Piezoresistive biochemische Sensorarrays für medizinische Anwendungen

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Arbeitsgebiet und Motivation

Zielstellung

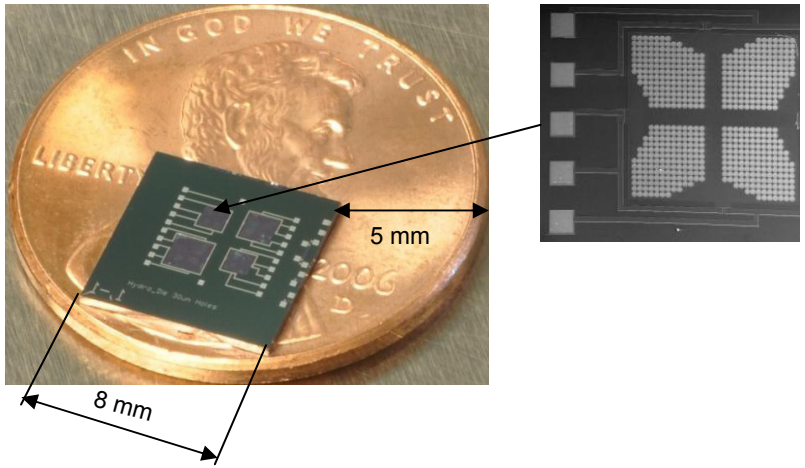
Piezoresistive biochemische Sensoren für:

- Glucose
- pH
- Ionenstärke

Zusammenfassung

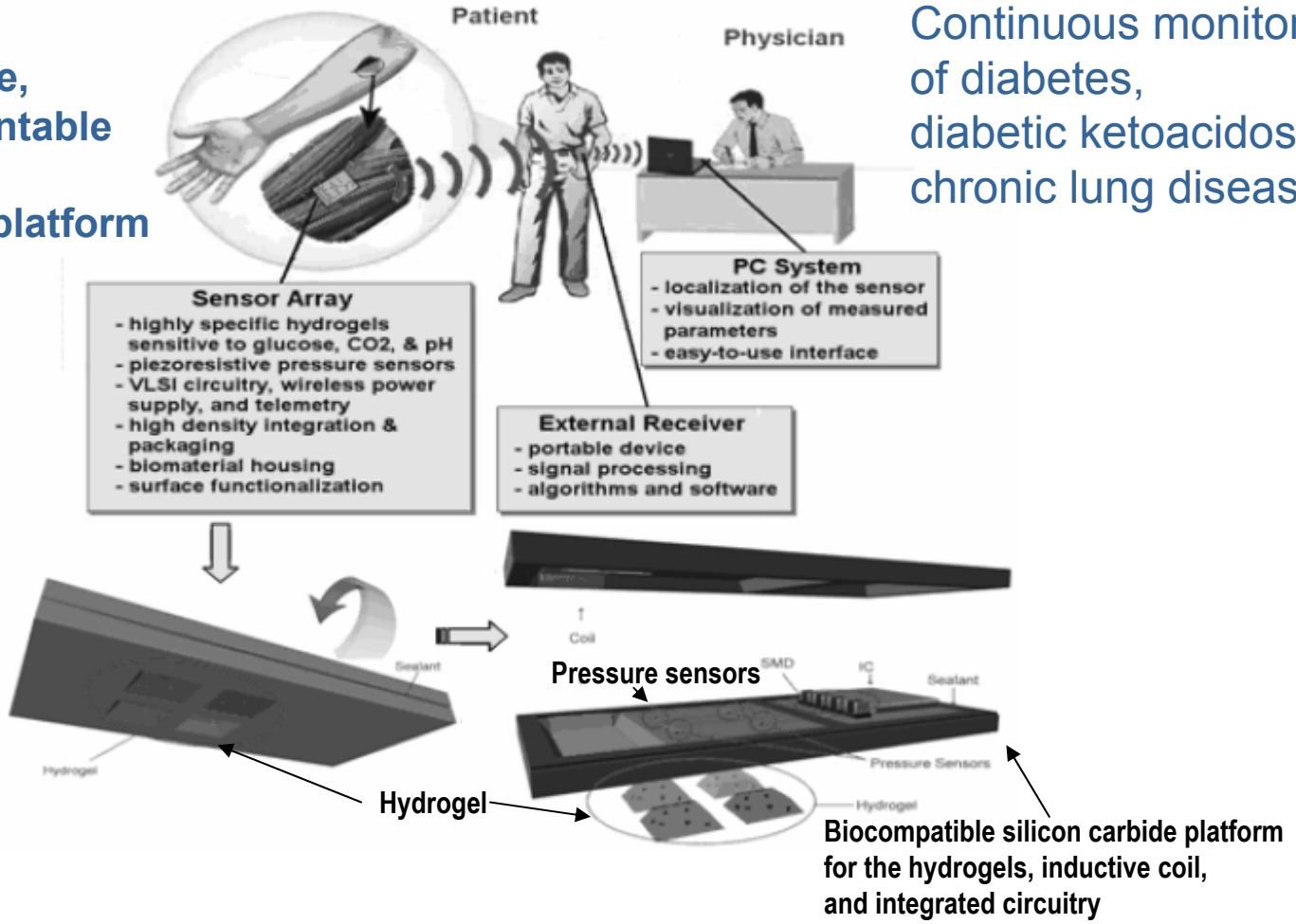
Ausblick

Sensorcharakteristiken:
Sensitivität
Selektivität
Reproduzierbarkeit
Ansprechzeit
Langzeitstabilität

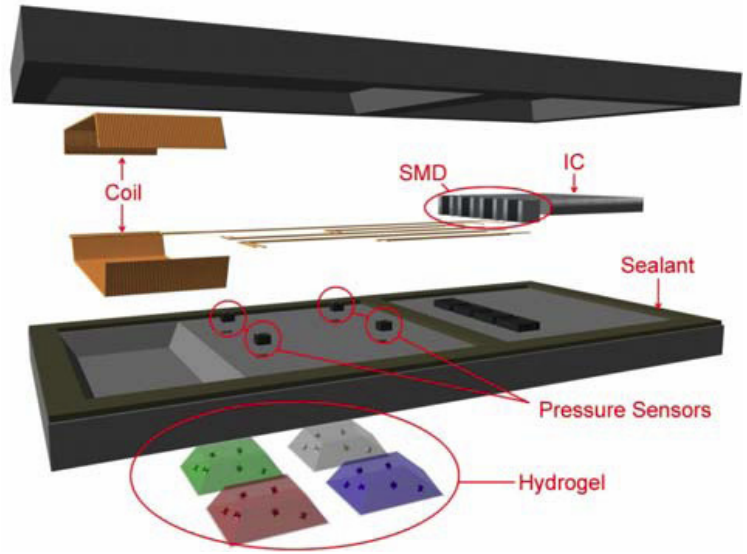


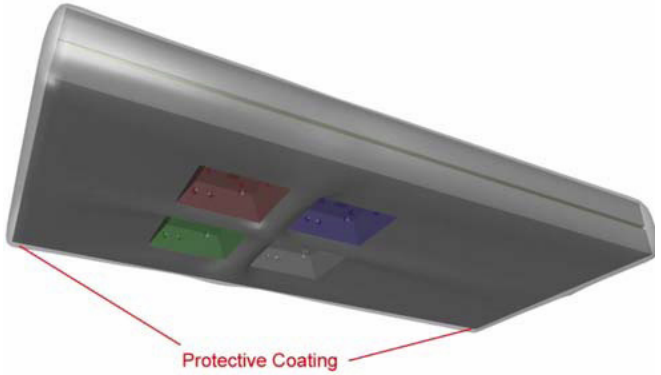
Glucose/pH/CO_2 sensor array

Minimally invasive, chronically implantable wireless hydrogel sensor platform



Continuous monitoring of diabetes, diabetic ketoacidosis, chronic lung disease



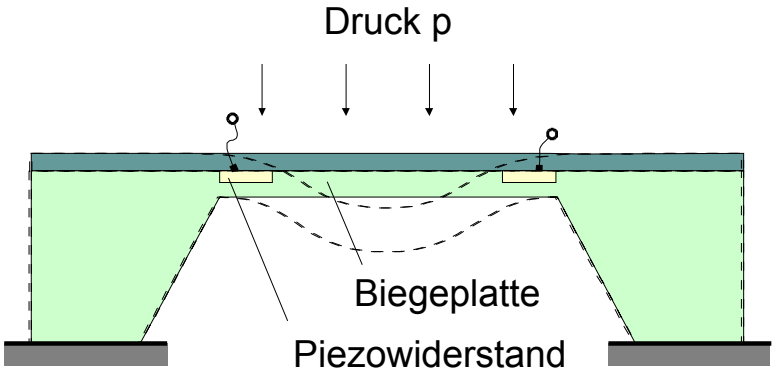


Teilaufgaben:

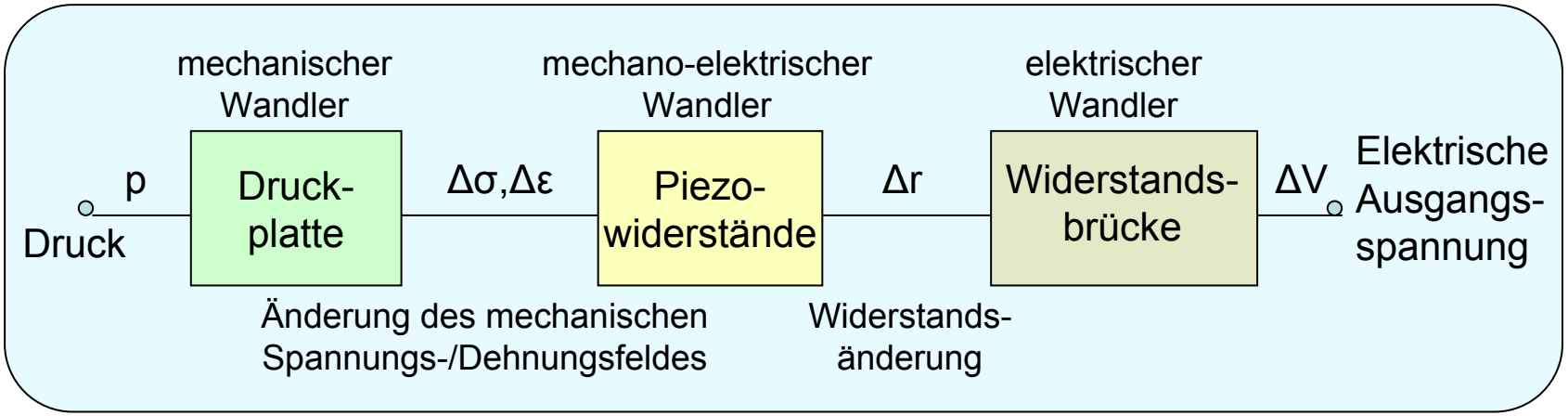
- 2x2 Array piezoresistiver Drucksensoren
- Analyt-sensitive Hydrogele
- Hydrogel-basierte Biosensoren
- Telemetrieeinheit zur drahtlosen Datenübertragung
- Einheit zur induktiven Energieversorgung
- Bioverträgliche hermetische Verkapselung
- Minimal invasive Implantation

Kooperation: University of Utah

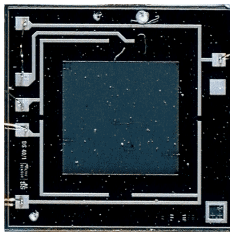
IMPLANTIERBARES DRAHTLOSES SENSORSYSTEM

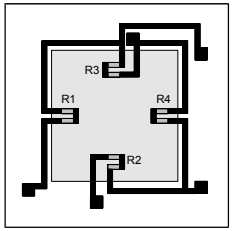


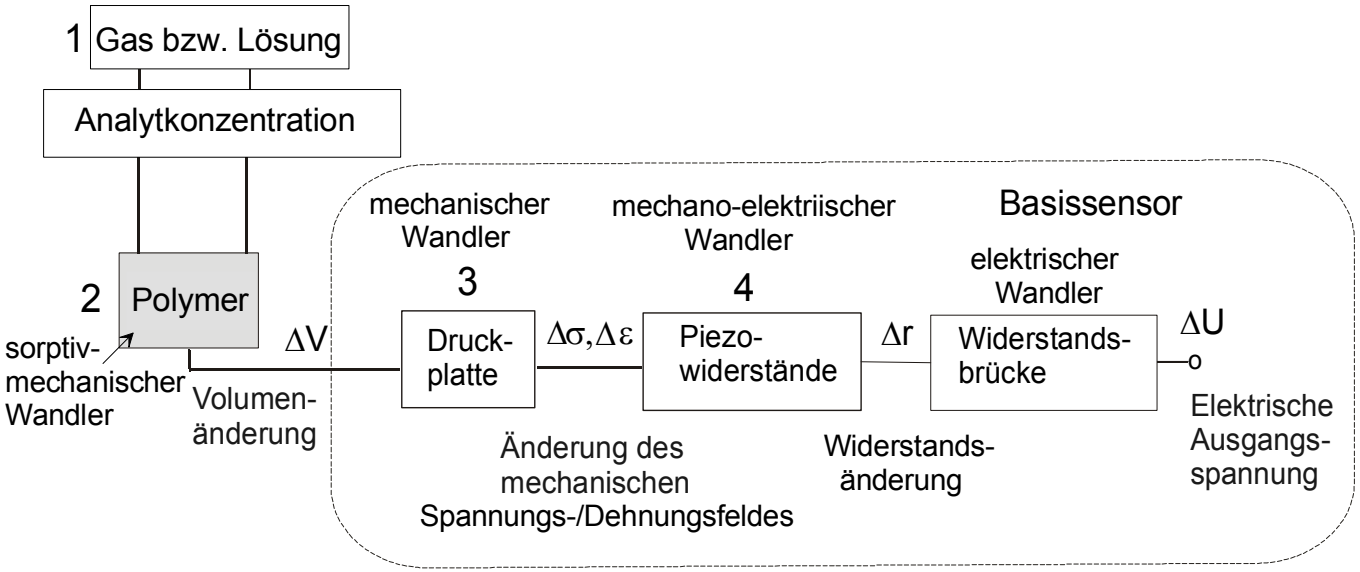
Piezoresistiver Drucksensorchip



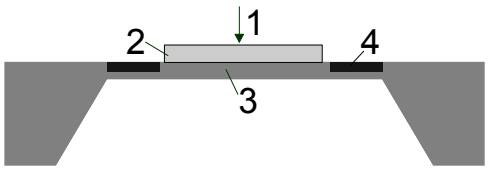
Piezoresistive chemische Sensoren



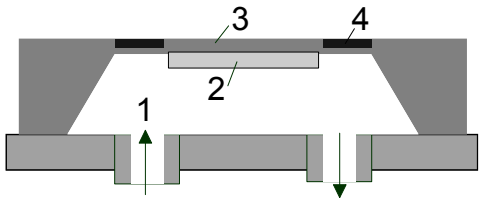




G. Gerlach et al., Feuchtesensor, Patentschriften:
DD 236.173 vom 28.05.1986,
DE 4312 788 C2 vom 20.04.1993,
DE 198 53 732 C1 vom 23.11.1998



bimorpher Gassensor

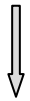


Flüssigkeitssensor

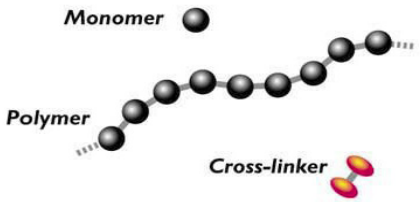
G. Gerlach et al., Sensor zu Messung der Anwesenheit und der Konzentration von Komponenten in einer Flüssigkeit, Patentschriften:
DE 101 29 985 C2, DE 101 29 986 C2,
DE 101 29 987 C2 vom 12.06.2003

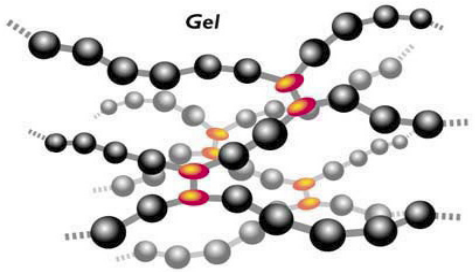
1 Messgas bzw. -flüssigkeit; 2 Polymerschicht; 3 Si-Biegeplatte; 4 Piezowiderstände

Hohe
• Sensitivität,
• Genauigkeit und
• Stabilität
piezoresistiver biochemischer Sensoren



1. Auswahl geeigneter Polymere,
2. Geeignete
• Herstellungstechnologie
und Funktionsregime der Polymerschichten,
• Sensorkonstruktionen





Hydrogel

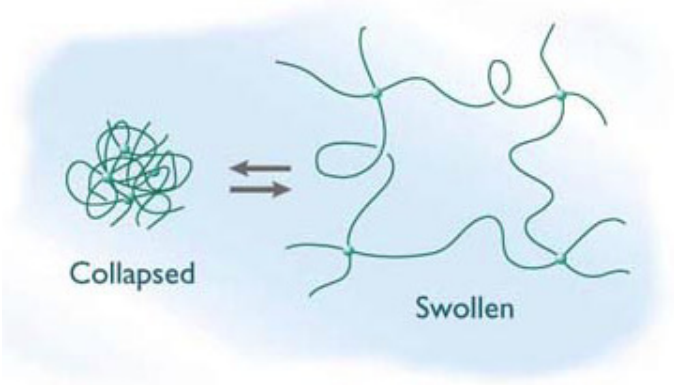
3-D vernetztes Polymernetzwerk, enthaltendes Wasser

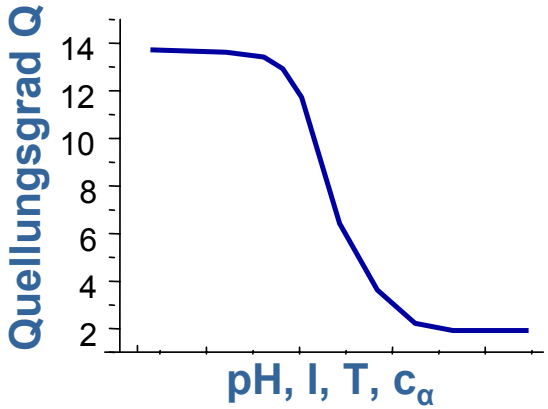
funktionale Gruppen →

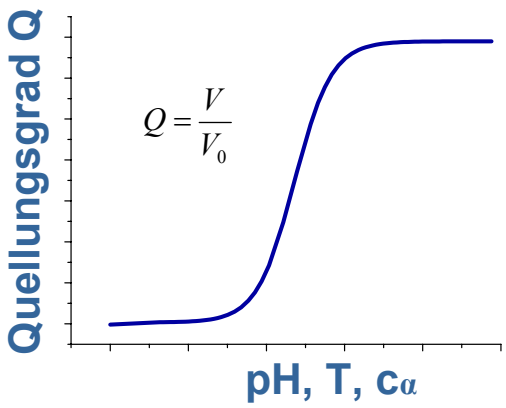
- Analytendiffusion
- Chemische Reaktion
- Änderung der Polymerhydrophilie
- Wasseraufnahme

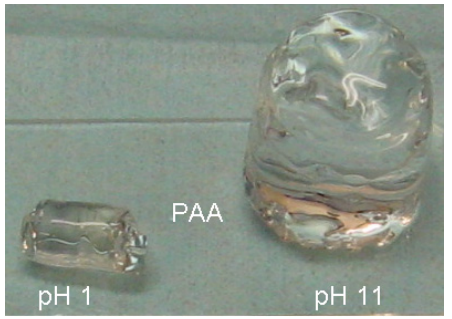
Stimuli-sensitives Hydrogel

ist fähig zu einem Volumenphasenübergang unter dem Einfluss der äußeren Erregungen









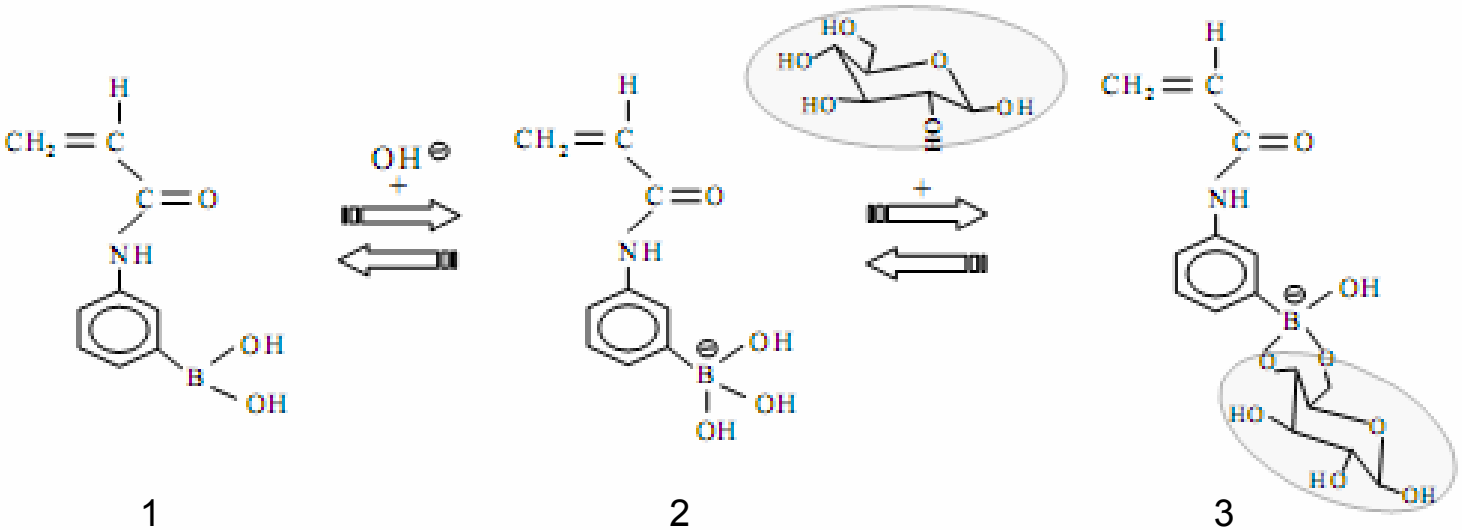
Äußere Erregung: pH-Wert, Ionenstärke, Temperatur, Konzentration von Zusätzen in Wasser

Glucose sensitive hydrogels

P(AAm/3-APB/BIS) (79.75 / 20 / 0.25)

Acrylamide (AAm), 3-acrylamidophenylboronic acid (3-APB), N,N-methylenebisacrylamide (BIS)

Glucose binding to PBA



1
De-swelling form

2
Transition form

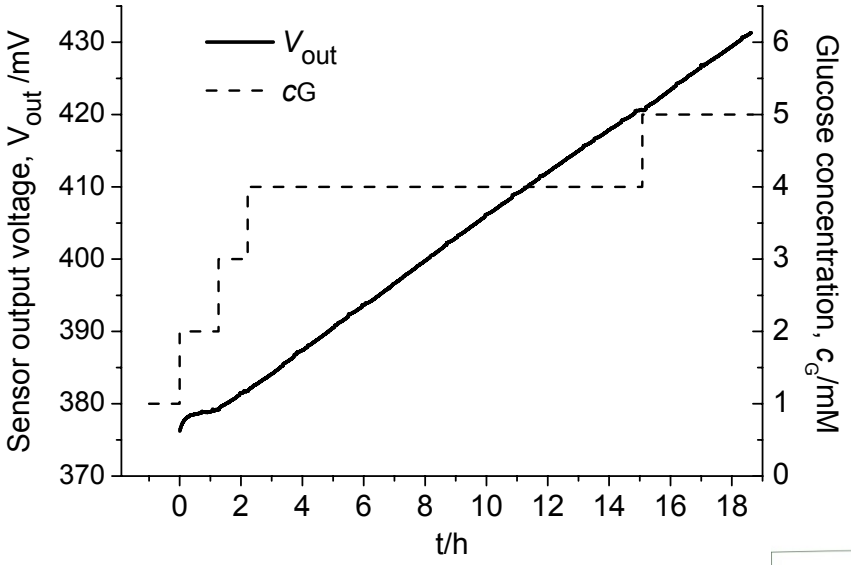
3
Swelling form

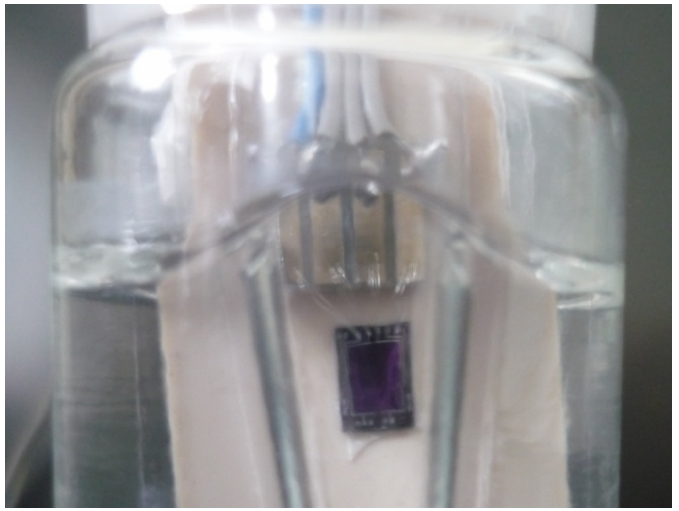
$$\alpha = \frac{1}{1+\lambda \cdot 10^{pK_0 - pH}}$$

$$\alpha = \frac{1+c_G / K_G}{1+\lambda \cdot 10^{pK_0 - pH} + c_G / K_G}$$

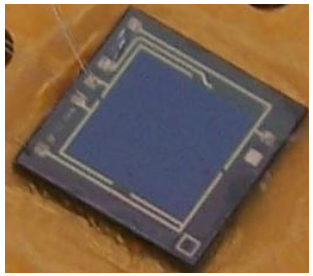
$pK_0 = 8.86$

$K_G = 9.1\text{mM}$

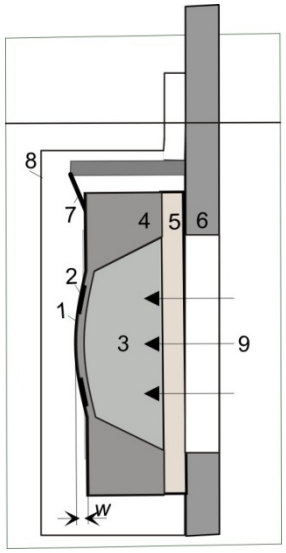




Dip biosensor with a porous Anopore™ membrane at the backside of the chip

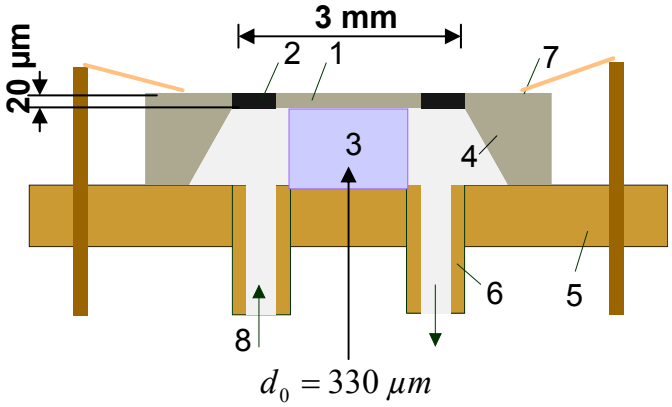


Frontside of the piezoresistive pressure sensor chip



Design of hydrogel-based biochemical sensor:
1 bending plate (3 mm x 3 mm x 0.02 mm);
2 mechano-electrical transducer (piezoresistive bridge);
3 swellable hydrogel; 4 Si chip (5 mm x 5 mm x 0.4 mm);
5 porous membrane; 6 substrate; 7 interconnect; 8 cap;
9 measuring solution.

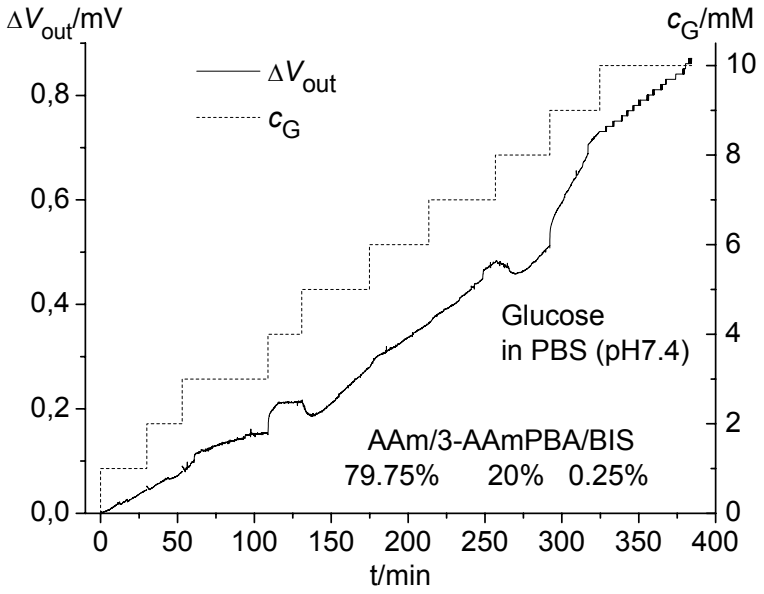
TAUCHSENSOR FÜR GLUCOSE



1 – bending plate
2 – mechano-electrical transducer (piezoresistive bridge)
3 – swellable hydrogel layer
4 – Si chip
5 – socket TO-8
6 - tube
7 - interconnect
8 - solution

$$\tau \sim d^2 / D_{coop}$$

D_{coop} = 3x10^{-11} m^2/s

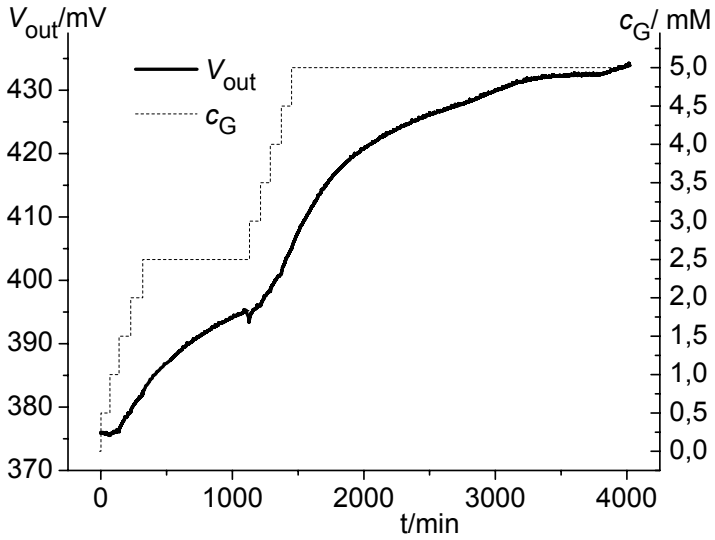


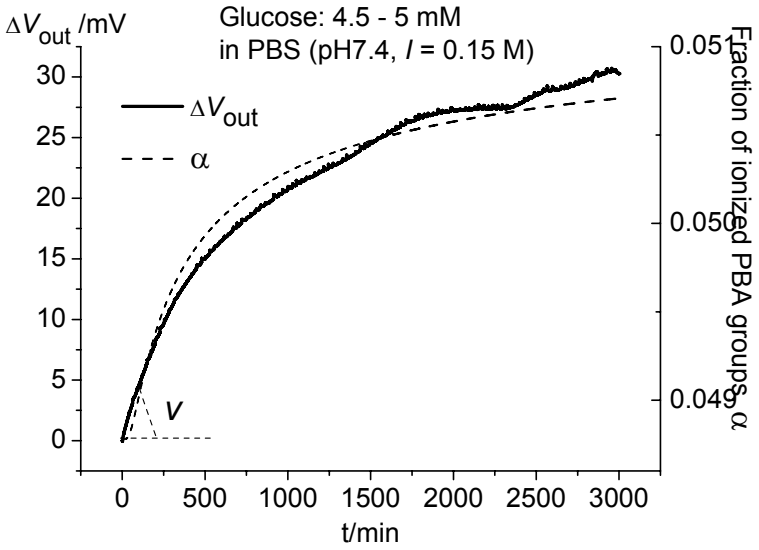
M. Guenther et al.,
Proc. SPIE, 7642 (2010)

GLUCOSE-SENSOR: DURCHFLUSSPRINZIP

Quellungskinetik

Analytendiffusion → Chemische Reaktion → Erhöhung der Polymerhydrophilie → Zusätzliche Wasseraufnahme





$$c_\alpha = c_{\alpha 0} + (c_\alpha^0 - c_{\alpha 0})\, f(d,t)$$

$$f(d,t) = \left[1 - erf\ (d / 2\sqrt{D_\alpha t})\right]$$

$$erf\ (\delta) = \frac{2}{\sqrt{\pi}} \int_0^\delta e^{-\varsigma^2} d\varsigma$$

Rate of gel groups ionisation

$$\dot{c}_{gi} = k_f c_\alpha (c_g - c_{gi}) - k_b c_{gi}$$

Fraction of ionized polymer groups α = c_{gi}/c_g

$$\alpha = \frac{1 + c_G / K_G}{1 + \lambda \cdot 10^{pK_0 - pH} + c_G / K_G}$$

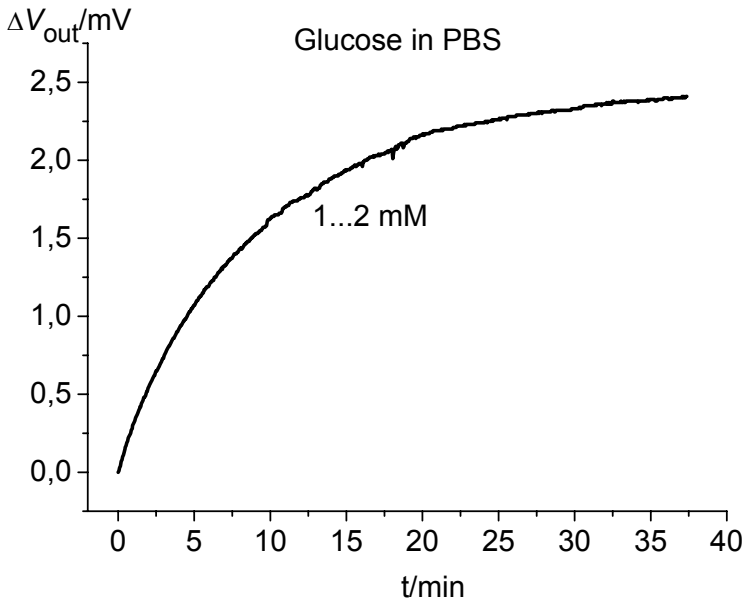
D_G = 4.8x10^{-12} m^2/s

$d = d_0 + \Delta d$

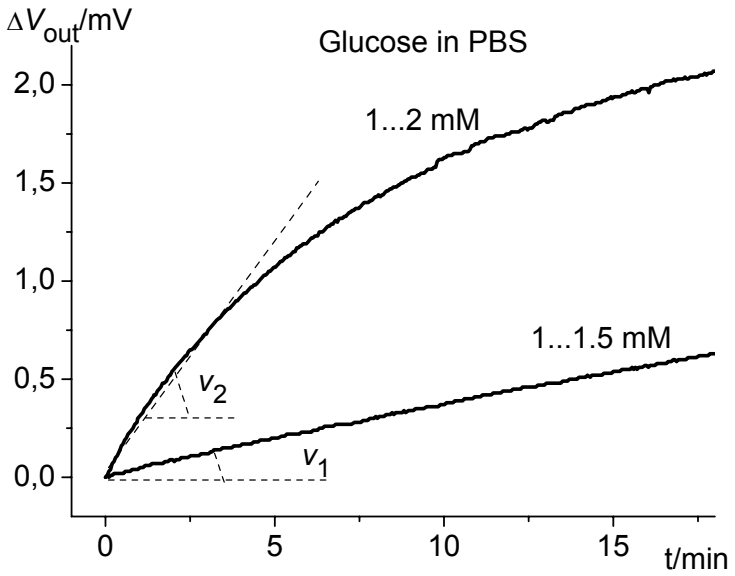
d_0 = 330 µm

λ = 1.5

GLUCOSE-SENSOR: ANSPRECHZEIT



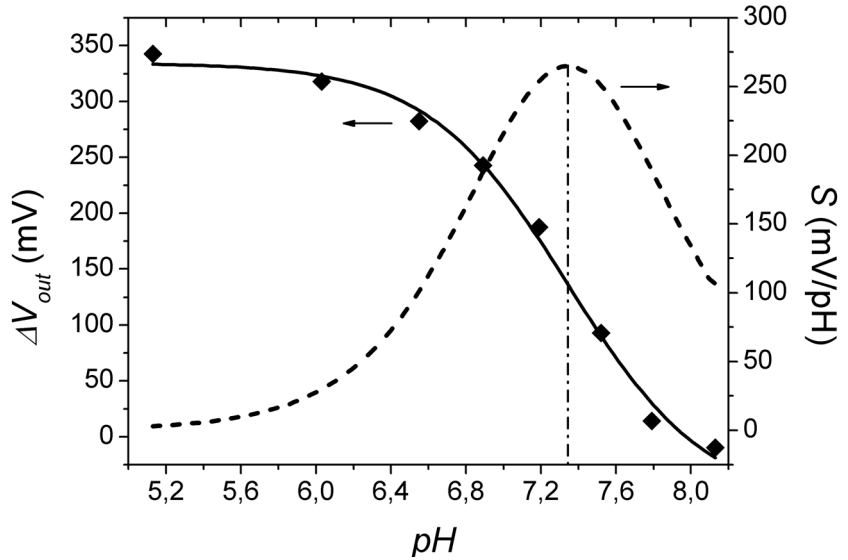
$t_{eq} \rightarrow t_m$



$$(c^0_{\alpha,2} - c_{\alpha 0,2}) = (c^0_{\alpha,1} - c_{\alpha 0,1})(v_2 / v_1)$$

M. Guenther, G. Gerlach, In: Hydrogel Sensors and Actuators. Eds.: G. Gerlach, K.-F. Arndt. Springer Series on Chemical Sensors and Biosensors, vol. 6. Springer-Verlag. Berlin. 2009, p.165-195

GLUCOSE-SENSOR: ANSPRECHZEIT



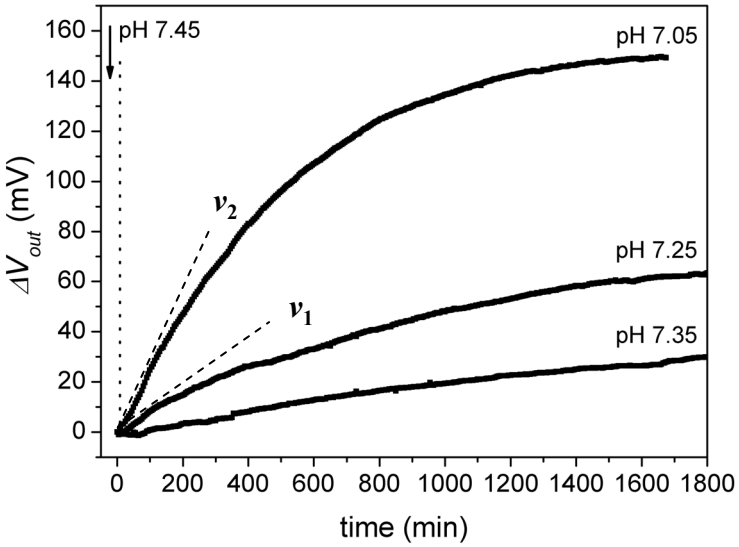
HPMA / DMAEMA / TEGDMA
68% 30% 2%

pH-sensitives Hydrogel
poly(hydroxypropyl methacrylate – (N,N-dimethylamino)ethyl methacrylate)-tetraethylene glycol dimethacrylate)

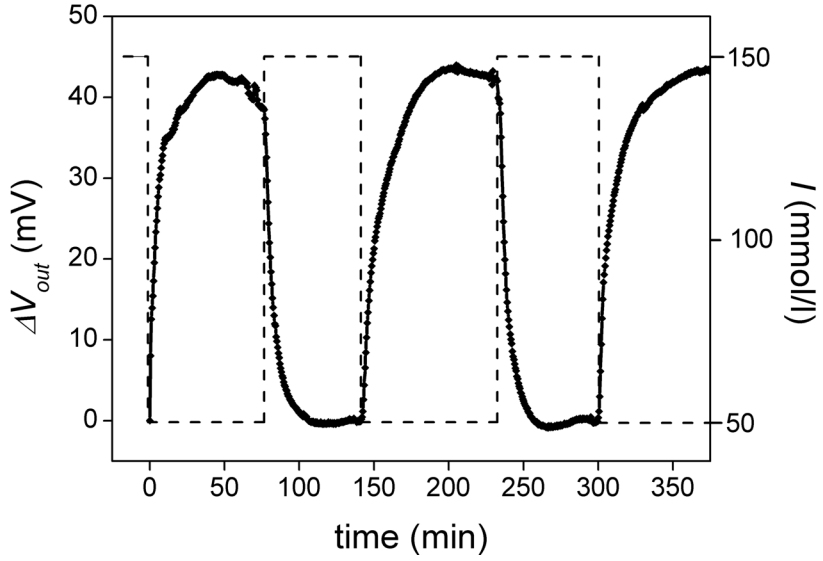
V. Schulz et al., Techn. Messen, 3 (2010)

Sensorsensitivität

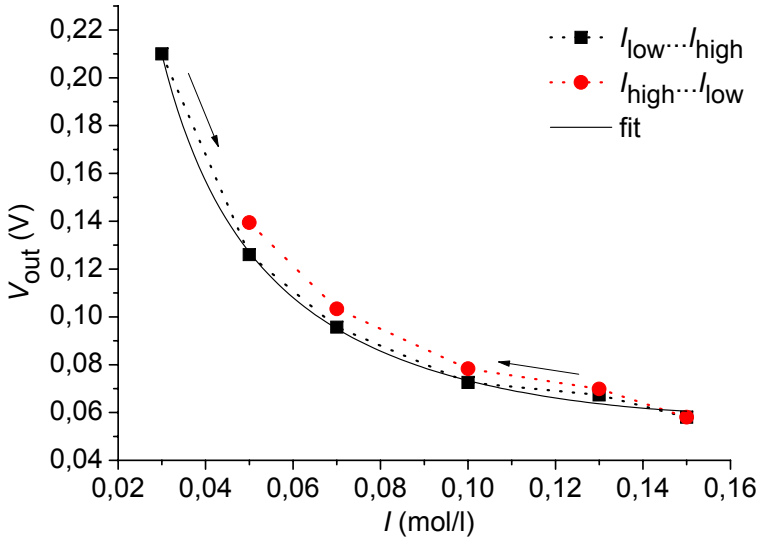
$$S = \frac{\partial \Delta V_{out}}{\partial pH}$$



$$\lg(c^0_{\alpha,2} - c_{\alpha 0,2}) = \lg(c^0_{\alpha,1} - c_{\alpha 0,1}) + \lg(v_2 / v_1)$$



HPMA/DMAEMA/TEGDMA-Hydrogel



V. Schulz et al., Techn. Messen, 3 (2010)

„Intelligente“ Hydrogele

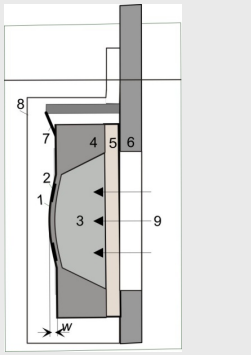
PVA/PAA
PNIPAAm (BIS 4)
P(AAm/3-APB/BIS)
PNIPAAm-DMIAAm
P(N,N-DMAEMA-DMIMA)
PNIPAAm-DMAAm-DMIAAm
HPMA / DMAEMA / TEGDMA
P2VP-block-P(NIPAAm-co-DMIAAm)
P4VP-block-P(NIPAAm-co-DMIAAm)
P2VP-block-P(NIPAAm-co-DMIAAm)quart
P4VP-block-P(NIPAAm-co-DMIAAm)quart

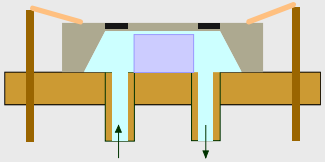
Schichtdicke: 4… 330 µm

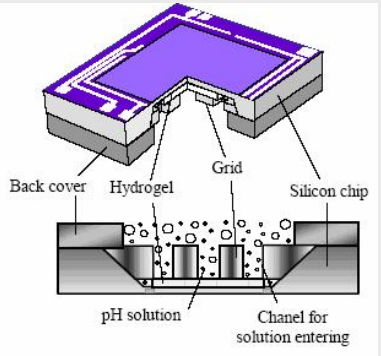
Messspezies

Glucose,
H^+, OH^-
Salze

Sensor-Konstruktionen







Sensor-Charakteristiken

Sensitivität
Selektivität
Reproduzierbarkeit
Ansprechzeit
Langzeitstabilität

Lebensdauer

S1, P(AAm/3-APB/BIS): Glucose-Sensor
0,8 Jahr, 75 Messungen

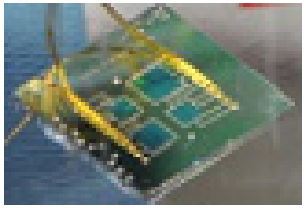
S2, P(AAm/3-APB/BIS): Glucose-Sensor
0,5 Jahr, 50 Messungen

S3, PVA/PAA: pH-Sensor
2,8 Jahre, 144 Messungen

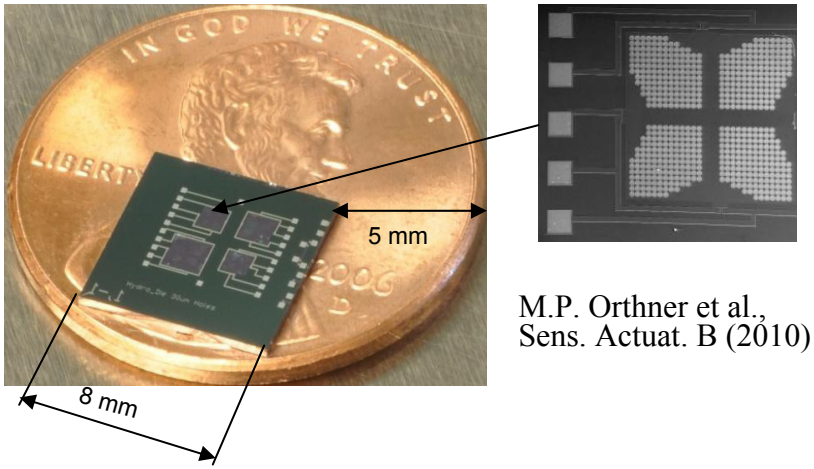
S9, PNIPAAm (BIS4): T, Alkohol-Sensor
4,5 Jahre, 156 Messungen

S14, P2VP-block-P(NIPAAm-co-DMIAAm) Multisensor
0,5 Jahr, 125 Messungen

ZUSAMMENFASSUNG



Integrated and encapsulated implantable glucose, CO_2, and pH sensor array



M.P. Orthner et al., Sens. Actuat. B (2010)

Hydrogels:

1) **Glucose sensitive**
poly(3-acrylamidophenylboronic acid-co-acrylamide)
2) **pH sensitive (for CO_2 sensor)**
poly(hydroxyethyl methacrylate-co-(N,N-dimethylamino)ethyl methacrylate)
3) **pH sensitive**
poly(hydroxypropyl methacrylate – (N,N-dimethylamino)ethyl methacrylate)-tetraethylene glycol dimethacrylate)
4) **Neutral (for ionic strength)**
copolymer of N-isopropylacrylamide

Integrated sensor solution

Arrays combining

- **Biochemical sensors (analytes: glucose, CO_2)**
- **pH sensor**
- **Sensor for ionic strength measurements**
- **Temperature sensor**

Finanzielle Unterstützung:
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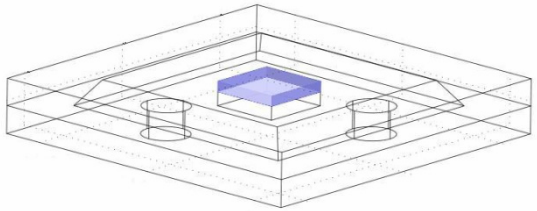
University of Utah: F. Solzbacher, J. Magda, G. Lin, M. Orthner, P. Tathireddy

TUD / IFE: V. Schulz, U. Lehmann



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