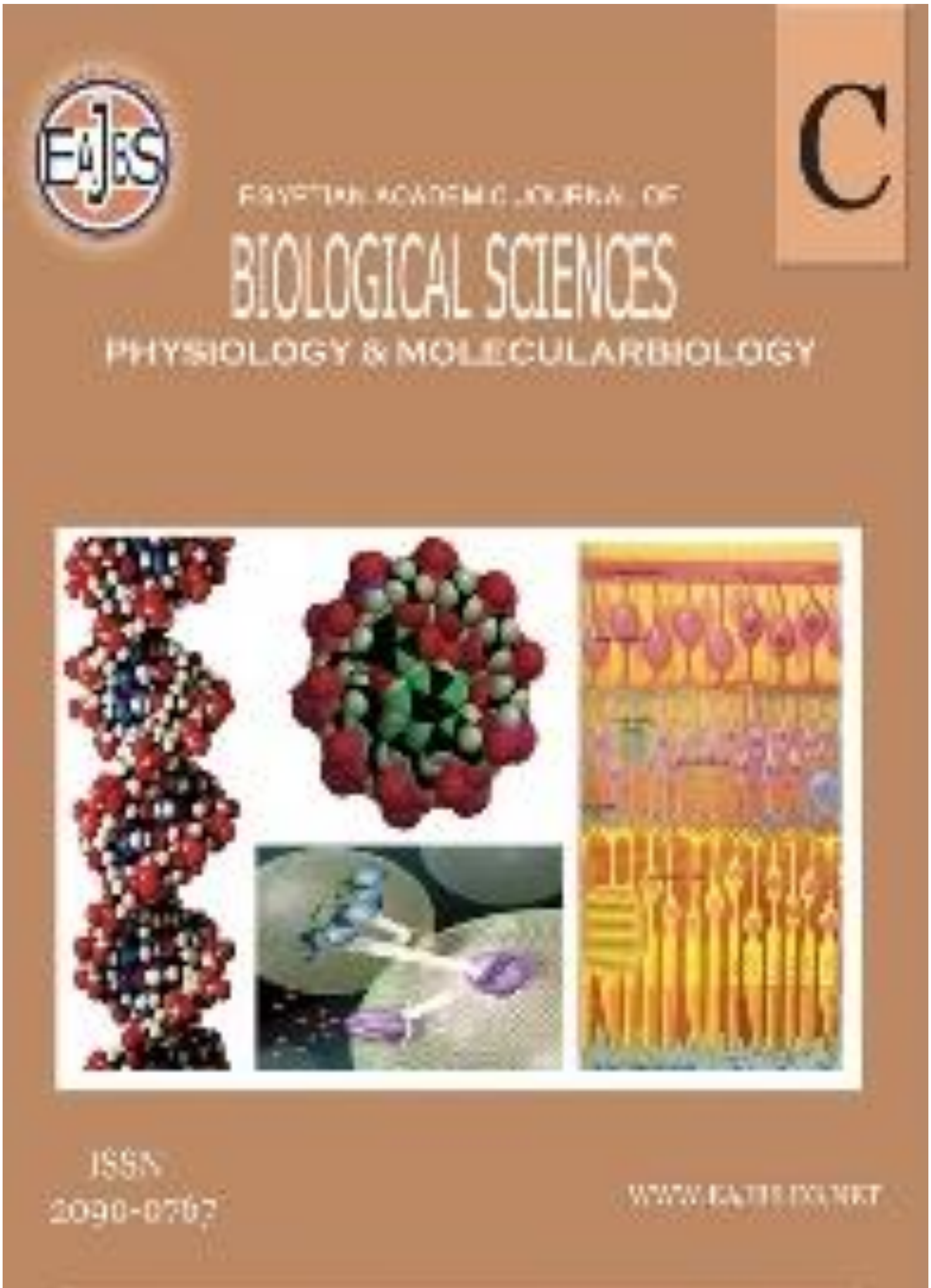

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The Potential Impact of Artificial Intelligence-Assisted Carbon-Nanotube Field-Effect-Transistor (CNT-FET)-Based Nano-Biosensors on The Diagnosis of The Disease Caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

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ABSTRACT

Rapid, appropriate, and reliable diagnosis is paramount for selecting a suitable therapeutic intervention for the clinical management of COVID-19. Several serological and molecular diagnostic methods are available, however, biosensor-based diagnosis has been employed in the diagnosis of viral diseases including COVID-19 due to its high specificity, sensitivity, expeditiousness, low cost, and capability to detect the analyte even at low concentrations, especially during the initial stage of infection and pathogenesis. Due to the high conductivity, and thermal and mechanical stability of CNT, it is considered a potential candidate for biosensor development, for instance, CNT-FET-based biosensors. However, the designing and simulating a high-performance, low-power, and miniaturized CNT-FET nanoelectronic device suitable for diagnostic applications, especially, point-of-care testing (POCT) is crucial for rapid and appropriate diagnosis of COVID-19 and other related viral diseases. Taking the leverage of the advancement of artificial intelligence, attempts have been made to boost the CNT-FET technology and the development of efficient CNT-FET-based biosensor models with accurate performance. This article explains the fundamental concept of the biosensor-based diagnosis of the COVID-19 disease, application of the artificial intelligence to increase the accuracy of the high-performance model, and the approach to standardize the design variables and performance parameters of the nanoelectronic circuit suitable for diagnosis. Moreover, the article highlights the current challenges and meaningful insights into their application in viral disease diagnosis beyond COVID-19 and the future perspective of the CNT-FET-based sensors in viral disease diagnosis.

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 2021). 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-bio-sensors 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; Ghafar-Zadeh 2015; Ke *et al.,* 2020; Kim *et al.,* 2021; Ovais *et al.,* 2022; C Wang *et al.*, 2020) (Fig. 1).

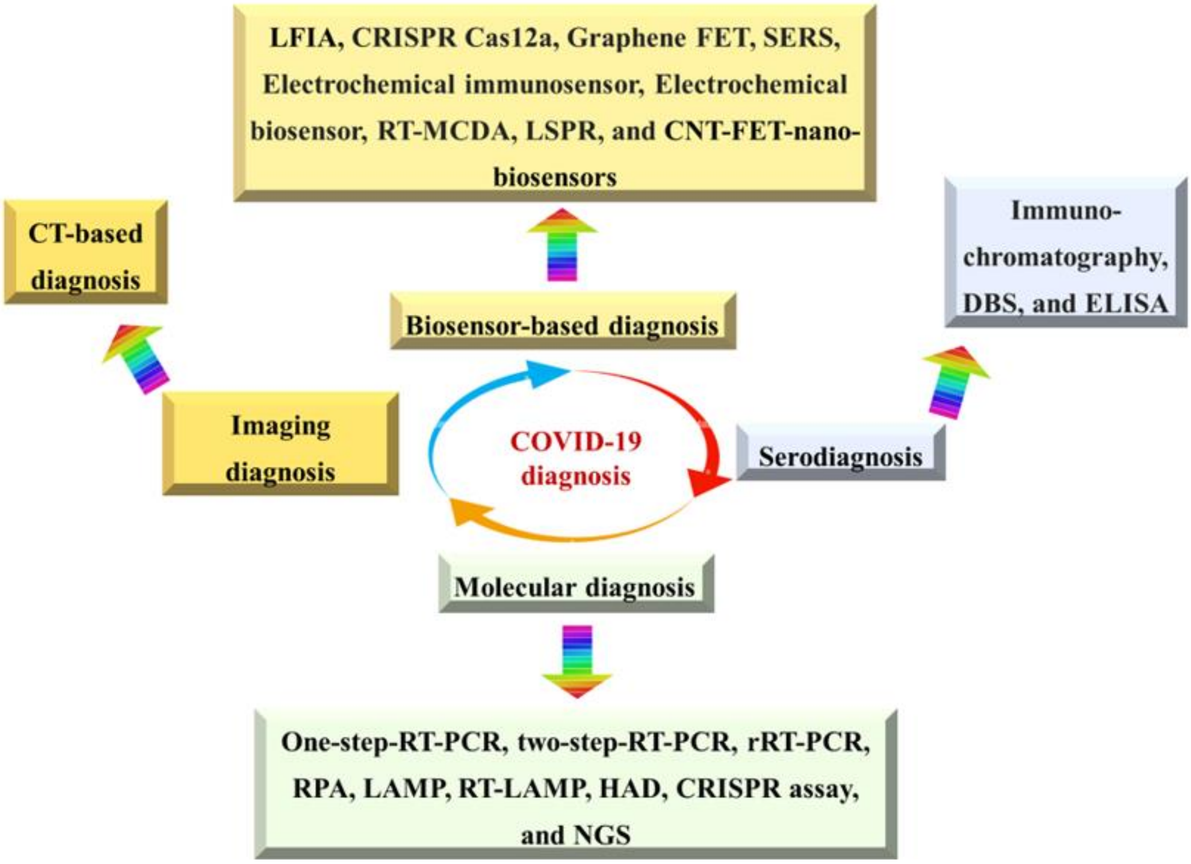

Fig. 1. Illustration of the COVID-19 diagnostic techniques and methods. RT-PCR = reverse-transcription-polymerase-chain-reaction; rRT-PCR = real-time-RT-PCR; RPA = recombinase-polymerase-amplification; NGS = next-generation-sequencing; CRISPR = *clustered regularly interspaced short palindromic repeats; ELISA = enzyme-linked-immunosorbent-assay; DBS = d*ried-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.

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).

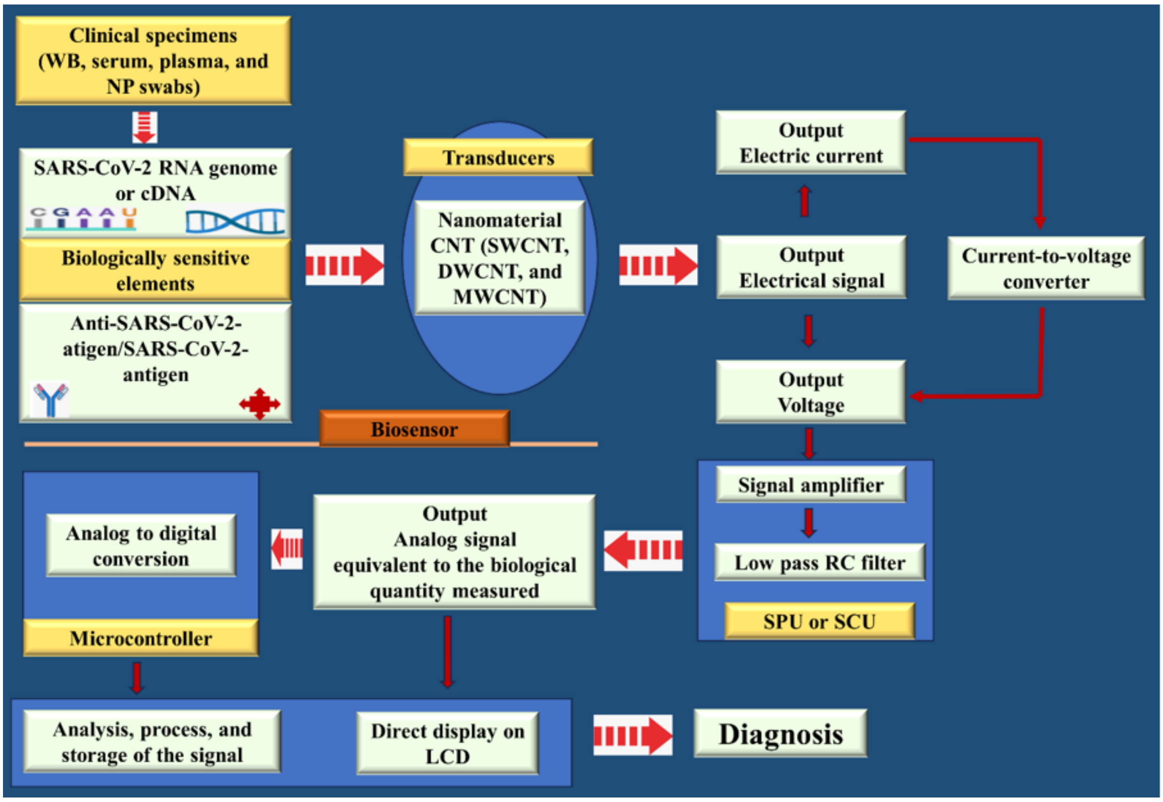

Fig. 2. Principal components of the CNT-based biosensor for the COVID-19 disease diagnosis. LCD = Liquid crystal display, SPU = Signal processing unit, SCU = Signal conditioning unit, RC = Resistor-capacitor, CNT = carbon nanotube, SWCNT = single-walled CNT, DWCNT = double-walled CNT, and MWCNT = multi-walled CNT.

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

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

CNT = carbon nanotube, FET = field-effect transistor, DFLAPRB = dual-functional-LSPR-biosensor; PTT = combining the plasmonic photothermal (PPT); 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.

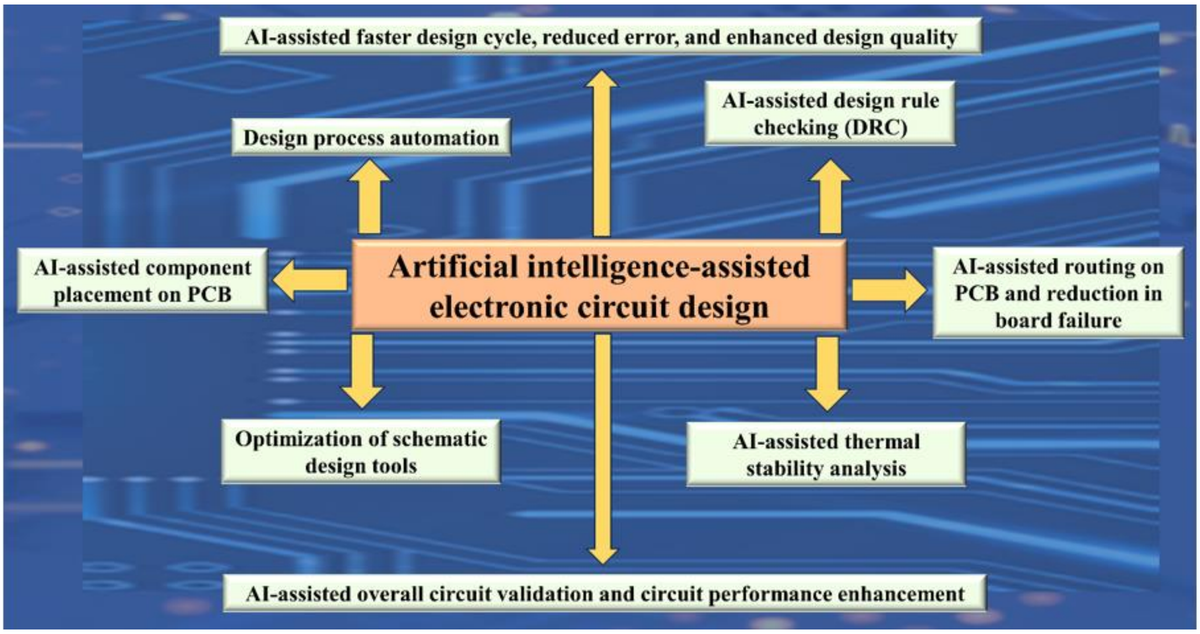

Fig. 3. Multifaceted impact of artificial intelligence on electronic circuit design. PCB = physical printed circuit board, DRC = Design rule checking, and AI = artificial intelligence.

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 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).

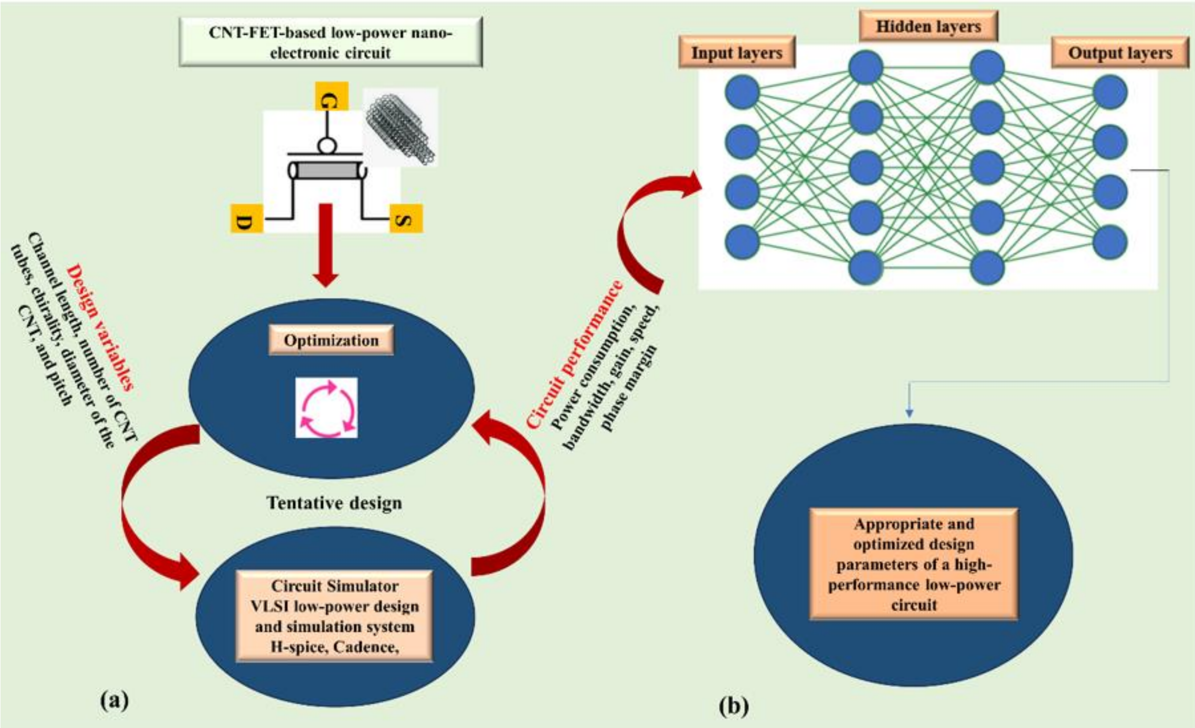

Fig. 4. Impact of AI on electronic circuit design: (a)-design variable to performance inverse approach (inverse approach), and (b)-electronic circuit performance to design variables using AI-artificial neural networks.

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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