

Implantable Microsystems for Monitoring and Neural Rehabilitation, Part I

Thomas Stieglitz

Fraunhofer Institute for Biomedical Engineering, St Ingbert, Germany

Miniaturised implantable biomedical microsystems are offering completely new product possibilities for diagnosis and therapy. Some of the latest developments are discussed here. Part I of this two-part article describes microdevices for diagnosing and monitoring blood, brain and intraocular pressure inside the body, and a retina implant system.

Tracking today's reality

For a long time, humans have dreamed of monitoring body functions and performing surgical interventions with tiny systems. In the science fiction movie *Innerspace* (1987) scientists build a submarine that is miniaturised so that it can travel inside the body. Today, this fiction has almost become a reality. Miniaturisation has been driven by the microelectronic developments of memory chips and microprocessors. Using micromachining methods, a microsubmarine of approximately 2 mm was built in 2000 by Microtec

(Duisburg, Germany) (see Figure 1).¹ However, form without function is not enough. If electronic and mechanic components could be included to develop a real micro-electromechanical system, the dream of monitoring a journey through the human body may become true in the near future. This two-part article describes some remarkable system approaches that demonstrate developments in implantable biomedical microdevices.

Invasive monitoring

Monitoring body functions is an

essential tool in medical diagnosis. Repeated measurement of blood pressure at short intervals is mandatory for some diseases. However, often these measurements are accompanied by procedures that can stress patients and consequently may falsify the results or prevent patients from sleeping when applied during a 24-hour monitoring period. As a result, changes may only be detected when organs have already been damaged. Microsystems offer the opportunity to miniaturise the functional components and integrate data acquisition and transmission into microelectronic circuitry. If these microsystems become implants, continuous measurement would be possible after just one surgical intervention, which could be a minimally invasive surgical procedure.

Monitoring blood and brain pressure

An invasive system for monitoring intracorporeal pressure consists mainly of a sensor that is connected to a telemetric unit. One basic implantable microsystem to monitor pressure has been developed in a German joint project for an

Figure 1: Microsubmarine built by Microtec.

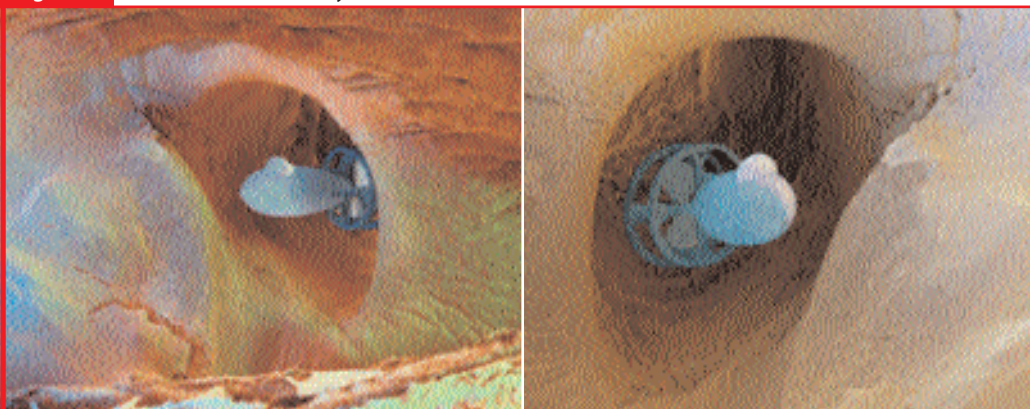


Figure 2: Implantable telemetric endosystem to monitor pressure, for example, intravasally. Left: schematic view; right: components of the prototype.

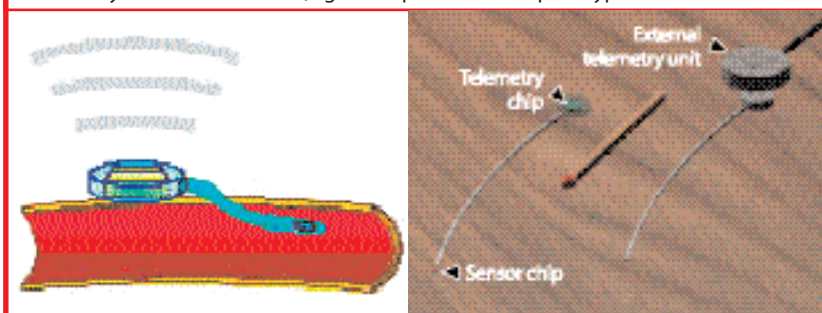
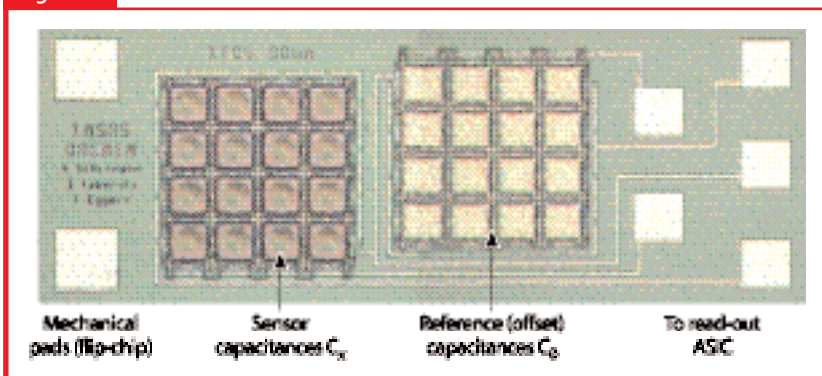


Figure 3: Pressure sensor.



implantable telemetric endosystem (ITES).^{2,3} The technical concept is based on the inductive telemetric transmission of energy to an implant, and the transmission of data through the skin to an external monitoring and data logging unit using a passive absorption modulated method (see Figure 2).⁴ The application specified integrated circuits (ASICs) were based on silicon semiconductor technology. They were assembled on a 50-micron thick polyimide substrate. The pressure sensor chip (0.8 mm x 2.0 mm) at one end of the device was made with surface micromachining methods. It was directly connected to a read-out electronics chip (0.8 mm x 2.0 mm). The complete implant was approximately 60 mm long and 0.7 mm wide (interconnection between telemetry chip and sensor). This design eliminates the need for an active power source such as a battery, which limits the lifetime of the implant. The disadvantage of inductive transmission is the short operation distance of only a few millimetres, which is a direct result of the magnetic near-field effect.

The pressure sensor (4.6 mm x 7.1

mm) that has been developed in the same project (see Figure 3) was fabricated with surface micromachining in a standard complementary metal oxide semiconductor (CMOS) microelectronics process. It was designed as a capacitive pressure sensor that must be connected to a read-out electronics chip and requires a telemetry chip to connect it to the ITES.⁵

Monitoring intraocular pressure

One of the major causes of blindness in the West is pathologically increased intraocular pressure, commonly called glaucoma. The loss of vision is caused by the apoptotic death of nerve fibres from the retinal ganglion cells, which is a result of elevated intraocular pressure. Glaucoma is responsible for the loss of vision in 15% of the registered blind people in Germany. The disease does not usually cause pain or any other symptoms except loss of vision in the later stages. Therefore, glaucoma has typically already destroyed more than 80% of the nerve fibres before it is detected.⁵ Using microsystem technology, some research groups have

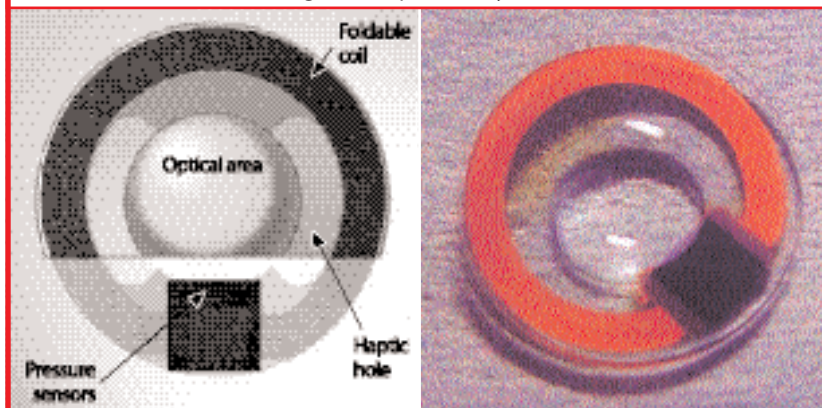
worked on intraocular pressure sensors that were built as implants in the shape of an artificial intraocular lens (see Figure 4).^{6,7} These implantable systems are currently undergoing clinical trials as long-term implants in animals. Continuous pressure monitoring allows the objective control of therapy strategies in glaucoma and may give insights into the mechanisms of glaucoma.

Functional neural rehabilitation

Neural rehabilitation is another application field for implantable microdevices. Diseases and traumatic incidents may lead to damage or lesions in the central or peripheral nervous system. When the information flow between the brain, spinal cord, nerves, biological sensors and actuators, and muscles is interrupted, sensoric inputs are lacking and vision or hearing is lost. If motor commands from the brain do not reach the muscles, paralysis occurs. The objective of neural rehabilitation is the restoration of lost functions using therapeutic programmes and technical aids. Because of the tremendous complexity of the human nervous system, technical aids only lead to restricted restoration in function. However, what may seem to be a small improvement to a healthy person may be a great improvement in quality of life for a disabled person.

Neural prostheses are one group of technical aids. These are technical systems that interface with nerves and muscles to record bioelectric signals or electrically stimulate the nerves and muscles. Implantable stimulators and electrodes of this type have been established for more than two decades. Heart and phrenic pacemakers can restore vital functions and neuromuscular stimulation can help paralysed people to micturate or to grasp. Sensory neural prostheses such as the cochlea implant are used in clinical practice and electrical stimulation has been introduced to allay chronic pain or to suppress tremor in Parkinson's disease. So far, the following implantable systems have been developed and optimised separately:

Figure 4: Implantable pressure sensor with telemetric system in an artificial intraocular lens. Left: schematic overview; right: the implantable system.



- electrodes for the stimulation of nerves and muscles
- implant housings with a power supply and microelectronics for control
- long cables to interconnect all the electrodes from a central implant.

Using precision mechanics, the implants are made to be robust, stable and functional for a long life span. However, they are space consuming, and the complexity of the implant and the number of electrodes are limited by the constraints of precision mechanics technology and the spatial and biological constraints of the human body. With microsystem technology active implants that have a higher degree of miniaturisation and an increased number of electrodes are now possible.

Implants not only have to be

biosafe and biostable in terms of cytotoxicity and degradation, they also have to satisfy biological system solutions with respect to smooth edges, low weight and high flexibility to prevent mechanic nerve traumatization. Therefore, material selection by IBMT leaned towards using flexible, light-weight substrates based on polyimide,⁸ and developing a mainly hybrid integration that utilised a special assembly method that involved its Microflex interconnection technique (patent pending by IBMT).⁹ In this technique a ball-wedge bonder is used to establish an electronic contact, and a mechanical connection between electronic chips and flexible substrates employs special kind of micro-rivets. Three examples of products fabricated in this way are described below.

A microsystem in the eye

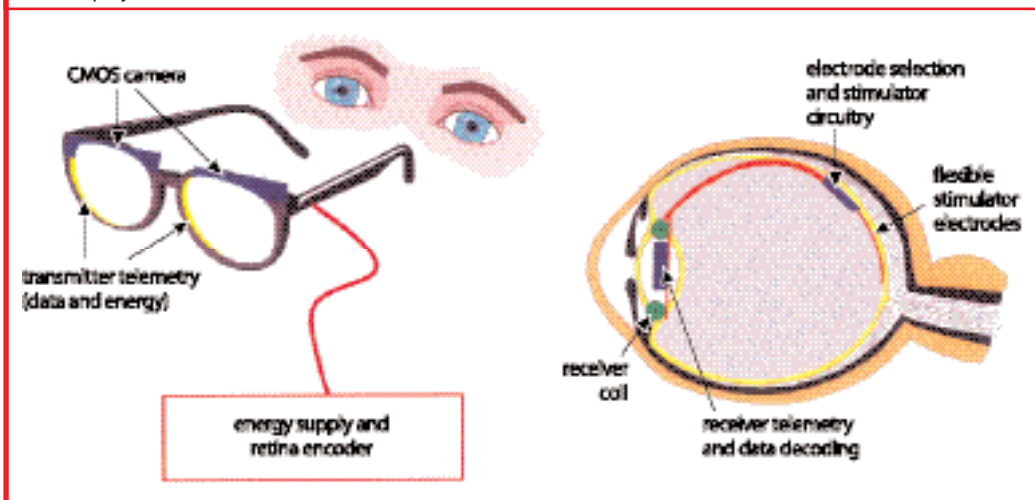
A large number of patients suffer from retinal degenerative defects, especially retinitis pigmentosa (RP) and macular degeneration. There is a progressive loss of rod and cone photoreceptors. However, the ganglion cell layer, which forms the optic nerve and subsequent parts of the visual system, remain intact. One study has demonstrated that local electrical stimulation of the retinal ganglion cell layer in blind RP patients yielded useful, localised visual sensations.¹⁰ These phosphenes were seen as dots or lines in defined locations in the visual space.

Two different implantation and stimulation locations are under investigation for a device to directly stimulate the retina: a subretinal location with photodiode arrays in the region of the degenerated photoreceptor cells, and an epiretinal location for ganglion cell stimulation with conventional stimulation contacts.¹¹ Components for the ganglion cell stimulation implant are currently being developed by several groups in the USA¹² and Germany.¹³

The retina implant system comprises several functional units (see Figure 5). The external part includes a high-speed camera to generate the images. It sends the data to a portable box that includes the energy supply that is powered by rechargeable batteries and a signal-processing unit, the retina encoder. This encoder is used to simulate the spatio-temporal properties of the different layers of the retina and it processes the signals from the camera and generates stimulus patterns for the ganglion cells. These data are led to a telemetric unit for transmission to the implantable part of the system. Inside the eye, a telemetry receiver is located in an artificial intraocular lens (7-mm diameter) decodes the data and the electrodes will be spatio-temporally selected for the stimulation of the ganglion cells.

Polyimide-based substrates with integrated electrodes have been developed that overcome the classical separation of substrate and insulation layers and allow the integration of

Figure 5: Illustration of the retina implant system for ganglion cell stimulation as envisioned in the German EPI-RET project.



interconnects and electrodes.⁸ The flexible polyimide foils were used as substrates for the assembly and hybrid integration of retina implant systems. Discrete components such as a coil, a capacitor, and a diode were soldered onto contact pads that had solderable metallisation. Integrated microelectronic circuitry demands a high integration density of contact pads. The MicroFlex interconnection technique is designed for the assembly of standard or custom-made microelectronic dice for the thin polyimide foils.⁹ Two different approaches for retina implant systems were realised.

■ System 1 is a system that integrates the microelectronics into an artificial intraocular lens. Flexible interconnects are leading to the macula region where the stimulation chip is located directly beneath the electrode area.

■ In system 2, all parts are assembled onto a foil for implantation directly on the retina near the macula region. Both systems of the flexible, lightweight devices for retina implants were designed and fabricated with integrated electrode areas and pads for hybrid electrode assembly, respectively (see Figure 6). The substrates on which the integrated circuits were assembled have a thickness of 15 µm. Integrated circuits (CMOS) with thin-film pads for signal and energy transmission, electrode selection and stimulus pulse forming were obtained from IBMT's partner in the work, FhG-IMS (Duisburg, Germany).¹⁴ The integrated circuits were mechanically fixed and electrically contacted to the flexible substrate using the MicroFlex interconnection technique.

In the systems described here, additional components (capacitor and diodes) and a receiver coil were soldered to the corresponding contact pads by hand. The contact pads were coated with a thin layer of epoxy resin for protection.

Two alternative concepts for signal and data transmission are undergoing competitive tests. System 1 may be equipped with an electromagnetic, inductive transmitter that has a coil soldered to contact pads. In addition, an optoelectronic telemetry device

with photovoltaic cells and a photodiode were developed by another project partner, the University of Duisburg, Germany¹⁵ and built onto System 1 and System 2. The assembled systems were given to the project partners for the encapsulation of the microcircuitry and subsequent implantation into a rabbit model.¹⁶ In recent studies in cats, acute electrical stimulation of the retina, delivered by the polyimide-based electrode arrays at levels from 4 µA to approximately 100 µA, and at a pulse width of 250 µs, resulted in the spatially correlated activation of the nerve fibre ensembles in the optic tract and the visual cortex.

Part II of this article discusses recent work on distributed and intelligent electrodes and a biohybrid neuroprosthesis for the restoration of skeletal muscle function.

Acknowledgement

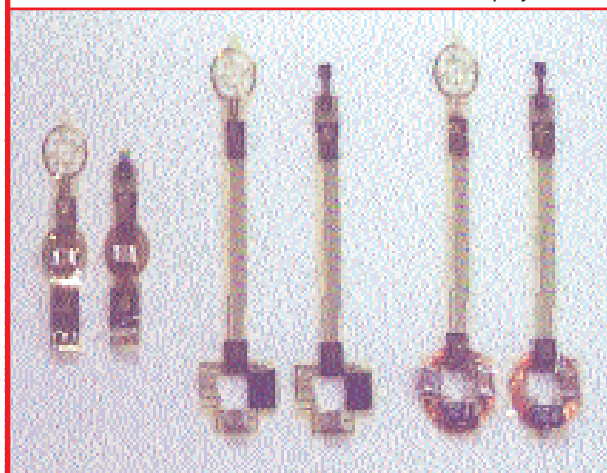
Part of this work was funded by the EU within the ESPRIT program (INTER and GRIP) and by the German Ministry for Education and Science (EPI-RET and Neuronenmikrosonde). The author would like to thank all project partners for their constructive collaboration. Special thanks go to all the author's coworkers at IBMT, especially to the neural prosthetic unit, Dipl.-Ing. Martin Schuettler, Dr. Oliver Scholz and Dipl.-Ing. Klaus Peter Koch for their

excellent work.

References

1. www.microtec-d.com
2. C. Hierold et al., "Implantable Low Power Integrated Pressure Sensor System for Minimal Invasive Telemetric Patient Monitoring," paper presented at MEMS98, Heidelberg, Germany, 1998.
3. T. Eggers et al., "Advanced Hybrid Integrated Low-Power Telemetric Pressure Monitoring System for Biomedical Applications," paper presented at MEMS2000, Miyuzaki, Japan, 2000.
4. www.bergmannsheil.de/akm
5. P. Walter and U. Bartz-Schmidt, "Perspectives of Intraocular Microsystems Retina Implants, Pressure Sensors, and Intraocular Vision Aids," MICRO.tec 2000, Proceedings, pp. 433–436 (2000).
6. T. Eggers et al., "Wireless Eye Pressure Monitoring System Integrated into Intraocular Lens," MICRO.tec 2000, Proceedings, pp. 255–258 (2000).
7. S. Kolnsberg et al., "CMOS Microtransceivers in Ophthalmology," MICRO.tec 2000, Proceedings, pp. 249–253 (2000).
8. T. Stieglitz et al., "Micromachined, Polyimide-Based Devices for Flexible Neural Interfaces," *Biomedical Microdevices*, 4, 2, 283–294 (2000).
9. T. Stieglitz, H. Beutel and J.-U. Meyer "Microflex, A New Assembling Technique for Interconnects," *J. of Intelligent Material Systems and Structures*, 6, 11, 417–426 (2000).
10. M.S. Humayun et al., "Visual Perception Elicited by Electrical Stimulation of Retina in Blind Humans," *Arch. Ophthalmol.*, 114, pp. 40–46 (1996).
11. J.L. Perlman, A.Y. Chow and N.S.

Figure 6: Illustration of the retina implant system for ganglion cell stimulation as envisioned in the German EPI-RET project.



- Peachey, "Subretinal Implantation of a High Density Microphotodiode Array in the Cat Retina," *Invest. Ophthalmol. & Vis. Sci.*, 37, (Suppl.), p. 96 (1996).
12. J. F. Rizzo et al., "Electrically-Evoked Potentials from Stimulation of Rabbit Retina with a Microfabricated Electrode Array," *Invest. Ophthalmol. & Vis. Sci.*, 37, (Suppl.), p. 707 (1996).
 13. R. Eckmiller "Retina Implants with Adaptive Retina Encoders," RESNA Research Symposium, Proceedings pp. 21–24 (1996).
 14. M. Schwarz et al., "Single Chip CMOS Imagers and Flexible Microelectronic Stimulators for a Retina Implant System," *Sensors and Actuators A*, **83**, pp. 40–46 (2000).
 15. M. Gross et al., "Optical Signal and Energy Transmission for a Retina Implant," First Joint Meeting of BMES and EMBS, Atlanta, USA, 13–16 October 1999, Proceedings, p. 476 (1999).
 16. P. Walter et al., "Successful Long-Term Implantation of Electrically Inactive Epiretinal Microelectrode Arrays in Rabbits," *Retina*, **19**, 6, 546–552 (1999).

Thomas Stieglitz

is Head of Resources, Neural and Prosthetics and Micromechanics, Fraunhofer Institute for Biomedical Engineering, Biohybrid Systems Department, Neural and Prosthetics Unit, Ensheimer Strasse 48, D-66386 St. Ingbert, Germany, tel. +49 6894 980 160, fax +49 6894 980 400, e-mail: thomas.stieglitz@ibmt.fhg.de, www.ibmt.fhg.de 