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Review Article

Nanostructured quartz crystal microbalance biosensors: Emerging frontiers in diagnostic applications

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ABSTRACT

The diagnostic field is undergoing a quiet revolution, driven by the convergence of nanotechnology and acoustic sensing. This review, for the first time, captures this transformative shift, charting the rise of nanostructured Quartz Crystal Microbalance (QCM) biosensors from a specialized research tool into a versatile, high-performance platform poised to redefine point-of-care diagnostics. We explore how the strategic integration of nanomaterials - such as gold nanoparticles, magnetic beads, and 2D composites - directly overcomes the traditional limitations of QCM, unlocking unprecedented sensitivity, specificity, and robustness in complex biological media. By acting as dynamic signal amplifiers and smart interfaces, these nanostructures enable the detection of elusive, low-abundance biomarkers critical for early disease intervention, from cancer antigens and neuro-inflammatory signals to viral pathogens. This work provides a synthesized analysis of the underlying principles, material innovations, and diagnostic applications that define this emerging frontier. We highlight how nano-engineering transforms QCM into a label-free, real-time sensing platform capable of revealing conventional laboratory methods. Furthermore, we critically assess the translational pathway of these technologies, addressing key challenges and future directions for integration into portable, affordable, and clinically validated diagnostic devices. Ultimately, this review illuminates nano-structured QCM biosensors not merely as an incremental improvement, but as a foundational technology bridging the gap between centralized laboratories and the urgent need for decentralized, actionable health insights.

1. Introduction

The diagnostic landscape is starkly divided. For a handful of conditions, rapid, point-of-care (PoC) testing is a reality; for many others, including neurodegenerative diseases and cancers, diagnosis remains tethered to centralized laboratories. This reliance on complex instrumentation creates critical delays and exacerbates global health inequities, leaving early detection - a cornerstone of effective treatment - out of reach for many. The challenge is not merely to miniaturize existing tools, but to reinvent the sensing paradigm itself, creating devices that are not only portable and affordable but also capable of detecting subtle, low-concentration biomarkers with high fidelity. Among these, quartz crystal microbalance (QCM) biosensors are particularly promising for their portability, simplicity, and rapid turnaround time [1]. Originally developed for electronic applications, QCM sensors are mass-producible and scalable, making them highly accessible for clinical use [2,3]. Their ability to function in both vapor and liquid environments [4,5], coupled with minimal energy dissipation [6,7], chemical inertness [6], and mechanical stability [8], enhances their adaptability across diverse biosensing contexts [9–11]. A key advantage of QCM technology is its label-free nature, which eliminates the need for fluorescent or radioactive tags, reducing assay cost and complexity while preserving native biomolecular behaviour and enabling real-time kinetic studies [12,13]. Yet, despite these compelling advantages, QCM has remained a relatively underrated and underexplored tool in the modern diagnostic landscape, often overshadowed by more established optical and electrochemical methods. Its perceived limitations - particularly its insufficient sensitivity to low-molecular-weight analytes [4,14], restricted active surface area for bioreceptor immobilization [15], nonspecific binding in complex media [16], and acoustic damping in liquids [17] - have largely confined it to the research bench. This historical relegation, however, has begun to reverse. The integration of nanotechnology is fundamentally rewriting QCM's diagnostic potential. Although QCM technology has been known for decades, its analytical potential has only recently been redefined through the integration of engineered nanostructured materials. This

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convergence represents a genuinely new chapter in acoustic biosensing. By introducing nanomaterials - such as gold nanoparticles [18], magnetic nanobeads [19], functionalized quantum dots [20], and others [21–25] - researchers have transformed QCM from a relatively simple mass-sensing device into a highly tunable, multifunctional diagnostic platform. These nanostructures act as signal amplifiers, selectivity enhancers, and capacity multipliers, directly addressing the core limitations that have held QCM back. They enhance the surface area, mass loading efficiency, and binding affinity of the QCM interface, thereby amplifying the signal response and improving selectivity. This enables the precise detection of minute biomolecular interactions, including antigen–antibody binding and nucleic acid hybridization, that underpin early disease diagnostics [26–28].

It is this pivotal transformation that we review here. While previous discussions have treated QCM as a mature, niche technology, this work synthesizes recent and rapid advances that are reshaping its diagnostic capabilities. For the first time, we comprehensively examine how nanostructure integration unlocks the latent potential of QCM biosensors, elevating their performance beyond conventional limits. This review provides a structured overview of recent advances in nano-QCM biosensors for diagnostic applications, detailing underlying detection principles, surface functionalization strategies, and nanomaterial-assisted performance enhancements. We also offer critical insights into their analytical capabilities and clinical potential, concluding with current challenges and future directions for translating nano-QCM biosensors into reliable, scalable, and commercially viable diagnostic tools.

2. Fundamentals of QCM biosensors

2.1. Piezoelectric effect and biosensor principle

The operational principle of QCM biosensors is fundamentally distinct from the optical or electrochemical platforms dominant in clinical diagnostics. This distinction stems from the piezoelectric effect, which enables the direct, label-free transduction of mechanical interactions - such as mass adsorption - into an electrical signal. While the requirement for precisely fabricated quartz resonators can increase initial complexity and cost, the core advantages of piezoelectric transduction are significant for diagnostic applications. Most notably, QCM eliminates the need for enzymatic or fluorescent labels, simplifying assay workflows, reducing reagent consumption, and minimizing waste. Furthermore, the direct mechanical-electrical coupling facilitates robust device architectures that are amenable to miniaturization, supporting the development of portable and wearable diagnostic systems where the piezoelectric element can also contribute to low-power or self-sustained operation [29]. To understand how nanomaterials enhance this platform, it is first essential to detail its underlying physical principles.

The performance of these systems is based on the piezoelectric effect, which was first described by Jacques and Pierre Curie in 1880 [30]. This effect refers to the ability of certain anisotropic, non-centrosymmetric materials to generate an electric charge in response to applied mechanical stress. Conversely, the reverse piezoelectric effect occurs when an electric field induces mechanical deformation in these materials, enabling a two-way conversion between mechanical and electrical energy. This bidirectional interaction is central to the functionality of piezoelectric sensors [30,31]. For this reason, piezoelectric biosensors are classified as mass-sensitive biosensors, as they transduce minute mass variations on the sensor surface into measurable electrical signals. Owing to these principles, piezoelectric biosensors, and QCM in particular, have been applied across a diverse range of diagnostic areas (Table 1).

Among the different piezoelectric transducers, bulk acoustic wave (BAW) and surface acoustic wave (SAW) devices represent the two main categories. BAW sensors operate via acoustic waves propagating through the bulk of the crystal, whereas SAW devices confine wave propagation to the surface [28,56].

Table 1
Summary of major application areas of piezoelectric biosensor technologies.

Application Area	Specific Examples	Notable Features	Ref.
Biomolecule Analysis	Identification, estimation, and interaction studies of biomolecules	Label-free, real-time analysis	[32]
Immunosensing	Detection of pathogens via antigen–antibody interaction	Highly selective & sensitive	[33]
DNA Detection	HPV16 detection using RCA; VHSV virus diagnosis; *Bacillus anthracis* detection with AuNPs; Detection of orchid viruses	Label-free and labeled methods; rapid hybridization detection	[33–37]
Protein and Amino Acid Studies	Arginine enantiomer detection; Type IV collagenase sensing; Protein-MIP characterization; Protein C via microcontact imprinting; Tumor necrosis factor α; Trypsin sensing; Carcinoembryonic antigen detection	Useful for structural, kinetic, and binding studies	[22,38–43]
Microorganism and Pathogen Detection	Avian influenza (aptasensor); *E. coli* O157:H7; *Salmonella typhimurium*; *Campylobacter jejuni*; *E. coli* biofilm stages	Aptamer- and nanoparticle-enhanced detection methods	[44–47]
Chemical and Environmental Monitoring	Pesticide detection; Monitoring industrial/chemical trace elements	On-site monitoring capability	[48,49]
Polymer and Material Science	Polymerization kinetics; Nanoparticle deposition; Dye–polymer interaction studies	Surface interaction quantification	[50,51]
Medical and Clinical Diagnostics	Exosome immunosensing; Saliva glucose sensors; MicroRNA detection; Point-of-care antibody assays	Non-invasive, fast, portable diagnostics	[1,52–54]
Gas Sensing	CO_2 and other gas detection applications	High selectivity; not limited to biological samples	[55]

Within the BAW family, the QCM has emerged as the most extensively employed platform due to its nanogram-level mass sensitivity and suitability for operation in liquid environments [57]. By detecting even subtle shifts in resonance frequency resulting from biomolecular adsorption, QCM enables precise and real-time detection of biomolecular interactions at the solid-liquid interface. These characteristics make QCM-based immunobiosensors particularly advantageous for the detection of disease-associated biomarkers in clinical diagnostics [58,59](Table 2).

Materials exhibiting piezoelectricity include natural crystals like quartz and tourmaline, as well as synthetic materials such as zinc oxide, aluminum nitride, and polyvinylidene fluoride [87]. Even some biological structures, such as bone, DNA, and proteins, display piezoelectric properties [2,88,89]. However, their piezoelectric response is typically orders of magnitude weaker and stems from more complex molecular-scale mechanisms (e.g., ion displacement, dipole alignment) than the robust, crystal lattice-based effect harnessed in engineered piezoelectric materials like quartz or ZnO for sensing applications. Quartz, in particular, is favored in sensing applications due to its thermal stability, mechanical robustness, and well-characterized properties. These characteristics make quartz crystals highly suitable for converting mechanical perturbations, such as mass loading into measurable electrical signals [90,91]. QCM devices exploit this principle by placing an AT-cut

Table 2
Clinical and diagnostic applications of QCM biosensors: targets, strategies, and performance.

Primary Category / Strategy	Target Analyte	Application / Context	Sensing Strategy / Recognition Element	LOD	Ref.
Immunosensing / Cancer Diagnostics	Prostate-specific antigen (PSA)	Prostate cancer diagnosis	Anti-PSA antibody + AuNP (sandwich assay)	48 pg mL^{-1}	[60]
	PSA (glycosylation patterns)	Prostate cancer diagnosis	QCM-D + SERS hybrid; PSA-specific aptamer	1.9 ng mL^{-1}	[61]
	Carcinoembryonic antigen (CEA)	Colorectal cancer monitoring	HRP nanosphere-based sandwich, EBCP amplification	7.8 pg mL^{-1}	[22]
	Heat shock proteins (HSPs)	Early cancer diagnosis	Lateral-field resonator; phage antibodies	7.5 pg mL^{-1}	[62]
	Metastatic breast cancer cells (Notch-4)	Cancer cell detection	Antibody attached via PHEMA NPs	50 cells mL^{-1}	[63]
Immunosensing / Infection & Inflammation	Procalcitonin	Sepsis and infection marker	Antibody–AuNP conjugate	37.8 ng L^{-1}	[64]
	Tumor Necrosis Factor α (TNF-α)	Inflammatory marker	Antibody + magnetic particle enhancement	1.6 pg mL^{-1}	[42]
	C-reactive protein (CRP)	Inflammatory marker	Antibody-conjugated nanomagnetic beads	–	[65]
Aptamer-based Biosensors	Thrombin	Coagulation marker	Aptamer on gold nanocages; cargo release	1.2 nM	[66,67]
	Matrix Metalloproteinase-9 (MMP-9)	Cancer metastasis	Dual aptamer sandwich	6.8 pM	[68]
	Lactoferrin (LF)	Diagnostic marker	Sandwich assay with aptamer-functionalized magnetic beads	8.2 ng mL^{-1}	[24]
	K562 cells	Chronic myeloid leukemia (CML)	T2-KK1B10 aptamer	263 cells	[69]
	Okadaic acid	Marine toxin	Capture aptamer + AuNP signal enhancement	–	[67]
Nucleic Acid Sensing	miR-106b	Exosomal miRNA for cancer	$LiTaO_3$ SAW biosensor; hairpin loop probe	0.0034 pmol L^{-1}	[70]
	miR-21	Cancer biomarker	Sandwich hybridization + TiO_2 NP & silver enhancement	0.87 pM	[71]
	miR-21 (alternative)	Cancer biomarker	DNA heteroduplex intercalation + AuNP	3.6 pM	[72]
	N6-methyladenine in DNA	Epigenetic biomarker	QCM; Transcription activator-like effector (TALE)	0.63 pmol L^{-1}	[73]
	Hepatitis C virus RNA	Viral infection	Oligonucleotide capture probes + RT-PCR	–	[74]
	Listeria monocytogenes DNA	Foodborne pathogen	LAMP amplification + direct binding	–	[75]
Molecularly Imprinted Polymers (MIPs)	Glucose in saliva	Diabetes monitoring	Microgel network with boronate binding sites	–	[76]
	Phosphoprotein casein	Food safety	TiO_2 NPs on aminated mercaptoundecanoic acid SAM	5.3 μg mL^{-1}	[77]
Microbial / Pathogen Detection	*Staphylococcus aureus*	Foodborne pathogen	Anti-*S. aureus* antibodies	10 CFU mL^{-1}	[78]
	Salmonella Typhimurium	Foodborne pathogen	Antibody-based; short precultivation (2 h)	10 CFU mL^{-1}	[79]
	Campylobacter jejuni	Foodborne pathogen	Antibody + magnetic particle preconcentration	20 CFU mL^{-1}	[80]
	Bacillus atrophaeus spores	Biothreat detection	Antibody immobilization	–	[81]
Enzymatic Activity Detection	PARP-1	Cancer therapy target	Poly(ADP-ribose) formation + CTAB-Au nanorods	0.04 nM	[82]
	Blood coagulation (fibrin)	Coagulation monitoring	Parylene-C coated QCM-D; dissipation monitoring	–	[83]
	Collagenase-IV	Cancer metastasis	Peptide substrate on QCM + AuNP label	1 ng mL^{-1}	[39]
Extracellular Vesicle / Exosome Analysis	Exosomes (via CD63)	Cancer diagnostics	Capture antibody on QCM-D	1.4–2.9 × 10^8 particles mL^{-1}	[52]
Viral Serology	SARS-CoV-2 antibodies	COVID-19 diagnosis	SAW biosensor; polyclonal anti-spike protein	–	[84]
Therapeutic / Toxin Monitoring	Sulfathiazole in honey	Food safety	Competitive immunoassay with monoclonal antibody	100 ng kg^{-1}	[85]
	Sulfur mustard (chemical warfare)	Security/defense	Hapten-conjugated albumin; direct binding in organic phase	–	[86]

quartz crystal between two metal electrodes. When an alternating voltage is applied, the crystal oscillates at a precise resonant frequency, which is highly sensitive to changes in the mass or viscoelastic properties of materials adsorbed onto its surface. Even nanogram-scale interactions such as biomolecule binding can induce measurable frequency shifts, making QCM an extremely sensitive and label-free analytical tool [92–94]. The quantitative relationship between frequency shift (Δ*f*) and mass change (Δm) was first described by Günter Sauerbrey in the 1950s [95] The Sauerbrey equation (Eq.1), which remains foundational in QCM theory, is given by:

$$\Delta f = -\left(\frac{2f_0^2}{\left(A\sqrt{\rho_q \mu_q}\right)}\right)\Delta m \quad (1)$$

where Δm is the change in the mass, Δ*f* is frequency shift of quartz oscillator due to mass change, ρ_q is the density of the quartz, μ_q is the shear modulus of a quartz crystal, f_0 is the resonant frequency of the QCM and A is its area. This linear relationship confirms that even minute changes in mass can be precisely measured by monitoring the resulting frequency shifts. All mass-sensitive piezoelectric sensors, including QCM, utilize the Sauerbrey equation to detect nanogram-level mass changes [96,97].

However, it is important to note that the Sauerbrey model assumes a rigid, evenly distributed mass layer in a vacuum or gaseous phase where no additional damping forces interfere. In liquid or viscoelastic environments, the crystal's oscillation is dampened by the surrounding medium's density and viscosity, causing deviations from ideal Sauerbrey behaviour [93,98]. This limitation led to further advancements, most notably by Kanazawa and colleagues [99], who introduced corrections for viscoelastic loading (Eq. 2). They demonstrated that in liquid media, resonance frequency shifts are influenced not only by mass changes but also by acoustic-fluid interactions, resulting in a phenomenon known as

acoustic damping. In these cases, both the resonance frequency and dissipation factor change due to energy loss as shear waves travel through or interact with non-rigidly bound layers on the crystal surface [9,29]. From a general standpoint, the contact of a QCM sensor with a liquid causes changes in oscillation that are proportional to the absolute viscosity (η_l) and density (ρ_l) of the liquid, (Eq. 2) allowing QCM to be used in assays sensitive to these physical parameters [29].

$$\Delta f = -2f_0^{\frac{3}{2}}\sqrt{\frac{\eta_l \rho_l}{\pi \rho_q \mu_q}} \quad (2)$$

In viscoelastic or biological environments, QCM responses are fundamentally categorized into two distinct regimes: gravitational (rigid) loading and viscoelastic loading. Gravitational loading, where adsorbed layers are thin, stiff, and uniformly distributed, adheres to the Sauerbrey equation, with frequency shift (Δf) being directly proportional to mass change. In contrast, viscoelastic loading occurs with soft, hydrated, or uneven layers (common for proteins, cells, and polymers). Here, the oscillation energy is dissipated into the layer, causing measurable changes not only in resonance frequency (Δf) but also in the dissipation (ΔD) or resistance (ΔR). This viscoelastic information is crucial for interpreting complex bio-interfaces, as it reveals structural properties, hydration, and mechanical changes beyond simple mass adsorption.

To fully leverage and interpret these viscoelastic effects, advanced QCM techniques have been developed. Quartz Crystal Microbalance with Dissipation monitoring (QCM-D) and Quartz Crystal Microbalance with Resistance monitoring (QCM-R) are the two primary methodologies that extend the capabilities of traditional QCM [100] .

The following table (Table 3) outlines the key operational and application differences between these two advanced techniques:

In practice, QCM-D has been extensively validated in complex clinical scenarios [101,102]. Its ability to deconvolute mass from viscoelastic effects has proven essential for detecting exosomes, analyzing protein glycosylation patterns relevant to cancer, and performing label-free coagulation assays that show strong agreement with standard clinical methods [103–105]. Conversely, QCM-R is emerging as a powerful alternative, particularly where a streamlined yet precise measurement of damping is paramount [106,107]. Its utility in detecting neuroinflammatory markers in accessible biofluids like perspiration highlights its potential for developing simpler, portable diagnostic devices for neurodegenerative conditions [21,108]. Together, QCM-D and QCM-R represent complementary advanced acoustic sensing platforms, with the choice of technique depending on whether detailed viscoelastic profiling (QCM-D) or precise, robust damping measurement (QCM-R) is better suited to the specific diagnostic challenge.

Table 3
Key operational and application differences between QCM-D and QCM-R.

Feature	QCM-D (with Dissipation Monitoring)	QCM-R (with Resistance Monitoring)
Primary Measured Parameters	Frequency shift (Δf) and Energy Dissipation (ΔD).	Frequency shift (Δf) and Motional Resistance (ΔR).
Core Principle	Measures the damping of the crystal's oscillation by quantifying the energy loss per cycle. A higher ΔD indicates a softer, more viscoelastic film.	Measures the damping by tracking the electrical resistance of the oscillating crystal. An increase in ΔR correlates with increased viscous loading.
Information Obtained	Provides detailed insights into the viscoelasticity, hydration, and structural rigidity of the adlayer. Enables modeling of layer thickness and shear modulus.	Provides a direct measure of damping losses at the interface. Often more sensitive to changes in viscosity and surface roughness in immediate contact with the sensor.
Typical Applications	• Studying protein conformational changes, polymer swelling, and cell adhesion mechanics. • Characterization of soft, hydrated biolayers (e.g., lipid bilayers, hydrogels).	• Environments where high precision in damping measurement is critical. • Detection in complex, high-viscosity media. • Applications benefiting from a simpler, potentially more robust electronic design.
Advantages	• Rich, quantitative data on film softness/rigidity. • Excellent for kinetic studies of layer formation and transformation. • Well-established model for data interpretation.	• Can offer higher precision in resistance measurement with a potentially simpler and more cost-effective electronic design. • May be more robust for certain point-of-care (POC) device integrations.

3. Nanomaterial-enhanced interfaces: overcoming the physical limits of QCM biosensing

The introduction of nanostructured materials into QCM platforms represents a targeted engineering solution to the core physical constraints outlined. While the intrinsic piezoelectric transduction of QCM offers label-free, real-time monitoring, its diagnostic utility has been bounded by fundamental trade-offs between sensitivity, selectivity, and operational stability in complex media. Nanotechnology provides a multifaceted toolkit to break these constraints by redesigning the sensor interface at the molecular and supra-molecular level.

3.1. Nanoscale solutions to intrinsic QCM challenges

The performance limits of conventional QCM arise from its reliance on acoustic wave propagation and mass loading at a solid-liquid interface. Nanomaterials are uniquely positioned to address each limiting factor:

- Overcoming Mass Sensitivity Limits: the Sauerbrey equation dictates that the frequency shift (Δf) is proportional to adsorbed mass. For low-concentration, low-molecular-weight analytes (e.g., cytokines, miRNAs), the resultant Δf is often indistinguishable from noise. Nanostructures act as mass amplifiers, either by providing high-surface-area scaffolds for increased analyte capture or by serving as secondary labels (e.g., enzymatic precipitation, metallic deposition) that add significant mass post-binding.
- Expanding the Functional Surface Area: the planar gold electrode of a standard QCM severely limits the density of immobilized bioreceptors. Nanoparticles, porous nanocomposites, and 2D materials increase the effective surface area by orders of magnitude, enabling higher loading of antibodies, aptamers, or molecularly imprinted polymers and thus improving the probability of target capture.
- Mitigating Non-Specific Binding and Damping: in biological fluids, fouling by irrelevant proteins and the viscoelastic damping of the acoustic wave (described by the Kanazawa-Gordon equation [99]) obscure specific signals. Engineered nano-architectures can incorporate highly oriented bioreceptor presentation and antifouling chemistries (e.g., PEGylated layers [12], hydrogel coatings [44]) to enhance specificity. Furthermore, certain nanomaterials (e.g., magnetic beads [24]) enable sample purification and magnetic-field-assisted signal modulation, separating target binding from matrix effects.
- Enabling Novel Transduction and Readout Strategies: Beyond passive mass loading, nanomaterials introduce new signal modalities. Magnetic nanoparticles allow for external field modulation, photocatalytic nanomaterials (e.g., WO_3 [109]) enable light-triggered mass amplification, and conductive nanocomposites (e.g., MXenes [25]) can transduce electrochemical events into acoustic signals.

By directly interfacing with the piezoelectric transducer, these nanoscale components do not merely modify the surface - they redefine

the sensing paradigm, transforming QCM from a generic mass balance into a tunable, high-performance diagnostic platform.

3.1.1. Gold nanoparticles

Gold Nanoparticles (AuNPs) have emerged as a remarkable class of nanomaterials, possessing properties that make them highly desirable for various applications, such as biomedicine and biosensors. These unique properties include controllable synthesis steps, low toxicity, and high biocompatibility [96]. The combination of the general properties of nanomaterials with the unique properties of gold enables them to offer an enhanced surface for the immobilization of biomolecules, making them exceptional candidates for the development of biosensing platforms. In various sensor designs, AuNPs have been used to facilitate the immobilization of recognition elements, amplify signal transduction, and improve the limit of detection for biomarkers [96].

One clinically relevant example that demonstrates the impact of nanoscale interface design in QCM biosensing is the detection of prostate-specific antigen (PSA), a key biomarker for prostate cancer diagnosis and disease monitoring [96]. Conventional QCM sensors often exhibit limited sensitivity in detecting PSA at clinically meaningful concentrations, particularly in complex biological matrices. To address this limitation, a nanostructured QCM biosensor modified with gold nanospikes (AuNS) was developed to enhance analyte immobilization and signal transduction efficiency for PoC applications [96]. In this system, the introduction of AuNS onto the QCM surface substantially increased the effective surface area and density of accessible binding sites, thereby improving the likelihood and strength of PSA-antibody interactions. Importantly, the nanospike morphology could be finely tuned by adjusting the pulse-current deposition parameters, with lower duty cycles (e.g., 20%) yielding sharper, more uniformly distributed nanostructures. This nanoscale control directly translated into enhanced frequency response sensitivity, while also maintaining oscillation stability an aspect commonly compromised in QCM platforms with excessive mass loading [96]. To further improve selective biomolecule attachment and long-term assay stability, PSA recognition elements were covalently immobilized using l-cysteine, avoiding weaker affinity-based immobilization strategies such as protein A. This strengthened the interfacial binding layer, reduced signal drift, and increased reproducibility under clinically relevant conditions [96]. As a result of these combined nanoscale and surface-chemistry optimizations, the AuNS-modified QCM biosensor achieved a broad PSA detection range of 0.1–100 ng mL^{-1}, with a limit of detection as low as 24 pg mL^{-1}, outperforming unmodified QCM platforms and matching the sensitivity of advanced nanoparticle-enhanced clinical assays [96]. The improved analytical performance is directly attributable to increased analyte capture efficiency and more effective coupling of binding events to the piezoelectric transduction process (Fig. 1). Overall, this study demonstrates how rational nanoscale surface engineering not merely the addition of nanomaterials can fundamentally enhance QCM biosensor performance, enabling label-free, clinically actionable POC diagnostics for early cancer detection [96].

Another significant advancement in QCM-based biosensing is demonstrated by the development of a AuNPs-enhanced immunosensor for the detection of *Salmonella typhimurium*, a major pathogenic agent associated with foodborne outbreaks [110]. In this system, the QCM surface was modified with a self-assembled monolayer of 4-mercaptobenzoic acid, enabling covalent attachment of antibody-functionalized AuNPs [111,112]. The introduction of AuNPs onto the QCM surface served not simply as a mass amplifier, but as a nanostructured scaffold that increased the density and spatial organization of the immobilized antibodies, thereby improving the efficiency of target capture and the transduction of binding events into measurable frequency shifts [110] (Fig. 2). A key finding of the study was the critical influence of nanoparticle size on biosensor sensitivity. Two AuNPs populations (25 nm and 62 nm) were evaluated, revealing that smaller AuNPs (25 nm) resulted in significantly greater frequency shifts upon *S. typhimurium* binding compared to the larger particles. This enhancement was attributed to the higher surface-area-to-volume ratio of the smaller nanoparticles, which enabled denser and more accessible antibody presentation, minimizing steric hindrance and improving biorecognition efficiency. Conversely, the 62 nm particles exhibited reduced immobilization efficiency and lower analytical response, demonstrating that nanoparticle size is a decisive parameter in maximizing QCM sensitivity. Importantly, the optimized AuNP-QCM platform enabled rapid, label-free pathogen detection with measurable frequency responses at clinically relevant bacterial concentrations (10^8 CFU mL^{-1}) [110]. Beyond providing a practical strategy for food safety and public health surveillance, this work underscores a broader principle central to nano-enabled

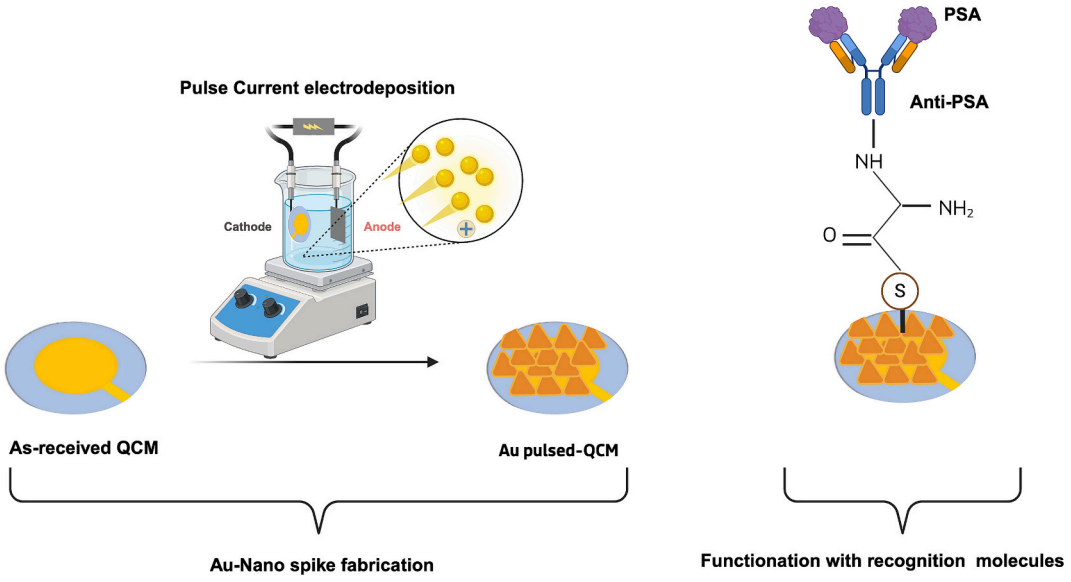

Fig. 1. Nanostructured QCM biosensor for PSA detection. (A) Pulse current deposition (PCD) process for fabricating gold nanospikes (AuNS) on the QCM electrode, including electrode setup, magnetic stirring, and pulsed current parameters to control nanospike morphology. (B) Schematic of the AuNS-modified QCM biosensor construction and PSA detection procedure, highlighting covalent immobilization of biomolecules via l-cysteine and EDC/NHS chemistry for enhanced stability and sensitivity [96].

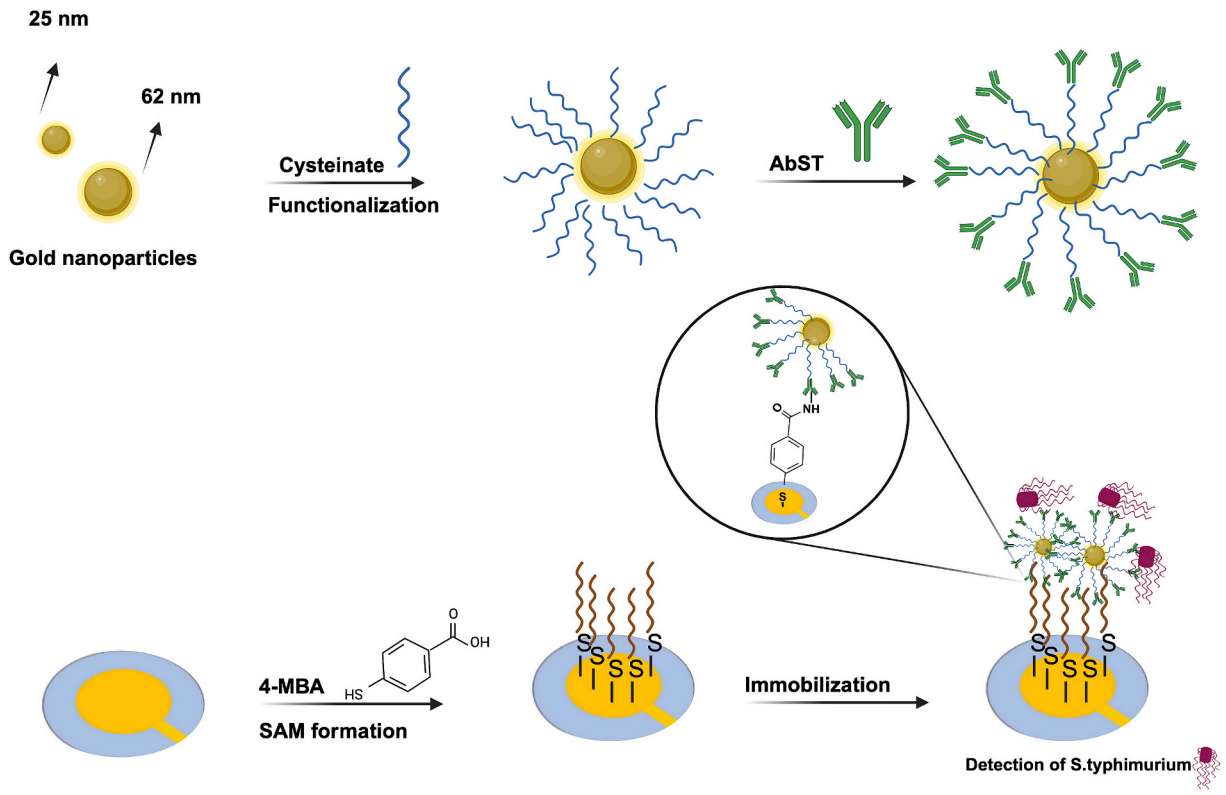

Fig. 2. AuNP-enhanced QCM immunosensor for rapid Salmonella typhimurium detection. (A) Schematic of AuNP synthesis and functionalization. (B) Fabrication of the QCM immunosensor via covalent immobilization on electrodes using a 4-mercaptobenzoic acid self-assembled monolayer (SAM) and EDC/NHS chemistry, followed by monoclonal antibody conjugation. The schematic also highlights nanoparticle size optimization (25 nm vs. 62 nm) and bacterial capture for enhanced frequency response [110].

QCM biosensor design: performance gains arise not merely from adding nanomaterials, but from engineering nanoscale interfacial architectures that improve analyte accessibility, bioreceptor organization, and mass energy coupling to the piezoelectric sensor.

One more notable example of nanostructure-assisted QCM biosensing for clinical diagnostics involves the detection of hepatitis B surface antigen (HBsAg), a key biomarker for hepatitis B virus (HBV) infection [113]. To address the limited sensitivity and slow turnaround time of conventional serological assays, a QCM immunosensor was developed using gold nanoparticle–polyethyleneimine (AuNP–PEI) nanocomposites as the functional sensing interface. The PEI provided a dense surface rich in primary amine groups, enabling high antibody-loading capacity, while the AuNPs enhanced the mass sensitivity of the QCM transducer. This synergistic nano structuring increased the number of accessible binding sites and improved analyte-capture efficiency, resulting in a stronger and more distinguishable frequency shift upon HBsAg binding. Importantly, the use of the AuNP–PEI architecture led to a significantly improved analytical performance, with a linear detection range of 1–1000 ng mL^{-1} and a limit of detection of 1.49 ng mL^{-1}, alongside 100% sensitivity and specificity in clinical serum samples, showing excellent agreement with ELISA results ($R^2 = 0.961$) (Fig. 3) [113]. In this case, the nanostructured layer was not simply a surface modification, but a functional signal amplification strategy, enabling real-time detection in a format that is potentially adaptable to PoC diagnostics. However, while promising, the sensor still depends on antibody stability and may be susceptible to fouling in complex biological matrices, suggesting that future designs may benefit from integrating antifouling or receptor-replacement strategies (e.g., aptamers or MIPs) to improve robustness.

While AuNPs significantly enhance sensitivity, their application in point-of-care formats is constrained by several factors. The functionalization chemistry (e.g., EDC/NHS) used for antibody immobilization can be susceptible to hydrolysis, affecting shelf-life and batch reproducibility. Furthermore, nonspecific adsorption of proteins from complex matrices like serum onto the high-surface-area gold nanostructures can lead to signal drift and false positives, necessitating robust yet often complex antifouling strategies. Scalable and uniform deposition of nanostructures (e.g., nanospikes) on QCM electrodes also remains a manufacturing challenge.

3.1.2. *Solid lipid nanoparticles*

In parallel with inorganic nanostructures such as gold nanoparticles, soft-matter nanomaterials have emerged as powerful tools for enhancing QCM biosensor performance, particularly in applications requiring biocompatibility, controlled surface chemistry, and improved receptor orientation. Among these, solid lipid nanoparticles (SLNs) offer a unique combination of structural stability, low toxicity, and tunable surface functionalization, positioning them as promising carriers for antibody immobilization and signal amplification [114,115]. Their relevance becomes particularly evident in the context of neurodegenerative disease (ND) diagnostics, where reliable detection of inflammation-related biomarkers remains a major challenge. NDs, despite their distinct etiologies, share convergent pathological features including neuroinflammation, oxidative stress, and dopaminergic neuronal loss that are closely associated with elevated systemic levels of haptoglobin (Hp), an acute-phase glycoprotein [116]. Conventional Hp assays, however, typically rely on labor-intensive, time-consuming, and costly analytical platforms and often require invasive cerebrospinal fluid sampling for ND biomarker assessment.

To overcome these challenges, Lettieri and co-workers [21] introduced the first QCM immunobiosensor employing hyaluronic acid–-coated solid lipid nanoparticles (HA-SLNs) as an advanced nano-interface for selective Hp detection in human serum. At the core of this system is a custom-designed QCM-R device [21,108] capable of

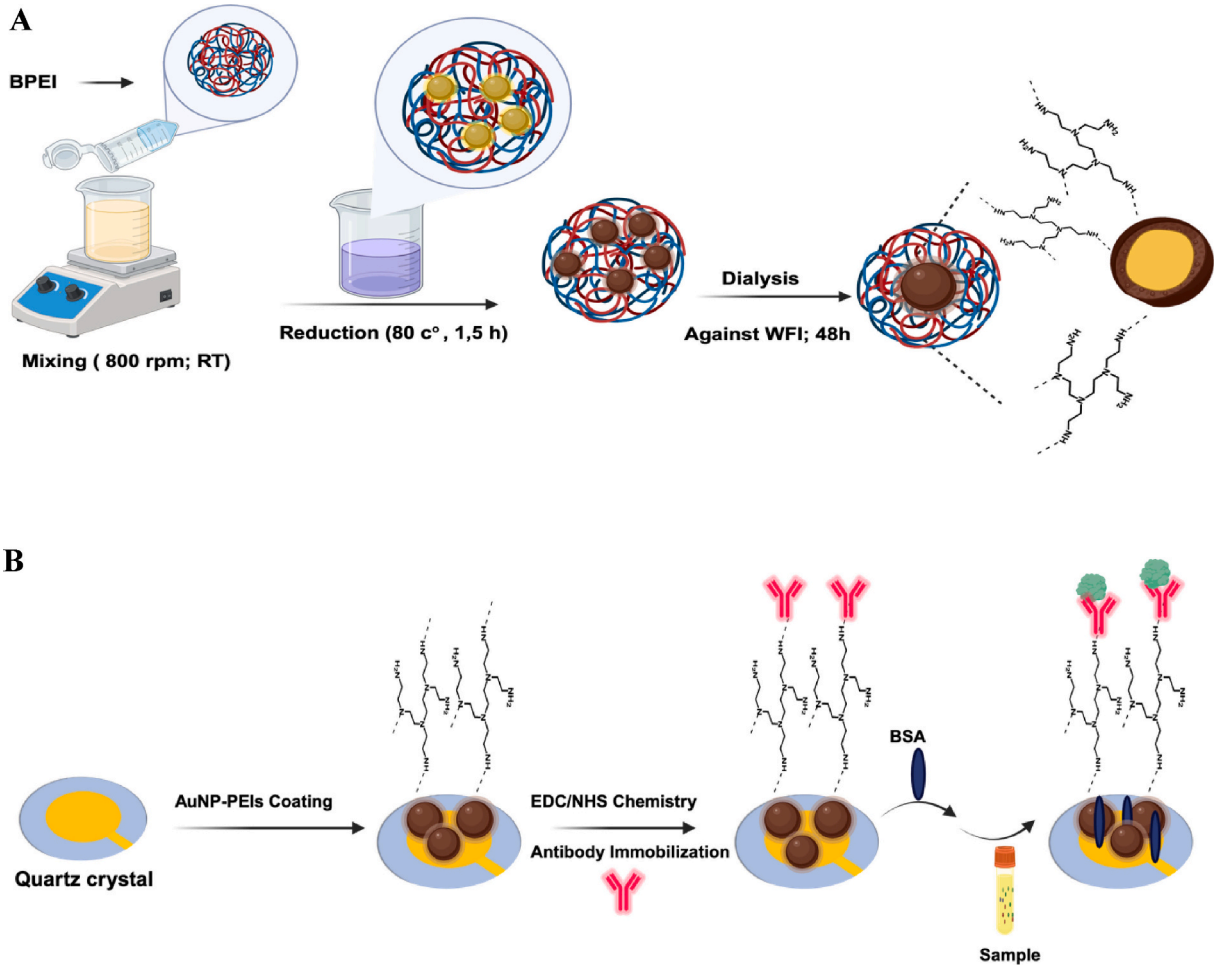

Fig. 3. AuNP–PEI-based QCM immunosensor for hepatitis B surface antigen (HBsAg) detection. (A) Schematic of AuNP–PEI synthesis, highlighting PEI's role as reducing, capping, and stabilizing agent. (B) Fabrication of the QCM immunosensor, including AuNP–PEI coating on the gold electrode, covalent antibody immobilization via EDC/NHS chemistry, surface blocking with BSA, and the detection procedure for HBsAg [113]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

simultaneous frequency and resistance measurements, enabling enhanced resolution of viscoelastic changes occurring at the sensor surface. The fabrication strategy involved functionalization of the quartz electrode with a thiolated polyethylene glycol amine self-assembled monolayer, anchoring of HA-SLNs to create a hydrated and bioactive nanoarchitecture, and subsequent covalent immobilization of anti-Hp antibodies. This configuration resulted in a highly responsive and stable immunosensing surface, demonstrating excellent analytical performance with high sensitivity (612.10 ± 28.14 μg mL^{-1}), outstanding reproducibility (CV_av% = 0.50%), and low limits of detection (0.063 ± 0.003 μg mL^{-1}) and quantification (0.21 ± 0.01 μg mL^{-1}). Surface modification and nanoparticle integration were rigorously validated through ToF-SIMS, AFM, and EIS analyses. Collectively, this SLN-assisted QCM-R platform provides a cost-effective, minimally invasive, and clinically relevant strategy for monitoring systemic neuroinflammation, offering significant promise for early detection and longitudinal assessment of ND progression [21] (Fig. 4).

3.1.3. Tungsten(IV) oxide (WO3) nanoparticles

Beyond receptor design, recent work has highlighted the use of photocatalytic nanomaterials as efficient mass-amplification elements in QCM-based immunoassays [109]. Tungsten(IV) oxide (WO_3) nanoparticles, in particular, have gained attention due to their tunable bandgap, chemical robustness, and strong oxidative activity under UV or visible irradiation [117–119]. Upon photoexcitation, WO_3 generates electron-hole pairs that readily drive surface redox reactions, enabling the rapid photoreduction of Ag^+ ions into metallic silver. The resulting silver deposition markedly increases the mass accumulated at the sensor interface, thereby amplifying the resonance frequency shift and improving the analytical performance of QCM measurements. This strategy was recently applied to the detection of alpha-fetoprotein (AFP) a clinically significant biomarker for hepatocellular carcinoma and for monitoring disease progression or recurrence. In the reported WO_3-mediated silver-enhanced QCM immunosensor, photocatalytic mass amplification improved the limit of detection by 6.5-fold (from 286 pg mL^{-1} to 43.7 pg mL^{-1}), demonstrating how photocatalytic nanomaterials can substantially strengthen both sensitivity and clinical relevance in QCM-based biomarker assays [109].

3.1.4. Horseradish peroxidase nanoparticles

In addition to photocatalytic amplification strategies, enzyme-assisted nanolabels have also been engineered to enhance mass transduction in QCM immunoassays. Traditional enzyme or nanoparticle labels often suffer from limited sensitivity, restricting their utility in detecting low-abundance biomarkers relevant to clinical diagnostics and biosecurity [22,120]. To overcome these limitations, a high-efficiency QCM immunosensing platform was developed for the detection of carcinoembryonic antigen (CEA) [22], an established tumor marker used for colorectal cancer diagnosis, prognosis, and monitoring of post-operative recurrence. In this approach, horseradish peroxidase (HRP)

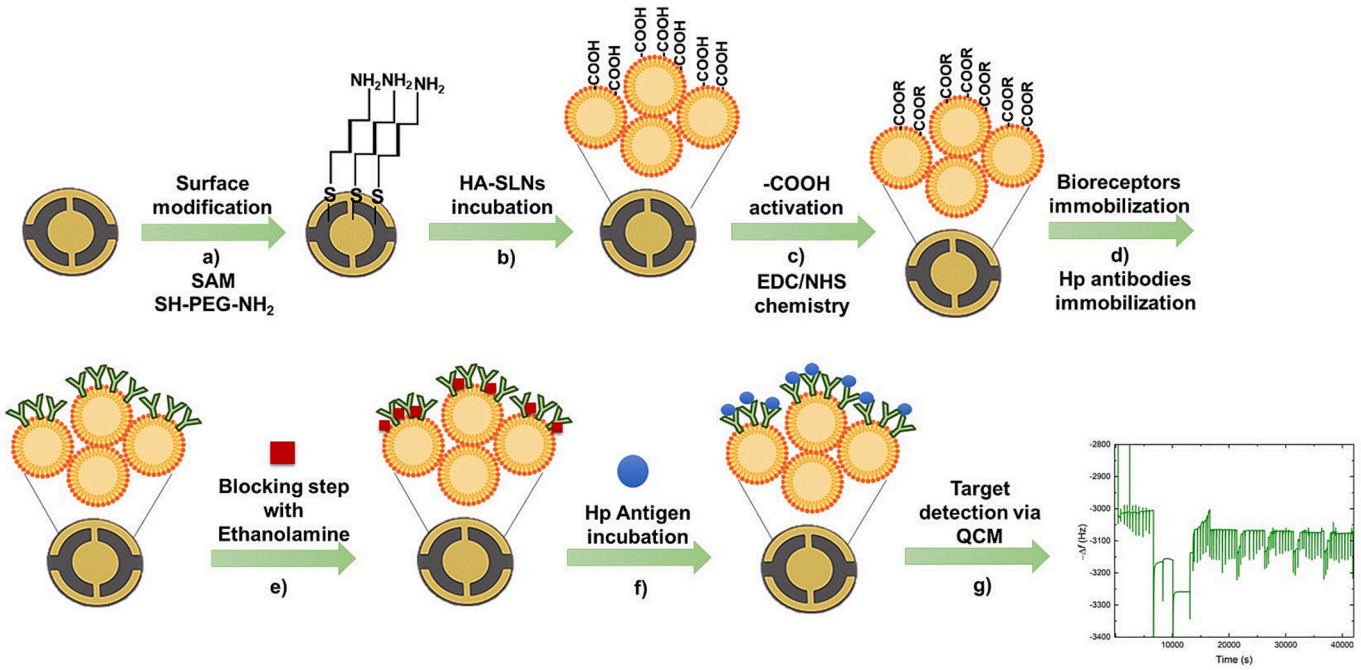

Fig. 4. Schematic representation of immunosensor assay for haptoglobin (Hp) detection: (a) incubation of the crystal in a solution containing a self-assembled monolayer of SH-PEG-NH2, (b) injection of HA-SLN and their immobilization on the crystal surface, (c) activation of the carboxyl groups of HA for subsequent binding of (d) Hp antibodies, (e) blocking of remaining active sites using ethanolamine, (f) injection of Hp, and (g) detection via the QCM device [21].

nanospheres were synthesized using a reverse micelle method with glutaraldehyde cross-linking and subsequently conjugated to anti-CEA detection antibodies. A complementary QCM probe was prepared by immobilizing monoclonal anti-CEA capture antibodies on an L-cysteine-modified gold electrode. Following sandwich immunorecognition with the target analyte, HRP nanospheres were anchored to the sensor surface, enabling enzymatic biocatalytic precipitation (EBCP) of 4-chloro-1-naphthol (4-CN). The formation of insoluble oxidation products on the electrode significantly increased the mass loading, producing amplified frequency shifts relative to conventional HRP labeling strategies. Under optimized conditions, the assay achieved a dynamic linear range of 0.01–100 ng mL^{-1} and an impressive detection limit of 7.8 pg mL^{-1}, with repeatability and intermediate precision as low as 10.7%. The method exhibited high specificity, excellent storage stability, and strong agreement with commercial ELISA measurements, underscoring its potential for sensitive and reliable clinical quantification of CEA in human serum. While natural receptors such as antibodies and enzymes are widely used in biosensing, their inherent limitations, including instability, environmental sensitivity, limited shelf life, and batch-to-batch variability, pose significant challenges for robust, long-term applications. To address these issues, researchers have developed core/shell molecularly imprinted nanoparticles (CS-MI-NPs), synthetic receptors offering enhanced thermal and chemical stability, reusability, and high selectivity [23] (Table 4).

In a study by Gagliardi and Cecchini [23] CS-MI-NPs were synthesized using a controlled sol-gel process via the Stöber method [137], to form the silica core. The silica core provided a rigid and chemically stable scaffold, while the imprinted polymer shell generated selective binding cavities complementary to target molecules such as streptavidin or tannins. Unlike antibody-based functionalization, which can suffer from denaturation and limited shelf-life, the CS-MI-NPs maintained structural integrity and recognition capability under varied environmental conditions. When integrated onto QCM-D transducers, the CS-MI-NP layers displayed low dissipation, indicating the formation of compact and mechanically robust sensing films an advantageous property for real-time, label-free detection in complex samples. The imprinted nanoparticles achieved an imprinting factor of 2.65 and relative affinity of 1.44, demonstrating significantly improved binding selectivity compared to non-imprinted controls. The system achieved a detection limit of 2.8 nM for streptavidin and showed effective molecular discrimination among structurally similar tannins, confirming that the synthetic recognition layer can operate in chemically complex matrices (Fig. 5) [23].

This work illustrates the potential of CS-MI-NPs as durable, reusable alternatives to biological receptors offering selective, sensitive detection in complex environments such as clinical samples, food matrices, and environmental media. While nonspecific adsorption and imprinting of large biomolecules remain challenges, ongoing research is focused on optimizing polymerization conditions and expanding applicability across a wider range of analytes [23].

3.1.5. *Magnetic nanobeads (MNBs)*

Enhancing mass loading is a well-established strategy for improving QCM sensitivity, particularly when detecting low-abundance biomarkers. Nanomagnetic beads serve as highly effective signal amplifiers because they introduce a substantial and controllable mass increase upon target capture while preserving high binding specificity [93] . Two general amplification modes have been demonstrated in QCM systems. In the first, nanomagnetic beads act as secondary labels in sandwich-type immunoassays, increasing the total mass bound to the QCM surface and thereby producing larger resonance frequency shifts. For example, in the detection of lactoferrin, Wu et al. employed aptamer-functionalized beads to build a secondary capture layer, markedly amplifying the mass signal and achieving a detection limit of 8.2 ng mL^{-1} [24]. The strength of this approach lies in the high surface-to-volume ratio of the beads, which supports dense loading of recognition units and efficient target capture (Fig. 6).

The second strategy leverages the superparamagnetic properties of the beads, where the application of an external magnetic field generates a measurable modulation of the QCM response. Thies et al. demonstrated that the introduction of antibody-conjugated nanomagnetic beads for C-reactive protein (CRP) detection significantly enhanced the QCM signal due to improved mass coupling and controlled bead positioning at the surface [65]. Extending this concept, Chen et al. designed

Table 4
MIP based biosensors for the selective detection of different biomarkers.

Target	Imprinting / Recognition Strategy	Sensor Material / Coating	LOD/LOQ	Ref.
C6-HSL (quorum sensing molecule)	NanoMIPs	Direct coating on QCM	-	[121]
Human Serum Albumin (HSA)	NanoMIPs	Spherical nanoMIPs on QCM	-	[122]
Ovalbumin	Oligomer immobilization imprinting	MIP film on QCM	-	[123]
IgM	MAPBA + Mannose functional imprinting	MIP thin layer on QCM	-	[124]
HSA	Epitope imprinting	MIP film	0.050–0.500 μg mL^{-1}	[125]
Salivary proteins	Thin-film bulk MIP imprinting	MIP-coated QCM	pM range	[126]
fbpA (N. meningitidis protein)	Epitope-imprinted EQCM	EQCM MIP	1.39 ng mL^{-1}	[127]
α1-Acid glycoprotein	Hybrid MIP synthesis	MIP-Cu_2O-GO composite	0.25 ng mL^{-1}	[128]
E. coli	Bulk & whole-cell imprinting	MIP-QCM	3.72×10^6 CFU mL^{-1}	[94]
B. subtilis	Bulk imprinting	MIP-QCM	-	[129]
M. leprae	Epitope-imprinted EQCM	EQCM MIP	0.161 nM; 0.536 nM	[130]
P.aeruginosa	Overoxidized polypyrrole MIP	MIP-QCM	10^3 CFU mL^{-1}	[131]
Dengue Virus (Type 1)	GO-enhanced viral template MIP	Graphene oxide + MIP composite	0.58 PFU mL^{-1}	[132]
HIV-1 gp41	Epitope imprinting in urine	MIP-QCM	2 ng mL^{-1}	[133]
Dengue Virus	Epitope-imprinted QCM film	MIP thin film	-	[134]
Classical Swine Fever Virus (CSFV)	Whole-virus imprinting	MIP-QCM	1.7 μg mL^{-1}	[135]
HRV & FMDV	Polyurethane MIP	MIP-QCM	-	[136]

a magnetic-modulation differential QCM system for the rapid and ultra-sensitive detection of prostate-specific antigen (PSA) using magnetic bead markers [139]. This setup employed two QCM sensors and an alternating magnetic field. PSA antibodies were functionalized onto nanomagnetic beads to facilitate antigen capture. The beads not only provided a high surface area for antigen binding but also exploited their superparamagnetic nature. By comparing the magnetic responses of bound and unbound beads under an applied magnetic field, Brownian motion noise in the solution was effectively suppressed, resulting in a remarkably low detection limit of 0.064 ng mL^{-1} [139]. Collectively, these studies show that nanomagnetic beads improve QCM biosensing not merely by increasing mass, but by enabling controlled, tunable, and noise-reduced signal amplification. However, optimal bead size, surface chemistry, and magnetic modulation parameters must be carefully tuned to avoid steric hindrance and non-specific aggregation, which could otherwise compromise sensor performance.

3.2. Nanocomposites-based QCM biosensors

3.2.1. MXene-Cu/Cu_2O/C nanocomposites

Since their introduction by Gogotsi and colleagues in 2011 [140] MXenes ($M_{n+1}X_nT_x$) have become attractive candidates for biosensing due to their tunable surface chemistry, high conductivity, and large accessible surface area [141–144] . Their surface terminations (—O, –OH, —F) facilitate strong interfacial interactions with biomolecules, while their 2D layered structure supports the formation of stable nanocomposite architectures. When combined with metal organic framework (MOF)-derived carbon materials, MXenes can additionally improve electron transport and structural robustness, making them suitable for non-enzymatic sensing applications [145–150]. Addressing the limitations of enzyme-based glucose sensors such as poor storage stability and susceptibility to denaturation a recent study developed a non-enzymatic QCM sensor based on MXene–Cu/Cu_2O/C nanocomposites for real-time glucose detection [151]. Here, MXene nanosheets act as a conductive, hydrophilic support that enhances surface adsorption and rapid charge transfer, while Cu/Cu_2O nanoparticles provide intrinsic electrocatalytic activity toward glucose oxidation. The resulting hybrid interface induces a larger frequency shift upon glucose binding, effectively translating chemical interaction into a measurable piezoelectric response with improved sensitivity. The sensor exhibited a linear response across 3–10 mM glucose and a limit of detection of 1.70 mM, which is directly relevant to physiological glucose monitoring. Additionally, the system demonstrated rapid signal stabilization and

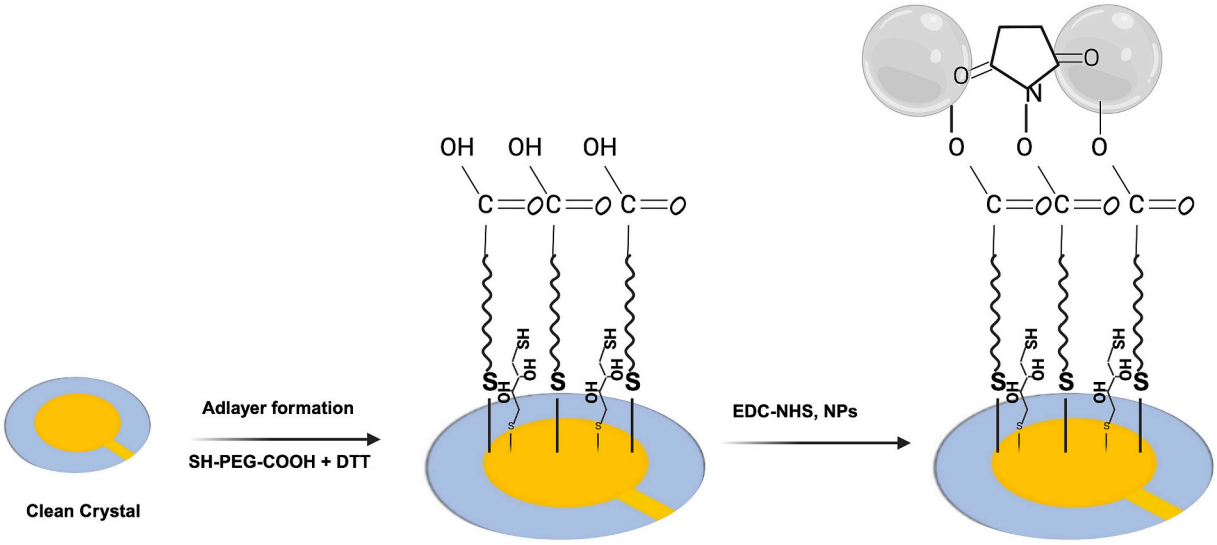

Fig. 5. Schematic representation of CS-MI-NP functionalization and subsequent integration onto QCM-D sensors. The process involves initial formation of the adlayer using HS-PEG-COOH and DTT, followed by activation of carboxylic groups via EDC/NHS chemistry and immobilization of the probe [23].

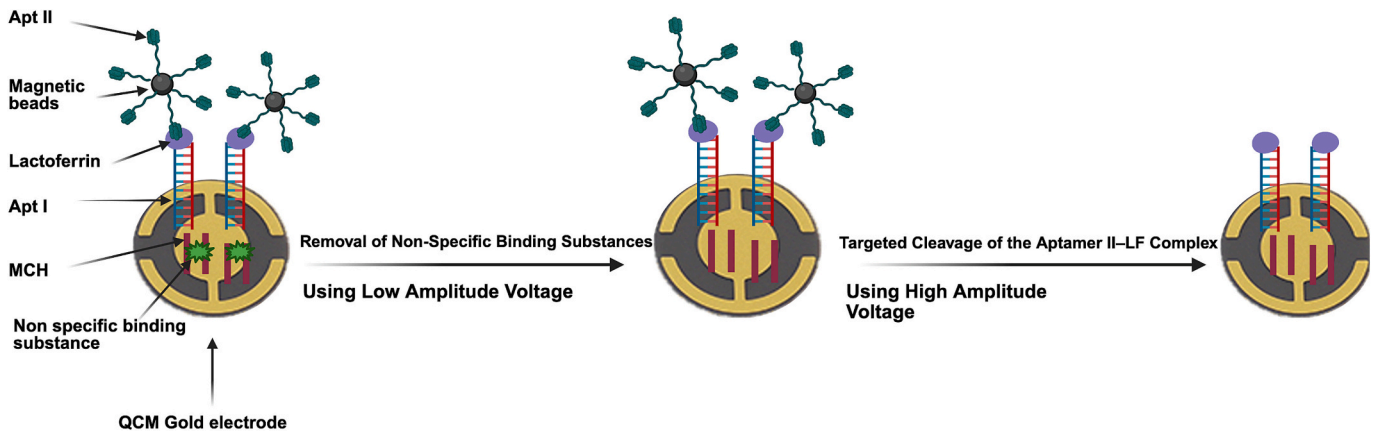

Fig. 6. High-frequency QCM aptamer biosensor for lactoferrin (LF) detection. Schematic of the sandwich assay-based detection strategy using aptamer-functionalized gold electrodes and nanomagnetic beads. The molecular bond capture technique is applied by controlling the excitation voltage to selectively break weak non-specific bonds and strong aptamer–bead complexes, with resulting frequency shifts corresponding to LF concentration [138]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

high operational durability, features that address major practical challenges faced by enzymatic and polymer-coated QCM glucose sensors [25]. Critically, the analytical enhancement arises not from increased surface roughness alone, but from the synergistic coupling of MXene conductivity and Cu/Cu_2O catalytic sites, which together enable enzyme-free, real-time glucose quantification with clinically meaningful precision. This work highlights how rational nanointerface engineering can shift QCM glucose sensing from bioreceptor-dependent recognition toward robust, catalyst-driven detection, supporting future miniaturization into portable monitoring formats.

4. Translational pathways and barriers to clinical adoption

The preceding sections have detailed the remarkable analytical advances enabled by nanostructured QCM biosensors, showcasing their enhanced sensitivity, selectivity, and potential for PoC diagnostics. However, the journey from a high-performing laboratory prototype to a clinically adopted, commercially viable device is complex and fraught with translational challenges. The majority of nano-QCM biosensors reported in the literature reside at low Technology Readiness Levels (TRLs 3–4) [152], representing proof-of-concept demonstrations in controlled laboratory settings. Advancing to higher TRLs (6–7) [152] required for clinical prototyping involves overcoming significant integration hurdles. A primary challenge is the transition from a sensor measuring a purified or spiked analyte to a fully integrated "sample-in-answer-out" system. This necessitates the incorporation of upstream sample preparation modules (e.g., for plasma separation from whole blood, filtration, or analyte preconcentration) and downstream fluidic handling and waste containment, all while maintaining the integrity of the functional nano-interface. Furthermore, the design of the electronic readout must evolve from benchtop impedance analyzers to miniaturized, low-power, and stable circuitry suitable for portable or handheld use. Long-term stability of the bioactive surface - a composite of nanostructures and bioreceptors - under variable storage conditions (temperature, humidity) is another critical parameter that requires extensive optimization for PoC deployment.

While impressive LOD are routinely reported, these metrics, often obtained in buffer solutions, are only the first step in clinical validation. The true test of a diagnostic biosensor is its performance in authentic clinical matrices (e.g., whole blood, serum, saliva, sweat) from a diverse patient population. Comprehensive analytical validation must follow established guidelines (e.g., *Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures* - CLSI EP17 [153]) to determine not only sensitivity and specificity but also the limit of quantitation, linear range, precision, and robustness against interferents endogenous to the sample (e.g., lipids, heterophilic antibodies, other proteins). Following analytical validation, clinical utility must be established through prospective trials. These studies must demonstrate that the sensor's output correlates strongly with gold-standard laboratory methods and, more importantly, that it provides actionable information leading to improved patient outcomes or more efficient clinical pathways. For early disease detection markers, this involves large-scale longitudinal studies to define clinically relevant cutoff values and predictive power. Collectively, these factors emphasize that while QCM biosensors hold significant promise for clinical and PoC applications, successful translation will require coordinated progress in standardization, regulatory compliance, clinical validation, and manufacturability.

5. Conclusions

The integration of nanotechnology into QCM-based biosensing platforms has driven transformative advancements in sensitivity, selectivity, signal amplification, and device miniaturization. Among the various nanomaterials employed, gold nanostructures (AuNS) have been particularly effective in enhancing biomolecule immobilization and improving signal response. Nevertheless, further investigation is required to optimize the size and configuration of Au-NS on QCM electrode surfaces to maximize detection efficiency for specific biomarkers. Despite meeting key performance benchmarks, persistent challenges include precise calculation of the limit of detection, ensuring long-term sensor stability, and enhancing resilience in complex biological and environmental matrices.

Core-shell molecularly imprinted nanoparticles also continue to demonstrate significant potential due to their high selectivity and compatibility with acoustic detection systems. Their tunable binding affinities and increased surface areas mark a substantial leap in biosensor capability. However, real-world deployment requires validation against complex interferences to confirm their practical effectiveness. Similarly, nanomagnetic beads are gaining attention for their superparamagnetic behaviour, fast responsiveness to magnetic fields, and ease of surface functionalization. These traits make them excellent candidates for sample preconcentration and separation in biosensing. Yet, current detection platforms lack direct quantification mechanisms for these beads, often relying on indirect signals that can compromise accuracy. Moreover, their limited role in multi-analyte detection frequently necessitates integration with other nanomaterials, increasing system complexity and material compatibility concerns.

Moreover, the development of MXene/MOF-functionalized QCM electrodes has opened new opportunities for enzyme-free glucose detection. These biosensors have shown excellent selectivity and

reproducibility within physiological ranges. However, improvements in film uniformity and electrode surface architecture remain necessary to enhance sensitivity and push detection limits even lower [25].

In summary, QCM-based biosensors augmented with advanced nanomaterials have made remarkable strides. However, critical limitations related to surface engineering, quantitative signal interpretation, real-world reliability, and system integration persist.

6. Future outlook

To advance beyond the recognition of these challenges and toward their resolution, a deeper analysis of their root causes and corresponding solution pathways is essential. The limitations in long-term stability and reproducibility often stem from fundamental issues such as nanomaterial batch-to-batch variability, inconsistent bioreceptor orientation, and the inherent instability of biological recognition elements (e.g., antibodies) in point-of-care formats. Corresponding solutions include the adoption of synthetic, robust receptors (e.g., engineered aptamers or molecularly imprinted polymers), standardized nanofabrication protocols, and advanced stabilization techniques (e.g., lyophilization, hydrogel encapsulation). Similarly, the challenge of non-specific binding in complex matrices is rooted in the non-selective physicochemical interactions between nanostructured surfaces and background biomolecules. This can be mitigated by integrating multi-functional interfaces that combine high-affinity capture elements with ultra-low fouling coatings (e.g., zwitterionic polymers, polyethylene glycol derivatives). Finally, the scalability and manufacturability hurdles arise from the incompatibility of lab-scale, multi-step functionalization processes with high-throughput production. Future efforts should therefore prioritize scalable nanomaterial deposition methods (e.g., inkjet printing, roll-to-roll coating) and modular sensor designs that decouple the stable transducer from disposable, pre-functionalized cartridges. By shifting the research focus from mere performance metrics to the underlying materials and engineering bottlenecks, the field can strategically accelerate the translation of nano-structured QCM biosensors into reliable, commercially viable diagnostic platforms.

To translate this potential into clinical reality, a clear roadmap with specific milestones and realistic timelines is necessary. Within the next 1–3 years, key milestones should include: (1) the establishment of consensus standards for nano-QCM performance validation in clinically relevant matrices (e.g., pooled human serum), moving beyond buffer-based detection limits; (2) the demonstration of integrated, prototype point-of-care devices that couple sample preparation (filtration, dilution) with nano-QCM sensing in a single, automated workflow. The subsequent 3–7 year horizon should focus on: (3) conducting robust analytical validation and multi-center clinical studies to correlate sensor output with gold-standard diagnostic methods and clinical outcomes; (4) forging industry partnerships to address manufacturability, scaling up nano-interface fabrication via techniques like inkjet or slot-die coating. An actionable strategy involves adopting a phased “test strip” model, where the stable, reusable QCM reader is paired with disposable, mass-produced sensor chips pre-functionalized with nanostructured capture elements. This approach separates the engineering challenges of reader durability from those of assay reproducibility and shelf-life.

The advancement and adoption of nano-enhanced biosensors are also hindered by challenges in regulatory approval, ethics, scalability, reproducibility, and biocompatibility. Regulatory agencies such as the Food and Drug Administration (FDA) and European Medicines Agency (EMA) require rigorous validation, made more complex by the integration of nanomaterials and bioreceptors [154]. Ethical concerns, particularly around privacy and consent in wearable or implantable devices, highlight the need for robust frameworks to safeguard patient rights [155]. Scalability and reproducibility remain critical, as large-scale production must preserve performance despite variability in nanomaterials.

Concurrently, emerging computational and engineering technologies are providing powerful new tools to navigate this complex translational landscape. For instance, machine learning (ML), deep learning techniques, especially convolutional neural networks (CNNs) and recurrent neural networks (RNNs), are expanding the analytical potential of biosensors [154] . These models are adept at managing high-dimensional datasets, enabling more accurate and faster analyte identification. Their integration with high-throughput platforms, such as microarrays and microfluidic chips, is pushing the boundaries of real-time diagnostics and personalized healthcare. In addition, new technologies like 3D printing, Internet of Things (IoT) and artificial intelligence (AI), accelerates biosensor prototyping, while AI and IoT improve functionality through real-time data handling and advanced diagnostics [156–158]. Innovations in other label-free sensing paradigms, such as liquid crystal (LC)-based biosensors enhanced by smart nanostructures, also offer complementary paths forward due to their high sensitivity, low cost, and minimal power consumption [155].

Ultimately, the path forward lies in continued interdisciplinary collaboration bridging materials science, nanotechnology, data science, and biomedical engineering. By tackling the outlined materials, engineering, and translational bottlenecks through a structured roadmap, the next generation of biosensors can revolutionize diagnostics, personalized medicine, and environmental monitoring.

CRediT authorship contribution statement

Anahita Darbandi: Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Data curation. **Mariagrazia Lettieri:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Conceptualization. **Gemma Leone:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition. **Agnese Magnani:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Formal analysis. **Marco Consumi:** Writing – review & editing, Visualization, Supervision, Resources, Project administration.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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