing the proteolytic activities of the proteases produced by these two bacteria to hydrolyze a synthetic peptide sequence used as substrate. Peptide nucleic acid-based biosensors use peptide nucleic acids (PNAs) as the sensing element to detect specific nucleic acid sequences. PNAs are synthetic molecules that mimic the structure of DNA and RNA and can be designed to bind specifically to target nucleic acid sequences. PNAs can be used in hybridization applications with tighter binding and higher specificity, leading to faster and easier procedures. It can also be used in affinity electrophoresis and biosensor procedures to detect complementary strands or mismatches (60). Computational methods can be used to optimize the design of the PNAs for maximum binding affinity and specificity.

2.4 Antibody-based computational biosensor

Antibody-based computational biosensors use antibodies as the sensing element and integrate computational methods to analyze and interpret the data generated by the biosensor. Antibodies are proteins produced by the immune system in response to a specific antigen, and it can bind to their target antigens with high specificity and affinity, making them ideal for use as sensing elements in biosensors (61). In an antibody-based computational biosensor, the antibody sensing element is immobilized on a transducer surface and interacts with the target analyte to produce a measurable signal. The signal is then processed using computational methods, such as machine learning algorithms, to analyze the data and provide quantitative measurements of the target analyte (62). Antibody-based computational biosensors have several advantages over traditional biosensors, including improved sensitivity, specificity, and stability. There are several examples of antibody-based computational biosensors, including monoclonal antibodies to detect specific proteins or pathogens and recombinant antibodies to detect small molecules or other targets.

In a sandwich assay, two antibodies are used, one as a capture antibody and the other as a detection antibody. The capture antibody is immobilized on the biosensor surface. It binds to the target analyte, while the detection antibody is labeled with a signal-generating molecule and binds to a different site on the target analyte. ELISA-based analysis can detect foodborne pathogens, such as C. fetus (63)and E. coli O157:H7 (64), using digital signals interpreted by a computer-aided readout. In a competitive assay, a labeled target analyte competes with the unlabeled target analyte for binding to the immobilized antibody. The amount of labeled analyte that attaches to the antibody is inversely proportional to the concentration of the unlabeled analyte in the sample. A highly sensitive competitive Single molecule array was created by scientists for the detection of small molecules. We demonstrate that the sensitivity of the competitive Single molecule arrays is roughly 50 times greater than that of the traditional ELISA (65). This improved analytical sensitivity makes it possible to measure small molecules at previously impossible concentrations and provides access to previously unobservable biological phenomena.

Antibody-fragment-based biosensors use antibody fragments, such as single-chain variable (scFvs) or Fab fragments, as the sensing element (66). The antibody fragments are smaller and more stable than full-length antibodies and can be designed using computational methods to optimize their binding affinity and specificity. This biosensor is envisioned as a small, portable device that can be produced in large quantities, minimized for development into a handheld point-of-care device. It is useful in remote or developing areas without easy access to sophisticated laboratory facilities (67). Aptamer-antibody hybrid biosensors use a hybrid molecule consisting of an antibody and an aptamer as the sensing element. Amyloid beta-peptide can be used as a biomarker of Alzheimer's disease, and a glassy carbon electrode was modified with carboxyl graphene, BSA, and an aptamer probe. A linear response range was observed with a detection limit of 100 pM (68). An antibody-aptamer assay detects C-reactive protein with a detection limit of 0.4 mgmL-1 (69). The aptamer is designed to bind to the target analyte with high affinity and specificity, while the antibody provides a

second binding site for the analyte. Computational methods can be used to optimize the design of the aptamer and the antibody for maximum binding affinity and specificity and to analyze the data generated by the biosensor.

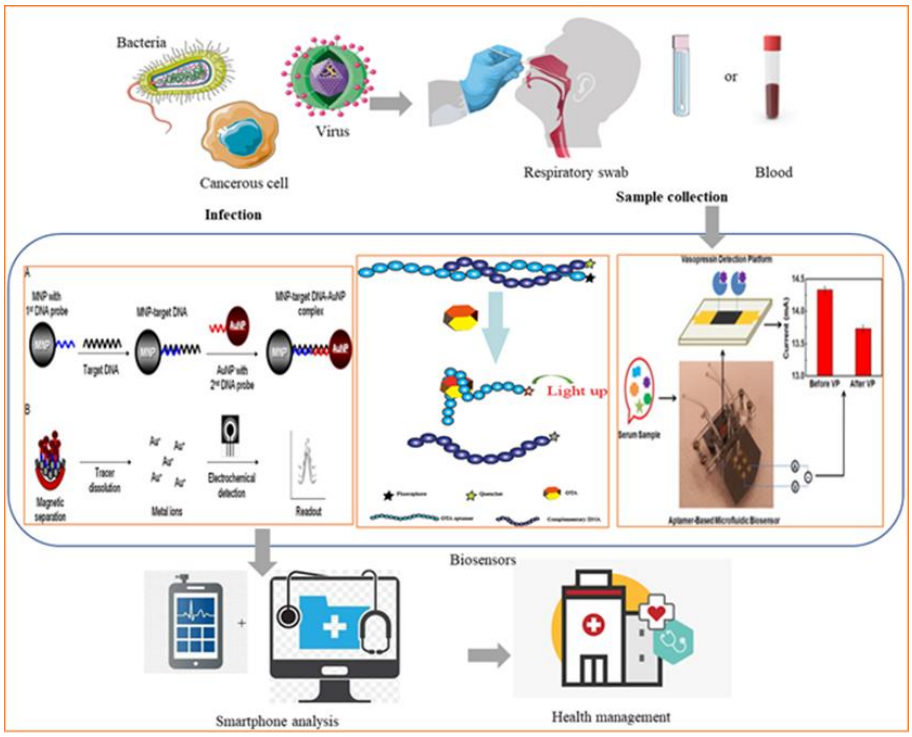

Fig 4. Antibody-based computational biosensor (70)

2.5 Nucleic acid-based computational biosensor

Nucleic acid-based computational biosensors use nucleic acids, such as DNA or RNA, as the sensing element and integrate computational methods to analyze and interpret the data generated by the biosensor. Nucleic acids can selectively recognize and bind to specific target molecules, making them ideal for sensing in biosensors (3). In a nucleic acid-based computational biosensor, the nucleic acid sensing element is designed to recognize and bind to the target analyte, producing a measurable signal that a transducer can detect. Computational methods, such as DNA computing or machine learning algorithms, can be used to analyze the data generated by the biosensor and provide quantitative measurements of the target analyte (4). There are several examples of nucleic acid-based computational biosensors.

Aptamer-based biosensors rely on the specific binding between an aptamer and its target molecule to detect and quantify the presence of the target molecule (52). Computational methods can be used in various stages of developing aptamer-based biosensors, including design, optimization, and analysis. Computational methods are used in aptamer-based biosensors to design and optimize aptamer sequences with high binding affinity and specificity to the target molecule (71). These methods consider the structural and chemical properties of the target molecule, as well as the binding affinity and specificity of the aptamer. Molecular docking simulations can be used to predict the compulsory mode and energy of an aptamer-target complex; structural analysis can be used to analyze the 3D structure of the aptamer-target complex, and signal processing and data analysis can be used to process and analyze the signals generated by biosensors (72). DNA microarrays use thousands of DNA probes to detect the presence and abundance of specific DNA or RNA sequences in a sample. The probes are attached to a solid support, such as a glass slide, and the hybridization of the target nucleic acids to the probes is detected (73). PCR-based biosensors use PCR amplification to detect and quantify specific DNA or RNA sequences in a sample. The PCR amplification products of human coronaviruses are detected (74). CRISPR-based biosensors use the CRISPR-Cas system, a natural defense mechanism in bacteria against foreign DNA. The system can be programmed to recognize specific DNA or RNA sequences, and the binding of the target nucleic acids to the CRISPR-Cas system is detected. Scientists discussed the CRISPR/Cas system for detecting various pathogenic bacteria like *L. monocytogenes, M. tuberculosis, Methicillin-resistant S. aureus, Salmonella, E. coli, P. aeruginosa, and A. baumannii*. (75). Hybridization-based biosensors use the hybridization of complementary nucleic acid strands as the recognition element to detect target analytes. The complementary strands are designed to specifically bind to the target analyte and trigger a change in the electrical or optical properties of the biosensor. Biosensors have become increasingly popular due to their physicochemical stability and ability to discriminate between organism strains. DNA biosensors (Geno sensors) are used for their physicochemical stability and suitability to distinguish different organism strains (76).

2.6 Whole-cell-based computational biosensor

A whole cell-based computational biosensor uses intact cells as the sensing element and integrates computational methods to analyze and interpret the data generated by the biosensor. Cells possess and express a series of molecular recognition

elements, such as receptors, ion channels, and enzymes, which are usually sensitive to their corresponding analytes (77). Whole cell-based biosensors can continuously monitor and analyze various physiological parameters under external stimulation, such as changes to the cell's metabolism, impedance, and action potential (78). This has led to these biosensors becoming widely applicable to many fields in biomedicine, such as cellular physiological analysis, pharmaceutical evaluation, and medical diagnosis. Whole cells can be genetically engineered to produce a specific response in the presence of a target analyte, making them ideal for use as the sensing element in biosensors (78). In a whole cell-based computational biosensor, the cells are genetically engineered to produce a specific reporter gene, such as green fluorescent protein (GFP), in response to the presence of the target analyte. The amount of reporter genes produced by the cells can be quantified and analyzed using computational methods to measure the target analyte (59) quantitatively. The genetic mutation in drug targets, such as G protein-coupled receptors (GPCRs), and changes in their response to medications is a current research goal of precision medicine. For instance, a novel label-free, whole-cell-based biosensor was developed to characterize GPCR-mediated drug responses in lymphoblastoid cell lines (LCLs) (79). This suggests whole-cell-based biosensors may be applied in precision medicine as a cellular model system for studying GPCR pharmacology in vitro. The field of micronutrients is another area where whole-cell sensors are used. Riboflavin is a vital vitamin for human health, and a deficiency can cause serious conditions like cancer, cataracts, and metabolism disorders (58). A key objective in disease diagnosis is the swift and precise detection of pathogens. Since patient blood and urine samples must first be precultured enough for their detection, conventional microbiological methods can take several days to weeks. For the precise and direct detection of bacteria, a novel approach based on whole-cell biosensors was created that did not require this time-consuming culture step (81). Such targets can be monitored using computational methods for quantitative and qualitative measurements. Whole cell-based biosensors have special advantages that have developed in part due to their ease of use and quick application to provide results for diagnosing various diseases. As a result, whole-cell biosensor-based biomedical diagnosis techniques exhibit great promise and potential.

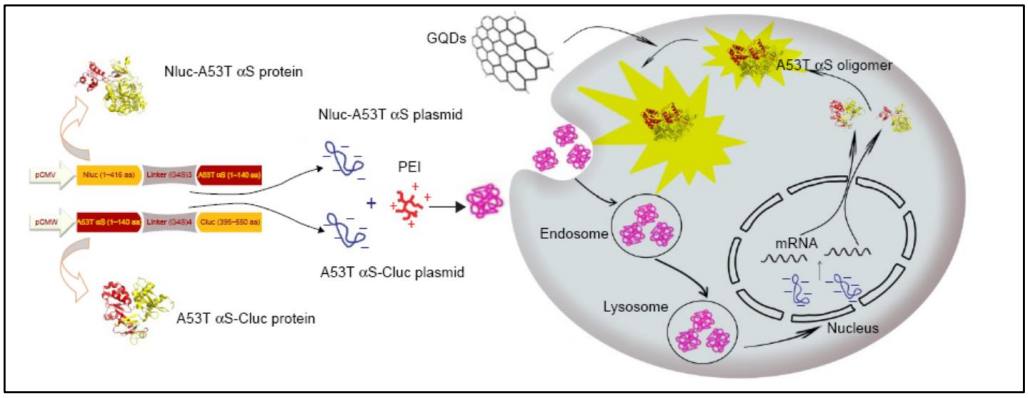

Fig 5 Whole-cell-based computational biosensor (82)

Table 1 Computational biosensors applications

Biosensor Type	Description	Application	References
Nucleic acid-based	Use nucleic acids (adenine, thymine, cytosine, and guanine) to detect specific sequences or mutations.	Detection of genetic disorders, identification of infectious agents	(83,84)
Microfluidics-based	Use microfluidic technology (Chips, lab-on chips, droplets) to detect analytes	Point-of-care diagnostics, monitoring of drug levels in the blood	(85,86)
Optical based	Use light to detect changes in analytes.	Measuring oxygen saturation, monitoring protein-protein interactions	(9,87)
Whole cell-based	Use living cells to detect changes in their environment, often through genetic engineering	Detection of toxins in the environment, monitoring of cell metabolism	(88,89)
Protein-based	Use proteins (Insulin, Collagen, Myosin) to detect analytes	Detection of cancer biomarkers, tracking of infectious diseases	(90,91)
Antibody-based	Use antibodies (Alemtuzumab, Adalimumab) to detect analytes	Detection of infectious diseases, monitoring of autoimmune disorders	(92,93)
Enzyme-based	Use enzymes (RNA/RNA polymerase, Proteases) to detect and quantify analytes	Glucose monitoring in diabetes, lactate measurement in sports medicine	(94,95)
Peptide-based	Use peptides (Oxytocin, Glucagon, Angiotensin) to detect analytes	Detection of toxins and pathogens in food and water	(96,97)

3.0 Computational methods for improvement of biosensors

In recent years, computational methods have emerged as valuable tools for designing and optimizing biosensors (10). These computational approaches enable researchers to predict and understand the behavior of biomolecules and the interactions between biomolecules and target analytes. By leveraging computational methods, scientists can accelerate the development and enhance the performance of biosensors (3,4). Integrating computational methods with experimental approaches in biosensing research holds great promise. It enables researchers to make informed decisions in the design and development of biosensors, saving time and resources by identifying the most promising candidates for experimental validation. Through a comprehensive understanding of the computational methods utilized in biosensing, we aim to showcase the potential of these approaches to drive innovation, improve biosensor performance, and contribute to advancements in human health and well-being.

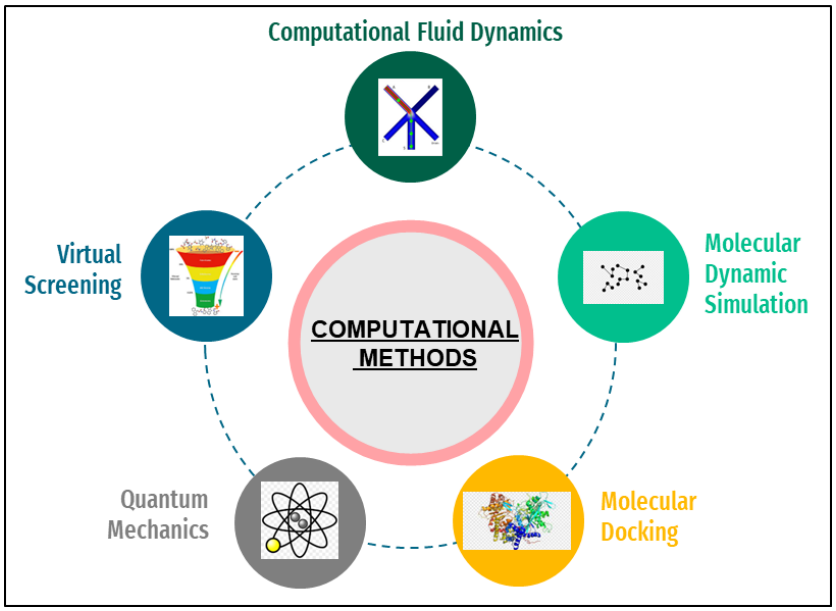

Fig.6 Computational methods used in biosensor development.

3.1 Computational fluid dynamics

Computational fluid dynamics (CFD) used to study the behavior of fluids, such as liquids and gases, in motion. CFD is a powerful tool in biosensing, as it can provide valuable insights into the behavior of fluids in microfluidic devices, which are commonly used in biosensing applications with enhanced efficiency and lower operating costs (98). Murthy K S N et al. proposed designing and simulating MEMS microcantilever sensors for identifying Mycobacterium tuberculosis from a blood sample. Here researcher used COMSOL Multiphysics to define the structural mechanics of microcantilever. (99). Komen et al. (81) created a microfluidic system that can expose cancer cells to a medication concentration profile that mimics that found in vivo and quantify the effectiveness on-chip. A transparent membrane was used to divide the drug-dosing channel from the cell culture chamber in this system, protecting the drug from shear stresses and enabling label-free growth quantification. Scientists experimented with cell exposure and confirmed that the blood concentrations determined in vivo were followed.

To achieve the right cell responses, optimizing the physical features of nanoparticles (NPs), such as their size and shape, is important. Nanoparticles (NPs) have drawn interest for their potential application as drug delivery systems (100). The impact of gold nanoparticles on IDE systems for impedance-based biosensing approaches is demonstrated through COMSOL Multiphysics simulations. Additionally, the best design parameters to provide the highest sensitivity can be discovered using these simulations. (101). To replicate the essential characteristics of complicated drug and nanoparticle transport inside a tumor microenvironment, Kwak and colleagues (102) created a tumor-microenvironment-on-chip. Scientists gained more in-depth knowledge of the dynamic transport behavior of NPs through the combination of computational simulations and experimental tests, and researcher concluded that NPs should be designed with consideration for their interactions with the tumor microenvironment. Scientists investigated a report of a study biosensor based on silicon into an effect on the dimensions of conductance design and simulation nanowire surface with molecular DNA for sensitivity. By leveraging computational methods, scientists can accelerate the development and enhance the performance of biosensors used COMSOL Multiphysics software to provide interaction within the DNA. researcher computed surface nanowire charge using the Poisson equation with Boltzmann statistics. (103)

Researchers discovered A photonic crystal fiber (PCF) biosensor based on surface plasmon resonance (SPR) to obtain maximum sensitivity for detecting unknown analytes. Sensing performance is numerically investigated by the finite element method (FEM) based on commercially available tools COMSOL Multiphysics. The amplitude sensitivity of the proposed sensor is 442.11 RIU^{-1} with sensor resolution 1.66×10^{-5}. (104) To optimize the exposure period for autophagy,

a biological mechanism where proteins are digested and recycled to provide another source of energy to cells, Karakas and coworkers (105) designed a microfluidic device for screening individual cancer cells (Figure 7a). Researchers were able to save time and resources during experimental tests by using this numerical investigation to establish the minimal exposure duration necessary to guarantee the success of the studies. On the other hand, Zhang et al. (106) investigated the change in the blood and buffer inlet flow rates affected the ability of circulating tumor cells to be separated in a microfluidic chip and modified the operating parameters to improve separation effectiveness.

Jun-Shan et al. (107) developed a microfluidic chip with micropillar arrays for 3D cell culture, and using numerical simulations, the space between micropillars was optimized, allowing nutrients in the medium to diffuse quickly into the chamber and cell metabolites to diffuse out of the chamber on time. This method was another way to increase a device's accuracy. Chen and colleagues conducted a similar investigation using micropillars (108). In this instance, the authors looked at pillars with square, elliptical, and circular cross-sections arranged in aligned and staggered patterns. The latter situation results in fluid flowing through the array's Centre and surrounding the pillars, the researchers discovered through numerical simulations. These findings prompted the study team to examine this strategy since the fluid is more evenly dispersed throughout the device in staggered patterns. To simulate mechanical interactions between flow and particles (cells) for cells-on-a-chip systems, Zhang et al. (109) developed a two-way Euler/Lagrange multiphase model. Using three alternative designs, the authors investigated the effect of using varying cell densities, intake flow velocities, and inlet cell numbers. The findings demonstrated that greater cell densities were found in locations with lower strain rates and at lower inflow velocities (10 and 20 m/s). However, scientists discovered that some cells could get to the outlet at a speed of 40 m/s while others could not. Microfluidic devices are small-scale systems that can manipulate and analyze fluids at the microliter or nanoliter scale. CFD simulations can predict the behavior of fluids in microfluidic devices, optimize the design of microfluidic devices, and study the transport of analytes in microfluidic devices. CFD is a valuable tool in biosensing, as it can provide insights into the behavior of fluids and help to optimize their design for improved performance.

Table.2 CFD Applications

Disease	Biosensor Type	CFD Application	Reported accuracy (%)	References
Cancer	Electrochemical	Simulation of fluid flow and mass transport to optimize electrode design and maximize sensitivity	90-95	(110)
Diabetes	Optical	Modeling of microfluidic channels to improve the accuracy and reliability of glucose measurements	+/- 5	(111)
Cardiovascular disease	Electrochemical	Investigation of flow patterns and mixing in microchannels to enhance the detection of cardiac biomarkers	93	(112)
Infectious diseases	Surface plasmon resonance	Optimization of surface functionalization and fluid flow to improve detection limits and reduce false positives	92-99	(113)
Alzheimer's disease	Electrochemical	Investigation of transport phenomena to optimize electrode design and enhance the sensitivity of detection	Not reported	(114)
Parkinson's disease	Optical	Modeling of fluid flow and mass transport in microfluidic channels to improve detection limits	Not reported	(115)
Tuberculosis	Electrochemical	Simulation of flow and transport to improve sensor sensitivity and reduce false positives	94-98	(116)
Hepatitis B	Surface plasmon resonance	Investigation of surface chemistry and flow conditions to optimize detection limits	Not reported	(117)
HIV/AIDS	Optical	Modeling of microfluidic channels to enhance specificity and sensitivity of detection	95-100	(118)
Malaria	Electrochemical	Simulation of transport phenomena to optimize electrode design and enhance the sensitivity of detection	90-98	(119)

3.2 Molecular dynamic simulation

Molecular dynamics (MD) simulation is a powerful tool in biosensing, as it can provide valuable insights into the interactions between biomolecules and biosensors. By simulating the behavior of biomolecules at the atomic level, MD simulations can help to understand the binding mechanisms between the biomolecules and the biosensor, as well as predict the performance of the biosensor under different conditions (120). Scientists are trying to understand how proteins and other biomolecules react with each other on an atomic level. A biomolecule's atomic-level structure is incredibly useful and often yields significant insight into how the biomolecule functions. However, because the atoms in a biomolecule are constantly in motion, the dynamics of the individual molecules affect both their intramolecular connections and molecular function. The capacity to observe these biomolecules in action, to disturb them at the atomic level, and to observe how

biomolecule react depends on the dynamic or biomolecules involved. Observing the motions of individual atoms and disturbing them in a desirable way is challenging. This problem can be minimized using an atomic-level computer simulation of the necessary biomolecules.

In recent years, molecular dynamics (MD) simulations have significantly increased their influence on molecular biology and drug development. These simulations completely capture the atomic level details and extremely fine temporal resolutions of the behavior of proteins and other biomolecules. The appeal of biomolecular modeling to experimentalists has expanded due to significant advancements in simulation speed, accuracy, and accessibility, as well as the abundance of experimental structure data. The understanding of the workings of proteins and other biomolecules, the discovery of the structural underpinnings of disease, and the design and optimization of small molecules, peptides, and proteins have all benefited from simulations. (121)

MD simulation can be performed by using several program packages, such as CHARMM (122), GROMACS (123), NAMD (124), AMBER (125), LAMMPS (126), and GROMOS (127). Typically, GROMACS computes the MD parameters 3-10 times more rapidly than other programs. NAMD can efficiently run on parallel machines to study large molecules. Scientists describe the first method for predicting the three-dimensional structures of single-stranded DNA needed for aptamer applications. By combining 2D and 3D structural tools like Mfold, assemble 2, Chimera, VMD, and Molecular Dynamics (MD) simulations, the method accurately predicts the representative resolved structures contained in the Nucleic Acid Database (NDB) and Protein Data Bank (PDB) databases. Specifically, scientists create similar 3D ssRNA models, convert the 3D ssRNA models into ssDNA 3D structures, and then explicitly build ssDNA secondary structure from sequence. Finally, we refine the resultant ssDNA 3D structures by energy minimization.(128).

MD simulations are a valuable tool in biosensing as it can provide insights into the behavior of biomolecules at a level of detail that is not possible through experimental methods alone. MD simulations can be used to investigate the binding of a ligand to a protein target in a biosensor and to study the interactions between a biosensor and a lipid bilayer in biological membranes.

3.3 Molecular docking

Molecular docking used to predict small molecules or ligands' binding modes and affinities to a receptor or target protein. This method generates multiple ligand and protein conformations and then computationally indicates their optimal orientation and interactions at the binding site (129). Molecular docking involves two steps: ligand preparation and receptor preparation. Ligand preparation involves removing solvent molecules and optimizing their conformation, while receptor preparation involves removing any ligands or co-crystallized molecules and optimizing their conformation. Docking simulation involves generating multiple conformations of the ligand and protein and evaluating their binding affinity and energy. Analysis and visualization are used to identify the ligand's most likely compulsory mode and affinity to the receptor (130).

The behavior of tiny molecules at the binding site of a target protein is investigated by molecular docking methods. Conventional methods like NMR (Nuclear magnetic resonance, X-ray crystallography and cryomicroscopy) determine a huge amount of protein structure. Hence, molecular docking is increasingly used as an emerging tool in biomedical engineering (131). A few researchers used the AutoDock Vina to conduct a molecular docking analysis to examine the binding mechanism between the ZEN and aptamers. The secondary structure of the linear ssDNA was predicted using the Mfold web service. The Vienna output format file was utilized to create the aptamer's three-dimensional (3-D) structure. Using the ChemBioDraw Ultra14.0 program, the ZEN molecule's structure was drawn with the correct two-dimensional (2-D) orientation, and the drawing was reviewed for flaws. Using the software ChemBio3D Ultra 14.0, ZEN's energy was reduced. The docking input files were created using the AutoDockTools 1.5.6 package. Unless otherwise stated, the default settings were used for Vina docking. (132)

In another study, peptide aptamer was used for the detection of L-arginine. From the protein sequences of four species, Homo sapiens, Mus musculus, Rattus norvegicus, and Sus scrofa, eight-mer peptide aptamers were isolated. The UniProt database yielded 29,185 protein sequences for the four species. A sliding window of eight amino acids was used to scan the protein sequences, and a total of 2,854,481 peptide fragments were produced. The eight-mer peptides were constructed into -helices using PyMol, and these conformations served as the starting point for the molecular dynamics simulations. Using AutoDock 4.2.6, simulations were run to test the stability of eight-mer peptide and L-Arg complexes (133). Xiongfei Zhao et al. also developed a fluorescent probe DNC for point-of-care detection of Albuminuria. Scientists studied the Albumin-sensing mechanism by molecular docking using the software Autodock. Their work provides a novel design strategy for reducing the interference from urinary fluorescence on the detection result. (134)

Computer-based applications play a crucial role in biosensing by enabling the analysis, interpretation, and management of the vast amounts of data generated by biosensors. Examples include machine learning algorithms to analyze biosensor data, computer simulations to model the behavior of biosensors, and databases to store and retrieve large amounts of data. These applications are essential to developing and implementing biosensing technologies, enabling researchers and

practitioners to analyze, interpret, and manage the complex data generated by biosensors and optimize their performance for a wide range of applications (135,136).

3.4 Quantum mechanics

Quantum mechanics has also been applied to computational biosensing, which involves using computational methods to analyze and interpret biosensor data. Quantum computing, in particular, has the potential to greatly improve the speed and efficiency of computational biosensing by allowing for the processing of large amounts of data and the simulation of complex biochemical processes (3).

One example of using quantum mechanics in computational biosensing is the development of quantum algorithms for analyzing biological data. Quantum algorithms are designed to run on quantum computers, which use quantum mechanical phenomena to process information fundamentally differently than classical computers. Quantum algorithms have been developed for various biosensing applications, including protein folding prediction, DNA sequencing, and drug discovery (137). Another example is using quantum mechanics to simulate biological processes, such as protein-protein interactions or enzyme catalysis. Manufacturing these processes using classical computers is often computationally intensive and time-consuming, but quantum computing can greatly accelerate these simulations. This could lead to the discovery of new drugs or the development of more efficient biosensors (138). Juliana Khecheto and coworkers developed a label-free capacitive design interface using quantum mechanics to diagnose dengue viral infection. Researchers used DFT Hamiltonian analysis for requiring minimal manipulation of patient samples to detect DENV. The minimal need for manipulating biological samples is attributed to the reagent-less nature of electrochemical capacitive assays. This capacitive method can potentially compete with traditional serological laboratory assays, with the advantage of being inexpensive and compact, especially when compared with ELISA methods which require labeled secondary antibodies, or expensive NAAT assays. (139)

Quantum mechanics has also been applied to the design of biosensors with improved sensitivity and specificity. For example, quantum coherence effects have been used to develop biosensors that can detect the presence of single molecules with high accuracy. These biosensors use quantum mechanical phenomena to detect changes in the electronic properties of the sensing material caused by the binding of a target molecule (140). Overall, the application of quantum mechanics to computational biosensing has the potential to greatly improve the speed, accuracy, and efficiency of biosensing. However, the development of quantum computing and quantum algorithms is still in its early stages, and much research is needed to realize their potential in biosensing fully.

3.5 Virtual screening

Virtual screening has ability to predict small molecules' binding affinity to a target protein or biomolecule (141). It can be applied to developing biosensors by predicting the binding of small molecule probes to specific biomolecules of interest (142). In biosensors, small molecule probes are often used to detect and measure the presence of specific biomolecules, such as proteins or nucleic acids. Virtual screening can identify small molecule probes with high binding affinity and selectivity for the target biomolecule (143). This can significantly reduce the time and cost required for experimental screening of large compound libraries. Virtual screening in biosensors is the development of small molecule probes for protein kinase activity (144). Protein kinases are enzymes that play a critical role in cell signaling and are often dysregulated in diseases such as cancer (145). Small molecule probes that selectively bind to specific protein kinases can be used to monitor their activity in cells and tissues. Virtual screening can also identify small molecule probes to detect pathogens or toxins (146). Virtual screening can identify small molecule inhibitors of bacterial toxins such as cholera toxin and anthrax toxin, which could be used as probes for detecting these toxins in food or water samples. Viirtual screening is a powerful tool for the development of biosensors, as it allows for the rapid identification of small molecule probes with high binding affinity and selectivity for specific biomolecules of interest.

4.0 Critical discussion

Combining computational biosensors and computational methods such as fluid mechanics, molecular dynamics, molecular docking, quantum mechanics, and virtual screening offers numerous opportunities to develop advanced biosensors with enhanced sensitivity, specificity, and accuracy. Enzymes, proteins, antibodies, peptides, and whole cells are commonly used as sensing elements in biosensors, and computational methods can help optimize their performance by predicting their interactions with target analytes and optimizing their binding affinity and selectivity. Computational fluid mechanics can aid in designing microfluidic systems for biosensing applications, indicating the flow behavior of fluids, and optimizing the flow patterns to enhance analyte transport and detection efficiency (11). Molecular dynamics simulations and quantum mechanics calculations can be used to predict the behavior of biomolecules at the atomic level and to study the binding kinetics and thermodynamics of enzyme-substrate, protein-ligand, and antibody-antigen interactions (147). Virtual screening methods can be used to screen large databases of compounds and identify potential ligands with high affinity and specificity for a given target. However, there are also limitations to these computational methods. Molecular dynamics simulations are limited by the size of the systems that can be studied and the accuracy of the force fields used. Virtual screening methods rely on accurate structural models of the target and may miss important conformational changes that occur upon ligand binding (146). The accuracy of molecular docking methods is also limited by the accuracy of the scoring functions used to evaluate ligand binding (148). Therefore, integrating multiple computational methods and using

hybrid approaches can help overcome some of these limitations and improve the accuracy and reliability of biosensor design and optimization. Combining computational biosensors and computational methods is a promising approach to developing advanced biosensors for various applications, including healthcare, environmental monitoring, and food safety (149–151). However, further research and development are needed to optimize these methods, overcome their limitations, and demonstrate their effectiveness in real-world applications.

5.0 Conclusion and future prospective

The development of biosensors that can detect multiple targets simultaneously or targets with high sensitivity and specificity in complex biological matrices is an area of active research. Furthermore, integrating biosensors with other technologies, such as microfluidics and wearable devices, is expected to enable new applications in personalized medicine and point-of-care testing areas (152,153). Furthermore, integrating different computational methods and developing hybrid approaches that combine multiple methods are expected to enable the study of complex phenomena that cannot be studied using a single method alone. Integrating molecular dynamics simulations with quantum mechanics calculations can provide a more accurate description of electronic structure and chemical reactions. In contrast, integrating virtual screening with molecular docking can enable the identification of novel drug candidates with high specificity and affinity (154).

The combination of computational biosensors and computational methods, including enzyme, protein, antibody, peptide, and whole cell-based biosensors, along with computational fluid mechanics, molecular dynamic simulation, molecular docking, quantum mechanics, and virtual screening, offers tremendous potential for the development of advanced biosensors with enhanced sensitivity, specificity, and accuracy. These computational methods can optimize sensing elements' performance by predicting their interactions with target analytes and optimizing their binding affinity and selectivity. Additionally, computational fluid mechanics can aid in designing microfluidic systems for biosensing applications. In contrast, molecular dynamics simulations and quantum mechanics calculations can be used to predict the behavior of biomolecules at the atomic level and study the binding kinetics and thermodynamics of interactions (155). However, there are limitations to these computational methods, and the accuracy and reliability of biosensor design and optimization can be improved by integrating multiple computational methods and using hybrid approaches (10). Further research and development are needed to optimize these methods, overcome their limitations, and demonstrate their effectiveness in real-world applications.

Looking towards the future, the continued development and refinement of these methods are expected to further advance our understanding of molecular systems and their interactions, accelerate the growth of new drugs, materials, and technologies, and enable the development of biosensors with increasingly enhanced sensitivity and specificity (156,157). Furthermore, integrating these methods with emerging technologies such as machine learning and artificial intelligence is expected to improve the accuracy and predictive power of biosensors and computational methods, enabling the development of more complex and sophisticated biosensing systems (158). Advances in computational methods, such as machine learning and artificial intelligence, are expected to improve biosensor design, optimization accuracy, and efficiency. Additionally, the development of novel materials, such as nanomaterials and biomimetic materials, is expected to enhance the sensitivity and specificity of biosensors (159). The future of computational methods is bright, and these technologies are poised to play an increasingly important role in a wide range of fields, from healthcare to environmental monitoring to materials design. The continued development and refinement of these methods are expected to advance our understanding of molecular systems and their interactions and accelerate the development of new drugs, materials, and technologies.

6.0 Conflict of interest

There are no conflicts of interest to declare.

7.0 Ackowledgement

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