



REVIEW

Implantable Flexible Electronic Devices for *In Vivo* Diagnosis and Therapy

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Received: 07 September 2026; Accepted: 12 October 2026; Published: 27 October 2026

ABSTRACT: Implantable flexible electronics have emerged as an important technological pathway for *in vivo* diagnosis and treatment, owing to their ability to directly achieve continuous sensing and localized intervention at target tissues. Compared to traditional methods relying on *ex vivo* sampling or intermittent examinations, such systems are better suited for capturing dynamic changes in complex physiological environments, including electrical activity, metabolism, temperature, and mechanical states. This review summarizes recent advances in implantable flexible electronics from the perspective of the complete technological trajectory of *in vivo* adaptation, theranostic implementation, and system-level applications. First, it discusses the requirements for crossing the two major engineering thresholds of *in vivo* operation and theranostic implementation: on one hand, adhesion, mechanical coupling, biocompatibility, and degradable or antibacterial designs to ensure *in vivo* survival; on the other hand, functional interface construction, system architecture integration, and signal chain processing strategies required to establish theranostic interaction. Second, it summarizes representative diagnostic applications in electrical, chemical, thermal, and mechanical sensing, as well as localized therapeutic progress in drug delivery, thermal regulation, optical stimulation, and electrical stimulation. On this basis, it analyzes major development trends such as theranostic integration, data-driven operation, and precise intervention, and discusses common challenges that still restrict its widespread translation, including long-term interfacial stability, power supply, packaging, communication, and clinical evaluation. Overall, the field is evolving from single-function signal acquisition or stimulation toward integrated, closed-loop theranostic systems, and future progress will depend on whether reliable connections can be simultaneously established among materials, interfaces, systems, algorithms, and clinical translation.

KEYWORDS: Flexible electronics; implantable devices; biointerfaces; biosensing; theranostics

1 Introduction

Modern clinical medicine still primarily relies on imaging examinations, biochemical assays, and routine physical examinations for organ function evaluation, early lesion identification, and dynamic postoperative monitoring [1–5]. While indispensable in daily clinical practice, these methods typically provide information derived from *ex vivo* samples or discrete time points, making it difficult to continuously capture the dynamic changes within the microenvironment surrounding the lesion [5–8]. For many *in*

vivo diseases, the continuous evolution of local electrical activity, metabolic status, temperature, and mechanical environment often reflects disease progression and the optimal timing for intervention more accurately than a single examination result [8–13]. Without *in situ*, continuous *in vivo* readouts, early abnormal signals between examination intervals are highly prone to being missed, and local therapies are difficult to implement based on the true real-time state of the lesion [5–7,9,14]. Consequently, implantable electronic devices capable of continuously acquiring information and delivering local interventions near target organs or lesions have emerged as an important technological direction for *in vivo* diagnosis and therapy [2,5,15–18].

Once introduced into the body, these devices must overcome two major engineering thresholds: *in vivo* operation and theranostic implementation [18–20]. The first challenge is long-term interface stability. Traditional rigid devices differ significantly from soft tissues in terms of modulus, thickness, and deformation modes [19,21–25]. During long-term implantation, interfacial sliding, local friction, and stress concentration can easily induce tissue damage, chronic inflammation, and fibrous encapsulation, subsequently leading to degraded recording quality and elevated stimulation thresholds [21–23,26–30]. Concurrently, the wet physiological environment and immune responses continuously cause device corrosion, biofouling, and failure [29,31–34]. Therefore, the devices must meet stringent requirements for stable adhesion, mechanical coupling, and biocompatibility [15,21–26,30,35–38]. Secondly, upon satisfying these conditions for *in vivo* survival, the devices must establish an effective engineering foundation for diagnosis and therapy [18,19,39–41]. This requires constructing low-impedance, interference-resistant functional interfaces between the tissue and the device, accomplishing the systemic architectural integration of power, communication, and actuation components within an extremely limited implantation space, and establishing a signal chain capable of processing weak *in vivo* signals and precisely outputting intervention commands [17–19,39,40,42–46]. Flexible design continues to garner attention precisely because its low-modulus materials, ultrathin structures, and conformal capabilities provide a more realistic engineering basis for synergistically addressing the aforementioned challenges of *in vivo* adaptation and systemic interaction [15,16,34,47].

The development of implantable flexible electronic devices has gradually formed a technological pathway from *in vivo* adaptation to theranostic implementation, and ultimately to system-level applications [2,5,15,16,18,41]. *In vivo* adaptation determines whether the device can maintain stability in complex internal environments, whereas theranostic implementation determines whether local signals can be reliably acquired and further translated into effective interventions [1,5,9,10,19,39,41]. Building upon this, electrical, chemical, thermal, and mechanical signals have been utilized for *in vivo* detection and diagnosis [48–56], while drug delivery, thermal regulation, optical stimulation, and electrical stimulation have been employed for local regulation and therapy [57–65]. Accordingly, theranostic integration, data-driven operation, and precision medicine have become crucial development directions in this field [66–71]. Based on this framework, this article unfolds across five interconnected aspects (Fig. 1): engineering foundations for stable *in vivo* operation; functional interfaces, system architectures, and signal-chain design for theranostic implementation; diagnostic applications; therapeutic applications; and future perspectives and translational challenges.

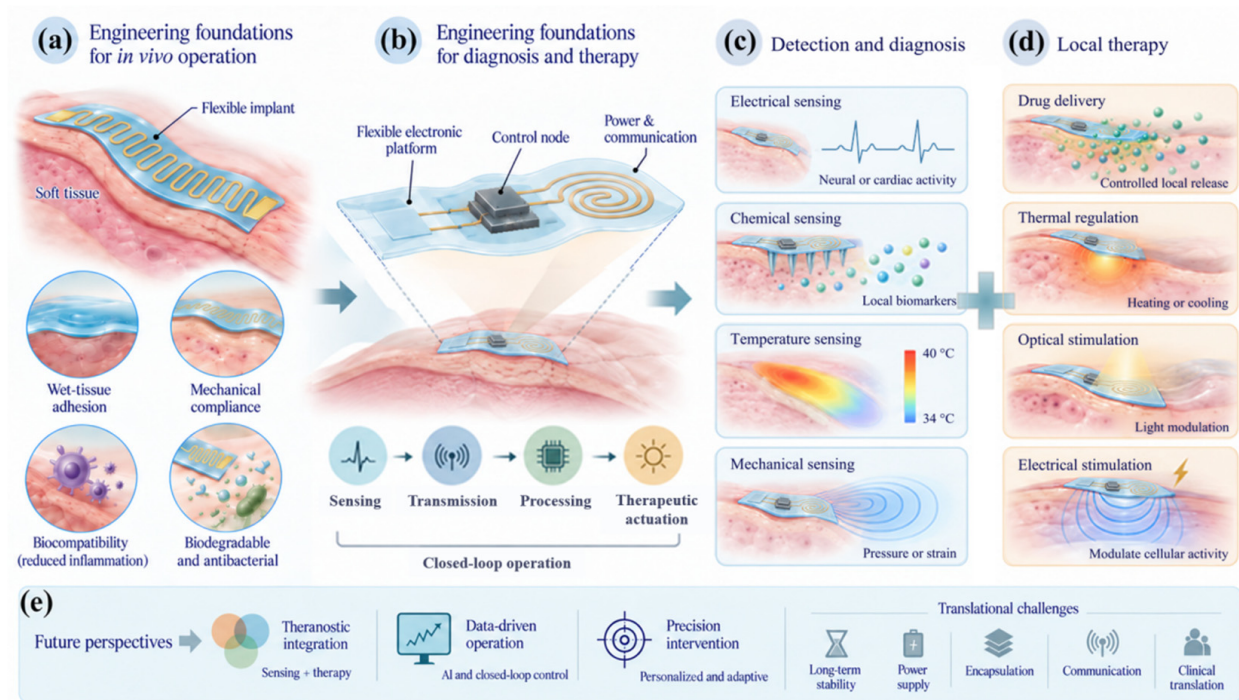


Figure 1: Overview of implantable flexible electronic devices for *in vivo* diagnosis and therapy. (a) Engineering foundations for *in vivo* operation, including wet-tissue adhesion, mechanical compliance, biocompatibility, and, in specific scenarios, biodegradable and antibacterial properties, which collectively support stable tissue-device interfacing. (b) Engineering foundations for diagnosis and therapy, involving the construction of functional biointerfaces, integration of flexible electronic platforms with control, power, and communication modules, and establishment of closed-loop signal input, transmission, processing, and therapeutic actuation. (c) Representative applications in detection and diagnosis, including electrical, chemical, temperature, and mechanical sensing for monitoring local physiological and pathological states. (d) Representative local therapeutic modalities enabled by implantable flexible electronics, including drug delivery, thermal regulation, optical stimulation, and electrical stimulation. (e) Major future perspectives and translational considerations in this field, highlighting theranostic integration, data-driven operation, precision intervention, and key challenges related to long-term stability, power supply, encapsulation, communication, and clinical translation.

2 Engineering for *In Vivo* Operation

Before implantable flexible electronic devices can perform their intended functions *in vivo*, they must first contend with interaction with the complex physiological environment. Compared with *ex vivo* electronic systems, *in vivo* devices must withstand the combined constraints of wet environments, tissue motion, immune responses, and limited implantation space over extended periods. Accordingly, design must begin with adaptation between the device and biological tissue. Around this objective, relevant studies have optimized adhesion, mechanical coupling, biocompatibility, and, in specific scenarios, biodegradability and antibacterial performance. Together, these requirements constitute the engineering foundation for long-term *in vivo* application of such devices [21–23,26].

2.1 Adhesion

Adhesion is one of the prerequisites for stable *in vivo* operation in most implantable flexible electronic devices. Whether a device is intended for signal acquisition, local stimulation, or drug delivery, its function

depends on sustained and reliable interfacial contact with the target tissue. If interfacial detachment, local lifting, or positional drift occurs after implantation, not only can signal quality decline and stimulation thresholds or delivery efficiency fluctuate, but local friction and tissue injury may also be induced. This issue is especially prominent in continuously moving organs such as the heart and gastrointestinal tract, where the interface must simultaneously withstand cyclic tensile, shear, and peeling loads. Under these conditions, the problem of adhesion expands from simple surface attachment to stable fixation at a dynamic wet interface [26,35,36]. The difficulty of this issue arises mainly from the specific nature of *in vivo* interfaces. First, the internal environment is generally wet, and interfacial water can shield binding interactions and weaken effective contact between the material and tissue. Second, tissue surfaces are often soft, rough, and continuously deforming, making it difficult for conventional planar adhesive layers to maintain uniform stress distribution over time. Third, adhesion in implantable devices cannot simply pursue higher strength. Excessively strong or overly stiff adhesion may also cause bleeding, tearing, and secondary inflammation during implantation and removal. These factors together pose major design challenges [26,35,36].

Strategies to enhance adhesion in implantable flexible devices can be broadly divided into two categories. The first is structural design, in which actual contact area is increased through microstructures and interfacial topography control, or attachment strength is enhanced through effects such as mechanical interlocking, capillary forces, and negative-pressure adsorption. Representative structures include micropillars, mushroom-shaped structures, and suction-cup microcavities. As one example, bioinspired adhesion based on suction-cup structures has shown good durability and engineering feasibility in recent years [26,35,36], and many devices capable of repeated adhesion under wet conditions have been developed within this framework. The second category is molecular design, which introduces tissue-compatible adhesive groups and wet-adhesive polymers to establish more stable molecular interactions between materials and tissues. The most common examples are catechol-containing molecules and mussel-inspired systems, such as dopamine and tannic acid. In addition, chemical strategies such as NHS ester-amine coupling, Schiff-base formation, and boronate ester chemistry are widely used in tissue-adhesive hydrogels and injectable interfacial materials. More comprehensive solutions that combine both approaches have also been developed in order to achieve adhesion across different time scales and environmental conditions. Structurally engineered approaches favor repeated attachment on dynamic wet tissues, whereas molecular anchoring may be stronger but can complicate atraumatic removal; hybrid designs are therefore particularly relevant to longer-term usages such as neural and cardiac interfaces [26,35,36]. For temporary applications, reversibility and atraumatic removal may be prioritized, whereas chronic implantation requires sustained adhesion and interfacial stability. Applying these concepts, Moon et al. reported an adhesive bioelectronic interface for peripheral nerves (Fig. 2a). This work focused on neural interface fixation, using a hydrogel adhesive layer with NHS-amine covalent anchoring to establish a stable, low-fibrosis interface on multiple peripheral nerves, including the vagus and sciatic nerves, thereby extending interfacial stability to 12 weeks [27].

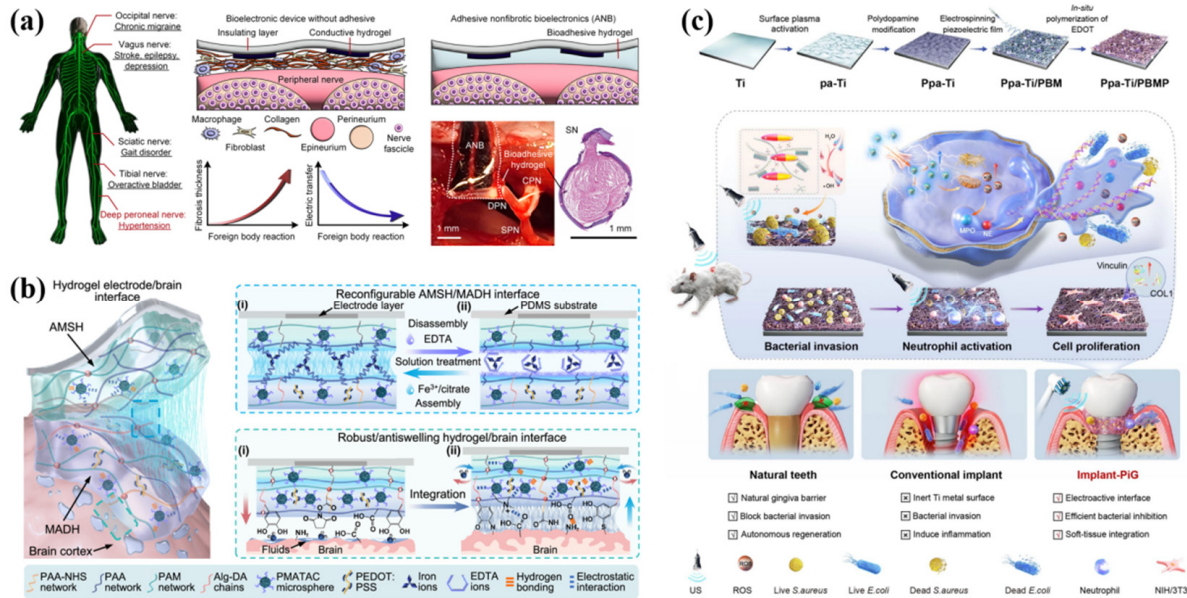


Figure 2: Practical examples of engineering for *in vivo* operation. (a) Design and mechanism of constructing non-fibrous bioelectronic devices using adhesive hydrogels [27]. (b) Electrode array design with reconfigurable hydrogel interfaces, achieving intracranial neurophysiological monitoring in rabbit models through mechanical coupling [72]. The soft electrode array can adhere to the soft brain surface, supporting stable brain–electrode coupling. (c) Piezoelectric-conductive peri-implant interface for antibacterial therapy and soft-tissue integration [73].

2.2 Mechanical Coupling

Mechanical coupling is one of the core conditions required for stable *in vivo* operation of implantable flexible electronic devices. Human tissues generally exhibit low modulus, viscoelasticity, and continuous deformation, and the magnitude of these properties varies substantially among organs. For example, the Young's modulus of brain tissue is typically only 0.1–10 kPa, whereas myocardium is generally in the range of 10–15 kPa, and the epineurium of peripheral nerves can reach approximately 0.4 MPa. By contrast, silicon and common metallic probes typically exceed 100 GPa, far higher than most soft tissues. Among flexible polymer materials, polyimide is approximately 2.5–9 GPa, Parylene-C is around 3 GPa, and PDMS is typically about 1–3 MPa. Even though these materials are much softer than silicon, they may still differ from brain or myocardial tissue by several orders of magnitude. If an implantable device cannot approach the mechanical properties of the target tissue as closely as possible, it is difficult to maintain a stable and low-injury tissue interface during long-term service [7,10,21–23,74].

The consequences of mechanical mismatch are both complex and severe. Devices with excessively high modulus cannot readily follow tissue stretching, bending, or twisting, and therefore tend to generate local stress concentration, causing edge lifting, micromotion, or interfacial separation. In addition, tissue motion, such as respiratory micromotion, cyclic cardiac contraction, and gastrointestinal peristalsis, can amplify relative sliding at the interface, thereby inducing inflammation and fibrotic encapsulation. These biological effects will be further discussed in the next subsection. The resolution of mechanical mismatch is itself difficult, because implantable devices are usually composed of multiple layers, including substrates, interconnects, electrodes, encapsulation layers, and adhesive layers. Even if one layer is intrinsically soft, ideal mechanical coupling may still not be achieved if the overall thickness remains large, if local stiffness transitions are abrupt, or if interlayer coupling is poorly designed. Therefore, mechanical coupling

involves not only material selection but also structural scale, material modulus, and interfacial force-transfer pathways as systemic design issues [21–23,74]. Reconfigurable hydrogel interfaces have also been used to improve mechanical coupling between soft electrode arrays and the brain surface, enabling high-fidelity intracranial neurophysiological monitoring in rabbit models (Fig. 2b) [72].

Strategies for improving mechanical coupling can be broadly divided into two directions. One is structural softening, which reduces effective stiffness and improves deformation compliance through ultrathin designs, serpentine interconnects, mesh layouts, or island-bridge integration. The advantage of this route is that even if the core functional materials remain relatively rigid, strain can be released and local stress dispersed through structural design, thereby yielding a more compliant mechanical response at the macroscopic level. The other direction is material softening, which directly lowers the modulus of the device body or interfacial layer so that it more closely resembles soft tissue. Commonly used materials include soft elastomers, hydrogels, soft electrolytes, and tissue-like interfacial layers. Hydrogels in particular can reach the range of 1–100 kPa and are therefore closer to soft tissues such as the brain and myocardium. In recent studies, some novel electronically conductive or ionically conductive hydrogels have further reduced modulus to the range of a few to several tens of kilopascals while simultaneously maintaining low-impedance interfaces and stability in aqueous environments. Structural softening is useful when functional components remain relatively rigid, whereas material softening offers closer modulus matching but can complicate handling and encapsulation [7,23,74–77].

2.3 Biocompatibility

Biocompatibility is the primary safety prerequisite that implantable devices must satisfy upon entering the body. Unlike *ex vivo* electronic systems, implantable devices often need to come into direct contact with bodily fluids, cells, and tissues over long or intermediate periods. If a device has insufficient biocompatibility, it may cause local irritation, inflammation, and tissue remodeling in mild cases, and rejection, increased infection risk, functional deterioration, or even the need for premature removal in severe cases [21,26]. Biocompatibility can be understood at several levels. First, at the molecular and material levels, toxic monomers, residual solvents, ion leaching, and harmful degradation by-products must be avoided. Second, at the cellular and blood levels, nonspecific protein adsorption, cytotoxicity, thrombosis, and uncontrolled immune activation must be minimized. Third, at the tissue level, devices should reduce long-term foreign-body responses, fibrotic encapsulation, and chronic inflammation, because even when these processes do not immediately cause a safety event, they progressively weaken material and signal exchange between the device and tissue. For example, thickening of fibrotic encapsulation around electrodes lengthens ion transport pathways and thereby increases interfacial impedance and stimulation thresholds. In flexible electronic devices, the issue becomes even more complicated because electrodes, interconnects, encapsulation layers, adhesive layers, and interfacial modification layers often derive from different material systems, and any release products, surface defects, or mechanical wear from any component may become a long-term source of risk [21,23,26,74].

There are several approaches to improving biocompatibility. The first is to select milder material systems that more closely resemble biological environments at the bulk-material level, such as soft elastomers, synthetic polymers, hydrogels, or tissue-like polymers, in order to reduce the initial stimulation caused by device implantation. The second is to suppress adverse biological responses at the interface, including through antifouling surfaces, low-protein-adsorption interfaces, antifibrotic coatings, and stable encapsulation, so as to reduce foreign-body response and surface contamination. A common route here is the introduction of zwitterionic interfaces, which can suppress nonspecific adhesion of proteins and cells

through a stable hydration layer, thereby improving antifouling performance and long-term interfacial stability. The third is active regulation of the local microenvironment at the functional level, for example through drug release, anti-inflammatory molecules, or dynamic adaptive interfaces, in order to attenuate chronic inflammation and promote tissue integration. More commonly, recent work has focused on constructing adaptive soft interfaces that reduce damage while improving interaction between the device and tissue [21,26,75,78,79].

Turrin et al. functionalized the surface of polyimide commonly used in neural implants by covalently binding dexamethasone to BPDA-PDA-type polyimide, thereby achieving local sustained release for at least 9 weeks. Their results showed that this strategy not only reduced macrophage-associated inflammatory markers but also decreased inflammatory cell infiltration and fibrotic capsule thickness after implantation *in vivo* [78]. It should be emphasized that biocompatibility is not independent of the adhesion and mechanical coupling discussed above. In many cases, device-induced inflammation does not arise solely because the material itself is toxic, but rather because of the long-term accumulation of mechanical mismatch, surface contamination, interfacial detachment, and microdamage. For this reason, recent studies on soft active materials, adaptive interfaces, and hydrogel electronics often discuss mechanical coupling, interfacial stability, and biological integration simultaneously, rather than treating biocompatibility as an isolated toxicological index. In this sense, improvement in biocompatibility essentially relies on coordinated design of materials, structures, encapsulation, and interfaces to establish a long-term functional interface that can be tolerated by tissue [21,23,26,74,78].

2.4 Other Requirements

In addition to adhesion, mechanical coupling, and biocompatibility, implantable flexible electronic devices often face more specific requirements under different application scenarios. The most common are biodegradability and antibacterial performance. The former determines device exit timing and exit mode, whereas the latter determines the ability of the device to suppress infection and interfacial destabilization during service. Although these are not mandatory properties for all implant systems, they often directly determine whether a device concept is viable in scenarios such as short-term postoperative monitoring, transient therapy, long-term implantation, and sites with high infection risk [26,31,32].

Biodegradability provides a lifecycle-management mode fundamentally different from that of conventional inert implants for devices that do not need to remain permanently in the body. For tasks such as postoperative monitoring, short-term stimulation, and stage-specific drug regulation, a device that can gradually degrade and be absorbed by the body after completing its required service period may reduce the need for secondary surgical removal and the associated bleeding, infection, and additional trauma. This requires not only material degradation itself, but also strict matching between the degradation process and device functional requirements: the device must maintain sufficient mechanical strength, electrical performance, and structural integrity throughout the target time window, while also avoiding toxic by-products, residual fragments, or metabolic burden during the exit phase. Biodegradability is therefore also a problem of balancing operational stability with safe *in vivo* degradation, clearance, and metabolic elimination [31–33,80–83].

The realization of biodegradable implantable devices requires simultaneous consideration of two categories of functional components. One category is biodegradable conductors or electrode materials, such as magnesium, zinc, and molybdenum, which mainly support signal conduction, stimulation, or electrochemical interfacial functions. The other category is biodegradable substrate or encapsulation materials, such as PLGA, PCL, silk fibroin, and biodegradable hydrogels, which mainly determine structural

support, interfacial buffering, and overall degradation behavior. Material degradation behavior can be designed chemically. Taking PLGA as an example, the degradation rate changes significantly with the ratio of lactic acid to glycolic acid, and systems near 50:50 or 1:1 typically hydrolyze more rapidly and can reach the timescale of 1–2 months. Biodegradable design is therefore not simply a matter of choosing a single material, but of precisely defining the working window of a device through the combination of conductors, substrates, and encapsulation [31–33,80].

Antibacterial performance mainly addresses infection control at long-term implantation sites and high-risk interfaces. Once implanted in the body, the device surface may become a starting point for bacterial adhesion, biofilm formation, and local infection spread. Once infection occurs, it not only causes tissue injury and exacerbated inflammation but also significantly degrades device performance. This is especially important for nerve cuffs, peri-implant interfaces, and long-term adherent devices, where biofilm formation not only increases infection risk but also progressively destroys the low-impedance contact and stable adhesion originally established. Implantable electronic devices often contain more complex surface morphologies, multimaterial interfaces, and microstructured regions, all of which may provide conditions favorable for bacterial adhesion and biofilm development. Accordingly, antibacterial performance is a basic requirement for long-term safe operation in certain implantation scenarios [26,73,75].

Several antibacterial designs have already been applied to implantable flexible electronic devices. The first category is anti-adhesive or antifouling surfaces, whose goal is to reduce the initial attachment of bacteria and protein contamination on the device surface, thereby suppressing subsequent biofilm formation at the source; PEGylation and zwitterionic interfaces are common examples. The second category is bactericidal coatings or release systems, which achieve local antibacterial or bactericidal effects through active components such as metal ions, quaternary ammonium compounds, or chitosan. The third category is stimulus-responsive antibacterial strategies, in which on-demand antibacterial action is triggered through photothermal, electrothermal, ultrasonic, or piezoelectric-conductive coupled interfaces. More representative recent work has focused on simultaneous optimization of antibacterial function, soft-tissue integration, and functional interfaces [26,73,75]. For example, Han et al. proposed an artificial piezoelectric-conductive integrated peri-implant gingival interface (Fig. 2c). This work combined piezoelectric effects, conductive interfaces, bacterial inhibition, and soft-tissue integration within a single artificial interface, thereby improving both peri-implant bacterial suppression and soft-tissue bonding [73].

Beyond the adhesion, mechanical coupling, biocompatibility, biodegradability, and antibacterial properties discussed above, *in vivo* engineering also involves additional considerations such as encapsulation protection and miniaturized layout. The interaction between implanted devices and the physiological environment depends on systematic engineering design, and the various physical and biological requirements are interdependent. Only when a stable and safe tissue interface can be established *in vivo* can the device subsequently perform substantive diagnostic and therapeutic functions.

3 Engineering for Diagnosis and Therapy

After a device has achieved basic adaptation to the *in vivo* environment, it must further realize effective diagnostic and therapeutic functions. At this stage, the key issue is how the device exchanges signals, energy, and matter with tissue. In this review, engineering design for diagnosis and therapy is divided into three levels: constructing task-matched functional interfaces, organizing multiple components into an implantable system, and establishing stable input, output, and processing chains for signals [9,10,14,15,39,84–86]. These aspects are discussed below.

3.1 Construction of Functional Interfaces

The core role of a functional interface is to improve the efficiency of matter, information, and energy exchange between the device and tissue. For implantable flexible electronic devices, diagnosis and therapy ultimately depend on the cross-interface transfer of some physical or chemical quantity, such as the conversion between ionic and electronic currents, the propagation of photons in tissue, the diffusion of heat in local regions, the coupling transmission of ultrasound, or the synchronized strain between the device and tissue. Accordingly, the functional interface is the key working layer that determines transfer efficiency and precision [15,40,84,87–89]. Taking functional hydrogel interface materials as an example, Yang et al. systematically summarized their role in bridging devices and soft tissues (Fig. 3a,b) [37]. As illustrated, hydrogels can not only act as double-sided interface hydrogel adhesives to physically connect bioelectronic devices with the underlying tissue, or as surface hydrogel coatings to isolate biological fluids; more importantly, they can establish multimodal coupling between soft and hard interfaces. Through this water-rich, three-dimensional polymer network, the interfacial layer can simultaneously mediate optical coupling, chemical molecule exchange, electrical conduction, heat transfer, and dynamic mechanical coupling [37]. This strategy of simultaneously satisfying physical buffering and multimodal functional transduction through a single material system reflects the fundamental logic of current functional interface design, a logic that must be tailored to specific application modalities [37,87–89].

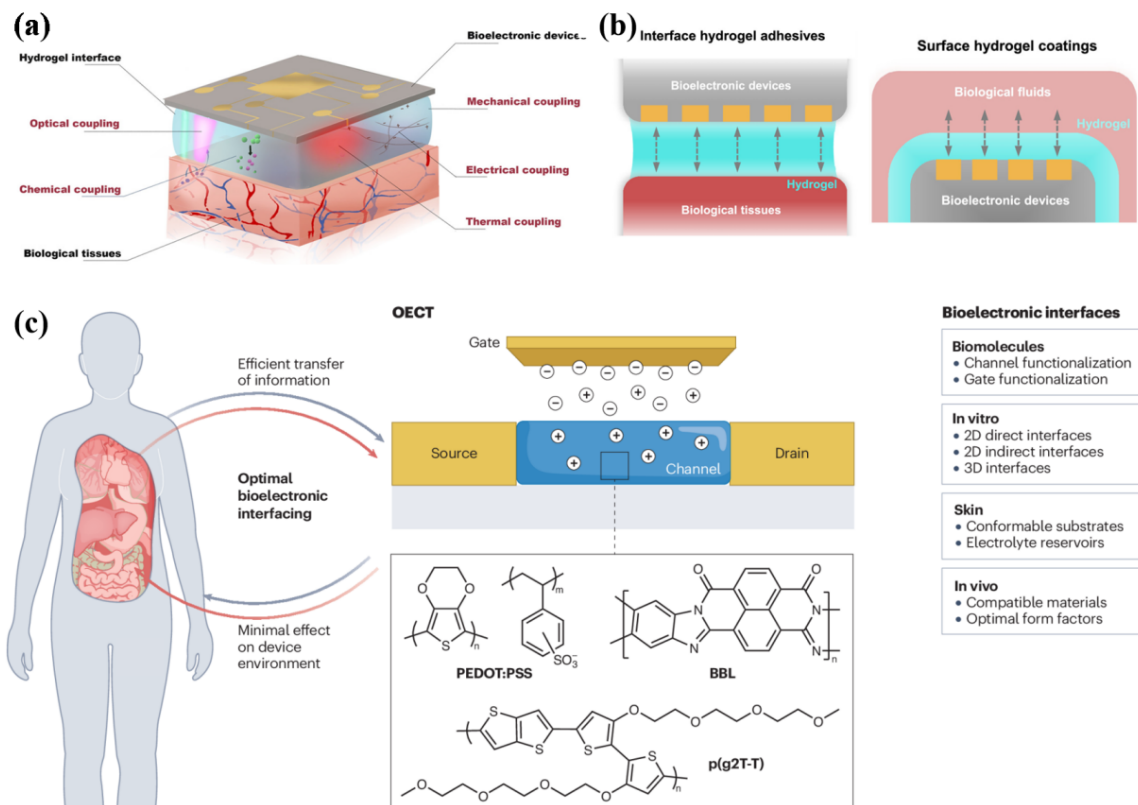


Figure 3: Functional bioelectronic interfaces for multimodal coupling and active signal transduction. (a) Schematic illustration of a hydrogel-based interface bridging a bioelectronic device and biological tissue, simultaneously mediating mechanical, optical, chemical, electrical, and thermal coupling [37]. (b) Structural configurations of functional hydrogels, serving as either double-sided tissue adhesives or protective surface coatings [37]. (c) OECT-based active bioelectronic interface for ionic-to-electronic signal transduction [43].

Different diagnostic and therapeutic tasks correspond to different interfacial matching requirements. The most basic and common is the electrical interface. Whether for bioelectrical recording or electrical stimulation, the device must establish stable conversion between ionic conduction in tissue and electronic conduction in the circuit. Therefore, low impedance, stable charge injection, and long-term interfacial integrity are central criteria. To achieve these goals, common optimization strategies include increasing the effective specific surface area of electrodes, introducing low-impedance coatings such as PEDOT:PSS and IrOx, and using conductive hydrogels, ionic conductors, and ion-electron hybrid interfaces to improve signal coupling in soft tissue [9,75,84]. PEDOT:PSS is more commonly used to reduce recording-interface impedance and improve readout of weak signals, whereas IrOx is more commonly used to enhance charge-injection capability for stimulation applications. The shared purpose of these strategies is not simply to improve material conductivity, but rather to reduce interfacial polarization, suppress noise and stimulation-induced injury, and maintain stable recording and output capability under chronic implantation conditions. For example, as an important branch of electrical interfaces, active functional interfaces based on organic electrochemical transistors (OECTs) further demonstrate the system-level advantages of mixed conductor materials in ion-electron coupling. Saleh et al. systematically summarized the role of OECTs in constructing bioelectronic interfaces (Fig. 3c) [43]. As illustrated, by employing conductive polymers such as PEDOT:PSS, BBL, or p(g2T-T) as the channel material between the source and drain, the device can directly convert ionic fluctuations from the gate (biological fluids or tissue) into electronic current within the channel. This volumetric doping mechanism not only achieves efficient transfer and local amplification of biological information, but also minimizes interference with the surrounding microenvironment, thereby providing optimized engineering solutions for bioelectronic interactions across multiple levels, including molecular, *in vitro*, skin, and *in vivo* [43].

In addition to electrical interfaces, optical, thermal, and acoustic modalities also impose interfacial requirements. Optical interfaces must minimize scattering and reflection losses introduced by encapsulation layers, interfacial layers, and tissue itself, while improving local irradiation precision and optical flux utilization. Accordingly, transparent electrodes, ultrathin encapsulation, and miniaturized light-emitting devices have become common design approaches [42,84,85,88,90]. Thermal interfaces emphasize how heat can be delivered more controllably into target tissue in order to avoid local hotspots and off-target injury, and are therefore often designed together with heat-spreading layers, flexible temperature-sensing units, and local thermal-isolation structures [40]. The key issue in acoustic interfaces is reducing acoustic-impedance mismatch between the device and tissue in order to improve ultrasonic energy-coupling efficiency as well as imaging or stimulation precision [40,86,91]. Although the interfacial requirements of different physical fields differ, they all serve the same goal: enabling energy or information introduced into the body to act on target tissue as efficiently, controllably, and locally as possible.

Functional interfaces also involve the coordination of multiple modalities. For example, even if a certain electrode material has relatively low impedance, stable recording may still be difficult if it cannot adhere to tissue over long periods or if obvious relative sliding occurs under organ motion. Accordingly, the more mature current approach is not to optimize each physical field separately, but to integrate low-impedance coatings, transparent conductors, flexible adhesive structures, and related features into a single interface as needed, thereby forming a composite functional interface with multiphysics synergy [15,26,40,75]. This strategy has become common in cardiac and neural implant systems. For example, flexible optoelectronic interfaces for cardiac theranostics typically require coordinated integration of micro-LEDs, transparent electrodes, flexible substrates, and conformal adhesive structures, so that local electrical activity can be stably recorded on one side while high-spatial-resolution optical stimulation or optical therapy is performed

on the other [42,85]. Functional-interface matching and construction are thus prerequisites for subsequent system integration, signal processing, and specific diagnostic or therapeutic applications.

3.2 Component Integration and System Architecture

System-level implantable flexible electronic devices rarely operate as isolated single components. Instead, they typically execute diagnostic and therapeutic tasks through system integration. Downstream of the interfacial units mentioned above, a complete implant system usually requires both functional units and system-support units at the architectural level. Functional units carry out specific tasks such as sensing, stimulation, light emission, or drug release, whereas system-support units are responsible for power supply, communication, data processing, and encapsulation protection. Device design must couple these units into an integrated system capable of long-term operation and reliable data transmission and reception [14,15,39,92,93]. It is worth noting that Li et al. systematically summarized two core routes for the structural integration of multimodal flexible hybrid epidermal electronic devices: the all-in-one strategy and the assembled strategy (Fig. 4a,b) [69]. Although developed for epidermal systems, this classification provides a conceptual framework for implantable system design. The all-in-one structure typically adopts a soft-stiff stacked integration, tightly binding the flexible substrate, soft encapsulation, and rigid electronic components within a single entity. In contrast, the assembled structure employs heterogeneous separation integration technology, physically separating the flexible modules from the rigid modules and connecting them via dedicated soft-stiff interfaces, thereby avoiding direct conflict between the rigid components and the flexible tissue interface [69]. This clear delineation of system architectures provides important engineering guidance for balancing the mechanical compliance of the device with the complexity of system functions across different application scenarios [69,92,93].

This modular logic is broadly applicable across devices with different form factors and implantation modes. For example, in patch-type electrode systems, the front end may consist of epicardial or cortical electrode-array interfaces and functional units, while the back end integrates wireless power and telemetry modules as support units. In cuff-based neural recording systems, the front end often comprises a nerve-wrapping recording interface, with communication or control units connected at the back end. Different systems thus follow the same architectural division, in which the front-end interface performs local interaction and the back-end modules provide energy and communication support [9,14,15,39,94,95]. Among these support modules, power-supply and communication-link design directly determines system architecture. Traditional percutaneous leads or rigid batteries entail infection risk and limit long-term application, and therefore wireless power transfer, wireless telemetry, and battery-free operation have become frontier directions. Widely used schemes currently include electromagnetic coupling, magnetoelectric coupling, ultrasound, RF backscatter, and hybrid wireless links.

The challenge in integration lies in trade-offs among modules. Biointerfacial units must remain soft, ultrathin, and conformal in order to minimize tissue injury, whereas support units such as chips, coils, antennas, and energy-storage elements generally have greater thickness and stiffness. Implant systems must complete interconnection, thermal management, and encapsulation protection simultaneously within a limited volume. An increase in the size or stiffness of any single support module can constrain overall compliance, implantation pathways, and long-term stability, and this limitation is especially pronounced in deep implantation and multimodal therapy [14,15,39,92,93,96]. In addition, different power-supply and communication schemes involve different trade-offs among implantation depth, bandwidth, alignment tolerance, and system power consumption [14,39,86]. Clinically translatable system architectures require integrated arrangement of power supply, communication, control, and interfacial layout under constraints

including anatomical location, power budget, communication distance, encapsulation volume, and long-term reliability [14]. As the underlying architecture matures, implant systems are evolving from monofunctional devices toward reconfigurable platform designs. Kang et al. developed a wireless modular implantable neural device that uses magnetic assembly to interchange neural-interface modules for optical stimulation, drug delivery, and electrical stimulation on a single platform, thereby enabling task-specific switching of operating modes (Fig. 4c,d) [97]. This modular architecture significantly improves adaptability across different diseases and organ scenarios [9,14,15,39].

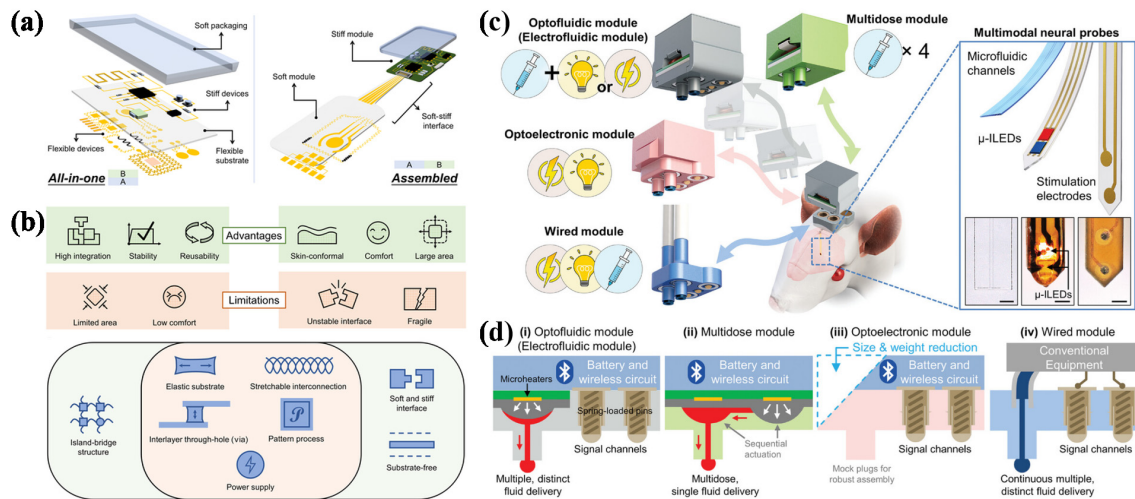


Figure 4: System architecture design ideas and examples for flexible electronic devices. (a) Common ideas include integrated solutions and modular solutions. Integrated solutions use stacking to achieve the integration of soft and hard structures [69]. The whole generally includes flexible components, flexible substrates, rigid components and flexible encapsulation layers. Modular solutions rely on the heterogeneous integration idea of separating soft and rigid modules to avoid direct contact between flexible and rigid components. The interface structure between the two types of modules is the core part of the system. (b) The unique components of each solution and the common components that overlap with each other, as well as their respective advantages and disadvantages [69]. (c) Schematic illustrating the architecture of a wireless modular implantable neural-interface device [97]. (d) Representative interchangeable modules for optical stimulation, electrical stimulation, and drug delivery [97].

3.3 Signal Input, Output, and Processing

Signal input, output, and processing determine whether an implantable device can truly convert *in vivo* information into interpretable diagnostic evidence, or convert control instructions into effective intervention in a stable manner. For such systems, front-end interfaces, functional modules, and system architecture can only be considered fully realized when the required signal pathways are complete. In other words, the device must not only sense or act on tissue, but also deliver acquired weak signals intact into the downstream processing chain, or accurately return control instructions generated by the back end to stimulation, drug-release, light-emission, or heating units [1,9,10,14].

The signal chain of implantable flexible electronic systems typically includes acquisition or stimulation output, front-end conditioning, analog-to-digital conversion, multichannel multiplexing, data transmission or storage, and subsequent analysis and feedback control. Acquisition tasks often face raw signals with very low amplitude, strong noise sensitivity, and substantial drift, such as weak bioelectrical signals, electrochemical currents, and analog variations caused by changes in impedance or temperature. For example, cortical potentials, ECGs, and peripheral nerve signals are often on the microvolt-to-millivolt

scale, whereas temperature and impedance readouts more often appear as slowly varying analog quantities. Stimulation tasks, by contrast, require parameters generated in the digital domain to be reconverted into controllable electrical pulses, optical pulses, thermal inputs, or drug-release actions, with direct control parameters including amplitude, frequency, pulse width, or duration. Thus, although the input and output chains run in opposite directions, both rely on strict timing control, noise management, and power constraints [1,9,10].

Within this chain, front-end conditioning is the first critical determinant of system quality. For recording tasks, low-noise amplification, band-pass filtering, common-mode rejection, and artifact suppression directly determine whether downstream signals are usable. For chemical and multimodal sensing tasks, the front end also often involves potentiostatic control, current-to-voltage conversion, and baseline-drift compensation. Once the chain enters the analog-to-digital conversion stage, the system must again balance sampling rate, resolution, and power consumption, because although high channel counts and high temporal resolution preserve more information, they immediately impose greater data throughput and energy burden. For this reason, multichannel multiplexing, event-driven sampling, compressed transmission, and on-chip preliminary feature extraction are increasingly common, as they attempt to reserve limited power for information that truly has diagnostic or control value [9,10,14].

Traditional implant systems often operate on fixed thresholds or preset programs. Although this approach is simple and stable, it is difficult to accommodate individual differences, chronic drift, and disease-course variation. By contrast, recent closed-loop studies increasingly emphasize adaptive analysis and dynamic updating. For closed-loop theranostic systems, the signal chain must further complete judgment and trigger feedback within a limited time window. In scenarios such as closed-loop neuromodulation or on-demand drug delivery, the system often needs to first identify a certain biomarker change and then immediately adjust stimulation timing, amplitude, or release intensity on the basis of a preset threshold or algorithmic output [9,51,67]. In this process, edge-side processing becomes increasingly important, because if all raw data must be transmitted outside the body for analysis, latency, power consumption, and communication burden often become unacceptable. Accordingly, an increasing number of systems have begun to move threshold detection, feature extraction, state classification, and even part of decoding algorithms to the implant side or to proximal processing units, thereby endowing devices with preliminary local decision-making capability. The RONDO framework proposed by Lee et al. is one such example. This framework introduces online recursive learning under resource-constrained conditions for embedded neuromodulation systems, improving neural decoding accuracy by 35%–45% relative to offline learning while avoiding dependence on cloud-based high-performance computing [68]. This indicates that signal processing in implant systems has expanded from filtering and transmission to embedded decoding, edge learning, and real-time adaptive control [66,68]. In summary, the core of signal input, output, and processing lies in compressing the entire chain into an appropriate range of volume, power consumption, and latency according to the specific diagnostic and therapeutic task. A mature implant system should ensure that the front end can stably acquire or deliver effective signals, that the intermediate chain can sustain long-term operation at sufficiently low energy cost, and that the back end can return intervention instructions in a timely manner when needed [1,9,10,14,51,67].

4 Signal Detection and Diagnosis

At the application level, implantable flexible electronic devices can transform diagnostic approaches that traditionally depend on *ex vivo* sampling or short-term examination into continuous, *in situ*, and dynamic *in vivo* monitoring. In *in vivo* diseases, many key pathological changes are not static, but evolve

continuously over time and space, such as transient abnormalities in neural activity, fluctuations in local metabolite concentration, and changes in tissue temperature. Therefore, if a device can operate stably near a lesion over long periods, it can convert the disease process itself into a trackable spatiotemporal signal [1,9]. The categories of detection covered in Section 4 reflect this idea. Electrical sensing more directly reflects organ function, especially in nerves and muscles; chemical sensing is closer to metabolism and the molecular microenvironment; and temperature and mechanical sensing can supplement information related to inflammation, perfusion, and tissue motion. More advanced current approaches organize different modalities into complementary diagnostic systems around specific clinical tasks. Accordingly, the focus of this chapter is not only the detection targets themselves, but also the application of specific devices in specific *in vivo* scenarios [1,9,15].

4.1 Electrical Sensing

Electrical sensing is one of the most mature and representative application directions for implantable flexible devices. EEG, cortical potentials, ECG, EMG, and peripheral nerve electrical signals all directly reflect organ functional status and therefore have irreplaceable value in epilepsy monitoring, arrhythmia recognition, brain-computer interfaces, and neural function assessment. Its engineering core lies not merely in placing conductive materials on tissue surfaces, but in simultaneously solving the problems of low-impedance coupling, dynamic adhesion, resistance to motion artifacts, and long-term recording stability. For this reason, a major recent focus in electrical sensing has been whether sufficiently high-fidelity signals can be continuously acquired under real *in vivo* conditions to support diagnostic judgment [1,9,15,98–101]. In terms of device form, current mainstream electrical-sensing routes can be roughly divided into two categories. One comprises conformal recording interfaces for organ surfaces, such as patch-type or cuff-type electrode arrays for the cortical surface, epicardium, and peripheral nerves. The other comprises fibers, probes, and navigable interfaces for deep structures, whose aim is to improve spatial resolution while reducing tissue injury. The former emphasizes large-area coverage, multipoint synchronous recording, and mechanical compliance, whereas the latter emphasizes spatial targeting, long-term stability, and accessibility of implantation pathways [9,10,74,95,96,102–104].

Choi et al. reported a sutureless adhesive epicardial bioelectronic patch that uses an ionically conductive tissue-adhesive layer, a viscoelastic network film, and a fatigue-resistant conductive composite layer to form a recording interface capable of instant attachment to the wet and beating heart surface (Fig. 5a) [28]. The device can adhere in less than 0.5 s, exhibits less than 0.2% resistance change after 1000 cycles at 50% tensile strain, and can record cardiac signals in awake rats for up to 4 weeks while also performing spatiotemporal mapping of electrical activity in an ischemia-reperfusion model [28]. This indicates that the feasibility of electrical recording depends to a large extent on whether the interface can remain stable and low-injury over time. Wu et al. reported a flexible cardiac patch based on orbit-symmetry-broken MXene. By lowering bioelectronic-tissue interfacial impedance and improving interlayer charge transport, this device achieved spatiotemporal epicardial mapping and long-term real-time recording on the left ventricular epicardium in rodents and pigs [105]. Such studies show that electrical sensing remains central in implantable flexible devices because it most directly connects organ function with electronic readout. However, transforming this advantage into true diagnostic capability still depends on whether stable interfaces, high-fidelity acquisition, and long-term system operation can all be established simultaneously. Only when materials, structures, and system architectures are jointly optimized can electrical sensing progress from short-term signal demonstration to diagnostically meaningful chronic *in vivo* monitoring [1,9,28,105].

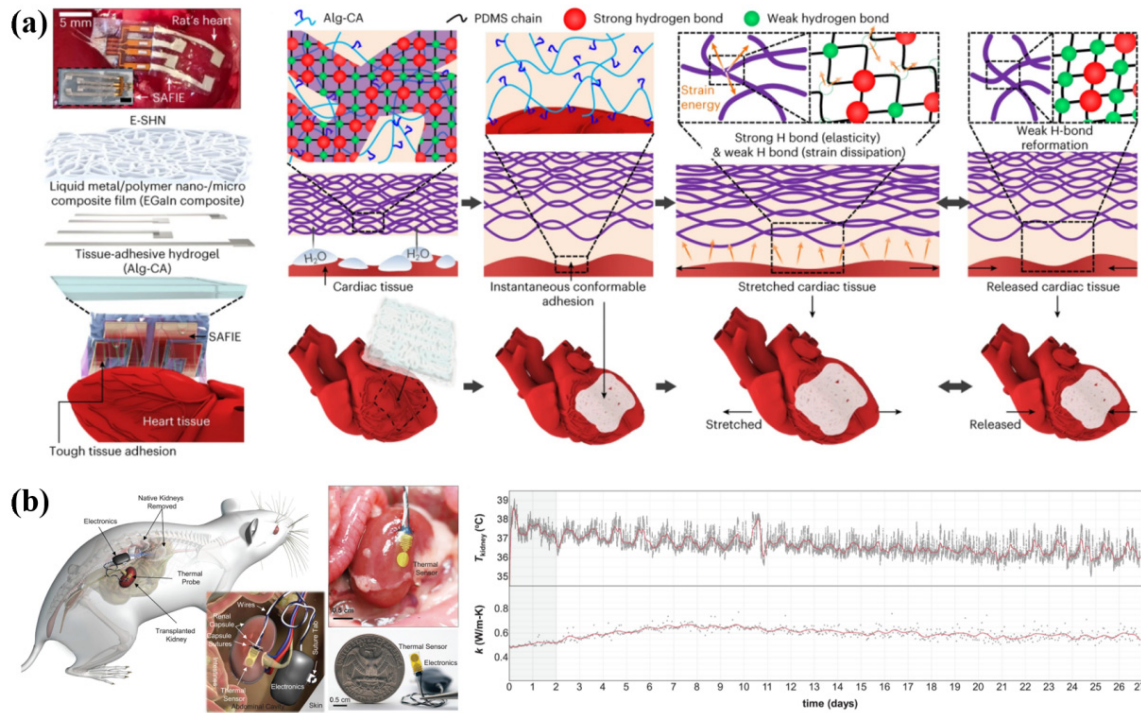


Figure 5: Representative applications of implantable flexible electronics for *in vivo* monitoring. (a) Design and application of a strain-isolating flexible patch (SAFIE) for sutureless epicardial interfacing [28]. (b) Implantable bioelectronic system for continuous monitoring of kidney-transplant rejection [6].

4.2 Chemical Sensing

Chemical sensing further expands the dimensions through which implantable devices acquire *in vivo* information. Compared with bioelectrical signals, chemical indicators such as glucose, lactate, and oxygen more directly reflect local metabolic status and therefore have unique value in scenarios including infection warning, ischemia assessment, and postoperative monitoring. The mainstream implementation paradigm still centers on electrochemical sensing, including amperometric, voltammetric, impedance-based, and field-effect transistor-based strategies. In specific implementations, these can be further divided into direct *in situ* detection, microneedle-assisted detection, and continuous molecular monitoring routes that rely on nucleic acid aptamers or enzyme recognition layers [1,52].

Chemical sensing faces even more stringent engineering constraints. First, analytes *in vivo* are often present at low concentrations, diffuse slowly, and are strongly influenced by local convection, so the device must maintain sufficient sensitivity within an extremely small sampling volume. Second, protein adsorption, cell adhesion, and fibrotic encapsulation rapidly alter interfacial mass-transfer conditions, leading to baseline drift and sensitivity loss. Third, many chemical sensors depend on enzymes, aptamers, or other recognition elements, and these active layers themselves are prone to deactivation during long-term implantation. Thus, the challenge of chemical sensing is not merely recognizing a certain molecule, but maintaining selectivity, stability, and calibratability over time within complex body-fluid environments [1,52].

An important direction has been to extend electrochemical monitoring from surface-limited sampling to deep organs and perioperative scenarios. Li et al. reported a programmable bioresorbable electrochemical microneedle sensor array that uses independently addressable three-dimensional microneedle arrays to probe the parenchyma of deep organs [53]. This system can monitor key indicators such as electrolytes,

metabolites, and oxygenation in parallel, and in animal models it achieved real-time spatialized monitoring for at least 7 days in conditions including renal ischemia and intestinal abnormalities [53]. This work advanced multi-index electrochemical readout into deep organs [53]. Another key line of progress has focused on improving long-term *in vivo* stability. Chen et al. proposed a biochemical sensing system termed SENSBIT, which significantly extended sensor lifetime in complex biological fluids through the combination of three-dimensional nanoporous gold electrodes and a mucus-mimicking protective layer [8]. After one month in undiluted human serum and one week of intravascular implantation in living rats, the system still retained more than 50% of its baseline signal and remained repeatedly calibratable, while also continuously tracking changes in drug concentration after several days of exposure to flowing blood [8]. This again shows that, for implantable chemical sensing, overcoming *in vivo* fouling and deactivation is just as important as improving sensitivity. Chemical sensing expands the readout target of implantable devices from functional activity to molecular state, but it still must simultaneously address the problems of recognition selectivity, interfacial antifouling, long-term drift, and system calibration.

4.3 Temperature Sensing

Temperature is one of the most fundamental yet most easily overlooked types of physiological information *in vivo*. Local temperature changes are often directly associated with inflammation, perfusion, metabolic activity, infection spread, and external therapeutic processes. As a result, temperature sensing can be used not only for state monitoring but also for real-time evaluation of treatment safety. Compared with surface thermometers or single-point thermocouples, the value of implantable flexible temperature devices lies in their ability to conform to lesion surfaces or wound surroundings and to continuously provide spatial temperature distributions that more closely reflect the true local microenvironment. For this reason, the engineering focus of temperature sensing is not only single-point thermometry itself, but also the establishment of stable thermal contact on soft, wet, and continuously deforming tissue surfaces, while maintaining sufficiently high spatial resolution and measurement consistency over larger areas [6,11]. In terms of implementation, current mainstream routes mainly include metal-resistive temperature sensors, semiconductor thin-film temperature sensors, and array designs for large-area distributed monitoring. The first two emphasize single-point sensitivity and response speed, whereas the latter is better suited for scenarios such as inflammation localization, postoperative observation, and treatment feedback, where temperature distribution rather than a single value is of concern. Compared with electrical and chemical sensing, the temperature signal itself is relatively stable, but the real difficulty lies in avoiding false signals caused by device lifting, heat diffusion, and environmental disturbances, and in stably preserving temperature readout in actual *in vivo* scenarios [6,40].

In recent studies, Madhvapathy et al. leveraged the physiological significance of temperature signals to design a temperature-monitoring system for kidney transplantation (Fig. 5b) [6]. This work integrated a flexible temperature-sensing unit with a wireless readout module into an implantable platform for continuous monitoring of local graft-kidney temperature and thermal conductivity, thereby enabling identification of abnormal signals associated with rejection [6]. This study directly placed local thermal readouts into the concrete clinical problem of early detection of renal-transplant rejection, and the warning signal appeared earlier than conventional serum creatinine and blood urea nitrogen indicators [6]. In addition, temperature sensing is moving from single-point thermal monitoring toward continuous thermal-field monitoring. Many pathological processes and treatment side effects present as spatially heterogeneous local thermal abnormalities, such as infection boundaries, inflammatory hotspots, regions of insufficient perfusion, and thermal spillover zones. Without arrayed and conformal thermal interfaces, this information

is often averaged out by single-point readings, whereas distributed readout is more conducive to identifying local abnormalities and changes in thermal boundaries. Accordingly, in actual systems, temperature sensing often simultaneously serves local abnormality identification and treatment-safety window constraint [11,40]. As a realization of this concept, Han et al. reported a catheter-integrated soft multilayer electronic array [59]. This system can establish conformal contact with curved endocardial surfaces during cardiac surgery and perform high-density spatiotemporal mapping of local temperature distribution, thereby identifying the boundary of thermal diffusion while providing feedback control and safety-window constraints for radiofrequency ablation [59].

4.4 Mechanical Sensing

Mechanical sensing is concerned with dynamic information such as tissue motion, pressure, strain, and deformation. Such information can be used for cardiovascular hemodynamic monitoring, assessment of gastrointestinal peristalsis, bladder-state recognition, and observation of tissue loading after suturing or reconstruction. More specifically, pressure readout is more suitable for reflecting local compression and dynamic fluctuations, whereas strain readout more directly corresponds to tissue stretching, graft laxity, or loading during repair. Compared with traditional rigid pressure probes, flexible implantable devices can better conform to soft tissue surfaces and record complex mechanical changes without significantly interfering with their natural motion. Mechanical sensing provides long-term continuous and quantitative physical-state information about disease progression and recovery [1,48]. From the standpoint of technical routes, common mechanical-sensing structures currently include resistive, capacitive, piezoelectric, and inductively coupled devices, among which wireless and battery-free pressure sensors have developed most rapidly because they are especially suitable for long-term implantation and rapid intraoperative assessment. Mechanical sensing usually does not rely on active recognition layers and therefore suffers less from drift, but it faces another more prominent challenge: the device itself must be sufficiently soft, stretchable, and fatigue-resistant, otherwise tissue motion will be transformed into sensor failure. For this reason, the competitive focus of mechanical sensing devices often lies in system-level issues such as structural compliance, spatial coverage, wireless readout, and implantation stability [1,48].

As one example, Kim et al. reported a liquid-metal-based wireless soft implantable pressure sensor, demonstrating the potential of flexible mechanical sensing for local pressure monitoring [48]. This work used eutectic gallium-indium simultaneously as the deformable electrode of a capacitive sensor and as the low-resistance conductor of an inductive unit, thereby constructing a thin-film, battery-free LC wireless sensing platform. Through microfabrication, scalable pressure arrays were further realized, supporting large-area pressure mapping [48]. The authors also integrated the sensor with soft magnetic and self-healing layers into a cuff-like structure, allowing the device to autonomously fold under an external magnetic field and achieve suture-free implantation, while being paired with a wearable glove for real-time wireless readout [48]. This work showed that mechanical sensing is already capable of providing continuous local pressure readout on real tissue surfaces. Yang et al. reported an implantable wireless suture sensor that directly embeds a mechanical sensor into the surgical repair pathway to continuously track changes in tissue loading [54]. This work integrated the sensing unit and communication coil onto medical suture to form a double-helical structure suitable for surgical implantation, achieving a strain-monitoring range of 0–10%, a minimum detection threshold of 0.25%, and stability after more than 300,000 stretching cycles [54]. In models of lateral collateral ligament injury and anterior cruciate ligament reconstruction, the system could distinguish graft stretch, reinjury, and laxity while providing real-time wireless readout [54]. Mechanical sensing is thus moving toward long-term, *in situ*, and continuous monitoring of mechanical state. Its value

lies not merely in adding another detection channel, but in providing physical information such as tissue loading, interfacial contact, and motion state that cannot be readily replaced by other modalities in *in vivo* diagnosis [48,54].

Overall, electrical, chemical, thermal, and mechanical monitoring together constitute a multimodal representation of *in vivo* state. On the one hand, they improve the ability to identify disease progression and local tissue status. On the other hand, they provide real-time information that supports subsequent diagnostic judgment and therapeutic decision-making [1].

5 Therapeutic Applications

Compared with detection and diagnosis, therapeutic applications more directly reflect the active intervention capability of implantable flexible electronic devices in *in vivo* processes. Their shared feature is that the device actively inputs drugs, heat, optical signals, or electrical stimulation into target tissue to achieve local and temporally controllable intervention. This mode of *in situ* regulation is especially suited to lesions and organs that are difficult to cover precisely with conventional systemic drug administration or external devices [1,40]. The core objective is to confine the therapeutic dose to the target tissue and target time window as much as possible, while minimizing influence on surrounding normal tissue and the systemic environment [1,40].

5.1 Drug Delivery

Drug delivery is one of the most intuitive directions in implant-based therapy. Compared with conventional systemic administration, implantable delivery places greater emphasis on localization, temporal control, and on-demand release, thereby increasing effective drug concentration at the lesion while reducing systemic side effects. Current technologies mainly rely on reservoir-based or microfluidic micropump-driven delivery, microneedle- or microchannel-assisted delivery, and electrochemical or other stimulus-responsive release strategies. As device-design capability improves, drug-delivery systems are gradually evolving from passive diffusion platforms into active-release platforms capable of quantitative and programmable temporal control [49,51]. From an engineering perspective, the main challenge in implantable drug delivery is how to realize drug loading, encapsulation, driving, quantitative release, and long-term stable operation simultaneously within a limited volume. Devices optimized for high drug-loading capacity often sacrifice flexibility and miniaturization, whereas devices optimized for ultraminiaturization and compliance are easily constrained by drug payload and transport capacity. In addition, many *in vivo* scenarios do not require sustained high-dose administration, but rather intermittent, on-demand, and region-selective release. This means that the delivery module must provide explicit start-stop control, dose control, and release consistency, rather than functioning merely as a passive drug depot [49,51].

Qi et al. reported an electrochemically programmable drug-release platform [51]. In this study, drug molecules were modified onto gallium-based liquid-metal nanoparticles, and electrochemical corrosion was used to precisely control release rate, drug type, and release sequence. The fastest release time was less than 1 s, and the platform was compatible with multiple classes of drug molecules containing amine, thiol, hydroxyl, and carboxyl groups [51]. More importantly, this platform has been integrated into stretchable films and can be used in both epidermal and implantable settings, with *in vivo* experiments demonstrating treatment of wound infection with antibiotics and treatment of subcutaneous melanoma with antitumor drugs [51]. In a more clinically specific example of on-demand delivery, Ciatti et al. reported an implantable device termed Naloximeter for preventing fatal respiratory depression caused by opioid overdose [55]. This device contains a naloxone reservoir and release mechanism and can initiate drug release when overdose-related abnormalities

appear. In both small- and large-animal experiments, it rescued animals from otherwise lethal overdose states within minutes [55]. Future development in this direction is likely to focus more strongly on whether the release process can be controlled more precisely, more stably, and in closer alignment with specific therapeutic needs.

5.2 Thermal Management

Implantable thermal management centers on active regulation of local temperature, including both heating and cooling. Heating can be used in mild thermal regulation, antibacterial treatment, and tumor ablation, whereas cooling is more suitable for suppressing nerve conduction and establishing reversible analgesia. The common requirement of both routes is to establish a predictable temperature distribution within the limited *in vivo* space, confine temperature change near the target tissue, and reduce the risk of thermal injury to adjacent tissues. Common current implementation methods include resistive heating, photothermal conversion, microfluidic cooling, and local temperature-control modules coupled with other physical fields. Temperature monitoring, thermal isolation, and output constraints generally need to be designed together with encapsulation and control systems [6,40].

The core issue in the heating route is whether the thermal boundary can be controlled. Cai et al. reported an implantable thermal therapeutic device [61]. This system combines foldable electronics with an insulating pad to realize closed-loop heating, *in situ* temperature monitoring, and thermal protection of neighboring tissues around the lesion, and it was used for tumor thermal ablation in animal experiments [61]. Such a design maintains a stable balance among local treatment range, ablation efficiency, and protection of normal tissue.

The cooling route corresponds to another class of thermal-management task. Reeder et al. reported a bioresorbable soft neural cooler (Fig. 6a) [60]. This system uses microfluidic evaporative cooling to achieve local cooling of peripheral nerves within a flexible cuff interface, and combines this with real-time temperature-feedback control to realize reversible nerve conduction block [60]. In rat models of neuropathic pain, this class of device can rapidly and precisely cool peripheral nerves and thereby provide on-demand and localized analgesia [60].

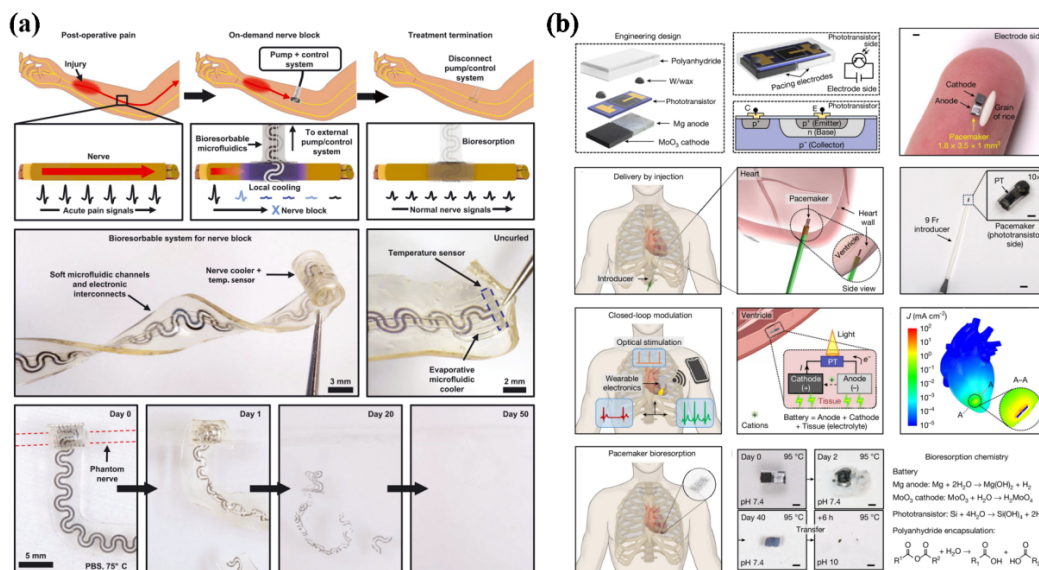


Figure 6: Representative applications of bioresorbable flexible electronics for localized therapy. (a) A soft, bioresorbable, evaporative microfluidic cooling system for on-demand peripheral nerve block [60]. (b) Injectable bioresorbable optoelectronic system for temporary cardiac pacing [58].

Once the device enters the therapeutic setting, the key issue in thermal management is no longer whether heating or cooling can be achieved, but whether the thermal boundary can be maintained over time. The temperature-monitoring examples discussed in the previous chapter have already shown that continuous *in vivo* thermal readout itself can provide local-state information [6,59]. During thermal therapy, synchronized temperature readout, thermal-diffusion management, and output constraints further determine whether the therapeutic window is stable, whether the thermal boundary is predictable, and whether the device can continue to function under tissue motion and perfusion-related heat dissipation [6,40,60,61].

5.3 Optical Stimulation

The advantage of optical stimulation lies in the relative ease with which input parameters can be precisely defined: wavelength, power density, irradiation time, and irradiation position can all be controlled independently. It is therefore particularly suitable for therapeutic scenarios with strict requirements on dose window and spatial boundary, such as photodynamic therapy and localized photobiomodulation. The difficulty lies in the strong scattering and absorption of light by biological tissue. Especially within the visible range, external irradiation often cannot deliver a sufficiently stable optical dose to deep lesions. What implantable optical stimulation must truly solve is how to use miniaturized light sources, waveguides, or structures implanted near the lesion to deliver light effectively to the vicinity of the target tissue while avoiding ineffective exposure and thermal injury to neighboring tissue [40,42,90,106]. From an engineering perspective, one representative current route is to decompose optical-therapy systems into two coupled problems: first, how to place the light source as close to the lesion as possible so as to shorten the optical propagation path in tissue; and second, how to match different wavelengths and different irradiation programs with specific treatment steps. In photodynamic therapy for tumors, for example, the former determines whether deep lesions can be illuminated, whereas the latter determines whether different stages of optical input can act on the lesion in the intended sequence. For this reason, implantable optical-stimulation systems increasingly emphasize programmed irradiation [40,42,57]. In addition, implantable devices face the continuing challenge of balancing small volume, low thermal burden, and long-term stability [40,42,57].

For photodynamic therapy of deep liver tumors, Liu et al. constructed a wireless dual-wavelength implantable micro-LED system that decomposed the therapeutic process into two sequential irradiation steps using 405 nm and 580 nm optical inputs [57]. From the standpoint of optical-stimulation implementation, the key feature of this system lies in assigning two different resonant-frequency wireless transmitting coils to the two wavelengths, thereby allowing deep lesions to receive programmed, near-lesion optical input. In an orthotopic rat liver-tumor model, this sequential low-dose irradiation strategy achieved effective PDT while keeping tissue heating within an acceptable range, with maximum temperature rises of approximately $1.3 \pm 0.5^\circ\text{C}$ and $5.2 \pm 0.7^\circ\text{C}$ for the 405 nm and 580 nm channels, respectively [57]. This work demonstrates that optical input in deep lesions can be implemented as an implantable, programmable, and quantifiable therapeutic process.

5.4 Electrical Stimulation

Among several implantable therapeutic approaches, electrical stimulation remains the most mature and the closest to routine clinical practice. It acts directly on excitable tissues such as myocardium, nerves, and muscle by setting stimulation sites, pulse width, frequency, amplitude, and timing in order to alter tissue activity. For this reason, the therapeutic effect of electrical stimulation is usually the easiest to quantify. However, its engineering challenges include stability of the electrode-tissue interface, infection

risk associated with leads and power-supply systems, and encapsulation and reliability under long-term implantation [9,50].

In recent progress, some studies continue to optimize conventional electrode stimulation itself in pursuit of more stable chronic interfaces and higher spatial selectivity, whereas others focus on reducing implantation burden by minimizing leads, percutaneous power connections, and the need for subsequent surgical removal from the therapeutic process as much as possible. The latter has given rise to design concepts such as wireless operation, self-powered function, biodegradability, and miniaturization. Their value lies in making electrical-stimulation therapies that were originally only feasible for short-term and constrained use easier to deploy during postoperative recovery, on fragile organ surfaces, or within confined anatomical spaces [9,50,58].

Zhang et al. developed a millimeter-scale bioresorbable optoelectronic system for electrotherapeutic tasks such as temporary cardiac pacing. The device carries its own power supply and is triggered wirelessly through external optical control, with a size already small enough for percutaneous injection or endovascular delivery (Fig. 6b) [58]. The authors demonstrated both single-site and multisite pacing in mice, rats, pigs, dogs, and *ex vivo* human hearts, indicating that such highly miniaturized and bioresorbable electrical-stimulation devices can still accomplish effective therapy [58].

In summary, drug delivery emphasizes the input of chemical substances, whereas heat and light are more closely related to local energy coupling, and electrical stimulation directly regulates the activity of excitable tissue. These approaches correspond to different pathological mechanisms and different engineering constraints. Their common trend is toward localization, on-demand operation, and quantifiability, that is, confining sufficiently well-defined intervention to the tissue region that truly requires treatment while imposing the smallest possible burden *in vivo* [51,55–58].

6 Conclusion and Perspectives

In summary, the use of implantable flexible electronic devices for *in vivo* diagnosis and therapy is, in essence, a continuous engineering process extending from *in vivo* adaptation to functional realization and then to system-level application. Section 2 discussed adhesion, mechanical coupling, biocompatibility, biodegradability, and antibacterial performance, which address how devices can stably exist in wet, dynamic, and immunologically active internal environments. Section 3 discussed functional interfaces, component architectures, and signal-chain design, which address how devices effectively exchange electrical, optical, thermal, acoustic, and chemical information with tissue. Sections 4 and 5 further demonstrated how, once both *in vivo* engineering and diagnostic-therapeutic engineering are established, detection functions based on electrical, chemical, thermal, and mechanical signals, as well as therapeutic functions based on drugs, heat, light, and electricity, can be stably realized. At the same time, the field has shown several major development trends, which are summarized below.

6.1 Trend toward Theranostic Integration

One of the clearest future directions is the transition from purely diagnostic or purely therapeutic systems toward theranostic integration. For implantable systems, the key point is not to mechanically stack sensors, actuators, and communication modules, but to allow front-end sensing results to directly participate in subsequent intervention decisions, thereby enabling the device to move from simply reading *in vivo* states to carrying out interventions on the basis of those states. This also implies a change in evaluation criteria. In the past, emphasis was often placed on the sensitivity of a single module, stimulation thresholds, or wireless distance. By contrast, systems aimed at closed-loop theranostic integration must address whether they can

form a stable chain of sensing, judgment, and execution around a specific pathological process. Here, a closed-loop system links sensing, decision-making, and actuation through feedback, whereas devices that merely co-integrate sensing and therapy are multifunctional [1,9].

Multiple examples discussed above already illustrate this trend. The implantable bioelectronic system developed by Madhvapathy et al. for kidney-transplant rejection shows that the value of continuous *in situ* monitoring lies not merely in obtaining more data, but in providing an earlier time window for subsequent clinical intervention [6]. Ciatti et al.'s Naloximeter similarly shows that the significance of implant systems lies not merely in storing drugs within the body, but in enabling on-demand intervention when a high-risk event occurs [55]. The closed-loop vagus-nerve stimulation study by Kilgard et al. further shows that state-dependent stimulation can already be used to improve functional recovery after injury [67]. Together, these studies illustrate a progression from monitoring and multifunctional integration toward closed-loop capability, which requires *in situ* state identification linked to feedback-guided targeted intervention.

Theranostic integration does not imply that increasing the number of integrated functions necessarily improves device performance or clinical utility. In *in vivo* systems, once sensing, analysis, and therapy are placed on the same platform, instability in any one link can propagate downstream and be amplified. For closed-loop theranostic systems, a more meaningful question is whether the device can construct a sufficiently simple, reliable, and clinically meaningful closed-loop pathway around a clearly defined pathological target. This will also be a key criterion in determining whether future closed-loop theranostic systems can move from proof of concept to actual use [1,9,67].

6.2 Data-Driven Trend

The data-driven trend is another major line of development that is becoming increasingly evident. As implantable devices evolve from single-channel, short-duration readout toward multimodal, long-duration, and continuous acquisition, traditional analysis methods based on fixed thresholds and empirical rules are becoming insufficient to fully exploit such information. This is especially true in scenarios such as neuromodulation, chronic disease monitoring, and continuous physiological assessment, where *in vivo* signals often show large interindividual variation, obvious temporal drift, and complex background noise. If analysis remains at the level of static threshold judgment, early abnormalities can easily be missed and on-demand intervention becomes difficult to support. Accordingly, algorithms are no longer merely back-end analysis tools, but are beginning to enter the working chain of implant systems themselves for abnormality identification, state estimation, risk prediction, and stimulation-parameter adjustment [14,66].

Daraie et al. systematically reviewed adaptive neuromodulation in drug-resistant epilepsy and pointed out that artificial intelligence has already been applied to key steps such as patient selection, stimulation-target identification, seizure-risk prediction, and individualized parameter optimization [66]. The embedded online-learning neural-decoding framework proposed by Lee et al. further shows that parameter updating and model correction are moving from offline analysis to edge-side operation, thereby preserving the ability of implant systems to adapt to individual changes during long-term use [68]. These advances indicate that a data-driven approach is not simply a matter of introducing machine learning, but of transforming data processing from an auxiliary step into part of the functional definition of the device itself.

At the same time, the data-driven trend is also influencing device design in the opposite direction. Multimodal continuous acquisition means that the burdens of power supply, storage, communication, and computation all increase simultaneously. As a result, sampling strategies, feature compression, event-driven readout, and edge-side computing will gradually become prerequisites of system design rather than merely algorithm-level optimization items [14,15]. In the future, competition among implant systems will concern

not only how much data can be acquired, but also whether key information can be transformed into reliable decisions under limited *in vivo* resources. This is the engineering significance of the data-driven trend.

6.3 Precision Trend

The precision trend is reflected in the increasing emphasis on tailoring devices to specific lesions, anatomical sites, temporal patterns, and individual requirements. Compared with earlier, more generic implantable devices, newer systems place greater emphasis on local deployment, on-demand activation, and disease-specific design. The representative works discussed above already show that the value of implantable devices is gradually shifting toward whether they can operate stably at a defined location, within a defined time window, and at a defined intensity. Whether for local temperature monitoring in kidney transplantation [6], bioresorbable neural interfaces for local thermal pain block [56], or programmed photodynamic therapy for deep lesions [57], the common logic is to confine action as much as possible to clearly defined tissue targets. For example, in the reported thermal nerve-block system, nerve temperature was controlled at $\leq 45^{\circ}\text{C}$, whereas programmed PDT relies on sequential dual-wavelength irradiation to confine optical input to predetermined treatment steps.

This precision first manifests as contraction of spatial scale. The sutureless adhesive epicardial bioelectronic device reported by Choi et al. shows that devices are moving from organ-level fixation toward precise adhesion at specific functional interfaces [28]. The modular implantable neural device developed by Kang et al. shows that functional modules can be reassembled on demand for different targets and tasks, rather than being preset into a single pathway [97]. The millimeter-scale bioresorbable electrotherapeutic system developed by Zhang et al. further shows that miniaturization and biodegradability can embed short-term intervention more naturally into specific clinical windows [58].

Precision also manifests in customization across time and individual dimensions. On-demand drug delivery, on-demand thermal stimulation, and online-learning neural decoding all indicate that future implant systems will no longer provide only fixed program outputs, but will increasingly adjust their operation in response to individual disease-course changes and evolving organ states [51,56,68]. In this sense, implantable flexible electronic devices are likely to evolve from general-purpose implant platforms into precision diagnostic and therapeutic terminals more closely aligned with the logic of individualized medicine.

6.4 Common Challenges and Summary

Despite rapid progress in this field, several common bottlenecks remain before broader practical application can be achieved. First, long-term interfacial stability remains the most central challenge. The fact that a device adheres well initially and exhibits reasonable modulus matching does not mean that the same interfacial state will be maintained after weeks or months. Protein adsorption, inflammatory responses, interfacial contamination, material fatigue, and microstructural damage can all gradually erode the advantages established at the beginning [15,28,105]. Therefore, future evaluation of implantable devices must focus not only on short-term performance peaks, but also on the time-dependent decay of interfacial performance under real *in vivo* conditions.

Second, the issues of power supply, encapsulation, and communication have not truly been solved by wireless design, but have merely taken on a different form of engineering constraint. Wireless and battery-free systems can substantially reduce the burden of leads and secondary surgery, but significant tension remains among deep implantation, miniaturization, long-term reliable operation, and tissue safety [14,39]. Likewise, the more implantable devices move toward theranostic integration and multimodality, the more

complex encapsulation layers, thermal management, data transmission, and module coupling become, and any weak point may become the origin of long-term failure.

Third, clinical translation still requires the field to move from laboratory prototypes toward stable manufacturing, standardized evaluation, and clinical acceptance. Problems such as manufacturing consistency, sterilization compatibility, quality control, encapsulation lifetime prediction, and scalable production of complex multimodule systems remain some distance from the standards required for true clinical deployment. Reproducible implantation and, where applicable, retrieval routes, together with validation in large-animal models and ultimately in humans, are also essential [14,15]. At the same time, continuous *in vivo* data also raise issues in algorithm validation, data security, regulatory evaluation, and accumulation of clinical evidence, none of which can be solved by a single discipline alone.

Overall, implantable flexible electronic devices for *in vivo* diagnosis and therapy have advanced from the stage of proof of concept to the stage of system integration and application expansion. What will truly determine the upper limit of this field in the future is whether reliable chains can be established simultaneously at the four levels of *in vivo* engineering, diagnostic-therapeutic engineering, data and algorithms, and clinical translation. Only when devices can both remain stable *in vivo* and accomplish interpretable, reproducible, and verifiable diagnostic and therapeutic tasks around clearly defined clinical objectives can implantable flexible electronic devices truly progress from frontier research to broad practical application [14,15].

Acknowledgement: None.

Funding Statement: This work was supported by National Natural Science Foundation of China (Nos. 81930048 and 82330061), Guangdong Science and Technology Commission (No. 2019BT02 × 105), Hong Kong Research Grant Council (Nos. 15125724, 15217721 and C7074-21GF), Shenzhen Science and Technology Innovation Commission (No. JCYJ20220818100202005), and Hong Kong Polytechnic University (Nos. P0039517, P0043485, P0045762, and P0048314). The Faculty Development Scheme (FDS) of the Research Grants Council (RGC), Hong Kong (Grant No. UGC/FDS24/M02/24), and the CPCE Research Fund of the College of Professional and Continuing Education, The Hong Kong Polytechnic University (Grant No. SEHS-2024-351(I)).

Author Contributions: Wenzhao Li and Siyang Zheng contributed equally to this work. Wenzhao Li and Siyang Zheng: conceptualization, Literature search and synthesis, visualization (figure preparation), writing—original draft. Chi Man Woo and Yuchen Song: Literature review, writing—review & editing. Yingying Zhou, Puxiang Lai, and Tianting Zhong: supervision, writing—review & editing. Qitao Tan: conceptualization, supervision, funding acquisition, writing—review & editing. All authors discussed the outline, critically reviewed the manuscript, and approved the final version. All authors reviewed and approved the final version of the manuscript.

Availability of Data and Materials: Not applicable.

Ethics Approval: Authors declare human or animal ethics approval was not needed for this study.

Conflicts of Interest: The authors declare no conflicts of interest.

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