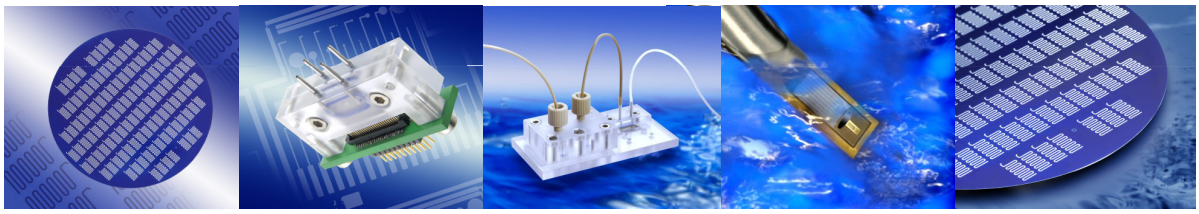
# Fraunhofer Institute for Silicon Technology (ISIT)

## Microfluidics for Electrical Biochip Technology

8th Workshop Low Flows in Medical Technology, September 24th 2014



Lars Blohm, Department „Biotechnical Microsystems“

*lars.blohm@isit.fraunhofer.de*



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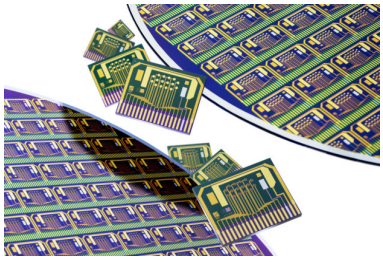
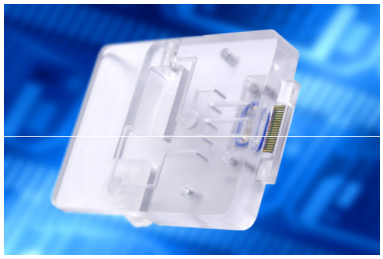


## Biotechnical Microsystems

- Continuous Enzyme Sensors
  - Glucose and Lactate Monitoring
- Multi-Pore Membrane Chips
  - Bioprocess Analytics
- Electrical Biochip Arrays
  - Protein and DNA Detection
- Chromatography On-Chip
  - Small Molecule Detection
- Mass Flow Sensors





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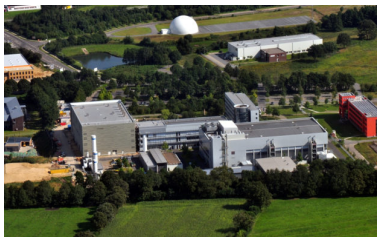

## Research and Production at one Location

Microelectronics and Microsystems Technology

- IC Technology and Power Electronics
- Micro Electrical Mechanical System (MEMS)
- IC Design
- Biotechnical Microsystems
- Packaging Technology for Microsystems and Microelectronics
- Quality and Reliability of Electronic Assemblies
- Integrated Power Systems



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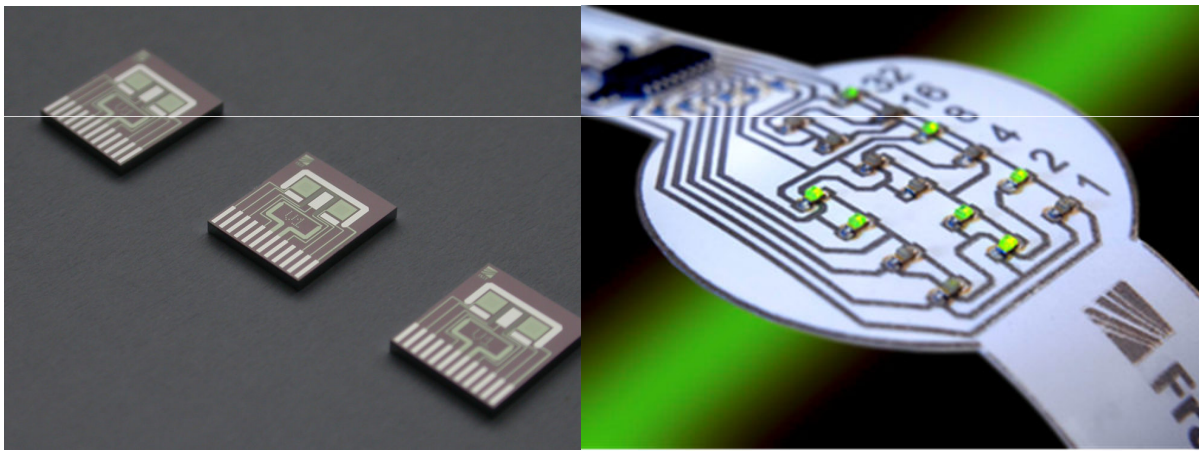
# Electronic detection of lactate (ELaN)

organic and printed electronics north

## Continuous monitoring of lactate in sweat during exercise for sports medicine

Gefördert durch:
Bundesministerium für Wirtschaft und Technologie
impulse ZIM für wachstum Zentrales Innovationsprogramm Mittelstand
aufgrund eines Beschlusses des Deutschen Bundestages





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## Motivation for continuous monitoring of lactate in sweat

- Individual check of endurance performance
- Non-invasive measuring of lactate during exercise
- Recognition of anaerobic threshold for continuous training control
- Bio-compatible disposable sensor system for monitoring
- Low production costs by printed electronics
- Evaluation of fitness status via Smartphone, PC or internet portal



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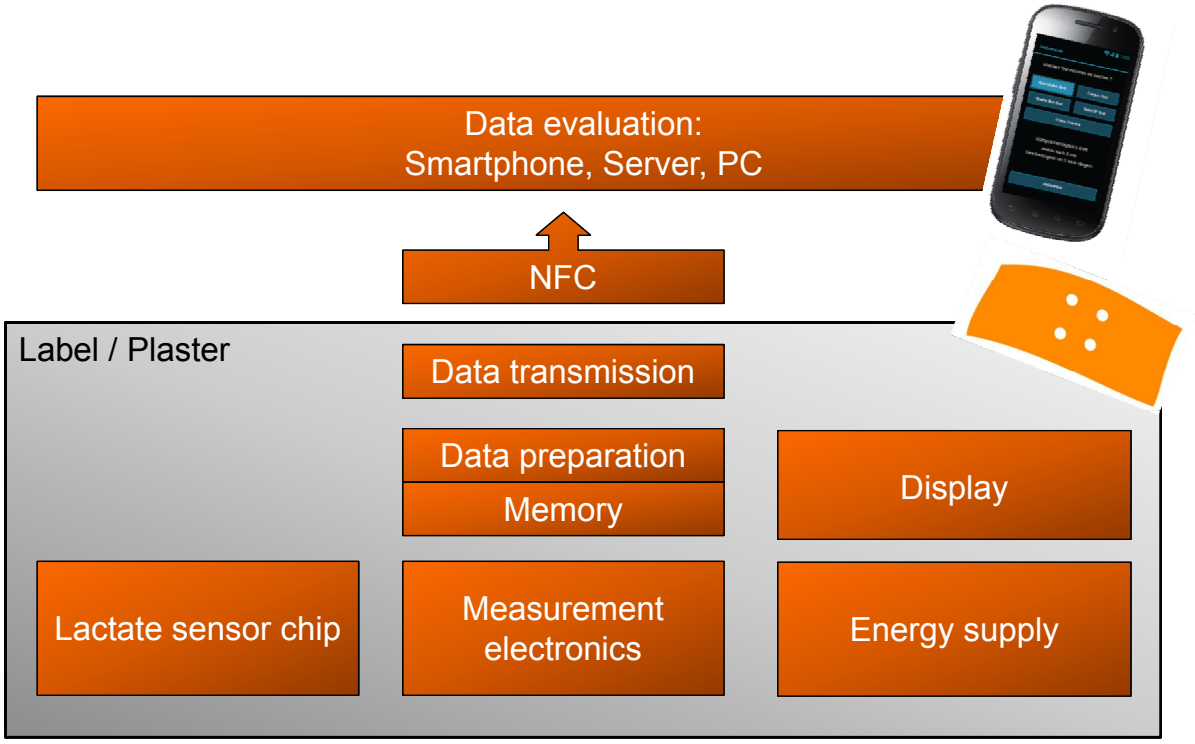
## Concept of the project (ELaN)



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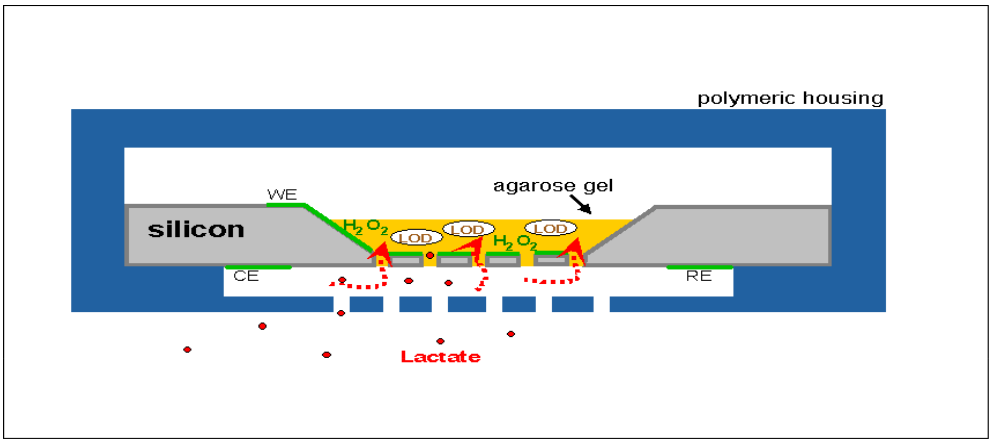
## Principle of the enzyme sensor




- Diffusion of the analyte through the pore membran
- Enzymatic reaction (e.g. lactate – lactate oxidase)
- Amperometric detection of hydrogen peroxide

- G. Piechotta et al., “Novel micromachined silicon sensor for continuous glucose monitoring”, Biosensors and Bioelectr. 21 (2005) 802–808



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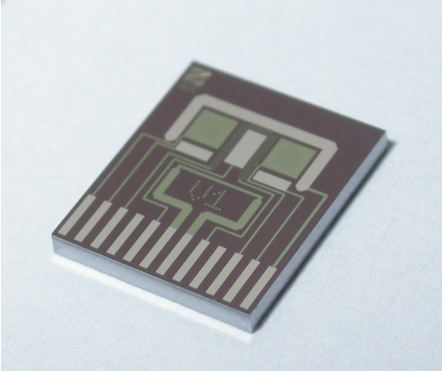
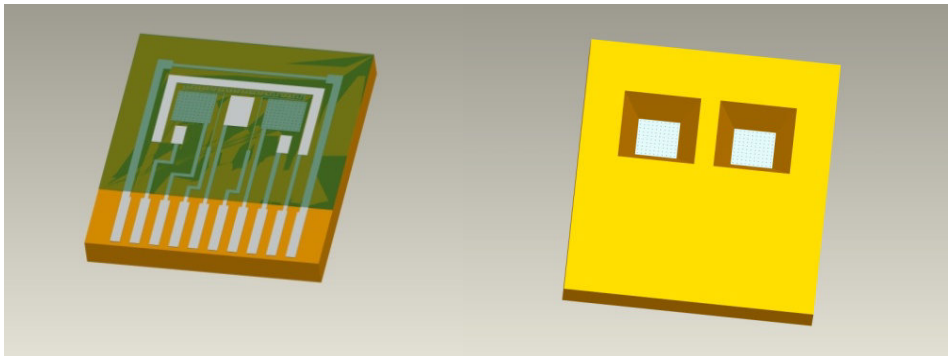
## Layout and dimensions of the current lactate chips

- Chip size: 6 mm x 7 mm
- Pore membrane: 0,65 mm x 0,65 mm
- Pore size: 5 µm or 10 µm
- Amount of pores: 9, 25, 100







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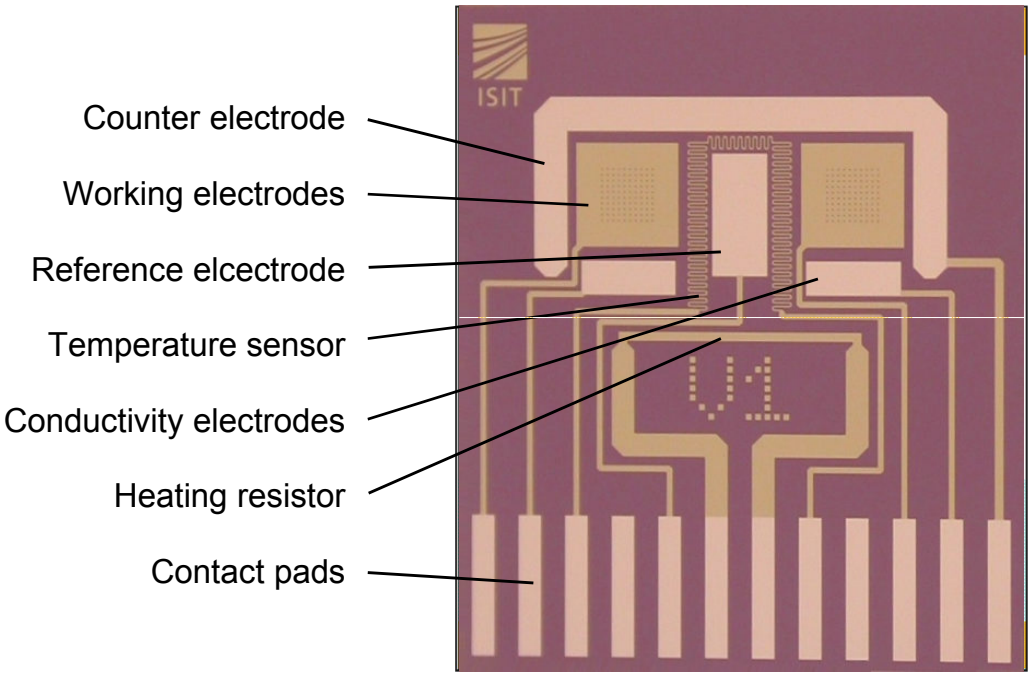
## Layout and dimensions of the current lactate chips



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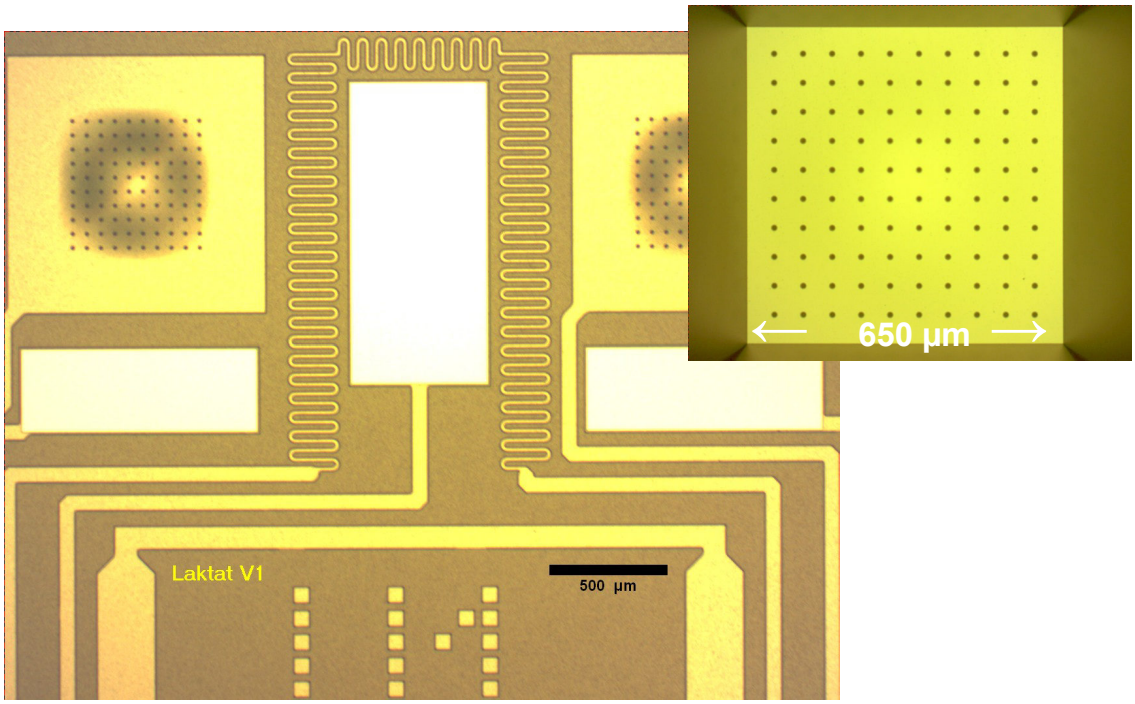
## Lactate chip and pore membrane with 100 Pores (⌀10µm)



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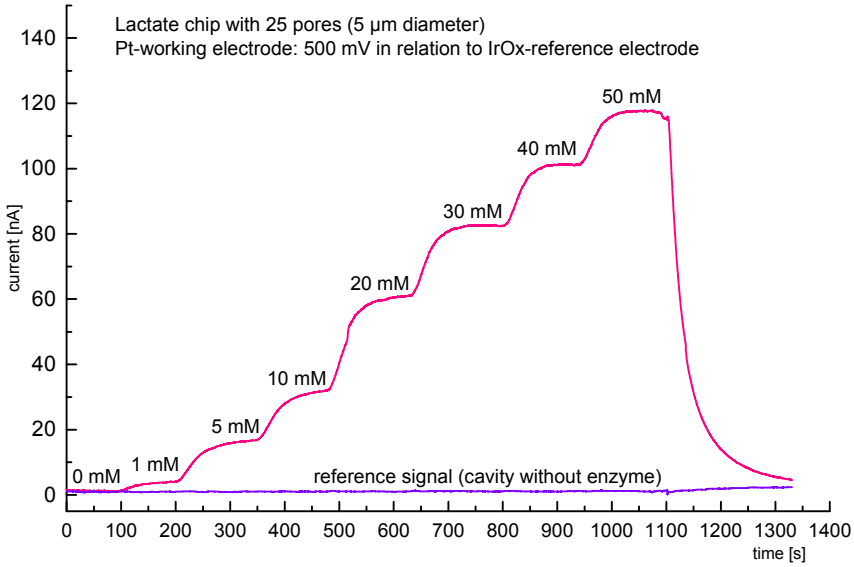
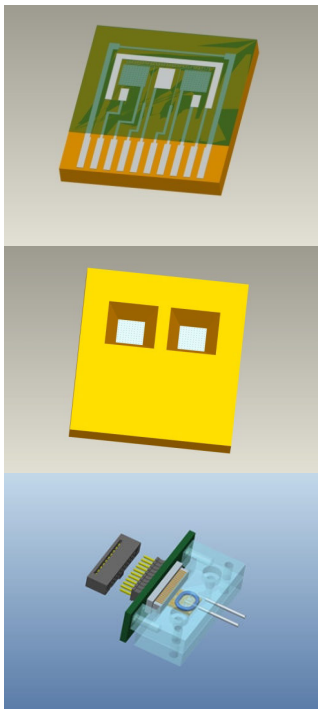
## Concentration series with lactate chip in a flow through cell

- Differential measurements for compensation of interfering substances
- Flow rates ~ 50µl / min.





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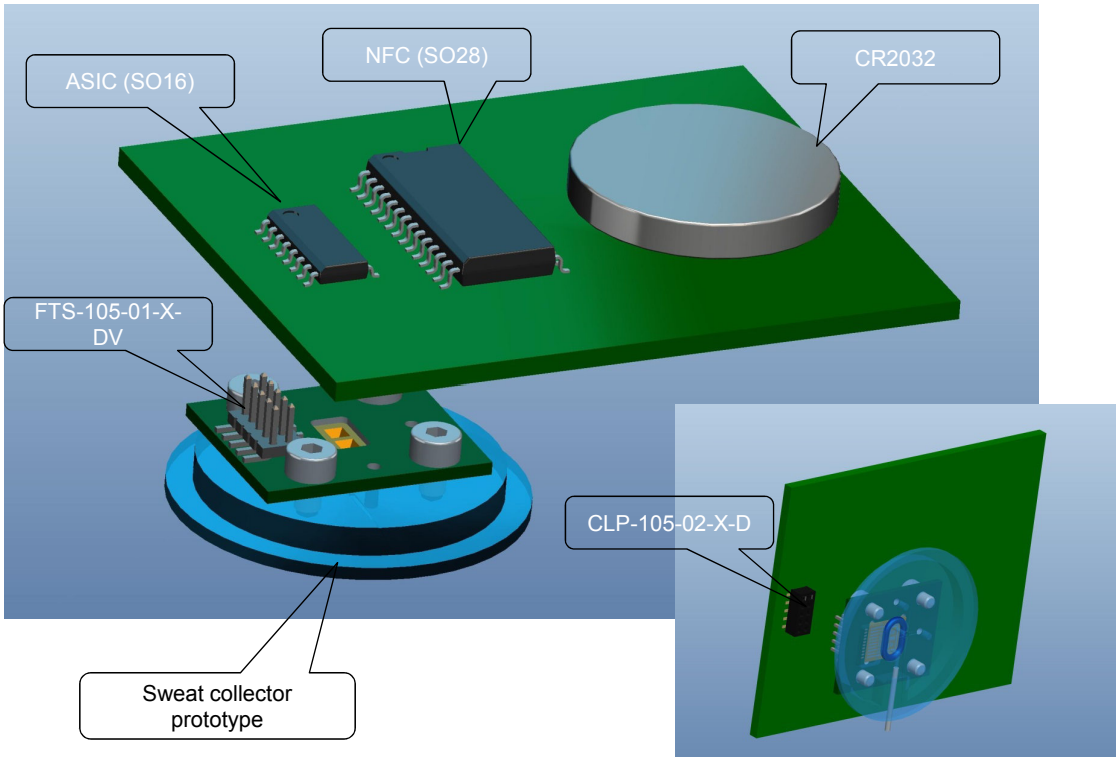
## Sweat collection by microfluidic cartridge



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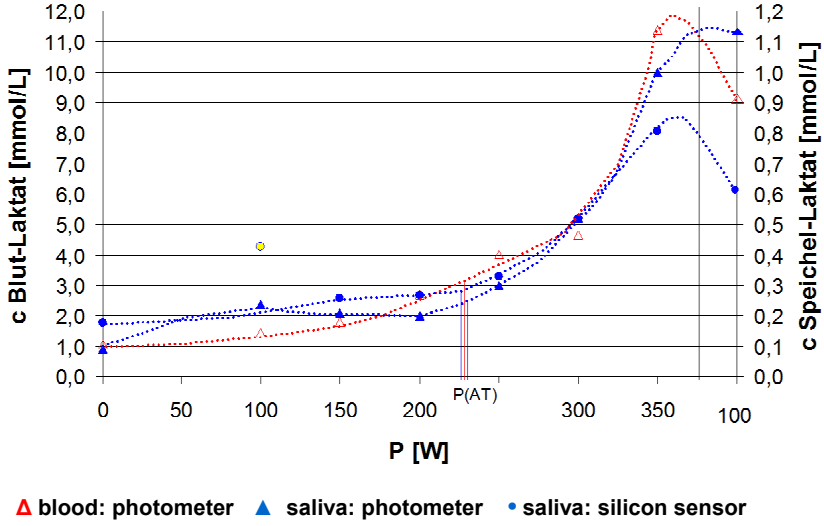
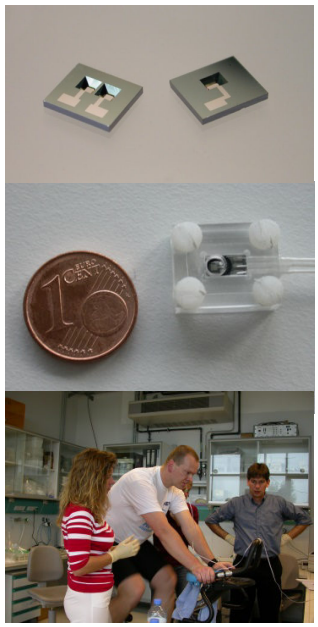
## Comparison of different measuring methods in an Ergometer test

- Increase in steps of 50 W
- Interval 3 min.



- C.G.J. Schabmueller et al., « Micromachined sensor for lactate monitoring in saliva", Biosensors and Bioelectronics 21 (2006) 1770–1776



GLAD Gesellschaft für laborgestützte Entwicklung mbH

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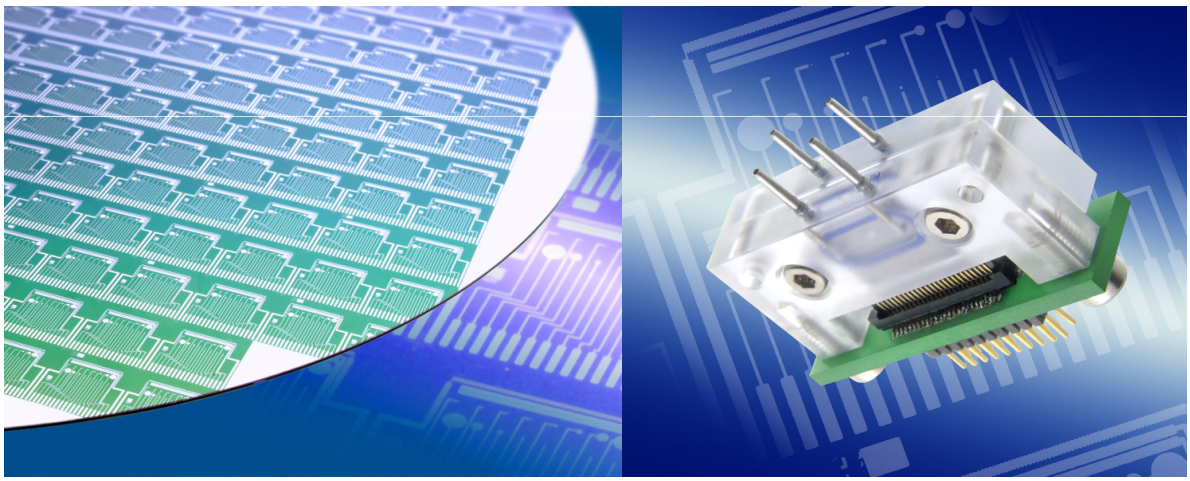
# Cell-Free Bioproduction

## Fraunhofer Lighthouse Project

(IBMT, IGB, IME, IPA, IPK, ISiT, ISI, IZM)

BIOMOLEKÜLE VOM BAND

GEFÖRDERT VOM Bundesministerium für Bildung und Forschung





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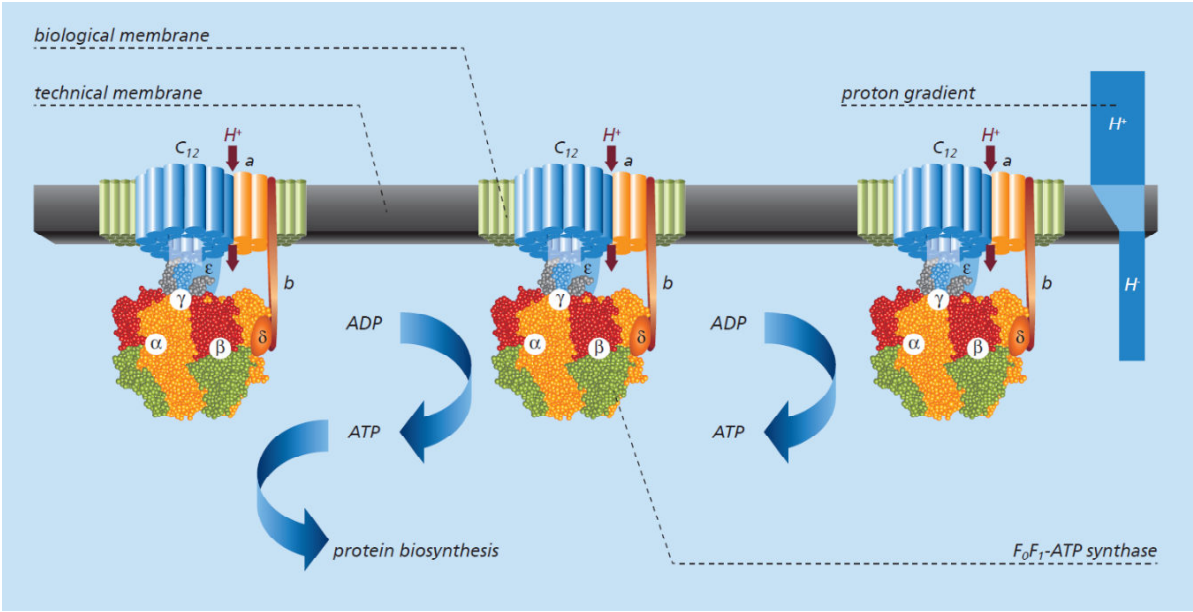
## Cell-free protein production with integrated energy supply

- Scheme of pore membrane for ATP synthesis
- ATP-Synthase is just active in lipid double layer



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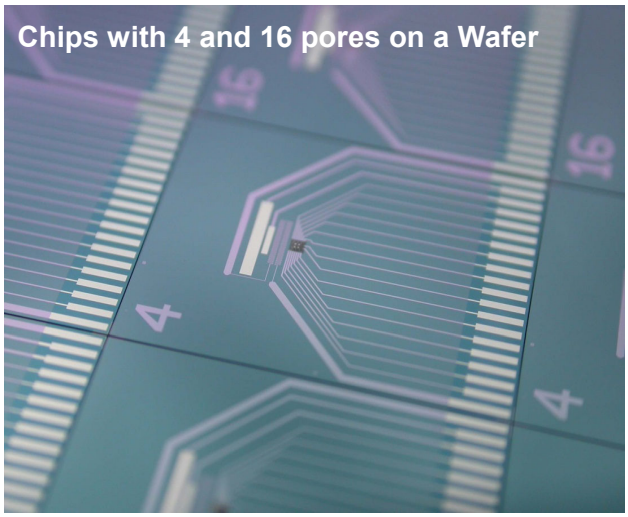
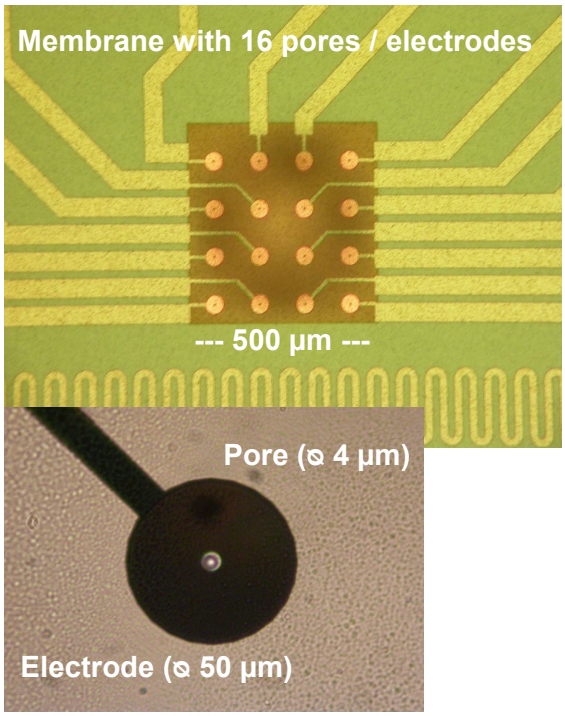
## Micro-pores in silicon membranes and integrated micro electrodes




Membrane (1.8 µm thick)

on the bottom of a cavity



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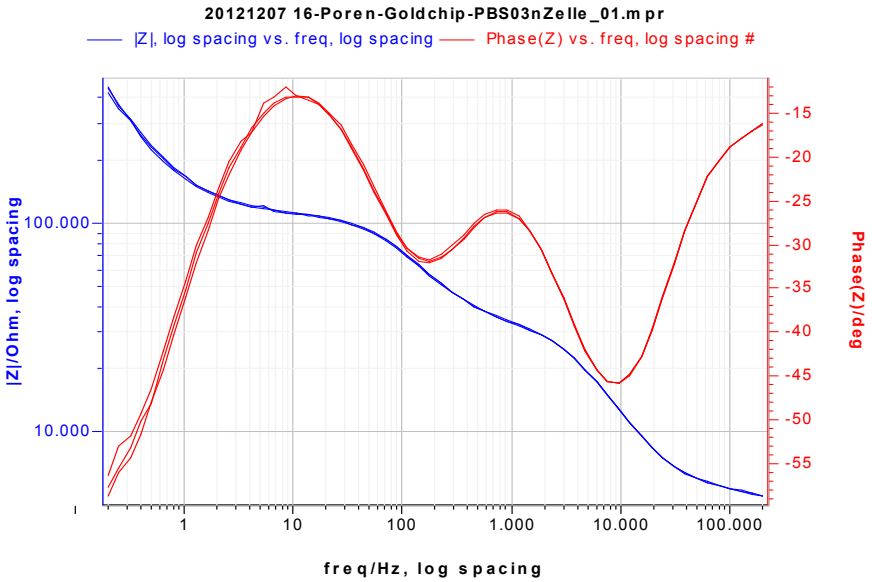
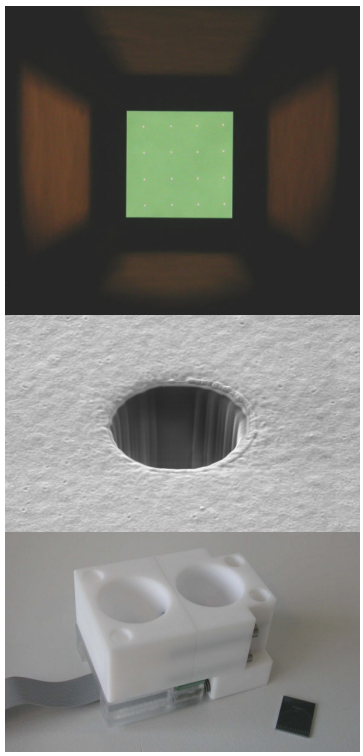
# Technical membrane with16 Pores on a silicon chip

- Impedimetric detection of lipid double layer
- Electrochemical impedance spectroscopy





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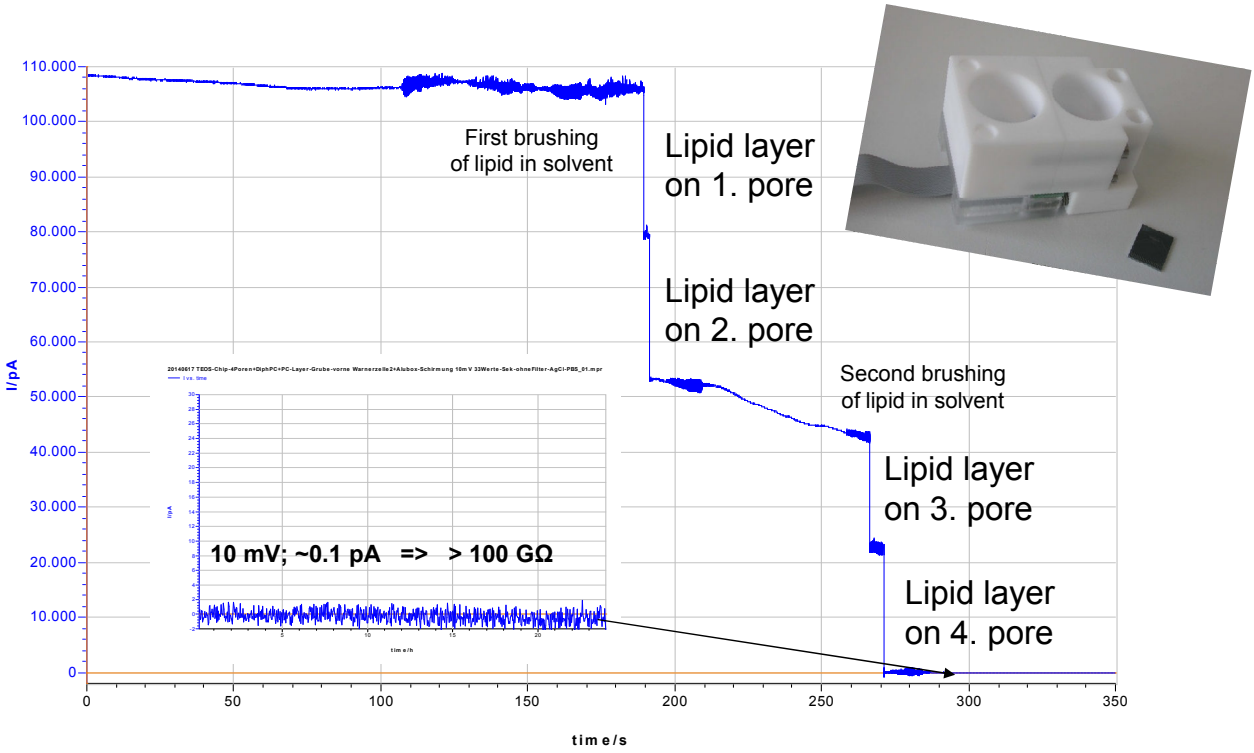
# Formation of lipid bilayer on membrane chips with 4 pores



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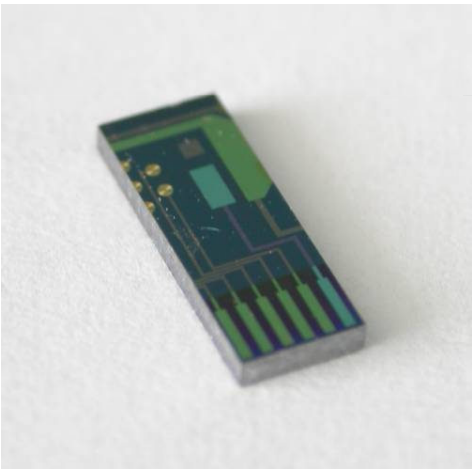
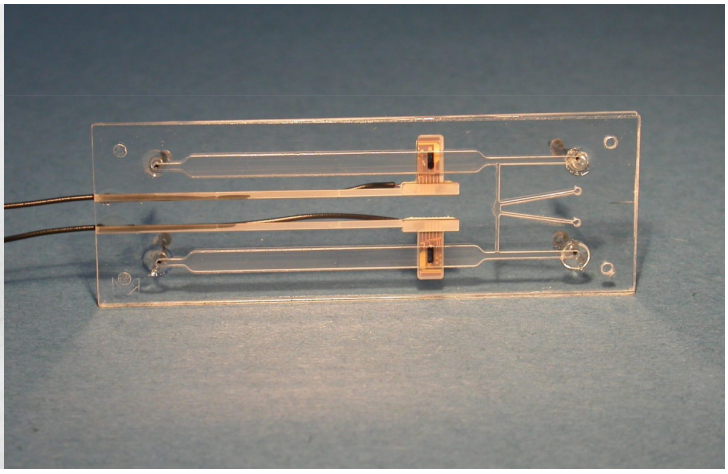
# pH-measurement in bioreactors for cell-free bio production

- pH-sensitive iridium oxide microelectrodes
- Integration of the sensor chips in microfluidic bioreactors
- Measuring of proton gradient on micro pore membranes







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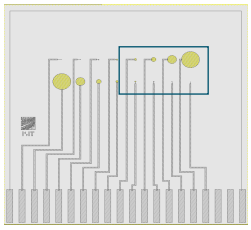
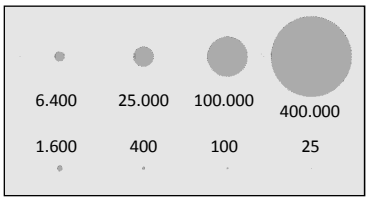
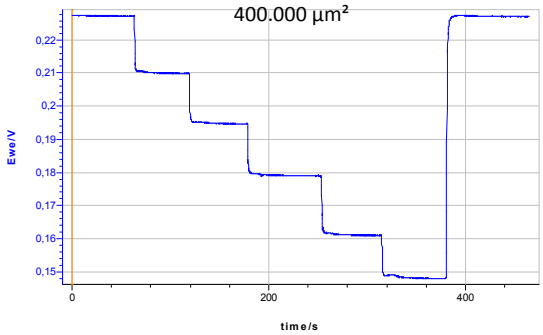
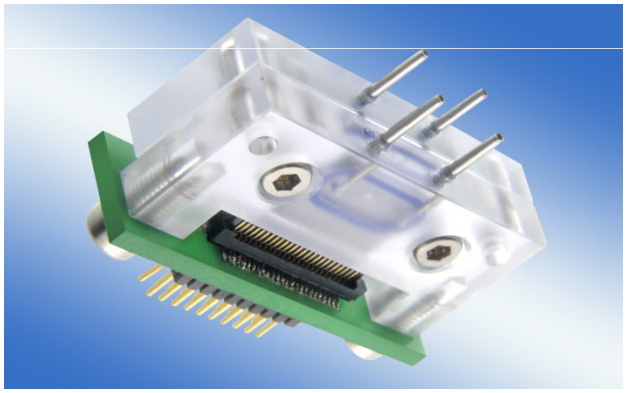
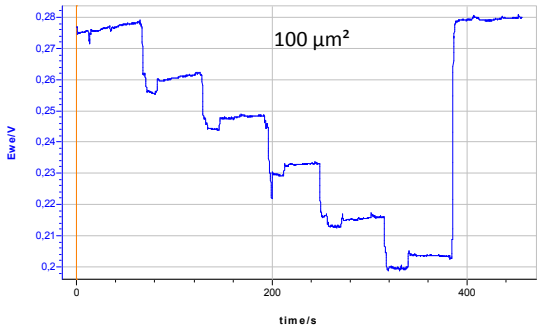
# Evaluation of IrOx-microelectrodes for pH-measurement on micro pore membranes







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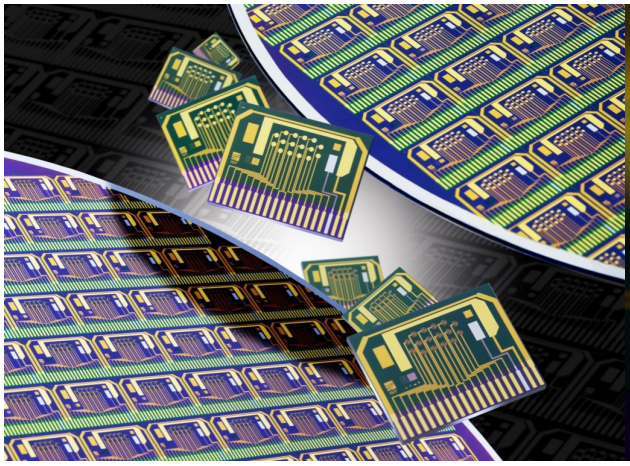
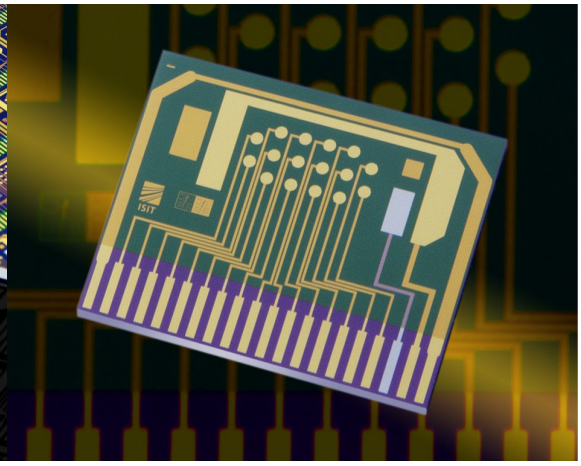
# Biotechnische Mikrosysteme

## Electrical Array-Biochips







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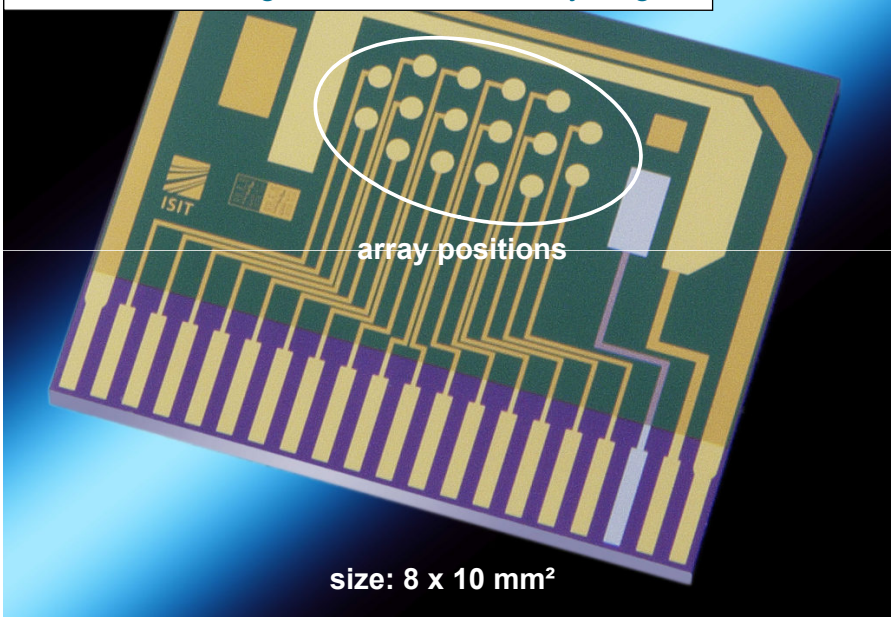
## Technology of the electrical array biochips

Principle:
Sandwich-ELISA on gold electrode arrays.
Detection via single electrode redox-cycling.



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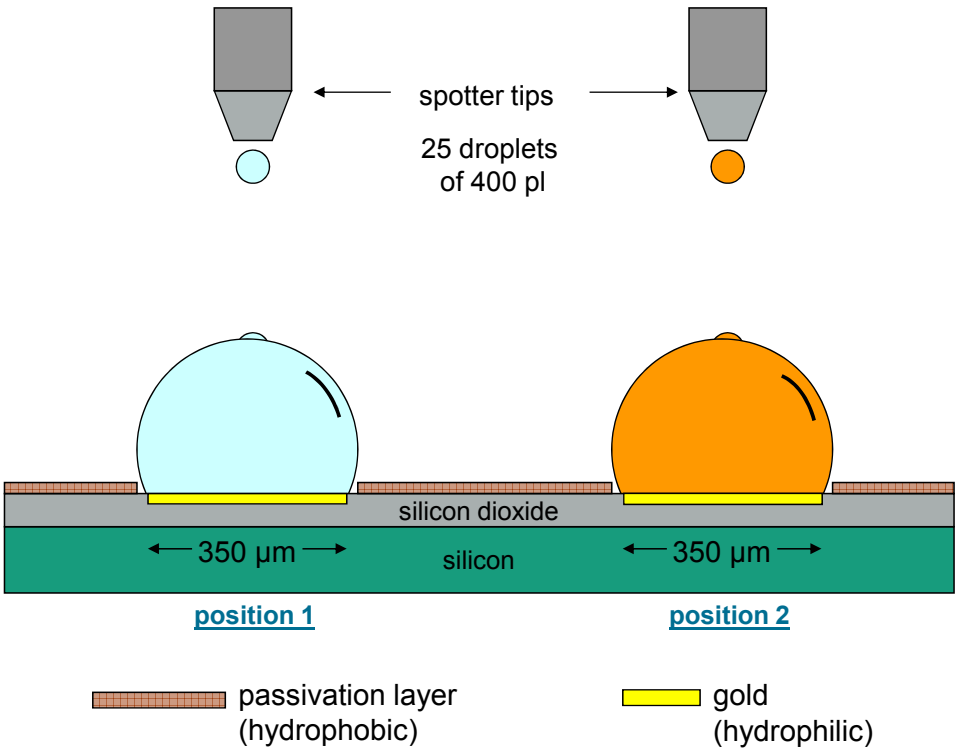
## Position specific dispensing of biological components



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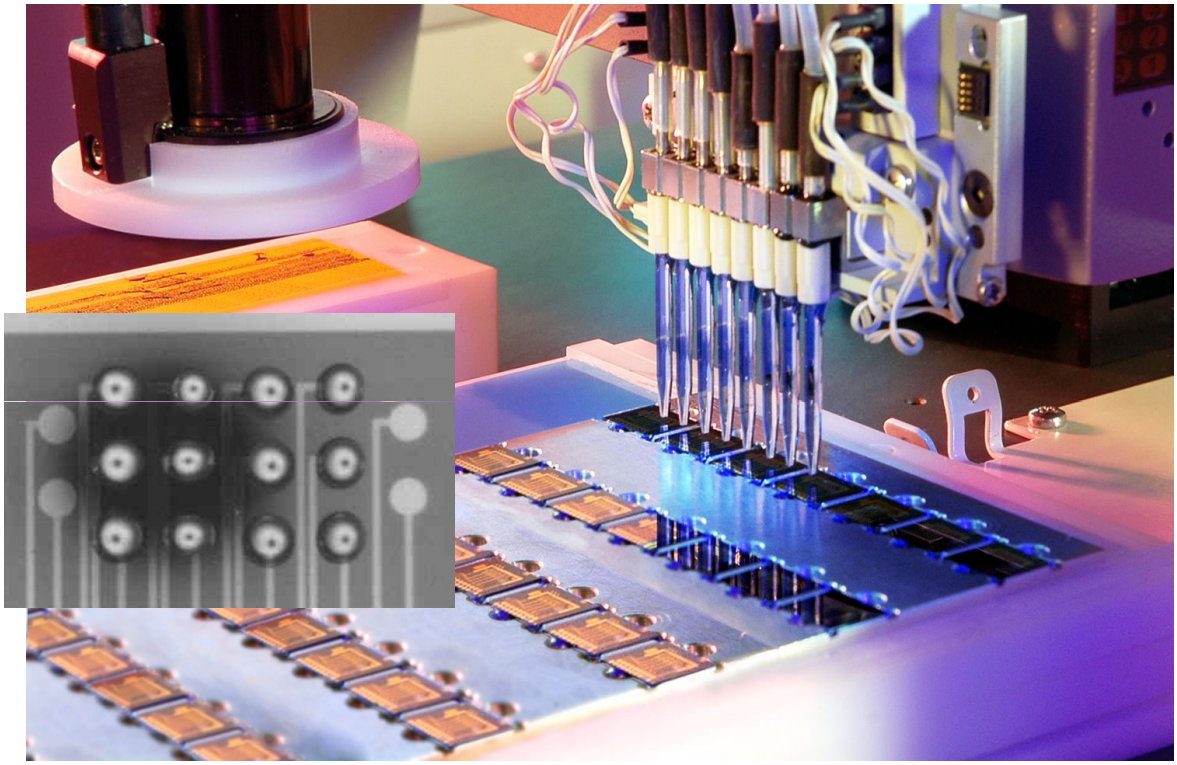
## Piezoelectric nanodispensing device





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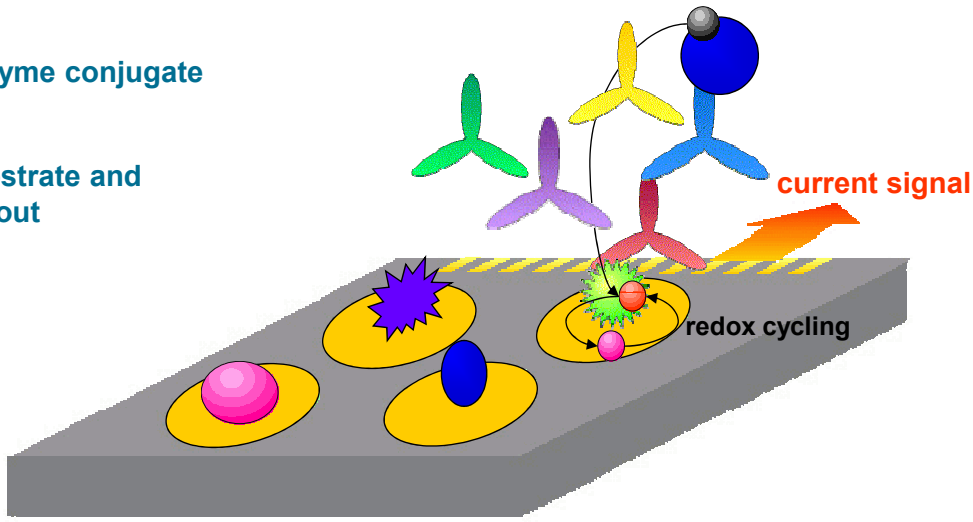
# Immunoassay on an electrical biochip

## Biochip spottet with different capture molecules

1. Adding a diluted serum or whole blood sample
2. Adding the enzyme conjugate
3. Adding the substrate and electrical read out



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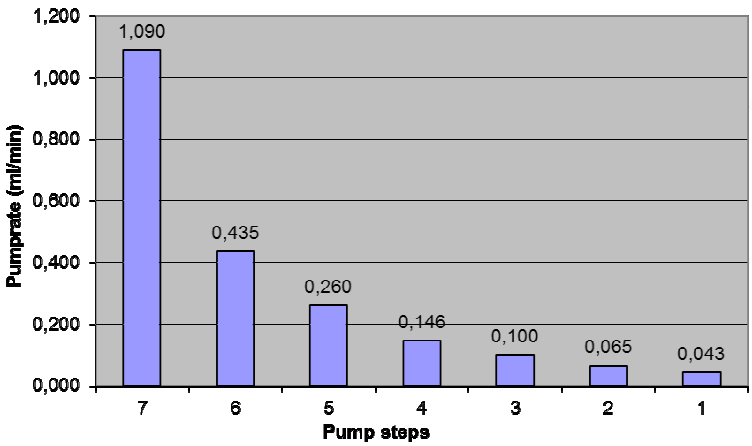
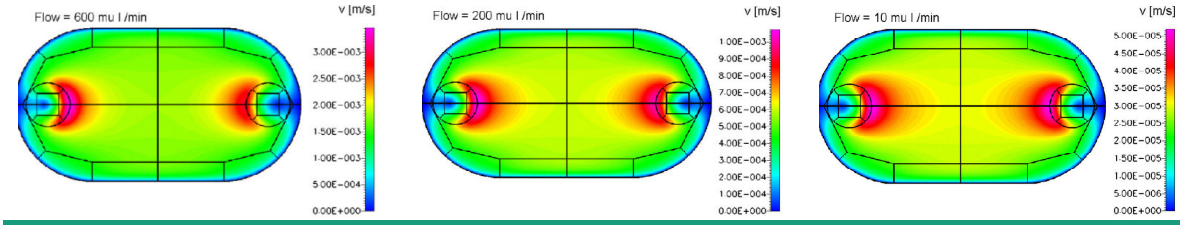
# Pump and flow rates for assay procedure



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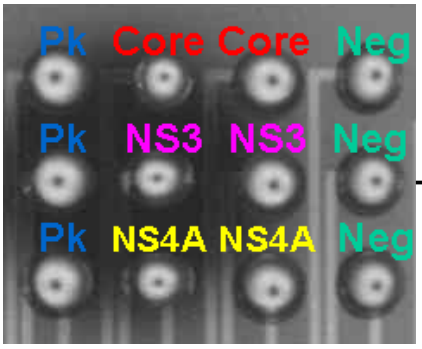
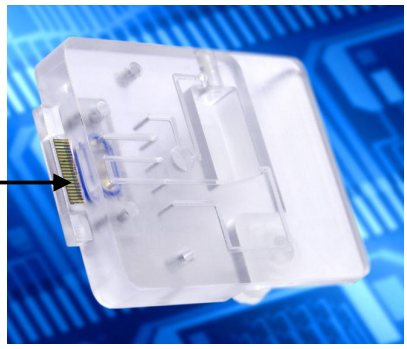
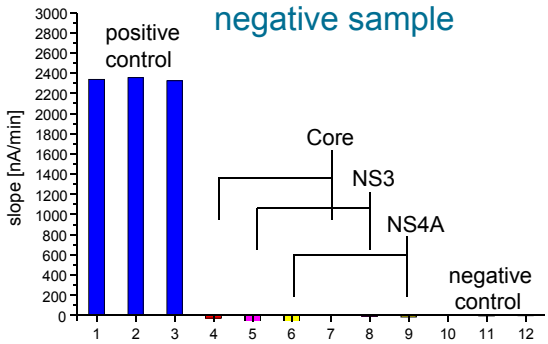
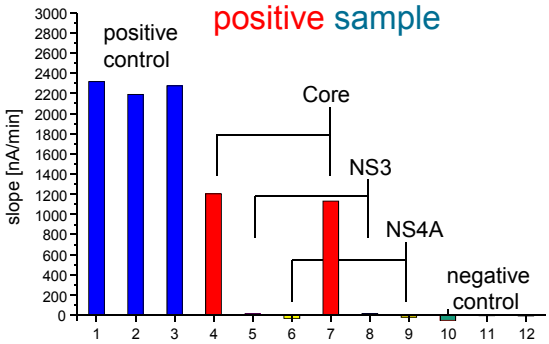
# Hepatitis-C (HCV) detection with the electrical biochip system




assay time: <15 min.



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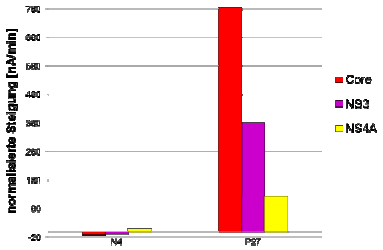
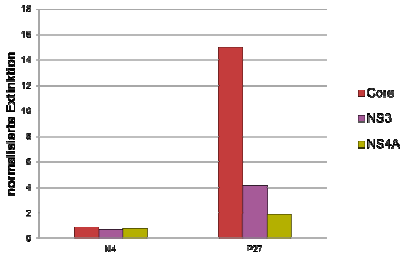
# Comparison of the biochip system with standard ELISA by HCV-Assay

| 32 positive HCV samples<br>39 negative HCV samples | Standard ELISA | Biochip |
|---|---|---|
| Correctness of the test | 88,7% | 94,4% |
| Duration of the test | 4 h | 15 min |




- Universal platform for protein detection
- High sensitivity and selectivity
- Small volume whole blood analysis
- Fast, user friendly and reproducible system
- Portable device for on-site detection

L.Blohm *et al.*, “Rapid detection of different human anti-HCV immunoglobulins on electrical biochips”, Antibody Technology Journal 2014:4 23–32



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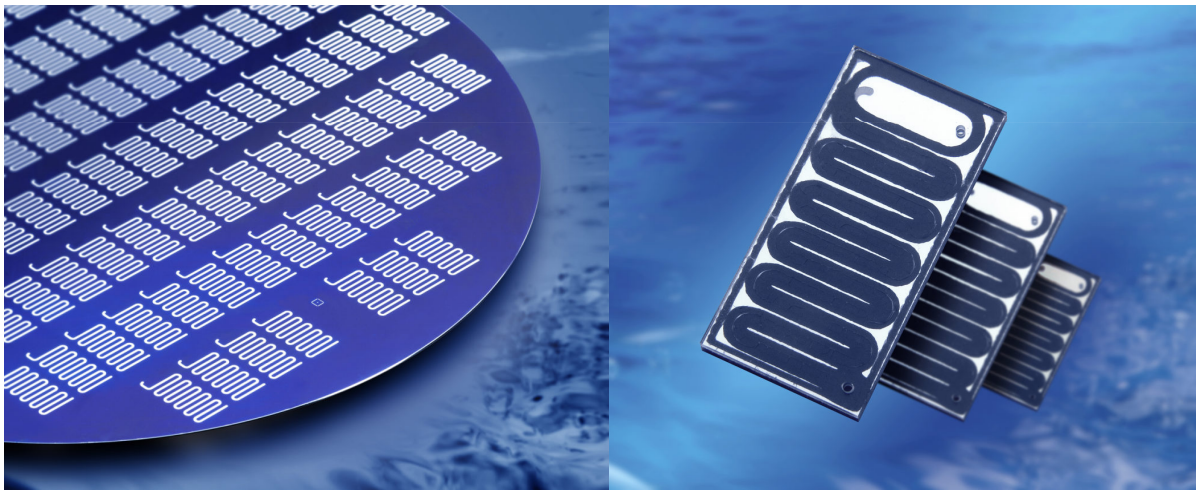
# Biotechnical Microsystems

Microsystem for mobile analysis of biochemical molecules

“MEMS-Chromatography”





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## Development of a portable analytical system on the basis of liquid chromatographic separation processes

- Separation column with very large surface (porous material)
  - Compatible with silicon technology
- Components for detection of biochemical substances
  - Electrochemical detection methods
- Integration of 3D-Column structures and detection in a microsystem
  - Process- and module integration on wafer level



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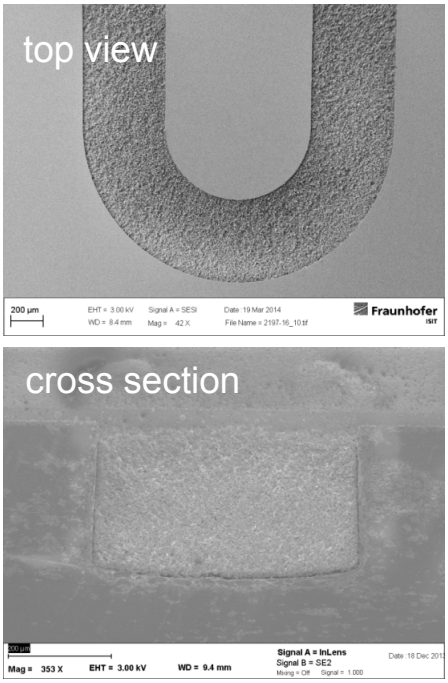
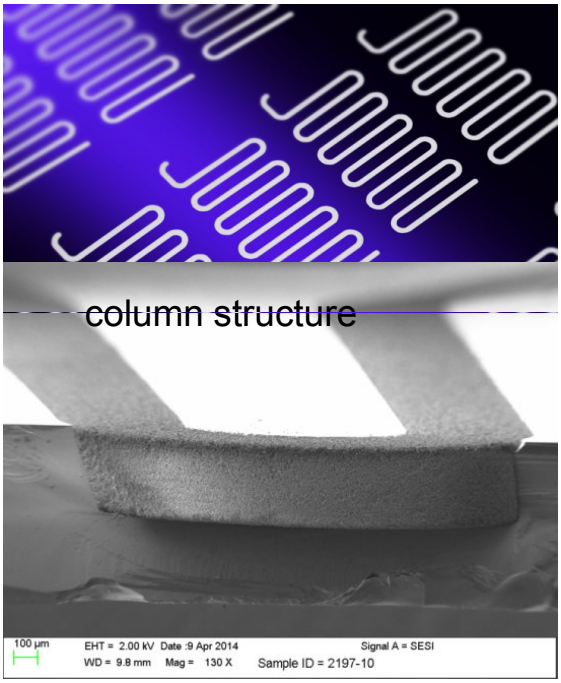
## 3D-MEMS process for porous separation column



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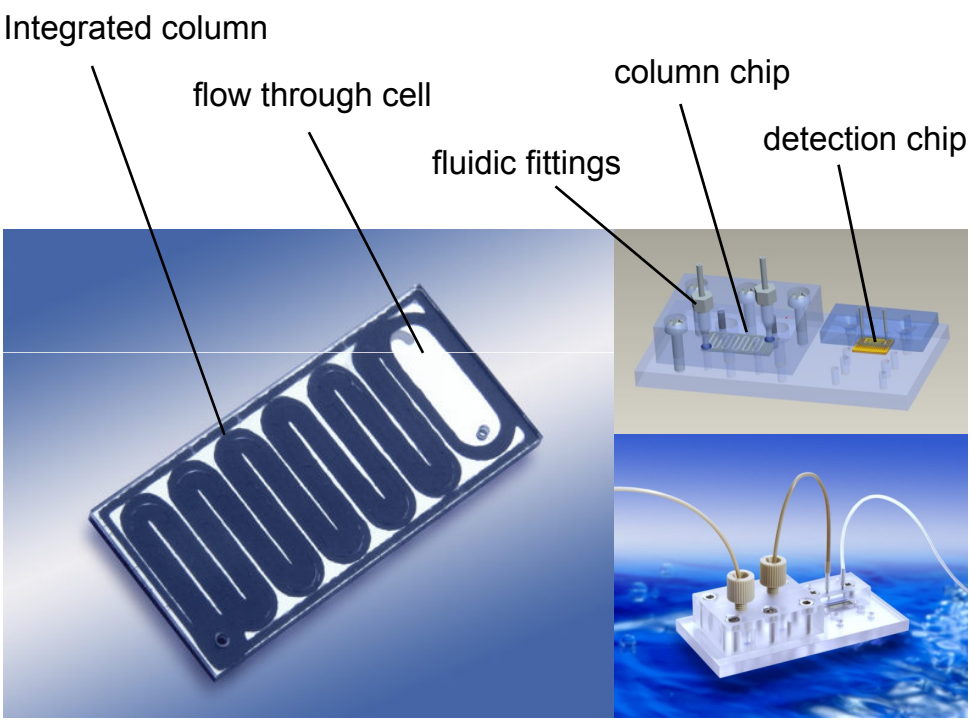
## Column chip and test cartridge



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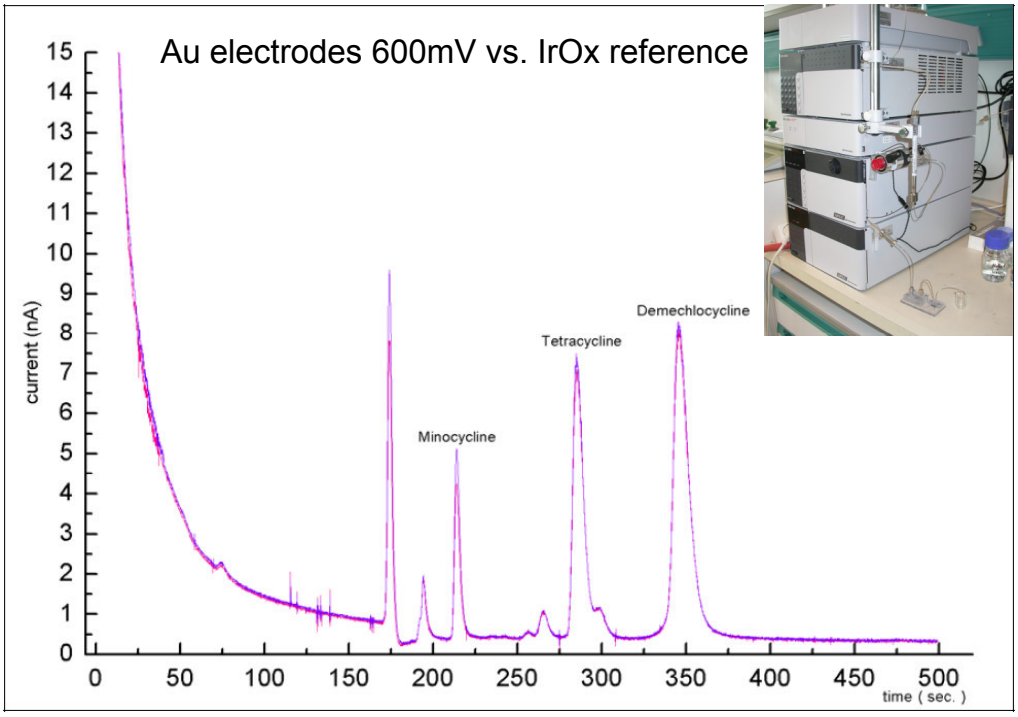
## Electrochemical detection of three different antibiotics with a commercial column and gold microelectrodes



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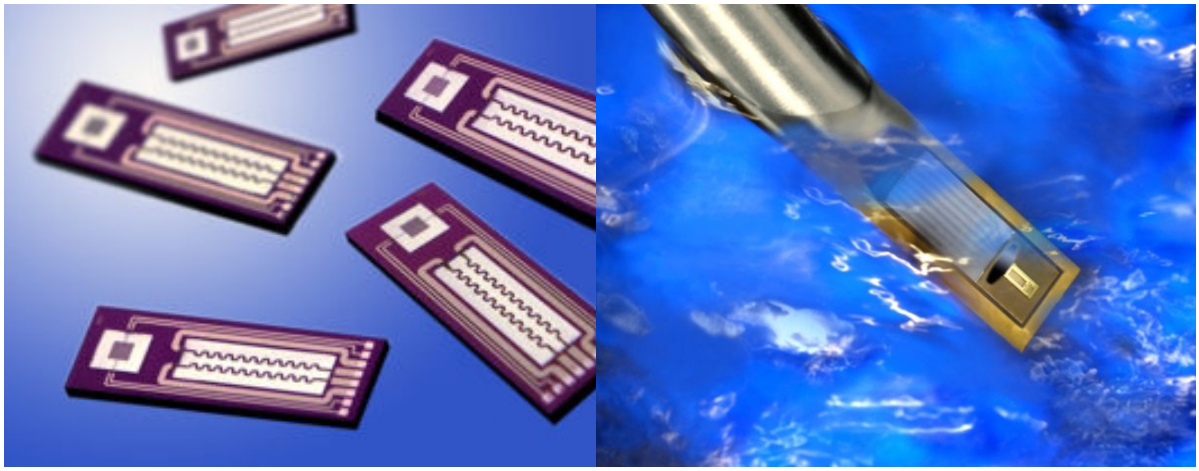
# Microsystem Technology

## Micro Electrical Mechanical Systems (MEMS)

## „Mass Flow Sensors"





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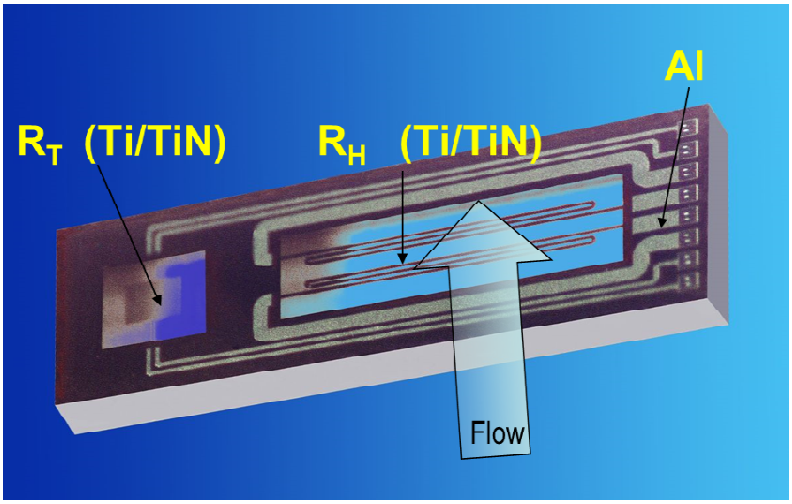
## Temperature compensated Hot-Wire Mass Flow sensor with recognition of direction

- Suitability
  - for Gases and Fluids
  - Recognition of Flow Direction
- Fields of Application
  - Automotive
  - Public Water Supply
  - Medical Technology



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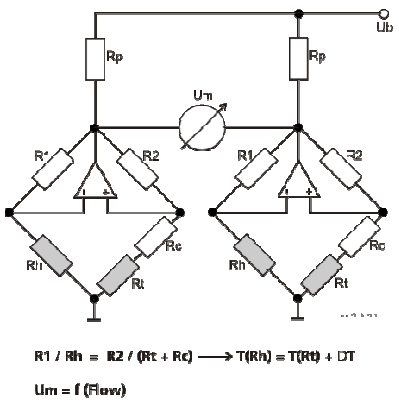
## Principle and test of the mass flow sensor

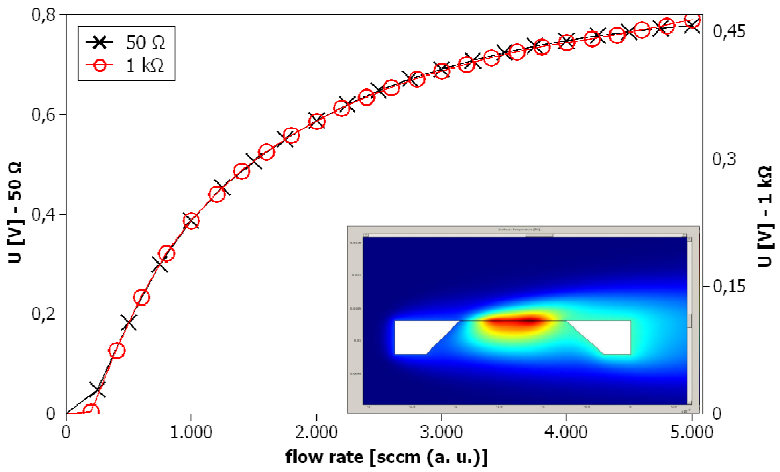
Flow Sensor Concepts

- 2 Heaters
- 2 Temperature Sensors

Response function of flow rate in volume per minute

- Wide dynamic range
- Independence of T (ambient)



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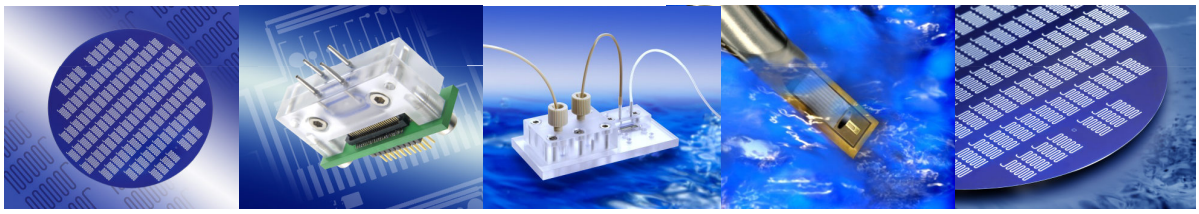

Thank you for your attention!



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