IMPLANTED DEVICES

Ultrasound-powered tiny neural stimulators

Wireless and leadless millimetre-scale implantable pulse generators, powered and controlled by ultrasonic links, enable the electrical stimulation of neural pathways in anaesthetized rats.

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A promising approach for restoring impaired bodily functions is to artificially input information into selected neural pathways. This can be achieved non-invasively through transcutaneous stimulation[1], but only for superficial nerves and with limited neural selectivity. Implantable devices that target neural pathways selectively are thus desirable, but their development has been hindered by a myriad of technological challenges. A device aiming to artificially introduce information into the nervous system must be comprised of at least an electrode and a stimulator (Fig. 1). The stimulator requires power for delivering electrical pulses on demand via a control logic; however, the inclusion of a power supply (such as a battery) and dedicated electronics results in large devices that must remain external to the body and away from their neural targets, with centralized units connected by leads to percutaneously implanted electrodes. Although a percutaneous approach can remain functional for several years and be useful in a research setting for short-term applications[2], it is a sub-optimal solution as the leads can be easily pulled out and are an infection risk. Fully implantable systems with a centralized stimulator and embedded battery, although avoiding percutaneous components, must be placed in a spacious anatomical location and still require leads to reach the neural targets. Although considerable work has been devoted to optimizing leads and connectors[3] — as their failure can compromise the whole system — currently not all neural targets are accessible with this approach.

By using wireless electromagnetic links for power and communication to an external controller, small (millimetre scale) and distributed implantable stimulators have eliminated the need for leads, batteries and a centralized stimulation unit[4–7]. In this approach, each device has its own stimulation unit and electrode, and thus can be distributed independently of each other and in direct proximity to neuromuscular targets. Nevertheless, current distributed implantable stimulators use relatively inefficient passive components, deliver voltage-controlled pulses that are dependent

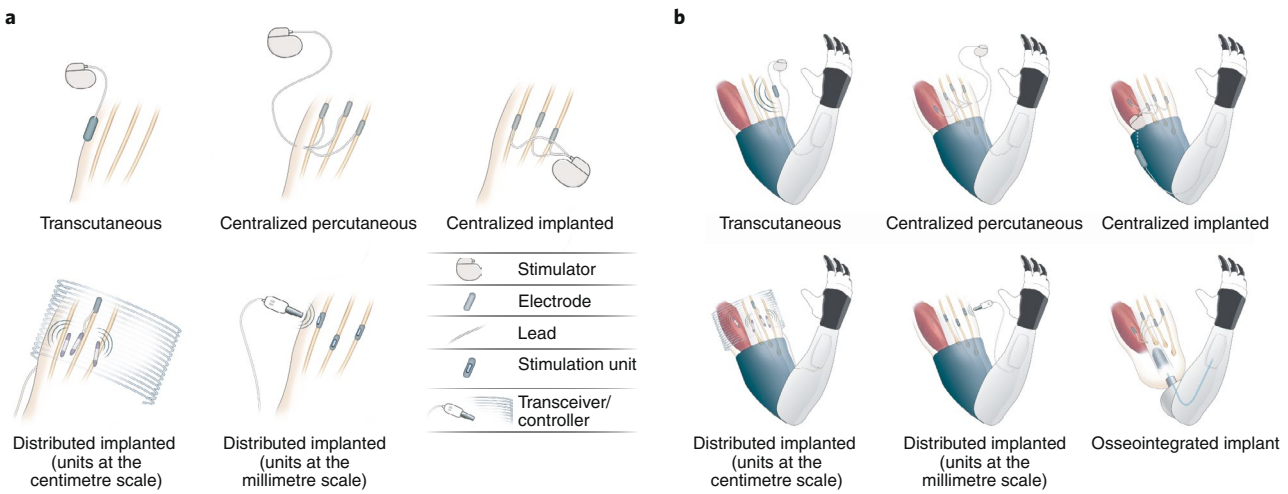

Fig. 1 | Neural interfacing technologies and their use for inputting somatosensory information from a prosthetic hand into the severed nerves of a person. **a**, Transcutaneous: stimulation is delivered via an electrode over the skin and thus no component is implanted[1]. Centralized percutaneous: the electrodes are implanted on the neural targets, but the stimulator remains external to the body; therefore, the leads must cross the skin percutaneously to link the electrodes with the stimulator[2]. Centralized implanted: the electrodes and stimulator are implanted with leads connecting each electrode to a centralized unit that communicates wirelessly with an external controller. Distributed implanted (centimetre scale): several stimulation units with embedded electrodes[4,5] or extension leads[15] are placed on neural targets and powered by a wireless link that also commands their activation. Distributed implanted (millimetre scale): several stimulation units embedded with electrodes that are powered and commanded wirelessly using electromagnetic[6,7] or ultrasonic[8] links. Some implanted stimulators can also be injected. **b**, The same neural interfacing technologies as in **a**, implemented to transmit information from a prosthetic hand attached via a socket. Lower right panel: osseointegrated implant for skeletal attachment and bidirectional communication with implanted electrodes[12]. The prosthesis is attached via an osseointegrated implant. Sensors in the prosthetic hand gather tactile and proprioceptive information collected by a central controller. The controller commands the neural stimulator to input the somatosensory information into the severed nerves at the stump of the subject by a predefined encoding algorithm. Image courtesy of Jason Millenaar.

of the power received (limiting precision), lack monitoring capabilities for securing an effective delivery of stimulation and are limited to superficial placements owing to the limited range of electromagnetic links. Writing in *Nature Biomedical Engineering*, Muller and colleagues describe a wireless, millimetre-scale and current-controlled stimulation unit within a neural electrode[8] for selective, precise and self-contained neural stimulation. The device, which the authors named 'StimDust', does not require leads or batteries and can be implanted at centimetre depths owing to the use of an ultrasonic (rather than an electromagnetic) wireless link.

The StimDust system comprises a piezoceramic transducer, an energy-harvesting capacitor and an integrated circuit, all contained within a volume of 1.7 mm^3. The capacitor is used to secure the proper powering of the integrated circuit, which in turn controls the current stimulation for delivery independently of the power received. The small size of the integrated circuit was optimized by avoiding registers to store stimulation parameters, which are instead obtained in real time from the wireless ultrasonic link. No battery is needed within the device as it uses the ultrasonic link for powering its operation and for the generation of electrical stimulation pulses. The same ultrasonic link provides binary feedback on the state of the stimulators to the external controller. Whereas stimulators typically rely on an embedded clock to ensure accurate stimulation timing, the StimDust decodes the shape of the incoming ultrasound envelope for timing, thus saving power and allowing for greater flexibility in stimulation protocols than when pre-programmed registers are used.

Muller and co-authors show the operation of the device at a depth of 55 mm through heterogeneous layers of tissue explanted from a porcine hind limb (in an ultrasound gel, the maximum operation depth was 70 mm). In in vivo measurements in three anaesthetized rats with StimDust devices implanted in the sciatic nerve, the authors observed the generation of compound action potentials at amplitudes dependent on the stimulation parameters (a varying amplitude of 50–400 μA with a fixed 392 μs pulse width, and a fixed amplitude at 400 μA with a varying 12–392 μs pulse width). The authors also observed different muscular activation responses dependent on the stimulation frequency: single twitches up to 10 Hz, an unfused tetanus at 32 Hz (that is, when the muscle fibres do not completely relax before the next stimulus), a fused tetanus at 100 Hz and 320 Hz (that is, when there is no relaxation of the muscle fibres between stimuli during high-rate stimulation) and an initial twitch followed by relaxation (interpreted as a potential nerve block) at 2 kHz and 2.2 kHz (stimulation pulses of 52 μs and 400 μA).

To avoid adverse tissue reactions resulting from the toxic materials that are typically used in electronic devices, the electronic components of StimDust were coated in parylene and the electrode was electroplated in poly(3,4-ethylenedioxythiophene) polystyrene sulfonate. Whereas such measures are usually enough for animal experimentation, more stringent measures are needed to ensure long-term biocompatibility in humans, such as the hermetical sealing of the stimulation unit and the application of electrical communication only via sealing feedthrough connectors. These two challenges could considerably increase the size of a millimetre-scale implantable device. Hence, a major challenge for the clinical translation of StimDust will be for it to comply with regulatory requirements on biocompatibility while preserving its compact size and reported performance. Notably, although distributed centimetre-scale implantable stimulators had been implanted in humans[5], none of the smaller distributed technologies have reached that stage.

Interfacing severed nerves with an artificial limb for control and sensory feedback is one application where both recording and stimulation are required. Such closed-loop control is a feature that distributed implanted devices still lack, as current distributed devices were designed for either recording or stimulation. Inputting information in severed afferent nerves has restored somatosensory perception to varying degrees using transcutaneous[1] and percutaneous[2,9,10] stimulation, whereas distributed implants have been used for recording motor intent alone[11]. Whether an analogous millimetre-scale device with recording capabilities only[12] (known as 'Neural Dust') and StimDust can be used simultaneously for recording and stimuation is unknown. Alternatively, osseointegrated implants for the skeletal attachment of the prosthesis and bidirectional communication with implanted electrodes allow for both recording and stimulation[13].

Wireless technologies that allow for distributed implantable devices solve problems associated with power and transcutaneous communication. Yet achieving highly selective stimulation — a major issue in neuroengineering — remains a significant obstacle[14]. Current neural electrodes can only interface a small fraction of the ensemble of axons within their hosting nerve[14]. More importantly, a fundamental constraint for increasing stimulation selectivity is the difficulty in constraining the propagation of electric fields in the conductive neural milieu. Unless the selectivity problem can be solved, inputting information into neural pathways will continue to be sub-optimal via blunt stimulation of mixed-nerve fibre types. ❐

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Competing interests

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