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AI-driven and IC-enabled advanced closed-loop neuromodulation for practical clinical applications

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Highlights:

- Provide an overview of state-of-the-art AI-driven algorithms and IC-enabled technologies.
- Summarize the CLNM landscape which emphasizes the clinical practice-oriented perspective.
- Clarify the effectiveness of implementing CLNM in clinical settings.
- Describe the roadmap for integrating AI and IC innovations to address unmet clinical needs.

Abstract: Closed-loop neuromodulation (CLNM) has emerged as a transformative approach for treating neurological disorders, enabling precise and adaptive interventions through real-time monitoring and modulation of neural activity. Although advancements in artificial intelligence (AI) have unlocked new possibilities for more accurate closed-loop systems, and significant progress has been made in this area within academia, challenges persist in translating these technologies into clinical practice. Similarly, integrated circuits (IC) have been pivotal in optimizing power consumption, latency, and device miniaturization. However, further innovations are still required to meet the stringent demands of clinical environments. This review not only provides an overview of state-of-the-art AI-driven algorithms and IC-enabled technologies that are reshaping the neuromodulation landscape but also emphasizes a clinical practice-oriented perspective. Through analysis of related clinical trials, we highlight both the effectiveness and the obstacles of implementing these technologies in clinical settings. Finally, we propose a roadmap for integrating AI and IC innovations to address unmet clinical needs, offering insights into the future of CLNM.

Keywords: closed-Loop neuromodulation; artificial intelligence (AI); application specific integrated circuits (ASIC)

1. Introduction

Neuromodulation has long served as a cornerstone in the treatment of neurological and psychiatric disorders, offering therapeutic interventions through electrical or chemical modulation of neural

circuits [1,2]. Traditional open-loop systems, such as deep-brain stimulation (DBS) for Parkinson's disease [3] or spinal cord stimulation (SCS) for chronic pain [4], rely on static stimulation parameters programmed during periodic clinical visits. While effective for many patients, these systems inherently lack the ability to adapt to dynamic neural states, resulting in suboptimal therapeutic outcomes, persistent side effects, and inefficient energy consumption [5].

Recent advancements in sensing technologies and computational power have catalyzed a paradigm shift toward closed-loop neuromodulation (CLNM) [6,7]. Unlike their open-loop counterparts, CLNM systems operate via a "sense-analyze-act" framework, continuously monitoring neural biomarkers (e.g., local field potentials, beta-band oscillations) and dynamically adjusting stimulation parameters in real time [8,9]. Early clinical successes, such as the NeuroPace RNS System for epilepsy, have demonstrated the feasibility of this approach. After five months of treatment, it achieved seizure reduction rates of 40%–50% in refractory patients [10,11].

However, the widespread adoption of CLNM remains constrained by computational and hardware limitations [12–14]. Current systems often employ handcrafted thresholds for biomarker detection, which struggle to accommodate interpatient variability or disease progression [15]. Furthermore, conventional integrated circuits (ICs) used in implantable devices face trade-offs between processing speed, power consumption (typically > 10 mW), and miniaturization, hindering long-term chronic use [16].

The integration of artificial intelligence (AI) and next-generation IC technologies promises to overcome these barriers. AI-driven algorithms, such as deep neural networks (DNNs) [17,18] and reinforcement learning (RL) [19] models, enable adaptive decoding of complex neural patterns, while specialized ICs—featuring low-noise analog front ends (AFEs) [20], event-driven analog-to-digital converters (ADCs) [21,22], and near-threshold computing architectures—address the critical need for energy efficiency and miniaturization [23,24]. Together, these innovations pave the way for truly personalized therapies, capable of self-optimizing stimulation parameters based on individual patient responses [25].

To systematically review the development trajectory of CLNM systems, this article is organized as follows. First, we define the fundamental principles and key components of CLNM, and summarize its main clinical indications and regulatory effects. We highlight the advantages of closed-loop approaches in terms of precision and responsiveness, while pointing out current limitations—particularly the need for efficient algorithms and low-power chip designs to support personalized therapy. Next, we review mainstream commercial CLNM products and categorize the current technical pathways of AI-assisted systems, including traditional machine learning methods, the integration of deep learning, and advancements in integrated circuit (IC) design. Finally, based on recent research trends, we outline future directions for next-generation AI-assisted CLNM systems, emphasizing the co-development of low-power ICs and high-performance AI algorithms, and discussing key challenges that need to be addressed. This review aims to provide valuable insights for advancing CLNM from bench to bedside.

2. Definition, principles, and commercial landscape of CLNM

2.1. Definition and foundational principles

CLNM represents a transformative paradigm in neurotherapeutic intervention, defined by its capacity to dynamically integrate real-time biophysical feedback with adaptive control algorithms to optimize therapeutic outcomes. Unlike conventional open-loop systems that deliver static predetermined stimulation parameters (for example, chronic deep brain stimulation [DBS] for Parkinson's disease), closed-loop systems operate through a continuous detect-analyze-actuate cycle. Figure 1 shows a general wearable or implantable closed-loop epileptic seizure detection or prediction scheme. This architecture enables context-aware modulation, where intervention parameters (e.g., frequency, amplitude, or spatial targeting) are iteratively adjusted based on moment-to-moment neural state assessments. For instance, in epilepsy management, such systems autonomously detect interictal epileptiform discharges or high-frequency oscillations (HFOs > 80 Hz) through intracranial electroencephalography (iEEG) and deliver responsive electrical stimulation to abort ictal progression, achieving seizure reduction rates exceeding 60% in drug-resistant cases [26–28].

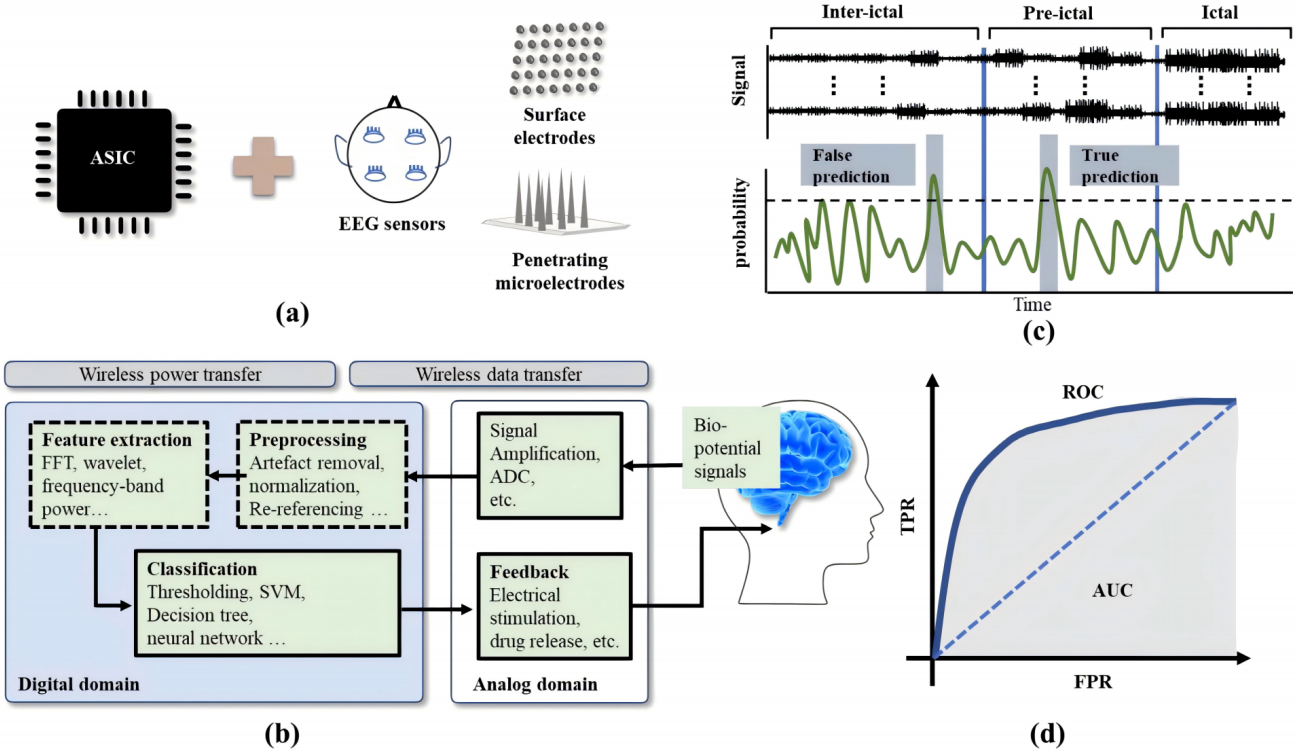

Figure 1. Typical seizure prediction system: **(a)** Highly integrated seizure prediction system including a bio-interface or micro-electrode array to collect bio-signals such as EEG, ECoG, and an integrated circuit for analog and digital processing. **(b)** Key digital and analog hardware blocks to building a closed-loop neuromodulation (CLNM) system. **(c)** The goal of the system is to classify different seizure stages based on the captured bio-signals. **(d)** Performance of the system is characterized by various metrics such as receiver operating characteristic curve (ROC), area under curve (AUC), which are determined by true positive rate (TPR) and false positive rate (FPR) of the system.

The conceptual framework of CLNM is based on three pillars:

- Time-sensitive biosensing: High-fidelity acquisition of neural signals with millisecond temporal resolution is critical. Emerging technologies, such as flexible nanoelectronics or optogenetic voltage reporters, enable chronic monitoring of both local field potentials (LFPs) and single-unit activity across distributed networks. These signals are processed to extract clinically relevant biomarkers—for example, beta band oscillations (13 to 30 Hz) in the subthalamic nucleus serve as proxy for bradykinesia severity in Parkinsonian states [29].
- Adaptive decision algorithms: Machine learning models, including recurrent neural networks (RNNs) [30] and hidden Markov models [31], analyze streaming data to classify neural states (e.g., pre-seizure, dyskinetic, or depressive phases) and predict pathology trajectories. Reinforcement learning frameworks further optimize stimulation policies by maximizing reward functions tied to therapeutic efficacy metrics (e.g., tremor suppression or mood stabilization) [32].
- Precision intervention: Closed-loop systems orchestrate multimodal actuators, such as demand-controlled DBS [33], optogenetic silencing of hyperactive neuronal populations, or closed-loop vagus nerve stimulation (VNS) [34] titrated to heart rate variability. Innovations in magnetogenetics and ultrasound-mediated drug release now permit spatiotemporally precise modulation of deep brain structures without invasive implants [35].

A critical distinction from open-loop approaches lies in bidirectional interactivity: therapeutic actions not only modulate neural circuits but also alter subsequent feedback signals, creating a self-reinforcing optimization loop. This dynamic interaction mirrors homeostatic neurophysiological processes, where endogenous control mechanisms (e.g. hippocampal theta-gamma coupling during memory encoding) are coopted or enhanced. The adaptability of the system is particularly advantageous for disorders that exhibit temporal fluctuations (for example, the interictal-ictal continuum of epilepsy) or variability between patients in circuit pathophysiology (for example, the heterogeneous frontolimbic connectivity patterns of depression).

By bridging neurophysiological insights with advances in artificial intelligence and bioengineering, CLNM establishes a new standard for personalized neurotherapy. Its capacity to evolve with patient-specific disease dynamics positions it as a cornerstone for next-generation treatments of refractory neurological and psychiatric disorders, as will be explored in subsequent discussions of clinical applications.

2.2. The role and mechanism of CLNM in neurodegenerative disease treatment

In the treatment of neurological diseases, neuromodulation techniques have become pivotal in improving patient outcomes. Traditional open-loop neuromodulation systems deliver continuous stimulation with fixed parameters, lacking the capability to respond to the patient's real-time neural states, which may result in limited efficacy or increased side effects. In contrast, CLNM systems dynamically adjust stimulation parameters by continuously monitoring neural activity, enabling personalized and adaptive therapeutic strategies. This approach has demonstrated significant advantages in various neurological disorders.

The following contents will explore the advantages of CLNM over traditional open-loop methods and examine specific clinical cases of its application in neurological disease treatments, highlighting its

pivotal role in modern neuromodulation.

2.2.1. Comparative advantages over traditional therapies

In the field of neuromodulation, traditional open-loop stimulation methods have been widely employed in treating various neurological disorders, including Parkinson's disease, epilepsy, and chronic pain. However, as our understanding of the complexity of neural networks deepens, CLNM systems—capable of real-time monitoring and adaptive regulation—are emerging as a focal point in both research and clinical applications. The following table (Table 1) compares the primary characteristics and clinical applications of traditional open-loop methods versus CLNM systems, providing a comprehensive overview of their differences and respective advantages [36–38].

Since CLNM has huge advantages compared with traditional solutions, CLNM has gradually increased in clinical applications.

Table 1. Closed-loop *vs.* open-loop therapeutic profile.

Dimensions	Closed-Loop	Open-Loop
Response Speed [39]	< 50 ms intervention	Fixed-rate stimulation
Personalization [40]	Covers 95% individual variations	One-size-fits-all approach
Side Effects [41]	40%–60% reduction	Non-target activation risks
5-Year Efficacy [42]	30% lower recurrence	15% annual efficacy decline

2.2.2. Clinical applications in major neurodegenerative diseases

CLNM is an advanced therapeutic strategy that involves real-time monitoring of a patient's neural activity and dynamically adjusting stimulation parameters based on feedback to achieve individualized treatment for neurodegenerative and other neurological disorders. Its clinical applications have demonstrated significant efficacy in conditions such as Parkinson's disease (PD), Alzheimer's disease (AD), and epilepsy. Next, we will introduce the application of closed-loop neural regulation in several major neurodegenerative diseases: Parkinson's disease, Alzheimer's disease and epilepsy.

In the treatment of Parkinson's disease, traditional deep brain stimulation (DBS) delivers continuous stimulation with fixed parameters, which may lead to increased side effects. Adaptive deep brain stimulation (aDBS), a form of closed-loop system, monitors beta-wave activity in the subthalamic nucleus (STN) in real-time and provides stimulation only when abnormal activity is detected, thereby enhancing efficacy and reducing side effects. Studies have shown that aDBS selectively suppresses prolonged beta bursts, improving motor function and decreasing stimulation-related adverse effects in patients [43,44].

For Alzheimer's disease patients, memory impairment is associated with abnormal activity in hippocampal-related neural circuits. Deep brain stimulation targeting the fornix has been investigated to improve memory function [45,46]. Closed-loop stimulation systems monitor specific neural activity patterns and adjust stimulation in real-time to optimize therapeutic outcomes. In the ADvance trial,

researchers implemented fornix DBS in patients with mild Alzheimer's disease. Results indicated that some patients experienced cognitive improvements, suggesting that closed-loop DBS may modulate memory-related neural circuit activity and slow cognitive decline. However, the study also found variability in treatment effects among individuals, highlighting the need for further research to optimize patient selection and stimulation parameters [47–49].

In epilepsy treatment, the Responsive Neurostimulation System (RNS) monitors electroencephalographic (EEG) activity in real-time and delivers electrical stimulation upon detecting seizure precursors or abnormal discharges to prevent or mitigate impending seizures. Long-term studies have evaluated the efficacy and safety of the RNS system in patients with drug-resistant partial epilepsy. Results showed that after nine years of follow-up, the median seizure frequency was reduced by 75%, with 73% of patients experiencing at least a 50% reduction in seizure frequency. Additionally, patients exhibited significant improvements in quality of life and cognitive function, with no severe stimulation-related adverse events observed [50].

In summary, CLNM offers personalized therapeutic strategies by real-time monitoring and dynamically adjusting neural stimulation based on individual pathophysiological states. Clinical studies have demonstrated its potential advantages in treating Parkinson's disease, Alzheimer's disease, and epilepsy, though further large-scale clinical trials are necessary to validate its long-term efficacy and safety, suggesting that CLN may become a crucial modality for future neurological disease treatments [51–56]. Beyond these validated clinical uses, closed-loop neuromodulation is being explored in a variety of novel therapeutic and augmentation scenarios, which will be further discussed in Section 4.4.

2.3. Commercial landscape of CLNM

Closed-loop neuromodulation (CLNM) systems offer distinct advantages over traditional open-loop approaches by enabling real-time adaptive regulation of neural activity. Unlike open-loop systems that deliver fixed stimulation regardless of neural state, CLNM systems continuously monitor physiological signals and dynamically adjust stimulation parameters based on the individual's current condition. This real-time feedback mechanism not only optimizes therapeutic efficacy but also minimizes adverse effects by avoiding overstimulation. For instance, in epilepsy treatment, CLNM systems can detect abnormal brain activity patterns and intervene before seizures fully develop, significantly improving patient outcomes.

Another major benefit of CLNM lies in its ability to reduce unnecessary stimulation. By delivering stimulation only when needed, these systems can conserve energy, reduce side effects associated with constant stimulation, and extend the operational lifespan of implanted devices. These features collectively contribute to improved patient comfort and satisfaction, while also enhancing the long-term sustainability of the therapy.

Driven by these clinical and technological advantages, a variety of CLNM products have emerged in the commercial landscape, targeting diverse neurological conditions. One prominent example is the Responsive Neurostimulation System (RNS), primarily developed for patients with drug-resistant epilepsy. RNS devices continuously monitor brain signals and deliver targeted stimulation upon detecting early signs of seizure activity. Clinical studies have consistently demonstrated the superiority of RNS over open-loop stimulation in reducing seizure frequency and improving quality of life [57–63].

Similarly, Adaptive Deep Brain Stimulation (aDBS) systems have shown great promise in treating movement disorders such as Parkinson's disease. These systems modulate stimulation intensity in real time based on specific neural biomarkers, enabling more precise symptom management while minimizing side effects commonly associated with continuous stimulation [64–69]. In the domain of chronic pain management, Closed-Loop Spinal Cord Stimulation (SCS) systems adjust stimulation dynamically according to neural feedback, leading to better pain relief and higher patient satisfaction compared to traditional open-loop SCS approaches [70–73].

Beyond these leading technologies, other emerging closed-loop modalities such as vagus nerve stimulation (VNS) and deep transcranial magnetic stimulation (Deep TMS) are also under active exploration. These alternative approaches further diversify the technical landscape of CLNM and hold potential for addressing a wider range of neuropsychiatric and somatic conditions.

In conclusion, closed-loop neuromodulation represents a transformative advancement in the field of neurotherapeutics. Through real-time adaptability, enhanced therapeutic precision, and efficient stimulation management, CLNM systems have opened new avenues for personalized and effective treatment strategies. The following section will explore in detail the clinical indications and outcomes associated with these systems, while critically analyzing the advantages and limitations of current technologies.

3. The evolution of AI and IC technologies in CLNM: from independent development to deep integration

CLNM, as a cutting-edge neuromodulation technology, has shown great potential in the treatment of neurological diseases in recent years. By monitoring neural activity in real time and dynamically adjusting stimulation parameters based on feedback signals, CLNM can achieve precise and personalized treatment effects. This technology has made significant progress in the treatment of neurological diseases such as Parkinson's disease and epilepsy, but its further development still faces technical challenges.

In this chapter, the introduction of AI and IC technologies has provided new possibilities for CLNM. AI technology can significantly improve the adaptability and accuracy of the system by intelligently analyzing and optimizing neural signal processing; while IC technology provides guarantee for the real-time and miniaturization of CLNM through hardware support and efficient processing capabilities. With the continuous advancement of technology, the combination of AI and IC is becoming an important direction for the development of CLNM.

This chapter will discuss the technological development route in CLNM from three perspectives: first, analyze the application and limitations of pure AI technology in neural signal processing; second, discuss the role and challenges of pure IC technology in hardware support and signal processing; Finally, we will conduct in-depth research on the synergistic effect of the combination of AI and IC to reveal its potential and future development direction in CLNM.

3.1. Development and limitations of pure AI approaches in CLNM

The early CLNM systems primarily relied on manually designed features and simple classification algorithms. In the early 2000 s, researchers employed Support Vector Machines (SVM) to classify time-frequency features (such as wavelet coefficients and entropy of energy) of Electroencephalography (EEG) signals, aiming to predict epileptic seizures [74–76] or Parkinsonian tremors [77,78]. For instance, studies have utilized sample entropy and fractal dimension of temporal lobe EEG, combined with a logistic regression model, achieving a seizure prediction sensitivity of 65% (AUC 0.72) [79]. Although these methods preliminarily validated the feasibility of data-driven approaches, their reliance on expert experience revealed significant shortcomings: the substantial inter-patient variability in the High-Frequency Oscillations (HFOs) band (70–250 Hz) led to high misclassification rates, with false positive rates reaching up to 25% when fixed feature thresholds were applied [80].

The limitations of manual features prompted the rise of deep learning post-2010. Convolutional Neural Networks (CNNs) demonstrated advantages in directly extracting spatiotemporal features from raw signals [81–85]. Researchers have utilized CNNs to process intracranial EEG, achieving high detection sensitivities for epileptic seizure periods, surpassing traditional methods by significant margins. Figure 2 shows a typical 5-channel neural recording and the signal training and inference steps. However, the computational demands of deep networks soon conflicted with hardware limitations—clinical-grade neurostimulators' processing units offered limited processing capabilities, resulting in real-time inference delays exceeding acceptable thresholds for optimal seizure intervention windows.

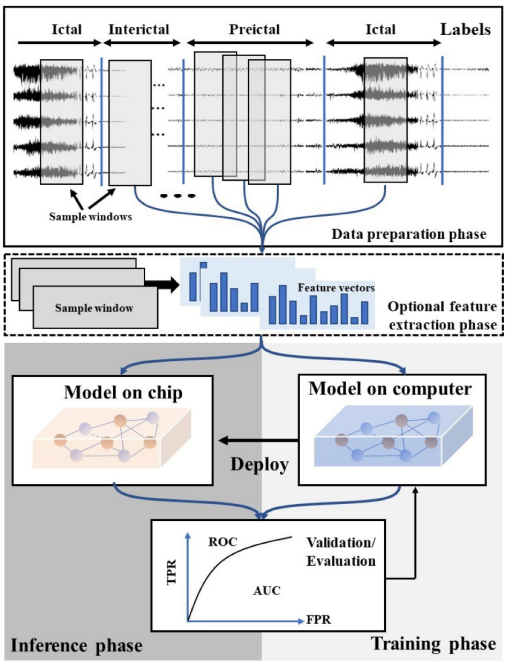

Figure 2. Typical training and inference process.Training phase: brainwave signals database are labeled with different epileptic states and passed on to a deep learning network on computer to find a set of optimized parameters. The performance of the predictive model can be evaluated with RoC and AUC metrics. Inference phase: training obtained parameters will be deployed to a SoC, brainwave signals obtained from users will be passed to the SoC.

To address computational constraints, research after 2018 focused on model simplification. Knowledge Distillation techniques, transferring knowledge from large teacher networks to smaller student networks, gained widespread adoption [86–88]. Models developed with pruning and quantization techniques reduced parameter counts significantly, enabling real-time processing with low power consumption on microcontrollers [89–92]. However, this approach unveiled new challenges: the simplified models' reduced sensitivity led to higher miss rates for low-amplitude high-frequency oscillations. This performance fluctuation reflects the diminishing returns of algorithm optimization—merely reducing parameter count cannot transcend the physical boundaries of signal-to-noise ratio and hardware energy consumption.

The introduction of online learning was once viewed as a potential breakthrough [93–95]. The MetaEEG framework [96] in 2021 employed Meta-Learning to pre-train base models, requiring only 5 minutes of fine-tuning data for patient-specific adaptation. However, practical memory limitations hindered its implementation. Implantable devices typically offer less than 512 KB of SRAM [97], while Meta-Learning necessitates caching gradient information from multiple tasks, leading to memory overflow [98]. Moreover, the non-stationary nature of neural signals (e.g., circadian fluctuations in Parkinsonian β waves) [99] demands continuous algorithm updates, yet hardware's finite write endurance (e.g., NAND flash's 10,000 erase cycles) further widens the gap between theoretical requirements and engineering realities.

The current surge in large models and generative AI, such as aligning EEG signals with clinical data using Transformer architectures [100–102], seemingly offers new possibilities for personalized treatment. However, this path exacerbates traditional conflicts: training models of GPT-4 scale requires GPU clusters with tens of thousands of cores, whereas implantable devices' energy budgets are insufficient for even a trillionth of the computational load [103–106]. This disparity is particularly evident when diffusion models generate synthetic EEG data—while data augmentation can enhance model robustness, the reliance on cloud-based computing architectures is entirely disconnected from the device's stringent low-power requirements [107–110].

While artificial intelligence algorithms have demonstrated remarkable capabilities in decoding neural states and predicting stimulation parameters, their deployment in real-world closed-loop neuromodulation systems remains tightly constrained by hardware limitations. Specifically, the high computational complexity and latency requirements of many AI models pose significant challenges for real-time, low-power, and implantable neurotechnology applications. To enable practical and efficient AI deployment, integrated circuits (IC) serve as the foundation for bridging advanced AI inference with energy-efficient, on-chip processing. The following section delves into the role of ICs in supporting AI functionality and enabling closed-loop neuromodulation at the hardware level.

3.2. Application of integrated circuit technology in CLNM systems: from analog integration to intelligent reconfiguration

In closed-loop neuromodulation, integrated circuits (IC) play a pivotal role in realizing the low-latency, power-efficient, and real-time execution required for clinical applications. From analog front-end signal acquisition and filtering to digital control and stimulation modules, IC underpin the physical interface

between the brain and intelligent algorithms. More critically, the fusion of AI and IC technologies has become essential for achieving intelligent autonomy in implanted systems. This section explores key components of IC-based neuromodulation systems, highlights emerging AI-accelerated circuit designs, and lays the groundwork for AI–IC co-optimization strategies in future neurotechnologies.

In the development of CLNM driven by IC technology, the evolution of hardware architectures has consistently focused on enhancing the efficiency of signal pathways and the intelligent progression of functionalities. As shown in Figure 3, various biosignals with rich physiological information are recorded and digitized by analog front-end chips and analog to digital converters and processed by digital signal processing chips or remote devices such as cell phones or computers. Early solutions emphasized the high integration of analog circuits [111–114]. For instance, the early neural recording ASIC, introduced in 2006 [115], utilized a 0.5 mum CMOS process to integrate 16 parallel amplifier channels into a single-chip design. This chip supported multi-channel signal conditioning for neural recording probes, achieving a gain of 59.5 dB and a high cutoff frequency of 9.1 kHz, with a power consumption of 75 muW per channel. The low cutoff frequency was independently tunable on each channel to accept or reject field potentials. This design was small enough for chronic packaging in awake behaving animals and could be integrated into a fully implantable neural recording microsystem. Another version of the front-end, implemented in a 3 mum CMOS process, included 64 to 8 site selection, 8 per-channel amplifiers with a gain of 50.2 dB, a tunable low cutoff frequency, and a 7 kHz upper cutoff frequency, dissipating 142 muW. Real-time site impedance and circuit testing were also integrated into this design.

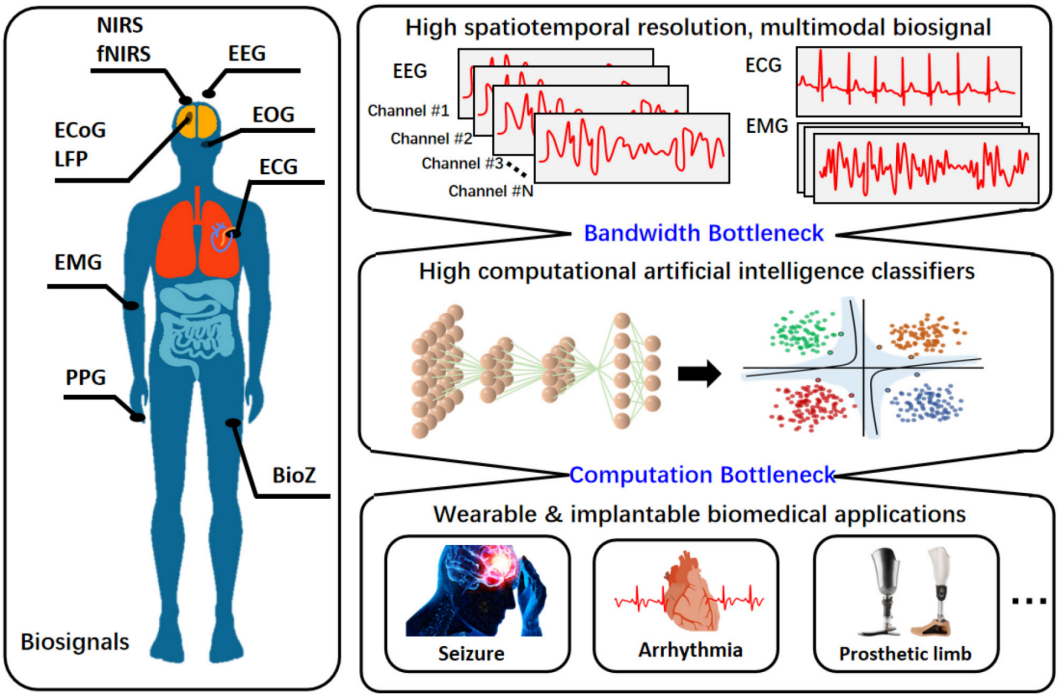

Figure 3. Building blocks of conventional biomedical devices. EEG, EMG, and ECG are among the biosignals used for various applications, including seizure prediction, arrhythmia detection, and gesture recognition.

Post-2010, fully integrated mixed-signal chips significantly improved closed-loop real-time capabilities [116–120]. An example is NeuroPace's responsive neurostimulation system (RNS) [121], whose dedicated SoC integrated an analog front-end (± 5 mV dynamic range), digital filters

(programmable bandwidth of 1–200 Hz), and current-driving modules to give electrical stimulations, all within a 7.2 mm² area using a 65 nm process. Fixed-parameter decisions of stimulations were managed via state machine logic, reducing stimulation trigger latency to 15 ms. However, the solidification of the algorithm results in the need to replace the firmware when adapting to different conditions, highlighting a need for reconfigurable hardware solutions.

After 2018, dynamic voltage and frequency scaling (DVFS) and event-driven architectures became prevalent [122–126]. Medtronic's Percept™ chip [127,128], employing a 22 nm FD-SOI process, achieved hardware-level energy efficiency adaptation. Its core logic monitored computational load demands, dynamically adjusting clock frequencies (1–50 MHz) and core voltages (0.5–1.0 V), optimizing average power consumption to 300 μW. Additionally, asynchronous ADCs were introduced, initiating conversions only during signal events (e.g., HFOs in epilepsy), reducing energy consumption by 90% compared to traditional periodic sampling methods.

The focus in current technological advancements is on intelligent decision units and high-precision clock synchronization. IBM's NorthPole chip [129] demonstrated the potential of compute-in-memory (CIM) architectures, enhancing convolution operation efficiency to 5 TOPS/W through in-memory computing, enabling direct processing of spatiotemporal features from multi-channel EEG data. However, existing CIM architectures face challenges in efficiently processing the temporal signals inherent in neuromodulation [130], such as theta-gamma cross-frequency coupling, due to their matrix computation models not aligning with the dynamic causal network analysis requirements.

Technological boundaries, constrained by physical limits, also present significant challenges [131–135]. For example, SRAM access under the von Neumann architecture accounts for 65% of total system power consumption, prompting innovations like near-memory computing or compute-in-memory (CIM). Similarly, multi-channel electrophysiology systems face critical limitations in data throughput, which hinder real-time, data-informed experiments in both experimental neurobiology and next-generation neuroprosthetics. Addressing these challenges, a novel 68-channel, highly-integrated neural signal processing PSoC has been developed using 22nm FDSOI technology. This chip integrates 68 recording frontends, spike detectors, codecs, and a MAC-assisted processor in a compact 9 mm² area, achieving ultra-low power consumption (0.41 µW/channel for analog frontends, 0.87–4.39 µW/channel for action potential codecs, and 0.32 µW/channel for local field potential codecs). The system supports on-chip training for compression, spike sorting, and inference, reducing data transmission bottlenecks by up to 91% space saving ratio while enabling fully autonomous operation under stringent low-power constraints. These innovations demonstrate how advanced integration and on-chip processing capabilities can overcome physical limitations, paving the way for next-generation implantable neuroprosthetics and experimental neurobiology research [136].

In summary, the evolution of IC technology in CLNM has transitioned from fixed-function analog integration to intelligent, reconfigurable hardware. Future breakthroughs will heavily rely on deep collaboration between algorithms and circuit topologies—for instance, adapting the temporal sparsity of spiking neural networks (SNNs) to event-driven clock granularities [137]. Through cross-domain optimization, we can achieve the ultimate leap from "mechanical functional execution" to "biological intelligence extension" in neuromodulation.

3.3. Supporting circuit modules for AI-enabled CLNM systems

Beyond core modules such as neural signal acquisition, AI processing, and stimulation control, closed-loop neuromodulation (CLNM) systems also rely on several critical supporting circuits. These modules ensure robust, safe, and energy-efficient operation in real-time, particularly in resource-constrained or implantable environments. This section highlights key supporting circuits, including impedance measurement, electrode voltage monitoring, and power management, and discusses their roles and design considerations.

Impedance measurement modules monitor the electrode–tissue interface impedance to assess contact quality and adapt stimulation parameters accordingly. A typical implementation involves injecting a known current and measuring the resulting voltage to compute impedance in real time. Such modules often use low-noise transimpedance amplifiers (TIAs), lock-in amplifiers, or sinusoidal excitation with demodulation [138,139]. Impedance tracking is particularly critical for adaptive stimulation systems to ensure safe and targeted delivery.

Electrode voltage monitoring circuits provide insights into both the applied stimulation waveform and the evoked biological response. These circuits enable real-time feedback and fault detection (e.g., open/short conditions). Common implementations include differential sensing amplifiers followed by ADCs [140]. The captured voltage waveforms can also be fed into AI algorithms for pattern recognition or anomaly detection.

Power management units (PMUs) are essential to support both AI inference and high-power stimulation events. PMUs typically include low-dropout regulators (LDOs), switched-capacitor DC–DC converters, and energy harvesting interfaces [141–143]. In implantable settings, dynamic voltage scaling and on-demand power gating are employed to minimize heat generation and prolong battery life [144]. These supporting circuits are crucial for the full-stack integration of AI-CLNM systems, bridging the gap between intelligent signal processing and safe, reliable hardware-level execution.

3.4. Integrating AI and IC technologies in CLNM: advancements, applications, and challenges

To achieve closed-loop neuromodulation with high precision and efficiency, the co-design of artificial intelligence algorithms and integrated circuit hardware is becoming increasingly critical. AI-IC co-design refers to the joint optimization of algorithmic performance and hardware constraints, enabling intelligent functionality to be embedded directly within neuromodulation devices. The evolution of CLNM technology has been intricately linked with the collaborative advancement of integrated circuit (IC) design and artificial intelligence (AI) algorithms. Early systems, such as neural stimulators from the 2000 s, primarily relied on analog circuit-based hardware architectures, including low-noise amplifiers and fixed-threshold comparators. While these designs achieved micro-watt level power consumption through 350 nm CMOS processes, their decision-making logic was entirely based on preset rules. This rigidity resulted in interventions for conditions like epilepsy or Parkinson's disease that lacked dynamic adaptability. This phase exemplifies the "pure IC approach," where hardware met stringent low-power requirements but lacked the intelligence necessary for real-time, individualized therapy based on physiological feedback. Table 2 provides a comparison of representative systems that integrate AI algorithms into hardware neuromodulation platforms.

Table 2. Representative AI–IC systems for closed-loop neuromodulation.

System/Platform	AI Model Type	IC Architecture	Applications	Power (mW)	Latency (ms)	Key Features
Medtronic Percept PC [128]	Fixed classifier	Custom DSP Core	DBS for Parkinson	∼100	< 100	First commercial adaptive DBS, sensing + stimulation
IBM NorthPole [129]	Quantized DNN	Digital neurosynaptic	Cortical decoding	∼200	1–10	Event-driven edge inference, high parallelism
Intel Loihi [145]	SNN	Neuromorphic SoC	Seizure detection	< 50	< 1	Supports online learning, low power
Edge TPU (Google) [146]	Quantized CNN	ASIC for inference	EEG classification	200–500	∼2–10	General-purpose edge AI chip
MetaEEG (Research) [96]	LSTM/ Transformer	FPGA/ mixed-signal	Real-time EEG AI	∼300	∼5–20	High flexibility, research-stage only

The independent evolution of algorithms, such as the use of support vector machines (SVMs) for seizure prediction, briefly spurred attempts at cloud-assisted decision-making. However, communication delays ($\geq$ 500 ms) failed to meet real-time requirements, and data privacy concerns hindered clinical applications. During this period, AI and IC technologies remained physically separate, interacting mainly through interface protocols like SPI, essentially functioning as discrete systems. A significant breakthrough occurred with the 2013 release of the NeuroPace RNS system. This system's dedicated system-on-chip (SoC) integrated mixed-signal chains with fixed-logic state machines using a 65 nm process, enabling digital threshold-based decisions (e.g., triggering stimulation upon specific LFP amplitude events). This integration marked the initial embedding of algorithmic functions at the chip level. However, the fixed hardware logic remained inflexible in addressing the non-stationary nature of neural signals, such as beta rhythm frequency drifts.

Starting in 2018, the co-design of lightweight AI models and reconfigurable chip architectures gained prominence [147–151]. For example, NeuralTree [152] is a system-on-chip (SoC) that integrates a 256-channel neural signal acquisition, a low-power neural network classifier, and a 16-channel neurostimulator. The chip adopts a tree-like neural network structure, which can achieve high-precision detection of epilepsy and Parkinson's disease states with an energy consumption of only 0.227 μJ/classification, and trigger neural stimulation in real time. Tests in vitro and animal models showed a sensitivity and specificity of more than 95%, verifying the potential of deep integration of AI and IC in closed-loop neural regulation.

The introduction of event-driven architectures and spiking neural networks (SNNs) signified a deeper integration of AI and IC technologies. IBM's NorthPole chip demonstrated the potential of compute-in-memory (CIM) architectures by enhancing convolution operation efficiency to levels hundreds of times greater than traditional GPUs. However, its design was not specifically tailored for neuromodulation, leading to inadequate support for the temporal characteristics of neural signals. To address the limitations of fixed-logic neuromodulation systems, researchers at the University of California, Berkeley, developed the Wireless Artifact-free Neuromodulation Device (WAND) in 2018 [153]. This device integrates custom application-specific integrated circuits (ASICs) and an on-board FPGA to enable

simultaneous recording and stimulation across 128 channels. WAND's architecture allows for real-time cancellation of stimulation artifacts and dynamic adjustment of stimulation parameters based on detected neural biomarkers. *In vivo* experiments with non-human primates demonstrated WAND's capability to disrupt movement preparatory activity during a delayed-reach task, highlighting its potential for treating neurological disorders such as Parkinson's disease and epilepsy. However, challenges remain in translating this technology to clinical settings, including ensuring long-term biocompatibility and managing the power consumption associated with high-channel-count, real-time processing systems.

The core advantages of AI-IC co-optimization have become evident in three key areas [154–165]:

To overcome the limitations imposed by the memory wall in traditional von Neumann architectures, algorithm-circuit co-compression strategies have been developed. Techniques such as low-bit quantization combined with analog multiply-accumulate units have demonstrated the potential to significantly improve energy efficiency, with reported gains of 5–10 times in energy density. These advancements enable the deployment of neuromodulation systems that are both power-efficient and capable of real-time processing.

Furthermore, dynamic power management has become an essential component of modern closed-loop neuromodulation systems. By implementing confidence-based model switching, these systems can adjust their computational complexity according to the real-time quality of neural signals. This allows for the selective activation of lightweight or high-precision models, enabling the average power consumption to drop below 1 mW without compromising accuracy.

Equally important is the integration of safety constraints into the decision-making process. Rather than relying solely on AI or rule-based heuristics, modern architectures combine global safety boundaries—such as hardware-defined limits on stimulation current—with localized, real-time decisions made by intelligent agents. This hybrid approach ensures biological safety while maintaining the flexibility needed to address a wide range of complex and evolving neurological conditions.

Compared with purely AI-based systems that depend heavily on cloud computing—with associated drawbacks such as high carbon emissions and unpredictable latency—or purely IC-based designs that are often rigid and lack adaptability, this collaborative paradigm offers a compelling balance between personalization and sustainability. It enables on-device intelligence while respecting the stringent constraints of implantable or wearable neurotechnology.

Despite its promise, this cross-disciplinary integration presents several formidable challenges. As semiconductor manufacturing continues to advance toward smaller process nodes, mixed-signal circuit precision becomes increasingly difficult to maintain. In FinFET-based technologies, for instance, elevated leakage currents can degrade the linearity of analog-to-digital converters, impairing the fidelity of neural signal acquisition. Similarly, compute-in-memory (CIM) architectures, while beneficial for in-situ processing, suffer from physical limitations such as resistance drift in resistive memory elements. These variations can disrupt the precise timing of neural signal encoding, ultimately affecting the accuracy of spatiotemporal models.

Moreover, aligning biologically inspired neuromorphic algorithms with rigid, silicon-based substrates remains a fundamental hurdle. Spiking neural networks (SNNs), for example, often operate at firing rates and learning dynamics that diverge significantly from real synaptic plasticity observed in biological systems. The mismatch between algorithmic models and physical hardware must be resolved to ensure

functional fidelity and therapeutic safety.

A concrete example of this mismatch is found in AMD-Xilinx's Versal ACAP platform [166], which incorporates embedded FPGAs capable of dynamically adjusting precision between 4 to 16 bits. While this flexibility is commendable, the platform's reconfiguration latency, which exceeds 1 ms, fails to meet the sub-millisecond temporal resolution demanded by real-time neuromodulation applications. These limitations underscore the necessity for end-to-end innovation, from materials science (e.g., integrating two-dimensional semiconductors to reduce power leakage and improve signal integrity) to architectural design (e.g., developing compilers capable of spatiotemporal co-optimization). Only through such holistic collaboration can truly efficient, adaptable, and clinically safe closed-loop neuromodulation systems be realized.

4. Future directions and challenges of next-generation AI-assisted CLNM systems

4.1. The importance of deep integration between AI and IC technologies

Next-generation CLNM systems aim to achieve real-time monitoring and modulation of neural activity for precise and personalized interventions in neurological disorders such as epilepsy and Parkinson's disease. Traditional open-loop systems lack adaptability and may cause habituation, reduced efficacy, and undesired side effects due to continuous stimulation. The integration of artificial intelligence (AI) holds promise in identifying pathological states and dynamically adjusting stimulation based on patient-specific neural biomarkers. As shown in the Figure 4, with the combination of AI and IC, wearable or implantable sensors collect physiological signals of various modalities, allowing the patient's status to be monitored in real time. However, directly deploying complex AI models on implantable devices introduces significant challenges in terms of real-time processing, ultra-low power consumption, and thermal constraints.

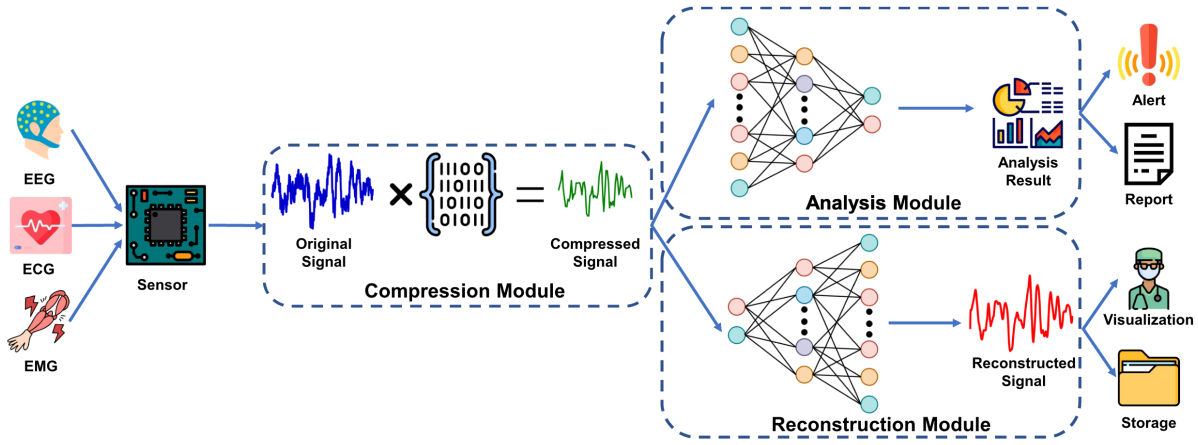

Figure 4. Physiological signals of various modalities are collected by wearable or implantable sensors and compressed via the compression module. The sampled measurements are then utilized for monitoring task analysis and signal reconstruction by the analysis module and reconstruction module, respectively. The compression matrix, analysis network and the reconstruction network are optimized simultaneously during training.

Conventional systems often rely on offloading data to external or cloud-based platforms, which increases latency and introduces network dependency, hindering real-time responsiveness. Therefore, the

development of future closed-loop systems relies critically on the deep integration of AI algorithms with integrated circuits (ICs), enabling on-device intelligence.

Recent advancements propose the concept of neuromorphic neuromodulation, wherein brain-inspired computing architectures are used to perform *in situ* signal processing and AI-based decision making. These architectures can drastically reduce data volume by several orders of magnitude during feature extraction, thereby improving power and storage efficiency. This integration becomes a foundational driver of the next generation of implantable brain-machine systems, enabling high-resolution, patient-adaptive therapies with long-term reliability.

4.2. Key roles of AI–IC co-design in system evolution

The co-design of AI algorithms and custom ICs has emerged as a transformative approach in enhancing the performance and applicability of CLNM systems. By embedding highly optimized AI models into ASICs, these systems achieve ultra-low power consumption while maintaining high computational efficiency. Techniques such as hardware-aware binary neural networks (BNNs) and compact CNNs have been successfully implemented in neuromodulation ASICs, offering energy-efficient inference within minimal chip areas—an essential prerequisite for long-term implantability and continuous operation.

In addition to energy efficiency, edge intelligence plays a pivotal role in enabling real-time therapeutic intervention. The integration of intelligent computing directly within the neuromodulation device eliminates dependence on remote servers, thereby reducing communication latency and ensuring that responses to neural events occur within milliseconds. This capability is crucial for precise and timely modulation of neural activity, particularly in applications such as seizure interruption or tremor suppression.

Another critical advancement is the ability to deploy compact AI models directly on-chip. Models such as quantized decision trees, lightweight LSTM networks, and spiking neural networks (SNNs) are increasingly adapted for neuromorphic hardware, offering a balance between interpretability, computational efficiency, and biological plausibility. These models are particularly suited for resource-constrained implantable systems, where size, power, and thermal limits pose stringent constraints.

Collectively, these innovations drive the evolution of CLNM systems toward solutions that are not only personalized and miniaturized but also capable of real-time adaptation to dynamic physiological states. The synergy between AI and ICs thus forms the foundational architecture for next-generation neuromodulation technologies, enabling more intelligent, efficient, and clinically responsive systems.

4.3. Development trends of next-generation AI-driven closed-loop neuromodulation systems

With the deepening integration of neuroscience and AI, CLNM systems are evolving toward enhanced intelligence, personalization, and energy efficiency. These advancements address critical demands for real-time performance, adaptability, and safety in the treatment of neurological disorders. One of the most significant trends in this field is the adoption of neuromorphic computing and corresponding hardware platforms. Conventional AI models, when deployed on implantable devices, are constrained by limited computational resources and high power consumption. In contrast, neuromorphic processors based on

SNNs emulate the sparse and event-driven nature of biological neurons, enabling real-time neural signal processing with power consumption at the microwatt level. This makes them exceptionally well-suited for edge computing in implantable systems.

To further enable AI capabilities in power- and memory-constrained environments, researchers are focusing on the development of lightweight AI models. Techniques such as pruning, quantization, and knowledge distillation have led to the creation of compressed CNNs, BNNs, and efficient variants of SNNs, with memory footprints reduced to under 100 KB. These models can be deployed on ultra-low-power chips for real-time classification of neural activity and detection of disease states, without sacrificing inference accuracy.

Beyond computational models, event-driven and asynchronous computing architectures are increasingly being adopted to reduce power consumption. Unlike traditional clock-based or periodic sampling approaches, event-driven systems activate data acquisition and processing only upon detecting specific neural events, such as high-frequency oscillations. This approach not only conserves energy but also aligns with the non-stationary and sparse characteristics of neural signals, improving system efficiency and responsiveness.

Personalization is another key frontier in the development of intelligent neuromodulation. Due to the high inter-individual variability in neural signals, universal models often struggle to generalize across patients. To address this, researchers are exploring cross-modal data fusion strategies and personalized training paradigms. Approaches such as generative adversarial network (GAN)-based data augmentation and knowledge distillation from generalized models to patient-specific instances have been shown to improve both adaptability and classification accuracy across diverse subjects and disease states.

Lastly, achieving optimal system performance requires a holistic co-design of hardware and software. Rather than treating hardware and algorithms as separate components, next-generation designs embed algorithmic considerations into chip architecture from the outset. This includes optimizing data pathways, memory hierarchies, and computational logic for target AI models. Reconfigurable chip platforms that support various neural network architectures provide the flexibility needed to address different clinical scenarios and application requirements, enabling broader deployment of neuromodulation therapies.

In summary, the future of AI-driven closed-loop neuromodulation lies in the convergence of neuromorphic computing, lightweight edge models, event-driven architectures, personalized training strategies, and tight hardware–software integration. These synergistic advancements will lead to systems that are not only miniaturized and energy-efficient, but also intelligent and adaptable, meeting the rising clinical demand for precision, real-time, and patient-specific neurological therapies.

4.4. Potential applications of AI-driven closed-loop neuromodulation

AI-driven closed-loop neuromodulation (CLNM) systems are poised to reshape future neurological care by enabling real-time, adaptive, and personalized therapeutic interventions. Going beyond currently approved clinical applications, emerging AI-augmented platforms are being explored in advanced seizure prediction, fine-grained motor control optimization, and the integration of brain-computer interfaces (BCIs) for dynamic stimulation management. These technologies promise greater precision, reduced side effects, and enhanced responsiveness in treating complex and fluctuating neurological conditions. Although some

of these applications share common therapeutic goals with existing CLNM systems, they remain in the exploratory or preclinical stage, supported by emerging AI and IC advancements.

Beyond symptom suppression, future CLNM applications may focus on enhancing cognitive functions and facilitating neuroplasticity. In neurodegenerative disorders such as Alzheimer's disease, closed-loop interventions driven by real-time biomarkers—such as hippocampal oscillations or cortical slow waves—may enable memory circuit reactivation and delay functional decline. Similarly, in post-stroke rehabilitation and disorders of consciousness, real-time EEG-guided neuromodulation combined with adaptive stimulation algorithms holds promise for promoting cortical reorganization, restoring motor pathways, and assessing residual neural responsiveness in severely impaired patients.

The advancement of wearable CLNM devices is further expanding their utility toward decentralized and home-based neurological care. Integrated with smart exoskeletons and rehabilitation robots, these systems can collect multimodal physiological data, apply embedded AI models for movement analysis, and deliver personalized neuromodulatory feedback. Such platforms enable precise and continuous neural rehabilitation in everyday environments. In parallel, non-invasive techniques such as temporal interference stimulation are being enhanced with AI-driven targeting, neuroimaging fusion, and digital twin modeling to achieve deep brain modulation without the need for surgical implants—broadening accessibility and improving patient safety.

Collectively, these emerging applications reflect the vast technological potential of AI-driven CLNM systems—not only for managing a broader spectrum of neurological disorders but also for enabling continuous, personalized care beyond hospital settings. Future CLNM architectures integrating wearable sensors, on-chip AI, and real-time adaptive control may define the next generation of intelligent neuromodulation and brain–machine interfacing.

4.5. Outlook

Future AI-assisted closed-loop systems will benefit from advances in neuromorphic chips, flexible biocompatible electrodes, and interpretable AI. These systems are expected to transition from disease treatment to broad neurological health enhancement. With continued interdisciplinary integration combining neuroscience, AI, materials science, and clinical medicine, next-generation CLNM will not only restore lost functions but also augment human capabilities in real-world environments.

5. Conclusion

CLNM has become a foundational paradigm in the evolution of neuromodulatory technologies, shifting from traditional single-modality electrical feedback systems toward more advanced frameworks that integrate multimodal biosensing. This transformation is largely driven by the convergence of AI algorithms and IC technologies, enabling systems that are not only adaptive but also capable of intelligent decision-making in real time. While current systems have shown considerable efficacy in dynamically regulating neurological disorders with relatively stable symptomatology, such as Parkinson's disease and epilepsy, they remain constrained by several unresolved technical challenges.

One major limitation lies in the real-time performance of brain–machine dynamic coupling algorithms. Many current solutions, such as those based on recurrent neural networks (RNNs), suffer from

computational delays that misalign stimulation timing with neural events, diminishing therapeutic efficacy. Additionally, the computational and energy demands of advanced personalized models cannot be met by existing implantable ICs; highly expressive models that could enable fine-grained precision therapy, akin to those used in protein folding prediction, are too resource-intensive for current low-power chip architectures. Moreover, the variability of neural activity across different neurological and psychiatric disorders leads to significant generalization decay, making it difficult to develop universal control strategies that function reliably across diverse patient populations and conditions.

Addressing these limitations requires a multifaceted strategy. Future efforts should prioritize the development of low-latency brain–machine coupling algorithms that can respond within biologically meaningful time windows, ensuring timely and context-aware interventions. Simultaneously, breakthroughs in IC design must be achieved to deliver implantable chips with both ultra-low power consumption and sufficient computational headroom to support more complex, adaptive models. The integration of multimodal biosensing, including electrophysiological, biochemical, and behavioral data, will also be essential for building a comprehensive understanding of neural states, enabling more precise and individualized regulation. Finally, cross-disease research aimed at uncovering shared circuit mechanisms and decoding disorder-specific signatures could greatly enhance the robustness and generalizability of future closed-loop systems.

Through continued interdisciplinary innovation spanning AI algorithms, chip architecture, and systems neuroscience, CLNM will be well-positioned to overcome current bottlenecks. This evolution will enable next-generation therapies that are not only intelligent and efficient, but also scalable and broadly applicable, marking a significant step forward in the convergence of precision medicine and AI.

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Author's contribution

Junzhe Wang: conceptualization, investigation, data curation, writing—original draft, writing—review & editing; Yunsheng Liao: conceptualization, investigation, data curation, writing—original draft, writing—review & editing; Jie Yang: conceptualization, supervision, writing—review & editing; Mohamad Sawan: supervision, writing—review & editing. All authors have read and agreed to the published version of the manuscript.

Conflicts of interests

The authors declare no confilict of interest.

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