The Potential Impact of Artificial Intelligence-Assisted Carbon-Nanotube Field-Effect-Transistor (CNT-FET)-Based Nano-Biosensors on The Diagnosis of The Disease Caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

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INTRODUCTION
SARS-CoV-2, a lethal virus causing the coronavirus-disease-2019 (COVID-19) pandemic(Dong et al., 2020; Spychalski et al., 2020), resulted in high global mortality and morbidity (Almalki et al. 2023; Dong et al. 2020). The evidence suggests that SARS-CoV-2 causes injury beyond the pulmonary clinical manifestations, for instance, thrombotic complications, acute coronary syndromes, renal damages, and hepatocellular injuries (Gupta et al., 2020). Moreover, regional outbreaks caused by emerging variants or subvariants pose a remarkable challenge for early diagnosis, appropriate therapy selection, and effective management of pulmonary and extra-pulmonary sequelae of COVID-19 (Izhari et al., 2024).
The primary step in the management of COVID-19 is accurate, reliable, and speedy pathogen detection (R Liu et al., 2020). Genome (RNA), genome-encoded protein components, and nucleocapsid of the SARS-CoV-2 are the major and reliable molecular targets for the diagnosis of the disease (Yong et al., 2020), however, the most precise diagnostic method is genome detection and/or viral load determination by real-time reverse-transcription–polymerase-chain-reaction (RT–PCR) (Kevadiya et al., 2021; H Wang et al., 2020). Additionally, culture-based-test (C-G Huang et al. 2020), and immunoassay (Antigen and/or antibody detection) using several techniques including lateral-flow rapid assay have also been employed for the diagnosis of COVID-19 (C Li et al., 2020; Mathuria et al., 2020). These diagnostic methods are rigorous, however, they need sophisticated diagnostic laboratories with costly reagents/enzymes and consume time(Islam & Iqbal 2020; Jefferson et al., 2021) which highlights the necessity of cost-effective, simple, highly sensitive, and accurate biosensors/ nano-biosensors/ immune-biosensors for rapid detection of the SARS-CoV-2 /components of the SARS-CoV-2 (Patel et al., 2022; Samson et al., 2020).

Recently, Biosensors-assisted diagnosis of the viral infection has gained remarkable momentum post-COVID-19 pandemic(Mukherjee et al., 2022; Saylan et al., 2019; Trinh et al., 2023). Biosensors have been leveraged for the delineation of the potential biomarkers in the specimens of clinical significance on account of their high sensitivity and reliability (Banakar et al., 2022; Cesewski & Johnson 2020) which is paramount for the diagnosis of SARS-CoV-2 infection (Abid et al., 2021). Biosensors-based detection of pathogens/molecular components of pathogens is advantageous over traditional culture-based or molecular diagnosis (Kaya et al., 2021; Shokeen et al., 2022; Vidic & Manzano 2020). Successful applications of the electrochemical biosensors in viral disease (Hepatitis C virus, influenza A virus, avian influenza virus, and Middle East-Respiratory-syndrome coronavirus) diagnosis have been reported (Antiochia 2020; Sayhi et al. 2018; Timurdogan et al., 2011; Xu et al., 2007). Biosensing devices based on the field-effect-transistor (FET) have been reported to be highly sensitive and instantaneous in measuring the biomarkers using a very small amount of clinical specimens making these devices highly suitable for point-of-care testing (POCT) and rapid management of the disease (Alnaji et al. 2023; Janissen et al., 2017; Nehra & Singh 2015). In the recent past, a CNT-FET-based miniature device for the detection of antibodies (anti-SARS-CoV-2 spike antigen) has been reported which exhibited a very narrow determination range of 5.5 femtogram/ml to 5.5 picogram/ml of the sample (Shao et al., 2021). Additionally, spike (S1) antigen detection CNT-FET-based nano-electro-immuno-biosensor with enormous sensitivity and selectivity has been reported (Mazin A. Zamzami et al., 2022). With the excellent features of CNT, fast-sensing, cost-effective, and miniaturized portable devices (nano-size) can be devised which could pave the way for large-scale, rapid, onsite diagnosis of SARS-CoV-2 infection using CNT-FET-based nano-immuno-sensors even from patients saliva (Bertacchini et al., 2020). Efficient circuit design and circuit-parameter optimization are the key components of the nano-biosensor developmental process and to achieve the desired performance of the biosensing circuit, automation in circuit design is an important factor (Fayazi et al., 2021). Computer-aided design (CAD) tools have been meeting the demand of automating circuit optimization for considerable performance (Back 1996). In the last decades, in many studies, the leverage of Artificial Intelligence (AI) has been taken for analog circuit design leading to the development of high-performance nano-biosensors for biomedical applications (Fayazi et al., 2021). Therefore, this study aimed to summarize the CNT-FET-nano-biosensors,
CNT-FET-nano-biosensors-based diagnosis of SARS-CoV-2 infection, and potential impact of AI on the development of CNT-FET-nano-biosensors along with the future direction of the rapid diagnosis of the SARS-CoV-2 infections.

**COVID-19 Diagnostic Approaches:**

Several technical approaches have been undertaken to diagnose COVID-19 appropriately to curb the large-scale transmission of SARS-CoV-2 and effective clinical management of the disease in a time-bound fashion.

**Genome-Based Diagnosis:**

PCR-based diagnostic assays with high specificity and sensitivity are considered the gold-standard molecular diagnostic methods in viral pathogen genome detection (Hernández-Huerta et al. 2021). Additionally, clustered regularly interspaced short palindromic repeats (CRISPR)-based molecular diagnostic assays (Rahimi et al., 2021) and several genome sequencing techniques have been the most reliable tools in the diagnosis of COVID-19 (Falzone et al., 2021). However, the necessity of sophisticated laboratories (Maurer 2011), trained specialists, the high purity level of clinical specimens, expensive reagents, and prolonged assay reaction time highlight the drawbacks of these diagnostic methods (Afzal 2020; Corman et al., 2020). To address the time-consuming process of genome detection, recently, isothermal nucleic acid amplification-based assays such as recombinase-polymerase-amplification (RPA), reverse-transcription-RPA (RT-RPA) (Liu et al., 2021), loop-mediated-isothermal-amplification (LAMP), reverse-transcription LAMP (RT-LAMP) (W E Huang et al. 2020), helicase-dependent amplification (HDA), and RT-HAD (Shanmugakani & Wu 2022) have been employed for COVID-19 rapid molecular diagnosis (Fig. 1).

**Serodiagnosis:**

Moreover, reliable, rapid, inexpensive, and onsite diagnostic alternatives for large-scale surveillance to curb the transmission of SARS-CoV-2 and to minimize its clinical impacts are required urgently (Larremore et al., 2021). Detection of anti-SARS-CoV-2 antibodies (immunoglobulin G and M: IgG and IgM) (W Liu et al. 2020) and SARS-CoV-2-antigens (Ernst et al., 2021) in blood, plasma, tissue fluids, and other tissue samples using immunological (Zhang et al. 2020), immunochromatographic (Z Li et al., 2020), and dried-blood-spot (DBS) (Amendola et al., 2021) methods is carried out by researchers to meet the desired diagnostic requirements (Fig. 1). Nonetheless, SARS-CoV-2 antigen exhibits identity with antigens of other SARS-CoV viruses which highlights the false positive results (Zhang et al., 2020). Furthermore, anti-SARS-CoV-2 exhibits cross-reactivity with SARS-CoV antigen which is a major challenge for the development of the serological tests for the diagnosis of COVID-19 (Lv et al., 2020). In addition, an immunochromatography-based test does not confirm the presence of the virus and determines only recently infected individuals which highlights the limitation of the method. Anti-SARS-CoV-2 antibodies’ cross-reactivity flags the specificity and sensitivity issue of the technique (Liu & Rusling 2021). Therefore, to address this issue these serological techniques are frequently used in tandem with molecular methods to achieve the confirmatory diagnostic goals.

**Radiodiagnosis:**

Furthermore, the role of radiodiagnosis (cross-sectional image-based) by computer-tomography (CT) (Lee et al., 2020) based on identifying abnormal radiological features (unifocal/multi-foci plaque-consolidation and/or ground glass opacity) (Chung et al., 2020) is crucial in the diagnosis of infection and the clinical manifestations of the disease (X Li et al., 2020) (Fig. 1). Nonetheless, studies showed that chest CT-scan does not appropriately diagnose at the initial stage (Bernheim et al., 2020), also RT-PCR-positive individuals exhibited normal CT at the early stage of the disease (Ai et al., 2020) which explains the probability of missing a few lesions due to low resolution or SARS-CoV-2 might have
targeted other organs than the lungs. However, CT-based diagnosis needs a professional radiologist, and expensive equipment and is often used in conjunction with RT-PCR for confirmatory diagnosis which emphasizes its limitation as a diagnostic tool alone.

Carbon-Nanotube (CNT) and Sensor-Based Diagnosis:

Nacked-eye, non-invasive, sensitive, cost-effective, convenient, biocompatible, and suitable for POCT diagnostic techniques are urgently required to expedite the diagnostic processes for better management of infectious diseases which led to the development of biosensors for biomarker detection. Also, the remarkable application of electronics in the determination of biomolecular markers for the diagnosis of various infections has taken center stage due to the demand for surveillance and early diagnosis with high sensitivity and specificity, recently (Behera et al., 2020). Electrochemical immuno-sensors/optical biosensors/electrical biosensors, very-large-scale integration (VLSI) chip-based biosensors, and FET/CNTFET-based nano biosensors have been used to improve diagnosis (Eissa & Zourob 2020; Ghafer-Zadeh 2015; Ke et al., 2020; Kim et al., 2021; Ovais et al., 2022; C Wang et al., 2020) (Fig. 1).

![Fig. 1. Illustration of the COVID-19 diagnostic techniques and methods. RT-PCR = reverse-transcription-polymerase-chain-reaction; rRT-PCR = real-time-RT-PCR; RPA = recombinase-polymerase-amplification; NGS = next-generation-sequencing; CRISPR = clustered regularly interspaced short palindromic repeats; ELISA = enzyme-linked-immunosorbent-assay; DBS = dried-blood spot; CT = computer-tomography; LFIA = lateral flow immunoassay; FET = field-effect transistor; SESR = surface-enhanced Raman resonance; RT-MCDA = reverse-transcription multiple cross displacement amplification; LSPR = localized-surface plasmon-resonance; CNT = carbon-nanotube; LAMP = loop-mediated-isothermal amplification; RT= reverse-transcription; HAD = helicase-dependent amplification.](image-url)
An electronic digital system is based on logic circuit design and simulation for optimizing the key performance parameters. CNTs are identified to be an efficient building block material that renders the development of ultra-sensitive bio-sensing devices (Zhou et al., 2019). CNTs have imprinting features for rendering supreme quality circuit manufacturing for biosensor development due to their metallic properties, high carrier mobility, and ballistic conduction. (Mohammaden et al., 2022). CNTs’ behavior is dependent on the atomic arrangement along the nanotube termed a chiral vector which is described by indices (m, n). The CNT’s circumference is expressed as a chirality vector (Ch= na_1+ma_2). Thus, CNT-based nanoelectronic circuits could potentially impact the biosensing of molecular biomarkers of diagnostic significance. Moreover, device simulation and device characteristics analysis using several simulators are crucial for improving the circuit performance. Furthermore, the presence of CNTs as a channel in CNTFETs makes ultra-high-speed CNTFET nanoelectronic circuits consume low power making them suitable for biomedical applications (Mehrabani et al., 2017). The fundamental concept of the CNT-FET biosensing of the analytes is illustrated in Figure 2 (Yang et al., 2015).

Fabrication of CNTFET-nano-immuno-biosensor was carried out to use for the convenient and speedy diagnosis of SARS-CoV-2 infection with high specificity as the sensor differentiated the SARS-CoV-1 antigens from spike antigens of other SARS-CoV (Ovais et al. 2022). One of the most fascinating uses of tungsten-disulfide-MWCNT (WS2-MWCNTs) in conjunction with hybridization reaction for ultra-sensitive genomic detection with ultra-sensitivity was spectacular which led to the development of a
diagnostic tool (Liu et al. 2016). An electrochemical biosensor (SWCNTs-based nanocomposite) with ultra-sensitivity was developed to identify nucleic acid target sequences in clinical samples for the diagnosis of infections (Chen et al., 2016). Such efficient biosensors could also be used to diagnose other human coronaviruses such as Middle East Respiratory Syndrome (MERS) (Antiochia 2020). However, there are various potential challenges in the development of the CNT technology which include controlled synthesis, placement of CNTs, and poor interfacial metal-CNT interaction (Daneshvar et al., 2021). Several developed biosensors for laboratory diagnosis of SARS-CoV-2 are summarized in Table 1.

### Table 1. Biosensors employed in diagnosis of SARS-CoV-2 infections

<table>
<thead>
<tr>
<th>Biosensors</th>
<th>Bio-sensor design</th>
<th>Molecular targets (biomarkers)</th>
<th>Specific features</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNT-FET-based electrochemical biosensor</td>
<td>CNT printed Si/SiO2 surface was developed as a biosensor. Non-covalent immobilization of Anti-SARS-CoV-2 S1 on the CNT surface (between the S-D using PBASE linker)</td>
<td>SARS-CoV-2-2-S1-sub-unit antigens</td>
<td>High sensitivity (LOD = 4.12 femtogram/milliliter)</td>
<td>(Mazin A Zamzami et al. 2022)</td>
</tr>
<tr>
<td>EDL-FET-based biosensor</td>
<td>The sensing electrode is coated with anti-SARS-CoV-2 nucleoprotein-antigen and the results are displayed on a smartphone through Bluetooth device</td>
<td>SARS-CoV-2 nucleoprotein-antigen</td>
<td>Sensitivity (LODs = 0.34 nanogram/mL)</td>
<td>(P-H Chen et al. 2022)</td>
</tr>
<tr>
<td>FET-biosensor</td>
<td>Graphene sheet of FET-coated with anti-SARS-CoV-2-spike-antibody</td>
<td>Spike-protein antigen</td>
<td>High sensitivity (LOD = 2.42 × 10² copies/milliliter)</td>
<td>(Seo et al. 2020)</td>
</tr>
<tr>
<td>RT-MCDA-based biosensor</td>
<td>Two primer sets: ORF-1a/b and SARS-CoV-2 nucleoprotein genes.</td>
<td>ORF-1a/b and nucleoprotein gene sequences</td>
<td>LOD = NA, total reaction completion time = 1 hours</td>
<td>(S Li et al. 2020)</td>
</tr>
<tr>
<td>DF-LSPRB</td>
<td>Two-dimensional-AuNIs-DNA receptors (complimentary)/detection based on nucleic acid hybridization</td>
<td>Any selected SARS-CoV-2 marker sequence</td>
<td>High sensitivity (LOD = 0.22 pM)</td>
<td>(Qiu et al. 2020)</td>
</tr>
<tr>
<td>FTO/AuNPs immunobiosensor</td>
<td>FTO-electrodes/AuNPs complex conjugated with anti-SARS-CoV-2 spike-S1-subunit</td>
<td>SARS-CoV-2 spike S1-subunit antigen</td>
<td>High sensitivity (LOD = 0.63 fMP)</td>
<td>(Roberts et al. 2021)</td>
</tr>
<tr>
<td>LFIA biosensor</td>
<td>Phage-display technology to generate fusion antibodies to trap NP-antigens</td>
<td>SARS-CoV-2 nucleoprotein-antigen</td>
<td>High sensitivity (LOD = 10 copies/microliter)</td>
<td>(Kim et al. 2021)</td>
</tr>
<tr>
<td>LFIA-nano biosensor</td>
<td>SARS-CoV-2-nucleoprotein-antigen coupled with selenium nanoparticle</td>
<td>Anti-SARS-CoV-2 NP antigen (IgG and IgM)</td>
<td>anti-NP IgG-LOD 20 and anti-NP IgM-LOD 60 ng/mL</td>
<td>(C Chen et al. 2022)</td>
</tr>
</tbody>
</table>

CNT = carbon nanotube, FET = field-effect transistor, DF-LAPRB = dual-functional-LSPR-biosensor, PTT = combining the plasmonic photothermal (PTT); LSPR = localized surface plasmon resonance; AuNIs = gold-nanoislands, LOD = Limit of detection, pM = picomole, LFIA = Lateral-flow immunoassay, PBASE = 1-pyrenebutanoic acid succinimidyl ester, FTO = fluorine-doped tin oxide, EDL = electrical double layer, RT = reverse transcription, MCDA = multiple cross-displacement amplification.
Impact of Artificial Intelligence (AI) in CNT-FET-Based Circuit Design:

Accuracy in electronic circuit design is paramount. AI advancements offer huge potential in circuit design and optimization. Manual calculation of the significant design parameters of the nanoelectronic circuit poses a greater challenge, and inefficiency due to the model complexity, especially during the downscaling process (Lyu et al., 2018). Furthermore, following the design, the simulation studies are also a lengthy, time-consuming process, and error-prone. Therefore, automation in design and simulation is highly needed to meet the growing market demands for low-power and miniaturized integrated circuits (ICs) for various applications (Zhang et al., 2019). In the recent past, many studies have attempted to leverage the potential of AI in electronic circuit design. Using AI automated circuit-sizing optimization and accuracy of the performance models can be successfully achieved. AI-based design tools and algorithms not only automate the design process but also offer the design of an efficient circuit by analyzing the avalanche of complex design and performance-related data to predict the suitable combinations of the circuit components with high efficiency resulting in the development of low-power consuming, least signal interference and reduced heat generation (Li et al. 2021). Various aspects of the impact of AI on electronic circuit design are illustrated in Figure 3.

Fig. 3. Multifaceted impact of artificial intelligence on electronic circuit design. PCB = physical printed circuit board, DRC = Design rule checking, and AI = artificial intelligence.

AI or its sub-domain machine learning (ML) has been recognized as a potential analytical tool to address circuit design-related issues with its potentialities to make automated calculations and predictions of design parameters by deeply mining complex data (Zhao et al., 2020). AI operation is based on training with pre-labeled data to provide appropriate predictions on fresh data input which plays a crucial role in expediting the experimental and computational analysis (Floreano & Mattiussi 2008). In addition, AI in combination with other methods could be used to figure out the yield estimation and to generate high-order models (Lin et al., 2018). ML is advantageous over traditional qualitative and quantitative algorithms because it can analyze high-dimensional datasets efficiently and find significant connections and patterns among the various aspects of the design.
parameters (Volk et al. 2020). The appropriate applications of random forests, decision trees, support vector machines, and artificial neural networks ML algorithms have been reported in recently published scientific reports (Bhatti et al., 2023; Charbuty & Abdulazeez 2021; Ding et al., 2011) that could play a crucial role in nanoelectronic circuit design (Rosa et al., 2020). The conventional inverse approach is compared with artificial intelligence-based, especially, the neural networks-based direct approach of electronic circuit design in Figure 4 (Rosa et al., 2020).

Fig. 4. Impact of AI on electronic circuit design: (a)-design variable to performance inverse approach (inverse approach), and (b)-electronic circuit performance to design variables using AI-artificial neural networks.

Conclusion and Future Outlook:

The burden of the disease caused by emerging viruses, in the recent past, has drastically increased. Error-prone viral replication generates a vast range of variants, subvariants, and covariants of a wild-type virus, especially RNA viruses, for instance, SARS-CoV-2. Therefore, molecular diagnostic procedures based on detecting some conserved genomic elements of the virus sometimes give inappropriate diagnoses. In addition, direct electron microscopy and viral culture-based diagnosis are time-consuming and costly. Rapid immune-chromatographic tests and immunoassays based on antigen-antibody interaction are comparatively less time-consuming, however, the specificity and sensitivity are not remarkably high. Therefore, the development of biosensors with high sensitivity for diagnosing viral disease has recently gained the attention of researchers globally. Several classes of biosensors have been used in the successful diagnosis of COVID-19 disease leading to the increasing demand for high-performance biosensors. Using nanomaterial, for instance, CNTs to enhance the performance level of biosensing devices has been paramount. CNT-based biosensors, especially, CNT-based FETS offer ultra-sensitivity and reduced-noise analyte detection systems which facilitate the biomolecules even in a narrow concentration range. Such low-concentration (typically analyte is in low concentration at an early stage of the
infection) detection systems facilitate the early diagnosis of the viral infection. CNT-FET-based biosensors exhibited remarkable diagnostic potential in diagnosing COVID-19 disease which underlines the commercial interest in CNT-FET-based biosensors development. Therefore, the design and simulation of the CNT-FET with high performance is crucial to meet the diagnostic necessities. Taking the leverage of the advancement of artificial intelligence to analyze complex simulation data, and predict appropriate design variables and vital performance parameters suitable for the diagnostic application. Taking advantage of the combination of the CNT-FET and artificial intelligence, the diagnostic challenges for the COVID-19 diagnosis could be minimized, and a promising, accurate, speedy, and cost-effective diagnostic solution could be achieved. However, CNT production and its solubility are some of the major challenges.

**Declarations:**

**Ethical Approval:** Not applicable

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