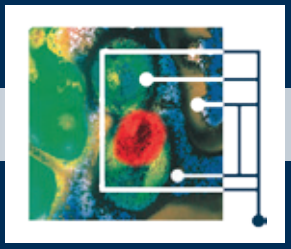
Medizinische Elektronik

Science Report



Technische Universität München
Heinz Nixdorf-Lehrstuhl
für Medizinische Elektronik

Steinbeis-Transferzentrum
Medizinische Elektronik und
Lab on Chip-Systeme

Medizinische Elektronik
Science Report

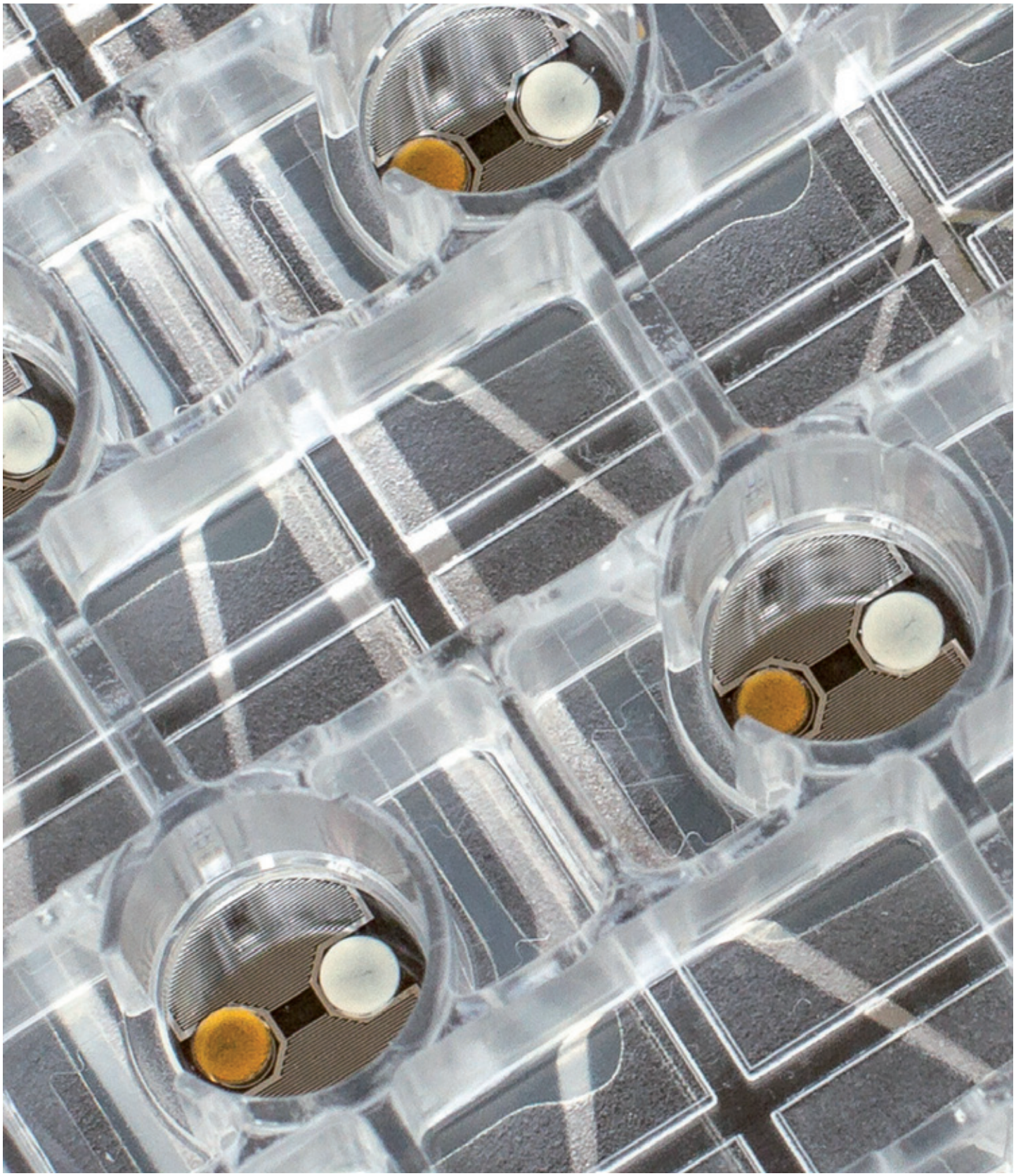
Table of contents

contents

Table of contents

contents

- Watch the videos of our research projects: http://www.stw-med-chip.de/filme
- View a list of our patents: http://www.stw-med-chip.de/patente



Foreword

During the past 50 years, advances in microelectronics have given rise to devices and systems that have significantly influenced our everyday lives. In the field of medicine, we have seen two major developments: new technologies for modern imaging, and a large number of medical microsystems and microsensors as a result of the inherent miniaturizing potential of microelectronics.

Smart medical systems and miniaturized analytical systems have become more and more widespread – with some even being implanted into the human body. A “silicon pill”, i.e. a chip that can be swallowed, is already within reach now that we have a growing understanding of the electrical processes taking place in cells and tissues. With these new insights, completely new forms of therapy, such as therapeutic implants, can be developed. One concept already widely used today is cochlear implant surgery. Retinal implants may soon become a routine surgical intervention, and in the distant future we may be able to ease the lives and the pain of those suffering from chronic and advanced diseases.

These and other aspects are the focus of the research we have been doing at our department, the Heinz Nixdorf-Lehrstuhl für Medizinische Elektronik at Technische Universität München, in collaboration with the Steinbeis-Transferzentrum Medizinische Elektronik und Lab on Chip-Systeme, as well as with spin-offs and partners. This book provides an overview of our activities. Many of our projects have meanwhile attracted industrial partners who have put our systems into production and are using them in real patients.

We would like to express our gratitude to Heinz-Nixdorf-Stiftung for constantly supporting our visions and projects. Many of our most important and in the meantime very successful projects would otherwise not have survived the lean periods of cautious public funding. Our thanks also go to Dr. Horst Nasko for his continued commitment to our research unit, whose input is always very much appreciated. We would also like to thank our partners from industry and science who have helped us to continue pursuing our joint scientific endeavors through our Steinbeis-Transferzentrum (http://www.stw-med-chip.de).

Prof. Dr. Bernhard Wolf
Munich, March 2016

Sensor Technology

Microsensor system for measuring surface contamination - [KONTAMIN]

In short

Surface contamination can be determined with a special multilayer sensor chip. The impedance variations caused by the bacteria that accumulate on the surface of the sensor can be measured.

The aim of KONTAMIN, a cooperative project funded by the Bundesministerium für Bildung und Forschung, was to develop a bacterial sensor to enable the electronic measurement of microbe contamination (e.g. on a butcher's meat counter).

So far, the standard method for determining surface contamination has entailed the use of tests involving luminescence measurement. To this end, a defined wipe of the contaminated surface is used to collect a microbe sample which is then placed in a measurement solution.

The results of the KONTAMIN project revealed that the electronic measurement of the germ concentration in liquids is actually possible with relatively low germ content, provided that the germs can be accumulated in the direct vicinity of the sensor. This was achieved by using a dielectrophoretic method. In an inhomogeneous electric field, forces are exerted on polarisable microparticles – in this case the bacteria – that move the microbes towards the strongest field gradient. If adequately designed electrodes are used, the bacteria thus accumulated will change the electric impedance of the sensor. Sensor sensitivity can be

To determine the degree of contamination of a surface, a sensor suitable for use in a two-step measuring method was developed. The bacteria are first accumulated on the surface of the sensor and then determined by measuring the sensor impedance variations caused by the accumulated bacteria. The field distribution in the sensor structure was optimised by means of numeric field computations. The sensor itself was manufactured using a photolithographic process well-known in semiconductor technology. A considerable sensitivity of 105 bacteria / ml has been achieved.

In principle, it is possible to further increase

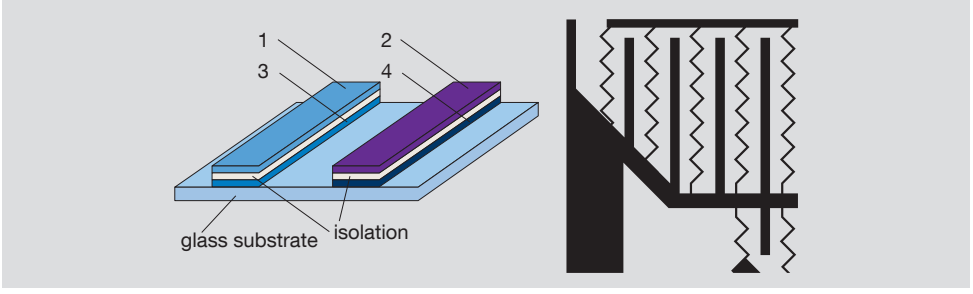


Fig. 1: Left: multilayer sensor design for a two-step measuring principle;
a). Accumulating the microbes by means of dielectrophoresis (conductive tracks 1, 2);
b) Measuring the impedance variation (conductive tracks 1, 3 and 2, 4); Right: final sensor structure on a glass substrate, in the form of a sandwich sensor.

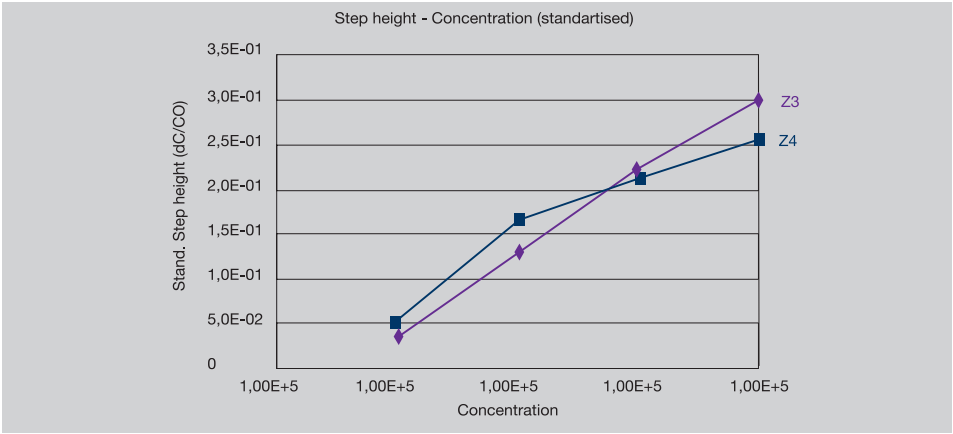


Fig. 2: Bacteria / ml in de-ionised water

this sensitivity: on the one hand by utilising nanoparticles with coupling properties for bacteria, and on the other hand by using a larger liquid reservoir and by extending the bacterial accumulation stage accordingly.

Selected publications

- *T. Weyh, K. Wendicke, B. Gleich, B. Wolf, „Optimisation of a Bacteria Sensitive Sensor“; in 2nd European Medical and Biological Engineering Conference,Vienna, December 2002. IFMBE Proceedings Vol I, pp. 332 – 333.*

- *T. Weyh, K. Wendicke, B. Wolf „Simulation and Design of a Bacteria Sensor“, Sensor 2003 Conference, Nuremberg, May 2003.*

- *T. Weyh, B. Gleich, B. Wolf „Design of a Bacteria Sensitive Biosensor“; DECHEMA; Jahrestagung der Biotechnologen, Posterbeitrag, Munich-Garching, April 2003.*

- *T. Weyh, K. Wendicke, B. Gleich, B. Wolf, „Empfindlichkeitssteigerung von Biosensoren zur Bestimmung von Bakterienkonzentrationen durch Mikropartikel“, 6. Dresdner Sensor-Symposium, Dresden, December 8-10, 2003. Dresdner Beiträge zur Sensorik (Tagungsband), J.G. Baselt und G. Gerlach (Hg.), w.e.b. Universitätsverlag, Dresden 2003, pp. 239-242.*

- *Wolf, B., Scholze, C., Grothe, H., Brischwein, M., „‘Medizin 4.0‘ – Die Bedeutung von Elektronik, Informationstechnik und Mikrosystemen in der modernen Medizin“, in: Gausemeier, J. (ed), Vorausschau und Technologieplanung, 11. Symposium für Vorausschau und Technologieplanung, 29. - 30.09.2015, Berlin 2015, pp. 379 – 401.*

This research was funded by the Bundesministerium für Bildung und Forschung.
Project title: Kontamin; project life span: 2000 to 2003

Biohybrid sensor system with living cells and electronic components [cellristor®]

In short

Biohybrid sensor systems, called cellristors®, are able to convert the biological signal responses of cells into electronically readable signals. For example, they may be used as a sensitive component in addition or as an alternative to existing measuring instruments for environmental monitoring.

In recent years, advances in microelectronics and biotechnology have facilitated the development of stable constructs made of living cells combined with electronically active components. In the cellristor® project, the biological signal response of cells is converted into electronically readable signals (Fig. 1). Analogue to transistors (transfer resistors), this type of biohybrid sensor system is defined as a cellristor®.

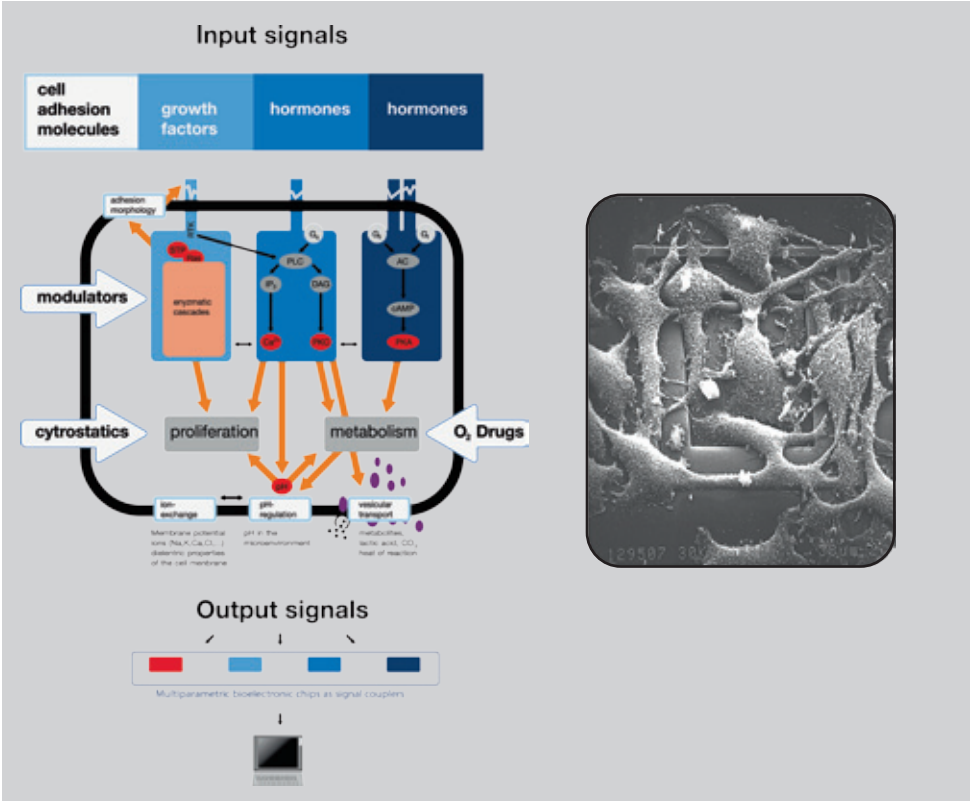
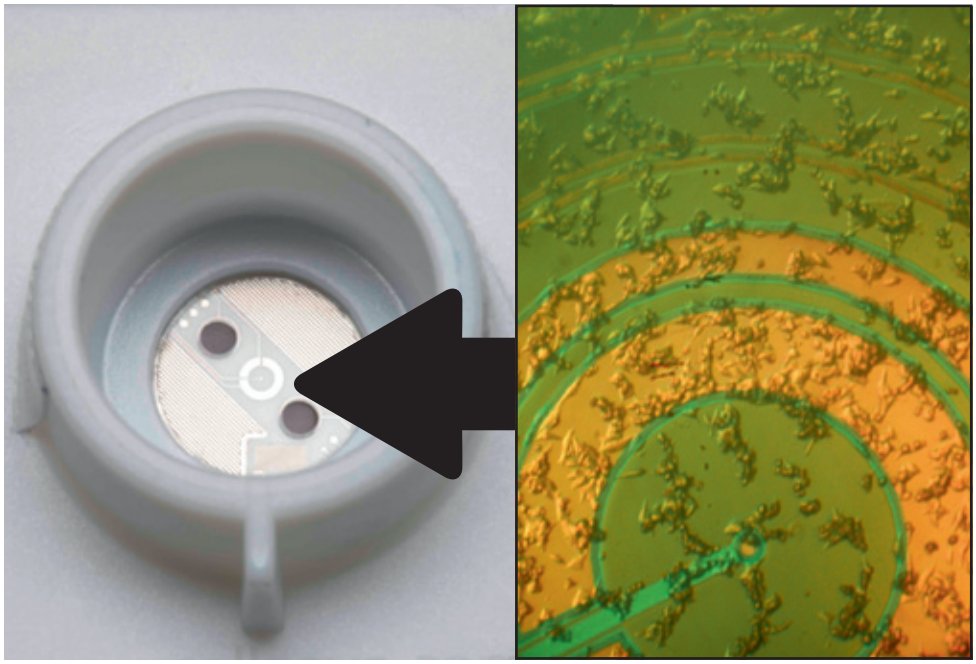


Fig. 1: Left: diagram of a cellristor®; right: scanning electron microscope (SEM) image of cells on a transistor array in a tentative project.



F ig. 2: Example of the technology in practice

There are multiple ways to achieve the physical basis for a cellristor® along with a wide variety of measuring principles. Film-type resistors, diodes, transistors (e.g. ISFETs), planar capacitances and electrode systems from technical sensor structures can be utilised in the same way as the corresponding components used in polymer electronics.
If living cells are used, it is also necessary to ensure appropriate living conditions. This can be achieved by adequate design and connection technologies, and increasingly by microsystem technology.

Fig. 2 illustrates an example of the technical implementation of a cellristor®. The sensor chip comprises the physical sensors by which the signals of a living organism (e.g. an animal cell, a yeast, an alga) are captured. A technical life support system provides a micromilieu for the organism similar to the in-vivo situation.

Figure 3 illustrates the variation in the vitality parameters (pH und pO_2) of green algae Chlorella Kessleri used as biological part of the cellristor® in this case over time. A study of the sensitivity to the herbicide Metramitron revealed the following findings: In the characteristic signal curve, the amplitude changed after the toxic substance was added. The measuring cycle revealed the metabolic activity of the algae to be decreased. In the following measuring cycle, the culture medium had returned to a non-contaminated state which again regenerated the cells.

The biosensor system described here, which uses living cells as signal converters, can be used as a sensitive component in addition

or alternative to existing measuring instruments for environmental monitoring. Due to its low operational costs and by involving the mobile radio network, it is possible to achieve a degree of flexibility that allows for extensive detection of environmental parameters. The automatic analysis and evaluation of the measured data permits rapid detection of environmental influencesor the occurrence of unusual water pollution. By using living organisms, it is possible to respond to any type of toxin which can otherwise only be selectively detected by means of elaborate chemical methods.

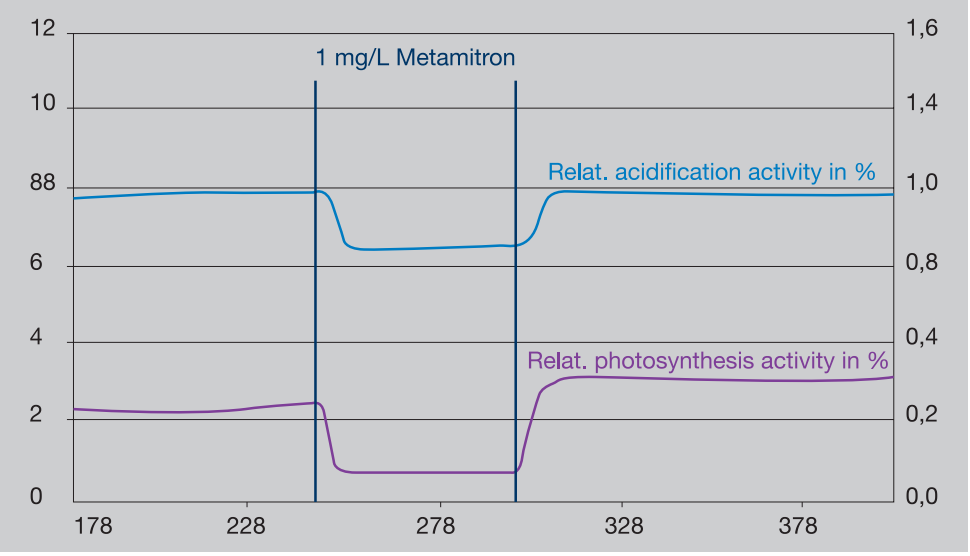
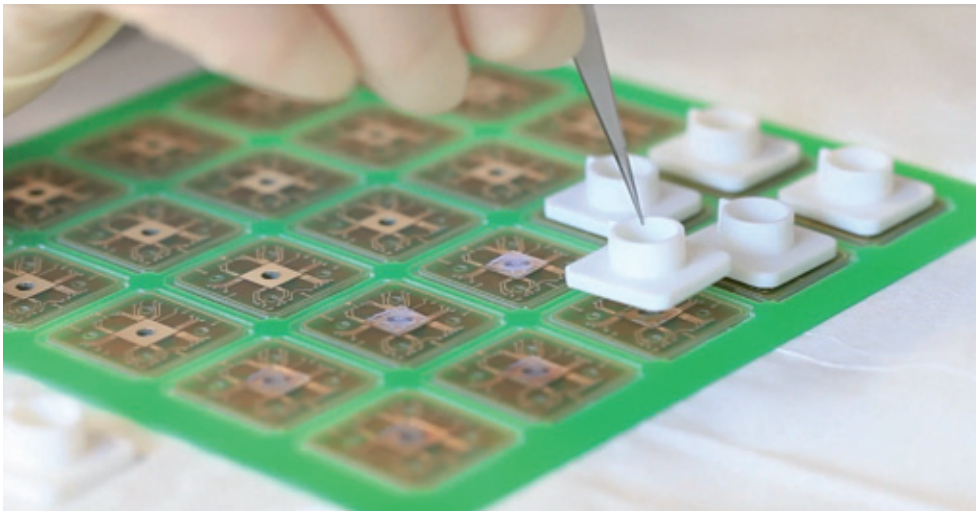


Fig. 3: Cell vitality parameters, pH and pO_2, measured from green algae Chlorella Kessleri. After approx. 235 minutes, the herbicide Metamitron was added and decreased cell metabolism was detected. Regeneration of this test organism can be observed after removing the herbicide. These data were generated in a joint research project between our deparment and the Limnologic Institute of the Technische Universität München in Iffeldorf.



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- *T. Stadthagen: „Entwicklung eines online Gewässermonitoringssystems mittels Biosensorchips zum Nachweis ausgewählter Xenobiotika“, Dissertation, Technische Universität München, 2007.*

- *M. Brischwein, G. Scarpa, H. Grothe, B. Wolf, S. Thalhammer, „Toward printable lab-on-a-chip technologies for cell analytics“, in: Biological and Medical Sensor Technologies, Kryzysztof Iniewski, ed. CRC press 2012, p. 125-148, Print ISBN: 978-1-4398-8267-2, eBook ISBN: 978-1-4665-5257-9*

- *D. Weiss, H. Grothe, B. Wolf, J. Wiest: “BioChip-based Electrochemical Platform for the Label-free Monitoring of Living Cells”, ATLA, 40, 2012, A35*

This research was funded by the Heinz Nixdorf Stiftung and the company Erwin Quarder Gruppe. Project title: Cellristor® (Cellristor® is a registered trademark of the Heinz Nixdorf-Lehrstuhl für Medizinische Elektronik, Technische Universität München). Project life span: 2011 to 2012

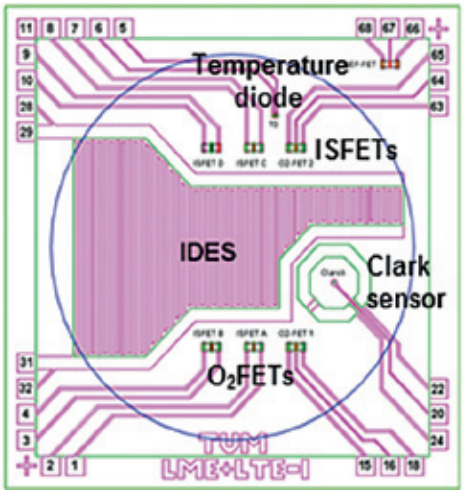
ISFET (ion-sensitive field effect transistor) as a planar pH sensor on multiparametric cell chips

In short

This innovative process for manufacturing multiparametric silicon sensor chips enables the integration of impedance, oxygen and pH sensors as well as temperature sensitive diodes and microelectrodes on one single chip.

This project entailed the development of an NMOS technology process for manufacturing multiparametric silicon sensor chips (Fig. 1), enabling the integration of all the sensors needed for cytoscopy on one single chip.

Besides impedance and oxygen sensors, these include in particular ion-sensitive field effect transistor structures (ISFET) serving as pH sensors. In these structures, the isolated, unplated gate is activated by the ionic charges in the intracellular fluid above.



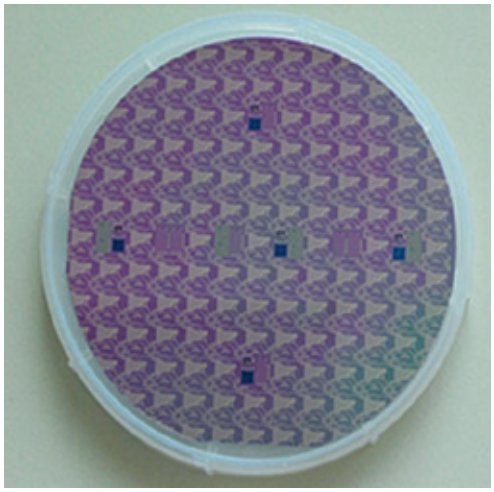


Fig. 1: Layout of the multiparametric silicon sensor chip and corresponding 4“ wafer. Besides the ISFETs for measuring the pH, the sensor chip includes a Clark sensor and O_2-FETs for measuring oxygen, as well as an impedance sensor (IDES) and a temperature sensitive diode.

The manufacturing process is carried out as follows (Fig. 2):
The starting material comprises p-doped, oxidised Si wafers (1). The source and drain areas of the FETs are defined by a photolithographic process and then etched (2) and doped by means of an n-diffusion process (3).

The next step involves removal of the oxide ridge above the gate area (4) and formation of the gate oxide. A silicon nitride layer acting as an ion-sensitive membrane is deposited directly on the gate oxide (5).
The silicon dioxide layer deposited thereon (6) is only removed in the area of the source

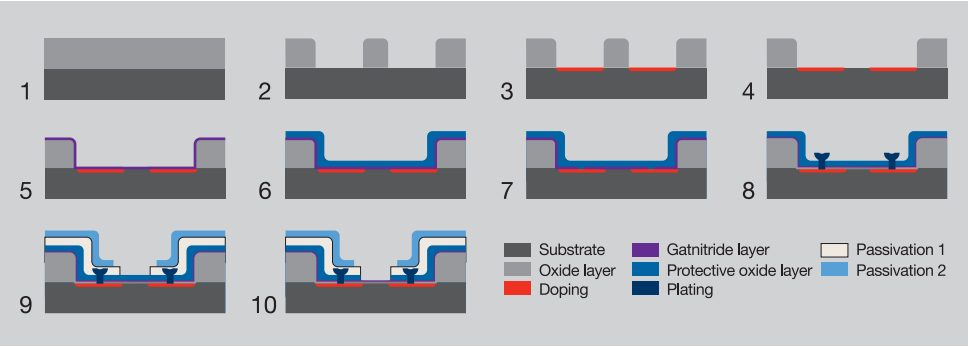


Fig.2: Manufacturing process for the sensor chip

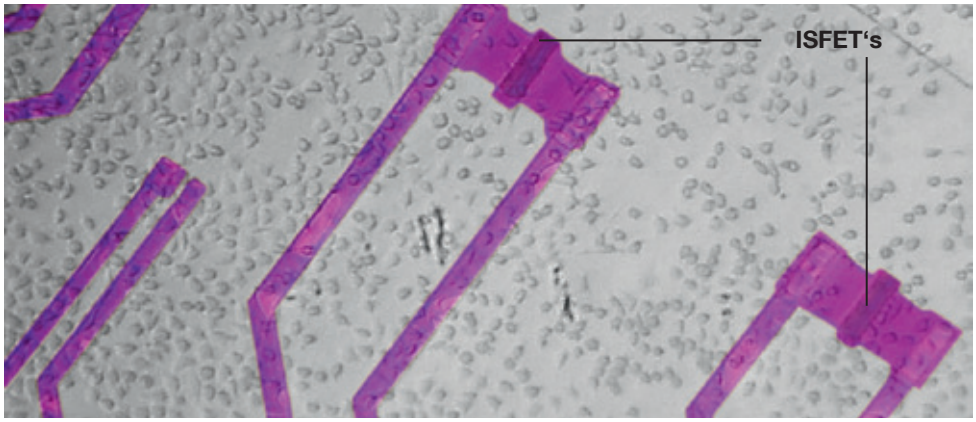


Fig. 3: Cells grown on a sensor chip

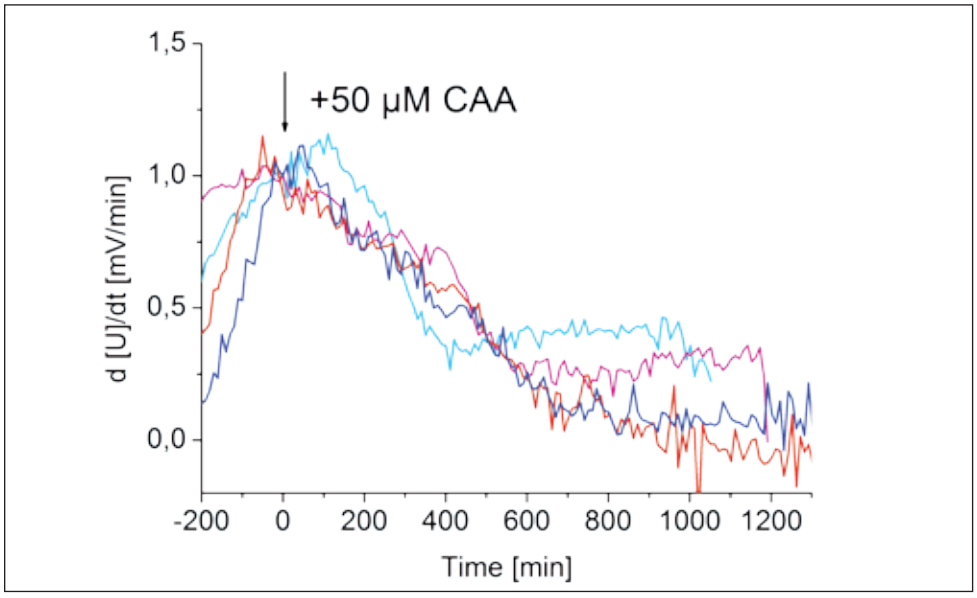


Fig. 4: Response of LS 174 T cells (human colon adenocarcinoma) treated with 50 µM of the alkylating agent chloracetaldehyd. The derivative of the ISFET output voltage dU/dt is a measure of the extracellular acidification. The graph shows the results obtained with four ISFETs in separate on-chip cell cultures.

and drain contacts (7), which are then metal-plated (8).
Two additional stress compensated silicon oxide/nitride passivation layers insulate the sensors against short circuits in liquids (e.g. a cell culture medium) (9); and beyond that they serve as an etching mask for exposing the ISFET gate area (10). Alternatively, a photo-resist coating (SU-8) can also be applied for the purposes of passivation.
Fig. 3 shows a microscopic image of a sensor chip with ISFETs overgrown by cells, Fig. 4 gives an example of a tumour chemosensitivity experiment using these sensors.

Selected publications

- *B. Wolf, M. Brischwein, A.M. Otto, H.Grothe, „Microelectronics meets life sciences: Biohybrid microelectronic components for multiparametric lab-on-chip systems“, mstnews No. 1/02, pp. 37-38, 2002.*

- *H. Grothe, M. Brischwein, A.M. Otto, E. Motrescu, C. Stepper, T. Henning, B. Wolf, „Bioelectronic chips and systems for life science applications“, 21. DECHEMA- Jahrestagung der Biotechnologen, Techn. Univ. München, Garching, April 2-4 2003, in: Book of Abstracts V 87- 90, 2003.*

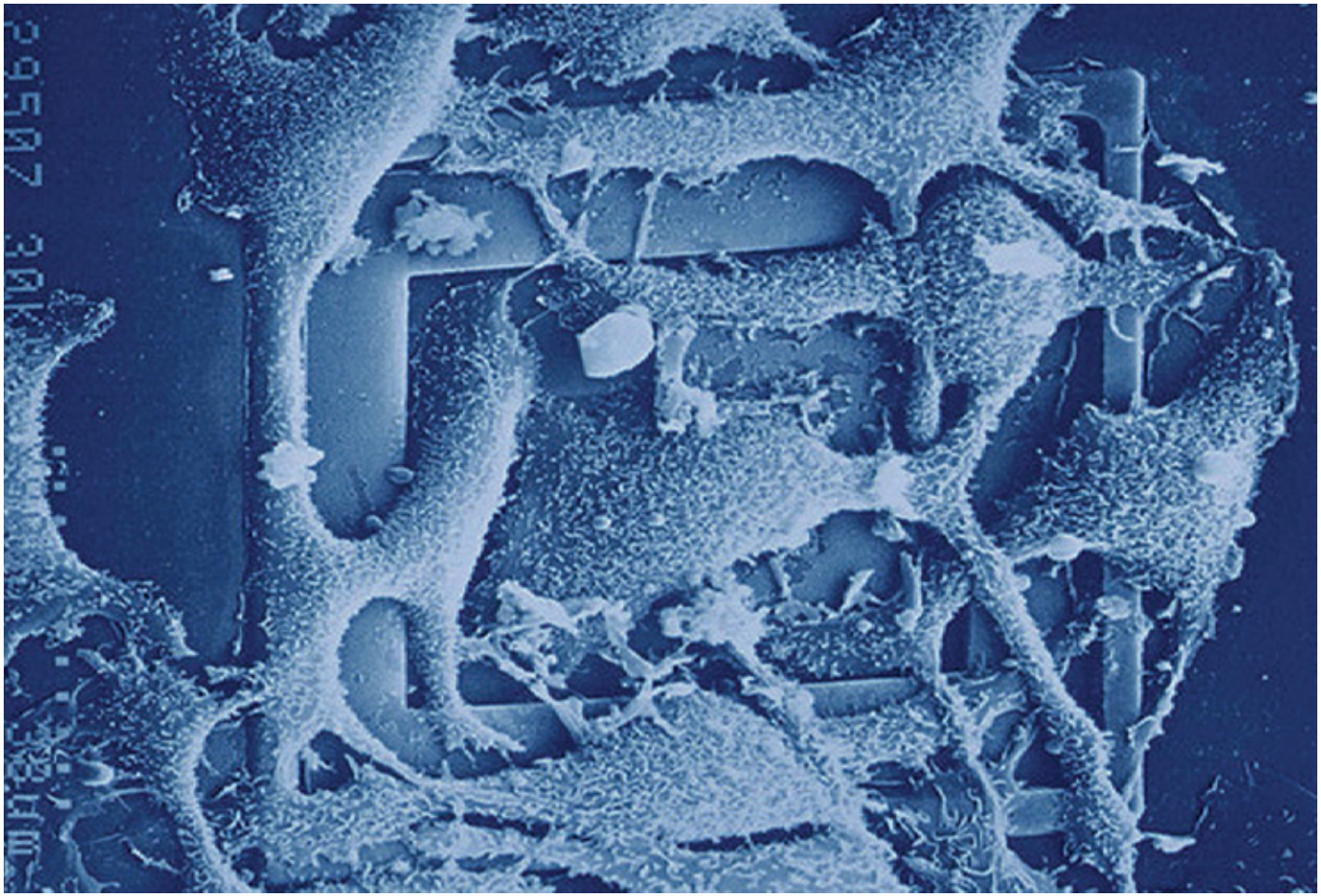
- *M. Brischwein, H. Grothe, A.M. Otto, C. Stepper, E. Motrescu, T. Weyh, B. Wolf, „Living Cells on Chip: Bioanalytical Applications“, in: Ultrathin Electrochemical Chemo- and Biosensors. Mirsky, V.M. (ed.), 159-180. Springer-Verlag, Berlin 2004.*

- *B. Wolf, M. Brischwein, H. Grothe, C. Stepper, J. Ressler, T. Weyh, „Lab-on-a-chip Systems for Cellular Assays“, in: G. Urban (ed.), BioMEMS. Series: Microsystems, Vol. 16, pp. 269-308, Springer-Verlag, Dordrecht (NL) 2006, ISBN-10:0-387-28731-0, ISBN-13: 978-0-387-28731-7.*

- *B. Wolf, B. Neumann, J. Wiest: „Metabolische Signaturen“. Technisches Messen (2013), (7-8), 243-248.*

- *P. Wolf, M. Brischwein, R. Kleinhans, F. Demmel, T. Schwarzenberger, C. Pfister, B. Wolf: “Automated platform for sensor-based monitoring and controlled assays of living cells and tissues”. Biosensors and Bioelectronics (2013), 50, 111-117*

This research was funded by the Heinz Nixdorf Stiftung.
Project title: „ISFET (ionensensitiver Feldeffekttransistor) als planarer pH-Sensor auf multiparametrischen Zellchips“ (ISFET (ion-sensitive field effect transistor) as a planar pH sensor on multiparametric cell chips)
Project life span: 2001 to 2004



Selective coupling of cells by means of suitable materials, electrodes and layer structures for the development of cell-based testing systems („cell-based“ assays)

In short

The multiparametric sensor chips created in this project are able to examine the influence of an agent on cell metabolism. For example, they may detect the effectiveness of a chemotherapeutic agent after adding it to a tumour cell sample taken from a cancer patient.

By using cell-based testing systems, living cells and tissues can be analysed on bioelectronic sensor chips in an environment that is very similar to the in-vivo setting. In this project, sensors detecting cellular metabolism from the acidification of the surrounding medium (pH sensor) and the oxygen consumption of the cells within this medium (oxygen sensor), were integrated on a chip. Cell adhesion is measured with impedance sensors, and temperature is monitored with a thermal sensor.
To examine the influence of an agent, the variation rates in the pH and pO_2 sensor signals typical of normal cell metabolism are used as reference values. By adding a chemotherapeutic agent to a tumour cell sample taken from a cancer patient, for example, the effectiveness of the applied drug can be evaluated. This is done by observing the change in the acidification rates and the oxygen consumption of the tumour cells. This method allows the potential effect of chemotherapy to be verified prior to starting treatment. Consequently, on the one hand the highly unpleasant side effects of chemotherapeutic drugs can be reduced, and on the other hand treatment costs can be significantly decreased by avoiding multiple courses of chemotherapy.

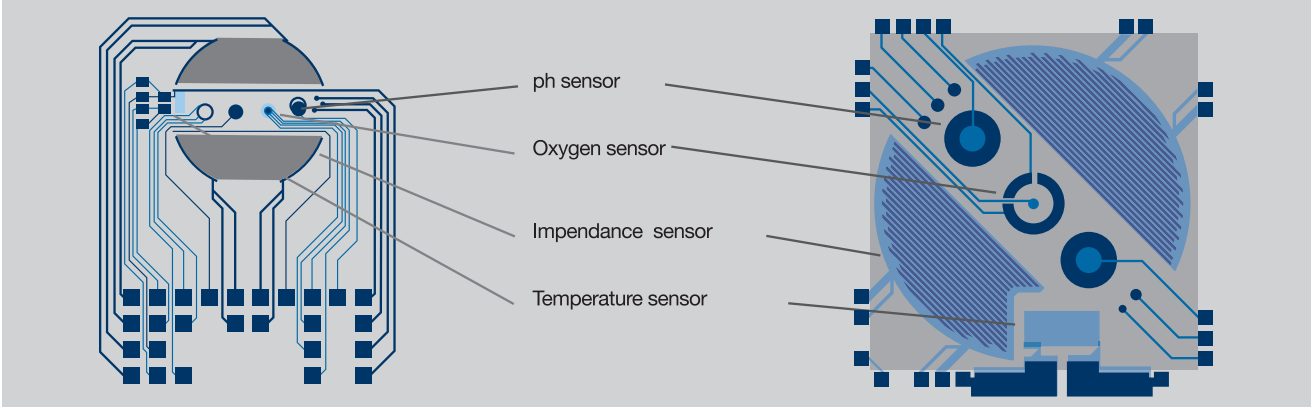


Fig. 1: Multiparametric sensor chips for cellular assays; left: microscopable glass chip with integrated sensors; right: ceramic chip with the same functionality

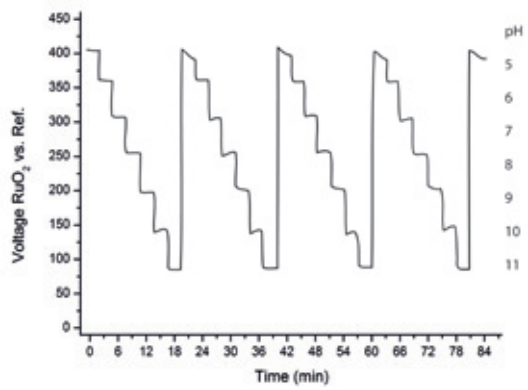


Fig. 2: Output signal of the RuO_2 sensor upon a pH variation in the fluid

Among others, the pH sensor plays an important role in these measurements. A particular focus of this project was to study the applicability of pH sensors that are simple to integrate on the sensor chip at low cost as a replacement for ISFETs. To this end, use is made of the pH sensitivity of metal oxides, with RuO_2 proving to be particularly suitable.

Fig. 1 depicts a multiparametric sensor chip on a transparent glass substrate that allows visualization of cellular assysays using an inverted microscope, as well as a ceramic chip with the same functionality, both developed in the course of this project.
The RuO_2 sensor can be used over a wide pH range and reacts to pH variations within seconds.

Selected publications

- *J. Wiest, M. Brischwein, J. Ressler, A.M. Otto, H. Grothe, B. Wolf, „Cellular Assays with Multiparametric Bioelectronic Sensor Chips“ ,Chimia 59, pp. 243-246, 2005.*

- *J. Ressler, H. Grothe, M. Brischwein, B. Wolf, „Low-cost biosensors: ceramic-based multiparametric sensorchip for functional screening“, Biomedizinische Technik Vol. 50, Supplementary vol. 1, Part 1, pp. 531-53, 2005.*

- *J. Wiest, T. Stadthagen, M. Schmidhuber, M. Brischwein, J. Ressler, U. Raeder, H. Grothe, A. Melzer, B. Wolf , „Intelligent Mobile Lab for Metabolics in Environmental Monitoring“, Analytical Letters, Vol. 39, Issue 8, Jul 2006, Pages 1759 - 1771, DOI 10.1080/00032710600714089, URL http://dx.doi.org/10.1080/00032710600714089.*

This research was funded by the Stiftung Industrieforschung.
Project title: „Selektive Verknüpfung von Zelleigenschaften mittels geeigneter Werkstoffe, Elektroden und Schichtaufbauten“ (Selective combination of cell properties by means of suitable materials, electrodes and layer structures)
Project life span: 1 April 2004 to 31 March 2006

Intelligent multi-well plate

In short

The “intelligent multi-well plate” permits real-time, label-free monitoring of the responses of living cells and tissues to experimental influences (e.g. pharmaceuticals).

Living cells and tissue samples respond to experimental influences (e.g. applied pharmaceutical drugs) by means of a highly complex intracellular signal network. Their response may lead to cell division, metabolic activation or even to cell death. If cellular specimens are cultured on a planar chip with appropriate sensors, such responses can be monitored in real time and in a label-free way. A research group at our department has developed an automated cell-chip platform, the so called „Intelligent Microplate Reader” (IMR) for recording of multiple parameters in parallel (see also chapter “Automated high-troughput analysis platform for personalized cancer therapy - AHA”). The system permits to study the dynamic response behaviour of cells to applied agents under realistic conditions (see Fig.1 and 4).

The researchers working on the „Intelligent Multiwellplate“ project designed a micro-well plate with optochemical sensors for pH

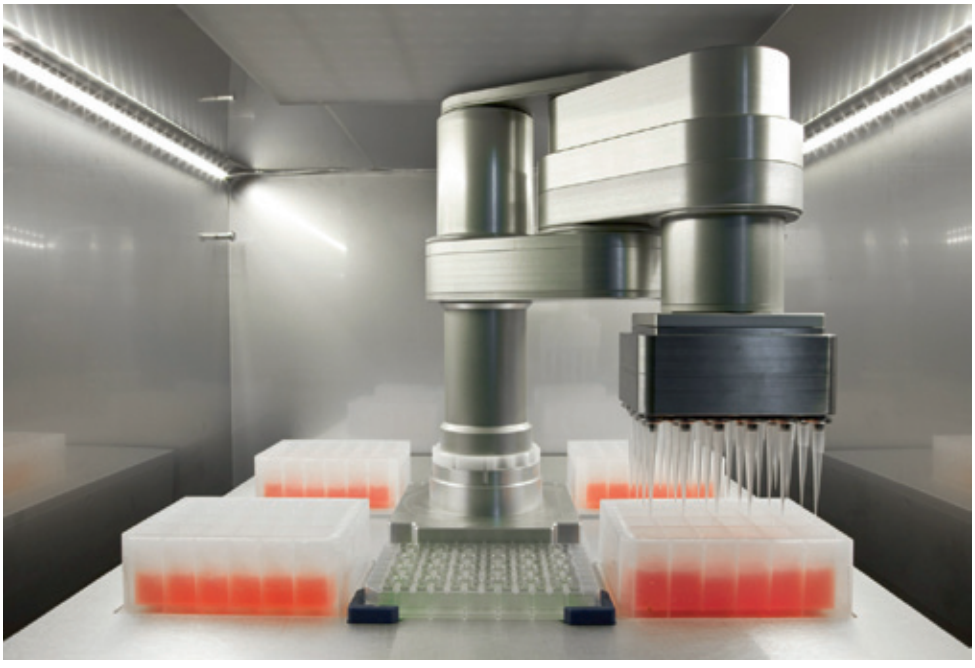


Fig. 1: Pipetting robot of the Intelligent Microplate Reader

Link to a video showing the operation of the IMR

and dissolved oxygen, analysing metabolic signatures of the cells and electrochemical impedance sensors for the detection of cell morphologic alterations. A pipetting robot actuates a fluidic system for controlled supply of the specimens with fresh culture media or the required drug solutions. The sensor-based plate has 24 wells and consists of a glass bottom connected to the polymer corpus (Fig. 2). In the centre of each well an area is left free from sensors to allow for bright field and fluorescence microscopy.

The cell and tissue samples are cultured directly in the sensor area of the well. In order to measure rates of extracellular acidification and cellular oxygen consumption with a reasonable time resolution, microreaction chambers have to be created to reduce the volume of surrounding cell culture medium. This is achieved by a cover lid confining a flat volume of approximately 23 µl that is regularly exchanged according to the selected experimental protocol. The pipetting tips of the robot have access to side vessels adjacent to the microreaction chamber of each well (Fig. 3). Small hydrostatic pressure differences emerging by the action of the robot cause a controlled regeneration of the media inside the microvolumes.

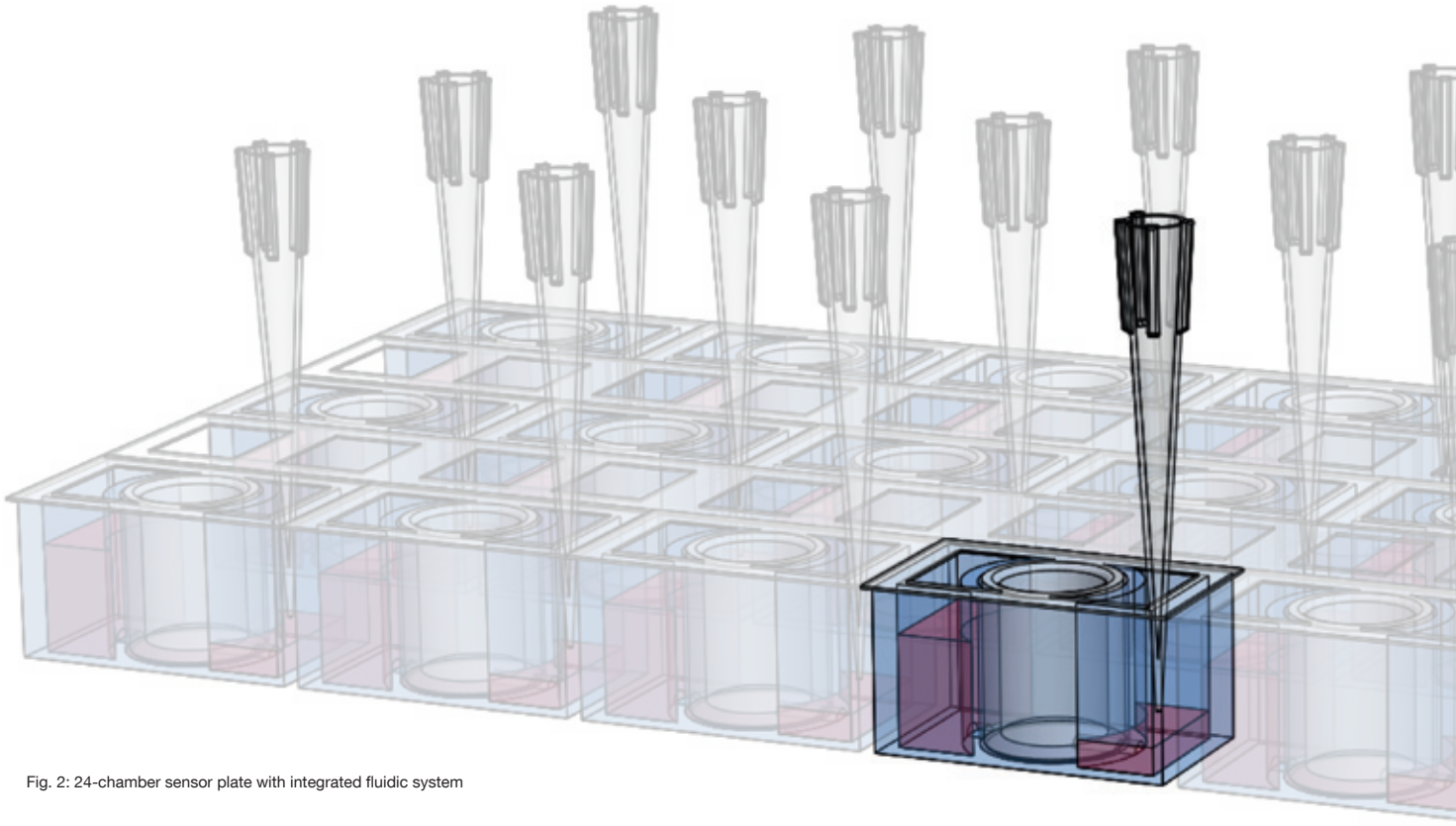


Fig. 2: 24-chamber sensor plate with integrated fluidic system

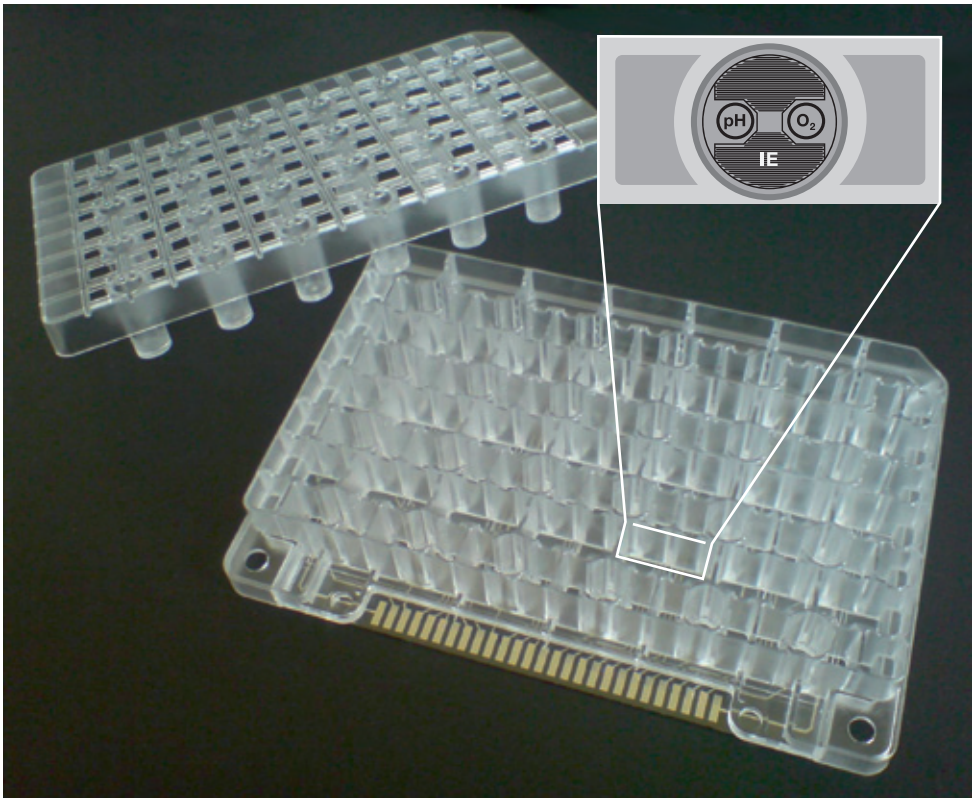


Fig.3: Sensor-based multi-well plate

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- *M. Brischwein, T. Geisler, V. Lob, J. Wiest, J. Ressler, B. Wolf, „Chip statt Maus: Microsensorarrays zur Chemikalienprüfung“. Nachrichten aus der Chemie, Vol. 54, pp. 115-120, February 2006.*

- *T. Geisler, J. Ressler, H. Harz, B. Wolf, R. Uhl, „Automated Multiparametric Platform for High-Content and High-Throughput Analytical Screening on Living Cells“, IEEE Transactions on automation science and engineering, Vol. 3, No. 2, pp.169-176, April 2006.*

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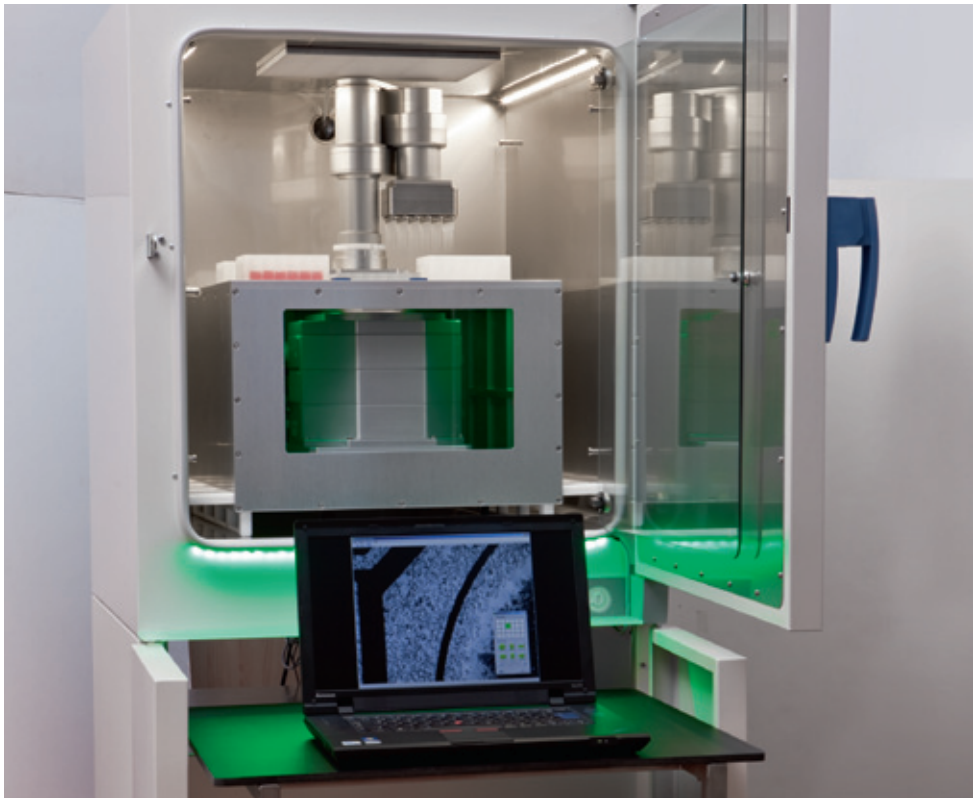

Fig.4: Intelligent Microplate Reader in open state. The incubator contains the pipetting robot, the sensor plate with the impedance electronic and an insertion with a digital microscope, underneath. A work surface with the notebook through which the device is controlled, can be pulled out from the base.

➢ *P. Wolf, M. Brischwein, R. Kleinhans, F. Demmel, T. Schwarzenberger, C. Pfister, B. Wolf, "Automated platform for sensor-based monitoring and controlled assays of living cells and tissues", Biosensors and Bioelectronics (2013), 50, 111-117.*

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➢ *F. Demmel, M. Brischwein, P. Wolf, F. Huber, C. Pfister, B. Wolf, "Nutrient depletion and metabolic profiles in breast carcinoma cell lines measured with a label-free platform", Physiol. Meas. 36 (2015) 1367-1381.*

This research was funded by the Bayerische Forschungsstiftung.
Project title: „Intelligente Multiwellplatte“ (intelligent multi-well plate)
Project life span: 1 August 2004 to 31 July 2007

Electrochemical multi-well plate

In short

Refinement of the intelligent multi-well plate will permit a large variety of measurement techniques to be performed at the same time in one chamber without any interference. In the future, it will be possible to use this system to test the metabolism of cells and tissues for a great number of different substances.

In cytological analysis, the sizes of the samples being examined are becoming smaller and smaller – a development that calls for more sophisticated measuring technologies. Electrochemical systems, which offer high sampling rates and a good signal-to-noise ratio, could be the answer. With the precision they provide, it is even possible to discern the signals of a single cell.

With the aim of developing a system that can compete with optical systems, we examined and enhanced the high throughput capabilities of electrochemical sensors. As described on the preceding pages, we had already developed the "Intelligente Multiwellplatte", a microtitre plate with electrochemical sensors in each of its 24 wells. We subsequently adapted the sensor design (see Fig. 1) and the read-out electronics (see Fig. 2). Multiparametric reading was therefore possible, enabling us to take various measurements at the same time from one well without any interference. A pH and oxygen sensor can thus be used in addition to a bioimpedance analysis system for examining cell morphology.

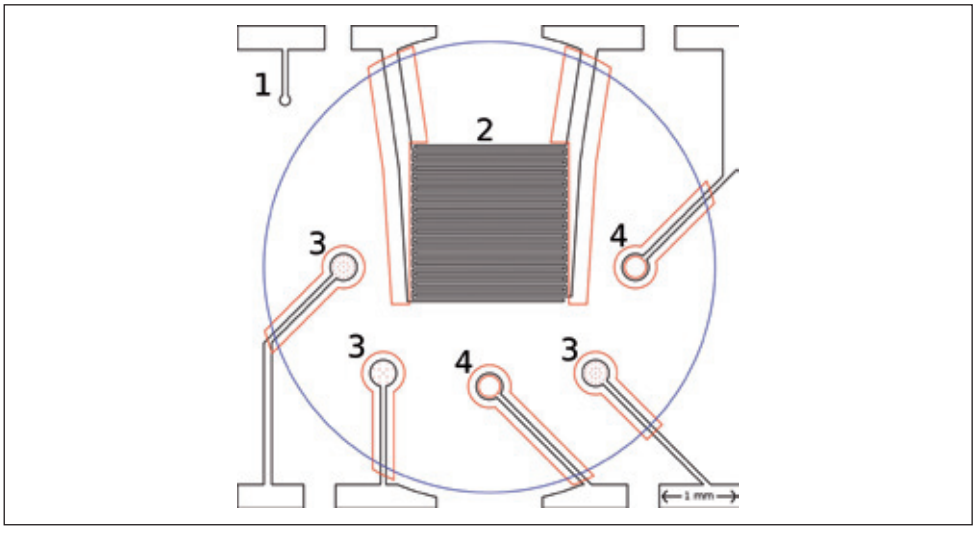

Fig. 1:
Sensor design in the wells of the electrochemical multi-well plate: Each of the sensors comprises (1) an external reference electrode (for absolute measurements), (2) an interdigital electrode structure (IDES) for bioimpedance measurements, (3) microelectrode structures for pH and oxygen sensors, and (4) circular electrodes for the internal reference electrode. The thin-layer and replica structures made of platinum (or gold) are shown in black, the isolation layer covering the supply leads in red. The cell culture is placed inside the area marked in blue.

Bioimpedance, oxygen and pH measurement were chosen as placeholders in this sophisticated new system for the three main principles of electrochemical analysis (impedance, amperometry, and potentiometry). The target parameters can thus be changed by adapting the respective sensor. Through appropriate biofunctionalisation in each specific target, it will be possible to detect a wide variety of substances in different materials. A conceivable application would be glucose measurement using glucose oxidase as in commercial glucometers, for instance. Detection of urea and the neurotransmitter dopamine are just two further examples of how the system could be used in the future.

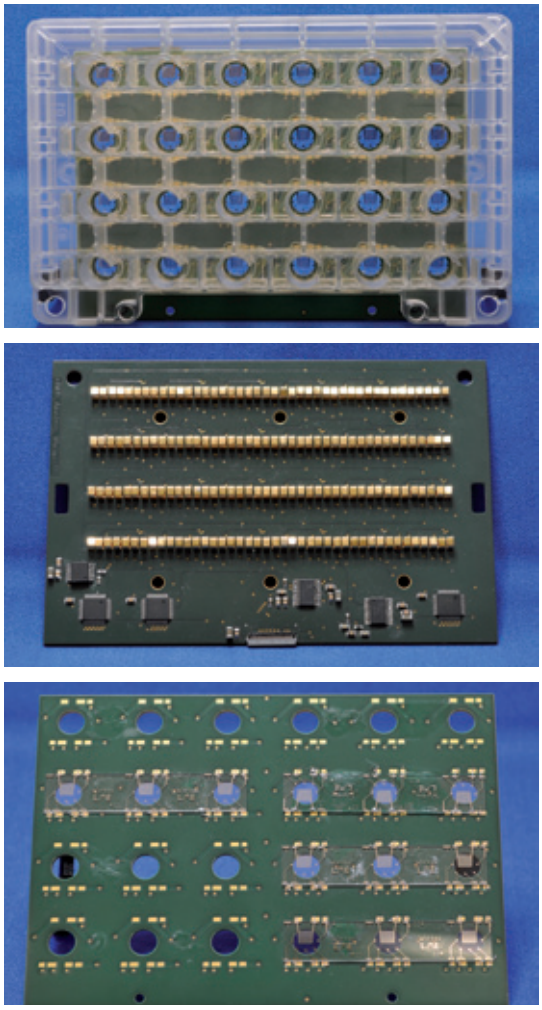

Fig. 2:
Refinement of the intelligent multi-well plate
a) 24-well plate equipped with electrodes for oxygen, pH and impedance measurement
b) Read-out unit for connecting to the electrochemical sensors
c) Thin-film sensors were produced on a glass substrate and placed on a PCB, and the electrical connection established by wire bonding

Project life span: since 2012 • Project funded by: private sponsor
Network partner: Erwin Quarder Systemtechnik GmbH

i³ screen project – passive electrical properties and active biosignals from cardiocyte cultures

In short

The cell screening device being jointly developed with Nanion Technologies GmbH supports parallel and highly precise, time-resolved measurements of bioimpedance and extracellular field potentials, particularly for cardiomyocyte cultures. An important aspect of the project was the improvement of the planar electrode interface properties.

Every novel pharmaceutical compound has to be tested intensively for possible cardiac side effects. Early signs of such effects can be found with indirect electrophysiological methods – but without additional analytical investigation, there is a danger that drug development will come to an end prematurely. High-throughput and high-content in-vitro screening for cardiac risks is therefore urgently needed.

The joint "i³ screen" project pursues a combination of bioelectric impedance measurement and extracellular recording of altered electric potentials over time in millisecond resolution. Both yield valuable information about the pharmacological responses of cardiocytes. The project tasks encompass the development of multifunctional electrodes fabricated on flexible boards, suitable hardware and software, and testing with different cell models.

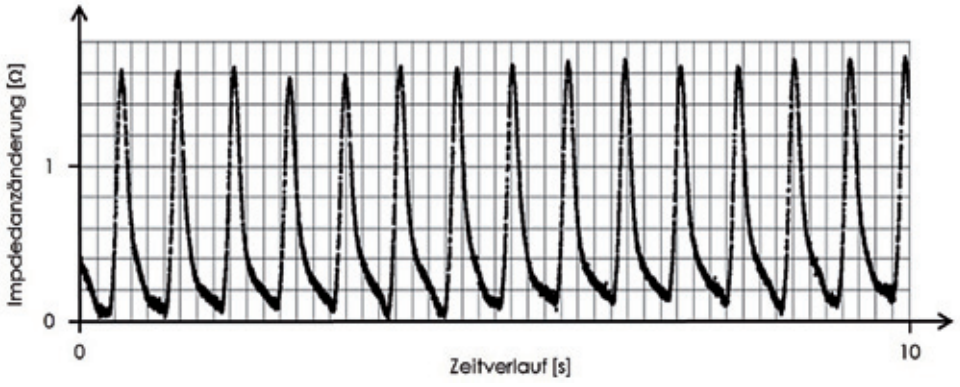

Fig. 1:
Impedimetric pattern of contractile (primary) murine cardiocytes growing on a Ø 290 µm electrode array (1 ms sampling rate, 10 mV/10 kHz measurement input signal). Using an electric circuit based on an impedance converter chip and the existing electrodes, we were able to detect the contractile patterns of cardiocytes by measuring impedance at 10 kHz. These pivotal experiments were important in defining the specifications for highly parallel and precise electronic circuitry.

Rapid impedance recording has now been implemented in a 96-well test plate prototype with complete electronic circuitry, data processing and software user interface. The integration of extracellular field potential (EFP) recording as well as active electric stimulation of cell cultures is in progress. Fig. 2 illustrates a short sequence from EFP measurement on the same electrode as for bioimpedance recordings. It was clearly demonstrated that the bioimpedance signal results from the mechanical "beating" of the cardiomyocyte layer, while the EFP signal arises from transient electric cell depolarisation.

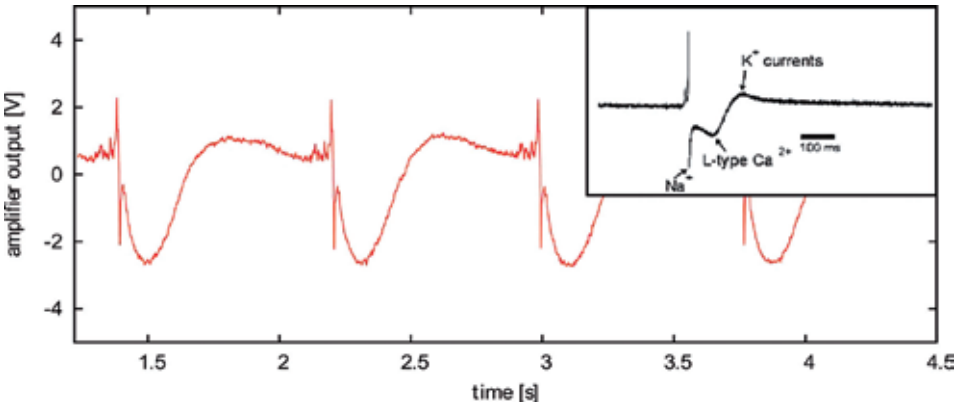

Fig. 2:
Result of extracellular field potential measurement. Sum of the signal from contractile cultures of human cardiomyocytes (Cor4U, Axiogenesis), growing on a Ø 500 µm electrode, recorded with a single-channel amplifier.

➢ *Name: "i³ screen – in-vitro Impedanz Screening System für die Sicherheitspharmakologie"*
(i³ screen – in vitro impedance screening system for use in safety pharmacology)

➢ *Duration: 2013 to 2015*

➢ *Project partner: Nanion GmbH, www.nanion.de*

Supported by: Bayerische Forschungsstiftung (Bavarian Research Foundation)

Development of methods for non-invasive measurement of blood glucose

In short

Blood glucose levels affect several parameters such as temperature and pH on the surface of the skin. A novel approach to non-invasive "multivariate" blood glucose monitoring was taken in this project: the parallel analysis of several values correlated with blood glucose.

A lot of energy has been invested, and multiple studies performed in the field of „diabetes" worldwide to create a more convenient way for patients to monitor their blood glucose levels. Modern „blood glucose test strips" require only a few microlitres of blood taken from less painful areas such as the arm or the thigh.

However, invasive methods with intermittent measurements are always associated with poor or insufficient blood glucose monitoring, e.g. while resting at night or during physical activities hyperglycaemic and hypoglycaemic episodes may go undetected. Furthermore, the invasive sampling of blood involves risks for the patient such as infections, nerve damage and a general risk of non-compliance.

The challenge of finding a suitable non-invasive transdermal method of measurement lies in the development of sensors with a high level of sensitivity and reliability which are able to translate small variations in the blood glucose level into an easily detectable variation of the monitoring signal, while accounting for the layers of tissue between the sensor and the capillary system. A possible drawback is the influence the following factors may have on the measurement results: sweat, pigmentation, texture and thickness of the skin, artefacts caused by breathing or body movements, ambient temperature, contact pressure exerted by the sensor, as well as the data acquisition time. Under ideal conditions, the blood glucose concentrations should be detected within less than five minutes in a range of 18-540 mg/dl at a magnitude of error under 5%.

Non-invasive sensors can be based on the following two principles: either a direct concept based on chemical analysis of the glucose molecule, or an indirect method for detecting the effect the blood glucose has on secondary values such as skin temperature or pH variations.

During this research, a more or less novel approach to „multivariate blood glucose monitoring" was investigated: the parallel analysis of several values correlated with blood glucose which allows for significantly reduced artefacts in the prognosis of blood glucose levels – without any negative effects on the patient's compliance. The multivariate analysis is performed by using algorithms based on so-called „neuronal networks". The resulting prognosis of the blood glucose level is then compared with the values taken from the gold standard of invasive measurement and entered in a „Clarke Error Grid" (Fig. 1).

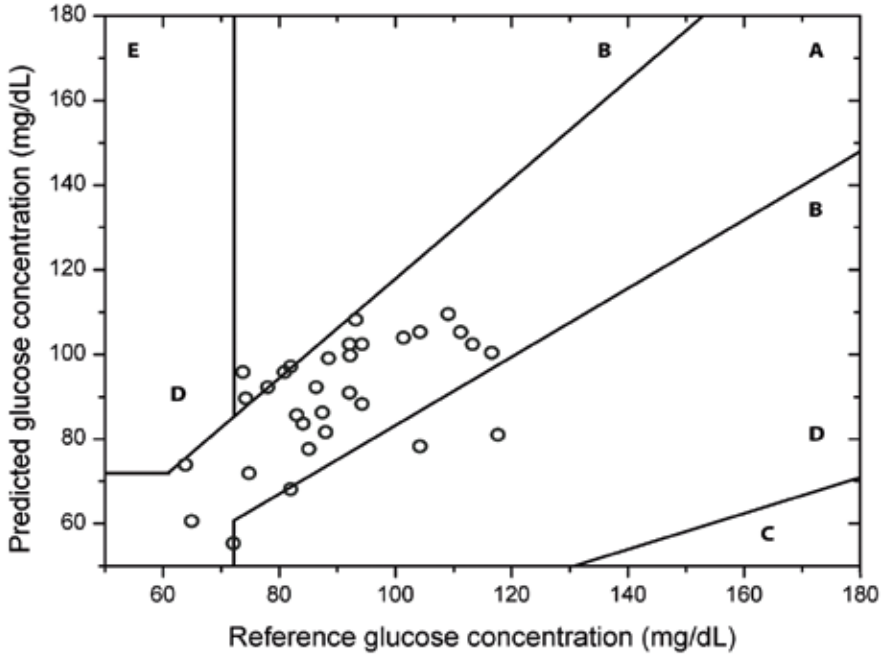

Fig. 1: Clarke Error Grid as a graphical representation of the multivariate analysis results. This method categorises the measurement value obtained from the device into five zones, A to E. Zone A represents clinically correct values, the other zones are for incorrect diagnoses with varying degrees of risk potential.

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- *C. E. F. Amaral, B. Wolf, „Cell-Electrode Interface in Bioimpedance applications“. 4th IEEE Conference on Nanotechnology. Munich, August 16-19, 2004, IEEE Proceedings (CD, ISBN:0-7803-8537-3).*

This research was possible thanks to a scholarship C. E. F. Amaral was granted by the Deutscher Akademischer Austauschdienst and was also supported by the Heinz Nixdorf Stiftung.
Project title: „Entwicklung von Methoden zur nicht-invasiven Blutzuckerbestimmung“
(Development of methods for non-invasive measurement of blood glucose)
Project life span: 2004 to 2007

Implantable wireless sensor system for monitoring bone healing

In short

This independent, wireless implantable measuring system was developed with the aim of monitoring the process of bone healing based on the measurement of oxygen saturation at the fracture site.

Bone healing has so far been monitored by diagnostic imaging methods such as X-ray, CT and MRI, or surgical intervention. Clinical experience provides reference values for determining the permitted degree of mechanical stress on implants, e.g. dental implants. Continuous monitoring of bone healing by means of microelectronic implants would enable physicians to individually control the healing time, the stress on the implant, the timing of transplantation and removal of the material used for osteosynthesis. The data continually acquired during this project are being used to better understand and study the processes taking place during bone healing.

The project team has developed an independent, implantable wireless measuring system. The aim is to record the healing progress by measuring oxygen saturation at the fracture site and provide the physician with the information thus acquired. The implant system comprises an electrochemical oxygen sensor, a microcontroller and wireless communications system, and is powered by a primary cell. The data on oxygen saturation are acquired periodically and sent to an external receiver via a radio interface, which in turn forwards the data via a radio or USB connection to an Internet database. The researchers involved or the attending physician can then view the data in a web browser. The implant is coated with a biocompatible material to protect it against external influences.

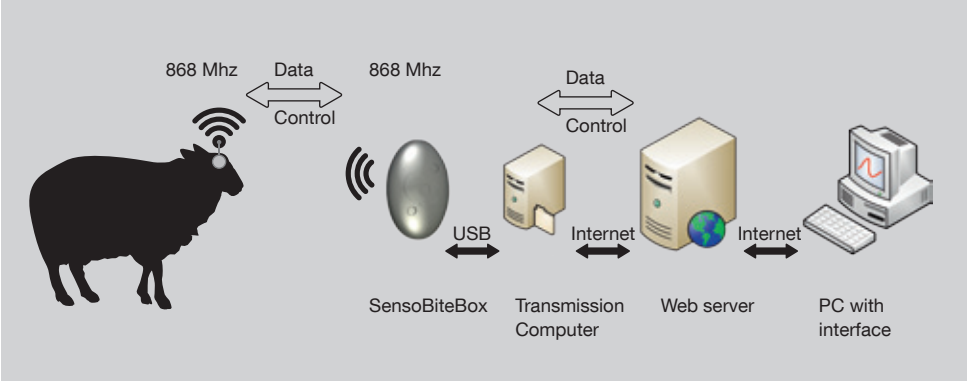

Fig. 1: Signal transmission link of a telematic implant

The system was implanted in a bone defect on the cranial calvarium in sheep as a means of demonstrating the functionality of the implant system as well as the correct operation of the wireless communications system. During the experiment, the electrochemical sensors revealed a strong drift due to increasing biofouling at the sensor, thereby causing unsatisfactory long-term stability. These findings initiated the development of an in-vivo calibration system for the oxygen sensor and an innovative membrane coating for the sensor surface as parts of the follow-up project „IntelliTUM“ at Heinz Nixdorf-Lehrstuhl für Medizinische Elektronik.

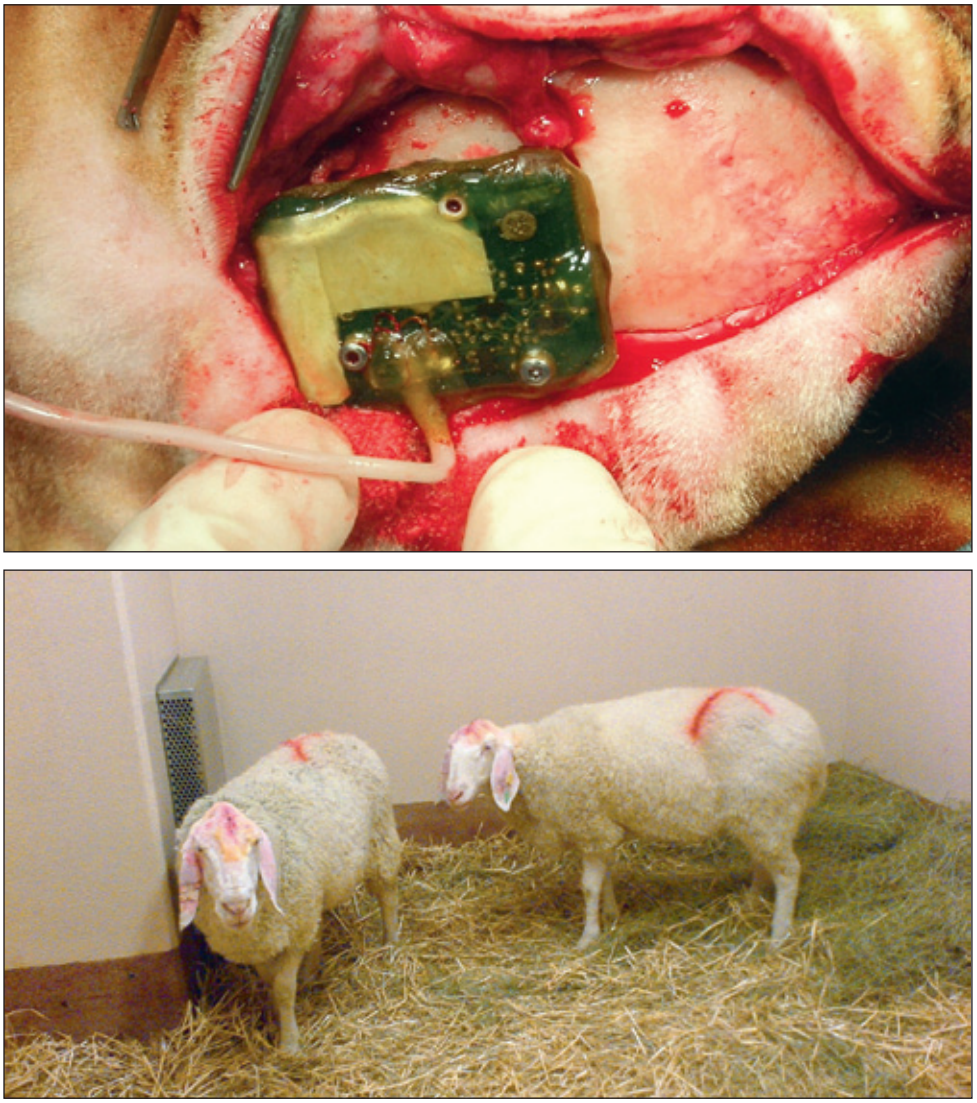

Fig. 2: Implanting the monitoring system in an animal model

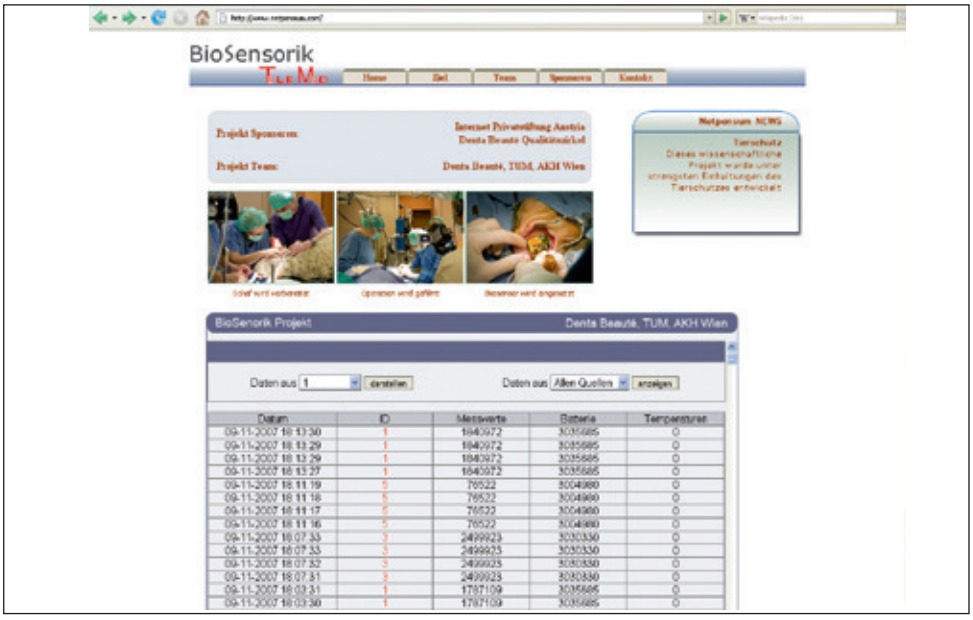

Fig. 3: Internet-based evaluation of the real-time measurement data obtained at the animal research institute

Selected publications

- *M. Sattler, J. Clauss, M. Schmidhuber, J. Belsky, B. Wolf, „Implantable sensor system for the moni-toring of bone healing“, In: Ratko Magjarevic, Olaf Dössel und Wolfgang C. Schlegel (Hg.): IFMBE Proceedings. Berlin, Heidelberg: Springer Berlin Heidelberg, pp. 281–284, 2009.*

- *S. Becker, B. Wolf: „Smart Electronic Systems for Therapy Support“, mstnews (2010), 1, 6-7.*

- *S. Becker, T. Xu, F. Ilchmann, J. Eisler, B. Wolf, „Concept for a gas-cell-driven drug delive-ry system for therapeutic applications“, Proc. IMechE Part H, J. Engineering in Medicine (2011), 225(12), 1196-1201.*

- *S. Becker, D. Hofsoey, Y. Eminaga, J. Clauss, J. Wiest, M. Brischwein, H. Grothe, B. Wolf, „Aktive Implantate in der Tumortherapie“, Deutsche Zeitschrift für klinische Forschung (DZKF), 3/4, 2012, S 38-41.*

This research was funded by the Internet Privatstiftung Austria,
Denta Beauté Qualitätszirkel
Project title: „Implantierbares drahtloses Sensorsystem zum Monitoring der Knochenheilung“ (Im-plantable wireless sensor system for monitoring bone healing)
Project life span: 2007

„PRINTS“ – Printed nanomaterials for microsensor technology

In short

The PRINTS project aims to fabricate sensors, conductive tracks, and actuators from nano-materials by means of inkjet printing and other printing techniques. This will permit the use of sensor applications in disposables as well as in environments where sensors so far have been too bulky or intrusive.

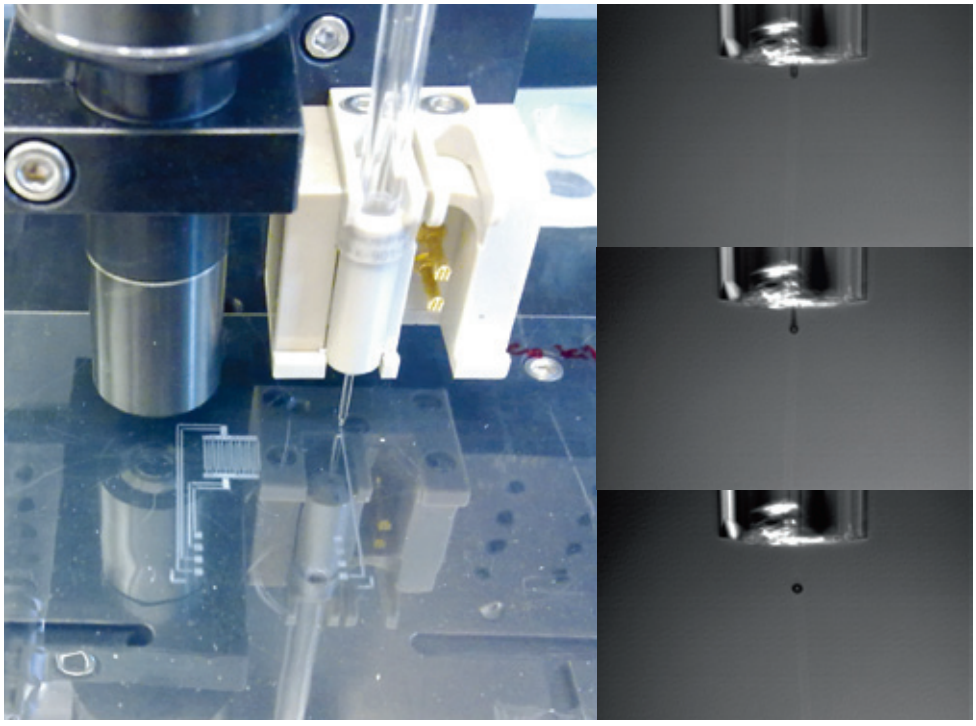

Fig. 1:
Left: Inkjet printing of nanomaterials. A glass capillary tube is used for printing and a camera for monitoring the printed lines on a transparent polymer film.
Right: Droplet ablation from the printing glass capillary tube, recorded by a stroboscopic camera.

The PRINTS project aims to fabricate sensors, conductive tracks, and actuators from nano-materials by means of inkjet printing and other printing techniques. The team's objective was to simplify the fabrication process and maintain or even enhance the functionality of the sensors in comparison to other production techniques. This should enable sensor applications to be used in disposable articles as well as in an environment where sensors so far have proved too bulky or restrictive.

The printable sensor technology investigated in this project entails both electrochemical and optochemical sensors. Actuators in the form of electrodes are used to stimulate the culti-

vated neurons and muscle cells. Uses for the printable multiparametric sensor chips include biomedicine and cell analysis, drinking water quality tests, as well as electrochemical gas microsensor technology. While impedimetric pH sensors can be manufactured with inkjet printing techniques, optochemical sensors are preferably produced with a compressed air dispenser, while protective and selective membranes for both sensor types can be obtained with either method. Conducting path structures have also been produced by screen printing with layer thicknesses of a few µm.

The ability to print electrically conductive structures is an attractive alternative to conventional photolithography, especially since it requires neither expensive templates nor high-temperature or vacuum processes. It offers a fast and contactless fabrication method that is suitable for flexible substrates and minimises material consumption and process steps. Nano-material or polymer solutions can be printed on various substrates to form conductive, semiconductive and insulating structures. Structures on PI foils, for instance, can be annealed by heating up to 300°C, but we also use room-temperature processes for both metallic and carbon structures which improve the conductivity of the printed patterns and their adhesion on the substrate. In printed Ag nanoparticle lines, a conductivity of 50% has been achieved with the bulk material. The lifetime of printed structures for disposable sensor chips was found to be up to 11 weeks under ac voltage in aqueous media.

The inkjet printing process itself is performed using a glass capillary tube (see Fig. 1) which ejects the ink from a small orifice using precise shock waves generated by a piezo actuator (Fig. 2). Fig. 3 illustrates conductive line structures in the form of impedance sensors printed on polymeric films. The interdigital electrode structures (IDES) are printed with a carbon nanotube/nanoparticle ink whereas the conducting lines consist of silver nanoparticles. The impedance spectra of pH-sensitive IDES are shown in Fig. 4. Fig. 5 depicts a screen-printed sensor foil for an “Intelligent Multiwellplate”.

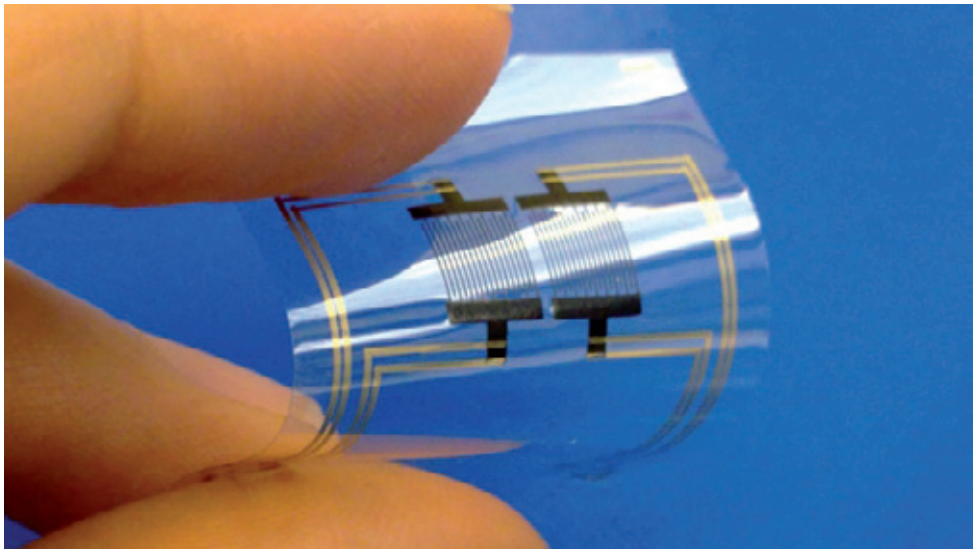

Fig. 2:
Impedance sensors printed on flexible film for integration in cell-based assays for diagnostic use.

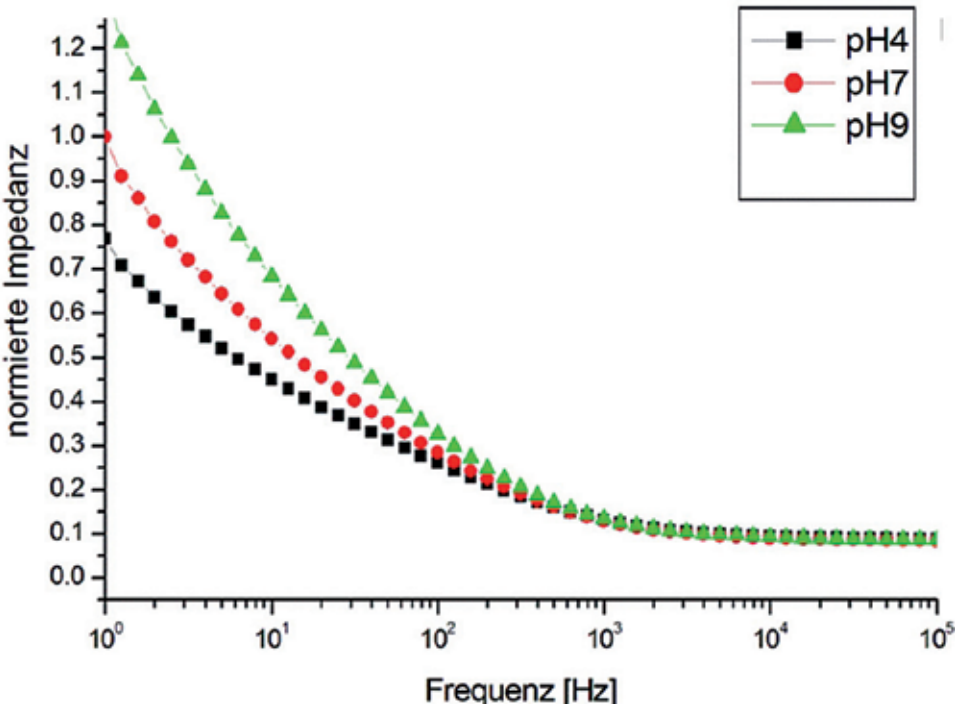

Fig. 3:
Normalized impedance spectra of SWCNT sensors at different pH levels. Increasing sensitivity is obtained at lower frequencies.

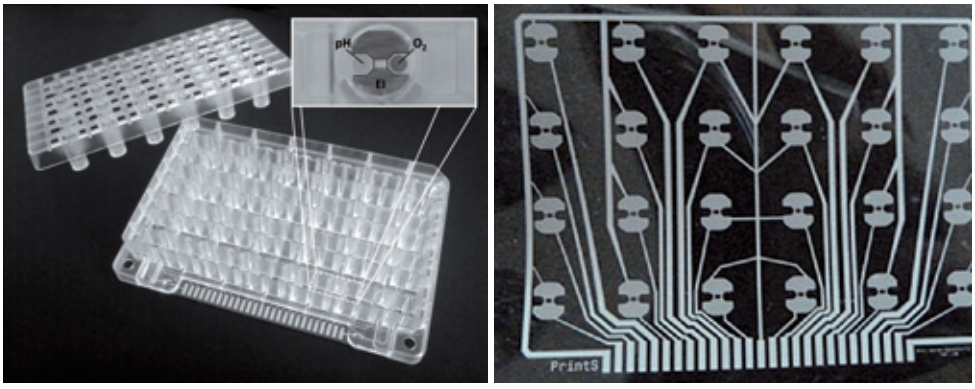

Fig. 4:
Left: „Intelligent multi-well plate“ with detailed view of a sensor.
Right: Screen-printed sensor foil for an „intelligent multi-well plate“.

Selected publications

- *T.B. Neumann, N. Mzoughi, H. Grothe, B. Wolf: „Nanosensoren. Inkjet Printing of Nanomaterials for Microsensors“, Biomedizinische Technik/Biomedical Engineering, Vol. 56, No. s1, pp. 1–8, ISSN 0013-5585, DOI: 10.1515/BMT.2011.819, September 2011.*

- *N. Mzoughi, B. Neumann, H. Grothe, B. Wolf: „Sensorik Chemo/Bio. Inkjet printed electrodes on PET substrate for biosensing applications“, Biomedizinische Technik/Biomedical Engineering, Vol. 56, No. s1, pp. 1–12, ISSN 0013-5585, DOI: 10.1515/BMT.2011.844, September 2011.*

- *N. Mzoughi, A. Abdellah, Q. Gong, H. Grothe, P. Lugli, B. Wolf, G. Scarpa: „Characterization of novel impedimetric pH-sensors based on solution-processable biocompatible thin-film semiconducting organic coatings”, Sensors & Actuators B: Chemical, 2012, 171, pp. 537-543.*

- *N. Mzoughi, Y. Eminaga, H. Grothe, B. Wolf, G. Scarpa, P. Lugli: „pH-Sensoren auf Basis biokompatibler halbleitender Polymere“, In: Bernhard Wolf (Hg.): Bioelektronische Diagnose- und Therapiesysteme. m3: microelectronic meets medicine. 1. Aufl. 2012, Aachen: Shaker Verlag, pp. 237–246. ISBN: 978-3-8440-0831-9.*

- *S.-L. Steffan, N. Mzoughi, H. Grothe, J. Wiest, B. Wolf: Evaluation of an Inkjet Printed Biochip, 35th Annual International Conference of the IEEE EMBS, Osaka, Japan, 3 – 7 July 2013, Transactions of Japanese Society for Medical and Biological Engineering, 51, Supplement, U-1.*

- *B. Wolf, C. Scholze, H. Grothe, M. Brischwein, „‘Medizin 4.0‘ – Die Bedeutung von Elektronik, Informationstechnik und Mikrosystemen in der modernen Medizin“, in: J. Gausemeier (ed), Vorausschau und Technologieplanung, 11. Symposium für Vorausschau und Technologieplanung, 29. - 30.09.2015, Berlin 2015, pp. 379 – 401.*

This research was funded by the Bundesministerium für Bildung und Forschung
Project title: „PRINTS - Gedruckte Nanomaterialien für die Mikrosensorik“
(PRINTS – Printed nanomaterials for microsensor technology), FKZ 16SV5393
Project life span: 2011 to 2014

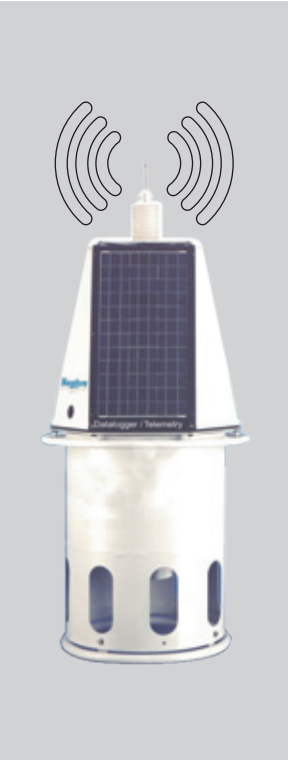

Fig. 2: Floating autonomous support unit suitable for various water monitoring sensors. The acquired data are radio-transmitted to a central office. The project group investigated how chip-based biomonitors may be integrated into this type of support unit. (Joint project with the company Rhode und Schwarz GmbH, Munich)

Silicon-algae hybrid sensor for remote monitoring of surface waters

In short

Monocellular green algae colonisation on a silicon sensor chip is the central element of this biomonitoring system, which can be used for monitoring lakes, rivers or waste water. The algae metabolism reacts even to low degrees of contamination in the test water.

Continuous monitoring of lakes, rivers or municipal and industrial water discharges is an appropriate means of complying with European quality standards for surface water reservoirs. Further, such an approach enables water to be monitored for reasons of environmental protection.

Currently, only in isolated cases „environmental monitors“ (Umweltmonitore) are used for water conservation purposes. This is done, for example by visually monitoring the swimming behaviour of fish or water fleas. Usually, this kind of biomonitoring is achieved by observing an „effect“ on a target organism, in contrast to determining the concentrations of certain substances as is the aim of chemical analysis. Currently, there are only few publications on the investigation of portable cell-based testing systems for long-term monitoring outside the lab.

This project, which was initiated in cooperation with a local dairy in the Ammersee region near Munich, involved colonising monocellular green algae on silicon sensor chips. The pH sensors on the silicon chip are able to measure changes in the microenvironment of the algae which are permanently influenced by their own aerobic or photosynthetic metabolism. The resulting „biohybrid element“, comprising the living organism and solid state sensors, permits detection of the synergistic effects of potential pollutants depending on the respective sensitivity profile of the algae species used.

The sensor chip is the central component of the biomonitor system. Further components are peripheral systems such as a controlled fluidic system with a filter unit for supplying the water to be tested, an illumination system to allow photosynthesis, radio modules for wireless data transmission, as well as a central electronic control unit. Since the complete system is designed to work independently between the servicing intervals (several months),

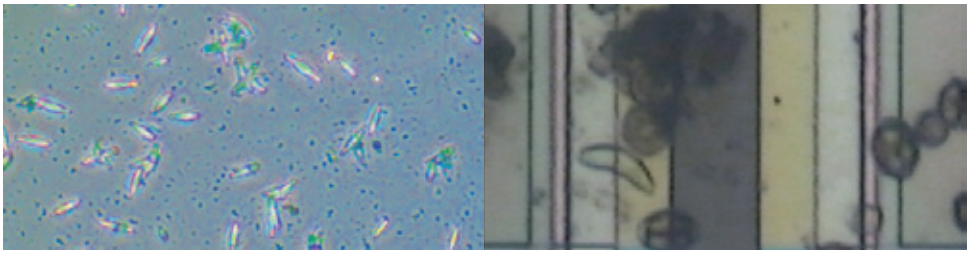

Fig. 1: Diatoms colonised on a silicon chip with ion-sensitive field-effect transistors

it is also important to ensure minimum energy consumption in all components.

Fig. 3 is an illustrative example of the water quality monitoring system and shows how living algae on a sensor chip are used to monitor the quality of aquarium water. The algae metabolism reacts even to low degrees of contamination in the test water, which is replaced in intervals of a few minutes. ISFETs measure the pH value directly under the algae. The vitality of the algae, which is an important indicator of water quality, is analysed by examining the pH variations.

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- *Wiest, J., „Toxizitätstest mit Grünalgen als Testorganismus“, energie | wasser-praxis, 7+8, 2009, p.90, 2009.*

This research was funded by Bayern Innovativ, the Andechser Molkerei Scheitz GmbH, as well as the Rohde und Schwarz GmbH München.
Project life span: September 2001 to September 2002
In 2008, the department was awarded the E.ON Umweltpreis (E.ON environmental award) for this work.

Fig. 3: Monitoring of water quality: (1) Aquarium water inflow and outflow; (2) Sensor module with pH-ISFETs, algae culture on silicon sensor chips and LED light source for ensuring photosynthesis; (3) Electronic unit for the pH-ISFETs with data display.

Intelligent mobile lab for bioelectronic analytics [IMOLA]

Fig. 1: BioChip-C (side length: 24 mm) with two pH sensors, two bioimpedance sensors, a sensor for measuring dissolved oxygen, a temperature sensor and various test electrodes.

In short

Real-time monitoring of cellular behaviour is a key technology in the development of cell-based methods and therapies. The IMOLA system may be used in such applications as individual anticancer chemotherapy, pharmaceutical drug development and environmental monitoring.

The Intelligent Mobile Lab (IMOLA) provides information on the metabolism and morphology of living cells. This system is able to perform a label-free detection of cellular responses to any experimental stimulation. The real time monitoring of cellular behavior is a key technology for the development of cell-based methods and therapies. The cellular specimens are examined by measuring rates of extracellular acidification (pH), cellular respiration (pO_2) and variations in cellular morphology (modulating the electric impedance of electrodes). Extracellular acidification and cellular respiration provide insight into the metabolic signature of the cell or tissue sample. Bioimpedance measurement provides information about variations in proliferation and morphology.

Cells are cultivated directly on a „BioChip" comprising the electrochemical microsensors for pH value, dissolved oxygen concentration and bioimpedance, plus an integrated temperature sensor for temperature control.
The BioChip as a self-contained cell culture vessel is placed into the IMOLA system and connected to a closed fluidic system.
The software module DALiA (Data Acquisition and Link Application) supplied with the IMOLA system serves for configuration and monitoring of ongoing experiments. It permits the adjustment of experimental protocols. Additional features are the graphical display of the measured data and a database for data storage.

When taking measurements from the cells, the driving pump is alternately switched on and

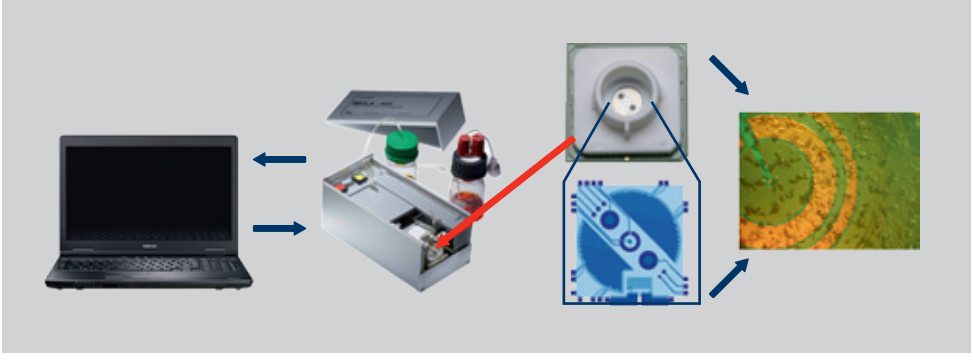


Fig. 2: The complete system

off. When in the „off“ position, the BioChips take measurements from the cellular specimens on the chip surface. During the subsequent pump phase, the microsensors are recalibrated and the cells are supplied with fresh cell culture medium or drug solutions. The duration of continuous cell monitoring may be up to several days.

A variety of cell types have already been investigated on the IMOLA System, including cells growing in suspension (e.g. yeasts and algae), adherent cell lines (e.g. MCF-7, L929, HeLa), cell cultures prepared from primary human tissue or three-dimensional spheroids.
Key experiments have shown a potential for applications in individualised anticancer chemotherapy, pharmaceutical drug development, regenerative medicine, alternatives to animal testing and environmental monitoring. The spin-off cellasys GmbH (www.cellasys.com) has further developed and commercialised the IMOLA technology.

Selected publications

- *B. Wolf, M. Brischwein, V. Lob, J. Ressler, J.Wiest, „Cellular signaling: aspects for tumour diagnosis and therapy“, Biomedizinische Technik, Vol. 52, pp. 164-168, DOI 10.1515/BMT.2007.030, 2007.*

- *M. Brischwein, H. Grothe, J. Wiest, M. Zottmann, J. Ressler, B. Wolf, „Planar Ruthenium Oxide Sensors for Cell-on-a-chip Metabolic Studies“, Chemical Analysis (Warsaw), Vol. 54, pp.1193-1200, 2009.*

- *J. Wiest, U. Schnakenberg, Ch. Koch, W. Wirths, F. Stadler, T. Bachinger, H. Grothe, B. Wolf, „An Iridium-oxide pH sensor for cell based assays“, Biomed Tech , 56 (Suppl. 1) DOI 10.1515/BMT.2011.276, 2011.*

This research was funded by the Heinz Nixdorf Stiftung.
Project life span: 1 December 2005 to 30 June 2006

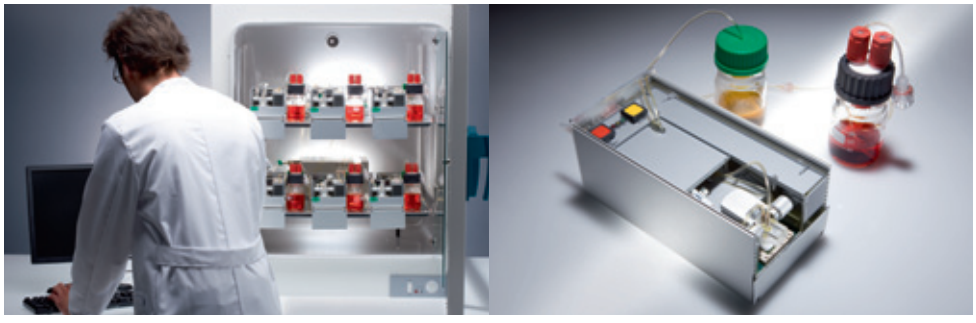
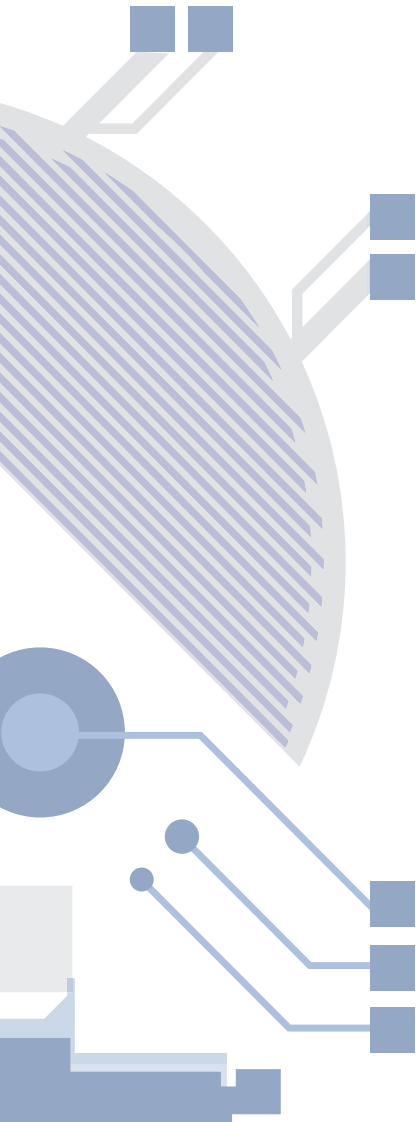


Fig. 3: The 6xIMOLA-IVD device enables examination of six cell samples at the same time. For optimum temperature control, the system is integrated into an incubator.

Chips not mice: biohybrid microelectronic components as an alternative to animal testing

In short

Our biohybrid systems may be regarded as “test benches” for living cells or tissues. They can be used instead of animal testing for example to detect side reactions in new pharmaceutical compounds.



Today, animal testing is still the method of choice for many issues of pharmaceutical product development and toxicological research. Legislation in the European Union however is increasingly restrictive towards use of animals for biological or medical testing, mainly due to ethical reasons.

Targeted effects and side reactions of new pharmaceutical compounds are to be tested thoroughly prior to the launch of clinical trials with humans. Numerous other chemicals, which are brought into the environment need to be evaluated with respect to their toxicology. Although it appears to be difficult to replace animal testing – with its distinct capability to map complex inter-organ relationships and pharmacodynamics – completely, their number can be reduced by the application of appropriate in-vitro alternatives based on well-differentiated cells from human origin. Sensor-based and label-free cell assays allow a continuous recording of cell responses to applied compounds in time scale from minutes to many days, including the possibility to test recovery effects [1, 2].

There are various approaches to such biohybrid devices comprising cellular target and microscaled sensing elements. We selected sensor chips based on glass, ceramic and silicon substrate integrating sensors for pH value, dissolved oxygen value and electric impedance (Fig. 1). Cells or tissues are directly cultured on the surface of these sensor chips.

Necessary additional components to arrive at practical instruments are cell culture maintenance systems including fluidics for regular exchange of culture media or drug solutions and devices for temperature control. In general it is important to strictly keep stress-free environmental conditions resembling the physiological in-vivo situation as close as possible.

As in the world of technology, these systems may be regarded as „test benches“ for living cells or tissue enabling the observation of both rapid, acute and cytotoxic effects and slower, chronic or cytostatic responses of cells to nearly any applied chemical compound [3, 4].

Selected publications

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- *[2] J. Wiest, "Extracellular acidification and changes in bioimpedance of L929 cells", ALTEX 28, p. 76, 2011.*
- *[3] M. Brischwein, E.R. Motrescu, A.M. Otto, E. Cabala, H.Grothe, B. Wolf, „Functional Cellular Assays with Multiparametric Silicon Sensor Chips", Lab on a Chip 3, pp. 234-240, 2003.*
- *[4] M. Brischwein, H. Grothe, A.M. Otto, B. Wolf, „Microphysiological Testing of Tumour Cells for Chemosensitivity: Use of Bioelectronic Sensor Chips", mstnews 1, pp. 34-36, 2004.*
- *[5] F. Demmel, M. Brischwein, P. Wolf, F. Huber, C. Pfister, B. Wolf, "Nutrient depletion and metabolic profiles in breast carcinoma cell lines measured with a label-free platform", Physiol. Meas. 36 (2015) 1367-1381.*
- *[6] C. Pfister, C. Bozsak, P. Wolf, F. Demmel, M. Brischwein, "Cell shape-dependent shear stress on adherent cells in a micro-physiologic system as revealed by FEM", Physiol. Meas. (2015), 36, 955-966.*

This research was funded by the BMBF, the Heinz-Nixdorf-Stiftung, Bayern Innovativ and the Bund der Freunde der Technischen Universität München e.V., as well as the Softwarehaus Zuleger GmbH.
Project title: „CHIP STATT MAUS: Planare und miniaturisierte mikroelektronische Sauerstoff-Sensoren für Tumor – Chemosensitivitätsanalysen“ (CHIPS NOT MICE: Planar and miniaturised microelectronic oxygen sensors for tumour chemosensitivity analyses.)
Project life span: 2006

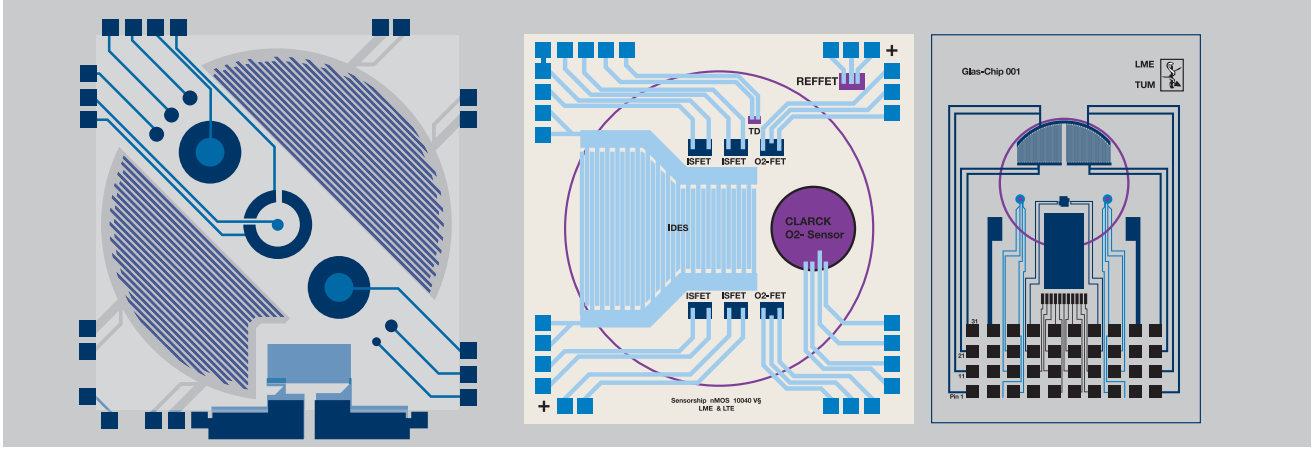


Fig. 1: Glass-, ceramic- and silicon sensor chips for cell and tissue analytics. The circle indicates the cell culturing surface

Handheld system for mobile cell-based assays [µLA]

In short

The novel µLa (microLab) testing device is easy to operate; it has been developed as a first step towards on-site food analysis. For the first time, evidence has been obtained that living cells can be used as signal transducers for food tests.

In recent years there have been an increasing number of reports about food contaminated with pesticides. While parts of this increase may be attributed to improved analytical methods, these findings have generally sensitized the public for food quality. Currently foodstuffs can only be analysed in time-consuming, costly tests in specialized laboratories. Novel testing devices such as the µLA (microLab) have been developed by a project group in our department as a first step towards food analyses to be performed on site with a handheld device that is easy to operate. An existing table-top version (IMOLA) was the basis for successfully miniaturising the system, resulting in a wireless handheld device for measuring the vitality of living cells.

Contaminated samples are placed on test cells in the system. If their vital state deteriorates, the system will detect this change, compare the values detected with reference values in an Internet database via a wireless connection, and display the result for the user.

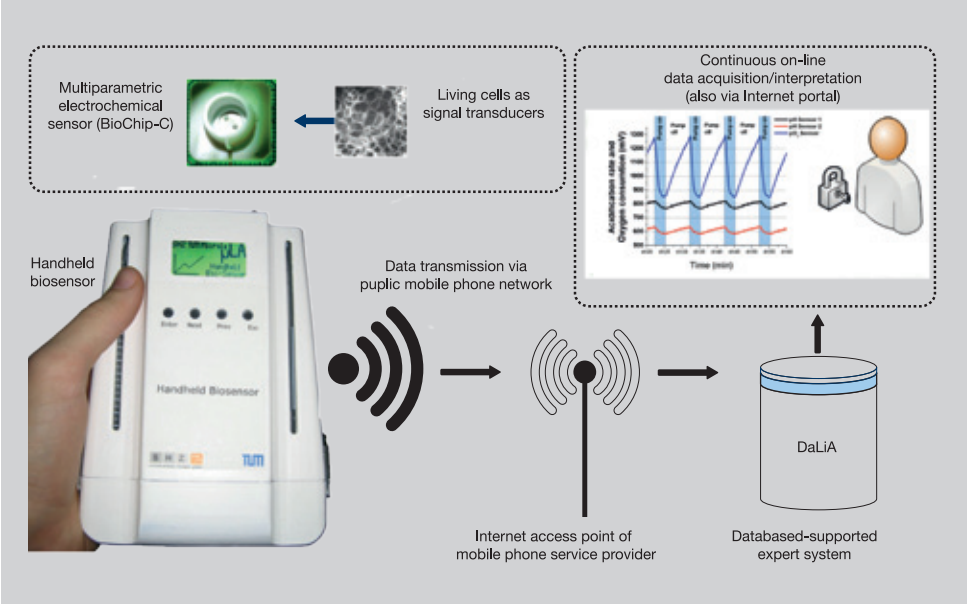


Fig.1: µLA Handheld Biosensor system for mobile cytobiologic assays and cellristor-application.

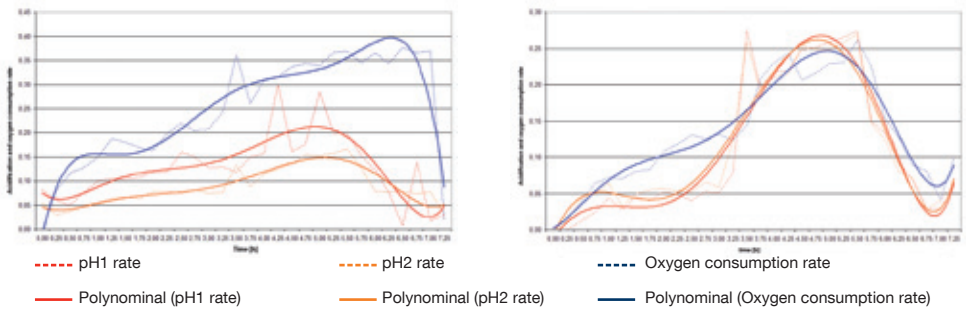


Fig. 2: Energy drink A was added to the yeast „Vita Vegan“. As a result, the metabolism values increased substantially. After about 5h, the „energy drink“ medium was replaced by the initially used medium. Analysis method: gradient analysis of the pH value and partial oxygen pressure in the surrounding micromilieu.

Fig. 3: Energy drink B was added to the yeast „Vita Vegan“. The metabolic values did not increase as much as with energy drink A. After about 5h, the „energy drink“ medium was replaced by the initially used medium. Analysis method: gradient analysis of the pH value and partial oxygen pressure in the surrounding micromilieu.

This research project employed an initial, miniaturised prototype with the name „µLA“ (micro Lab) to perform a pivotal food testing experiment. The influence of conventional sprays (fungicides) used in fruit farming on the vitality of yeast cells was examined, revealing that the lowest concentration as recommended by the manufacturer affected cell vitality.

This is a big step toward providing a handheld system for analysis of food quality. For the first time, there was evidence that living cells can be used as signal transducers for food tests. Figures 2 and 3 provide an illustrative example: „energy drinks“ were added to a test culture of yeast cells (Bioavailability-Test / “Bioverfügbarkeits-Test”).

Selected publications

- *M. Schmidhuber, J. Wiest, A.M. Otto, M. Brischwein, H. Grothe, B. Wolf, **„Microelectronic Cellular Vitality Monitoring“**. In Noll, T. (ed.), Cells and Culture, ESACT Proceedings, Volume 4, Part 2, 2010, 89-93, DOI: 10.1007/978-90-481-3419-9_15.*

- *M. Schmidhuber, B. Becker, J. Wiest, B. Wolf, **„Development of a Multiparametric Handheld Biosensor for use in Mobile Applications“**, The IEEE Region 8 Eurocon 2009 Conference, May 18-23, 2009, Saint-Petersburg, Russia, ISBN 978-1-4244-3861-7, pp. 114-121, IEEE Catalog Number CFP09EUR-CDR 2009 IEEE, Library of Congress Number 2009900519.*

- *M.Schmidhuber, J. Wiest, B. Wolf, **„A Multiparametric Handheld Biosensor for Mobile Metabolomics“**, The IET Conference on Synthetic Biology, Systems Biology and Bioinformatics, March 23-25, 2009, Cambridge, UK, pp. 192-193.*

This research was funded by the Bayerische Forschungsstiftung.
Project title: „IMOLA - Intelligent Mobile Lab“
Project life span: 1 April 2006 to 31 March 2009

Virtual Lab – an interactive telemedicine system for personalised diagnosis and therapy

In short

Virtual Lab is an ideal development project and test platform for personalised treatment as well as for other therapeutic concepts involving long-term assistance and individual coaching.

When treating chronic diseases such as hypertension, diabetes mellitus, obesity or respiratory disorders, a change in the patient's habits and lifestyle is usually the key to sustainable therapeutic success. Such patients need long-term assistance and individual coaching.

In this context, telemedical assistance systems can help to save resources and provide a personalised solution. Our COMES® system (see article New therapy options with „COMES®") offers a flexible concept involving a monitoring of body functions and therapeutical recommendations.

The virtual telemedicine lab as implemented with COMES® includes a large variety of options for use in diagnostics and therapy. Individual data patterns can be recorded from the patient's real-life environment using various sensor-based measuring devices with feedback and evaluation options. The Virtual Lab is an ideal development and test platform for personalised treatment as well as for other therapeutic concepts. The measurement of various parameters such as blood pressure, blood glucose or activity allows both the patient and the attending medical professional to give direct behavioral feedback. The efficiency of therapeutic interventions or recommended relaxation exercises in an authentic setting can be controlled immediately. Pharmaceutical interventions and behavioural therapies may be tested under realistic conditions.

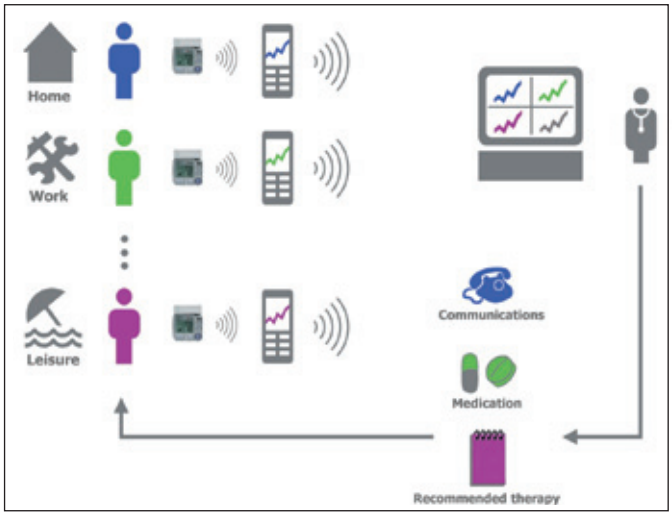


Fig. 1: The structure and principle of the Virtual Lab

The system is particularly suitable for assisting the patient during therapy. This has been demonstrated, for example, in preclinical research studies of bioa-

coustic hypertension therapy. In particular, by using pieces of music chosen to suit the individual patient, we used the anti-hypertensive effect of selected iterative sound patterns as a possible intervention in patients suffering from essential hypertension. This means that acoustic signals can modulate metabolic and central nervous functions and evoke physiological effects in humans. We also intend to investigate the described effects of different light qualities on humans as a future extension of the Virtual Lab.

Fig. 2: The first generation of the measuring devices connected to COMES© to be used as Virtual Lab equipment: 1) blood glucose meter; 2) wrist sphygmomanometer; 3) Blackberry telephone with Bluetooth connection; 4) step counter; 5) upper arm sphygmomanometer

Selected publications

- *P. Friedrich, J. Clauss, A. Scholz, B. Wolf, „Sensorik für telemedizinische Anwendungen“, in: Goss, Middeke, Smetak (Hrsg.), Praktische Telemedizin in Kardiologie und Hypertensiologie, Georg Thieme Verlag (2009), ISBN 978-3-13-149931-8, S. 6-14.*
- *P. Friedrich, T. Spittler, S. Tübinger, W. Tiedge, B. Wolf, „COMES® - ein Konzept zur personalisierten telemedizinischen Assistenz - oder - auf Anruf Arzt“, in e-Health 2011 Informationstechnologien und Telematik im Gesundheitswesen / Frank Duesberg (Ed.) Solingen, Medical Future Verlag, 2010.*
- *B. Wolf, M. Brischwein, H. Grothe, P. Friedrich, M. Schmidhuber, D. Grundl, T. Spittler, E. Cabala, S. Becker, B. Gleich, J. Clauss, A. Scholz, J. Wiest, B. Becker, P. Wolf, „Komponenten und Systeme für die personalisierte Assistenz“, in: W. Niederlag, H.U.Lemke (ed.), Personalisierte Medizin, Health Academy Bd. 14, 2010, S. 215-234.*
- *J. Gausemeier, B. Wolf, J. Clauss, P. Friedrich, K. Herzog, A.-C. Lehner, M. Lehner, M. Placzek, T. Schierbaum, T. Spittler, T. Westermann, „Telemedizinische Assistenzsysteme – Technik, Markt, Geschäftsmodelle“, Heinz Nixdorf Institut, Universität Paderborn, Heinz Nixdorf-Lehrstuhl für Medizinische Elektronik, Technische Universität München, Paderborn/München, 2014.*
- *B. Wolf, H. Grothe, K. Herzog, F. Demmel, J. Wiest, W. Wirths, J. Clauss, M. Brischwein, C. Dormeyer, M. Gül, K.-U. Hinderer, P. Friedrich, “Von der TUM in den Markt: Mikroelektronik für Diagnose und Therapie“, in: F. Duesberg (ed), e-Health 2015 Informations- und Kommunikationstechnologien im Gesundheitswesen, Solingen/Mittweida, medical future verlag, 2014, 120-127.*

The Virtual Lab is the result of the research performed as part of various telemedicine projects between 2005 and 2010, which was funded by the Heinz Nixdorf Stiftung and the Siemens AG.

Non-invasive sensor technology for stress analysis as a means of maintaining mobility in the 50 plus generation – [FBA, (FahrerBeanspruchungsAnalyse) driver stress analysis]

In short

Development of a system for analysing a driver's stress level using electrodes integrated in the steering wheel. By incorporating this system into the electronic system of a vehicle, it is possible to offer the user support and assistance.

Mobile individuals are socially more active and are found to be in better health. As for other generations in our society, it is very important that the fastest growing age group, namely those over 65 years of age, maintain their mobility.

In the future, the so-called „50 plus generation" will increasingly outweigh other age groups as drivers of personal vehicles. Potential driver assistance systems should therefore include an additional driver monitoring function. Such systems would provide individual support adapted to the situation according to the driver's stress level: by means of a non-invasive sensor system, vital parameters could be measured and the stress level could be calculated from physical, emotional and mental stress factors. The stress level data thus obtained could be used to configure the driver assistance and emergency assistance sys-tems. In this context, our fdepartment has developed a system for analysing a driver's stress level by means of a mobile platform. This unit also records the vital parameters that enable the assessment of cardiac irregularities, derived from ECG sensors integrated in the seat or the steering wheel of the vehicle. If this system for „driver stress analysis and emergency detection" is incorporated into the electronic system of a vehicle, it is possible to offer support and assistance to the user.

The FBA system consists of four main components: Data acquisition from one or several vital parameter data streams is complemented by an input feature for the required configuration. The central feature of this application is the driver stress analysis unit performing the evaluation. All stress levels calculated by the system as well as stress trends are displayed on a special screen. As far as possible, these parameters are transmitted to the vehicle assistance systems in order to generate the support and assistance described above, thereby closing the feedback patch (see Fig. 1). The options provided by the database include trend analyses and long-term monitoring as well as a self-learning configuration feature.

The driver test bench developed in this project enables ECG data to be captured by gold-plated copper electrodes integrated in the steering wheel. A monitoring amplifier is placed directly in the steering wheel, with all further electronic processing equipment integrated in a central board where all the parameters are digitalised by a data acquisition and measu-

ring card with real-time capabilities. Data reduction and analysis of the measured values is then performed synchronously by MATLAB/Simulink software in a mobile computer.
By selecting specific filters and processing steps, the stress level can be calculated and retrieved by external applications. The graphics display can be seen in Fig. 3.
The system was incorporated into a passenger car and was successfully tested in urban traffic.

Selected publications

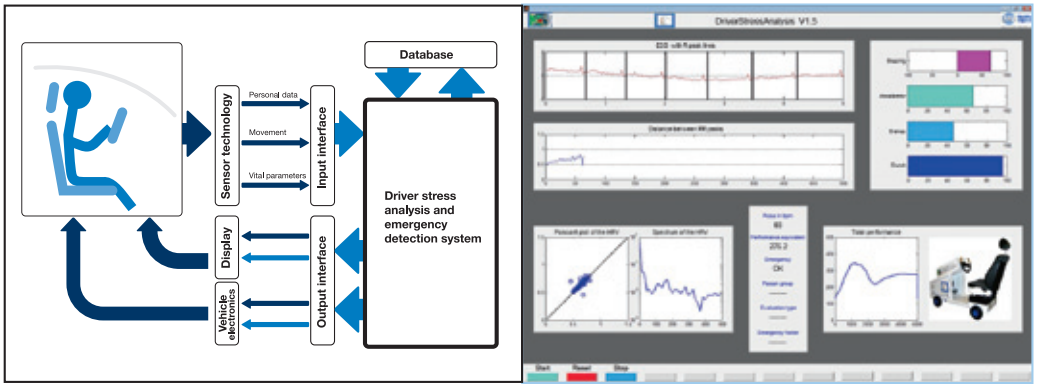
Zauner, P.; Wolf, B.: „Der Autofahrer der Generation Plus“. München 2007.

This research was carried out in 2007 for the purposes of a dissertation on the topic „Fahrerbeanspruchungsanalyse und Notfallerkennung mittels biomedizinischer Vitalparameter“ (Driver stress analysis and emergency detection by means of vital biomedical parameters), in the context of a project initiated by Ambient Assisted Living (AAL).

Fig. 1: Driver stress analysis concept

Fig. 2: User screen of the FBA

Fig. 3: System test set-up



Sensocopter: a flying multisensor platform

In short

With the aid of integrated sensors (gas sensors, radioactivity sensors, image sensors, chemical sensors), the sensocopter enables acquisition of various environmental and situational parameters related to fires, disasters, or other incidents on the ground.

Sensocopters are flying objects belonging to the helicopter family generating lift via four propellers arranged in one plane. By tilting the propeller plane, quadrocopters are able to move freely in all directions. In recent years, scientists have not only been interested in sensocopters due to their agility but also because of the wide range ofpossibilities they offer for unmanned aviation, irrespective of the fact that engineers have not yet been successful – or not sufficiently so – in developing these aircrafts for manned aviation.

There have been more and more media reports about the most recent scientific achieve-ments in this field. Powerful video systems enable monitoring applications at minimum effort and cost. By combining the copters with GPS or other tracking methods, their range of application can be extended without needing to consider the RC pilot‘s range of vision. Sensocopters equipped with appropriate sensor and control systems could be used in areas that are virtually inaccessible to humans or pose a substantial risk to the pilot‘s health. The drones may be able to detect contamination of all kinds, thus enabling their extent and the associated risks to be assessed. The sensocopter used at the Heinz Nixdorf-Lehrstuhl für Medizinische Elektronik is able to fly on GPS-tracked routes and transmit images from an on-board camera to a mobile ground station via radio. Via a Bluetooth interface, the data acquired by the on-board sen-sors (gyroscope, acceleration sensors and altimeter) as well as the GPS position can also be displayed at the mobile ground station. It is this same interface that can be used to send pre-defined GPS routes to the sensocopter, which will then start to fly along these routes when activated by remote control.

With the help of the integrated sensors (gas sensors, radioactivity, image sensors, chemical sensors), such a system permits an initial impression to be obtained of the situation on the ground, thereby enabling the acquisition of various environmental and situational parameters related to fires, disasters or other incidents without risking the health of emergency workers. Currently, further interfaces and sensors are being tested to enhance and extend the range of obtainable data and enable better assessment of potential uses.

This research was carried out during the student project „Quadrokopter: Eine fliegende Plattform für Sensoranwendungen“ (Quadrocopter: a flying platform for sensor applications) from 2011 to 2013.

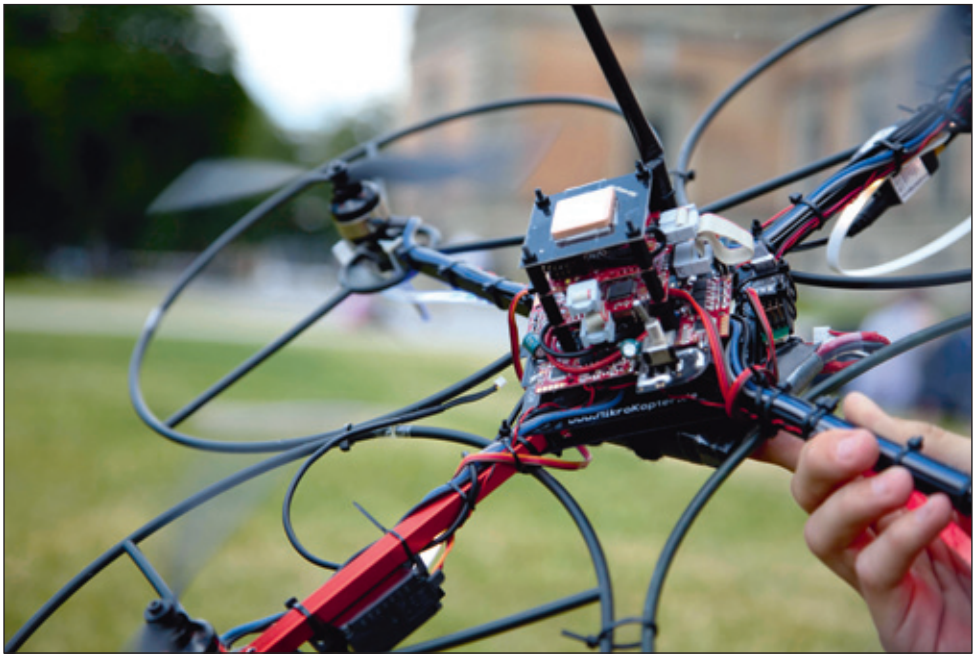


Fig. 1: The sensocopter in starting position, with sensor interface and camera

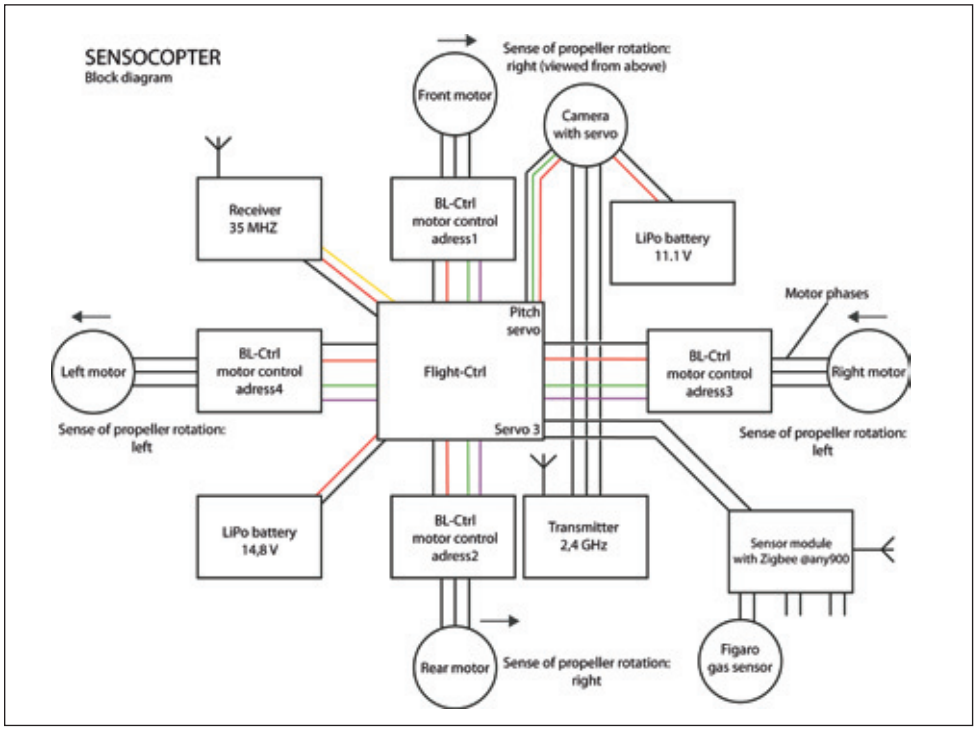


Fig. 2: Wiring of the sensocopte

Tumour diagnostics

Development of a patient-specific tumour chemosensitivity test based on a silicon sensor chip [CST]

In short

Microfabricated, silicon-based sensor chips have been developed for the purposes of cell cultivation and multiparametric monitoring of pericellular pH and dissolved oxygen. After integration into a fluidic system, they constitute a versatile, label-free, cell-based assay platform ready for use in pharmaceutical and toxicological research.

Despite the advances that have been made in the field of chemotherapeutic drugs, patients still only receive certain therapies (known as the „stratification of patient groups“) on the basis of little or relatively vague individual diagnostic data. It is general knowledge that patients suffering from tumours of the same histopathologic class may respond very differently to medication.

Our „chemo-sensitivity-testing” (CST) project saw the development of planar silicon-based sensor chips as a culture substrate of human tumour cells. The integrated sensors record the functional cell reaction to agents that are applied to the chips. Specifically, these sensors measure electrical impedance (Fig. 1), the dissolved oxygen concentration and extracellular pH value. This multiparametric approach increases testing safety and facilitates data interpretation. The fact that this system does not require the cells on the chip to be marked in any way allows for several days of continuous monitoring, a period necessary also for detecting delayed cell reactions or potential recovery effects.

The measurement parameters are values that are closely interrelated with the cellular signal network: cell death for example is regularly coupled with cytomorphological changes that are reflected by the electrical impedance values.

As a result of this project, we developed a six-channel device (Fig. 2) in cooperation with our clinical and industrial partners. This device forms the basis for further developments using

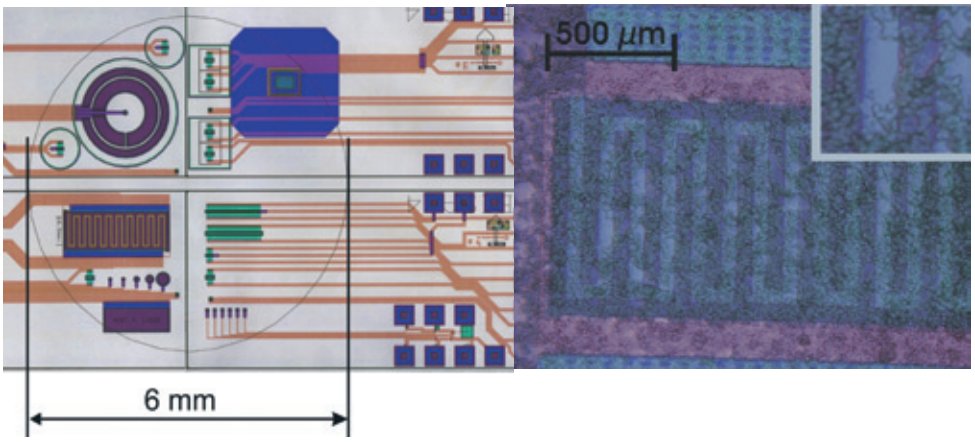


Fig.1: (Left) Layout of the silicon sensor chip for measurements from the cell cultures. Within the indicated area, with a diameter of 6 mm (identified by the two vertical lines), there are planar sensors that are in direct contact with the cells and the cell culture medium. (Right) Section of a silicon sensor chip with an interdigitated electrode structure for electrical impedance measurements. A culture of LS 174 T cells derived from human colon carcinoma is growing on the surface. The right upper window provides a detailed view at higher magnification.

clinical samples such as tissue collected during surgical interventions or exploratory excisions (biopsies).
The company Bionas GmbH, a spin-off founded in cooperation with Micronas GmbH introduced a follow-up model of that system into the market (www.bionas.de).

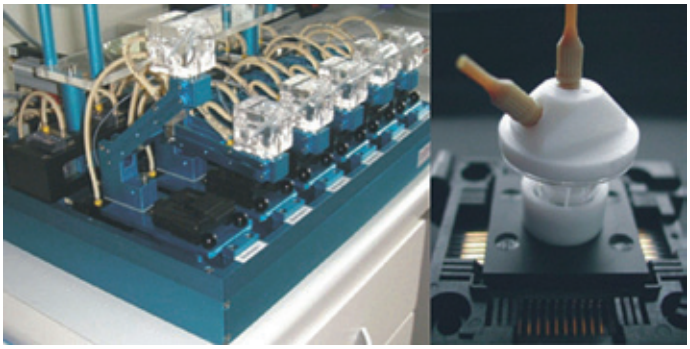


Fig. 2: Left: six-channel testing device. Right: sensor chip with „Package“ and a fluidics adapter (white) on an electronic socket

Selected publications

- *M. Brischwein, E.R. Motrescu, A. M. Otto, E. Cabala, H. Grothe, B. Wolf, „Functional Cellular Assays with Multiparametric Silicon Sensor Chips“, Lab on a Chip 3 (4), pp. 234-240, LabChip 2003.*
- *A.M. Otto, M. Brischwein, E. Motrescu, B. Wolf, „Analysis of drug action on tumour cell metabolism using electronic sensor chips“, Archiv der Pharmazie 337, 682-686 2004.*
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- *C. Pfister, C. Forstmeier, J. Biedermann, J. Schermuly, F. Demmel, P. Wolf, B. Kaspers, M. Brischwein, “Estimation of dynamic metabolic activity in micro-tissue cultures from sensor recordings with an FEM model”. Med Biol Eng Comput, 2015.*

This research was funded by the Bundesministerium für Bildung und Forschung.
Project title: „Entwicklung und Erprobung eines patientenspezifischen Tumour-Chemosensitivitäts-Assays auf der Basis eines Silizium-Sensor-Chips“ (Development and testing of a patient-specific tumour chemosensitivity test based on a silicon sensor chip)
Project life span: November 2000 to June 2004

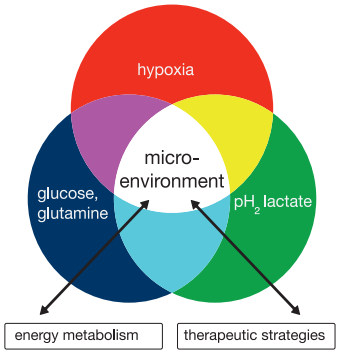


Fig. 1: Soluble substances in the tumour micro-environment. Hypoxia represents an insufficient oxygen level in the tumour tissue. At the same time, the milieu exhibits a low pH, excessive lactic acid (lactate) and low concentrations of nutrients such as glutamine and glucose. The interrelationships of these values regulate the metabolic patterns of the cells and also affect their sensitivity to therapeutic measures.

Tumour micro-environment and tumour metabolism: systemic analysis using sensor chip technology

In short

This project systematically analysed basic metabolic parameters in tumour cell cultures. We aim to use the resulting data to develop new, efficient diagnostic and therapeutic concepts in the field of oncology.

To understand the regulatory mechanisms of the energy metabolism, proliferation and cytolysis of tumour cells, it is essential to learn about the characteristics of the micro-environment of tumour tissues. The microenvironment of a tumour cell encompasses not only the surrounding cells and the so-called extracellular matrix, but more importantly the soluble compartment containing growth factors, cytokines, nutrients and waste products, and ions. The interplay between the micro-environment and the metabolic activity of a cell or a cell population may provide diagnostic and prognostic indicators of cancer growth as well as information useful for developing more efficient (chemo) therapeutic strategies

The aim of the project entitled „Cell-based assays using bioelectronic sensor chips for the dynamic analysis of tumour cell metabolism and chemosensitivity“ was to systematically analyse basic metabolic parameters in tumour cell cultures by selecting predefined conditions representing different tumour microenvironments (Fig. 1)

Two well-characterised human breast cancer cell lines serve as a model for tumours of differing malignancy: Characteristic of one of these cell lines is the preservation of hormonal sensitivities and cell contacts and low metastatic potential (MCF-7), while the other has lost these differentiated functions and has a high metastatic potential (MDA-MB231). To modulate their metabolism, the tumour cells are cultivated under predefined conditions as outlined in Fig. 1. For clinical use, certain inhibitors of specific paths of energy metabolism are tested for their efficacy under different microenvironmental conditions.

Our methodical approach comprises a defined number of different assay systems. These include established biochemical and cytobiological assays for measuring specific cellular activities. Using a newly developed technology based on multiparametric microsensor chips on which cells are cultivated directly, rapid changes in pH and oxygen concentrations (closely associated with cellular metabolic activity) as well as in the electrical cell-substrate impedance (changes in which are linked with the morphological parameters of the cells) can be monitored in real-time. Using a fluidic perfusion system, it is furthermore possible to not only simulate pre-defined microphysiological conditions, but also to maintain culture conditions for long-term incubation studies.

The results demonstrate, for example, that by combining extracellular glutamine and glu-cose

levels with different pH values the said parameters interact in a non-linear fashion with the energy metabolism – but do not correlate with the cell proliferation rate.
During our investigations, we obtained data suitable for describing the systems biology of tumour cell metabolism in interaction with the tumour microenvironment. Moreover, it is our aim to use this data to develop new options for efficient diagnostic and therapeutic concepts in oncology.

Selected publications

- *A.M. Otto, M. Brischwein, E.R. Motrescu, B. Wolf, „Analysis of drug action on tumour cell metabolism using electronic sensor chips“, Archiv der Pharmazie , Vol.337, pp. 682-686, 2004.*
- *E.R. Motrescu, A.M. Otto, M. Brischwein, S. Zahler, B. Wolf, „Dynamic analysis of metabolic effects of chloroacetaldehyde and cytochalasin B on tumour cells using bioelectronic sensor chips“, J. Can. Res. Clin. Oncol. Vol. 131, pp. 683-691 DOI 10.1007/s00432-005-0015-2, 2005.*

This research was funded by the Deutsche Forschungsgesellschaft.
Project title: „Cell-based assays using bioelectronic sensor chips for dynamic analysis of tumour cell metabolism and chemosensitivity“
Project life span: 2005 to 2007

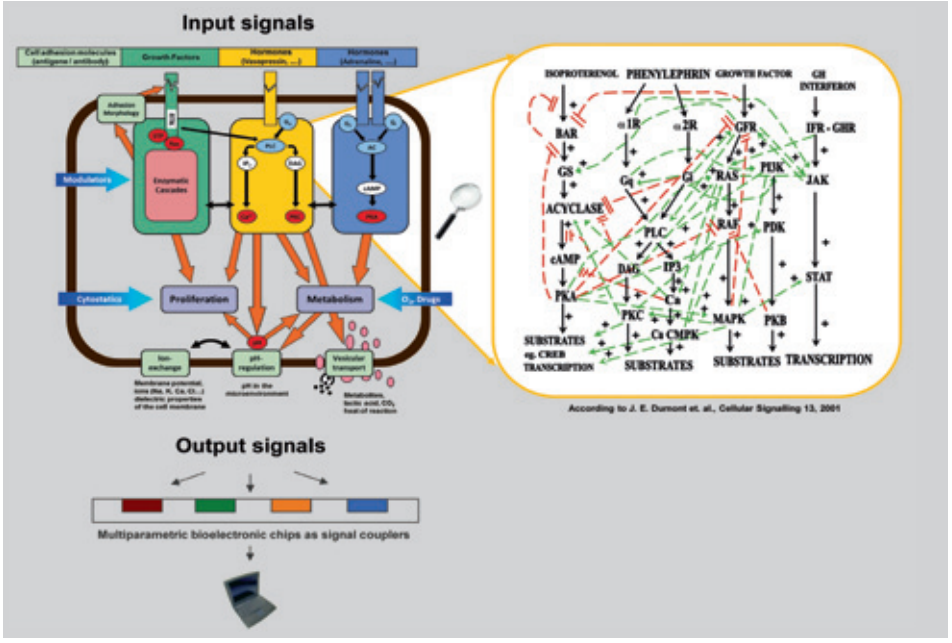


Fig. 2: Diagram of mitogenetic signal transfer in a cell

Automated high-throughput analysis platform for personalised cancer therapy [AHA]

In short

This innovative assay platform permits real-time analysis of the response of explanted human tumour tissue without the need for biomarkers. If data on cell metabolism is used, it is possible to determine whether or not significant chemosensitivity exists.

Personalised cancer chemotherapy depends on reliable assay methods, based either on so-called „predictive biomarkers" or on the direct functional assessment of the tumour cells. While the first strategy is designed to indirectly associate molecular profiles with a certain therapeutic response, the latter is aimed at directly assessing cellular chemosensitivity. The aim of the AHA project was to evaluate the chances of success with either approach.

As a step in this direction, we developed a new assay platform using innovative technologies (Figs. 1, 2). This platform analyses the response of explanted human tumour tissue (the project focused on breast cancer) in real time and without any marking steps. If data on cell metabolism are used, it is possible to determine whether or not significant chemosensitivity exists. It is also possible to derive molecular parameters from treated and untreated samples, though there has been no evidence so far to show whether this information has any predictive value.

The assay protocol focused in particular on defining the preparation process of the tissue samples: from the conditions for explanting the tissue and its transport to the lab (as fast as possible), to the clearly defined preparation routine. The variability of every single step must be kept at a minimum when it comes to testing.

For the preparation protocol, thin, vital tissue slices obtained with a vibratome proved to be well suited for the breast cancer tissue samples, since this method reduces the manipulative impact on the three-dimensional tissue structure to a minimum. The test itself is performed mainly in an automated manner on a 24-well assay plate. The normal duration of short-time culture and testing of the tissue samples is 96 hours, and an agent is added after 24 hours.

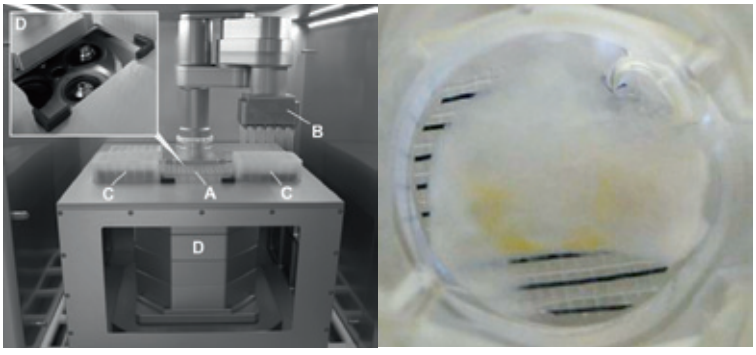


Fig. 1. Left: assay platform, indicating the position of the sensor plate (A), the pipetting head (B), the storage ves-sels (C) and the process microscope (D). Right: section of breast cancer tissue in the sensor plate. A nylon mesh facilitates sample transfer and enhances the mass transfer between the sample and the sensors.

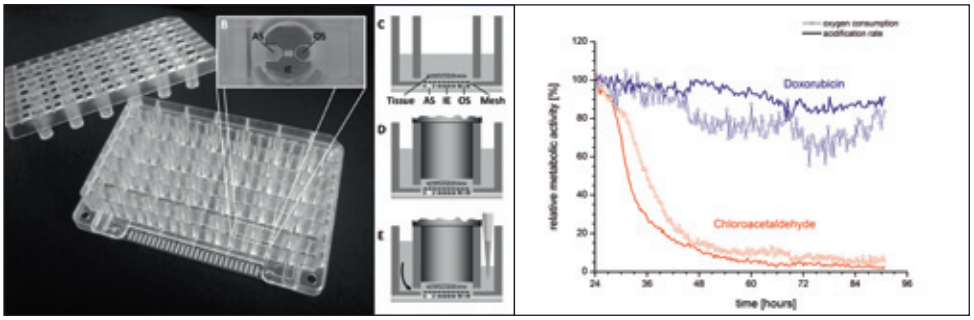


Fig. 2: 24-well sensor plate with cover (A). Top view of a well (B) with optical sensors integrated in the base for measuring the pH value (pH) and the concentration of dissolved oxygen (pO_2) in the culture medium. Interdigi-tated electron structures (IE) enable cell impedance to be recorded. Longitudinal section of a well (C). By placing the cover on the 24-well plate, the volume of the culture medium is reduced (D), forming a microreaction chamber (MR). The medium exchange in the cell culture area results from the pipetting process and is achieved by hydro-static pressure compensation between the interconnected chambers (E).
Fig. 3: Measuring the chemosensitivity of a human mammary carcinoma tissue sample. Adding the metabolite chloracetaldehyde (CAA, formed from ifosfamide or cyclophosphamide) results in a substantial decrease of the acidification activity and oxygen consumption in this sample, while only little effect of doxorubicin can be seen here. By means of statistical tests including controls, it is possible to assess the degree of sensitivity that must be expected and to personalise the therapy for this patient accordingly.

Selected publications

- *R. Kleinhans, F. Demmel, B. Becker, T. Schwarzenberger, M. Brischwein, A. M. Otto, P. Wolf, B. Wolf, „Real-time screening of the chemosensitivity of human tumour slices to chemotherapeutical drug treatment“, European Journal of Cell Biology, p.55, Vol. 89S1, Suppl. 60, ISSN 0171-9335, Elsevier, 33. Annual meeting of the DGZ, Regensburg 2010.*
- *M. Zottmann, F. Demmel, B. Becker, R. Kleinhans, M. Brischwein, B. Wolf, „Multiparametric real time assay of cellular drug response: kinetics of cell metabolism and proliferation“, 34. Jahrestagung der Deutschen Gesellschaft für Zellbiologie, March 30 - April 2, 2011, Bonn, p.75, 2011.*
- *R. Kleinhans, F. Demmel, B. Becker, T. Schwarzenberger, M. Brischwein, P. Wolf, B. Wolf, „Personalisierte Medizintechnik (2). Real-time screening of the chemosensitivity of human tumour slices to chemotherapeutical drug treatment“, Biomedizinische Technik/Biomedical Engineering, Volume 56, No. s1, pp. 1–6, ISSN 0013-5585, DOI: 10.1515/BMT.2011.834, Sept. 2011.*
- *R. Kleinhans, M. Brischwein, P. Wang, B. Becker, F. Demmel, T. Schwarzenberger, M. Zottmann, A. Niendorf, B. Wolf, „Sensor-Based Cell and Tissue Screening for Personalized Cancer Chemotherapy“, Medical and Biological Engineering and Computing, vol. 50, pp. 117–126, 2012.*
- *B. Wolf, B. Neumann, J. Wiest: „Metabolische Signaturen“. Technisches Messen (2013), (7-8), 243-248.*
- *P. Wolf, M. Brischwein, R. Kleinhans, F. Demmel, T. Schwarzenberger, C. Pfister, B. Wolf: “Automated platform for sensor-based monitoring and controlled assays of living cells and tissues”. Biosensors and Bioelectronics (2013), 50, 111-117.*

This research was funded by the Bundesministerium für Bildung und Forschung.
Project title: Verbundprojekt (joint project) „Automatisierte High-Content-Analyseplattform zur Entwicklung individualisierter Therapiestrategien (AHA)“ (Automated high-content analysis platform for development of individualised therapy strategies (AHA))
Project life span: 1 Sept. 2008 to 31 Aug. 2011

Personalised Chemosensitivity Testing (pCST project)

In short

This explorative clinical study, involving direct analysis of human tissue explants, aims to establish a very fast and efficient procedure for preclinical research and clinical routine, helping to provide improved, personalised data as a basis for therapeutic decisions in oncology.

Personalised cancer chemotherapy can be performed without using biomarkers, as was clearly demonstrated by the AHA project described in the previous chapter. Assessing cellular chemosensitivity directly from data on cell metabolism could potentially be far superior to genetic methods, since the environmental conditions to which tumour cells are exposed are also considered. Enviromental conditions dramatically affect the chemosensitivity of tumours.

Our pCST project is an explorative clinical study involving direct analysis of human tissue explants with the aim of personalising pharmaceutical anti-cancer therapy. It follows on from previous work undertaken as part of the AHA project for predictive testing of cancer cells. The “AHA” cell and tissue monitoring platform is now being used in collaboration with the Asklepios Klinik Hamburg-Barmbek to test its applicability in colorectal carcinoma.

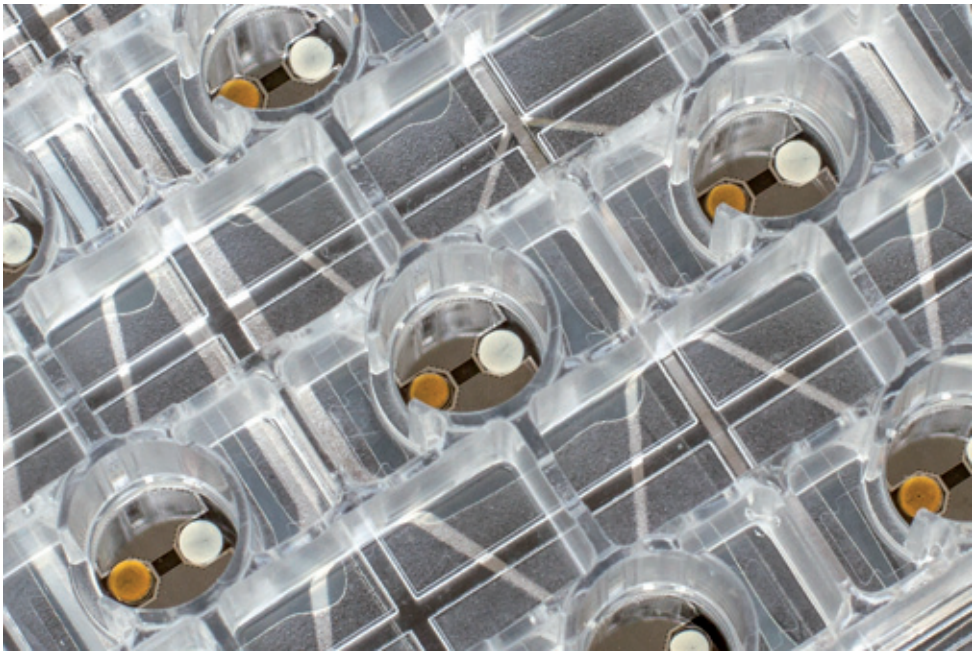


Fig. 1.
Cutout of a test plate with 24 wells for tissue slices. Each of the wells has optochemical sensors for pH and dissolved oxygen, facilitating the read-out of cellular oxygen uptake and extracellular acidification. Following transfer of the slices into the wells, the plate is closed with a lid to guarantee the micro reaction volumes necessary for highly sensitive recordings of cellular metabolic activity.

The pCST project utilises not only patient-derived tissue from primary colorectal carcinomas, but also tissue from liver metastases. The inclusion of such bioptic specimens considerably broadens the clinical relevance and the spectrum of therapeutic situations in which predictive tests can be introduced. Examples are tumours that are detected early or are inoperable. Another advantage of predictive testing on biopsy material is that the results from comparative, prospective studies will be available much earlier given that the clinical efficacy of the pharmacological treatment can be gauged directly from easily accessible clinical response parameters.

In each test process, the piece of biopsy tissue is cut into slices of ≈ 0.3 mg using mechanical techniques in order to preserve as much of the native tissue structure as possible and avoid extensive tissue cultivation procedures. Given the typical cell densities and viabilities, it should be possible, even in such small specimens, to determine the activities of oxidative and non-oxidative metabolic pathways using appropriate pH and O_2 sensors in micro reaction volumes. Fig. 1 illustrates the test plate with the wells into which the tissue slices are transferred. The miniature reaction volume in each well is further reduced by lowering a lid. Thereafter, different concentrations of chemotherapeutic drugs are added to the different sample micro-volumes by a pipetting robot and the metabolic reactions of the cells are detected by the sensors in the base of the test plate (see Fig. 2). The dynamic sensor read-out demonstrates the properties of each of the tissue slices before, during and after ex-vivo treatment. This process of self-referencing improves the precision of the assay.

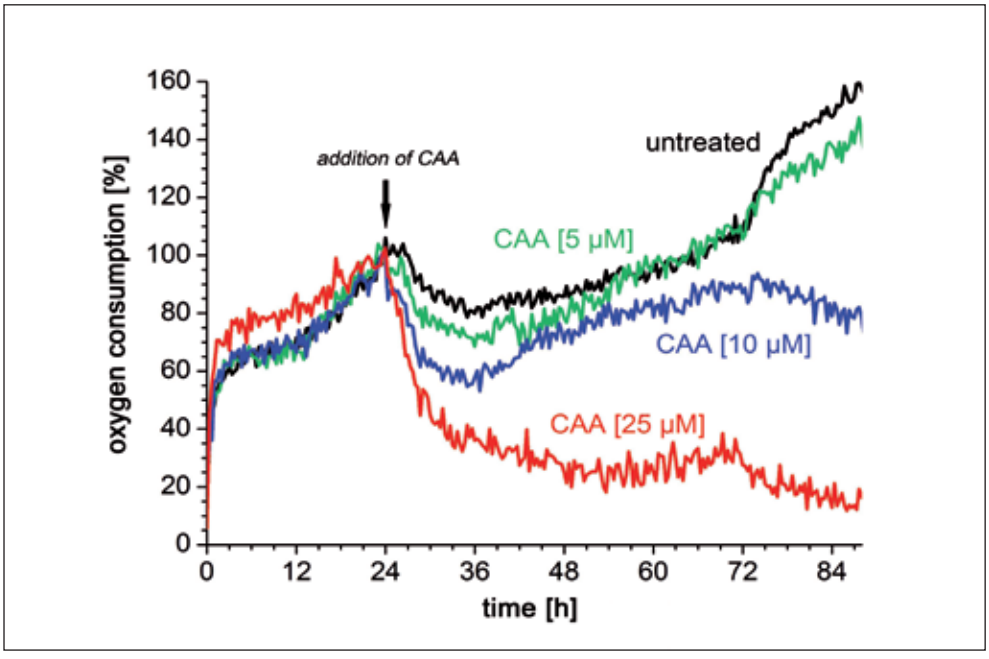
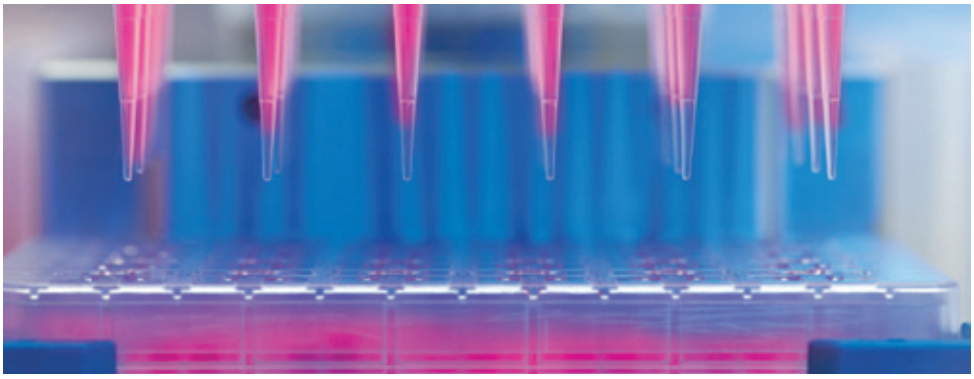


Fig. 2:
Measuring the chemosensitivity of human carcinoma cells. Depending on the concentration, addition of the metabolite chloracetaldehyde (CAA) results in a weak, diminishing decrease or a strong, lasting decrease in the oxygen consumption and also the viability of the cells. Using statistical tests, including controls, it is possible to assess the degree of sensitivity with which a patient's therapy can be personalised.

The main benefit of the predictive test platform would be in its clinical use, providing doctors with a powerful method for making rational and personalised decisions on pharmacotherapies. Beyond the clinical application, however, an ex-vivo organotypic model with dynamic sensor read-out would be a fascinating tool for tumour research: It can be used to assess the efficacy of targeted therapies (with single compounds or drug combinations) and novel approaches in the context of "companion diagnostics" prior to the initiation of expensive clinical trials.



Selected publications

- *R. Kleinhans, M. Brischwein, P. Wang, B. Becker, F. Demmel, T. Schwarzenberger, M. Zottmann, A. Niendorf, B. Wolf, „Sensor-Based Cell and Tissue Screening for Personalized Cancer Chemotherapy" Medical and Biological Engineering and Computing (2012), 50, 117–126.*
- *P. Wolf, M. Brischwein, R. Kleinhans, F. Demmel, T. Schwarzenberger, C. Pfister, B. Wolf: "Automated platform for sensor-based monitoring and controlled assays of living cells and tissues". Biosensors and Bioelectronics (2013), 50, 111-117.*
- *B. Wolf, C. Scholze, H. Grothe, M. Brischwein, „'Medizin 4.0' – Die Bedeutung von Elektronik, Informationstechnik und Mikrosystemen in der modernen Medizin", in: J. Gausemeier (ed), Vorausschau und Technologieplanung, 11. Symposium für Vorausschau und Technologieplanung, 29. - 30.09.2015, Berlin 2015, pp. 379 – 401.*

Project life span: October 2014 - March 2017
Project funded by: Heinz Nixdorf Stiftung and private sponsor
Network partners: Erwin Quarder Systemtechnik GmbH; Asklepios Klinik Hamburg-Barmbek; Asklepios Medizinisches Versorgungszentrum Hamburg

Intelligent implant for tumour monitoring [IntelliTUM]

In short

An intelligent implant with an oxygenation detection sensor placed in the direct vicinity of a tumour may provide important information on tumour activity. This information can then be used as the basis for individualised therapy at the appropriate dosage.

Active implanted systems are becoming more and more important in modern medicine – not only due to our increasing life expectancy. Intelligent implants are also increasingly used to record microphysiologic information from selected organs or tissues and for customising therapy.

During the „IntelliTUM“ project, we developed an implant system for monitoring levels of dissolved oxygen. The saturation of tissues with dissolved oxygen plays a leading role in invasive processes in malignant tumours, with the hypoxia (oxygen deficiency) found in many solid tumours correlating to abnormal metabolic profiles and also sensitivity to radiation therapy. A sensor placed in the direct vicinity of such a tumour may detect increasing hypoxia and provide important information on tumour activity. This may then be used as the basis for individualised therapy at the appropriate dosage.

Our aim was to utilise the sensors for long-term measurements in vivo: to this end, the sensors that had already undergone many years of in-vitro testing were further enhanced during a research project at our faculty that again took several years. This was possible with the aid of novel technology for recalibrating the sensor in vivo. Further, the sensor was coated with a specific ionomer membrane which is permeable to oxygen, while preventing proteins from being adsorbed on the sensor and thus minimising biofouling at the electrodes of the tissue-sensor interface.

Fig.1: Packaging of the implant: the pc board is folded into the housing. Subsequently, a cover with a window for the sensor is placed onto the housing.

Via a bi-directional wireless radio circuit the implant remains in constant contact with a receiver box transmitting the data to a control station. If signal patterns potentially hazardous to the patient are detected, the control station can quickly prompt therapeutic intervention. This approach allows for continuous monitoring of the effects of therapy, thus eliminating the need for the patient to stay in hospital. In case of a relapse, early interventions are possible at any time.

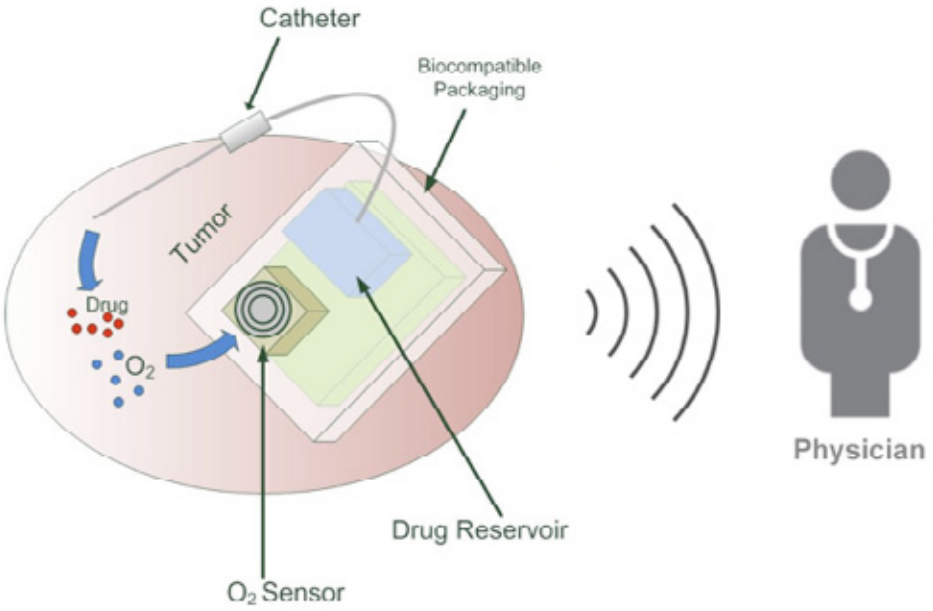


Fig. 2: Vision of the implant system as a closed-loop application. Depending on the functional state of the sensor, it is possible to deliver a chemotherapeutic agent.

By using closed-loop implant systems with a topical intracorporeal drug delivery system, it would also be possible to restore a normal quality of life in patients suffering from diseases that require a systemic treatment involving many side effects. The required actor interface for the implant was implemented in a follow-up project entitled THEMIC.

Monitoring the oxygenation of organ tissue is a further field in which this technology can be used. The oxygenation of the tissue can be an important indicator of the condition of a transplanted or partially resected organ during follow-up diagnostics, e.g. in tumour patients. With such a diagnostic application, which is only needed for a short period after a surgical intervention, the implant can be powered externally by means of inductive energy transmission. Therefore, these implants can have very small dimensions (with a diameter of approx. 16 mm, i.e. the size of a Euro cent coin, and a thickness of 3 mm), permitting their later removal by means of minimal invasive surgery.

Selected publications

- *S. Becker, Y.Eminaga, D. Hofsöy, J.Clauss, J.Wiest, M.Sattler, M.Brischwein, H.Grothe, B.Wolf, „Implantable dissolved oxygen sensor system for monitoring disease and healing processes“, Proceed-ings Deutsches Biosensor Forum 2011, ISBN 978-3-00-034073-4, p.30, April 3-6, 2011, Bad Heiligenstadt.*

- *S. Becker, Y. Eminaga, D. Hofsöy, K.-U. Hinderer, H. Zhang, A. Sifferlinger,M. Brischwein, H. Grothe und B. Wolf, „Towards a closed-loop diagnostic and therapeutic implantable system for tumours“, Proceedings Smart Systems Integration 2011, ISBN 978-3-8007-3324-8, paper 41, March 22-23, 2011, Dresden.*

- *S. Becker, T. Xu, F. Ilchmann, J. Eisler B. Wolf, „Concept for a gas-cell-driven drug delivery system for therapeutic applications“, Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine, DOI: 10.1177/0954411911423348.*

- *S. Becker, Y. Eminaga, D. Hofsöy, J. Wiest , J. Clauss, M.Sattler, und B.Wolf, „Intelligent implants for monitoring the hypoxia status of tissue“, BMT 2010; 55 (Suppl 1) pp.4-5, 44. DGBMT Jahrestagung, October 5-8, 2010, Rostock.*

- *S. Becker, B.Wolf, „Aktive Implantate in der Tumortherapie“, DZKF Deutsche Zeitschrift für klinische Forschung, 16. Jahrgang (16th year), 03/04 2012.*

- *J. Clauss, S. Becker, M. Sattler, B. Wolf, „In vivo Diagnostik mit intelligenten Implantaten“, In: Bern-hard Wolf (Hg.): Bioelektronische Diagnose- und Therapiesysteme. m3: microelectronic meets medicine. 1. Aufl. 2012 (1st edition), Aachen: Shaker Verlag, p. 237–246. ISBN: 978-3-8440-0831-9.*

This research was funded by the Bundesministerium für Bildung und Forschung.
Project title: „Realisierung eines sensorgestützten intelligenten Implantats zum minimalinvasiven Tumormonitoring mit Telemetrieanbindung – Intellitum“ (Implementation of a sensor-based intelligent implant for minimally-invasive tumour monitoring with a telemetry link – Intellitum)
Project life span: 1 March 2009 to 30 April 2011

Closed-loop microsystem for tumour therapy [THEMIC]

In short

An implantable closed-loop system was developed in this project, enabling a precisely defined dose of a chemotherapeutic agent to be delivered in the direct vicinity of a tumour in response to a validated sensor signal.

In modern diagnostics and therapy, the role of in-situ measurements and the in-situ delivery of drugs is becoming more and more important. Physiological parameters, such as dissolved oxygen in close proximity to a tumour, are important indicators for tumour growth and therapeutic response. In the preceding „IntelliTuM“ project, an intelligent implant for measuring dissolved oxygen was developed which can be used for tumour monitoring.

The THEMIC project investigated the key technologies needed to extend the existing im-plant system (a purely diagnostic system) to become a closed-loop system. The system enables a precisely defined dose of an agent used in local chemotherapy to be delivered in the direct vicinity of the tumour in response to a validated sensor signal. Drug delivery according to tumour growth and substantially smaller total drug volumes allow for a substantial reduction in side effects for the patient compared to systemic therapy, while leading to a higher local drug concentration due to localised application. The research work focuses on the actuator technology required for local drug delivery and on new power supply concepts for meeting the increased energy requirements of such closed-loop systems.

Commercially available systems for microdosing are either too large or unsuitable for implantation. We designed a prototype for a drug delivery system in this project based on a gas generation cell for producing electrochemical gas within in chamber, causing expansion of a latex membrane and enabling the administration of very small amounts of a drug.

As the functionality of the closed-loop system expands, the power consumption of these implants will also increase. Wireless power transmission would offer a long product lifetime without having to explant the system in order to replace the battery. As a part of the THEMIC project, we have developed an inductive wirel-

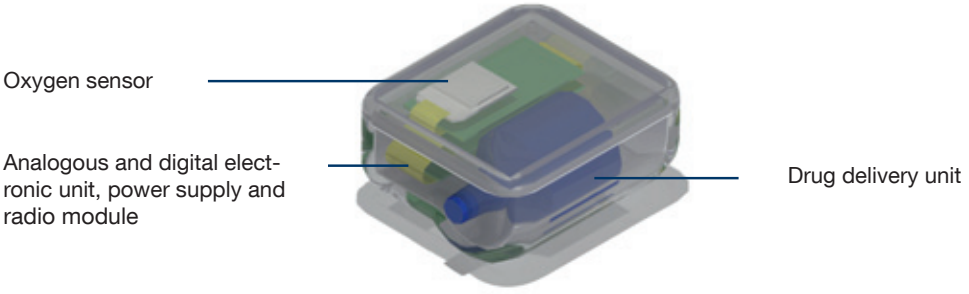


Fig. 1: Diagram of a prototype system with foldable electronic unit, sensor chip and integrated drug delivery system.

ess energy transmission system designed to power an intelligent implant system.
The THEMIC and IntelliTUM projects have demonstrated the basic feasibility of an implantable pO_2 sensor system for tumour therapy, with the results having been validated experimentally. The next step will be to test this implant system in eligible in-vivo models.

Selected publications

- *S. Becker, T. Xu, F. Ilchmann, J. Eisler B. Wolf, „Concept for a gas-cell-driven drug delivery system for therapeutic applications“, Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine, 2011.*
- *S. Becker, Y. Eminaga, D. Hofsöy, K.-U. Hinderer, H. Zhang, A. Sifferlinger,M. Brischwein, H. Grothe und B. Wolf, „Towards a closed-loop diagnostic and therapeutic implantable system for tumours“, Proceedings Smart Systems Integration 2011, ISBN 978-3-8007-3324-8, paper 41, March 22-23, 2011, Dresden.*
- *J. Clauss, S. Becker, M. Sattler, B. Wolf, „In vivo Diagnostik mit intelligenten Implantaten“. In: Bern-hard Wolf (Hrsg.): Bioelektronische Diagnose- und Therapiesysteme. m3: microelectronic meets me-dicine. 1. Aufl. (ed.) 2012, Aachen: Shaker Verlag, pp. 237–246. ISBN: 978-3-8440-0831-9*
- *Y. Eminaga, M. Brischwein, S. Becker, J. Wiest, J. Clauss, B. Wolf, “Self calibration of a planar dissolved oxygen sensor”, Sensors & Actuators B 177 (2013), 785-791.*

This research was funded by the Bundesministerium für Bildung und Forschung.
Project title: Verbundprojekt „Biomechatronisches Therapie-Mikrosystem für die Tumortherapie – THEMIC“ (Joint project „Biomechatronic therapy microsystem for tumour therapy – THEMIC“)
Project life span: 1 April 2010 – 30 June 2011

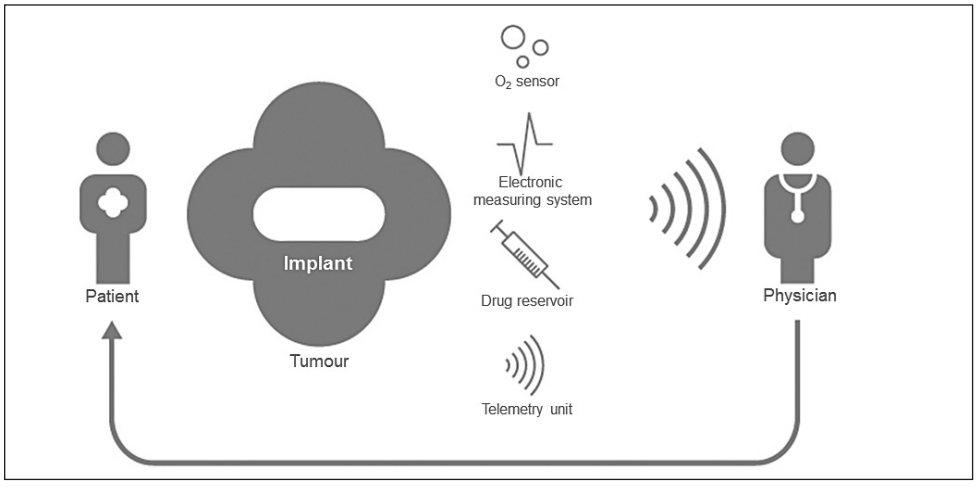


Fig. 2: Concept of a closed-loop system

Therapy modules and systems

“Der Arzt im Gepäck” (A doctor always at hand)

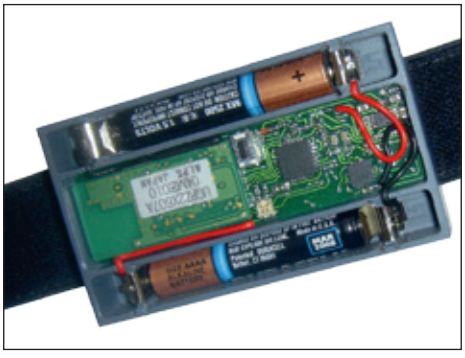
In short

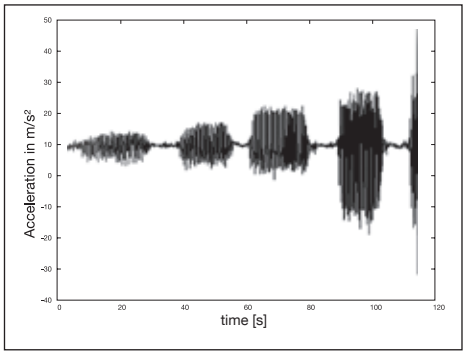
A movement detector strap worn across the chest is used to detect various gaits, the number of steps taken, and the physical load. This is part of an authentication system for assigning individuals to medical devices based on their unique patterns of movement.

The project „Der Arzt im Gepäck“ was used to develop a gait pattern authentification unit for use with telemedical support systems. The aim of this project was to develop an authentification system for assigning individuals to medical devices based on their unique patterns of movement. To this end, a person‘s unique kinetic pattern is used for identification. A movement detector strap worn across the chest is used to detect the degree of two-dimensional acceleration, with the data obtained permitting the individual gait type to be identified using a pattern detection system. This pattern is assigned to the corresponding individual. The signals are processed in the chest strap itself, and the data thus acquired are transmitted to a mobile phone. A mobile phone enables the creation of a self-organised network and facilitates connection to medical databases and health care providers. This system is particularly useful if it detects the individual kinematic movements while correlating these data with the pulse rates measured at the same time. Figure 1 depicts the chest strap system, enabling telematic detection of movements and loads.

Fig.1: Left: Prototype for kinetic pattern detection, implemented as a multiparametric chest strap with integrated acceleration measurement system, real-time clock, ECG recording system, and a Bluetooth transmission unit.

Right: Using the kinetic data recorded by the chest strap, various gait patterns may be identified based on the signal patterns measured.





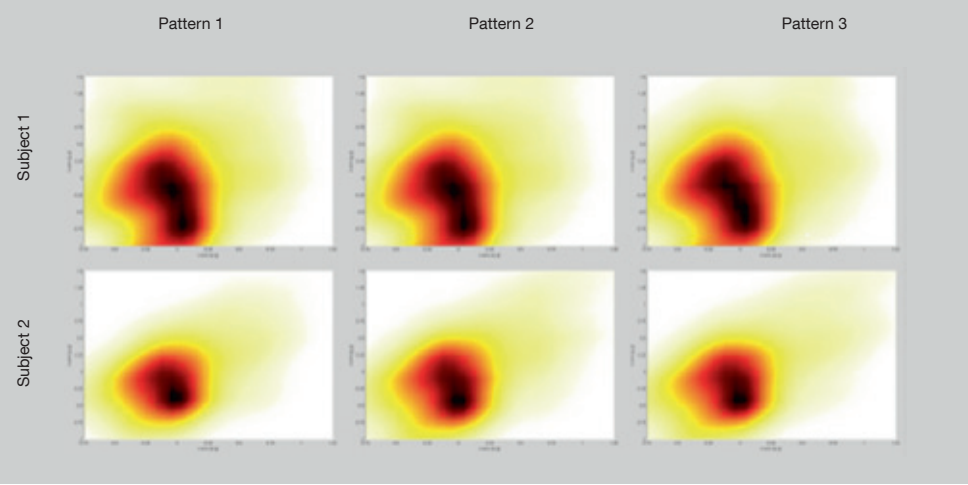


Fig. 2: Histograms of the individual gait patterns of two different test persons

Kinetic types may be classified according to various criteria: On the one hand they may be classified according to a person‘s energy consumption, on the other hand kinematic movement patterns may be used as classification parameters. The system is thus able to differentiate between various gaits (slow walking, fast walking, jogging, running), the number of steps taken as well as the physical load (see Fig. 1, right).

By developing a time series algorithm, we have produced a method suitable to detect individual gait patterns, as illustrated in Fig. 2.

Selected publications

- *A. Scholz in Jörg Eberspächer, Arnold Picot, Günter Braun: „eHealth: Innovations und Wachstumsmotor für Europa“ chapter 18, pp. 261- 268, Springer 2005.*
- *A. Scholz, V. Lob, J. F. Clauss, J. M. Herrmann, B. Wolf: „Einbindung von Sensorsystemen in das TPHM-System“, Biomedizinische Technik Vol. 49, pp. 224-225, 9/2004.*

This research was funded by the co-operation partner Siemens AG Communications, München.
Project title: „Der Arzt im Gepäck“ eine Entwicklungsplattform zur selbstorganisierten drahtlosen Vernetzung physikalischer und biomedizinischer Sensoren, („A doctor always at hand“, a platform for the development of self-organised wireless linking of physical and biomedical sensors)
Project life span: December 2004 to December 2007

An intelligent splint for the diagnosis and treatment of teeth grinding

In short

With the “SensoBite” splint, the patient’s chewing activities are measured by means of a piezo-electric sensor system integrated in a conventional occlusal splint. A wireless radio transmitter sends the measured data to a receiver. This system monitors the bruxism levels during the day and night.

Bruxism is defined as the non-functional grinding, gnashing and chattering of the teeth, and clenching of the jaw. Today, 5 - 10 % of all adults suffer from bruxism. Bruxism may occur during the daytime, as well as when sleeping, and is largely a subconscious habit. In most cases, the habit of teeth grinding is caused by emotional factors, since bruxism is a way of compensating for feelings of stress, anxiety or depression. Typical symptoms include wear on the teeth, pain in the muscles and jaw, but also headache and neck pain. For initial therapy, patients often wear a custom-made plastic splint (occlusal splint) to protect the teeth.

One of our projects, funded by the „Exist-Seed Förderung“ foundation of the Bundesministerium für Wirtschaft und Technologie, involved the development of a wireless measuring system for bruxism („SensoBite“) which can be integrated into conventional occlusal splints thanks to its minimal size (see Fig. 1).

The patient‘s chewing activities are measured by means of a piezo-electric sensor system. A wireless radio transmitter sends the measured data to a receiver the size of a matchbox which may be placed at the patient‘s bedside or worn on the body. The receiver is able to receive and store the data over a period of several months. Via a USB interface, the stored data can be transmitted to the computer of the attending physician. This system allows the bruxism activity to be monitored both during the daytime and during sleep without disturbing the patient.

Software for analysing the timing, intensity and frequency of the teeth grinding activity complements this system. From the recorded measurements, it is possible to identify the individual causes for bruxism and to derive an appropriate and personalised therapy for the patient. This system can also prompt immediate tactile (vibration) or acoustic biofeedback via the receiver. In the long run, this biofeedback stimulation will help to condition the patient and to reduce his/her bruxism activity.

Fig. 1: Occlusal splint with integrated sensor chip

Fig. 2: Complete system including: occlusal splint (1); tactile biofeedback system (2); front-end computer (3)

Selected publications

- *K. Vahle-Hinz, J. Clauss, W.-D. Seeher, B. Wolf, A. Rybczynski, M.O. Ahlers,"Development of a wireless measuring system for bruxism integrated into occlusal splint". Journal of Cranio-mandibular Function vol. 1, No. 2, pp. 125, 2009.*
- *K. Vahle-Hinz, J. Clauss, W.-D. Seeher, B. Wolf, A. Rybczynski, M.O. Ahlers,"Development of a wireless measuring system for bruxism integrated into occlusal splint". World Congress on Medical Physics and Biomedical Engineering 2009, IFMBE Proceedings 25/XI, pp.108.*
- *K. Vahle-Hinz, J. Clauss, B.Wolf, O.Ahlers, „Vergleich eines drahtlosen Bruxismussensors zur Integration in eine Okklusionsschiene mit EMG-Messungen", DGFDT 2008 – 41. Jahrestagung der Deutschen Gesellschaft für Funktionsdiagnostik und Therapie – Bad Homburg, 28 Nov. - 29 Dec. 2008.*
- *B. Wolf, M. Brischwein, H. Grothe, P. Friedrich, M. Schmidhuber, D. Grundl, T. Spittler, E. Cabala, S. Becker, B. Gleich, J. Clauss, A. Scholz, J. Wiest, B. Becker, P. Wolf, „Komponenten und Systeme für die personalisierte Assistenz", in: W. Niederlag, H. U. Lemke (ed.), Personalisierte Medizin, Health Academy Bd. 14, 2010, S. 215-234.*
- *B. Wolf, C. Scholze, H. Grothe, M. Brischwein, „'Medizin 4.0' – Die Bedeutung von Elektronik, Informationstechnik und Mikrosystemen in der modernen Medizin", in: J. Gausemeier (ed), Vorausschau und Technologieplanung, 11. Symposium für Vorausschau und Technologieplanung, 29. - 30.09.2015, Berlin 2015, pp. 379 – 401.*

This research was funded by the Bundesministerium für Bildung und Forschung (Exist-Seed).
Project title: „System zur Diagnose und Therapie von Bruxismus"
(System for the diagnosis and therapy of bruxism)
Project life span: 1 May 2005 to 30 April 2006.

Tone and tonus

In short

Acoustic signals can modulate metabolic and central nervous functions, and induce physiological effects in humans. The antihypertensive effect of certain iterative sound patterns in particular, as a possible means of intervention in essential hypertension, has been investigated in our virtual laboratory with the aid of telemedical systems.

The „Tone and Tonus“ project examined the acoustic intervention options relevant to the treatment of hypertension and other stress-related disorders. Our research team investigated the options for modulating the autonomic nervous system with non-pharmacological therapies and the related control mechanisms in human physiological processes.
We use modern information and communications technologies as an interdisciplinary and practical approach. Telemedical assistance systems and consumer electronic devices must be closely interlinked with medical applications. We used our „Virtual Lab“ (cf. article 13) to specifically investigate the antihypertensive effect of certain iterative sound patterns as a possible intervention in patients suffering from arterial hypertension. The antihypertensive effect of particular pieces of music and iterative sound patterns is a frequently described phenomenon [1, 2].

It has been demonstrated that when collecting physiological data from humans, quality very much depends on parameters like location and time [3,4]. The so-called „white coat effect“ is just one example of the influence psycho-physical reactions may have on physiological measurement signals. The use of a virtual lab supported by telemedicine results in increased patient compliance and better correlation of the patient‘s own blood pressure measurements with his/her current state of health compared with measurements taken in the clinical setting [3]. Furthermore, the virtual lab enables us to find solutions to the practical medical problems we are facing today.

The system is not limited to measuring blood pressure, however; it can also be used to generate complex intervention-correlated data patterns by integrating further sensors.
Since our system can collect and transport any type of physiological data, it it can be used in the development of various physical or musical biofeedback therapies. In order to allow for individualised therapy, an evaluation of the circadian or gender-specific efficacy and compliance structures is also necessary. The virtual lab environment is therefore an ideal development and test platform for personalised treatments as well as for other music therapy concepts. Acoustic interventions have already been integrated into our cognitive medical system COMES®.
Further scientific questions in this context are addressed by integrating the fields of psycho-education, surrogate therapies, activity focused prevention and rehabilitation, as well as Ambient Assisted Living (AAL).

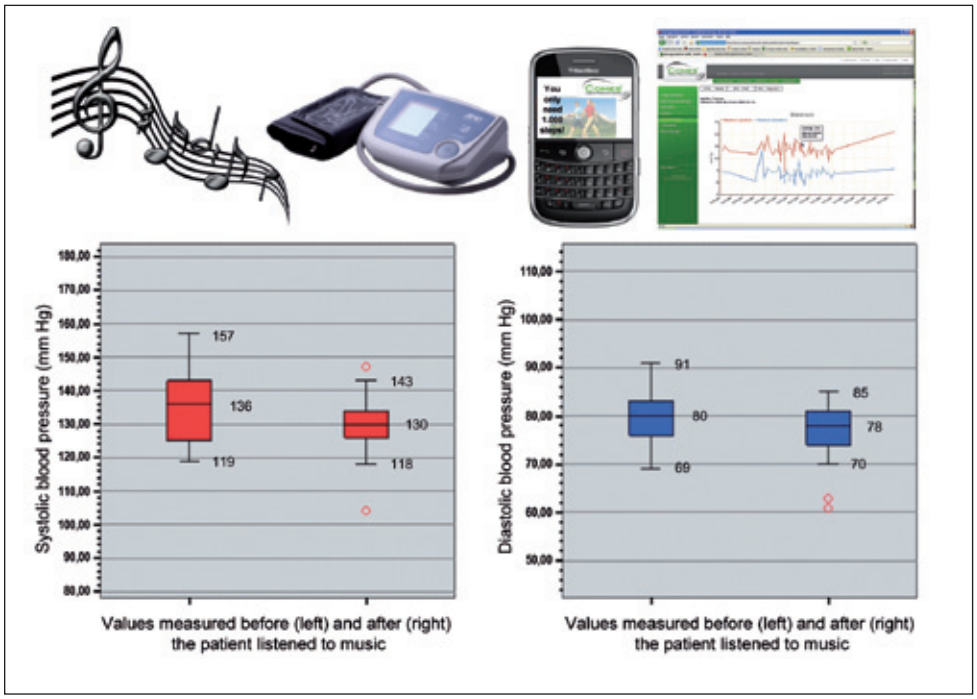


Fig.1: Acoustic interventions as a component of our cognitive medical system COMES© (Cognitives Medizinisches System)

[1] R. Spintge, R. Droh, „MusicMedicine“, Barcelona Publishers 1992.
[2] H.-P. Hesse, „Musik und Emotion“, Springer, Vienna 2003.
[3] F. McAlister, ”Measurement of blood pressure”, BMJ: 322, 2001.
[4] M. Middeke, „Arterielle Hypertonie“, Stuttgart 2005.

Selected publications

➢ *P. Friedrich, „Etablierung einer telemedizinisch gestützten bioakustischen Hypertonie-Therapie mittels Virtual Lab“, Dissertation at the Heinz Nixdorf-Lehrstuhl für Medizinische Elektronik, Technische Universität München, 2010.*

Research has been ongoing in this field since 2005. Until 2011 this research was funded by the Heinz Nixdorf Stiftung and the Siemens AG. Meanwhile, this project has been continued and expanded by the KoKeTT institute at the Hochschule Kempten in cooperation with the Heinz Nixdorf-Lehrstuhl für Medizinische Elektronik of Technische Universität München.

Enrichment and detection of molecules secreted by tumour cells using magnetic nanoparticles and LC-MALDI-TOF mass spectroscopy

In short

This innovative method for detecting and characterising peptides and proteins renders screening for "tumour biomarkers" more efficient. We assume, however, that it may also be used for follow-up tests in cancer patients.

Cells communicate through a network of different substances, including cytokines, interleukins and hormones. The synthesis and partly also the secretion of such substances reflect the functional state of the cells. In the case of tumour cells, the progression to states of increasing malignancy is accompanied by changes in gene expression.

Peptides or proteins that are secreted by tumour cells at different stages during the process of neoplastic degeneration could be possible candidates in the search for new biomarkers to further improve tumour diagnostics. However, cancerous cells secrete only very low amounts of peptides or proteins (concentrations in the range of 10-12 to 10-9 mol/L). Therefore, a large number of cells (108 to 109) are needed to obtain sufficient material for successful mass spectrometric analysis. Cancer cells are usually cultivated in a medium containing foetal calf serum, though this entails considerable background noise in the spectra.

In this study, MCF-7 and MDA-MB231 cells (model lines for various stages of progression of human breast cancer) were successfully cultivated and propagated under serum-free culture conditions. We also successfully isolated the secreted substances from the serum-free supernatant, and concentrating them with magnetic reversed-phase particles. Microparticles and nanoparticles offer the advantage of having an extremely large surface which is able to efficiently and reversibly bind proteins and peptides from complex solutions. It is particularly important to adapt the chemical surface of these particles precisely to the desired process. After binding, the particles are washed and the substances eluted. After separating the substances by liquid chromatography (LC), it is possible to generate reproducible signal patterns by using a method called „matrix-enabled laser desorption", coupled with a „time-of-flight" analysis of the substances.

The signal patterns thus obtained from one cell line differ substantially from those of the other cell line. It was possible to detect small volumes of the substance even down to 100 femtomole/mL.

A primary goal of this project was more efficient screening for „tumour biomarkers", but we

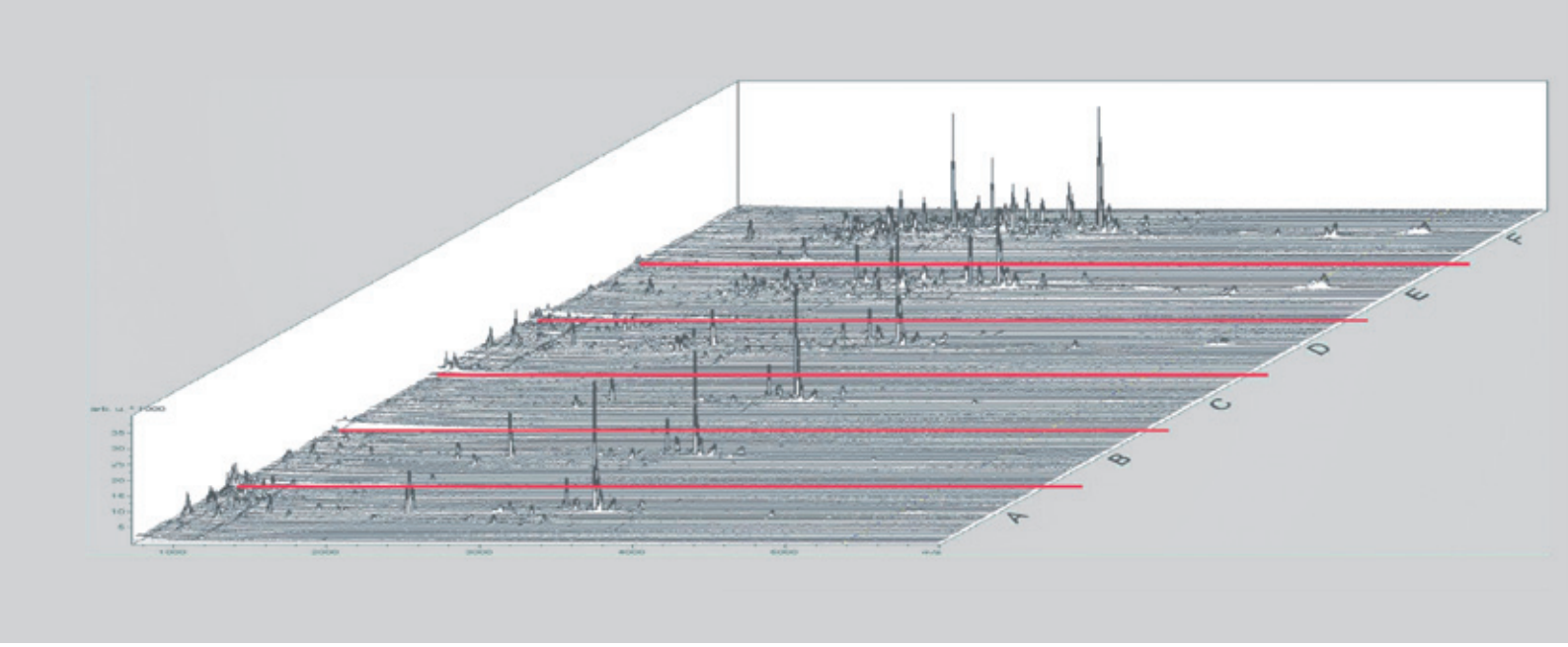


Fig. 1: Profiles of peptides secreted by MCF-7 and MDA-MB231 cells, represented in a 3D diagram. The vertical dimension stands for the relative substance volumes, the horizontal one for the retention time in liquid chroma-tography. Cell-culture supernatants (DMEM + 5% serum surrogate) collected 0 h and 48 h after changing the medium were purified and analysed. (A) Cell-free control after 0 h, (B) MC F-7 cells after 0 h, (C) MD A-MB231 cells after 0 h, (D) cell-free control after 48 h, (E) MC F-7 cells after 48 h, (F) MD A-MB231 cells after 48 h. The diagram clearly depicts the different cell-specific secretion profiles that provide data on functional behaviour.

assume that the methods employed may also be used for follow-up tests in cancer patients. They could help with early detection of recurring tumour activity after therapy. We are currently doing intensive research in order to solve the issue as regards the serum background.

In principle, the sampling process can be aligned with the IMOLA and AHA platforms, making it possible to also detect the relevant peptide profiles in addition to unaddressable profiles.

Selected publications

➢ *J. Peter, A. Otto, B. Wolf, „Enrichment and Detection of Molecules Secreted by Tumour Cells Using Magnetic Reversed-Phase Particles and LC-MALDI-TOF-MS“, Journal of Biomolecular Techniques, Volume 18, Issue 5, December 2007, pp. 287-297.*

The method introduced in this article is currently one of the most sensitive methods for the simulta-neous detection and characterisation of peptides and proteins. For his research in this field, Dr. Jochen Peter received the Outstanding Scientist/Technologist award from the international organisa-tion ABRF in the USA in March 2007, and the Young Investigator Award in Proteomic Sciences from the HUPO in Korea in October of the same year.
This research was funded by the Heinz Nixdorf Stiftung.

Cell transfection, targeting and positioning of agents marked with nanoparticles using static and dynamic magnetic fields

In short

This promising new method for transporting magnetic nanoparticles coupled with an appropriate drug to any site of the human body, by applying an external magnetic field, could prove useful in cancer therapy. The aim is to direct high concentrations of a therapeutic substance solely at the area of the tumour.

This project entailed the investigation of a method for directing magnetic nanoparticles coupled with an appropriate drug to any site of the human body by applying an external magnetic field (Magnetic Drug Targeting, MDT). This is done after endovascular application of the particles. This promising new method could be useful in cancer therapy, its aim being to direct high concentrations of a therapeutic substance solely to the area of the tumour. In practice, the medicine could be administered into an artery or vein and could then be controlled by an external magnetic field and directed towards the desired region. It is also conceivable that such localised cancer treatment could be applied in the form of an aerosol for pulmonary diseases.

In the past, several carrier systems were developed for specifically transporting therapeutic agents. The MDT method allows the drug chosen for the patient to accumulate in a particular part of his/her body by means of magnetic nanoparticles and magnetic fields. The molecules of a pharmaceutical substance are chemically coupled to active components (e.g. magnetite) and thus transferred to a pharmaceutically stable micro-carrier system.

For clinical applicability, it must be ensured that the nanoparticles are biocompatible, e.g. by coating the magnetic particles with biopolymers such as starch. Recent studies have revealed that with particles treated in this way,

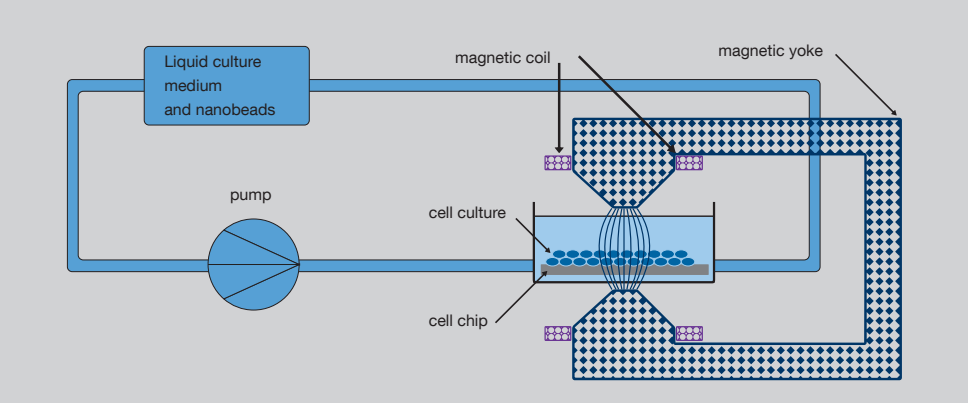
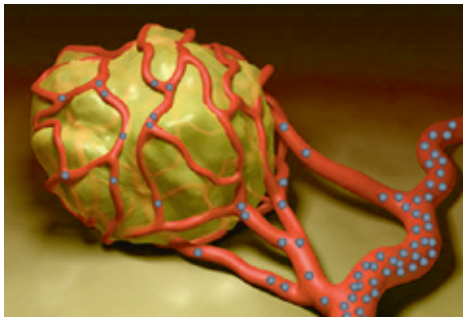


Fig. 1: This model illustrates a blood vessel in which particles get immobilized against the blood flow through magnetic fields.



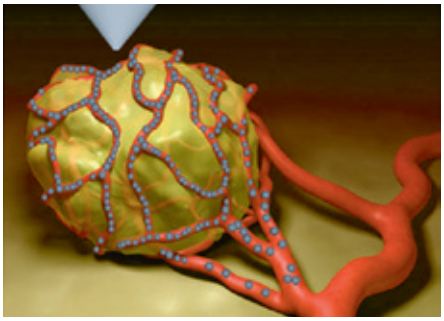


Fig. 2: Illustration of the Magnetic Drug Targeting system (right) compared to a passive method (left). When the magnetic particle/active agent complexes reach the perfusional area of the tumour, only a few will flow into the tumour if no magnetic field is applied, whereas a large number will migrate if a magnetic field is present. Thanks to the magnetic field, the particles are drawn into the tumour and will also remain there. [Image modified according to www.gcarlson.com].

undesirable side effects can almost be eliminated entirely. This coating is also necessary for preventing the particles from aggluti-nating due to Van der Waals forces. Further, in the case of intravascular application of nanoparticles it is extremely important to take the local flow characteristics within the bloodstream into account. Among others, these are influenced by the size and the material of the particles. These characteristics are crucial to pharmacokinetics and the attainable enrichment factor.

We developed a physical model in this project that simulates various types of flow characteristics in order to be able to predict the behaviour of the individual particles.

Selected publications

- *C. Dahmani, T.Weyh, H.-G. Herzog, „A simplified Approach for Nanoscale Magnetic Moment Measurement and a Study of the Impact of Nanoparticle Interaction on their total Magnetic Moment“, Pro-ceedings of the conference Seeing at the Nanoscale VII - Exploring the future of Nanotechnology Using SPM and related Techniques, Santa Barbara, California, 28-31 July 2009; California NanoSys-tems Institute; 2009.*
- *C. Dahmani, S. Götz, T. Weyh, R. Renner, M. Rosenecker, C. Rudolph, „Respiration triggered Magnetic Drug Targeting in the Lungs“, Proceedings of the 31st Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Minneapolis, 2-6 September 2009; IEEE; 2009.*
- *C. Dahmani, F. Helling, T. Weyh, C. Plank, „An Innovative Rotational Magnetic System to enhance Cell Transfection with Magnetic Nanoparticles“, Proceedings of the World Congress for Medical Physics and Biomedical Engineering 2009, München, 8-11 September 2009; VDE; 2009.*

This research was funded by the Bundesministerium für Bildung und Forschung.
Project title: „Verbundvorhaben Nanomagnetomedizin: Teilvorhaben: Zell-Transfektion, Targeting und Positionierung von Nanopartikel-markierten Wirkstoffen durch statische und dynamische Magnetfelder“ (Joint project Nano-magneto-medicine: Subproject: cell transfection, targeting and positioning of agents marked with nanoparticles using static and dynamic magnetic fields)
Project life span: 1 January 2007 to 31 December 2009

Investigation of the inhibition of pathogen adhesion to intestinal cells caused by oligogalacturonic acids (OGA) using chip-based in vitro test systems

In short

Measurements with a sensor-enabled in-vitro test system revealed that certain oligogalacturonic acids (OGA) exert a negative effect on the metabolic activity of E. coli bacteria. This system may be used for therapeutic purposes in cases of diarrhoea.

The human gastrointestinal tract is a biotope-like environment in which intestinal epithelia and non-pathogenic (i.e. symbiotic and commensal) bacteria co-exist. This sensitive equilibrium may be perturbed by the appearance of pathogenic strains such as Escherichia coli O157:H7 (EHEC), leading to an infection of the gastrointestinal tract. The adhesion of pathogenic bacteria to the cells of the intestinal epithelium is assumed to be a key step in this infection process, which will finally out-compete the physiological intestinal flora. Figure 2 is a microscopic image of a Caco-2 cell culture used as an in-vitro model for the intestinal epithelium. The cell culture has been colonised by E. coli bacteria ,some of which are already firmly adhered to the cells.

In collaboration with the Deutsches Institut für Lebensmitteltechnik e.V. in Quakenbrück and the Bundesinstitut für Risikobewertung in Berlin, we investigated the detectability of the adhesion of pathogenic bacteria to intestinal epithelial cells, and studied options for preventing or at least reducing the effects of such adhesion through the use of food additives. The additive analysed in this project was a hydrolytic breakdown product of pectin (a component of plant cell membranes), available as a compound of so-called oligogalac-

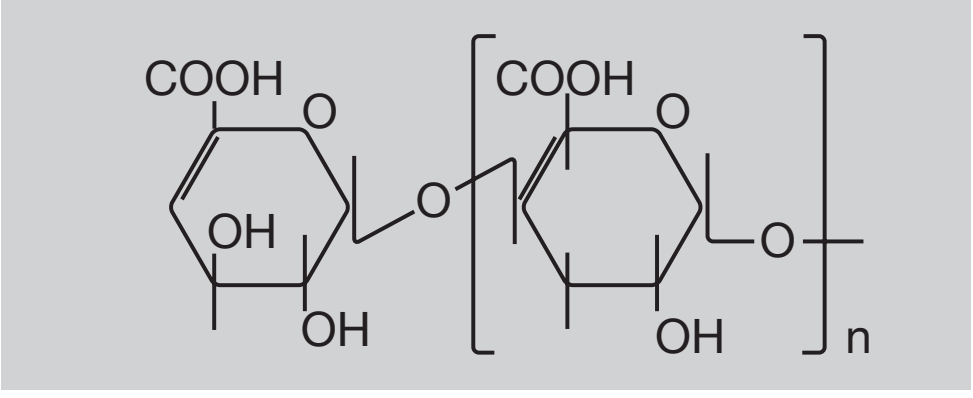


Fig. 1: Unsaturated OGA molecule. During the hydrolysis of pectin, trimers or tetramers usually develop (n=2-3).

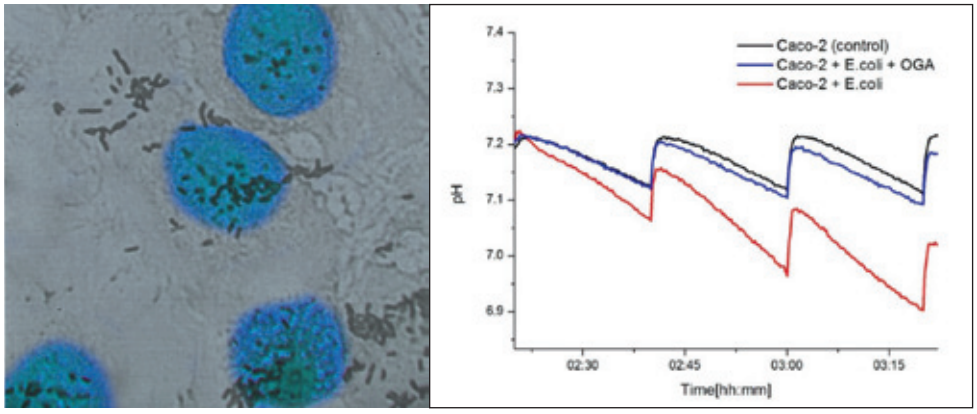


Fig. 2: Left: microscopic image of Caco-2 cells in co-culture with E.coli H10407 cells (1 x 108/mL, 1 hour after co-culture) - image reproduced with the kind permission of: Deutsches Institut für Lebensmitteltechnik e.V., Abt. Mikrobiologie. Right: extracellular acidification rates of co-cultures of Caco-2 cells and E.coli C.25 (added at 2 h 15 min). While E.coli cells preincubated with OGAs do not lead to increased acidification, untreated bacteria rapidly colonise the Caco-2 cell culture. The data on extracellular acidification suggest that the E.coli cells prein-cubated with the OGAs are affected with respect to their metabolic activity, and presumably also with respect to their adhesion to the Caco-2 cells. This result suggests that OGAs have an antibacterial effect, but it still remains to be seen whether they have a toxic effect on Caco-2 cells.

turonic acids (OGAs). Quite large amounts of these pectin fractions and OGAs are found in carrot juice, for example, which is thought to have a preventive or even a therapeutic effect in cases of diarrhoea. In measurements with a sensor-enabled in-vitro test system, we have in fact found that certain OGAs exert a very negative effect on the metabolic activity of E.coli bacteria and may thus be used for therapeutic purposes.

Selected publications

- *D. Grundl, T. Flurschütz, J. Wiest, B. Becker, M. Brischwein, B. Wolf, „Mathematische Verarbeitungs- und Interpretationsmethoden von metabolischen Signalen lebender Zellen auf biohybriden Sen-sorchips Biosensor“, 6. Deutsches BioSensor Symposium, 29 March - 1 April 2009, Freiburg, p. 60, 2009.*
- *B. Becker, D. Grundl, M. Schmidhuber, F. Ilchmann, M. Brischwein, B. Wolf, „Automatisches Lab-on-a-Chip Testsystem für cell-based assays“, 6. Deutsches BioSensor Symposium, 29 March - 1 April 2009, Freiburg, p. 147, 2009.*
- *K. Jeongyun, M. Hegde , A. Jayaraman, „Co-culture of epithelial cells and bacteria for investigating host–pathogen interactions“, Lab on a chip 10, pp. 43-50, 2010.*

This research was funded by the Bundesministerium für Bildung und Forschung.
Project title: „Verbundprojekt: Gewinnung und Charakterisierung von Oligogalacturonsäuren sowie Untersuchungen zur Inhibierung der Anheftung pathogener Keime und Cytotoxine an Intestinalzellen mittels in vitro-Testsystemen“ (Joint project: Sampling and characterising oligogalacturonic acids and investigating the inhibition of pathogenic germs and cytotoxins to intestinal cells by means of in-vitro test systems)
Project life span: 1 January 2007 to 31 May 2010

Isolation of human pancreatic islet cells and quality control: quality control and toxicological testing of immunodepressants with chip-based test systems

In short

A quality-control platform based on bioelectronic sensor chips was developed in this project, suitable for testing the vitality of pancreatic islets prior to transplantation with various methods, and at the same time enabling immunosuppressant drugs to be tested.

Pancreatic islet cells are transplanted in patients suffering from a serious form of type I diabetes. Despite considerable success in restoring insulin production, in most cases patients experience a relapse after a short period of time. This occurs on the one hand because the cells die after transplantation, whilst on the other hand immunodepressants have been found to exert unexpected toxicity on the islet cells.

For improving the success rates in the transplantation of pancreatic islets, we require a quality platform allowing for testing the functionality of the donor islets and their sensitivity to immunodepressants prior to transplantation. A viable approach is measuring the vitality of isolated islet cells on a bioelectronic sensor chip in real time.

The goal of this project, therefore, was to develop a quality-control platform suitable for testing the vitality of the isolated islets prior to transplantation using various methods, and at the same time enabling immunosupressant drugs to be tested. We had intended to equip this platform with bioelectronic sensor chips on which the islets may be cultivated in order to measure their metabolic activity in real time.

The primary functionality testing of isolated islets and islet cells in culture was first per-

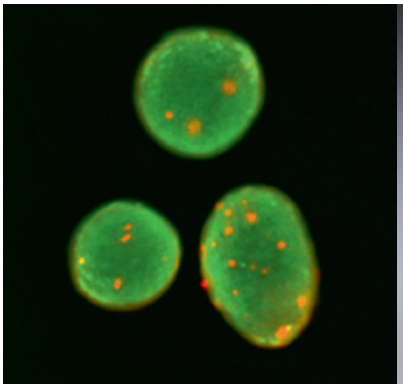


Fig. 1: Mouse islet cell samples marked with a fluorescent dye (green: living cells, red: dead cells). Fig. 2: Singular measuring device for a bioelectronic sensor chip (IMOLA)

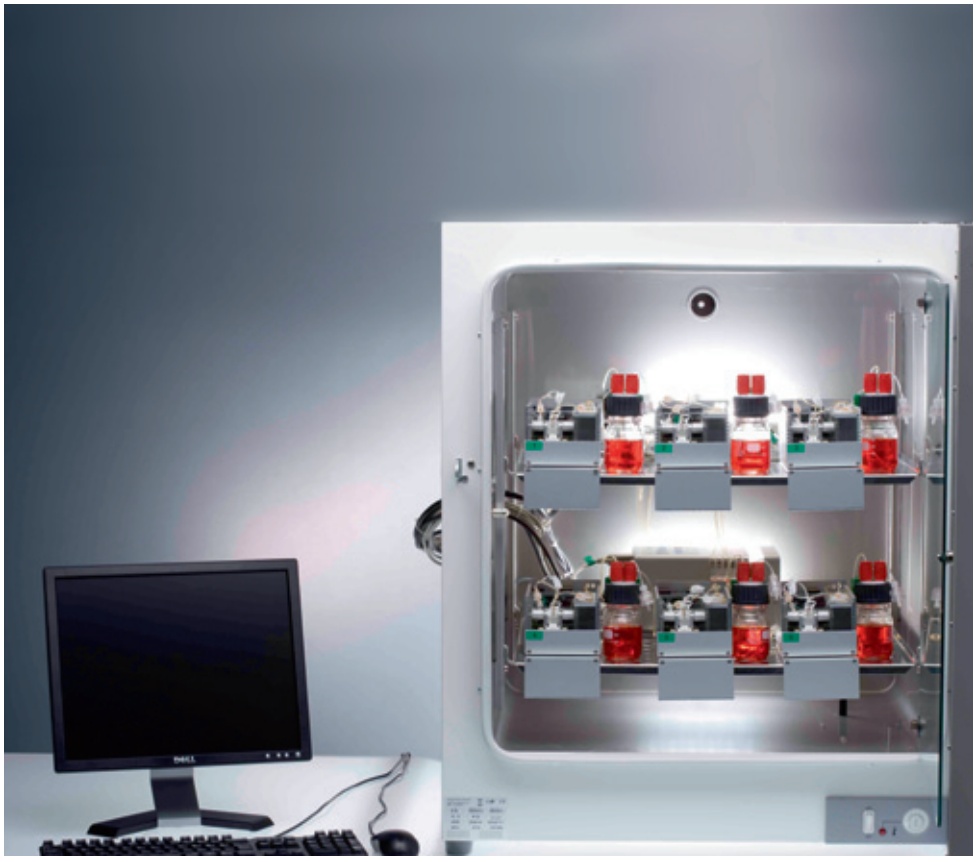


Fig. 4: The test was performed on 6 parallel chips in an IMOLA incubators.

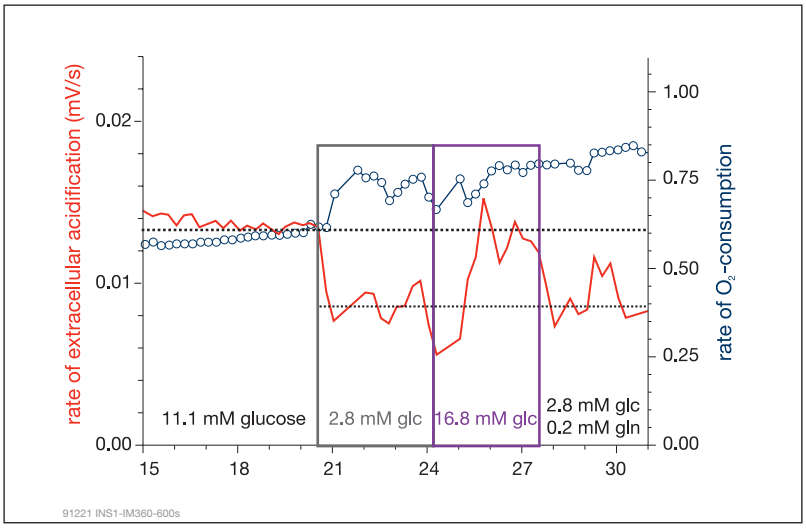


Fig. 3: Measuring the metabolic activity of islet cells in culture (INS1E) prior to and after stimulation with a high glucose concentration leading to insulin secretion.

formed by means of antibody detection of glucose-stimulated insulin secretion. At the same time, islets were cultivated on sensor chips in order to continually monitor the metabolic activity, by measuring the acidification rate and oxygen consumption during glucose stimulation. The test system was then used to analyse the effect of immunosuppressants. The sensor chips also permit the vitality of various liver cells (the islets are injected into the recipient's liver) to be measured. To provide conditions similar to the physiological situation, the islets were cultivated with matrix proteins and inflammatory substances which are produced by immunologically competent cells (interleukins). The laser microdissection method was employed for differential characterisation since it allows defined areas to be excised from the islets and their function to be analysed using molecular biology techniques.

All in all, we found that the cultivation of isolated islets on bioelectronic sensor chips allows for multiparametric analysis of cell vitality and also offers a good basis for further applications in medicine.

Selected publications

- *F. Yilei, „Optimierung der Kultivierungsbedingungen für die INS-1E Zelllinie im Hinblick auf die Insu-linsekretion“, Semesterarbeit (assignment), submitted at the Technische Universität München, October 2009.*

- *B. Bergmann, „Funktionale Charakterisierung von INS-1E-Zellen unter verschiedenen Bedingungen zur Stimulation der Insulinsekretion“, Diplomarbeit (dissertation submitted for a diploma) at the Hoch-schule für Angewandte Wissenschaften, Munich, March 2010.*

- *R. Kleinhans, J. Wiest, A.M. Otto,, „Effects of cytokines on growth and energy metabolism of insulin secreting cells“, European Journal of Cell Biology 88S1, Suppl.59. p76, Jahrestagung der Deutschen Gesellschaft für Zellbiologie, Universität Konstanz (Constance), 24-27 March 2009.*

- *B. Bergmann, V. Auer, Y. Fu, J. Wiest, A. M. Otto, „Metabolism of beta-cells stimulated to secrete insulin: real-time monitoring using sensor chips“, Jahrestagung der Deutschen Gesellschaft für Zell-biologie, Universität Regensburg,10–18 March 2010.*

- *B. Bergmann, V. Auer, E. Janas, V. Ninichuk, J. Wiest, A. M. Otto, „Monitoring Metabolism of Pancreatic Beta-Cells in Real-time by Using Sensor Chip Technology“, Heinz-Nixdorf-Symposium, Munich, 12-13 October 2010.*

- *A.M. Otto, „Cell Cultivation and Sensor-based Assays for Dynamic Measurements of Cell Vitality“, BetaSys - Systems Biology of Regulated Exocytosis in Pancreatic Beta-Cells Eds: Booß-Bavnbek,B.; Klösgen,B.; Larsen,J.; Pocoit,F.; Renström,E.. Springer Series Systems Biology 2 Ch. 10, p.221-240, 2011.*

This research was funded by the Bayerische Forschungsstiftung.
Project title: „Humane pankreatische Inselisolation und Qualitätskontrolle“ (Isolation of human pancreatic islet cells and quality control)
Project life span: 15 August 2007 to 31 December 2010

Development and evaluation of a monitoring and treatment system for sleep-related breathing disorders

In short

An innovative monitoring and treatment system for sleep-related breathing disorders was developed in this project. It permits parameters such as snoring, heart rate, respiratory movement and sleeping position to be measured by means of a single acceleration sensor in a headband or dental splint.

Studies have shown that more than 20 % of the adult population snore regularly during sleep and that 2 % - 4 % suffer from obstructive sleep apnoea (OSA), leading to obstruction of the respiratory tract and causing patients to repeatedly wake up. OSA mostly leads to severe daytime sleepiness and entails an increased risk of cardiovascular diseases. It is therefore an

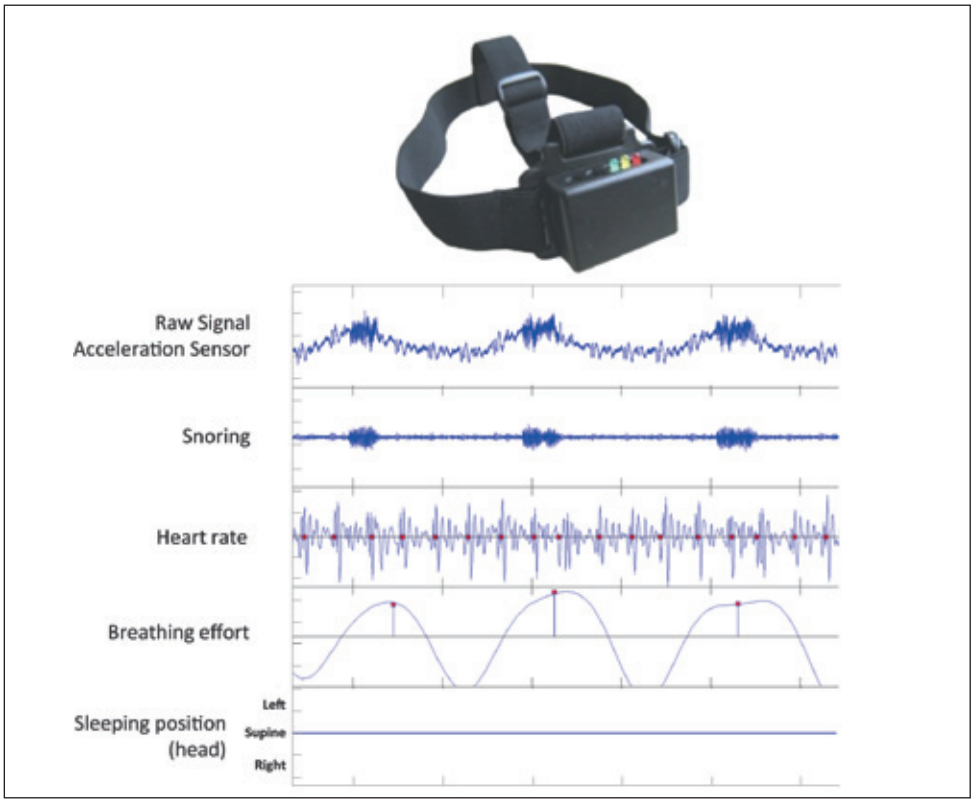


Fig. 1: Detection of the signals of snoring and respiratory movement by the acceleration sensor

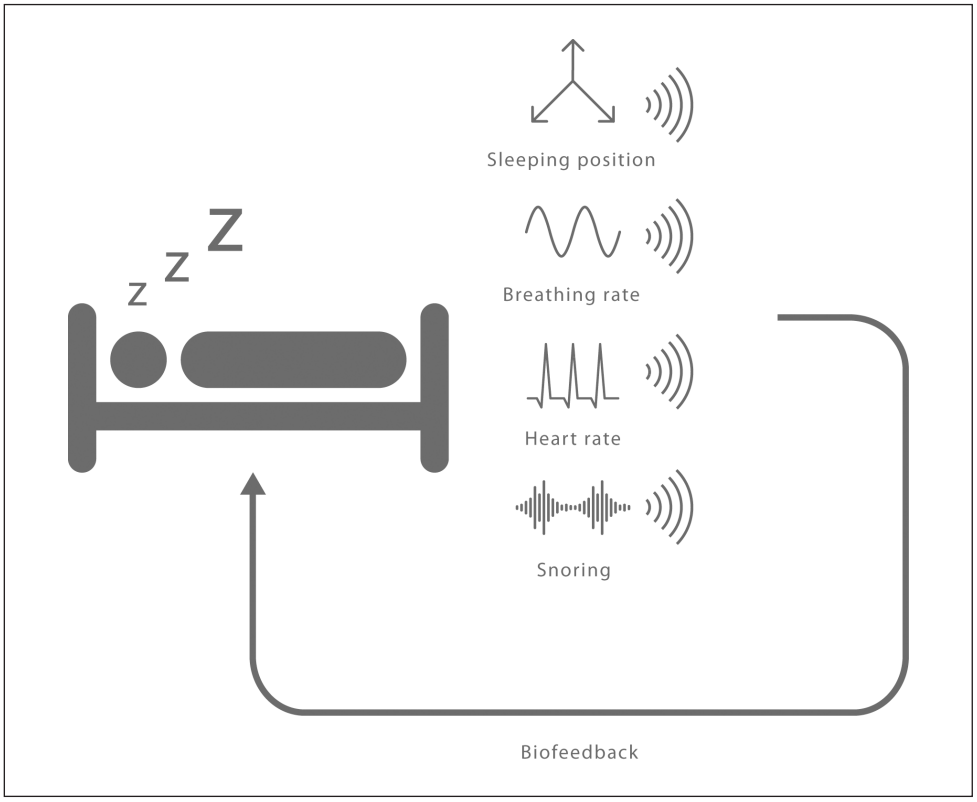


Fig. 2: Complete system: the different parameters measured on-line are used to control therapy

alarming fact that over 70 % of sufferers are yet to be diagnosed, a procedure that normally takes place at a sleep laboratory. As treatment, patients usually need to wear a continuous positive airway pressure mask (CPAP mask). However, almost half of snorers and OSA patients could benefit from an efficient therapeutic approach which prevents them from lying on their backs during sleep, since these patients suffer from what is referred to as positional sleep apnoea with snoring and OSA, which is mainly caused by sleeping on one's back.

For these reasons, an innovative monitoring and treatment system for sleep-related breathing disorders (SRBD) has been developed and evaluated. The innovative feature of this system allows parameters such as snoring, heart rate, respiratory movement and sleeping position to be measured by means of one single acceleration sensor in a headband or dental splint (see Fig. 1). We were able to demonstrate in a clinical study that it is possible to automatically detect snoring and provide an indication of the severity of SRBD.

Hence the miniature wireless measuring system may be used for making a diagnosis, but also for long-term monitoring: it enables routine monitoring of the patient for disease progression and therapeutic efficiency.
Follow-ups delivering conclusive results

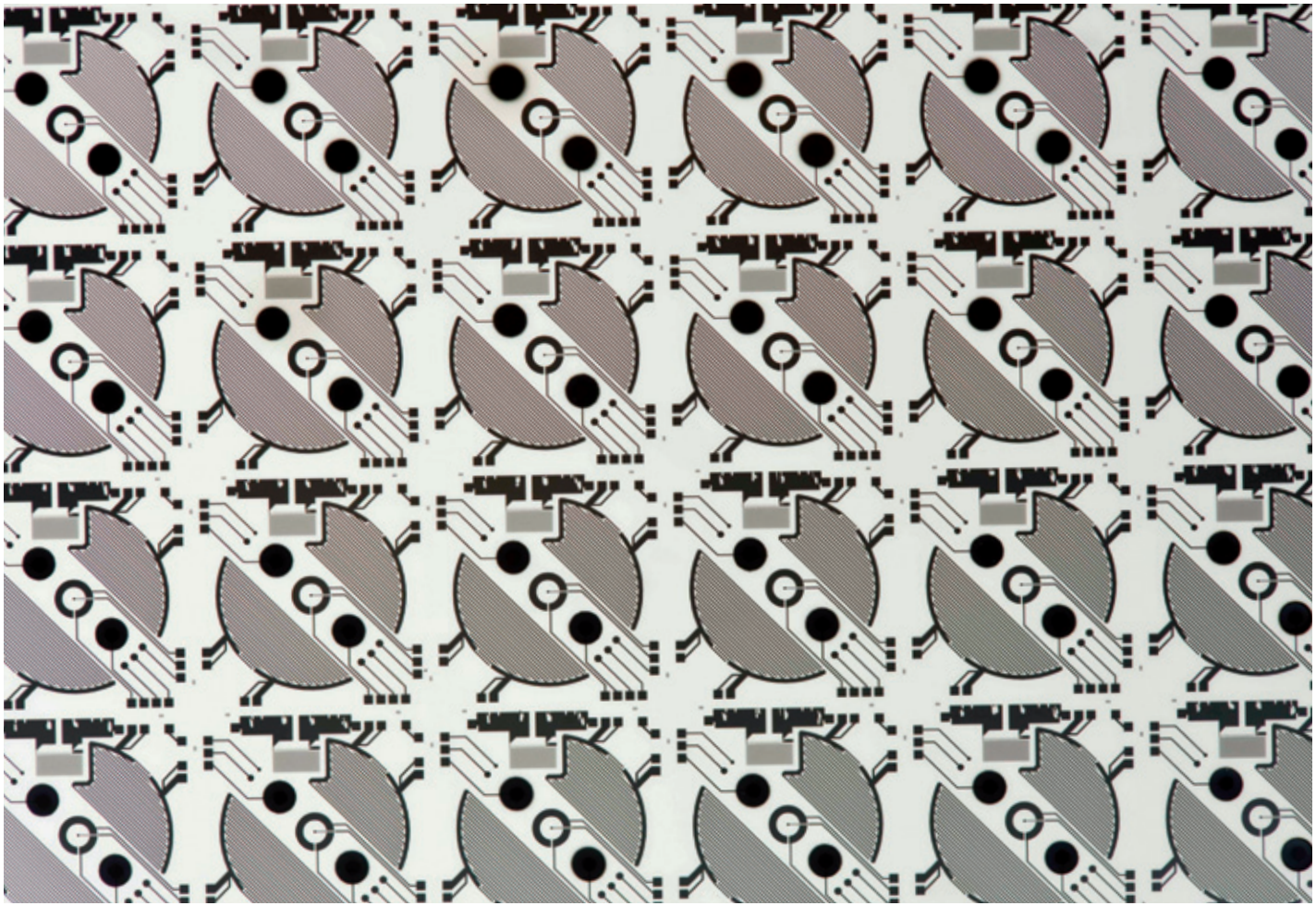
have so far necessitated elaborate tests in a sleep laboratory.
The automatic detection of snoring and OSA combined with recording the patient's sleeping position make it possible to identify those patients suffering from a positional disorder as well as to monitor the efficiency of positional therapy. By using vibration signals for biofeedback, implemented as a vibration motor in the headband, we have been able to demonstrate the success of this intelligent approach to positional therapy. Compared to the inconvenience of the breathing mask, our system is a comfortable alternative for a large number of patients suffering from positional sleep apnoea.

Selected publications

- *D. A. Hofsøy, J. Clauss, B. Wolf, „An intelligent implant system for monitoring and biofeedback therapy of snoring“, World Congress on Medical Physics and Biomedical Engineering, September 7–12, 2009, Munich, Germany, ISBN 978-3-642-03472-5, pp. 196-199, IFMBE Proceedings, Volume 25/VIII, Olaf Dössel and Wolfgang C. Schlegel, Springer Heidelberg, 2009.*

- *D.A. Hofsøy, J. Clauss, B. Wolf, „Monitoring and therapy of sleep-related breathing disorders“, 6th International Workshop on Wearable Micro and Nano Technologies for Personalized Health (pHealth), June 24– 26, 2009 in Oslo, Norway, ISBN 978-1-4244-5252-1, DOI 10.1109/PHEALTH.2009.5754827, pp. 41-44, IEEExplore, 2009.*

This research was funded by the Bund der Freunde der TU München e.V. and the Heinz Nixdorf Stiftung.
Project title: „Intelligentes Implantatsystem zur Diagnose und Therapie von Schnarchen und Schlafapnoe“ (Intelligent implant system for the diagnosis and treatment of snoring and sleep apnoea)
Project life span: 5 August 2008 to 4 August 2009



Analysing the therapeutic relevance of the transmembrane potential of tumour cells [EvoPot]

In short

The EvoPot project demonstrated that the growth rate of cells may be influenced by applying electric and magnetic fields, and that growth may be reduced significantly under certain conditions. To achieve a therapeutic effect, a permanent field exposure over a period of at least one hour is required.

Cells are electrodynamic systems and may be described by defined input and output variables. Electric activity at the cellular level is caused primarily by moving ions, leading to generator potentials at selective membranes permeable to ions. Fig. 1 is an electron microscope image of a colonic epithelial cell. It is clear from this picture that the structural cell components mainly consist of membranes, and that the nanostructured compartmentation of the cell is elicited by electroactive membranes.

Binggeli and Weinstein (see Fig. 2) have shown that with almost all the cell types ex-amined, the transition from stationary to proliferative behaviour is characterised by a change in the transmembrane potential. The trigger threshold was found to be approx. 37 mV, and depending on whether the potential is increased or decreased, the tendency of the cells to divide will also change [1].
Surprisingly, this value is true for both tumour and non-tumour cells, which suggested that an evolutive concept must be the underlying principle.
The EvoPot project demonstrated that the growth rate of cells may be influenced by applying electric and magnetic fields, and that growth may be reduced significantly under certain conditions.
In therapies involving electric fields, the field strengths are within a technically feasible range most unlikely to pose any regulatory problems when it comes to developing a new cancer therapy. Surprisingly, however, we have found that therapy using magnetic fields requires very high magnetic field strengths. Nevertheless, we also found that the influence of magnetic fields reduces growth by approx. 30 - 40 %.

From the data obtained during the EvoPot project, it can be seen that a permanent field exposure over a period of at least one hour is required for a therapeutic effect. In this project, the principles of using a field-enabled influence on the membrane potential for cancer therapy were investigated for the first time ever. During our experiments, we found that not all information found in literature was correct, as was the case with some assumptions as regards an available apparatus system that may be appropriate here. However, thanks to the presently available technical options some of which were provided by other project

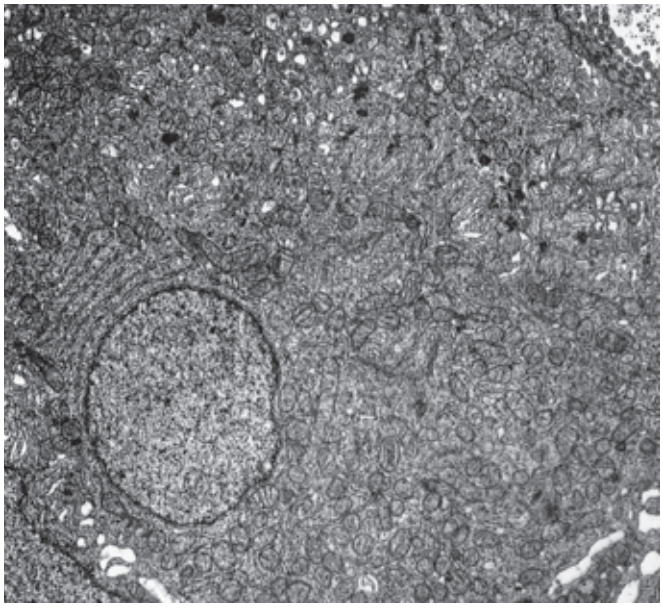


Fig. 1: Electron microscope image of a colonic epithelial cell

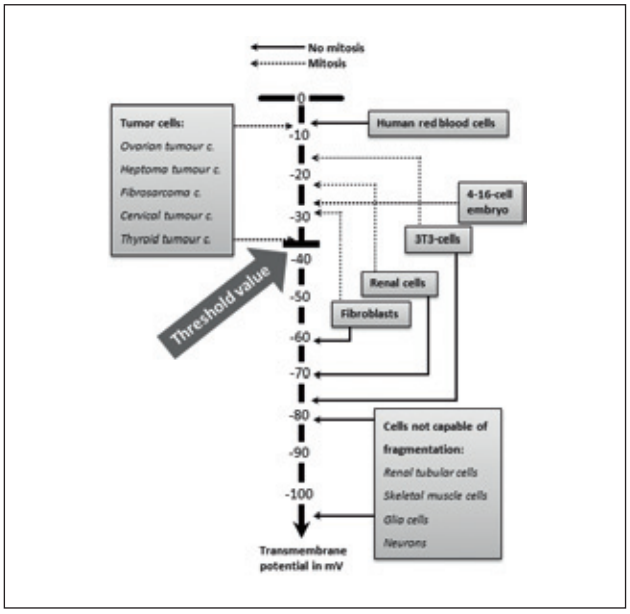
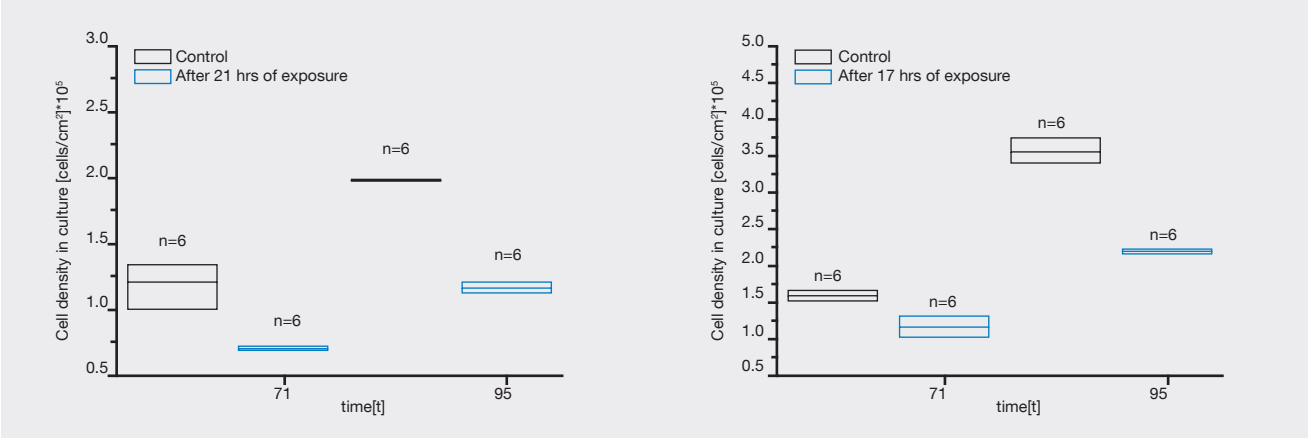


Fig. 2: The transmembrane potential of normal animal cells (right) and of transformed tumour cells (left). It can be seen that proliferating cells have a transmembrane potential exceeding a threshold value of approx. -37mV. Cells able to assume a transitory mitotic state thereby decrease the value of their transmembrane potential. The red blood cell, an anuclear cell with special functions, is an exception to this rule. According to data provided by Binggeli and Weinstein 1986.

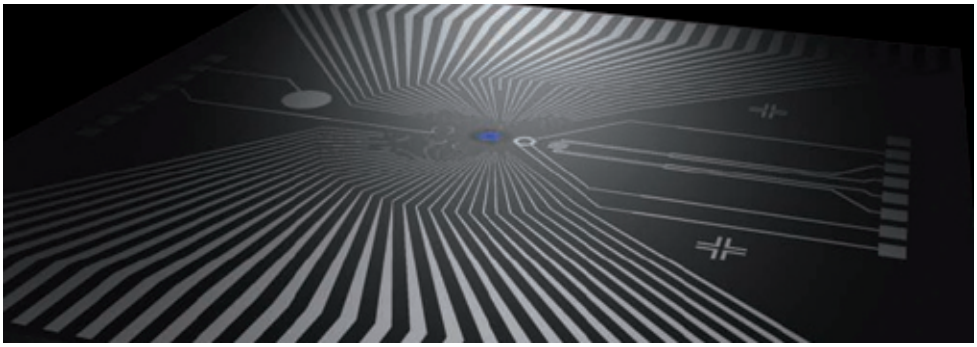
Fig. 3: Influence of the exposure of MDA-MB231 cells to an electric field on their growth after 71h and 95 h in culture on glass chips (electric field strength: E=250 V/m).

Fig. 4: Influence of the exposure of L929 cells to the magnetic field on their growth after 71h and 95 h in culture on glass chips (magnetic field strength: B=35 mT).



groups, we are able to perform the experiments that are still necessary in a highly parallel and a statistically well-established manner. Further, the data thus acquired were used for designing therapeutic implants

[1] R. Binggeli, R.C. Weinstein, Membrane potentials and sodium channels (1986): Hypotheses for Growth regulation and cancer formation based on changes in sodium channels and gap junctions, J.theor. Biol.123, 377-401



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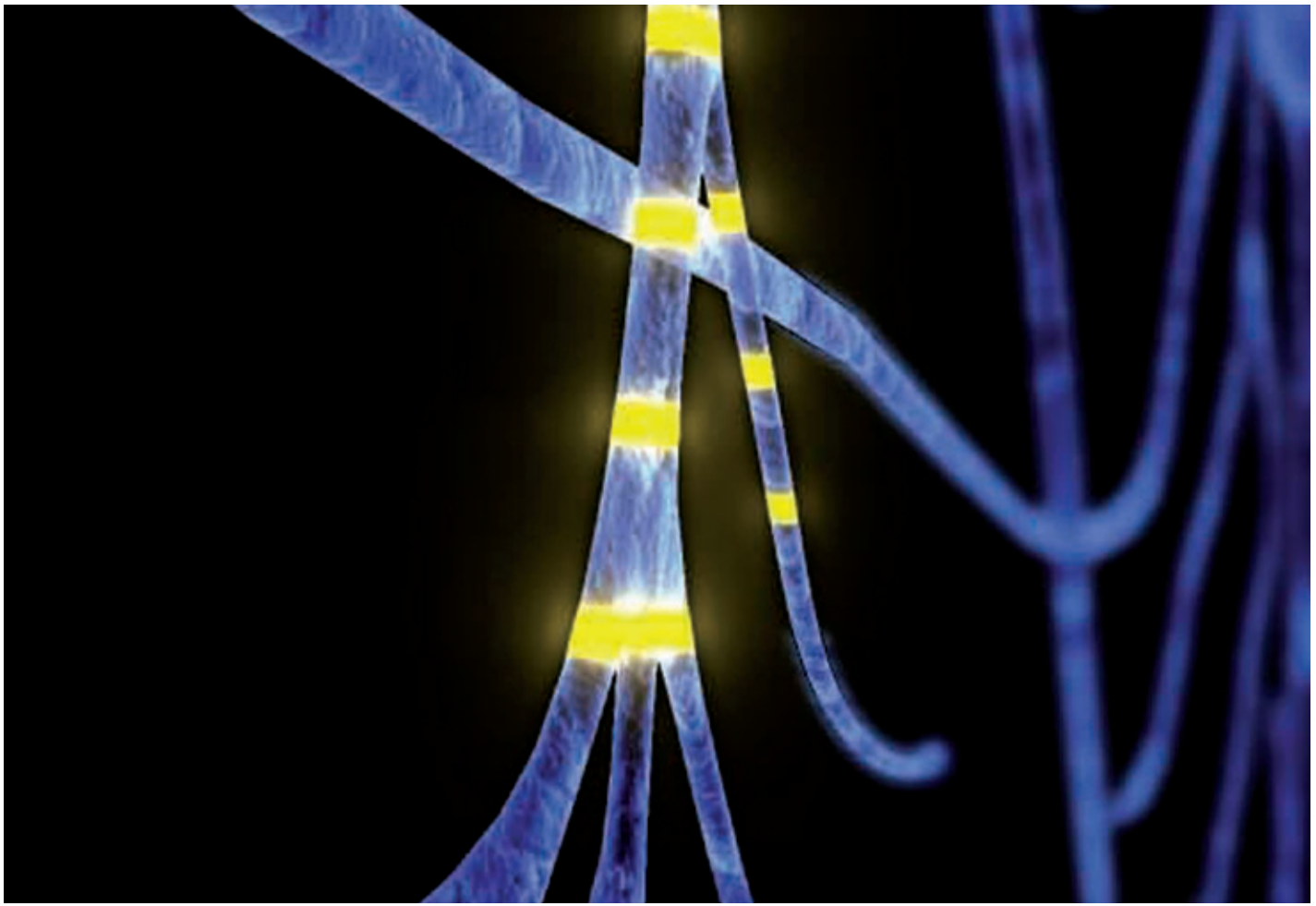
- *B. Wolf, L. Hafner, M. Brischwein, H. Grothe,M. Remm, A. Michelfelder: **EvoPot: Konzepte für eine bioelektronische Tumortherapie.** In: Bernhard Wolf (Hg.): Bioelektronische Diagnose- und Therapiesysteme. m³: microelectronic meets medicine, 1. Aufl. 2012, Aachen: Shaker Verlag, pp. 139–146. ISBN: 978-3-8440-0831-9*

- *L. Hafner, B. Wolf: **Feldinduzierte metabolische Veränderungen an Tumorzellen.** In: Bernhard Wolf (Hg.): Bioelektronische Diagnose- und Therapiesysteme. m3: microelectronic meets medicine, 1. Aufl. 2012, Aachen: Shaker Verlag, pp. 139–146. ISBN: 978-3-8440-0831-9*

- *L. Hafner, M. Brischwein, B. Wolf, **„Effect of electric field on tumor cell growth“,** Beiträge zur 49. Jahrestagung der Deutschen Gesellschaft für Biomedizinische Technik im VDE – BMT 2015, 16. – 18.09.2015, Lübeck.*

This research was funded by the Heinz Nixdorf Stiftung.
Project title: „EvoPot - Analyse der therapeutischen Relevanz des Transmembran-Potenzials von Tumorzellen mittels multiparametrischer bioelektronischer Chipsysteme“ (EvoPot - Analysing the therapeutic relevance of the transmembrane potential of tumour cells by multiparametric bioelectronic chip systems)
Project life span: 2008 to 2010



Multiparametric system for automated high-throughput analysis of nerve cells [neuroscreening]

In short

The “NeuroPlate” was created to detect various metabolic and morphological parameters in coherent neuronal networks. This is important for developing drugs, for example to treat neurodegenerative diseases such as Alzheimer’s or Parkinsons’s disease.

In recent years, the investigation of living cell cultures using miniaturised sensor systems has become more and more important in medicine and in pharmaceutical research. Nerve cells are used as biological sensors and signal conductors in a large number of our research endeavours. This includes the evaluation of the effectiveness of new drugs and the investigation of their neurological side effects, as well as environmental analytics for testing the neurotoxicity of pollutants.

Based on the know-how gained during the preceding „EvoPot“ project, one of our teams has focused on detecting various metabolic and morphological parameters in coherent neuronal networks. Since nerve cells, the so-called neurons, communicate via electric potential variations, it is of great importance to find a way of detecting these signals in order to investigate complex interneuronal relationships, as well to develop drugs for influencing these functions, e.g. drugs for the treat-

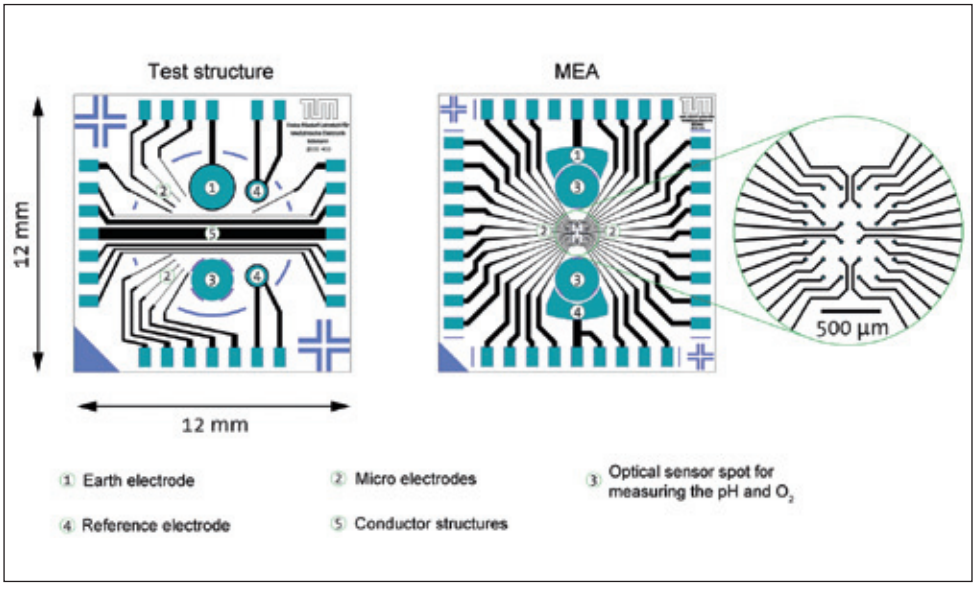


Fig. 1: Layout of the chip structures used. The insulated conductor patterns are shown in green, de-insulated ones in blue

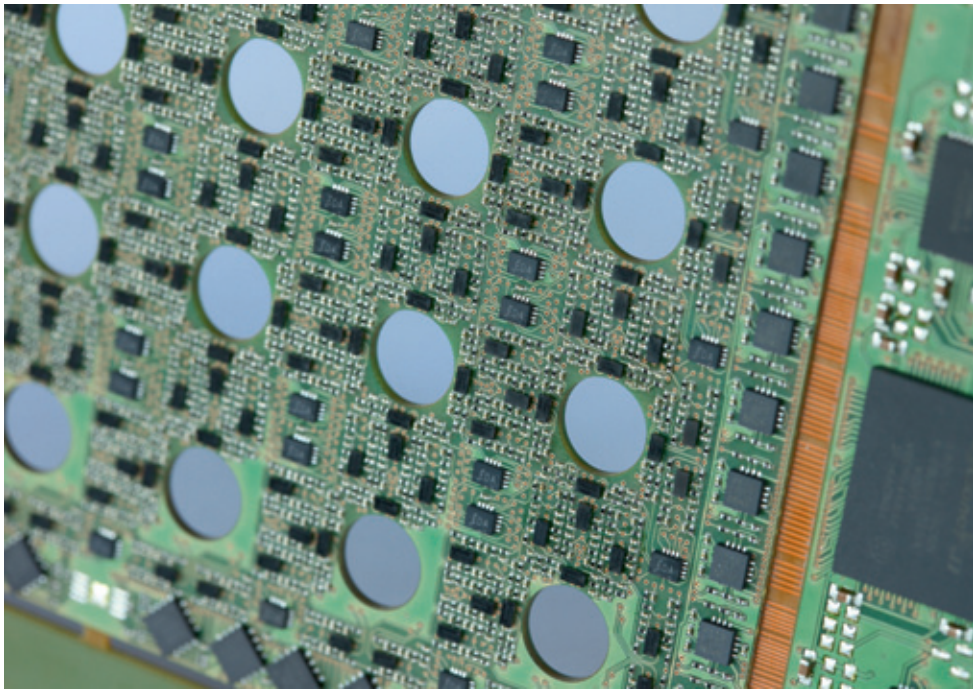


Fig. 2: Detailed view of the NeuroPlate.

ment of neurodegenerative diseases such as Alzheimer‘s or Parkinson‘s disease.

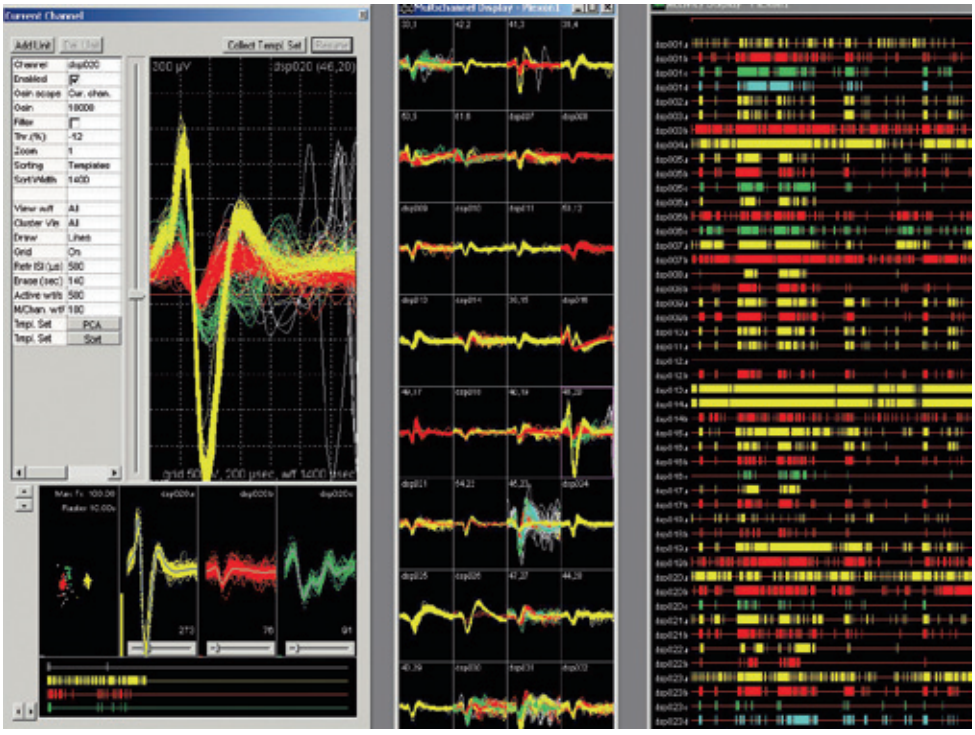
Aiming to investigate the behaviour of neuronal cell layers in greater detail, and to find a solution for measuring their interactions, we make use of extracellular measuring techniques. These do not harm the neurons and therefore allow for long-term measurements. The multi-electrode arrays (MEAs) we had developed and miniaturised particularly for this purpose are able to detect the electric cell signals with an array of tiny conductive electrode structures and to transmit them to external monitoring amplifiers which are part of the so-called NeuroPlate.

For statistical validation of the data thus acquired, we also developed a specific system for collimating the individual measurements. The basis of the NeuroPlate is formed by a carrier in the format of a multi-well plate with 24 individually equippable wells for the MEA glass sensor chips (neuro-chips) that can be microscopied during measurement. Every neuro-chip already has a vessel fixed to it, holding the culture medium required for the long-term measurements.

The central feature of the NeuroPlate is its integrated signal processing unit. The electrical signals derived from the 32 microelectrodes of every single chip undergo analog pre-amplification and filtering, a process performed separately in each chip. The channels may be controlled separately and amplified with variable amplification factors, and A/D conversion of the signals may be performed within the NeuroPlate. An optional data compression function helps to transmit the data volumes to a computer.

Fig 4: visualisation of the derived action potentials in a cell culture at the measurement station; right:

Fig. 3: Display depicting the activities in a cell culture.



Selected publications

- *Ilchmann, F., Grundl, D., Lob, V., Becker, B., Wolf, B., „Zell-Chipsysteme - Mikrosensorarrays für die biologische Grundlagenforschung und Diagnostik“, GIT Laborfachzeitschrift, 52. Jahrgang (52nd year), 3 March 2008, pp. 260-285.*

- *Ilchmann, F.; Weiß, R.; Trappendreher, D.; Becker, B.; Schmidhuber, M.; Wolf, B.: Multiparametrisches NeuroScreening-System für automatisierte Hochdurchsatz-Analyse. In: Bernhard Wolf (Hg.): Bioelektronische Diagnose- und Therapiesysteme. m3: microelectronic meets medicine, 1. Aufl. 2012, Aachen: Shaker Verlag, pp. 139–146. ISBN: 978-3-8440-0831-9*

- *J. F. Meyer, F. Kamp, T. Bartels, T. N. Kinney, F. Ilchmann, K. Beyer, B. Wolf, „MEA supported corti-cal cultures as a novel tool in Alzheimer’s research“, Proceedings 6th International Meeting on Sub-strate-Integrated Micro Electrode Arrays, Reutlingen, 2008*

- *F. Ilchmann, J. F. Meyer, J. Ressler, H. Grothe, B. Wolf, „Multiparametric NeuroLab recording chamber with MEA and integrated metabolic sensors“, Proceedings 6th International Meeting on Substrate-Integrated Micro Electrode Arrays, Reutlingen, 2008*
  Ilchmann, F.; Trappendreher, D.; Becker, B.; Heise, G.; Wolf, B.: Laserbasierte Herstellungsverfahren individualisierbarer Biosensorchips. In: Bernhard Wolf (Hg.): Bioelektronische Diagnose- und Thera-piesysteme. m3: microelectronic meets medicine. 1. Aufl. 2012, Aachen: Shaker Verlag, pp. 131–138. ISBN: 978-3-8440-0831-9

- *Becker, B., Etzbach S., Schmidhuber M., Grundl D., Ilchmann F., Grothe H., Wolf, B. Real-time Screening System using living cells for chemosensitivity testing, The IEEE Region 8 Eurocon 2009 Conference, 18 -23 May 2009, Saint-Petersburg, Russia, ISBN 978-1-4244-3860-0, pp. 87-93, INSPEC Accession Number: 10791108, Digital Object Identifier: 10.1109/EURCON.2009.5167609*

This research was funded by the Heinz Nixdorf Stiftung.
Project title: „EvoPot - Analyse der therapeutischen Relevanz des Transmembran-Potenzials von Tumorzellen mittels multiparametrischer bioelektronischer Chipsysteme“ (EvoPot - Analysing the therapeutic relevance of the transmembrane potential of tumour cells by multiparametric bioelectronic chip systems)
Project life span: 2008 to 2010

Structuring of biosensor chips by laser ablation for low cost applications

In short

In this project, a new method for fabricating low-cost biocompatible sensor chips with laser structuring was developed. For applications with modest demands for spatial resolution, such as sensor chips for impedance spectroscopy, this method is a less expensive alternative to common techniques like photoetching.

The recording of electrical and electrochemical signals by planar sensor chips has become an important application for in-vitro drug and toxicity screenings. These include metabolic profiles like alterations of the oxygen consumption and the extracellular acidification, as well as cellular growth, morphological changes and activity patterns of electrically active cells. Ideally, these recordings should be entirely non-invasive, long-term stable, economical as well as efficient and highly reproducible. In the ongoing work at the Heinz Nixdorf-Lehrstuhl für Medizinische Elektronik, a new way of fabricating low-cost biocompatible sensor chips by laser structuring could be established. In order to reduce chip size and to keep costs to a minimum the layouts were designed for a final chip size of 12 mm × 12 mm.

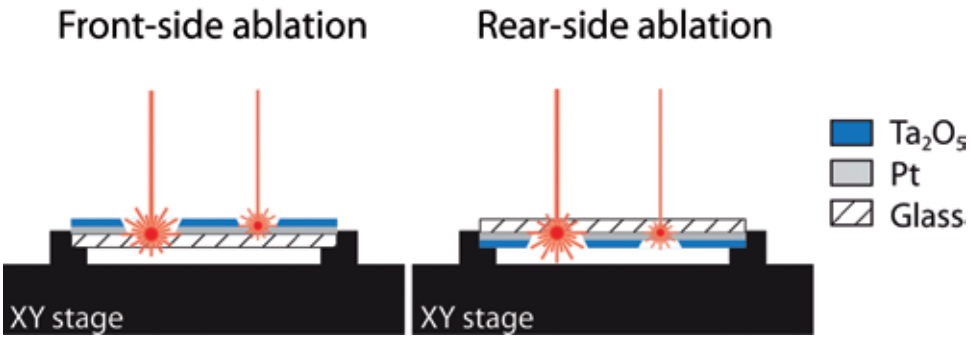


Fig. 1:
Principle arrangements of front-side (A: Direct laser ablation (l.a.); B: Indirect induced l.a.) and rear-side (C: Direct induced l.a.; D: Only Ta2O5 l.a.) picoseconds laser structuring

A novel low cost method for structuring both circuit paths and the insulation layer in sensor chip fabrication has been developed to overcome the disadvantages SU-8 photoresist or silicon nitride (Si3N4) shows regarding its long term stability. Therefore a thin film layer system consisting of platinum and tantalum pentoxide was utilized, where platinum represents the conductive layer and tantalum pentoxide the insulation layer. Thin films were deposited onto glass wafers by sputtering and electron beam evaporation, respectively. For

applications in cell culture optical transparency is crucial when monitoring cell viability or morphological alterations. In addition tantalum pentoxide displays high chemical and thermal stability and can withstand a wide range of sterilization procedures like autoclaving and mechanical stress, which supports the reuse of the biosensor chips.

Multiple ways of structuring and process parameters have been investigated in order to obtain optimized results. Both, complete removal and selective ablation of platinum and tantalum pentoxide thin films were possible by irradiating the substrate with ultra-short pulses of a Nd:YVO4 laser with 10 ps pulse duration at 1064 nm wavelength. For a deeper understanding of the selective structuring front-side and rear-side ablation were compared as well as different film thicknesses. We showed, that best results could be obtained by utilizing rear-side structuring of the platinum layer followed by front-side ablation of the tantalum pentoxide layer.

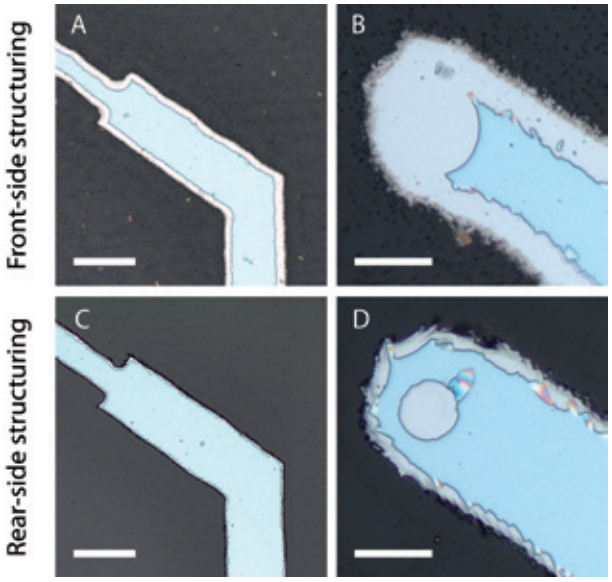


Fig. 2:
Comparison of simultaneous front-side structuring (A, B) and rear-side structuring (C, D). A and C show an electric line, B and D the tip geometry (200 nm Pt + 100 nm Ta2O5).
(Bar (A, C) = 100 µm; Bar (B, D) = 25 µm)

Impedance spectroscopy performed with laser structured sensor chips indicated the need of sequential structuring due to high unspecific coupling of electrical signals when utilizing simultaneous structuring. In the latter case the ratio between the area of bare platinum at the edges of the produced structures and the effectively isolated area is much higher compared to the sequential process. Furthermore, an unexpected reduction of the fluence level for the complete removal of the platinum layer was observed when it was covered with an additional dielectric layer.

For applications with modest demands for spatial resolution like sensor chips for impedance spectroscopy, the presented method is a cheaper alternative to common techniques like photoetching. Confocal microscopic examinations indicated a minimal reproducible path width of about 10 µm.

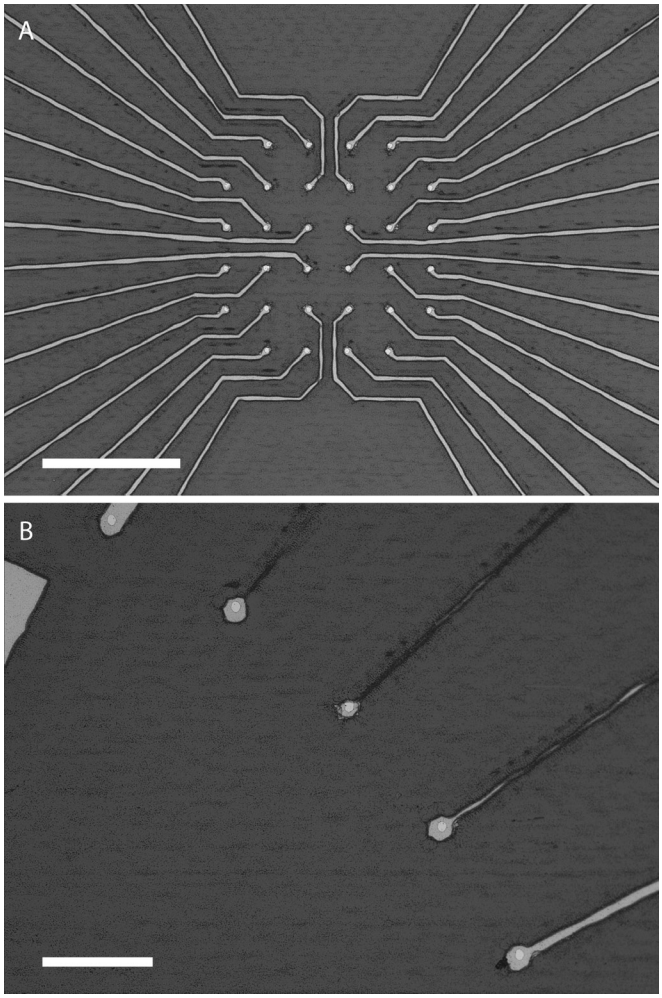


Fig. 3:
Microscopic pictures of a sequentially laser-structured multi-electrode array (A) and electrodes of different widths (50 µm, 2 µm, 5 µm, 10 µm and 20 µm, from upper left to lower right) of a test structure (B). (200 nm Pt + 300 nm Ta2O5; Bar A = 500 µm; Bar B = 200µm)

This research was funded by the Heinz Nixdorf Stiftung.

It was part of the project “EvoPot – Analyse der therapeutischen Relevanz des Transmembran-Potentials von TUMOURzellen mittels multiparametrischer bioelektronischer Chipsysteme” (EvoPot – Analysing the therapeutic relevance of the transmembrane potential of tumour cells by multiparametric bioelectronic chip systems).

Project Life Span: 2008 to 2010

Selected publications

- *Becker, B., Etzbach, S., Schmidhuber, M., Grundl, D., Ilchmann, F., Grothe, H., Wolf, B. Real-Time Screening System Using Living Cells for Chemosensitivity Testing. The IEEE Region 8 Eurocon 2009 Conference. pp. 87-93.*

- *Ilchmann, F., Becker, B., Grundl, D., Meyer, J., Wolf, B. Automated 24 Well Neuro-Screening System with Life Support. World Congress on Medical Physics and Biomedical Engineering. 2009*

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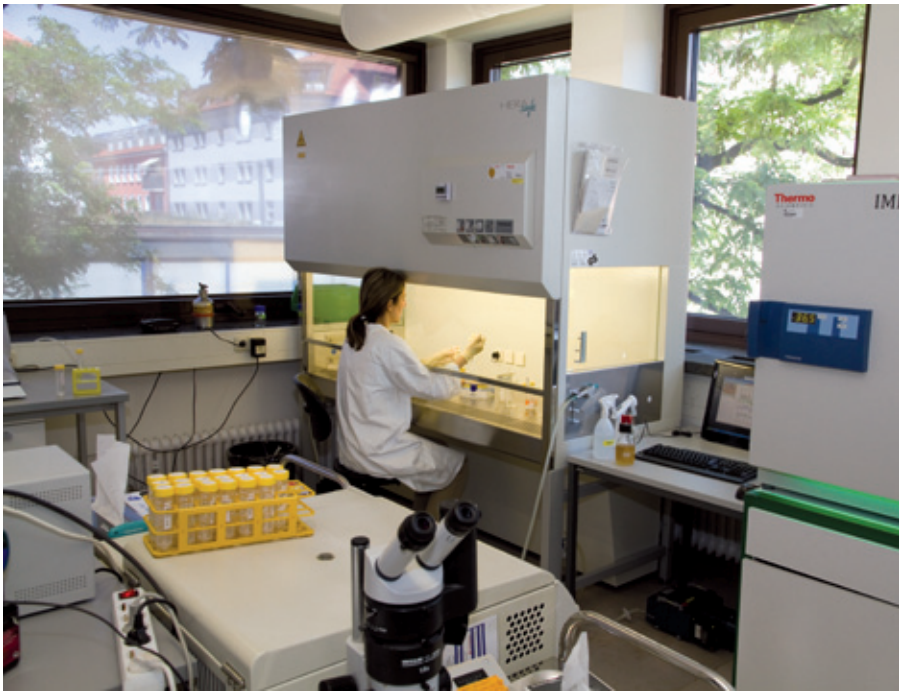
- *Heise, G., Englmaier, M., Hellwig, C., Kuznicki, T., Sarrach, S., Huber, H.P. Laser Ablation of Thin Molybdenum Films on Transparent Substrates at Low Fluences. Applied Physics Materials Science & Processing. 102, 2011, pp. 173-178.*



Therapeutic magnetic stimulation

In short

In contrast to electrical stimulation of large muscular surfaces, this novel magnetic stimulation system permits muscle contraction to be triggered without activating the pain pathways, and penetrates deeper into the muscular tissue.

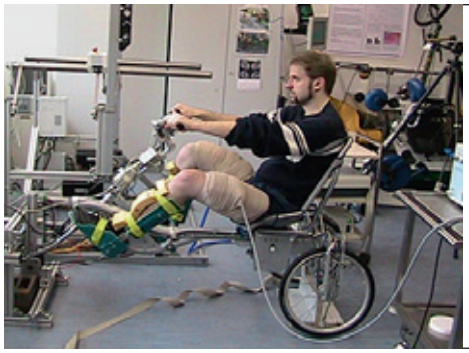
In neuro-rehabilitation, magnetic stimulation has been postulated as a promising treatment option. Our „Therapeutic magnetic stimulation“ project involved the development and design of a new magnetic stimulation system for therapeutic purposes for testing in humans.

In medicine, the electric and magnetic stimulation of nerves and muscles is an established method for diagnostics, therapy and rehabilitation. This project aimed at significantly enhancing the efficiency of the relatively new „Therapeutic magnet stimulation“ method and opening the door to new fields of application in medicine.

The electrical stimulation of large muscular surfaces is associated with substantial pain in the patient/subject, and only allows for the stimulation of muscles lying under the skin surface. In contrast, magnetic stimulation permits muscle contractions to be triggered without activating the pain pathways, and penetrates deeper into the muscular tissue. Due to the beneficial magnetomotive force acting on the muscle, it is possible to make use of substantially stronger muscle forces while causing less fatigue.

In our project, we developed, designed and tested a new magnetic prototype system which for the first time ever uses a high-frequency polyphase „BURST“ as a stimulation pulse. With a view to clinical use, the new stimulation system was tested in humans for its therapeutic and rehabilitative effects and its energy efficiency.

Test series were performed to determine the optimum number of cycles in subjects with total paraplegia compared to healthy subjects. We found that the effectiveness of peripheral repetitive magnetic stimulation may be increased by using pulse trains (BURSTs) with 3-4 cycles. We further assume that peripheral repetitive magnetic stimulation may have a strong alleviating effect on spasticity.



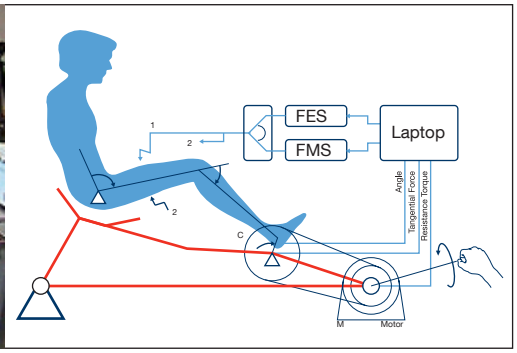


Fig.1: Real-life measurement set-up (photo: Dr. Szecsi, Klinikum Großhadern)

Fig. 2: Principle of the test installation for rehabilitative magnetic stimulation

Selected publications

- *Therapeutische Magnetstimulation, BFS-Forschungsberichte 2010, p. 38.*
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This research was funded by the Bayerischen Forschungsstiftung.
Project title: „Therapeutische Magnetstimulation“ (Therapeutic magnetic stimulation)
Project life span: 2008 – 2010

The “Lufttacho”: Sensors get wings

In short

The “Lufttacho” is a spirometer developed especially for children. Its innovative hot-wire anemometry technology permits even low-volume flow rates to be detected. Our collaborative partner Sendsor GmbH has since brought the product onto the market.

The measurement of air flows may be useful in medicine and also in many other fields of research. While the principle of hot-wire anemometry for measuring the mass flow of gas has long been known, the fabrication of such a sensor has remained too elaborate and cost-intensive. In cooperation with the company sendsor GmbH, we have worked on finding a new and cost-effective production process for this type of sensor. Compared to conventional mass flow sensors, these sensors offer the advantage of a broader measurement range and higher measurement accuracy, especially in the case of lower flow.

Plating any type of metal structure intended for electronic circuits on injection-moulded carrier substances offers a very efficient option for the production of microsensor devices. Figure 1 gives an example of a simple structure made from a nickel-galvanised polymer, the surface of which reveals meander-like structures formed by means of a CO_2 laser. Thanks to the geometrical design and the selection of various metals, it is possible to fabricate structures with the desired resistance value and temperature dependence or resistance in a fast and cost-effective manner.

Thanks to the simplified fabrication process, it is also possible to rapidly adapt the specific characteristics of the sensors to the requirements of every application.

The spirometer, or „Lufttacho“, which was especially developed for children, entails the direct use of the hot-wire anemometry principle mentioned above. The innovative hot-wire anemometry technology allows even for small volume flows to be detected.

Owing to the simplicity of this technology, the pre-calibrated sensor unit may be replaced in a similar way as the mouthpieces of comparable spirometers. Hence this system does not needs to be calibrated by the user, a process which often is a source of error in other measurement systems. The tube may be disinfected and disposed of after a predetermined number of applications, which helps to minimise cross-infections.

The „Lufttacho“ was developed by sendsor GmbH and is the first electronic spirometer specifically designed for children. The measurement range was adapted to the small lungs of children and allows for the precise and reliable measurement even of values under 300 L/min. The „Lufttacho“ is the first ever system to enable the patient and physician to use one and the same device for measurement. Besides its diagnostic feature, the device also comprises a game that was specifically developed for children and enables them to use the

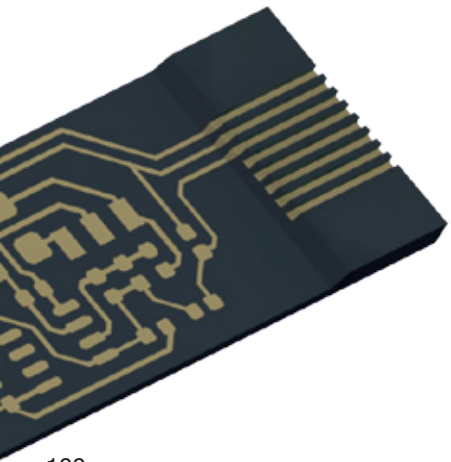

Fig. 1: Sensor base made of plastic with sensor structures made by electrodeposition. At first, the entire surface exhibits sensor activity; in a further step, the sensor capacity on the surface in the area of the layout struc-ture is deactivated by applying a gold layer.

device for respiratory training. The colour display with its speedometer-like appearance (displaying the respiratory volume in %) makes it possible to easily read and understand the measured values, even for children under the age of 6 years.

Fig. 2: The „Lufttacho“ is a medical device for children suffering from asthma comprising a gas mass flow sensor made of plastic.
http://www.sendsor.de

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- *A. Scholz, J.M. Herrmann, B. Wolf, „Etablierung neuer Therapiekonzepte durch den Einsatz von Telemetric Personal Health Monitoring Systeme“, DGBMT 2004., Berlin, pp. 256-257.*
- *A. Scholz, V. Lob, J. F. Clauss, J. M. Herrmann, B. Wolf: „Einbindung von Sensorsystemen in das TPHM-System“, Biomedizinische Technik Vol. 49, pp. 224-225, 9/2004.*
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- *B. Wolf, H. Grothe, K. Herzog, F. Demmel, J. Wiest, W. Wirths, J. Clauss, M. Brischwein, C. Dormeyer, M. Gül, K.-U. Hinderer, P. Friedrich, „Von der TUM in den Markt: Mikroelektronik für Diagnose und Therapie“, In: Duisberg, F. (Hrsg.), „E-Health 2015“, Solingen, 235-242, 2014.*
- *C. Dormeyer, A. Scholz, F. Prenzel, „Lungenfunktionsmessung bei Vorschulkindern – führt ein Spiel zum Erfolg?“, ALLERGOLOGIE, 37(4), 161-+, 2014.*

This research was funded by the Bundesministerium für Bildung und Forschung.
Project title: „GaSeMed“ -Einweg-Gasfluss-Sensor für medizinische Anwendungen“ („GaSeMed” - disposable gas flow sensor for medical applications)
Project life span: 1 March 2008 to 28 February 2012

New therapeutic options with COMES®

In short

COMES® is a new mobile diagnostic and therapeutic platform that offers patients the possibility to lead a healthy and independent life.

In view of the fact that age-related diseases such as cardiovascular disorders, primary hypertension, diabetes, heart failure or stroke are on the rise, a team at our faculty is working on a systemic care approach for patients suffering from these diseases. In this context, the Cognitive Medical System (abbreviated to COMES®) developed in this project plays quite an important role.

COMES® is a new mobile diagnostics and therapy platform that offers patients the possibility to lead a healthy and independent life. It has resulted from various development projects involving sensor-enabled systems during the past ten years, and helps to measure, transmit and verify biomedical data by means of established measuring techniques and communications structures [1, 3].

COMES® was conceived in the middle of 2009 with the support of the companies Synergy Systems GmbH and Pasife GmbH. Since November 2010, COMES® has been funded by Heinz Nixdorf Stiftung as part of the „Kompass“ project and is being gradually expanded and modernised. Our aim with COMES® is to enable medical diagnostics and intervention at any time, anywhere. To this end, intelligent databases are used as an important support system for individualised therapy and follow-up – and for motivating the patient.

Thanks to the use of modern databases, physicians can offer personalised information or establish a dialogue with a particular patient.

A wide variety of sensors – some of which were developed at our faculty – are already available for the COMES® system. Not only can patients measure their blood pressure, weight and activity in a familiar and comfortable environment, but values relating to diabetes, bruxism, breathing volume and breathing-related sleep disorders can also be monitored. The data thus obtained are then automatically transmitted via smartphone to the COMES® Trust Center, while guaranteeing compliance with the applicable data safety standards. The patient may further complete questionnaires directly on his/her smartphone, tablet PC or computer and provide additional information useful to his/her physician that can be stored in the system.

We are currently doing research into the following points: user acceptance, expansion of the feedback system, application of personalised motivation methods.

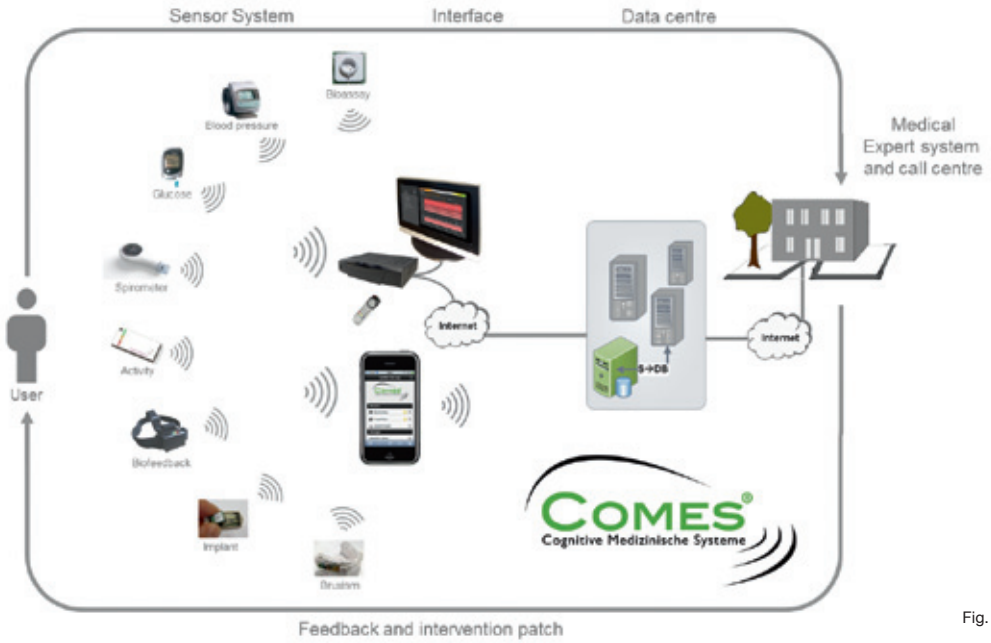

Fig. 1: The complete COMES® system

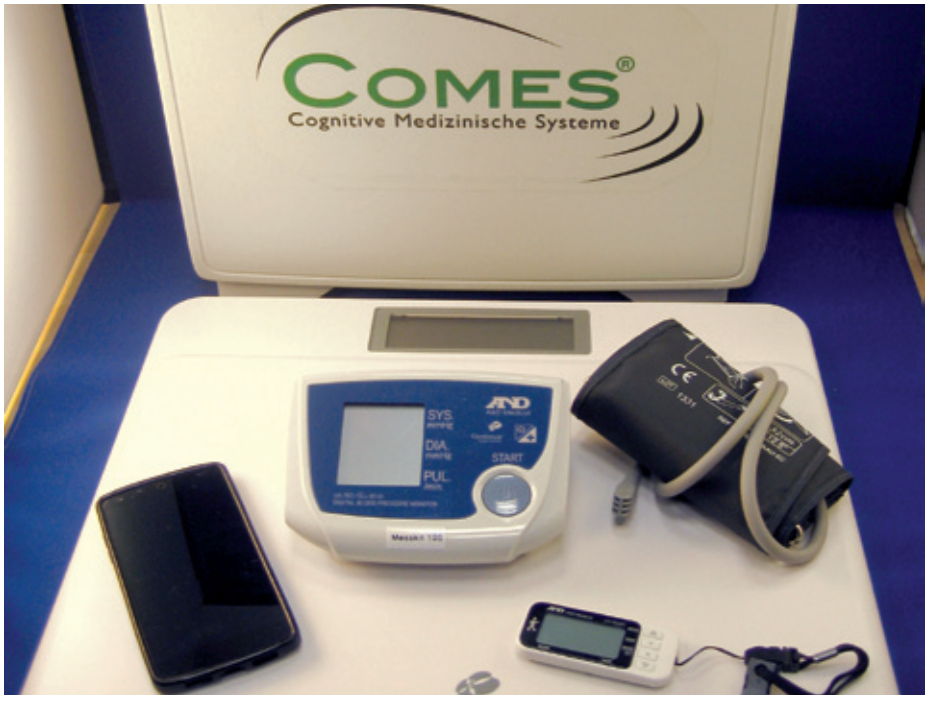

Fig.2 Measuring devices connected to COMES®

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- *[2] P. Friedrich, J. Clauss, A. Scholz, B. Wolf, „Sensorik für telemedizinische Anwendungen“, in: Goss, Middeke, Smetak (Hrsg.), Praktische Telemedizin in Kardiologie und Hypertensiologie, Georg Thieme Verlag (2009), ISBN 978-3-13-149931-8, S. 6-14.*
- *[3] B. Wolf, P. Friedrich, S. Becker, J. Clauss, D. A. Hofsøy, A. Scholz, „Ambient Medicine® - sensorgestützte Assistenzsysteme für die telematische Diagnose und Therapie“, in: F. Duesberg (ed), e-Health 2010, Informationstechnologien und Telematik im Gesundheitswesen, Solingen, 2010, pp. 230 – 236.*
- *[4] C. Türmer, D. Dill, B. Wolf, „Medizinisches Aktivitätsmonitoring“, in: F. Duesberg (ed): E-Health 2013 Informationstechnologien und Telematik im Gesundheitswesen. Solingen/ Mittweida, medical future verlag, 2012, S. 266 – 269.*
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- *[6] B. Wolf, T. Spittler, J. Clauss, A. Scholz, P. Friedrich, K. Herzog, „Telemedizin - rundum gut betreut“, Bulletin (2014), 4, 33-37.*
- *[7] T. Spittler, D. Polterauer, P. Friedrich, B. Wolf, „Rehabilitation’s Aftercare by COMES®”, European Congress on e-Cardiology & e-Health, 29.-31. Oktober 2014, Bern, Switzerland, European Journal of Preventive Cardiology, S. 42.*
- *[8] B. Wolf, P. Friedrich, „Therapieplattform COMES® - Für ein selbstbestimmtes Leben“, Deutsches Ärzteblatt, 4/2014, 24-27.*
- *[9] B. Wolf, C. Scholze, H. Grothe, M. Brischwein, „‘Medizin 4.0‘ – Die Bedeutung von Elektronik, Informationstechnik und Mikrosystemen in der modernen Medizin“, in: J. Gausemeier (ed), Vorausschau und Technologieplanung, 11. Symposium für Vorausschau und Technologieplanung, 29. - 30.09.2015, Berlin 2015, pp. 379 – 401.*

This research was funded by the Heinz Nixdorf Stiftung, the Synergy Systems GmbH and the Pasife GmbH. Project title: COMES® – „Cognitive Medizinische Systeme“ (COMES® – Cognitive Medical Systems)
Project life span: 1 September 2009 to 31 August 2012

KOMPASS – "Kognitives Medizinisches Personalisiertes Assistenzssystem" (Cognitive personalized medical assistance system)

In short

The "All-in-One" medical device that is integrated into the COMES® telemedical system and the newly developed business models have shown that systems like these can improve public healthcare and can be operated economically on a long-term basis.

Telemedical assistance systems offer a great opportunity to achieve improvements in public healthcare. They can help enhance the quality of patient care along the entire chain, from prevention, diagnostics and therapy to rehabilitation, as well as reducing costs and facilitating the provision of medical care to patients living in rural regions with little infrastructure. An important field of application is telemonitoring: By using communications and information technologies to exchange data, close monitoring is possible despite long distances between doctor and patient.

The project entitled "Development, evaluation and optimization of a telemedical assistance system for prevention, diagnosis and therapy" (KOMPASS, "Entwicklung, Evaluation und Optimierung eines telemedizinischen Assistenzsystems zur Prävention, Diagnostik und Therapie") was initiated and conceived by our faculty to investigate the use of cutting-edge sensors combined with communications and information systems. This work was done in collaboration with the Heinz Nixdorf Institut of the University of Paderborn (Professor Ordinarius: Prof. Dr. Jürgen Gausemeier). We have extended the COMES® telemedical assistance system introduced in the previous chapter and optimized the sensor system that had been developed to this end.

The aim of the "KOMPASS" project was to create a multi-sensory terminal device for integration into COMES® along with a suitable information management concept. The result is an "All-in-One" medical device which will be described in detail in the following chapter. A further important part of this project was to develop an appropriate business model to reveal the changes that could take place in the markets and society by 2030, and how the telemedical system may be operated economically in the long run.

The analyses revealed that companies offering telemedical services – who are fully aware of their business opportunities – nevertheless mainly offer insular solutions. Comprehensive market services are still lacking. One reason for this could be the as yet unanswered questions about financing, protection of privacy, legal issues and the acceptance of telemedical concepts in society. In order to present viable models, the Heinz Nixdorf Institut developed

three scenarios according to which telemedicine may develop in very different ways, depending on how the concept is accepted by the relevant stakeholders (Fig. 1). From what we know today, it is very likely that telemedicine will soon be widely accepted and commonly used. Various viable, long-term models were then designed with this in mind.

The novel All-in-One medical device integrates various measuring functions and is ergonomic and intuitive to operate – enabling patients to use it in almost all everyday situations. The integrated information management permits direct data exchange between patient and doctor. The doctor can thus access the measurements taken by his or her patients at any time (Fig. 2) and react quickly, if necessary. It is also possible to compare the patient data with a large population of similar patients. All in all the resulting system is a comprehensive solution and can be installed for regional, national or even international use.

The results of the KOMPASS project were summarized in an 84-page brochure (see next page).

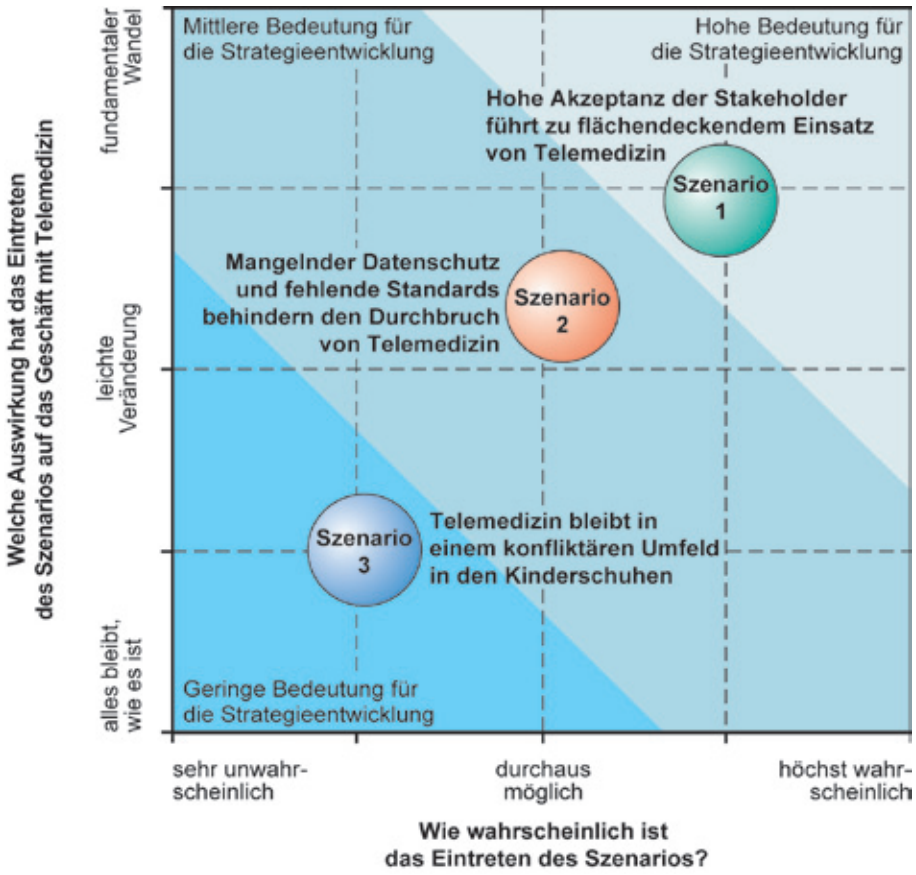

Fig. 1: In the three scenarios developed as part of the KOMPASS project, various factors with either a positive or a negative effect on telemedicine were taken into account. Current trends suggest that scenario 1 is most likely to evolve.

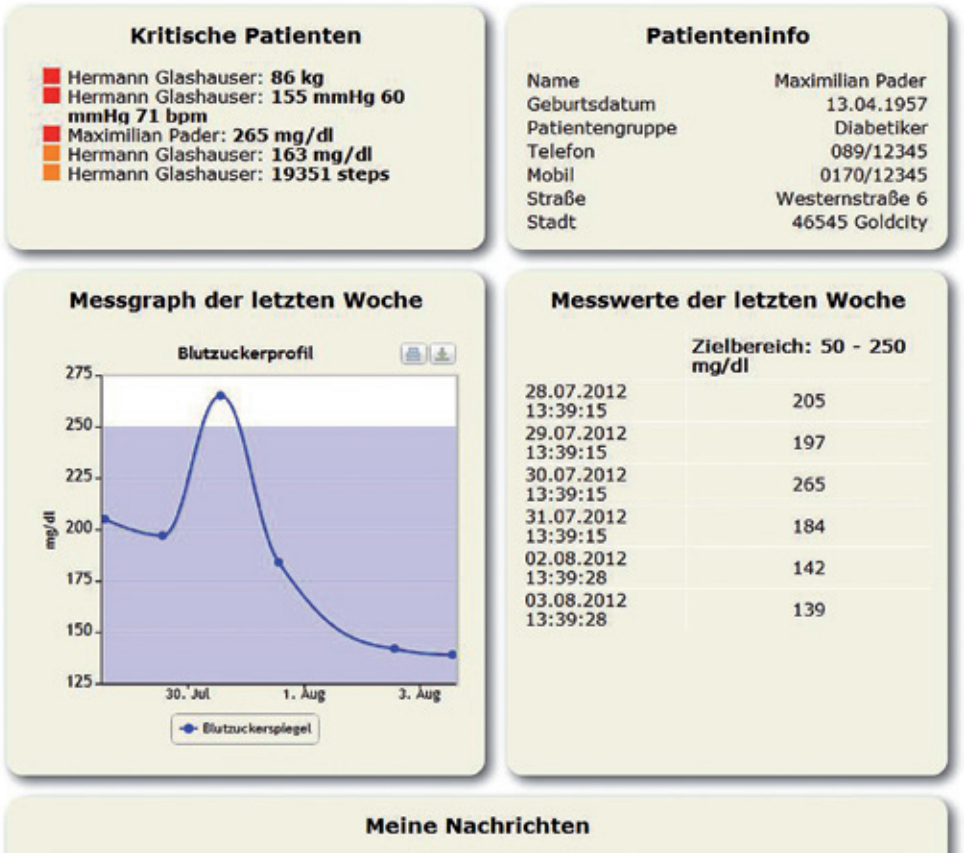

Fig. 2: Information management in the COMES® telemedical system: detailed view of the dashboard for the doctor (screenshot)

Selected publications

➢ *J. Gausemeier, B. Wolf, J. Clauss, P. Friedrich, K. Herzog, A.-C. Lehner, M. Lehner, M. Placzek, T. Schierbaum, T. Spittler, T. Westermann, „Telemedizinische Assistenzsysteme – Technik, Markt, Geschäftsmodelle", Heinz Nixdorf Institut, Universität Paderborn, Heinz Nixdorf-Lehrstuhl für Medizinische Elektronik, Technische Universität München, Paderborn/ München, 2014.*

This brochure may be ordered free of charge by sending an e-mail to info@stw-med-chip.de.

This project was conceived by the Heinz Nixdorf Stiftung.
Project title: "Entwicklung, Evaluation und Optimierung eines telemedizinischen Assistenzsystems zur Prävention, Diagnostik und Therapie" (Development, evaluation and optimization of a telemedical assistance system for prevention, diagnosis and therapy)
Project life span: 1 November 2010 to 31 March 2016

KOMPASS – The “All-in-One” medical device

In short

The “All-in-One” medical device enables patients to monitor their vital signs independently by using one single device. It utilises mobile radio services to automatically transmit the measurements to a database – the treating physician can access the data of his/her patients at all times.

As part of the “KOMPASS” project, the Heinz Nixdorf-Lehrstuhl für Medizinische Elektronik has been working with the Fachgruppe Produktentstehung, Heinz Nixdorf Institut, Universität Paderborn on the integration of a number of essential medical sensors into a single, handy device that is combined with a communication unit.

The resulting “All-in-One” medical device permits the blood pressure, temperature, electrical conductivity of the skin, as well as pulse and oxygen saturation to be measured with just one single device. To do so, the patient simply has to insert one finger into the provided sensor cuff and press the start button. The processes of taking the measurements and storing them in a central database are fully automated. Additionally, a measurement strip for glucose can be inserted into the device. A scale is connected via Bluetooth, and the data measured in such a way is also saved automatically to the database. The All-in-One medical device is illustrated in figure 1.

Fig. 1:
a) “All-in-One” medical device as developed by the Heinz Nixdorf-Lehrstuhl für Medizinische Elektronik, Technische Universität München, in collaboration with the Fachgruppe Produktentstehung, Heinz Nixdorf Institut, Universität Paderborn. Design: Abteilung für Industrial Design, Kunstuniversität Linz, Prof. Axel Thallemer b) Sensor sleeve, detailed view

The device is composed of two function blocks. The single sensors are connected by a microcontroller which records and pre-processes the data. The first function block comprises single sensors that are connected by a microcontroller and offers the following features: combined optical and oscillometric blood pressure measurement, optical measurement of oxygen saturation, conductivity measurement by means of gold electrode structures on the inside of the finger cuff, and a temperature sensor.

For glucose measurement, a drop of blood is taken and analysed using an amperometric test strip. The second function block comprises an embedded Android platform offering both an intuitive user interface and an automatic connection to the COMES® [1] web database, as well as an emergency call option. The wireless transfer of the measured data via a mobile internet connection means that the device can be used at any time of day regardless of the user’s location. Figure 2 illustrates the two function blocks in a block diagram.

Fig. 2:

Technical design of the All-in-One medical device comprising of Android embedded platform and microcontroller

A large touch screen is located on the front of the device, providing instructions on how to operate the device and displaying the measurement results. The user interface is intuitive. The patient can choose between “easy view” and “expert view”. “Easy view” offers just one large button for starting the measurement and displays the values last measured. It is also possible to connect automatically to an emergency center by means of an emergency call button. All the data stored in the database can be visualized in the “expert view” in order to show the progress in therapy. Messages, for instance from and to the general practitioner, can also be read and sent.

Fig.3:

All-in-One medical device showing the “expert view”.

To further develop the system, we are currently working on a sensor ring that can be worn on the finger. This will permit the parameters developed through the project presented above to be measured continually through a ring which can be comfortably integrated into everyday life and connected to a smartphone [2]. This is the reason why our current project has focused on a miniaturized, energy-saving concept for all the sensors and data-processing algorithms.

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- *B. Wolf, P. Friedrich, S. Becker, J. Clauss, D. A. Hofsøy, A. Scholz, „Ambient Medicine® - sensorgestützte Assistenzsysteme für die telematische Diagnose und Therapie“, in: F. Duesberg (ed), e-Health 2010, Informationstechnologien und Telematik im Gesundheitswesen, Solingen, 2010, pp. 230 – 236.*
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- *[2] Wolf, B.: Patent: Einrichtung zur Früherkennung von kritischen Gesundheitszuständen, insbesondere bei Risikopatienten (DE100 06 598)*
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This research project has been funded by the Heinz Nixdorf Stiftung. We thank the Fachgruppe Produktentstehung, Heinz Nixdorf Institut, Universität Paderborn, under the leadership of Professor Gausemeier, for their outstanding contribution to this project. We also thank OMRON Deutschland GmbH for supplying the blood pressure gauge.

Project title: “Entwicklung, Evaluation und Optimierung eines telemedizinischen Assistenzsystems zur Prävention, Diagnostik und Therapie” (Development, evaluation and optimisation of a telemedical assistance system for prevention, diagnosis and therapy)

Project life span: 1 November 2010 to 31 March 2016

CoKeTT Centre – mechatronic assistance systems for health and generations at the University of Applied Sciences Kempten

In short

The CoKeTT AAL User Centre offers the opportunity to test practical therapeutic management systems for conditions such as diabetes, obesity, cardiovascular diseases and psychosomatic disorders, as well as for patients who require rehabilitative care. It offers mechatronic assistance systems for healthcare across all generations.

The AAL Anwenderzentrum CoKeTT (CoKeTT AAL User Centre) was founded in the autumn of 2011 as part of a joint venture with the Hochschule Kempten. CoKeTT stands for COMES® Kempten Test- und Trainingszentrum (COMES® Kempten Test and Training Centre) and is a joint project with the Heinz Nixdorf-Lehrstuhl für Medizinische Elektronik of Technische Universität München. CoKeTT is the first AAL application centre for healthcare in the Allgäu region (south-western Germany) and is a Living Lab for systems, solutions and products designed specifically for elderly people.

Both research institutions are working closely together on this topic. We have therefore come to the conclusion that the application-oriented problems arising with the COMES® and KOMPASS project (Kognitives Medizinisches Personalisiertes Assistenzsystem) at the Heinz Nixdorf-Lehrstuhl für Medizinische Elektronik should be studied intensively at a specifically equipped laboratory of the University of Applied Sciences Kempten. The aim of CoKeTT is to test the systems developed at Technische Universität München in cooperation with existing and new user groups for their practical usability. In this context, CoKeTT can be used by all medical institutions intending to employ personalised assistance systems with modern information and communications technology or requiring support in the use of these systems.

CoKeTT enables the testing of practically oriented therapy management systems for conditions such as diabetes, obesity, cardiovascular diseases and psychosomatic disorders, as well as for patients who require rehabilitative care. For this purpose, the test and training centre is equipped with various telematic measuring systems, providing different configuration options and allowing for different settings according to the different ICT infrastructures of medical institutions. Landline and mobile communications-enabled analysis and therapy platforms can be used, by means of which problems such as telemonitoring and the development of personalised telematic therapy structures may be addressed. Together with CoKeTT, potential users may develop suitable test scenarios, enhance existing equipment and also perform on-site tests of new diagnostic and therapeutic systems.

One example is the PUMA project, “Prävention und Motivation am Beispiel von Adipositas” (PUMA – prevention and motivation concept for patients with adiposis), at the University of Applied Sciences Kempten in collaboration

with Heinz Nixdorf-Lehrstuhl für Medizinische Elektronik der Technischen Universität München, the Alpenklinik Santa Maria (Bad Hindelang/Oberjoch) and the St. Irmingard clinic (Prien/Chiemsee), which was sponsored by the Bavarian State Ministry of the Environment and Public Health (project life span November 2012 to December 2015).

The objective of PUMA was to manage sustainable lifestyle changes with the COMES® telemedicine platform using the example of obesity. The main element for controlling an individual's weight is a motion-controlled intervention mechanism for adjusting the caloric intake to the amount of mechanical energy required by the individual. The body weight is determined by means of a telemedicine scale and transmitted by smartphone to an interactive medical database. Further accompanying parameters (activity, optional blood pressure and blood sugar) can be determined by supplementary sensors and correlated with the weight data. On this basis, an assistance system was created which, depending on the desired scope, is able to ensure effective weight control and compliance with a target weight - with or without medical supervision.

Users of all ages may therefore test new technical solutions and therapeutic concepts. These include rehabilitation clinics, business users, senior researchers (70+), as well as medical practitioners. Further, AAL products are tested for feasibility, usability and ergonomics, and for technical or clinical characteristics. CoKeTT can also be used by the elderly and their relatives if they wish to fully test a desired product or solution prior to purchase. To demonstrate these activities, an AAL show apartment will soon be opened in Kempten.

The foundation for this test and training centre is a cooperative agreement made by the Heinz Nixdorf-Lehrstuhl für Medizinische Elektronik and University of Applied Sciences Kempten.

Fig. 1: CoKeTT research areas. Joint project with Heinz Nixdorf-Lehrstuhl für Medizinische Elektronik der Technischen Universität München

Fig. 2: Ambient Medicine® means using sensors, IT and devices for healthcare management at home, supported by consumer electronics and smart home technologies.

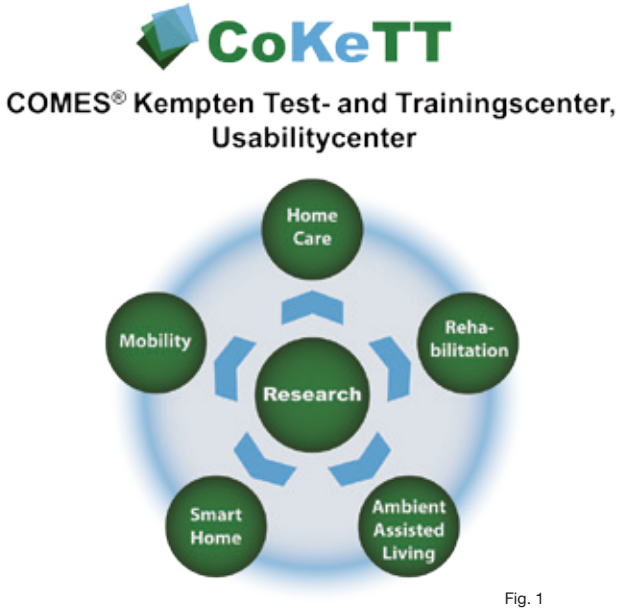

Fig. 1

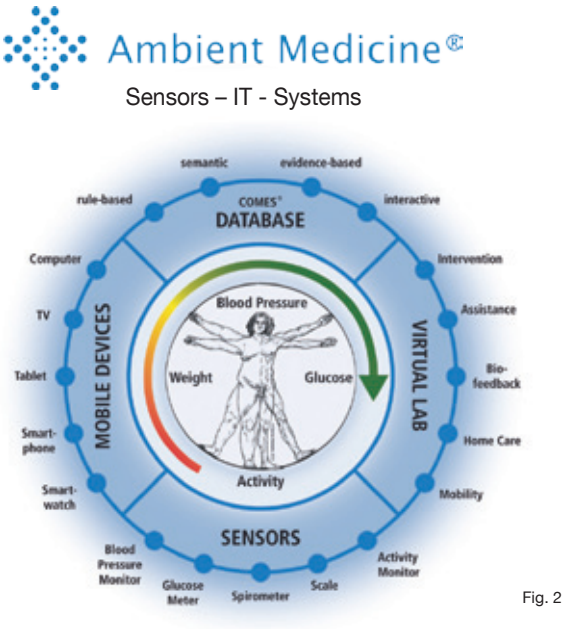

Fig. 2

Development of a personalised pedal exerciser [PREAM - Prevention and Rehabilitation through Activity and Motivation]

In short

This telemedical pedal exerciser is connected to a conventional television set via a DVB-T set-top box. The exercise programme is complemented by customised background information, and exercise and motivational instructions provided through the TV set that are easy to follow.

Many elderly persons suffer from disease-related mobility impairments that lead to a lack of flexibility and above all a lack of activity. There are many possible causes, including cardiovascular diseases, rheumatism, arthritis, as well as the consequences of a stroke or a fall.

In this context, a sufficient amount of activity is still important and makes therapeutic sense. As a solution to this problem, we have developed a telemedical pedal exerciser connected to a conventional television set via a DVB-T set-top box. The system enables users to continue their exercise at home after returning from a rehabilitation clinic, or prevent oedema or thrombosis, simply by doing pedalling exer-

Fig. 1: Integration of the therapeutic exerciser into the telemedical assistance system COMES® (image source: Pasife GmbH)

cises. The exercise programme is complemented by individually adapted background information, and exercise and motivational instructions provided through the TV set that are easy to follow. Feedback on the distance covered and the energy consumed (calories burned) is displayed constantly on the TV screen. The project aims to integrate further telemedical services.

We have succeeded in configuring the sensors of the pedal exerciser and its wireless link using the wireless standard ANT and the profiles ANT+ with the DVB-T set-top box, and have thus developed a cost-effective pedal exerciser called iBikos which is suitable for therapeutic use at home. We have also developed a concept for monitoring the amount and intensity of activity

Fig. 2: iBikos, the telemedical exerciser, offers an entertaining activity and health programme (image source: Pasife GmbH)

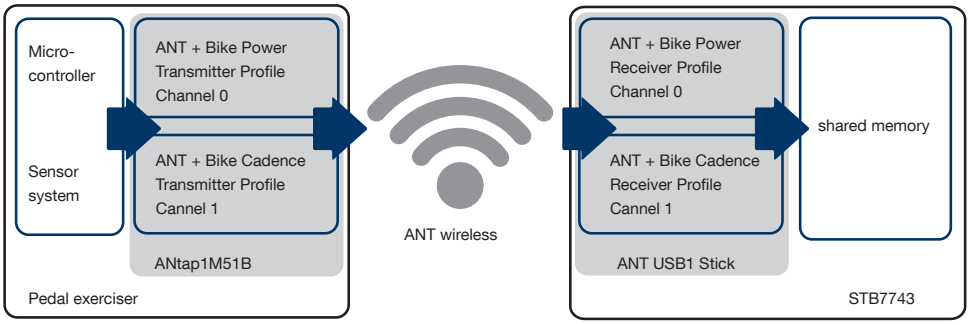

Fig. 3: Diagram of data transmission from the pedal exerciser to the DVB-T set-top box

This research was funded by the Bayerische Staatsministerium für Wirtschaft, Infrastruktur, Verkehr und Technologie.
Project title: „PREAM - Prävention und Rehabilitation durch Aktivität und Motivation“
(PREAM - Prevention and Rehabilitation through Activity and Motivation)
Project life span: December 2009 to December 2010

iBikos II - Development of a telematic exerciser as an integrated home rehab system

In short

This integrated home rehab system permits the user to exercise while watching TV. The captured training data are automatically transmitted to the COMES® database system for evaluation by a physician, who returns them to the patient with recommendations for further exercise.

The iBikos II project is a logical advancement to the system developed in the PREAM project. While the iBikos I exerciser is a low-cost version and is connected with the TV set in the user's home via a set-top box, the iBikos II incorporates the latest level of technology: it is based on a sophisticated rehabilitation exerciser, namely the Bluetooth-enabled THERA-vital device from Medica Medizintechnik GmbH. The design is compatible with the latest generation of Internet-ready television sets.

A system has been developed that comprises a telematic rehabilitation exerciser, a plug computer for mains operation and real-time animation. The idea behind the concept was to potentially expand the COMES® telemedical assistance system.

Fig. 1:
Top: Cycle race animation – the user plays the role of the cyclist in red and has two virtual training partners.
Bottom: Media content – for example, the popular German crime series "Tatort".

To process the live data recorded by the exerciser in real time, we have incorporated Java-based receiver software in the plug computer which screens the data received via a Bluetooth interface and transmits them to a database. These data are then converted by the web animation system into a racing game and displayed on the TV screen, partly superimposing the current image. The idea is that the remaining picture could be a TV or video image, or a Skype window, and that – thanks to the web-based concept – the remote device merely requires a browser (e.g. Smart TV) to facilitate the display. To increase motivation, the user exercises in front of the TV set while the captured data are visualised in an interactive display.

The captured training data are not only displayed on the TV screen, but are also stored in a database system which will be incorporated into the COMES® database. The results will be evaluated by a physician, who then returns them to the patient in message format along with recommendations for further exercise. The user will be motivated not only by an increase in ambition during training, but in particular by the long-term overview of the amount of exercise accomplished, as well as the pro-

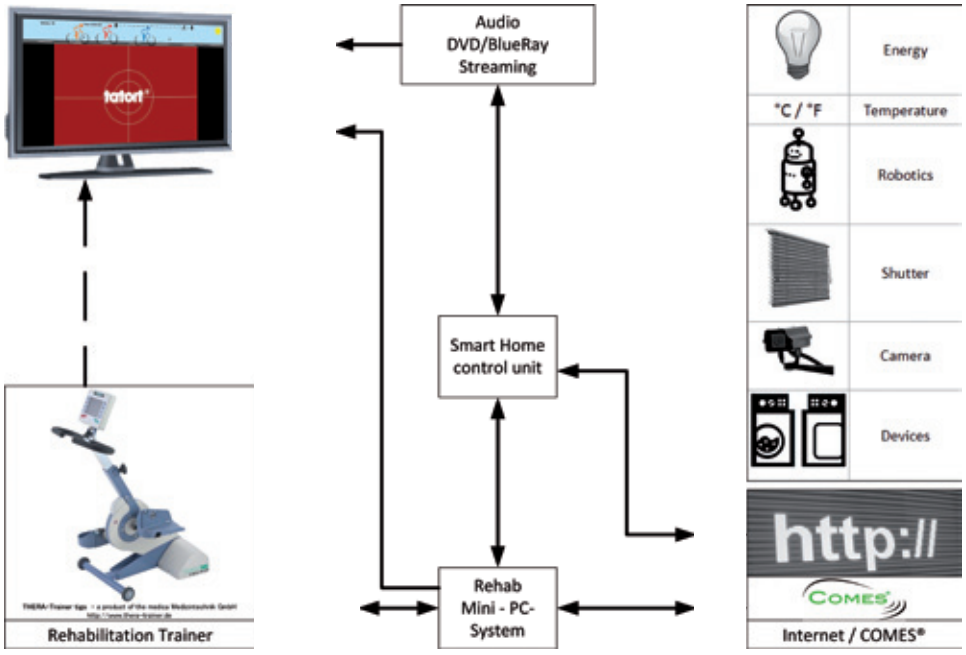

Fig. 2:
Schematic overview of the Smart Home system with its components and connections

fessional feedback provided by the physician. This will allow new goals to be set and ensure that training is consistent.

By using the Bluetooth-enabled THERA-vital device and linking it with the COMES® platform, we have created a system that provides an all-round picture of a patient's health at all times. The physician can use this information to determine what can be achieved and make training recommendations.

To enhance this approach even further, this system was integrated in a smart home environment so as to utilise the technological and communication infrastructure of the Smart Home system.

Through such modular integration, the motivation to employ telemedicine could possibly be increased. This will hopefully lead to greater acceptance and more widespread use of concepts such as COMES®, potentially helping to respond to the challenges of an ageing society.

Selected publications

- *K.-U. Hinderer, "Entwicklung eines telemedizinischen Bewegungstrainer als Home Care Produkt", Diplomarbeit am Heinz Nixdorf-Lehrstuhl für Medizinische Elektronik der Technischen Universität München, 2012.*

- *K.-U. Hinderer, P. Friedrich, B. Wolf, "Home Care: A Telematic Rehabilitation Exerciser", IEEE Second International Conference on Consumer Electronics, 2012, Berlin, pp 13-18, 978-1-4673-1547-0/12.*

This project was initiated in the autumn of 2011 and is a joint venture with Kempten University of Applied Sciences.

DorsiFlex: Device-based therapy for the lower extremities

In short

This innovative training device will deliver individualised treatment to patients with plantar flexor weakness (drop foot) – also at home, if necessary, with the aid of the COMES® telemedical assistance system.

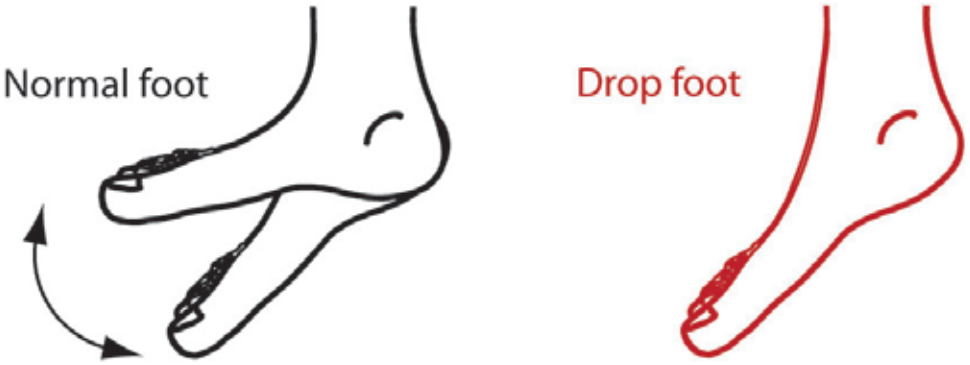

Fig. 1:
Illustration of a healthy foot vs drop foot

Mobility is essential to an active social life. The current rehabilitation system, however, does not offer appropriate options for treating weakened lower extremities, as caused by stroke, MS or diabetes. This is due to the fact that damage to the smaller muscles, which are essential for a natural gait, necessitates a costly, time-consuming personal training programme with numerous breaks and repetitions.

One solution to this problem is to relieve the strain on physiotherapists by moving the therapy sessions into the patient's home and supporting them via telemedical systems. This is only possible of course with device-based therapy.

A collaborative project was therefore initiated to develop a feedback-controlled treatment concept for the lower extremities. The purpose of this project is to offer individualised treatment to patients with plantar flexor weakness (drop foot).

An intelligent pedal senses the activity in the user's tibialis anterior and tibialis posterior muscles. By monitoring this muscular activity, spasms or certain motion patterns can be detected. A motor-driven unit uses this information to deliver fully individualised, adaptable treatment.

Moreover, a therapist can interact with the patient and prescribe therapy sessions online as part of the COMES® telemedical platform. Training results can be reviewed and prescriptions adapted.

The objective of the DorsiFlex project is to individually treat diseases which affect muscle coordination in the lower extremities. Further aims are to reduce the risk of falling and increase mobility.

This project was initiated in autumn 2012 and is a joint venture of the Heinz Nixdorf-Lehrstuhl für Medizinische Elektronik with medica Medizintechnik GmbH and the CoKeTT Centre at the University of Applied Sciences Kempten.

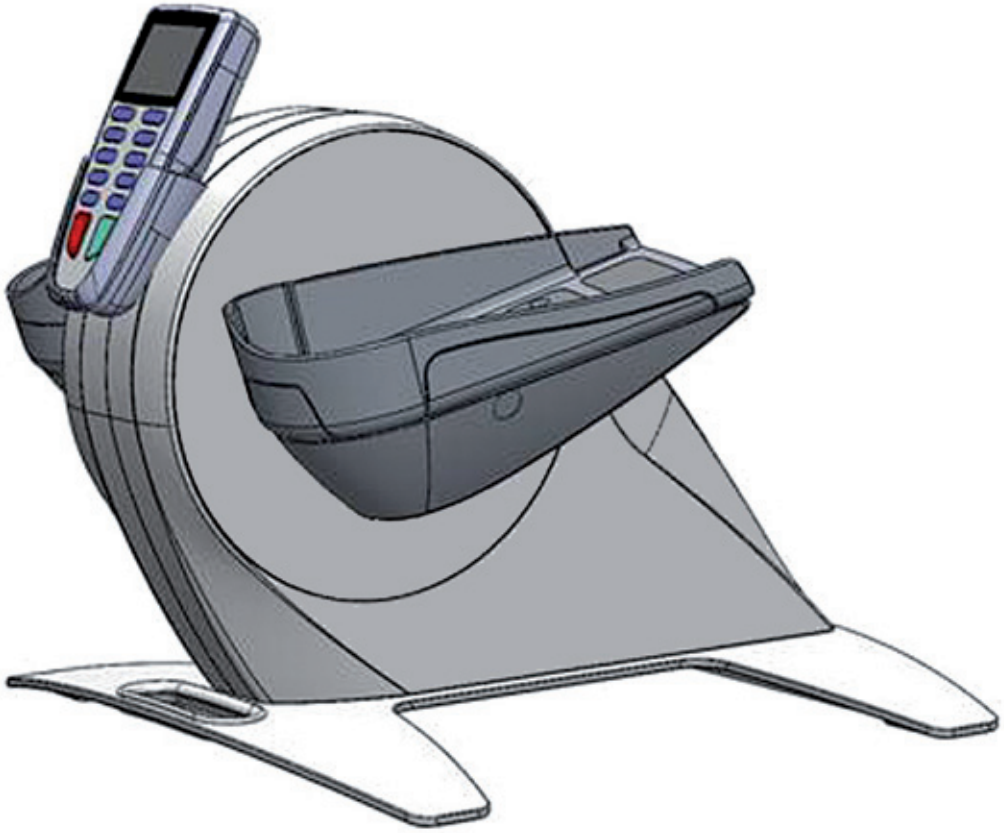

Fig. 2:
Design study for a therapeutic training device

iMob – Unlimited mobility for all ages at all times

In short

In this project, a new assistance system based on a stair-climbing wheelchair combined with a vehicle integration concept was developed, eliminating the difficulty and strain of transferring from wheelchair to car. This system offers a useful solution for the present and future driving generation aged 75.

In our aging society, mobility is a vital, basic need that is closely linked to quality of life. To limit this basic need would mean to deprive people of the possibility to maintain their social contacts and independence, which in turn would have psychological and social consequences. In our joint "iMob" project cooperated with the CoKeTT Centre of University of Applied Sciences Kempten, we developed a new assistance system in the form of a novel wheelchair for people with limited mobility.

Fig. 1:
iMob wheelchair; views from different angles

This system is based on a highly maneuverable wheelchair with which even obstacles such as stairs can be overcome unaided. The combination of a stair-climbing wheelchair and a vehicle integration concept which eliminates the difficulty and strain of transferring from wheelchair to car, offers a useful solution for the present and future driving generation aged 75+. With this car-wheelchair combination, the user does not expect his or her electric wheelchair to reach high speeds and long distances. Here, the focus was more on a design that offers easy maneuverability, both indoors and also over shorter distances outdoors. Furthermore, it was imperative that such a system offers easy and intuitive handling and a reliable stair-climbing mechanism.

Excellent maneuverability is achieved with a Segway-like chassis design which enables the

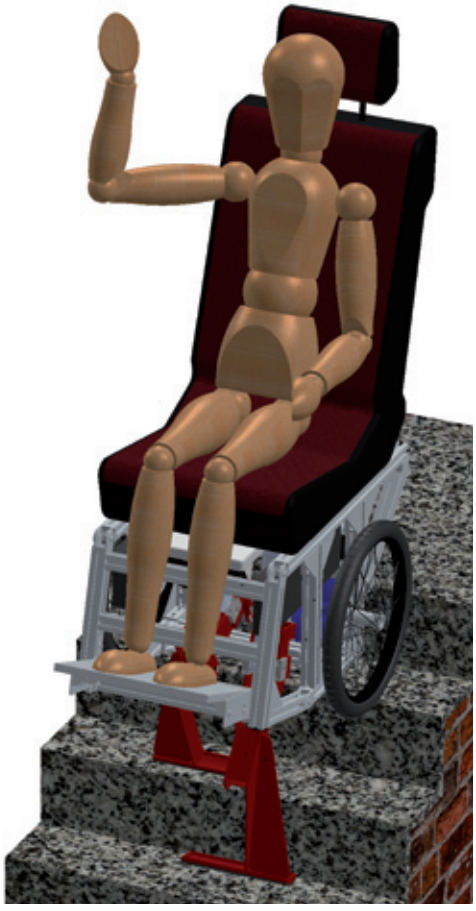

Fig. 2:

Climbing stairs with the iMob wheelchair

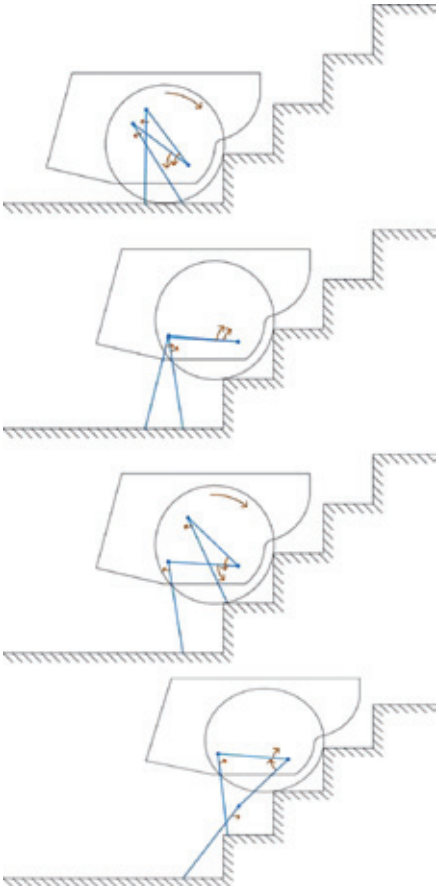

Fig. 3:

Climbing mechanism of the iMob wheelchair (schematic illustration)

Link to a video showing the iMob demonstration model

wheelchair to move on one axle and one pair of wheels only. To achieve this, each wheel is driven by a separate motor. Based on the principle of the inverse pendulum, these motors are dynamically actuated in order to always keep the center of gravity precisely above the wheel axle (Fig. 1 + 2). In stair-climbing mode, two fold-out legs which each consist of an upper and lower leg just like that of a human limb are located between the wheels. These legs push the wheelchair up or down the stairs as shown in Fig. 3. A 3D camera system combined with an intelligent control algorithm specifies the correct leg position for each step.

To travel longer distances in comfort, the iMob wheelchair is equipped with interfaces that can be easily integrated into a production vehicle. The automotive integration system is based on the seat transfer system produced by Autoadapt. An additional feature of this system developed during the project is the ability of the wheelchair chassis to unfold and drive autonomously from the trunk to the driver‘s door and return after use. The automated stowing process is illustrated in Fig. 4. Thus, the elderly driver‘s dream of independent mobility becomes a reality.

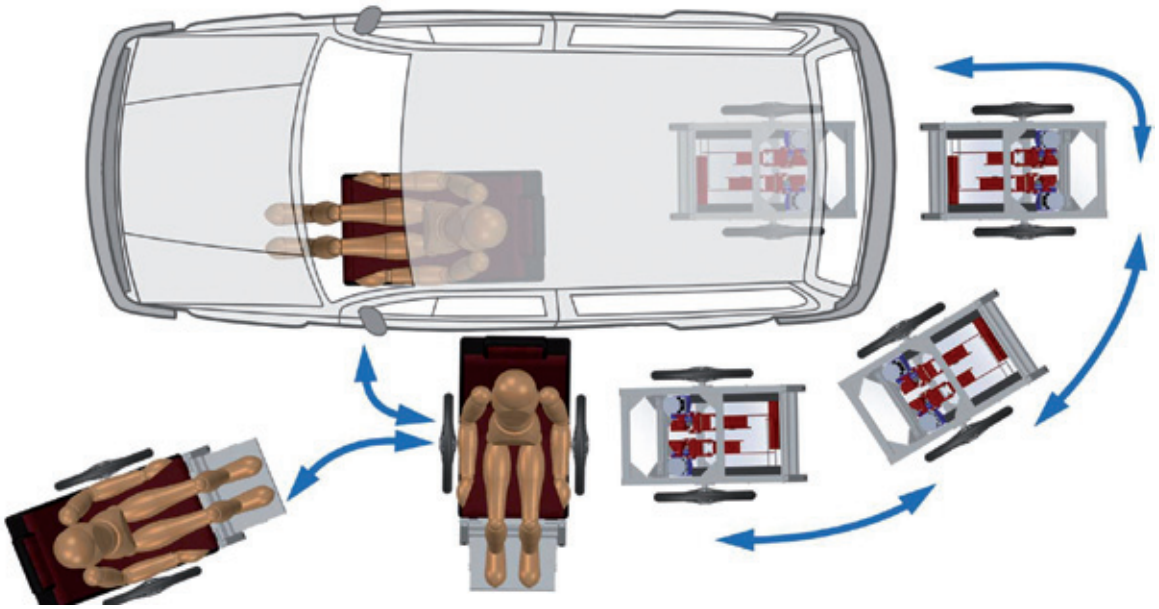

Fig. 4: Concept of the vehicle interface for the iMob wheelchair.

Selected publications

- *M. Häcker, P. Friedrich, M. Obermayer, B. Wolf:* ***Konzepte und Lösungen für Mobilität im Alter; Lebensqualität im Wandel von Demografie und Technik;*** *AAL Kongress Berlin 2013.*
- *M. Häcker, P. Friedrich, B. Wolf:* ***New mobility concepts for disabled and elderly people****; IEEE Third International Conference on Consumer Electronics - ICCE Berlin; page 39-43; 2013.*
- *M. Häcker, P. Friedrich, B. Wolf:* ***Neue Mobilitätskonzepte für ältere und behinderte Menschen****; Wohnen–Pflege–Teilhabe–„Besser leben durch Technik “; AAL Kongress Berlin 2014.*
- *M. Häcker:* ***Barrierefreiheit in der Stadt der Zukunft am Beispiel von iMob****; VDE Kongress Frankfurt am Main 2014*

This research was funded by the University of Applied Sciences Kempten and the Heinz Nixdorf Stiftung (partly from the KOMPASS project) and was realised in cooperation with the Institute of Ergonomics of the Technische Universität München (Prof. Dr. Klaus Bengler).

Project title: “iMob – Uneingeschränkte Mobilität in jedem Alter und zu jeder Zeit” (iMob – Unlimited mobility for all ages at all times)
Project life span: 2011 to 2015

Fig. 5: iMob demonstration model

Diabetes management from a student‘s viewpoint – the project „DiaManTUM“

In short

The DiaManTUM project team has designed and developed a “glucose stick” the size of a USB memory stick which permits the blood glucose level to be measured and the acquired data to be transmitted to a smartphone, ultimately reaching the COMES® Data Centre.

Diabetes mellitus is one of the most common metabolic diseases in western industrialised nations, with approximately 90 % of patients suffering from type II and approximately 5 % from type I diabetes. With over 8 million diabetes patients in Germany and an estimated 246 million diabetes patients worldwide, this disease has become one of the most widespread diseases in industrial nations of the west.

Besides the primary symptoms such as permanently increased blood glucose levels, diabetes entails the risk of constricted arteries and thus a significantly increased risk of myocardial infarction and stroke. Therefore, therapy focuses not only on correcting the blood glucose level, but also on managing the blood pressure, blood lipids and other disorders.
Since the beginning of 2011 this topic has been investigated by the DiaManTUM project, which is financed by tuition fees. A project team consisting only of students is working on the individual modules.
The aim of DiaManTUM is to help diabetes patients manage their condition. The telemedical assistance system COMES® is being used during this project. Via a platform, COMES® users may measure and record their individual parameters (here the blood glucose level) – without the assistance of a doctor, hospital or other care provider – by means of the certified COMES® measuring devices. In an easy, fast and reliable way, the measured values are transmitted to the COMES® Data Centre; the patient receives prompt feedback from the medical expert centre or – as an option – directly from a general practitioner sent to his/her personal mobile phone.

The DiaManTUM project team has designed and developed a „glucose stick“ the size of a USB memory stick as a prototype. This device allows the blood glucose level to be measured and the acquired data to be transmitted via a serial USB connection or via mobile communications to a smartphone, ultimately reaching the COMES® Trust Centre.
Measuring the blood glucose level is not the only important aspect of diabetes management, however. An appropriate diet and adequate exercise also play an important role. We are therefore working on a system that can record the approximate number of carbohydrate

units consumed by a patient using a smartphone. It should also be possible to make meal suggestions and provide the corresponding recipes or a shopping list. At the present stage of the project, it is possible to use the COMES® device to capture exercise data and provide the user with feedback as well as the motivation to keep exercising.

This research project has been financed by tuition fees of Technische Universität München.
Project title: DiaManTUM
Project life span: 2011 to 2014

Fig. 1: Glucose stick (size of a USB stick) with mobile phone

Appendix

Spin-offs

The company **sendsor GmbH** develops Telemetric Personal Health Monitoring (TPHM) systems: miniaturised medical devices that differ from conventional sensor systems by actively involving the patient in the therapeutic concept.

The key business of **Ambright GmbH**, a company focusing on intelligent, industry-specific lighting solutions, is the development of multi-purpose LED lights and accompanying control units. In cooperation with Heinz Nixdorf-Lehrstuhl für Medizinische Elektronik, the company is working intensively on the design of optical biofeedback systems as therapeutic lighting solutions in medical practice.

The company **cellasys GmbH** offers cell-based systems for continuously monitoring the vitality of living cells. These systems comprise on the one hand the requisite hardware and consumables such as biohybrid sensor chips, and on the other hand the necessary software components for data management and interpretation as well as consultation in the field of cell-based systems and their application.

Steinbeis GmbH is a decentralised network of independent transfer enterprises. The concept focuses primarily on the professional, unbureaucratic transfer of research and development projects on behalf of customers from academia and industry. Our **Steinbeis-Transferzentrum Medizinische Elektronik und Lab on Chip-Systeme** (Steinbeis transfer centre for medical electronics and lab-on-chip systems) offers interested parties diverse biomedical components on a lab-on-chip basis. For more information, go to: www.stw-med-chip.de

Facilities

Faculty lectures, workshops and events

Events	*Location*	*Year*
Continuous lectures of the Arbeitskreis Medizintechnik & Lifescience Electronic (Study group medical device technology & life science electronics) in cooperation with the VDE (Verband Deutscher Elektrotechniker)	Heinz Nixdorf-Lehrstuhl für Medizinische Elektronik , Munich	Since 2005 (please visit www.lme.ei.tum.de)
Symposium: Individualisierte Chip-basierte Chemosensitivitätstestung (Individualised chip-based chemosensitivity testing)	Bayerisches Staatsministerium für Wirtschaft, Infrastruktur, Verkehr und Technologie, Munich	3 June 2005
1. Omron / Heinz Nixdorf Ambient Medicine® Symposium	Technologiezentrum Bernried / Starnberger See	14 October 2005
Workshop Herbstuniversität – Mädchen machen Technik (Autumn college workshop – Girls do tech): „Mit dem iPod therapieren“ (iPod therapy)	Heinz Nixdorf-Lehrstuhl für Medizinische Elektronik, Munich	2-4 November 2005
IBM on Campus - IBM Deutschland Entwicklung GmbH	Technische Universität München	2 December 2005
m^3 Symposium: microelectronic meets medicine (m^3)	Bayerisches Staatsministerium für Wirtschaft, Infrastruktur, Verkehr und Technologie Munich	22 June 2006
Workshop Herbstuniversität – Mädchen machen Technik: „Der Arzt im Gepäck: Elektronik für die Gesundheit” (Autumn college workshop – Girls do tech: „A doctor always at hand: Electronics for your health“)	Heinz Nixdorf-Lehrstuhl für Medizinische Elektronik, Munich	29-31 October 2007
CeBit Future Talk „Unsere Zukunft in IKT“ („Our future in ICT“) Congress of the D21 Initiative	Hannover	8 March 2008

Events	*Location*	*Year*
Symposium: „Tools for Tissue Engineering“	Zentralinstitut für Medizintechnik der TU München / Garching	11 April 2008
Life Sciences live at IMETUM Open day	Zentralinstitut für Medizintechnik der TU München / Garching	13 June 2008
Special Seminar: Prof. Dr. G.W. Gross: NEUROENGINEERING – Emerging Concepts and Challenging Applications	Zentralinstitut für Medizintechnik der TU München / Garching	27 June 2008
1. Workshop of the ITG FA 9.3. Biomedizinische Informationstechnik (Biomedical information technology)	Zentralinstitut für Medizintechnik der TU München / Garching	5 November 2008
Interdisziplinäres Diskussionsforum: System-Medizin „Wider den Methodenzwang“ - Systemische Ansätze für neue Therapieformen (Interdisciplinary discussion forum: Systems medicine „Against methodological constraints“ - Systemic approaches to new forms of therapy)	Semper-Sternwarte, Zurich	25 March 2010
3. Ambient Medicine® Forum	Klinik Höhenried, Bernried	22 June 2010
Heinz Nixdorf Symposium 2010 m^3: microelectronic meets medicine Bioelektronische Diagnose- und Therapiesysteme (Bioelectronic diagnosis and therapy systems)	Business Center der BMW Welt Event Forum Munich	12-13 October 2010
Senior Research Day 2011	Heinz Nixdorf-Lehrstuhl für Medizinische Elektronik, Munich	13 April 2011

Events	*Location*	*Year*
Workshop Herbstuniversität – Mädchen machen Technik: „Hands-On Streifzug durch den Lehrstuhl“ (Autumn college workshop – Girls do tech: „Hands-on excursion: exploring the faculty“)	Heinz Nixdorf-Lehrstuhl für Medizinische Elektronik, Munich	3 November 2011
4. Ambient Medicine® Forum and Statuskolloquium zum Forschungsprojekt KOMPASS (Status colloquium on the research project KOMPASS)	Schloss Höhenried, Bernried	26 April 2012
1st Conference in eHealth and Telemedicine in Cardiovascular Prevention and Rehabilitation	Universitätsspital (Inselspital) Bern, Schweiz	07 June 2013
Conference: 3rd IEEE 2013 ICCE-Berlin	Messe Berlin	08-11 September 2013
Electronic goes Medical - Entwicklerforum 2013 (Developer panel)	Holiday Inn, Munich	09-10 October 2013
Health IT Forum (Health IT panel), trade fair "MEDICA"	Messe Düsseldorf	20-23 November 2013
Heinz Nixdorf-Symposium Telemedizin (Heinz Nixdorf symposium telemedicine)	Paderborn	09 December 2013
Entwicklerforum Medizinelektronik 2014 (Developer panel medical electronics 2014)	Holiday Inn, Munich	08-09 October 2014
European Congress on e-Cardiology and e-Health	Bern / Schweiz	29-31 October 2014
Hands-on-Workshops bei den 14. Münchner Wissenschaftstagen - Digitale Welten (Hands on workshop, 14. Munich Science Days)	Alte Kongresshalle Munich	08-11 November 2014
Health IT Forum (Health IT panel), trade fair "MEDICA"	Messe Düsseldorf	12-15 November 2014

Events	*Location*	*Year*
5. Ambient Medicine Forum zum Forschungsprojekt PUMA - Prävention und Motivation am Beispiel Adipositas (5. Ambient Medicine Panel, Research projcet PUMA - Prevention and motivation in case of the desease pattern adipositas)	Hochschule Kempten	25 February 2015
Münchner VDE-Kolloquium 2015: "Medizin 4.0 - Die Zukunft der Medizinelektronik" (Munich VDE-Colloquium 2015: "Medicine 4.0 - Medical electronics in future")	MDK Bayern, Bay. Staatsministerium für Gesundheit und Pflege, Munich	07 July 2015
Entwicklerforum Medizinelektronik 2015 (Developer panel medical electronics 2015)	Konferenzzentrum München (Munich)	28-29 October 2015
Health IT Forum (Health IT panel), trade fair "MEDICA"	Messe Düsseldorf	16-19 November 2015

Honours and Awards

Awards	*Award winner/topic*	*Year*
Praxis-Depeschen Award	Dr. Alexander Scholz, Prof. Bernhard Wolf	2004
Alfred Kärcher-Förderpreis	Bernhard Gleich, „Sensorentwicklung" (Sensor development)	October 2005
IFMBE Young Investigator's Award, 7th International Conference on Cellular Engineering	Dr. Johann Ressler, „24-well microplate with sensors for metabolic, morphologic and electrophysiologic parameters of living cell tissue"	September 2005
ABRF Award, Association of Biomolecular Resource Facilities	Dr. Jochen Peter	3 April 2007
HUPO Young Investigator's Award, The Human Proteome Organization	Dr. Jochen Peter „Proteomic Sciences"	October 2007
E.ON Umweltpreis (E.ON Environmental Award), E.ON Bayern	Heinz Nixdorf-Lehrstuhl für Medizinische Elektronik der Technischen Universität München, „Wasserqualitätsmonitoring mit biohybriden Sensorchips" (Water quality monitoring with biohybrid sensor chips)	22 July 2008
DGBMT Preis 2009, Deutsche Gesellschaft für Biomedizinische Technik im VDE	Dr.-Ing. Joachim Wiest, „Entwicklung und Erprobung von miniaturisierten, elektrochemischen Sensoren für die Gelöst-Sauerstoff-Messung zum Einsatz in Lab-on-Chip Systemen" (Development and testing of a patient-specific tumour chemosensitivity test based on a silicon sensor chip)	11 September 2009

Awards	*Award winner/topic*	*Year*
Mitgliedschaft Deutsche Akademie der Technikwissenschaften (Membership of the National Academy of Science and Engineering)	Professor Dr. Bernhard Wolf was admitted to the Deutsche Akademie der Technikwissenschaften	20 October 2009
Best Poster Award / ibai, Industrial Conference on Data Mining	Dipl.-Ing. Thomas Spittler, „COMES® - ein telemedizinisches Assistenzsystem zur Früherkennung von Depression bei Herzinsuffizienz“ (COMES® - a telemedical assistance system for the early detection of depression in patients with heart failure)	August 2011
Münchner VDE-Award 2011	Dr. Joachim Wiest, Erfolgreiche Firmengründung der cellasys GmbH (Successful establishment of the company cellasys GmbH)	November 2011

List of researchers

Research professor

Wolf, B.

Senior research associates

Grothe, H.

Brischwein, M.

Research associates

Clauss, J.		Otto, A.M.	2001-2010	Weyh, T.	2001-2009		
Scholze, C.		Gleich, B.	2007-2010	Wankerl, B.	2007-2009		
Herzog, K.		Dahmani, C.	2007-2010	Pilawa, P.	2001-2004		
Neumann, B.	2010-2015	Götz, S.	2008-2010	Schlichting, H.	2002-2004		
Barthel, J.	2011-2012	Ninichuk, V.	2010	Renger, J.	2003-2004		
Orban, A.	2012	Janas, E.	2010	Rampf, R.	2001-2003		
Friedrich, P.	2004-2011	Peter, J.	2005-2009				

Research staff

Ruppert, W.		Toldrian, J.		Sawatzki, J.	2010-2012		
Giorno, A.		Arbogast, R.	2000-2015	Szabados, I.	2005-2007		
Remm, M.		Teschner, G.	2000-2015	Zirm, W.	2000-2001		
Michelfelder, A.		Kaneppele, A.	2011-2014				
Franz, I.		Stein, S.	2010-2013				

External assistents

Wolf, P.	2009-2015	Lachner, A.	2009-2011				

Doctoral candidates

Zottmann, M.		Demmel, F.		Spittler, T.		Foderà, G.	
Kleinhans, R.		Eminaga, Y.		Türmer, C.		Iwert, O.	
Hafner, L.		Ilchmann, F.		Wirths, W.		Sattler, M.	
Gül, M.		Mzoughi, N.		Hinderer, M.		Weber, A.	
Dill, D.		Grundl, D.		Hinderer, K.-U.		Mengele, A.	
Aicher, M.							

Doctoral theses

Henning, T.	Studien zur Entwicklung eines prädiktiven Chemosensitivitätstests mit Mikrosensoren	2002
Koch, M.	Nicht invasiver Transport von Ladungsträgern in komplexen Materialien	2004
Motrescu, E.	Analysis of Biological Signals with Multifunctional Bioelectronic Sensor Chips on Living Cells	2004
Stepper, C.	Entwurf, Herstellung und Charakterisierung von Biosensorchips	2005
Cabala, E.	Monitoring multiparametrischer komplexer Mikrosensorarrays für zelluläre Analytik	2007
Gleich, B.	Aktiver Wirkstofftransport mit magnetischen Feldern	2007
Geisler, T	Echtzeitumgebung (Hard- und Firmware-Plattform) für ein Mikroskop-basiertes "Machine-Vision" System	2007
Wendicke, K	Optimierung von Stimulationsspulen für die induktive Nervenreizung	2007
Zantow, H	Optimierung des Strom-Zeitverlaufs für die Depolarisation von Nervenzellen	2007
Stadthagen, T	Entwicklung eines online Gewässermonitoring-systems mittels Biosensorchips zum Nachweis ausgewählter Xenobiotika	2007
Amaral, C.E.F.	Multiparameter Methods for Non-invasive Measurement of Blood Glucose	2008
Wiest, J.	Entwicklung und Erprobung von miniaturisierten, elektrochemischen Sensoren für die Gelöst-Sauerstoff-Messung zum Einsatz in Lab-on-Chip-Systemen	2008
Reßler, J.	Sensorchips für die multiparametrische zelluläre Bioanalytik und für biohybride Bauelemente	2008
Lob, V.	Design und Realisierung eines High-Content-Screeningsystems für lebende Zellen	2009
Friedrich, P.	Etablierung einer telemedizinisch gestützten bioakustischen Hypertonie-Therapie mittels Virtual Lab	2010
Meyer, J.	Evaluation of new bioelectronic cell based assays for diagnostic and therapeutic systems	2010
Scholz, A.	Konzepte für eine personalisierte telematische Medizin	2010
Clauss, J.	Intelligente Zahnschiene als Technologieplattform für sensorische Implantate	2011

Hofsøy, D.A.	Development and evaluation of a long-term management system for sleep-related breathing disorders	2011
Becker, B.	Automatisierung eines Cell-Based-Assay Systems zur prädikativen Tumorklassifikation	2011
Gruber, H.-G.	Telemonitoring-Systeme: Gesundheitsökonomische Evaluation und Innovationsbarrieren	2011
Schmidhuber, M.	Konzeption und Erprobung eines bioybriden nanoanalytischen Handheld Systems	2011
Becker, S.	Intelligente Implantate zur Therapieunterstützung	2012
Pfister, C.	Mikrofluidisch gestützte zellbasierte Assays mit gedruckter Sensorik für High-Content Analytik	2015

Diploma theses

Bahr, L.	Evaluierung planarer Sensorstrukturen zur Messung der Zellulären Respiration	2002
Neurauter	Optisch plethysmographische Signale	2002
Rinser, M.	Image Processing for Automated Measurement and Analysis of Cardiac function in Drosophila Melanogaster	2002
Scholz, A.	Bluetooth-Anbindung von Biomodulen zur Messdatenübertragung	2002
Steinmann, M.	Entwicklung einer Microcontroller-Steuerung mit CAN-Schnittstelle für einen magnetischen Neurostimulator	2003
Wiest, J.	Measurement of pH and pO_2 change at an ISFET surrounded by a noble metal electrode	2003
Loeser, M.	Behavior of polarizable micro-particles in inhomogeneous fields	2003
Schmidt, M.	Sensorarray for fetal ECG signals: simulation, sensor selection and source separation	2003
Ressler, J.	Entwicklung und Evaluierung von impedanzsensorgestützten Multiwellplatten zum zellulären Screening	2003

Holzinger, S.	Entwicklung und Aufbau eines biohybriden Monitors für Regenwasserqualität	2003
Gneiting, S.	Entwicklung eines röntgenbasierten 3D-Hüftprothesen-Plannungssystems	2003
Cabala, E.	Neuentwicklung von Software für ein multiparametrisches Meßsystem	2003
Kang, S.H.	Evaluierung eines nicht-invasiven Impedanzsensors zur Hydratationsmessung der Haut	2003
Fuchs, C.	Analyse und Implementierung ausgewählter Rauschunterdrückungsmethoden zur Anwendung bei optisch plethysmograyhischen Signalen	2003
Slusarczyk, M.	Optimisation of the power circuit of a magnetic neurostimulator	2003
Erl, T.	Entwicklung und Evaluierung analoger Messelektronik für ein LAPS-basiertes pharmakologisches Mehrfachtestgerät	2003
Lob, V.	Entwicklung eines Telemetric Personal Health Monitoring Systems für Bluthochdruckpatienten	2003
Gleich, B.	Entwurf und Dimensionierung eines EMG Messsystems	2004
Pelhak, S.	Sicherheitsfunktion für Magnetstimulator - metal detect	2004
Wagner, R.	Entwicklung und Realisierung der Steuerung und der PC-Schnittstelle für ein optoelektronisches pH-Meßsystem	2004
Kotzlowski, S.	Entwicklung und Integration einer mikrocontrollerbasierten Ethernetschnittstelle für biomedizinische Messsysteme	2004
Holbein, N.	Entwicklung einer Mikrocontrolleranbindung und Verbesserung von Messelektronik für impedanzsensorgestützte Mikrotiterplatten	2004
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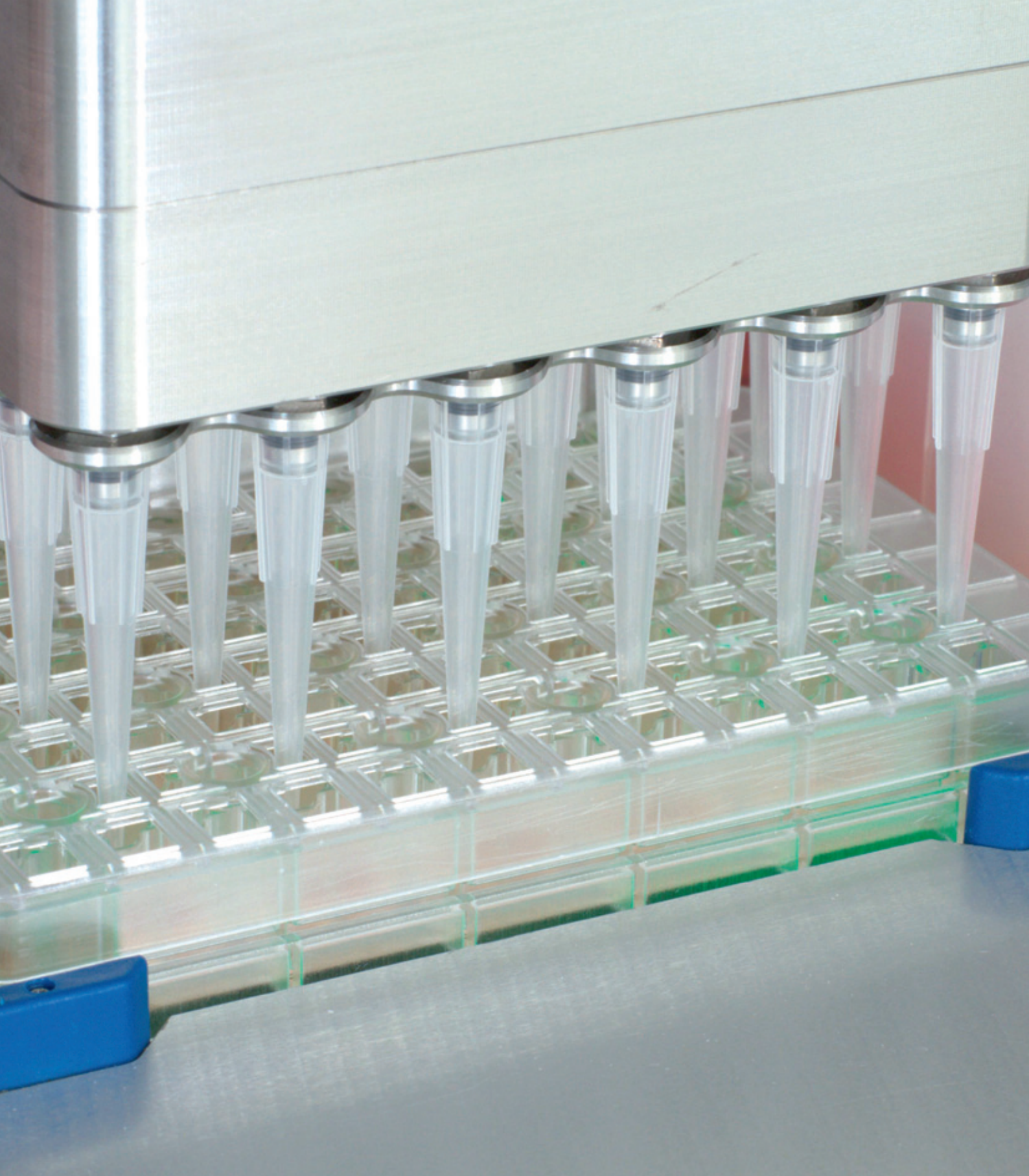

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Editor
Prof. Dr. Bernhard Wolf

Heinz Nixdorf-Lehrstuhl
für Medizinische Elektronik
Technische Universität München
Theresienstr. 90 / Gebäude N3
80333 München

Tel. 089 – 289 – 22948
Fax 089 – 289 – 22950

www.lme.ei.tum.de
christian.scholze@tum.de

Steinbeis-Transferzentrum
Medizinische Elektronik
und Lab on Chip-Systeme
Fendstr. 7
80802 München

Tel. 089 – 89 05 43 47
Fax 089 – 89 05 37 15

www.stw-med-chip.de
info@stw-med-chip.de

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Christian Scholze, Karolin Herzog, Ingrid Franz

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