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Closed-Loop Neural Interfaces with Real-Time Biofeedback: Intelligent On-Chip Systems for Adaptive Neuromodulation in Neurological Disorders

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ABSTRACT: The global burden of neurological diseases, including epilepsy, Parkinson's disease, and motor deficits following stroke, continues to rise due to the inefficacy of traditional treatments. Conventional approaches to neuromodulation, such as open-loop electrical stimulation, lack adaptive capabilities to adjust to dynamic neural activity and can lead to suboptimal treatment outcomes and diminished efficacy over time. This inherent shortcoming has spurred the advent of closed-loop neural interfaces with real-time biofeedback systems that allow adaptive regulation of neural activity via continuous monitoring of physiological activity.

Brain–computer interfaces (BCIs) and implantable neurostimulation technologies have recently emerged to incorporate intelligent feedback control into neurostimulation devices. Technology of the type adaptive deep brain stimulation (DBS) and responsive neurostimulation (RNS) shows enhanced therapeutic efficacy, with closed-loop modulation of stimulation based on neural correlates of disease (Rosin et al., 2015; Little et al., 2016; Sun & Morrell, 2014). Moreover, new technologies that include optogenetic stimulation afford fine-tuned control of neural circuits, broadening the applications of therapeutic interventions beyond conventional electrical stimulation (Deisseroth, 2015; Kim et al., 2017). Closed-loop systems are further improved by embedded artificial intelligence and machine learning capabilities to enable real-time, energy-efficient processing and decision-making within the devices themselves (Zhu et al., 2020; Liu et al., 2021).

These systems have been shown to be effective in epilepsy, motor control in Parkinson's, and stroke recovery through neuroplasticity (Pais-Vieira et al., 2016; Chaudhary et al., 2016; Daly & Wolpaw, 2018). The integration of real-time biofeedback, adaptive neurostimulation, and embedded artificial intelligence in the future is likely to lead to fully autonomous neuromodulation systems for self-optimising, personalised therapeutic control (Sitaram et al., 2017; Lebedev & Nicolelis, 2017; Arlotti et al., 2021).

Keywords: Closed-loop neural interfaces, real-time biofeedback systems, on-chip artificial intelligence, adaptive neurostimulation, brain–computer interfaces, optogenetic stimulation, neurorehabilitation technologies.

I. INTRODUCTION

The burden of neurological diseases like epilepsy, Parkinson's disease, and stroke is a great challenge in contemporary medicine, as these are chronic, multifactorial, and have a profound effect on motor, cognitive, and functional capacity. Epilepsy is a condition that involves excessive, synchronous firing of neurons, which results in recurrent seizures and requires strategies for chronic management, beyond drug therapy, to treat its effects. Parkinson’s disease is characterized by progressive degeneration of the dopamine pathways of the basal ganglia circuitry, leading to motor symptoms like tremor, stiffness, and slowness. Stroke, meanwhile, results from the sudden cessation of blood flow to the brain, resulting in irreversible damage to neurons and consequent motor or cognitive dysfunction, depending on the region of the brain affected.

Although medical therapies have improved, conventional stimulation-based treatments, such as conventional deep-brain stimulation (DBS) and other open-loop methods of brain stimulation, are limited in their effectiveness because they do not adapt to ongoing changes in brain activity. These methods provide open-loop fixed or pre-scheduled stimulation parameters, which do not adapt to the dynamic and non-stationary nature of brain functions. This can lead to variable therapeutic outcomes over time and the emergence of side effects or non-responsiveness, especially in progressive diseases.

For instance, in seizures, conventional stimulation paradigms do not adapt to continuously changing seizure precursors, while responsive neurostimulation shows that adapting to dynamic changes in the brain leads to better seizure reduction (Sun & Morrell, 2014; Pais-Vieira et al., 2016). In Parkinson's disease, anomalous beta-band oscillations in neural circuits of the basal ganglia are highly correlated with motor dysfunction, but traditional DBS does not automatically adapt to these dynamic neural indices (Little & Brown, 2014; Neumann et al., 2016; Tinkhauser et al., 2017). Likewise, in stroke recovery, fixed-stimulation approaches do not optimally leverage neuroplasticity-based recovery mechanisms that rely on feedback-based learning of motor skills (Ramos-Murguialday et al., 2016; Teo et al., 2016).

This has led to the recent development of adaptive neurotechnology, especially closed-loop neural interfaces that combine real-time biofeedback systems that adapt neural stimulation based on dynamic neural signals. This shift is greatly assisted by developments in brain–computer interfaces (BCIs), which provide real-time bidirectional interaction between the brain and computers, enabling real-time neural decoding and feedback-based activity modulation (Chaudhary et al., 2016; Lebedev & Nicolelis, 2017; Nicolas-Alonso & Gomez-Gil, 2016). Here, the adaptive control is based on real-time neural biomarkers, such as local field potentials (LFPs), EEG rhythms, and spike patterns.

Taken together, these advances represent a shift from non-adaptive to smart neurotechnology with feedback-based adaptive control for personalized therapies. This forms the basis of contemporary closed-loop neuroengineering, in which neural interfaces integrate neural sensing, processing, and stimulation into integrated adaptive systems to enhance therapeutic outcomes in epilepsy, Parkinson's disease, and stroke rehabilitation.

II. SYSTEM ARCHITECTURE OF CLOSED-LOOP NEURAL INTERFACES

Closed-loop neural interfaces are developed as multi-layered bioelectronic devices to continuously acquire, decode, and interactively stimulate the brain in response to current states. Closed-loop systems differ from traditional open-loop systems, which use fixed stimulation parameters, by creating a dynamic control structure that links signal acquisition, neural decoding, artificial intelligence (AI) decision making, and feedback stimulation in a closed loop.

The system starts at the sensor level, which acquires neural signals via implanted and wearable electrodes. This can be local field potentials (LFPs), electroencephalography (EEG), or intracortical spike trains, depending on the use case and invasiveness of the system. For instance, implantable BCIs (such as those used for deep brain stimulation or responsive neurostimulation) record signals directly from the brain regions of interest, whereas wearable BCIs mostly use non-invasive scalp recordings of electroencephalogram signals. This stage is crucial as the quality of the signal impacts decoding accuracy (Hasan & Berdichevsky, 2016; Liu et al., 2021).

The next step is signal decoding and preprocessing, which involves filtering, denoising, and converting neural signals into neural features. This may include spectral analysis, artifact filtering, and feature extraction methods that extract disease-specific features, such as beta rhythms for Parkinson's disease, or epileptiform spikes for epileptic seizures. This information is fed into models for analysis. Classic systems are based on rule-based detection, but contemporary systems increasingly include machine learning models that can adaptively learn patterns (Chou et al., 2015; Chapman et al., 2018).

The third component is the AI decision-making module, which constitutes the heart of closed-loop systems. In this stage, on-chip artificial intelligence (AI) or machine learning (ML) algorithms interpret the decoded signals and decide on the stimulation response. With recent developments in AI on the chip, these calculations can now be performed within the implanted devices themselves, thus reducing delay and energy consumption. This on-chip processing is crucial for applications such as seizure detection or tremor reduction, where even millisecond delays can impact effectiveness (Zhu et al., 2020; Liu et al., 2021; Chapman et al., 2018). The AI algorithms can also include learning algorithms to continuously optimise stimulation based on individual neural responses.

The last component is the stimulation feedback, which involves the delivery of electrical or optical stimulation to the neural circuits of interest. This then alters the abnormal neural activity, closing the loop. Stimulation can be continuous (such as for Parkinson's disease) or triggered in response to events (such as seizures in epilepsy). For example, adaptive deep brain stimulation (aDBS) will modulate the intensity of stimulation in response to real-time neural oscillations in Parkinson's (Little et al., 2016), and RNS will only stimulate when it senses potential seizures (Sun & Morrell, 2014; Rosin et al., 2015). New techniques also use optogenetic stimulation to specifically modulate genetically targeted neurons with light control (Deisseroth, 2015; Kim et al., 2017; Warden et al., 2016).

An important aspect of closed-loop neural interfaces is the hardware-software integration. Hardware aspects include electrodes, amplifiers, signal processors, and stimulators, and software aspects include signal processing, machine learning, and control algorithms. This requires low-power and miniaturised systems, and biocompatibility, particularly in the case of implanted systems. Neural chips and balanced stimulation circuits, based on silicon technologies, have enhanced the reliability and safety of the system (Liu et al., 2021; Hasan & Berdichevsky, 2016).

The other key difference is implantable vs wearable systems. Implantable systems, like DBS and RNS, offer high-resolution neural access and are generally used to treat severe brain diseases where direct brain stimulation is required. But they pose surgical risks and complications with implantation. Wearable systems, on the other hand, are non-invasive (using sensors like EEG caps) systems, and are broadly used for rehabilitation and neurofeedback for training, with better accessibility and lower resolution. Both approaches are now blending together with hybrid systems that utilize wearable monitoring to control implantable stimulation systems, offering improved accuracy and convenience (Chaudhary et al., 2016; Daly & Wolpaw, 2018; Nicolas-Alonso & Gomez-Gil, 2016).

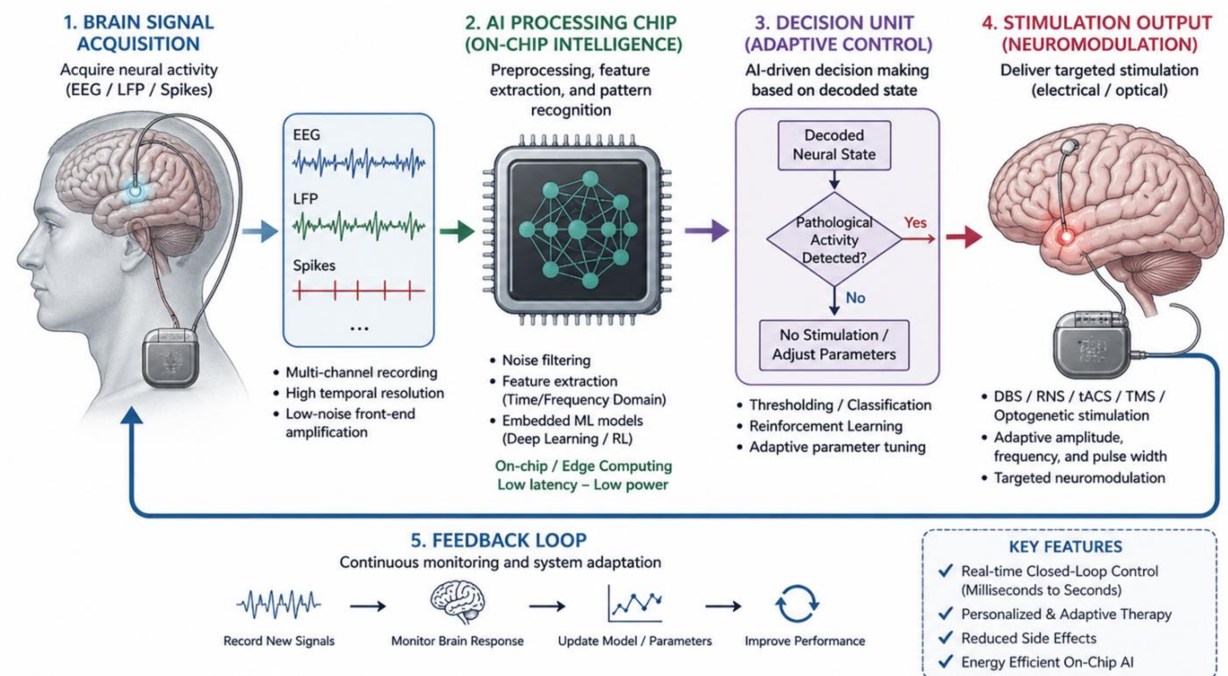

FIGURE 1: Closed-Loop Neural Interface Architecture

The basic structure of a closed-loop brain interface system is shown in Figure 1, where the brain activity and the targeted stimulation are in a dynamic bidirectional interaction. It starts with the acquisition of brain signals, in which the neural activity is measured by implanted or wearable electrodes, recording either electroencephalography (EEG), local field potentials (LFPs) or spiking activity. This data is then fed to an AI processing chip, which preprocesses, extracts features, and decodes (in real-time) them using onboard machine learning algorithms.

The neural information is then forwarded to a decision-making unit, which makes a therapeutic decision based on neural patterns or biomarkers of pathology. The decision is then carried out by the stimulation output module, which provides electrical or optical stimulation to particular neural circuits. This neural modulation leads to new brain signals that are re-acquired and the loop is closed. This feedback process allows real-time and patient-specific neuromodulation, which is the basis of closed-loop neural interfaces.

Table 1: Comparison of Neural Interface Architectures

System Type	Feedback Mode	Example Study	Application
Open-loop DBS	No feedback	Rosin et al. (2015)	Parkinson's
Adaptive DBS	Neural feedback	Little et al. (2016), Priori et al. (2018)	Parkinson's
RNS system	Seizure-triggered feedback	Sun & Morrell (2014), Pais-Vieira et al. (2016)	Epilepsy
AI-driven closed-loop	Embedded machine learning	Zhu et al. (2020)	Multi-disorder

III. REAL-TIME BIOFEEDBACK MECHANISMS

Real-time biofeedback is the main characteristic that sets closed-loop neural interfaces apart from traditional neural stimulation devices. It describes the ongoing cycle with the recording, interpretation, and use of the neural activity to modulate stimulation parameters in milliseconds to seconds. This process allows the nervous system and neurotechnology device to become a closed-loop, adaptive system, in which each component affects the other. The efficacy of this loop relies on three key factors: the kind of neural signals that are recorded, the latency (time delay) of the processing, and the biological understanding of neural dynamics such as brain oscillations and plasticity.

3.1 Modalities of Neural Signals: EEG, LFP, and Cortical Activity

Closed-loop systems can use various forms of neural signals according to the invasiveness and indication. The most common type of non-invasive signal is electroencephalography (EEG). It measures electrical signals from the scalp and reflects global brain activity. EEG is of particular importance in neurorehabilitation as it can be used to measure motor intentions and cognitive states in stroke patients. In the context of brain–computer interfaces, EEG feedback has been demonstrated to lead to motor recovery by reinforcing the correct activation patterns in the brain via feedback cycles (Wolpaw et al., 2017; Enriquez-Geppert et al., 2017). While EEG is less spatially informative than invasive techniques, it can be easily measured and is thus ideal for wearable closed-loop systems.

Local Field Potentials (LFPs) are invasive signals recorded from deep brain regions (e.g., subthalamic nucleus). LFPs give detailed information about the population activity of synchronised neurons, and are particularly important in Parkinson's disease. Pathological oscillatory activity in the beta frequency band (13-30 Hz) is closely related to motor dysfunction. Closed-loop deep brain stimulation (DBS) systems can use LFP to adapt the magnitude of stimulation to these oscillations (Tinkhauser et al., 2017; Neumann et al., 2016).

Microelectrode recordings of cortical spike activity offer the best temporal resolution and are frequently used for epilepsy suppression and sophisticated BCIs. These are fast-firing patterns that can be used as a presymptom of pathological activity such as epilepsy seizures (Sun & Morrell, 2014; Lebedev & Nicolelis, 2017).

3.2 Feedback Latency and Temporal Constraints

One of the key challenges in real-time biofeedback systems is the latency - or delay - between the acquisition of neural signals and the delivery of stimulation. In certain neurological diseases, such as epilepsy or Parkinson's disease, neural activities are fast evolving; thus, latencies greater than a few hundred milliseconds may severely diminish the efficacy of therapy.

Therefore, closed-loop systems have to beat tight timing constraints:

- Signal acquisition: milliseconds
- Feature extraction: real-time or near-real-time
- AI decision-making: ultra-low-latency inference
- Stimulation delivery: immediate response

Emerging technologies in embedded computing and on-board artificial intelligence have now enabled neural decoding on-board the implantable device, without the need for an external compute unit. This reduces the latency and enhances the reliability and efficiency of the system (Zhu et al., 2020; Liu et al., 2021). Hardware-software co-design is thus critical for delivering real-time control in the clinic.

3.3 Oscillations and Disease

Neural activity is not chaotic, but rhythmic oscillations that represent the interconnectivity of brain regions. These oscillations are important for closed-loop neuromodulation as they can be used as a biomarker of disease.

Parkinson's disease patients suffer from increased synchronisation in the beta band (13-30 Hz) across the basal ganglia, which interferes with motor control and leads to rigidity and bradykinesia (Little & Brown, 2014). Recent research has suggested that the oscillations are often seen in transient and brief episodes, called beta bursts, which are highly correlated with disease symptoms (Little & Brown, 2014; Tinkhauser et al., 2017). Closed-loop DBS can identify these bursts and only provide stimulation during these periods, which enhances effectiveness and minimises side effects.

Furthermore, oscillations in subcortical brain regions like the subthalamic nucleus have been shown to be directly responsible for motor dysfunction in Parkinsonian patients (Neumann et al., 2016). Real-time adaptive stimulation can focus on these oscillations to provide more selective symptom control than continuous stimulation.

3.4 Neuroplasticity and Adaptation to Biofeedback

In addition to symptomatic improvement, in real time, biofeedback systems also have a long-term effect on brain organisation through neuroplasticity, whereby the brain can reorganise itself in response to stimulation. This plays a key role in motor recovery and stroke rehabilitation.

Closed-loop brain-computer interface systems facilitate learning of the desired patterns of neural activity by providing feedback when the correct motor intention is identified. This learning process favours the formation of effective neural connections for recovery of motor function (Ramos-Murguialday et al., 2016; Teo et al., 2016). This turns neural interfaces from assistive to rehabilitative learning machines.

Neurofeedback also shows that people can regulate their own brain activity to change their cognition and behaviour by training them to regulate neural oscillations (Ros et al., 2016; Sitaram et al., 2017). But neurofeedback performance is dependent on signal fidelity, timing, and user motivation, and interpretation is still a work in progress from a clinical perspective (Thibault & Raz, 2017).

Table 2: Neural Signal Modalities in Closed-Loop Systems

Signal Type	**Source**	**Application**	**Key Study**
EEG	Scalp cortex	Stroke rehabilitation	Wolpaw et al. (2017)
LFP	Deep brain structures	Parkinson’s DBS	Tinkhauser et al. (2017)
Cortical spikes	Implanted electrodes	Epilepsy control	Sun & Morrell (2014)
Oscillatory patterns	Subthalamic nucleus	Motor control	Neumann et al. (2016)

IV. ON-CHIP ARTIFICIAL INTELLIGENCE IN NEURAL INTERFACES

On-chip artificial intelligence (AI) in implantable and wearable neural interfaces is a game-changing development in the field of closed-loop neuroengineering. Conventional neural interface systems usually rely on external processing platforms (e.g., bedside computers and cloud computing) to process the neural signals and determine the appropriate response to the neural stimulation. While such systems work well in laboratory environments, they introduce inherent latencies (due to data transfer), raise the power consumption levels, and diminish the overall reliability of the system, especially in real-world clinical scenarios. On the other hand, on-chip AI allows for processing and decision-making in situ and lays the groundwork for the development of fully autonomous and adaptive closed-loop neural interfaces.

Central to this new technology are embedded machine learning models tailored for real-time decoding of neural signals. These models are not merely miniaturized versions of traditional AI models but are specifically designed to work in the resource-constrained environment of implantable devices. Often run on hardware such as application-specific integrated circuits (ASICs) or neuromorphic chips, these models are able to efficiently process complex neural signals. In closed-loop systems, embedded machine learning algorithms are vital in recognising clinically significant neural activity, such as pre-ictal seizures in epilepsy, beta oscillations in Parkinson’s disease, and motor intention in the rehabilitation of stroke patients. Alongside classification, these models can also be used to preprocess signals, such as denoising, and extract features. One major breakthrough in this space is the use of deep learning classifiers that can accurately detect the precursor to seizures, while being highly efficient in terms of computational power, allowing for real-time delivery of therapy (Zhu et al., 2020).

But the use of AI in neural implants presents a challenge with respect to edge computing. In contrast to conventional computer systems with plentiful processing and memory resources, implantable systems possess a minute amount of available resources. These devices have limited size, battery life, and must be biocompatible for long-term use. Therefore, the design of neural interfaces should focus on extremely efficient processing, sparing data exchanges between different parts of the system, and latency-free real-time operation without real-time communication. To overcome these limitations, contemporary systems are increasingly turning to on-device inference, whereby all key processing stages - from decoding neural signals to making decisions - are carried out within the implanted system itself. This not only reduces latency but also increases system reliability and privacy by removing the need to constantly transmit data (Liu et al., 2021; Hasan & Berdichevsky, 2016).

A recent advancement in this regard is the advent of neuromorphic computing systems that draw inspiration from the organization and operation of the brain's neural networks. Rather than being based on the traditional serial processing of data, as in conventional computing systems, neuromorphic systems are based on event-driven, distributed processing, which is similar to how the brain works. This mode of operation is particularly advantageous for neural interfaces, given the event-driven nature of neural activity. Neuromorphic chips are extremely energy-efficient and highly efficient because they only process relevant events (e.g., spikes, bursts) in neural data. This is essential for implanted systems that need to operate for long periods of time and whose lifetime and effectiveness depend on energy consumption. Moreover, the parallel processing capability of neuromorphic chips is well-suited for the distributed nature of brain dynamics, facilitating scalable and biologically-inspired processing (Chapman et al., 2018; Liu et al., 2021).

Another key aspect of on-chip AI is the ability to deal with the non-stationarity of brain activity. Neural signals are dynamic and constantly change due to learning, disease progression, and other factors. This presents a challenge for fixed decoding models, whose accuracy could diminish due to changes in the underlying neural patterns. To address this issue, recent closed-loop systems use adaptive decoding models that continuously update their parameters. Methods like reinforcement learning enable the system to update its stimulation strategies based on the success of previous stimulation, effectively "learning" the effects of stimulation in each individual. Likewise, adaptive filtering techniques dynamically optimise the parameters of signal processing algorithms to cope with noise and variability in signals. These techniques allow neural interfaces to be effective and efficient in changing and challenging neural environments (Chapman et al., 2018; Chou et al., 2015).

These technological developments are all underpinned by hardware–software co-design, in which AI algorithms are designed to work seamlessly with the hardware design of the neural device. In contrast to the traditional approach of designing hardware and software separately, new systems are engineered using a co-design technique that optimises computational models for the particular hardware system at hand. This approach has resulted in the creation of new silicon-based neural chips, charge-balanced stimulators, and integrated digital signal processors that are coupled with AI algorithms. This has led to the development of a new generation of neural interfaces that consume less power, have faster response times, are more stable, and are safer over extended periods of time. Critically, such co-designed systems have already been shown to perform real-time on-chip neural monitoring and closed-loop stimulation, without the use of additional computational power (Liu et al., 2021; Hasan & Berdichevsky, 2016).

Overall, on-chip artificial intelligence is transforming the possibilities of closed-loop neural interfaces by providing real-time, adaptive, energy-efficient neural processing capabilities within lightweight and compact devices. By leveraging embedded machine learning, edge computing techniques, neuromorphic designs, adaptive algorithms, and hardware-software co-design, such systems are revolutionising neurotherapeutic systems to be fully autonomous, offering personalised and adaptive treatment.

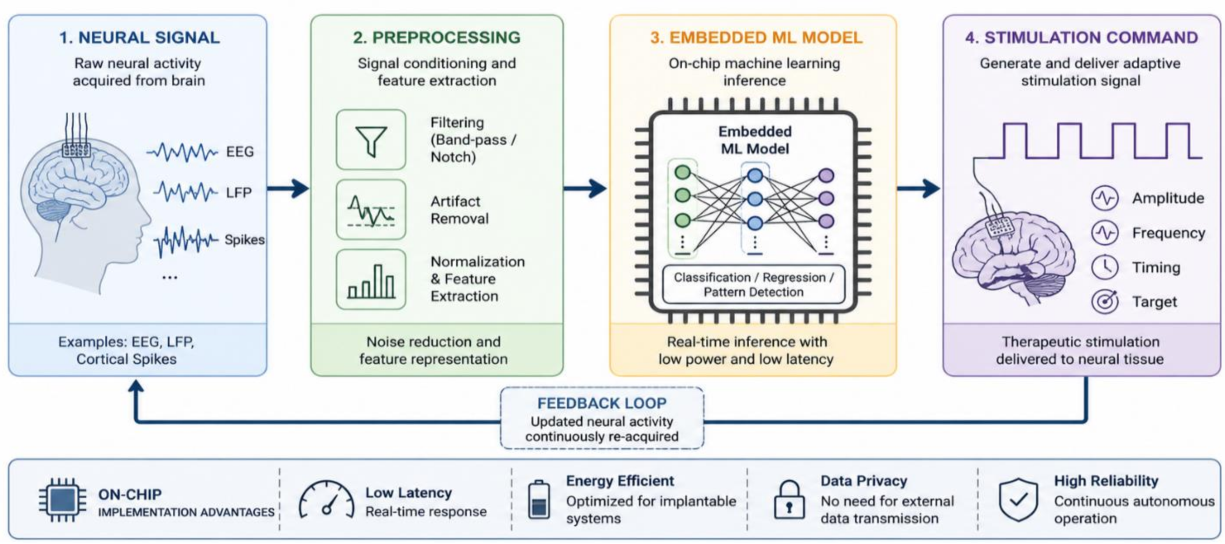

FIGURE 2: On-Chip AI Processing Flow

Table 3: AI Methods in Neural Interfaces

AI Method	Function	Advantage	Study
Deep learning classifiers	Seizure detection	High accuracy	Zhu et al. (2020)
Adaptive filtering	Signal decoding	Low latency	Chou et al. (2015)
Reinforcement learning	Stimulation tuning	Self-adaptive behavior	Chapman et al. (2018)
Embedded DSP + ML	On-chip neural control	Energy efficient processing	Liu et al. (2021)

V. ADAPTIVE NEUROSTIMULATION TECHNOLOGIES

Adaptive neurostimulation technologies represent the functional output interface of closed-loop neural interfaces, which translate the decoded neural information into therapy. Adaptive systems, in contrast to traditional neuromodulation approaches that apply pre-determined stimulation values, are able to adapt stimulation based on real-time biofeedback. This dynamic interaction is enabled by the real-time adjustment of critical stimulation parameters such as current amplitude, frequency, temporal and spatial profile, enabling precise engagement with disease-related neural networks. This enables adaptive neurostimulation to increase therapeutic benefit and reduce side effects, compared to conventional open-loop stimulation.

The most well-known type of stimulation is electrical stimulation. An example of electrical stimulation is deep-brain stimulation (DBS), commonly used for treating Parkinson's disease, which provides electrical stimulation to subcortical regions like the subthalamic nucleus or globus pallidus to correct abnormal neural activity. Though traditional DBS is delivered in a continuous manner, irrespective of the dynamic states of neural activity, recent advances in adaptive DBS (aDBS) have introduced a closed-loop control mechanism. aDBS involves adjusting the stimulation on the basis of neural biomarkers, such as beta-band oscillations, which are linked to motor dysfunction. By focusing on transient pathological oscillations such as beta bursts, adaptive DBS has been demonstrated to increase motor improvements, reduce adverse effects from stimulation, and reduce the energy required to deliver stimulation, compared with continuous stimulation (Little et al., 2016; Priori et al., 2018; Rosin et al., 2015). This shift from open- to closed-loop stimulation is part of the evolution towards precision neuromodulation.

Similarly, responsive neurostimulation (RNS) systems have proven to be a successful use of closed-loop stimulation in epilepsy. These devices track cortical electrical activity and provide stimulation in response to the detection of seizure precursors, thus facilitating early intervention to prevent seizure onset. This "on-demand" strategy is an alternative to continuous stimulation strategies, enabling suppression of pathological neural activity without interfering with normal brain activity. RNS has shown remarkable efficacy in reducing seizures in patients with intractable epilepsy, underscoring the value of real-time detection and intervention in the treatment of neurological disorders (Sun & Morrell, 2014; Pais-Vieira et al., 2016). RNS systems are usually implanted in the cortex at seizure foci, rather than deep brain structures, allowing for targeted and disease-specific treatments.

Electric stimulation is not the only method of modulating neural activity; optogenetics offers a new class of neural stimulation by allowing the selective activation of neurons through light-sensitive proteins. Optogenetic systems can be used to activate or inhibit specific neurons by genetically engineering them to express opsins (light-sensitive proteins), which can be activated by light of specific wavelengths. This selectivity is greater than that afforded by electrical stimulation, which tends to stimulate large areas of neural tissue. Optogenetics has been shown to be a powerful approach both in experimental neuroscience and potential clinical applications, such as the control of neural circuits in epilepsy, Parkinson’s disease, and neuropsychiatric disorders (Deisseroth, 2015; Kim et al., 2017; Warden et al., 2016; Yizhar et al., 2016). But while it offers benefits in terms of spatial and temporal specificity, its clinical application is limited by the difficulties of genetic engineering, efficient and safe light delivery, and biocompatibility over time.

The combination of these technologies has given rise to hybrid neurostimulation systems that combine multiple stimulation methods and computational control. These approaches seek to capitalize on the strength and versatility of electrical stimulation, with the specificity of optogenetics, while also including pharmacological manipulations or artificial intelligence-based control strategies. Through the use of multiple mechanisms of interaction with neural circuits, hybrid systems provide a more holistic approach to tackling complex brain disorders that involve multiple interacting brain networks. The addition of on-chip artificial intelligence also improves these systems by allowing dynamic adaptation of stimulation strategies to the changing state of the neural network, which moves towards fully autonomous therapeutic devices (Chapman et al., 2018; Zhu et al., 2020).

One of the main features of adaptive neurostimulation is its adherence to the principles of personalised medicine. Neural states are highly heterogeneous across individuals and time, with factors like disease progression, environmental changes, and learning playing a critical role. Closed-loop neurostimulation, with real-time biofeedback and on-board artificial intelligence (AI), can adapt to these variations and provide stimulation that is matched to the dynamic neural activity of the individual. This is especially critical for treatment of diseases like Parkinson's disease, in which the severity of symptoms varies, epilepsy, in which seizure patterns differ between individuals, and stroke rehabilitation, in which recovery is based on individual patient neuroplasticity. As technology advances, the combined features of adaptive stimulation, smart control, and multimodal sensing are expected to lead to fully autonomous neuromodulation devices that can autonomously enhance therapeutic outcomes.

Table 4: Neurostimulation Modalities

Modality	**Mechanism**	**Advantages**	**Limitations**	**Key Study**
DBS	Electrical deep brain stimulation	Clinically approved, effective for motor symptoms	Limited specificity	Rosin et al. (2015)
Adaptive DBS	Feedback-controlled electrical stimulation	Personalized, reduced side effects	Complex parameter tuning	Little et al. (2016); Priori et al. (2018)
RNS	Responsive cortical stimulation	Targeted seizure suppression	Invasive implantation	Sun & Morrell (2014)
Optogenetics	Light-controlled neuronal activation/inhibition	High spatial and cellular precision	Experimental, requires genetic modification	Deisseroth (2015)

VI. CLINICAL APPLICATIONS OF CLOSED-LOOP NEURAL INTERFACES

Closed-loop neural interfaces have evolved from basic neuroengineering research platforms to clinical-grade therapy systems that have been shown to be beneficial in a range of neurological conditions. Their therapeutic potential is based on their capacity to provide continuous recording of neural activity, real-time detection of pathological activity, and triggering of precisely timed therapeutic interventions. This chapter reviews their use for epilepsy, Parkinson's disease, and stroke, and how adaptive neurotechnology outperforms traditional therapeutic approaches.

6.1 Epilepsy: Adaptive Seizure Detection and Suppression

Closed-loop neurostimulation has been most successful in the treatment of epilepsy due to the clear electrical biomarkers associated with seizures, and the predictability of the patterns that lead to seizures in many patients. Conventional therapies (such as anti-epileptic medications and open-loop stimulation) either do not completely suppress seizures or can lead to considerable side effects, as a result of continuous stimulation.

Closed-loop neurostimulation, such as responsive neurostimulation (RNS), overcomes this issue by offering continuous monitoring of electrical activity in the cortex and stimulation only in the presence of biomarkers for an impending seizure. These include epileptic spike discharges, high-frequency oscillations, and progressive epileptiform discharges. Once these are detected, the system automatically delivers electrical stimulation to prevent clinical seizure onset.

The RNS system has been shown to effectively reduce seizure frequency in the long term, particularly in drug-resistant epilepsy, by stimulating the seizure focus using real-time feedback control (Sun & Morrell, 2014). Likewise, brain-controlled functional electrical stimulation has demonstrated that bidirectional neural interfaces can not only reduce seizures but may enhance long-term stability of the neural system (Pais-Vieira et al., 2016). More recently, advances in embedded AI have also been made to improve seizure detection through the use of machine learning models that can detect complex neural dynamics preceding seizures with high sensitivity and low latency (Zhu et al., 2020).

Crucially, these systems are a leap from reactive to predictive therapy, where the focus is not simply on treating seizures once they have occurred, but preventing them altogether through the detection and anticipation of seizures.

6.2 Parkinson's disease: beta band oscillations and motor function

Parkinson's disease involves degeneration of dopamine neurons in the basal ganglia, which results in pathological synchronization of neural activity, especially oscillations in the beta range (13-30 Hz). This activity is highly correlated with symptoms of rigidity, tremor, and slowness of movement.

Traditional deep-brain stimulation (DBS) offers continuous stimulation of the subthalamic nucleus or globus pallidus, reducing symptoms, but not responding to dynamic changes in neural activity. However, adaptive deep brain stimulation (aDBS) systems can use real-time feedback from the brain to modulate the amplitude of the stimulation based on the presence of beta oscillations and bursts.

Beta bursts, which are brief bursts, have been demonstrated to be more closely associated with motor dysfunction and are therefore very well suited as biomarkers for closed-loop systems (Tinkhauser et al., 2017). By focusing on bursts, aDBS systems can minimise unnecessary stimulation without compromising, or even enhancing, therapeutic effects (Little et al., 2016; Priori et al., 2018). In addition, synchronized oscillations in the subthalamic nucleus are correlated with the severity of motor impairment, highlighting the need for optimization of therapy using biomarkers based on oscillations (Neumann et al., 2016).

Closed-loop DBS systems have shown:

- Motor symptom reduction
- Reduced stimulation-induced side effects
- Lower energy consumption
- Increased device longevity (Rosin et al., 2015; Little & Brown, 2014)

These results show the need for a control signal using neural oscillations to modulate DBS, turning DBS from a passive to a neuroadaptive system.

6.3 Rehabilitation after Stroke: Motor Recovery using Brain–Computer Interfaces

Strokes can cause permanent changes in motor function due to damage in the motor cortex pathways, causing problems with voluntary movement and resulting in disability. Rehabilitation of stroke is different from epilepsy and Parkinson's disease - it is not only concerned with the suppression of symptoms, but also with neuroplastic recovery and restoration.

Closed-loop brain–computer interfaces (BCIs) have proved to be an effective stroke rehabilitation strategy by creating a feedback loop between the brain and assistive devices. Such interfaces interpret the intention to move from neural activity (such as the electroencephalogram or cortical activity) and use this to guide functional electrical stimulation (FES) or robotic assistance, thus promoting the desired movement.

This closed-loop feedback loop during motor training fosters activity-dependent plasticity, thereby facilitating the strengthening of damaged neural circuits and improving motor function with training (Ramos-Murguialday et al., 2016). BCI-based motor rehabilitation systems have been shown to result in greater motor improvement in patients compared with traditional therapy methods.

Interventions based on neuroplasticity also use repetitive feedback training, which rewards the correct brain activity with a stimulation, enhancing motor learning (Teo et al., 2016). What's more, long-term research indicates that such systems may promote long-lasting brain reorganization, promoting recovery.

Finally, the concept of neurofeedback has also been incorporated into rehabilitation to enhance therapeutic options, enabling patients to control their own brain activity during therapy (Wolpaw et al., 2017; Daly & Wolpaw, 2018). This converts stroke therapy from a passive to an interactive brain-led learning system, in which activity has a direct impact on recovery.

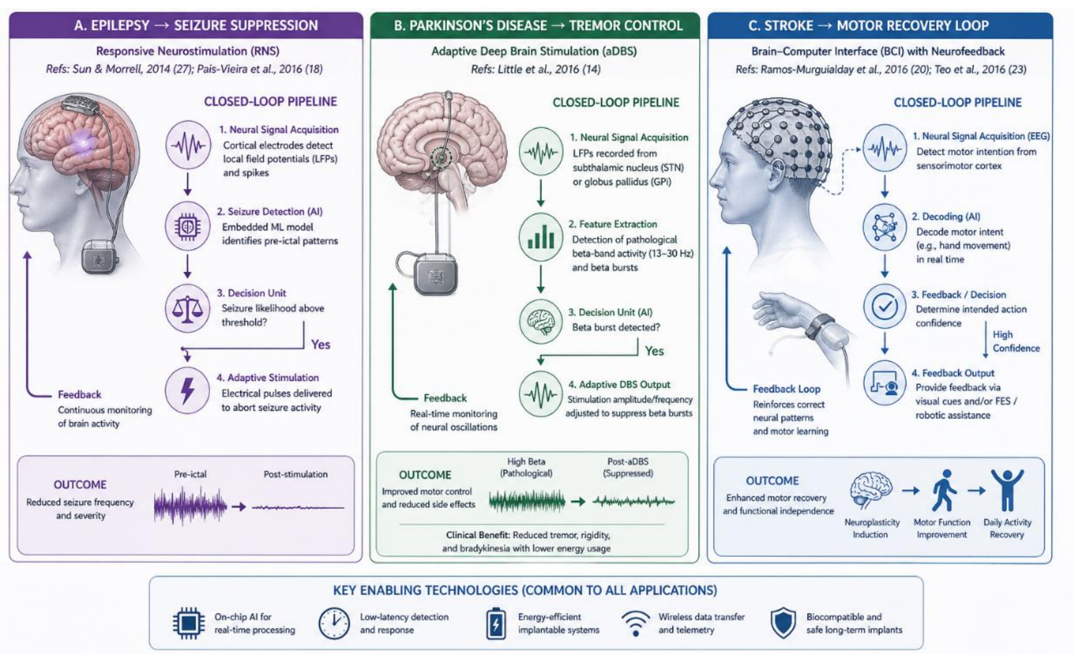

Figure 3: Disease-Specific Closed-Loop Applications of Neural Interfaces.

The figure illustrates common principles of real-time biofeedback and adaptive control across all three panels, showing how closed-loop systems adapt therapeutic interventions to the neural signatures of a particular disease or disorder, while preserving the system's integrity.

VII. CHALLENGES AND SYSTEM LIMITATIONS

As the field of closed-loop neural interfaces with real-time biofeedback rapidly advances, the integration of these systems into fully reliable and sustainable clinical practice is challenging, as is the case with any technology, because of the presence of engineering, biological, and ethical limitations. These constraints are intimately linked, such that gains in one aspect often come at the expense of others. This results in a constant trade-off in the design of clinically useful systems between performance, safety, and sustainability.

Delay and Latency

A major technological challenge in closed-loop neurotechnology is latency, the time delay between the recording of neural activity, computation, and stimulation. In neurotechnologies to treat conditions like epilepsy or Parkinson's disease, even a few milliseconds of latency can greatly diminish therapeutic outcomes, as neural dynamics can change on the order of milliseconds. For instance, epileptic seizures can proceed from pre-ictal (seizure precursor) states to seizure events within a few seconds and thus require immediate intervention.

In conventional systems, data from the neural system needs to be sent to external processing units, leading to delays in communication that hinder real-time processing. This issue is exacerbated in systems that use advanced algorithms, such as machine learning, for signal decoding. But recent advances in embedded machine learning and on-chip processing are ameliorating this problem by allowing for on-board processing within the implantable device. These systems avoid the need for external systems and thus greatly reduce system latency and reliability (Zhu et al., 2020; Liu et al., 2021). However, designing algorithms with extremely low latency and high accuracy presents an engineering challenge.

Artifact and Noise Elimination

A further source of limitations comes from the noisy nature of neural recordings. Neural recordings are frequently accompanied by various types of artifacts, such as electromyography (EMG) artifacts from muscle movements, eye blinks, electrical noise, and background noise. For invasive recordings like local field potentials (LFPs), other sources of noise can come from unstable electrodes or encapsulation of the tissue around the electrodes.

Effective decoding of neural signals relies on effective artifact rejection and processing to extract the relevant information from the raw signal in real time, without adding any delay. In closed-loop applications, decisions need to be made in real time, which is a challenge in the presence of such artifacts. Adaptive filtering and machine learning denoising techniques have been designed to address this issue by continually differentiating between the neural patterns of interest and noise (Chou et al., 2015; Chapman et al., 2018). But long-term stability of the quality of signals in clinical settings is still a major challenge.

Biocompatibility and Implant Stability

Closed-loop neural interfaces typically need to be implanted for extended periods, if not indefinitely, and thus biocompatibility is of paramount importance. Implanting materials into the brain triggers an immune response, which can cause inflammation, glial scarring, and a gradual loss of signal quality. This can lead to increased electrode-tissue interface impedance over time, leading to reduced fidelity of the neural recording and stimulation.

Biological responses are not the only consideration. The brain is an elastic, dynamic medium, while implants are generally rigid structures, which can lead to micro-damage in the brain. The development of flexible electrodes, protective coatings, and low-profile implants has enhanced the stability of implants, but complete suppression of the tissue response has yet to be achieved (Hasan & Berdichevsky, 2016; Liu et al., 2021).

Neural Autonomy and Ethics

With growing autonomy of closed-loop systems, ethical issues around neural control and autonomy have emerged. Such systems can monitor brain activity in real time and make decisions about neural stimulation, introducing issues of patient autonomy, consent, and control over the brain.

A key issue is the level of autonomy of the machine in treatment. Although AI-based systems may make better decisions than human operators in terms of brain stimulation, there is a degree of uncertainty about the decision-making process of such systems, particularly when using complex machine learning algorithms. This can pose challenges in terms of transparency and interpretability in clinical practice. Furthermore, the long-term effects of neural implants and impacts on cognitive or emotional states due to continuous brain stimulation are also being studied (Zhu et al., 2020; Chapman et al., 2018).

As such, ethical considerations are critical to ensure the safe and ethical use of these technologies in relation to patient safety, consent, and clinical responsibility.

Implantable System Energy Limitations

One of the key engineering challenges of implantable neural interfaces is energy. The systems need to be in operation for extended periods without the need for frequent battery changes or recharging, which is difficult due to the demanding nature of real-time data processing and stimulation.

Energy-hungry functions like machine learning inference, wireless telemetry, and high-frequency stimulation consume precious energy. This limitation leads system designers to focus on energy-efficient designs, at the cost of increased complexity or reduced accuracy. Recent advances in low-power ASIC designs, energy-efficient signal processing, and event-driven computation have significantly alleviated this problem, but it still remains one of the major bottlenecks to scaling up the system (Liu et al., 2021; Zhu et al., 2020).

Neuromorphic and on-chip AI systems present an interesting opportunity to emulate the brain's own energy-saving strategy, allowing for continuous operation of the system with low energy consumption. But such systems are only beginning to be used in clinical applications.

In summary, the progress in closed-loop neural interfaces is currently limited by a multitude of temporal, biological, computational, and ethical considerations. Temporal and computational delays reduce responsiveness and speed, the noise present in the data reduces decoding accuracy, biocompatibility issues reduce long-term stability, ethical considerations limit the ability of the system to make autonomous decisions, and energy limits scalability. Overcoming these limitations requires the ongoing integration of emerging technologies in embedded artificial intelligence, materials, and neuroengineering designs, along with the development of sound ethical and clinical guidelines for implementation.

VIII. FUTURE DIRECTIONS

Closed-loop neural interfaces with real-time biofeedback are increasingly moving towards increasingly adaptive but also increasingly autonomous, scalable, and embedded systems that are integrated into real-world clinical and non-clinical applications. With ongoing improvements in the existing latency, biocompatibility, and computational power constraints, the future of neurotechnology is likely to transition from assisted neural modulation to smart neural systems that can self-regulate and adapt over time.

One key futuristic trend will be the advent of truly autonomous neural AI devices, in which on-board algorithms continually process neural signals, adapt to individual patient patterns, and automatically modify stimulation variables independently. This transition from clinician-controlled programming to self-optimizing therapeutic agents marks a significant departure from current practice. The growing field of machine learning-based neurofeedback systems already shows that closed-loop systems can progressively learn optimal control policies, enhancing both accuracy and therapeutic effectiveness, in complex brain environments (Sitaram et al., 2017; Zhu et al., 2020). But this independence needs to be tempered by safety considerations to maintain clinically and ethically predictable adaptive responses.

Similarly, we are now beginning to explore the notion of brain-AI co-adaptation learning systems, where both the brain and artificial intelligence system co-learn through mutual adaptation. Here, neural plasticity is not just a biological process but also a computational outcome, with AI systems influencing and being influenced by neural plasticity. This bidirectional interaction has strong implications in rehabilitation, where repeated training paradigms that provide feedback have the potential to result in long-term neural reorganisation. Neural interface studies have already shown that repeated interactions in closed-loop brain–computer interfaces can boost motor pathways and increase volitional control in patients with neural impairments, suggesting the potential for long-term co-evolution between human cognition and artificial systems (Lebedev & Nicolelis, 2017; Chaudhary et al., 2016).

The other major trend is wireless implant ecosystems, which seek to remove physical barriers posed by wired neural implants. Existing implantable technologies typically incorporate transcutaneous cables or low-bandwidth wireless communication units, which limit mobility and risk infection. We anticipate that future systems will have a totally wireless design with energy harvesting, remote programming, and data telemetry. This will enable distributed, real-time, and unobtrusive neural sensing networks that could be used for chronic neurological disease and will greatly increase the potential applications of neural sensing (Nicolas-Alonso & Gomez-Gil, 2016; Wolpaw et al., 2017).

Meanwhile, translation of optogenetics to clinical practice offers another exciting yet formidable challenge in neurostimulation. Although optogenetics has already achieved unprecedented levels of precision in preclinical research, enabling cell-type-specific activation or inhibition of neural circuits, this approach faces many challenges in clinical translation, including gene therapy, light delivery, and safety. However, ongoing advancements in viral vector technologies, minimally invasive light delivery methods, and hybrid bioelectronic interfaces suggest that optogenetic control will eventually complement or even replace traditional electrical stimulation in terms of selectivity and functional resolution (Deisseroth, 2015; Yizhar et al., 2016; Warden et al., 2016).

Lastly, the proliferation of scalable neuroprosthetics is likely to extend the frontiers of human-machine interfaces in the field of neuroengineering. In contrast to current neuroprosthetics, which are usually aimed at a single pathology or neural circuit, future neuroprosthetic systems will likely be modular and scalable, and able to interact with multiple neural circuits. This will allow these devices to leverage breakthroughs in machine learning, dense neural recording, and distributed stimulation to restore motor, sensory, and cognitive function. Recent research in brain-machine interfaces has already shown that scalable decoders can map neural intent to ever more complex motor tasks, and lay the groundwork for more intuitive control of neuroprostheses (Lebedev & Nicolelis, 2017; Daly & Wolpaw, 2018; Ramos-Murguialday et al., 2016).

Overall, these advances indicate a future where neural interfaces transform into self-learning neurocomputational systems that operate in the brain–machine ecosystem. The integration of closed-loop biofeedback, artificial intelligence, and next-generation neuroengineering technologies is likely to take neurological therapy from reactive to real-time, adaptive neural regulation.

IX. CONCLUSION

Real-time biofeedback-based closed-loop neural interfaces mark a significant advancement in both understanding and treatment of neurological diseases, transitioning from traditional fixed stimulation-based approaches to adaptive, smart, and personalised neurotherapeutic systems. In the treatment of epilepsy, Parkinson's disease, and neurorehabilitation following stroke, the coupling of real-time neural monitoring with responsive stimulation systems has been shown to be more effective than open-loop systems, both in efficiency and therapeutic efficacy.

The evolution from conventional deep brain stimulation (DBS) to adaptive DBS and responsive neurostimulation (RNS) underscores the benefits of feedback-based control in enhancing therapeutic efficacy by online suppression of pathological neural activity, as opposed to fixed off-on stimulation (Rosin et al., 2015; Little et al., 2016; Sun & Morrell, 2014). Likewise, the development of brain–computer interfaces (BCIs) has broadened the applications of neurorehabilitation by harnessing the conversion of neural intent into pathways of recovery in stroke patients where neuroplasticity is integral to motor recovery (Ramos-Murguialday et al., 2016; Wolpaw et al., 2017).

The latest closed-loop systems are distinguished by the integration of artificial intelligence and machine learning capabilities on the device, allowing real-time decoding of neural activity and dynamic stimulation control without the need for off-chip processing and computing. This move towards local intelligence not only improves speed and efficiency but also autonomy and practicality in clinical applications (Zhu et al., 2020; Liu et al., 2021). In addition, recent research in neural engineering shows that multimodal systems that harness electrical stimulation, optical neuromodulation, and AI control may provide unmatched specificity and selectivity in modulating dysfunctional neural circuits (Deisseroth, 2015; Warden et al., 2016).

However, there are still critical issues around long-term biocompatibility, energy consumption, signal fidelity, and ethical considerations of autonomy in neural interfaces. These challenges underline the importance of interdisciplinary research efforts between neuroscience, biomedical engineering, materials science, and artificial intelligence to facilitate safe and scalable clinical translation (Hasan & Berdichevsky, 2016; Chapman et al., 2018; Zhu et al., 2020).

Overall, closed-loop systems are increasingly becoming fully autonomous neuroadaptive systems with self-optimising and personalised treatments. With the advancement in embedded AI and more biocompatible and energy-efficient neurotechnology, we anticipate these systems to transform the future of brain therapy through intelligent and continuous brain-machine interaction.

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