

Artificial nerve systems for use in bio-interactive prostheses

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Abstract

Artificial nerves aim to replicate the functioning of the biological nervous system and are expected to lead to important advances in bio-interactive prosthetics. Population ageing is expected to increase the number of patients with neurological deficits or disorders worldwide and to drive increasing global demand for effective prosthetic solutions. Most current bio-interactive prostheses use traditional complementary metal–oxide–semiconductor digital computing and are primarily focused on the restoration or rehabilitation of physiological functions from an electronics perspective. These devices often place little emphasis on neurological compatibility. By contrast, artificial nerve systems consisting of neuromorphic devices offer a promising and neurologically compatible method to either bypass damaged biological nerves or act as an interface between biological nerves and a prosthesis. Artificial nerves are designed to restore lost sensory and motor functions in a similar way to biological nerves by providing biologically plausible and simplified signal processing. Moreover, artificial nerves provide power-efficient control of prostheses and improve users' interactions with their environment. This Review explores the achievements and limitations of conventional bio-interactive prostheses and describes advances in artificial nerve systems that aim to increase functionality through the seamless integration and neuromorphic processing of biological signals.

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Key points

- Conventional bio-interactive prostheses that rely on bulky external computing architectures and complex algorithms have high power use and operational latency; their low biological plausibility mandates extensive user training.
- Artificial nerve systems based on neuromorphic hardware and principles of synaptic plasticity replace conventional computing with event-driven signal processing and analogue memory properties that reduce both complexity and power consumption.
- Artificial nerves convert stimuli into neural spikes and mimic afferent and/or efferent pathways to provide natural sensory feedback and smooth muscle control without extensive digital processing.
- Near-sensor and in-sensor neuromorphic processing are essential to reduce the data transfer load and enable real-time filtering and feature extraction for accurate decoding of motor intent and sensory pattern recognition.
- Artificial nerves that use closed-loop feedback and biocompatible signalling enable naturalistic bidirectional communication by dynamically adjusting motor outputs based on multimodal sensory inputs and the user's real-time physiological state.
- Flexible, stretchable materials and biocompatible encapsulants ensure long-term stable performance and allow on-skin or implantable artificial nerves to integrate seamlessly, reduce mechanical strain and enhance user comfort in daily life.

Introduction

Nerves are easily damaged, including by physical injury, genetic factors, secondary complications and ageing. Nerve damage impedes signal transmission and can lead to permanent loss of function^{1–3}. Various attempts have been made to repair damaged nerves via microsurgery and medication but full recovery of damaged or degenerated nerve function remains almost impossible. Moreover, despite considerable advances in medicine and biology, no major breakthroughs in these approaches are on the horizon. The development of bio-interactive prostheses that can restore these lost functions provides an alternative method to rehabilitate patients with neurological damage^{4–6}. Accordingly, artificial implementations of the key features of biological nerves (that is, artificial nerves) have gained considerable attention over the past 10 years. Research into artificial nerves that can imitate biological neural events has also surged, especially those with applications in bio-interactive prostheses. This neuromorphic approach to the development of bio-interactive prostheses aims to mimic the neural architecture and functions of the human nervous system, such as real-time information processing, event-driven responses and parallel operation.

Bio-interactive prostheses are artificial devices that can be designed to interact with various biological signals, including electrical signals detectable by electromyography (EMG), electroencephalography (EEG) or electrocorticography and chemical signals such as ions, neurotransmitters and hormones. The purpose of bio-interactive prostheses is to restore lost functions and, accordingly, these systems

are designed to interact dynamically with the user's nervous system, unlike passive prostheses, which offer strictly limited functionality and lack sensory feedback^{7,8}. Furthermore, the capabilities of bio-interactive prostheses go beyond simple movement; these devices are designed to provide simultaneous control of multiple degrees of freedom in real time and thereby to closely mimic the natural behaviour of the human body^{9–12}. The goals of developing these devices are to establish bidirectional communication between the biological central nervous system (CNS) and peripheral nervous system (PNS) and to provide sensory feedback that strengthens the user's interaction with the environment.

Current prosthetic technologies can be categorized as having non-biomimetic, biomimetic or neuromorphic approaches to signal processing (Fig. 1a). Non-biomimetic signal processing usually relies on heuristic rule-based operations and does not consider biological neurophysiology. Movement responses to input signals are generated by following predefined rules, which limit the degrees of freedom available for prosthetic operation. By contrast, biomimetic signal processing attempts to replicate at least some of the anatomical and physiological principles of biological systems. Such devices leverage biological models to process sensory inputs and generate movement patterns that closely resemble natural neural responses. Finally, neuromorphic signal processing focuses on replicating neuronal and synaptic principles using event-driven spiking neural networks (SNNs). The results closely mimic real neural activity and enable efficient, low-power, real-time adaptation to biological signals.

Bio-interactive prosthetic devices researched so far typically require substantial user training over extended periods of time^{10,13–15}. Moreover, many such devices have not yet exploited the full potential of synaptic functions. For example, most clinical trials have studied functional electrical stimulation (FES) devices, which merely generate a pulse signal regardless of how the prosthesis communicates with the biological system^{16,17}. These systems mainly use conventional complementary metal–oxide–semiconductor digital computing for both neural signal processing and electrical stimulation. This process requires bulky external computing units and processors for signal filtering, modulation and regression or classification that consume a large amount of energy^{18–21}.

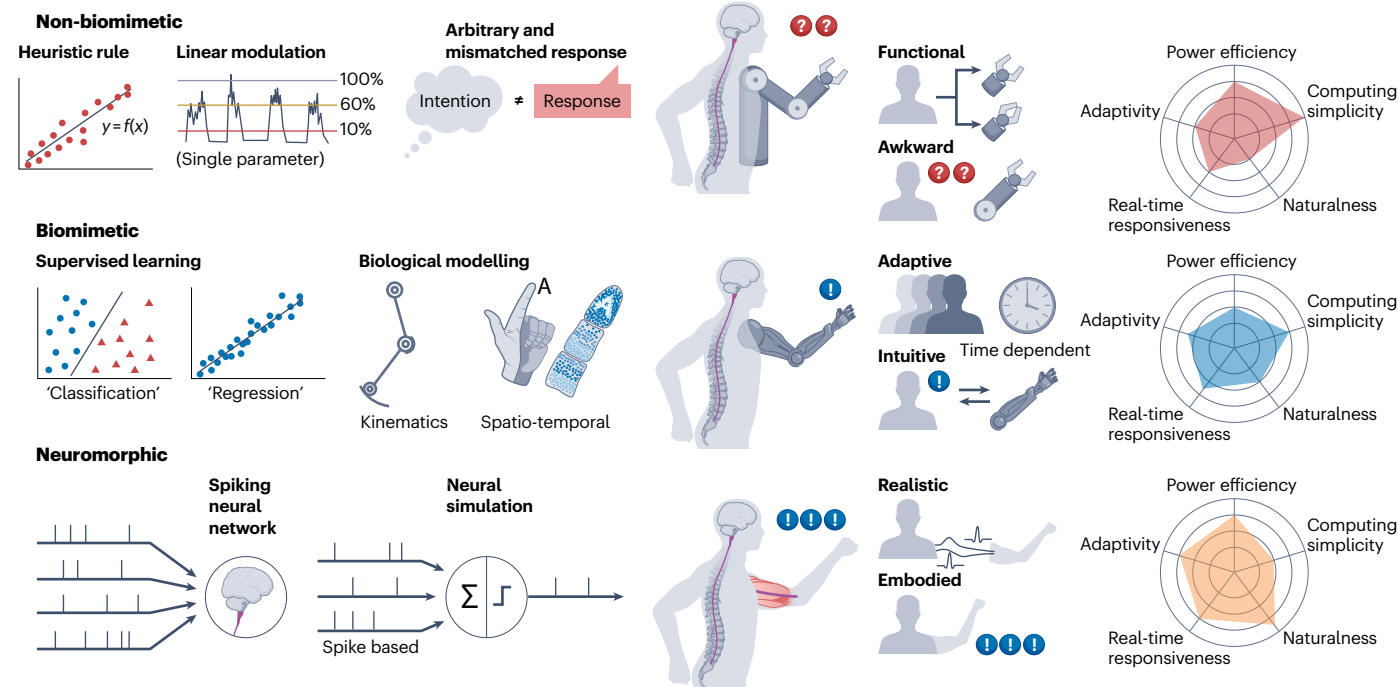
To overcome these demerits, the field of bio-interactive prosthetic technology is moving towards the use of neuromorphic hardware that emulates or replaces the function of impaired nerves and enables the sophisticated and naturalistic movement of paralysed limbs while minimizing the use of external high-power computing devices. Artificial nerves could simplify the signal processing pipeline in bio-interactive prostheses by permitting direct communication between the user and the prosthesis, and could reduce energy consumption by mimicking event-driven signal processing without relying on external complementary metal–oxide–semiconductor computing. Artificial nerves also aim to seamlessly integrate with the user's nervous system via control and feedback mechanisms that exploit the inherent adaptive and learning capabilities of neuromorphic devices (Fig. 1b). Thus, the use of neuromorphic engineering can not only overcome the limitations of conventional bio-interactive prostheses but also enable the development of advanced devices with improved functionality and an intuitive user interface. Ultimately, artificial nerves are expected to provide a key component of this technology, which might offer a future in which prosthetic devices feel and function similar to natural extensions of their users' bodies.

Review article

This Review provides a guide to the development of bio-interactive prosthesis operated by artificial nerves. We first explore the features and limitations of bio-interactive prostheses based on

conventional signal processing architectures. We then discuss the contributions of artificial nerve systems to bio-interactive prostheses. Finally, we discuss the essential components and strategies needed to

a Conventional bio-interactive prosthesis control



b Artificial nerve system

Neuromorphic hardware-implemented neural and/or synaptic properties

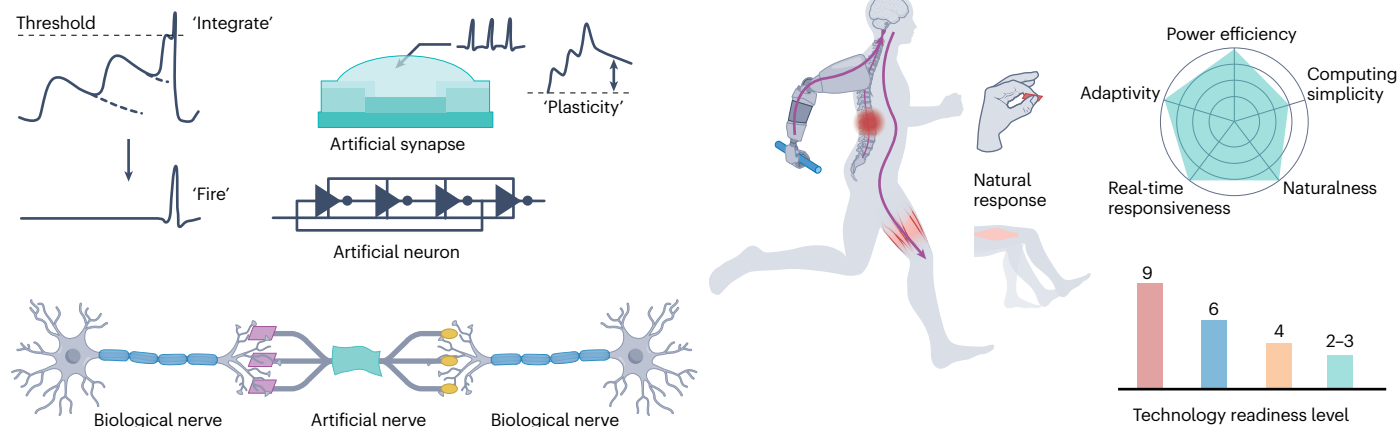


Fig. 1 | Development of bio-interactive prosthesis control. **a**, Non-biomimetic prostheses rely on algorithms that do not directly mimic neural behaviour or consider biological properties. Biomimetic prostheses replicate biological signals using conventional electronics, which requires prior modelling of neural activity. This approach enables more-intuitive control and enhanced interaction with the prosthesis by incorporating biological models, such as body kinematics and spatio-temporal mapping of neural signals. Neuromorphic prostheses directly adopt the neural dynamic principles of biological nerves by allowing event-driven signal processing in a spiking neural network (SNN) hosted in external complementary metal-oxide-semiconductor computing, which results in more-realistic responses. **b**, Artificial nerves mimic the characteristics

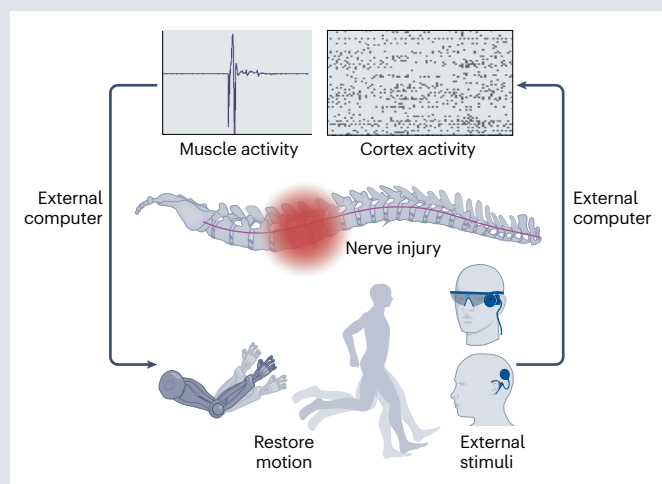
of biological nerves to establish a hardware-implemented neuromorphic bypass for neural signals without using external complementary metal-oxide-semiconductor computing. Through neuromorphic properties that mimic synaptic plasticity, artificial nerves communicate with biological nerves and restore afferent and efferent signal pathways that facilitate sensory feedback as well as actuation. Spider charts display representative performance components (namely power efficiency, computational simplicity, naturalness, real-time responsiveness and adaptability) of the four bio-interactive prosthesis types. The farther from the chart centre, the greater the degree of each component. Chart colours and bar heights indicate technological readiness levels.

Box 1 | Unidirectional bio-interactive prosthetics

Bio-interactive prosthetics interface with the nervous system to restore lost sensory and motor functions. These advanced prosthetics work by decoding neural signals to control prosthetic limbs, or by encoding sensory information to send to the brain. The best-known prosthetic devices that interact with our nervous system are the artificial cochlea and the artificial retina. The artificial cochlea restores hearing in individuals with hearing impairments by transforming sound waves into electrical impulses that stimulate the auditory nerve^{208–211}. The artificial retina restores sight in individuals with vision impairments by converting light into electrical signals to stimulate the retina^{212–214}, optic nerve^{215,216} or visual cortex²¹⁷. Additionally, thermal sensation on amputees' phantom hands can be provided by a non-invasive device worn at the amputation plane²¹⁸. The sensory signals generated by these bio-interactive prosthetics facilitate the interaction of these individuals with their environment.

When nerve pathways are damaged, they cannot conduct generated biological signals, the consequences of which can be severe²¹⁹. For example, spinal cord injuries disrupt sensory and motor communication and can cause permanent paralysis. However, this issue can be addressed by providing detours around damaged nerves. Decoding of electrophysiological signals from muscles (detected by electromyography (EMG)) or from the motor cortex in the brain (detected by intracortical or epicortical electrodes) enables the intention of movement to be transmitted to prosthetic, bionic or paralysed limbs. For example, the formation of new cortical connections in the primary motor cortex (M1) can bypass damaged areas²²⁰. Recordings from brain-implanted microelectrodes can predict motion intention²²¹ and thereby instruct an electrical stimulator to activate muscles in paralysed limbs, bypassing the

spinal cord. By using machine learning to analyse kinematic and EMG data, continuous locomotion can be predicted and appropriate signals can be conveyed to the spinal cord to form a closed-loop system (see the figure). This approach, which includes brain-signal recording and epidural electrical stimulation, has shown promise in restoring movement after spinal cord injury in rodents³³ and non-human primate models¹⁹⁹. Voluntary locomotion was restored in animals by using a closed-loop system with epidural stimulation and drug intervention^{199,222}. In people with spinal cord injuries, continuous decoding of EMG and brain signals, correlated with three-dimensional body kinematics, aids in restoring voluntary walking^{10,15}.



create improved bio-interactive prostheses that offer high signal processing efficacy, biocompatible signal communication and seamless integration with the human nervous system.

Conventional bio-interactive prostheses

Biomedical research aimed at the remediation of malfunctioning neural systems and injured or lost body parts has focused on restoring function using drug treatments, cell therapy^{22,23} and genetic engineering^{24,25}. In the past 50 years, electrical neuromodulation has considerably broadened the spectrum of strategies for restoring neural signal-transduction functions through the use of bio-interactive prostheses^{26,27} (Boxes 1 and 2). This technology has contributed to the rehabilitation of patients with neurological conditions such as paraplegia²⁸, quadriplegia¹⁵ and limb amputations²⁹.

Bio-interactive prostheses are engineered to bridge the gap between human tissue and prosthetic effector devices in an ordered structure that mimics that of the biological nervous system. These sophisticated prostheses incorporate high-level, mid-level and low-level controls, which are each important in ensuring efficient interaction between the user and the prosthesis³⁰. The overall signal communication loop is realized through a hierarchical control scheme that reflects the way in which biological nervous systems process signals and enables rapid responses to environmental changes while preserving device stability and functionality. An overview of these control strategies is provided below, along with

brief details of the signal conditioning or modulation used in each approach.

High-level controls

High-level controls detect the user's electrophysiological signals via methods such as EMG, EEG or electroneurography and translate them into commands sent to the prosthesis. This level of control is crucial for both capturing and interpreting the user's intentions. High-level controls also encode externally sensed stimuli into electrical signals, which enable the user to perceive these stimuli as natural sensory feedback through their neural pathways.

Thus, the essential function of high-level controls in a conventional prosthetic operating system is interaction with the user. This function is mediated by translation of the complex natural signals passed between the user and prosthesis into a format that can be interpreted by the prosthetic to enable the user's intended operation. Computational methods are used, along with components such as neural electrodes, signal filters and signal generators, to process very large amounts of unstructured data and extract meaningful information into the biological interface.

Operation of a prosthetic device typically starts with decoding the user's physiological signals. EMG signals^{31,32} originate from the electrical activity of muscle and provide direct relationships with motor intentions, whereas brain signals (detected by EEG^{33–35} or electrocorticography^{36,37}) and peripheral nerve signals (detected by

electroneurography^{38–41}) provide motor-related neural signals that are associated with movement planning and execution. High-level processing of these electrophysiological signals is typically mediated by either direct control or pattern recognition-based control. In the direct control approach, motor signals are mapped directly to prosthetic control signals on the basis of measurable features (in, for example, EMG traces). Parameters such as impedance or torque that produce either binary (on or off) outputs or proportionally modulated outputs can be determined with a direct control approach^{42,43}. This approach is computationally efficient and provides rapid responses to a user's volitional motor commands. Nonetheless, reliance on simple signal metrics or amplitudes might not effectively capture the non-linear features of neuromuscular systems. To address this limitation, researchers use biomimetic signal processing to extract additional features. For example, machine learning can be used to derive biomimetic models that approximate a realistic physiological state^{44,45} and enable prosthetic control signals to be more accurately mapped than is possible using electrophysiological signals alone. Even with this capacity, direct control cannot reflect variations in user intent and is sensitive to noise, one consequence of which is the need for frequent recalibration.

The pattern recognition-based control approach extracts a range of representative features (such as event timing or frequency) from multichannel electrophysiological recordings. Extracted features are analysed using classifiers that infer the user's motor intentions. The pattern recognition control approach is more commonly applied to EEG and electroneurography signals (which are not always tightly linked to muscle activity) than to EMG signals. Early pattern recognition control systems used heuristic rule-based classifiers such as finite state machines^{46,47} and decision trees^{48,49}. These methods rely

on predefined rules to categorize electrophysiological signals and translate them into corresponding prosthetic movements. Although these methods are effective for identifying fixed sets of patterns, they generate inflexible classification models and therefore have limited ability to capture the full range of user intentions. To overcome these limitations, machine learning classifiers have been developed that can recognize complex patterns in electrophysiological signals after training on extensive datasets. Supervised training classifiers such as support vector machines^{50,51}, linear discriminant analysis^{52,53} and other mechanisms^{54,55} can classify new signals by comparing their features with those of representative datasets. These machine learning classifiers have shown promise for increasing the accuracy and adaptability of signal interpretation. However, pattern recognition systems typically require extensive training and remain sensitive to inter-session variability and environmental disturbances⁵⁶.

High-level control systems can also process sensory feedback in the afferent pathway. High-level sensory signal processing begins with the collection of external stimuli from multiple sensors embedded in the prosthesis, followed by the extraction of spatio-temporal analogue signals and their encoding as electrical signals. High-level control uses patterned electrical pulses to map the resulting encoded sensory data onto the neural interface with the user. This process depends on the part of the body and the type(s) of sensory input, and provides the user with detailed and accurate feedback^{14,57–59}. These signals are designed to stimulate the user's sensory nerves in a way that provides biomimicry when perceiving stimuli and generating a neural response.

Unlike motor signals, which are mainly under the user's conscious control, sensory information remains largely unprocessed and in the form of continuous analogue signals. As a result, complex pattern

Box 2 | Bidirectional bio-interactive prosthetics

Even for a bio-interactive prosthetic that is capable of precise motor control, precise movement cannot be achieved without sensory feedback. Electrophysiological signals drive the movement of the prosthesis, but sensory signals are important to enable the user to determine the consequences of this movement^{223,224}. Sensory feedback in biological limbs conveys information not only from outside the body (about interactions with objects, such as pressure and texture) but also from within the body (such as movement and position). Thus, combinations of motor signals and somato-sensory signals provide the information that is essential for precise control. When prostheses do not provide such information, the user must rely on visual feedback to control them. For this reason, a prosthesis system that is designed to restore locomotion and enable manipulation of objects requires bidirectional communication of sensorimotor information to coordinate actions effectively.

Bidirectionally interactive prostheses not only decode the user's intentions with regard to movement but also deliver sensory feedback. For example, one type of upper-limb prosthesis is controlled by surface electromyography (EMG) signals, whereas sensory information is sent to the median and ulnar nerves. This sensory feedback is delivered by intraneural stimulation, in which the user must learn to interpret stimulation properties such as amplitude, pulse width and frequency. Several training sessions might be required to accustom the user to these feedback signals¹³. This arrangement enables patients to control the force applied by

the prosthesis and to handle different types of object; object size and compliance are differentiated by tactile and proprioceptive feedback, rather than by relying on visual or acoustic feedback. Tactile feedback alone is insufficient for position control and proprioceptive feedback alone is inadequate for force control, but the combination of both types of feedback enables the user to precisely control the prosthesis and restores dextrous and agile movement. Moreover, bidirectional feedback helps reduce phantom limb pain (the sensation of pain in a missing limb) by addressing the absence of sensory feedback from the lost part of the limb to the brain^{225,226}. When sensory feedback is provided through a bio-interactive prosthesis, patients report increased confidence, considerable relief from neurological pain and improved functional outcomes^{60,181,227–229}.

Interest is growing in applying neuromorphic approaches to neural prosthetics. For example, a neuromorphic system has been used to connect two neuronal populations in vitro, which enabled bidirectional interaction through a spiking neural network (SNN)²³⁰. This model demonstrates the potential of all-hardware neuromorphic prostheses to reconnect neural networks. Additionally, a neuromorphic human reflex model allowed amputees to handle 47% of the typical neural information levels of healthy individuals²³¹. Artificial synaptic devices have also achieved biological sensorimotor⁹⁷ and proprioceptive¹⁹ feedback loops without extensive computation.

recognition is not necessary and direct control is sufficient for transmitting this information. Direct control signal modulation rules can be applied to encode sensory signals into neural signals by first simply defining a sensory perceptual region in the corresponding impaired area^{57,59,60}. Early attempts at the restoration of sensation focused on adjusting the amplitude, frequency and pulse width of stimulation^{58,59,61}. However, these methods sometimes led to paresthesias due to the non-natural or excessive activation of nerve fibres. Therefore, more-advanced biomimetic simulation models have been proposed to emulate the spatial distribution and temporal dynamics of neural spikes for each type of sensory receptor. Several remarkable biomimetic simulation models have been developed for the palmar surface of the hand (TouchSim⁶²), foot sole (FootSim⁶³), retina (Virtual Retina⁶⁴) and cochlear hair cell auditory-nerve fibres⁶⁵. Biomimetic sensory restoration improves both prosthesis functionality and overall user experience, which can make the prosthesis feel like a natural extension of the user's body. However, the signal-encoding processes required to provide natural sensory feedback incur a massive computational load⁶⁶.

Mid-level and low-level controls

Mid-level controls are responsible for both precise signal transmission to the effector and accurate acquisition of signals that represent sensory information from sensors, whereas low-level controls are responsible for the execution of motor commands and the perception of external stimuli.

Mid-level and low-level controls for the processing of motor and sensory signals in conventional bio-interactive prostheses are vital for precisely and accurately executing the control commands generated by high-level signal processing. Motor execution steps are then planned according to biological kinematic models to emulate natural motor behaviours. In a direct control scheme, a high-level controller calculates these dynamic motor parameters and transfers this information to mid-level and low-level controls, which perform forward-kinematics calculations⁶⁷. By contrast, in pattern recognition-based control approaches, the high-level system identifies a particular motion category (for example, walking, standing or sitting) and leaves the mid-level and low-level controllers to execute the structured actions and steps required to generate this motion⁶⁸. For instance, in lower-limb prostheses, pattern recognition-based control recognizes cyclic gait patterns, whereas mid-level and low-level controls generate commands for continuous movement. These commands typically require real-time feedback about the internal state of the prosthesis to verify that the actual motion matches the user's intended trajectory. As an example, echo control exploits the phase-delayed mirror symmetry of leg movement during walking. This system records the position and trajectories of the intact limb, and then applies a phase delay and scaling before replaying them on the assisted limb^{69,70}. However, given that the prosthesis simply repeats the contralateral limb's motion automatically with a time delay, this method might not fully represent the user's intention. Therefore, complementary limb motion estimation has been adopted to restore natural limb motion. This method analyses the motion of the non-assisted limb to infer the intended motion of the contralateral assisted limb, and then maps this information onto a reference trajectory for the prosthesis⁷¹.

Additionally, in upper-limb prostheses, mid-level and low-level controls adjust motor commands in real time based on sensory feedback and motion planning algorithms that use Kalman filters or machine learning algorithms to estimate system states^{72,73}. These commands can preform a prosthetic hand to grasp an object and maintain a

stable grip without slipping⁷⁴. Also, sharing motor operating information with a sensor can enable the design of commands that extend the arm to an object, release an object and pause for appropriate intervals⁷⁵. These controls perform real-time monitoring and adjustment of the operation status of the prosthesis. Sensors embedded in the prosthesis continuously provide feedback on various parameters such as joint angles, velocity and force. However, the raw somato-sensory signals from these sensors are often noisy and require substantial preprocessing to render them usable. Signal processing techniques such as fast Fourier transform and wavelet transform are used to extract either time-domain or frequency-domain features from these signals^{76–78}. The status of the prosthesis can then be defined using proportional–integral–derivative control, which is widely used to ensure smooth and accurate movements of the prosthesis^{79,80}.

In sensory bio-interactive prostheses, mid-level and low-level controllers can preprocess external stimuli to reduce the computational burden on the high-level controller. The raw signals produced by external stimuli are encoded by applying filters, adjustments or other processing steps depending on the sensor's modality and performance parameters (such as resolution and sensitivity). However, biomimetic methods that fully replicate neural activity based on traditional von Neumann computing architectures require heavy computation to encode raw signals^{81,82}. Moreover, although conventional signal processing in prosthetic control systems is effective in bridging the gap between the user's intention and executed action, this approach often results in feedback that is delayed and less accurate than that provided by a biological nervous system^{83,84}. Thus, the control methods used in conventional bio-interactive prostheses can be regarded as rigid interpreters of biological signals. They are not capable of connecting the user and prosthesis in an embodied manner by enabling bidirectional communication based on wholly biocompatible signal processing methods.

Neuromorphic signal processing

The neuromorphic approach has been adopted in bio-interactive prosthetic control systems to both reduce power consumption and replicate biological neural activity in an intact yet computationally simplified manner that overcomes the drawbacks of conventional prosthetic control architectures.

In direct control systems, neuromorphic models often rely on equations that reflect biological neuron dynamics^{85–87} to convert the analogue sensor outputs into spiking neural signals that enable event-driven, asynchronous and parallel signal processing. Typically, embedded software calculates time-dependent changes in a simulated membrane potential and triggers spikes when a threshold is reached. In pattern recognition-based control systems, SNNs and spiking signal conversion circuits^{88,89} are used to mimic hierarchical neural connections^{90,91}. The SNN computing parameters require exposure to large training datasets to enable them to correlate sample input signals with accurate prosthetic command patterns. Therefore, SNNs not only improve the accuracy of pattern recognition but also adapt to an individual user's neural spiking patterns^{92,93} and time-varying biological activities based on adaptive learning⁹⁴. Furthermore, development of SNN hardware techniques into neuromorphic prostheses in industrial and academic research settings could further improve the efficiency of signal processing and decrease power consumption^{95,96}. In a similar vein, another strategy focuses on using artificial nerve systems that mimic the functional characteristics of biological synapses. These systems are expected to simplify signal processing compared with

conventional approaches that rely on externally modelled neuromorphic software. Building on this approach, artificial nerve systems that are capable of mimicking and seamlessly interfacing with the biological nervous system are anticipated to replace conventional prosthetic operating systems.

Whereas conventional bio-interactive prostheses have already reached technological readiness levels of 6–9, neuromorphic prostheses (especially those using artificial nerve systems) remain at an early stage of development (technological readiness levels 2–4). Artificial nerve systems, in particular, are still primarily at the concept validation and fundamental experimental stages. Although artificial nerve systems operate similarly to direct control-based methods, which likewise bypass neural signals and have a minimal computational load, the goal of artificial nerve systems is to provide a fully hardware-based neuromorphic signal processing bypass that connects the user directly with the bio-interactive prosthesis and mimics the principles and functions of biological nerve systems.

Artificial nerve systems

The advent of artificial nerve systems composed of artificial neurons and artificial synapses that enable efficient data processing using simple biomimetic device functions and circuit configurations has introduced a new paradigm in prosthetic technologies^{18,19}. Artificial nerve systems use SNNs and other hardware to drive biological activity by emulating the spike signal-transduction and signal-transmission behaviours of biological nerves as well as the plasticity of biological synapses. These devices aim to provide seamless integration with the human nervous system owing to the similarity of their signals to those of biological systems. Artificial nerve systems that are intended to interface directly with biological nerves also eliminate the need for additional signal processing (as is required in conventional prosthetic control systems).

The close connectivity of artificial nerves results in more-natural motion control and more-accurate sensory feedback than is possible with conventional signal processing. For this reason, artificial nerves are suitable for bio-interactive prostheses that require high energy efficiency, closed-loop operation, portability and stability. These characteristics enable their daily use in the form of on-skin or implantable electronics without the need for bulky external power sources.

Artificial synapses

Artificial nerves are connected to each other and to biological tissue by artificial synapses that emulate the functions and responses of biological synapses^{10,18,97,98}. These artificial synapses are designed to replicate the plasticity of biological synapses, which refers to the capacity to modulate signal-transmission efficacy (also known as synaptic weight) in response to experience. Synaptic plasticity is essential for the accumulation of memory and learning in biological systems and is characterized by both the potentiation (strengthening) and depression (weakening) of trans-synaptic signal-transmission efficacy in response to neural activity patterns^{99–101}.

Synaptic plasticity has been successfully emulated by devices with two-terminal and three-terminal structures that use various working mechanisms, including charge-trapping^{102–104}, formation of conductive bridges^{105,106} or ferroelectric tunnel junctions^{107–109}, ion migration^{110–112} and electrochemical reactions^{18,19,98–101,113–116}. Ion gel-gated organic synaptic transistors (IGOSTs) are an especially promising technology. When subjected to an electrical field, ions in a gel can migrate and form electric double layers on the polymer

channel surfaces or can even permeate and dope the channel. IGOSTs have demonstrated various kinds of synaptic responses, including long-term plasticity (LTP), short-term plasticity (STP) and the linear or symmetrical modulation of synaptic weights^{100,101,113}. LTP is exploited to achieve learning and memory, whereas STP is exploited for immediate responses and is considered a crucial feature of bio-interactive sensory and motor prostheses^{18,19,97,98}. Electric double layers are mostly exploited for STP-dominant operations, whereas electrochemical doping endowed by high volumetric channel capacitance is mainly exploited for LTP-dominant operations and enables both low-voltage operation and mimicry of biological synaptic mechanisms¹¹⁷. IGOSTs can exhibit STP and LTP simultaneously, depending on ion movement and electrochemical doping parameters. The operational reliability and functional versatility of IGOSTs render them particularly suitable for use in artificial nerves.

In artificial synapses, potentiation and depression are typically induced by applying voltage spikes that emulate presynaptic action potentials. The number and frequency of input spikes can alter the plasticity of the output signal of artificial synaptic devices. When a voltage spike is applied to the gate electrode of a synaptic transistor such as an IGOST, ions that have the same charge as the spike will move towards the channel wall and form an electric double layer. This process induces charge carriers in the transistor channel and thereby maintains its conductance during the period of electric double-layer formation, which yields STP^{118,119}. Under specific input conditions, ions can penetrate the active layer and induce additional charge carriers; the trapping of these ions in the active layer establishes LTP, which is maintained until the ions are de-trapped, even after the cessation of stimulating spikes^{99,117}. LTP characteristics can be exploited to achieve both localized memory and processing in memory, which together enable the preprocessing of signals used in bio-interactive prosthesis and cannot be achieved with STP alone. The synaptic plasticity responses of IGOSTs can be precisely regulated to implement diverse functions. For instance, the STP property is required to obtain immediate response to sensors and biological signals, whereas the LTP property is required for signal manipulation based on localized memory and subsequent processing. Several methods have been used to modulate the properties of artificial synaptic devices, including modifying the semiconducting material to meet the desired dynamic conductance range^{120,121} and controlling the microstructure of the semiconducting channel layer to modulate the duration over which conductance is retained^{100,101,113}.

Artificial neurons

Artificial neurons are the electrical component of an artificial nerve. The artificial neuron generates spike signals in response to integrated spatio-temporal inputs derived from sensory receptors or other neurons and then transmits this signal through artificial synapses between neural networks. This biomimetic approach enables artificial neurons to effectively replace damaged nerves and thus to provide the core element of next-generation bio-interactive prostheses.

The generation of spike signals in artificial neurons closely mimics the consecutive spiking behaviour of neural signals in the spiking frequency range of biological neurons (<200 Hz)¹²². Several artificial neurons have been implemented using a ring oscillator that consists of multiple transistors^{123,124}, but the use of numerous transistors and passive electronics yields bulky circuits that are not suitable for direct interfaces with biological nerves. By contrast, circuits that comprise components commonly used in artificial synapses (such as OECTs), along with capacitors and resistors can yield artificial neurons that can

both generate and propagate action potentials, and thereby simulate the electrical activity of neurons^{125,126}. For instance, when the number of applied electrical impulses (the input signal) exceeds a given threshold, the artificial neuron generates a voltage spike that propagates along its axon, similar to the action potential of a biological neuron. This process in an artificial neuron emulates the integrate-and-fire model of a biological neuron¹²⁷.

Artificial neurons can also operate using the threshold concept and the all-or-none law to determine whether an input stimulus should be included in signal processing. In this model, continuous stimuli accumulate and result in consecutive output spikes once a predetermined threshold is reached, a characteristic that effectively filters out noise. The signals from artificial neurons are integrated with artificial synapses to enable the incoming information to be summed both temporally and spatially to form an input signal for artificial neurons. This integration process enables external stimuli to be effectively processed concurrently. As a result, the neuron responds to complex input patterns and adjusts its output signals according to the cumulative activity of its synapses, which in turn determines whether the operating threshold voltage is exceeded and, therefore, whether the output signal is fired.

Artificial nerves

Artificial nerve systems represent a considerable advance in bio-interactive prostheses. Compared with conventional bio-interactive prosthetic systems, artificial nerve systems offer efficient and adaptive signal processing by mimicking biological event-driven signal transmission between the CNS and the PNS through both efferent (away from the CNS) and afferent (towards the CNS) pathways. Bidirectional signal processing enables neuromorphic hardware to provide both somato-sensory feedback and the recovery of natural motor behaviour.

Unlike traditional prostheses, which convert motor commands or detected sensory signals into pulsed digital information to stimulate nerves, artificial nerves generate an asynchronous spiking signal. Whereas digitized signals follow a fixed rhythm or clock, neuromorphic systems generate spikes (action potentials) irregularly and non-periodically, similarly to biological systems. These systems fire spikes in response to input stimuli rather than at predetermined intervals, which enables event-driven operation. Moreover, asynchronous spiking enables the encoding of additional information in the timing and pattern of spikes, which enables the integration of sensing and processing functionalities. In sharp contrast, conventional hierarchical systems require extensive software-mediated signal preprocessing and interpretation to provide meaningful feedback to the user^{76,77,79,80,128,129}. Moreover, artificial nerves also reduce energy usage by responding only when an event occurs, unlike conventional systems that continuously sample and process data. Thus, neuromorphic systems offer considerably improved energy efficiency.

Artificial afferent nerves. In the afferent pathway, artificial nerve systems can both detect spatio-temporally patterned stimuli and implement event-driven operations. An artificial receptor such as a neuromorphic sensor or electronic skin (e-skin)^{130–141} linked to artificial neurons can convert incoming stimuli to spike signals, which are transmitted via artificial synapses that are adapted to recognize spatio-temporal patterns. These spatio-temporal patterns can easily be analysed to accurately recognize sensory information and provide meaningful feedback. Artificial nerve systems replicate biological afferent nerve pathways by exploiting the functional characteristics

of artificial synapses and processing the external stimuli signals from artificial sensory receptors (Fig. 2a). For example, the linear modulation of signal frequency converts sensor data to signals that modulate neural activity. This process conveys information about the intensity of a sensation to the brain by varying the number or firing patterns of generated action potentials, in a manner that mimics biological adaptation.

The capacity to integrate tactile sensations into a bio-interactive prosthesis gives its users a tangible way to comprehend the world. Human tactile receptors include slow adaptation and fast adaptation types^{142–144}. Mimicking these two different responses implements a human-like sensory system that can detect pain as well as objects. Such systems are crucial for both achieving safety in daily life and providing lifelike functionality. The presence of stimuli that are likely to cause damage, such as high temperature^{145,146} or local high pressure^{147,148}, enables artificial nerves to generate a nociceptive warning. Harsh stimuli reach the signal threshold of the artificial nerve more quickly than mild stimuli, and therefore provide an early warning of potential harm. Additionally, the plasticity of artificial synapses enables the memorization of tactile sensations, which enables the output signals from the artificial nerve to shoot up rapidly again if the same noxious stimuli occur during the period that the synaptic device retains its memory.

Artificial synapse plasticity also provides adaptability and facilitates the formation of haptic memory. Haptic memory reduces computational loads by enabling the preprocessing of sensory signals within the trained memory. Therefore, neuromorphic prostheses can learn specific tactile patterns, such as English character writing¹⁴⁹ or various stimuli^{150–152}, and will respond with appropriate outputs in an easily recognizable form.

Other human senses can also be mimicked in artificial afferent nerves. Optical sensing can be achieved using an array of pixels that convert light stimuli to electrical signals and act as optically sensitive artificial nerves. Each pixel is integrated with a synaptic device^{153,154} or photonic synapse^{155–157} that directly emulates synaptic characteristics when stimulated by light, including by integrating temporal patterns of stimuli into each pixel that correspond to image-related information. For auditory sensing, spatio-temporal signal processing and noise filtration are crucial for reliable operation in the real world. These processes can be effectively implemented using artificial synapses integrated with triboelectric nanogenerators^{101,158}. For gustatory and olfactory sensing, which both rely on chemical detection, artificial chemical receptors can be trained by exposure to appropriate reactants. The artificial nerve can then discriminate between input signals according to the type and concentration of chemicals present and respond by modulating the frequency of output signals^{159,160}. These sensing primitives are also important in biomolecule sensing by visceral artificial nerves.

Rapid reactions to harmful situations can be obtained with an artificial nerve system that mimics the functions of a biological reflex arc. Such a system can be obtained by the integration of artificial afferent (sensory) nerves with an artificial efferent (motor) nerve¹⁸ that stimulates the biological motor nerves, thereby generating motion in response to external stimulation. One such artificial mechanosensory nerve system includes a sensor that detects applied pressure and acts as a mechanoreceptor. Artificial nerves convert the detected information into spike-shaped action potentials, which are sent to a synaptic transistor where they are processed to generate postsynaptic output signals. The synaptic transistor interfaces with a biological motor nerve, thereby forming a hybrid reflex arc that can activate an actuator, such as an isolated insect leg, in response to external pressure¹⁸.

a Artificial afferent nerve

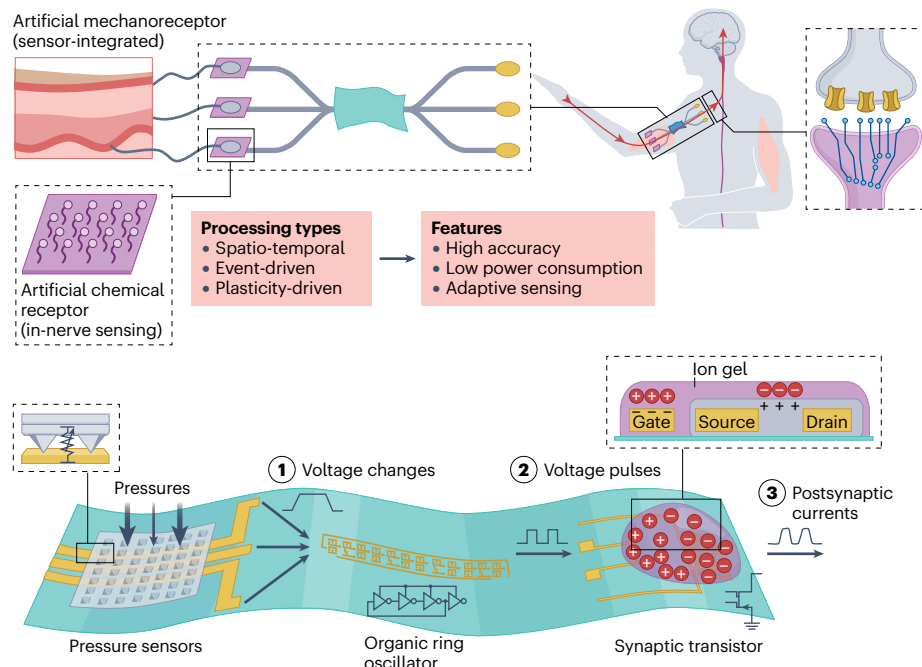
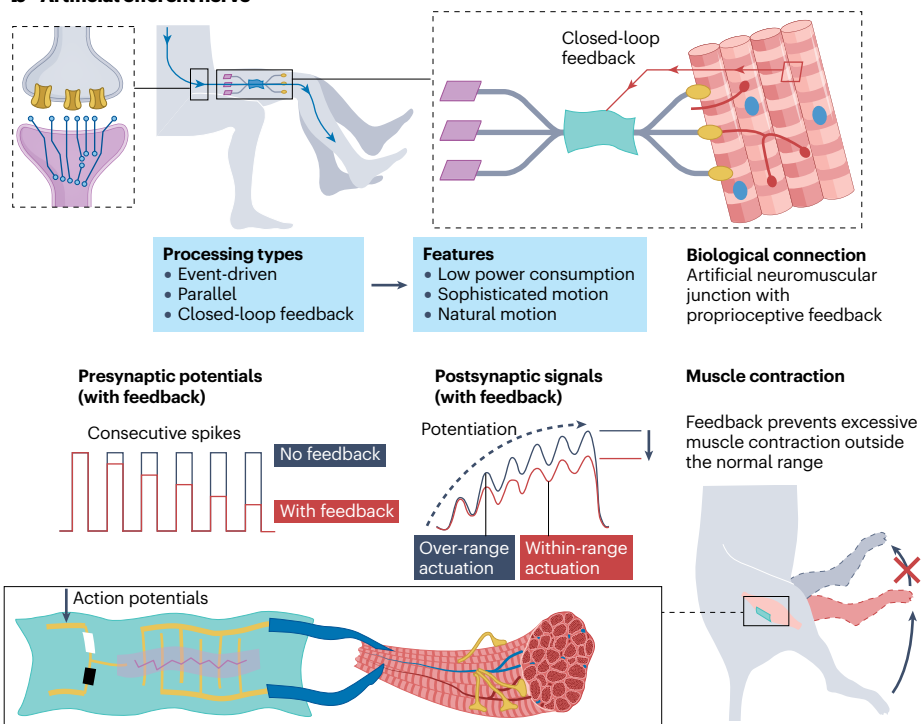


Fig. 2 | Artificial nerve systems. a, Configuration of an artificial afferent nerve interfaced with a biological system. Artificial sensory receptors sense incoming stimuli as electrical signals, which are converted into spike form by artificial neurons (step 1). The artificial synapse accumulates these signals according to their sensory information (step 2). The postsynaptic signals are converted into action potentials and transmitted to the biological system (step 3). Panel **a** adapted with permission from ref. 18, AAAS. **b**, Configuration of an artificial efferent nerve interfaced with a biological system (a rodent leg). Physiological signals are converted into several consecutive presynaptic voltage spikes. These presynaptic potentials are modulated by closed-loop feedback from the effector to control limb motion. The artificial synapse accumulates these signals and exhibits potentiation and depression based on synaptic plasticity. The artificial efferent nerve transmits signals to the motor neuron that cause a smooth contraction in biological muscle.

b Artificial efferent nerve



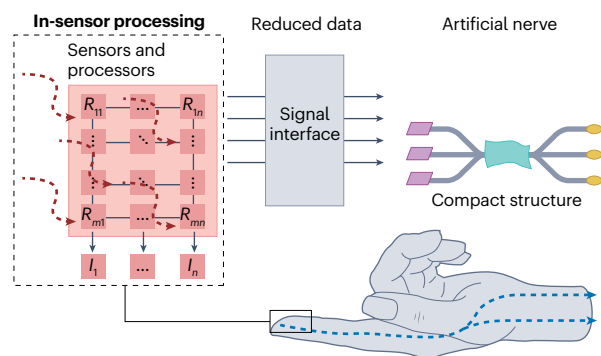
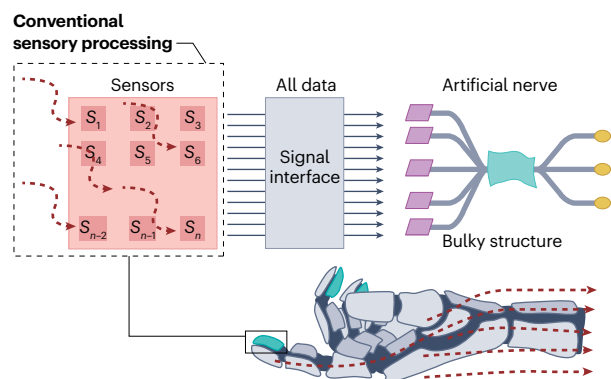
By mimicking natural reflexes, this system demonstrated the first use of artificial afferent nerves in a neural prosthesis.

Artificial efferent nerve. Artificial nerve systems in the efferent pathway offer the distinct advantage of exploiting synaptic plasticity to directly

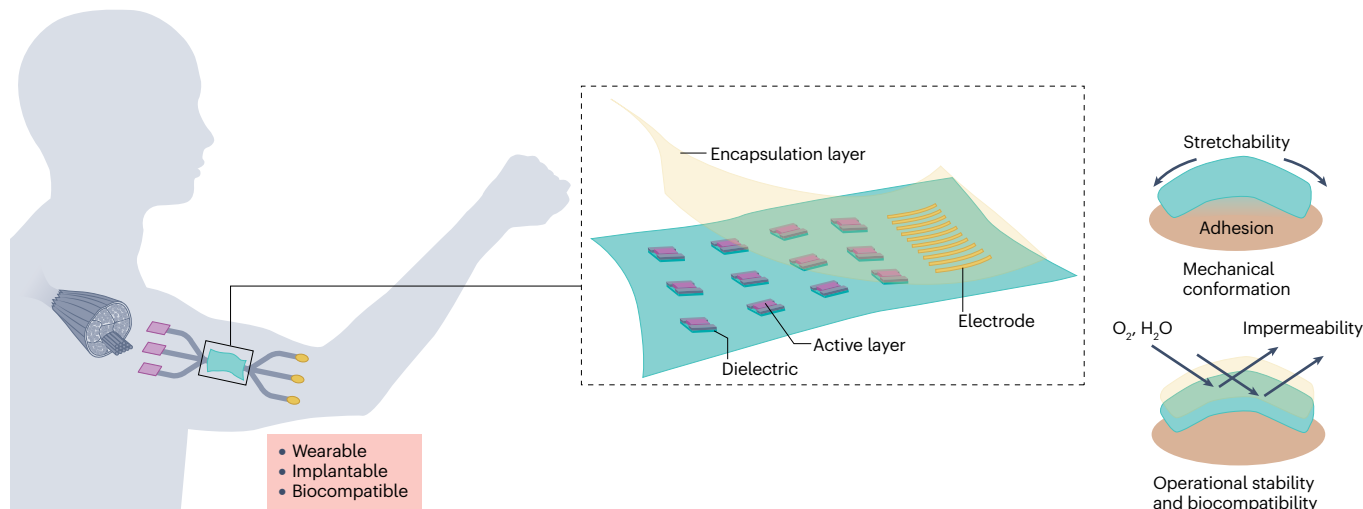
mimic the natural motion of biological effectors (Fig. 2b). This result is achieved by using artificial synaptic devices that emulate the synaptic plasticity of the neuromuscular junction in biological motor nerve systems. Conventional FES applies discrete electrical pulses of a constant amplitude, which induce an abrupt and drastic muscle contraction.

Review article

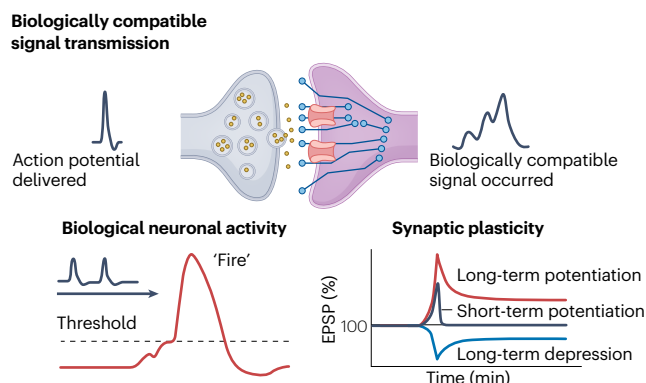
a Reduced complexity of signal processing



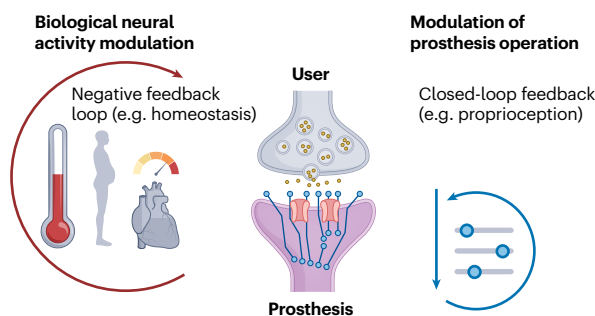
c Seamless integration and biocompatibility



b Communication with the body



Feedback loop communication



Difficulty in predicting the force of this muscle contraction can cause unpredictable twitching and cramping, which cause discomfort to the FES user¹⁷. By contrast, biological skeletal muscle contractions are categorized into three types: twitch, summation and tetanus¹⁶¹. Low frequencies of action potentials cause muscle twitches. As the frequency of action potentials increases, the induced twitches gradually undergo

summation, which smoothly changes the muscle response to a continuous and strong contraction. A further increase in the action potential frequency induces the muscle to contract with its maximum force (a tetanic contraction), which can take some time to relax after the stimulation is withdrawn¹⁶². Therefore, FES signals require additional processing to gradually ramp the voltage during both the onset and

Fig. 3 | Artificial nerves for future bio-interactive prostheses. **a**, In a conventional sensory processing prosthetic system, sensors simply convert external stimuli into electric signals, which incurs a huge cost in data transmission. In artificial nerves, in-sensor processing architectures preprocess information, which reduces the cost of data transmission. **b**, The biocompatible signals generated by an artificial nerve mimic biological neural activity and synaptic plasticity, and are controlled by feedback loops. Modulation of neural activity occurs via the delivery of negative feedback to biological nerves, which recovers the signal loop and maintains the stable status of the body (red arrow).

Closed-loop feedback inside the artificial nerve enables it to precisely adjust its operation (blue arrow). **c**, Artificial nerves made of stretchable semiconductors, conductors and dielectrics enable wearable or implantable applications owing to their ability to both conform to and maintain adequate adhesion to biological tissue. The biocompatible and stretchable encapsulant must also confer operational stability in the in vivo environment. EPSP, excitatory postsynaptic potential; I , output of intelligent sensors in in-sensor processing; R , responsivity of intelligent sensors; S , output of a conventional sensor array.

deactivation of stimulation. By contrast, the inherent potentiation property of artificial nerves enables the transmission of ramping signals and thereby increases both natural motion and patient comfort¹⁹. The gradual increase in muscle force response achieved by artificial nerves also eliminates the need for bulky electronic components such as function generators. A single artificial synapse enables the actuator^{163,164} to implement movements analogous to those found in biological systems⁹⁸. Biomimetic movement control cannot be achieved easily by conventional transistors, which only have binary (on and off) states. However, a light-responsive motor system composed of a soft ionic polymer–metal composite actuator that contracts artificial muscles in response to optical stimulation can provide a graded response without the need for additional components. This approach has been incorporated into an artificial nerve system consisting of an artificial synapse integrated with a photodetector⁹⁸. This artificial synapse can also respond to biomolecules, such as acetylcholine, which induce movement of the soft actuator¹⁶⁵.

The combined use of two or more artificial synapses can increase the sophistication of movement responses. For instance, parallel processing using both STP and LTP synaptic devices led to an increase in the displacement of chronic actuation that simulated biological conditions such as muscle growth¹⁶⁶ and muscle memory¹⁶⁷. Each effector was operated via an artificial synaptic device, which obviated the need for a conventional memory chip to control the whole prosthesis system. Also, the integration of multiple artificial synapses into a robotic hand enabled coordinated finger movements¹⁶⁸. The event-driven properties of artificial nerves enable spatio-temporal signal summation, which can yield various motor outputs that correspond to complex stimulating patterns.

Reciprocal inhibition via integrated artificial synapses can implement lifelike motion in an actuator¹⁶⁹. By connecting and controlling a soft actuator using both excitatory and inhibitory synaptic devices, the speed, range and direction of the actuator's motion can be precisely regulated. Implementation of these responses in conventional computing systems requires complex architectures or additional processing steps¹⁷⁰. Therefore, the use of artificial nerves minimizes device complexity.

Artificial multi-synapse systems can also be applied to biological muscles^{18,19,97}. Artificial efferent nerves have been connected to both extensor and flexor muscles using a soft hydrogel electrode. Adjusting the frequency of presynaptic spikes to the artificial nerves enabled precise control of the muscle's movement¹⁹. Additionally, control of muscle extension and flexion has been implemented using pre-recorded electrophysiological signals from the primary motor cortex (M1)¹⁹ (Fig. 2b). This system represents the first demonstration of synchronized movement achieved using artificial efferent nerves and provides a basis for the future development of bipedal walking locomotion controlled by artificial synapses.

Synchronized movement requires that artificial efferent nerves receive feedback about their response from effectors such as prosthetic limbs or their restored biological counterparts. For a conventional

system, the detection of internal device status and the fine adjustment of its movements to compensate for errors requires complicated signal processing and computing of inputs from multiple sensors. However, for artificial nerves, sensors can be integrated into the system itself and can both detect stimuli and provide feedback during signal processing. As an example, proprioceptive feedback from mouse leg muscles connected to an artificial efferent nerve can be exploited to control the signal potentiation ratio in the artificial synapse and thereby prevent the muscle from developing unwanted tetanic behaviour¹⁹. This feedback mechanism enabled the artificial nerve to modulate motor behaviour in paralysed mice. The mice regained not only their leg movement but also the ability to walk and run¹⁹ (Fig. 2b).

Future technological goals

Current research mainly focuses on artificial nerves that exploit neuromorphic electronics to enable them to communicate with prostheses. However, this concept is still in its early stages of development and several important challenges remain to be overcome. In particular, considerable research is focusing on the development of bio-interactive prostheses that can intuitively emulate natural biological functions.

Reduced complexity of signal processing

Increasing the precision of paralysed or artificial limb movements requires the development of high-resolution sensors that can detect high-density external stimuli and neural signal recording sensor arrays. These arrays must collect signals from many channels (Fig. 3a). Electrophysiological signals are in analogue form and are difficult to interpret owing to their small amplitude and noise, which makes them vulnerable to attenuation and the accumulation of additional noise (such as thermal noise) during signal transmission. Moreover, when signals collected at high sampling rates are transmitted from many channels to a centralized computing unit, the resulting transmission of large amounts of data can result in latency, insecurity and high power consumption¹⁷¹. Additionally, processing these analogue signals using conventional von Neumann digital computing units involves numerous steps of signal conversion and transmission, which further slows the process and increases energy requirements.

Processing-in-memory methods, such as in-sensor processing and near-sensor processing, could overcome this disadvantage. These methods process and compress data within or close to the sensors before transmission¹⁷² (Fig. 3a). By reducing the noise that accumulates during signal transmission and transmitting preprocessed and compressed data, these approaches can reduce both latency and the energy cost of substantial data transmission¹⁷³. One intelligent sensor network that emulates biological sensory systems directly processes incoming analogue signals without first converting them to digital form¹⁷⁴. This intelligent system enables neuromorphic localized signal processing, which reduces latency, power consumption and circuit complexity.

Intelligent systems with intensity-dependent and time-dependent plasticity characteristics enable the direct preprocessing of sensory information at a low-level stage, unlike conventional sensors that merely convert the intensity of stimulation into linear electrical signals for subsequent processing by back-end memory and processors¹⁷⁵. The front-end processing units perform preliminary low-level data processing, including noise and artefact reduction, filtering, background suppression and feature enhancement. The preprocessed data are then transmitted to back-end signal processing units for high-level processing, which enhances the computational efficiency of post-signal processing¹⁷⁶.

Near-sensor or in-sensor signal processing implemented by neuromorphic processors composed of artificial synapse arrays can provide an interface between sensors and post-processors that enables the preprocessing of the sensor's analogue signals at low power without complex and unnecessary signal conversion. Artificial nerves have demonstrated the potential for near-sensor and in-sensor processing of external stimuli, which represents a foundational step in the development of intelligent artificial nerve systems that are capable of processing complex biological signals. For example, an artificial mechanosensory nerve array composed of pressure sensors, artificial neurons and artificial synapses can form receptive fields where synapses integrate the signals from multiple neurons for preprocessing¹⁸. This near-sensor signal processing approach has shown potential for improving the accuracy of Braille recognition compared with systems that do not use artificial synapses. Another in-sensor neuromorphic processor that comprises vertically integrated pressure sensors and memristors carries out preprocessing of analogue signals from the pressure sensors in real time, which reduces noise in tactile patterns and detected edges and results in superior contrast enhancement, noise reduction and improved pressure pattern recognition rates¹⁷⁷. Optoelectronic in-sensor processing that emulates the functions and hierarchical connections of photoreceptors and bipolar cells in the retina enables real-time primary processing of visual information that results in image contrast enhancement and noise reduction^{175,178}. Moreover, multimodal sensory systems that simultaneously receive sensory information from various sources can exhibit improved recognition accuracy and reduced system complexity compared with single-sensor systems¹⁷⁹ as well as an increased dimensionality of the tasks that can be performed¹³⁰. These near-sensor and in-sensor neuromorphic sensory processors contribute to the development of advanced bio-interactive artificial nerve prostheses by providing both increased signal processing efficiency and improved perception accuracy in relation to sensory information^{18,149}.

Even in devices that use in-sensor and near-sensor signal preprocessing using intelligent multimodal sensors, the use of conventional back-end processors that rely on von Neumann architectures for high-level tasks can still hinder further improvements in processing efficiency. The use of neuromorphic devices to perform both low-level and high-level signal processing can considerably simplify circuit design and increase the device integration density. For instance, images can be preprocessed by front-end optoelectronic memory arrays that emulate the functions of the biological retina and then routed to back-end high-level image processors that use in-memory processing units, thereby increasing the speed and reducing the energy cost of signal processing¹⁸⁰.

Considerable research has been conducted on near-sensor and in-sensor processing systems that detect external multimodal stimuli, but strategies to increase the efficiency of processing of complex neural

signals remain largely unexplored. This gap must be addressed in the development of advanced, high-functionality, motor neural prostheses and bidirectional neural prostheses.

Communication with the body

Although bidirectional signal transmission has been achieved in bio-interactive prostheses (Box 2), participants must still undergo multiple learning sessions to map the artificial stimulation onto the sensory information from biological nerves^{10,13,14,181}. The biological nervous system can adapt to new sensory mappings, but whether people with amputations or spinal cord injuries can learn (from scratch) the extensive and complex information required to control each degree of freedom of movement of a prosthesis remains untested. To solve this problem, a method should be developed to enable communication between the body and the prosthesis without the need for additional signal-transducing devices or circuits. This advanced capability would open possibilities for future improvements by integrating increasingly natural and increasingly intuitive control mechanisms. In such systems, feedback loops enable precise control of the prosthesis by continuously sensing and responding to the status of both the prosthesis and the user's body, to ensure accurate and responsive movements.

Biologically compatible signal transmission. Mimicking of biological signal transmission is essential to ensure the seamless integration of a prosthesis with the nervous system (Fig. 3b). This approach results in intuitive and efficient communication that increases the functionality and usability of bio-interactive prostheses. Researchers have demonstrated that memristors can exhibit most of the known dynamics of biological neural systems¹⁸². Specifically, 23 types of biological neural behaviour have been experimentally demonstrated¹⁸².

To synchronize the active signal with biological cells, three-terminal artificial synapses have been created that connect previously uncoupled neurons by mimicking biological synaptic plasticity¹⁸³. Activity-dependent coupling eliminates the need for complex circuitry at the user–prosthesis interface. Moreover, artificial synapses can both modulate spiking probability and delay spike generation, capabilities that closely resemble the functions of biological synapses and therefore permit the emulation of biological signal-transmission processes. Such artificial synapses also eliminate the need for the bulky hardware and complex processing used in conventional approaches⁷⁸, and thereby facilitate the development of advanced bio-interactive prostheses. Artificial components that are intended to operate in biologically relevant environments and maintain physical, functional and temporal proximity with biological components must also interact in real time with biological parts. For example, connectivity with biological cells could be facilitated by the capacity to directly detect neurotransmitters such as dopamine, which would enable the immediate detection of biological neural signals^{126,184,185}.

In one proposed conceptual approach, features of the biological neural network could be 'copied' and 'pasted' onto a neuromorphic system to create a hybrid neural connectivity map¹⁸⁶. The functional synaptic connectivity map is first extracted from a biological neural network recorded from a nanoelectrode array¹⁸⁷. This map could then be transferred to a network of neuromorphic devices, in which each device stores the connection strength of a corresponding biological synapse. A similar idea involves recording the connectivity map generated from a nanoelectrode array and directly imprinting this map onto memristors, thereby bypassing the extraction process. Although this concept has not yet been realized, its groundbreaking aim is to

construct an electronic brain via the direct engineering of neural connectivity. The structures of such electronic brains could replicate the functional complexity of neurons by implementing characteristics of biological neurons, including ion-channel activity, routing and delay. This approach could eventually generate neuromorphic systems that function in the same way as biological neurons and are, therefore, highly suitable for communicating biological signals.

The development of artificial nerves that mimic the characteristics of biological neurons has already achieved a more-natural signal transmission than traditional methods such as FES. By seamlessly coupling disconnected nervous systems and mimicking the characteristics of biological neurons, artificial nerves offer a promising avenue for the development of next-generation bio-interactive prostheses.

Feedback loop communication. The incorporation of internal sensing of the prosthesis status provides a feedback mechanism that enables the prosthesis to adjust and adapt in real time, which results in smooth and continuous movements that closely mimic natural motion patterns (Fig. 3b). A prosthesis that can constantly monitor its own status could also detect and respond to changes or abnormalities.

Artificial nerves have also been evaluated for control of the body's homeostatic functions. In one study, artificial nerves that detected glucose and insulin levels could regulate a negative feedback loop necessary for maintaining homeostasis¹⁸⁸. This advanced capability enables the continuous monitoring and adjustment of physiological parameters to ensure that the body remains in a balanced state. Other negative feedback mechanisms, such as thermoregulation and blood pressure regulation, could be fulfilled by a body cooperating with an artificial nerve.

Proprioception is essential for motor activities such as standing and walking. Without proprioceptive feedback, locomotion deteriorates, muscles can be damaged and interactions between prosthesis users and their environment are suboptimal. Furthermore, a lack of appropriate proprioceptive response results in clumsy physical activity¹⁸⁹. An artificial proprioceptor has been designed to detect leg movements and prevent the over-extension of leg muscles under the control of an artificial nerve¹⁹. This artificial proprioceptor, in conjunction with an artificial synapse, forms a sophisticated feedback loop that mimics the natural sensory feedback mechanisms found in biological systems. This system increases the precision and adaptivity of responses to changes in muscle movement and contraction force, which helps prevent muscle damage and substantially improves the user's ability to perform complex motor tasks such as walking, running and kicking a ball¹⁹. The continuous feedback and adjustment enabled by this technology could markedly increase the intuitiveness and naturalness of movement, as well as improving interaction with the environment.

Importantly, artificial nerves trigger action potentials that travel simultaneously in both distal and proximal directions^{17,190}. Therefore, generated proprioceptive feedback and motor neuron activity can potentially cause signal interference that results in the loss of robust control. To avoid the cancelling out of proprioceptive feedback owing to signal overlap, the external electrical signal used to generate neuron activity can be spatio-temporally controlled¹⁹¹, for example by delivering a signal that has a sufficiently low amplitude and sufficiently high frequency to secure excitatory postsynaptic potential. Another possible approach involves the regeneration of cancelled proprioceptive feedback simultaneously upon providing motor signals. Finally, the action potential signals emitted by artificial nerves must not disturb

any biologically generated signals. The generation of biologically compatible feedback signals remains an ongoing challenge in artificial nerve research.

Seamless integration and biocompatibility

Artificial nerves that implement near-sensor and in-sensor processing must be positioned as close as possible to the signal source to reduce data transmission distances, minimize noise and efficiently process sensory and motor neural signals. As the signal source is on or inside deformable body tissues, these devices must be both flexible and stretchable to seamlessly integrate with the body (both externally and internally) and to minimize signal artefacts and noise caused by the host's activities. Additionally, to ensure stable long-term operation in both external and internal environments, these devices must be made of biocompatible materials (Fig. 3c).

Body parts that are critical for movement and sensory detection, such as the hands and knees, have high degrees of freedom and undergo considerable stress. Therefore, highly effective and intuitively functioning bio-interactive prostheses must be composed of highly reliable materials that can operate stably under these challenging conditions. Many studies have focused on neuromorphic devices that combine flexible sensors and memory arrays¹⁹², but few have described neuromorphic devices that operate stably under strains exceeding 5% (for reference, depending on its location on the body, the skin can experience strain of up to 40%¹⁹³). Research on sensory synapses for low-level processing, excluding those that sense strain, is still insufficient. Specifically, research on stretchable memory arrays for high-level processing is rare, possibly because memory arrays that are highly tolerant to strain are challenging to create given that the weights stored in the memory arrays have a critical effect on computation. Methods of increasing strain tolerance include the deposition of one-dimensional semiconductor and electrode materials in serpentine shapes^{19,98} and the use of compensation circuits¹⁹⁴. However, these approaches might limit miniaturization and increase the complexity of neuromorphic systems. An alternative idea is to use inherently stretchable polymers and nanomaterials^{97,195}. Polymer blends composed of semiconducting conjugated polymers and polymers with a low Young's modulus have been used as active materials to create stretchable synaptic transistors. A one-dimensional single nanowire or nanofibril network embedded in an elastomer matrix demonstrated reliable characteristics under mechanical strains of up to 100%^{19,97,98,196}. Additionally, a conjugated polymer with a moderately flexible polythiophene backbone did not develop cracks even under 100% strain, so a device that uses this material could operate stably under such conditions¹⁹⁷.

e-skin devices offer advanced characteristics and functionalities that traditional complementary metal–oxide–semiconductor-based electronic devices cannot provide¹⁹⁸. Therefore, e-skin is suitable for applications in the biomedicine, wearable robotics, healthcare, augmented reality and virtual reality fields. Nevertheless, improvements are still needed in e-skin electrical properties and long-term stability at the material level, memory retention at the device level, and integration density and processing technology at the system level.

Outlook

The development of artificial nerves presents considerable advantages for the field of bio-interactive prostheses. By mimicking the behaviour of biological nerves, artificial nerves enable more-direct and more-intuitive operation of prosthetic devices than is possible using conventional methods. The use of artificial nerves increases the

Glossary

All-or-none law

The principle that stimulation of a single nerve fibre always results in a maximal response; thus, an increased intensity or duration of stimulus does not alter the amplitude of the resulting electrical impulse.

e-skin

A type of thin-film device that mimics the high elasticity of the skin as well as its sensory receptors and actuators.

Integrate-and-fire model

An input current causes the neuronal membrane voltage to increase over time until it reaches a preset threshold, at which point an output electrical impulse occurs and the membrane voltage resets to its resting potential; more-sophisticated versions of this model incorporate various adaptation variables.

accuracy of signal processing, minimizes power consumption and enables coherent communication. Traditional prostheses often struggle to provide effective signal matching between biological nerves and the prosthetic device, primarily because of the inherent complexity of biological signals and their noisy nature¹⁹¹. This mismatch complicates the decoding and interpretation of biological signals and causes difficulty in achieving precise prosthesis control and adaptive responses^{11,12,199}.

Artificial nerves reduce the complexity of the processes of decoding and interpreting biological signals. This simplification can lead to an increase in the accuracy and reliability of communication between the prosthesis and the user's nervous system. By emulating the functions of biological systems, artificial nerves increase biocompatibility and reduce both errors and power consumption^{18,19}. Near-sensor and in-sensor processing can also clean up noisy signals and increase the reliability of signal transmission to the prosthetic device, thereby increasing the accuracy and responsivity of control. Artificial nerves that are designed to be biocompatible and flexible can integrate seamlessly with the body's tissues and withstand the mechanical stresses of movement. Moreover, artificial nerves that communicate with biological nerves through modalities other than electrical signals could greatly increase the versatility and effectiveness of artificial nerve systems. For instance, artificial nerves that detect and interact with biomolecules such as neurotransmitters, antigens and nucleic acids could facilitate communication with their biological counterparts²⁰⁰. These expanded abilities could include reading signals electrochemically^{201–203} using piezoelectric methods^{204,205} or applying other techniques to detect biomolecules²⁰⁰.

Preliminary results have demonstrated the feasibility of using artificial nerves for direct communication with biological systems^{18,19,97}. This approach could overcome the limitations of current bio-interactive prostheses by providing a naturalistic interface that adapts and responds to the user's needs in real time. The use of flexible, biocompatible materials further ensures that these devices can operate stably under the mechanical stresses of daily use. In particular, the artificial nerve must be wearable or implantable to enable in-sensor or near-sensor signal processing, which greatly increases the efficiency of a bio-interactive prosthesis. Thus, all materials used in artificial nerves must be soft and stretchable. In addition, the materials must have low cytotoxicity and immunogenicity to avoid long-term adverse effects when mounted on the skin or implanted in the body^{206,207}. Encapsulation materials must also be developed that can prevent biofluids from degrading the performance of artificial nerves without limiting the

mechanical stretchability of wearable and implantable devices, such as encapsulants based on elastomers with low water vapour transmission rates and low ionic conductivity.

The aim of using artificial nerves is to move away from purely mechanical prosthesis solutions and towards seamlessly replacing the functions of damaged nerves while preserving the body's natural form and function. The goal of this approach is the restoration of natural sensation and movement via a direct interface with the nervous system. This shift from mechanical to neural prosthesis represents a transformative step in the design and functionality of bio-interactive prosthesis technologies. Solving the existing challenges will enable the development of prosthetic devices that offer natural, intuitive and responsive control as well as novel methods of communication with biological systems. This vision holds great promise for improving both the user experience and quality of life for individuals with neurological impairments including limb loss, spinal cord injury and paralysis.

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Competing interests

The authors declare no competing interests.

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