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Bioelectronic Implantable Devices for Physiological Signal Recording and Closed-Loop Neuromodulation

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Bioelectronic implantable devices are adept at facilitating continuous monitoring of health and enabling the early detection of diseases, offering insights into the physiological conditions of various bodily organs. Furthermore, these advanced systems have therapeutic capabilities in neuromodulation, demonstrating their efficacy in addressing diverse medical conditions through the precise delivery of stimuli directly to specific targets. This comprehensive review explores developments and applications of bioelectronic devices within the biomedical field. Special emphasis is placed on the evolution of closed-loop systems, which stand out for their dynamic treatment adjustments based on real-time physiological feedback. The integration of Artificial Intelligence (AI) and edge computing technologies is discussed, which significantly bolster the diagnostic and therapeutic functions of these devices. By addressing elemental analyses, current challenges, and future directions in implantable devices, the review aims to guide the pathway for advances in bioelectronic devices.

1. Introduction

The contemporary landscape of medicine is witnessing a paradigm shift with the advent of bioelectronic implantable devices, revolutionizing the approach towards physiological signal recording and closed-loop neuromodulation in a wide spectrum of diseases across various organs. This transformative shift responds to the escalating prevalence of chronic conditions, extending from neurological disorders to metabolic dysfunctions. The World Health Organization (WHO) reports that chronic diseases account for 71% of global deaths, highlighting the pressing need for innovative therapeutic strategies.[1] Furthermore, the burgeoning impact of neurological disorders, affecting people worldwide,

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The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/adfm.202403562

DOI: 10.1002/adfm.202403562

underscores the expanding scope for bioelectronic applications. The rapid advancement in biomedical technologies, coupled with an aging population, is expected to surge the demand for long-term management of chronic conditions. This review paper explores the realm of implantable devices on organ systems including nervous,[2–32] cardiovascular,[33–42] respiratory,[43–45] digestive,[46–48] urinary,[49–53] and musculoskeletal systems[54–59] designed for both physiological signal recording and neuromodulation therapy, marking a notable advancement in the domain of electroceuticals (**Figure 1A** and **Table 1**).

The key to this technological innovation is the ability of these devices to measure an array of biophysiological signals, encompassing mechanical, thermal, electrical, optical, and chemical parameters. Mechanical biosensors,[2,21,42,50,58,60–61] for instance, are instrumental in monitoring hemodynamic changes in cardiovascular diseases and intracranial pressure in neurological conditions. Thermal biosensors[34,43,49,56,62–63] are increasingly used for detecting febrile responses in infectious diseases and monitoring metabolic rate disorders. Electrical biosensors[5–6,22,27,64–69] measure nerve and muscle signals throughout the body, providing critical information for understanding and diagnosing the various regulation and function systems inside the body. Optical biosensors,[10,38,46,48,70–74] utilizing technologies like fluorescence, bioluminescence, and photoplethysmography (PPG), are crucial in assessing tissue health, detecting neoplastic changes, and determining blood composition, as seen in applications like pulse oximetry for measuring oxygen saturation levels. Chemical biosensors[11,47,75–79] detect biomarkers for a variety of conditions, from renal dysfunction to neurotransmitter imbalances in neurological disorders, using electrochemical and enzymatic methods. The integration of these diverse bio-signal recording in implantable devices allows for comprehensive and continuous monitoring of health conditions, providing valuable insights for early and accurate diagnosis.

The therapeutic application of bioelectronic implantable devices, particularly in neuromodulation therapy, is equally compelling. Neuromodulation, involving the alteration of nerve activity through targeted delivery of electrical, optical, or chemical stimuli, finds application in a wide range of conditions. Electrical stimulation[29,31,52,80] methods like deep brain stimulation (DBS) and spinal cord stimulation (SCS) are employed for managing chronic pain, movement disorders, and psychiatric conditions. Optogenetics,[81–87] an innovative optical neuromodulation technique, is being explored for its potential in treating neurological diseases and modulating neural functions in nervous systems. Chemical neuromodulation, using targeted drug delivery systems,[18,88–92] is promising in managing conditions like Parkinson's disease, hormonal imbalances, and targeted chronic pain management. Moreover, these neuromodulation therapies extend their therapeutic reach to conditions like arrhythmias, chronic gastrointestinal disorders, urinary incontinence, and even mood disorders like depression and bipolar disorder, showcasing their versatility.

The integration of closed-loop systems[14,25,40,53,93–94] in implantable devices has marked a significant evolution in treatment methodologies (**Table 2**). These systems utilize real-time bio-signal feedback to dynamically adjust therapeutic interventions, ensuring personalized and adaptive treatment strategies. This approach is particularly beneficial for diseases with fluctuating symptoms, such as diabetes mellitus,[95–96] epilepsy,[97–98] cardiac arrhythmias,[99–100] and mood disorders,[101–102] where continuous monitoring and timely intervention can significantly improve patient outcomes. Furthermore, closed-loop systems are showing promise in managing complex conditions like Alzheimer's disease,[103–104] Parkinson's disease,[105–106] and spinal cord injuries,[107–108] providing adaptive therapies based on patient-specific needs. The incorporation of artificial intelligence (AI) and edge computing in these systems is enhancing their diagnostic and therapeutic capabilities. AI algorithms, through deep learning (DL) and machine learning (ML), provide predictive insights for customized treatment regimens, while edge computing facilitates on-device, real-time data processing, essential for efficient and responsive therapeutic interventions.[109–114]

Conclusively, this review explains present and future where bioelectronic implantable devices, particularly those in physiological signal recording, neuromodulation therapy, and closed-loop treatments, become integral to medical therapeutics across various specialties. Emphasizing the shift towards personalized, customized electroceutical solutions, these devices represent not just a technological innovation but a redefinition of electrical medicine. They offer individualized treatment strategies for diverse chronic conditions, ushering in an era of more effective and tailored medical care. This amalgamation of biomedical engineering with clinical practice is set to transform the boundaries of medical treatment, propelling the field towards an era of effective, personalized electroceutical interventions.

2. Bioelectronic Implantable Devices

2.1. Physiological Signal Recording and Closed-Loop Neuromodulation

The synergistic relationship between physiological signal recording and closed-loop neuromodulation is critical as it showcases why neuromodulation stands out as a principal and efficacious method among various therapeutic strategies. Physiological signal recording serves as the eyes and ears of bioelectronic systems, precisely capturing real-time data from various organ systems. This data collection spans mechanical, thermal, electrical, optical, and chemical signals that reflect the dynamic physiological state of the body (Figure 1B left). By accurately measuring these signals, implanted devices can detect early signs of dysfunction or disease, allowing for timely intervention. The transition from sensing to stimulation is where closed-loop neuromodulation serves a critical function. Unlike traditional treatment methods that might apply a static, one-size-fits-all approach, closed-loop systems utilize the continuous stream of physiological data to tailor and time interventions precisely.[115] For example, in patients with epilepsy, devices can detect the onset of abnormal electrical activity in the brain and immediately deliver electrical stimuli to halt the progression of a seizure.[116] This prompt and precise response not only prevents the physical manifestations of a seizure but also minimizes the potential side effects and disruptions to the patient's daily life.

Among various treatment methods, neuromodulation is particularly effective because it stands out as an optimal therapeutic approach due to its precision targeting, real-time responsiveness, and integration with natural biological functions.[117]

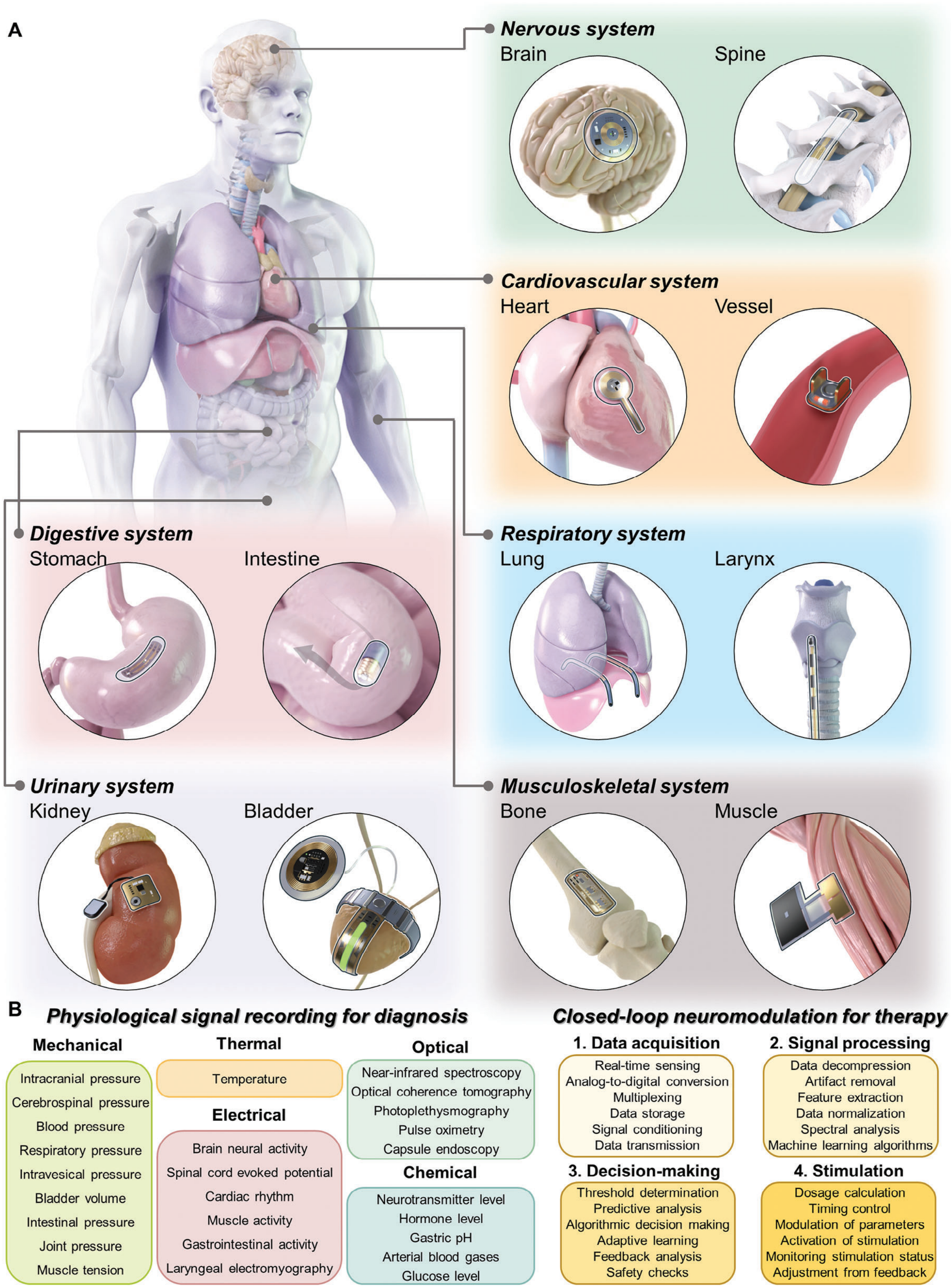


Figure 1. Organ-specific bioelectronic implantable devices. A) Classification of implantable devices for monitoring and therapy across various organ systems, including the nervous, cardiovascular, respiratory, digestive, urinary, and musculoskeletal systems. B) Examples of physiological signal recordings, categorized by specific modalities (left). Ordered elements of closed-loop neuromodulation systems designed for therapy (right).

Table 1. Clinical applications for implantable bioelectronic devices on various organs.

Organ system	Organ	Functions	Modality	Method	Clinical application	Ref.
Nervous system	Brain	Recording	Mechanical	Intracranial pressure	Brain injury	[2,3]
			Electrical	Electrical monitoring	Neural circuit study	[4–7]
					Brain disease	[8,9]
			Optical	Brain oxygenation	Tumor	[10]
			Chemical	Neurotransmitter monitoring	Brain disease (e.g. PD, Schizophrenia)	[11–13]
		Neuromodulation	Electrical	Electrical stimulation	Epilepsy	[14]
			Optical	Optogenetics	Behavioral control	[15–17]
			Chemical	Drug delivery	Behavioral control	[18,19]
	Spine	Recording	Electrical	Electrical monitoring	Spinal cord injury	[22,23]
		Neuromodulation	Electrical	Electrical stimulation	Spinal cord injury	[24]
	Peripheral Nervous	Recording	Electrical	Electrical monitoring	Nerve activity monitoring	[26–28]
		Neuromodulation	Electrical	Electrical stimulation	Pain management	[29]
					Nerve injury	[30,31]
			Optical	Optogenetics	Chronic pain	[32]
Cardiovascular system	Heart	Recording	Mechanical	Heart rhythm	Arrhythmias	[33,34]
			Electrical	ECG	Ischemia	[35,36]
			Thermal	Heart temperature	Arrhythmias	[37]
			Optical	Cardiac oxygenation saturation	Hypoxia	[38]
		Neuromodulation	Optical	Optogenetics	Heart failure	[39]
	Vessel	Recording	Mechanical	Hemodynamics	Cardiovascular diseases	[41,42]
Respiratory system	Lung	Recording	Thermal	Lung temperature	Homeostasis monitoring	[43]
	Larynx	Recording	Electrical	EMG	Laryngeal paralysis	[44]
		Neuromodulation	Electrical	Electrical stimulation	Voice fold paralysis	[45]
Digestive system	Stomach	Recording	Optical	Absorbed radiation dose	Gastrointestinal cancer	[46]
	Intestine	Recording	Chemical	Serotonin monitoring	Bowel disease	[47]
			Optical	Fluorescence endoscopy	Colon cancers	[48]
Urinary system	Kidney	Recording	Thermal	Kidney temperature	Graft rejection	[49]
	Bladder	Recording	Mechanical	Deformation of bladder	Detrusor underactivity	[50,51]
		Neuromodulation	Electrical	Electrical stimulation	Detrusor underactivity	[52]
Musculoskeletal system	Bone	Recording	Mechanical	Bone strain	Bone fracture	[54,55]
			Thermal	Local temperature	Bone fracture	[56]
	Muscle	Recording	Electrical	EMG	Neuroprosthetic application	[57]
	Tendon	Recording	Mechanical	Tendon strain	Tendon disorder	[58,59]

Table 2. Clinical applications for closed-loop implantable bioelectronic devices.

Organ system	Organ	Signal Monitoring	Neuromodulation Method	Clinical application	Ref.
Nervous system	Brain	Local field potential	Electrical stimulation	Behavioral control	[20]
		Electroencephalogram	Drug delivery	Seizure	[21]
	Spine	Electromyography	Optogenetics	Spinal cord injury	[25]
Cardiovascular system	Heart	Electrocardiogram	Electrical stimulation	Bradycardia	[40]
Urinary system	Bladder	Strain gauge data	Optogenetics	Urinary urgency	[53]

Techniques such as electrical stimulation, optogenetics, and pharmacological modulation allow for precise targeting of specific neurological pathways or biological processes, enabling devices to affect only the intended areas or systems without widespread systemic effects. This precision minimizes side effects and enhances treatment efficacy. Furthermore, neuromodulation can provide real-time adjustment of therapy based on continuous feedback from the patient's physiological signals, crucial for conditions with dynamic symptoms like epilepsy. Additionally, neuromodulation therapies work by harnessing the body's existing nervous or hormonal pathways, enhancing or suppressing their activity to achieve therapeutic goals. This integration helps maintain the natural balance of bodily functions, which is often less disruptive and more in line with the body's own regulatory mechanisms, making neuromodulation not just another treatment option but often the most strategic choice for managing complex medical conditions effectively and safely. Moreover, the application of neuromodulation in treating a wide range of conditions—from neurological disorders to metabolic dysfunctions—underscores its versatility and capacity for customization. The technology's adaptability is further augmented by advancements in AI and edge computing, which enhance the system's ability to analyze data, learn from patient responses, and predict future needs.

2.1.1. Mechanical Physiological Signal Recording and Closed-Loop Neuromodulation

Neuromodulation targeting the subarachnoid space within the brain manages intracranial pressure by modulating the absorption or secretion of cerebrospinal fluid (CSF), maintaining cerebral perfusion pressure crucial for brain tissue viability, especially in conditions like traumatic brain injury or hydrocephalus. Similarly, neuromodulation of the spinal cerebrospinal pressure involves regulating CSF dynamics to prevent nerve damage or dysfunction, utilizing pharmaceuticals implanted along the spinal column.[118–119] In cardiovascular health, baroreflex activation therapy (BAT) targets the carotid sinus to control systemic blood pressure. By electrically stimulating the baroreceptors, signals are sent to the nucleus of the solitary tract in the brainstem, leading to a decrease in sympathetic nervous system activity and an increase in parasympathetic output.[120] This results in vasodilation and reduced cardiac output, effectively lowering blood pressure.[121] This mechanism also prompts renal adjustments, enhancing diuresis and sodium excretion which further aids in blood pressure regulation.

In urology, devices monitoring intravesical pressure can regulate bladder function in patients with conditions like overactive bladder or neurogenic bladder dysfunction. These devices stimulate the sacral nerve to control detrusor muscle activity, facilitating coordinated bladder emptying or storage.[122,123] Similarly, bladder volume sensors can activate neuromodulation interventions to manage bladder contractions or retention based on real-time volume assessments.[124] Gastrointestinal motility disorders such as gastroparesis or chronic intestinal pseudo-obstruction can be managed by modulating the enteric nervous system to regulate intestinal motility and pressure, enhancing peristaltic movement, and alleviating symptoms like bloating and pain.

Neuromodulation in this context can adjust the release of motility drugs or directly stimulate nerve pathways to achieve effective gastrointestinal movement. Joint and muscle neuromodulation involve targeting the sensory nerves or muscle fibers respectively to manage pain and inflammation or control muscle tension and spasms. This is particularly beneficial in chronic pain conditions, arthritis, spasticity, or during rehabilitation from muscle injuries, where precise control over inflammatory and nociceptive pathways can significantly improve mobility and quality of life.

2.1.2. Thermal Physiological Signal Recording and Closed-Loop Neuromodulation

The physiological monitoring of body temperature through bioelectronic devices is an intricate process, vital particularly in conditions that impair the body's natural thermoregulatory responses, such as in patients suffering sepsis.[49] These devices are designed to continuously monitor body temperature and can initiate therapeutic responses to prevent dangerous fluctuations that could lead to further complications or mortality. Temperature regulation in the human body is a complex interaction between various systems, primarily controlled by the hypothalamus.[125] The hypothalamus receives input from peripheral and central thermoreceptors and integrates this information to maintain a set point of core body temperature through various mechanisms, including altering metabolic heat production, initiating sweating, shivering, and regulating blood flow to the skin. In neuromodulation therapy, devices that monitor temperature can utilize a variety of strategies to maintain normothermia.

In the context of neuromodulation therapy for hyperthermia management, electrical or pharmacological stimulation can be used to influence the hypothalamic set point in response to detected high body temperatures. Electrical stimulation could target the preoptic area of the hypothalamus, which is crucial for initiating physiological cooling processes such as sweating and vasodilation. By modulating this region, neuromodulators can lower the body's temperature set point, thus combating hyperthermia effectively. This approach is particularly advantageous in managing drug-resistant fevers or in conditions where traditional cooling methods pose risks or are ineffective. For hypothermia management, neuromodulation could involve electrical stimulation of heat production pathways. This could be done by targeting areas of the brain responsible for thermoregulation, such as the posterior hypothalamus,[126] to enhance metabolic heat production or reduce peripheral heat loss mechanisms like skin vasoconstriction. Additionally, electrical stimulation could be applied to peripheral nerves that control shivering, an involuntary response that generates heat.[127] Pharmacological neuromodulation might involve the controlled release of hormones like thyroxine, which play a crucial role in regulating basal metabolic rate and thus body temperature.[128] These neuromodulation strategies ensure precise control of body temperature, essential in critical care settings where maintaining normothermia is crucial for patient recovery.

It is important to recognize that while maintaining core body temperature is crucial for health status monitoring, the continuous measurement of internal localized temperatures presents unique challenges. The use of implantable devices allows for the ongoing surveillance of body temperature, providing critical insight into potential surgical site infections by monitoring localized increases in temperature.[63] Such a method is invaluable not only for detecting infections at surgical sites but also for identifying inflammatory responses associated with acute rejection in organ transplants and inflammatory diseases like Crohn's disease. Furthermore, the precision of temperature measurement is essential when administering regional thermal therapies, such as hyperthermia and hypothermia therapies, or photothermal therapy.[129] These treatments, used in the management of conditions like cancer, rely on the careful application of heat to targeted tissues. Without accurate temperature sensing, there is a risk of underheating or overheating, which can lead to thermal damage to normal tissues.[130] In hyperthermia therapy, specifically, maintaining a temperature above 41 °C is necessary to induce the denaturation of tumor cells, emphasizing the necessity for continuous monitoring to ensure the effectiveness and safety of the treatment.[131]

2.1.3. Electrical Physiological Signal Recording and Closed-Loop Neuromodulation

In neuromodulation of brain neural activity, devices such as deep brain stimulation (DBS) are surgically implanted to deliver electrical impulses directly to areas like the subthalamic nucleus or globus pallidus.[105] These regions are critical in motor control, particularly affected in Parkinson's disease. The electrical impulses can modulate the abnormal neural oscillations observed in Parkinson's, thereby reducing symptoms such as bradykinesia, rigidity, and tremors. This adjustment is believed to reset the neuronal network, allowing more normal motor signals to prevail. For spinal cord health, particularly after injury or during surgeries, neuromodulation devices can measure the integrity of pathways by monitoring spinal cord evoked potentials.[132] These devices can apply therapeutic electrical stimulation to specific regions of the spinal cord to promote neuroplasticity and possibly restore function. By adjusting the amplitude and frequency of stimulation, the therapy can facilitate the strengthening of neuronal connections within the spinal cord, enhancing signal transmission across injured or dysfunctional areas.

Cardiac neuromodulation involves the use of implantable cardioverter-defibrillators (ICDs) and pacemakers, which continuously monitor heart rhythm and automatically adjust electrical output to maintain a physiologically appropriate heart rate and rhythm.[133] The ICDs can detect arrhythmic events and deliver a precisely calibrated electrical shock to restore normal rhythm, while pacemakers can prevent too-slow heart rates by providing rhythmic electrical pulses. Functional electrical stimulation (FES) is used to restore muscular function, particularly in individuals with paralysis or severe muscle weakness. Sensors integrated into the neuromodulation system detect residual muscle activity, which guides the delivery of electrical impulses. These impulses stimulate the muscles or the nerves that control them, inducing contractions and promoting functional movement, such as enabling walking or standing in patients with spinal cord injuries.[134] In the gastrointestinal tract, neuromodulation devices can measure motility and secretory functions to modulate digestive processes. For instance, gastric pacemakers detect disruptions in the normal electrical rhythm of the stomach and deliver electrical pulses to normalize peristalsis, enhancing gastric emptying in patients with gastroparesis.[135] In laryngeal electromyography, sensors measure muscle activity in the larynx to detect dysfunction like vocal cord paralysis or laryngeal paralysis.[136] Implanted sensors detect the electrical activity generated by laryngeal muscles, and then this data guides neuromodulation, where targeted electrical stimulation is applied to the recurrent laryngeal nerve to restore muscle function, improving voice and swallowing.

2.1.4. Optical Physiological Signal Recording and Closed-Loop Neuromodulation

Regional tissue oxygen saturation ($rStO_2$) monitoring by implantable device can be important in neuromodulation strategies by providing real-time data on tissue oxygenation and hemodynamics. Near-infrared spectroscopy (NIRS) measures the oxygen saturation in the blood within microvascular tissues.[70] This is crucial for assessing the balance between oxygen delivery and consumption in tissues, which is vital for ensuring tissue health and function. By providing continuous insights into the oxygenation status and hemodynamics of targeted tissues, NIRS data can guide the development and adjustment of treatment protocols in neuromodulation.

Photoplethysmography (PPG) and pulse oximetry, commonly used for assessing blood flow and oxygen saturation, can indirectly influence neuromodulation therapies, particularly in sleep medicine and cardiology. In cardiology, PPG can help refine cardiac pacing parameters by providing real-time feedback on blood oxygen levels and peripheral blood flow, ensuring that cardiac pacemakers or resynchronization therapies are optimally adjusted to clinical needs.[137]

Optical coherence tomography (OCT) can be used for indirect applications in neuromodulation, particularly in surgical guidance. During procedures that implant neuromodulation devices, OCT can provide high-resolution, real-time images to ensure accurate placement of electrodes in target tissues such as the retina or superficial brain areas.[138] This precision is crucial for the success of optical neuromodulation therapies, such as optogenetic control of neurons, where light-sensitive proteins are used to modulate neuronal activity with high spatial resolution. Capsule endoscopy, while primarily diagnostic, has potential therapeutic implications by providing targeted visual data that can guide the delivery of localized pharmacological neuromodulation therapies. For example, the identification of specific gastrointestinal segments with inflammatory or dysmotile segments could lead to precise, segment-specific delivery of drugs or miniature bioelectronic devices that can electrically stimulate the enteric nervous system to modulate gastrointestinal motility or secretion.[139–140]

2.1.5. Chemical Physiological Signal Recording and Closed-Loop Neuromodulation

In neuromodulation for neurotransmitter regulation, sensors monitor specific neurotransmitters such as dopamine, serotonin, or GABA within the brain. Elevated or reduced levels of these chemicals can indicate neurological disorders such as depression, anxiety, or Parkinson's disease. Electrical neuromodulation can target specific brain areas, where electrodes deliver electrical pulses to modulate neurotransmitter activity. This stimulation adjusts the neural circuits' activity, restoring balance and alleviating symptoms. For instance, increasing dopamine transmission in Parkinson's patients can mitigate motor control symptoms, demonstrating the effectiveness of neuromodulation in restoring chemical balance.[141] Hormonal fluctuations detected by biochemical sensors can trigger neuromodulation interventions, such as in stress-related disorders. Vagus nerve stimulation (VNS) is employed to modulate the hypothalamic-pituitary-adrenal (HPA) axis indirectly.[142] By stimulating the vagus nerve, there is a reduction in the production and release of stress hormones like cortisol. This physiological adjustment can alleviate symptoms of stress, depression, and even epilepsy, showcasing how neuromodulation can stabilize hormone levels and contribute to homeostasis and well-being In cases of gastroesophageal reflux disease (GERD) or peptic ulcer disease, the detection of altered gastric pH levels can prompt the use of neuromodulation therapy.[143–144] Optogenetic control of neurons in the stomach lining that regulates acid secretion can adjust gastric pH levels. By controlling these neuronal signals, gastric acid secretion is decreased, which helps in managing the symptoms and physiological complications associated with high acidity, thereby restoring normal gastric function.

For patients with respiratory insufficiencies or during anesthesia, sensors that monitor arterial blood gases such as oxygen and carbon dioxide levels can inform neuromodulation strategies.[145] Phrenic nerve stimulation or diaphragmatic pacing can be used to adjust breathing patterns automatically. This form of neuromodulation helps maintain optimal oxygenation and CO_2 elimination, crucial in managing respiratory dysfunction or in critical care settings, ensuring the stabilization of arterial blood gas levels according to physiological needs. Neuromodulation can potentially influence glucose levels by targeting specific neural pathways that regulate endocrine functions, particularly those involving insulin secretion and glucose metabolism.[146–147] One promising area is the modulation of the autonomic nervous system, specifically the vagus nerve, which innervates the pancreas. Electrical stimulation of the vagus nerve has been studied for its potential to increase insulin secretion directly from the pancreas, thereby lowering blood glucose levels. This type of neuromodulation involves sending electrical impulses via an implanted device to the vagus nerve, which then stimulates pancreatic cells to produce and release more insulin in response to elevated glucose levels. This method could offer a more integrated and physiological approach to managing diabetes by harnessing the body's own regulatory mechanisms, enhancing the natural response to glucose changes, and maintaining blood glucose within a target range crucial for effective diabetes management.

2.2. Therapeutic Implantable Closed-Loop Neuromodulation Devices

The implementation sequence of closed-loop neuromodulation is a complex, multi-stage process that encompasses various technical and computational aspects, ensuring the system's effectiveness and adaptability (Figure 1B right). First, data acquisition involves real-time sensing of physiological signals, which is fundamental for closed-loop systems. The acquired analog signals are then converted into digital form through analog-to-digital conversion. Multiplexing is used to manage multiple signals, and signal conditioning is applied to refine the signals for accurate interpretation.[148] Finally, these processed signals are stored and transmitted for further analysis.[149] Next, signal processing is a critical stage where raw data undergoes comprehensive processing.[150] Data decompression is applied to manage the size and complexity of the data. Artifact removal eliminates noise and irrelevant data, ensuring the integrity of the information. Feature extraction is performed to identify specific characteristics of the collected signals, which are essential for accurate analysis. Data normalization standardizes the data, making it comparable across different time points or sessions.[151] Spectral analysis helps in understanding the frequency components of the signals, while machine learning algorithms are employed to interpret and learn from the data, enhancing the system's decisive and predictive capabilities. Then, decision-making is the stage where the system interprets the processed data to make therapeutic decisions.[152] Threshold determination is a process to set the limits or parameters for stimulation. Predictive analysis uses historical and real-time data to forecast the subject's physiological state. Algorithmic decision-making utilizes computational algorithms to determine the best course of action. Adaptive learning allows the system to modify its behavior based on subject response, enhancing treatment efficacy. Feedback analysis is conducted to evaluate the system's performance and make necessary adjustments. Safety checks are integrated throughout to ensure patient safety and system reliability. Lastly, stimulation is the stage where therapeutic intervention is delivered. Dosage calculation determines the amount of stimulation required. Timing control ensures that stimulation is delivered at the most effective moments. Modulation of parameters allows for adjustments in stimulation based on real-time data. Activation of stimulation is the process of delivering the therapeutic intervention. Monitoring stimulation status involves continuously assessing the delivery and effectiveness of the stimulation. Adjustment from feedback uses the system's feedback mechanism to fine-tune the stimulation for optimal therapeutic results. Each of these stages is intricately connected for the effective functioning of a closed-loop neuromodulation system.

Open-loop systems, which are the most basic form of neuromodulation, consist of sensors that measure physiological signals and stimulators that perform neuromodulation (**Figure** 2A left). These systems operate on pre-set parameters without the capacity for real-time adaptability or feedback. Open-loop systems have laid the groundwork for more advanced neuromodulation techniques. Conventional closed-loop systems[25,40,53] represent a significant advancement over open-loop systems by incorporating a feedback mechanism (Figure 2A middle). In these systems, physiological signals detected by sensors undergo processing in a processor. The processed data is used to deliver feedback and set stimulation parameters, which are then relayed to a controller. This controller enables the system to adjust its stimulation in response to real-time physiological data. This feedback loop is critical for enhancing the adaptability of the system, as it allows for the modulation of stimulation parameters in response to changing physiological needs. The integration of artificial intelligence (AI) significantly improves the performance of closed-loop systems for efficient and safe neuromodulation therapy (Figure 2A right). In AI-based closed-loop systems,[14,93–94] after initial signal sensing and processing, the data contributes to big data construction. AI algorithms, often through neural networks, learn from this data and continuously optimize the system's response. This process enables the system to make more informed decisions, adjusting the controller's output in an optimized manner. AI's capability to analyze vast datasets and learn from complex patterns allows for a level of precision and personalization previously unattainable. Each of these developmental stages reflects a deeper integration of technology with combining interdisciplinary science and engineering. The development from static, predetermined systems to dynamic, learning systems underscores the potential of technology to not only interface with biological systems but to adaptively treat and manage various diseases.

For examples on advanced conventional closed-loop systems, Choi et al. discussed a transient closed-loop system combining a network of wireless body-integrated devices with a bioresorbable pacemaker for autonomous electrotherapy (Figure 2B).[40] This system is used for cardiac pacing, where it provides autonomous rate-adaptive pacing capabilities, demonstrated in studies involving rats, canines, and human hearts. The system comprises several components including a bioresorbable pacemaker, power harvesting unit, skin-interfaced sensors for physiological monitoring, and a wireless module for power transfer. It addresses limitations of conventional pacing systems by eliminating physical tethers and reducing patient burden, ultimately dissolving in the body after a defined operational period. Otherwise, Kathe et al. described a wireless, closed-loop optogenetics system for spinal cord modulation in mice (Figure 2C).[25] The system incorporates microscale light-emitting diodes (μ-LEDs) and a stretchable strain gauge, conforming to the spinal cord's dura mater. This allows for precise, real-time modulation of neurons and pathways across the entire dorsoventral spinal cord. The system also integrates a head-mounted wireless platform for power and control, enabling experiments in untethered mice. The research demonstrates its utility in studying the control of locomotion, both in healthy and spinal-cord-injured mice, by selectively targeting and modulating specific neuronal subtypes and pathways. Lastly, Mickle et al. introduced a wireless closed-loop system for optogenetic peripheral neuromodulation (Figure 2D).[53] The study focuses on managing bladder function in rats through a fully implantable system comprising microscale inorganic light-emitting diodes (μ-ILEDs) and a low-modulus stretchable strain gauge. The μ-ILEDs optogenetically control inhibitory opsins expressed in bladder sensory afferents, while the strain gauge monitors bladder filling and voiding. The system operates in real-time, using data algorithms to identify and normalize pathological bladder behavior. This approach offers advantages over traditional electrical stimulation methods by targeting specific neuronal populations, providing a promising avenue for treating bladder dysfunction with minimal invasiveness and high specificity.

In studies on AI-based closed-loop systems, Topalovic et al. discussed the development of the Neuro-stack, a wearable,

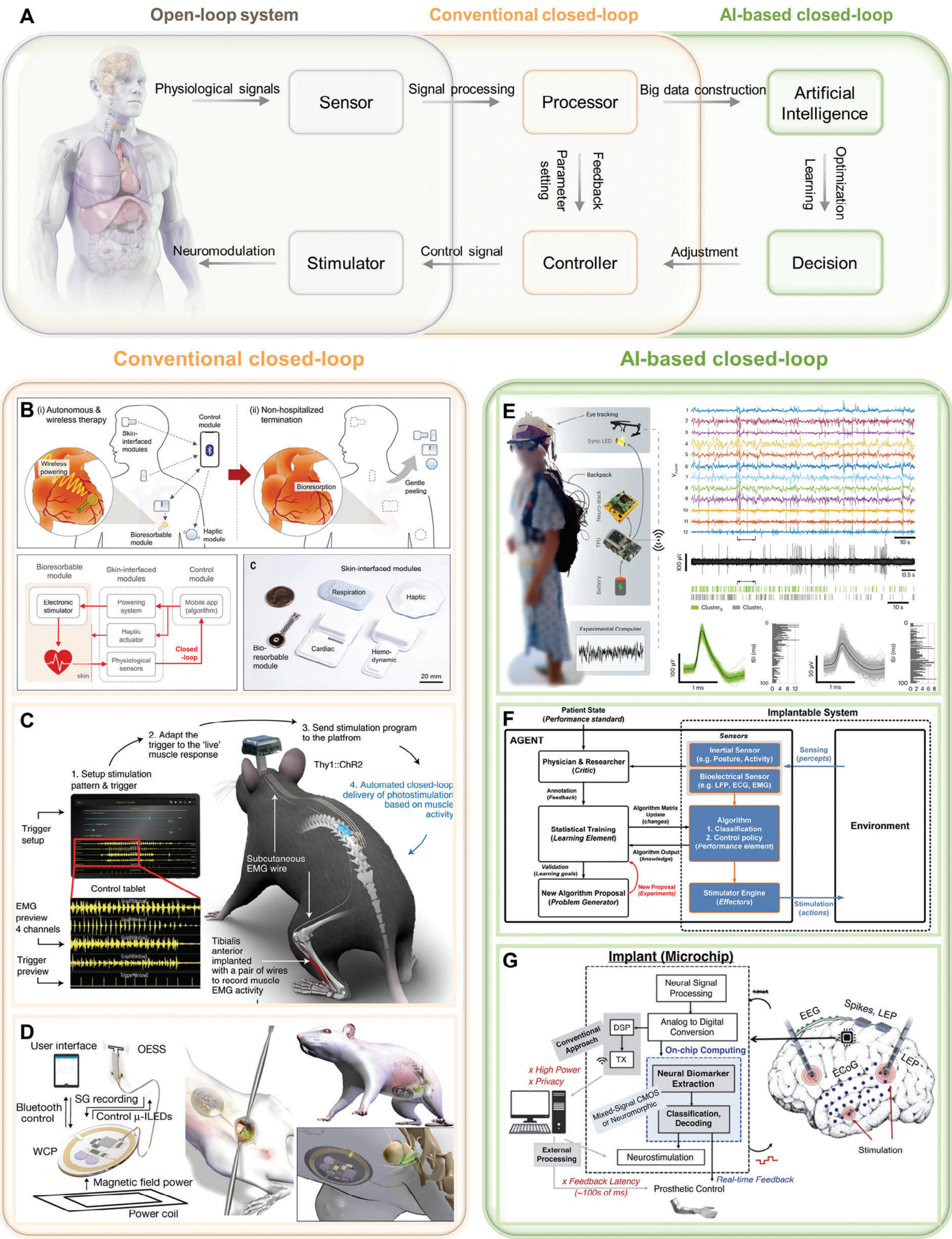


Figure 2. Therapeutic implantable closed-loop neuromodulation devices. A) Block diagram of open-loop, conventional closed-loop, and AI-based closed-loop systems. B) Transient closed-loop system with a bioresorbable pacemaker for autonomous electrotherapy in cardiac pacing. Reproduced with permission.[40] Copyright 2022, American Association for the Advancement of Science. C) Wireless optogenetics system for spinal cord modulation, enabling locomotion studies in untethered rodents. Reproduced with permission.[25] Copyright 2022, Nature Publishing Group. D) Wireless system for optogenetic peripheral neuromodulation in rats for targeting bladder. Reproduced with permission.[53] Copyright 2019, Nature Publishing Group. E) A

bidirectional closed-loop neuromodulation system (Figure 2E).[14] It is capable of recording single-neuron and local field potential (LFP) activity in freely moving humans. The system interfaces with implanted electrodes and enables simultaneous recording and stimulation. Key features include its compact size, flexible stimulation capabilities, and a high degree of programmability. The research shows the system's utility in recording neural activities during ambulatory behavior and its potential in developing personalized neuromodulation therapies for brain disorders. The study also underscores the importance of phase-locked stimulation in enhancing the effectiveness of neuromodulation therapies. In another study, Afshar et al. provided a comprehensive exploration of a closed-loop neuromodulation system integrated with artificial intelligence (Figure 2F).[93] The system's design includes an implanted sensing and stimulation device, an external tool for prototyping classifier and control-policy algorithms, and real-time telemetry for device firmware updates and monitoring. The system was tested in a large animal model focusing on hippocampal dynamics, where biomarkers of observed states and transfer functions of different stimulation amplitudes were studied. The findings revealed that moderate levels of stimulation suppress hippocampal beta activity, while higher levels produce seizure-like activities. The study demonstrates the system's capability to continuously adjust stimulation amplitude for desired network effects, emphasizing its potential for various neurological disorders. For future AI-based closed-loop systems, Yoo et al. discussed advancements in neural interface systems featuring on-chip computing capabilities (Figure 2G).[94] It focuses on integrating machine learning and neuromorphic architectures into these systems, which are crucial for developing next-generation clinically viable neural interfaces. The paper reviews recent developments in "on-chip" machine learning and neuromorphic architectures, highlighting their significance in creating low-power, smart, miniaturized therapeutic devices for a wide range of neurological and psychiatric disorders. The study emphasizes the trend of combining artificial intelligence with modern neural interfaces, leading to new generations of devices optimized for real-time and on-site processing of neural activity without the need for power-demanding telemetry.

3. Requirements for Bioelectronic Implantable Devices

In the upcoming chapter, we delve into the intricate world of bioelectronics, categorizing and examining the fundamental elements that constitute these advanced implantable devices. This comprehensive exploration aims to elucidate the significance of each component, its evolution, and the trajectory of its development (**Figure 3**).

The starting point for this discussion is the concept of "Operationality," which encompasses three main aspects: powering, functionality, and communication. The evolution of powering methods, transitioning from wired systems to advanced battery-free operations, promotes the technological strides made in ensuring device usability and effectiveness. Similarly, the functionality of these devices, whether for stimulation, recording, or both, represents the ability of implantable devices. The shift from wired to wireless communication epitomizes the advancements towards more patient-centric and less invasive treatments.

The "Integrity" of these devices is dissected through modality, integration, and performance. Modalities in bioelectronic devices have evolved from single-function units to complex systems capable of multiple forms of sensing and stimulation. Integration, from basic electrodes to fully autonomous systems, creates more sophisticated and clinically viable devices. Performance levels, from passive to AI-driven, indicate developmental phases of operational ability, with AI-driven devices representing the zenith of current technological advancements.

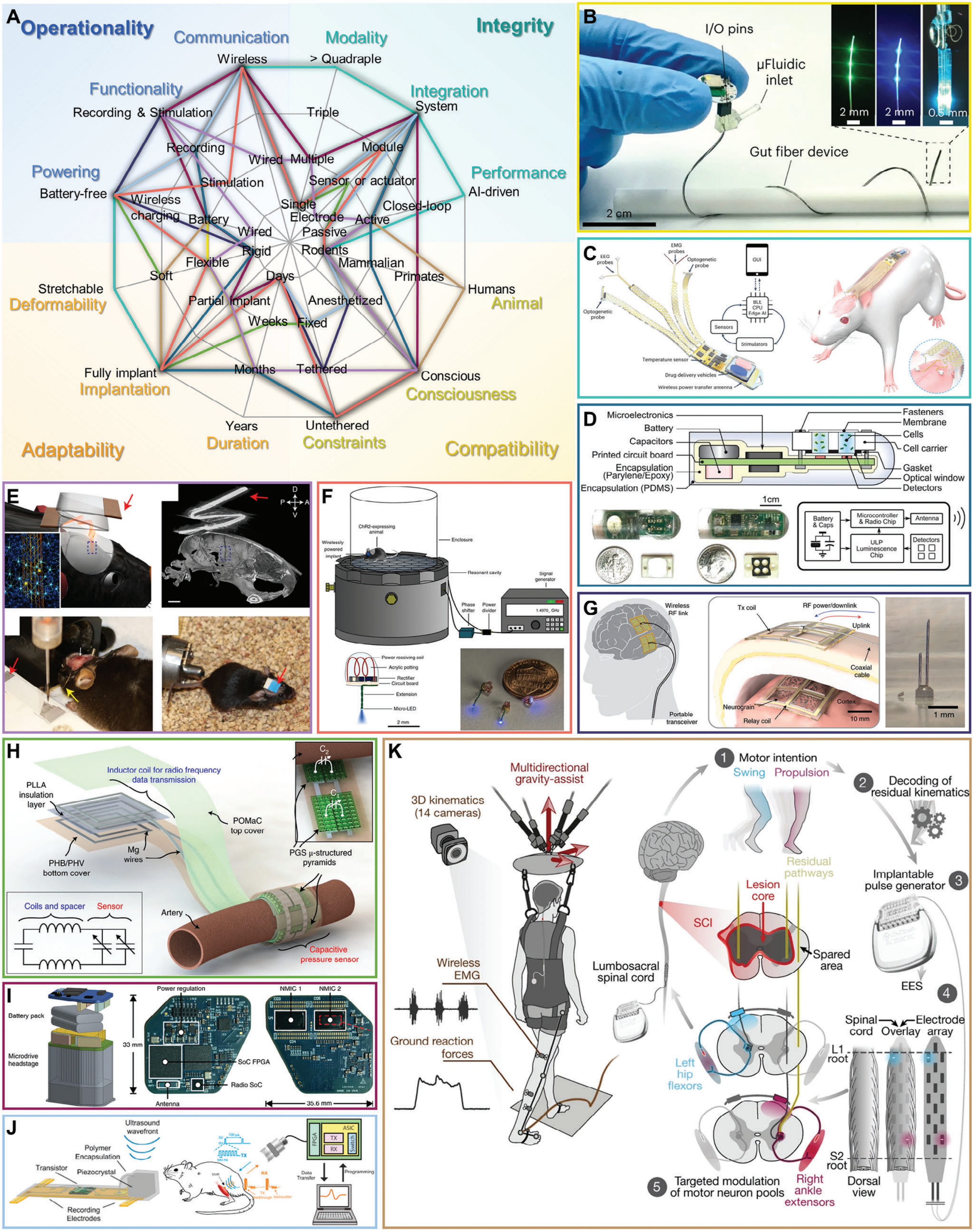
"Adaptability," another important aspect, is sub-categorized through deformability, implantation, and duration. Deformability, from rigid to stretchable designs, addresses the need for devices that align with the dynamic mechanical properties of anatomy. Implantation, spanning from partial to fully implantable devices, reflects the progression toward minimizing external dependencies. Duration, ranging from days to years, indicates the operational lifespan, with longer durations signifying advancements in device reliability and patient care.

The "Compatibility" section assesses the suitability of these devices across different stages of animal testing, from rodents to humans, and consciousness states, from anesthetized to conscious applications. This analysis is vital for understanding the safety and efficacy of the devices in diverse biological systems and procedural contexts.

A key feature of our analysis is depicted in Figure 3, a spider web diagram categorizing these elements into stages, and **Table 3**, a summary of implantable devices. This visual representation not only aids in understanding the complexity of these devices but also illustrates the interconnectedness of their components. By connecting the corresponding elements, the diagram vividly portrays the latest and most advanced forms of bioelectronic implantable devices. This section promises to be an insightful journey through the domains of bioelectronic implantable devices, providing a detailed, methodical, and academically rigorous analysis of their key components and developmental trajectory.

In operationality, studies such as those in Figure 3B,F showcase advances in powering methods from wired to battery-free operations, underscoring significant strides in device usability and effectiveness. For instance, Figure 3G,I discusses the integration of wireless power transmission and advanced communication protocols, which highlight evolutionary trends in the operational aspects of these devices. For integrity, the transition from single-function units to complex systems capable of multiple forms of sensing and stimulation is well illustrated through research in Figure 3C,H, where multifunctional devices with enhanced inte-

wearable neuromodulation system enabling bidirectional interaction in freely moving humans. Reproduced with permission.[14] Copyright 2023, Nature Publishing Group. F) Platform for developing closed-loop neuromodulation systems integrated with AI. Reproduced with permission.[93] Copyright 2013, Frontiers Media S.A. G) Integration of machine learning and neuromorphic computing architectures in neural interface systems. Reproduced with permission.[94] Copyright 2021, Elsevier.


A
Operationality
Communication
Modality
Integrity
Wireless
> Quadraple
Functionality
Recording & Stimulation
Triple
Integration
System
Recording
Wired
Multiple
Module
Powering
Battery-free
Stimulation
Sensor or actuator
Performance
AI-driven
Wireless charging
Battery
Single Electrode
Closed-loop
Active
Wired
Passive
Rigid
Rodents
Flexible
Mammalian
Soft
Days
Primates
Stretchable
Deformability
Partial implant
Anesthetized
Humans
Animal
Weeks
Fixed
Fully implant
Implantation
Months
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Conscious
Consciousness
Years
Duration
Untethered
Constraints
Adaptability
Compatibility
B
I/O pins
μFluidic inlet
2 mm
2 mm
0.5 mm
Gut fiber device
2 cm
C
GUI
Sensors
Stimulators
D
Microelectronics
Battery
Capacitors
Printed circuit board
Encapsulation (Parylene/Epoxy)
Encapsulation (PDMS)
Fasteners
Membrane
Cells
Cell carrier
Gasket
Optical window
Detectors
1cm
Battery & Caps
Microcontroller & Radio Chip
Antenna
ULP Luminescence Chip
Detectors
E
F
G
Tx coil
RF power/downlink
Uplink
Coaxial cable
Cortex
Neurograin
Relay coil
10 mm
1 mm
H
Inductor coil for radio frequency data transmission
PLLA insulation layer
POMaC top cover
Mg wires
PHB/PHV bottom cover
PGS μ-structured pyramids
Coils and spacer
Sensor
Artery
Capacitive pressure sensor
I
Power regulation
NMIC 1
NMIC 2
Battery pack
33 mm
Microdrive headstage
SoC FPGA
Radio SoC
Antenna
35.6 mm
J
Ultrasound wavefront
Polymer Encapsulation
Transistor
Piezocrystal
Recording Electrodes
Data Transfer
Programming
K
Multidirectional gravity-assist
3D kinematics (14 cameras)
1 Motor intention
Swing
Propulsion
2 Decoding of residual kinematics
Residual pathways
Lesion core
SCI
Spared area
Implantable pulse generator 3
Wireless EMG
Lumbosacral spinal cord
EES 4
Ground reaction forces
Left hip flexors
Spinal cord
Overlay
Electrode array
L1 root
S2 root
Dorsal view
5 Targeted modulation of motor neuron pools
Right ankle extensors

gration and performance metrics are elaborated. In adaptability, Figure 3D,E describes devices' adaptability in terms of deformability and implantation, showing how devices are designed to be less invasive and more compliant with anatomical dynamics. In compatibility, studies in Figure 3K address the compatibility of devices across different stages of animal testing, indicating a thorough evaluation of safety and efficacy that is critical for moving toward human applications.

3.1. Operationality: Powering, Functionality, Communication

3.1.1. Powering

Powering is the starting point of the operation in implantable devices. The evolution of powering methods reflects the technological advancements and design priorities within the field.[158] Initially, implantable devices were powered through wired connections. This method, being straightforward and reliable, ensures a consistent and stable power supply. However, it comes with significant disadvantages, including the risk of infection at the entry point of the wire, the potential for wire breakage, and the limitation on mobility, thereby confining its use to acute experiments or short-term applications. To overcome the limitations of wired systems, battery-powered devices were developed.[159] These devices offer greater mobility and eliminate the need for external wires. The advancement in battery technology, particularly the development of lithium-polymer batteries and all-solid-state batteries, has significantly improved the feasibility of these devices. Nonetheless, batteries have a finite lifespan and require periodic recharging or replacement, which can be a major drawback for long-term implantation. To address the limitations of battery lifespan and the need for recharging, wireless charging through inductive coupling became a popular method.[15,160] This method allows charging without direct physical connections, reducing the risk of infections and improving patient comfort. However, high-power wireless charging is limited by the need for close proximity between the charging device and the implant, leading to potential immobilization during charging. Additionally, there are concerns about heat generation, which can be detrimental to surrounding biological tissues. The most advanced and emerging method in powering implantable devices is battery-free operation.[161–163] These devices wirelessly received power by external electromagnetic fields,[164] ultrasound,[165–166] or light[167] through the skin. This approach eliminates the weight of the battery and associated risks such as explosions or electrolyte leakage. It also minimizes heat generation since the transmission system only needs to provide the power necessary for device operation. However, providing power wirelessly to implanted devices still faces physical limitations, such as the range and efficiency of power transmission at large distance.

3.1.2. Functionality

The functionality of implantable bioelectronic devices impacts their design and application. These devices can be categorized based on their primary functions: stimulation, recording, and a combination of both. Stimulation is a foundational function in many implantable devices for the treatment of various diseases. This process involves the flow of control signals from the device's central system to the electrodes, which then deliver therapeutic electrical stimulation to targeted areas of the body. Devices designed solely for stimulation are relatively straightforward from an engineering perspective, as they primarily require a reliable power source and control mechanism to deliver the necessary electrical impulses. However, recording function is more complex than stimulation. Recording in implantable bioelectronic devices means capturing physiological signals from the body. This function is more complex than stimulation, as it requires sophisticated signal processing algorithms to extract meaningful data from the recorded signals. The flow of information is from the electrodes to the device's central processing unit. Devices with recording capabilities are used in diagnostics and monitoring, providing valuable data on various health parameters. They can measure vital signs, neural activity, or other physiological markers, aiding in disease monitoring and management. The most advanced implantable bioelectronic devices combine both recording and stimulation functions. These devices can diagnose conditions based on recorded biosignals and then provide appropriate therapeutic stimulation based on the recording. This dual functionality enables a closed-loop system where the device can adapt its response based on real-time physiological data.[168]

3.1.3. Communication

Communication dictates how these devices transmit and receive data. Fundamentally, wired communication has been the most reliable and fastest method for data transmission in implantable devices. It is particularly advantageous for transmitting large volumes of data at high speeds, as required in applications like high-density brain neural signal monitoring,[169]

Figure 3. Requirements and advances of implantable devices. A) A spiderweb illustrating comparative results of fundamental components across various implantable device studies, with the web's color aligned to the corresponding study. B) Wireless, multifunctional fibers system capable of optical stimulation, drug delivery, recording electrophysiological signals and temperature. Reproduced with permission.[153] Copyright 2023, Nature Publishing Group. C) A wireless and battery-less device with autonomous closed-loop system. Reproduced with permission.[21] Copyright 2023, Nature Publishing Group. D) An ingestible device for biomolecular detection via biosensor bacteria and luminescence readout. Reproduced with permission.[154] Copyright 2018, American Association for the Advancement of Science. E) A flexible mesh electronics for single-unit recordings and electrical stimulation. Reproduced with permission.[155] Copyright 2016, Nature Publishing Group. F) An implantable, wireless optogenetic device powered by RF power source. Reproduced with permission.[84] Copyright 2015, Nature Publishing Group. G) Wireless system combining RF energy harvesting to record ECoG signals and provide intracortical stimulation. Reproduced with permission.[156] Copyright 2021, Nature Publishing Group. H) Biodegradable, wireless pressure sensor for blood flow monitoring. Reproduced with permission.[41] Copyright 2023, Nature Publishing Group. I) A wireless device capable of closed-loop control with on-board processing. Reproduced with permission.[20] Copyright 2019, Nature Publishing Group. J) A wireless ultrasonic system capable of recording EMG and electroneurogram signals. Reproduced with permission.[26] Copyright 2016, Cell Press. K) An implanted pulse generator for the control of paralyzed muscles in SCI injury. Reproduced with permission.[157] Copyright 2018, Nature Publishing Group.

Table 3. Summary of bioelectronic implantable devices.

Compatibility			Adaptability			Integrity			Operationality			Refs.
Animal	Consciousness	Constraints	Duration	Implantation	Deformability	Performance	Integration	Modality	Powering	Function	Communication	
Rodent	Conscious	Untethered	Months	Partial implant	Flexible	Active	System	> Quadruple	Battery	Recording & Stimulation	Wireless	[153]
Rodent	Conscious	Untethered	Months	Fully implant	Stretchable	AI-driven	System	> Quadruple	Battery-free	Recording & Stimulation	Wireless	[21]
Mammalian	Conscious	Untethered	Months	Fully implant	Rigid	Active	System	Single	Battery	Recording	Wireless	[154]
Rodent	Conscious	Tethered	Months	Partial implant	Flexible	Active	Electrode	Multiple	Wired	Recording & Stimulation	Wired	[155]
Rodent	Conscious	Untethered	Days	Fully implant	Flexible	Passive	Module	Single	Battery-free	Stimulation	Wireless	[156]
Rodent	Anesthetized	Tethered	Days	Partial implant	Rigid	Active	System	Multiple	Battery-free	Recording & Stimulation	Wireless	[41]
Rodent	Anesthetized	Fixed	Weeks	Fully implant	Soft	Passive	Sensor	Single	Battery-free	Recording	Wireless	[20]
Primates	Conscious	Untethered	Days	Partial implant	Rigid	Closed-loop	System	Multiple	Battery	Recording & Stimulation	Wireless	[26]
Human	Conscious	Untethered	Months	Fully implant	Soft	Active	System	Single	Battery	Recording	Wireless	[157]

which demands high sampling rates across numerous channels. However, the use of wires presents significant limitations, including the risk of infection at the penetration site, the physical constraint of wires which can restrict subject movement, and the potential for wire damage or breakage over time. Wireless communication eliminates the physical constraints of wires, offering greater flexibility of movements. This method of communication is achieved through various means such as ultrasonic waves,[26] light,[170] near-field communication,[171] and radio frequencies.[172] Wireless communication is indispensable for the development of fully implantable devices and is made easier with the availability of small, commercial integrated circuits (ICs). However, compared to wired communication, wireless communication typically has slower data transmission rates, so it can be limited when dealing with large-capacity and fast signals. Despite these limitations, wireless communication technology is continuously used for implantable device due to its ability to operate at low power, and it is evolving to meet the high data rate demands necessary for efficiently transmitting large volumes of biosignals.

3.2. Integrity: Modality, Integration, Performance

3.2.1. Modality

Modality refers to the types of interactions they offer, encompassing mechanical, electrical, thermal, optical, and chemical measurements, and electrical, optical, and chemical neural stimulations. The complexity of modality ranges from single to more than quadruple, enhancing variety of the device to diagnose and treat various conditions. This involves a device having a single type of sensor or stimulation method. Although limited in scope, it is highly specialized and efficient for specific functions. Devices with multiple modalities incorporate several types of sensors or stimulation methods, improving their diagnostic and treatment capabilities. This approach allows for a more comprehensive understanding of complex physiological interactions and can provide more detailed treatment options. The most advanced devices integrate three or more types of recording or stimulation technologies. This enables a more synergistic approach to diagnosis and treatment. For example, combining thermal and chemical sensors can yield more precise diagnostics in infection detection, as both C-reactive protein levels and body temperature might be elevated.[173] Similarly, measuring brain commands and corresponding muscular responses offers a deeper insight into neuromuscular functions.[174] The development of devices with multiple modalities presents engineering challenges, requiring efficient circuitry, communication, and integration of various sensors and stimulation modules. As these devices become more complex, they increasingly rely on internal programs and active control systems, necessitating advanced power management and data processing capabilities. Therefore, the modality of implantable bioelectronic devices defines their functionality, complexity, and application scope. As the field advances, the integration of multiple modalities in a single device will play a significant role in the evolution of personalized and precise medical treatments.

3.2.2. Integration

Integration implies how effectively various components work together. The levels of integration, ranging from the simplest electrode to a fully integrated system determine practicality of the device. At the basic level, electrodes serve as the primary interface, conducting measurements and stimulations. However, their functionality is limited when not integrated with other components. The next level involves sensors and actuators, which are essentially evolved forms of electrodes designed for specific functions. Their integration allows for more active interactions with biological systems. Moving further, a module encompasses functionalities like signal pre-processing or stimulus delivery, integrating multiple components into a modular unit. The highest level of integration is a system, where all elements, including measurement, processing, conversion, and communication, are cohesively combined into a single unit capable of programmable operation. This hierarchy from electrode to system-level integration emphasizes the progression towards more practical implantable devices, capable of higher clinical applicability.

3.2.3. Performance

Performance signifies how these devices function and operate. Performance can be categorized into four levels: passive, active, closed-loop, and AI-driven. Passive devices are the simplest form of implantable devices, requiring an external power or signal source to operate. They are limited in functionality but are minimally invasive because they often can be made with small size. Active devices, equipped with internal circuitry and a control unit, can process signals from various sensors or generate stimulation waveforms. They represent a more advanced level of implantable bioelectronics. Closed-loop devices operate on a feedback basis, adjusting their stimulation based on real-time measurements. This approach mimics the body's natural homeostatic mechanisms, making closed-loop devices particularly effective in continuous and responsive treatment scenarios. The most advanced in the spectrum, AI-driven devices utilize machine learning algorithms to analyse measured signals and make autonomous decisions for optimal treatment. This technology represents the cutting-edge in implantable bioelectronic devices.

3.3. Adaptability: Deformability, Implantation, Duration

3.3.1. Deformability

Deformability in bioelectronic devices affects tissue damage risk and device stability when implanted in living bodies. Rigid devices, often made from hermetically sealed metal or plastic, offer robust protection against biofluid and mechanical stress. However, their rigidity can lead to continuous pressure on soft biological tissues, potentially causing damage. To address this, the design of flexible devices has emerged, which conforms to the natural curvature of living tissues. These devices are particularly suitable for implantation in body areas that experience repeated folding and extension. Moreover, devices made from soft materials with an elastic modulus akin to biological tissues avoid exerting undue pressure within the body, enhancing long-term stability. The pinnacle of this development is stretchable devices, which offer flexibility and softness, and importantly, the ability to stretch. This attribute allows them to maintain stability and alignment with the movement of living tissues with minimized resistance. Compliant mechanical design ensures the stability of both biological tissues and the device. However, maintaining consistent device performance despite mechanical deformation remains a challenge.[175,176] Therefore, it is required to develop and identify materials with deformable structures that can withstand such deformations while retaining their functional integrity for more compatible with the dynamic nature of anatomy and physiology.

3.3.2. Implantation

Implantation refers to the degree to which a device is embedded within the body. Partially implantable devices only a portion of the device is implanted within the body, while other parts remain external. Partial implantation is typically easier to achieve compared to full implantation but may restrict subject's movement and increase the risk of infection and damage at the surgical site due to external connections. Fully implantable devices represent the most advanced form of implantation, where all components of the device are embedded within the body. The development of fully implantable devices is essential for ensuring subject freedom of movement and removing potential risks associated with external connections. However, achieving full implantation poses significant challenges, including the miniaturization and integration of all components, such as power sources and communication systems, without increasing the device's size.

3.3.3. Duration

Duration means the operational lifespan of devices once implanted in the body. The duration for which a device can function effectively is one of the major specifications, impacting patient care and device maintenance. Devices designed for a duration of days are typically used for short-term monitoring or therapeutic interventions. These devices are ideal for acute medical situations where temporary monitoring or treatment is required. Their short lifespan means they can be less robust. When a device is intended to last for weeks, it's usually aimed at intermediate medical needs, such as postoperative monitoring or short-term therapy. This duration allows for more comprehensive data collection and therapeutic impact than day-long devices, but still does not require the long-term commitment or durability of devices meant for months or years. Devices with a lifespan of months are used for more prolonged treatments or monitoring, such as chronic condition management. The extended duration demands higher reliability and sturdier construction to withstand longer periods within the body. These devices need to balance longevity with minimal impact on the body, ensuring patient comfort and safety over extended periods. The most advanced implantable bioelectronic devices are designed to last for years. These are typically used for long-term chronic condition management or permanent therapeutic interventions. Their design requires the highest level of durability, biocompatibility, and minimal maintenance, as they are intended to function effectively for extended periods without the need for replacement or significant intervention. Longer-duration devices need to address challenges like power management,[177] material degradation,[178–179] and long-term biocompatibility,[180–181] making them more complex but also more impactful in managing health conditions over time.

3.4. Compatibility: Animal, Consciousness, Constraints

3.4.1. Animal

Animal compatibility represents the suitability of these devices for use in different animal models during development, research, and clinical phases. Rodent models, primarily mice and rats, are the most basic and commonly used animal models in biomedical research. They offer several advantages, including their small size, ease of handling, and well-understood genetics and physiology. Rodent models are essential for initial testing of implantable devices, providing valuable data on biocompatibility, efficacy, and potential side effects.[182] Larger mammalian models,[183] such as pigs and sheep, are used after successful rodent testing. These animals have physiological systems more similar to humans than rodents. Studies in mammalian models help refine the device design and provide more reliable data on how the device will perform in human bodies. Primates, being closer to humans in terms of anatomy and physiology, are used for advanced testing of implantable bioelectronic devices.[184] Research in primate models is essential for assessing complex interactions between the device and the nervous system or other organ systems, offering insights that are more directly translatable to human applications. The ultimate goal of animal compatibility in implantable bioelectronics is to develop devices that are safe and effective for human use. Human trials are the final stage, where the device is tested in its intended user group. Data from human trials are crucial for obtaining regulatory approvals and for making the device available for clinical use.

3.4.2. Consciousness

Consciousness indicates the state of awareness of the subject during the use of these devices. Anesthetized applications of implantable devices involve subjects who are not conscious during the procedure. This approach is typically used in surgical implantations or therapies that might cause discomfort or require immobility. Anesthetized applications allow for more invasive procedures and can enable precise placement or calibration of the device without subject-induced variability. However, the lack of immediate behavioral feedback can be a limitation, requiring extensive preoperative planning and postoperative monitoring. In contrast, when implantable devices are used in conscious subjects, it implies that the subjects are awake and aware during the procedure or therapy. This state is needed for devices that require active subject participation or feedback, such as neuroprosthetics[185] or brain–computer interfaces.[186] In conscious applications, the device must be designed to ensure subject comfort and minimal interference with normal activities. It also allows for real-time monitoring of the subject‘s responses to the device, providing valuable data for adjusting treatments and improving device design. Understanding the requirements and implications of using implantable bioelectronic devices in both conscious and anesthetized states is vital for their successful application.

3.4.3. Constraints

Constraints imply the physical limitations or freedoms in the context of the subject's mobility during the use of these devices. Fixed constraint involves the subject being physically restrained or fixed in position during the use of the device. An example is experiments measuring brain nerve signals where a rat's head is fixed in a stereotaxic frame.[187] This setup is effective for precise and stable measurements but can be invasive and restrictive. In clinical settings, fixed constraints are generally limited to diagnostic or surgical procedures where patient mobility needs to be controlled. Tethered constraints refer to scenarios where the subject has some mobility but remains connected to an external component, such as a monitoring system or power source, via a physical connection. This allows for more freedom of movement compared to fixed constraints but still limits the range of activities that can be performed. It is commonly used in settings where continuous monitoring or power supply is necessary but complete immobilization is not required. Untethered constraints represent the ideal scenario where the subject has complete freedom of movement without any physical connection to external systems. This is achieved through wireless communication and power technologies with miniaturization of the device, allowing for normal activities and greater comfort. Untethered devices are particularly important in long-term monitoring and therapeutic applications, where minimally invasive and patient-friendly designs are crucial.

4. Physiological Signals Recording

In the evolving field of medical science, the imperative for bioelectronic devices in monitoring vital signals is increasingly recognized, especially in managing chronic diseases such as cardiovascular and neurological disorders.[36,188–192] The continuous monitoring of vital signs is essential for effective disease management. In bioelectronics, implantable devices address this need by offering real-time insights into the body's physiological state, enabling early detection and proactive intervention. This capability becomes increasingly crucial because of the rising incidence of chronic diseases, propelled by factors such as aging populations and lifestyle changes.[193–195] The ability of these devices to provide continuous, real-time data marks a significant leap from traditional episodic monitoring, offering a more dynamic and responsive approach to disease management.

The diversity of physiological signals and their importance cannot be overstated in the context of medical diagnosis. The human body, a complex network of systems, produces a range of signals that are key indicators of its health status. Mechanical signals like blood pressure provide insights into the cardiovascular system's functioning,[196–199] while thermal signals like body temperature can indicate metabolic or infectious conditions.[200–203] Electrical signals, such as those captured in electrocardiogram (ECG) and electroencephalogram (EEG), are crucial for assessing heart and brain health.[204–206] Optical signals, including tissue oxygenation measured through techniques like pulse oximetry, enable the monitoring of respiratory and circulatory health.[207–210] Chemical signals, like glucose levels, offer essential information about metabolic states and are crucial in managing conditions like diabetes.[211–213] The diverse array of these physiological signals, serving as direct or indirect biomarkers of health status, highlights the critical role of bioelectronic implantable devices in their measurement and monitoring.

Bioelectronic implantable devices measure bio-signals across multiple engineering stages. The initial stage entails the implementation of highly sensitive electrodes and precise sensors, designed to detect specific types of physiological signals. This precision is often achieved through advanced microfabrication technologies, allowing for the miniaturization and optimization of these components. Following signal detection, the data undergo a series of processing steps, including amplification to enhance signal strength, filtering to remove noise, and sophisticated processing to extract meaningful biomedical information. In recent years, it has become increasingly important to adopt cutting-edge signal processing techniques that incorporate artificial intelligence and machine learning.[214–217] These technologies allow for the interpretation of complex physiological data, transforming raw signals into actionable health insights.

In this context, bioelectronic implantable devices are reshaping the landscape of medical diagnostics, transitioning from traditional methods to more dynamic, real-time monitoring. This shift is crucial in the early detection and management of diseases, making these devices invaluable tools in modern medicine. This section further delves into the principles and types of devices employed in measuring these vital bio-signals, providing an encompassing overview of the technological foundations and innovations that underpin their diagnostic capabilities. It offers a comprehensive summary of the various bioelectronic devices, elucidating their design, operational mechanisms, and the types of bio-signals they measure, thereby laying the groundwork for understanding their integral role in modern diagnostic practices.

4.1. Mechanical Biophysiological Signals

Mechanical biophysiological signals originate from physical or mechanical changes within the body, encompassing a wide range of physiological activities. These signals are essential in medical diagnostics as they provide insights into the functioning and health of various bodily systems.

Sensors for these signals typically operate on principles like piezoelectricity,[218–220] capacitance,[221–223] and resistive strain.[124,224–225] Piezoelectric sensors utilize the piezoelectric effect, where certain materials generate an electrical charge in response to applied mechanical stress.[226] In crystallography, the piezoelectric effect is attributed to the asymmetrical nature of molecular chains or crystal structures.[227] This makes them highly sensitive to changes in pressure or vibration, ideal for dynamic physiological monitoring. However, their sensitivity can be a drawback, as they might register false signals from non-relevant vibrations.[226] Capacitive sensors work on the principle of capacitance change. When the distance between two conductive plates or the dielectric constant changes due to mechanical deformation, the capacitance changes.[228] This property is useful for detecting static or slow-changing phenomena like blood pressure.[229] Capacitive pressure or strain sensors, despite their high sensitivity and low power consumption, often face challenges related to susceptibility to external electromagnetic interference. This can compromise the accuracy of the sensor readings. Additionally, they typically require complex signal conditioning circuitry, which can increase both the cost and the complexity of the system.[230] Resistive strain sensors detect changes in electrical resistance due to strain. When stretched or compressed, the conductive path in these sensors changes, altering their resistance.[231] This principle is effective for measuring static strains. However, they often suffer from long-term stability issues and require calibration.[232]

The following sections will delve into specific types of mechanical biophysiological signals: hemodynamics, pressure, and strain. Hemodynamic signals provide crucial information about blood circulation and cardiovascular functions, while pressure and strain measurements inform about the physical forces exerted on or within the body.

4.1.1. Hemodynamics

Central to hemodynamics are key signals such as blood pressure and blood flow. They provide insights into the heart's pumping efficiency and the vascular system's integrity. Abnormalities in these signals can be early indicators of cardiovascular diseases, one of the leading causes of mortality globally.[233] Continuous monitoring of hemodynamic parameters is also vital in critical care settings, where rapid changes in blood pressure or flow can be life-threatening. Blood pressure, the force exerted by circulating blood on the walls of blood vessels, is a primary indicator of cardiovascular health. It is crucial in diagnosing and managing conditions like hypertension, which can lead to serious complications like stroke or heart failure.[234] Blood flow, on the other hand, refers to the volume of blood moving through vessels over a given period and is essential in assessing the efficiency of circulatory function. Disruptions in blood flow can lead to critical conditions such as ischemia or vascular diseases.[235–236] Recent advancements in bioelectronic implantable devices have significantly improved the accuracy and convenience of hemodynamic monitoring. These devices employ various sensors and measurement methods to provide real-time data on blood pressure and flow, enabling healthcare providers to make timely and informed decisions.[21,42,60]

Kwon et al. reported a novel bioelectronic implantable device for hemodynamic monitoring, utilizing silicon nanomembrane (Si-NM) sensors for enhanced sensitivity (**Figure 4A**).[21] This device, notable for its battery-less design, employs a Bluetooth Low Energy (BLE) communication system and wireless power transfer technology for operation. It is specifically engineered to monitor key hemodynamic parameters, including vascular pressure, flow rate, and temperature. Tested in large animal models, it demonstrates comparable performance to conventional clinical tools, indicating its potential in cardiac disease management.

The CardioMEMS system, as the FDA-approved remote monitoring system for heart failure (HF), represents a

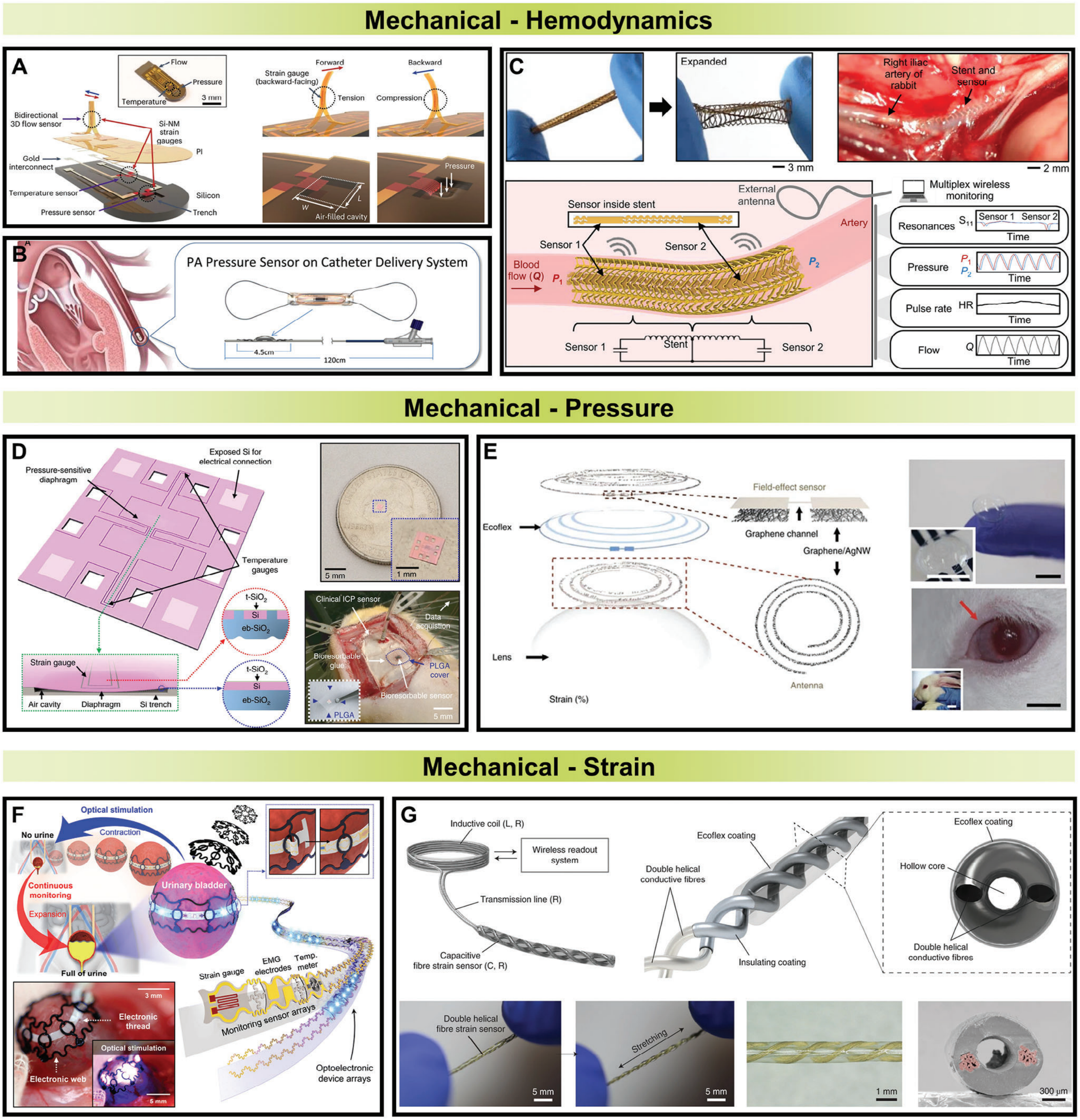


Figure 4. Bioelectronic implantable devices for mechanical biosignal recording. A) Silicon nanomembrane sensor-based implantable device for battery-less hemodynamic monitoring, including vascular pressure, flow rate, and temperature. Reproduced with permission.[41] Copyright 2023, Nature Publishing Group. B) The FDA-approved remote heart failure monitoring device, utilizing a pulmonary artery pressure sensor. Reproduced with permission.[60] Copyright 2020, Wiley-VCH. C) A fully implantable, wireless, and battery-less vascular monitoring system with a multimaterial inductive stent and soft capacitive sensors for real-time hemodynamic assessment, monitoring arterial pressure, pulse rate, and flow. Reproduced with permission.[42] Copyright 2022, American Association for the Advancement of Science. D) Bioresorbable silicon nanomembrane pressure sensors for intracranial pressure monitoring for chronic disease management. Reproduced with permission.[2] Copyright 2019, Nature Publishing Group. E) Wireless intraocular pressure sensors on soft contact lenses, merging transparency and stretchability for ocular health monitoring. Reproduced with permission.[61] Copyright 2017, Nature Publishing Group. F) Bioelectronic device for real-time urinary bladder activity monitoring using a strain gauge, designed to accommodate volume changes and enhance clinical applications in bladder health. Reproduced with permission.[50] Copyright 2020, American Association for the Advancement of Science. G) Stretchable and suturable fiber sensors for wireless connective tissue strain monitoring. Reproduced with permission.[58] Copyright 2021, Nature Publishing Group.

significant development in the management of cardiovascular condition (Figure 4B).[60] It utilizes a Cardio-Microelectromechanical system (CardioMEMS) for implantable pulmonary artery pressure (PAP) monitoring. The key feature of this system is its sensor implanted in the pulmonary artery, which monitors changes in PAP and communicates wirelessly to an external analyzer. The data is then uploaded to a web-based interface, allowing clinicians to track patient results and manage their condition effectively. Clinical studies have demonstrated the CardioMEMS system's efficacy in reducing heart failure-related hospitalizations and improving patient outcomes. For instance, the GUIDE-HF randomized trial included 1000 patients and showed a significant 19% reduction in heart failure hospitalizations. Similarly, the US Post-Approval Study involving 1200 patients reported a 57% reduction in HF hospitalizations. European studies, like the MEMS-HF study, further corroborate these findings, highlighting the system's effectiveness across different healthcare environments. The CardioMEMS system's success is partly due to its direct monitoring capability, offering a more accurate and real-time assessment of heart function compared to other device-based monitoring tools. This system represents a novel approach in HF management, integrating advanced sensor technology and telemonitoring strategies to enhance patient care in both acute and chronic HF scenarios.

Herbert et al. present a fully implantable, wireless, and batteryless electronic system for vascular monitoring (Figure 4C).[42] The system features a multi-material inductive stent, integrated with soft capacitive sensors, designed for the multiplexed sensing of arterial pressure, pulse rate, and flow. Utilizing advanced aerosol jet-printing technology, these flexible sensors are crafted for durability and effectiveness, even when subjected to bending. The device's functionality is showcased through artery model validations and an in vivo rabbit study, indicating its practical application in diverse vascular environments. This innovation in sensor design and integration within the vascular system offers enhanced capabilities for real-time hemodynamic monitoring, addressing the complexities of vascular disease management.

4.1.2. Pressure

Understanding and accurately monitoring various types of body pressures are fundamental in modern medical practice, significantly impacting the management of a wide range of critical health conditions. Intracranial pressure (ICP) is a key indicator of brain health, particularly crucial in managing conditions like traumatic brain injury, meningitis, and hydrocephalus. Elevated ICP can lead to brain herniation and death, making its monitoring vital in neurosurgical and intensive care settings.[237] Cerebral perfusion pressure (CPP), which is the difference between mean arterial pressure and ICP, is equally significant. Maintaining optimal CPP is essential to ensure adequate brain tissue perfusion, especially in patients with head trauma.[238] Intraocular pressure (IOP) is another vital measurement, primarily in the monitoring and management of glaucoma.[239] Elevated IOP is a significant risk factor for glaucoma, potentially leading to optic nerve damage and irreversible blindness.[240] Regular monitoring of IOP is essential for early detection and timely treatment to prevent vision loss. Additionally, joint pressure monitoring is crucial in orthopedics and rheumatology, particularly for conditions affecting the knees, hips, and elbows.[241] It provides vital information about the health and function of synovial joints, aiding in the monitoring and management of arthritis, joint effusions, and other joint-related disorders. Elevated joint pressure can indicate inflammation, fluid accumulation, or traumatic injury, necessitating prompt medical intervention. Continuous monitoring of joint pressure, especially in patients with chronic joint diseases or post-surgical recovery, can significantly aid in treatment planning, pain management, and rehabilitation strategies. Also, monitoring of intra-abdominal pressure is crucial in critically ill patients, particularly for the monitoring and management of abdominal compartment syndrome.[242] Increased intra-abdominal pressure can significantly impact organ function, leading to severe complications like renal failure and decreased cardiac output.

Shin et al. reported on bioresorbable pressure sensors using silicon nanomembrane (Si-NM) and thermally grown silicon dioxide (t-SiO_2) for enhanced durability and biocompatibility (Figure 4D).[2] These sensors, ideal for intracranial pressure monitoring, feature a pressure-sensitive diaphragm with piezoresistive properties, enabling precise measurements. The study highlights the sensors' biodegradability through in vivo animal model testing, assessing biodistribution, blood chemistry, and MRI compatibility. This research marks a significant advancement in bioresorbable electronics, offering stable, long-term pressure monitoring solutions for chronic disease management and postsurgical healing processes.

Kim et al. reported a novel approach in ocular diagnostics through a smart sensor system integrated on soft contact lenses (Figure 4E).[61] This system enables the wireless detection of glucose and intraocular pressure. It features a graphene-silver nanowire (AgNW) hybrid structure, ensuring transparency and stretchability, crucial for comfortable wear and unobstructed vision. The sensor operates using a resistance-inductance-capacitance (RLC) circuit at radio frequency, facilitating real-time, in-vivo glucose detection on a rabbit's eye and in-vitro monitoring of intraocular pressure of a bovine eyeball. These sensors, independent in their function, offer continuous, non-invasive monitoring of physiological conditions, presenting a significant advancement in managing ocular and systemic health.

4.1.3. Strain

Strain in the human body refers to the deformation or displacement of tissues under stress, a critical parameter in various medical fields (**Table 4**). In orthopedics, muscle and tendon strain are key indicators of injury or recovery progress.[243] Monitoring strain helps in the rehabilitation of musculoskeletal injuries, ensuring proper healing and avoiding re-injury.[244] In cardiology, myocardial strain measurement is vital for assessing heart muscle function, particularly in conditions like heart failure or myocardial infarction.[245] This type of strain analysis provides insights into the heart's contractility and overall health. Vascular strain is another important aspect, particularly in assessing the flexibility and integrity of blood vessels, crucial for diagnosing conditions like aneurysms or atherosclerosis.[246] Strain

Table 4. Gauge factor and materials of implantable strain sensors.

Organ	Gauge factor	Strain gauge Material	Substrate Material	Refs.
Bladder	1.5	Si NM	PI	[50]
	1.1	EGaIn	PAAm	[248]
Tendon	21.3	MWCNT	Polystyrene-*block*-polyisoprene-*block*-polystyrene	[249]
Heart	0.33	Si NM	Polyimide (PI)	[34]

Abbreviations: Si NM, silicon nanomembranes; PI, polyimide; EGaIn, eutectic gallium-indium alloy-based particles; PAAm, polyacrylamide; MWCNT, multiwalled carbon nanotubes.

measurement is also crucial in urology, particularly for assessing bladder strain. The bladder's ability to expand and contract effectively is essential for proper urinary function. Monitoring bladder strain helps in diagnosing and managing conditions like urinary incontinence, overactive bladder, and bladder outlet obstruction.[247]

Jang et al. reported on an innovative bioelectronic device designed to monitor and regulate the real-time activity of the urinary bladder (Figure 4F).[50] This expandable and implantable complex is particularly notable for its integration with the elastic bladder, accommodating substantial volume changes. The device's capabilities extend to precise monitoring and optogenetic manipulation, addressing issues such as detrusor underactivity (DUA), a syndrome that can lead to urinary infections or kidney damage. The system's design, which includes electronic and optoelectronic components, enables seamless integration onto the urinary bladder without adhesives, enhancing monitoring accuracy. This device has been validated through in vivo experiments, indicating its potential for practical applications in clinical trials related to bladder and other elastic organs. The study highlights the device's contribution to understanding and managing bladder-related conditions, showcasing the advanced engineering and medical relevance of such bioelectronic systems.

Lee et al. reported on stretchable and suturable fiber sensors for wireless monitoring of connective tissue strain, showcasing a novel approach in biomechanical sensing (Figure 4G).[58] These sensors feature a double helical capacitive fiber strain sensor made from silver nanoparticles and elastomeric fibers, providing high stretchability and conductivity. With a sensitivity of ≈12, these sensors accurately measure tensile strains on connective tissues like ligaments and tendons. The sensor's design, incorporating a passive resonant circuit without soldering, enhances flexibility and adaptability. Demonstrated in both ex vivo and in vivo settings, these sensors offer significant potential for clinical and rehabilitation applications, such as monitoring ligament and tendon strain, aiding in wound-closure monitoring, and potentially preventing hernia in postsurgical scenarios. This advancement represents a significant step forward in continuous strain monitoring technology in the medical field.

4.2. Thermal Biophysiological Signals

Thermal biophysiological signals originate from the body's heat-related processes. These include signals from metabolic activities, blood flow, and temperature regulation. Types of thermal signals include core body temperature, skin temperature, and infrared emissions from body tissues. Measuring these signals is medically important as they provide critical insights into a person's metabolic rate, circulatory health, and presence of inflammation or infection.[250] Sensors for measuring thermal biophysiological signals generally rely on thermoelectric,[251–254] resistive,[255–257] and infrared principles.[258–260] Thermoelectric sensors utilize the Seebeck effect, where a temperature difference across a material generates voltage.[251] This effect is pronounced in metals, offering a direct and linear response to temperature changes. However, they can be less sensitive compared to other types. Resistive sensors (Thermistors) change their resistance with temperature fluctuations. Made from semiconductor materials, these sensors offer high sensitivity and a rapid response to temperature changes. Their drawback is a non-linear response, requiring complex calibration.[261] Infrared sensors detect infrared radiation emitted from the body. They provide non-contact temperature measurement, ideal for continuous monitoring. While they offer ease of use and comfort, their accuracy can be affected by external factors like ambient temperature and distance from the body.

Thermal biophysiological signals are measured using sensors made from various materials like metals,[34,49] semiconductors,[56,62] and organics.[43,63] Metal-based sensors, often used in thermocouples, offer durability and wide temperature ranges but may lack sensitivity. Semiconductor sensors provide higher sensitivity and faster response times but can be more affected by environmental conditions. Organic materials, emerging in this field, offer flexibility and biocompatibility, making them suitable for implantable applications, but may have limitations in temperature range and long-term stability. In this section, we will further explore implantable thermal signal sensors, focusing on materials used in their construction: metals, semiconductors, and organics (**Table 5**)

Table 5. Resolution and measurement range of implantable temperature recording.

Organ	Temperature resolution	Measurement range	Refs.
Bone	0.01 °C	33–41 °C	[56]
Kidney	0.004 °C	30–41 °C	[49]
Brain	0.049 °C	25–50 °C	[62]
Lung	0.1 °C	25–50 °C	[43]

4.2.1. Metal-Based Temperature Sensor

Metal-based temperature sensors primarily operate on the principle of electrical resistance change with temperature variation. This is based on the fundamental property of metals where their electrical resistance increases with temperature. The choice of metal depends on factors like the required sensitivity, operating temperature range, and environmental conditions. Common metals used in these sensors include platinum,[262–263] nickel,[264–266] copper,[267–268] and gold[269] chosen for their predictable resistance-temperature relationship and stability. Platinum is often used in high-precision applications, such as in resistance temperature detectors (RTDs), due to its stable and linear response over a wide temperature range and strong durability.[270] Nickel offers a higher sensitivity compared to platinum but has a more limited temperature range.[271] Copper is used for its good thermal conductivity and lower cost but is less stable over because of corrosion. Gold is also used, especially where corrosion resistance and electrical conductivity are crucial, though it is more expensive.

Madhvapathy et al. reported on an implantable bioelectronic system for the early detection of kidney transplant rejection (**Figure** 5A).[49] The system employs a metal-based temperature sensor, specifically designed for implantation near the transplanted kidney. The lithographically patterned thin film serpentine structured gold, plays a crucial role in ensuring accurate and stable temperature readings in the long-term temperature measurement. The sensor's key feature is its sensitivity to subtle temperature variations, indicative of inflammation or infection – common signs of organ rejection. The study highlights the sensor's potential in improving post-transplant care, reducing the need for frequent biopsies. This development represents a significant stride in transplant medicine, offering a less invasive, more efficient method for monitoring transplant health.

Xu et al. reported on the development of 3D multifunctional integumentary membranes for cardiac applications (Figure 5B).[34] These membranes, utilizing gold as a functional material, are designed for comprehensive cardiac monitoring and stimulation. They provide spatiotemporal measurements across the entire epicardium, offering detailed insights into cardiac function. The device combines temperature sensing with other functionalities, like electrical and mechanical sensing, leveraging the conductive and flexible properties of gold. This integration allows for the simultaneous monitoring of various cardiac parameters, crucial in diagnosing and treating heart conditions. The system's 3D structure enhances its adaptability and reliability, marking a significant advancement in cardiac bioelectronics.

4.2.2. Semiconductor-Based Sensor

Semiconductor-based temperature sensors operate on the principle that the electrical resistance of a semiconductor changes with temperature. This change is more significant in semiconductors than in metals, primarily due to their bandgap energy properties. The existence of a bandgap in semiconductors means that they are insulators at absolute zero temperature. As the temperature increases, some electrons gain enough thermal energy to cross the bandgap, turning the material into a conductor. So, small changes in temperature can significantly alter their conductivity. Commonly used semiconductors for temperature sensing include silicon,[272–274] selected for its sensitivity and stability across various temperature ranges. Doping, the addition of impurities to a semiconductor, significantly affects its temperature sensitivity. For instance, adding boron or phosphorus to silicon changes its electrical conductivity and temperature response.[275] By adjusting the type and level of doping, the temperature sensitivity and operational range of the sensor can be optimized for specific applications. Semiconductor temperature sensors, compared to metal-based sensors, generally offer higher sensitivity and a faster response to temperature changes. However, they tend to have non-linear outputs, which might require more complex signal processing for accurate temperature readings. They are less stable at high temperatures than metal sensors but offer more flexibility in terms of design and integration into complex systems. Additionally, semiconductor sensors can be more affected by environmental conditions such as humidity and electromagnetic interference.

In the study by Cai et al., they explored the development of thin, wireless, battery-free, and multimodal musculoskeletal biointerfaces, known as Osseosurface electronics (Figure 5C).[56] The standout feature of this research was the incorporation of a commercial negative temperature coefficient (NTC) thermistor (NTCG064EF104FTBX, TDK), showcasing the effective use of established, reliable sensor technology in biomedical applications. This integration highlights the successful combination of semiconductor technology with commercial sensor solutions, ensuring precise and real-time temperature monitoring in the musculoskeletal area. The deployment of this commercially available temperature sensor emphasizes both the practicality and scalability of incorporating proven technologies into specialized biomedical devices, thereby enhancing their functionality and applicability in medical diagnostics.

In the study by Shi et al., a temperature sensor was developed using complementary metal-oxide-semiconductor (CMOS) technology, notable for its compact size and wireless capabilities (Figure 5D).[62] CMOS technology is well-suited for temperature sensors due to its high integration level, allowing for miniaturization and low power consumption. The CMOS-based sensor provided precise temperature measurements, an essential feature for in vivo medical applications. Its small size, combined with wireless functionality, makes it ideal for monitoring internal body temperatures in real time, demonstrating the versatility and potential of CMOS in advanced biomedical applications.

4.2.3. Organic Based Sensor

Organic-based temperature sensors operate using organic materials, which change their electrical properties in response to temperature variations. These materials include organic semiconductors[276–278] and conductive polymers.[279–281] Organic sensors typically utilize the property where their electrical conductivity or resistance alters with temperature changes. Popular organic materials for temperature sensing include poly(3,4-ethylenedioxythiophene) (PEDOT:PSS).[282–283] PEDOT:PSS is chosen for its stability and relatively linear response. Methods to enhance temperature sensitivity in organics involve doping or

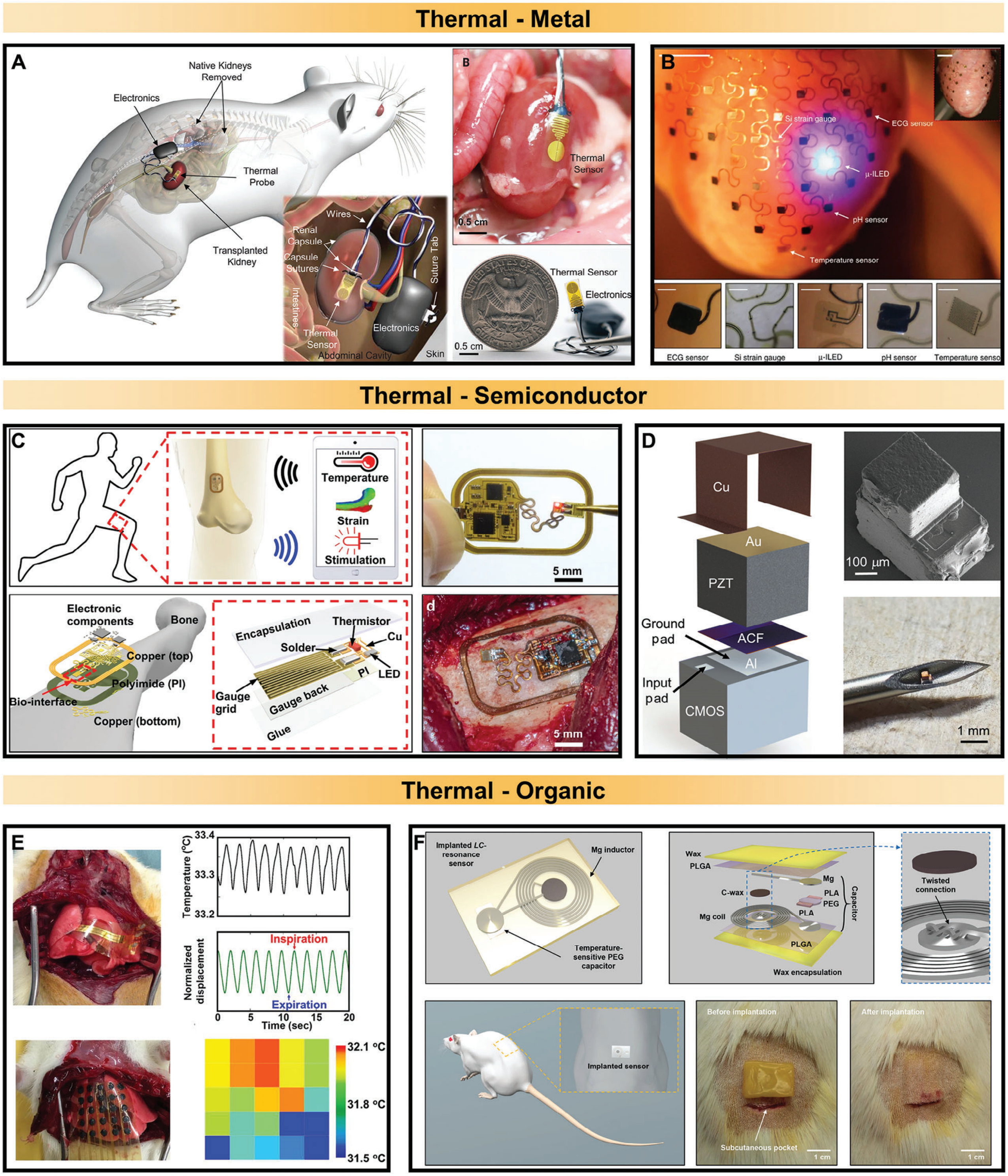


Figure 5. Bioelectronic implantable devices for thermal biosignal recording. A) Metal-based temperature sensor for early detection of kidney transplant rejection, sensitive to subtle temperature variations indicating inflammation or infection. Reproduced with permission.[49] Copyright 2023, American Association for the Advancement of Science. B) 3D multifunctional integumentary membranes for cardiac temperature monitoring. Reproduced with permission.[34] Copyright 2014, Nature Publishing Group. C) Osseosurface electronics employing a commercial NTC thermistor for precise, real-time musculoskeletal temperature monitoring. Reproduced with permission.[56] Copyright 2021, Nature Publishing Group. D) Compact, wireless temperature sensor using CMOS technology for precise in vivo medical applications. Reproduced with permission.[62] Copyright 2021, American Association for the Advancement of Science. E) Ultraflexible temperature sensors based on a composite of semicrystalline acrylate polymers and graphite for real-time temperature monitoring on tissue surfaces. Reproduced with permission.[43] Copyright 2015, National Academy of Science. F) Bioresorbable temperature sensors using PEG for internal body temperature monitoring. Reproduced with permission.[63] Copyright 2020, Wiley-VCH.

blending with other materials to modify their thermal response. Organic sensors are advantageous due to their flexibility, stretchability, and biocompatibility. They can conform to various shapes and surfaces, making them ideal for implantable devices. However, they generally have lower temperature ranges and less precision compared to metal or semiconductor sensors. Their stability and longevity can also be a concern, particularly in harsh environmental conditions.

The research by Yokota et al. presents a novel approach to temperature sensing in biomedical applications (Figure 5E).[43] The study introduces ultraflexible temperature sensors based on a composite of semicrystalline acrylate polymers and graphite. These sensors exhibit significant resistance changes near body temperature, making them highly sensitive and suitable for physiological conditions. The flexibility of these sensors allows for conformal application to living tissue surfaces, enhancing their practicality for in vivo measurements. The research demonstrates the use of these sensors for accurate, real-time temperature monitoring, successfully measuring minute temperature fluctuations in a rat's lung during breathing without interference from tissue motion. This achievement showcases the potential of these sensors in various medical applications, particularly in monitoring and managing health conditions that require precise temperature measurements. The integration of such advanced sensor technology into biomedical devices represents a significant step forward in the development of flexible, sensitive, and reliable diagnostic tools.

The study by Lu et al. focuses on developing bioresorbable temperature sensors for internal body temperature monitoring (Figure 5F).[63] The study utilizes polyethylene glycol (PEG) due to its temperature-dependent dielectric constant, particularly effective near body temperatures. A significant design aspect of these sensors is the use of natural wax as a water barrier, enhancing stability and operational lifespan. The sensors show stable performance for up to 6 days in buffer solutions and up to 4 days when implanted in rats. The research demonstrates the sensors' utility in monitoring subcutaneous and intracranial temperatures with high accuracy and minimal drift. This approach highlights the potential of bioresorbable materials in creating efficient, minimally invasive temperature sensors for medical applications.

4.3. Electrical Biophysiological Signals

Electrical biophysiological signals are fundamentally generated by nerve cells, or neurons, in the body. These neurons produce electrical signals as a response to various stimuli. These signals are created by the flow of ions across the neuron's membrane, a process governed by the ion channels. This electrical activity is essential because it serves as the primary means of communication within the nervous system, controlling all bodily functions and organ responses.[284]

The measurement of these signals is crucial because it offers a window into the functioning of the nervous system. For instance, abnormalities in brain signals can indicate neurological disorders. Various methods are used to measure these signals, including directly inserting electrodes into nerve tissue or wrapping electrodes around nerves. These techniques vary in their invasiveness and the type of data they provide, with some offering highly localized readings and others providing more generalized information.[285]

The nervous system is broadly divided into the central nervous system (CNS), comprising the brain and spinal cord, and the peripheral nervous system (PNS), which includes all other neural elements. The CNS is essential in processing and sending out instructions, while the PNS is crucial in transmitting signals to and from the CNS. Monitoring electrical activity in these areas is vital for diagnosing and treating various medical conditions. This chapter will focus on the advancements in implantable devices designed to interact with the nervous system.

4.3.1. Brain

The brain, a complex and essential organ, is central to neurofunctional processes. It coordinates mental and physical actions, from cognition to motor skills.[286] Understanding its neurological structure and composition is crucial for comprehending its diverse functions. The brain comprises various regions, each responsible for specific tasks, and is made up of billions of neurons interconnected through synapses.

Measuring brain neural signals is vital for diagnosing and treating neurological disorders. Techniques like electroencephalograms (EEG) provide insights into overall brain activity by region, making them useful in detecting conditions like epilepsy and sleep disorders. Electrocorticography (ECoG) involves surface-level measurements and is less invasive, making it suitable for long-term monitoring of brain activity. Local field potentials (LFP) offer localized activity data in specific brain regions, crucial for understanding the functioning of these areas, particularly in research and clinical interventions. Multi-unit and single-unit activities give detailed information on neuron clusters and individual neurons, essential for understanding complex neurological phenomena and monitoring target disease.[287]

Several methods exist for measuring brain neural signals (**Table 6**). The Utah array,[288–289] with its shallow insertion, offers high spatial resolution for brain-computer interface applications. The Michigan probe,[290–291] designed for deeper brain penetration, provides detailed data from specific brain regions, aiding in advanced neurological research. Recent advancements include the development of flexible and stretchable neural probes using thin film active layers embedded in polymers with low mechanical modulus, reducing brain damage and improving implant compatibility.[292–293]

The paper by Mestais et al. discusses the development of an implantable brain neural interface device designed for long-term wireless electrocorticography (ECoG) signal recording (**Figure 6A**).[64] This device, called WIMAGINE, is powered remotely through an inductive link and can record neural activity from 64 electrodes. It's designed with safety, reliability, and regulatory compliance in mind. Key features include a silicone-platinum electrode array for ECoG recording, a silicone-coated titanium cylinder housing, and antennae for remote power supply and data transfer. The device's architecture is modular and scalable, with off-the-shelf components and custom ASICs for low-noise signal amplification and digitization. In vivo evaluations with non-human primates demonstrated the implant's biocompatibility, functional performance, and potential for long-term

Table 6. Relevant parameters of implantable device for electrical brain activity recording.

Brain signal	Number of channels	Recording period	Neural probe substrate	Neural probe electrode	System integration	Refs.
ECoG	6	3 weeks	SiO_2	Mo/Si	Wired system	[294]
	64	11 months	Silicone rubber	Pt/Ir	Wireless system	[64]
LFP	128	25 days	Pt-Ag alloy	PI	Wired system	[295]
	12	33 weeks	Parylene	EGaIn	Wireless system	[296]
EAP	64	10 weeks	PFPE-DMA	Pt black	Wired system	[297]
	21	168 days	PEI	Sn	Wired system	[298]

Abbreviations: EcoG, electrocorticography; LFP, local field potentials; EAP, extracellular action potential; EGaIn, eutectic gallium-indium alloy-based particles; PFPE-DMA, perfluoropolyether dimethacrylate; PEI, poly(etherimide)

clinical applications in an area of brain-computer interface. This research highlights the advances in bioelectronic implantable devices, particularly for brain neural monitoring and interfaces.

In the study conducted by Zhao et al., the researchers developed a novel method to track neural activity from the same cells throughout the adult life of mice (Figure 6B).[5] This method leverages advanced bioelectronics to provide unprecedented insights into the long-term dynamics of neural activity. The core technology of this study is an implantable nano-mesh electrodes, intricately designed to minimize tissue damage and ensure long-term stability in the brain. The nano-mesh, fabricated using biocompatible materials, features high-density microelectrodes for precise neural signal acquisition. These electrodes, strategically positioned, allow for the consistent tracking of activity from specific neuron populations over extended periods. This is a significant advancement in neuroscience research, enabling continuous monitoring of neural development and degeneration processes.

D. A. Borton et al. reported a fully integrated and compact, subcutaneous microsystem housed in a titanium enclosure for brain neural recordings (Figure 6C).[65] This system connects to the brain using a 100-element silicon microelectrode array, with neural signals amplified, multiplexed, digitized, and wirelessly transmitted. The device operates on a rechargeable Li-ion battery, supporting 7 hours of continuous use and recharged via a wireless link. Tested in swine and non-human primates, it demonstrated stability, effectiveness in broadband neural data capture, and safety over a year. This technology holds significant potential for detection and monitoring of brain neurological diseases without physical constraints by wired components of the device.

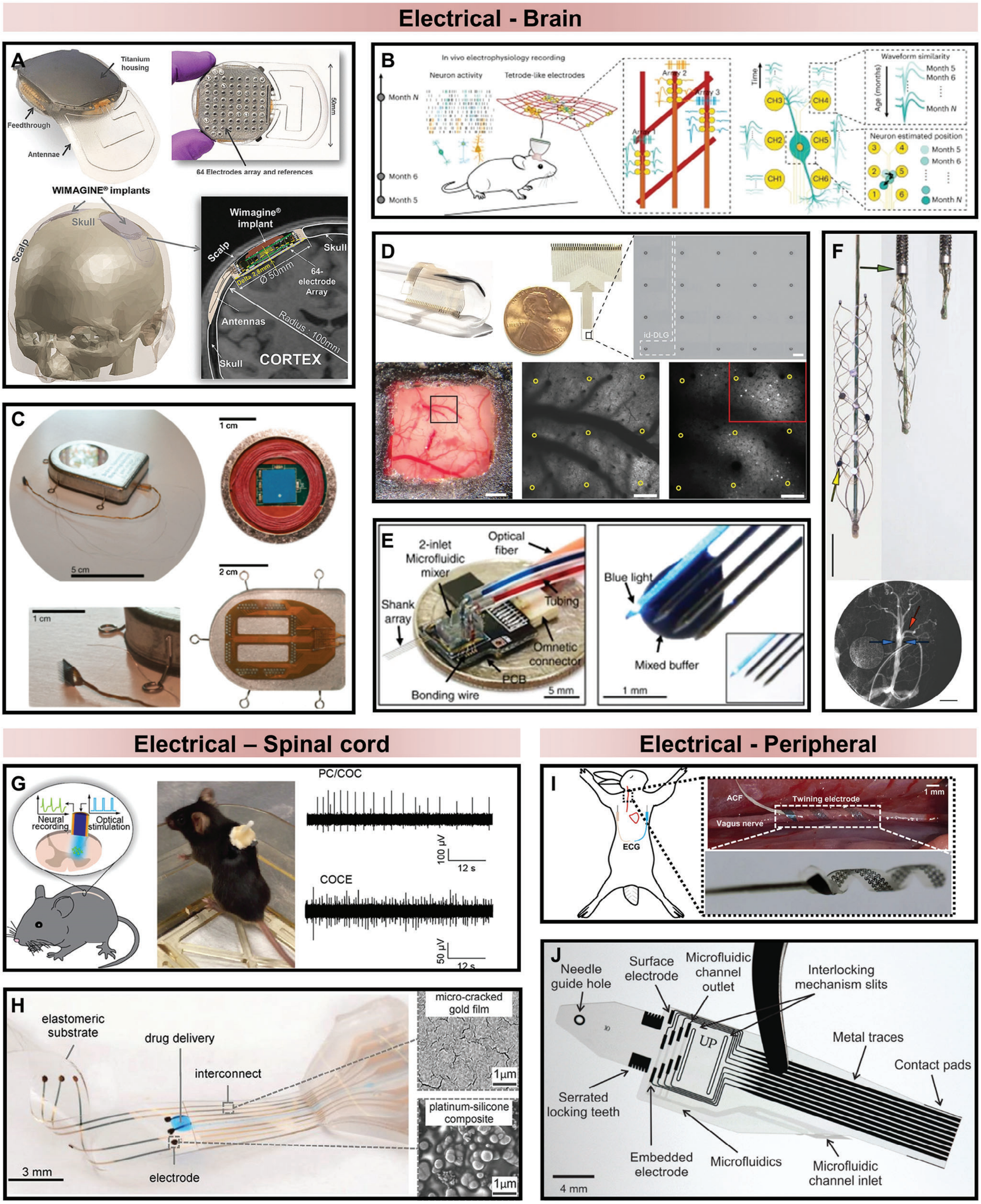
Ramezani et al. reported on the development of transparent graphene microelectrodes, significantly enhancing electrophysiological brain recordings (Figure 6D).[66] These microelectrodes, with ultrasmall 20 μm diameters and high-density arrays of up to 256 channels, were created using platinum nanoparticles and interlayer-doped double-layer graphene. This design facilitates simultaneous cortical potential recordings and two-photon calcium imaging, providing high spatial resolution over large brain areas. Through multimodal experiments on the mouse visual cortex, the study demonstrated the spatial localization of visually evoked responses and the correlation between multiunit activity power and cellular calcium activity. The study successfully decoded single-cell and average calcium activities from surface potentials using these transparent graphene arrays, integrating advanced dimensionality reduction techniques and neural networks.

Shin et al. developed a multifunctional multi-shank neural probe, uniquely engineered to study and modulate long-range neural circuits in vivo (Figure 6E).[6] This probe is distinctively integrated with an optical waveguide for targeted optical stimulation, microfluidic channels for precise drug delivery, and a series of microelectrode arrays for detailed neural signal recording. A key innovation of this probe is its ability to simultaneously record and modulate neural activities at multiple brain regions, specifically focusing on the hippocampal CA3 and CA1 regions. This dual functionality is pivotal for exploring intricate neural network interactions and understanding complex brain functions. The probe's design significantly reduces tissue damage, a common issue with larger probes, thereby enhancing its suitability for long-term studies. This multifaceted approach represents a significant advancement in neural technology, providing a powerful tool for comprehensively studying brain dynamics and interactions at a cellular level.

Oxley et al. have made a significant leap in the field of neural interfaces with their pioneering design of a stent-electrode array, named "stentrode," for recording brain activity (Figure 6F).[67] This innovative technology marks a departure from traditional intracranial electrode arrays that require invasive surgical implantation, presenting a minimally invasive solution to monitor and stimulate brain activity. The stentrode, ingeniously implanted into a superficial cortical vein via catheter angiography, successfully records neural signals in freely moving sheep for up to 190 days. This approach bypasses the need for open craniotomy, reducing the risk of inflammatory tissue responses and brain trauma. The spectral content and bandwidth of the stentrode's vascular electrocorticography (ECoG) recordings were found to be comparable to traditional epidural surface arrays, demonstrating its effectiveness in capturing high-quality neural data.

4.3.2. Spinal Cord

The spinal cord, an integral component of the central nervous system, plays a crucial role in transmitting information between the brain and the rest of the body. It is composed of nerve fibers that carry sensory and motor signals, and its structure includes various types of neurons, interneurons, and glial cells. Understanding the neurofunctional significance of the spinal cord is important, as it is involved in critical reflex actions and in the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Titanium housing
Feedthrough
Antennae
64 Electrodes array and references
50mm
WIMAGINE® implants
Skull
Scalp
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CORTEX
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In vivo electrophysiology recording
Neuron activity
Tetrode-like electrodes
Month N
Month 6
Month 5
Array 2
Array 3
Array 1
Time
CH3
CH4
CH2
CH5
CH1
CH6
Waveform similarity
Age (months)
Month 5
Month 6
Month N
Neuron estimated position
Month 5
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C
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1 cm
D
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E
2-inlet Microfluidic mixer
Optical fiber
Shank array
Tubing
Omnetic connector
PCB
Bonding wire
5 mm
Blue light
Mixed buffer
1 mm
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Electrical – Spinal cord
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Neural recording
Optical stimulation
PC/COC
100 μV
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COCE
50 μV
12 s
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elastomeric substrate
drug delivery
interconnect
electrode
3 mm
micro-cracked gold film
1μm
platinum-silicone composite
1μm
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I
ECG
ACF
Twining electrode
Vagus nerve
1 mm
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Needle guide hole
Surface electrode
Microfluidic channel outlet
Interlocking mechanism slits
UP
Metal traces
Contact pads
Serrated locking teeth
Embedded electrode
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mediation of sensory and motor functions. So, measuring spinal nerve signals is necessary for diagnosing a range of neurological disorders. These signals encompass both afferent (sensory) and efferent (motor) neural activities. Disorders that can benefit from spinal signal measurements include spinal cord injuries, which can cause loss of sensation or paralysis, multiple sclerosis.[25,299]

Traditionally, direct measurement methods like intradural electrodes have been used for spinal cord monitoring. These involve inserting electrodes in close proximity to the spinal cord, providing precise signal detection but with an invasive method. Modern advancements in implantable device technology have led to the development of less invasive yet highly effective methods for spinal cord signal monitoring. These include epidural electrodes that require minimal surgical intervention compared to intradural methods and provide reliable signal acquisition. Microelectrode arrays, which can be implanted along the spinal cord, allow for the mapping and monitoring of neural activity over a larger area with high spatial resolution. These arrays are particularly useful for studying the intricate neural networks within the spinal cord.[300–301]

In an innovative study, Lu et al. have developed flexible, stretchable probes for neural pathway studies in spinal cord injuries, marking a significant leap in neuroengineering (Figure 6G).[68] These probes, made from thermally drawn polymer fibers coated with conductive silver nanowire meshes, are designed to match the low elastic modulus of neural tissue, ensuring compatibility with the spinal cord's delicate structure. The hybrid probes are notable for their durability under strains exceeding those occurring in mammalian spinal cords, maintaining low optical transmission losses in the visible range and impedance suitable for extracellular recording. This feature is particularly crucial for recording electrophysiological activity in specific neurons, which is key to understanding loss and recovery of function following spinal cord injuries. The study's practical evaluation involved freely moving mice, confirming the probes' ability to record endogenous electrophysiological activity in the spinal cord.

Minev et al. developed a soft neural implant, termed "electronic dura mater" or e-dura, designed to overcome the mechanical mismatch between stiff neural implants and soft neural tissues (Figure 6H).[22] This pioneering implant closely mimics the elasticity and shape of the brain and spinal cord's natural protective membrane, the dura mater, enhancing the long-term performance of implantable neuroprostheses. The e-dura implant is a multifunctional device embedding electrodes, interconnects, and chemotrodes. These components are engineered to endure millions of mechanical stretch cycles, electrical pulses, and chemical injections, showcasing remarkable durability and versatility. This flexibility and resilience are key to its adaptability in various neuroprosthetic applications. In animal models, these soft implants successfully recorded cortical states for brain-machine interfaces, demonstrating their effectiveness in capturing neural activities.

4.3.3. Peripheral

Peripheral nerves act as conduits for transmitting signals between the brain, spinal cord, and the rest of the body. These nerves are composed of numerous nerve fibers bundled together, each encased in a protective myelin sheath. They are responsible for both motor functions, such as muscle movement, and sensory functions, like feeling pain, temperature, and touch. Understanding the structure and composition of peripheral nerves is meaningful for various body functions. These nerves consist of diverse types of neurons, including sensory neurons, motor neurons, and autonomic neurons, each with specific functions.

Abnormalities in peripheral nerve signals are indicative of various diseases or conditions, such as muscle disorders, and peripheral nerve injuries.[302–303] Effective measurement and interpretation of these signals are essential for diagnosing and managing these conditions. For measuring these signals, one common type of peripheral nerve electrodes is the cuff electrode,[304–306] designed to encircle a nerve and ensure contact for signal recording from the entire circumference. These are typically used for chronic applications and are known for their stability and selective stimulation capabilities. Hook electrodes,[307–308] shaped like hooks, are placed around the nerve fibers and are commonly used in acute settings like surgery. They allow for easy application and are suitable for short-term use.[309] Needle electrodes,[310] which are fine needles inserted directly into the nerve or muscle, provide direct access to targeted nerve fibers but are more invasive.

In the study by Zhang et al., the focus was on developing a novel 3D twining electrode for peripheral neuromodulation, addressing the challenges of mechanical and geometrical mismatches in current electrode-nerve interfaces (Figure 6I).[27] This innovative approach utilized stretchable mesh serpentine wires integrated onto a flexible shape memory substrate, capable of transforming from a 2D form to a 3D structure at body temperature. The electrode's design was inspired by the climbing mechanism of twining plants, enabling it to naturally self-wrap around nerves when exposed to 37 °C normal saline. This feature allows for a minimally invasive and more biocompatible

Figure 6. Bioelectronic implantable devices for electrical biosignal recording. A) A long-term, wireless ECoG recording device for brain-computer interfaces and neurological rehabilitation. Reproduced with permission.[64] Copyright 2014, IEEE. B) The nano-mesh electrodes for tracking neural activity in mice over their lifespan. Reproduced with permission.[5] Copyright 2023, Nature Publishing Group. C) Compact, subcutaneous microsystem for broadband neural data capture and wireless transmission, using a 100-element silicon microelectrode array. Reproduced with permission.[65] Copyright 2013, IOP Publishing. D) Transparent graphene microelectrodes for high-resolution electrophysiological recordings and two-photon calcium imaging. Reproduced with permission.[66] Copyright 2024, Nature Publishing Group. E) Multi-shank neural probe with integrated optical waveguide, microfluidic channels, and electrode arrays for simultaneous recording and modulation of neural activities. Reproduced with permission.[6] Copyright 2019, Nature Publishing Group. F) A minimally invasive stent-electrode array for brain activity recording via catheter angiography. Reproduced with permission.[67] Copyright 2016, Nature Publishing Group. G) Flexible, stretchable probes using conductive silver nanowire meshes for spinal cord injury studies. Reproduced with permission.[68] Copyright 2017, American Association for the Advancement of Science. H) A soft neural implant mimicking the dura mater's elasticity, embedding electrodes, interconnects, and chemotrodes. Reproduced with permission.[22] Copyright 2015, American Association for the Advancement of Science. I) The 3D twining electrode for peripheral neuromodulation, inspired by plant twining mechanisms. Reproduced with permission.[27] Copyright 2019, American Association for the Advancement of Science. J) The parylene C-based peripheral nerve interface combining electrodes and microfluidic channels. Reproduced with permission.[69] Copyright 2018, IEEE.

interaction with the nerves, significantly reducing the risk of neural damage like axonal degradation. The electrode's substrate offers distinct elastic modulus controllability, ranging from ≈100 MPa to 300 kPa, which ensures a gentle but secure attachment to the nerves. The study's in vivo animal experiments demonstrated the electrode's clinical utility, including applications like right vagus nerve stimulation for heart rate reduction and action potential recording from the sciatic nerve. These experiments highlighted the electrode's ability to form flexible neural interfaces with minimal constraint on the deforming nerves.

In their innovative research, Cobo et al. developed a multifunctional Parylene C-based peripheral nerve interface, ingeniously combining electrodes and microfluidic channels in an adjustable cuff (Figure 6J).[69] This interface, known as the lyse-and-attract cuff electrode (LACE), stands out for its minimally invasive approach and integrated drug delivery system. The LACE is designed to deliver lysing agents and neurotrophic factors directly to the nerve surface, enhancing fascicular selectivity by locally disrupting the epineurium. The device incorporates multiple platinum electrodes within the microfluidic channels, enabling both neural stimulation and recording. A key feature of the LACE is its simple locking mechanism, adjustable for snug fitting around nerves of varying diameters, ensuring close contact and effective interfacing. Fabrication using standard Parylene microfabrication techniques ensures high device yield and low variability, essential for consistent performance. The in vivo implantation procedure was successfully demonstrated around rat sciatic nerves, with the locking mechanism proving both secure and adaptable.

4.4. Optical Biophysiological Signals

Optical biophysiological signals originate from the body's interaction with light, either through reflection, absorption, or emission. These signals are useful in medical diagnostics as they offer a relatively non-invasive method to monitor various physiological functions and detect diseases. For instance, different materials within the body reflect and react differently to emitted light, providing valuable data on body composition and functioning.

Sensors for optical biophysiological signals typically use different wavelengths of light to probe and measure various substances within the body. Infrared light,[311,312] known for its deeper tissue penetration, is extensively used in brain imaging techniques like NIRS. Ultraviolet light,[313–315] with its shorter wavelength, is utilized in identifying and analyzing biomolecules. Due to its high energy, ultraviolet spectroscopy can break down molecular bonds, making it effective in analyzing the structure and concentration of biomolecules. This is particularly useful in diagnosing diseases that alter the molecular composition of body fluids. Otherwise, visible light, spanning from violet to red, is used in various diagnostic applications. For example, red and green wavelengths are employed in pulse oximetry to measure blood oxygen levels and heart rate.[316,317] Blue light, on the other hand, is often used in diagnostic imaging to enhance the contrast of bodily structures and fluids.[318] Each of these wavelengths has distinct advantages and limitations. Infrared light offers deeper penetration but may have lower resolution. Ultraviolet light provides detailed molecular information but can be harmful in high doses.

Table 7. Relevant parameters of an implantable device for oximetry recording.

Organ	Emission wavelength	Irradiances at the illumination surfaces	Refs.
Kidney	660 nm & 850 nm	8.13 mW mm^{-2} & 12.1 mW mm^{-2}	[70]
Heart	645 nm & 950 nm	9.21 mW mm^{-2} & 14.4 mW mm^{-2}	[38]
Brain	540 nm & 625 nm	N/A	[10]
Muscle	465 nm	N/A	[71]

N/A, not applicable.

Visible light is safe and versatile but may not penetrate as deeply as infrared light. These characteristics guide their use in specific medical applications, shaping the development of advanced optical sensing technologies in implantable devices.

The measurement of optical biophysiological signals often involves techniques like oximetry,[10,38,70–71] photometry,[72–74] and endoscopy.[46,48] Oximetry is widely used for measuring blood oxygen levels and can be crucial for monitoring respiratory and cardiac conditions. Photometry involves measuring light intensity to determine the concentration of substances in the body, which can be helpful in diagnosing various conditions. Endoscopy allows for visual inspection of internal organs and tissues, aiding in diagnosing a range of gastrointestinal diseases. These advanced devices, leveraging technologies like oximetry, photometry, and endoscopy, enable continuous and precise monitoring of internal physiological processes. The following section focuses on the examples and developments of implantable devices that utilize these optical measurement methods.

4.4.1. Oximetry

Oximetry is a technique that measures the saturation of oxygen in the blood. Its principle is based on the different light absorption properties of oxygenated and deoxygenated hemoglobin. Hemoglobin, a protein in blood, alters its configuration when bound with oxygen, influencing its light absorption characteristics. Oximeters use light-emitting diodes (LEDs) at specific wavelengths to detect these changes (**Table 7**). The variations in light absorption between oxygenated and deoxygenated blood are then translated into oxygen saturation levels (SpO_2) using the Beer–Lambert law.

Oximetry plays a critical role in medical diagnostics and patient management, especially for conditions affecting respiratory and cardiac functions. It allows for monitoring of oxygen saturation in the blood, providing crucial data for assessing patient's oxygenation status. This is particularly critical in managing diseases such as chronic obstructive pulmonary disease (COPD), heart failure, and various types of pulmonary disorders, where oxygen levels can significantly fluctuate.[319] There are several types of oximetry, each suited for different medical scenarios. Pulse oximetry,[320–322] the most common type, is used for continuous monitoring of oxygen saturation levels in critical care settings, during surgery, and for patients with severe respiratory issues. Transcutaneous oximetry measures oxygen levels through the skin and is useful in assessing wound healing and the viability of skin grafts.[323–325] Cerebral oximetry, on the other hand, monitors oxygen saturation in the brain, crucial during cardiac and major vascular surgeries.[326–327] Oximetry devices typically consist of LEDs and photodetectors. The LEDs emit light at specific wavelengths (usually red and infrared), which passes through the body tissue. The photodetector measures the amount of light absorbed, which varies based on the oxygen saturation of the blood.

In the study led by Guo et al., the researchers developed a novel wireless, miniaturized, near-infrared spectroscopic system aimed at providing continuous, real-time monitoring of local-tissue oxygenation (**Figure** 7A).[70] This technology is particularly imperative for microsurgical free tissue transfer and solid organ allotransplantation procedures, where early detection of anastomotic thrombosis is crucial. Unlike current technologies that have limitations such as intermittent measurements and the need for skilled personnel, this system offers uninterrupted monitoring with a bioresorbable, minimally invasive probe. The probe is anchored stably at implantation sites and connects to a skin-interfaced module for wireless access to essential physiological parameters.

In the study by Lu et al., a wireless, implantable catheter-type oximeter designed for cardiac oxygen saturation monitoring was developed (Figure 7B).[38] It operates based on near-infrared spectroscopy, enabling precise and continuous measurement of oxygen saturation in the heart. The catheter-type design facilitates direct and reliable monitoring inside the blood vessel by red, infrared LEDs and a photodiode, offering benefits over traditional methods that might be less accurate or more invasive.

Zhang et al. developed a wireless, fully implantable platform for in vivo, localized tissue oximetry (Figure 7C).[10] This advanced system is designed to monitor local hemoglobin dynamics in animal models, including deep brain regions in mice, without the need for physical tethers or anesthetics. It combines microscale optoelectronics and innovative wireless power delivery, offering continuous, tether-free operation. Such capabilities are crucial for studying O_2-mediated physiological processes in naturally behaving subjects.

In the study by Sonmezoglu et al., an ultrasonic implant for deep-tissue oxygenation monitoring was presented (Figure 7D).[71] This millimeter-scale device is designed for minimally invasive implantation, providing continuous, real-time monitoring of oxygen levels in deep tissue. The implant operates on ultrasonic energy transfer, eliminating the need for batteries. The core technology involves a miniaturized ultrasonic transducer, integrated with an oxygen-sensing module with custom-designed integrated circuit.

4.4.2. Photometry

Photometry in the biomedical field revolves around the measurement of light intensity to analyze various biological parameters. This technique has become a fundamental tool in modern medicine due to its ability to provide insights into the composition and function of biological tissues and fluids. Photometric methods vary based on the type of light used and the biological parameters being measured. Photometry is important medically as it allows for the monitoring of various biomarkers, such as blood components, glucose levels, or the presence of certain proteins. This makes it useful in diagnosing and monitoring a range of medical conditions, including diabetes, cardiovascular diseases, and cancer.

In medical photometry, several types are utilized to serve various diagnostic purposes. Fluorescence photometry is a popular technique that relies on the emission of light by a substance when excited by a specific wavelength.[328–330] This re-emission of light is then measured to detect particular molecules within tissue samples, making it especially valuable in cancer monitoring for identifying specific cancer markers. On the other hand, reflectance photometry,[331] often used in dermatology, measures the light reflected off the skin's surface, providing vital information for diagnosing various skin disorders and assessing skin health. In terms of engineering, photometric devices consist of various optical components like light sources (LEDs or lasers), detectors (photodiodes), and optical filters. These components vary based on the specific application of the photometer.

In the research by Chou et al., a multimodal multi-shank fluorescence neural probe was developed and used for the analysis of neural circuits (Figure 7E).[72] This probe uniquely integrates both electrophysiology and fluorescence-based photometry to allow cell-type-specific monitoring within various deep-brain regions, presenting high spatiotemporal resolution. The probe's photodiode and electrode-array pair, monolithically integrated into a compact silicon device, permit simultaneous measurement of both electrical and fluorescence signals. The probe captured neural spikes and identified specific cell types. The capacity to perform concurrent electro-optical recordings in multiple brain regions reveals the probe's versatility and innovative approach to understanding complex neural circuits. The fluorescence signal captured by the probe enables the identification of specific neural activities linked to particular cell types, supplementing the electrical signal data. This dual approach allows researchers to delve deeper into the functional connectivity and dynamics of diverse neural networks.

The research paper by Sych et al. presented a modular-type photometry system that significantly enhances the study of brain functions (Figure 7F).[73] This system, integrating advanced photometric sensors with high-density fiber optics, allows simultaneous monitoring of neural activities in multiple brain regions, offering a comprehensive view of brain dynamics. A key innovation is the multi-fiber arrangement, which marks an advancement over traditional single-fiber photometry systems. This approach provides a detailed understanding of brain activities, critical for both neuroscience research and clinical applications. The study also explores animal behavior, linking it to neuronal activity across brain-wide networks. The system's ability to perform simultaneous photometric calcium recordings in various brain regions, including optogenetic perturbations, emphasizes its versatility for in-depth brain circuit analysis.

The paper Lu et al. introduces a wireless, injectable fluorescence photometer that enhances the capability to record neural activities in freely moving animals (Figure 7G).[74] This advanced photometric system integrates a miniaturized light source and photodetector on a flexible, needle-shaped polymer support, enabling minimally invasive implantation into deep brain regions.

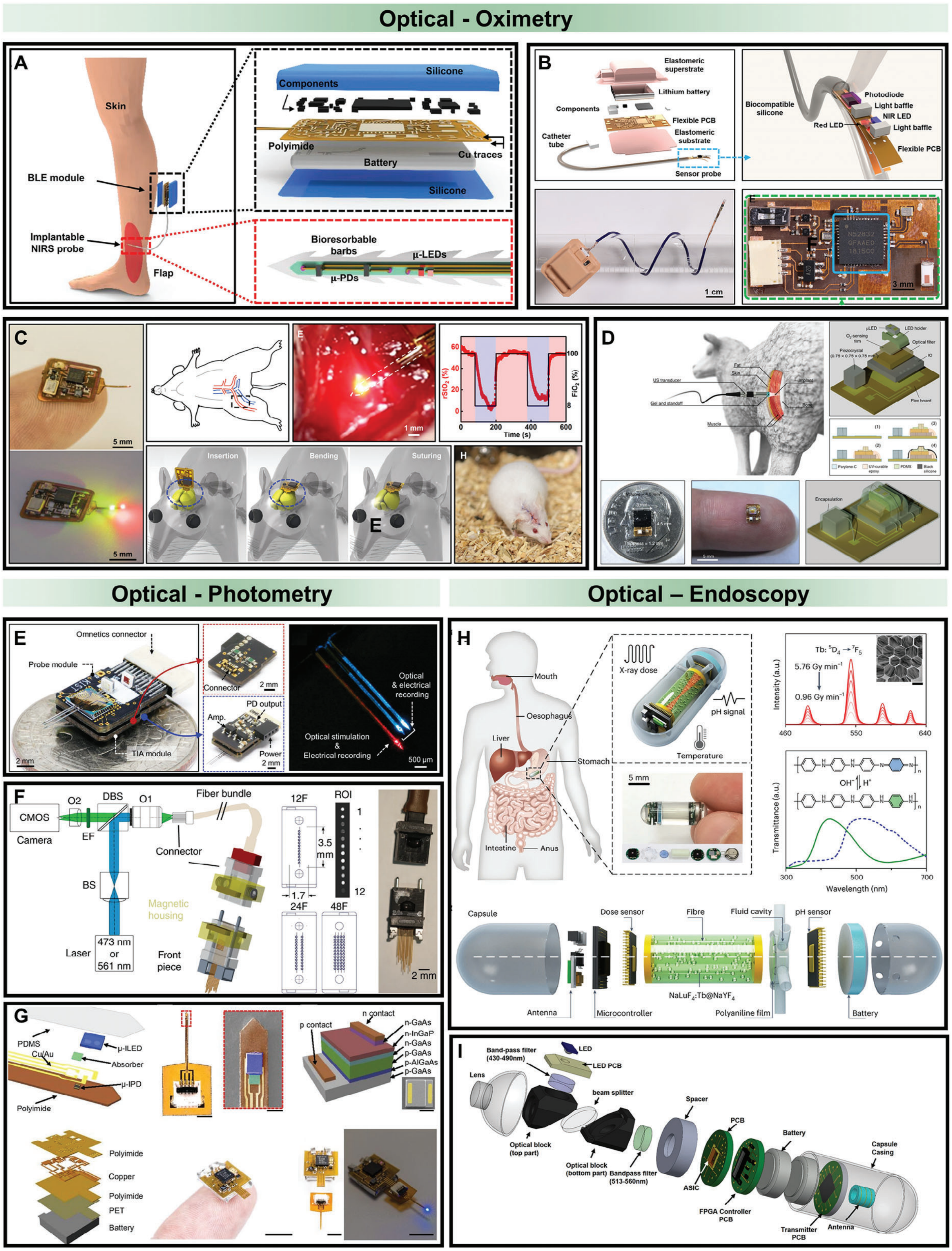

Figure 7. Bioelectronic implantable devices for optical biosignal recording. A) The wireless miniaturized near-infrared spectroscopic system for continuous monitoring of tissue oxygenation on postoperative care in transplant surgeries. Reproduced with permission.[70] Copyright 2022, Nature Publishing Group. B) The wireless, implantable catheter-type oximeter for cardiac oxygen saturation monitoring. Reproduced with permission.[38] Copyright 2021, American Association for the Advancement of Science. C) Fully implantable, wireless system for localized tissue oximetry. Reproduced with permission.[10] Copyright 2019, American Association for the Advancement of Science. D) Ultrasonic implant for deep-tissue oxygenation monitoring,

The design focuses on ultrathin geometry and compliant mechanics, ensuring stable, chronic operation with minimal physical constraints. Such features allow for high-fidelity recording of calcium fluorescence in the deep brain, matching the performance of traditional fiber photometry systems.

4.4.3. Endoscopy

Endoscopy is a medical procedure that allows doctors to view the inside of the body using an endoscope, a flexible tube with a light and camera attached. This technique is used for investigating symptoms in the digestive system, diagnosing conditions through biopsies, and for treatments like cauterization or removing foreign objects. Endoscopes can examine various body parts, including the gastrointestinal tract, respiratory tract, urinary tract, and more. The process is significant for diagnosing and managing diseases such as anemia, cancers of the digestive system, and Barrett's esophagus. While effective, endoscopy can have risks like infection or perforation.

Swallowable endoscopy capsules,[46,48] also known as capsule endoscopes, represent a significant advancement in gastrointestinal diagnostics, offering a minimally invasive alternative to traditional endoscopic procedures. These pill-sized devices are designed to be swallowed by the patient, and as they travel through the digestive system, they capture high-resolution images, providing a comprehensive view of areas often difficult to access with conventional endoscopes. This technology addresses the limitations and risks associated with traditional endoscopy, such as discomfort, sedation requirements, and the potential for infection or perforation. Furthermore, the capsule endoscopy is particularly useful for examining the small intestine and offers an excellent option for patients at risk of complications from standard endoscopic procedures or those requiring frequent examinations. The images captured by the capsule can aid in diagnosing a range of conditions, transforming the approach to gastrointestinal diagnostics.

The capsule endoscopy comprises a miniature digital camera or two, capturing detailed images of the intestinal lining.[332–333] This feature is essential for diagnosing conditions like small intestinal tumors, Crohn's disease, and celiac disease.[334–335] To illuminate the dark environment of the gastrointestinal tract, the capsule is equipped with LED lights, ensuring clear, well-lit images are captured. A tiny, long-lasting battery powers the capsule, designed to last the duration of the journey through the digestive system. Crucial to the functionality of the capsule endoscopy is a wireless transmitter, which sends the images captured by the capsule to a data recorder worn by the patient. This recorder collects and stores the images for subsequent analysis. An antenna within the capsule facilitates this wireless transmission of data, while control chips and sensors manage tasks like image capture frequency and data transmission.[336]

The study by Hou et al. introduced an approach to radiotherapy for gastrointestinal cancer, utilizing a swallowable X-ray dosimeter for enhanced precision in monitoring radiation exposure (Figure 7H).[46] The dosimeter, designed for ingestion and functioning within the gastrointestinal tract of rabbits, is a testament to the integration of biocompatible materials and sophisticated optoelectronic systems. Its composition includes lanthanide-doped persistent nanoscintillators, a pH-sensitive polyaniline film, and a miniaturized system for wireless luminescence readout. These components work in unison to measure absolute absorbed radiation dose, pH changes, and temperature in real-time, offering a comprehensive monitoring solution during radiotherapy. The device's standout feature is its ability to continuously monitor pH levels without external excitation, leveraging the persistent luminescence of the nanoscintillators post-irradiation. This aspect is particularly helpful for understanding the effects of radiotherapy on tumor pH and temperature, which can be critical indicators of treatment effectiveness. Moreover, the application of a neural-network-based regression model enables highly accurate radiation dose estimation from radioluminescence and afterglow intensity, along with temperature data.

In a fluorescence imaging (FI), Al-Rawhani et al. introduced a miniaturized wireless fluorescence endoscopy capsule (Figure 7I).[48] This capsule stands out for its low power consumption and enhanced sensitivity, making FI more accessible outside the conventional confines of laboratories and hospital examination rooms. The technological innovation of this capsule lies in its incorporation of a complementary metal oxide semiconductor single photon avalanche detector imaging array. This imaging technology, combined with miniaturized optical isolation and wireless capabilities, enables the device to deliver high-quality fluorescence images while consuming only a minimal amount of power—just 30.9 mW. The use of low-level 468 nm illumination further underscores its efficiency and safety. This capsule captured imges of tissue autofluorescence and targeted fluorescence via fluorophore labeling. It demonstrates the potential to replace traditional, power-hungry optical fiber-based endoscopes and to extend the range of clinical examination to areas previously inaccessible, such as regions below the duodenum. To validate the device's performance, comprehensive testing was conducted, including imaging fluorescence phantoms incorporating principal tissue fluorophores like flavins and absorbers such as hemoglobin. Moreover, the effectiveness of marker identification was proven through imaging of a fluorescein isothiocyanate (FITC) labeling solution on mammalian tissue.

utilizing ultrasonic energy transfer for continuous, real-time oxygen level assessments. Reproduced with permission.[71] Copyright 2021, Nature Publishing Group. E) Multimodal multi-shank fluorescence neural probe integrating electrophysiology and fluorescence-based photometry for cell-type-specific monitoring in deep-brain regions. Reproduced with permission.[72] Copyright 2022, Wiley-VCH. F) Advanced photometry system with high-density fiber optics for simultaneous monitoring of neural activities across multiple brain regions. Reproduced with permission.[73] Copyright 2019, Nature Publishing Group. G) Wireless, injectable fluorescence photometer for high-fidelity calcium fluorescence recording. Reproduced with permission.[74] Copyright 2018, National Academy of Science. H) Swallowable X-ray dosimeter for precision radiation exposure monitoring in gastrointestinal cancer radiotherapy. Reproduced with permission.[46] Copyright 2023, Nature Publishing Group. I) Miniaturized wireless fluorescence endoscope capsule for low-power, high-sensitivity tissue imaging. Reproduced with permission.[48] Copyright 2015, Nature Publishing Group.

4.5. Chemical Biophysiological Signals

Chemical biophysiological signals are key indicators of various physiological processes and health conditions. These signals, originating from cellular and molecular interactions, provide essential insights into the body's chemical composition, metabolic activities and signaling processes.

Regarding the configuration of these sensors, two common types are the two-electrode and three-electrode systems. In a two-electrode system, one electrode acts as the working electrode where the biochemical reaction occurs, and the other serves as the counter/reference electrode. This simpler setup is beneficial for its compact design and ease of use but may have limitations in terms of measurement accuracy and sensitivity compared to more complex systems. The three-electrode system, a more sophisticated arrangement, includes a working electrode (WE), a counter electrode (CE), and a reference electrode (RE). The working electrode is where the redox reaction of the analyte occurs, the counter electrode helps complete the circuit, and the reference electrode provides a stable voltage for accurate measurements. This setup enhances the precision and reliability of the measurements but is typically more complex and costly to implement.[337]

In terms of electrode material, gold, platinum, and carbon are commonly used for seed layer due to their good conductivity and chemical stability.[338] Modification techniques include the deposition of nanomaterials or biomimetic compounds, which can enhance the electrode's surface area and catalytic activity. This is crucial for detecting low concentrations of analytes and for achieving specific responses to particular biochemicals. Materials like transition metal complexes, oxides, and nanomaterials are used for modification. For example, the synthesis and modification of nanodendrite electrodes have been explored for the analysis of substances like hydrogen peroxide.[339–341] These modifications aim to increase the sensor's sensitivity, selectivity, and stability, particularly in various biological media analyses. Enzymes are also crucial in modifying electrodes for biosensors.[342–344] Techniques like protein engineering, designer polymers, and the introduction of nanomaterials are used to improve the electron transfer rate between the enzyme and the electrode surface. This enhances the sensor's sensitivity and power output.[345–347] Nanoparticles or nanorods can act as scaffolds for immobilizing enzymes, either through adsorption or chemical reaction, thereby improving the electrode's functionality.[348–350]

To measure chemical biophysiological signals, several methods are employed. Amperometric,[11,47,75] voltammetric,[76–77] and potentiometric[78–79] methods are commonly used (**Table 8**). Amperometry measures the current produced by the oxidation or reduction of a chemical substance, making it useful for detecting specific molecules in body fluids. Voltammetry involves measuring the current as the potential is varied, allowing for the detection of different substances based on their oxidation or reduction potentials. Potentiometry measures the voltage of a solution to determine the concentration of ions, useful in assessing electrolyte balance and other conditions. These methods have been incorporated into implantable devices, enabling continuous monitoring of chemical physiological signals within the body. Such devices are crucial for managing chronic conditions, such as diabetes, where continuous monitoring of glucose levels is essential. They also play a role in neurological studies, where neurotransmitter levels can be tracked, and in cardiology, for monitoring electrolyte imbalances that might affect heart function.

Table 8. Relevant parameters of implantable device for chemical biosignal recording.

Method	Target material	Sensitivity	Refs.
Amperometric	Dopamine	4.299 nA μM^{-1}	[75]
	Glucose	6.18 nA mM^{-1}	[11]
	Lactate	0.62 nA mM^{-1}	
	Glutamate	7.03 pA μM^{-1}	
	Choline	19.82 nA μM^{-1}	
Voltametric	Dopamine	0.06 nA μM^{-1}	[76]
	Corticosteroids	16.55 nA μM^{-1} cm^{-2}	[351]
Potentiometric	Ca^{2+}	37.8 mV/$\log_{10}$ [[Ca^{2+}] (mM)]	[352]
	K^+	66.7 mV/$\log_{10}$ [[K^+] (mM)]	
	Na^+	86.3 mV/$\log_{10}$ [[Na^+] (mM)]	
	Ca^{2+}	24.9 mV/$\log_{10}$ [[Ca^{2+}] (M)]	[78]

4.5.1. Amperometric Sensor

Amperometry is a refined electroanalytical method that measures electric currents produced by the chemical reactions of analytes in a solution. Amperometry involves the electrochemical reaction at the electrode surface. When a potential is applied, substances in the body, such as glucose or neurotransmitters, undergo oxidation or reduction at the electrode surface. This electrochemical reaction causes a current to flow, which is directly proportional to the concentration of the analyte. By measuring this current, amperometry can quantify the amount of the specific substance in the sample.[353] This method's sensitivity and selectivity make it valuable for monitoring physiological changes and detecting disease markers. The significance of amperometry in biomedical research and diagnostics stems from its high sensitivity and specificity, making it a valuable tool for detecting various biochemical compounds, including neurotransmitters. There are various types of amperometric devices, each characterized by specific electrode materials, designs, and measurement techniques, such as single-potential and pulsed amperometry.[354–355] These variations are tailored to meet different analytical needs, including sensitivity, selectivity, and resistance to electrode fouling.

One review introduces NeuroString, a novel bioelectronic tool designed for in vivo monitoring of neurotransmitter dynamics in the central and peripheral nervous systems, including the gastrointestinal tract (**Figure 8A**).[47] This tool addresses the challenge of measuring neurotransmitters in soft, complex, and actively moving organs. NeuroString is crafted from a metal-complexed polyimide, laser-patterned into an interconnected graphene/nanoparticle network within an elastomer, making it tissue-mimicking and stretchable. This unique construction allows for chronic, real-time, multichannel, and multiplexed monoamine sensing in the brain of mice and serotonin dynamics in the gut without causing undesirable stimulations or affecting peristaltic movements. NeuroString's flexible and conformable biosensing interface shows promise for exploring the influence of neurotransmitters on gut microbes and brain-gut

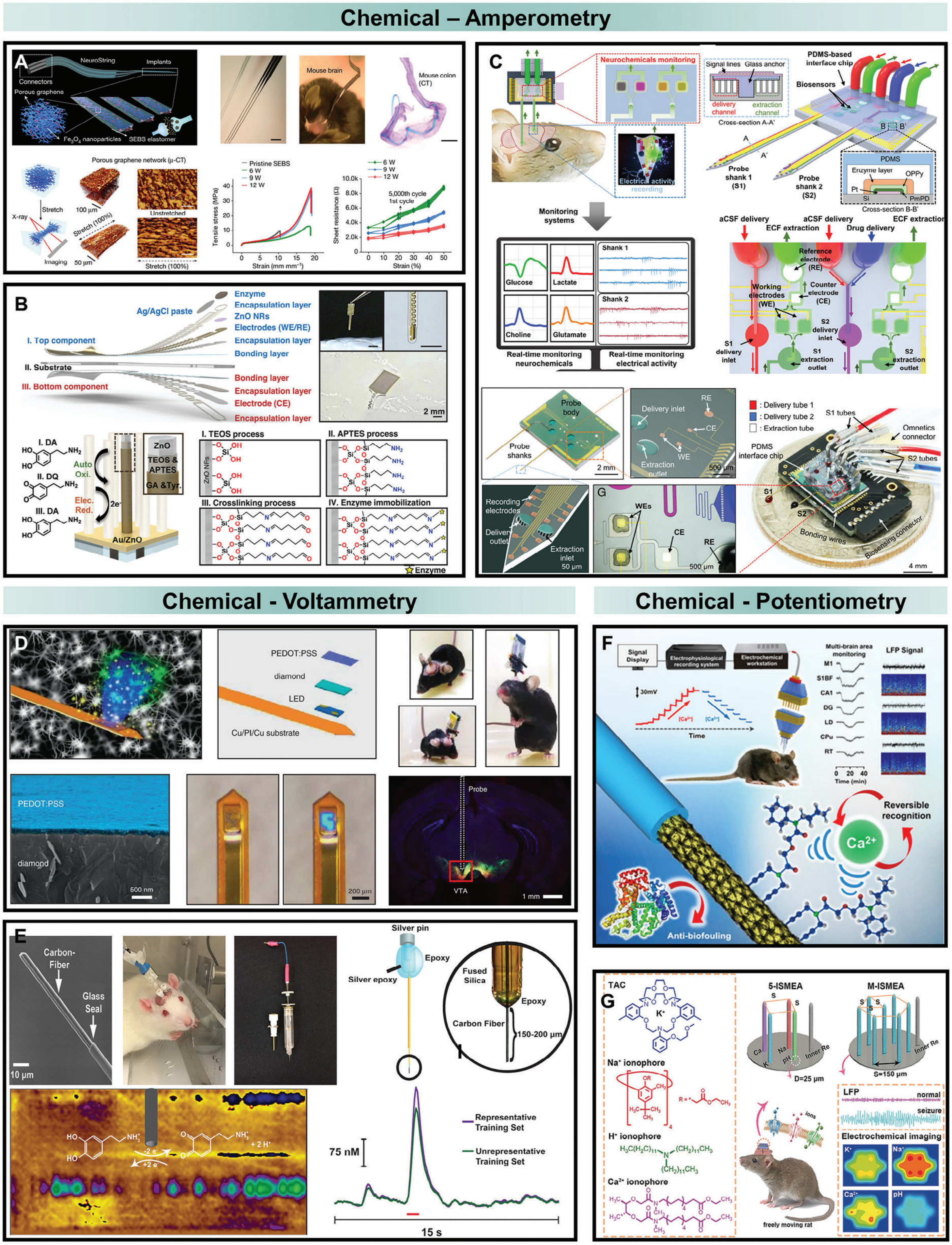

Figure 8. Bioelectronic implantable devices for chemical biosignal recording. A) A neurotransmitter sensor using a stretchable, tissue-mimicking metal-complexed polyimide for real-time monoamine and serotonin sensing. Reproduced with permission.[47] Copyright 2022, Nature Publishing Group. B) Double-sided neural probe for dopamine detection with enzyme-immobilized 3D nanostructures. Reproduced with permission.[75] Copyright 2024, Wiley-VCH. C) The enzyme-based sensor enables measurement of glutamate, choline, glucose, and lactate. Reproduced with permission.[11] Copyright 2023, National Academy of Science. D) Wireless, implantable optoelectrochemical probe for concurrent optogenetic stimulation and dopamine

communication, potentially extending to biomolecular sensing in various soft organs.

The study by Jung et al. presents a highly deformable, double-sided neural probe named the "Multi-Deformable Double-Sided (MDD) DA-Sensing Probe" for real-time in vivo detection of dopamine, especially for Parkinson's Disease research (Figure 8B).[75] This double-sided probe integrates a three-electrode system (working, reference, and counter electrodes) into a single, all-in-one form. The design incorporates enzyme immobilization on 3D nanostructures grown on the working electrode, enhancing dopamine sensitivity and selectivity. Its unique serpentine design allows the electrodes to withstand various deformations, managing stress induced on the probe. The study demonstrates the probe's effectiveness through in vivo experiments on rodents, monitoring dopamine dynamics before and after treatment with L-DOPA in hemi-Parkinsonian mice. This research features the probe's potential for studying and treating neurodegenerative diseases, offering precise and reliable monitoring of dopamine dynamics with minimal brain tissue damage.

The research by Chae et al. introduces a Real-Time Bimodal (RTBM) microelectromechanical systems (MEMS) neural probe for concurrent monitoring of various neurochemicals and electrical neural activity in multiple brain regions in vivo (Figure 8C).[11] This sensor features a multishank design integrating enzyme-based biosensors, enabling simultaneous measurement of neurochemicals like glutamate, choline, glucose, and lactate. The RTBM probe utilizes a three-electrode system and a polydimethylsiloxane (PDMS)-based microfluidic chip for efficient neurochemical extraction and analysis, minimizing crosstalk between sensors. The research demonstrates the probe's capabilities through in vivo experiments in mice, emphasizing its potential in studying neural circuits and brain diseases such as schizophrenia, with implications for drug development and neurochemical-related brain disorders.

4.5.2. Voltammetric Sensor

Voltammetry relies on varying the potential and measuring the resultant current to analyze the electrochemical properties of a solution. This method is characterized by its ability to provide detailed information about the redox potential and concentration of analytes. Voltammetry allows for a more comprehensive understanding of electrochemical reactions, making it particularly useful for analyzing complex mixtures and understanding reaction mechanisms by measurement of changing voltage and current.

The study by Liu et al. introduces a wireless, implantable optoelectrochemical probe for concurrent optogenetic stimulation and dopamine detection in the brain (Figure 8D).[76] This microprobe system integrates μ-ILEDs and PEDOT:PSS-coated diamond films, offering real-time capabilities for both optical stimulation and electrochemical sensing. The study demonstrates the performance of microprobe in experiments with mice, particularly in the ventral tegmental area for understanding complex neural dynamics.

The research paper by Rodeberg et al. introduces methodologies of fast-scan cyclic voltammetry (FSCV) for real-time neurotransmitter measurement in vivo (Figure 8E).[77] This study focuses on carbon-fiber microelectrodes (CFMs) encased in borosilicate glass or fused silica for acute and chronic applications, respectively. These electrodes offer high sensitivity and spatial resolution, enhancing the study of rapid neurotransmission in awake and behaving animals. The paper discusses the construction, optimization, and application of these electrodes in monitoring neurochemicals like dopamine in brain regions.

4.5.3. Potentiometric Sensor

Potentiometry is an electrochemical measurement technique where the potential of an electrochemical cell is measured under static conditions, with little to no current flowing through the sample. This method is highly valuable for its quantitative analytical capabilities. The fundamental principle involves measuring the potential difference between an indicator electrode, which responds to changes in the analyte's activity, and a reference electrode with a known, fixed potential.[356] The potential at the interface between the electrode and the analyte solution correlates with the amount of analyte present. Ion-selective electrodes (ISEs) are a crucial aspect of potentiometry, offering high selectivity for specific ions.[357] These electrodes are extensively used in clinical laboratories for measuring various ion concentrations in blood. The instrumentation for potentiometry is relatively simple and cost-effective, involving an indicator electrode, a reference electrode, and a potential measuring device. This simplicity, along with the minimal perturbation to the sample during measurement, makes potentiometry a versatile technique applicable in diverse fields like clinical analysis. For instance, measuring calcium levels in blood can provide critical information for various medical conditions.[358]

The study by Liu et al. presents a groundbreaking approach for long-term, dynamic quantification of extracellular Ca^{2+} changes in multiple brain regions of freely moving animals (Figure 8F).[78] They developed an anti-biofouling microfiber array capable of real-time tracking with high reversibility and selectivity. The microelectrodes, modified with gold particles and alternately wrapped with graphene oxide microbands, demonstrated exceptional anti-fouling properties, maintaining sensitivity for 60 days of continuous brain monitoring. The study conducted in vivo experiments in mice, focusing on ischemia-reperfusion processes and the influence of reactive oxygen species (ROS) on Ca^{2+} overload and neuron death.

The paper by Zhao et al. presents an electrochemophysiological microarray (ECPM) designed for real-time monitoring and quantification of multiple ions, such as K^+, Ca^{2+}, Na^+, and pH, in the brain of a freely moving rat (Figure 8G).[79] The ECPM uses open-circuit potentiometry with specific recognition ionophores

detection. Reproduced with permission.[76] Copyright 2020, Nature Publishing Group. E) Carbon-fiber microelectrodes for real-time neurotransmitters via FSCV. Reproduced with permission.[77] Copyright 2017, American Chemical Society. F) An anti-biofouling microfiber array capable of recording extracellular $Ca2^+$ changes. Reproduced with permission.[78] Copyright 2021, Wiley-VCH. G) Electrochemo-physiological microarray for real-time monitoring of ions in the brain. Reproduced with permission.[79] Copyright 2020, Wiley-VCH.

optimized for each ion. This approach allows simultaneous mapping and biosensing of chemical signals alongside electrical signals without cross-talk. The study demonstrates the ECPM's application in dynamic monitoring of ion changes in the brain during seizure events, providing insights into the physiological and pathological functions of these ions.

5. Closed-Loop Neuromodulation for Therapy

The necessity of bioelectronic implantable devices for neuromodulation within the body is paramount, driven by the important role of the nervous system in regulating various physiological processes. Neuromodulation is integral to addressing a spectrum of diseases and medical needs, as it directly influences neural activity, ultimately impacting bodily functions and organ systems. It alters neural dynamics, thereby influencing physiological states, ranging from pain perception to motor control, and even emotional and cognitive functions. Neuromodulation through bioelectronic implantable devices is increasingly recognized for its potential in treating various diseases and maintaining homeostasis. For instance, in the management of metabolic functions, neuromodulation plays a key role. It involves the regulation of metabolism through the central nervous system (CNS), which directly senses metabolic states and releases neuroendocrine signals. These signals influence various metabolic functions such as energy expenditure and blood glucose levels.[146–147] The hypothalamus in the CNS plays a pivotal role in monitoring the body's metabolic state and maintaining homeostasis by regulating neuroendocrine signaling. Neuromodulation can also be used to control metabolic dysfunctions by influencing the sympathetic and parasympathetic nervous systems, which have direct effects on organs like the pancreas and liver, crucial in metabolic regulation.[359] In the context of heart disease, neuromodulation offers an effective approach for treatment.[360] It addresses the imbalance in the autonomic neural control systems associated with the heart. Techniques like spinal cord stimulation and vagal nerve stimulation are being explored to dampen the sympathetic nervous system and stabilize the heart.[361–362] These approaches show promise in addressing the progression of cardiac diseases by modulating abnormal afferent signaling, which is often a contributing factor in cardiovascular disorders. Overall, the application of neuromodulation in bioelectronic devices presents a promising future in the medical field, offering targeted and effective treatment options for a range of conditions, particularly those involving organ dysfunctions.

In the dynamic field of bioelectronic implantable devices, neuromodulation unfolds through a series of interconnected stages, each leveraging the latest advancements in science and engineering. Initially, powering the device is crucial for initiating the neuromodulation process. This involves sophisticated energy management systems to ensure continuous and efficient operation.[161] The device then sets stimulation parameters, a critical step where the intensity, duration, and frequency of the neural stimulation are tailored based on individual needs. The actual delivery of stimulation is a central moment in neuromodulation. Here, the device applies the predetermined waveforms to the targeted neural pathways. This process is made accurate and minimally invasive thanks to advancements in microfabrication technology, which enable the development of highly compliant electrodes that are conformally attached to neural tissues.[29,161] These electrodes can stimulate specific neural circuits, reducing side effects and enhancing therapeutic outcomes. Finally, managing feedback is essential for the efficacy and safety of neuromodulation. The device constantly monitors physiological responses to the stimulation and adjusts its parameters in real-time.[40,363] This closed-loop system ensures that the treatment adapts to changing physiological conditions, optimizing therapeutic effects while minimizing potential risks. Overall, this harmonious integration of powering, waveform generation, parameter setting, stimulation delivery, and feedback management exemplifies the seamless operation of bioelectronic devices in neuromodulation therapy. Each element plays a critical role in transforming these devices from mere concepts into powerful tools for treating various health conditions, thereby revolutionizing modern medical therapies.

A critical aspect of these systems is the closed-loop control, which utilizes real-time physiological feedback for neuromodulation therapy. This approach eliminates the risk of overstimulation and enhances the efficacy of the treatment. For example, in managing chronic pain, these devices can adjust stimulation levels based on real-time feedback from pain receptors, providing effective pain relief while minimizing side effects.[364] In Parkinson's disease, devices can modulate dopaminergic neurons to control motor symptoms, enhancing patient mobility and quality of life.[365] For epilepsy, they can detect early signs of a seizure and deliver targeted stimulation to prevent its onset.[366] In mood disorders like depression, neuromodulation can regulate neurotransmitter levels, helping to stabilize mood swings.[367] This closed-loop approach ensures personalized, efficient, and responsive treatment, adapting to the patient's changing physiological state and providing targeted intervention when needed. The integration of Artificial Intelligence (AI) in these systems allows for autonomous diagnostics and optimized treatments, maintaining health states through personalized medical interventions.

5.1. Neuromodulation Modalities and Associated Devices for Therapeutics

5.1.1. Electrical: Electrical Stimulation

Electrical stimulation operates by directly applying electrical currents to targeted nerve cells, bundles, or specific regions within the nervous system (**Figure 9A**). This method induces a change in the transmembrane potential of the target neuron, causing depolarization or hyperpolarization.[368,369] The controlled application of electrical currents can modulate the activity of neuronal circuits, influencing various physiological functions.

When considering the application methods, surface placement involves electrodes placed atop the targeted nerve area. This method is safer and easier to implant, but it may offer less precise stimulation due to its limited depth of penetration.[370] In terms of application, spinal cord stimulation (SCS) involves the placement of electrodes in the epidural space, targeting specific spinal cord segments for localized neuromodulation in spinal cord injury (SCI).[371,372] On the other hand, invasive methods, like deep brain electrode insertion, provide direct and precise stimulation but carry risks associated with surgical procedures.

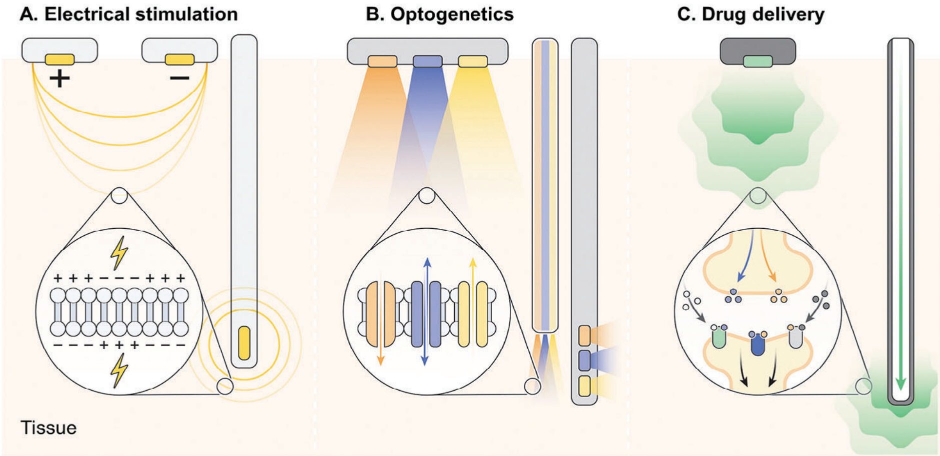

Figure 9. Neuromodulation modalities for therapeutics. Conceptual illustration of mechanisms of A) Electrical stimulation, B) Optogenetics, and C) Drug delivery.

For example, deep brain stimulation (DBS) involves implanting electrodes within specific brain regions for delivering precise electrical impulses to targeted brain areas, modulating abnormal neural activity.[373]

In electrical neuromodulation, multifaceted engineering strategies are essential for effective therapy. Electrode properties such as large charge storage capacity (CSC) are critical for effective therapy. A large CSC allows the electrode to store and release a higher amount of charge, which is important for maintaining effective stimulation over time.[374] Additionally, low impedance is also important for reducing the amount of energy required for stimulation and ensuring a stable and reliable signal.[375] Materials like PEDOT:PSS and iridium oxide are often used in electrode materials to achieve these properties, enhancing both the performance and longevity of the electrodes.[376] The selection of waveform shape, like monophasic or biphasic, influences stimulation impact, with biphasic waveforms generally preferred due to their reduced tissue damage risk. Duty cycle and frequency are tailored to each treatment, affecting therapeutic outcomes. Additionally, determining optimal intensity levels can avoid under or overstimulation.

Silvera Ejneby et al. presented a new method for chronic electrical stimulation of peripheral nerves using deep-red light (**Figure 10A**).[80] The device involves an implanted organic electrolytic photocapacitor that transduces light into electrical signals. This approach offers a minimally invasive, wireless solution for peripheral nerve stimulation, highlighting its potential in chronic applications and clinical translation. On the other hand, Lee et al. introduced a bioresorbable peripheral nerve stimulator, designed for pain management (Figure 10B).[29] The device's bioresorbable material ensures it degrades after fulfilling its therapeutic purpose, eliminating the need for surgical removal. Focusing on a minimally invasive approach, Chen et al. described a wireless, millimeter-sized magnetoelectric implant for endovascular nerve stimulation (Figure 10C).[31] The device's small size and wireless capabilities offer a promising solution for peripheral nerve disorders. In the development of system-level electrical stimulation device, Lee et al. detailed a therapeutic device for the urinary bladder's neuromodulation (Figure 10D).[52] This wireless and fully implantable device is not only expandable but also capable of bidirectional neuromodulation.

5.1.2. Optical: Optogenetics

Optogenetics starts with genetically modifying neurons to express light-sensitive proteins (opsins) (Figure 9B). When illuminated with light of specific wavelengths, these opsins trigger changes in ion transportation of ion channels, enabling precise control over their activity. Channelrhodopsins, depolarize neurons under blue light, while halorhodopsins and archaerhodopsins, activated by yellow or green-yellow light hyperpolarize neurons.[377] These opsins enable precise modulation of neurons, either exciting or inhibiting them, and have been altered through genetic engineering for enhanced functionality in research and potential therapeutic uses.

Optogenetic stimulation devices can be placed on the surface of the neural tissue, for example, targeting cortical areas in the brain. This method is less invasive than deep brain insertion and is suitable for modulating activities in the cerebral cortex.[378] However, its effectiveness is limited to superficial brain regions and light's penetration depth. For deeper brain regions, optogenetic fibers with optical waveguides or probes with μ-LEDs must be surgically inserted. This allows for targeted stimulation of deep-seated neural circuits, crucial in studying and potentially treating disorders like Parkinson's disease or epilepsy.[379]

In optogenetic neuromodulation, achieving optimal opsin expression requires careful selection of viral vectors and control over expression levels. The stimulation parameters, including light intensity, wavelength, and duration, must be finely tuned to effectively activate or inhibit neurons while minimizing heat generation and phototoxicity. The method of light delivery, whether using external light source or implanted optical elements, affects the spread and intensity of light, influencing opsin activation. Additionally, the temporal precision and frequency specificity are needed to align with neuronal refractory periods and natural firing patterns. These considerations enable successful optogenetic

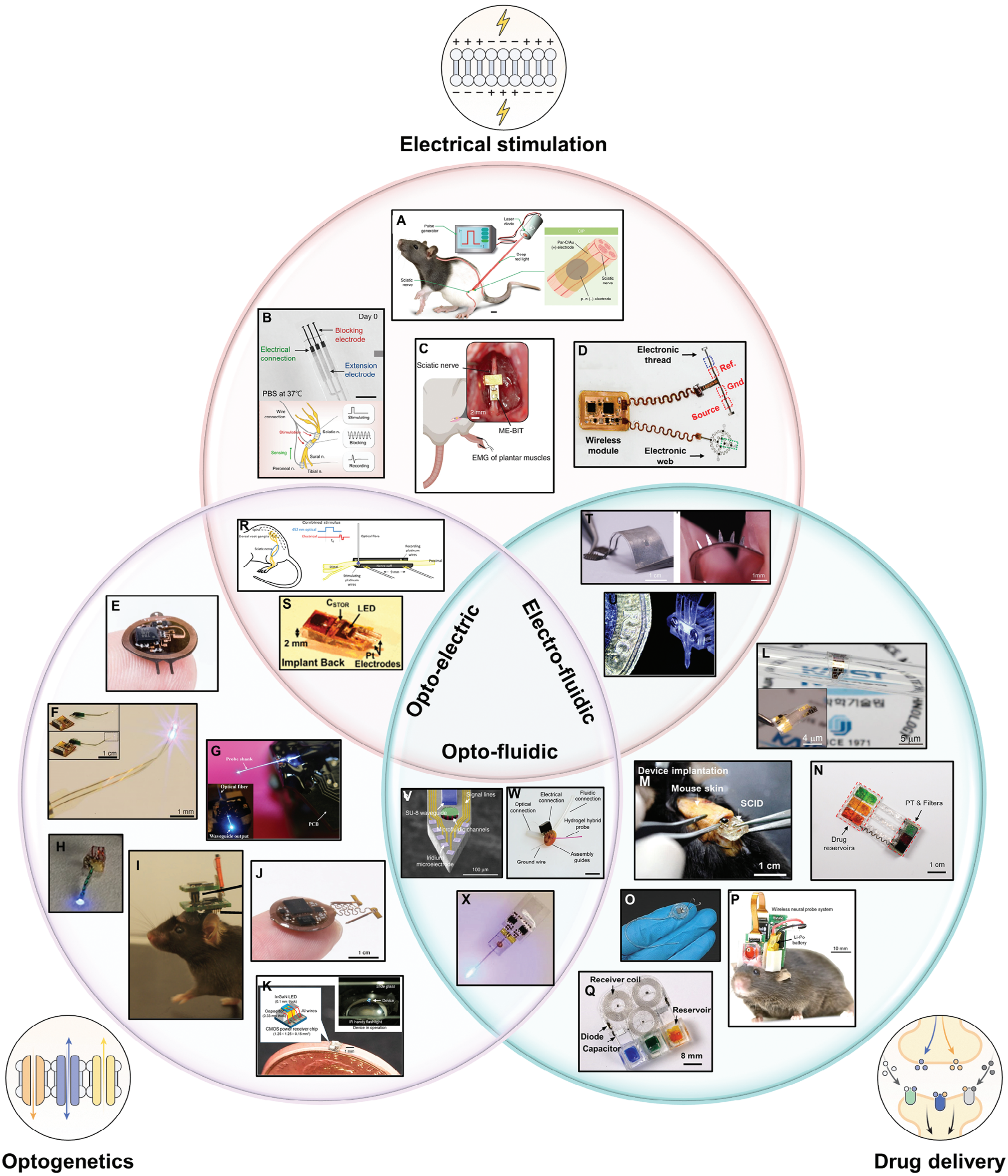

Figure 10. Therapeutic implantable neuromodulation devices. A) Implantable device for electrical stimulation of peripheral nerves using deep-red light via an organic electrolytic photocapacitor. Reproduced with permission.[80] Copyright 2022, Nature Publishing Group. B) Bioresorbable nerve stimulator for pain management. Reproduced with permission.[29] Copyright 2022, American Association for the Advancement of Science. C) Wireless magnetoelectric implant for peripheral nerve stimulation. Reproduced with permission.[31] Copyright 2022, Nature Publishing Group. D) Wireless and fully implantable device for urinary bladder electrical stimulation. Reproduced with permission.[52] Copyright 2023, American Chemical Society. E) Battery-free optoelectronic system for optogenetic system for freely moving rodents. Reproduced with permission.[81] Copyright 2018, Nature Publishing Group. F) Injectable, cellular-scale optoelectronic device. Reproduced with permission.[82] Copyright 2013, American Association for the Advancement of

modulation of neural activity, ensuring precision and minimal side effects in both research and therapeutic applications.[380]

In the flexible optogenetic stimulation devices, the report by Philipp Gutruf et al., presents a compact optoelectronic system for optogenetics. This system is fully implantable and operates in a battery-free manner, allowing for more freedom in behavioral studies without physical constraints (Figure 10E).[81] This device allows for precise and minimally invasive manipulation of neural circuits without wired components. Its design enables precise control over optical stimuli, ensuring spatially independent operation across large areas. While the research by Tae-il Kim et al. introduced a class of injectable, cellular-scale optoelectronics, which are capable of providing wireless control over complex behavioral patterns in freely moving animals (Figure 10F).[82] Furthermore, Yiyuan Yang et al. introduced wireless multilateral devices that enable the study of both individual and social behaviors in animals through optogenetics (Figure 10J).[86] They developed head-mounted and back-mounted devices to offer experimental versatility. The fully wireless operation allows for dynamic programming and control, facilitating intricate studies of social interactions and behaviors in animal models.

On the other hand, in the field of conventional silicon-based optogenetic studies, the study by Fan Wu et al., introduces a neural probe that is equipped with a monolithically integrated dielectric waveguide alongside recording electrodes, specifically designed for optogenetic applications (Figure 10G).[83] This probe allows for more targeted and effective optical excitation of neurons and simultaneous recording of neural activity, making it a valuable tool for exploring complex neural circuits. Also, Christian T. Wentz et al. reported a wirelessly powered and controlled device that significantly advances the study of neural activity in freely moving animals (Figure 10I).[85] The device's lightweight and efficient power management offers a less intrusive and more versatile approach to studying complex neural circuits and behaviors.

For emphasizing minimal-invasive approach, Montgomery et al. detailed the development of a fully internal, wirelessly powered device for optogenetic stimulation, significantly smaller and lighter than other devices (Figure 10H).[84] This implant allows for optogenetic control throughout the nervous system, including the brain, spinal cord, and peripheral nerve endings in freely moving mice. The device's small size and wireless performance minimize interference with natural behavior, broadening the potential for optogenetic experiments in various settings, including more naturalistic environments for the study subjects. Additionally, Tokuda et al. presented a highly compact neural stimulator, notable for its miniature size (1 mm^3) and integration of a photovoltaic power receiver using CMOS technology (Figure 10K).[87] The stimulator operates with blue LED, powered by infrared light for optogenetic applications. Similarly, the small size of the device is a major advantage, as it can be implanted in various parts of the body with minimal invasiveness to deliver photostimulation.

5.1.3. Chemical: Drug Delivery

Chemical neuromodulation involves the localized delivery of pharmacological agents directly to the nervous system (Figure 9C). This targeted approach can significantly enhance the efficacy of drugs while minimizing systemic side effects. Drugs can modulate neural activity by altering neurotransmitter levels, interacting with specific receptors, or affecting ion channel function, thus influencing neuronal excitability and signaling.[381]

Non-invasive application, like transdermal patches, offers ease of use but lack the precision and localization of drug delivery to specific nerve tissues. Invasive methods, such as intrathecal or intracerebral drug delivery systems, provide targeted medication administration directly to the nervous system using microfluidic channels, enhancing efficacy and reducing systemic side effects. However, these methods require surgical intervention and careful management.[19,382]

In drug delivery devices, especially when utilizing microfluidic systems for chemical neuromodulation, several critical factors need to be considered for optimal design and functionality. The dimensions and surface properties of microfluidic channels are crucial for effective drug release. The size and shape of these channels determine the flow rate and distribution of the drug, impacting the precision of delivery. The pressure or flow rate at which the drug is released plays a significant role in the efficacy of the delivery. Controlled release mechanisms ensure a consistent

Science. G) A neural probe with integrated waveguides and electrodes for optogenetic stimulation. Reproduced with permission.[83] Copyright 2013, IOP Publishing. H) A miniaturized, wirelessly powered optogenetic device. Reproduced with permission.[84] Copyright 2015, Nature Publishing Group. I) A head-mounted device integrated with LED and resonant RF power link system. Reproduced with permission.[85] Copyright 2011, IOP Publishing. J) The optogenetic platform with head-mounted and back-mounted LED for social behavior studies. Reproduced with permission.[86] Copyright 2021, Nature Publishing Group. K) A neural stimulator integrated with a photovoltaic power receiver using CMOS. Reproduced with permission.[87] Copyright 2018, American Institute of Physics. L) A wirelessly powered microdevice for targeted drug delivery to the cerebral cortex. Reproduced with permission.[89] Copyright 2018, Elsevier. M) A soft implantable drug delivery device for monitoring EEG and triggering drug release. Reproduced with permission.[92] Copyright 2021, American Association for the Advancement of Science. N) A bioresorbable device utilizing external light to trigger drug delivery. Reproduced with permission.[88] Copyright 2023, National Academy of Science. O) A self-powered drug delivery system using TENG. Reproduced with permission.[90] Copyright 2017, Wiley-VCH. P) A battery-powered neural probe system capable of bi-directional wireless drug delivery. Reproduced with permission.[18] Copyright 2022, Nature Publishing Group. Q) A bioresorbable drug delivery system with electrochemically degradable valves. Reproduced with permission.[91] Copyright 2020, American Association for the Advancement of Science. R) Implantable device combining optogenetic and electrical stimulation targeting the sciatic nerve. Reproduced with permission.[387] Copyright 2018, IEEE. S) Wireless device for combined electrical and optical stimulation of peripheral nerves. Reproduced with permission.[388] Copyright 2023, Frontiers Media S.A. T) Implantable device with bioresorbable microneedles for electrotherapy and drug delivery. Reproduced with permission.[389] Copyright 2022, The Royal Society of Chemistry. U) Intracranial implants for electrical stimulation and local drug delivery. Reproduced with permission.[390] Copyright 2022, American Chemical Society. V) A multifunctional multi-shank neural probe with microfluidic channels and SU-8 waveguides. Reproduced with permission.[6] Copyright 2019, Nature Publishing Group. W) Hydrogel hybrid probes for electrophysiological and optogenetic studies. Reproduced with permission.[298] Copyright 2021, Nature Publishing Group. X) An opto-fluidic device for wireless pharmacology and optogenetics studies. Reproduced with permission.[391] Copyright 2018, Wiley-VCH.

and targeted delivery to the intended site. The mechanism used for pumping the drug from the chamber, such as heaters, osmotic pumps, or pneumatic systems, influences the delivery rate and volume.[383–385] Each mechanism offers unique advantages in terms of control and consistency. The material of the drug chamber needs to be considered for preventing drug oxidation from biofluids and ensuring long-term storage stability. Biocompatible and inert materials are preferred to maintain drug integrity. Ensuring that the drug is released at a consistent rate and volume is necessary for reliable treatment outcomes. The system should be designed for repeatable performance over its intended usage period. For complex treatments, the ability to deliver multiple drugs through separate chambers and channels is advantageous. This allows for a more comprehensive treatment regimen, addressing different aspects of a condition simultaneously. Each of these factors contributes to the overall effectiveness and safety of the drug delivery system.[386]

For wirelessly powered drug delivery devices, the study by Sung et al. reported a flexible, wirelessly powered drug delivery microdevice, specifically designed for precise and controlled drug administration directly to the cerebral cortex (Figure 10L).[89] This allows for minimally invasive implantation and targeted drug delivery in the brain, addressing the challenges of treating neurological disorders and minimizing side effects. Koo et al. presented a new approach to controlled drug delivery (Figure 10Q).[91] This study introduces a unique bioresorbable drug delivery system that uses electrochemically degradable valves to regulate drug release. The device operates wirelessly, enabling on-demand drug release. The use of crevice corrosion as a mechanism for valve activation offers rapid and energy-efficient drug release. Joo et al. introduced the development of a soft implantable drug delivery (SID) device that is wirelessly integrated with wearable devices for real-time monitoring and rapid drug administration in response to fatal seizures (Figure 10M).[92] The SID's design is characterized by its softness and minimization, moving bulky components like batteries and control electronics to the wearable segment. This ensures minimal invasiveness and maximizes patient comfort.

There are also studies that rely on other power sources instead of wireless power to operate drug delivery systems. Yoon et al. presented a miniaturized and battery-powered wireless neural probe system capable of bi-directional drug delivery and simultaneous electrophysiological recording in socially interacting mice (Figure 10P).[18] This system can modulate neural activity and behavior through controlled drug delivery for investigating the neural basis of social interactions and the effects of pharmacological agents. The integration of drug delivery with neural monitoring in a socially relevant context enables the study of behavioral neuropharmacology. The paper by Zhang et al. introduced a technology combining self-powering using electrochemical corrosion and light-control schemes in a bioresorbable platform for targeted drug delivery (Figure 10N).[88] This approach utilizes external light sources to trigger an electrochemical cell structure in the device, allowing precise control over drug release. Song. P. et al., introduce a self-powered drug delivery system harnessing biokinetic energy (Figure 10O).[90] This system features a triboelectric nanogenerator (TENG) that converts mechanical energy from body movements into electrical energy to power the drug delivery process. This self-sustaining system eliminates the need for external power sources or batteries, enhancing the practicality and longevity of implantable drug delivery devices.

5.1.4. Multimodal: Opto-Electric, Electro-Fluidic, and Opto-Fluidic

Multimodal neuromodulation therapies that combine opto-electric,[387–388] electro-fluidic,[389–390] and opto-fluidic[6,298,391] modalities are at the forefront in neuroscience research. These therapies offer unique benefits due to their ability to provide precise and controlled stimulation to neural tissues through various modalities that were not previously possible. Furthermore, the combination of neuromodulation modalities in a single platform allows for more comprehensive approaches to studying and manipulating neural functions.

In the opto-electric category, one study explored a combination of optogenetic and electrical stimulation (Figure 10R).[388] This approach targets the sciatic nerve to achieve selective control over sensory fibers, a technique that could have substantial implications for pain management and neurological therapies. The second paper presented a combined approach in neuromodulation techniques using a millimeter-sized wireless device (Figure 10S).[387] This device offers a dual-function platform for electrical and optical stimulation of peripheral nerves. The device enables precise stimulation of targeted neural tissues without the need for cumbersome equipment.

In the realm of electro-fluidic neuromodulation, the first paper introduces a hybrid fabrication method for multimodal intracranial implants (Figure 10T).[389] These implants are capable of both electrical stimulation and local drug delivery. The paper underscores the potential of these implants in studying and modulating neural functions, particularly in the context of intricate brain activities and disorders. The second electro-fluidic paper discusses an implantable device featuring bioresorbable microneedles (Figure 10U).[390] This device is designed for wireless electrotherapy and drug delivery, integrating the benefits of minimally invasive application with advanced control over therapeutic delivery.

In the opto-fluidic domain, one study developed a miniaturized, battery-free optofluidic system designed for wireless pharmacology and optogenetics (Figure 10X).[391] This system integrates microscale light-emitting diodes and microfluidic drug delivery systems, offering a fully wireless, independent control of light and fluid delivery. This design allows for precise and minimally invasive manipulation of neural circuits in freely moving animals. The second opto-fluidic paper introduces hydrogel hybrid probes for long-term neural sensing and modulation (Figure 10W).[298] These probes are adaptive and multifunctional, designed for sustained use in neural applications. Hydrogels enable reducing foreign body response and enhance biocompatibility by similar mechanical and chemical properties from the biological tissue. The third opto-fluidic paper presents a multifunctional multi-shank neural probe (Figure 10V).[6] This probe is particularly effective for investigating and modulating long-range neural circuits in vivo. The multifunctionality of the device, coupled with its design for probing extensive neural networks.

6. Advances, Challenges, and Futures on Implantable Devices

The development of implantable bioelectronic devices has undergone a remarkable evolution, shifting from basic implantable components to complex systems that integrate advanced hardware and software. Initially, these devices were simple, fulfilling basic medical needs like cardiac pacing. However, the field has witnessed a substantial transformation, driven by the integration of sophisticated hardware—such as miniaturized electrodes, sensors, and intricate circuit systems—and advanced software capable of complex signal acquisition, processing, conversion, interpretation, and judgment.[392–394] Each engineering discipline contributes uniquely to the development of these devices, from the creation of biocompatible materials to the design of energy-efficient microelectronics and the development of algorithms for data interpretation. Moreover, a deep understanding of biology, physiology, and medicine is crucial. This interdisciplinary approach facilitates the creation of devices that are not only technically proficient but also medically relevant and safe for long-term use in the implanted environment. Bioelectronic implantable devices have become integral in the treatment of various medical conditions, focusing therapeutic possibilities. As we continue to explore this field, we are not only witnessing the progress in the devices themselves but also facing new engineering challenges and envisioning future possibilities in medicine and healthcare.

6.1. Engineering Challenges

6.1.1. Water-Resistance and Biocompatibility

Waterproofing in implantable bioelectronic devices is mandatory due to the need for long-term stability and functionality in a wet biological environment. As materials engineering advances, various materials and associated modifications have been discussed for achieving effective waterproofing.[395] These materials can be categorized into different groups based on their properties and applications. One category includes rigid hermetic encapsulations that offer robust protection but lack flexibility such as titanium casing.[396] Another category involves soft, conformable materials like silicone, while offering some degree of flexibility and biocompatibility, may not provide the same level of hermetic protection as rigid encapsulations.[397] Parylene-C, deposited via chemical vapor deposition (CVD), emerges as a promising material due to its biocompatibility and high water-resistance property.[398] When applied in thin layers, it maintains waterproofing efficacy over years. Overall, rigid encapsulations, while providing excellent protection, can cause discomfort and are not suitable for dynamic or soft tissue interfaces. Flexible and soft materials, on the other hand, may not offer the same level of protection and can be prone to degradation over time. For future directions, the researchers should focus on developing materials that combine the best of both worlds—soft with flexibility and robust hermetic sealing. This could involve innovative use of nanomaterials, hybrid structures combining rigid and soft elements, or new fabrication techniques that allow for better integration of the encapsulation with the device's functional parts. The goal is to achieve long-term reliability, biocompatibility, and mechanical compatibility with the dynamic environment of the biological organism.

6.1.2. Invasiveness

Invasiveness refers to the extent of physical intrusion and interaction of a device with biological tissues. Invasiveness in implantable devices is important for ensuring effective treatment while minimizing tissue damage and adverse reactions. Non-invasive or minimally invasive devices are preferred as they typically result in fewer complications and are better tolerated by subjects. The degree of invasiveness varies among different implantable devices. For instance, neural cuff electrodes for stimulation of peripheral nerves represent a minimally invasive approach. In contrast, more invasive devices, such as traditional injectable brain neural interfaces, might require direct implantation into neural tissue, posing greater risks of tissue damage and inflammation. Invasive devices, while often necessary for certain treatments, pose challenges such as potential tissue damage, inflammation, and scarring. This can lead to a foreign body response.[399] Advances in materials science and bioengineering are focusing on reducing the invasiveness of implantable devices. This includes the modification of the materials, such as nanostructured coatings and anti-biofouling material coatings, which enhance biocompatibility and reduce tissue inflammation.[400–402] These coatings can serve as a buffer layer, reducing the adhesion of cells that cause scar tissue formation and offering a more conducive environment for neuronal cell adhesion. The future of these devices lies in innovative design approaches and material choices that minimize physical and biochemical intrusion while maximizing therapeutic benefits.

6.1.3. Mechanical Mismatch

Mechanical mismatch in implantable bioelectronic devices is a significant challenge, primarily due to the disparity in mechanical properties between soft substrates and rigid components like integrated circuits (ICs). This mismatch can lead to issues like delamination, cracks, or even breakage at the interface between these components. To address these challenges, research is being conducted on various fronts. One approach is the integration of thin inorganic materials, which are miniaturized towards nanometric formats and then embedded in elastomer supporting layers.[403] This method aims to achieve a uniform or controlled stress distribution during bending, twisting, or multi-axial deformation of the device. To achieve this, inorganic materials must be placed on the neutral plane of a soft polymer substrate. In another approach, the chemical engineering of organic electronic materials with built-in mechanical compliance is used to form fully elastic microfabricated electronic circuits.[404] Another innovative approach to overcoming mechanical mismatch is the development of rigid-soft composite structures based on 'rigid islands'.[405] These structures are designed to maintain the necessary rigidity for electronic functionality on rigid components while being embedded in a softer, more flexible matrix that matches the mechanical properties of biological tissues. This design helps to mitigate the stress concentrations at the interface between rigid and soft components, thus enhancing the overall mechanical integrity and reliability of the device. Overcoming the challenge of mechanical mismatch in implantable bioelectronic devices requires unique engineering solutions that blend rigidity for electronic functionality with flexibility for biocompatibility. The development of new materials and structural designs is key to achieving this balance.

6.1.4. Integrated Circuit (IC)

The limitations of integrated circuits (ICs) in bioelectronics restrict the performance of implantable devices. These limitations primarily revolve around IC's limited inputs, low data rates, and limited computing speeds, each of which has specific implications. First, a common issue with ICs in bioelectronic devices is the restricted number of inputs they can handle. For instance, Intan's RH series ICs, which are widely used as commercial biopotential amplifiers, have a maximum capacity of 64 channels. However, when used with advanced neural probes like the Neuropixel,[169] which possesses over 1000 electrodes, multiple ICs are required. This necessity for multiple ICs not only complicates the system but also increases the overall size of the device, making it less practical for implantable devices. Focusing on low data rates, Bluetooth Low Energy (BLE) technology serves as a relevant example in this context. The BLE is often employed for wireless communication in fully implantable devices due to its high data rate and stability coupled with low power consumption. BLE allows communication over distances of several meters and has gained widespread usage. However, despite significant improvements in data throughput following updates to BLE 5.0 and later, certain limitations remain. The maximum theoretical data speed for current BLE technology is 2 Mbps, but in practical terms, the maximum achievable speed is ≈120 kBps. This limitation becomes particularly evident in applications like extracellular single/multi-unit recording, which demands high speed sampling rate (≈30 kSa s^{-1}). In such applications, the actual speed limit for a system using BLE technology is around four channels, posing a constraint on the volume and speed of data that can be transmitted. To address this challenge, future advancements in implantable bioelectronic devices will need to focus on enhancing wireless communication technologies like Wi-Fi, ionic communication,[406] and Li-Fi.[407] This includes improving data transmission rates to handle larger volumes of high-speed biomedical signals efficiently. Additionally, exploring alternative wireless technologies or developing new protocols that can offer higher data rates while maintaining low power consumption will be crucial for the advancement of implantable bioelectronic devices.

The limitation of computing speed in microcontrollers (MCUs) used in implantable bioelectronic devices is a significant challenge, particularly for real-time feedback applications like closed-loop control or AI-based algorithms. One of the key aspects contributing to this challenge is the limited memory and storage capacity of these MCUs. For instance, research from MIT on tiny machine learning (TinyML)[408–411] in microcontrollers introduces these limitations. The MCUs typically used in implantable devices have memory sizes of ≈256 kilobytes and storage capacities up to 1 megabyte. In contrast, mobile AI on smartphones and cloud computing may have memory capacities of 256 gigabytes and storage in terabytes, with significantly higher processing capabilities. Such limited memory and storage capacities in MCUs impact their ability to efficiently run complex neural network models, like convolutional neural network (CNN), which are essential for processing visual data in medical applications. The research showed that optimizing memory usage in these devices can improve their computational efficiency. MCUNetV2,[412] a TinyML vision system developed at MIT, exemplifies how these challenges can be addressed. Despite having only a fraction of the memory and storage capacity of larger AI models, MCUNetV2 was able to achieve high accuracy in object detection and classification tasks, demonstrating the potential for advancements in the computational capabilities of MCUs for implantable bioelectronics. By optimizing memory usage and rethinking the architectural design of neural networks, it's possible to enhance the computational capabilities of these devices for efficient medical applications.

6.2. Next-Visions

6.2.1. Flexible and Soft IC

The limitation of mechanical mismatch between rigid ICs and soft substrates can be resolved by changing rigid ICs to flexible or soft ICs.[413–415] Despite the advantages, the development of flexible or soft ICs faces several challenges. The difficulties in performance degradation of flexible or soft ICs primarily arise from the inherent properties and behaviors of materials used in these circuits. In organic material-based flexible or soft ICs, have different electrical properties such as low charge carrier mobility compared to traditional silicon IC.[414,416] At the atomic level, the arrangement and stability of atoms and molecules in flexible materials can be less consistent compared to rigid ICs. This inconsistency can lead to variable electrical properties, impacting the performance and reliability of the ICs. Also, the mobility of charge carriers (electrons and holes) in organic materials is generally lower than in silicon. This is due to the disordered arrangement of these materials at the atomic level, which can create traps and barriers for charge carriers, leading to reduced mobility and slower transistor speeds. Furthermore, achieving a balance between mechanical flexibility and optimal electrical conductivity is challenging. Flexibility often requires molecular structures that can bend without breaking, but these structures may not be conducive to the best electrical conductivity. Moreover, the interfaces between different materials in flexible ICs (such as between the semiconductor and the dielectric or electrodes) can introduce additional traps and defects. These imperfections can affect the overall performance of the ICs by increasing the likelihood of charge scattering and recombination. In addition, flexible materials can be more sensitive to environmental factors like temperature, humidity, and oxygen.[417] These factors can cause atomic or molecular level changes in the materials, such as oxidation or moisture absorption, leading to performance degradation over time. In terms of fabrication, the methods used for depositing and patterning flexible materials can introduce additional defects and inconsistencies. Techniques like printing or solution processing, while advantageous for flexibility and cost, might not achieve the same precision and uniformity as traditional semiconductor manufacturing processes.[418] Addressing these challenges involves innovative material science and engineering approaches to develop new materials and fabrication techniques that can maintain high electrical performance while providing the desired flexibility or softness.[419]

6.2.2. AI Algorithms for Implantable Device

AI algorithms are becoming increasingly essential in enhancing the diagnostic capabilities of implantable devices, particularly through the analysis of physiological signals.[420] Unlike conventional monitoring devices, implantable devices can be implanted within the patient's body, continuously recording high-quality signals over extended periods. This capability allows for a robust dataset, which facilitates more reliable and personalized diagnosis in real-time with the proper algorithm.[421]

Among AI algorithms, deep learning algorithms such as CNN and recurrent neural networks (RNN) integrate feature extraction layers and can achieve superior performance compared to conventional algorithms, particularly in identifying hidden features critical for classification. The CNN was originally developed for image recognition, utilizing feature extraction layers with convolutional filters. When applied to implantable devices, electrophysiology signals are often analyzed using time-domain signals or time-frequency representations, which can be used as input values for 1D or 2D CNN.[422–423] In the application of CNN to electrophysiology signals recorded by implantable device, the focus is typically on diseases that necessitate urgent treatment, such as arrhythmias and seizures. Thus, both accuracy and detection speed are critical. Consequently, it is essential to minimize the parameters required for training CNN architecture to enhance the efficiency of the diagnostic system.[424] On the other hand, RNN is applied to analyze and predict chemical signals, leveraging their suitability for sequential data. An example is predicting glucose levels in Type 1 diabetes patients using continuous glucose monitoring (CGM) data.[425] To enhance prediction accuracy, the CGM data is processed using Kalman smoothing, and advanced long-short-term memory (LSTM) architecture is employed.[426] In addition to deep learning, traditional machine learning algorithms also play an important role in the analysis of physiological signals, such as spike sorting. Unlike deep learning algorithms, traditional machine learning algorithms require additional feature extraction steps. For example, in spike sorting, the measured spikes are first processed using principal component analysis to reduce dimensionality and extract features. Subsequently, these features are clustered using machine learning algorithms such as K-means clustering and DBSCAN to group similar spikes together, facilitating further analysis.[427]

These deep learning and machine learning algorithms are being integrated to enhance the efficiency of diagnostic system in implantable devices.[14] However, these devices still face challenges such as high power consumption when AI algorithms require high-frequency neural signals. To address these challenges, AI algorithms for signal reconstruction are being employed in implantable device research. For example, the SwinIR model, a transformer-based algorithm originally used for enhancing image resolution, is being adapted to reconstruct high-frequency neural signals from lower-frequency signals. This approach extends the operational lifespan of devices by reducing the need for high sampling rates, without necessitating changes to the hardware structure.[428]

6.2.3. Edge-AI Computing

Edge-AI computing is increasingly important in futuristic bioelectronics, especially from diagnostic, therapeutic, and closed-loop system perspectives.[109–112] The integration of edge-AI in these devices significantly enhances their functionality, responsiveness, and efficiency, making them more adaptable to the dynamic needs of medical care. Edge-AI computing allows for real-time data processing and analysis directly within the implantable device. This capability is crucial for timely diagnostics, enabling the device to identify patterns or anomalies in physiological data, which could indicate the onset of a medical condition. Immediate processing at the edge minimizes delays compared to cloud-based analyses, allowing for quicker responses to potential health issues.[429] In therapeutics, edge-AI empowers devices to deliver personalized treatments and enhancing privacy as data processing occurs locally. Perhaps most importantly, edge-AI enables the creation of powerful closed-loop systems in implantable devices. These systems can monitor physiological signals, process this data to make decisions, and automatically adjust therapy delivery without external intervention. For instance, in patients with neurological disorders, edge-AI can analyze neural signals in real-time and adjust stimulation parameters for optimal therapeutic outcomes.[430] This adaptability ensures that treatments are not only timely but also tailored to the individual's current physiological state. Despite the significant benefits of edge-AI computing in implantable devices, challenges such as limiting memory and processing power can hinder the implementation of complex AI models. Nevertheless, the growing interest in edge AI and ongoing research are leading to more extensive use in implantable devices.[431] The evolution of hardware, such as more advanced miniaturized processors with neuromorphic architecture,[432] is necessary to support the increased computational demands of advanced AI algorithms. This hardware must be optimized for low power consumption and miniaturized for integration into implantable devices.

6.2.4. Advanced Powering Methods

Advanced powering methods should be developed due to the inherent limitations of traditional power sources like batteries, especially as devices become more miniaturized. Two common powering methods in this domain are biofuel power[433–434] and wireless power transfer (WPT),[161] both of which address the need for sustainable, long-term power solutions in these devices. Biofuel cells convert biochemical energy (like glucose and oxygen in the body) directly into electrical energy. This method is particularly appealing for implantable devices due to the abundance of biofuels in the human body.[435] However, quantifying the exact energy harvesting potential of biofuel cells in terms of numerical values is complex, as it depends on various factors such as enzyme efficiency, the concentration of biofuels, and the design of the cell itself. The current power output of biofuel cells is relatively low which is suitable for low-power implantable devices but limited to systems that require about over tens of milliwatts.[161,436] Future research may focus on enhancing the efficiency and longevity of biofuel cells, possibly through advanced enzyme engineering or nanotechnology. WPT technology, particularly using near-field inductive coupling at the frequency band at 13.56 MHz, is gaining popularity for powering implantable devices. It involves an external coil generating an alternating magnetic field, transferring energy through tissues to an implanted coil.[81,437] In addition, implantable devices utilizing the UHF and RF bands like 915 MHz and 2.45 GHz are being developed.[438–440] The efficiency of these systems is significantly improving, with advanced designs focusing on optimizing the matching network and rectifier performance to maximize power delivery to the implanted device. The future of WPT lies in improving the transmission efficiency and range, especially for deep-implanted devices in a broad area. This may involve developing more efficient antennas, advanced meta-materials for better power transmission through tissues, and smart power management systems to optimize energy usage by the implant.[441–442]

6.2.5. Biodegradation

Biodegradation in implantable bioelectronic devices is promising because of minimizing long-term adverse effects on the body, avoiding the need for additional surgeries to remove the device, and reducing environmental impact.[443–445] In the field of biodegradable electronics, materials are classified into organic and inorganic types. Organic materials include natural polymers like poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), and polyglycolic acid (PGA), known for their biocompatibility and controlled degradation rates.[446–450] These materials can degrade over periods ranging from several months to a few years, depending on their composition and environmental conditions. Inorganic materials include metal-based materials for conductive networks like magnesium, molybdenum, and zinc, and their alloys, designed to degrade over time under physiological conditions.[29,451–452] Their degradation times vary from months to a couple of years, depending on alloy composition and physiological environment.

The future development in biodegradable implantable bioelectronic devices is likely to focus on enhanced biocompatibility and safety to minimize immune response and potential toxicity. There will be efforts to achieve precise control over degradation rates to match the functional lifetime of devices and integrate biodegradable materials into more complex devices like multi-functional sensors and stimulation systems without compromising performance. Sustainability will also be emphasized, focusing on the sustainability of material production and degradation in biomedical applications. This rapidly evolving field aims to develop materials that are not only functionally effective but also safe and eco-friendly.[453–454]

7. Conclusion

We present a comprehensive review of the current state and advancements in bioelectronic devices for biomedical applications. The paper details the integration of various types of biosensors, including mechanical, thermal, electrical, optical, and chemical, into implantable devices. These physiological signal recordings proceed with continuous health monitoring and early diagnosis, providing data about the physiological state of different organ systems. The paper further explores the therapeutic applications of these bioelectronic devices in neuromodulation. It describes how these devices can manage a wide range of conditions by delivering electrical, optical, or chemical stimuli to targeted areas. One of the key areas of focus in the paper is the development of closed-loop systems in implantable devices. These systems are significant for their ability to provide adaptive treatment strategies. The paper focuses how closed-loop systems can monitor physiological signals and adjust the therapy. Furthermore, we discuss advances, challenges, and futures of implantable devices. Elemental analysis of bioelectronics is also discussed for highly integrated devices. The integration of AI and edge computing in bioelectronic devices significantly enhances the diagnostic and therapeutic performance of these devices. We expect that this paper will guide broad engineering concepts and specific designs for bioelectronic implantable devices.

Acknowledgements

S.O. and J.J. contributed equally to this work. This work was supported by the National Research Foundation of Korea (NRF) funded by Ministry of Science and ICT (RS-2024-00430782, RS-2024-00415347, RS-2023-00234581); NAVER Digital Bio Innovation Research Fund, funded by NAVER Corporation (Grant No. 3720230070); and DGIST R&D Program of the Ministry of Science and ICT (24-SENS2-02).

Conflict of Interest

The authors declare no conflict of interest.

Keywords

bioelectronics, biosensors, closed-loop, implantable devices, neuromodulation

Received: February 28, 2024
Revised: May 4, 2024
Published online: July 8, 2024

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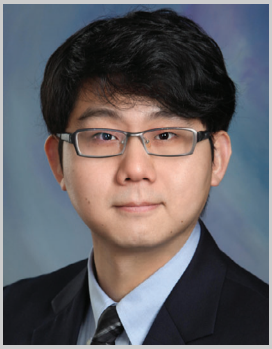

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