Implantable Microsystems for Monitoring and Neural Rehabilitation, Part II

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Miniaturised implantable biomedical microsystems are opening up completely new markets for diagnosis and therapy products. Part II of this article discusses recent work on distributed intelligent implants and biohybrid systems, which combine microsystems with cells and tissues.

Emerging new markets

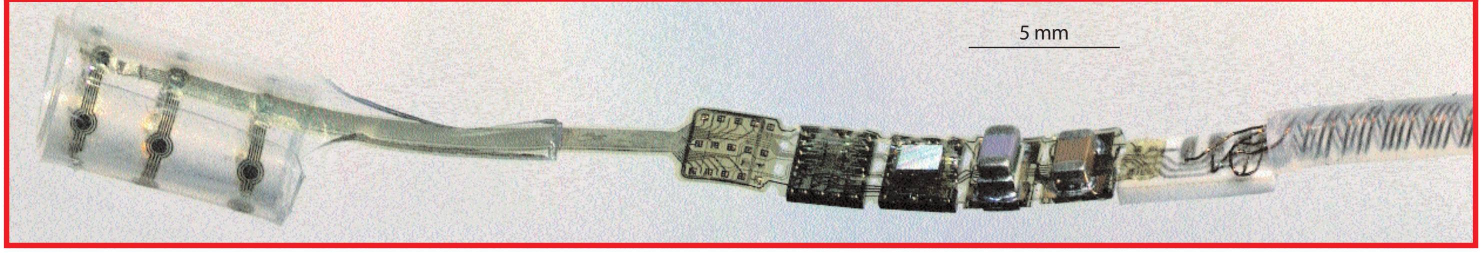
Miniaturisation gives new potential to implants for neural rehabilitation. Implantable stimulators for the prevention of drop foot after strokes, the restoration of limb function after paralysis and the control of artificial limbs after amputation trauma are a few examples of this new market. This two-part article highlights some exciting developments in miniaturised implantable biomedical microsystems. Part I described microdevices for diagnosing and monitoring blood, brain and intraocular pressure inside the body, and a retina implant system. Part II looks at two recent developments: a distributed neuroprosthesis for the restoration of skeletal muscle function and a biohybrid system for functional neural rehabilitation.

Distributed implants and intelligent electrodes

Most neural prostheses consist of one central implant connected via a restricted number of cables to the recording and stimulation electrodes. For several applications such as the ability to grasp or to stand-up-and-walk it would be better to have a number of distributed implants that are implanted in different locations in the body. It is preferable to control these implants using a wireless link rather than cables, which would increase the level of surgical complexity and the risk of cable breakage. Surgical interventions increase the risk of infection, and procedures in the spinal cord or brain such as the implantation of a sacral anterior root stimulator increase the risk of leakage of corticospinal fluid. For these reasons, a design for distributed implants that can be controlled by one external control unit is under development.

If only one external unit is used for the transmission of energy and data via an inductive link to the different implants, it is necessary to generate a magnetic field of sufficient strength through the coil of each implant. This means that two or more smaller external coils or one large external coil are required to produce a suitable magnetic field. This type of system needs a great deal of energy and is not comfortable for the patient to wear. To solve this problem, a "guide" for the magnetic field can be pro-

Figure 1: Intelligent electrode system with 18-polar cuff electrode (left), multiplexer circuitry (middle) and four-strand Cooper cable (right).



vided. The coil of the external system is placed in the front abdomen area to ensure a comfortable placement without a lot of pressure on the skin. One implantable coil is placed subcutaneously beneath the external coil to guarantee a good magnetic coupling. The subcutaneous coil is connected to satellite implanted coils via cables. These satellite coils are placed near the active implants to provide an inductive link. An implantable stimulator system previously developed at the Fraunhofer Institute for Biomedical Engineering was modified to extend it into a distributed stimulator system. The system was modified to permit collision-free communication between the external control unit and the different implants, thus enabling the continuous modulation of the stimulation parameters and the simultaneous stimulation of more than one implant. It was necessary to change the transmission protocol of the inductive data interface and the software of the stimulator's on-board micro-controller; the stimulator hardware could be used with only minor changes.

At the other end of the implantable stimulators, the number of cables often limits the number of electrodes from one contact site to the nerve. Because of this constraint, the idea of a smart electrode with integrated intelligence was born. In the first design of a modular system (see Figure 1), an 18-polar hybrid cuff electrode was connected to a miniaturised multiplexer circuitry that reduced the number of cables from twelve to four.[1,2] Further designs could integrate current sources or amplification units, depending on the application.

Biohybrid systems

The combination of microsystems with biological cells and tissues, known as biohybrid systems, has become an interesting research area. These systems have helped increase understanding of bioelectronic mechanisms and the development of new analysis systems and therapies for diseases that, so far, have not been treatable, for example, peripheral nerve lesions that result in flaccid paralysis.

Recent work on a biohybrid system aims to provide functional neural rehabilitation after peripheral nerve lesions. The traumatic lesion of a peripheral nerve interrupts bioelectrical signal transmissions and leads to paralysis and the degeneration of the truncated axons in the distal nerve stump. Healing a lesion of this type can occur only under favourable conditions and involves the outgrowth of axons from the proximal nerve stump, sprouting along the distal nerve stump as a guidance structure, and the reinnervation of the target muscles. For cases where natural or neurosurgical-assisted healing is not successful, embryonic spinal cord cells have been transplanted into a container made of a piece of a vein, which is placed at the distal nerve stump to restore skeletal muscle function.[4, 5] If control of the reinnervated muscles is desired, technical systems can help to electrically stimulate the neurons.

A biohybrid neuroprosthesis was conceived for the restoration of skeletal muscle function after peripheral nerve lesions (see Figure 2). The neuron microprobe measuring 2mm in diameter consists of a microfabricated flexible polyimide structure with microelectrodes and integrated biological cells (guest neurons and glial cells in a container structure). This microsystem is intended to be implanted on the distal nerve stump. The axons of the guest neurons will grow through the holes in the polyimide sieve into the distal nerve stump to reinnervate the muscle. Signals on the axons of the guest neurons will be recorded from the ring electrodes that surround some of the holes in the polyimide sieve. The coupling between the electronic and biological systems utilises a biohybrid approach: the coupling of ring microelectrodes and axons of specially primed neurons, which then achieve coupling to the target muscle. Thus, the guest neurons serve as mediators for a long-term, functional coupling between the microelectrodes and target muscles.

At the end of the micromachining

Figure 2: The concept of the neuron microprobe, a biohybrid system to restore nerve regeneration after peripheral nerve lesion.

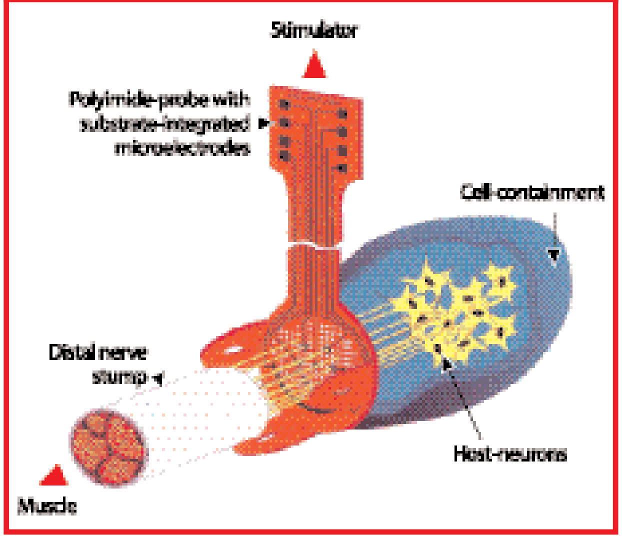
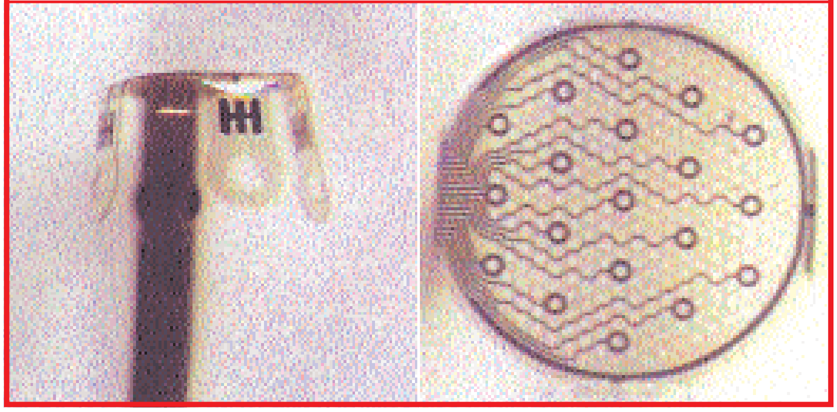


Figure 3: Implantable polyimide-based microstructure with integrated electrodes for recording and stimulation. Left: device with flaps for nerve fixation, counter electrodes integrated onto the straps; right: 19 ring electrodes distributed over the sieve.



process the polyimide sieve structures are planar (flat). The flaps for fixation and the cable were bent in a thermal treatment to an angle of 90° with respect to the sieve area (see Figure 3) to allow an adaptation, that is, a tight neurosurgical fixation of the microprobe with neurosurgical sutures on the nerve. Counter electrodes were placed on each flap and the interconnecting cable. They were connected to a single contact pad and 19 ring electrodes were distributed over the sieve area with 286 holes arranged in a hexagonal shape. So far, more than 100 sieve like devices have been fabricated in small series production. After adaptation of the microprobe on a nerve, the container made of a piece of a vein is fixed on the nerve microprobe assembly and cells injected into that container.

Biocompatibility in chronic implantations has been demonstrated at the proximal nerve stump of an amputee, that is, the nerve stump above the lesion site.[6] Electrophysiological evaluation of the peripheral nerve was conducted 11 weeks after implantation. Compound nerve action potentials have ben recorded from the sieve electrodes after stimulation of the nerve in the vicinity of the spinal cord. Later, electrical stimuli over the sieve electrodes elicited somatosensory-evoked potentials that were recorded with subcutaneously placed needle electrodes. Ongoing work will focus on implantation with cell containers and cell-electrode coupling to monitor cell behaviour and stimulate regenerated axons.

The future

Because the number of elderly people in society is steadily increasing, the topic of incontinence and neuromodulation will gain significant importance. Looking towards biohybrid systems, the combination of microsystems with cells and the tools and methods from molecular biology and biotechnology suggest many applications in diagnosis and therapy. Drug delivery and release via implantable transgenic cells could allow more efficient as well as patient-specific treatment of diseases. Monitoring systems could be included in prostheses and other technical implants to help patients stay as healthy as possible during rehabilitation and after in daily life.

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