Fundamentals of Biosensors and Electronic Biochips. EE515 EPFL Master

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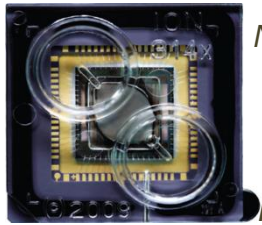
Bioanalytics. Key issues 1/2

Continuous demand for **higher throughput**

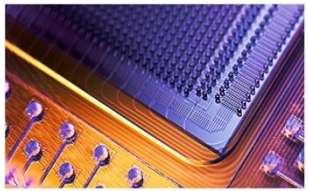
Large number of sequences to be read
Eg DNA/RNA sequencing



Next generation sequencing

Ion Proton, Life Technologies

Extreme parcellization of samples
Eg Digital PCR



Digital PCR

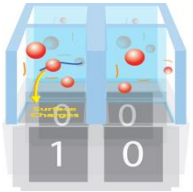
Fluidigm

In-flow manipulation of biological elements
Eg Cell separation, droplet formation

Bioanalytics. Key issues 2/2

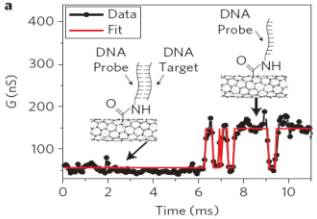
Targeting ultimate **sensitivity/resolution** in analytical samples

Single-copy detection in nanoliter wells
Eg: Digital PCR



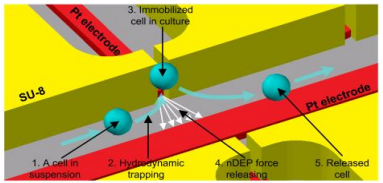
C. Guiducci, et al.
Nature Methods

Single-molecule kinetics observation
Eg: DNA hybridization on a nanodevice



Sorgenfrei et al.,
Nature Nanotechnology

Precise manipulation and measurement of single cells
Eg: Single-cell level analysis



A. Hierlemann, ETH,
Lab on a Chip

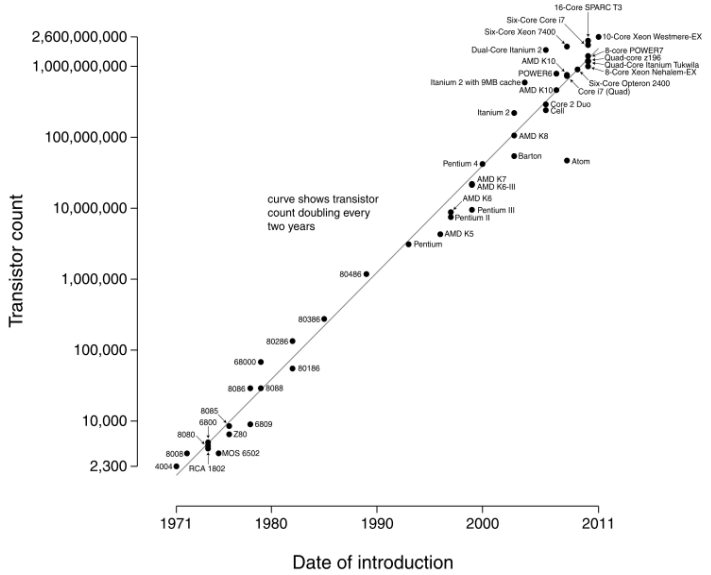
Drivers for the development of Biosensors and electronic biochips

- Multi-target/screening systems
- Sensitivity and robustness to interfering agents
- Miniaturization and adapted packaging for wearable and portable applications

Integration and complexity from electronic chips to biochips

Genesis. Electronic chips

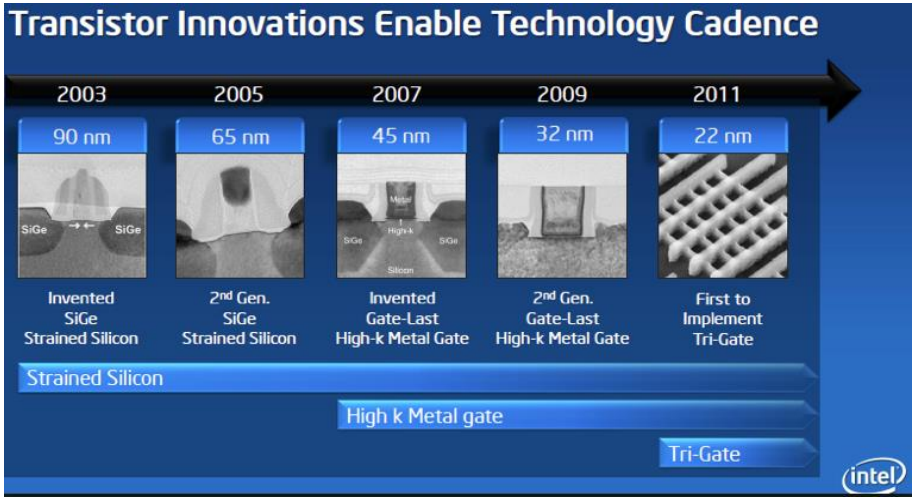
- Gordon E. Moore. “Cramming more components onto integrated circuits“. Electronics, 1965

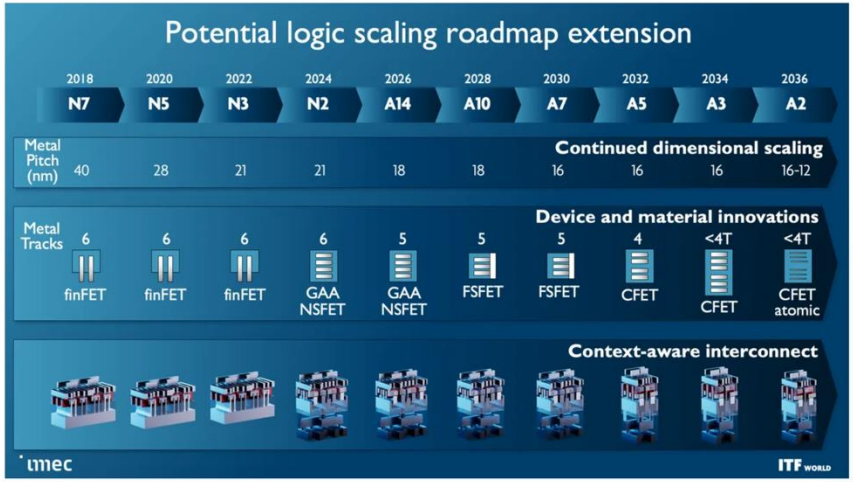


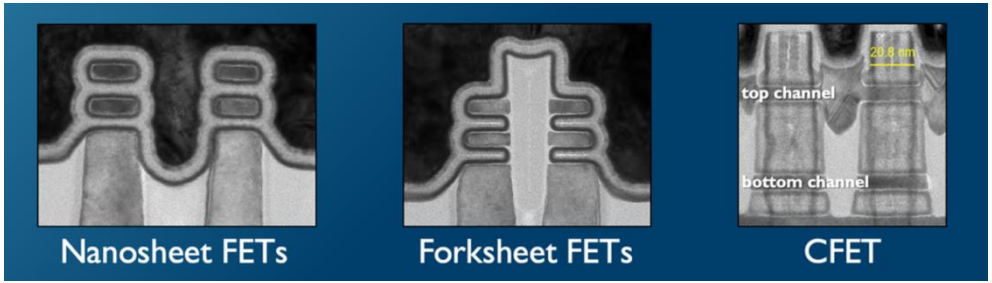
The Moore’s law is a prediction on Complexity (number of transistors per IC), foreseeing it would have increased of a factor of 2 approx. every 18 months.

1950, first planar transistor

Scaling


Transistor Innovations Enable Technology Cadence
2003
2005
2007
2009
2011
90 nm
65 nm
45 nm
32 nm
22 nm
SiGe
SiGe
Metal
High-k
SiGe
SiGe
Silicon
Invented SiGe Strained Silicon
2nd Gen. SiGe Strained Silicon
Invented Gate-Last High-k Metal Gate
2nd Gen. Gate-Last High-k Metal Gate
First to Implement Tri-Gate
Strained Silicon
High k Metal gate
Tri-Gate
intel

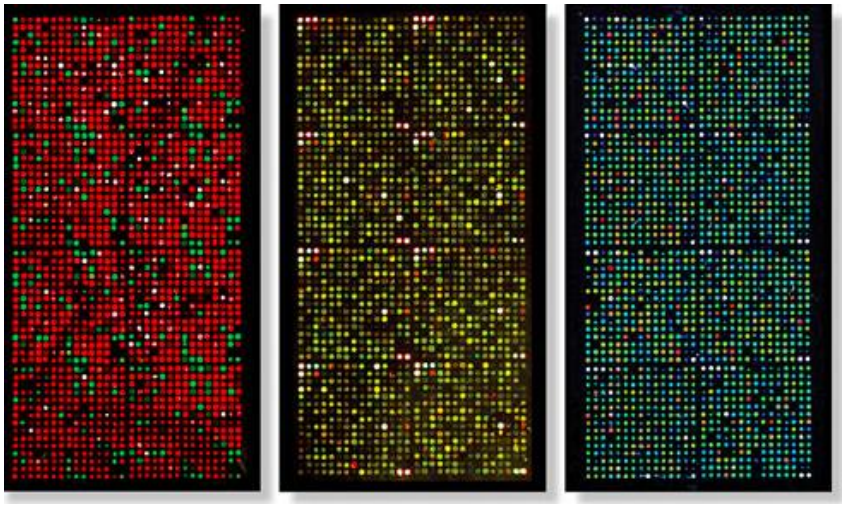

Potential logic scaling roadmap extension
2018 2020 2022 2024 2026 2028 2030 2032 2034 2036
N7 N5 N3 N2 A14 A10 A7 A5 A3 A2
Metal Pitch (nm)
40 28 21 21 18 18 16 16 16 16-12
Continued dimensional scaling
Metal Tracks
6 6 6 6 5 5 5 4 <4T <4T
finFET finFET finFET GAA NSFET GAA NSFET FSFET FSFET CFET CFET CFET atomic
Device and material innovations
Context-aware interconnect
imec
ITF WORLD


20.8 nm
top channel
bottom channel
Nanosheet FETs
Forksheet FETs
CFET

Advantages of increasing integration/complexity in electronics

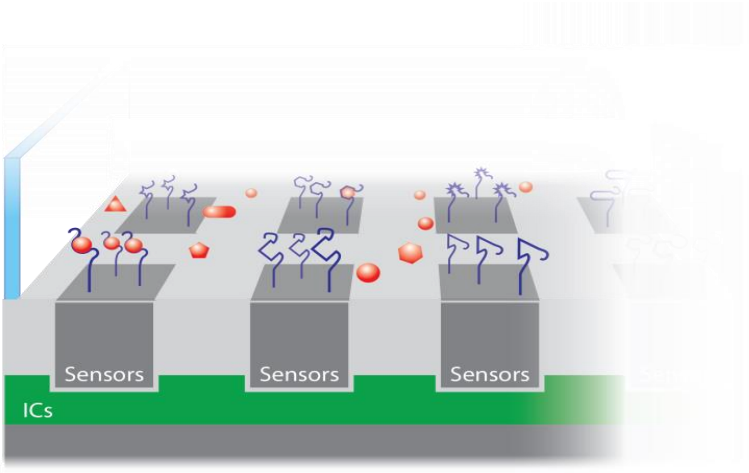
1. Improving complexity through integration by keeping costs steady
2. Reducing **size** of transducer without scaling the **signal**
3. **Integration** grants lower **noise and parasitics**

Complexity in biochips



DNA microarrays on glass or silicon substrates.

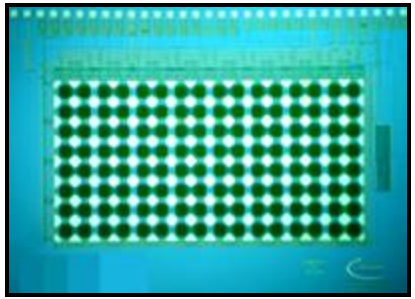
External readout systems (optical)



Molecular affinity arrays on sensing arrays

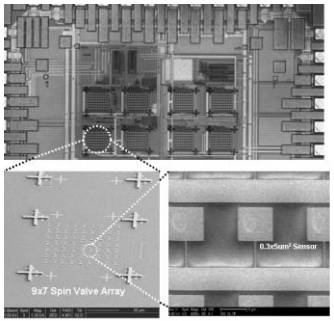
Integrated readout systems

Examples of Molecular affinity arrays on sensing arrays



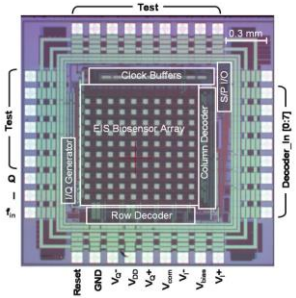
Infineon Technologies

CAPACITIVE



Stanford U.

MAGNETIC



Austin U

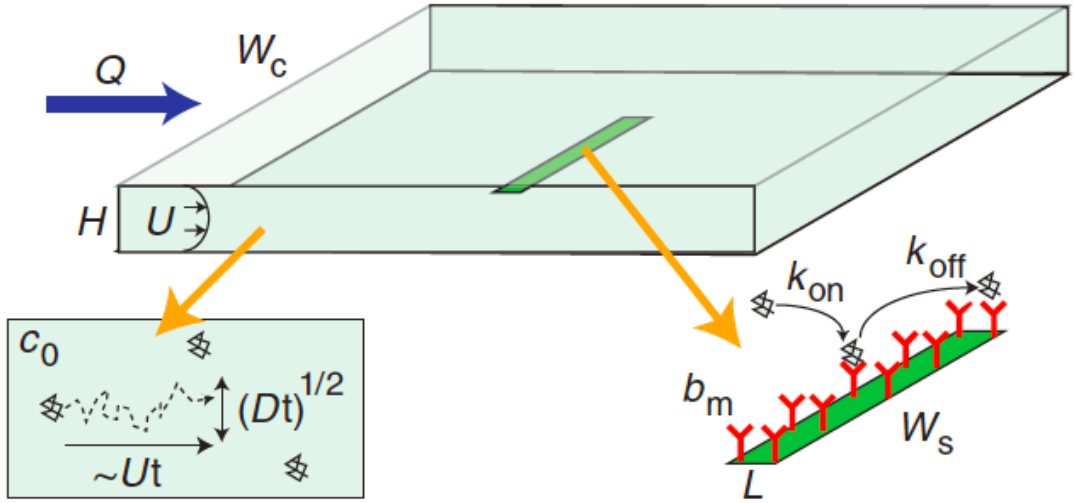
ELECTROCHEMICAL

ELECTROCHEMICAL

i-Stat. Abbott

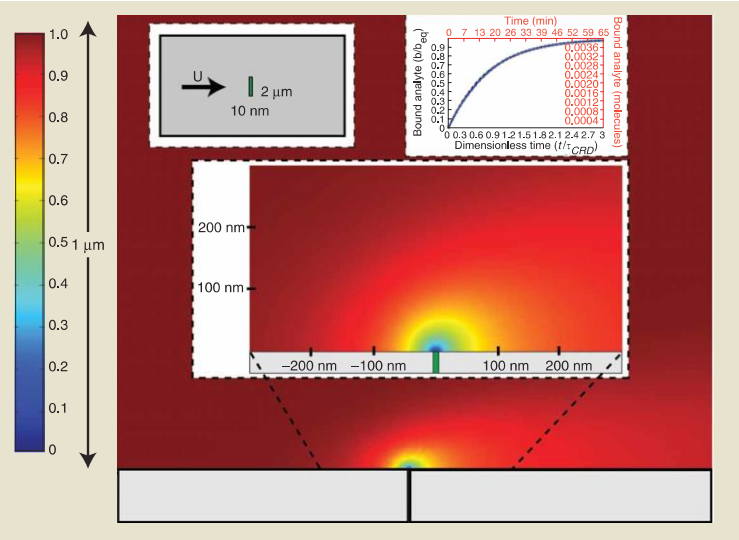
Biochips. Discussion on the Intrinsic limitations to complexity

Surface sensor, in flow injection of sample.
Role of the sensor surface size



Squires T.M. et al, Nat.Biotech. 2008

Surface sensor, in flow injection of sample.
Role of the sensor surface size



Collection rate: $J_D = D\ C\ W_S\ L/\delta$

$1/J_D \approx 208$ min

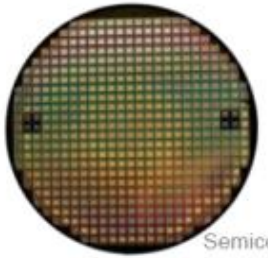
$1/k_{off} \approx 17$ min !!!

Collection is a rare event!

D diffusion constant 10 $\mu m^2/s$
C concentration 10 fM
W_s width of sensor 2 µm
L length of sensor 10 nm
δ depletion region
J_D collection rate 8×10^{-5} s

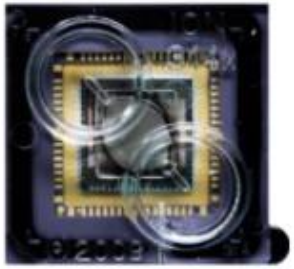
Mass transport issue!

DNA sequencing: large-scale pH-based systems. Overcoming mass transport issues



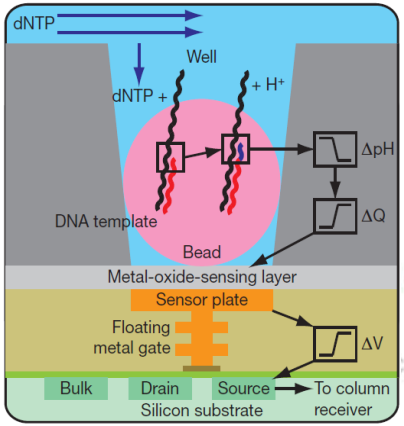
Wafer

Semiconductor Manufacturing



Chip

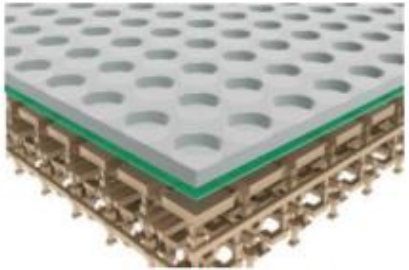
Semiconductor Packaging



TCGTACC...

Single Sensor

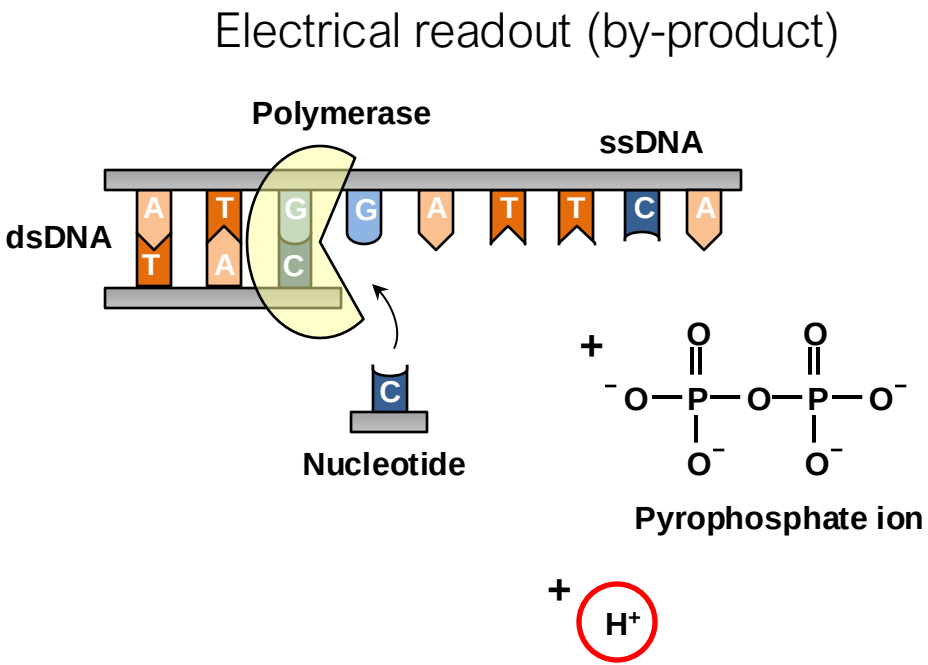
Chemical to Digital Sequence



Millions of Sensors

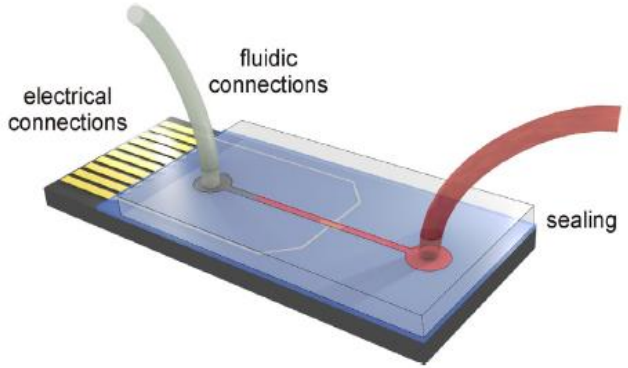
Semiconductor Design

Biochemical Readout of strand elongation

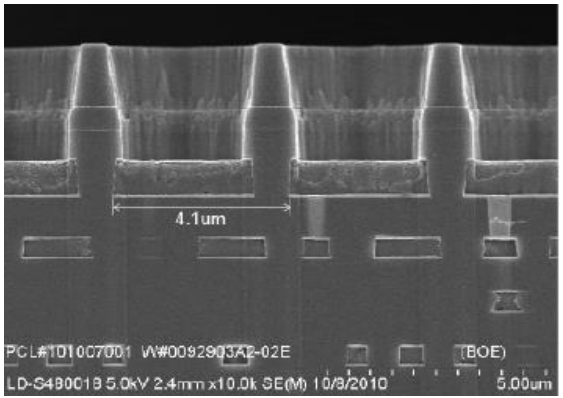


Translation of lab-on-chip technologies. Cost drivers

interfacing, robustness and user friendliness



Increased costs when deviating from standard microfabrication processes



Ion Torrent

System configuration and Sample manipulation strategies

Example: Impedance-based cytometry

Multiple wells

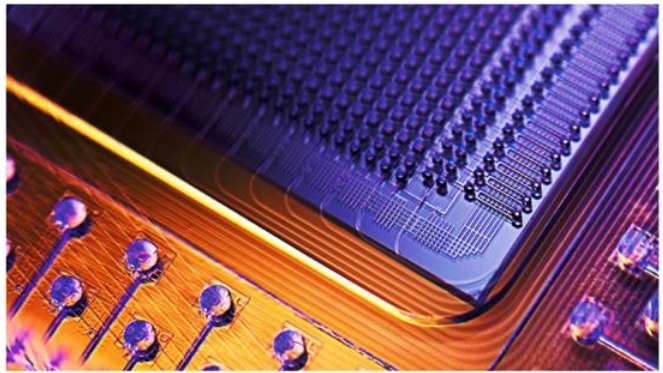
xCelligence

Flow cytometry, single cells through a channel

Fluigent

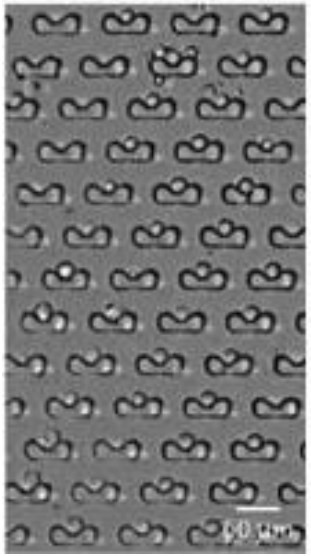
Sample isolation/parcellization

Sample parcellization down to nliter volume per chamber.
Issues of
-evaporation
- complex microfluidics



FLUIDIGM Quake lab

Cell isolation in flow.
Challenges to retrieve single cells



Hydrodynamic traps