Engineering two-dimensional electronic biosensors

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Abstract

The combination of exceptional electrical, mechanical, geometrical and chemical properties of two-dimensional materials has enabled highly sensitive detection of biological and environmental signals and opened new frontiers in biosensing. Graphene has pioneered much of this progress, yet the broader landscape of two-dimensional materials, comprising hundreds of experimentally validated and thousands of theoretically predicted materials, offers vast, largely untapped potential. The field is now at a critical stage where device sensitivity must be matched by improvements in selectivity, stability, reproducibility, and operation under physiological conditions. This Perspective reviews the current state-of-the-art in two-dimensional materials-based biosensors, highlighting their key advances and drawbacks. We argue that further progress will depend on linking biosensing performance more directly to the intrinsic structures and properties of individual materials. Emerging strategies to overcome persistent challenges, such as biocompatibility, selectivity, functionalization, drift, reproducibility and stability under physiological conditions will be central to translating laboratory demonstrations into reliable translational sensing technologies. The diversity of two-dimensional materials also creates opportunities to move beyond graphene and match specific material properties to unique sensing functions. Their integration into flexible and portable point-of-care devices would support applications ranging from continuous health monitoring to the Internet of Medical Things.

[H1] Key points

- Two-dimensional materials couple biomolecular recognition directly to charge transport, enabling amplification-free highly sensitive biosensing applications.
- Graphene derivatives, transition-metal dichalcogenides, hexagonal boron nitride and elemental X-enes, offer distinct trade-offs in sensitivity, stability and functionalization routes.
- Structural and chemical variability (defects, terminations, contamination and thickness) often outweighs intrinsic material properties in real devices.
- Biofunctionalization strategy (covalent, non-covalent attachment, linker chemistry and receptor choice) controls stability, drift and usable lifetime of the 2DM biosensors.
- Standardized benchmarks and testing workflows are central to comparing biosensing performance across materials, devices and laboratories.

[H1] Introduction

Two-dimensional materials (2DMs) **[G]** have been at the forefront of materials science and electrical engineering research for more than a decade. With their atomically thin geometry, 2DMs offer unparalleled sensitivity **[G]** to environmental and biological changes, making them prime candidates for next-generation sensors. This blend of electrical, geometrical, mechanical and chemical properties positions them as ideal platforms for biosensors – devices capable of detecting a variety of biomolecules or bioelectronic signals.

Graphene **[G]**, the most extensively investigated 2DM, has demonstrated outstanding biosensing performance[1z]. Majority of the reported 2DM-based biosensors are focused on graphene due to its structural versatility, biocompatibility, sensitivity, faster response times and extended stability in liquid environment[1]. However, it suffers from some limitations, such as the lack of an intrinsic bandgap **[G]**. Beyond graphene, more than one hundred of 2DMs have been experimentally[2] validated, and more than three thousands have been theoretically predicted to be exfoliable[3]. Transition-metal dichalcogenides (TMDs) **[G]**, hexagonal boron nitride (hBN) and emerging elemental 2DMs (X-enes) offer diverse electronic structures and surface chemistry that can be tuned for specific biosensing functions (see Box 1). These materials open up new possibilities for tailoring sensitivity, selectivity **[G]** and stability, especially when integrated in flexible, wearable or implantable formats. This vast material landscape poses critical questions – which of them holds the greatest promise for biosensing, and how can their intrinsic properties be best exploited to achieve the highest sensitivity, selectivity, environmental stability and biocompatibility?

In this Perspective, we provide a guide to the effective engineering of 2DM-based biosensors. We synthesize current knowledge into a structured, principle-based framework. Specifically, we review the foundational principles of two-dimensional (2D) biosensors, examine the biosensing potential of key material families, including graphene,TMDs, hBN and X-enes, introduce a seven-part framework based on structural, electrical, environmental, empirical and translational criteria, and offer forward-looking insights into both challenges and opportunities that lie ahead. Rather than attempting to cover every biosensor architecture or analyte, our goal is to provide a guiding lens for evaluating new materials and device designs with greater consistency and impact.

[H1] Fundamentals of 2D electronic biosensors

2DMs have emerged as a transformative platform for bio-sensing and stimulation. Their atomic thickness and maximal surface-to-volume ratios maximize sensitivity to environmental electronic variations. Unlike conventional biointerfaces **[G]**, such as thin-film metals reliant on metallic bonding, 2DMs leverage covalent bonding and Van der Waals (VdW) interactions **[G]**, enabling highly controllable covalent[4] or non-covalent[5,6] functionalization **[G]** and bypassing complex nanofabrication processes, like atomic layer deposition. Among 2DMs (Box 1), graphene stands out as the first discovered and most widely studied, owing to its exceptional biocompatibility[7,8], optical transparency, for example, about 98% for graphene[9], carrier mobility even under extreme deformation, for example, 1200 $cm^2 V^{-1} s^{-1}$ at uniaxial bending at 50-65° angle[10], electrochemical stability[11], corrosion resistance[12] and mechanical flexibility[13]. Beyond

electrochemical and transistor-based sensing, 2DMs also enable optical and catalytic biosensing modalities. For example, graphene and TMDs have been widely explored as fluorescence quenchers, surface-enhanced Raman scattering (SERS) substrates and plasmonic platforms, and MXenes and molybdenum disulfide (MoS_2) exhibit nanozyme-like catalytic activity, enabling colorimetric detection. This section is organized focusing on electronic biosensing capabilities of 2DMs.

[H2] Graphene Biosensors

Graphene field-effect transistors (GFETs) have emerged as powerful platforms for biosensing due to their electronic properties. In their pristine form, without surface functionalization, GFETs enable detection of target biomolecules via direct interactions with the graphene channel; although selectivity remains a significant challenge, particularly in complex biofluids[14]. Functionalization with ad-hoc molecular receptors or probe molecules improves selectivity by enabling GFETs to sense target-specific charge variations[15,16] (Fig. 1a). The GFET biosensor interface can be modeled as a simplified equivalent circuit coupled to the graphene channel, consisting of the solution potential V_{sol}, which is the effective gate bias applied through the electrolyte, the electrical double layer (EDL) capacitance C_{EDL} and the parallel charge-transfer resistance R_{ct}. Pristine or high-quality chemical vapour deposition (CVD) graphene exhibits high impedance in aqueous environments, with interfacial resistivity of ~10 MΩ cm^2 and areal capacitance of ~5 µF cm^{-2}, arising from the series combination of the electric double-layer capacitance, 10–20 µF cm^{-2}, and graphene's quantum capacitance, ~10 µF cm^{-2}) [refs [17,18]]. Combined with ultralow electrical noise[19,20], these properties make GFETs best suited for transconductance-based sensing applications[21,22].

In biosensing based on GFETs, biomolecular adsorption or binding events near the graphene surface can modulate the channel conductance through electrostatic gating. The response is typically transconductance-based and appears in the direct current (DC) transfer characteristics, for examples, Dirac-point shift and drain-current variations. GFET responses can also be attributed to charge-transfer effects, although the underlying mechanisms require further clarification[23].

Graphene is a semi-metal portrayed by a V-shaped energy band structure (Fig. 1b) near the Dirac point **[G]**, also referred to as the charge neutrality point (CNP) **[G]**, which corresponds to zero gate voltage in undoped graphene. In GFETs, the Fermi level of charge carriers within the graphene channel shifts in response to electrostatic potential variations. This gating effect allows tuning of the carrier density via the applied gate voltage (V_{g}), resulting in a V-shaped I-V_{g} curve indicative of ambipolar conduction (Fig. 1c)[24,25]. The lowest point of this curve, the minimum current, occurs at the transition between hole and electron conduction and corresponds to the CNP. However, this minimum is non-zero due to the presence of electron–hole puddles near the CNP[26].

For biosensing applications, GFETs are typically biased in either the electron- or hole-conducting branch of the I-V_{g} curve, where the current changes monotonically with V_{g} and the carrier mobility (μ) remains approximately constant[27]. Studies show that graphene' sensitivity is maximized near the CNPs due to the reduced noise level[28]. Although the intrinsic carrier mobility

of graphene is remarkably high, which is ~200,000 cm^2 V^{-1} s^{-1}), theoretically making it an exceptional platform for biosensing applpications[29], real-world GFET devices typically exhibit much lower mobility. This reduction can be attributed to defects, impurities and grain boundaries introduced during synthesis[30–33], for example, CVD, and subsequent device fabrication. In addition to diminishing mobility, such structural imperfections can create false interactions with analytes, potentially jeopardizing the selectivity and reliability of the sensing response[34].

Although GFETs exemplify the transistor-based modality of graphene biosensing, graphene can also be exploited in electrode-based devices. Graphene electrodes offer a simpler engineering pathway compared with transistor platforms. Their high interface impedance, however, limits charge transfer and often necessitates covalent functionalization or basal-plane modification to enhance interfacial conductivity[35]. Paradoxically, this same high impedance enables stable, low-density interfacial currents (~nA cm^{-2}) [ref. [17]], driven by electric double-layer potential with minimal perturbation. Coulometric methods measure these low-level currents at graphene biointerfaces without auxiliary electrodes, achieving detection of subtle pH changes (± 0.1 pH units), charge transfer through protein pores and flow rates as low as 0.5 µm s^{-1} within a 1 Hz bandwidth[36].

Graphene electrodes also lend themselves naturally to wearable sensor platforms[37]. Much like conventional electrophysiology electrodes, they can be used for monitoring heart rate, brain activity or muscle activity, and extended to more complex physiological parameters, such as blood pressure[38,39]. Unlike conventional electrodes, graphene-based wearables are atomically thin, flexible, transparent and ultimately compliant with the human skin making the most imperceptible interface. Further functionalization of graphene channels allows these wearable devices to serve as sweat biosensors.

[H2] Transition-metal dichalcogenide-based biosensors

Transition-metal dichalcogenides (TMDs), with the general formula of MX_2 (M = transition metal, X = chalcogen), are a class of 2DMs whose surface chemistry plays a central role in biosensor design. Structurally, each monolayer features a layer of metal atoms sandwiched between two chalcogen layers, which further form a Van der Waals-stacked lattice[40–42]. TMDs typically exhibit multiple polymorphic phases, such as 2H, 1T, and 1T′, each with distinct stability, crystallographic symmetry, electronic structure and surface properties[43,44]. These phase distinctions are not only structural, they fundamentally influence how TMDs conduct electrons, interact with biomolecules and function in biosensing systems[45,46]. The emergence of a particular phase depends on the d-orbital configuration of the transition metal, interlayer interactions and synthesis conditions, such as exfoliation, doping or strain[47,48]. Phases of TMDs fundamentally dictate the biosensing behaviour of TMDs by modulating charge transport, active site availability, and functionalization potential.

Figure 1d shows the TMD analogue of biosensors with functionalized channel for biorecognition. The transfer (I-V_g) characteristics of TMD field-effect transistors (FETs) **[G]** exhibit intrinsic bandgap-induced gate (Fig. 1e), enabling switching between off- and on-states (Fig. 1f). For n-type TMDs such as MoS_2, at low gate voltage, the Fermi level lies within the bandgap,

resulting in negligible carrier density and a low off-current. As the gate voltage (V_g) approaches threshold voltage (V_{Th0}), the Fermi level shifts towards the conduction band, leading to exponential current (I) increase in the subthreshold regime and accumulation of carriers in the channel when $V_g > V_{Th0}$. When V_g is further increased, the I-V_g relation becomes linear due to strong charge carrier accumulation in the channel. This transfer characteristic allows biosensing in linear, saturation and subthreshold region, where the sensitivity modulates linearly, quadratically and exponentially, respectively[49]. The biosensor sensitivity quantification for TMDs is expressed as either change in threshold voltage (ΔV_{Th}) or change in drain current (ΔI_{DS}) at constant gate voltage. When channel is coated with thin layer of an insulator, ΔV_{Th} provides information on biomolecular concentration whereas ΔI_{DS} is used for channel directly exposed to sensing environment. In presence of insulating layer, the target biomolecules electrostatically modulate free-carrier concentration and induce V_{Th} shift, whereas I_{DS} shift dominates due to reduction in transconductance (g_m) **[G]** when channel is exposed to biomolecules directly. Biomolecules generate disordered and corrugated potential distribution in channel, enhancing scattering and localization probabilities of moving carriers and in turn degrading transconductance. Insulating layer acts as buffer to such disordered potential and maintain flat equipotential surface[50]. Many TMDs, such as MoS_2, molybdenum ditelluride ($MoTe_2$), and tungsten diselenide (WSe_2), can undergo reversible phase transitions under stimuli, such as chemical intercalation, electron doping, strain or plasma treatment, providing a tunable platform for tailoring sensor performance[45,51].

The 2H phase, defined by trigonal prismatic coordination, represents the most thermodynamically stable structure for semiconducting TMDs, like MoS_2 and tungsten disulfide (WS_2). With bandgaps typically ranging from 1.2 to 2.0 eV [ref. [52]], 2H monolayers exhibit direct bandgaps and strong electrostatic sensitivity, features that make them attractive for FET biosensors[49,53,54]. 2H-MoS_2 FETs have been widely used for detecting deoxyribonucleic acid (DNA), proteins and small molecules through charge perturbation upon biorecognition[55,56]. Their wide-range bandgaps also lend themselves to optoelectronic biosensing, where direct optical transitions and strong light–matter interactions enable detection based on photoluminescence, fluorescence resonance energy transfer (FRET), or photoelectrochemical responses[53]. WS_2's 2H structure supports fluorescence-based detection due to strong photoluminescence and exciton quenching, which have enabled FRET-type ribonucleic acid (RNA) sensors[57]. In addition, the catalytic activity of MoS_2 has been exploited in colorimetric glucose sensors[58]. Chemical functionalization approaches often involve the use of thiols to heal lattice defects or non-covalent π–π interactions, facilitated by edge sites and moderate polarity of the basal plane[59,60]. Several comprehensive reviews have summarized the evolution of TMD-based biosensing platforms, ranging from discussions on layered MoS_2 and WS_2 for sensing and biosensing applications to analyses of nanomaterial functionalization strategies and healthcare-oriented biosensors[61–64]. These reviews collectively provide a systematic overview of material design principles, biomolecule immobilization strategies and electrochemical signal transduction mechanisms in TMD-based biosensors, thereby framing the context for the work on 1T-phase engineered systems.

The 1T phase, in contrast, is an octahedrally coordinated metallic form, typically induced by chemical exfoliation or lithium intercalation[65]. With a near-zero bandgap and high conductivity from overlapping conduction and valence bands, 1T-TMDs support rapid electron transfer kinetics. Such metallic-phase TMDs display catalytic activity at both edge and basal planes, along with enhanced charge transfer to the electrode surface, enabling superior heterogeneous electron transfer kinetics[66]. In this configuration, the basal planes become more chemically active, allowing for stable covalent attachment of redox probes, enzymes or aptamers. Such traits make 1T-phase TMDs highly suitable for electrochemical biosensors[67]. For instance, hemoglobin immobilized on 1T-WS_2 nanosheets has demonstrated fast and sensitive detection of hydrogen peroxide[68], 1T-phase WS_2 decorated with gold (Au) nanoparticles has been employed to construct an esterase-based electrochemical biosensor for organophosphate pesticide detection[69]. 1T-phase WX_2 (X=S, Se, Te) decorated with titanium dioxide (TiO_2) nanoplatelets achieving high electron transfer rates in enzyme-based biosensors[70]. Similarly, two-dimensional 1T-phase TMDs have been employed as nanocarriers to enhance and stabilize enzyme activity in electrochemical pesticide biosensors, where the metallic 1T structure promotes efficient electron transfer and improves enzymatic signal amplification[71].

Importantly, TMDs exhibit a wide range of bandgaps and band-edge positions depending on composition and phase, as summarized in Fig. 2. This intrinsic variation enables careful selection and pairing of materials to control the band alignment at metal–semiconductor junctions. When semiconducting TMDs, such as 2H-MoS_2, are contacted with metallic phases, such as 1T-WS_2 or graphene, a Schottky barrier **[G]** is typically formed at the interface[72]. Although often considered an obstacle in conventional electronics, Schottky barriers can be advantageous in biosensing, where small perturbations in the local environment, like the binding of target biomolecules, significantly modulate the barrier height, thereby amplifying the electrical response. For instance, a graphene and MoS_2 Schottky junction FET that utilizes the interface barrier to detect trace levels of ascorbic acid and dopamine has achieved high sensitivity and stability under physiological condition[73]. Similarly, a photodetector-type biosensor based on a 2H-MoS_2/1T'-$MoTe_2$ hetero-phase junction utilized a Schottky barrier to facilitate efficient charge separation and amplify the photoresponse generated by target molecule recognition[74]. Moreover, a MoS_2-based bio-FET where copper (II) ion (Cu^{2+})-DNA modulation altered the Schottky barrier at the MoS_2–Titanium interface, enabling ultrasensitive, label-free detection of doxorubicin with excellent signal amplification and reusability[75].

Beyond Mo- and W-based dichalcogenides, indium selenide (InSe) has emerged as a particularly promising TMD for biosensing applications. Its atomic structure enables high electron mobility and consequently strong electrostatic response to adsorbed biomolecules. InSe FETs have demonstrated ultrasensitive detection of nucleic acids and proteins, with outstanding signal-to-noise ratio even under physiologically relevant conditions, highlighting their potential for next-generation biosensors[76,77].

Another exciting direction lies in platinum diselenides ($PtSe_2$) and ditellurides ($PtTe_2$). These materials exhibit a unique predisposition to undergo layer-dependent electronic transitions, shifting from metallic to semimetallic or semiconducting behaviour depending on thickness, which is the number of atomic monolayers. Such properties open the possibility of

fabricating complex 2D FET circuits using a single material platform, simplifying device manufacturing and preserving high electronic performance[78,79].

[H2] Other 2DM biosensors

Beyond graphene and TMDs, a plethora of emerging elemental and compound 2DMs is beginning to demonstrate significant biosensing potential. These systems offer diverse electronic structures, surface chemistry and functional properties that can be tailored for targeted applications at hand.

Among elemental 2DMs, silicene, germanene, stanene and phosphorene are of particular interest. For example, phosphorene has drawn strong attention due to its puckered lattice structure, direct bandgap and high carrier mobility, which together enable highly responsive electrochemical and transistor-based biosensors. Experimental studies have demonstrated its utility in detecting gases, nucleic acids and small biomolecules with high selectivity[80–82]. Despite these advantages, phosphorene suffers from poor ambient stability, degrading rapidly in air or aqueous environments and thus requires encapsulation strategies for practical use.

Hexagonal boron nitride, in contrast, is chemically inert and functions primarily as a wide-bandgap insulator. Although hBN is not typically used as a stand-alone electronic sensing layer, it plays a crucial role in heterostructure engineering, where it can be used as an ultrathin dielectric or as atomic passivation layer. Incorporation of hBN into graphene or TMD-based devices has been shown to reduce charge inhomogeneities, suppress leakage currents and improve long-term stability in biological environments[83].

MXenes represent another rapidly expanding subfamily of 2DMs. These carbides, nitrides and carbonitrides are derived from M-A-X phases by selective etching of the A-layer[84]. Their metallic conductivity, surface terminations and hydrophilicity have made them highly attractive for biosensing. However, because MXenes constitute a distinct field with its own fabrication and integration challenges, we do not cover them in detail here, instead referring readers to dedicated review[85] and perspective[86].

Finally, 2D oxides, such as tin dioxide (SnO_2) and indium oxide (In_2O_3), are noteworthy for their ambient stability and compatibility with thin-film transistor platforms. SnO_2 nanosheets have been used in chemical and biological sensing applications due to their strong surface reactivity and high sensitivity[87,88]. Similarly, In_2O_3-based FETs, including amorphous thin-film variants, have demonstrated stable operation and reproducible biosensing performance[89,90].

[H1] 2D Biosensor Framework

The study of 2DM-based biosensors has been propelled by a combination of experimental validation and theoretical modeling. The electronic structure, surface bonds and biocompatibility of 2DMs, all contributing crucial insights into their performance, sensitivity and selectivity. Experimental studies confirm real-world feasibility, and theoretical predictions provide deeper understanding and guide material optimizations for enhanced detection capabilities. Fig. 3 provides a complete framework for 2DM biosensors, including their design, form-factor, integration, performance metrics, choice of nanomaterial and application-receptor-linker functionalization strategies.

[H2] Electronic structure, surface bonds and selectivity

The remarkable sensitivity of 2DMs to external stimuli due to their atomically thin structure, ultimately high surface-to-volume ratio, and direct exposure of active sites has positioned them as promising candidates for chemical and biosensing applications[91]. Their diverse electronic structures, ranging from direct bandgaps in semiconducting monolayers, like MoS_2 and WSe_2 [refs [40–42,92,93]], to high carrier mobility in metallic systems, such as graphene and MXenes, enable strong responsiveness to molecular adsorption[94,95]. Apart from the electronic structure, highly accessible and tunable surface chemistry plays crucial role in sensitivity. In atomically thin materials, atoms reside at or near the surface, making interfacial chemical interactions central to biosensor performance. Surface chemistry in 2DMs encompasses intrinsic functional groups, lattice defects, for examples vacancies and grain boundaries, edge terminations, surface terminations, for examples –OH, –O, –F in MXenes, and non-covalent interaction sites. These features collectively determine how biomolecules adsorb, bind or are immobilized on the material surface. Equally important, their surfaces can support both covalent bonding, primarily at edge defects, vacancies, healing or molecular linkers, and non-covalent interactions, likeπ–π stacking, hydrogen bonding, electrostatics and polymer functionalization[96,97]. These properties establish a versatile foundation for attaching receptors, such as antibodies, aptamers and enzymes.

Pristine or un-functionalized 2DMs, such as graphene, graphene oxide (GO), and TMDs like MoS_2, can serve as sensitive platforms for label-free biosensing[98,99] **[G]**. Graphene offers a highly conductive and chemically accessible pristine surface (Fig. 4), where analytes interact through π–π stacking, Van der Waals forces or electrostatic interactions, which is particularly effective for detecting aromatic compounds and charged biomolecules. GO, which exposes abundant oxygen-containing functional groups, like hydroxyl, carboxyl and epoxy moieties, promotes additional hydrogen bonding and electrostatic interactions, enabling affinity towards nucleic acids, peptides and proteins[100]. In TMDs, intrinsic chalcogen vacancies, such as sulfur vacancies in MoS_2, serve as active sites for the adsorption of electron-donating analytes like amines, thiols, or polar volatile organic compounds[101]. These interactions often result in measurable changes in conductivity or surface potential.

Although unmodified 2DMs offer high sensitivity, their lack of specificity limits their practical use, as different analytes can bind non-selectively[97]. Enhanced selectivity can be achieved upon decoration of the 2D surface with molecular recognition elements, such as aptamers, antibodies or enzymes (Fig. 4)[102,103]. The optimal strategy depends on the sensing application, requiring careful balance of sensitivity, selectivity and stability. A benchmarking comparison of functionalization strategies across major 2DM families is summarized in Table 1, highlighting attachment types, linker chemistries, receptor compatibility and environmental stability.

One common approach is direct covalent functionalization, in which receptors are bonded to intrinsic functional groups or surface defects (Fig. 4). In GO, the surface is rich in oxygen-containing groups, enabling covalent attachment of receptors via amide, ester or epoxy bonding[104]. Likewise, amine ($-NH_2$) and thiol (-SH) functionalization forms carbon-nitrogen (C-N) and Carbon-Sulfur (C-S) bonds[105]. In TMDs like MoS_2 and WS_2, sulfur vacancies allow for direct covalent linkage with aminated or thiolated receptors[45,106]. These strong covalent modifications

provide excellent stability and resistance to desorption, making them particularly useful for developing reusable biosensors. However, covalent modifications can disrupt the electronic structure of the 2DM, potentially affecting conductivity, thus ultimately reducing the sensitivity. Optimized defect engineering and controlled functionalization balance selectivity and conductivity, making 2DM-based devices ideal for biosensing, medical diagnostics and environmental applications[107].

When direct covalent strategies are not feasible, for example, due to chemical incompatibility or risk of over-modifying the surface, indirect covalent functionalization provides an alternative[108]. This method involves the use of an intermediate linker molecule exposing a terminus that can specifically bind to the anchoring site of 2DM and have a Tethering Unit (TU) on the other side for immobilization of the receptors (Fig. 4). Linkers, such as silanes, thiols, azides or others can bridge the two components, enabling effective functionalization. One of the main advantages of this method is the greater versatility it offers in receptor selection, orientation and spatial arrangement, which is particularly valuable when working with delicate or structurally complex biomolecules. However, this strategy often requires multi-step synthesis and precise control over the linker design and positioning, which can introduce practical challenges in reproducibility and large-scale sensor fabrication.

Alternatively, non-covalent functionalization represents a milder, reversible route for receptor attachment[109]. Based on weak interactions, such as π–π stacking, hydrogen bonding or electrostatic forces, this method preserves the pristine electronic properties of the 2DM (Fig. 4)[110]. Receptors can be directly adsorbed onto the surface or introduced via a non-covalent linker that stabilizes their attachment. A well-known example includes the use of pyrene derivatives, which non-covalently anchor onto graphene through π–π interactions and serve as platforms for biomolecule attachment[111]. Non-covalent strategies are advantageous in that they maintain the intrinsic conductivity of the 2DM and allow for dynamic sensing applications, where reversible binding is desired. However, their long-term stability is limited, especially in complex biological or high-ionic-strength environments, where desorption of receptors can compromise sensor reliability. Table 1 provides an overview of the attachment chemistry, linker strategies, receptor compatibilities and environmental stability benchmarks across different 2DM families used in field-effect transistor biosensors.

Beyond conventional amide coupling and π–π anchoring strategies, emerging surface chemistries are increasingly being explored to improve control, reproducibility and stability of 2D biosensor interfaces. Among these, click-chemistry approaches, such as copper(I)-catalyzed azide–alkyne cycloaddition and strain-promoted azide-alkyne cycloaddition, offer bio-orthogonal, high-yield and selective conjugation under mild conditions. These reactions enable site-specific immobilization of biomolecules and minimizing non-specific adsorption and preserving electronic integrity of the 2D channel. Additional strategies, including thiolene and thiolyne coupling, Diels–Alder cycloadditions, and dynamic covalent chemistries such as boronic ester or imine formation, allow reversible and even stimuli-responsive attachment. These approaches enable modular control over receptor density, orientation, and spacing, which is critical for tuning binding kinetics, signal transduction efficiency, and long-term device stability. Importantly, these advanced

chemistries align well with the atomically thin nature of 2DMs, enabling precise interfacial engineering without excessive disruption of charge transport pathways.

[H2] Electrical properties

The performance of 2D transistor-based biosensors is fundamentally governed by their charge transport characteristics. In-plane source–drain current (*I*) in a 2D FET can be modeled using the Drude formalism[112]:

$$I = \frac{enμWV_{ds}}{L} \quad (1)$$

where *e* is the elementary charge, *n* is the charge carrier density, *W* and *L* are the channel width and length, respectively, and V_{ds} is the source-drain voltage.

Because the carrier density (*n*) depends on the applied electrostatic potential, the current can also be expressed as:

$$I = μ\frac{W}{L}CV_{ds}\left(V_g - \frac{1}{2}V_{ds} - V_x\right) \quad (2)$$

where *C* is the areal capacitance of the gate dielectric, V_g is the gate potential, and V_x denotes either V_{Dirac} for GFETs indicating Dirac voltage offset or V_{Th} for other 2D FETs with finite bandgap, where V_{Th} denotes threshold voltage. Conjugation of target molecules on functionalized sensing channel with receptor molecules perturb the local electrostatic environment, modulating carrier density and producing a measurable change in current (Δ*I*).

Although this general framework applies to a wide range of 2D materials, the presence or absence of a bandgap introduces critical differences in device behaviour. In graphene, the zero bandgap prevents complete current suppression, resulting in the absence of a true off-state. On the contrary, semiconducting 2DMs exhibit a finite bandgap that enables efficient switching between low off-state and high on-state currents, which is essential for sensitive detection. Subthreshold slope (SS) indicates switching efficiency, where smaller magnitude depicts faster switching behaviour crucial for higher sensitivity.

$$SS = \left(1 + \frac{C_{Ch}}{C_g}\right)\frac{k_B T}{q} ln10 \quad (3)$$

where SS is subthreshold slope, C_{Ch} is channel capacitance, C_g is gate capacitance, k_B is Boltzmann constant, T is temperature and q is electron charge.

In the subthreshold region, the sensitivity (S_n) exponentially depends on the biomolecular concentration and expressed as[49]:

$$S_n = 10^{\left(\int_{\varphi_i}^{\varphi_f}\frac{1}{SS}d\varphi\right)} - 1 \quad (4)$$

Where φ_i and φ_f denotes surface potential on gate dielectric before and after biorecognition event. In above threshold region, all 2D FETs carrier density (*n*) varies linearly with gate voltage and current (*I*) can be expressed as:

$$I \propto \left(V_g - V_x\right) \quad (5)$$

V_x denotes either V_{Dirac} for GFETs indicating Dirac voltage offset or V_{Th} for other 2D FETs with finite bandgap.

Furthermore, in subthreshold region of semiconducting 2D FETs carrier density (*n*) thus current (*I*) shows exponential dependance on gate voltage, which can be denoted as $I \propto exp^{V_g}$, and the sensors demonstrate enhanced sensitivity to small electrostatic perturbation. Hence, equation (2) can be rewritten as:

$$I=\mu \frac{W}{L} C V_T^2 \, exp\left(\frac{V_g - V_{Th}}{SS}\right)\left(1 - exp\left(-\frac{V_{ds}}{V_T}\right)\right) \quad (6)$$

where V_T is thermal voltage:

$$V_T = \frac{kT}{q} \quad (7)$$

In bioanalytical applications, the current response (ΔI) is proportional to the number of adsorbed charged biomolecules, and thus the analyte concentration (C). This relationship is described by the Hill–Langmuir equation, which can be split into two options:

In linear (GFETs) or above threshold regime (2D FETs):

$$\Delta I \propto \frac{\left(C/K_D\right)^a}{1+\left(C/K_D\right)^a} \quad (8)$$

In subthreshold regime (2D FETs):

$$\Delta I \propto exp\left(-\frac{\alpha}{SS}\frac{\left(C/K_D\right)^a}{1+\left(C/K_D\right)^a}\right) \quad (9)$$

where K_D is the equilibrium dissociation constant, and *a* is the Hill coefficient. Equations 8 and 9 highlight that the electrical readout of a 2DM biosensor is determined by two coupled contributions: the biomolecular binding thermodynamics, described by the Hill–Langmuir isotherm and the charge transport physics of the transistor channel. This coupling between molecular recognition and electronic amplification represents a defining advantage of 2D transistor-based biosensors over conventional detection platforms.

[H2] Environmental properties: stability and cytotoxicity

The environmental performance and safety of 2DMs differ substantially and must be evaluated on a case-by-case basis. For instance, device stability is generally reliable for graphene and hBN. By contrast, more reactive 2DMs, such as TMDs, silicene, germanene, phosphorene and MXenes, are prone to rapid oxidation under ambient conditions, necessitating careful encapsulation or surface engineering to preserve functionality[113,114]. Stability is further influenced by factors, such as the number of layers, crystal phase and integration strategy. For example, metastable phases like 1T-MoS_2 can degrade unless they are stabilized with dielectric capping or surface treatments[115,116].

Equally critical is the cytotoxicity of 2DMs, which can vary dramatically even within a single material class depending on synthesis route, flake size and post-processing conditions[117]. Flake-based 2DMs, although attractive for their large surface-to-volume ratios beneficial for electrochemical sensing, have been shown to induce higher cytotoxicity levels compared with bulk or CVD-grown counterparts[118]. Importantly, CVD-grown electronic-grade graphene is

considered biocompatible, even promoting cell growth[119–121]. In contrast, some nanoscale graphene or graphene oxide sheets have been linked to cell toxicity[122–124], driven by small lateral dimensions, fabrication-related contamination, or reactive surface functional groups. However, reducing lateral size mitigates these effects in certain cases[125]. These seemingly contradictory findings highlight that biocompatibility is highly case-specific and warrants further investigation **[Au: this sentence is a little too long. Please revise]**. Accurate cytotoxicity assessment requires standardized nomenclature and comprehensive testing regimes, extending well beyond isolated in vitro assays. Robust evaluation should cover skin irritation, acute and chronic toxicity, immunological responses, genotoxicity, and systemic effects across multiple organ systems[126,127]. An example of such systematic study is the comparison between large-scale electronic grade CVD graphene, MoS_2, $PtSe_2$, and $PtTe_2$, and flaky MoS_2 used as culture substrates for neural stem cells, showing robust neuronal differentiation and neuronal maturation[128]. Such broad toxicological profiling is particularly important for implantable biosensors **[G]** that maintain prolonged contact with tissue or biofluids.

[H2] Experimental data: Performance and Validation

Experimental research has consistently demonstrated the ultrasensitive nature of 2DM-based biosensors, especially when configured as FETs. Devices based on graphene, TMDs and MXenes have achieved detection limits down to femtomolar concentrations for DNA, proteins and small molecular analytes[94]. The unmatched sensitivity arises from their high surface-to-volume ratio, allowing even minor interactions with analytes to produce measurable changes in conductivity or surface potential.

Key factors influencing biosensor performance include material purity and defect engineering, surface functionalization, and electrostatic and dielectric effects. Pristine monolayers generally offer the highest sensitivity, whereas controlled defect engineering or doping can improve selectivity by introducing additional binding sites[129]. Surface functionalization via covalent and non-covalent chemistries improves molecular recognition specificity and target discrimination[130]. Finally, environmental factors such as pH, ionic strength, and dielectric screening, significantly influence device stability and overall sensing performance[131].

Previous studies highlight the translation of these properties into flexible and wearable formats, where 2D biosensors demonstrate promise for real-time, point-of-care diagnostics[94]. Furthermore, multiplexing strategies are being actively explored to enhance selectivity in complex biological fluids, where simultaneous detection of multiple analytes remains a critical challenge[129].

[H2] Theoretical Predictions and Further Optimization

Theoretical modeling provides essential insights into the mechanisms of 2D biosensors and complements experimental validation. Methods, such as density functional theory (DFT) and molecular dynamics simulations, elucidate charge transfer processes, adsorption energetics and sensing mechanisms. For example, both graphene and MoS_2 have been shown computationally to undergo charge redistribution upon biomolecule adsorption, resulting in detectable conductivity shifts[130]. Similarly, simulations have revealed that defect engineering via

introduction of vacancies, dopants, for examples nitrogen and sulfur), or strain can be leveraged to fine-tune selectivity for specific biomolecules[94].

Beyond single-material devices, theory has predicted the benefits of hybrid heterostructures **[G]**. MoS_2 and graphene junctions, for instance, are modeled to enhance signal transduction efficiency through favourable bandgap alignment[131]. Computational studies also quantify analyte binding strengths, guiding experimentalists in selecting the optimal material–target pairings[130]. For example, DFT indicates that sulfur vacancies in MoS_2 enhance binding with gas molecules, and modeling of graphene-based FETs suggests functionalization strategies that maximize specificity and minimizes false positives signals[94].

Artificial intelligence (AI) has accelerated the exploration of 2DMs[132–134]. Machine learning (ML) and deep learning approaches offer efficient pathways to validate theoretically predicted structures, especially when combined with DFT[135,136]. ML frameworks have been used to identify exfoliatable 2D candidates from vast materials databases, thereby expanding discovery beyond traditional computational screening[137]. On the fabrication side, ML-assisted process optimization has improved growth quality of MoS_2 and enabled circuit-level integration by analyzing key parameters that dictate FET performance[138].

[H2] Bridging Experiment and Theory

The most impactful advances in 2D biosensors emerge when experimental validation and theoretical prediction are combined. Experimental studies provide real-world evidence of feasibility, sensitivity and stability, and theoretical models reveal the underlying mechanisms of charge transfer, binding energetics and interfacial interactions. Together, these complementary approaches provide systematic optimization of biosensor architectures, guiding material choice, device design and functionalization strategy.

In practice, theoretical insights are often key towards sensor designs before fabrication, reducing costly prototyping cycles and accelerating the development of high-performance biosensors. For example, DFT-predicted defect states or heterostructure alignments can direct experimentalists towards specific synthesis routes, and experimental feedback on stability or reproducibility informs refinements in computational models. This closed feedback loop transforms both domains, ensuring that modeling remains realistic and fabrication becomes more targeted.

As computational techniques advance, ML and other data-driven approaches are increasingly integrated into the development and operation of 2D biosensors. Beyond accelerating materials discovery, ML algorithms are being applied to analyze complex sensing datasets, extract weak signals from noisy backgrounds, multiplex, and correct for baseline drift and device-to-device variability-persistent challenges in electrochemical and transistor-based platforms. Supervised learning methods can classify subtle shifts in transfer characteristics, impedance spectra, or time-dependent current fluctuations, improving selectivity in complex biological environments.

In multiplexed systems, where multiple analytes generate multidimensional electrical responses, pattern-recognition algorithms and dimensionality reduction techniques enable decoupling of overlapping signals, enhancing analytical specificity beyond receptor chemistry

alone. Importantly, these models can be combined with theoretical simulations and experimental feedback in closed optimization loops, guiding defect engineering, functionalization density and engineering parameters. As 2D biosensors progress towards wearable and Internet-of-Medical-Things applications, intelligent signal processing will be essential to achieve robust, real-time and clinically reliable performance in multimodal and personalized sensing[129].

[H2] Technology readiness level

The technological maturity of 2D biosensors can be mapped using the technology readiness level (TRL) framework (see Fig. 5). Within this landscape, graphene-based electronic devices are significantly ahead of other 2DMs, owing to advances in large-area, scalable and cost-effective synthesis. In 2026, Paragraf[a] and Graphenea[b] commercially produce graphene micro and nanoarray devices, which place them at TRL 9 as chip provider for biosensing. These chips are being used mostly by academic labs for proof-of-concept devices and TRL 7-8 start-up like GrapheneDx. Moreover, several spin-offs from academic labs have received external private equity and venture capital firms funding, showing the commercial promise of this industry. These start-ups include for instance Xsensio[c] that commercializes graphene-based biosensors, and Persperity Health[d] that utilizes MXene-based biosensors to continuously monitor female hormones. At this rate, more companies will reach matured states with significant data for regulatory approval in coming years. By comparison, TMD-based biosensors remain at earlier TRL stages, primarily due to challenges in scalable manufacturing. Nevertheless, their long-term potential is considerable, as TMDs can be integrated directly into chip-scale architectures, enabling system-level solutions beyond what graphene alone can achieve[139,140].

In terms of applications, point-of-care diagnostics are closest to market, generally reaching TRL 6-7, where pilot prototypes are being validated in operational environments. Flexible biosensors[141] and environmental sensors[142] such as wearables, are typically positioned at TRL 6, reflecting advanced prototyping. Multi-target biosensors and many TMD-based devices are at TRL 5, representing fully functional laboratory prototypes that have yet to undergo real-world testing. Graphene electronic tattoos and implantable 2D biosensors currently remain at TRL 4: these platforms have demonstrated feasibility on skin and tissue interfaces but are limited to short-term, lab-scale studies[143].

At earlier stages, several promising concepts are still confined to the proof-of-concept phase (TRL 3). These include Debye-unlimited sensing biosensors[144,145], e-skin, smart e-health platforms[141], drug discovery interfaces, and biosecurity biosensors. In spite of showing strong performance in controlled laboratory conditions, these technologies require improvements in robustness, reproducibility and system integration. Early-stage disease sensing, such as for cancer diagnostics, represents TRL 2, where fundamental sensing schemes have been explored but remain far from clinical translation[146,147]. At the lowest stage, fully 2D integrated systems that combine sensing, signal processing and wireless transmission entirely from VdW materials remain at TRL 1 that are visionary concepts without functional prototypes.

This TRL stratification highlights the maturity gap between graphene-based technologies, which reached industrial momentum, and other 2D platforms, which currently remain largely at

laboratory scale. Efforts are being made towards upscaling the 2D material growth as well as device fabrication[148,149]. Bridging this gap will require overcoming persistent barriers in materials manufacturing, system integration and long-term device reliability, ensuring that the broader promise of 2D heterostructures can be fully realized.

[H1] Outlook: challenges and opportunities

Despite rapid progress, several key challenges still hinder the full translation of 2DM biosensors into real-world applications. Addressing these limitations, ranging from biointerface stability to manufacturing scalability, will be critical to realizing their clinical and commercial potential.

[H2] Debye Layer

The inherently short Debye length **[G]** in physiological fluids remains a fundamental barrier to achieving high sensitivity in 2DM-based field-effect biosensors. Under these conditions, electrostatic perturbations from biomolecular binding are rapidly screened, limiting the transduction efficiency of surface recognition events. To overcome this constraint, several engineering strategies have been explored. One approach involves elevating the sensing interface above the screening layer using molecular spacers[150]. Another uses crumpled 2DMs to create nanoconfined sensing volumes that bring analytes closer to the conductive channel[151,152]. Interrogation of graphene transistor current spectra as a function of target–probe molecular vibration frequency has been demonstrated[27], as operating devices at higher frequencies makes water behave more like a dielectric, reducing electrostatic screening[153].

On the molecular side, the use of ultrashort biorecognition elements, such as aptamers and nanobodies, has gained particular traction[154]. Their compact size positions binding events within the Debye screening length, and also provide advantages, such as signal regeneration, robust performance in complex biological environments and high target specificity.

[H2] Manufacturability and reproducibility

Fabrication challenges remain a primary roadblock to the reliable deployment of 2DM biosensors. Contamination introduced during microfabrication steps, such as etching, metallization and passivation, can compromise the 2DM surface and degrade functionalization fidelity. Surface cleanliness is therefore essential, and standardized protocols for ultraclean transfer and processing must be established. For TMD-based devices, performance and uniformity are further limited by grain boundaries, since most large-area growth methods still produce polycrystalline films with grain sizes on the order of 10–50 μm. As a result, unlike graphene, TMD-based biosensors currently rely on precise microfabrication, which only amplifies contamination risks. Significant advances in material science, particularly in large-area, single-crystal TMD growth, are needed to enable scalable deployment.

Industrialization of 2DM biosensors also depends on achieving wafer-scale uniformity, device-to-device reproducibility and reliable batch processing. This requires multilayer fabrication compatibility, seamless integration of functionalization steps and robust packaging tailored for biological environments. Standardization efforts will be critical to bridge lab-scale innovation with

manufacturable product lines[149]. Furthermore, moving beyond normalized response, defined as percentage change in output current, towards calibrated protocols that relate current to transconductance has been proposed to mitigate device-to-device variability and reduce coefficients of variation.

[H2] Sensor drift and hysteresis

Drift and hysteresis **[G]** remain one of the most persistent yet underreported limitations in 2DM biosensing. Although their precise origins are not fully understood, they likely arise from multiple factors. At the device level, residual contamination and surface charge instabilities on the 2DM surface prior to functionalization can create unstable baselines. Substrate has significant effect on the hysteresis of the FET-based sensors. For example, GFET on Si and SiO_2 substrate shows hysteresis in buffer which is dominated by Si and SiO_2 surface chemistry. CNP hysteresis often occurs due to adsorbed strongly bound water on graphene sheet or hydroxylated SiO_2 surface and the change of dipoles upon direction change of gate voltage sweep causes hysteresis[155]. Hydration of near-surface bulk silanol groups due to low-temperature diffusion of water into SiO_2, induces electron traps and the lag in capture and emission processes from electron traps in SiO_2 substrate causes transconductance hysteresis[156]. Similarly, charge trapping at the SiO_2 substrate defects in contact with graphene is the origin of drift, which often jeopardizes the detection capability by inducing continuous change in sensor output[157]. Unstable output signal in buffer makes the quantification of biomolecules recognition event challenging. In addition to these material- and process-driven sources, drift and hysteresis can also result from environmental variations, such as operating temperature, humidity and ionic strength of surrounding media. Even minor fluctuations in these conditions can shift baseline responses and compromise reproducibility.

Such effects emphasize the necessity for built-in calibration that continuously compensates for and corrects drift during operation. Several strategies have been proposed to mitigate these issues. For example, pre-functionalization purification protocols[158] improve surface stability by removing contaminants before receptor attachment. Real-time calibration schemes, including those informed by ML algorithms[159,160], can dynamically account for baseline fluctuations and environmental noise. Together, these approaches suggest that sensor drift **[G]**, although persistent, is not overwhelming and can be addressed via a combination of material processing, device engineering and intelligent signal correction.

2DM-based optical and catalytic approaches are not constrained by Debye screening effects that limit FET-based devices in high-ionic-strength environments, and they are often less susceptible to baseline drift associated with interfacial charge instability[161,162]. These complementary strategies highlight the broader versatility of 2DMs in biosensing, although their underlying physics and engineering challenges differ substantially from electrochemical transduction mechanisms discussed here.

[H2] Sensor recyclability

Another critical challenge for 2DM-based biosensors is recyclability, as the majority of current devices are designed for single use. This limitation is driven in part by the irreversible nature of biorecognition events, where antibody–antigen binding or other reactions permanently occupy active sites. Although such single-use formats might be acceptable for disposable point-of-care diagnostics, they are less suitable for long-term monitoring applications, implantable devices, or resource-limited settings where sensor reuse is essential. Several strategies have been explored to enable sensor regeneration. Chemical approaches, such as treatment with urea or other denaturing agents[150,163], can disrupt non-covalent interactions and release bound analytes, partially restoring the sensing surface. Electrical methods, including the application of voltage pulses or electrochemical desorption[164], have been shown to "refresh" electrode surfaces without extensive chemical processing. Optical techniques, such as localized photoexcitation, offer another route to selectively weaken or dissociate receptor–analyte interactions and at the same time maintaining overall device integrity[165].

Key challenges here include maintaining the stability and activity of immobilized recognition elements across multiple refresh events, preventing degradation of the underlying 2DM channel and minimizing signal drift after regeneration. Integrating recyclable architectures with intelligent calibration schemes or modular receptor replacement strategies could further advance this goal, enhancing the sustainability and cost-effectiveness of 2DM-based biosensors.

[H2] Functionalization

The biointerface is the cornerstone of 2DM-based biosensor performance, often serving as the true limiting factor in sensitivity, specificity and overall utility. Even when the underlying 2DM channel provides excellent electronic responsiveness, poor functionalization can compromise recognition fidelity and device reproducibility. Effective functionalization therefore requires careful balancing of multiple parameters, including selectivity, binding strength, regeneration capability and long-term stability in complex biological environments.

Both covalent and non-covalent strategies are widely used, each with distinct trade-offs. Covalent approaches offer strong attachment but risk disrupting the electronic structure of the channel. Non-covalent methods preserve pristine conductivity and allow reversible sensing but are less durable. In both cases, variability in linker density, orientation and surface coverage results in batch-to-batch inconsistencies, underscoring the importance of site-specific functionalization, optimized linker chemistries and robust passivation techniques. Beyond simple immobilization, receptor kinetics must be tuned to ensure consistent signal generation in physiological conditions. Strategies that enable controlled receptor orientation and spacing, such as DNA origami scaffolds[166,167] or engineered protein adapters[168], are beginning to emerge as promising solutions.

To expand sensing capabilities, hybrid functionalization approaches are gaining momentum. For example, integrating 2DM platforms with signal amplification schemes, such as hybridization chain reaction or clustered regularly interspaced palindromic repeats (CRISPR)-based recognition, has enabled ultrasensitive detection of nucleic acids and other low-abundance biomarkers[169] **[G]**. These combinations not only extend the detection range but also improve

resilience in complex sample matrices, advancing diagnostic and environmental monitoring applications.

Equally important is the development of benchmarking tools to quantitatively evaluate the quality and stability of the functionalization layer across device platforms. Assessing coverage uniformity, binding kinetics, long-term stability and regeneration efficiency will be critical to move beyond proof-of-concept demonstrations towards standardized, reproducible devices.

[H2] Stability

Long-term stability of the sensors is a crucial roadblock for commercialization. Graphene has demonstrated stability and robustness, retaining sensitivity for over half a year when used as a biosensor[36], but few other 2D nanomaterials maintain ambient stability and long-term performance, especially in highly ionic biofluids, which remains a major challenge. Although point-of-care sensors are expected to provide results in a short time, continuous monitoring for wearable and implantable sensors requires extended stability. Encapsulation strategies, such as few-nanometre dielectric or oxide coatings, can improve durability but often reduce sensitivity. Therefore, the development of specialized packaging approaches that simultaneously preserve sensitivity and prevent degradation is critical for advancing stable, long-lived 2DM-based biosensors.

[H2] Translation

The translational potential of 2DM-based biosensors is vast. Achieved sensitivities already surpass many conventional methods, with detection limits extending into the zeptomolar (zM) range. Such extreme sensitivity enables the detection of subtle molecular changes associated with the earliest stages of disease including cancer, diabetes and Alzheimer's, through monitoring of microenvironmental shifts, microRNAs, proteins and metabolites. This level of molecular granularity could represent the 'killer application' of 2DMs. Realizing this vision, however, will require reproducible multi-channel sensor arrays with device uniformity of more than 99%, supported by robust readout systems. Because these platforms will generate highly complex datasets, AI and ML algorithms will be indispensable for real-time analysis, not only for pattern recognition and disease classification but also for mitigating persistent challenges, such as sensor drift and batch-to-batch variability.

Importantly, the inherent mechanical flexibility of 2DMs allows seamless integration with soft substrates, making them ideal for next-generation wearables, such as graphene e-tattoos, sweat biosensors and even implantable devices. Yet, these applications must contend with sensing in high-molarity biofluids, where short Debye lengths severely restrict the performance of transistor-based biosensors. Approaches to overcome the Debye layer are presented earlier.

Beyond transistor-based biosensing, 2DMs enable other valuable applications. Graphene's ambipolarity, for example, enables low-power multi-channel sensing applications[28,170]. Multianalyte detection and multiplexing can be achieved either through controlled functionalization with multiple receptors or by harnessing the compositional and

functional complexity of VdW heterostructures[171]. Going forward, the integration of multimodal sensing, combining physical and chemical signals, with advanced data analytics in the context of the Internet of Medical Things (IoMT) **[G]** could enable the early detection of complex diseases with unprecedented precision. The convergence of 2DM-based biosensors with AI-driven analysis and wireless IoMT ecosystems would unlock continuous, personalized monitoring at population scale.

Finally, transitioning 2DM-based biosensors from laboratory prototypes to deployable technologies will depend as much on standardization and regulation as on technical advances. Extreme sensitivity to fabrication conditions, surface treatments and environmental variability continues to complicate reproducibility and comparability across groups. The absence of universally accepted benchmarks for performance metrics remains a major barrier for both scientific progress and regulatory approval. To bridge this gap, the field must establish unified protocols for material characterization, biofunctionalization validation and device testing. Equally important will be alignment with emerging regulatory frameworks. Community-driven initiatives, including interlaboratory studies, shared datasets and consensus guidelines, are essential to ensure rigour, reproducibility and regulatory readiness. Such collective efforts will ultimately accelerate the translation of 2DM-based biosensors into impactful clinical and environmental technologies.

[H1] Concluding Remarks

2DMs have demonstrated extraordinary biosensing capability, yet their translation into translational technologies demands systematic optimization of the trade-offs between sensitivity, selectivity, stability and manufacturability. Success requires multiple converging elements: standardized protocols for benchmarking performance in complex biological matrices, scalable fabrication achieving >99% device uniformity, and long-term continuous sensing in physiological complex conditions. As graphene biosensors achieve commercial maturity and TMD-based platforms advance through TRL stages, integrated strategies combining engineered heterostructures, multiplexed detection arrays and AI/ML-driven signal processing will define the next generation of 2D electronic devices. The field stands at an inflection point where material science innovation must couple equally with rigorous experimental validation and regulatory readiness to unlock the full potential of 2D biosensors.

[H1] Glossary

Two-dimensional materials – Atomically thin layered crystals with unique electrical, mechanical and chemical properties. Examples include graphene, transition-metal dichalcogenides, and hexagonal boron nitride.

Graphene – A monolayer of sp^2-hybridized carbon atoms with a hexagonal lattice structure.

Transition-metal dichalcogenides – A broad class of layered materials comprising a transition-metal atomic planes sandwiched between two chalcogen atomic planes

Field-effect transistor – A semiconductor device in which current flow is modulated by an applied electric field, controlled through a gate electrode.

Dirac point – The point where conduction and valence bands meet in graphene's energy band structure, corresponding to the charge neutrality point where the minimum conductivity occurs.

Bandgap – The energy difference between the conduction band and valence band in semiconductors.

Charge neutrality point – The gate voltage at which the Fermi level of graphene aligns with the Dirac point, resulting in minimum conductivity and low noise, making it optimal for biosensing applications.

Debye length – The characteristic length scale over which electrostatic perturbations from charged species are screened in ionic solutions.

Transconductance – The ratio of change in drain current to change in gate voltage in a field-effect transistor, representing the device's amplification capability.

Schottky barrier – An energy barrier formed at the interface between a metal and a semiconductor, advantageous in biosensing where biomolecule binding modulates barrier height to amplify electrical response.

Van der Waals interactions – Weak intermolecular forces between atoms and molecules.

Functionalization – Chemical modification of 2D material surfaces through covalent or non-covalent attachment of molecular receptors, linkers and functional end groups to achieve selective biomolecule recognition.

Heterostructure – Engineered stacked structure of different 2D materials to combine their properties.

Label-free biosensing – Detection of biomolecules without use of fluorescent or other labels.

Selectivity – The ability of a biosensor to distinguish target analytes from non-target species and background interference.

Sensitivity – The magnitude of change in sensor output per unit change in analyte concentration.

Biomarker – Measurable biological indicators of disease state or physiological condition, including microRNAs, proteins, metabolites, or small molecules.

Wearable biosensors – Flexible bioelectronic devices integrated into clothing, skin patches or electronic tattoos for continuous, non-invasive monitoring of physiological parameters and biomarkers.

Implantable biosensors – Biocompatible 2D devices surgically placed within tissue for long-term monitoring of internal physiological conditions.

Sensor drift – Gradual, continuous change in baseline sensor output over time arising from surface charge instabilities, contamination, charge trapping and environmental variations.

Hysteresis – Lag or history-dependent behavior in sensor response, particularly in transfer characteristics, resulting from charge trapping, adsorbed water and substrate effects.

Internet of Medical Things (IoMT) – Interconnected ecosystem of wearable and implantable bioelectronic devices that continuously collect health data, transmit wirelessly and integrate with AI-driven analysis for personalized, population-scale clinical monitoring.

Biointerface – The junction between a 2D material and biological environment.

[H1] References

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Author contributions

All authors contributed equally to the preparation of this manuscript.

Competing interests statement

The authors declare no competing interests.

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Category		Graphene family			MXene	TMDs					2D-P	2D oxides	
Material		Graphene	GO	rGO	Ti_3C_2	MoS_2	$MoSe_2$	WS_2	WSe_2	InSe	P	SnO_2	In_2O_3
Surface atom		C	-O	C*	O, OH	S	Se	S	Se	Se	P	O	O
Ambient stability		✓	✓	✓	☐	**1L: ☐ ML: ✓**	☐	**1L: ☐ ML: ✓**	☐	☐	☐	✓	✓
Attachment type	Pristine	✓	✓	✓	☒	○	✓	✓	○	✓	○	☒	☒
	Covalent	✓	○	○	✓	✓	○	○	✓	○	✓	✓	✓
	Non-covalent	✓	✓	✓	○	✓	○	✓	○	☐	☐	✓	○
Linker	PBASE	✓	○	✓	☒	○	○	○	○	☐	○	☒	☒
	EDC/NHS	✓	○	✓	✓	☐	☐	☐	✓	☒	☐	☒	☒
	APTES	☐	○	○	✓	✓	○	○	✓	○	☐	✓	✓
	AuNPs	✓	○	✓	○	✓	○	✓	○	☒	✓	✓	○
Linker end groups	Ester	✓	○	✓	✓	○	○	○	✓	☐	☐	☒	○
	Amine	✓	○	✓	✓	✓	☐	☐	○	☒	☐	✓	✓
	Thiol	✓	○	○	○	○	○	○	○	☒	○	○	○
	Aldehyde	○	○	✓	○	✓	☐	☐	✓	☒	✓	☒	✓
Receptors	Antibody/ Nanobody	✓	✓	✓	✓	✓	○	○	✓	○	○	✓	✓
	Aptamer	✓	○	✓	✓	✓	○	✓	○	✓	○	✓	✓
	Enzyme	✓	○	✓	○	○	○	○	✓	○	○	○	✓

Table 1 | **A benchmarking comparison of 2DM-based field-effect transistor biosensors.**

✓ Reported in literature, ○ Possible (Pristine/modified), ☐ Not ideal, ☒ Not possible.

For ambient stability: ✓ Stable**,** ☐ Poor stability.

GO, graphene oxide; rGO, reduced graphene oxide; MXene, two-dimensional transition metal carbide, nitride, or carbonitride; Ti_3C_2, titanium carbide; TMD, transition metal dichalcogenide; MoS_2, molybdenum disulfide; $MoSe_2$, molybdenum diselenide; WS_2, tungsten disulfide; WSe_2, tungsten diselenide; InSe, indium selenide; In_2O_3, indium(III) oxide; P, phosphorene; SnO_2, tin(IV) oxide; 1L, monolayer; ML, multilayer; PBASE, 1-pyrenebutyric acid N-hydroxysuccinimide ester; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; NHS, N-hydroxysuccinimide; APTES, (3-aminopropyl)triethoxysilane; AuNPs, gold nanoparticles.

Figure captions

Fig. 1 Device concept, band structure and transfer characteristics of 2DM-transistor biosensors. a, Schematic of a liquid-gated GFET biosensor functionalized with specific receptors. **b,** Band structure of graphene showing the linear dispersion of the conduction band (red) and valence band (blue), which meet at the Dirac point. Unlike conventional semiconductors, graphene has zero bandgap, making it a semimetal with charge carriers that behave as massless Dirac fermions. **c,** Transfer characteristics of a GFET upon exposure to charged molecules. The pristine device (solid) exhibits a characteristic V-shaped curve with a minimum conductivity point at the charge neutrality point V_{CNP}, reflecting ambipolar characteristic, where the device conducts through both electrons and holes. This adsorption of positively charged molecules shifts V_{CNP} to lower gate voltages (left), and negatively charged a shift it to higher gate voltages (right), consistent with electrostatic gating by the adsorbed charges. The direction and magnitude of this V_{CNP} shift enables identification of both the polarity and concentration of adsorbed analytes, highlighting advantage of GFET as a label-free, highly sensitive biosensor. **d,** Schematic of a liquid-gated TMD FET. **e,** Band structure of TMDs as representative of 2DMs with bandgap, for example, monolayer MoS_2 showing direct bandgap between the conduction band (red) and valence band (blue). **f,** Transfer characteristics of a TMDs (MoS_2) transistor upon exposure to charged molecules. The pristine device (grey) turns on at the intrinsic threshold voltage V_{Th0}. Adsorption of positively charged molecules induces a negative shift in V_{Th} (red), and negatively charged molecules shift V_{Th} in the positive direction (blue). This gate-voltage shift reflects charge transfer between the analyte molecule and the MoS_2 channel, demonstrating the potential of monolayer MoS_2 as a sensitive field-effect transistor-based biosensor. 2DM, two-dimensional material; FET, field-effect transistor; GFET, graphene field-effect transistor; TMD, transition metal dichalcogenide; MoS_2, molybdenum disulfide; V_{CNP}, charge neutrality point voltage; V_{Th}, threshold voltage; V_{Th0}, intrinsic threshold voltage.

Fig. 2 Two-dimensional materials and their bandgaps. Band alignments of representative 2D semiconductors, metals and insulators relative to the vacuum level (E_{VAC}). The shaded bars indicate conduction (red) and valence (blue) bands. Atomic schematics of each material are shown. *highlights materials whose bandgap depends on the number of atomic monolayers. 2D, two-dimensional; E_{VAC}, vacuum energy level.

Fig. 3 The 2DM biosensor framework. Schematic illustration of the key components and design considerations governing 2DM-based biosensors. The framework considers an interplay of intrinsic material properties (growth quality, dimensions, sensing principle), interface engineering (linkers, functional end groups, receptors, passivation), and device-level factors (solution environment, form factor, integration and connectivity). 2DM, two-dimensional material.

Fig. 4 Functionalization strategies for 2DM biosensors. Schematic overview of common approaches used to immobilize biological receptors on 2DM surfaces. Pristine graphene surfaces contain intrinsic functional

groups and defect sites (*e.g.,* –OH, –COO^-, –O) that can serve as anchoring points for functionalization. Covalent functionalization can happen either through direct attachment of the recognition element (*e.g.,* antibody, aptamer, enzyme, ssDNA) to reactive surface sites or through linker-mediated coupling, in which an intermediate tethering unit (*e.g.,* maleimide, NHS ester, aldehyde, azide–alkyne chemistry) provides controlled immobilization of the receptor. Alternatively, non-covalent functionalization can be imposed via common strategies such as π–π stacking (*e.g.,* pyrene derivatives), electrostatic adsorption, polymer-mediated interactions, or hydrogen bonding to attach molecules to the 2DM surface without disrupting the lattice. 2DM, two-dimensional material; –OH, hydroxyl group; –COO^-, carboxylate group; –O, oxygen-containing functional group; ssDNA, single-stranded DNA; NHS, N-hydroxysuccinimide; π–π, pi–pi stacking interaction.

Fig. 5 Technology readiness levels of 2DM-based electronic biosensors and remaining challenges. The schematic maps emerging applications of 2DM-based biosensors onto the TRL scale, illustrating their emerging progression from early proof-of-concept concepts to matured platforms. Early TRLs (1-3) include foundational sensing mechanisms, such as fully 2D integrated technologies, Debye-length-unlimited sensing strategies and initial demonstrations of e-Health and drug discovery. Mid-stage developments (TRL-6) encompass device integration and application-driven systems, including graphene electronic tattoos, TMD biosensors, and multi-target and implantable sensing platforms, as well as flexible and wearable biosensors **[G]**. Advanced stages (TRL 7-9) highlight translational and deployment-oriented technologies, such as point-of-care diagnostics and graphene-based biosensors approaching commercial maturity. Remaining challenges that must be addressed to enable widespread adoption of 2DM-based biosensors are highlighted. 2DM, two-dimensional material; TRL, technology readiness level; TMD, transition metal dichalcogenide; e-Health, electronic health.

Box 1 | Structural diversity of 2D materials. Two-dimensional materials comprise a broad family of layered crystals, each with unique lattice geometries and surface chemistries that define their electronic and chemical properties for biosensing. Graphene, a monolayer of sp^2-hybridized carbon atoms, features a hexagonal lattice that can host oxygen-containing groups (hydroxyl, carboxyl, epoxy), enabling diverse functionalization routes. Group IV elemental X-enes, such as silicene, germanene and stanine, adopt buckled honeycomb lattices with highly reactive surfaces amenable to halogenation, alkylation, or organo-functionalization, thereby tuning their surface reactivity for sensing. Phosphorene, with its puckered lattice, exhibits strong anisotropy and high surface reactivity, allowing covalent bonding and hybrid functionalization strategies. Hexagonal boron nitride (hBN) provides chemical stability and insulating behavior, serving as an atomic passivation or dielectric layer in heterostructures. Transition-metal dichalcogenides (MX_2, M = Mo, W, Pt…, Sn; X = S, Se, Te…) consist of a transition-metal plane sandwiched between two chalcogen planes, yielding semiconducting, metallic, or even superconducting phases depending on thickness and composition, making them versatile for transistor-based biosensors. MXenes (*e.g.,* Ti_3C_2), derived from selective etching of MAX phases, feature abundant terminal groups (–OH, –O, –F) that provide rich functionalization sites but pose challenges in stability and integration. Finally, 2D oxides (*e.g.,* SnO_2, In_2O_3) offer ambient stability, facile thin-film growth and established applications in gas and biosensing. 2D, two-dimensional; X-enes, two-dimensional elemental materials; hBN, hexagonal boron nitride; MX_2, transition metal dichalcogenide; M, transition metal; X, chalcogen; MXenes, two-dimensional transition metal carbides, nitrides, or carbonitrides; MAX phases, layered ternary carbides and nitrides; Ti_3C_2, titanium carbide; –OH, hydroxyl group; –O, oxygen-containing terminal group; –F, fluorine terminal group; SnO_2, tin oxide; In_2O_3, indium(III) oxide.

ToC blurb

Two-dimensional materials offer exclusive electronic and chemical properties for biosensing. This Perspective outlines their fundamental principles, functionalization strategies and applications, and discusses key challenges and opportunities for translating these platforms into real-world use.