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CRITICAL REVIEW

Low-dimensionality carbon-based biosensors: the new era of emerging technologies in bioanalytical chemistry

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Abstract

Since the last decade, carbon nanomaterials have had a notable impact on different fields such as bioimaging, drug delivery, artificial tissue engineering, and biosensors. This is due to their good compatibility toward a wide range of chemical to biological molecules, low toxicity, and tunable properties. Especially for biosensor technology, the characteristic features of each dimensionality of carbon-based materials may influence the performance and viability of their use. Surface area, porous network, hybridization, functionalization, synthesis route, the combination of dimensionalities, purity levels, and the mechanisms underlying carbon nanomaterial interactions influence their applications in bioanalytical chemistry. Efforts are being made to fully understand how nanomaterials can influence biological interactions, to develop commercially viable biosensors, and to gain knowledge on the biomolecular processes associated with carbon. Here, we present a comprehensive review highlighting the characteristic features of the dimensionality of carbon-based materials in biosensing.

Keywords Carbon nanomaterials · Low dimensionality · Biosensors · Graphene · Bioanalytical chemistry · Biotechnology

Abbreviations

0D	Zero-dimensional
1D	One-dimensional
2D	Two-dimensional
3D	Three-dimensional
AuNC	Gold nanocages
BOD	Bilirubin oxidase
BSA	Bovine serum albumin
CDs	Carbon dots
CNDs	Carbon nanodiamonds
CNFs	Carbon nanofiber
CNHs	Nanohorns
CNTs	Carbon nanotubes
COVID-19	New coronavirus disease
CQD	Carbon quantum dots
CSCNTs	Cup-stacked carbon nanotubes
CVD	Chemical vapor deposition
DA	Dopamine
DNA	Deoxyribonucleic acid
Dox	Doxorubicin
ds-DNA	Double-stranded DNA
FCF	Flexible carbon fibers
FEG-SEM	Field emission–scanning electron microscope
FET	Field-effect transistor
fM	Femtogram
GFET	Graphene field effect transistor
GO	Graphite oxide
GOx	Glucose oxidase
GQD	Graphene quantum dots
Gr	Graphene
HA	Hyaluronic acid
HRP	Horseradish peroxidase
IgG	Immunoglobulin G
ITO	Indium tin oxide
Lamp	Loop-mediated isothermal amplification
LB	Langmuir–Blodgett technique
LbL	Layer-by-layer technique
lncRNA	Non-coding RNA
LOD	Limit of detection
miRNA	MicroRNA
MWCNTs	Multiwalled carbon nanotubes

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M*v*BOD	*Myrothecium verrucaria* BOD
NIR	Near-infrared spectroscopy
OCP	Open circuit potential
OGB	Oxidated graphene bilayer
ORR	Oxygen reduction reaction
PEI	Polyethyleneimine
PL	Photoluminescence
pM	Picogram
PNR	Poly-neutral red
POC	Point-of-care testing device
QD	Quantum dots
RBD	Receptor-binding domain
rGO	Reduced graphene oxide
RNA	Ribonucleic acid
RT-PCR	Reverse transcription polymerase chain reaction
SEM	Scanning electron microscope
ss-DNA	Single-stranded DNA
SWNTs	Single-walled carbon nanotubes
TCVD	Monolayer graphene-based three-component vertically designed device
UV	Ultraviolet
WOR	Water oxidation reaction
XA-NSEC	X-ray absorption nanospectroelectrochemistry
XAS	X-ray absorption spectroelectrochemistry
XPS	X-ray photoelectron spectroscopy

Introduction

Diagnostic technologies represent one of the market's top sectors, especially because around 70% of medical choices are supported by diagnostic devices [1]. Depending on the application, biosensors can be constructed using proteins, whole cells, aptamers, RNA, or DNA [2, 3]. Due to these broad capabilities, carbon-based material usage in biosensors is established as successful, as seen in academic research and commercial products [3–5]. In particular, carbon-based materials can be used for the electrochemical detection of various analytes due to their distinctive electrochemical characteristics, including a broad potential window, low cost, and a negligibly small background current [6]. Additionally, the biocompatibility of carbon materials has completely transformed their potential application [7].

Carbon can form long chains of atoms, consequently exhibiting the phenomenon of polymerization. Despite having the same chemical composition, carbon atoms possess an electronic structure and atomic size that enable them to display various physical structures and distinct physical attributes; further, the fundamental standard for categorizing nanomaterials (Fig. 1) is the geometrical structure of the particles [6, 8]. The particles may include spheres and

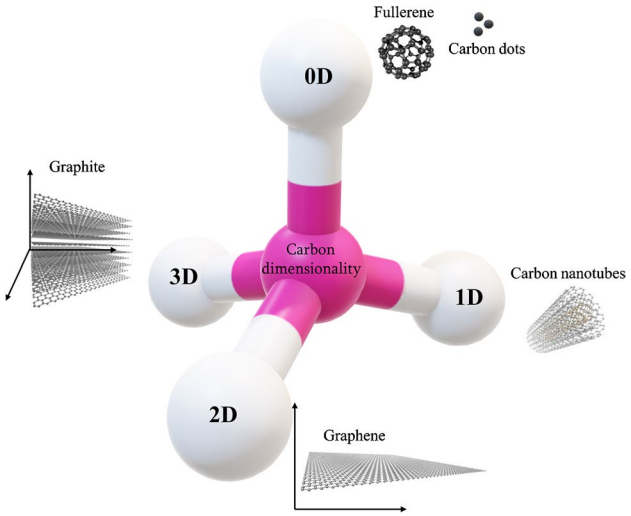

Fig. 1 Examples of 0D, 1D, 2D, and 3D carbon-based nanomaterials

ellipsoids (presented as fullerene structures), carbon nanotubes (CNTs), and nanohorns (CNHs). Allotropes of carbon, such CNTs, graphene, fullerene, carbon dots (CDs), and carbon nanodiamonds (CNDs), are typically used in biosensing applications. Commonly, the dimensionality is classified as follows [9]: (i) zero-dimensional (0D)—including graphene quantum dots (GQD), fullerenes, and carbon quantum dots (CQD); (ii) one-dimensional (1D)—CNTs, single-walled carbon nanotubes (SWNTs), multiwalled carbon nanotubes (MWCNTs), or cup-stacked carbon nanotubes (CSCNTs); (iii) two-dimensional (2D)—graphite and graphene; (iv) three-dimensional (3D)—carbon nanofibers (CNFs), carbon sponges felt, and a myriad of composites [10]. The 2D and 1D nanomaterials are gaining popularity, laying the groundwork for a profound revolution in the flexible electronics/sensors sector [11]. Functionalization [6] and immobilization of biomolecules [3] are common for preparing carbon-based materials for biosensing/sensing purposes.

Carbon nanotechnology has already had a notable impact on different fields, such as energy storage [12], catalyst [13], energy conversion [14], electromagnetic shielding [15], bioimaging [16], drug delivery [17], artificial tissue engineering, DNA sequencing [7], and biosensors [18–23]. Efforts are underway to understand how nanomaterials can influence biological interactions [24]; further, to develop an appropriate sensor platform, integrated knowledge about carbon structure and biomolecular events is necessary. The use of carbon-based nanomaterials in biosensing is very versatile to create distinct biosensor platforms [16, 25–28], and relies on the enhanced signal and/or the immobilization of the target analyte and bioreceptor [29]. For example, biomolecule immobilization together with carbon-based nanomaterials can be obtained in undemanding experimental setups by using nanostructured films, for example, via

the layer-by-layer (LbL) and Langmuir–Blodgett (LB) techniques, providing new biosensor nanoarchitectures [30–34]. Those architectures can be diverse and provide different types of sensing platforms depending on the application [6]. However, new biosensor platforms can be designed and chosen according to the dimensionality and structural characteristics of carbon nanomaterials, which encouraged us to write the present review article. Here, we highlight the characteristic features of dimensionality of carbon-based materials in biosensing, with a focus on the literature of the last years.

0D carbon nanomaterials

The most explored examples of 0D carbon nanomaterials are quantum dots, either in the form of CQD or GQD, fullerenes, and nanodiamonds [16, 35]. GQD is considered a small piece of graphene with a length of less than 100 nm; ideally, for GQDs, a length of less than 30 nm is considered a practical benchmark size that greatly enhances quantum confinement effects [36]. An intrinsic characteristic of quantum dots is that they possess an optical absorption peak in the UV region relative to the π–π* transition, relative to the sp^2 hybridization. The electronic spectroscopy characteristics of QDs are greatly influenced by the presence of doping elements, often nitrogen, phosphorus, and sulfur; defects, such as the alterations of C = O bonds; or surface functionalization, which lead to additional n–π* transitions; additionally, some photoluminescence (PL) mechanistic–associated pathways are being under discussion [37].

A great extent of QD usage relies on their PL properties; GQDs showing a higher emission yield than CQDs, yet often still low, with the emission wavelength being greatly dependent on the particle size, amount of defects, functionalization types, or doping concentration, renders GQDs highly versatile and amenable for light emission tunability through bandgap engineering strategies, as represented in Fig. 2(A) [38]. The same is noticed for electroluminescence, in which the fluorescence emission results from the quantum confinement of sp^2 domains and is modulated through sp^3 defects and doping elements [39]. In GQDs, it is known that the surface functionalization associated with the delocalization of electrons and holes affects the recombination of electron–hole pairs, leading to enhanced photoemission due to decreased graphene symmetry [40]. When graphene is used in the form of GQDs, a particular practical case occurs if the material is highly oxidated, often named as graphene oxide quantum dot, with distinct spectral features and implications for QD–solvent interactions [41].

The synthetic strategies include the arc discharge of graphite, laser ablation, and electrochemical oxidation as top–down examples, and CVD, micro/nanoemulsion, microwave irradiation, and hydrothermal protocols as bottom–up examples [39]. More recently, biological and green routes have also been explored [42]. The commonplace balance of top–down versus bottom–up approaches certainly applies here, with the former group of methodologies requiring dispendious facilities and instrumentation while enabling the rapid production of nanoparticles and allowing usage of less noble carbon sources as precursors, at the cost of limited size control. The latter requires less expensive instrumentation but often lengthy protocols, with the advantage of the controllable products' size, doping level, and overall properties, especially via the cautious selection of carbon precursors.

The surfaces of both CQDs and GQDs can be functionalized through a myriad of strategies, either simple physisorption or via exploring reactions, such as amide coupling, coupling streptavidin–biotin for affinity binding [43], and even click-chemistry [44]. Zero-dimensional carbon nanomaterials have a wide range of applications in bioanalysis literature, especially driven by the thrilling advances in liquid biopsy and point of care [45, 46], owing to their photoluminescence and electroluminescence properties, which makes these materials unique compared to 2D or 3D carbon nanomaterials, or via electrochemical approaches. Additionally, readers can find examples and future expectations concerning the use of 0D carbon nanomaterials in recent reviews [16, 47]. Here, some frontier applications associated with biosensing and bioimaging are highlighted as they represent some of the major advances in using CQDs and GQDs for bioanalysis.

The optical features of both CQDs and GQDs show exciting versatility for their practical usage, as the wavelength of their maximum photoluminescence can be easily tuned via the introduction of distinct groups at the edges of the material and modulating the bandgap and producing redshifts of up to 200 nm either by inducing the formation of an additional π character or by creating n-orbitals to the structure, as exemplified (Fig. 2(A)) [38].

In electrochemistry-based biosensors, the use of CQDs has found success in improving the early detection of biomarkers for life-threatening conditions, such as myocardial infarction and heart failure, which are often detected or monitored through biomarkers such as troponin-I and troponin-T, creatine kinase, and myoglobin. A screen-printed electrode decorated with graphene quantum dots and gold nanoparticles, followed by anti-cardiac troponin-I, was recently developed [50]. The electrochemical analyses were performed using human serum, providing quantitative results in ca. 10 min with square-wave voltammetry, until concentrations as low as 0.5 pg mL^{-1}. In a similar context, a study explored the photoelectrochemical sensing of troponin-I using a modified electrode capable of generating a large variation in photocurrent and charge-transfer impedance via antigen–antibody interactions [51]. Zinc stannate (Zn_2SnO_4) cubes were deposited onto an indium–tin oxide

(ITO) glass conducting electrode, followed by subsequent modification with N,S-GQDs and CdS, employed to co-sensitize the cubic particles, narrow down the bandgap, and enhance the photoelectric properties of zinc stannate. Using this approach, troponin-I concentrations as low as 0.3 pg mL^{-1} were detected in serum.

In electrochemical experiments, it is very important to consider the complexity of the samples, which frequently translates to the requirement of the anti-fouling ability of the biosensor surface. As an example, a research engendered a sensing platform comprising of vertically ordered mesoporous silica–nanochannel film, with channels < 5 nm in size perpendicular to the underlying gold electrode, resulting in an anti-biofouling ability [48]. The nanochannel platform was modified with OH– and NH_2–GQDs through electrophoresis, as shown in Fig. 2(B), to act as a recognition element or signal amplifier. Their GQD-based platform enabled the detection of Hg^{2+}, Cd^{2+}, Cu^{2+}, and dopamine through differential pulse voltammetry in complex samples such as seafood, soil-leaching mixtures, and serum, achieving quantification in the pM to nM range. This approach complements the widely reported sensing of heavy metals due to their affinity to functionalized GQDs (affinities of HO-GQDs for Hg^{2+} and Cd^{2+} for H_2N-GQDs), therefore inducing a fluorescence quenching optical effect; in complex samples, however, the selectivity of these photoluminescence quenching approaches is a challenge.

In another example, GQDs were employed as substrates for horseradish peroxidase (HRP) to provide an amplified electrochemical signal for the biosensing of a specific miRNA chain, accompanied by a change in the color of the solution [52]. The GQD-based miRNA enzymatic biosensor platform was used to analyze human serum samples and achieved the detection of the analyte in the fM to pM range. The detection of miRNA was recently explored, designing a biosensing platform for the quantification of a specific pancreatic cancer–derived miRNA, expressed as pre-miR-132, based on the fluorescence variation of N-doped GQDs when bound to a bait ss-DNA sequence or the bait-target assemble, in a likely charge-transfer event [53]. The minimal concentration in the micromolar range indicates that these important biomarker sensors possess the potential for achieving ultrasensitive detection. It must be highlighted that despite the interesting electrochemical properties of CQDs and GQDs, the optical features of these materials, especially their photoluminescence, are pivotal properties that make them unique, compared to commonplace carbon nanomaterials with higher dimensionality. For this reason, the PL of carbon-based nanomaterials is often explored in the bioimaging field.

As a clear example of CQD usage as a fluorescent nanoprobe, a research developed an assembly of polyethyleneimine (PEI)–modified CQDs (P-CD) and hyaluronic acid–conjugated doxorubicin (Dox, a chemotherapy drug), which show only weak photoluminescence emissions in the normal cellular environment (NIH-3T3) [49]. In the aforementioned study, the authors explored the high affinity of hyaluronic acid (HA) to CD44 receptors, which are overexpressed on the membranes of several cancer cells. HA is cleaved by hyaluronidases after endocytosis; further, it is commonly more abundant in cancer cells. Hence, the P-CD/HA-Dox probe is easily absorbed by cancer cells, and after cleavage of HA-Dox, the fluorescence of P-CDs is restored, and the cells become optically identifiable (Fig. 2(C)). Additionally, as Dox is then cleaved from HA, it can intercalate with DNA pairs and inhibit efficient replication; therefore, these probes acted as both bioimaging and drug-delivery probes.

For additional examples of CQDs and GQDs applied to biosensing and bioimaging, especially for circulating nucleic acid bioanalysis, the readers can refer to the selected literature [54, 55]. Although we highlighted quantum dots, applications of fullerenes can be found in literature as photoactive materials bound to dyes, such as methylene blue [56], and as a charge-transfer mediator, especially for nucleic acid sensing [57, 58]. Nanodiamonds represent the other class of 0D-carbon nanomaterials of interest, showing high biocompatibility, the typical chemical inertness of diamonds, a high surface area, the possibility to functionalize surface regions (as in $–NH_2$ and –COOH-terminated nanodiamonds), and the ability to be used for drug delivery and bioimaging, especially with tailored structure defects that drive photoluminescence [59].

1D carbon nanomaterials

The group of 1D carbon-based nanomaterials commonly explores carbon nanofibers and carbon nanotubes, either in the form of a single cylindrical graphitic sp^2-hybridized carbon network denominated single-walled carbon nanotube (SWCNT), or in the form of concentrical multiple cylindrical structures, in the so-called multiwalled carbon nanotubes (MWCNT); other less common presentations are also possible, such as the cup-stacked carbon nanotubes (CSCNT), with higher edge content and, therefore, oxidized functional groups, with crucial consequences to electrostatic interactions and charge transfer [26]. These nanomaterials can be produced by arc discharge and laser ablation [60], but catalytic chemical vapor deposition is a classic and very efficient method of producing nanotubes of a wide range of diameters and lengths, with good helicity control—although still a challenge—due to the initial hemispherical pentagon cap formation, driving, and defining the elongation of the CNTs [26]. In these materials, the optical and chemical properties are greatly affected by the doping—either electron donors or acceptors [61], and some methods have been shown to promote controllable doping [62]. Structural topological and

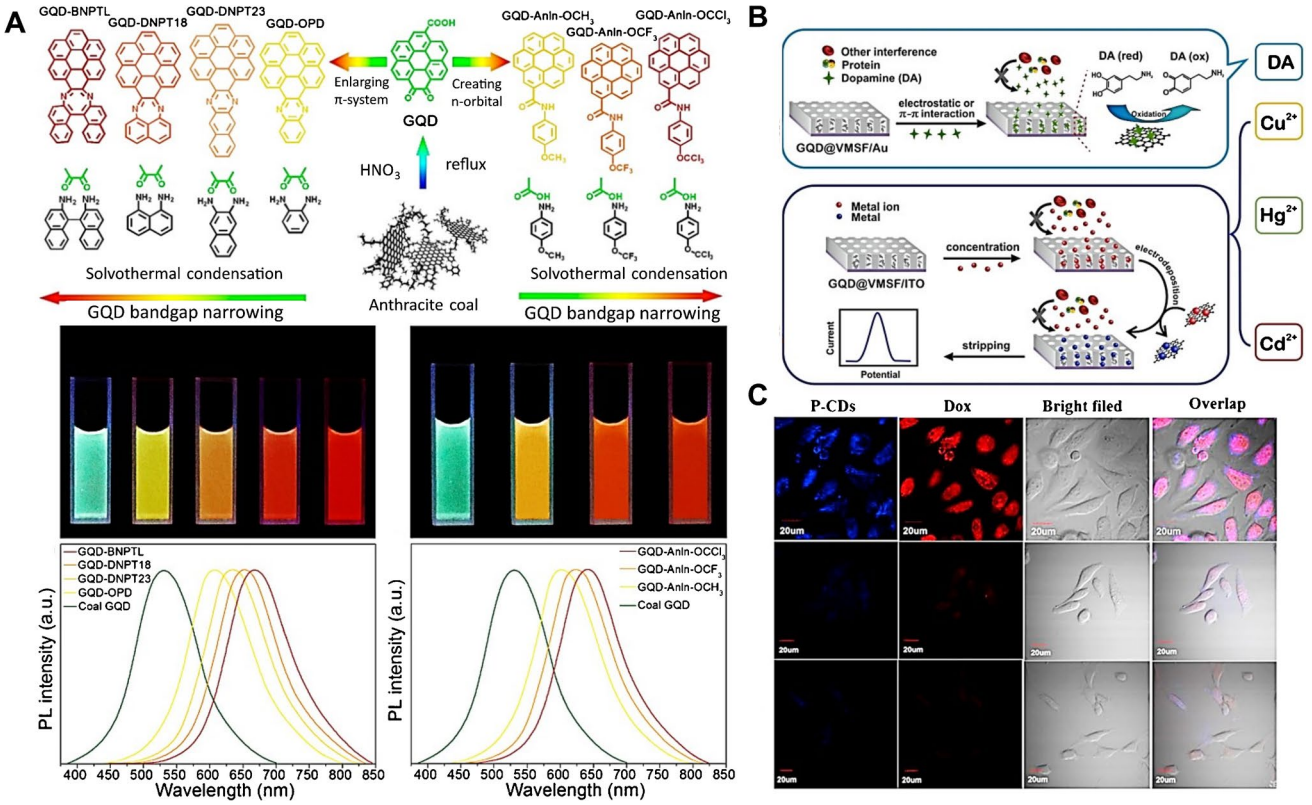

Fig. 2 (A) (Top) Schematic representation of the tuneable photoluminescence redshift caused by the introduction of n-orbitals or by the enlargement of π-systems in GQDs, with their photographs under a UV lamp (middle) and the respective spectra (bottom). Reproduced from [38] with permission from the American Chemical Society. (B) Incorporation of GQDs into a mesoporous silica–nanochannel film through electrophoresis, resulting in anti-fouling properties for the electrochemical sensing of Hg^{2+}, Cd^{2+}, Cu^{2+}, and dopamine (DA) in complex samples, such as food, soil, and serum. Reproduced (adapted) from [48], with permission from the American Chemical Society. (C) Bioimaging of HeLa cancer cells based on the fluorescence of CQDs after endocytosis due to preferential hyaluronic acid–CD44 interactions compared to normal cells, in blue and red channels, and the corresponding bright field (first row); HeLa cancer cells pre-treated with hyaluronic acid, showing weak PL (middle row), and non-cancer NIH-3T3 cells indicating weak PL (bottom row). Reproduced from [49], with permission from Elsevier

incomplete bonding defects, such as vacancies, pentagons, and heptagons disrupt carbon hexagons' regularity and, therefore, cause important electronic charge localization and produce changes to the density of states [63].

When it comes to CNT properties, the regularity of the structure as a rolled-up graphene sheet promotes high conductivity in the length axis, thermal stability, and mechanical resistance, leading to a wide presence of these materials in bioanalytical devices, most often as electrical conductivity enhancers for transduction [18]. While MWCNTs behave as metallic conductors, SWCNTs are more versatile as a semiconducting characteristic can also be obtained depending on the diameter and helicity control, and the present bandgap in this case is responsible for near-infrared fluorescence emission [64]. The anisotropy relative to the edge regions, with a higher amount of oxidized groups, also provides a central role in electron transfer and electrocatalysis [65]. Additionally, as commonplace routes for CNT production employ metallic precursors, researchers should be extremely careful about metallic impurities which can promote catalytic artifacts and undesired contamination in biological environments [66].

In terms of 1D carbon-based material applications in bioanalytical devices, there is a wide range of well-succeeded examples in literature, mostly for biomarker sensing and cell bioimaging, with recent interests boosted by the point-of-care (POC) development trend and the exciting research pathway toward ultrasensitive biosensing for liquid biopsy. In this context, an ultrasensitive and selective biosensor was developed for quantifying breast cancer exosomal miRNA21 [67]. For this, the authors employed CNTs as the channel material in a field-effect transistor (FET), as in Fig. 3(A), with subsequent incorporation of gold nanoparticles onto which a thiolated DNA probe is chemically linked as the recognition element. The hybridization of the miRNA leads to a current change in the CNT-FET device, and authors reached an attomolar limit of detection, with satisfactory performance in clinical samples.

A p-type CNT-FET strategy was also employed for the fast detection of the SARS-CoV-2 surface spike protein S1, employing CNTs as charge-transfer transducers and relying on anti-SARS-CoV-2 S1 antibodies to grant selectivity to the protein [68]. The variation of current induced by the antigen–antibody coupling in the affinity sensor in the case of a positive response was evaluated in fortified saliva, and the platform was able to achieve a limit of detection of 4.12 fg mL^{-1}.

In the context of POC bioanalytical development, CNT-FETs are also showing important advances to allow the early diagnosis of health conditions, such as through blood biomarkers, which brings the additional challenge of low biomarker concentration and high protein concentration that promotes surface biofouling [45, 69]. A CNT-FET biosensor for the β-amyloid, using aptamers as the recognition element in the affinity sensor and 6-mercapto-1-hexanol, tween 20, and bovine serum albumin (BSA) for anti-biofouling, was proposed [69]. The sensor delivered high selectivity ratios for two tested amyloid peptides and a limit of detection in the attomolar range.

The usage of MWCNTs as electroactive materials for the anchoring of metallic nanoparticles and biorecognition elements is also being frequently explored [74–76]. In recent work, the detection of a long non-coding RNA (lncRNA), a molecule with regulatory roles and with an increased circulating concentration in conditions such as lung adenocarcinoma, was performed by the engineering of a disposable electrode strip based on amidated MWCNTs as a conducting supporting element for the incorporation of gold nanocages (AuNC) and a specific probe DNA (Fig. 3(B)) [70]. The recognition of the target DNA in this affinity sensing platform promotes a current variation and limit of detection in the femtomolar range, with good results in human serum samples.

When it comes to exploring bioanalytical imaging, carbon nanotubes have been employed with success with multiple distinct strategies. A single-chirality SWCNT probe was used for biosensing due to their optical properties as NIR bands and Förster resonance energy transfer (FRET), developing a set of functionalized CNTs coated with helical polycarbodiimide polymers with distinct functionalities [71]. By differential interaction of each functionalized SWCNT with sub-cellular structures, the authors were able to observe internanotube FRET and image separate parts of the cell, such as the nuclear and cytosolic regions (Fig. 3(C)). This work emphasizes the exciting room for CNT-based FRET nanoprobes for multiplexing sub-cellular bioimaging. SWCNT uptake via cell membrane transport is still not explored as needed, and recent works acquired important pieces of information regarding the role of CNT length and surface charge for uptake in prokaryote cyanobacteria for fluorescence imaging [77]. Also, it was elaborated a CNT-based biosensing platform for circulating tumor cells (CTCs) in an antigen-independent capture fashion, where the preferential attachment of CTCs to a CNT-decorated surface is advantageously explored (Fig. 3(D)) [72]. In this kind of platform, the absence of antigen dependence enables the isolation of distinct CTC phenotypes and imaging without major disturbances of microfluidic devices, as no transfer is needed for microscopy analyses. The ingenious platform enabled the capture of multiple breast cancer phenotype CTCs from the same patient and offers a high impact for future studies of metastasis evolution, dynamics, and therapeutic selection with observations at a single-cell level.

1D materials such as flexible carbon fiber can also be explored combined with other carbon nanomaterials such as graphene oxide (a 2D material) to enhance the electron-transfer process in enzymes as glucose oxidase, as represented in Fig. 3(E), with a decreased activation energy of the process and a shorter distance to the electrode [73].

2D carbon nanomaterials

Graphene has attracted great attention with regard to biosensing platforms. It is considered a two-dimensional nanomaterial with outstanding electronic properties that are widely envisioned in analytical and bioanalytical applications [78, 79]; herein, we refer to graphene as a single sp^2-hybridized layer of carbon atoms, in its monolayer or isolated form [8, 80]. When in its isolated form, whether obtained from mechanical exfoliation [81] or chemical vapor deposition (CVD) [82, 83] process, graphene is characterized by its unique structural, electronic, and interfacial properties at the basal plane [84], isolated graphene edge [85–87], and an edge periphery [88, 89]. Graphene can also be easily handled, given its high surface area and suitable physical properties [90], in some cases, in its single-crystal form [91, 92]; further, it is a promisor candidate for use in the fabrication of bioelectronic devices due to its high carrier mobility [93], physical stability and the ease of modifying its chemical characteristics [94], and characteristics of electro-transfer depending on functionalization and modification [73, 95], which can be achieved by oxidative or non-oxidative experimental protocols [96, 97].

There are still many difficulties associated with graphene use, for example, when reproducible sizes of single sheets or surface contamination from the fabrication process hamper its practical applications [98–100]; chemical or electrochemical (*e-etching*) [101, 102] protocols were reported in the last years as methods to overcome such limitations. In addition, for the miniaturization of devices, it is crucial to examine edge effects in the diffusion mechanism of electroactive species in low-dimensional electrodes [103].

With regard to the development of graphene-based bioelectronics, there is much progress in the biosensing

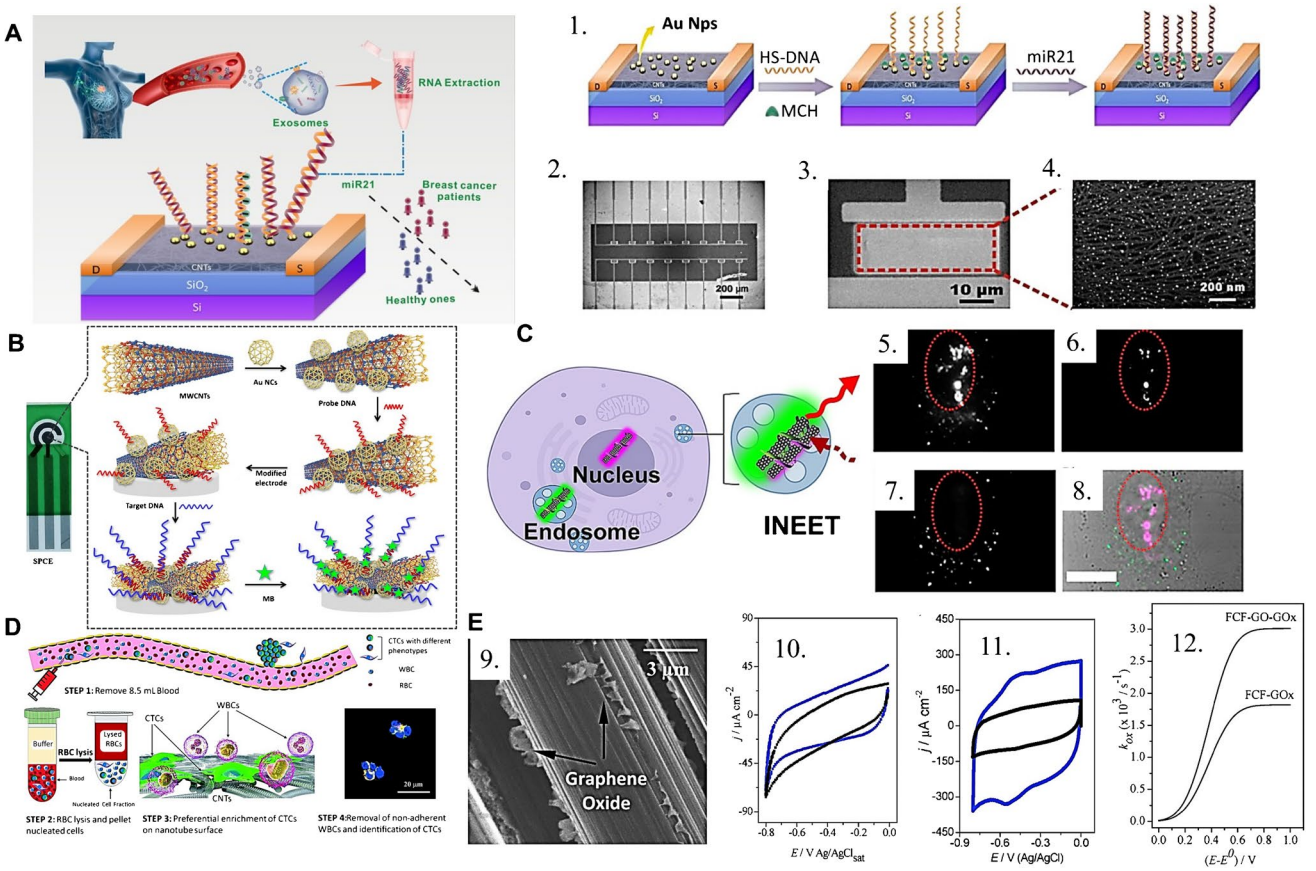

Fig. 3 (A) (Left) schematic of the CNT-FET based biosensing platform for the detection of breast cancer exosomal miRNA21, in an example of affinity sensing relying on CNTs and a designed probe DNA. The probe is built by (1) the incorporation of gold nanoparticles and thiolated DNA; (2–3) SEM images of the biosensor chip. (4) Part of the device channel with AuNPs uniformly distributed on the Y_2O_3/CNT film. Reprinted (adapted) from [67] with permission from the American Chemical Society. (B) Representation of the electrochemical sensing pad designed by the incorporation of gold nanocages (AuNCs) and probe DNA onto MWCNTs; methylene blue adsorbed after the sensor's exposition to the sample with the target DNA. Reproduced from [70], with permission from *Nature*. (C) Application of CNT-based FRET nanoprobes to the bioimaging of sub-cellular structures as (5, 6) the nuclear region and (7) cytosolic region, generating (8) a combined artificially colored image through multiplexed spectral analysis. Reprinted (adapted) from [71], with permission from the American Chemical Society. (D) Operational schematic for the CNT-based antigen-independent capture of circulating tumor cells in human blood serum, exploiting the preferential interaction of CTCs to CNTs and enabling the observation of multiple phenotypes of breast cancer cells. Reproduced from [72] with permission from the Royal Society of Chemistry. (E) (9) FEG–SEM image of the flexible carbon fibers with graphene oxide exfoliated directly onto the filaments' surface, (10) cyclic voltammograms of FCF and FCF-GO and (11) FCF-GOx and FCF-GO-GOx in sodium phosphate buffer, (12) oxidative electron-transfer rate constant as a function of the overpotential for FCF-GOx and FCF-GO-GOx. Reproduced from [73], with permission from the Royal Society of Chemistry

of metabolites, to the understanding of the interactions of graphene with peptides [104], DNA [105], or neurotransmitters [106]. Bioanalytical measurements are traditionally performed in vitro or in vivo [107], using body fluids [108], via the design and integration of electronic devices on the body or the implantation of the devices into living tissues [109]. Interfacing electronics with tissues for bioanalysis has been an area of interest for decades, but many of these devices involve the use of rigid and bulky substrates with robust physical connections; this can make the acquisition of experimental data more difficult, since mechanical properties may influence the signal captured [110]. These physical characteristics limit the integration of such electronic devices in soft or curvilinear surfaces, such as human skin or brain tissues; hence, the discovery of graphene emerged as a versatile and promisor material for the future fabrication of biomedical devices in the future [110].

Another example is the regular monitoring of glucose which involves the conventional measurement of its levels in blood via invasive finger-stick procedures, which are substituted by using temporary implantable microneedles or monitoring glucose levels in saliva, tears, or sweat. As a more reliable material for measuring the levels of glucose in body fluids, owing to its high specificity and low selectivity for

detection, large-area graphene has been recently shown as a non-invasive and promising material. The development of a graphene-based sensor with thermoresponsive microneedles for diabetes monitoring in human skin is reported [108]. Large-area graphene is also a very versatile material and has been reported as a promising platform to detect neuronal activity in the brain. Also, it is reported [106] that single-layer graphene increases neuronal firing by tuning the distribution of extracellular ions at the neuronal interface.

The detection, manipulation, and sequencing of single DNA molecules are both scientifically and commercially relevant. As an example, a study [111] reported the fabrication of nanopores onto single and suspended graphene ribbons to detect the translocation of single DNA molecules. In this case, the simultaneous ionic and electrical current of graphene was recorded when DNA molecules flow through an isolated graphene nanopore (single event or translocation of DNA). As other examples of ultimate advances in graphene-based technology, graphene has been investigated for its use in electrical–electrochemical point-of-care devices, DNA sensing, and electrical–electrochemical sensing devices (Fig. 4).

The development of novel technologies for the detection of bacteria [112] or viruses [113] is of great importance to our society. The early diagnosis of emerging pathogens is very critical for human health. With respect to the COVID-19 pandemic, graphene has also shown powerful potential for the development of hybrid electrical electrochemical devices [114]. The importance of such protocols for early detection can be substantiated by their specificity and speed of detection compared to those of the conventional molecular RT-PCR methods [115, 116]. For instance, graphene was reported as a powerful miniaturized platform for the development of POC serologic COVID-19 diagnosis (Fig. 4(A)), with an analysis time of up to 15 min [113]. The application of an electrical–electrochemical vertical device (EEVD) was proposed, based on hybrid electrical and electrochemical working principles [113]. Different from a G-FET, it utilized a hybrid system operating under a quasi-circuited mode and comprising a Ag/AgCl/Cl electrode as the gate. This innovation produces 10× more signal when compared to a traditional G-FET. Figure 4(B) shows the EE I_{ds} vs. V_{ds} curves that were acquired within a potential range with no faradaic process, considering the bare graphene and all following modification onto its surface. Fig. 4(C) shows the wide linear dynamic range of IgG concentrations varying from 10^{-12} to 10^{-7} g mL^{-1}, and Fig. 4(D) shows the distribution of OCP displacement values for $n = 9$ for positive and negative IgG detections in diluted patient serum samples by G-PNRAuNP/RBD EEVD. This is clearly exampling that graphene technologies could be adapted for use in other emerging bioanalytical strategies for controlling pandemic diseases with a high probability of success.

Monolayer graphene-based three-component vertically designed device (TCVD) has also been used as a biosensing platform for DNA, either by ds-DNA adsorption onto graphene or DNA hybridization from the bulk solution (Fig. 4(E)). Interestingly, the interface properties of the device change according to the characteristics of the components used and can be adjusted due to its versatileness. For example, the absence of a semicircle in the EIS spectra and the Nyquist plots indicates a diffusive response for the graphene monolayer deposited onto the gold (Au) electrode. From the Nyquist plots, the characteristic linear lines indicate the absence of charge transfer, as well as the diffusive response for the pristine graphene on the Au electrode (Fig. 4(F, I); black curve). The electrochemical impedance response changes either for the adsorption of ferrocene (Fc) or ds-DNA (concentration of 0.2 µmol L^{-1}). The total interfacial capacitance values of the graphene monolayer electrodes in the presence or absence of ds-DNA are shown in Fig. 4G, H and J, K, respectively, and were acquired from the simulation of the equivalent circuit.

Graphene monolayers show a high sensitivity to any change on the surface and can be monitored by measuring the capacitance of the electrodes. In this case, the TCVD ($C = 2.5 \pm 0.08$ µF cm^{-2}) showed a higher decrease in the capacitance after Fc adsorbed onto the surface of the graphene monolayer ($C = 1.6 \pm 0.06$ µF cm^{-2}, $C = 2.4 \pm 0.10$ µF cm^{-2}, respectively), and a threefold higher sensitivity for detecting ds- than biosensors in which graphene monolayers deposited onto Si/SiO_2 substrates. EEVDs have also been reported to be constructed via the combination of horizontally aligned graphene–ferrocene heterojunctions as a powerful electrode configuration for DNA sensing. The EEVD was composed using two working and auxiliary electrodes in a short-circuit configuration and compared with the field-effect conventional device (Fig. 4(M)). The quantification of ss-DNA with EEVD graphene-Fc devices that were able to reach an LOD of 5×10^{-21} mol L^{-1} for the detection of ss-DNA is shown in Fig. 4(N).

Beyond the graphene monolayer, bilayer-based devices have been proposed as a new strategic design of biosensors and its fundamental study on the atomic behavior of defects and stacking layers of oxidated graphene bilayer (OGB) provides devices with superior electrochemical performance, when compared to pristine graphene electrodes [118]. The electrochemical impedance spectroscopic study showed that the charge transfer of the OGB electrodes improved by 90% as a result of the existence of edge-like defects 100 times greater than those of pristine electrodes. Attributable to the superior electrochemical activity of the OGB electrode and conciliating the surface modification on the upper layer with exceptional electron transport of the bottom layer (that remained intact), this study provided a new insight into the superior electrochemical properties of OGB electrodes, making it a potential electrode for application on-chip devices. Additionally, the presence of high-oxygen content has been

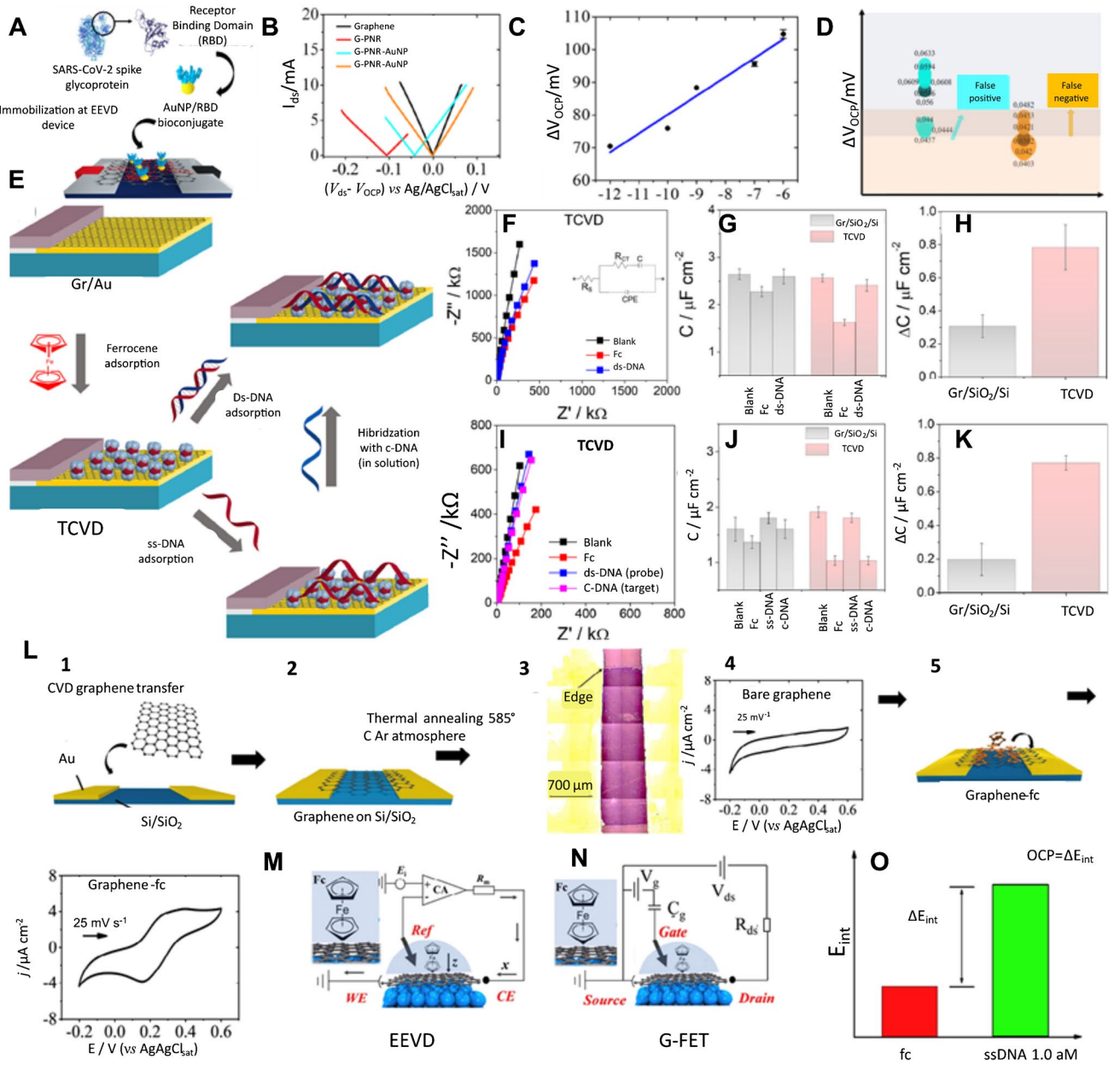

Fig. 4 Graphene-based bioelectronics. (A) Schematic representation of the method for immobilizing AuNP/RBD onto G-PNR. (B) Hybrid I_{ds} vs. V_{ds} EE curves for bare graphene (black), G-PNR (red), G-PNR-AuNP/RBD (cyan), and G-PNR-AuNP/RBD after interactions with human IgG (orange) in PBS buffer. (C) Calibration curve for IgG detections from 1.0 pg mL^{-1} to 1.0 μg mL^{-1} in PBS as support electrolyte by hybrid I_{ds} vs. V_{ds} EE experiments. (D) Distribution of OCP displacement values positive and negative IgG detections in diluted patient serum samples by G-PNRAuNP/RBD EEVD. Reproduced from [5], with permission from Elsevier. Monolayer graphene-based three-component vertically designed (TCVD) device. (E) Schematic illustration of the detection of ds-DNA adsorption and hybridization in solution using the TCVD device. (F) Nyquist plots obtained during the adsorption of Fc and ds-DNA onto the device surface. (G) Plot of the measured capacitance of the TCVD and Gr/SiO_2/Si electrode fitting the Nyquist plots to the equivalent circuit (inset of F). (H) Plot of the change in the capacitance after the adsorption of ds-DNA to the electrode surface. (I) Nyquist plots of the TCVD electrode obtained during the adsorption of Fc, ss-DNA, and complementary DNA to the electrode surface. (J) Plot of the measured capacitance of the TCVD and Gr/SiO_2/Si electrode obtained from fitting the Nyquist plots to the equivalent circuit (inset of J). (K) Plot of change in the capacitance after the hybridization of the DNA on the electrode surface from the solution. Reproduced from [117], with permission from Elsevier. (L) Electrical–electrochemical vertical device (EEVD) device preparation description. Steps 1 and 2 correspond to graphene wet transfer methodology. Step 3 presents an optical micrograph of graphene on SiO_2/Si. Step 4 depicts an electrochemical response of typical pristine graphene. Step 5 illustrates ferrocene in ethanol drop casting and its adsorption onto graphene, forming a graphene-fc vdW heterojunction. Step 6 illustrates a typical final cyclic voltammogram obtained for graphene-fc in phosphate buffer solution. (M) Schematic representation of the working principles of an EEVD with the proposed graphene-fc heterojunction. (N) Schematic representation of a GFET's working principles for comparison with M. (O) Representation of ss-DNA quantification using EEVD graphene-fc devices. Reproduced from [113], with permission from Elsevier

shown to affect molecule adsorption, including eventually hindering the process [119].

3D carbon nanomaterials

The class of 3D carbon–based materials can be regarded as a network of lower-dimensional structural elements, such as carbon felts comprising carbon fibers [120], carbon nanotube weaves [121], graphene-based composites [122, 123], and combined hierarchical materials [124, 125]. These carbon materials can be presented as stand-alone matrices or combined with other materials as a multitude of polymers and biopolymers, gels, metallic particles, and oxides. Among the advantages of 3D carbon-based materials is their capability to offer a high surface area for the adsorption and immobilization of biomolecules, practical manipulation for the construction of biosensing platforms, and versatility, regarding both chemical functionalization and mechanical properties. Here, we will highlight some studies using different platforms to produce nanoblisters for flexible biosensors, wearable biosensors, and porous and mesoporous structures to provide a relevant increase in both sensitivity and molecular recognition.

As the orientation of adsorbed redox-active enzymes onto electrodes deeply affects the electron transfer from the enzyme's active center to the electrode, a research employed a carbon fiber matrix decorated with reduced graphene oxide (rGO) as inter-fiber sheets and cup-stacked carbon nanotubes (CSCNTs) coating the fibers' surface, as seen in Fig. 5(A), enabling favorable surface–enzyme interaction, efficient electron transport, and high accessibility to the active sites to drive effective electrochemical communication [120]. This platform was employed to study glucose oxidase (GOx) as a model redox enzyme, and the results indicated that not only does a kinetic improvement depend on the presence of rGO and CSCNT combined, that is, a 3D composite, but also that a considerable conformational change of GOx is evident when it is adsorbed onto the modified felt electrode, which exposes its active center at the same time, compromising the biocatalytic activity.

Flexible carbon fibers can also be applied to produce carbon-based nanoblisters, as represented in Fig. 5(B). Nanoblisters can improve the electrocatalytic processes for high-performance glucose dehydrogenase [126]. When it comes to wearable devices, carbon nanotubes have been employed combined with hydrogels to construct conducting, adhesive, and mechanically resistant stretchable materials for sensing. A study exploited the remarkable conductivity of CNTs modified with polydopamine in a composite with agarose hydrogel and glycerol (Fig. 5(C)) [127]. The composite presented humidity retention, skin biocompatibility, and thermal stability across a wide temperature range, underscoring its promising applicability for use in skin-based wearable biosensors.

3D carbon-based nanomaterials can also be employed for coupled technique studies [117, 118], such as the study of the oxygen reduction reaction process by bilirubin oxidase (BOD) using in situ X-ray absorption spectroelectrochemistry. Mesoporous 3D carbon nanoparticles can form matrices, as in Fig. 5(D), and maximize BOD loading while maintaining high electronic conductivity.

The production of 3D hierarchical and structured platforms with carbon nanomaterials is another exciting possibility, especially when combined with smart materials, such as thermoresponsive polymers. A multilayered porous graphene oxide coating onto ITO electrodes was proposed using the breath-figure method [129]; the porous graphene oxide surface inside and outside the pores was then locally functionalized with brushes of poly(N-isopropylacrylamide), a thermoresponsive polymer, generating a platform that blocks the access of species from the external medium to the electrode at room temperature, while enabling the access of these species to the electrode after heating; this, in turn, causes the reversible contraction of the polymeric brushes and the opening of the pores, reversibly (Fig. 5(E)). This 3D carbon-based thermoresponsive physical gate platform opens the room for smart chemical sensors that are self-activated through external stimuli, such as body temperature, and can be extrapolated to light, pressure, and chemical activation.

A similar rationale can be obtained using a glassy carbon electrode decorated with MWCNTs to improve enzyme immobilization and communication [128]. In their work, a carbon cloth loaded with carbon nanoparticles was employed to maximize BOD loading while maintaining high electronic conductivity. A similar rationale was explored elsewhere [130], using a glassy carbon electrode decorated with MWCNTs, BOD and Nafion for acquiring XAS data for water oxidation reaction (WOR) in multiple steady-state electrochemical potentials (Fig. 5(F)).

Additionally, mesoporous structures of electrodes applied with different in situ analytical techniques facilitate the in-depth study of interface elements and signal transduction and provide relevant information for the fabrication of more sensitive and stable biosensors. The combination of carbon nanomaterials has been a new trend to support, mainly, new configurations of biosensors operating under either direct or mediated bioelectrocatalysis [131–133].

Challenges and perspectives

With regard to commercial prospects, it is reported that the carbon material market is segmented as follows: MWNTs, CNTs, other categories, and end-user industries (electronics, healthcare, energy, aerospace and defense, automotive) [134, 135], and its global market is projected to reach almost $32.8 billion by 2030 [135]. Although these numbers involve the utilization

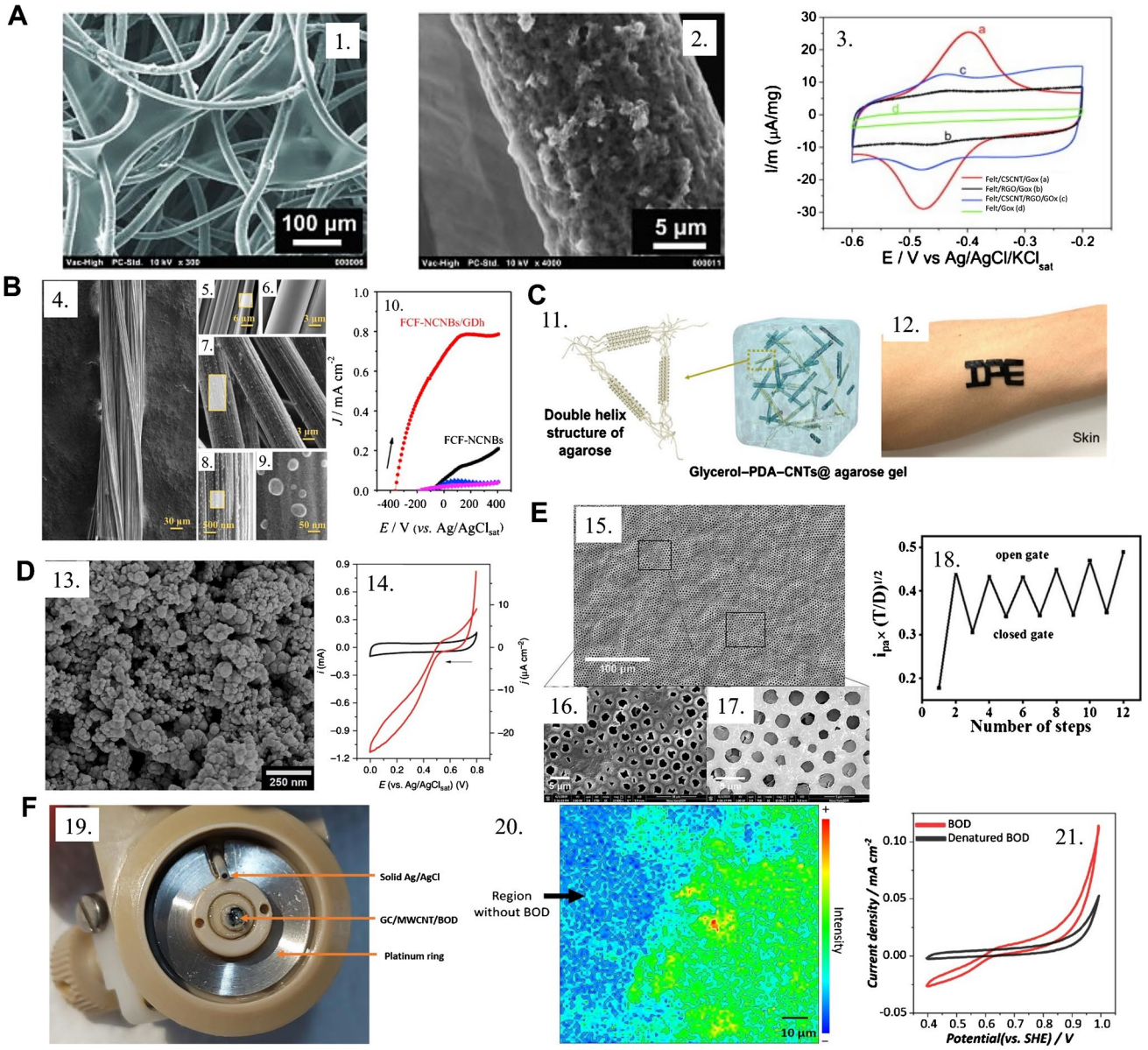

Fig. 5 (A) Scanning electron microscopy images of (1) felt/CSCNTs/graphene oxide material, (2) felt/CSCNTs/graphene oxide image at higher magnification, and (3) CSCNT/RGO-coated fibers and the corresponding voltammograms in the presence of immobilized GOx in 20 mmol L^{-1} PBS and 0.1 mol L^{-1} KCl. Reproduced from [120], with permission from Elsevier. (B) (4–9) Micrographs of carbon fibers and carbon nanoblisters generated through chemical processing and (10) the electrochemical response to glucose. Reprinted (adapted) from [126], with permission from Elsevier. (C) (11) Fabrication and mechanical tests of a 3D CNT-agarose hydrogel composite for (12) application in skin-based wearable biosensors. Reprinted (adapted) from [127] with permission from the American Chemical Society. (D) (13) SEM micrographs of the mesoporous carbon matrix with high carbon nanoparticle loading employed as the working electrode for BOD immobilization, (14) cyclic voltammogram of *MvBOD*-modified electrode in (red line) O_2-saturated electrolyte performing the ORR and (black line) Ar saturated demonstrating no process for the bioelectrocatalysis of ORR. Reprinted (adapted) from [128], with permission from *Nature*. (E) (15–17) SEM micrograph of a graphene oxide/poly(N-isopropylacrylamide) porous formed after a polymerization time with the (18) electrochemical signals from redox probes in the external medium before and after sequential thermal opening of the polymeric brushes gate, operating in a smart-sensing thermal stimulus-activated electrochemical sensor. Reprinted (adapted) from [129], with permission from the American Chemical Society. (F) (l9) A MWCNT-based bioelectrode for BOD immobilization to a XAS-analysis assembly; (20) a chemical Cu K-edge XA-NSEC mapping onto a MWCNT/BOD/Nafion bioelectrode, enabling the localization of high enzymatic loading; (21) biocatalytic water oxidation reaction obtained with the MWCNT/BOD/Nafion bioelectrode. Reprinted (adapted) from [130], with permission from Wiley

of carbon-based materials in the automotive industry, healthcare represents a critical area of focus for these materials, given that they can be used for assessing medication-associated aspects, e.g., tissue imaging. MWCNTs are the principal material of the carbon nanotube market, particularly for clinical applications [135]. There are many possibilities contained in the properties of carbon-based materials discovered so far. However, additional adjustments/revisions or even modifications for commercial-level applications are necessary, especially when aiming at the production of biosensing platforms.

Among the main perspectives, one can secure that the future of carbon nanomaterials will roam through the pursuit of new technologies, applications, and also the assurance of safe handling and in vivo safety, based on current research [136]. Recently, discussions concerning CNT safety and pressure for restricted usage have been presented, including the addition to the Substitute It Now (SIN) List by ChemSec, in a decision taken after reports indicating potential carcinogenicity, reproductive deleterious effects, and additional long-term health damage in in vitro and mice studies [137]. An immediate response by multiple researchers was issued, with a worry that an unclear depiction of the facts would hinder relevant advances and safe usage of CNTs [138]. It is clear that the risk assessment of a wide class of materials with an immense presentation variation as CNTs is an extremely difficult task, and reports from other agencies emphasize the importance of avoiding the absorption of long, aggregated, and concentrated CNTs with metallic particles as remaining impurities from catalytic production. The data heterogeneity in toxicity studies implies that CNT concerns should be narrowed down to specific ranges of length, diameter, concentration, aggregation, and purity.

Concerning the applications, the purity, form, presence of heteroatoms, and oxidation levels have a notable impact on carbon-based biosensor performance, since these factors frequently affect electrical conductivity, binding interactions between the surface and biomolecules, and the ability of biomolecules to adsorb onto the biosensor surface. Additionally, to construct biological sensors, it is crucial to evaluate the overall design concept, production techniques, and real-world application based on these materials. There are numerous scientific publications using the keywords "carbon-based sensors" and "carbon-based biosensors," with most of them being original research articles. Certainly, modern-tech advances, such as portable, flexible, and wearable devices, are relevant for a multitude of applications. However, only a minority are currently commercially available. Although many biosensors show promise for a variety of technological and scientific applications, they are associated with several challenges in terms of mobility, selectivity, sensitivity, and multi-analyte detection in commercial fields. To overcome these challenges, the devices need to be low cost and suitable for large-scale production; demonstrate rapid, robust, and efficient performance; and achieve quick data acquisition and transmission, which will aid the construction of databases to monitor a specific disease or target analyte.

Regarding carbon-based materials, an expansion of novel carbon forms, especially in academic fields, including new precursors, especially those obtained via sustainable methods, such as the use of biomass, and the combination of different hybridization states (sp, sp^2, and sp^3), synthesis routes, functionalization, heteroatoms, or even new carbon forms, is expected. All these improvements are closely related to our interdisciplinary knowledge; innovation in technologies can lead us into a new era of the transformation and synthesis of materials, especially aiming at the ecofriendly manufacturing process for these materials. Additionally, it is important to mention that to achieve this goal, theoretical studies are needed, given their valuable contribution to predicting the structures, electron mobility, functionality, and reactivity of carbon surfaces. The functionalization of carbon-based materials is also an upcoming trend, since it provides the ability to customize the chemistry of the surface required for a specific application. It is worth mentioning that the standardization of the biomolecule immobilization procedure is a notable challenge that can affect the interactions of the target biomolecules with the carbon-based material. Synthesis methods that combine different carbon-based materials with dimensionalities are not a simple task, and achieving this goal could represent a breakthrough as it could simplify the construction of miniaturized devices.

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Declarations

Conflict of interest The authors declare no competing interests.

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