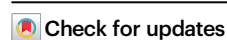


Advancing neuroengineering with Neuromorphic Twins

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Michela Chiappalone ^{1,2} & Timothée Levi ³  & 

Neuromorphic engineering, originally focused on replicating the biophysics of neurons and synapses in hardware, has progressively expanded to explore novel computational principles, materials, and applications. With their unique ability to emulate brain functions, neuromorphic devices are emerging as prime candidates to advance the treatment of brain disorders, addressing the current limitations of electroceutical-based strategies, particularly their lack of flexibility and personalization. In this Perspective, we introduce and elaborate on the concept of the ‘Neuromorphic Twin’ and explain why this emerging technology is both timely and relevant. By integrating Digital Twin approaches for modelling the brain’s functions with neuromorphic engineering, Neuromorphic Twins offer the potential to address major challenges, such as dealing with brain complexity in real-time, enabling adaptive and personalized interventions, and tracking the progression of neurological diseases over time. Moreover, they can be embedded in low-power devices, thus marking a transformative shift in biomedical interventions and promising to open new frontiers for neuroengineering and brain repair.

Brain disorders and their debilitating effects on patients have emerged as one of the most significant public health challenges of the 21st century, and the situation will worsen in the years to come due to the ageing of the population¹. In response to this pressing issue, the scientific and medical community has been actively explored neuroengineering-based alternatives, often centered on electroceutical approaches² to treat neurological diseases or their symptoms, support rehabilitation, reduce healthcare costs, and, most importantly, improve patients’ quality of life. Significant progress has been made in the last decades, resulting in neurotechnologies such as Brain Machine/Computer Interfaces (i.e., BCI for simplicity), brain modulators and neuroprostheses able to replace and retrain either brain^{3,4} or somatosensory functions^{5–7}, block seizures in epilepsy⁸ and relieve symptoms in neurodegenerative diseases, such as Parkinson’s^{9,10}. Interestingly, implanted neuroprostheses, at both preclinical and clinical levels, have proven to be a promising tool for neurorehabilitation post brain¹¹ or spinal cord injury^{12,13}. A different type of neuroprostheses (i.e., cognitive neuroprostheses), aimed at replacing the

function of damaged brain circuits in the hippocampus, have been tested in vivo^{14–16} and in humans¹⁷ for memory restoration. Recently, commercial initiatives such as Neuralink, founded by E. Musk (<https://neuralink.com/>), have also announced the implantation of BCI devices in humans, although detailed information on their intended clinical applications and scientific validation remains still limited.

Even if important results have been achieved so far, current neuroengineering solutions still present drawbacks, including lack of flexibility and personalization, and difficulty in tracking both disease progression and/or possible side effects of the therapeutic treatment. Indeed, state-of-the-art electroceutical strategies are associated with stimulation parameters that may change over time due to the physiological process of development or ageing and with the progression of the disease, potentially resulting in a decline in stimulation effectiveness and thus requiring several sessions of manual reprogramming¹⁸.

Digital Twin technology has recently emerged as a promising and powerful solution to tackle the above limitations¹⁹. By creating

¹Department of Informatics, Bioengineering, Robotics and Systems Engineering (DIBRIS), University of Genova, Genova, Italy. ²LisTechLab, IRCCS Ospedale Policlinico San Martino, Genova, Italy. ³University of Bordeaux, CNRS, Bordeaux INP, IMS, UMR 5218, Talence, France.

 e-mail: michela.chiappalone@unige.it; timothee.levi@u-bordeaux.fr

dynamic replicas, these *in silico* models of the brain (i.e. Virtual Brain Twins) can offer adaptable and personalized support for patients^{20,21}, taking into account the multiscale nature of the brain²². Nevertheless, they require the collection of several data types, such as MRI and electrophysiology, and their use is currently limited to specific medical decision-making and actions, such as identifying the best location for surgery in drug-resistant epilepsy^{23,24} or the optimal stimulus location for Parkinson's disease²⁵. Importantly, Virtual Brain Twins developed so far, although dynamic and capable of simulating complex neural processes, differ from classical Digital Twin technology^{26–28}, as they do not enable the bi-directional communication in real-time with their physical counterparts. Instead, they function as powerful predictive tools to simulate disease progression and treatment effects, possibly supporting *in silico* experimentation and virtual clinical trials^{29,30}. Therefore, while valuable, this modeling approach does not provide the continuous, adaptive interaction required for treating chronic brain injuries or neurodegenerative diseases, highlighting the need for a new class of Digital Twins that can interactively co-evolve with the brain over time.

In this Perspective, we introduce a still nascent but potentially revolutionary technology named 'Neuromorphic Twin', which aims to overcome the above-mentioned limitations. The Neuromorphic Twin is a digital model designed to emulate, interact with, and adaptively co-evolve alongside a biological neural network. The biomimetic approach is central for the emulation component because the Neuromorphic Twin requires mechanistic fidelity that brain-inspired abstractions cannot provide (cf. Box 1 for more details). It integrates real-time neuromorphic hardware with adaptive software components to enable continuous bi-directional communication and long-term personalization. Its main features are: (i) real-time, bi-directional coupling with the biological system, enabling continuous information exchange; (ii) a hardware-level biomimetic emulation of neuronal and synaptic activity across neurons, synapses, and network scales; (iii) a software layer for non-real-time personalization, which periodically tunes the network topology and parameters to maintain alignment with the evolving biological counterpart.

Neuromorphic engineering was initially conceived as an interdisciplinary field, aiming at building hardware systems by mimicking the intricate biophysics of real neurons and synapses³¹. Recent advancements have expanded its horizons, exploring novel computational principles, materials, and applications^{32–37}. With their unique ability to emulate even complex brain functions, neuromorphic devices emerge as the prime candidates for the realization of physical (i.e., hardware) neural digital twins. The term Neuromorphic Twin is not entirely new, as it has been recently used in contexts such as system and communication engineering^{38,39}. Within the field of neuroengineering, the neuromorphic components and means to create the Neuromorphic Twins are partially in place^{40–43} and some ideas have been introduced, even mentioning the term itself^{44,45}. However, the holistic integration and vision that would bring the Neuromorphic Twins to fruition within the neuroengineering context is currently lacking. Indeed, only a few concrete examples exist to date^{46–49}. Inspired by the use of neuromorphic technology for biomimetic stimulation to restore sensations⁴⁹, we foresee that a similar strategy could be expanded to create Neuromorphic Twins capable of restoring neural functions to a broader extent. This technology can also benefit from Artificial Intelligence (AI), which would form the software core of the twin, allowing it to adaptively track and co-evolve with the brain's dynamics over extended timescales. This is the central aim of this Perspective, which is organized as follows. First, we describe the hardware and software architecture of the Neuromorphic Twin, emphasizing the critical real-time bi-directional communication between the Neuromorphic Twin and the brain network(s). The closed-loop interaction with the living brain, mirroring the way industrial digital twins continuously communicate with their physical

counterparts, is a key aspect of the Neuromorphic Twin. Moreover, the tight integration of software and hardware components is fundamental to its functioning, enabling it to operate as a dynamic extension of the brain. Therefore, we present applications for this technology, focusing on its potential impact on healthcare and on the development of biohybrid intelligence, which could represent a crucial driver for the next generation of AI. Finally, we propose a roadmap for the adoption of the Neuromorphic Twin technology, outlining future challenges, a prospective timeline, and ethical considerations.

We are confident that this technology has the potential to advance biomedical interventions by driving a global therapeutic shift in the treatment of neural disorders, thereby representing a transformative leap forward for the field of Neuroengineering.

Architecture of the Neuromorphic Twin

The Neuromorphic Twin relies on an architecture composed of three main elements (Fig. 1), two implemented in hardware and one in software. In this section, we first focus on the hardware for neural feature extraction (cf., "Hardware-based signal processing"), we then describe the hardware biomimetic network component (cf., "Hardware biomimetic network"), we present the software module for automatic tuning of the network parameters (cf., "Software automatic tuning") and finally we describe the interaction among all these elements (cf., "Communication between interconnected layers").

Hardware-based signal processing

A key feature of the Neuromorphic Twins lies in their ability to process and decode neural signals in real-time, enabling feedback that can modulate or replace neural functions within a closed-loop architecture³⁶. This process poses several technological challenges, particularly the requirement for rapid and complex computation of extensive data, along with the extraction of meaningful features for stimulation control⁵⁰. Indeed, current acquisition systems allow to record from a large number of electrodes (Fig. 1, Neural Recording block), i.e., hundreds up to thousands at the same time, both *in vivo*^{51–53} and in humans^{54,55}. To tackle these challenges, the integration of neuromorphic-based systems for edge computing functions, such as detection and classification of neural events, can greatly enhance the overall performance of the Neuromorphic Twins (Fig. 1, Neuromorphic Twin–Hardware for signal processing).

To date, real-time neural processing remains limited by the lack of fully unsupervised algorithms capable of handling large volumes of neural data autonomously. While Deep Learning (DL) has shown impressive performance in pattern recognition tasks with large labeled datasets, its applicability in real-time, closed-loop neural interfaces is hindered by its dependence on labeled data and high computational demands, often requiring specialized hardware such as GPUs. These constraints make DL unsuitable for closed-loop neuro-engineering applications, where rapid calibration (within minutes) and millisecond-level adaptive stimulation are essential. In contrast, Spiking Neural Networks (SNNs) offer a compelling alternative. Their event-based processing makes them particularly well-suited for real-time analysis of neuronal signals. SNNs rely on biologically inspired plasticity rules like Spike-Timing-Dependent Plasticity (STDP) and often require fewer parameters and less data to train than conventional DL models. Several neuromorphic circuit architectures have already been developed to extract specific features of interest directly from neural signals. These circuits operate at the hardware level to perform low-latency, energy-efficient processing by mimicking the biophysics of neural computation. For instance, implementations of circuits such as event-driven edge detectors, adaptive threshold spike detectors, or temporal correlation filters have been used for real-time spike detection, burst classification in multi-electrode recordings⁵⁶. Recent studies have demonstrated the efficacy of SNNs in real-time detection and classification of neural activity^{57–61}, showing their potential to autonomously

BOX 1

Why brain emulation matters: from Digital to Neuromorphic Twins

Notwithstanding the recent progress and the huge impact of AI in our everyday life, current artificial systems lack the intelligence and learning capabilities of the brain. To bridge this gap, any technology aimed at emulating brain functions must focus on three key requirements: (i) replicating the anatomy and/or physiology of brain networks, (ii) guaranteeing a bi-directional, real-time communication with a living brain for continuous adaptation and (iii) prioritizing parallel brain architecture to ensure efficient, low-power solutions that move beyond conventional silicon-based methods. To address the first and the second requirements, we can leverage Digital Twin technology. For the third, we can rely on neuromorphic engineering. The combination of these approaches enables the creation of a Digital Twin that not only replicates key brain dynamic properties and their evolution over time but also continuously interacts with and is updated by the real brain. The result of this co-creation process is the 'Neuromorphic Twin', as schematically depicted in Fig. Box 1.

Achieving a high level of emulation is made possible by drawing inspiration from nature through the concept of 'biomimicry'. Biomimicry is based on the study of properties and processes of nature and adapting them to create more efficient technologies. It is an approach widely used in domains such as engineering, materials and robotics^{200–203}. Nonetheless, biomimicry serves as the foundation for two distinct approaches: bio-inspired and biomimetic. The first draws inspiration from nature to develop novel materials and devices, whereas the second one focuses on faithfully reproducing nature. Digital twins can be considered inherently biomimetic models, as they accurately replicate their physical counterparts. Specifically, digital

brain twins are now achieving remarkable levels of detail as they integrate multiscale spatial and temporal dimensions to reproduce the brain's intrinsic complexity²². Building on this foundation, the Neuromorphic Twin aspires to replicate this complexity, offering a new paradigm for modeling brain function for real-time, continuous interaction. Although the Neuromorphic Twin primarily models electrical behavior, anatomical and physiological aspects can be integrated through the emulation of either structural or functional connectivity or both^{204,205}. Examples of such an approach for neuromorphic emulation have been recently proposed in the literature, for modelling the somatosensory cortex⁴⁸ and the central pattern generators in the spinal cord²⁰⁶. This raises an important question: is this level of emulation actually necessary in the Neuromorphic Twin?

Emulation through biomimetic modelling is grounded on the theory that replicating the natural topology and/or dynamics of a biological system can enable more natural and intuitive interactions with its physical counterpart. This idea was explored in the literature for biomimetic stimulation within neuroprosthetics applications^{120,207}. Indeed, biomimetic neural firing patterns generated by neuromorphic hardware have been recently proposed and exploited to evoke more natural and intuitive sensations^{49,159,208}. Along the same line of thinking, we pose that neuromorphic technology can be a unique means to both provide models able to emulate the natural neural dynamics of different neurons embedded into brain networks as well as to learn and adapt to different inputs over time⁴⁹. To this end, it constitutes not only the best approach to emulate brain functions but also to interact in real-time with the brain itself.

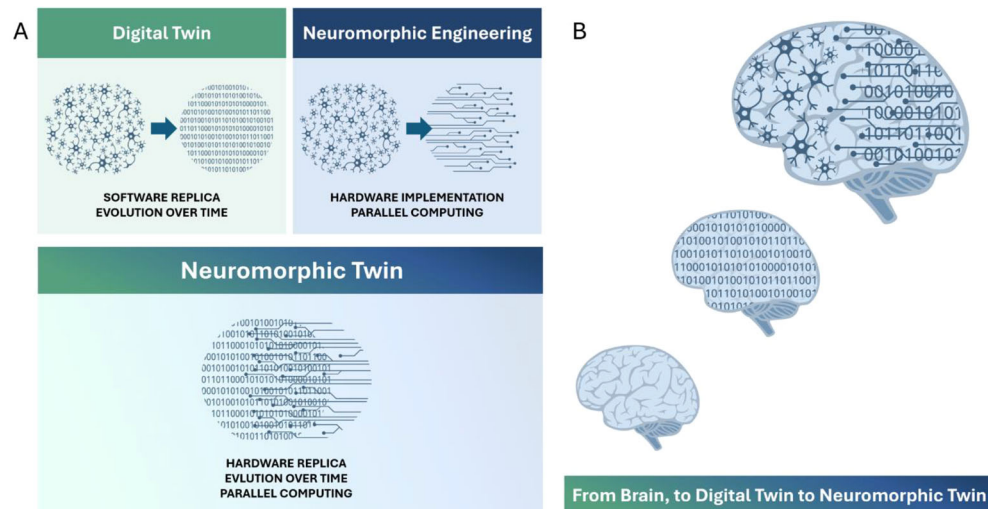


Figure Box 1. From Digital to Neuromorphic Twin. A. The concept of Neuromorphic Twin emerges from the integration of two technologies: Digital Twin (green panel, on the top left) and Neuromorphic Engineering (blue panel, on the top right). The Digital Twin allows to create virtual (software), biomimetic replicas of physical systems like neuronal networks, neural tissue, or the entire brain, making it ideal for studying and predicting both physiological (e.g., aging) and pathological processes (e.g., neurodegenerative diseases). Neuromorphic engineering, on the other hand, enables the physical (hardware) implementation of neuronal networks, mostly leveraging the brain's parallel computing capabilities, its intrinsic learning and plasticity principles. The Neuromorphic Twin (green-to-blue gradient panel, on the bottom) integrates advantages from both technologies, allowing the implementation of a biomimetic hardware replication of neuronal networks according to the principles of neuromorphic computing but evolving over time and continuously interacting with their physical counterpart (not represented in the cartoon), as done in Digital Twins. B. A graphical representation of the progress of intelligent systems, from the natural brain (i.e., the biological system) to the digital brain twin (i.e., software system) to the Neuromorphic Twin (i.e., integration of software and hardware), which will evolve over time thanks to the bi-directional interaction with a living brain.

self-configure using local learning rules to recognize hidden patterns in data. Table 1 reports the various applications of SNNs for detecting and classifying different forms of biological events, such as spikes, spike trains, Local Field Potentials (LFPs), and even Electroencephalogram (ECoG) and Electroencephalography (EEG) signals.

Despite their promise, practical implementations of neuromorphic systems (Table 1), especially SNNs, face challenges in scaling to large numbers of parallel channels. Current implementations often remain limited to a small number of channels^{62,63}. However, the coupling of analog-mixed signal (AMS) circuits with the high parallelism of Field Programmable Gate Arrays (FPGAs) offers a promising path forward. Particularly, FPGA-based System-on-Chip (SoC) architecture combining real-time hardware processing with Linux-based software environments provide an adaptable platform capable of real-time tuning for the Neuromorphic Twin. These advances not only enable detection but also allow sophisticated classification of spatiotemporal patterns, such as spike sorting⁶⁴, vocal⁶⁵ or neuropathological⁶⁶ patterns (e.g., epileptic seizures), which are crucial for understanding neural dynamics and guiding the Neuromorphic Twin's response.

For example, in spike sorting, a fundamental task in neural signal processing aimed at identifying the actual sources of the acquired neuronal signals, SNNs can detect and classify spikes from raw extracellular recordings. A simple SNN architecture⁶⁷, comprising layers for signal encoding, pattern detection, and classification, uses STDP and low-threshold spiking (LTS) neurons to learn and recognize spike patterns efficiently (Fig. 2). This architecture processes raw input without requiring precise spike timing, ensuring no events are missed, and achieves real-time classification across multiple channels using only minimal FPGA resources (e.g., <6% LUT and <15% URAM on the Kria KR260 SoC). Unlike traditional spike sorting pipelines, which cannot scale efficiently to multi-channel real-time processing, this SNN-based approach provides a lightweight, parallelizable, and energy-efficient solution—ideal for embedded neuromorphic applications such as the Neuromorphic Twin. Still, challenges remain in scaling these models further while maintaining low power consumption and unsupervised learning capabilities, particularly for complex time-varying pattern extraction.

Hardware biomimetic network

Choice of neural network, synapse, and neuron models. To emulate neural dynamics in the brain, several neuroscience-inspired computational structures can be used. Winner-Take-All (WTA) circuits with lateral inhibition capture aspects of sensory cortex competition⁶⁸; canonical microcircuits simplify the organization of various cortical regions^{69,70}; Central Pattern Generators (CPGs)⁷¹, and Kuramoto oscillators⁷² model rhythmic or oscillatory behavior; and Liquid State Machines (LSMs) reproduce recurrent cortical dynamics⁷³. These models are attractive because they allow fast implementation and tuning on microcontrollers.

For the initial biomimetic implementation of the Neuromorphic Twin, Artificial Neural Networks (ANNs) can serve as a practical starting point. ANNs provide an efficient computational framework capable of reproducing certain aspects of neural processing. They are widely used for tasks such as image recognition, classification, or facial identification through Feedforward Neural Networks (FNNs)⁷⁴ or Convolutional Neural Networks (CNNs)⁷⁵. For example, Kheradpisheh et al.⁷⁶ demonstrated STDP-based CNNs for object recognition. Recurrent Neural Networks (RNNs)⁷⁷, on the other hand, support applications involving sequential data, such as speech recognition or time-series prediction. However, despite these advances⁷⁸, traditional ANNs remain fundamentally limited for biologically realistic modeling. They are optimized for specific computational tasks rather than for reproducing the fine-grained temporal and biophysical dynamics of real neurons. In particular, they do not naturally encode or exploit temporal information, which is essential for implementing biologically

plausible unsupervised learning rules. These limitations have motivated the development of Spiking Neural Networks (SNNs), which emulate neuronal communication through discrete action potentials⁷⁹. By capturing both spatial and temporal aspects of neural activity, SNNs provide a more faithful representation of biological neuronal networks than conventional ANNs. This is achieved through sophisticated neural connectivity patterns and plasticity mechanisms that reflect the brain's natural processes. Unsupervised learning remains one of the most biologically plausible and computationally efficient strategies for training SNNs, making it particularly well-suited for neuromorphic systems. Among the most prominent mechanisms is STDP, a local rule that adjusts synaptic weights based solely on the relative timing of spikes, enabling networks to autonomously discover and encode meaningful spatiotemporal patterns in the input data. Such learning rules operate without the need for labeled datasets or global error signals, aligning naturally with the architecture and operational constraints of neuromorphic hardware. As highlighted in these review articles^{80,81}, unsupervised plasticity mechanisms enable continual learning, adaptability, and low-power consumption in embedded systems.

A table comparing the advantages and disadvantages of both ANNs and SNNs, and the best choice for each criterion for the Neuromorphic Twin technology, is reported below (cf. Table 2). Table 2 highlights that, aside from learning and implementation criteria, SNNs emerge as the most suitable candidate for biomimetic emulation. While ANNs currently have an advantage in terms of learning algorithms and ease of implementation, this gap is expected to narrow over time as SNN frameworks continue to evolve.

In terms of emulation of biological networks, SNNs can operate in real-time, providing a sufficiently high level of biological coherence to accurately depict and mimic the dynamics of biological networks⁸². They are able to autonomously evolve through learning and plasticity rules^{83,84}, similar to how the brain learns through experience. This is achieved through specific rules that allow the network to change its structure or function based on what it learns. Because of this, SNNs can improve their performance on their own, without needing to be reprogrammed. SNNs can also model different types of neurons and their interactions, which is important for accurately simulating the complex dynamics of the brain, where different neurons have specialized roles. Additionally, SNNs are good at capturing both where neurons are located and how they connect (spatial organization), as well as the timing of their signals (temporal organization). This makes them particularly useful for tasks that involve understanding patterns over time and space. Hardware SNNs employ generic biological parameters for updating the neural model and aim at emulating biological neural networks as accurately as possible in experiments. The use of complex models that closely mimic biology and have the same parameters allows for easier communication and interactions with neuroscientists. In particular, conductance-based models (see Table 3) such as the Hodgkin-Huxley type allow for precise identification of neuron parameters like the equilibrium voltage by biologists, thereby facilitating smooth interdisciplinary communication between designers and biologists. Furthermore, for emulation purposes and especially for reproducing neurological diseases, conductance-based models are essential, as certain disorders, such as ALS, involve dysfunctions at the level of ionic currents. Finally, since our goal is to replicate brain function, the backpropagation plasticity rule is not compatible with biological reality. We therefore turn to biologically plausible forms of plasticity, such as STDP or Hebbian learning.

The choice then remains between single or multi-compartment models to reproduce the topology and the various interactions between neurons. Single-compartment models, such as the Hodgkin-Huxley model⁸⁵, allow for high prediction rates of action potentials and biophysical coherence⁸⁶. Several cortical simulations exist, particularly using specialized software such as NEURON and NEST. However, real-

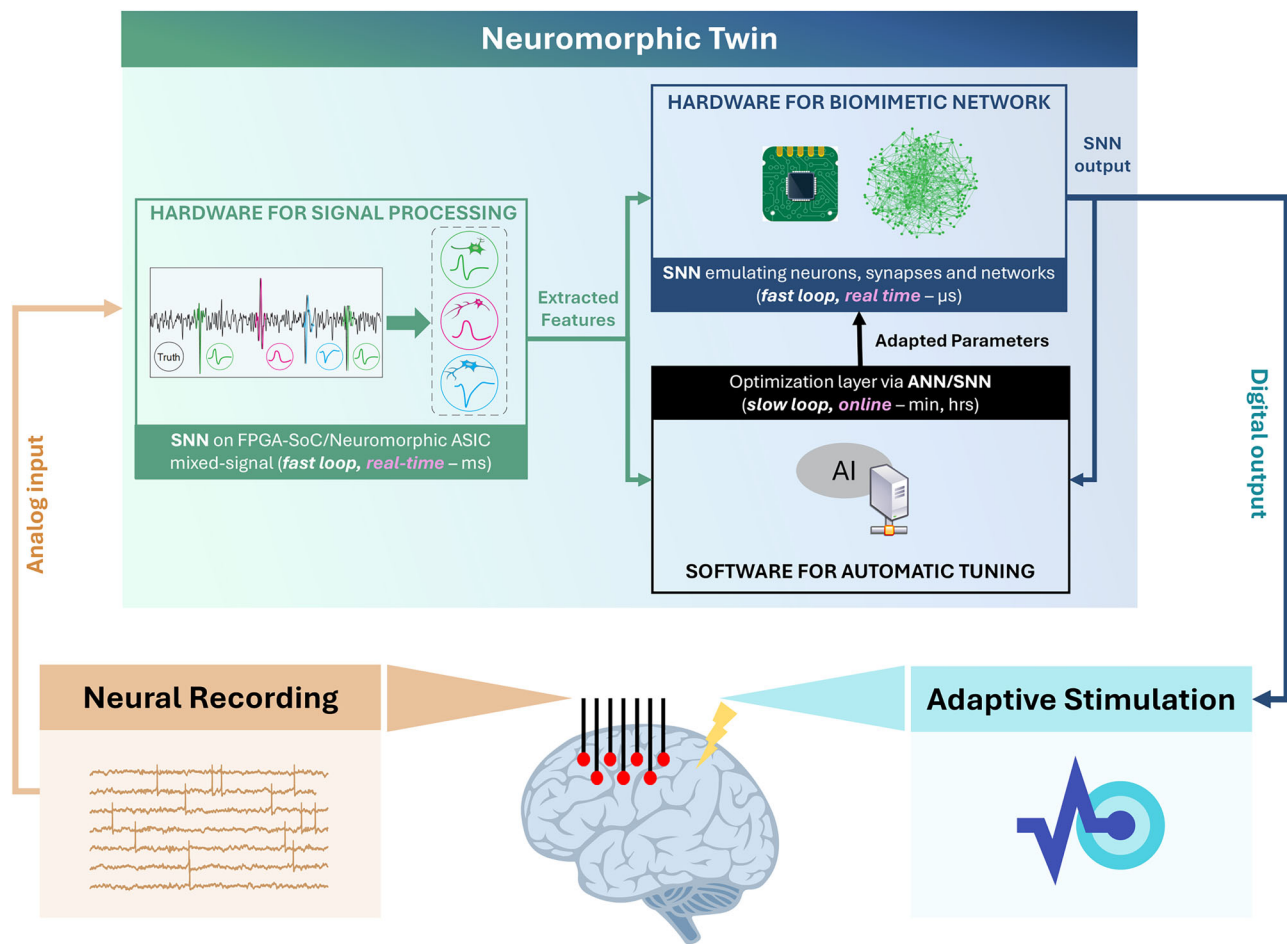
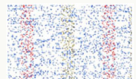


Fig. 1 | Main components of the Neuromorphic Twin and its closed-loop interaction with a living brain. *Neural recording.* Electrodes from an implanted multichannel probe capture single neuron activity across one or more brain regions. The acquired analog signals constitute the input for the Neuromorphic Twin. *Neuromorphic Twin.* The Neuromorphic Twin consists of three main blocks. Starting from the neural measurements coming from the implanted brain, all feature extractions (e.g., sorted spikes) from the recording channels are performed by the signal-processing hardware (typically, Spiking Neural Network (SNN)-based) and then sent as input to both the biomimetic-network hardware and the software for automatic tuning blocks. The biomimetic network, implemented as an SNN and configured offline, emulates the brain network(s) and reproduces the neuronal

activity at the single neuron level, operating in real time to maintain a closed-loop interaction with the biological brain. To personalize and accurately replicate the biological component, the SNN output is also fed into the automatic-tuning software block, which uses ANN (Artificial Neural Network)/SNN-based optimization to adjust the model parameters and plasticity rules online, enabling adaptive tuning in response to the current state of the brain. This update does not need to operate in real-time; a delay of minutes or even hours/days is sufficient for rewiring the biomimetic SNN's network and the topology. *Adaptive Stimulation.* The digital output of the Neuromorphic Twin, directly coming from the biomimetic SNN, consists of a train of events through which adaptive, personalized stimulation is generated to treat the impaired brain network(s).

Table 1 | SNN-based detection and classification

Signal	Spike	Spike trains	LFP	ECoG	EEG	Audio
Template						
SNN-based platform	SoC with FPGA	Microcontroller	Analog chip NET-TEN	Analog chip DYNAP-SE	Analog chip DYNAP-SE and FPGA	Simulation
Application	Spike sorting	Hidden pattern of spikes	Epileptic seizures	Epileptic pattern	High Frequency Oscillations	Vocal pattern
Reference	67	178	66	60	58	65

The table outlines the current state of the art in neural detection and classification based on the use of SNN across multiple scales, from spikes to EEG and ECoG, including LFPs. The type of platforms (i.e., analog, using ASICs, digital, typically FPGA-based, or hybrid) and the primary neural applications are also provided, as well as the literature references. All the reported publications are very recent, highlighting the utility and efficiency of hardware-based SNNs for these applications.

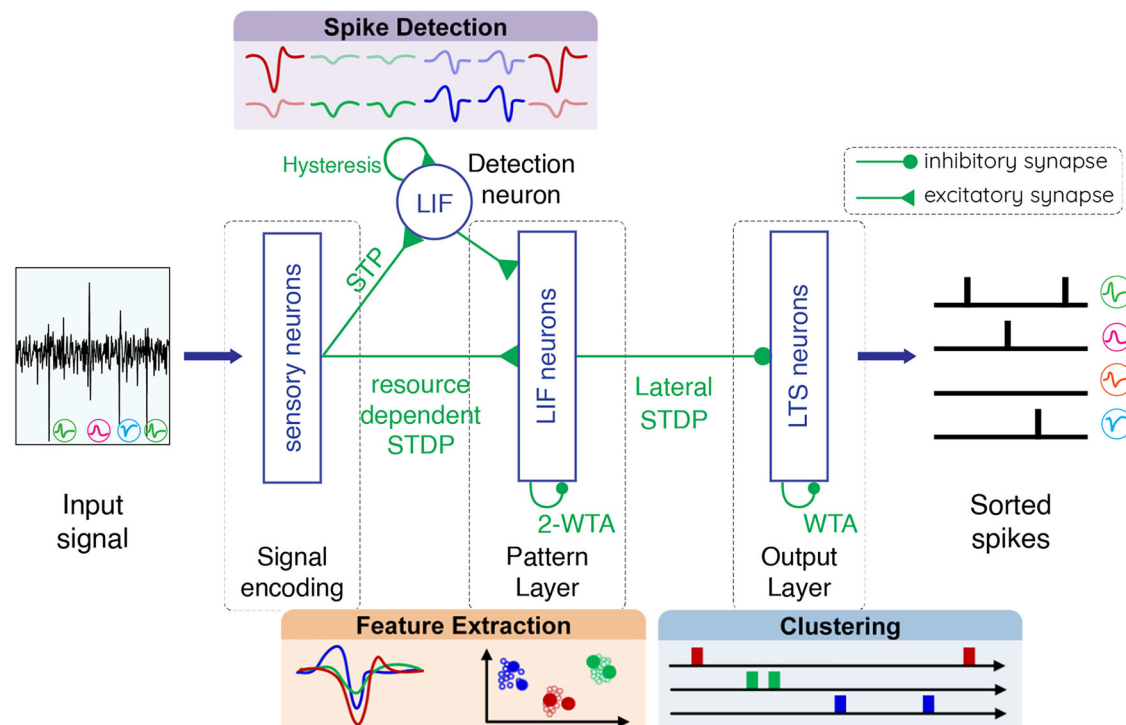


Fig. 2 | SNN-based spike sorting. Description of a Spiking Neural Network (SNN)-based algorithm for spike sorting. Each layer is used for completing the three main tasks of classical spike sorting: spike detection, feature extraction, and clustering. Figure 2 is reproduced with permission from ref. 67, copyright 2024, IEEE.

time execution is generally not achieved, except in rare cases using huge GPU system⁸⁷ or supercomputers⁸⁸, which are incompatible with the Neuromorphic Twin approach in terms of cost and embedded system.

Multicompartmental models offer a more comprehensive and biologically realistic approach, thus providing deeper insights into neuronal function and information processing. It is particularly important as regions such as dendrites are the center of vital computations linked to their spatial morphology⁸⁹ and are affected by some neurodegenerative diseases like Amyotrophic Lateral Sclerosis -ALS⁹⁰. Multicompartmental modeling also allows the investigation of the role of dendrites in neurons. They are also known to display physiological and morphological abnormalities during postnatal development in motor neurons with ALS⁹¹. However, there are still few real-time multicompartmental neuron implementations in the state of the art⁹².

Hardware implementation. Several commercial neuromorphic systems have emerged in the recent years. Neuromorphic chips, such as Intel's Loihi and IBM's TrueNorth⁹³, are designed to execute SNNs more efficiently than traditional processors by mimicking neuronal and synaptic structures. However, these chips were primarily developed for SNN-based processing rather than for reproducing and emulating biological systems. Notably, they lack support for complex neuronal models. The most well-known hardware systems are SpiNNaker, a digital hardware platform, and BrainScaleS, an analog hardware platform, both developed during the Human Brain Project. Some real-time implementations have successfully replicated cortical models^{94–96}. Recent articles show some interesting results in real-time emulation of biological networks. The Neurogrid system, which is a hybrid analog-digital architecture that simulates various cortical cell types and dendritic effects^{97,98}. BioemuS system⁹⁹ emulates with high precision 1000 HH neurons and millions of synapses for brain organoid emulation. DYNAP-SE2¹⁰⁰ implements 1024 AdEx I&F neurons for part of somatosensory cortex.

Several technologies can be used to implement these SNNs in hardware. They can be analog, digital, or a combination of both. However, emerging technologies could be the next target, particularly for synapses and plasticity. Indeed, spintronic^{101,102} and memristor^{103,104} technologies enable reduced power consumption and a smaller implementation footprint. Moreover, these systems inherently integrate both synapses and plasticity. However, these technologies are not yet mature enough for easy integration with analog or digital neurons. The challenge with these models remains their implementation, which requires significant hardware resources while maintaining real-time computation. The substantial number of parameters that require tuning also poses a problem. Leveraging AI to efficiently explore the parameter space can greatly accelerate the discovery of optimal network parameters that accurately replicate biological dynamics. Consequently, the Neuromorphic Twin and the biological network will establish a connection facilitating mutual adaptation, learning, and self-correction (Fig. 1 - Software automatic Tuning and section "Hardware biomimetic network"). Being intrinsically adaptive, the Neuromorphic Twin can thus naturally follow the evolution of the biological neural network and take the corrective action to counterbalance disease progression, by delivering the electrical therapy with the updated stimulation parameters.

Software automatic tuning

To design the Neuromorphic Twin, the biomimetic SNN must be able to adapt over time. The objective is therefore to continuously adjust the network's dynamics based on biological recordings. To achieve this, several optimization algorithms can be used, including meta-heuristic algorithms, Bayesian optimization, and gradient descent. Table 4 presents the advantages and disadvantages of the different possible methods.

The objective is to readjust the dynamics in case of a significant change in the biological network, while not knowing the future dynamics in advance. Table 4 shows that optimizing the parameters of

Table 2 | Comparison between ANN and SNN based on different criteria

Criteria	ANN	SNN	Neuromorphic twin
Biomimicry	Far from biology	Close to biological principles	SNN
Learning	Many techniques (backpropagation)	More complex learning rules (STDP)	ANN
Applications	Vision, image processing	Robotics, BMI	SNN
Robustness	Sensitive to perturbations	Robust to noise and perturbations	SNN
Implementation	Advanced tools (PyTorch, Tensorflow)	Difficult and time-consuming	ANN
Energy	High power consumption	Low power consumption	SNN
Real-time	Challenging	Efficient	SNN
Platform	Conventional CPU or GPU	Neuromorphic platforms (Loihi, etc.) or custom hardware	SNN

Table 3 | Comparison of various neuronal models based on the biological fidelity of the neuron, synapse, and plasticity rules

Neuron model	IF	LIF	Izhikevich	AdEx I&F	FitzHugh-Nagumo	Hindmarsh-Rose	Morris-Lecar	Hodgkin-Huxley
High biological fidelity of the neuron model	X	X	X	X	X	X	O	O
Synapse model	Current-Based				Conductance-based			
High biological fidelity of the synapse model	X				O			
Plasticity rule	Backpropagation				STDP, Hebbian learning			
High biological fidelity of the plasticity rule	X				O			

The O indicates the inclusion of the corresponding property, while the X denotes its absence.

an SNN using evolutionary algorithms is an effective approach to reproducing the spike frequencies of a biological network. Among these algorithms, Particle Swarm Optimization (PSO) is particularly well-suited for small-scale SNNs, as is the case for the Neuromorphic Twin, offering fast convergence and easy embedded implementation, although it may be sensitive to local optima. For more complex models, Evolution Strategies (ES) provide a robust alternative, capable of handling a large number of parameters and well-suited for execution on GPUs, TPUs, or FPGAs. On the other hand, Differential Evolution (DE) is useful for exploring complex parameter spaces, but it converges more slowly. However, the resources required for implementation and the simulation time are significant. Thus, it is necessary to carefully consider which software/hardware platform and programming language will be most effective.

For software implementation, frameworks such as PyTorch¹⁰⁵ (used via Norse or Tonic) and SpikingJelly¹⁰⁶ are well-suited for SNN optimization, because they support GPU-based parallel computation and biomimetic learning algorithms such as STDP. In contrast, PyNN¹⁰⁷ is mainly designed for simulating biologically realistic SNNs on platforms such as NEST and NEURON, making it less relevant for our Neuromorphic Twin application.

As previously discussed, the Neuromorphic Twin already includes SNNs for signal processing and the replication of biological networks. The choice of hardware for implementing these algorithms can be based on: (i) FPGAs, which offer high performance but require a very long development time; (ii) GPUs or AI SoCs, which provide more flexible software execution but are less optimized for low latencies and get less I/Os; (iii) neuromorphic chips like Loihi¹⁰⁸ and Akida¹⁰⁹, which are well-suited for SNNs with bio-inspired learning rules, although native support for ES or PSO is limited. A hybrid approach would involve training the SNN with PSO or ES in PyTorch or SpikingJelly on a GPU, then exporting it to an FPGA or neuromorphic chip for embedded execution. This solution combines efficient optimization and embedded system, making it ideal for integration into a biological setup. Recent articles are using optimization algorithms based on DE^{110,111} or Bayesian optimization¹¹² implemented on GPU for the hyperparameter optimization of SNN. Ethernet or SPI communication can be used from the GPU to the SoC FPGA device.

Communication between interconnected layers

In the previous sections, we introduced the three interconnected layers of the Neuromorphic Twin (Fig. 1): the signal processing module (cf. “Hardware biomimetic network”), the emulation module (cf. “Hardware biomimetic network”), and the optimization layer for parameter tuning (cf. “Software automatic tuning”).

The signal processing block acts as an edge-level preprocessor (edge computing), implemented on FPGA-SoC platforms or through mixed-signal analog–digital neuromorphic circuits (Fig. 1, green box). It runs algorithms for neural signal feature extraction, such as spike detection, burst classification, and spectral estimation, in real time, achieving latencies on the order of 1 ms for event detection and -10 ms for classification. The extracted features are transmitted directly to the emulation module (Fig. 1, blue box), which hosts the biomimetic SNN hardware reproducing the dynamics of biological neural networks in real time (approximately 100 μs to emulate synaptic and ionic current dynamics). Using SNN-based architectures for both the signal processing and the emulation layers (although relying on different neuronal and synaptic models) offers the advantage of co-implementing them on the same hardware platform, thereby simplifying communication protocols, reducing latency, and enabling fully embedded operations. The two hardware blocks are functionally coupled through a software optimization layer (Fig. 1, black box), based on either ANN or SNN architecture, which adaptively tunes neuronal and synaptic parameters. The latency associated with this update does not need to operate in real time; update cycles on the order of minutes/hours are sufficient since neuronal dynamic changes occur over slow timescales. Usual communications such as ZeroMQ can be used as the usual latency is around 300 μs, large enough for the update timing.

This three-tier co-design ensures continuous adaptation of emulation fidelity while maintaining high energy efficiency. From a system-level perspective, this hardware–software co-optimization defines the operational metrics of the Neuromorphic Twin. Real-time performance and latency are primarily governed by the hardware interface between the signal processing unit and the SNN core, where analog front-ends enable fast feature encoding, while FPGA or neuromorphic ASICs handle large-scale parallel computation. High-bandwidth interconnects, such as AXI buses between microcontrollers and FPGAs or Ethernet links between recording and stimulation systems, can be

Table 4 | Advantages and disadvantages of the different algorithms for SNN optimization parameters (excluding unsupervised methods such as STDP) for Neuromorphic Twin applications

Method	Advantages	Disadvantages
Surrogate Gradient Descent ¹⁷⁹	Allows the use of backpropagation techniques. Fast and efficient optimization with labeled data.	Requires an approximation of spike gradients. Less biologically plausible than other methods.
Evolutionary Optimization (DE, ES) ¹⁸⁰	Does not require gradients. Excellent exploration of the parameter space.	High computational cost. Slower convergence compared to gradient-based methods.
Particle Swarm Optimization (PSO) ¹⁸¹	Simple to implement. Good exploration-exploitation balance.	Less effective for very large parameter spaces.
Bayesian Optimization ¹⁸²	Works well with few evaluations. Effective for hyperparameter tuning.	Less suitable for highly dynamic systems like a real time trained SNN

leveraged to sustain low-latency real-time communication (range of 40 μ s for an AXI DMA in loopback clocked at 200 MHz¹¹³).

Energy efficiency and scalability depend on the hardware technology choice: hybrid analog–digital architectures typically achieve one to two orders of magnitude higher energy efficiency than GPU-based simulations. For reference, the average power consumption of SNNs on FPGA is in the range of 3 W for the emulation part on a KR260 kit⁹⁹. Therefore, the selection of the FPGA target defines the trade-off between energy efficiency, flexibility, and embedded capability. A future ASIC can be designed to optimized performances.

Overall, the Neuromorphic Twin demonstrates how hardware–software co-optimization can bridge low-level signal processing with high-level biomimetic computation. The interplay between analog neuromorphic circuits, FPGA-based SNN acceleration, and evolutionary software adaptation defines the main design trade-offs in terms of real-time capability, power efficiency, and scalability. These considerations are central to advancing neuromorphic hardware for next-generation brain–machine interfaces and digital twins of the nervous system. Finally, this hierarchical co-design enables the Neuromorphic Twin to maintain long-term biologically faithful personalization of neural emulation without compromising its real-time responsiveness, a prerequisite for future clinical and biohybrid applications.

Neuroengineering applications of Neuromorphic Twins

The applications of Neuromorphic Twins encompass a paradigm shift in neuroengineering, offering a diverse array of possibilities. The first example of a Neuromorphic Twin was envisaged in recent paper⁴⁴ under the name “evolving neuromorphic Twin” (enTwin). The authors proposed that the hypothetical chip enTwin would be based on flexible neuromorphic arrays featuring learnable synaptic connectivity and a neuromorphic architecture, designed for implantation in the human body¹¹⁴ and the brain¹¹⁵. Even if they did not provide any timeline for such a development and the description was extremely general, they were confident about its feasibility just by looking at the state of contemporary neuromorphic research. Indeed, research in the last few years showed promising advancements in terms of components for the Neuromorphic Twin^{36,37,116}, including biohybrid systems for brain repair as a novel tool for regenerative medicine^{36,117}. We have already presented examples of neuromorphic-based solutions for the real-time processing. Another notable application lies in the real-time emulation of biological neural networks, which not only aids in understanding natural neural processes but can support investigating the influence of neurological and psychiatric disorders on the network dynamics, as recently underlined¹¹⁸.

Computational models capable of replicating natural neural responses can be adopted to guide neural stimulation strategies. By modulating stimulation across multiple parameters and channels in space and time, it becomes possible to evoke more complex and natural patterns of activity in the recruited neuronal population. Potential applications range from the sole peripheral interventions^{49,119,120} to central nervous system interfaces¹². The

evolution then extends to smart neuromodulators for treating a disease and its symptoms, where the Neuromorphic Twin can contribute to restoring the correct neural dynamics thanks to its ability to deliver a neural-like/biomimetic stimulation. Indeed, the importance of biomimicry in tailoring the neurostimulation protocols has been very recently underlined for both restoring naturalistic sensations^{49,120} and for improving personalization in vagal nerve stimulation¹²¹. Tangible progress in the biomimetic emulation of brain circuits lies at the forefront of current research. A recent study⁴⁸ realized the neuromorphic implementation of a bio-realistic model of layer IV of the somatosensory cortex of the rodent brain (Fig. 3A top). That Neuromorphic Twin is an ASIC featuring 1024 neurons distributed across four cores, each implementing the AdEx I&F model (Fig. 3A bottom). According to the study, this physical emulation of cortical circuits provides a powerful tool for understanding and predicting the behavior of the somatosensory cortex under neurostimulation.

Along the same line, another study demonstrated that a hardware-based biomimetic SNN made up of 1,024 Hodgkin-Huxley neurons successfully reproduced key electrophysiological features of the rat premotor cortex, i.e., the Biological Neural Network - BNN¹²². By exploiting the Bioemus framework⁹⁹, a small-world like topology¹²³ was designed (Fig. 3B top). Using this set-up, 325 different SNN configurations, varying in neuron types, excitation/inhibition balance, were deployed on an FPGA board (Fig. 3B bottom). A comparative analysis was carried out between a set of BNNs, considered as the reference, and the 325 SNNs (Fig. 3 C). The SNN better approaching the key electrophysiological features was indeed matching well the global activity patterns, as depicted in the representative raster plots of Fig. 3D. Using a former version of the Bioemus set-up⁹⁹, a hardware-based SNN was exploited to deliver neural-like stimulation patterns to deeply anesthetized healthy rats¹²⁴ according to a purely open-loop modality. That study reported that the SNN-based stimulation increased spontaneous firing in both the primary somatosensory and in the premotor area, a result typically seen only with closed-loop stimulation^{125,126}. All the previous studies highlight the feasibility of the Neuromorphic Twin technology, also for delivering brain-like stimulation patterns.

Given the above results, it is then clear that the Neuromorphic Twins can pave the way for a new generation of neuro/brain prostheses where the “twin” can replace the damaged brain network/region/area, providing adaptive and restorative treatment, typically in the form of stimulation. Neuromorphic Twins interacting bi-directionally with their biological counterpart are schematically depicted in Fig. 4A. Preliminary examples of their implementation show the closed-loop interaction between a neuromorphic-based model and neuronal cultures coupled to Micro-Electrode Arrays - MEAs in vitro^{46,127,128}, to mimic the restoration after a traumatic lesion. Other applications involving brain slices of the hippocampus⁴² as well as in vivo animal models^{16,42}, have been also presented in the literature. Even if those studies claim the use of such a technology for restoring neural activity after brain injury, most of the current implementations are still limited to healthy animal models.

For clinical applications in humans, we foresee that the architecture of Neuromorphic Twins, with their advanced properties, will enable complex analysis of neuronal signals, replication of biological behavior, and personalized treatments especially in the case of stroke, epilepsy and neurodegenerative disease such as Parkinson's (cf. see also the Roadmap section). These treatments may include electroceuticals⁴⁷ and other types of brain stimulation strategies, such as ultrasound¹²⁹ or optogenetics^{130,131}.

In parallel with clinical applications, the neuromorphic community has progressively advanced the development of increasingly bio-inspired and biomimetic models like SNN and efficient architectures, exploring various approaches at the intersection of electronics, chemistry, and biology. Three main research directions are currently emerging. The first involves using technologies other than electronics, such as chemistry, with molecular networks replicating neuromorphic architectures. For example, Okumura¹³² developed DNA-encoded enzymatic neurons with tunable weights and biases, assembled into multilayer architectures capable of classifying non-linearly separable regions. Similarly, Cherry and Qian¹³³ implemented Winner-Take-All neural networks based on DNA strand displacement reactions for pattern recognition. The second is using organic technology for designing neuromorphic architecture. The use of organic materials offers many advantages, notably better integration with biological systems even at ionic level, thereby facilitating sensing, signal processing, and stimulation within a close-loop system¹³⁴. Harikesh¹³⁵ presented organic electrochemical neurons (OECNs) with ion-modulated spiking, integrated with organic electrochemical synapses exhibiting both short-term and long-term plasticity. The last axis will take advantage of biological intelligence and its tremendous energy efficiency (approximately 20 W for a brain with billions of neurons). An innovative approach involves the direct employment of biological neurons for computational tasks^{136–138}. This is made possible by the synergistic emergence of bidirectional hybrid systems⁹⁹ and biologically realistic AI algorithms¹³⁹, further expanding the concept of Neuromorphic Twin and combining it with the idea of organoid intelligence^{140,141}. Indeed, it is possible to create novel forms of intelligence where biological and artificial systems are able to dialogue in a truly bi-directional way (Fig. 4B, top left). A recent work by Beaubois and colleagues⁹⁹ showcased this hypothesis and anticipated a preliminary concept of Neuromorphic Twin, by putting in communication a connectoid (i.e. two connected cortical organoids from human induced pluripotent stem cells) and a biomimetic organoid implemented as a biomimetic SNN (Fig. 4B, bottom left and right). These innovative approaches hold immense promise in advancing neuroprosthetic technologies, opening avenues for unprecedented levels of integration and adaptability in the realm of neural interfaces.

Roadmap to support the feasibility of Neuromorphic Twin technology

In the previous paragraphs, we have provided a picture of the current status of the research related to the new technology named Neuromorphic Twin, as witnessed by the reported results. Recent advances in this technology have shown significant potential for modeling brain dynamics, with early applications targeting small-scale, well-defined neural circuits and specific pathologies. These models have enabled researchers to explore the feasibility of personalized preliminary therapeutic interventions at the preclinical level, laying the foundation for more complex and adaptable systems. However, it is clear that the Neuromorphic Twin still is in the early stages of development, with most applications confined to the research settings. Although promising, the path toward the clinical adoption of the technology remains long and challenging. Looking ahead, the goal is to create fully personalized Neuromorphic Twins that can be used routinely in clinical environments for diagnostics, treatment planning, and real-time monitoring. Achieving this will require a well-defined roadmap that

includes progressive refinement of models, extensive preclinical validation, and ultimately, regulatory approval for clinical use. In this section we present the technical limitations and challenges for the full exploitation of the technology together with a possible timeline for the use of the Neuromorphic Twin in clinics.

Technical barriers and challenges to technology adoption

Real-time signal processing. Recent advances in electrode array technologies, increasing from 64 to 1024⁵³ and even up to 10,000¹⁴² and 300,000 electrodes¹⁴³, pose significant challenges for real-time signal processing. Edge computing (including detection and classification) will become essential to extract only the relevant biological signatures for analysis. Emerging techniques, such as attention-based SNNs¹⁴⁴, show promise in classifying action potential shapes with greater precision. A key focus for ongoing research is the development of methods capable of extracting multivariate temporal patterns in a fully unsupervised manner, which would significantly enhance our understanding of complex neural dynamics. Despite the demonstrated potential of SNN hardware in applications like spike sorting, adaptive control, and brain signal recording, existing systems still fall short in terms of accuracy and online adaptability achieved by modern AI techniques. Bridging this gap will require the development of algorithms capable of real-time, parallel computation that are also suitable for low-power embedded systems, enabling the full potential of SNNs to be realized.

Real-time emulation. Regarding emulation, research efforts focus either at the single-cell level, which involves the electrical reproduction of neurons and networks¹⁴⁵, particularly through the neuron model used, or at the functional level of the brain¹⁴⁶, which focuses on topologies, connected neural circuits, and oscillations between networks. To achieve an efficient emulation that encompasses the different hierarchical levels, it is essential to combine these two approaches¹⁴⁷. Real-time emulation is possible through hardware implementations of parallel computing such as GPUs, SoC FPGAs, ASICs—whether analog or digital—and neuromorphic chips. To maintain a real-time closed-loop interaction with biological systems, integrating the SNN-based signal processing solutions from section 6.1.1 allows both the interface and the emulation to be implemented within a single neuromorphic system.

Scalability. Fortunately, new technologies, particularly SoCs¹⁴⁸ and the development of analog and mixed neuromorphic chips^{100,149,150}, make it possible to address challenges related to scalability, power consumption, and parallelism, which are mandatory requirements for the Neuromorphic Twin. Networks with generic parameters are essential to allow the tuning of dynamics over time. The reproduction and personalization of networks are achieved through the internal parameters of the SNN and evolve with their plasticity; however, occasional re-adjustment of the network may be necessary to re-fit the real biological dynamics of the patient. This re-adjustment does not need to occur in real time, as it operates on a slower timescale (from few seconds to some hours for the fully rewired network and the updated topology).

Hardware miniaturization. While neuromorphic chips are powerful, they still face challenges related to both scalability and miniaturization, which are critical for integration into usable biomedical applications. To bridge this technological gap, the SNN hosting the Twin can be miniaturized using an analog or digital ASIC, enabling its deployment in medical implants¹⁵¹. The generic parameters can be uploaded and modified over time via wireless transmission to embedded hardware (such as SoC or microcontroller board). A hybrid system (ASIC – SoC – IoT network) appears to be an ideal solution, allowing for miniaturization (ASIC implant), parameter control and plasticity (SoC),

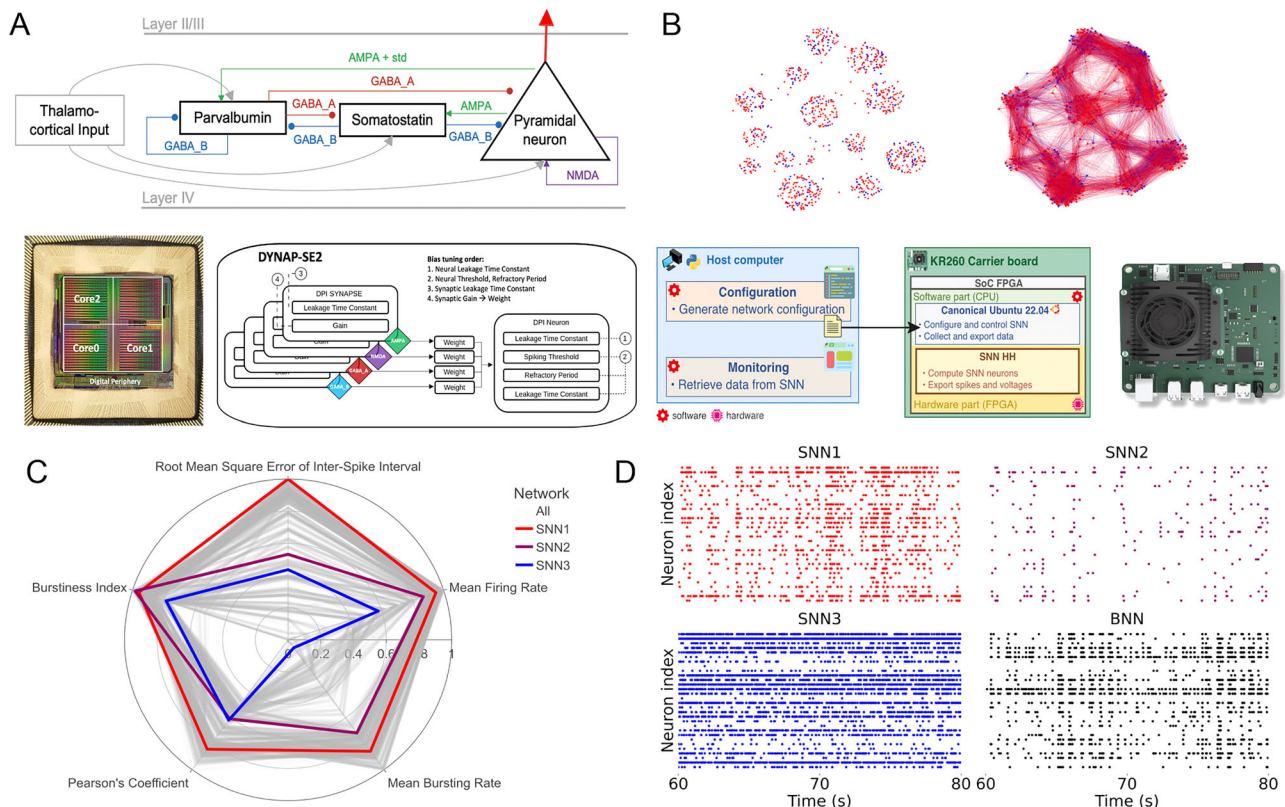


Fig. 3 | Real-time emulation with the Neuromorphic Twin. A Top. Model of the brain architecture within layer-IV of the somatosensory cortex. **Bottom Left.** Microphotograph of the ASIC (Application-Specific Integrated Circuit) called DYNAP-SE2 used to implement the Neuromorphic Twin of the somatosensory cortex, depicted on the top panel. **Bottom Right.** Diagram of the tuning scheme within each core of both neuron and synaptic parameters. **B Top Left.** Position of the nodes (neurons) in a simulated model of a neuronal network emulating the functional behavior of the premotor cortex of a rat. **Top Right.** Connections among the nodes of network reported on the left. **Bottom Left.** Block diagram of the BioemuS system architecture, detailing each component and indicating software and hardware elements with pink and red symbols, respectively. **Bottom Right.** Microphotograph of the board hosting the configured FPGA (Field-Programmable

Gate Arrays). **C** Radar plot of selected network features computed by the analysis of spiking activity obtained through the simulation of 325 SNNs (Spiking Neural Networks) emulating the rat premotor cortex (i.e., the Biological Neural Network - BNN). They include the Root Mean Square Error of the Inter-Spike Interval, Mean Firing Rate, Mean Bursting Rate, Pearson's Correlation Coefficient, and Burstiness Index. Each configured SNN is shown in grey. Three representative SNN are highlighted: SNN1, in red, exhibits the largest area; SNN2, in purple, shows a median area; and SNN3, in blue, covers one of the smallest areas. **D** Raster plots of the SNNs highlighted on the left, together with the BNN of origin. **A** Is reproduced with permission under CC BY 4.0 license from ref. 48. **B–D** Is reproduced with permission from ref. 122, copyright 2024, IEEE.

and parameter and network tuning (IoT network). An IoT network^{152–154} applied to an ASIC brain implant enables continuous communication between the implant and external devices, such as a smartphone, a computer, or a cloud infrastructure. Thanks to this connectivity, brain activity can be monitored in real time, allowing for dynamic and remote adjustment of stimulation or tuning parameters. Learning or parameter optimization algorithms for the digital twin, hosted in the cloud, can adapt the implant's behavior to the patient's specific and evolving needs. Finally, medical doctors can track the progression of the electroceutical protocol and modify remotely, enhancing both the responsiveness and personalization of care.

Invasiveness. The problem related to electrodes' invasiveness into brain tissue has been extensively faced in previous studies since the birth of brain-computer interface technologies, highlighting strategies to reduce tissue reaction and prolong the lifetime of chronic implants^{155,156}. Invasiveness in the context of Neuromorphic Twin is important as both recording and stimulation need to as much selective as possible⁴⁹. In a recent review, Shen and co-workers¹⁵⁷ examined the key features of neural probes that may support the clinical translation of invasive neural interfaces, by focusing on abiotic and biotic factors that can lead to their failure, and highlighting emerging architectures in neural interface design. Notably, to support the use of invasive

electrodes for the exploitation of Neuromorphic Twin, it is important to acknowledge that some studies already reported about patients having long-term implants without experiencing adverse reactions^{158,159}. We feel that, in the years to come, this will become a less demanding issue, considering all the progress done so far.

Integration of multimodal data. The current approach for the Neuromorphic Twin implementation focuses on electrophysiological signals as the primary data input. However, additional data types, such as MRI scans, can be used to improve the model (i.e., the Twin) at its initial definition, providing important details related to the anatomical (i.e., structural) and functional connectivity. In the coming years, as both neuromorphic and imaging technologies continue to advance, the Neuromorphic Twin will be able to integrate a broader range of data to refine its models over time, an approach already explored in recent studies on data and sensor fusion with neuromorphic systems^{37,160}. Moreover, behavioral and performance-related inputs, such as motor task execution, also represent a key dimension. Incorporating this data into the loop can improve patient monitoring and enable adaptive therapy adjustments based on real-time functional status, also thanks to AI-related markerless algorithms, which can accurately track behavior and performance without the need for wearable sensors^{161–163}.

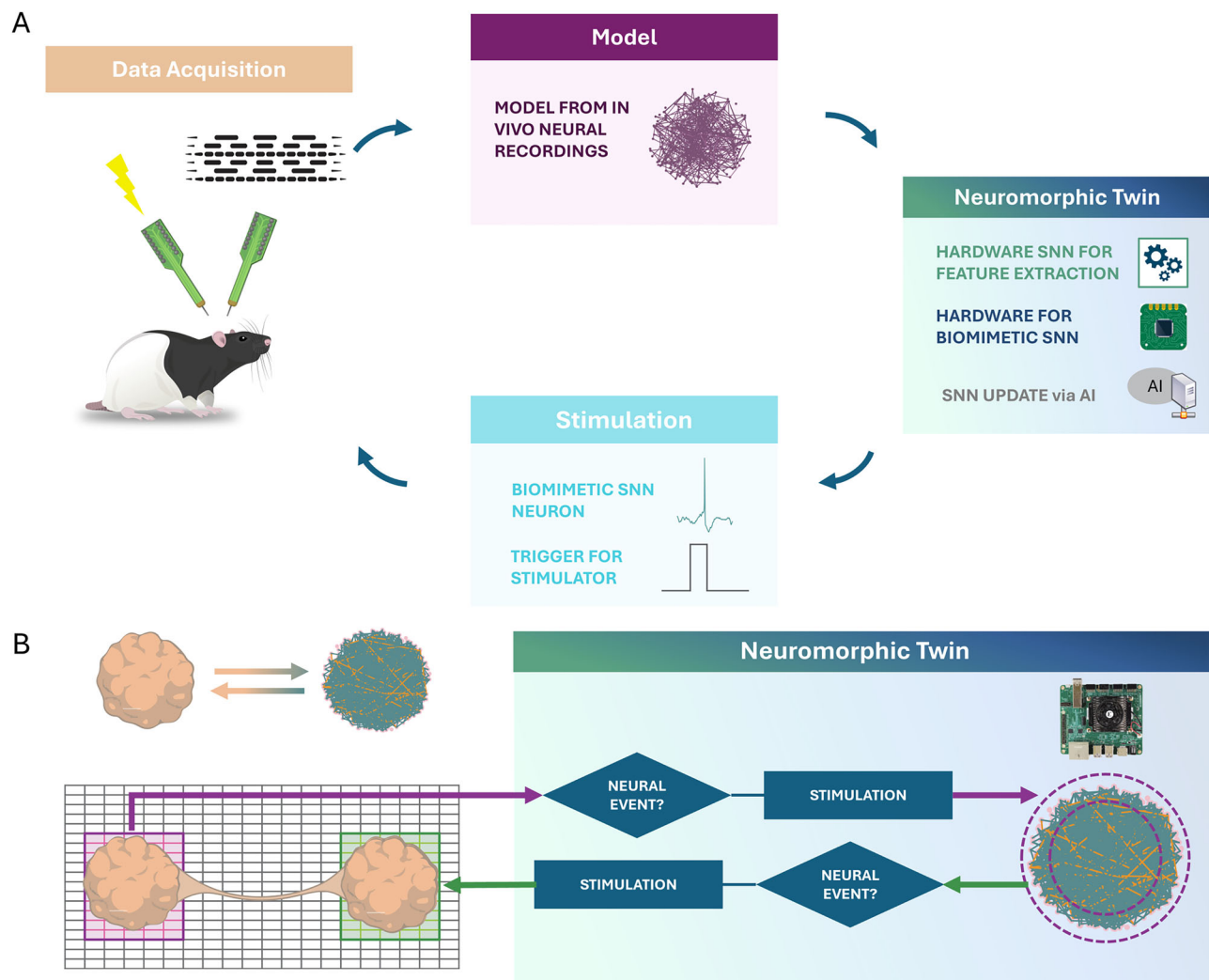


Fig. 4 | Neuromorphic Twins for neuroengineering. **A** Neuromorphic Twin at the preclinical level. This diagram illustrates the key components required to integrate Neuromorphic Twin technology with in vivo experiments in rodent models. Neural recordings are obtained from a specific brain area using an implanted Micro Electrode Array (MEA). The collected data creates a library of electrophysiological parameters necessary for designing the biomimetic SNN, which is then deployed into the Neuromorphic Twin. The Twin also contains the hardware needed to process neural signals in real time and can be periodically updated based on network dynamics adjustments from monitoring the animal's activity and behavior. The output of the Neuromorphic Twin is a signal, or a combination of signals, coming from a subset of neurons of the biomimetic SNN, which serves as a trigger

for delivering stimulation to the animal via a second implanted MEA. Modified from refs. 99,124. **B Top Left.** Schematic of a biohybrid interaction between a brain organoid and its artificial counterpart (i.e., biomimetic SNN). **B Two connected organoids (Bottom Left)** are placed over a planar high-density MEA. The Neuromorphic Twin (**Right**) allows the artificial communication between the two via a biomimetic SNN emulating one organoid, implemented thanks to the Bioemus framework⁹⁹. Neural events of interest (e.g., synchronized spikes, network burst, or even single spikes) are used to trigger stimulation from the left (i.e., purple shaded) organoid to the SNN and from the SNN to the right (i.e., green shaded) organoid. **B** takes inspiration from ref. 99.

Long term-personalization. Brain networks' emulation over long-term scales is necessary to guarantee a personalized therapy as the neural disease progresses. Thanks to the integration of multimodal data, even acquired through the patient's body (cf. section "Integration of multimodal data"), and the scalability of the system (cf. section "Scalability"), it will be possible for the Neuromorphic Twin to co-evolve and continuously adjust the stimulation's parameters for the electroceutical treatment. Occasional refinement of the Twin's parameters can occur through the software for automatic tuning block (cf. Fig. 2), but it does not need to operate in real time.

Ethical issues

As new technologies emerge, especially before they become fully integrated into society, it is crucial to engage in early ethical and social reflection. The development of advanced neural interfaces based on a real-time, two-way connection between the brain and autonomous

ANNs, such as the case of the Neuromorphic Twins, prompts critical questions about how those technologies might affect human subjectivity, i.e., the continuous process by which individuals develop identity, agency, and self-awareness, thus remaining the "subject" of their life¹⁵⁸. This specific topic has been recently discussed by Yvert and Fournier⁴⁵. To protect the user's autonomy, these technologies must be designed to clearly explain how they make decisions, to ensure that the human user stays in control. If this is not guaranteed, the device could act more like an independent agent than a simple tool, contributing to ongoing debates about the ethical and legal status of advanced non-human systems¹⁶⁴. Similarly, a recent research paper first introduced the concept of the enTwin (basically our Neuromorphic Twin, cf. "Introduction") and discussed the ethical related issues. The authors suggested that artificial brains designed thanks to neuromorphic engineering, as in the case of the enTwin, are becoming more and more similar to biological ones⁴⁴. They also introduced a new

Table 5 | Timeline, goals, key actions, and challenges for the adoption of the Neuromorphic Twin up to the clinical trials in humans

Phase	Timing	Task name	Task goal	Key actions	Target metrics	Challenges & Mitigation
Early development (i) Building of initial proof-of-concept biomimetic models and validation with small-scale data; (ii) Refinement of the technology and make it embedded and compact.	1–3 years	Functional Emulation of Biological Neural Circuits	Accurately reproduce the behavior of biological neural circuits using SNNs.	• Acquisition/exploitation of datasets from preclinical models and human subjects – whenever possible – relevant for the building of the Neuromorphic Twin^{40,185–185} • Definition of the main electro-physiological and non-electrophysiological features for the initial definition of the model, in terms of structural/functional connectivity. • Integration of realistic dynamics: delays, stochastic variability, synaptic plasticity (STDP, homeostatic regulation)⁸⁰. • Definition of algorithms for the parametrization of the SNN to achieve bio-realistic emulation (e.g., Indicator-Based Evolutionary Algorithm - IBEA¹⁸⁶, Simulation-Based Inference- SBI^{187,188}).	• 10^3 neurons / 10^6 synapses • Computation latency $\leq$ 1 ms per spike event • Parallel computation of recording channels (64) • bandwidth $\geq$ 20 MB/s • 10^2 to 10^4 electrodes • Energy efficiency: $\leq$10 pJ/synaptic event • Power <100 mW / module • Closed-loop latency $\leq$ 10 ms • Continuous operation $\geq$ 7 days in vitro	• High model complexity → Use modular, scalable architectures • Data heterogeneity → Standardize and curate datasets early • Complex parametrization → Reduce the number of parameters and focus on those that have the greatest influence on network dynamics.
		Development of Embedded, Compact Neuromorphic Platforms	Design low-power hardware (ASICs, FPGAs, or mixed-signal analog systems) capable of interfacing with living tissue.	• Hardware-efficient SNN implementations on neuromorphic chips (e.g., Loihi, SpiNNaker, BrainScaleS)^{99,149,150,189}. • Miniaturization and biocompatible neural interfaces (e.g., MEAs, optoelectronic probes)^{190,191}. • Development of embedded-friendly learning algorithms (unsupervised, Hebbian, reward-modulated STDP)^{192,193}.		• Many options for the hardware platform → use the one which guarantees fastest results • Biocompatibility constraints → Use flexible substrates and organic coatings
		Closed-Loop interaction I	Enable real-time action of SNNs on biological neural network	• Real-time coupling with in vitro biological systems over long-term time scales, i.e. days^{40,192}. • Development of adaptive control strategies for noisy and dynamic signals⁶⁷.		• Latency and jitter → Use hardware system and fast communication protocol to compute the SNN and the interaction with biological neural network under one millisecond (neuron and synapse update) • Long-term monitoring → exploit in vitro systems to evaluate the robustness of the algorithms and the stability of the response over time
Preclinical testing (i) Develop and refine Neuromorphic Twins for specific brain pathologies; (ii) Conduct testing with larger datasets and animal models	3–5 years	Adaptive and Personalized Therapeutic Protocols	Use SNNs to dynamically modulate stimulation protocols for clinical applications. Target pathologies: Epilepsy, PD, stroke. Preclinical testing.	• Preclinical testing in epilepsy: detect and suppress seizures in real-time⁸⁸. • Preclinical testing in Parkinson's disease: perform adaptive deep brain stimulation (DBS)⁹⁰. • Preclinical testing in stroke: perform Intracortical Microstimulation - ICMS for motor recovery⁷¹. • Preclinical testing in neurorehabilitation: closed-loop prosthetics⁹⁴.	• 10^8 neurons / 10^{10} synapses • Closed-loop latency $\leq$ 1 ms • Power <100 μW per channel • Parallel computation of recording channels (1024) • On-chip learning update latency $\leq$ 1 min • Continuous operation $\geq$ 15 days in vivo	• Inter-subject variability → Use personalized modeling, introduce subject-specific parameters (i.e. elements from structural connectivity from MRI scans) • Interfacing robustness → Focus on chronic stability and immune response, perform long-term studies (weeks, months)
		Closed-Loop interaction II	Enable real-time long-term closed-loop interaction between the SNN and the biological Network	• Evaluate long-term stability, safety mechanisms, and signal integrity. • Monitor the behavioral performances of the subject and verify their integration in the loop (as part of the software for automatic tuning block). • Monitor feedback and plasticity over		• Long-term implant reliability → Accelerated aging and safety testing

Table 5 (continued) | Timeline, goals, key actions, and challenges for the adoption of the Neuromorphic Twin up to the clinical trials in humans

Phase	Timing	Task name	Task goal	Key actions	Target metrics	Challenges & Mitigation
Clinical trials (i) Initiate controlled clinical trials; (ii) Initiate regulatory certification	5–10 years	Ethics I	Address ethical concerns in preclinical neuromorphic interfacing	• Define acceptable risks • Evaluate dual-use potential • Engage early with bioethics committees		• Societal skepticism → Emphasize transparency, scientific education, and oversight
		Quality/Medical Device Regulations	Achieve regulatory compliance for human use	• Identify the best implantable device for recording and stimulation in humans^{33,35} • Implement quality procedures for the medical devices (e.g. ISO 13485 and IEC 60601 standards) • Request pre-market approval (EU MDR / FDA IDE) • Prepare a risk management plan	• Power <10 μW per channel • Parallel computation of recording channels (8192) • System latency $\leq$ 1 ms • On-chip learning enabled • Reliability $\geq$ 99.9% • Continuous operation $\geq$ 30 days	• Rapidly evolving standards → Collaborate with notified bodies early • Software as Medical Device (SaMD) issues → Design modular, auditable firmware
		Clinical trials	Test safety and efficacy in humans	• Recruit patients with epilepsy, PD, stroke. • Configure patient-specific models, also including patient-specific data, e.g., imaging scans²⁴. • Monitor over time the motor performance of the patient by means of wearable sensors. Implement sensor-fusion strategies to inform the software for automatic tuning block. • Monitor adaptive learning over time⁹⁵. • Enlarge the sample size by means of virtual clinical trials^{29,30}.		• Small initial sample sizes → Use adaptive trial design, exploit clinical virtual trials. • Regulatory delays → Run parallel applications
		Integration with organic and bio-compatible materials	Build flexible, printable, and bio-integrated neuromorphic systems to improve long-term implant performance	• Adoption of flexible organic neurons and synapses^{91,196,197} • Use of additive manufacturing (e.g., inkjet printing, microfluidics) for tailored designs¹⁹⁰. • Coupling with biological tissues for smart biohybrid interfaces^{198,199}.		• Long-term degradation → In vitro + in vivo studies • Integration mismatch → Use hydrogels and soft-tissue mimicry
Clinical integration Achieve widespread clinical use for personalized therapy	10+ years	Ethics II	Extend ethical analysis to human applications	• Informed consent models for adaptive systems (i.e., dynamically informed consent). • Address autonomy, privacy, and data rights.		• Lack of explainability → Ensure clinicians can understand and trust system decisions
		Personalized neuromorphic therapy deployment	Deploy certified neuromorphic systems in hospitals and clinics	• Create cloud-assisted platforms for configuration and monitoring^{152,154}. • Train clinical staff in device operation.	• Latency $\leq$ 1 ms (system-level) • Power <1 μW per channel • Cloud communication delay $\leq$ 100 ms	• Integration into hospital infrastructure → Collaborate with hospital staff. • Insurance and cost challenges → Demonstrate value
		Continuous monitoring and upgrades	Ensure safety, software updates, and model retraining	• Secure cloud pipeline for data collection + updates¹⁵³. • Ensure cybersecurity measures.	• Adaptive personalization $\leq$ 1 min • Cybersecurity certified (ISO/IEC 27001)	• Data privacy risks → Comply with GDPR/HIPAA. • Misuse → Implement rollback and alert systems
		Ethics III	Governance for post-deployment AI in medicine	• Define limits of autonomy. • Patient feedback channels. • Transparent performance metrics.		• Diminishing clinical decision authority → Maintain human oversight policies

The references are related to some recent studies implementing the reported key actions, with results which might be relevant for the Neuromorphic Twin realization.

model, called the Conductor Model of Consciousness, that explains how both humans and machines might develop an inner understanding of the world by organizing and interpreting information. The model also poses ethical questions, especially as artificial systems become more human-like in cognition and emotion, calling for a new ethical framework to guide human-AI relationships. In general, a multidisciplinary approach, incorporating neuroscience, philosophy, and technology policy, is essential to ensure that the integration of humans and machines benefits society as a whole¹⁶⁵. Of course, the ethical framework for adopting the Neuromorphic Twin is tightly related to ongoing discussions about brain-body interface technologies^{166,167} and AI¹⁶⁸. These fields have already raised important questions about human autonomy, agency, safety, and responsibility^{164,169,170}. As the Neuromorphic Twin integrates elements of both advanced brain technology and AI, it inherits the ethical concerns of both domains and the importance of maintaining human control. Establishing a clear and anticipatory ethical framework will be essential to ensure that these technologies support human well-being, respect for individual rights, and are treated in a socially responsible way. Moreover, adaptive neuromorphic systems, such as the Neuromorphic Twins, present specific ethical challenges because the biomimetic model can evolve over time in response to neural activity, potentially altering its behavior after initial deployment¹⁷¹. This adaptability raises further concerns regarding patient autonomy, ongoing consent, and the ability to monitor or predict system adaptations¹⁷². To address these issues, strategies such as dynamic informed consent^{173,174}, where patients are periodically updated on changes in the system's behavior, and clinician-mediated oversight of the system's adaptive behavior can be implemented. These approaches aim to ensure that patient autonomy is respected, ethical standards are maintained, and regulatory requirements are met throughout the system's lifecycle^{175,176}.

Clinical translation timeline and adoption pathway

Although several open issues remain, spanning technical, experimental, clinical, and ethical dimensions, the development of the Neuromorphic Twin is steadily progressing. As previously mentioned in this Perspective, the fundamental components required to enable biohybrid interaction between the Twin and the central nervous system are already in place^{4,36,117,177}. However, these elements must be coherently integrated within a structured development framework. This calls for the definition of a clear and realistic timeline to guide the transition from current prototypes to functional systems that can be tested in relevant biological and, later on, clinical settings. To this end, we propose a phased roadmap for the adoption of the Neuromorphic Twin in clinical applications. The timeline spans approximately a decade and is structured into four main stages, with early-stage clinical testing potentially starting within the next 7 to 10 years (cf. Table 5).

As outlined in the reported Roadmap, Neuromorphic Twins are expected to represent a major innovation in neuroengineering by enabling real-time interaction with, and emulation of, complex brain dynamics. By integrating digital twin technology with neuromorphic engineering, this approach has the potential to overcome key limitations of current electroceutical strategies, enabling more adaptive and personalized interventions. Although still at an early stage of development, Neuromorphic Twins open promising clinical perspectives, ranging from the restoration of impaired neural functions to the management of neurological disorders. Their energy efficiency and suitability for implantable implementations further support their use in a new generation of compact, closed-loop neuroprosthetic systems. Overall, advances in this field may drive a substantial shift toward truly personalized neurotherapies and improved patient quality of life.

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MC and TL co-wrote this perspective and made the figures. Both authors edited and proofread the manuscript and authorized the submission of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to Michela Chiappalone or Timothée. Levi.

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