Advances in Carbon Nanotube Field-Effect Transistor Biosensors: Structure, Applications and Future Prospects

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Abstract: Nanomaterial possesses unique features that make them attractive for biosensing applications. Among various nanomaterials, carbon nanotubes (CNTs) stand out due to their exceptional sensitivity to biomolecules, making them ideal candidates for next generation biosensing technologies. CNT-based field-effect transistors (CNTFETs) have shown great promise in the development of biosensors. CNT-FET not only offer heightened sensitivity and selectivity but are also well-suited for point-of-care diagnostics. CNTs provide an excellent platform for biomolecule immobilization, enabling the precise detection of disease biomarkers. In this research paper, we have provided a comprehensive review of CNT-FET-based bio-sensors, highlighting their application for detecting extremely low concentrations of biologically relevant molecules. Additionally, we discuss the major challenges and future prospects of CNT-FET-based bio-sensors.

Keywords: Carbon nanotubes, CNT-FETs, functionalization, cytotoxicity, biocompatibility.

1. Introduction

Carbon nanotubes (CNTs) have garnered significant attention over the past two decades, emerging as one of the most widely utilized nanomaterials in various fields, particularly in biosensing applications. The unique structure of CNTs, which are seamless cylinders of one or more layers of carbon atoms, endows them with extraordinary properties such as high surface area-to-volume ratios, excellent electrical conductivity, chemical stability, and mechanical strength[1]. These attributes make CNTs particularly advantageous for use in chemical and biological sensors, which play critical roles in healthcare, environmental monitoring, food quality control, and defence. [2] The first true biosensor was developed in 1956 by Clark et al., who are regarded as the pioneers of this technology [3]. Over the years, the integration of CNT based FETs into biosensors has revolutionized the field, offering unprecedented sensitivity and specificity. The high aspect ratio and exceptional electrical properties of CNTs allow for the detection of minute changes in biological systems, which are crucial for applications such as disease diagnosis and environmental monitoring [4]. These devices offer several advantages over traditional sensing technologies, including high sensitivity, fast response times and the ability to operate at low temperatures. The ability of CNTs to be functionalized with biorecognition elements further enhances their utility in biosensors, enabling the selective detection of target analytes. Recent advancements have demonstrated the potential of CNTFETs in detecting various pathogens, including viruses like SARS-CoV-2, where they have been employed to create highly sensitive and selective diagnostic tools. [5]

As the field of CNT-FET based biosensors continues to advance, the focus remains on optimizing the functionalization and transduction processes to ensure reliable and rapid detection. The integration of CNT-FETs into biosensing platforms not only holds promise for enhancing diagnostic capabilities but also offers new avenues for addressing global health challenges. The ongoing research and development efforts are poised to further solidify the role of CNT-FETs in the next generation of biosensing technologies, driving innovations in medical diagnostics and beyond.

This research paper discusses the development of CNT- FET based biosensors focusing on device structures and functionalization. Recent applications of CNT-FET based biosensors in the medical field is also reviewed. Finally, we discuss the major challenges and future prospects of CNT-FETs.

2. Related Work

Carbon nanotubes (CNTs) have emerged as highly promising platforms for biosensing applications. Recently, CNT field-effect transistors (CNT-FETs) based biosensors have been extensively utilized in the detection of various cancer biomarkers, showcasing their potential in early diagnosis and real-time monitoring [6] . One of the significant advancements in this domain was the development of a novel method for real-time detection of breast cancer cells . This method utilized a CNT-FET based biosensor, which was linked with antibodies to detect the presence of cancer cells without the need for labelling [7]. The label-free nature of this biosensor not only simplified the detection process but also enhanced its sensitivity, allowing for more accurate and timely identification of cancerous cells .

Similarly, another technique introduced was both simple and highly sensitive, aimed at the real-time monitoring of the PSA-ACT complex, a well-known prostate cancer biomarker . The CNT-FET biosensor employed in this study was modified with specific linkers and spacers, which played a crucial role in preventing non-target proteins from interacting with the sensor.[8] This selective blocking allowed for the precise detection of the target protein within human serum samples, demonstrating the biosensor's potential for clinical applications.

Expanding on these findings, a comprehensive investigation was conducted into the feasibility of using CNT-FETs based biosensors as diagnostic tools for quantifying cancer biomarkers in serum . This research highlighted the advantages of CNT-FET based biosensors, such as high sensitivity and the ability to function in complex biological environments. This study laid the groundwork for future developments in CNT-FET based diagnostics, particularly in the context of cancer detection [9][10].

In another significant contribution, an innovative bio-sensing platform was proposed that utilized a horizontally aligned single-walled carbon nanotube field-effect transistor (SWCNT-FET). This platform was designed to enable real-time and highly sensitive detection of proteins, which are critical in various diagnostic processes. The horizontally aligned structure of the SWCNT-FET allowed for more consistent and reliable sensor performance, making it a valuable tool for medical diagnostics [11].

A rapid and label-free method for detecting Interleukin-6 (IL-6), a cytokine involved in inflammation and immune responses, was demonstrated. This approach employed CNT microarrays functionalized with IL-6-specific aptamers, which served as molecular recognition elements. The conjugation of these aptamers with PASE (a chemical linker) enhanced the sensitivity and specificity of the CNT-FET biosensors, enabling the detection of IL-6 in biological samples without the need for additional labelling steps. This method offered a streamlined approach to cytokine detection, which could be particularly beneficial in clinical settings where quick and accurate results are essential [12][13]. Continuing the exploration of CNT-FET biosensors, a highly sensitive and user-friendly assay for IL-6 detection using liquid-gated FET sensors was presented. This study highlighted the advantages of using liquid-gated FETs, which included improved sensitivity and ease of use, making this technology accessible for broader applications in biomedical research and diagnostics [14].

An innovative biosensing approach was introduced that combined a floating gate FET with a semiconducting CNT film and an undulating yttrium oxide (Y_2O_3) dielectric layer. This unique combination of materials and design features allowed for enhanced biosensing capabilities, particularly in the detection of specific biomolecules [15]. The floating gate design also contributed to improved signal stability and sensitivity, making this approach a significant advancement in the field of biosensing [16].

Additionally, the application of CNT-FET-based biosensors for monitoring the pH of solutions was explored, a crucial parameter in various biological and chemical processes. This study also investigated the use of CNT-FETs biosensors in virus detection, a topic that gained increased attention during the COVID-19 pandemic[17]. Virus detection using CNT-FET biosensor typically involves either immobilizing the DNA or RNA of the virus on the sensor surface or directly detecting the virus by immobilizing antibodies or peptides [18]. This approach offers the potential for rapid and specific virus detection, which is critical in managing infectious diseases. Moreover, the COVID-19 pandemic highlighted the urgent need for sensitive, specific, and rapid diagnostic tests to facilitate timely treatment and prevent the spread of infectious diseases. While the polymerase chain reaction (qPCR) remains a commonly used method for virus detection, it involves time-consuming amplification steps. CNT-FET based biosensors offer a promising alternative by providing faster results without the need for amplification [19]. These biosensors have demonstrated their potential in quickly and accurately detecting viral infections, making them valuable tools in the fight against pandemics.

3. Device Structures of CNT FET based Biosensors

Carbon nanotubes (CNTs) possess unique electrical properties that make them highly sensitive to environmental changes, a characteristic that is key in their role in biosensing applications. CNTs, known for their exceptional electrical conductivity, can function as conductive channels in sensing devices [20]. When these CNTs are functionalized with specific biomolecules, such as antibodies or aptamers, they can selectively bind to target analytes like cancer biomarkers. This binding event alters the electrical conductivity of the CNTs, either through charge transfer or changes in the charge distribution near their surface. By measuring these conductivity changes, the presence and concentration of the target analytes can be detected, enabling label-free sensing [21]. In CNT-FET based biosensors, either single-walled carbon nanotubes (SWCNTs) or multi-walled carbon nanotubes (MWCNTs) are employed as the conductive channel[22]. When integrating

SWCNTs into electronic biosensors, various sensing mechanisms come into play, including electrostatic gating, charge scattering, Schottky barrier modulation, and capacitance modulation. The specific mechanism depends on the design of the device structure employed [23]. CNT-FET based biosensors devices are typically configured as two-end devices, back-gate devices, electrolyte-gated devices, or dual-gate devices.

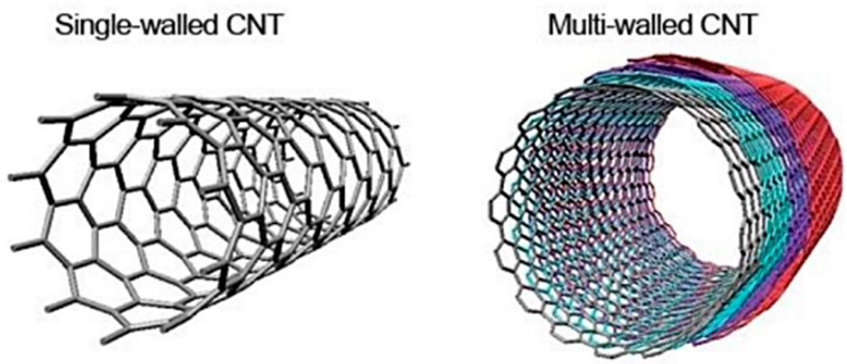

Figure 1: Single walled and Multi walled Carbon Nanotubes

Among these, electrolyte-gated devices are particularly noteworthy for their versatility and potential in biosensing applications. The back-gated Bio-CNTFETs is a relatively straightforward device where the gate and source-drain are positioned on opposite sides of the silicon substrate. This design minimizes potential damage to the channel layer during processing. The channel conductivity is modulated by applying a potential to the highly conductive silicon substrate, allowing for control over a wide range of back-gate voltages [24]. Back-gated devices are typically used to measure device performance in dry environments by applying a gate voltage to the substrate. However, these FETs are not suitable for real-time measurements in liquid environments due to the absence of electrode passivation. Liquids can interfere with the electrical signals necessary for proper FET function, leading to inaccurate readings and potential corrosion, which compromises device stability and reliability. Back-gated CNT-FET based biosensors has lower gate control efficiency and sensitivity compared to liquid-gate structures. Additionally, they cannot perform real-time measurements in liquid environments, which restricts their potential for high-performance biosensing applications [25][26].

Electrolyte-gated devices can be classified into two types: channel-exposed and channel-isolated configurations. When target analytes interact with the biomolecules on the device, changes in the electrical properties of CNTs, such as resistance or field-effect behaviour, can be detected by measuring the output current [27]. Another common configuration involves the use of a liquid gate with a reference electrode. In this setup, the gate voltage is applied to the solution between the source and drain, with the solution acting as the gate layer of the FET [28]. The dual-gate Bio-CNTFET enhances the detection of small biological signals by several orders of magnitude through capacitive coupling between the top and bottom gates of the channel, resulting in better signal-to-noise ratios compared to single-gate devices. However, most research on dual-gate Bio-CNTFETs is theoretical, with practical applications being limited by the complexity of device fabrication. The electrolyte-gated isolated-channel Bio-CNTFET, also known as a floating-gate Bio-CNTFET, avoids the detrimental effects of electrolyte solutions on channel materials by introducing a dielectric layer between the electrolyte and the channel. In this design, the source and drain electrodes are passivated by an insulating layer to prevent current leakage and electrochemical reactions, thus eliminating Schottky barrier modulation effects. The charge variations induced by the hybridization of target biomolecules on the gate are capacitively coupled with the semiconductor channel, leading to a threshold voltage shift in the FET, which is crucial for biosensing as shown in the figure 2 [29[30].

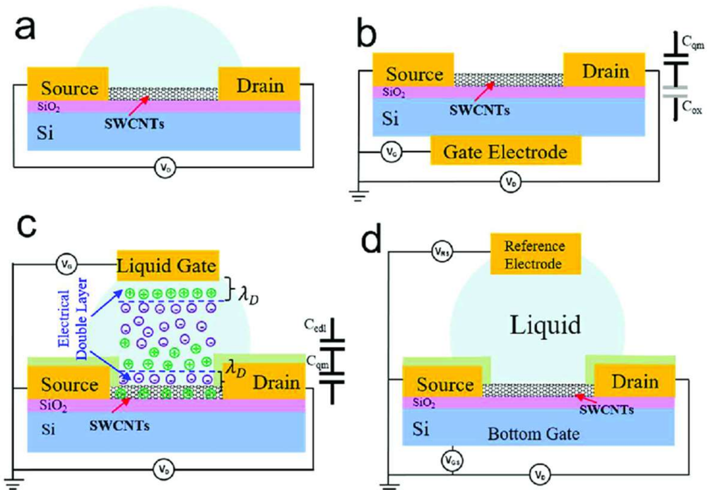

Figure 2: Three device structure of CNT-FET based biosensors. (a) Two electrode sensors. (b) Back-gate control device structure. (c) Electrolyte- gated control device. (d) Electrolyte trench isolation type.

4. Functionalization of CNT – FET based biosensors

Functionalization is a vital process in enhancing the utility of carbon nanotubes (CNTs) for biosensing applications [31]. The inherent high hydrophobicity of CNTs and tendency to aggregate limit their practical use in biological environments [32]. Functionalization modifies the CNT surface to improve solubility, enhance interaction with biological molecules, and tailor their properties for specific applications [33]. The functionalization process on CNTFETs using different biochemical molecules and chemical treatments is achieved through covalent and non-covalent configuration methods [34].

A) Non-covalent functionalization: This involves modifying the CNT surface through weak interactions such as π-π stacking, van der Waals forces, and hydrophobic interactions. This method preserves the intrinsic properties of CNTs while improving their dispersion and solubility[33].

- **π-π Stacking and Hydrophobic Interactions:** Non-covalent approaches often utilize π-π stacking between CNTs and polyaromatic molecules. Pyrene derivatives, for example, are frequently used due to their strong π-π interactions with CNTs. This method allows for the attachment of various biomolecules, such as proteins and DNA, without altering the CNT structure . This approach has been employed to develop biosensors with enhanced stability and sensitivity[33].

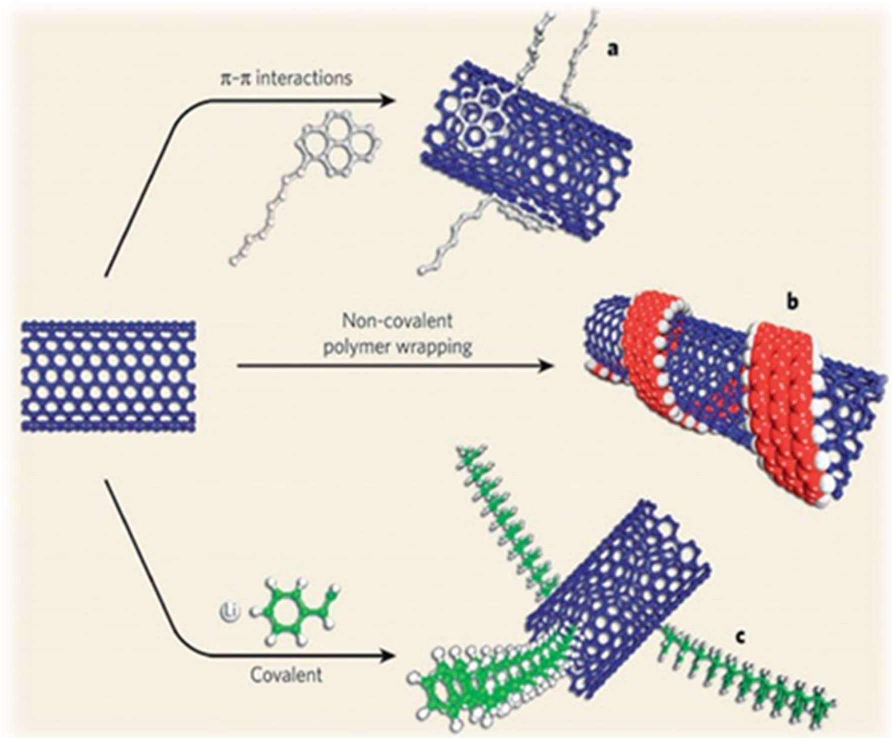

Figure 3: a) π- π stacking interactions b) Non covalent polymer wrapping c) Covalent functionalization.

- **Surfactants and Polymers:** Surfactants like sodium dodecyl sulphate (SDS) and polymers such as polyethylene glycol (PEG) are used to improve CNT dispersion in aqueous solutions. SDS helps to individualize single-walled carbon nanotubes (SWCNTs) through sonication and ultracentrifugation. PEGylated phospholipids and other polymers can also be used to create highly water-soluble CNTs, facilitating their use in diagnostic tools and drug delivery systems[35].

B) Covalent functionalization: This involves creating strong chemical bonds between CNTs and functional groups, which can significantly alter their solubility and compatibility. This approach is used to introduce specific functional groups that enhance the interaction of CNTs with target molecules [36].

Chemical Modification: Covalent functionalization methods include attaching functional groups such as carboxyl (-COOH), hydroxyl (-OH), or amine (-NH2) groups to the CNT surface. These groups provide reactive sites for further chemical modifications and biomolecule attachment. For instance, carboxyl groups can react with amine-containing biomolecules to form stable amide bonds, enabling the immobilization of antibodies or aptamers on CNTs [37][38].

5. Applications of CNT-FET Based Biosensors

CNT-FET based biosensors offer highly sensitive and selective detection of biomarkers associated with various diseases, including cancer, infectious diseases, and genetic disorders[39]. The ability of CNT-FETs to detect specific DNA sequences makes them invaluable for early disease diagnosis. For instance, by incorporating nucleic acid probes on the CNT surface, these biosensors can identify mutations in genes linked to cancer, enabling early intervention and personalized treatment plans[40].

CNT-FET biosensors are also being developed for environmental monitoring applications. These sensors can detect DNA sequences from microorganisms or contaminants in water, soil, and air, making them valuable for assessing environmental pollution and its impact on ecosystems. For example, CNT-FET biosensors can be used to monitor the presence of harmful pathogens in water supplies, ensuring safe drinking water for communities [41]. Additionally, these biosensors can detect pollutants such as heavy metals and pesticides, aiding in the protection of natural resources and public health [42].

In the pharmaceutical industry, CNT-FET biosensors are emerging as valuable tools in drug discovery and development. These biosensors can be used to screen potential drug candidates by detecting interactions between drugs and their target biomolecules, such as enzymes or receptors [43]. CNT-FET biosensors allow for the rapid identification of promising compounds, accelerating the drug development process. Moreover, these biosensors can be integrated into high-throughput screening platforms, enabling the simultaneous analysis of multiple drug candidates[44].

Recently, CNT-FET biosensors have been used in defence and security, particularly in the detection of chemical and biological warfare agents [45]. These biosensors are engineered to recognize specific DNA sequences or proteins associated with pathogens or toxins, providing early warning systems for potential bioterrorism threats use latest research focuses on the use of CNT-FET biosensors in implantable and prosthetic devices [46]. These biosensors can monitor biological signals, such as glucose levels in diabetic patients or biomarkers associated with cardiovascular diseases, providing real-time data that can inform treatment decisions [47]. For instance, CNT-FET biosensors integrated into pacemakers could monitor the levels of certain proteins that indicate heart stress, allowing for timely adjustments to the device's operation [48]. Additionally, these biosensors could be used in prosthetic devices to monitor tissue health, ensuring the long-term success of the implant.

6. Challenges of CNT-FET Based Biosensors

Despite the promising potential of CNT-FET based biosensors in biomedical applications, several significant challenges need to be addressed for their widespread adoption and practical implementation:

1. **Surface Passivation and Non-Specific Binding**: Surface passivation is essential to prevent non-specific binding of biomolecules, which can lead to false positives and reduce the specificity of the biosensor [49]. However, achieving effective surface passivation without compromising the sensitivity of CNT-FET biosensors is challenging. Non-specific interactions can also complicate the detection of target molecules in complex biological samples[50].

2. **Cytotoxicity and Biocompatibility**: The cytotoxicity of CNTs remains a significant concern, especially for in vivo applications. While functionalization can improve biocompatibility, there is still a need for comprehensive studies to understand the long-term effects of CNTs on biological systems. Ensuring the safety of CNT-FET biosensors for clinical use is paramount [51][52].

3. **Regulatory and Standardization Issues**: As with any emerging technology, CNT-FET biosensors face regulatory hurdles. The lack of standardized protocols for the synthesis, functionalization, and testing of CNTs can hinder the development and approval of these devices for clinical use [53]. Establishing clear guidelines and standards is necessary to facilitate the transition of CNT-FET biosensors from the lab to the market [54].

4. **Consistency and reproducibility:** The consistency and reproducibility of CNT-FET biosensors is another significant challenge. Variations in the size, chirality, and purity of CNTs during synthesis can lead to inconsistencies in sensor performance. Additionally, the stability of functionalized CNTs over time, especially under physiological conditions, is critical for the long-term reliability of these biosensors [55]. The consistency and reproducibility of CNT-FET biosensor devices' performance is crucial, as it directly impacts the reliability and accuracy of the results. Therefore, every process—including materials synthesis, device fabrication, and biomodification—needs to be handled carefully [56].

7. Conclusion

The use of CNT-FET based biosensors present both opportunities and challenges. Due to the high performance, high sensitivity and small size CNT-FET biosensors have the ability to detect very low concentration of largest molecules. Biosensors have developed as a reliable, fast and inexpensive method of diagnostic techniques. Moreover, these CNT-FET based biosensors have been widely used in medicine, environmental monitoring and security. It is found that in CNT-FET based biosensors, enzymes often need to be immobilized onto the surface of CNTs which can potentially damage their biological activity, biocompatibility and structural stability. Hence, there is a need to standardize the structural stabilization and surface characteristics of CNTs. Overall, we can say that the market of CNT-FET based biosensors is steadily increasing driven by their good sensitivity, low cost and low power consumption.

8. Future Prospects

The future of CNT-FET biosensors is promising, with opportunities for the development of multi-target and multi-functional arrays and the integration of microfluidic and CNT signal processing circuits for self-adaptive disease diagnosis. The capability of Bio-CNTFETs to detect low-concentration biomarkers without the need for labelling is expected to provide new insights into the roles of various biomarkers in the etiologic of specific diseases and create new opportunities for medical diagnosis. Also, the low-temperature fabrication process of CNTs enables low-effort 3D integration and high-throughput processing of sensitive data. Currently the main focus is to optimize the functionalization techniques and improve the stability and reproducibility of CNT-FET based biosensors. Thus, continued research is going on to overcome these challenges. As these developments progress, CNT-FET based biosensors are likely to play a significant role in advancing healthcare and enabling early and accurate disease detection.

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