

BioFETs with Magnetic Microbeads for Enhanced Biosensing and Early Disease Detection

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ABSTRACT: Biological field-effect transistors (Bio-FETs) have demonstrated strong potential for biosensing and early disease detection with the new advances in nanomaterials, wafer fabrication, and integrated microfluidic devices. However, the intrinsic challenges, such as Debye length screening, electrical impedance interference, and biofouling effects from complex biological samples still exist in conventional Bio-FETs. Among emerging strategies, magnetic microbeads offer distinct advantages for enhancing sensing performance. Magnetic microbeads provide a high surface-to-volume ratio, enabling efficient conjugation and active capture of target biomolecules. Magnetic microbeads possess unique magnetic properties to allow precise manipulation by magnetic fields, such as controlled concentration, positioning, and mixing. Conjugated magnetic microbeads can be detected by both Bio-FETs and giant magnetoresistance (GMR) sensors, with improved robustness and sensitivity. This review focuses on Bio-FETs with magnetic microbeads, highlights key concepts, device types, manipulation, and signal detection mechanisms, and discusses remaining challenges and future opportunities for rapid, sensitive, portable, and wearable systems in precision healthcare.

KEYWORDS: Bio-FETs, Magnetic Microbeads, Conjugation, Microcoils, Detection.

■ Introduction

Over the past several decades, the semiconductor industry has undergone continuous innovations driven by Moore's law, leading to modern metal-oxide-semiconductor field-effect transistors (MOSFETs) with critical dimensions approaching the sub-2 nm node technology. As noted in the International Roadmap for Devices and Systems, advanced logic technology nodes have reached gate lengths and feature sizes on the order of a few nanometers, where atomic-scale effects increasingly dominate device behavior.¹ At these dimensions, transistor structures become comparable in size to fundamental biological molecules. For example, the DNA double helix has a uniform diameter of approximately 2 nm,² while single-stranded RNA molecules typically have an effective diameter of about 1 nm.³ Proteins occupy an intermediate nanoscale regime, as most globular proteins have diameters ranging from about 2 to 10 nm,⁴ with antibodies measuring approximately 10-15 nm in overall dimension.⁵ In contrast, viruses are larger nanoscale assemblies; they range in size from approximately 20-300 nm in diameter.⁶

As MOSFET dimensions are now comparable to biological entities, they are capable of detecting individual biomolecular or cellular components rather than bulk-averaged signals from large populations. Advanced 1D and 2D MOSFET layouts enable the fabrication of dense sensor lattice arrays, making simultaneous, massively parallel detection of millions of targets on a single chip feasible. Most importantly, because MOSFET operation is governed by electric-field changes of channel conductivity, these devices are intrinsically sensitive to nanoscale electrostatic and electromagnetic signals, enabling ultrafast detection on ps-ns timescales. Together, MOSFET dimensional matching, scalable array integration, and ultrafast electrical re-

sponse have driven the rapid adoption of specialized biological field-effect transistors (Bio-FETs) for biological and biomedical applications.

Bio-FETs are biosensors that utilize field-effect transistors to convert biological recognition interactions directly into electrical signals. The fundamental operating principle was first introduced by Bergveld, who pointed out that changes in the ion concentration at the gate surface cause corresponding shifts of the transistor channel current.⁷ In Bio-FETs, the traditional metal gate is replaced or functionalized with biological recognition elements such as DNA probes, antibodies, enzymes, or aptamers. When target biomolecules bind to the sensing surface, such as DNA hybridization, protein binding, or antigen-antibody interactions, their intrinsic charges change the surface potential, leading to a measurable shift in threshold voltage or channel conductance. Because Bio-FETs can operate at the nanoscale and measure the intrinsic electrostatic interactions without optical or chemical labels, they are particularly attractive for label-free and real-time detection.⁸

Despite significant advantages, Bio-FET sensors face several fundamental and practical limitations. One of the most critical challenges is electrostatic screening in physiological environments, commonly described by the Debye length. The Debye screening length in high-ionic-strength solutions can be reduced to less than 1 nm, severely limiting the sensitivity of charge-based biosensors.⁹ This effect makes it difficult for Bio-FETs to detect biomolecules or binding events occurring several nanometers away from the sensing surface, such as antibody-antigen complexes. In addition, device-to-device variation, instability of surface functionalization, biofouling, and long-term signal drift are key engineering challenges. While Bio-FETs demonstrate exceptional sensitivity under

controlled conditions, reproducibility and robustness in real biological samples remain major obstacles.¹⁰

Therefore, future developments in Bio-FETs research have increasingly focused on engineering strategies that overcome Debye screening and improve robustness and reproducibility, including nanostructured and nanoporous channels,¹¹ reduced ionic strength, and signal-amplification approaches. Among these, the integration of magnetic microbeads has emerged as a particularly promising direction.¹² With a high surface-to-volume ratio for bioreceptor immobilization and active manipulation of target biomolecules using external magnetic fields, magnetic microbeads effectively increase the amount of molecular charges to the gate surface with pre-concentration and reduced background noise. Moreover, in addition to charge-based detection alone, magnetic microbead-based Bio-FETs also support hybrid sensing schemes, where electrical readout is combined with magnetic sensors, enhancing detection reliability in complex samples. Consequently, magnetic microbead-enhanced Bio-FET development represents a key future trend from high-sensitivity laboratory testing toward robust, scalable, and clinically capable biosensing platforms for early disease detection.

This review, therefore, focuses on the integration of magnetic microbeads with Bio-FET platforms, citing the capture of extracellular vesicles and exosomes for cancer biomarker detection as a clinical application for a promising noninvasive liquid biopsy strategy for early and sensitive diagnosis. The Bio-FET mechanism, different types, and the Debye length concept are introduced to establish the foundational understanding of Bio-FET systems. The review then examines microbead-based biosensors, with particular emphasis on available functionalization strategies and magnetic microbeads as mobile carriers and mobile nets for selective target conjugation and capture. Magnetic microbeads can be actively manipulated, especially by using microfabricated platforms, including planar micro-coils, PCB-based coils, and 3D micro-solenoid structures, to achieve precise control at the targeted sensing interface. The increased charge concentration near the Bio-FET gate surface helps to overcome the limitations caused by Debye screening and poor mass transport.

The review compares the major post-manipulation detection strategies that convert bead accumulation into measurable outputs, including optical, electrochemical, electrical, and magnetic detection. Optical methods provide simple visual confirmation but are mostly qualitative. Electrochemical techniques such as cyclic voltammetry and impedance spectroscopy offer high sensitivity for clinical biomarker assays, but they often require redox-active labels, enzymes, or additional chemical modification steps rather than being fully label-free. They also suffer from nonspecific adsorption and unwanted side reactions from other molecules present in complex biological samples, as well as electrode fouling. Magnetic detection using giant magnetoresistance (GMR) and tunnel magnetoresistance (TMR) sensors enables highly quantitative bead counting without being affected by Debye screening; however, the major limitation is the complexity of device fabrication and integration with highly specialized magnetic sensor structures.

Overall, Electrical detection using Bio-FETs and magnetic microbeads enables ultrasensitive detection of targets such as exosomal miRNA and DNA through charge-based sensing, creating a highly promising platform for early disease detection by reducing sample pretreatment, minimizing false signals, and enabling direct analysis in minimally processed biological samples.

■ Discussion

Clinical Aspects of the Applications:

Cancer remains one of the leading causes of death worldwide, with approximately 20 million new cases and 9.7 million deaths reported globally in 2022.¹³ Lung, breast, and colorectal cancers are among the most common and deadliest types. However, patient survival rates are strongly dependent on the stage at which the disease is diagnosed. Early-stage detection results in survival rates as high as 90% for breast and ovarian cancer and approximately 80% for lung cancer, while survival rates drop sharply to 15% or lower when the disease is diagnosed at advanced stages. This huge difference highlights the urgent need for early, sensitive, noninvasive, and point-of-care diagnostic methods. Improving technologies for early disease detection, particularly through liquid biopsy approaches that can identify biomarkers before symptoms appear, has the potential to lower cancer-related deaths and help patients receive treatment earlier and more effectively.

Extracellular vesicles (EVs), including exosomes, are nanoscale extracellular vesicles found in bodily fluids such as blood, saliva, urine, and breast milk. EVs contain proteins and RNA that represent the biological state of the parent cells, making them unique carriers of disease-related biomarkers.¹⁴ By isolating and analyzing these molecular contents, EV-based liquid biopsy approaches can support early cancer detection, monitor treatment response, and help predict disease progression, enabling noninvasive analysis and personalized healthcare.

Despite significant progress, EVs/Exosomes detection using Bio-FET sensors has encountered the electrostatic screening of the nanometer-level Debye length.¹⁵ Magnetic microbeads functionalized with capture probes have been proven to effectively enable selective binding and active manipulation of EVs as an interim medium, and for low-concentration detection effectively.^{16,17} Solovicova *et al.* provided a comprehensive overview of magnetic-bio-affinity capture applied to the detection of exosomes or exosomal cargo as disease markers using different affinity capture ligands.¹⁸ Wu *et al.* developed the Mag-Net platform, which uses magnetic beads to capture and enrich EVs from plasma while depleting background proteins, thereby enabling sensitive downstream detection of EV-associated proteins in low-concentration clinical samples.¹⁹

Fundamentals of Bio-FET and Bio-FET Types:

A Bio-FET is constructed by integrating biological detection with an FET platform. The fundamental structure of a Bio-FET consists of the following key components: 1) Semiconductor Channel as the conduction pathway between the source and drain electrodes. 2) Gate Dielectric Layer as both

an insulating layer and a sensing interface. 3) Source and Drain Electrodes and 4) Functionalized Sensing Surface as shown in Figure 1.

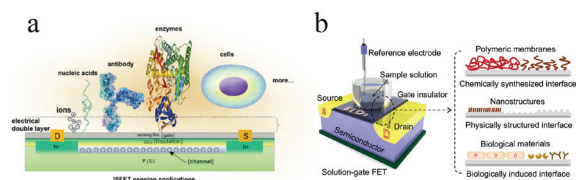


Figure 1: (a) Schematic illustration of the BioFET-sensing applications for different analytes. Reprinted with permission from Electrochemical Science Advances.²⁰ (b) Conceptual structure of potentiometric FET biosensor, consisting of a biological sample, a signal transduction interface, and a detection device. Reprinted with permission from Commun. Chem.²¹

Pandey *et al.* provided a comprehensive and up-to-date review of bio-field-effect transistors (Bio-FETs), systematically covering the fundamental operating principles of FETs, as well as the structural design and fabrication strategies specific to Bio-FET devices.²² The review categorizes and analyzes major Bio-FET types based on their applications, including DNA-FETs, enzyme-FETs (ENFETs), immuno-FETs, ion-sensitive FETs (ISFETs), and aptamer-based FETs, supported by detailed comparisons of different case studies for each type. In addition, the paper provides an in-depth discussion of the most widely reported materials in Bio-FET development, such as laser-induced graphene, carbon nanotubes, reduced graphene oxide, and molybdenum disulfide (MoS₂).

Instead of categorizing Bio-FETs by applications and detection materials, this review will follow Rai *et al.* by structuring the analysis around the various FET architectures and their performances, as shown in Figure 2, including MOSFET, ISFET (Ion Sensitive Field Effect Transistor), FGFET (Floating Gate Field Effect Transistor), EGFET (Extended Gate Field Effect Transistor), Carbon-Based FETs (Carbon Nanotube FET and Graphene FET), TFET (Tunnel Field Effect Transistor).²³

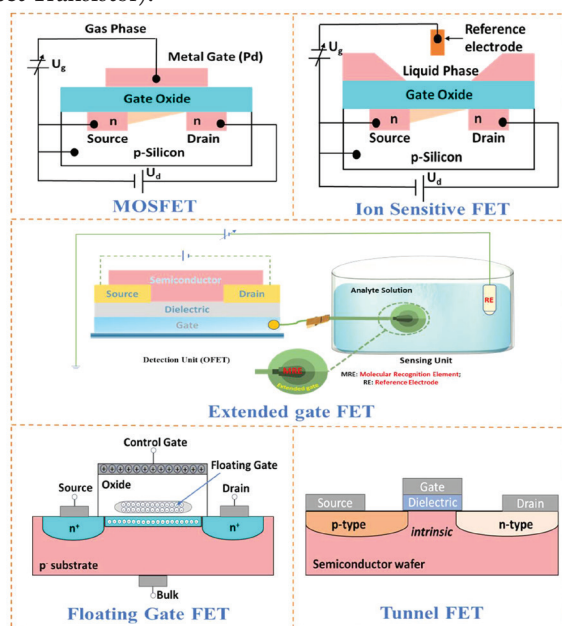


Figure 2: Various architectures of FET technology. Reprinted with permission from Talanta Open.²³

In biosensing applications, MOSFET-based sensors allow small changes induced by biomolecular interactions to produce measurable current variations directly. Sadighbayan *et al.* developed a commercial MOSFET-based biosensor to detect C-reactive protein (CRP).²⁴ The device identifies CRP by measuring changes in the drain current that occur when CRP binds to its specific antibody. Jieun Lee *et al.* reported a silver nanowire used to detect the target in Figure 3a, and a hybrid MOSFET converted this signal into an electrical output.²⁵ Both parts were integrated on a single chip using conventional CMOS fabrication.

ISFETs (Ion Sensitive Field Effect Transistors) are similar to MOSFETs, except that the metal gate is replaced by a reference electrode or sensitive membrane deposited on top of the gate, which is used to provide bias voltage (V_g) in an ISFET. Manimekala *et al.* covered a wide range of ISFETs on Dopamine, Glucose (non-enzymic), Nucleic Acid (DNA), Protein, Virus, and Cancer Biomarkers detection using nano-materials, especially 1D nanowires and nanoparticles, as well as 2D graphene in Figure 3b.²⁶

FGFETs (Floating Gate Field Effect Transistors) physically isolate the transistor channel from the electrolyte with improved device robustness. Panahi *et al.* have successfully utilized FGFETs for pH sensing, enzymatic reaction monitoring, and bioelectronic recording in Figure 3c.²⁷

EGFETs (Extended Gate Field Effect Transistors) are standard MOSFETs, with the gate extended to the reference electrode, electrolyte, and sensing layer, making them disposable sensor heads, with ease of packaging, resistance to light and temperature variations, and straightforward replacement of sensing films. Liu *et al.* presented a molecularly imprinted polymer (MIP)-based EGFET sensing system that is used for the measurement of CRP concentration in human serum.²⁸ Janićjević *et al.* illustrated the evolution of EGFETs in Figure 3d as an advanced class of FET biosensors that balance the high sensitivity of field-effect transduction with practical benefits.²⁹

Carbon-Based FETs, including CNTFETs and GFETs, have emerged as powerful biosensing platforms due to their exceptional electrical, mechanical, and surface properties. Yixi Deng *et al.* focus on applying CNTFET biochemical sensors to detect biomarkers, as shown in Figure 4a.³⁰ The functionalization step is key to making CNTs interact specifically with target analytes (e.g., DNA, proteins). Jiahao Li *et al.* demonstrated an AuNP-decorated GFET nanosensor for rapid and amplification-free SARS-CoV-2 identification, as shown in Figure 4b.³¹ Importantly, the nanosensor exhibited strong anti-interference capability and promising clinical applicability.

TFETs (Tunnel Field Effect Transistors) are novel biosensors based on a complementary metal oxide semiconductor (CMOS)-compatible silicon nanowire tunneling field-effect transistor (SiNW-TFET).³² A TFET works by band-to-band tunneling instead of electrons going over a barrier. The mechanism is illustrated in Figure 4c. Gao *et al.* fabricated a "top-down" TFET with a low-cost anisotropic self-stop etching technique.³³ Real-time measurements highlighted the ability to use clinically relevant samples such as serum. A

TFET is a special type of transistor designed to use much less power than conventional transistors. Like other transistors, it has a source, drain, and gate, but it works in a different way, as shown in Figure 4d. Ongoing improvements in device structure and materials are making them promising candidates for next-generation, energy-efficient biosensors.^{34,35}

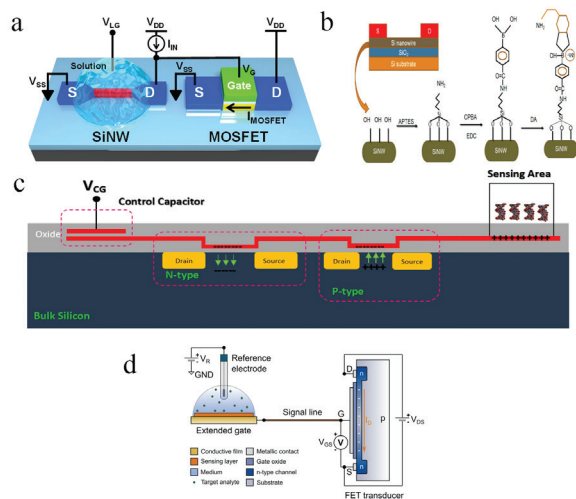


Figure 3: Fundamental Bio-FET types: (a) Schematic diagram of the demonstrated biosensor composed of an n-type SiNW and a MOSFET. Reprinted with permission from Sci. Rep.²⁵ (b) ISFET - A SiNW Bio-FET for DA detection. Reprinted with permission from J. Electron Mater.²⁶ (c) The FGFET structure and a real chip designed for Label-free DNA analysis. Reprinted with permission from Biosensors.²⁷ (d) Illustration of the EG-FET sensing concept using the example of an n-type enhancement mode MOSFET transducer. Reprinted with permission from Next Nanotechnology.²⁹

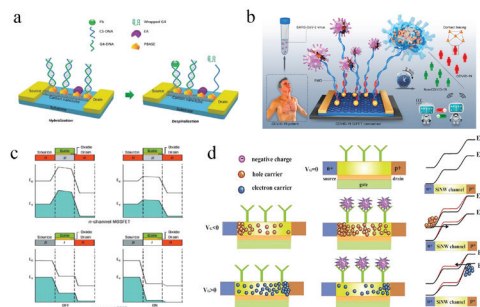


Figure 4: Advanced Bio-FET types: (a) Hybridization and desalination of CNT-FET sensors. Reprinted with permission from Biosensors.³⁰ (b) GFET nanosensor. Reprinted with permission from Biosens. Bioelectron.³¹ Copyright 2021 Elsevier. (c) An n-channel MOSFET and an n-channel TFET turn on and off by showing their energy band diagrams. MOSFET ON: electrons go over the barrier. TFET ON: electrons tunnel through the barrier.³² Copyright 2016 Elsevier. (d) SiNW-TFET mechanism. Reprinted with permission from Sci. Rep.³³

A summary of different types of Bio-FETs and their applications is presented in Table 1. The table compares the various Bio-FET types, including their gate or interface structures, key sensing mechanisms, major advantages and limitations, and typical applications.

Table 1: Different Types of Bio-FETs and Their Applications.

FET Type	Gate / Interface Structure	Key Sensing Mechanism	Major Advantages	Main Limitations	Typical Applications
MOSFET ^{24, 25}	Metal gate + oxide (SiO ₂)	Gate-voltage-modulated channel conductivity	High sensitivity, CMOS-compatible, low noise	Back-gate limited for neutral species	Protein-sensing CRP, Hybrid CMOS biosensors
ISFET ²⁶	Ionic solution and membrane + reference electrode	Ion-induced surface potential modulation	Small size, low cost, scalable arrays	Reference electrode, drift	pH sensing, Enzymatic biosensors, SoC platforms
FGFET ²⁷	Floating sensing gate + control gate	Chemical-to-electrical signal conversion	No reference electrode, robust, CMOS-compatible	Structural complexity	pH, Enzyme sensing, Bioelectronics arrays
EGFET ^{28,29}	Extended external gate with sensing film	Remote gate modulation	Disposable head, high stability, high sensitivity	Limited scaling, CMOS integration gap	pH, Enzyme detection, Protein
Carbon-Based FET ^{30,31}	CNT or graphene channel	Charge transfer at the nanomaterial surface	Ultra-high sensitivity, fast response, low power	Fabrication variability	Gas sensing, Virus, Neurotransmitter
TFET ³²	p-i-n structure with tunneling	Band-to-band tunneling	Ultra-low power, steep sub-threshold swing (SS)	Low ON current, ambipolarity	Low-power biosensors

Debye Length:
The Debye length refers to the characteristic length scale over which electric potentials are screened by mobile ions in an electrolyte, and it essentially defines the thickness of the electrical double layer adjacent to a charged surface, as pointed out by H.-C. Chang *et al.*³⁶ The Debye length is the distance from the charged surface where the potential has decayed to the 1/e point or 36.7% of the surface potential. Physically, it characterizes the thickness of the diffuse part of the electrical double layer (EDL) formed when an electrolyte solution is in contact with a charged surface. The Debye length quantifies how quickly the electric field is screened by ions in solution, and it appears explicitly in the Poisson-Boltzmann model of the EDL - a foundational concept of double layers.

Debye length λ_D scales inversely with the square root of concentration and also scales inversely with the valence of the ions in solution for electrolytes. Therefore, the high ionic strength subsequently leads to a short Debye length; the Debye length λ_D for a divalent ion is half that for the monovalent ion. To put λ_D into perspective for operational systems, at an electrolyte concentration of 1 μ M for a 1:1 electrolyte, λ_D =304 nm, but at 1 M, it is 0.3 nm. For typical biological Phosphate buffer solutions (PBS) containing a mixture of potassium monohydrogen phosphate (K2HPO4) and potassium dihydrogen phosphate (KH2PO4), in 1x PBS, the Debye length is typically ~0.7 nm or less than 1 nm, where most biomolecular charges are screened.³⁷ For 0.1x-1x PBS, reported Debye lengths range from ~0.7 nm up to ~2 nm as the buffer is diluted (lower ionic strength gives longer Debye length), as shown in Figure 5.³⁸

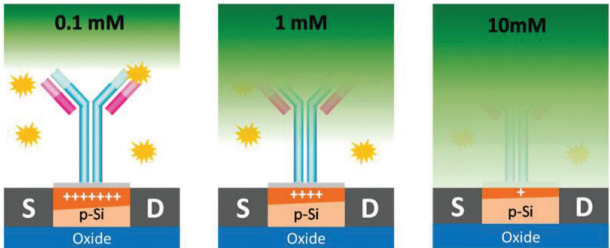


Figure 5: Debye Length Effects under different electrolyte concentrations. Reprinted with permission from J. Am. Chem. Soc.³⁸

Zhang and Zheng discuss the reduced FET sensitivity using the example of the negatively-charged streptavidin molecules, which are surrounded by positively charged ions due to the electrostatic force.³⁹ Conventional FET sensors sense the concentration of the target species by their intrinsic charge. The charges of solution-based molecules, however, can be screened by dissolved counterions in the solution. Their work shows that the Debye length can be increased by using diluted, low-ionic-strength buffers without significantly affecting biomolecular interactions such as oligonucleotide hybridization; however, additional strategies to mitigate Debye screening are still required to improve FET sensitivity.

Microbeads and Magnetic Microbeads: Properties and Functions:

Microbead-based biosensors have emerged as a promising platform due to their versatility, strong signal responses, and ability to detect multiple targets simultaneously, offering several inherent advantages such as high surface-to-volume ratio, rapid response, high throughput, and minimal sample volume. Hui-Pin Cheng *et al.* compare the advantages and disadvantages of microbead-based biosensors in Table 2 and categorize different microbead-based biosensors by their different materials as shown in Figure 6, highlighting the magnetic beads for improving specificity and reducing background noise.⁴⁰

Table 2: Advantages and disadvantages of microbead-based biosensors.⁴⁰

Pros	Cons
High Surface to Volume Ratio High Throughput Fast Response Reduced Matrix Effects Enhanced Sensitivity and Dynamic Range Multiplexed Detection Minimal Sample Volume Miniaturization and Portability	Reproducibility and Standardization Cross-Reactivity Instrumentation Complexity Clinical Translation

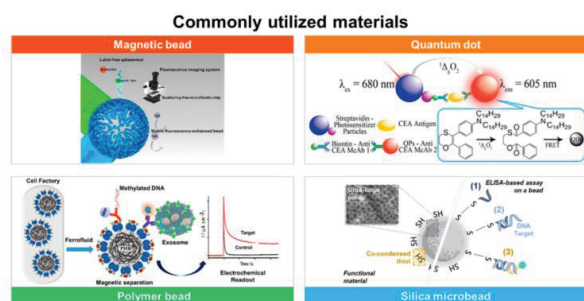


Figure 6: Commonly utilized materials in microbead-based biosensors. Reprinted with permission from Sensors.⁴⁰

Magnetic microbeads, typically composed of iron oxide or iron oxide within embedded polymer matrices, can be precisely controlled to mitigate Debye Length screening effects. Under an applied magnetic field, magnetic microbeads undergo directed motion and mixing, generating localized fluid flows. Although the Debye length remains fixed by electrolyte ionic strength, these localized fluid flows enhance mass transport and reduce diffusion limitations. As a result, target molecules are delivered more efficiently to the BioFET sensing surface, improving effective signal response despite strong Debye screening.

In addition, magnetic microbeads have a high surface-to-volume ratio, which can be biofunctionalized with target molecules, and the conjugates can be concentrated

using magnetic fields, increasing both the sensitivity and specificity of detection in complex biological samples. Magnetic microbeads benefit from the absence of magnetic background signals in biological samples, resulting in inherently low noise and high specificity. Therefore, unlike fixed sensing substrates, magnetic microbeads act as mobile carriers and mobile nets that transport captured biomolecules to defined sensing regions, diminishing the difficulties posed by the Debye length layer, mixing at low Reynolds numbers, or high flow resistances at small scales.

Furthermore, magnetic microbeads are commercially available in different sizes, magnetic properties, and surface coatings, making them very versatile, indispensable tools in biosensing, especially to realize integrated and miniaturized technologies based on small fluid volumes.

Magnetic Microbead Conjugation for Biosensing Applications:

Magnetic microbead conjugation is a key step that transforms simple manipulable particles into highly selective biosensing tools. By attaching antibodies, aptamers, peptides, or nucleic acids onto their surface, magnetic microbeads can specifically recognize and capture target biomolecules such as proteins, exosomes, and cancer biomarkers. This makes magnetic bead conjugation an important strategy for improving sensitivity and specificity in Bio-FETs and clinical diagnostic applications.

Modh *et al.* have reviewed magnetic microbeads in biosensing with different detection methods.⁴¹ For selectivity, magnetic microbeads are decorated with different biological recognition elements, as shown in Figure 7a: (1) Antibodies target specific protein biomarkers or pathogens in immunoassays. (2) Aptamers – synthetic single-stranded DNA or RNA sequences selected by SELEX (Systematic Evolution of Ligands by EXponential enrichment) – offer advantages such as ease of chemical modification, high stability, and the ability to design unique sensing formats (e.g., structure switching, induced dissociation). (3) Peptides and other small ligands can also be used, depending on the target and application. Functionalization strategies typically rely on established bioconjugation chemistry, e.g., covalent linking through reactive surface groups, streptavidin-biotin interaction, or linker arms for aptamer immobilization.

Yue *et al.* have developed a label-free electrochemical biosensor based on magnetically induced self-assembly. $\text{Mg}_0.5\text{Cu}_0.5\text{Fe}_2\text{O}_4\text{-Au}$ nanocomposites are prepared and assembled on a magnetic glassy carbon electrode (MGCE) under a magnetic field, forming the active sensor interface. A thiol-modified single-stranded DNA aptamer specific to CA125 is attached to the Au surface via Au-S bonds, without using a coupling agent.⁴² The CA125 antigen, which is an important indicator for early detection of ovarian cancer, is captured directly by the aptamer through specific binding (aptamer – antigen interaction). After aptamer immobilization and antigen capture, BSA is used for surface blocking to reduce nonspecific adsorption.

Xiaoxia Fang *et al.* have developed a magnetic bead selective adsorption strategy (MagExo) for easy-to-operate extracellular vesicles (EVs) isolation, as shown in Figure 7b and 7c.⁴³ EVs can be selectively adsorbed on the surface of magnetic microbeads in the presence of a hydrophilic polymer and can be separated from biological fluids with high purity by simple permanent magnetic separation. The MagExo procedure captured 2X higher yield and comparable purity of the harvested EVs to that obtained by ultracentrifugation (UC). The target RNA amount of the isolated EVs by MagExo was almost dozens and hundreds of times higher than the gold standard Density gradient ultracentrifugation (DG-UC) and ultracentrifugation (UC) methods, respectively. More detailed and latest magnetic affinity-based methods for isolating and detecting exosomes can be found in the review of Veronika Solovicová *et al.*, including antibody-based capture, DNA aptamer-based capture, peptides and glycan recognition, and other recognition schemes.¹⁸

Lin *et al.* addressed two main problems when using ISFETs to detect proteins.⁴⁴ First, antibodies on the sensor surface are often longer than the Debye length (~0.7 nm) in biological solutions, which makes it difficult for the bound proteins to be tightly attached to the sensor surface. Second, many proteins carry a small electrical charge and can be easily affected by the pH of the surrounding solution, leading to weak changes in surface potential and poor signal response. To solve these issues, the authors used a magnetic bead-based detection approach, as in Figure 7d, where an external magnetic field pulls the bead-protein complexes close to the sensor surface. After protein capture, DNA strands are attached to the microbeads as labels. DNA carries a high and well-defined negative charge, which is much easier for semiconductor sensors to detect than protein charges. Their work demonstrates a hybrid system combining magnetic microbeads, DNA-based signal amplification, and a semiconductor sensor within a microfluidic chip, enabling sensitive and fast protein biomarker detection while overcoming Debye screening limitations.

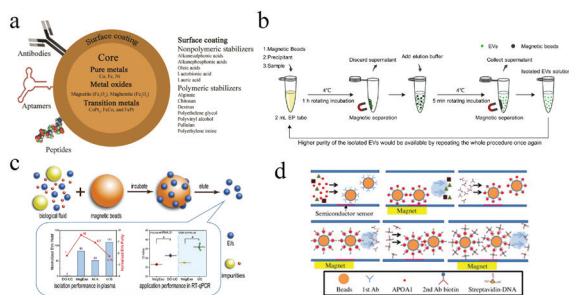


Figure 7: Magnetic microbead conjugation: (a) Composition of magnetic microbeads (MBs) used in analytical applications. Reprinted with permission from Sensors.⁴¹ (b) and (c) Schematics of MagExo for EV extraction. Reprinted with permission from Acta Biomater.⁴³ Copyright 2021 Elsevier. (d) Magnetic microbeads conjugated with multiple antibodies. Reprinted with permission from Anal. Chim. Acta.⁴⁴ Copyright 2015 Elsevier.

Magnetic Microbead Manipulation in Microfabricated Systems:

Besides using permanent magnets, magnetic microbeads can be effectively integrated with microfabricated microcoil

or micro-solenoid systems, which can be used to generate a localized magnetic field and magnetic field gradient to attract, trap, move, or concentrate magnetic microbeads near a sensing region (e.g., a Bio-FET gate or microfluidic channel). Micro-coils can be applied with different magnetic actuation modes, including DC current for static bead trapping, AC current for bead agitation and mixing, and pulsed current for capture - release cycles. These actuation modes enable efficient bead concentration, washing steps, and controlled contact between magnetic beads and the sensing surface. This allows more precise bead manipulation and supports a wide range of magnetic biosensors based on magnetic, electrical, optical, and electrochemical detection methods.

Vania Silverio *et al.* have developed the manipulation of magnetic microbeads for therapeutic drug monitoring with thin film microelectromagnet traps, taking into consideration both magnetic trapping and integrated efficient cooling as in Figure 8.⁴⁵ Six different designs (thickness, width, number of turns, positioning of coils, etc.) of planar microelectromagnet traps (MEMT) with four external coils in series and one central coil connected for an opposite direction of manipulation of magnetic microbeads in microfluidic flows. The yield of local concentration was highly dependent on coil design, but the optimized design showed a 210% increase. Their work demonstrated planar microelectromagnet can be fabricated and utilized in magnetic microbead concentration and manipulation for higher-sensitivity detection.

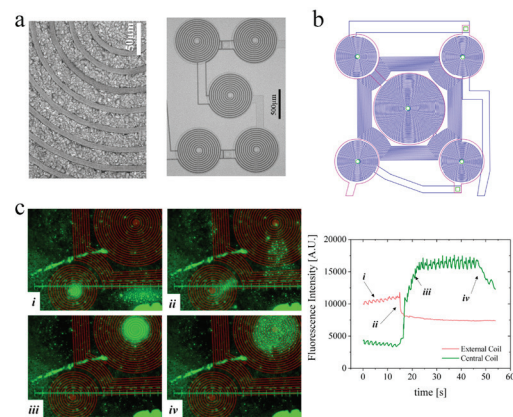


Figure 8: Magnetic microbead in microfabricated systems: (a) and (b) Microfabricated microcoil designs. (c) Experimental activation and deactivation pulses resulting in MB concentration. Reprinted with permission from Micromachines.⁴⁵

Planar microfabricated copper coils can be produced using standard photolithography and electroplating processes. In addition, printed circuit board (PCB)-based fabrication offers a cost-effective and scalable alternative for implementing microcoils without the need for complex microfabrication steps. Roer Eka Pawinanto *et al.* have proposed using PCB technology to fabricate planar micro-coils for driving magnetic MEMS actuators, as shown in Figure 9a.⁴⁶

3D (out-of-plane) microcoil or solenoid structures differ from planar spiral coils and are commonly employed when strong vertical magnetic fields and field gradients are required for magnetic bead manipulation near sensors. Heuberger *et*

al. developed a deep-UV lithography-based 3D microforming process capable of fabricating thick, high-aspect-ratio microstructures up to 200 μm thick with steep sidewalls in Figure 9b.⁴⁷ Hoa Thanh Le *et al.* have reviewed the advances in MEMS inductor fabrication, including Planar MEMS Inductors, 3D MEMS Inductors, and especially 3D air-core and magnetic-core designs as shown in Figure 9c.^{48,49} The authors shared the discussions on how advances in microfabrication, materials, and 3D architectures have transformed inductors from bulky passive components into high-performance, chip-scale devices. A comparison of planar microcoil and 3D micro-solenoid is listed in Table 3.

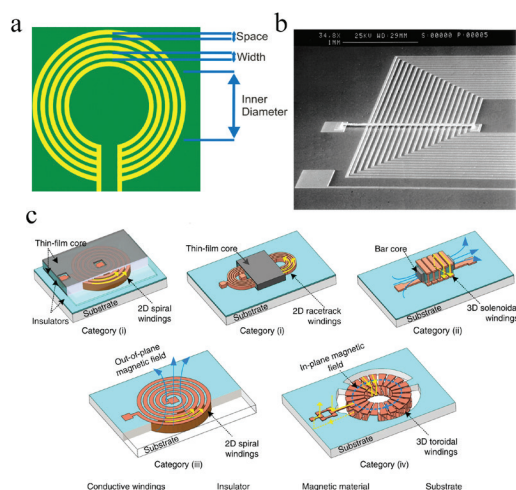


Figure 9: Microcoil designs (a) Microcoil for magnetic MEMS actuator by PCB technology.⁴⁶ (b) Planar gold microcoil with integrated contact bridge with optical DUV-lithography for high microstructures.⁴⁷ (c) 3D illustrations of different categories of MEMS inductors. Reprinted with permission from Microsyst Nanoeng.^{48,49}

Table 3: Comparison of Planar Microcoil and 3D Micro-solenoid:

Feature	Planar Coil	3D Solenoid
Coil geometry	Flat spiral (2D)	Vertical windings (3D)
Main field direction	In-plane	Out-of-plane (vertical)
Vertical bead force	Moderate	Strong
Bead localization	Broad area	Highly localized
Drive current	Higher	Lower
Fabrication complexity	Low	Medium - High
CMOS compatibility	Excellent	Partial/Hybrid
Best use case	Mixing, transport, and large-area trapping	Bead capture, pre-concentration, Bio-FET sensing

Magnetic Microbead Manipulation in Microfluidic Chips:

Precise magnetic microbead manipulation in microfluidic chips has also been widely studied, and these systems provide valuable design strategies for integrating microcoils with Bio-FET sensors.

Lefebvre, O. *et al.* have built a microfluidic chip with integrated planar microcoils that can effectively trap magnetic nanobeads (~300 nm) and also track temperature rise during operation (important because coil current causes Joule heating).⁵⁰ Their work includes design, fabrication, and operation for trapping magnetic nanobeads with embedded planar microcoils inside a microfluidic chip, providing a practical framework to optimize planar coil geometry (e.g., line width/spacing, inner/outer dimensions) rather than trial-and-error. Cai *et al.* provide a thorough, in-depth overview of how mag-

netic microbeads are manipulated within microfluidic chips and how these manipulation strategies are applied in biological and diagnostic workflows.⁵¹ The review provides the physical basis for magnetic manipulation, including superparamagnetism and magnetic bead properties, magnetic forces and magnetophoresis, and bead surface chemistry and surface modification methods. The review systematically explains how bead manipulation techniques are used in real biological applications, such as biomarker and analyte capture, cell sorting, immunoassays and ELISA variants, and extraction/enrichment of nucleic acids or extracellular vesicles.

Detection Strategies for Manipulated Magnetic Microbeads:

After magnetic microbeads are concentrated, several practical detection strategies can convert the bead accumulation into measurable signals. These approaches include simple visual observation and advanced electrical and magnetic sensing techniques. In general, four main detection methods are used: optical detection, electrochemical detection, electrical detection using Bio-FETs, and magnetic detection based on giant or tunnel magnetoresistance sensors.

Optical Detection:

Optical detection is the simplest and most commonly used method to observe magnetic microbeads after they are concentrated by a microcoil. After bead concentration, the region near the coil or sensor surface can be examined using a standard optical microscope, or a fluorescence microscope if fluorescent microbeads are used. Bead accumulation is identified by an increase in bead density or changes in brightness or fluorescence intensity, as in Figure 10a.⁴¹ This method is very easy to implement and provides direct visual confirmation; however, it is mostly qualitative and has limited sensitivity when detecting low numbers of microbeads. As a result, optical detection is mostly for proof-of-concept demonstrations and microfluidic experiments.

Electrochemical Detection:

Cyclic Voltammetry (CV) and Electrochemical Impedance Spectroscopy (EIS) are the main electrochemical techniques, as shown in Figure 10b. Magnetically induced self-assembly of functionalized microbeads enables highly sensitive electrochemical detection of cancer biomarkers in complex samples, where the measured current or impedance change is proportional to bead concentration.⁵² This strategy offers high sensitivity and robustness in real biological matrices, since electrochemical methods are less affected by sample complexity. However, because the approach relies on enzyme or redox labeling, it is not fully label-free and requires additional chemical modification steps. Therefore, electrochemical bead-based detection is particularly well suited for clinical assays and protein biomarker detection, as discussed by Cheng, H.-P. *et al.*⁴⁰

Electrical Detection for Bio-FETs with Magnetic Microbeads:

Magnetic bead-assisted Bio-FET detection represents a highly sensitive strategy due to its superparamagnetic prop-

erties, a key advantage for mixing, isolating, or concentrating targets from complex samples. In the following three studies, magnetic microbeads demonstrated their abilities to effectively and selectively capture important disease biomarkers under various situations. External magnetic fields help pull these targets closer to the graphene FET sensing surface, which improves target delivery and makes the electrical signal stronger and easier to measure at extremely low levels like femtomolar and picomolar concentrations.

Yu *et al.* have developed an integrated microsystem that combines magnetic bead-based exosome isolation with a FET biosensor to enable selective capture and highly sensitive detection of tumor-derived exosomal microRNA (miRNA), specifically miRNA10b.⁵³ The system uses magnetic microbeads functionalized with two antibodies - GPC-1 and EpCAM - which bind to surface proteins highly expressed on pancreatic cancer-derived exosomes. These dual-antibody microbeads selectively recognize and isolate pancreatic cancer exosomes from plasma samples before sensing. After concentration, the isolated exosomes are processed to release their internal miRNA. The released miRNA10b is then detected using a Peptide Nucleic Acid (PNA)-functionalized reduced GFET biosensor. PNAs hybridize selectively with the target miRNA, enabling highly specific and sensitive electrical detection down to an ultrasensitive detection limit of ~ 78 fM for miRNA10b. The method was validated with 40 clinical plasma samples, effectively distinguishing pancreatic cancer patients from healthy controls. The detailed process is illustrated in Figure 10c.

Sun *et al.* developed a GFET by transferring a chemical-vapor-deposited graphene film onto a substrate to serve as the conductive channel, as shown in Figure 10d.⁵⁴ Graphene's high surface area and excellent electronic properties make it an attractive material for sensitive FET biosensing. To enable specific DNA detection, the graphene surface was chemically modified with 1-pyrenebutanoic acid succinimidyl ester (PBASE), which acted as an anchoring layer for immobilizing a probe aptamer. The aptamer selectively binds complementary single-stranded DNA targets. Target complementary DNA strands were magnetically labeled using magnetic nanobeads. These magnetically tagged DNA targets could be manipulated by applying an external periodic magnetic field, causing them to interact dynamically with the graphene surface. Under the periodic magnetic field, the impedance of the GFET exhibited periodic oscillations, and the amplitude of these impedance changes correlated with DNA concentration. The biosensor demonstrated high sensitivity, with a detection limit on the order of ~ 1 pM for single-stranded DNA.

Zhu *et al.* developed a magnetically controlled GFET biosensor for highly sensitive detection of cardiac troponin I (cTnI), an important biomarker for acute myocardial infarction.⁵⁵ In this system, graphene films transferred onto Indium Tin Oxide (ITO) conductive glass served as the conductive channel, while a cTnI-specific aptamer was immobilized on the graphene surface using PBASE as the linker for selective target capture. Magnetic nanobeads functionalized with cTnI antibodies were then introduced to form an aptamer/cTnI/antibody/magnetic bead sandwich structure. By applying an

external magnetic field, the magnetic beads were actively pulled closer to the graphene sensing surface, significantly enhancing the electrical signal and improving detection sensitivity to a low detection limit of 10 pM for cTnI.

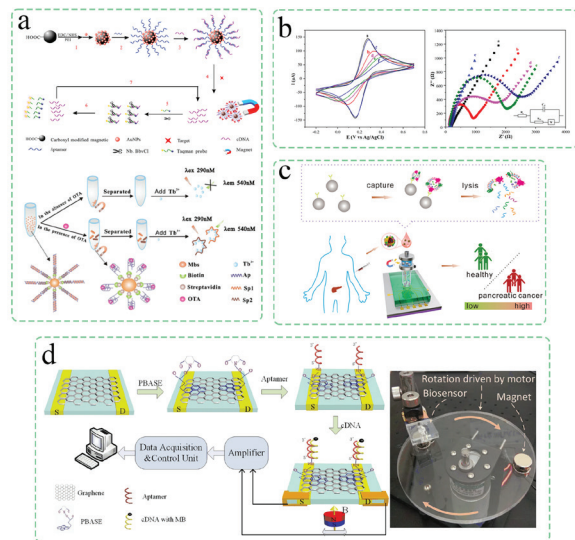


Figure 10: Different detection strategies for manipulated magnetic microbeads: (a) Fluorescence-based assays. Reprinted with permission from Sensors⁴¹ (b) CV profiles for Electrochemical Detection. Reprinted with permission from Arab J. Chem.⁵² (c) Integrated FET sensing microsystem for specific detection of pancreatic cancer exosomal miRNA10b. Reprinted with permission from Anal. Chim. Acta.⁵³ Copyright 2023 Elsevier. (d) Magnetic Graphene Field-Effect Transistor Biosensor for Single-Strand DNA Detection. Reprinted with permission from Nanoscale Res.⁵⁴

The research gap is that most studies either focus on magnetic bead-assisted Bio-FET sensing or microcoil-based bead manipulation separately, while very few directly integrate on-chip microelectromagnets with Bio-FET detection on the same platform. This makes microcoil-driven magnetic bead Bio-FET systems a strong and still novel research direction for early disease detection. Preliminary work at Chang's Lab has demonstrated the feasibility of this concept. A microcoil-driven magnetic bead Bio-FET system can be described as follows: Magnetic microbeads are introduced into the biological sample with conjugation agents and act as magnetic carriers to capture target biomolecules. When current is applied to the on-chip microcoil, the generated localized magnetic field and field gradient actively pull the magnetic microbeads toward the Bio-FET sensing surface. After the beads are concentrated near the gate region, only the correctly conjugated bead-target complexes specifically bind ("dock") to the functionalized Bio-FET surface, while non-target or non-conjugated beads are released once the magnetic field is reduced. The retained magnetic microbeads change the local charge environment at the Bio-FET surface, resulting in a stronger and more measurable electrical response through changes in gate voltage or channel current for Bio-FET detections.

Magnetic Detection:

Magnetic detection using giant magnetoresistance (GMR) or tunnel magnetoresistance (TMR) sensors provides a direct and quantitative way to detect magnetic microbeads concentrated by a microcoil. In this approach, magnetic microbead

core elements can be detected by a GMR or TMR device positioned above or in close proximity. The presence and number of microbeads are reflected as a measurable change in sensor resistance, enabling quantitative bead counting. Because this method relies on magnetic signals rather than electrical charges, it is not affected by Debye screening in physiological solutions and offers very high sensitivity. As a result, GMR/TMR-based detection is particularly sensitive for quantitative bead counting and bioassays. In general, magnetic detection requires integration of specialized magnetic sensors and involves more complex device fabrication; however, it holds strong potential for advanced biosensing applications.

GMR-based biosensors utilize changes in electrical resistance from variations in local magnetic fields to enable highly sensitive detection of biomolecular interactions. Sun *et al.* have reported the development of a GMR-based biosensing system specifically designed for the separable detection of *E. coli* O157:H7, a pathogenic strain of *Escherichia coli* commonly associated with foodborne illness.⁵⁶ This work, as in Figure 11a and 11b, demonstrates how magnetic labeling and GMR sensing can be combined to identify whole bacteria with improved sensitivity and specificity.

Wang *et al.* have focused on how GMR biosensors perform when combined with superparamagnetic nanoparticles (MNPs) used as magnetic labels, as in Figure 11c.⁵⁷ They built a GMR detection system with a 64-sensor array fabricated by photolithography, allowing multiplexed measurements. DNA hybridization was used as a model assay: probe DNA was immobilized on the sensor surface, and target DNA hybridization brought different types of MNPs close to the surface for GMR measurement.

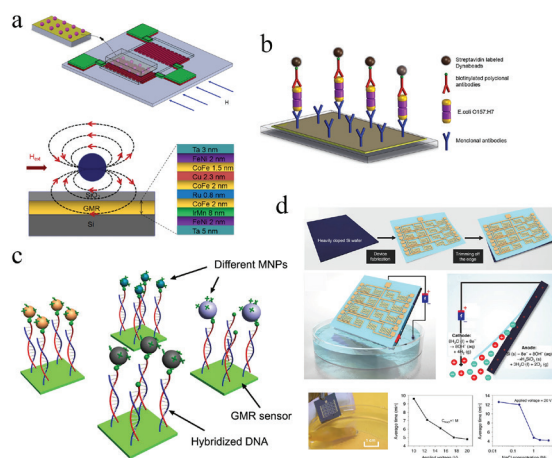


Figure 11: GMR magnetic detections (a) and (b) Microfabricated GMR sensor combined with double antibody sandwich immunoassay and streptavidin-biotin binding assay. Reprinted with permission from Biosens. Bioelectron.⁵⁶ Copyright 2016 Elsevier. (c) Magnetoresistive performance and comparison of supermagnetic nanoparticles on a GMR sensor-based detection system. Reprinted with permission from Sci. Rep.⁵⁷ (d) Typical electrochemical delamination process of a GMR sensor. Reprinted with permission from Microsyst. Nanoeng.⁵⁸

Recent progress in giant magnetoresistance (GMR) sensors has moved the technology beyond rigid chips toward printable, flexible, and skin-like (eSkin) devices. New materials and fab-

rication methods now allow GMR sensors to be made thinner, lighter, and more flexible, while still maintaining high sensitivity and fast response in real-world applications. Zhang *et al.* have developed an ultrathin, flexible giant magnetoresistive (GMR) sensor array that forms the core of a magnetoelectronic e-skin, as in Figure 11d.⁵⁸ An electrochemical delamination process was used, which enables rapid, non-destructive peeling of the ultrathin magnetic sensor array from a rigid substrate onto a flexible platform. These ultrathin, flexible, and skin-like GMR sensors are powerful for next-generation biosensing and wearable diagnostics.

■ Conclusion

The rapid evolution of integrated circuit (IC) fabrication technology has fundamentally promoted the development of biological field-effect transistors (Bio-FETs). Continuous scaling of MOSFET dimensions, progress in EUV lithography, and the widespread adoption of three-dimensional (3D) device architectures such as 3D NAND have enabled unprecedented integration density and device performance. These developments point toward a natural transition of Bio-FETs from planar designs to 3D sensing architectures, where vertical stacking and increased active surface area can further enhance sensitivity and throughput. As device dimensions approach the length scales of biomolecules, Bio-FETs are no longer limited to ensemble-averaged measurements, making single biomolecular or single-event detection increasingly feasible and establishing Bio-FETs as a powerful platform for next-generation biosensing and early disease diagnostics.

Magnetic microbead-based strategies offer significant advantages for Bio-FET applications. Magnetic microbeads provide convenient bioconjugation and enable selective capture of target biomolecules. Their motion and spatial positions can be precisely controlled using microcoils or microsolenoids. Such magnetic manipulation significantly improves detection efficiency and signal reliability, while remaining compatible with microfluidic and on-chip integration. Developments in the hard disk drive (HDD) industry have shown that GMR sensors can achieve ultrahigh sensitivity, gigahertz-speed operation, and large-scale manufacturability. Translating this maturity to biosensing suggests a future in which a single chip or “one-disk” platform could rapidly test multiple biomarkers in parallel, using magnetic beads as universal labels and GMR or Bio-FET readout for quantitative detection. Such convergence of semiconductor electronics, magnetic sensing, and biofunctional materials points toward scalable and programmable biosensing architectures with transformative potential in precision early disease detection.

■ Acknowledgments

I am deeply grateful for the step-by-step guidance and support of Dr. Hamidreza Shaye, whose mentorship in scientific writing and thoughtful suggestions were essential to the completion of this paper.

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