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Review

Neuromorphic neuromodulation: Towards the next generation of closed-loop neurostimulation

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Abstract

Neuromodulation techniques have emerged as promising approaches for treating a wide range of neurological disorders, precisely delivering electrical stimulation to modulate abnormal neuronal activity. While leveraging the unique capabilities of AI holds immense potential for responsive neurostimulation, it appears as an extremely challenging proposition where real-time (low-latency) processing, low-power consumption, and heat constraints are limiting factors. The use of sophisticated AI-driven models for personalized neurostimulation depends on the back-telemetry of data to external systems (e.g. cloud-based medical mesosystems and ecosystems). While this can be a solution, integrating continuous learning within implantable neuromodulation devices for several applications, such as seizure prediction in epilepsy, is an open question. We believe neuromorphic architectures hold an outstanding potential to open new avenues for sophisticated on-chip analysis of neural signals and AI-driven personalized treatments. With more than three orders of magnitude reduction in the total data required for data processing and feature extraction, the high power- and memory-efficiency of neuromorphic computing to hardware-firmware co-design can be considered as *the* solution-in-the-making to resource-constraint implantable neuromodulation systems. This perspective introduces the concept of *Neuromorphic Neuromodulation*, a new breed of closed-loop responsive feedback system. It highlights its potential to revolutionize implantable brain–machine microsystems for patient-specific treatment.

Keywords: bio-inspired algorithms, on-chip learning, neural networks, neuromodulation, neuromorphic

Introduction

Electrical brain stimulation has evolved significantly over the past half a century. It started in the 50s when it was found that emotional responses can be triggered by electrical brain stimulation (1). Penfield and Jasper's work (2) was pivotal in mapping cortical functions, which they used to enhance the understanding of seizure semiology. Since then, there has been an increasing number of studies on the safety of brain stimulation (3, 4) and its applications as therapy of intractable epilepsy (5–7), spinal cord injury (8), psychiatric illness (9), Parkinson's disease (10), dystonia (11), refractory depression (12), and Alzheimer's disease (13, 14). However, there is yet to be an effective, scalable, personalized, and truly responsive stimulation solution for refractory epilepsy or neurological diseases in general. The market share of neurostimulation devices was more than US$6 B in 2020 and is projected to pass US$11B by 2026 (15). Key manufacturers of neurostimulation devices include Medtronic, Boston Scientific, Abbott, LivaNova, Nevro, NeuroPace, Beijing Pins, and Synapse Biomedical. Figure 1(a and b) depicts the history of implantable neurostimulation devices and the trend in advanced neurostimulation. Although it does not perform neurostimulation, we consider the first pacemaker (16) the first important milestone on the roadmap, as it shares the same core idea: electrical stimulation. A decade after the first pacemaker, in 1967, the first implantable stimulation device was introduced for chronic pain relief. Since then, neurostimulation has shown consistent effectiveness in reducing chronic pain (17). This is followed by the first implantable defibrillator reported in 1980 (18). Neurostimulation has been explored for its potential as a treatment or therapy for other diseases such as epilepsy, Parkinson's disease, Alzheimer's disease, and spinal cord injury. The year 1997 marks the first FDA-approved vagus nerve stimulation (VNS) device in treating intractable epilepsy (19, 20). The device, NeuroCybernetic Prosthesis, is based on the finding that stimulating the vagus nerve modulates cortical activity via thalamocortical pathways, though the precise mechanism is not yet fully understood (21). Deep brain stimulation (DBS) was first used in 1980 for the reduction of tremors (22) and has since become an effective treatment

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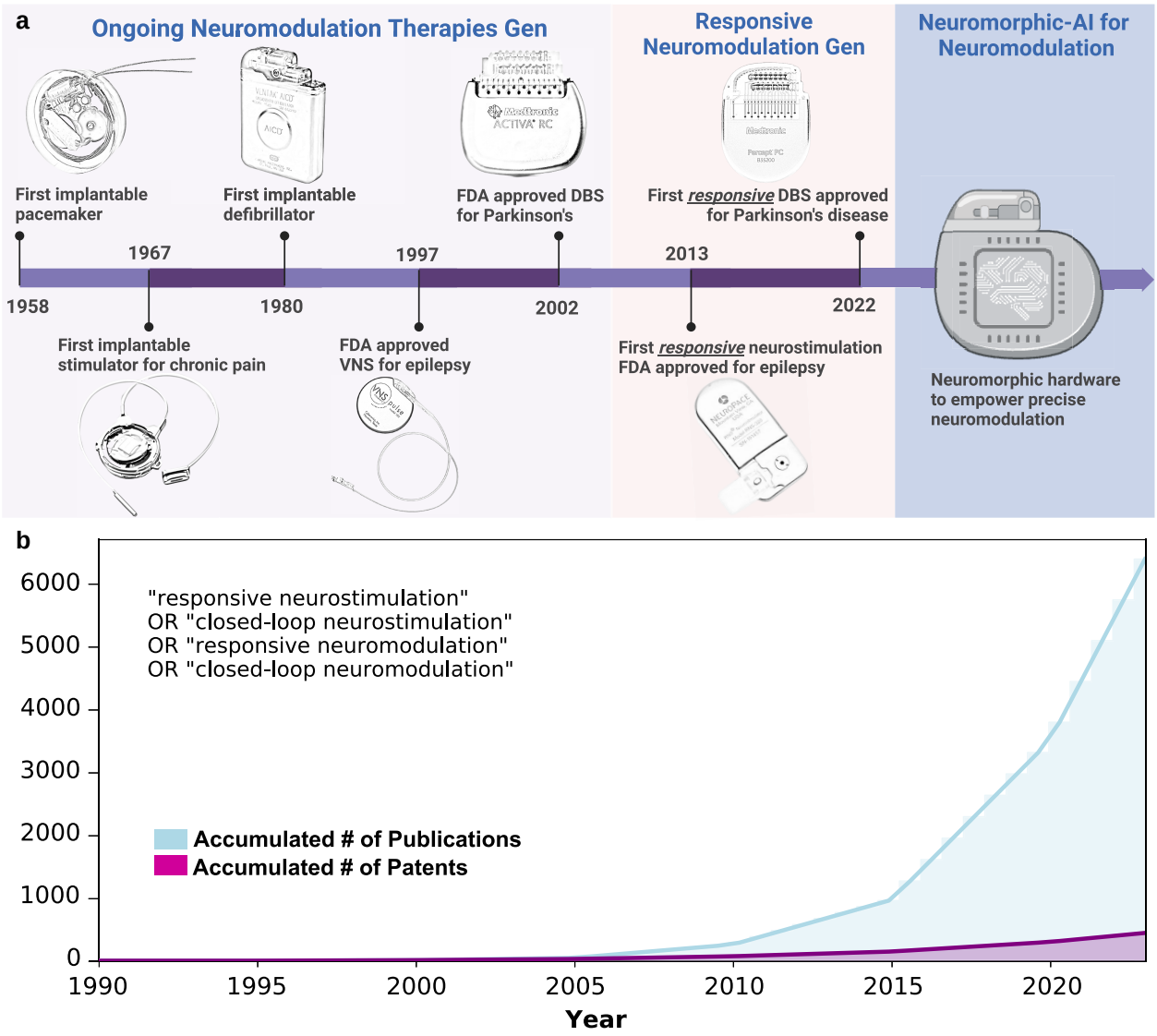

Fig. 1. a) Brief history of neurostimulation devices and possible future directions (16, 18, 20, 27–31). The first generation of neuromodulation devices primarily involved the delivery of constant electrical stimulation to targeted brain regions. Responsive stimulation generation represents a significant leap forward, incorporating closed-loop systems that dynamically adjust stimulation parameters based on real-time feedback from neural activity or physiological markers. Inspired by brain computing, the future generation should be focused on neuromorphic neuromodulation, which holds great potential for revolutionary and precise therapeutic interventions. b) Accumulated number of publications in responsive or closed-loop neurostimulation. An evident gap exists in closed-loop systems about the requirement for on-chip devices capable of continuous learning.

of Parkinson's disease with impressive clinical outcomes in terms of motor and nonmotor effects and quality of life improvements (10, 23). Neuromodulation has been tried with more acute conditions such as spinal cord injuries, where epidural electrical stimulation is applied to stimulate specific sensorimotor functions (8). Closed-loop VNS has shown promising evidence of the prolonged effects in restoring neural circuitry with a study on rats (24). Less commonly, neurostimulation has also been explored with other conditions such as psychiatric illness (9) and loss of control eating (25). Recent advancements in neuromodulation underscore its growing flexibility in targeting precise brain regions or networks, facilitated through various administration methods such as one-time treatments, continuous delivery, or adaptive responses to physiological changes. These advancements are pivotal for enhancing the efficacy and versatility of neuromodulation devices, particularly through the integration of advanced algorithms and responsive feedback mechanisms, as projected by 2035 (26).

Future brain stimulation devices will use advanced algorithms that combine predictive models and responsive feedback mechanism

In responsive neurostimulation, a neurostimulator device is surgically implanted within the patient's brain or near the affected area. This device ideally has electrodes that constantly monitor the brain's electrical activity in real time, which is not a trivial in terms of implementation. It is programed to detect abnormal electrical patterns or seizure onset based on predefined algorithms. One example is to treat epilepsy by continuously monitoring intracranial EEG and providing stimulation only when epileptiform activity is detected. NeuroPace developed the first Responsive Neuro-Stimulation (RNS) systems for epilepsy that detects abnormal brain activity and responds in real time (32). This reduces the amount of stimulation required and improves the accuracy of the treatment. This closed-loop system utilizes databases, modeling, and machine learning to enhance performance

while gathering data necessitates additional telemetry and data storage. Another example is the Mayo Epilepsy Personal Assistant Device (EPAD) that combines an implanted device with intracranial EEG telemetry, electrical stimulation, behavioral state classifiers, remote parameter control, a handheld computational device, and a cloud training for managing neurological diseases (33, 34). Consequently, neuromodulation will increasingly depend on data science for better outcomes.

Challenges with current responsive neurostimulation devices

Almost 55% of neurostimulation devices are intended for pain management (15). For more acute diseases like epilepsy, despite promising reports showing a reduction of around 50% in seizure frequency with responsive neurostimulation (35, 36), people with refractory epilepsy still develop seizures that prevent them from joining the workforce or performing certain daily activities (e.g. driving). There are several reasons for the low efficacy in preventing/suppressing seizures. Firstly, the stimulation is activated based on the detection of anomalies, presumably epileptic seizures, in brain signals which are manually predefined by physicians (35, 37–42). We argue that stimulating the brain after seizure onset is detected is sub-optimal. Activation of stimulation before the onset is likely more effective in preventing seizures. This idea was proposed back in 2003 (6) and was taken up in several patents (43, 44) but has not been tested in clinical trials yet. What prevents such a system from being effective is the lack of a high performance neurological event or seizure prediction model. Seizure prediction is more challenging than the detection counterpart and its performance relies on long-term and patient-specific EEG recording (45–48). Nevertheless, having access to ultralong-term EEG recordings is just one part of the overall solution for robust developing seizure prediction models. The EEG recording needs to be labeled such that it can be used to train a machine learning model, e.g. a deep neural network. This process is not only time-consuming, but it requires manual reading and labeling to be performed by neurologists, and must be regularly repeated as underlying physiological patterns are subject to changing over time (49). This corresponds to data set drift. Furthermore, interpreting brain data obtained chronically or in real time requires advanced analytics that rely on deep-learning algorithms and intensive computational capabilities, which are unsuitable for current hardware and software approaches for on-chip learning (50).

Can these devices be smarter, extraordinarily energy-efficient and perform truly real-time closed-loop therapy?

Neurotechnology research has seen a surge in startups and companies over the past decade, but on-chip computation is currently limited to simple signal processing and feature extraction. Existing systems such as the RNS, Percept family: (PC/RC) and Summit RC +S (31, 51, 52) rely on external systems with advanced machine learning algorithms for accurate symptom tracking.[a] For instance, the investigational Medtronic Summit RC+S utilizes an embedded dual Linear Discriminant Classifier that consumes 5 μW/channel, and its parameters can be upgraded through telemetry. Percept family includes the PC and RC. The PC device incorporates BrainSense technology, specifically designed for acquiring brain signals (known as local field potential or LFP) utilizing the implanted DBS lead. Concerning the utilization of BrainSense technology, for a patient with Parkinson's Disease, the system typically consumes a moderate amount of energy over 2 months with the BrainSense technology incorporated. This energy usage is expected to sustain the device for a duration of five years. The FDA approved the latest innovation of the Percept (RC) in early 2024 and includes the rechargeable neurostimulation. The RC is the smallest and thinnest dual-channel neurostimulator available for DBS that offers at least 15 years of service life with consistent and fast recharge performance (53). Brain Interchange ONE is the first version of the CorTec Brain Interchange technology, which is currently approved for the first study by the FDA. It consists of a closed-loop neuromodulation bi-directional device, in which the energy supply is done via induction and can record and stimulate brain activity in 32 channels. This device relies on external artificial intelligence that runs in a designed software (54).

The RNS system continuously monitors ECoG at the seizure focus and delivers closed-loop electrical stimulation when abnormal (epileptiform) patterns are detected. Two versions have been available in the market: The RNS-300 and RNS-320, with the latter incorporating the most recent advancements. Both versions depend on the telemetry component used for communication, a storage and access to historical neurostimulator data. However, one significant design feature, or lack thereof, in these devices is the demand for external transmission of information as continuous data telemetry drains their battery quickly. This system which are being said to be continuous monitoring are partially true. For instance, one of the RNS models can only record a maximum of 4 min of ECoG and it can be scheduled to repeat this up to four different times in a 24 h clock. That means, information of the whole day is not present, just instance of times. As well, this device passively records multiple seizures, which aids in developing detection algorithms tailored to the patient. By analyzing these recordings, the algorithms can identify seizure patterns and apply responsive stimulation using techniques like line length and half-wave detection. Existing deep-learning models outperforms such algorithms. These alternatives faces challenges such as increased power consumption due to wireless data telemetry and significant latency in the feedback loop (several hundred milliseconds) relative to potential latency for an on-device equivalent. Integrating this alternative approach could reduce the effectiveness of closed-loop stimulation and an increased need for more frequent battery replacements or recharges of implanted batteries. The goal is to design the next generation of intelligent neuromodulation systems with more on-chip computing, energy efficiency, and overall miniaturization (55).

In this perspective, we aim to explain why neuromorphic computing may represent a potential solution for making embedded smart electroceuticals devices. These ground-breaking devices use electrical impulses to precisely modulate the body's neural circuits (56–58). We discussed the practical advantages of our approach with a feasible application, study cases with potential improvements, challenges, and opportunities in this emerging field.

Neuromorphic neuromodulation: driving the next generation of on-device AI-revolution in electroceuticals

Data telemetry is power hungry

The rapid advancement of AI and neural networks has led to computers exhibiting impressive cognitive abilities. However, reducing computational costs and achieving brain-like efficiency remains a challenge. Deep neural networks form the basis of state-of-the-art AI as it stands, and these networks rely on computing systems,

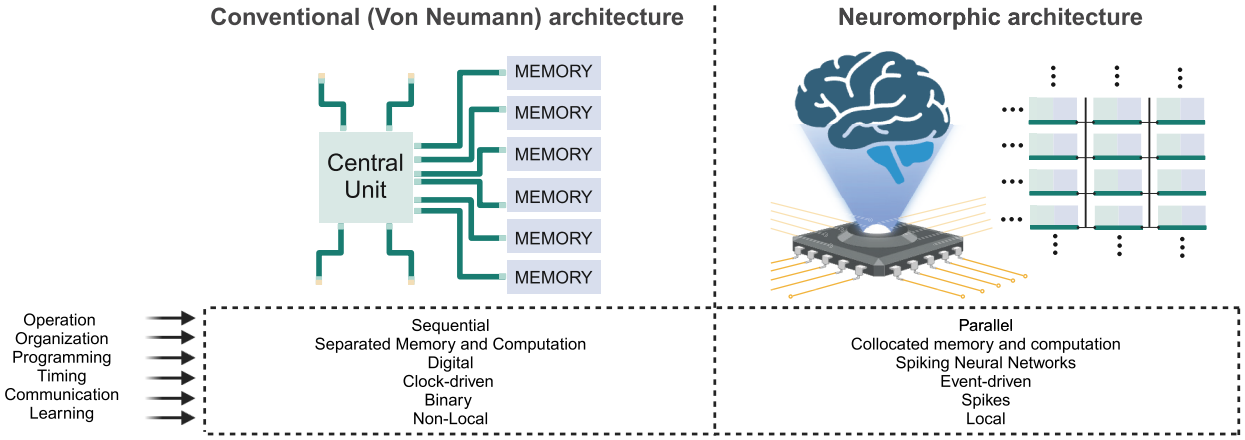

Fig. 2. Contrast between conventional (von Neumann, e.g. CPUs) architecture with bio-inspired (non-von Neumann, e.g. neuromorphic) architecture. Conventional computers rely on sequential, clock-driven (synchronous) binary operations, separating memory, and computation units. In contrast, the human brain employs event-driven (asynchronous), neural action potentials (spikes), with a great network capacity for parallel processing and capability for local learning mechanisms. These basic, seemingly shallow, yet fundamental distinctions contribute to the brain's inherent superiority in terms of energy efficiency, positioning it as a promising avenue for custom or general-purpose integrated circuits and computing architectures development.

from the transistors to hugely memory-intensive graphics processing units (GPUs), which consume substantial energy in their general-purpose and conventional computing architectures. Training these networks on energy-intensive servers yields high accuracy but also high energy consumption. For example, running a model on an intelligent glass-embedded processor would exhaust its battery (2.1 Wh) within a span of 25 min (59). This high power consumption makes such systems unsuitable for bio-electronic medicine applications, which prioritize low energy usage. External data processing in implantable devices requires wireless data telemetry, which is limited by bandwidth, communication range, interference, and, crucially, energy requirements. As real-time processing is a need, such external interaction would hinder timely response to signal features and potential efficacy issues. Conversely, on-device (edge) computing solutions enable the immediate processing of recorded signals and facilitate closed-loop interventions (60, 61). Expanding edge computing capabilities beyond inference-only to on-device learning would significantly enhance the personalization and efficacy of these devices.

Can we take inspiration from the brain through neuromorphic?

The human brain possesses a remarkable computational power ranging from 10^{13} to 10^{16} operations per second, with a power consumption of approximately 20 W.[b] In contrast, a computer performing a classification task requires around 250 W. The brain consists of billions of neurons ($\sim 9 \times 10^9$) connected by trillions of synapses ($\sim 3 \times 10^{14}$), allowing for information processing at a rate of approximately 6×10^{16} bits per second (62, 63). Recent investigations explores the prospects of neuromodulation over a decade (64), where it discusses the potential of neuromorphic chips for implanted body-machine systems, which mimic the co-location of logic and memory, hyper-connectivity, and parallel processing of the human brain, as shown in Fig. 2. The field of neuromorphic computing has seen significant advancements in industry and academia (63). Several notable neuromorphic chips, like IBM's TrueNorth and Intel's Loihi, cater to specific applications with dedicated software ecosystems. In the European Union Human Brain Project, chips like BrainScales, SpiNNaker, NeuroGrid, IFAT, and DYNAPs excel in tasks such as object detection and medical image analysis. There's a growing focus on versatile neuromorphic platforms integrating hardware and software, like the Tianjic chip supporting both spiking neural networks (SNNs) and traditional artificial neural networks (ANNs). Spinnaker serves as a general-purpose accelerator for diverse workloads. These chips employ digital, analog, or mixed-signal configurations based on their functional needs (65–75). Table 1 overviews some of the most prominent current neuromorphic chips. Notably, there is a wide range of neuromorphic chips, but we consider the mostly commercially available for demonstration. Research notes limitations in current devices for peripheral nervous system stimulation and suggests neuromorphic circuits as an ideal solution for enhancing bioelectric medicine. Adaptive closed-loop systems using neuromorphic engineering can improve symptom control by continuously monitoring physiological signals and adapting in real time (76). These systems use mixed-mode analog/digital transistors and consume ultra-low power. Neuromorphic engineering can overcome bandwidth and power consumption limitations, improving neural data acquisition and processing (77). Analog neuromorphic front-ends offer a low-power solution for high-bandwidth neural recording and multichannel processing needs. They process analog signals directly, converting them into spikes for SNN use. Recent neuromorphic computing advances enable on-chip training with minimal power usage and a small device size. Frenkel et al. (78) demonstrate on-chip training in a 32-mm^2 silicon area, achieving 95.3% accuracy with the MNIST dataset, slightly lower than off-chip training's 97.5% accuracy. Existing neuromorphic chips, such as the well-known IBM TrueNorth and Intel Loihi chips, are general-purpose chips that support various types of networks and configurable parameters (i.e. number of layers, kernel sizes, etc.). However, their versatility comes with a cost of higher power consumption and heat dissipation. For implementation of neural networks with learning capability, a neuromorphic chip should be fully optimized for one specific application if continuous active learning is to be coupled with a medical device, especially implants that have strict constraints on temperature.

Feasible application for neuromorphic neuromodulation

Figure 3 demonstrates three main categories of neuromodulation devices, including those which are commercially available (Fig. 3a and b)

Table 1. A benchmark of neuromorphic chips. This list is not extensive but considers the breakthroughs.

Features/chips	CPU	TrueNorth	Loihi2	Tianjic	SpiNNaker	Brain ScaleS-2	DYNAP SEL	Akida	Human brain
Event-driven	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Analog or digital	Digital	Digital	Digital	Digital	Analog	Analog	Analog	Analog	Analog
Node (nm)	5	28	7	28	130	65	28	28	–
In-memory computing	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Neurons/Synapses count	–	1 M/256 M	1 M/120 M	40 K/10 M	16 k/8 M per chip	–	1 K/78 K	1.2 M/10 B	20 B/200 T
Cores	Vary	4,096	128	156	18 per chip	8	5	80	–
Neurons/Synapses per core	–	256/64 K	8 K/900 K	256/64 K	800/1 M	512/130 K	256/	15 K/125 M	–
On-device learning	Backprop/STDP	No	STDP /Surrogate backprop	No	STDP	STDP, R-STDP, homeostatic plasticity	STDP	Few-shot training	Diverse learning
Network compatibility	ANN	SNN	SNN	Hybrid	Hybrid	SNN	SNN	ANN, SNN	SNN
Key properties	Limited to on-chip training	First commercial neuromorphic chip	Fully programable chip	First hybrid chip	Scalable SNN simulation	Hybrid Plasticity	One plastic core	Continuous and few-shot learning	–
ASIC/FPGAs	–	ASIC	ASIC	ASIC	ASIC	BOTH	FPGAs	ASIC	–
GSOPS/W	–	400	~ 10 × Loihi1[a]	649–1,278	0.033	>10	33	Akida	–
Memory type	–	SRAM/ DRAM	SRAM /DRAM	SRAM	SRAM	SRAM	SRAM	SRAM	Different brain regions
Routing schemes	–	Grid/2D mesh	Grid/2D mesh	2D mesh	Grid/2D mesh	Hierarchical tree	Hierarchical tree	Grid/2D mesh	Stochastic
Refs.		(79, 80)	(81)	(82, 83)	(65, 84)	(84–86)	(73, 87)	(88)	(62, 89)

[a] There are no direct data available, but it is stated to be 10 times more than Loihi1.

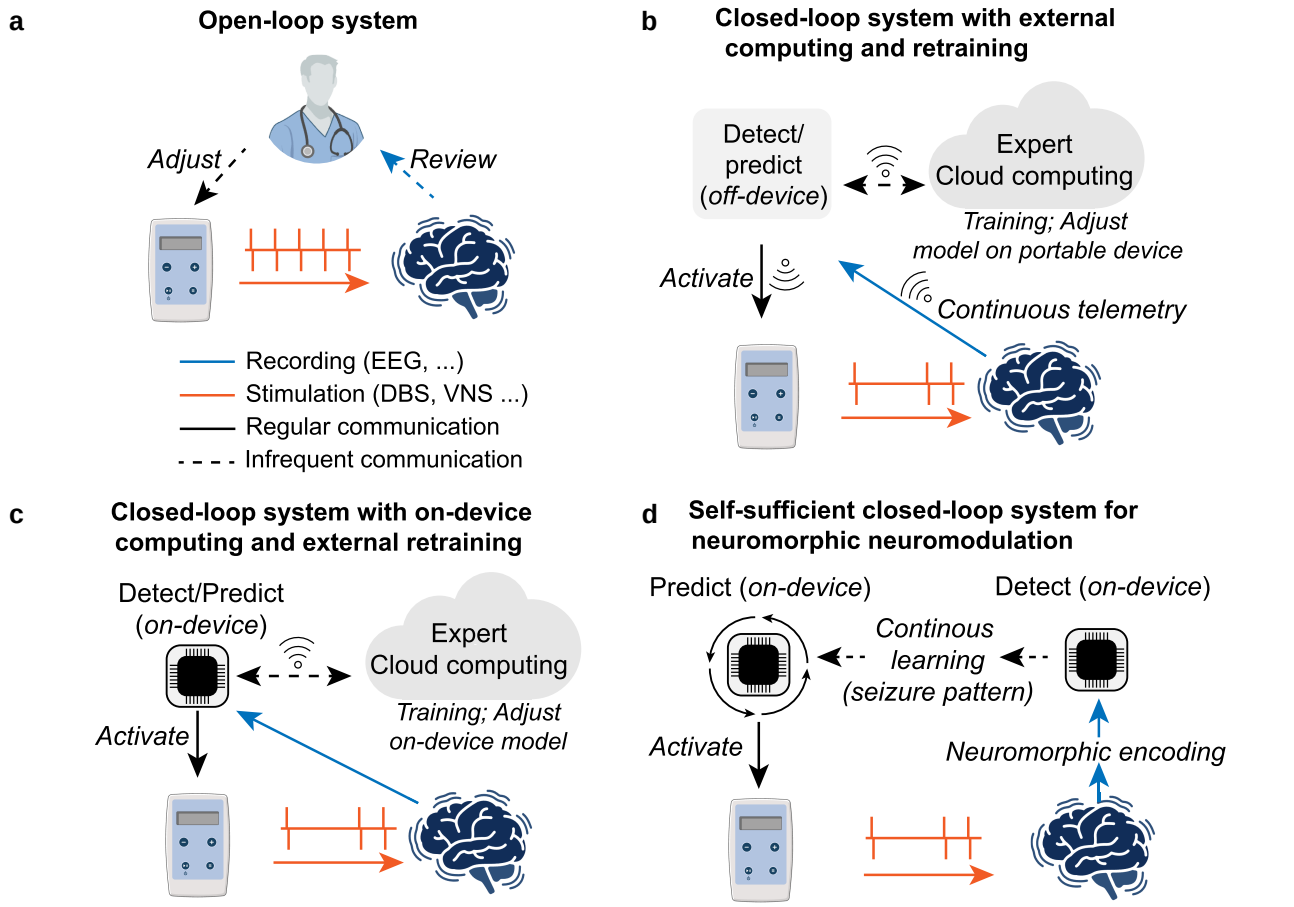

Fig. 3. Neuromodulation approaches. a) An open-loop system with an expert who occasionally reviews the effectiveness of the system and adjusts the stimulation parameters accordingly. Such system employs cyclic stimulation regardless of the current state of the target (e.g. brain state). b) A closed-loop system with external computing for accessing the state of the target to condition the stimulation. The external computing component can be in the form of a portable device, e.g. tablet, or a local computer. The recording device continuously streams data (e.g. EEG signals) to the external computing where trained algorithms are executed to determine the target's state. The deployed algorithms on the external computing component can be updated occasionally by involving a review from an expert(s) and big data/cloud computing (retraining). c) The computing component is embedded within the device, which eliminates the need for *continuous* streaming of data to the outside world (44, 97). However, the on-device algorithms need to be occasionally updated to reflect the change in physiological signals (e.g. change of seizure patterns in epileptic patients). The device must also have sufficient memory to store the signals for the expert(s) to review and for the retraining that takes place in the cloud. d) A neuromorphic neuromodulation system where the medical device can run and retrain its algorithm by itself without relying on external computing resources. The system utilizes labels generated by a detection model that has performance on-par with a human expert (101–103) and a continuous learning strategy that as a recorder to train a prediction model. The rapid improvements in neuromorphic computing (104, 105) have made on-device active learning possible. It's noteworthy that such system will intermittently transmit relevant snapshots or markers of the recorded bio-signal to comply safety-efficacy standards.

and under investigation (Fig. 3c). In an open-loop system (Fig. 3a), stimulation parameters such as amplitude, frequency, and duty cycle are predetermined by a clinician. Stimulation persists unless manually turned off by the patient or the clinician. The device can be reprogramed during a subsequent patient visit if the stimulation does not show effectiveness. In contrast, a closed-loop system triggers stimulation by responding to physiological changes. The system in Fig. 3b continuously senses the patient's state (e.g. EEG signals) and streams it wirelessly to a portable device (or a bedside computer) that is in charge of analyzing the signals by using threshold-based rules or machine learning models, and turning it into a control signal to the stimulation (48, 50, 52, 90–95). In epilepsy management, a portable device activates stimulation upon detecting or predicting a seizure onset. This closed-loop system, aided by external computing, minimizes unnecessary stimulation compared to traditional approaches. However, continuous data streaming to external resources consumes substantial power, limiting battery life or increasing device size. Moreover, wireless communication between the device and external computing poses challenges like connection loss, interference, and security risks. Figure 3c illustrates how an alternative closed-loop system can address the complications from continuous data stream of standard closed-loop systems by incorporating an on-device computing unit to the neuro-modulation device without reliance on external computational power to host the control algorithms (44, 96, 97). In these closed-loop system models (Fig. 3b and c), the optimization of models (on-device or off-device) must still be performed regularly and involves a human expert and/or cloud computation to adapt with the changes in the patient's conditions and/or in the underlying disease (49). This implies that the patient's data needs to be stored in the external device (Fig. 3b) or in the implantable device (Fig. 3c) and regularly be uploaded to the cloud. The data will also need to be analyzed or labeled by a human expert so it can be used to update threshold-based rules or to retrain the machine learning models. It should be noted that none of the aforementioned methods offer on-device training and retraining, and requires expert involvement for regular retraining (98), which limits the scalability of the system to a large number of patients (99). The idea of on-device active learning proposed in Ref. (100) relied on an ideal detection and deterministic feature extraction technique to actively train a prediction model without expert intervention or external computational resources.

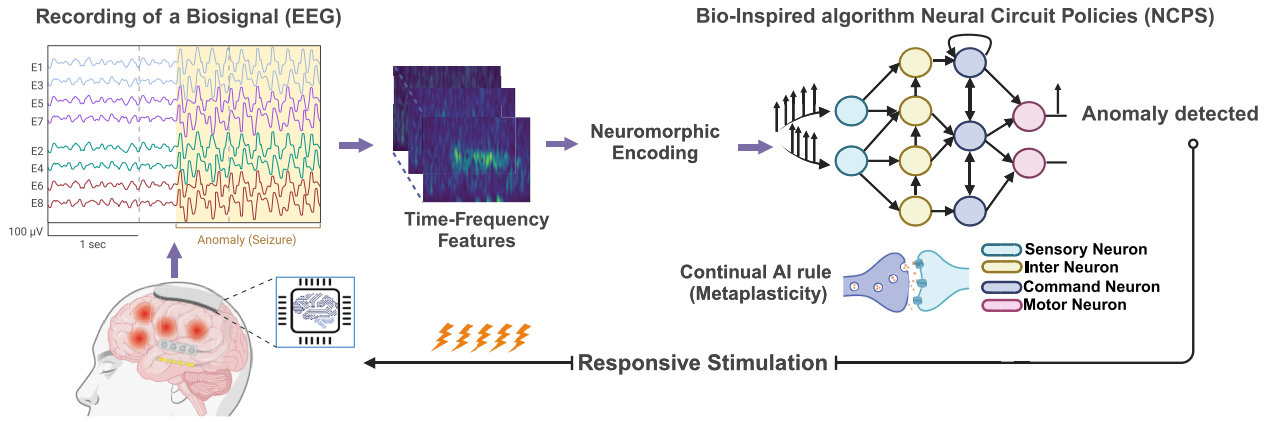

Fig. 4. Neuromorphic neuromodulation employing bio-inspired learning rules represents a cutting-edge paradigm in the field of neural systems. This innovative approach enables the development of on-device learning capabilities, thereby facilitating the seamless integration and real-time processing of continuous bio-signals. By leveraging this neuromorphic system, it becomes possible to dynamically adapt to extracted features, subsequently converting them into spikes. These spikes are then fed into a shallow, sparse, and bio-inspired algorithm that utilizes a continuous learning rule for precise adjustment, ultimately yielding responsive stimulation tailored to each individual patient. This approach eliminates the reliance on cloud computing.

However, we argue that deterministic feature extraction may lose its efficacy over time because the underlying disease is evolving. Our alternative is neuromorphic neuromodulation, a computationally self-sufficient closed-loop system, shown in Fig 3d. Our proposed system eliminates the requirements of continuous data telemetry and the reliance on external computational resources. We believe our self-contained system can provide an ultimate personalized closed-loop neuromodulation system. The vision is ambitious but not impractical.

Evaluating standards in a self-sufficient responsive neuromorphic system

Here, we discuss some fundamental standards and criteria that our system adheres for future neuromodulation devices.

Physiological event detection becoming more trustworthy

The field of automatic annotation of physiological data has seen significant advancements, with recent developments approaching the accuracy and reliability of human experts. Notable examples of these advancements include the detection and classification of arrhythmias (101), the identification of epileptiform discharges (102), and the marking of seizures (103). These technological improvements not only enhance automatic health monitoring, thereby reducing the burden on clinicians, but also create opportunities to leverage unlabeled data. For instance, algorithm-generated labels can be utilized to train other predictive models without the need for human expert intervention. While detecting seizures during or immediately after the onset has proven more successful than predictive methods, these advancements have led to the development of AURA, an Adaptive, Unlabeled, and Real-time Approximate-Learning platform (106).

On-device learning

AI systems utilizing Application-Specific Integrated Circuit (ASIC) with parallel multiply-and-accumulate (MAC) exhibit better inference and energy efficiency than GPUs. However, by performing MAC operations, the need for intensive data transfer between this units and data buffers limits energy efficiency and therefore and are restricted to functioning solely in inference mode, whereas the human brain has the remarkable ability to learn continuously. Consequently, on-device learning emerges as a significant characteristic of neuromorphic systems. On-chip learning is indispensable for tailoring and personalizing smart devices to cater to individual user requirements. Moreover, it bolsters privacy by eliminating the need to transmit user data to the cloud (107–110). At the core of AURA, on-device learning is achieve by a high performance physiological event (e.g. epileptic seizure) detection model that acts as an algorithmic "human expert" to generate labels on-the-fly as the signal arrives. The generated labels are paired with recorded signals from a loop recorder to be used as a training dataset for a predictive model (e.g. seizure forecasting). It is worth noting that while the detection model or label generator must have high performance, it does not necessarily need to be perfect. In fact, imperfect labeling from a mix of clinicians and medical students with varied levels of experience has shown to remain effective in training a deep-learning model to perform seizure detection at a high level of accuracy and generalization. AI models face limitations due to misaligned metrics with clinical needs, requiring validation through prospective data and real-world data testing (111).

Embrace multimodal signals

As part of physiological monitoring, it is usual that there are multiple signals being recorded. For instance, in the VNS device, multimodal approaches are also used in some cases, such as incorporating a heart rate sensor to activate stimulation when the heart rate exceeds a predetermined threshold since some seizures are associated with an acceleration in heart rate. Combining signals from multiple sources has the potential to improve the performance of a detection/prediction model (112, 113). It is important to note that depending on performance requirements, power consumption and/or heat dissipation, the detection model of AURA may use a different set of sensory modalities from the prediction counterpart.

Integrating bio-inspired algorithms for energy-efficient electroceutical systems

SNNs provide an alternative approach by mimicking the behavior of biological neurons and offering potential energy efficiency

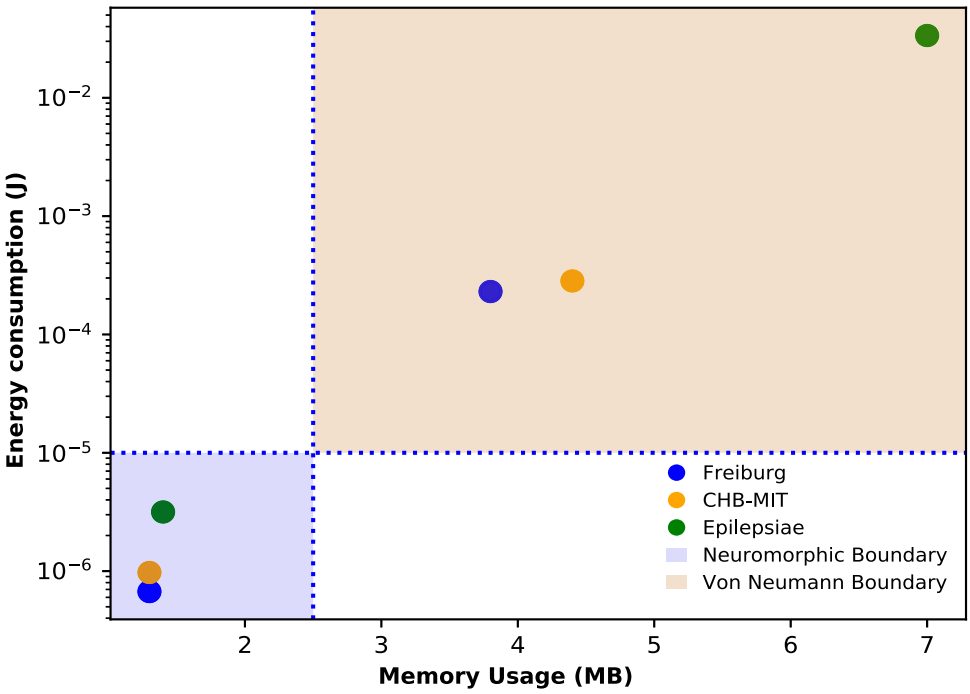

Fig. 5. Memory usage and energy consumption achieved by an inference-only task by a conventional AI model (ConvLSTM) run on a von Neumann computing architecture vs. a spiking ConvLSTM model that runs on a neuromorphic architecture.

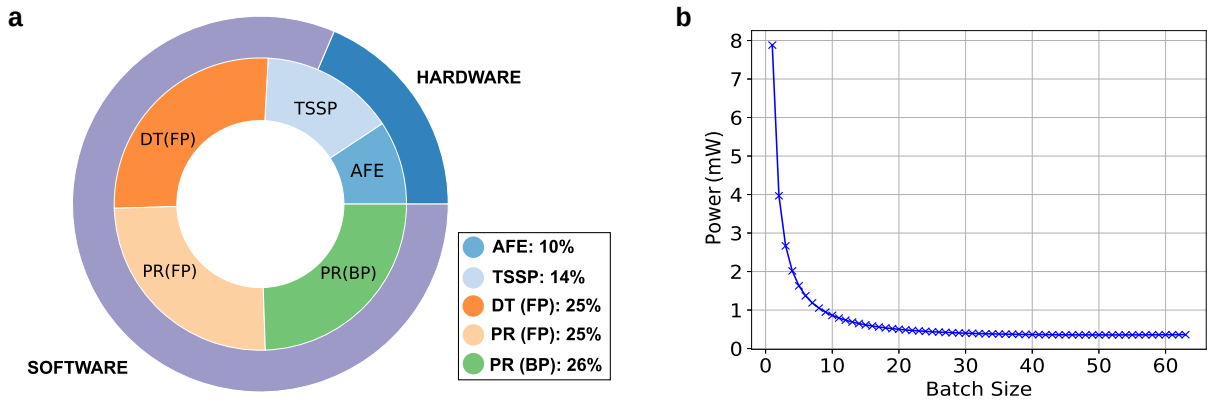

Fig. 6. Power breakdown of a Neuromorphic Device. Traditional algorithms used in neuromorphic often utilize Time-Series Signal Processing (TSSP) methods like Fast Fourier Transform (FFT) or Short-Time Fourier Transform (STFT) for feature extraction to enhance performance. All parts discussed are considered as one solely system (a). Power reduction can be address with the algorithm (software) development and this can even further be improve with the use of larger batch sizes in processing operations and the incorporation of more biological plausible algorithms for future implantable neuromorphic devices (b). AFE, analog front end; DT, detection; PR, prediction; FP, forward propagation; BP, backward propagation.

advantages, making them suitable for resource-constrained environments like edge devices (111). Training approaches can be categorized into different methods. One common approach is to directly train the SNN itself using surrogate gradient descend. Another approach involves training a traditional ANN and then mapping it into an SNN. The ANN is trained using conventional techniques, and the resulting trained weights and connections are then transferred to the SNN. Reservoir computing is another technique used in SNNs, where the network is structured with an input layer, a reservoir layer, and a readout layer. The reservoir acts as a dynamic memory, and the readout layer is trained to interpret the reservoir's activity. Lastly, spike-timing-dependent plasticity is an approach based on the synaptic plasticity mechanism, where the weights of the connections are adjusted according to the relative spike timings between pre- and post-synaptic neurons. These training approaches provide different strategies for training SNNs, each with its own advantages and applications. (114–121). The AURA system is built on conventional SNN architectures and training. Studies have investigated seizure detection using closed-loop direct neurostimulation devices in epilepsy with neuromorphic chips by successfully transferring a CNN to TrueNorth, demonstrating accurate detection with low memory usage and efficient runtime with a power consumption lesser than 40 μW. However, it is noted that CNNs' dependency on back-propagation can result in issues such as catastrophic forgetting and heightened computational costs (122–124).

Back-propagation: implausible biological way and issues with neuromorphic hardware

Artificial neural networks (ANNs) use back-propagation and gradient descent to adjust synaptic weights, but this leads to several

issues, including catastrophic forgetting, weight-symmetry problems (125), freezing of neural activity (126), and nonlocal weight updates (127). Back-propagation is also vulnerable to adversarial attacks (128) and requires excessive computational hardware in analog VLSI (129). Novel solutions, such as the forward-forward algorithm, aim to address these problems (130, 131). However, its current scope is limited to static datasets like CIFAR-10, with slightly worse test errors than current back-propagation framework. Nonetheless, in the following study cases we used biological-plausible solutions to tackle those problems and potentially served as framework for the proposed perspective solution.

Case studies for AURA: foundations of efficient, low-power, and biologically inspired models for seizure detection

In the realm of seizure detection/prediction, the quest for efficient, low-power models employing lifelong learning draws attention from bio-inspired algorithms, which can enhance the performance of the AURA system. Lifelong learning refers to the ability of a system to continuously learn and adapt to new information, similar to how biological systems function. Within this context, our exploration unveils three distinct yet impact success cases of studies. The following models stand as exemplars of effectiveness and power efficiency, showcasing an alternative approach to seizure detection, with the perspective for accurate neuromodulation. Leveraging the principles derived from biological systems, these algorithms manifest a prowess in lifelong learning, exhibiting adaptability and responsiveness.

Case 1: Continual learning with artificial metaplastic models

In computational neuroscience, the stability-plasticity dilemma revolves around AI models ability to acquire new memories while retaining existing ones. Synaptic plasticity, the basis of learning, involves neuronal connections adjusting their strength over time. This paradox is addressed through synaptic artificial metaplasticity, a bio-inspired approach to continuous learning. Using a binarized neural network (BNN), researchers implemented synaptic metaplasticity to mitigate catastrophic forgetting in multitask learning. This method modulates hidden weights via a function $fmeta(Wh)$, potentially applicable to neuromorphic platforms (132, 133). We applied this principles to our model MetaEEG, which is a low-power neuromorphic proof of concept for lifelong learning on EEG seizure. We proposed a BNN with artificial metaplasticity for stream learning setting to place the model in a close to wearable data-feed. We trained our model on the Temple University Hospital (TUH) dataset, dividing it into 300 subsets and sequentially presenting each to the model for 20 epochs. Every five subsets, we tested the model on unseen test data. We evaluated its performance on different EEG signatures to assess its adaptability to significant changes in seizure patterns. By generating five synthetic EEG datasets featuring different seizure signatures, we illustrated the model's ability to adapt without forgetting previous patterns, achieving an AUROC of nearly 0.80 (134). This feasibility proof paves the way for future studies focusing on integrating artificial meta-plastic behavior with SNN compatibilities for seizure prediction, addressing buffer limitations in the AURA system.

Case 2: Effective, sparse, interpretable, and low-power liquid time constant-based models

Liquid time neural networks are a class of time-continuous recurrent neural networks models that posses stable and bounded behavior, improving performance on time-series prediction tasks. Their low complexity allow for a better representation of the hidden states, and adapting to changing conditions such as autonomous driving and medical time-series data (135–142). We used Liquid Time Constant in different scenarios such as models on shallow bio-inspired models and spiking neural version of theirselves with a forward-propagation through time algorithm (143). We developed a dynamic spiking model for seizure detection across continental datasets utilizing spiking liquid-neuron networks with forward propagation through time (FPTT) (144). By training and validating in the TUH dataset, we evaluated generalization in the Royal Prince Alfred (RPA) Hospital dataset achieving an AUROC of 0.83 in 192 patients, which is slightly higher that a conventional algorithm based on ConvLSTM (145). By reducing the model's memory requirement by 10 times, we examined the model's robustness and found it to perform to the level of a large dynamic SNN, with an AUROC of 0.82. Subsequently, we applied a scaled-down model, which achieved an AUROC of 0.83 in the EPILEPSIAE Dataset. We provided a estimation of power consumption of the model with a 3.1 μJ/Inf (per inference) in Loihi. Further exploration should include this dynamic models with ECoG and LFP data.

Case 3: On-device fine-tuning with spiking liquid-base models: feasible application on hardware

We initiated a study exploring a Spiking Neural Circuit Policies (NCPS) model variant employing liquid time constant for Arrhythmia detection, incorporating for on-device fine-tuning (146). Our setup utilized the Radxa Zero SBC with an Amlogic 905Y2 processor and 4GB LPDDR4 memory. Refinement of the model on the Radxa Zero involved leveraging a pretrained model, initially trained for two epochs on the Telehealth Network of Minas Gerais dataset (TNMG) via GPU. Adjustments were implemented, including reducing the batch size to 8 during fine-tuning, utilizing 72% memory. The fine-tuning phase encompassed training on a dataset comprising 640 data points across five epochs, followed by validation on a subset of 320 data points. The evaluation of the fine-tuned model involved comparing its performance against the base model trained on GPU. Throughout the training iterations, the model displayed notable improvements in performance metrics. The average F1 score increased from 0.46 to 0.56, and the AUROC enhanced from 0.65 to 0.73. A fine-tuned model was tested on a larger dataset of 1,280 samples, where significant improvements are present with F1 score and AUROC increasing from 0.31 and 0.63 and from 0.45 and 0.72, respectively. These findings have motivated further investigation into its suitability for deployment on neuromorphic chips. Integrating these studies cases could be seen in a bio-inspired model as detailed in Fig. 4.

Estimation of power consumption of a fully integrated AURA system

A study conducted with spiking neural networks on EEG datasets (Freiburg, CHB-MIT, Epilepsiae) for seizure detection was proposed by (147) where they demonstrate the capabilities of neuromorphic approaches to reduce the memory usage and energy consumption from ten to thousands of magnitude in comparison like running in conventional GPUs devices with conventional AI algorithms. The results of this study are demonstrated in Fig. 5. Drawing inspiration from the aforementioned findings and case studies, these instances serve as a basis for projecting the power usage of a completely integrated system. For a fully integrated detection/prediction system, we assume the input signal (EEG) has

10 channels and a sampling rate of 128 Hz. For the sake of simplicity, both detection and prediction networks use similar convolutional long short-term memory (ConvLSTM) network architectures proposed in Ref. (148), which consists of three ConvLSTM layers followed by two fully connected layers. The detection and prediction algorithms use input windows of 10 and 30 s, respectively. The inputs are divided into 50% overlapping 1-s sub-windows to be fed to a ConvLSTM network. Using the Loihi neuromorphic chip as a reference and a real-time batch size of 1 (one input is processed at a time), the cost of inference for a single data sample is 25 mJ and 77 mJ for the detection and prediction algorithms, respectively. Since detection occurs every 10 s and prediction every 30 s, the energy can be amortized over time, with the total power consumption for inference of both networks being 5.1 mW (2.6 mW, detection; and 2.5 mW, prediction). Note that this power consumption can be reduced if inference is parallelized into batches and distributed across a longer time interval. For example, with a batch size 32, the total inference power consumption becomes 160 μW. Regarding the training of the prediction network, as the architecture is fixed, the backward pass can be completed simultaneously with the forward pass using a deterministic mode of forward-mode auto-differentiation; therefore, the gradient calculation cost is similar to the inference cost. Given the network has 31.5M parameters, and the energy for updating each additional weight is 120 pJ (Loihi), the total cost of weight update is 3.78 mJ. The total required energy for training the prediction algorithm is (77 mJ + 3.78 mJ) or 81.78 mJ. This training step occurs every 30 s, so its power consumption is 2.73 mW (batch size = 1) or 85 μW (batch size = 32). With a custom design, the EEG's Analog Front-End (AFE) power consumption can be optimized to less than 3 μW per channel (149). Considering the AFE solely, using a commercially available rechargeable Li-Po battery with a size volume of $2.7 \times 30 \times 34\ mm^3$ and a capacity of 240 mAh at 3.7 V (150), the system can be powered for at least 24 hours before a recharge. The battery life can be considerably extended with calculations in batches, with the only trade-off of a slight delay in obtaining results. Considering the size of the detection and prediction networks and adhering to the synaptic density of the TrueNorth chip, we estimate a required area of $\sim 62\ mm^2$ to implement the whole system. A power breakdown of a inspired neuromorphic device is provided in Fig. 6. To this extend there could be areas of opportunities in our algorithm by using more biological plausible algorithm. Studies had achieve efficient and energy-saving training of time-domain signals by incorporating dendrites into spiking neurons (151), potentially eliminating the dependency of TSSP blocks. Leveraging the model's capacity to interpret bio-signal data conserves power, prolonging implantable device lifespan.

Challenges and opportunities of neuromorphic-AI

We will need a better mapping of the neural circuits associated with the treated pathophysiology. At the signal level, we will need better decoders of the neural language associated with the pathophysiological states and more precise therapeutic patterns of electrical impulses targeting the rate, even the timing of spikes (76, 152). Generating such adaptive and precise neuromodulators will require a multidisciplinary effort: the development of neuromorphic circuits for real-time spike processing will translate the biological understanding of what is happening at the neural level in health and disease (153). The absence of standardized benchmarks in neuromorphic algorithm development makes it difficult to compare and assess hardware systems for specific applications. Neuromorphic hardware development involves extensive research into new materials and devices. Choosing appropriate materials are crucial for developing neuromorphic chips for neuromodulation, with carbon-based nanostructures suggested for bio-compatible probes and FDA-approved parylene utilized for neuromorphic building blocks (154, 155). Memristive systems based provides prospects for the hardware realization of ANNs for wearable and biomedical applications. Opportunites are present for software–hardware co-design, tailoring hardware to specific applications. It explores analog and mixed-signal computing, mimicking biological neural computation's stochastic nature. Nanowire networks (NWNs) offer a promising hardware approach to emulate the brain's physical structure, including neurons and synapses. NWNs mimic synaptic metaplasticity, strengthening synaptic pathways for memory consolidation. This highlights their potential for neuromorphic systems crucial in practical applications like robotics and sensor edge devices (156, 157). Neuromorphic processors, with their low-power consumption, are set to play a crucial role in various edge-computing and edge-learning applications in autonomous systems, robotics, remote sensing, implantable, wearables, and the Internet of *X* Things, where the *X* can be medical, industrial, etc. (114, 158).

Promises of neuromorphic AI

A CMOS-based neuromorphic device detects epileptic seizures by analyzing Local Field Potential (LFP) signals (159). It enables closed-loop intervention for early seizure control and seizure reduction using SNN with a delay of 64.98 ± 30.92 ms and consumes <50 pW for each ictal event detection. NET-TEN, a subsequent technology, enhances neuromorphic processors by reducing area and power consumption, making it suitable for implantable devices. Another study present a first feasible real-time neuromorphic detection system of high frequency oscillations, which utilizes mixed-signal neuromorphic computing system with high sensitivity (160, 161). Integrating neuromorphic technologies into neuroprosthetic devices could offer a promising strategy for enhancing the development of more intuitive human–machine interfaces, by improving performance and embeddability (152, 162–164). An study has unveil epilepsy seizure prediction system using deep learning and big data, compatible with low-power neuromorphic chip and wearable integration via closed-loop therapies (124, 165, 166).

Risk of false alarms or unnecessary stimulation

Ongoing neuromodulation has shifted towards adaptive, closed-loop stimulation from traditional open-loop methods. The key challenge now is ensuring stimulation is activated precisely when needed. Based on research findings showing that chronic brain stimulation can be performed safely with appropriate control of charge density (4, 167), we can allow the stimulation activation system to have as high a sensitivity as possible with an increased number of false positives as a trade-off. A responsive stimulation with many false positives can be considered equivalent to an open-loop system that performs cyclic stimulation, given that there is a control of charge density and stimulation frequency/duration in place. Saluda Medical conducted a pioneering study on responsive neurostimulation therapies, the first FDA-approved double-blind trial for Spinal Cord Stimulation. Patients were randomly assigned to either Evoke compound action potentials (ECAP)-controlled closed-loop stimulation or fixed-output, open-loop stimulation. Results showed a 21% higher

success rate in the closed-loop group at both 3 and 12 months, without adverse effects (168, 169).

Elimination of continuous data communication

Wireless data communication can consume half or more of the total power consumption of the whole EEG recording implant (170, 171). Neuralink reduces the frequency of sending data outside to every 25 ms and places a rechargeable battery and an inductive charger in the implant (172). Continuous data communication or a brain–computer interface is critical for disease diagnosis. It is also inevitable for responsive closed-loop neurostimulation systems where some computation (training of the event detection/prediction model) needs to be performed with an external device or on the cloud (93). The system's event detection/prediction model requires periodic retraining with recent data to adapt to patients' physiological changes. We propose that if the implant autonomously learns from the data itself to adapt to changes and becomes patient-specific, external data communication and model training on external hardware can be eliminated, except for debugging. This approach aligns with interventional medicine, where the device autonomously treats the condition based on diagnostics.

Data security, privacy, dangers of these techniques hazards and pitfalls

Neuromodulation devices must be developed to guard against this data being abused or hacked. Issues to be addressed include how long and where these data should be stored and who is in charge. If data can be "written to" the brain, we need systems to guard against undesirable intrusions. Access to data provided by a medical device can be empowering for patients. This allows them to receive reports on their health data and receive alerts for concerning events such as seizures. As examples, studies aimed to improve the security of insulin pump devices for diabetic patients. One employed an on-chip neural network system, while the other proposed an efficient deep-learning method to counter fake glucose dosage (173, 174). Unauthorized access to the device, often called *brainjacking*, could allow an attacker to manipulate the stimulation parameters or even cause harm to the patient. Interference on the wireless communication between the device and external equipment could disrupt therapy. Ensuring the security of communication in Implantable Medical Devices (IMDs) is a critical issue for patient safety, with several research groups focusing in addressing challenges for a reliable solution due to factors such as the device's battery life, adaptability, and the required level of security to avoid malicious software (111, 175, 176). Integrating Body Area Communications (BAC) or Body Channel Communication (BBC) into AI systems reduces reliance on external telemetry while enabling the capture of daily activity snapshots for safety-efficiency standards. This enhances self-sufficiency, privacy, and security (177).

Conclusions

Current challenges for designing implantable stimulation devices or electroceuticals, in general, include implant volume, safety, energy consumption, limited capacity in signal processing, and the need for data telemetry (55, 178). We envision that effective, responsive neuromodulation needs to be computationally self-sufficient in performing active on-chip learning to eliminate regular telemetry. Recent advancements in neuromorphic computing are critical to making our vision possible. We argue that neuromorphic computing in combination with highly low-power microelectronics for sensing (179, 180) and stimulation (181) will enable the emergence of neuromorphic neuromodulation device as a long-term solution for intractable neurological diseases.

Notes

[a] Some of these techniques are approved only for investigational use.
[b] This is an indicative figure based on whole body metabolic studies.

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Author Contributions

L.F.H.C.: conceptualization, data curation, software, formal analysis, validation, investigation, visualization, methodology, writing-original draft, writing-review and editing. N.D.T.: data curation, formal analysis, investigation, methodology, writing-original draft. J.K.E.: conceptualization, supervision, validation, investigation, methodology, writing-original draft. Z.X.: validation; visualization. Z.H.: validation, visualization. T.V.B.–V.: validation, visualization. I.A.: validation, visualization. W.H.L.: validation, visualization. A.N.: conceptualization, funding acquisition, validation, investigation, visualization. O.K.: conceptualization, resources, supervision, funding acquisition, validation, investigation, visualization, writing-original draft, project administration, writing-review and editing.

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Ethics Declaration

For this study, NSW Local Health District (LHD) ethics X19-0323-2019/STE16040 is approved in collaboration between The University of Sydney and the Comprehensive Epilepsy Services, the Department of Neurology, at the Royal Prince Alfred Hospital.

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