CMOS Sensor Arrays for Bio Molecule and Neural Tissue Interfacing

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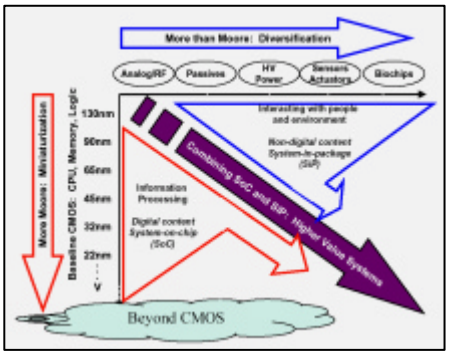
Dallas, TX

Outline

Introduction

- Beyond classical CMOS scaling driven performance increases, summarized as “More Moore”, the ITRS roadmap considers a second branch entitled “More than Moore”.
  There, CMOS generates value by functional diversification and application specific extensions.
- Among the related areas, “Biochips” are explicitly highlighted.



- Biotechnology and life sciences as such have gained huge attention in recent years due to the achievements of these disciplines on the one hand and due to the belief in their potential for forthcoming decades on the other.
- Purpose of this talk is to provide an overview about status, challenges, and opportunities where Silicon and CMOS meet these disciplines.

Outline

DNA* Microarray Chips

Purpose:
Highly parallel investigation concerning the presence / absence / quantitative amount of specific (pre-defined) DNA sequences in a given sample

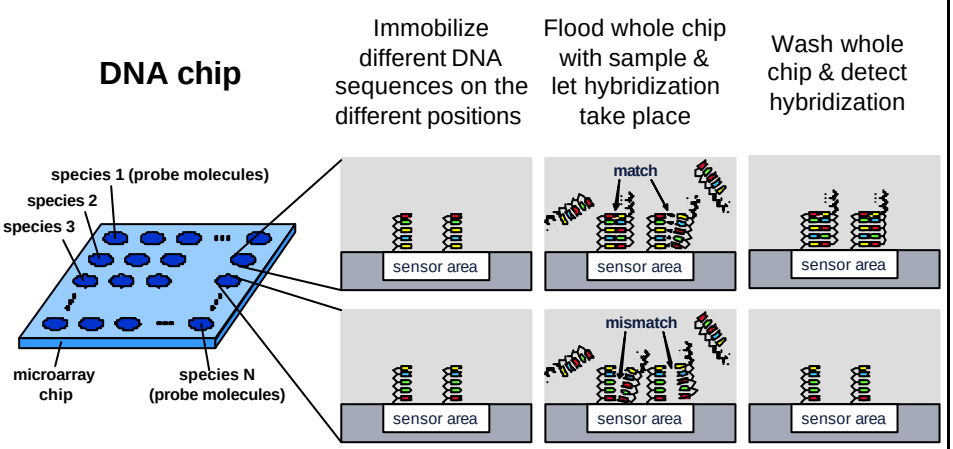
Basic setup:
Slide ("chip") of the order mm^2 ... cm^2 made of glass / polymer material / Si

Most important applications:
- Genome research
- Drug development
- Medical diagnosis

Application dependent requirements:
- Sensitivity / dynamic range (→ gene expression, drug development)
- Specificity (→ medical diagnosis)

** Within the context of this lecture, the DNA molecule is taken as a representative also for other important bio molecules such as proteins etc, since the biochemical boundary conditions required here can be easily explained by using the example of DNA only and since technical statements concerning CMOS extension etc. apply for other bio molecules as well.*

Basic Operation Principle of DNA Microarray Chips



Why Electronic Readout?

State-of-the-art commercially available DNA microarrays:

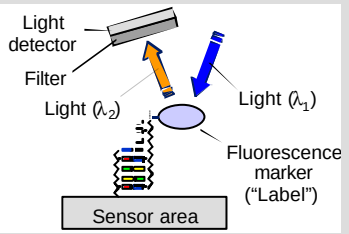
optical readout by labeling the target strands with fluorescence marker molecules

Opportunities provided by fully electronic readout techniques:

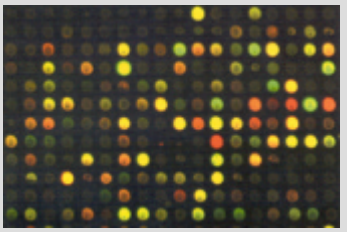
- increased robustness
- increased user friendliness
- decreased system cost
- increased flexibility
- …

Requirement of large arrays:

- CMOS integration ("large": = 10...100 sensor sites)

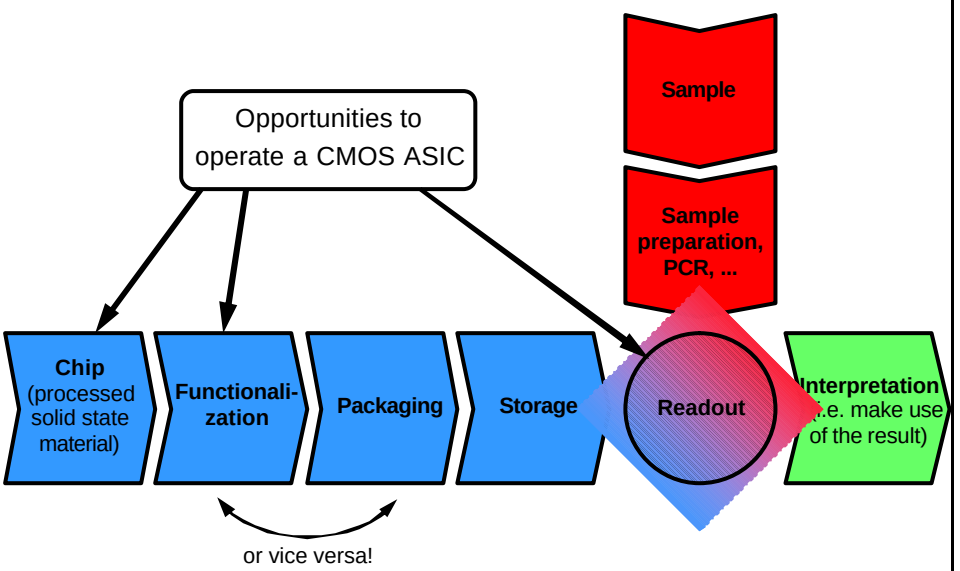


Basic principle: optical readout techniques



Typical result: overlay from a number of experiments (artificial color presentation)

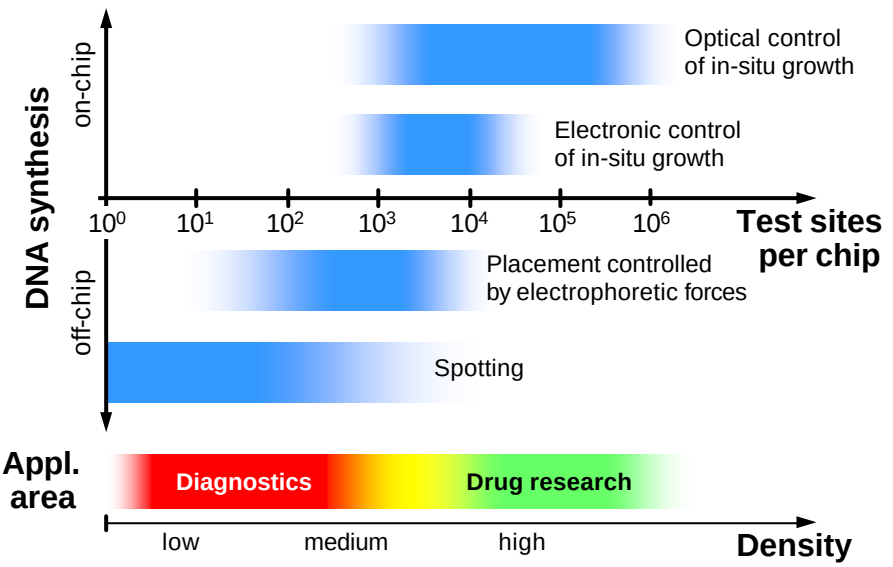
Entire Manufacturing / Application Chain of Microarrys



Outline

DNA Microarray Functionalization Techniques

... and related application areas



Functionalization by Spotting

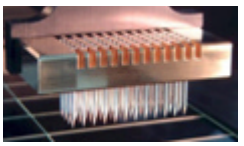
Spotter provides / contains:

- Pinhead with one or more pins, maneuverable in x-, y-, z- direction, positioning repeatability of order 10 µm
- Reservoirs (e.g. microplates) with probe molecules in solutions + washing solution
- Chips to be functionalized
- Optionally: Position recognition system

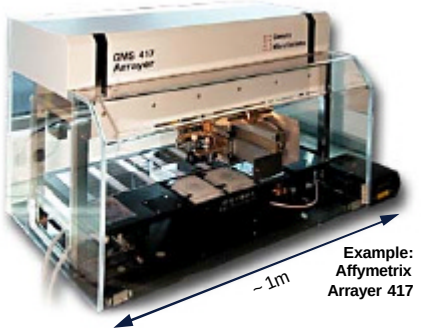
Procedure:

- Pins load solutions from reservoirs and deposit small volumes (of order: 1 nl, various deposition techniques in use) at microarray target positions

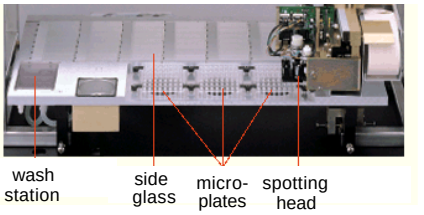
Pinhead with four pins



Stealth™ 48 pin printhead



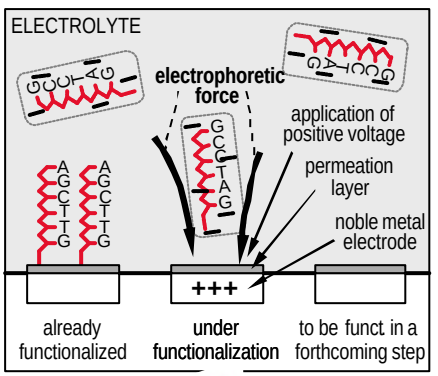
Example: Affymetrix Arrayer 417



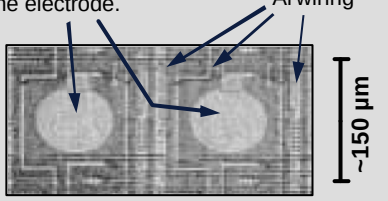
E. Zubritsky, Anal. Chem., 2000, December 1, 72(23), pp. 761A-767A.
V. G. Cheung et al., Nat Genet., 1999, January, 21(1 Suppl), pp. 15-19.
movies: www.bio.davidson.edu/courses/genomics/arrays/astart.html

Functionalization

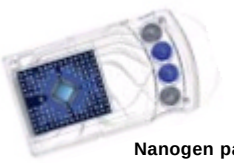
by electrophoresis driven movement of off-chip synthesized DNA receptor molecules to their on-chip target position (I)



Noble metal site with permeation layer to permit ion flow and to protect the DNA against damaging electrochemical reactions at the electrode.

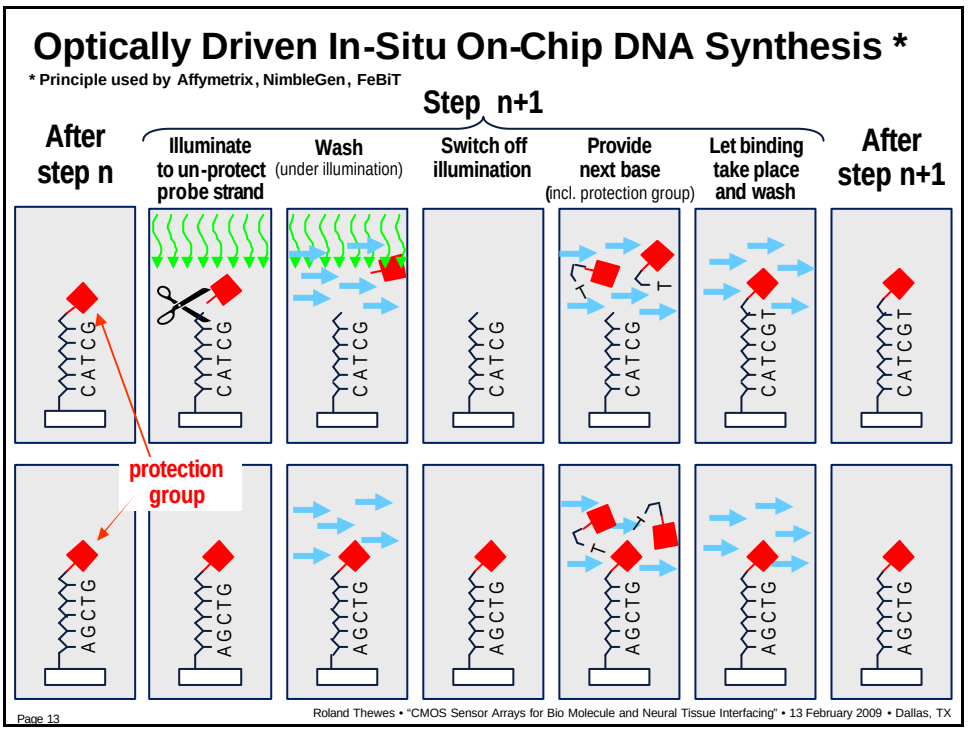


Sensor sites from a 20 x 20 Nanogen array using conventional optical readout.



Nanogen package

T. Sosnowski et al, Proc. Natl. acad. Sci. USA, 1997
M. Heller, IEEE Eng. Medicine and Biology Magazine, 1996


Optically Driven In-Situ On-Chip DNA Synthesis *
* Principle used by Affymetrix, NimbleGen, FeBiT
Step n+1
After step n
Illuminate to un-protect probe strand
Wash (under illumination)
Switch off illumination
Provide next base (incl. protection group)
Let binding take place and wash
After step n+1
protection group
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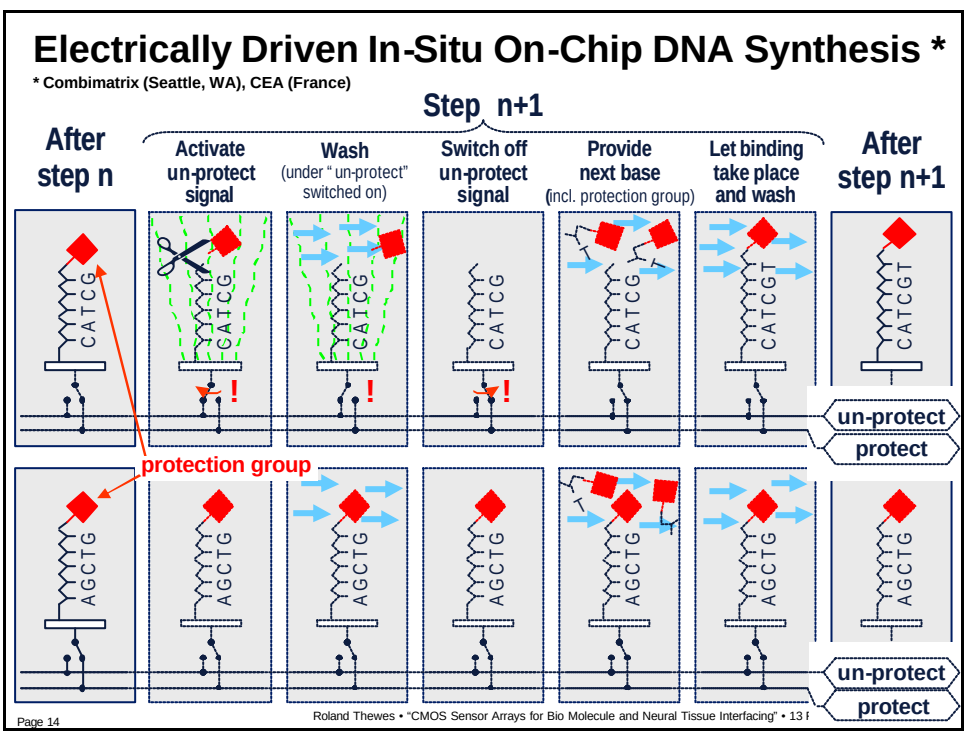
Electrically Driven In-Situ On-Chip DNA Synthesis *
* Combimatrix (Seattle, WA), CEA (France)
Step n+1
After step n
Activate un-protect signal
Wash (under "un-protect" switched on)
Switch off un-protect signal
Provide next base (incl. protection group)
Let binding take place and wash
After step n+1
un-protect
protect
protection group
un-protect
protect
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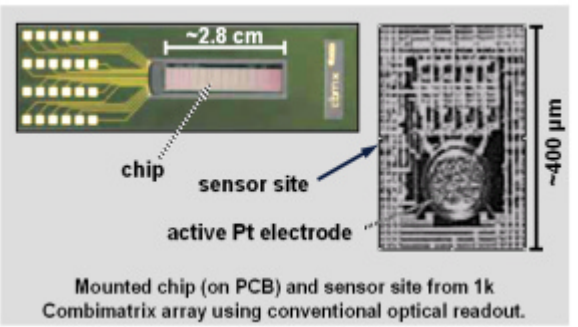
Commercially Available Platforms for In-Situ On-Chip DNA Synthesis

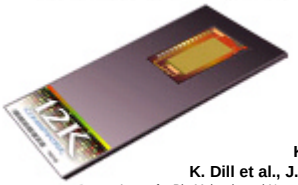
Affymetrix system:
optical synthesis / optical readout

Image courtesy of Affymetrix
www.affymetrix.com

Combimatrix system:
electrical synthesis / optical readout



Mounted chip (on PCB) and sensor site from 1k Combimatrix array using conventional optical readout.



Packaged 12k chip
Image courtesy of Combimatrix
www.combimatrix.com

K. Dill et al., Anal. Chim. Acta, 2001
K. Dill et al., J. Biochem. Biophys. Methods, 2004

CMOS Requirements For Electronically Driven Functionalization

- Chip must be chemically inert against applied fluidic samples and related compounds and withstand contact with "the wet world of biology"
- Introduction of noble metal electrodes / Extension of standard CMOS processes
- provision of *low-frequency* logic circuitry
- handling & switching of *large bias signals* to operate the electrodes

→ *relaxed requirements* concerning CMOS circuit design and CMOS process performance in case CMOS functionality is used for functionalization purposes only

→ requirements concerning *electrical readout* more challenging!

Outline

Extended CMOS Process Options

Required for Electronic DNA Microarrays

Frequently used approach:
CMOS + noble metal

+

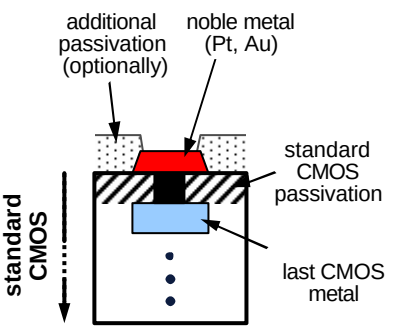
various application
specific extensions

+

various application
specific alternatives

+

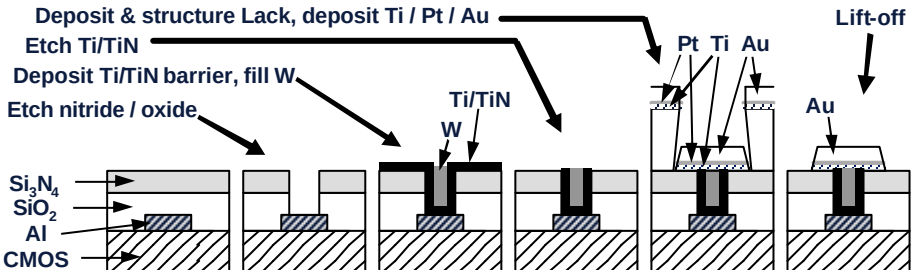
Flip-Chip solutions
with sensor chip + standard CMOS chip



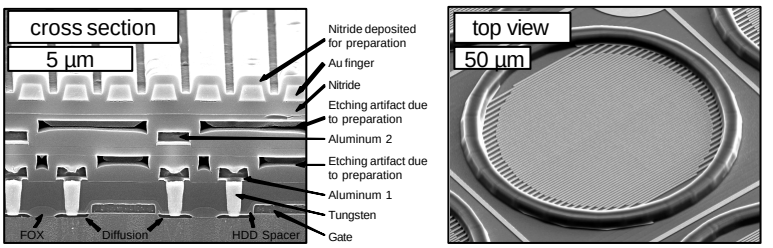
Extended CMOS Process Options

Example: Au on Standard 0.5µm, 6“ CMOS Process

Backend process flow:



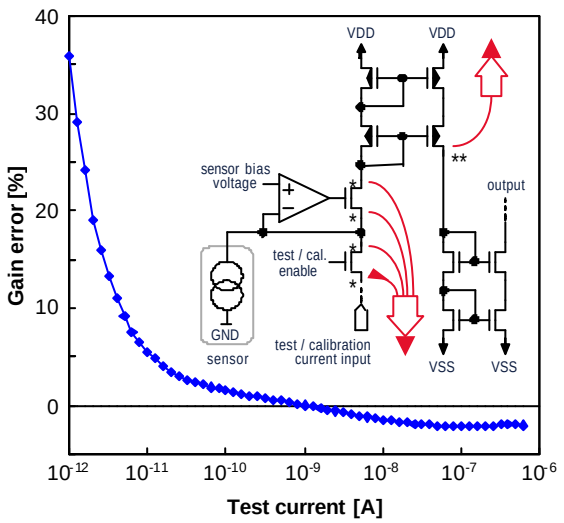
SEM photos:



F. Hofmann et al., IEDM 2002

Example CMOS + Au Processing

Device / Circuit Properties after Au Processing



Simple test circuit used for 100-fold current gain of sensor current with test input.

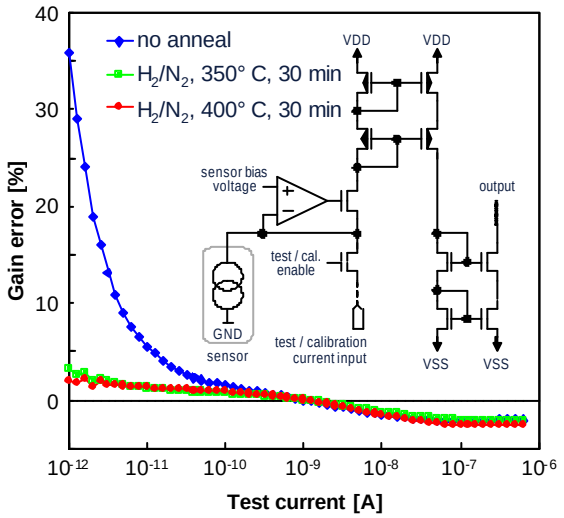
Specified sensor current:

10^{-12} A – 10^{-7} A

Insufficient behavior (high leakage currents) due to huge interface state density of > 10^{11} cm^{-2}

Example CMOS + Au Processing

Device / Circuit Properties after Au Processing + Extra Annealing Steps



imple test circuit used
r 100-fold current gain
f sensor current with
st input.

pecified sensor current:

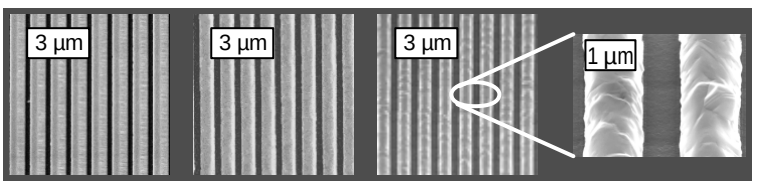
10^{-12} A – 10^{-7} A

Sufficient behavior after additional H_2/N_2 annealing step after Au processing

Definition of a Final Process Window

Considering frontend + backend parameters

	square resistance Au lines [mΩ/square]	resistance via holes (Al to Au) [mΩ]	square resistance Al 2 lines [mΩ/square]	interface state density [1/cm²]
CMOS only (i.e. without Au process)	-	-	-	~ 10^{10}
CMOS + Au process, no anneal	48	370	79	~ 2×10^{11}
CMOS + Au process, N_2/H_2 anneal with 350°C, 30 min	51	360	76	< 10^{10}
CMOS + Au process, N_2/H_2 anneal with 400°C, 30 min	61	340	74	< 2×10^9

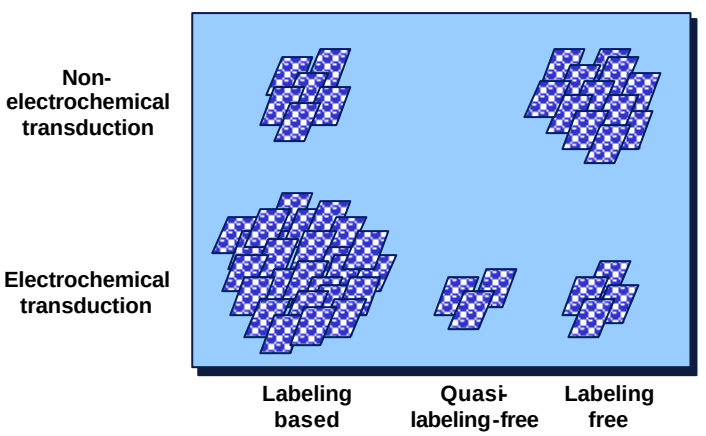


no annealing **350°C, 30 min** **400°C, 30 min** **F. Hofmann et al., IEDM 2002**

Outline

Overview

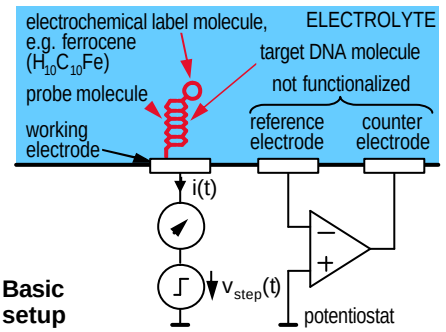
Classes of Electronic Bio Molecule Detection Techniques



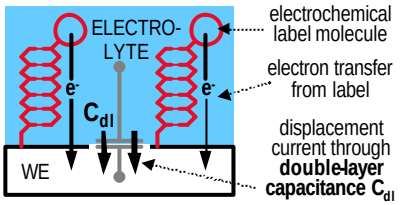
Estimated relative amount of chip- or CMOS-related publications.

Electrochemical Readout: Coulometry

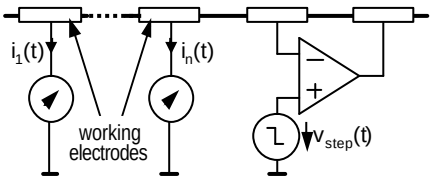
Three-Electrode-System



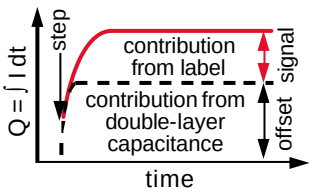
Basic setup



Voltage step leads to oxidation (or reduction) of the label if present at the considered test site



Alternative: step applied by potentiostat
→ in particular interesting for operation of arrays

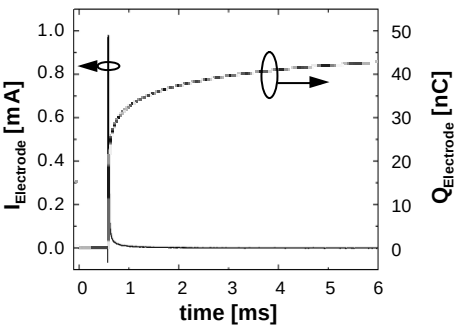


Result (schematic plot)

Coulometric Readout with Charge Evaluation

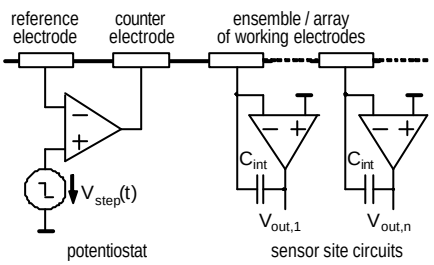
Typical signals

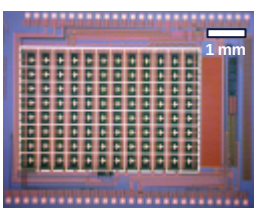
Example from large area electrode experiment
Signal magnitude:
Q_{total} / area ~ of order 10 nC / mm²



Straight-forward array design

Current integration within each sensor site

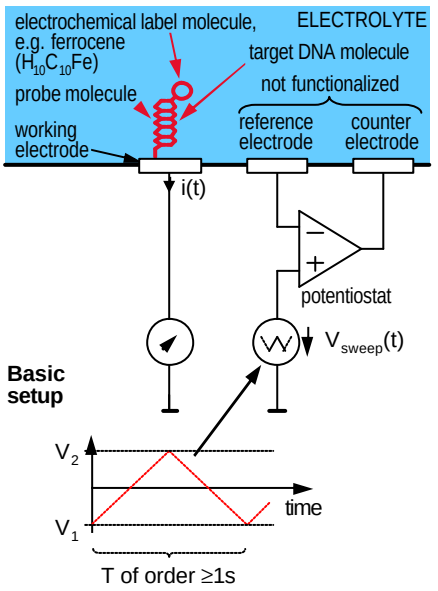




hardware realization in 3M 2P 0.5µm 5V CMOS + Au
M. Augustyniak et al., ISSCC 2006

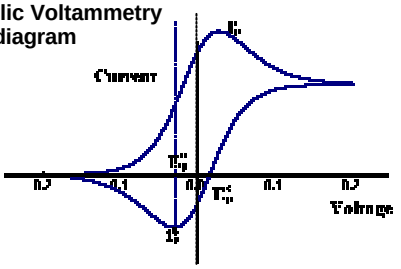
Electrochemical Readout: Cyclic Voltammetry

Three-Electrode-System



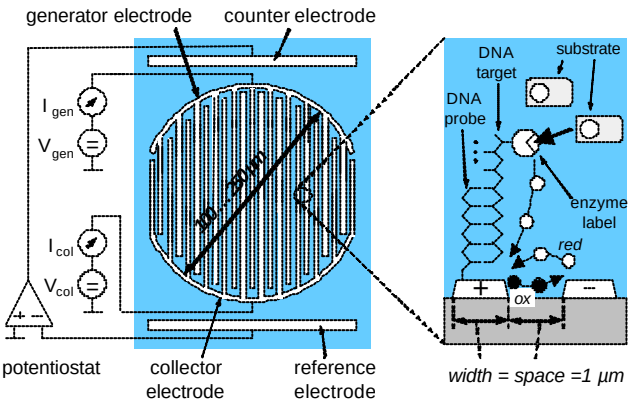
- Voltage is swept from V_1 to V_2 and back, so that a complete redox cycle is performed.
- Working electrode current is measured and
  - signal peak current
  - signal peak-to-peak current
  - area in between curves (∝ total charge) is evaluated.
- Note, that current depends on slew rate of potentiostat input voltage

Cyclic Voltammetry I-V diagram



Electrochemical Readout: Redox-Cycling

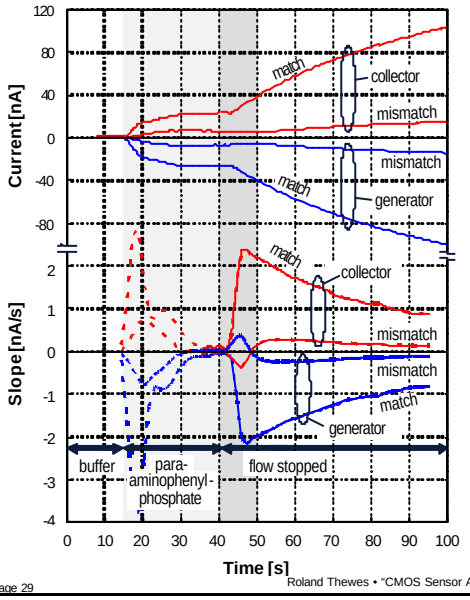
4-Electrode System with Interdigitated Working Electrodes



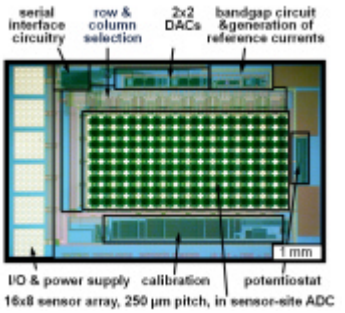
- Target DNA molecule labeled with enzyme molecule (not electrochemically active!)
- Application of an additional substrate, which is not electrochemically active in the provided form, but can be cleaved by the enzyme into electrochemically active sub-species
- Application of positive and negative voltages of order ±few 100 mV at neighboring electrodes starts redox-cycling (i.e. reduction and oxidation) process

Redox-Cycling

Typical signals



- Characterization time: **seconds**
- Evaluated signal: **¶ current / ¶ time**
  (reason: absolute current value may also consist of time-independent artifact)
- Required resolution: **1 pA ... 100 nA**
  (under assumptions:
  - sensor diameter of order 200 µm
  - electrode width and spacing ~ 1 µm
  - suitable for wide range of applications)

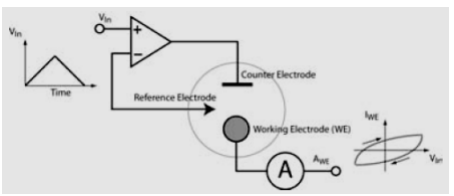


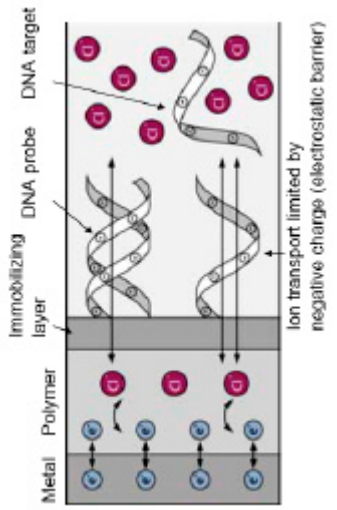
3M 2P 0.5 µm 5 V CMOS + Au
A. Frey et al., ISCAS 2005

Labeling-Free Electrochemical Readout
Example: Electropolymer Redox Reaction

Principle:

- cyclic voltammetry (3 electrode system) applied to oxidize and reduce an electropolymer (polypyrrole) covering the working electrode
- Hybridization hinders movement of the chloride counter ions and thus decreases the measured redox currents and related shapes of the cyclic voltammetry curves



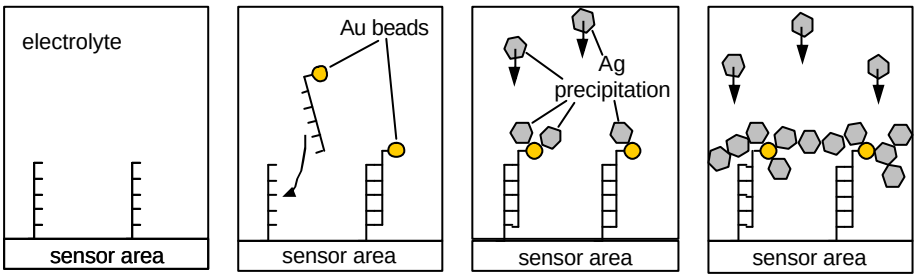


F. Heer et al., ISSCC 2008

Labeling-Based Non-Electrochemical Readout

Example: Gold Bead Labeling + Silver Precipitation

Basis principle:



sensor with probe molecules

hybridization phase: target molecules labeled with Au beads

application of Ag, Au beads form seed layer to bind Ag

formation of Ag layer under continuous Ag provision

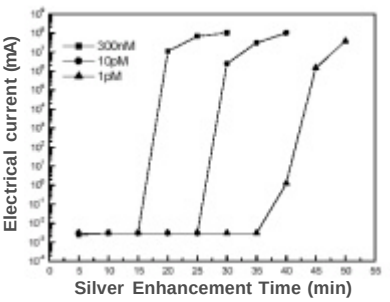
Hybridization-to-electrical signal transduction:

- Conductivity measurement between electrodes separated by isolating layer
- Impedance (or RF parameter) measurement between isolated electrodes
- Optical attenuation (detected by CMOS imager chip)

Au Bead Labeling + Ag Precipitation: Signal Generation

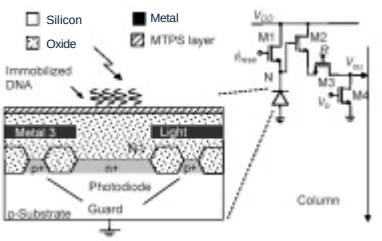
Conductivity readout

- probe molecules are immobilized on isolating layer between electrodes
- conductive Ag layer leads to a sharp decrease of ohmic resistance between the electrodes
- discrimination " match" / "mismatch" positions requires to consider temporal development



Optical attenuation

- Recent publications from the same group use optical attenuation
  → for that purpose a CMOS camera chip is used
- Other groups use pure optical setups

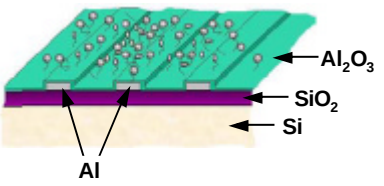


M. Xue et al., IEDM, 2002 (and ISSCC, 2003) (top)
J. Li et al., IEDM 2004 (bottom)

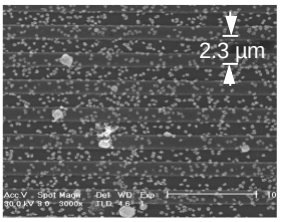
Readout Techniques: Au Bead Labeling + Ag Precipitation

Impedance readout

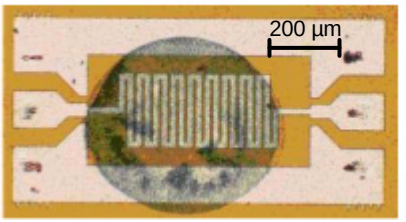
- probe molecules are immobilized on an isolating layer above capacitors with interdigitated electrodes, coil structures, meanders, ...
- conductive Ag layer leads to a change of impedance / RF parameters of the electrical device
- discrimination " match" / "mismatch" requires to consider temporal development



Schematic cross-section



Electrodes covered by silver grains after biological process



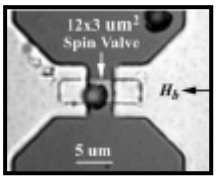
Spotted meander inductor structure

G. Laurent et al., ESSDERC 2003
L. Moreno-Hagelsieb, ESSDERC 2006

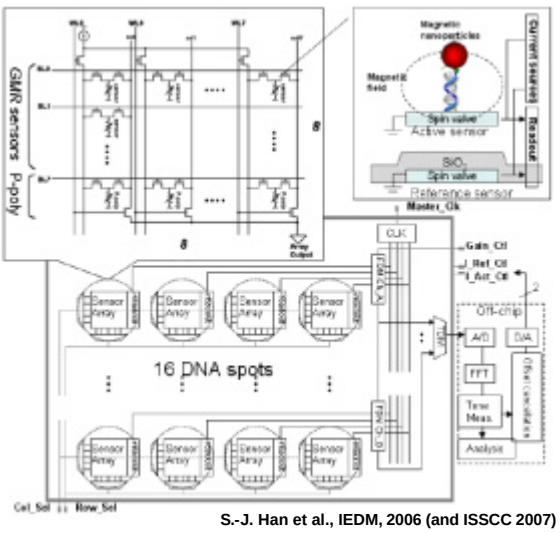
Further Readout Techniques / Labeling-Based Approaches

Magnetic Bead Labeling

- target DNA molecule are labeled with magnetic nano-particles
- after hybridization, magnetic properties are evaluated at the respective sites (e.g. using GMR sensors)
- today: most proof-of-principles done on post-processed PCBs and other substrates; very recently CMOS integration published

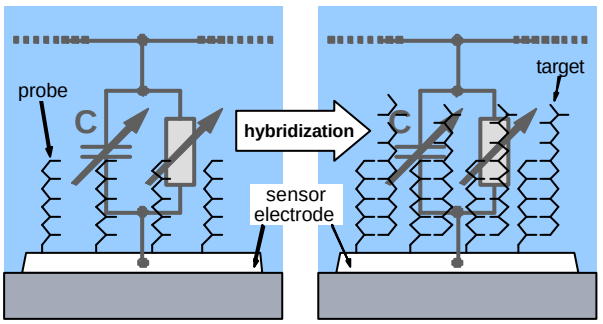


G. Li et al., J. Appl. Physics, 2003



S.-J. Han et al., IEDM, 2006 (and ISSCC 2007)

Labeling-Free Approaches
Impedance Method



Basic principle

C: parameter of interest

R: artifact dependent

⇩

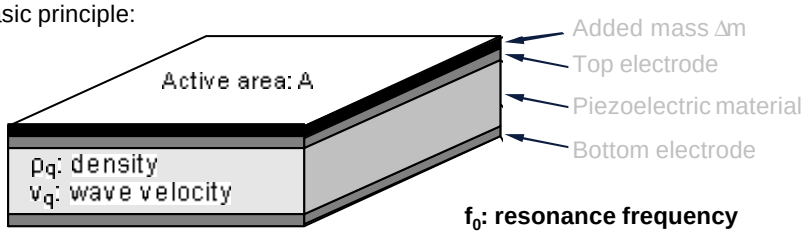
Phase sensitive characterization required to detect the biological information

(Literature: Different electrode arrangements / layouts in use)

- C, R, ΔC, ΔR depend on the quality of the layer of probe molecules (method is sensitive to pinholes in that layer)
- Literature reveals a number of proof-of-principles, but a consistent picture has not yet been achieved (data prone to measurement artifacts?)
- Active CMOS has the potential to avoid measurement artifacts due to signal processing close to the sensor and may thus help to evaluate the method

Labeling-Free Non-Electrochemical Readout
Example: Gravimetric Sensors (FBAR)

- Mass sensitive sensors (as considered here) are mechanical / electrical oscillating systems.
- Mass changes at the sensor surface change the oscillation frequency.
- Basic principle:



f_0: resonance frequency

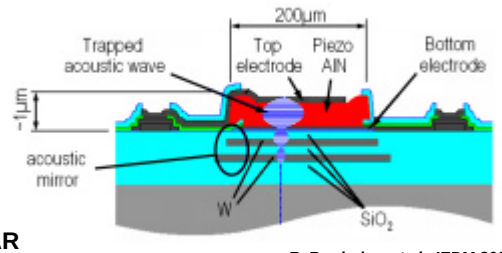
- Change of resonance frequency in air (Sauerbrey equation): $\frac{\Delta f}{f} = -\frac{2f_0}{Ar_q v_q} \times \Delta m$
  - → high sensitivity requires high f_0
  - → thin-film piezoelectric layers resonating in the GHz range are superior compared to conventional quartz-based sensors operating in the MHz...tens of MHz range
- Mechanical attenuation:
  quality factor in liquids (water) is significantly lower as in gases (air) **!**

Gravimetric Sensors

Film Bulk Acoustic Wave Resonator (FBAR)

Basic FBAR Technology

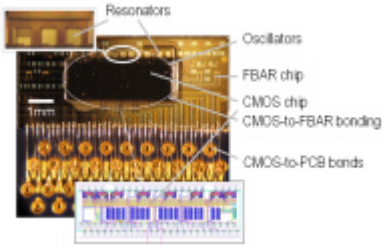
- Si substrate
- AlN used as piezoelectric
- acoustic mirror realized by buried W layers
- ?m deposited on top electrode

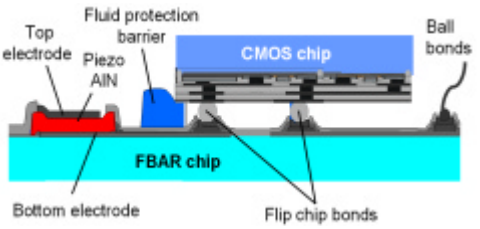


R. Brederlow et al., IEDM 2003

Flip-Chip Bonding CMOS-to-FBAR

Face-to-face flip chip bonding of 0.13 µm standard CMOS and FBAR chip
→ short interconnects between oscillator circuit and resonator



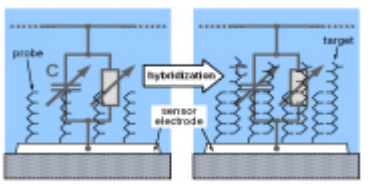


M. Augustyniak et al., ISSCC 2007

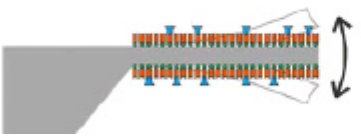
Further Detection Techniques

Demonstrated on Extended CMOS Chips

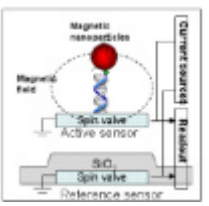
- **Impedance (Capacitance) Spectroscopy:**
  - Idea: Hybridization driven capacitance decrease between electrode and electrolyte
  - Implementation on CMOS:
    e.g. C. Stagni et al., Univ. Bologna, ISSCC 2006



- **Other Gravimetric Approaches:**
  (as compared to Bulk-Acoustic-Wave approaches)
  - Example: Mass increase driven decrease of cantilever oscillation frequency
  - System implementation on CMOS:
    K.-U. Kirstein et al., ETH Zurich, DATE 2005



- **Magnetic Bead Labeling:**
  - GMR-based detection
  - CMOS implementatio: S.-J. Han et al., UC Berkeley, IEDM, 2006 (and ISSCC 2007)

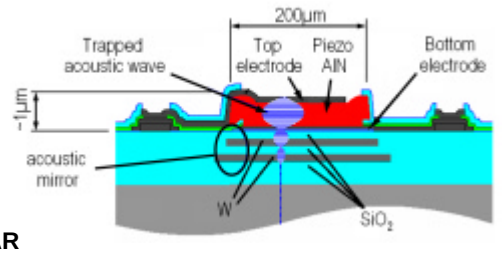


- **...**

Gravimetric Sensors
Example: Film Bulk Acoustic Wave Resonator (FBAR)

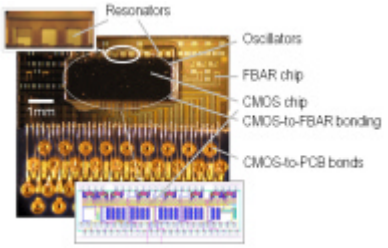
Basic FBAR Technology

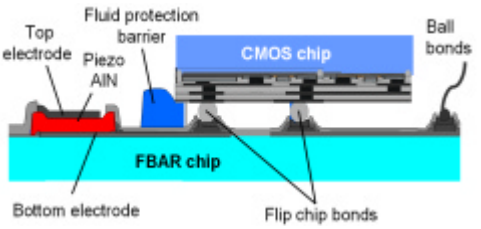
- Si substrate
- AlN used as piezoelectric
- acoustic mirror realized by buried W layers
- ?m deposited on top electrode



Flip-Chip Bonding CMOS-to-FBAR

Face-to-face flip chip bonding of 0.13 µm standard CMOS and FBAR chip
→ short interconnects between oscillator circuit and resonator



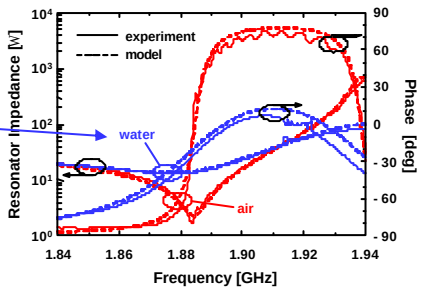


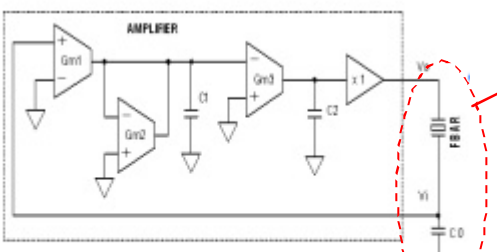
M. Augustyniak et al., ISSCC 2007

Gravimetric Sensors
FBAR - Oscillator Design

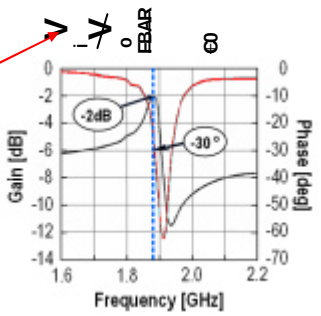
Challenge:
low Q-factor in water

Requirement:
precise gain / phase relationship (+5dB / 330°) at resonance frequency (1.86GHz)





$$\frac{V_o}{V_{in}} = -\frac{Gm1}{Gm2} \Big/ \left[\left(1+\frac{sC1}{Gm2}\right)\times\frac{sC2}{Gm3}\right]$$



M. Augustyniak et al., ISSCC 2007

Outline

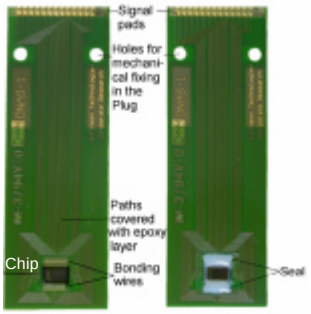
Packaging / Assembly Aspects

- Packaged electronic biochips require a fluidic and an electrical interface. Interfacing effort in case of optical biochips (fluidic + optical interface) is not higher!
- Electronic biochips: Cheap and reliable packaging solution required.
- Requirements concerning in-package (micro-) fluidics:
  - laminar flow
  - bubbles must be avoided (or trapped at predefined positions within package)
  - detailed requirement catalogue depends on detection method / assay / application

Insufficient packaging / micro-fluidic solutions may significantly deteriorate the performance of the entire system.

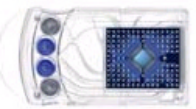
Chip Assembly

Examples: Published Assembly and Packaging Approaches

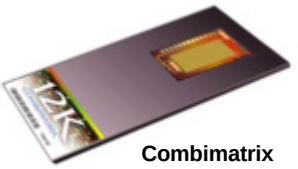


Infineon (until 2005)

- "open system"
- simple fluidic interface
- PCB-based electrical interface



Nanogen



Combimatrix

- fluidic interface with in-package microfluidics
- electrical interface with in-card electrical interconnects

Siemens (under development)

- fluidic + electric interface with in-package microfluidics and in-card el. interconnects
- in-card stored bio-chemical compounds

Complexity

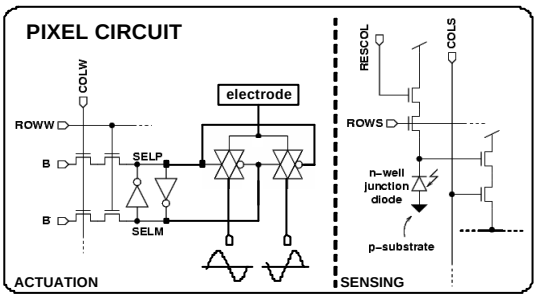
Outline

CMOS Chips for Cell Manipulation and Cell Sorting

Use of Dielectrophoretic Cages (I)

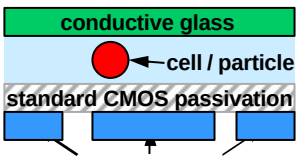
Goal: Highly parallel, individual, non-invasive cell manipulation

Applications:
- cell counting (→ blood analyses)
- individual cell isolation (→ biopsies)
- cell-to-cell interactions (→ immune response studies)
- compound delivery into cells (→ drug development)
- tissue assembly
- ...



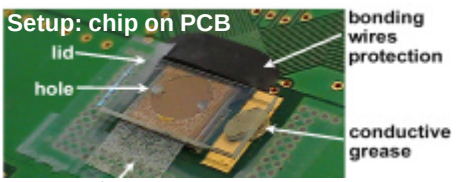
N. Manaresi et al., JSSC, 2003

Approach: CMOS chip to
- control AC voltages applied to electrodes (isolated from electrolyte), wich generate – together with a conductive lid of the microchamber – the required dielectrophoretic forces
- monitor the positions of the cells using photodiodes or capacitive sensing

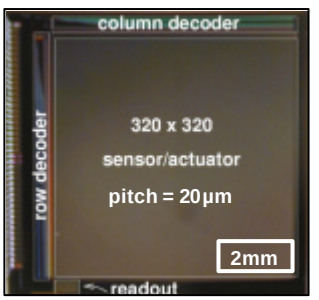


CMOS Chips for Cell Manipulation and Cell Sorting

Use of Dielectrophoretic Cages (II)



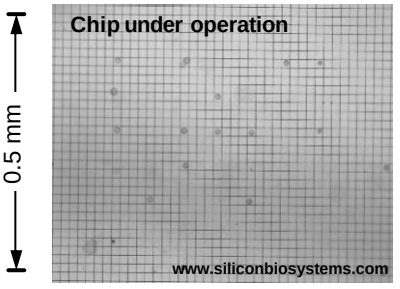
A. Romani, ISSCC 2004



3M 2P *standard* 0.35 µm CMOS

chip area	~64mm2
array size	320 x 320
pitch	20µm
microchamber - height - volume	 85...100µm <3.5...5µm
# of DEP cages	up to ~11000
VDD	3.3V
actuation - voltages - frequency	 3.3V (ext. applied) 100kHz – 10MHz
Clk frequency	20MHz

Summary specifications (opt. and cap. sensing chip)



Outline

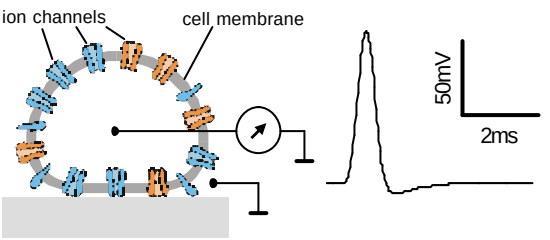
Nerve Cell and Neural Tissue Interfacing

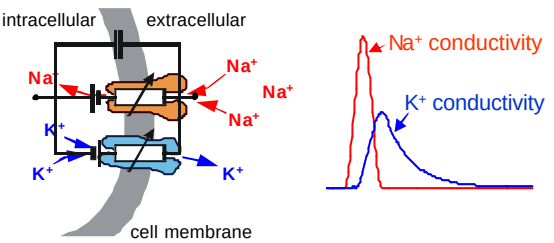
Nerve Cells

Goal:
Measurement of action potentials

Action potentials:
- are elementary neural signals
- are transient changes of the transmembrane voltage
- correspond to sodium and potassium ion currents through ion channels in the cell membrane.

Further remarks:
- typical cell diameters: 10...100µm
- steady-state potential of the transmembrane voltage also depends on amount of further ions such as Cl^-, Ca^{++}, ..., and on further mechanisms.

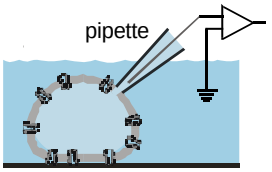




Nerve Cell and Neural Tissue Interfacing

Intracellular / Invasive Recording

Patch-Clamping



Setup

Micropipette manipulator

- Direct contact to intracellular space
- Gold standard in electrophysiology
- Used to characterize gating characteristics of ion channels
- Different patch techniques in use
- Different configurations in use

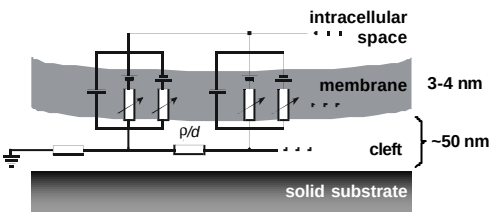
- Low throughput
- Time expensive
- Trained staff required
- Stable mechanical support obligatory
- **Not capable for multi-site recording** **!**

Nerve Cell and Neural Tissue Interfacing

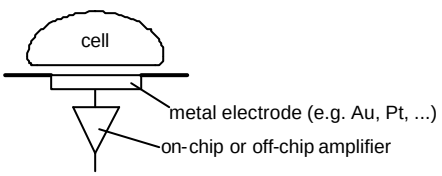
Extracellular Non-Invasive Recording

Principle of extracellular recording:

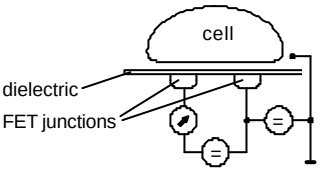
Ion currents flowing through cleft between cell and surface of solid state substrate lead to transient changes of cleft voltage with respect to electrolyte bulk potential



Cleft voltage monitoring techniques:



Noble metal electrode-to-electrolyte contact:
- contact via Helmholtz layer
- non- homogeneous surface



Electrolyte-Oxide-Semiconductor-FET (EOSFET):
- cleft voltage modulates OSFET current
- homogeneous (dielectric) surface

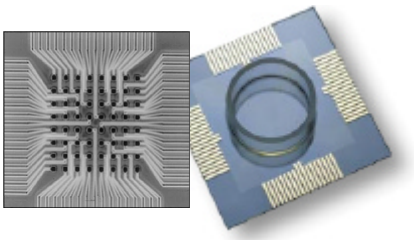
Typical peak-to-peak cleft voltages: 100µV – 5mV

Nerve Cell and Neural Tissue Interfacing

Non-CMOS Approaches

Passive Multi Electrode Arrays (MEAs) with Metal Electrodes:

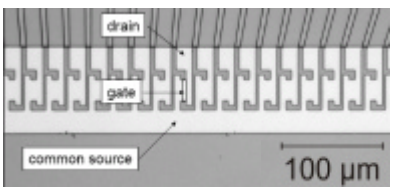
- no active electronic devices on chip
- commercially available
- transparent substrates
- simultaneous sensing and stimulation
- approximately 60 test sites per array
- pitch of order 200µm
- further increase of # of sites / of site density limited by interconnect restrictions



Alpha MED Sciences Co., Ltd., www.med64.com (subsidiary of Matsushita Electric Industrial Co., Ltd.)

EOSFETs:

- many proof-of-principles using metal-free processes (i.e. entire wiring in diffusion layer)
- simultaneous sensing and stimulation demonstrated
- 1D pitch of order few µm
- further increase of # of sites / of site density in 2D arrangements limited by interconnect restrictions



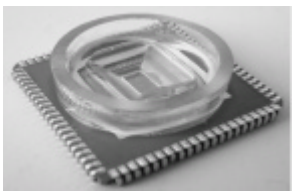
P. Fromherz, ISSCC 2005

Outline

Nerve Cell and Neural Tissue Interfacing

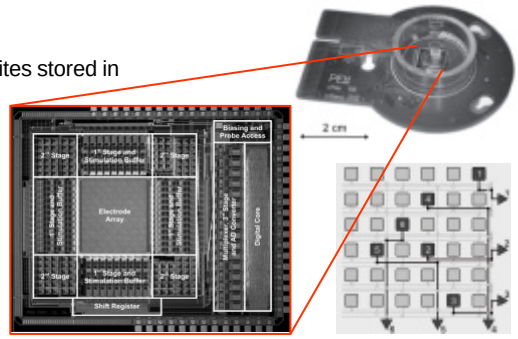
CMOS MEAs with Nobel Metal Electrodes on CMOS

- 16×8 electrodes, pitch: 250µm
- 3M 2P 5V 0.6µm CMOS process + 2 mask postprocessing
- Each site with integrated bandpass
- Simultaneous sensing and stimulation
- Fully digital chip interface, USB 2.0 system interface



F. Heer et al., ESSCIRC 2005

- 11k selectable sites, 126 channels (dedicated routing algorithm, selected sites stored in on-chip SRAM)
- 2.0×1.7 mm² array, pitch = 56µm
- 3M 2P 5V 0.6µm CMOS process extended by Pt electrodes
- Sensing + stimulation capability
- User-friendly system integration

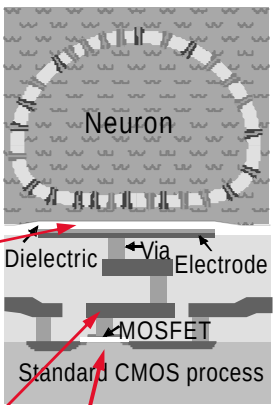


U. Frey et al., ISSCC 2007

Nerve Cell and Neural Tissue Interfacing

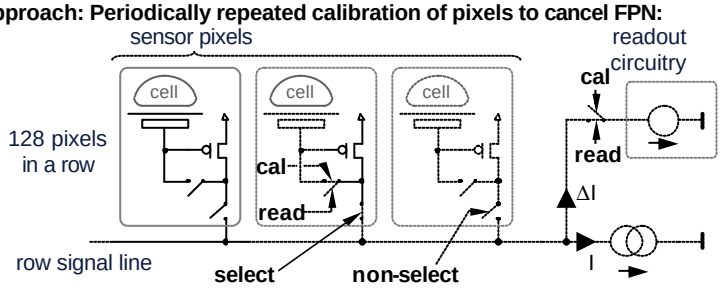
High-Density 2D Imaging

- **Goal:**
  Pitch of order 10µm or below, total sensor area 1mm²
- **Approach:**
  Extended EOSFET sensing
- **Challenges:**
  1. Sensor dielectric
     - high k / low thickness (e_r = 20…80, $t \approx$ 50 nm)
     - non-toxic, biocompatible
     - CMOS compatible
     - leak-proof
     - processed at T = 400° C
  2. Floating node realization impossible: operating point of sensor transistor prone to large uncontrollable processing-induced charging effects!
  3. Fixed pattern noise (FPN) resulting from sensor transistor $\sigma(V_t)$ >> signals to be detected

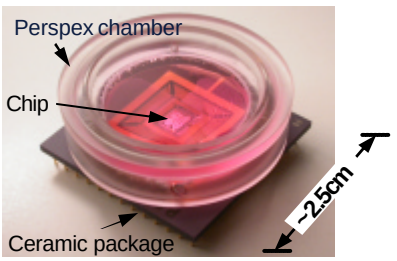


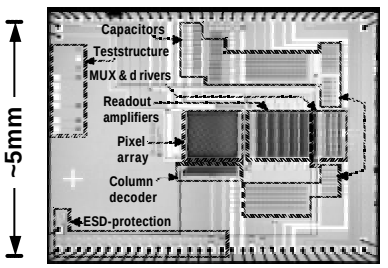
High-Density 2D Neural Tissue Imaging CMOS Chip

Design approach: Periodically repeated calibration of pixels to cancel FPN:



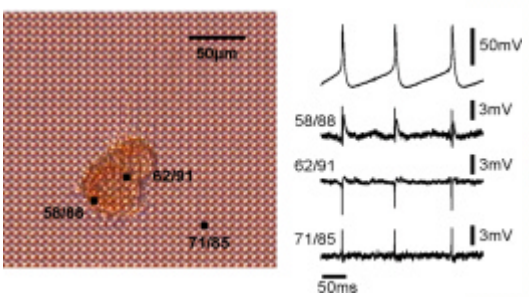
CMOS imager chip for extracellular monitoring of neural tissue w ith 16k Pixels on 1mm²:

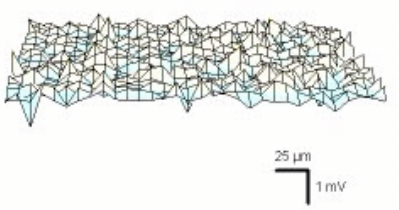




B. Eversmann et al., JSSC, 2004

Dynamic Imaging of Single Cells*



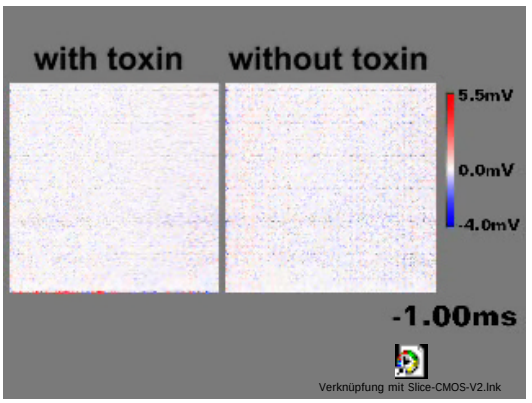


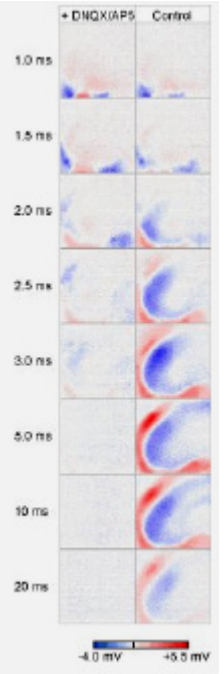
7600 frames per second

41 ms

* Max-Planck-Institute for Biochemistry , Martinsried

Cell-based Secondary Drug Screening
First Results





Cultured rat hippocampal slice measured with 16 k pixel neural imager chip. Recording area 1 mm x 1 mm.

Left column:
slice perfused with recording medium containing DNQX and AP5.
Right column: slice perfused with normal recording medium.

http://mnphys.biochem.mpg.de/mnphys/publications/06hutlameve/abstract.html

Outline

Summary

CMOS chips for in-vitro biotechnology applications - related to bio molecules as well as to nerve cells and neural tissue - have proven feasibility.

For such purposes, CMOS usually requires process extensions which must not deteriorate CMOS frontend properties.

Required/used CMOS minimum feature sizes are between 100 nm and 1 µm.

From the user's point of view the entire system (including packaging, storage, microfluidics, software, ...) must be considered.

The full potential of CMOS-based biosensor arrays is still under development as well as appropriate business models.

Thank you