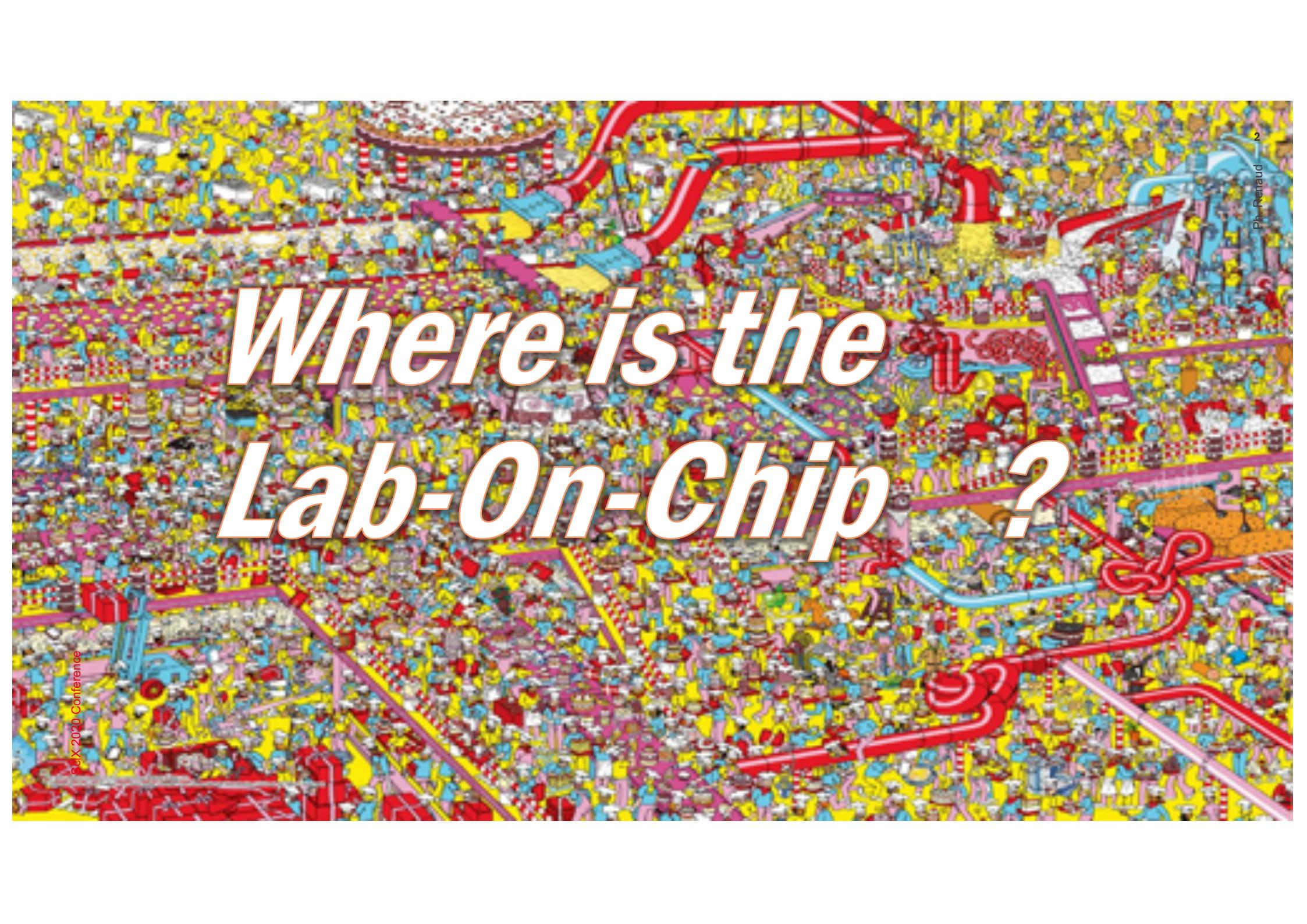


## Outline:

- History
- Some example
- Sample question

# *Where is the Lab-On-Chip ?*

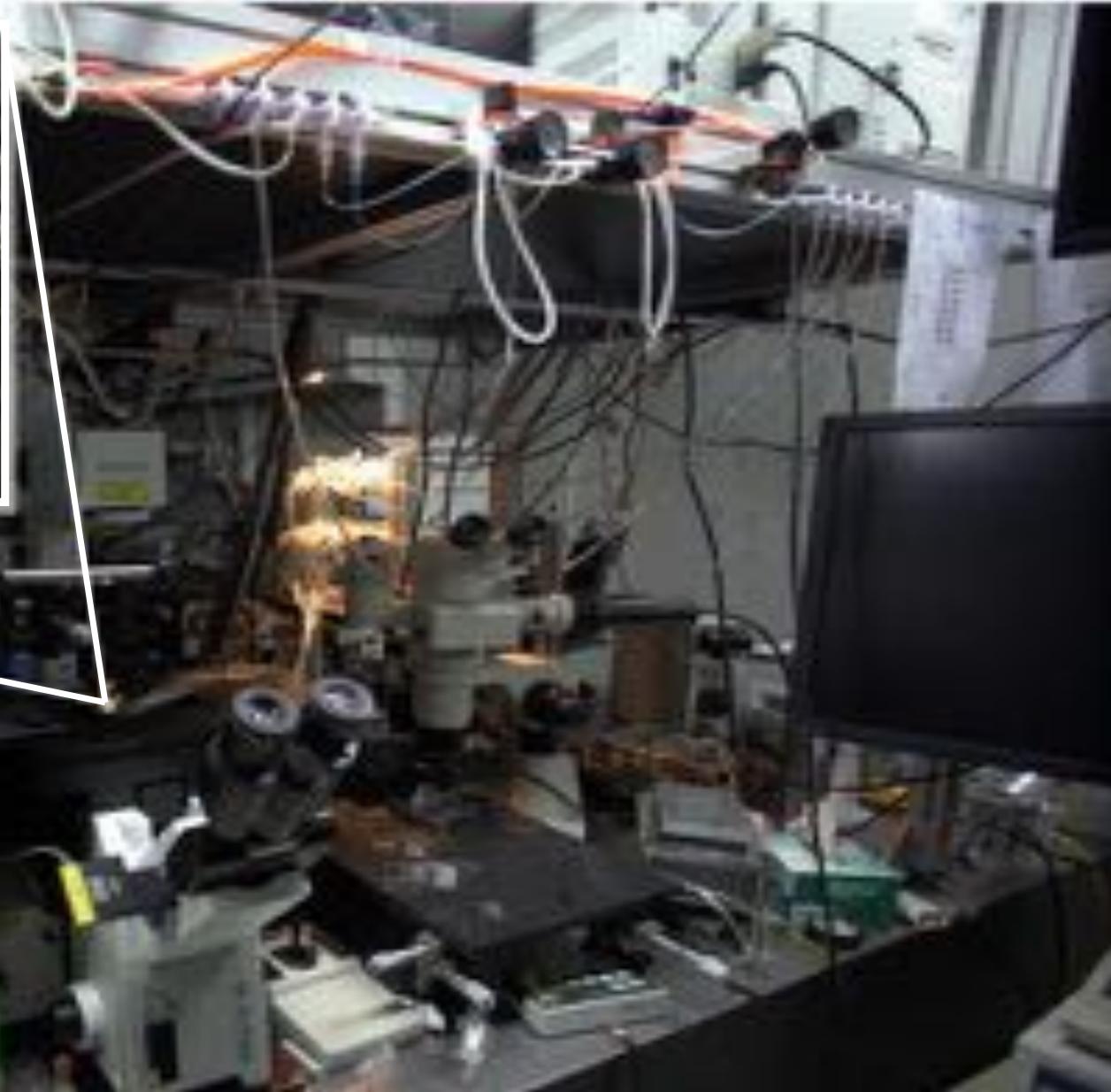
Prof. Philippe Renaud  
Microsystems Laboratory LMIS4  
EPFL, Lausanne, SWITZERLAND



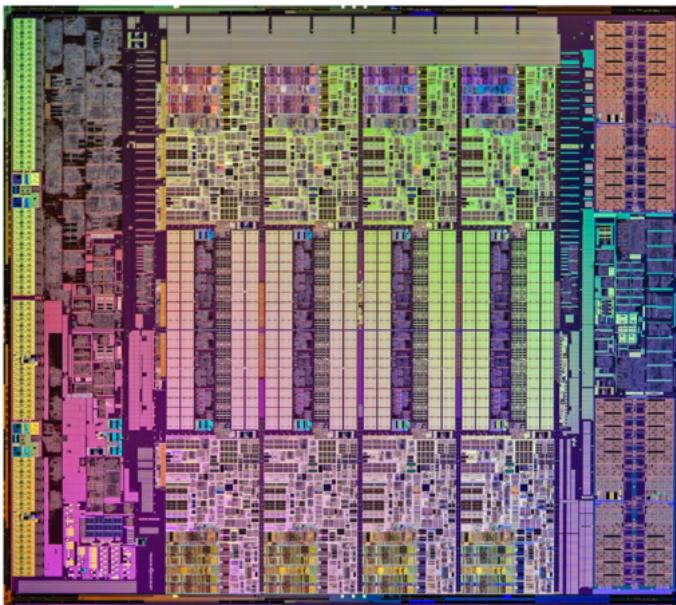
*Where is the  
Lab-On-Chip ?*



*Here !*



# Microelectronics inspiration



- Transistors and capacitors
- Electrical wiring
- MEMS sensors
  - Physical parameters
  - Light
  - (gas)

But lab-on-chip has to deal with a **large variety of samples**...

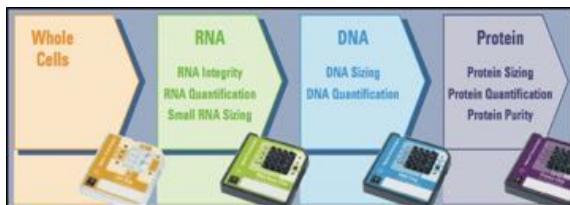
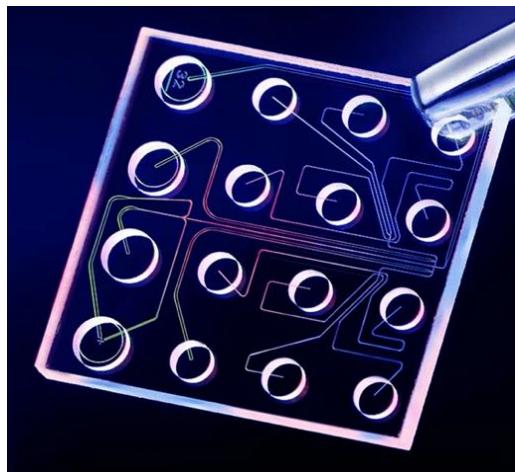
# Microelectronic-inspired technologies for miniaturization of (bio)chemical systems

- Reduced size **small** reagent volumes  
**fast** reactions  
high **throughput**
  - Mass production low **cost**, disposable
  - Integration : integrated **sensing**  
integrated **actuation**

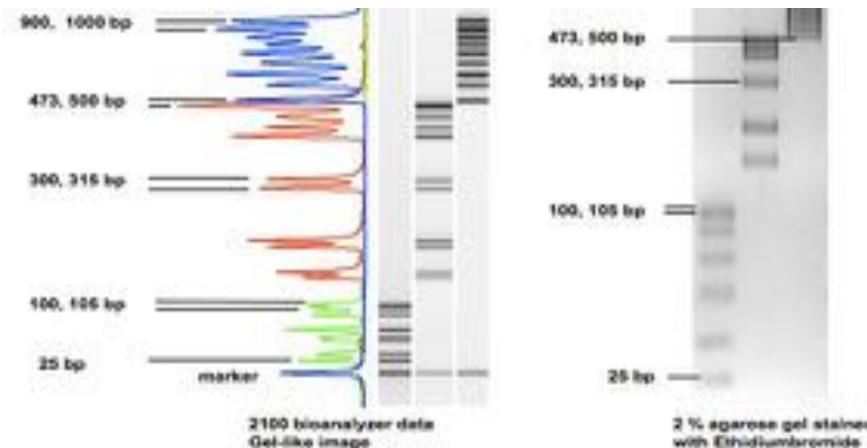
# Gartner Hype Cycle



# Microfluidic capillary electrophoresis



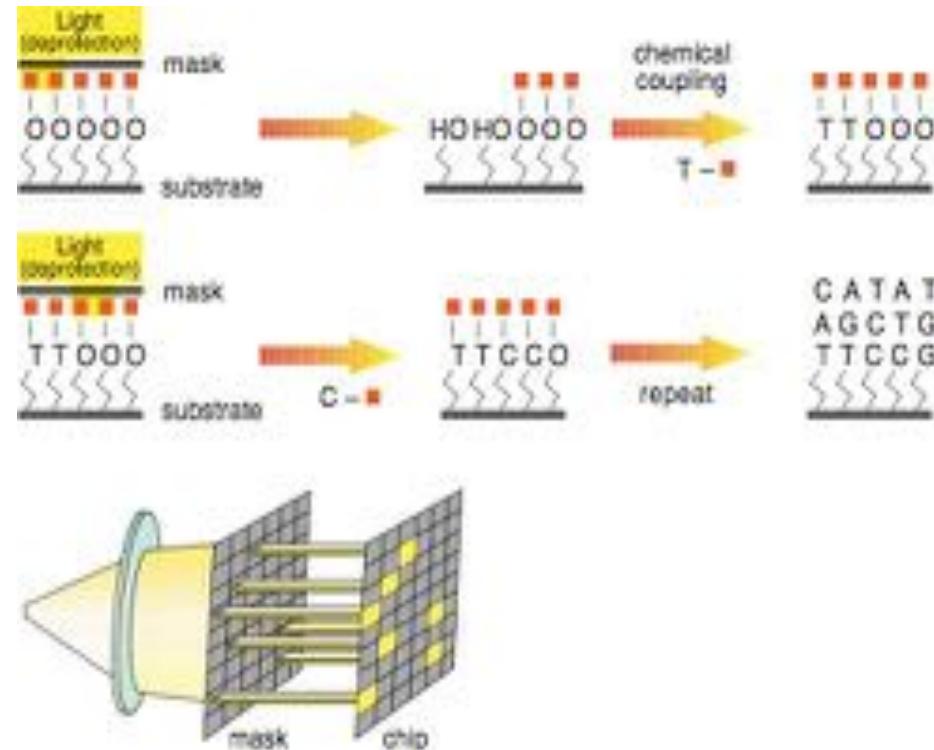
- Capillary electrophoresis **fast** separation of proteins or nucleic acids
- Glass chips with photolithography and glass etching for microchannels (20µm cross section)
- Injection cross: **zero dead volume** injection



Micromachining a miniaturized capillary electrophoresis-based chemical analysis system on a chip  
DJ Harrison, K Fluri, K Seiler, Z Fan, CS Effenhauser, A Manz  
Science 261 (5123), 895-897

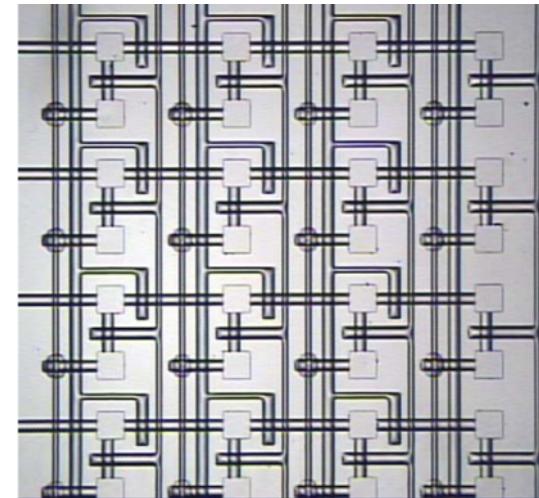
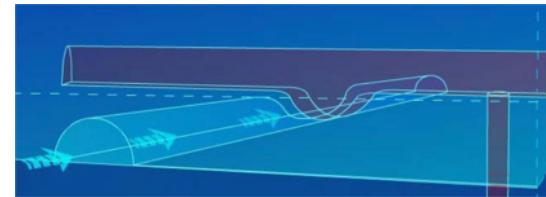


# High density DNA arrays



# VLSI microfluidics

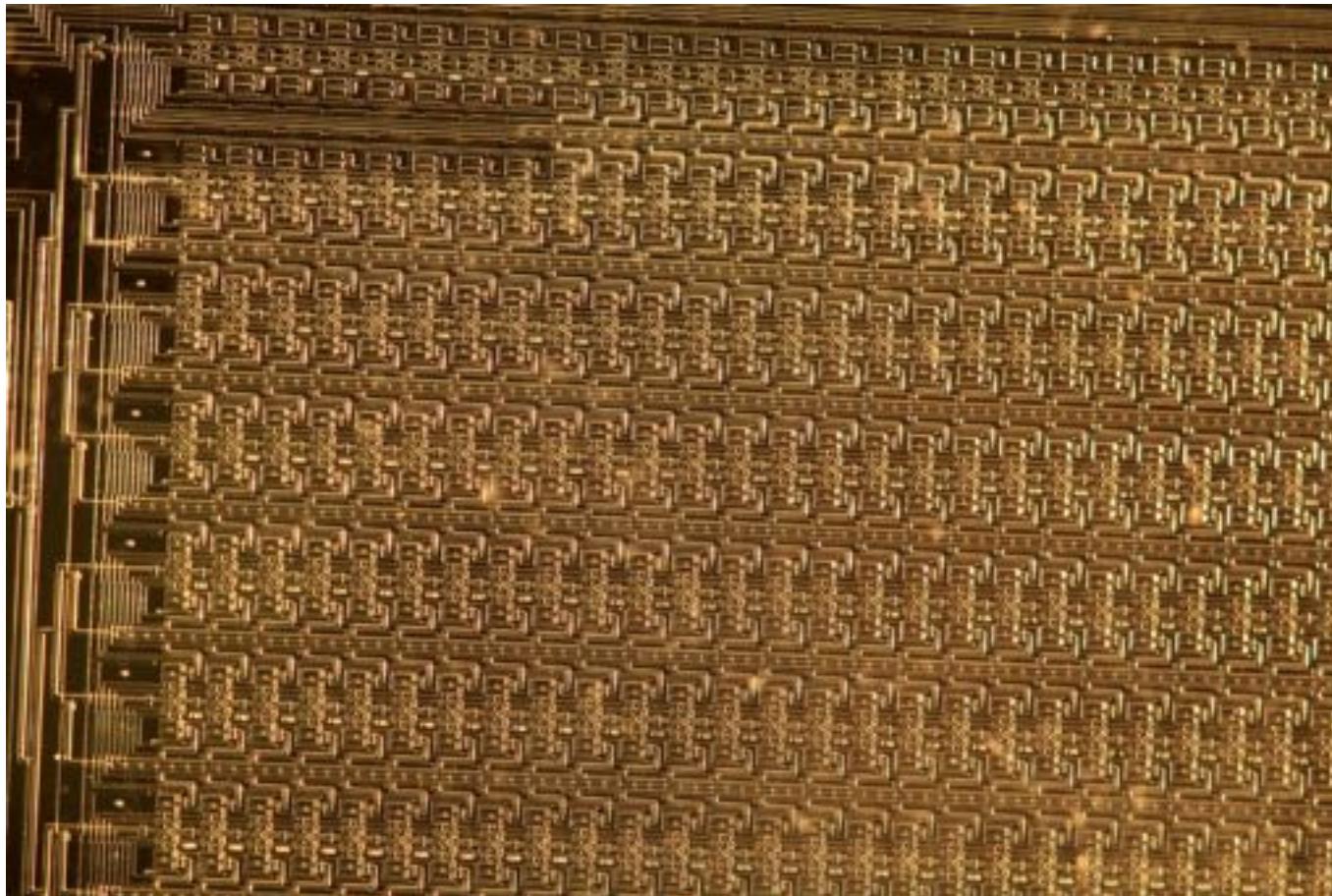
- 1000's of fluidic valves on a single chip



Monolithic microfabricated valves and pumps by multilayer soft lithography SCIENCE  
Unger, M. A., Chou, H. P., Thorsen, T., Scherer, A., Quake, S. R., 2000; 288 (5463): 113-116

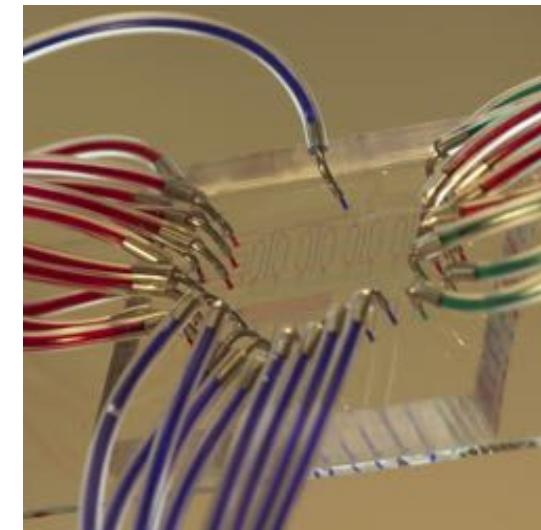


# *VLSI microfluidics*



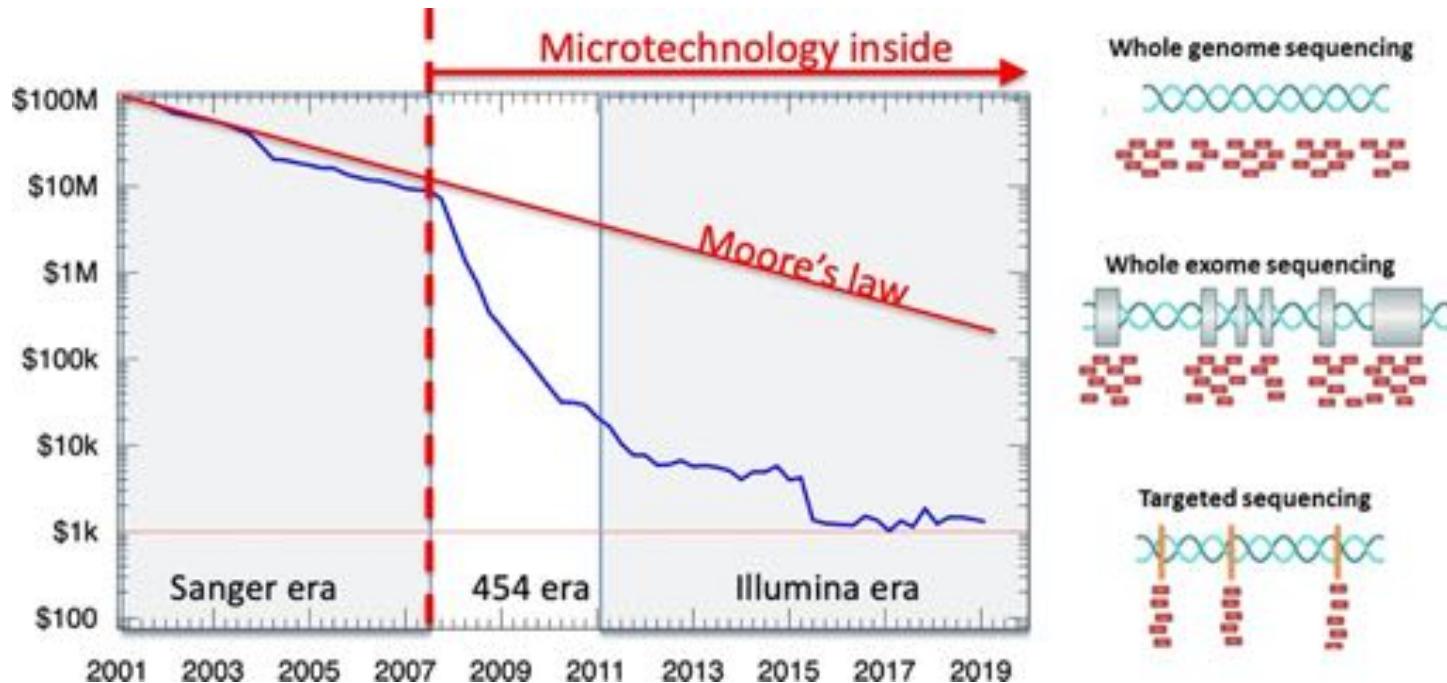
© Prof. Maerkli lab, EPFL

# *Integrated pumps and more....*



© Prof. Maerkli lab, EPFL

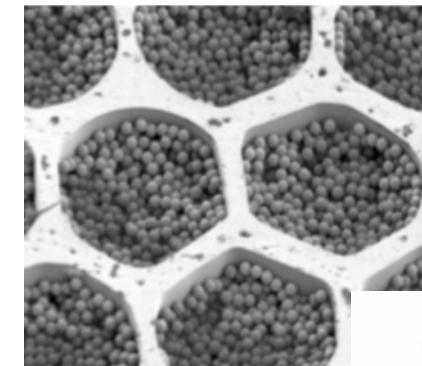
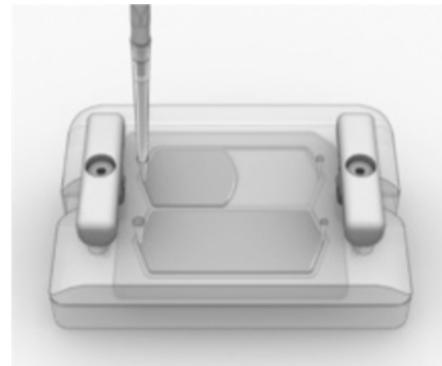
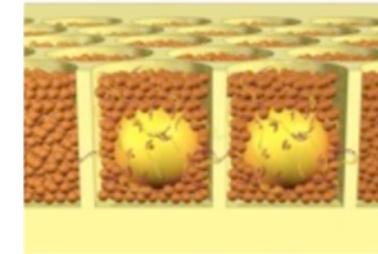
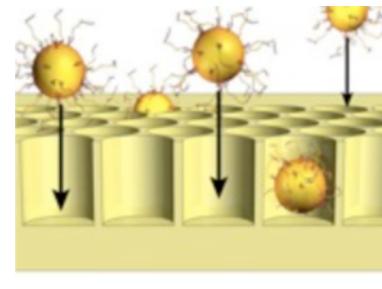
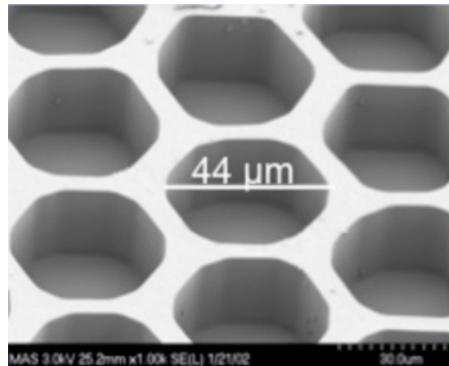
# Sequencing



- Sequencing: cost drop due to "array" technologies, sequencing by synthesis and **droplets**

# Sequencing

- Array of Micro-wells
- Microfluidic cartridge



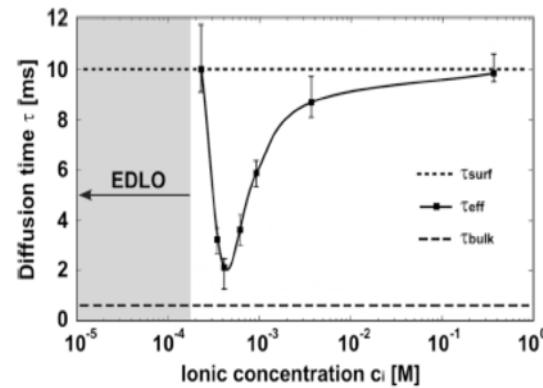
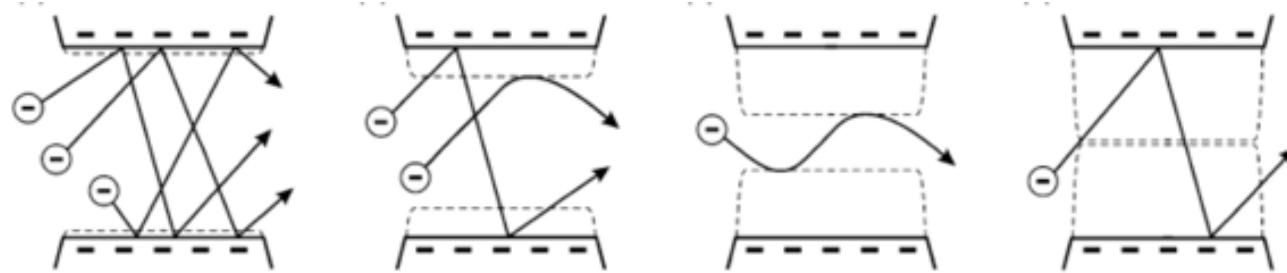
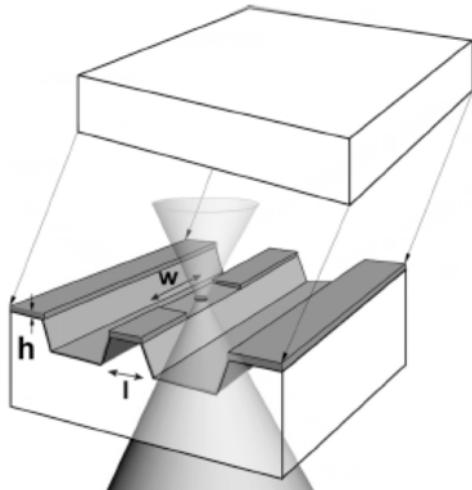
**454** LIFE SCIENCES

Measuring Life One Genome At A Time



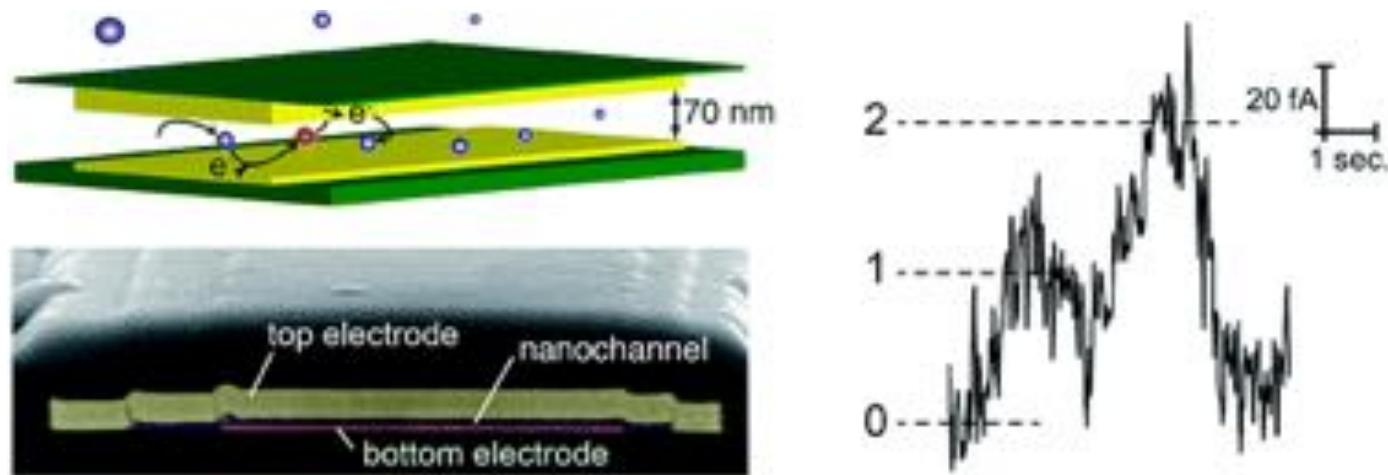
# *Sensing at micro-scale ?*

# Sensing in nano-gaps



Direct measurement of diffusing proteins in nanochannels using fluorescence correlation spectroscopy  
Durand, NFY; Dellagiacoma, C; Goetschmann, R; Bertsch, A; Märki, I; Lasser, T; Renaud, P  
ISSN: 1876-6196; DOI: 10.1016/j.proche.2009.07.335  
Procedia chemistry. , 2009, Vol.1(1), p.1343-1346

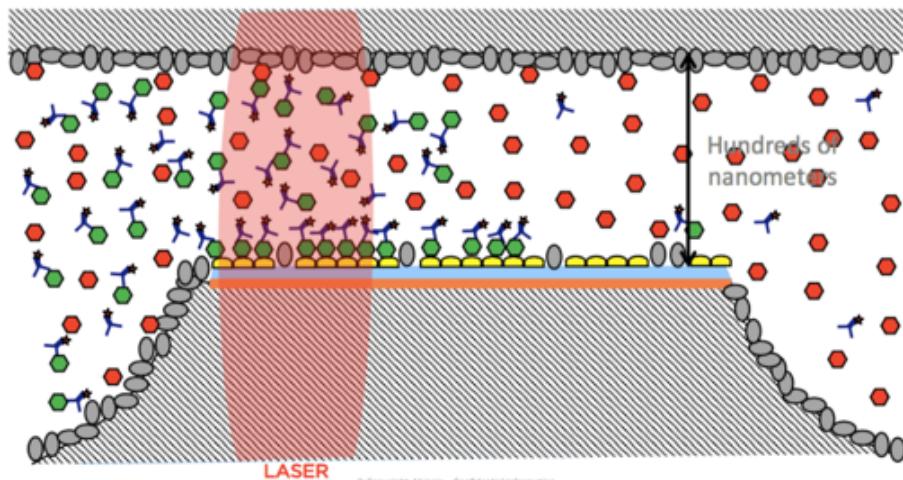
# Sensing in nano-gaps



Stochastic Sensing of Single Molecules in a Nanofluidic Electrochemical Device  
Marcel A. G. Zevenbergen, Pradyumna S. Singh, Edgar D. Goluch, Bernhard L. Wolfrum, and Serge G. Lemay  
Nano Letters 2011 11 (7), 2881-2886

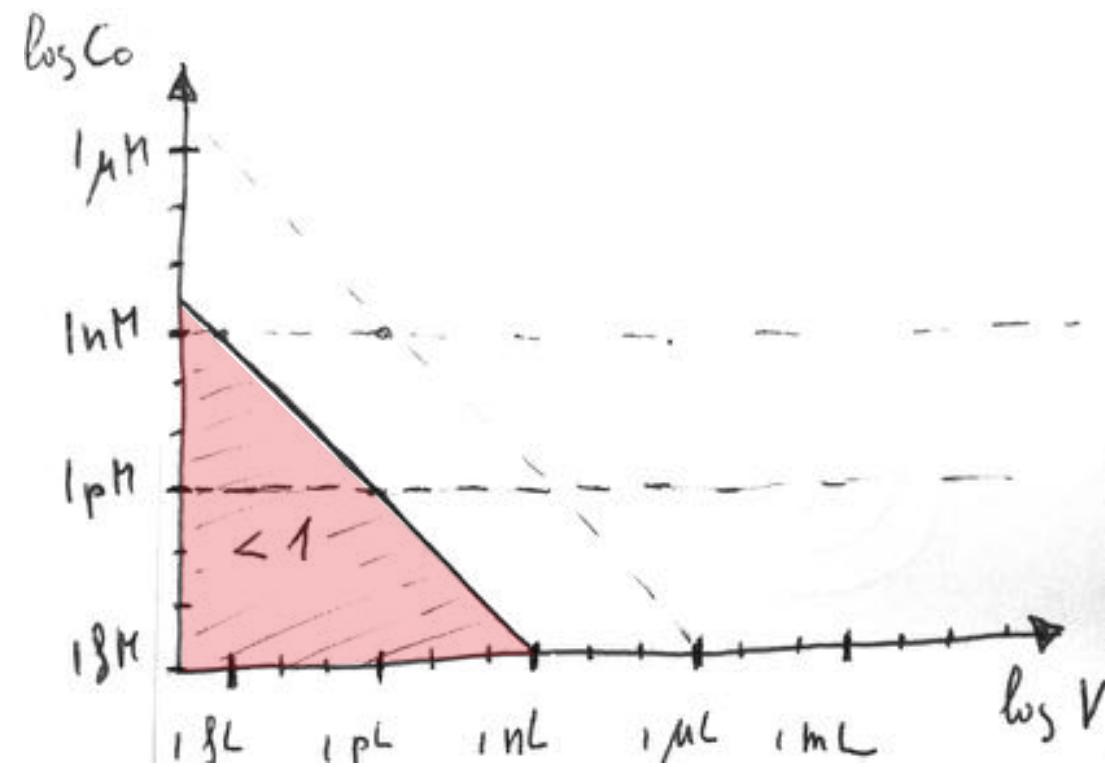
# ELISA in nano-gaps

- Adhesion layer
- Patient analyte (if present)
- Capture molecule
- Fluorescently labeled secondary antibody
- Blocker protein
- Other patient proteins



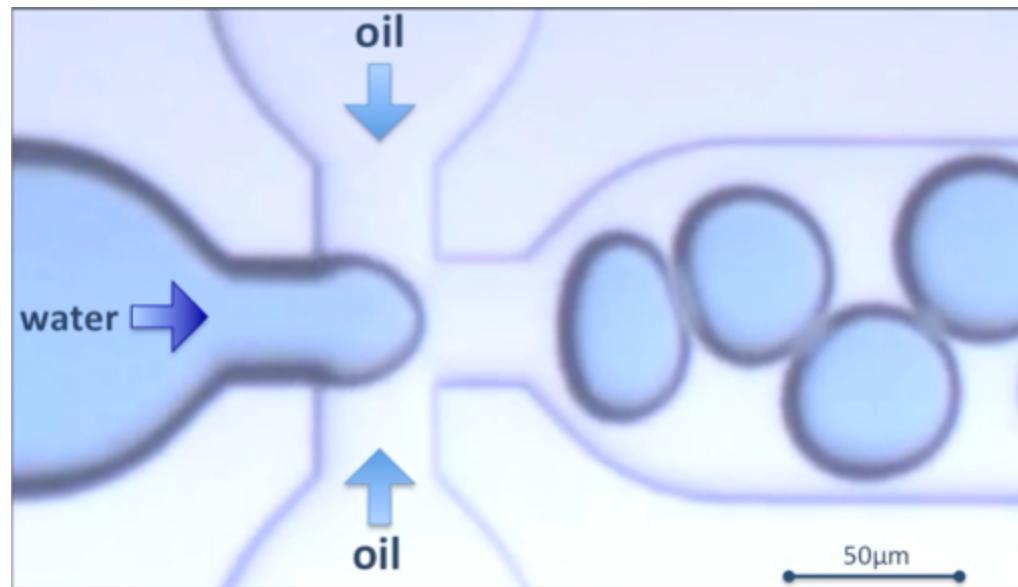
# Less than one molecule regime

"homeopathic limit"

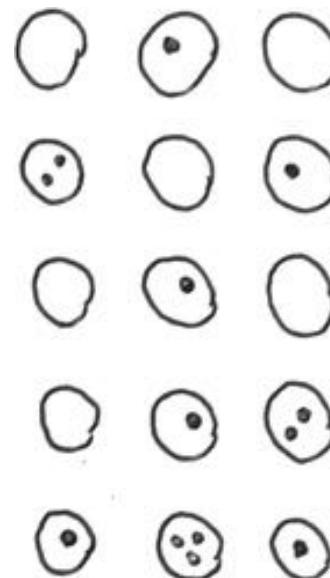
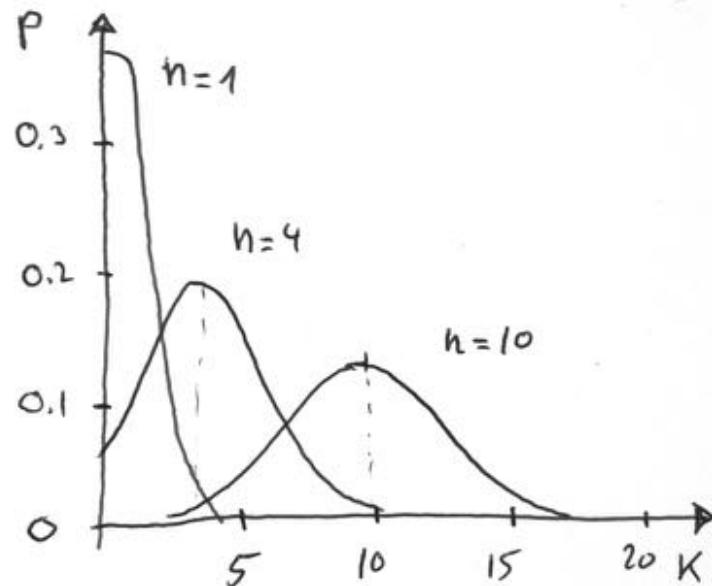


# Droplets microfluidics

- Small containers
- Large numbers
- High throughput



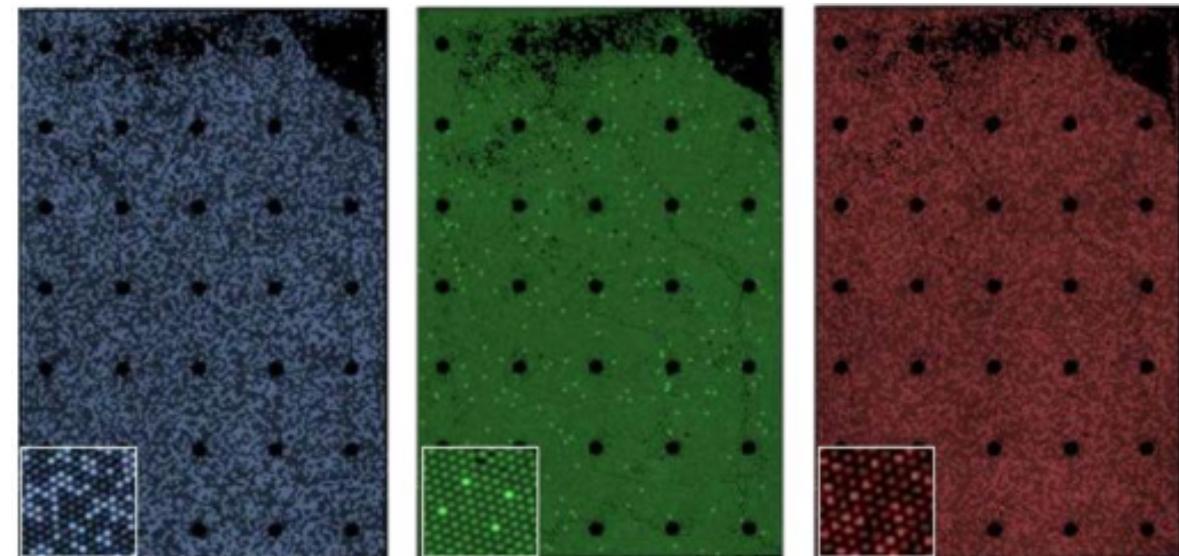
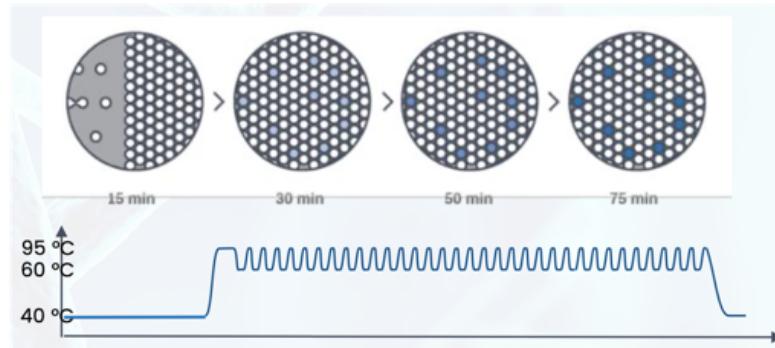
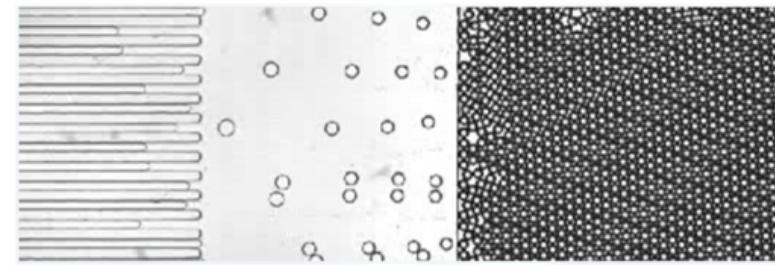
# Less than one molecule regime



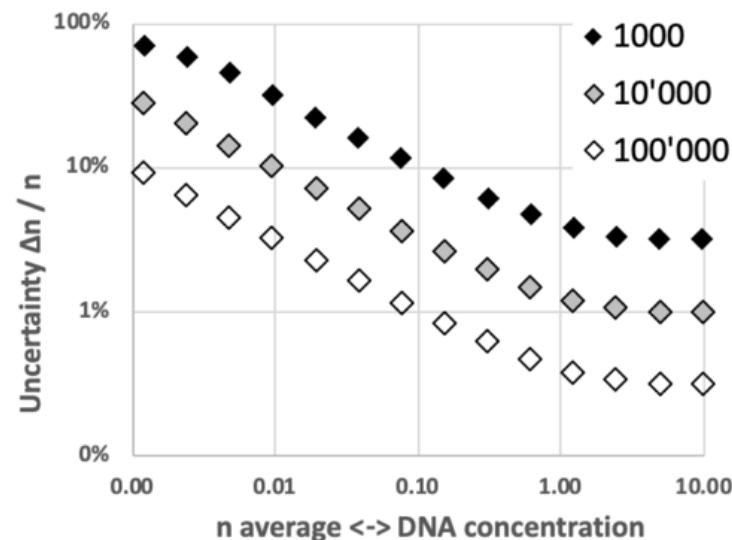
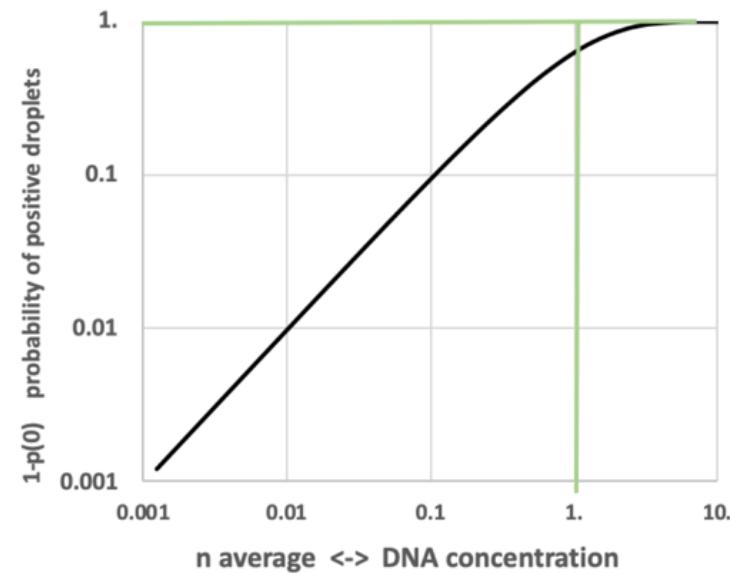
# Digital PCR



# Digital PCR



# Digital PCR

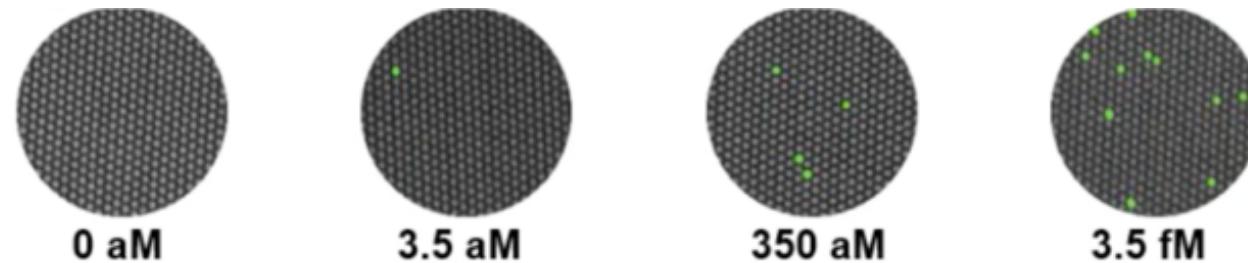


# Digital ELISA

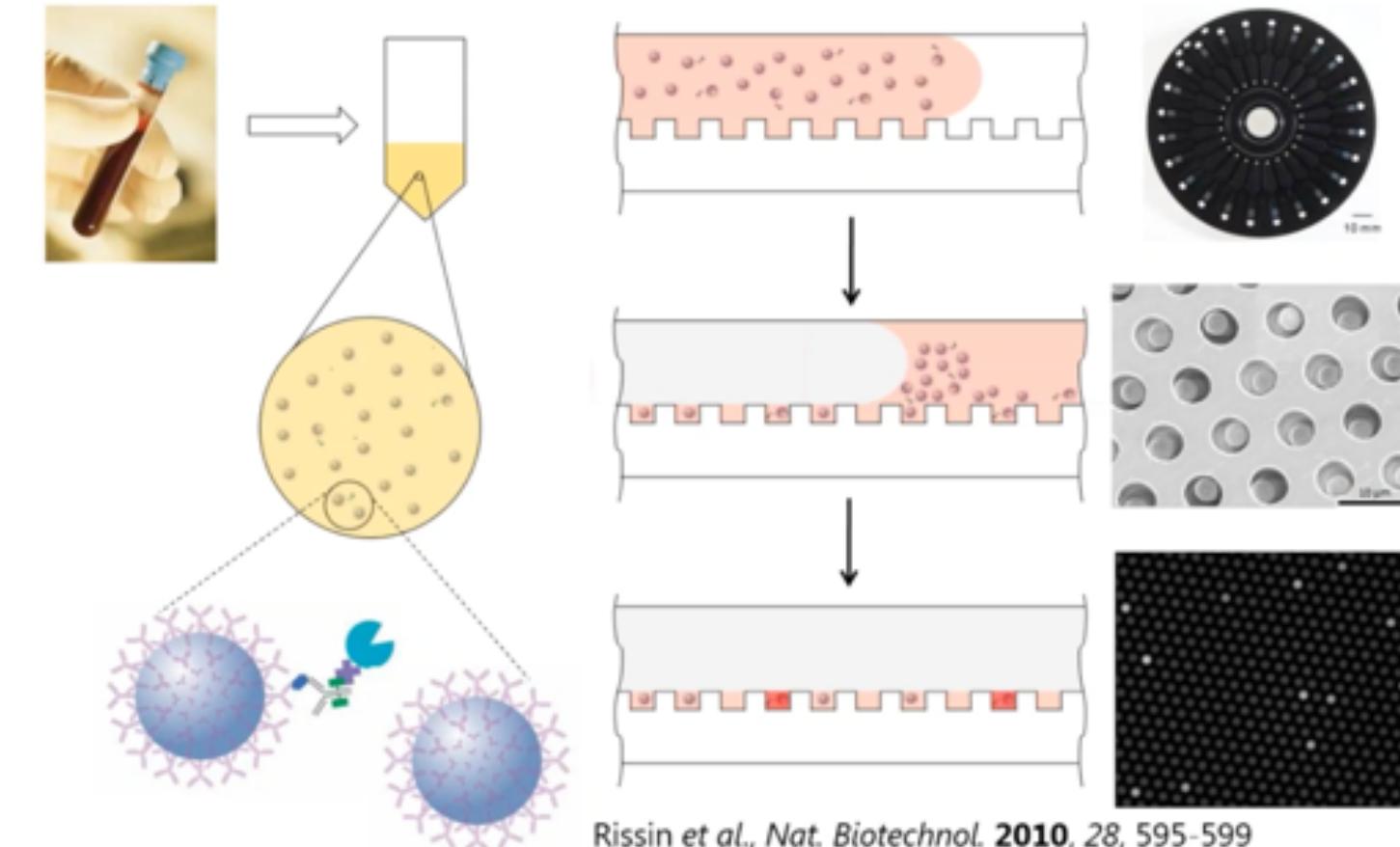
- Well plate
  - 100  $\mu$ l
  - 10E6 molecules LOD



- Digital
  - 0.00001  $\mu$ l
  - Single molecule LOD



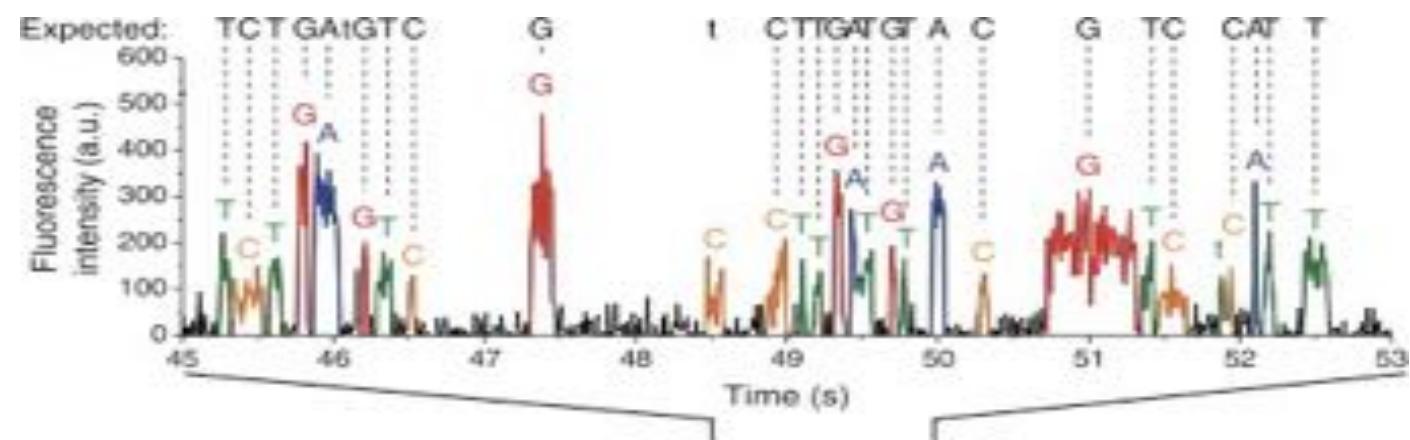
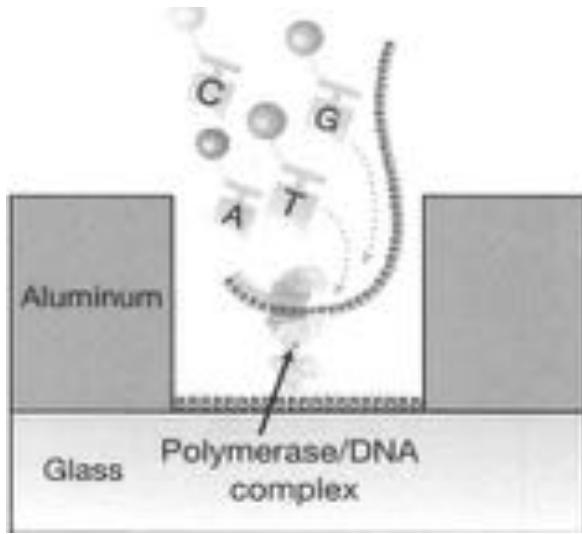
# Digital ELISA



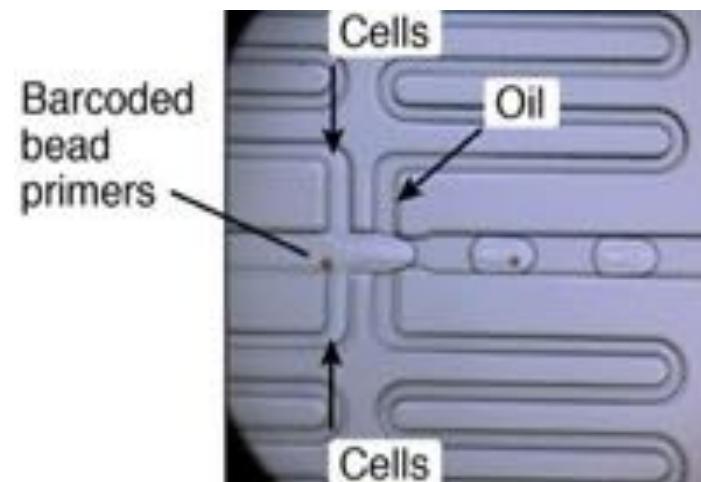
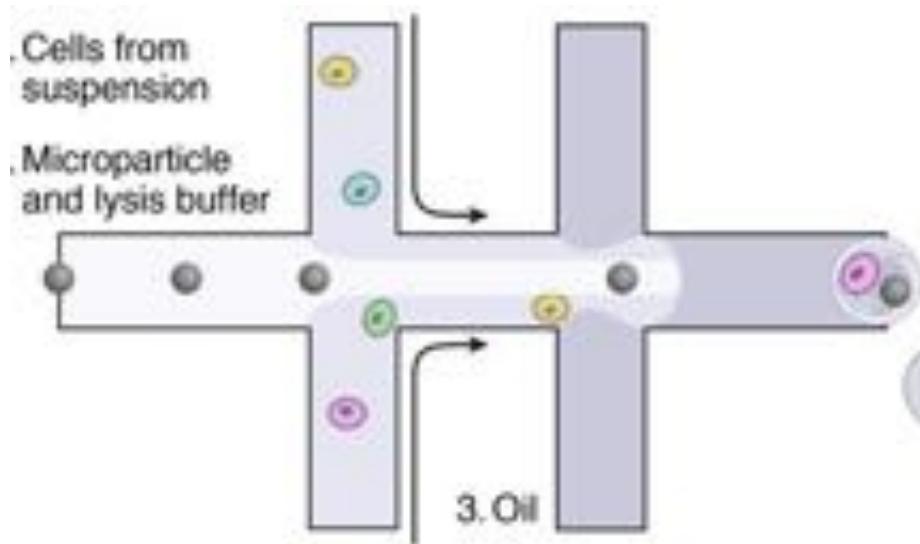
Rissin et al., *Nat. Biotechnol.* **2010**, 28, 595-599  
Kan et al., *Lab Chip* **2012**, 12, 977-985

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The Science of Precision Health

# Single molecule sequencing



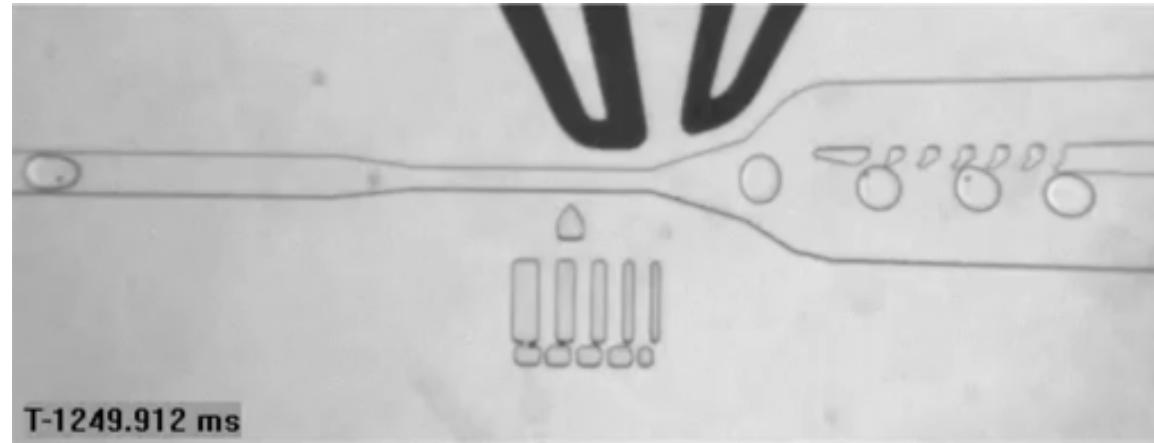
# Drop-Seq



Macosko EZ, Basu A, Satija R, et al. Highly Parallel Genome-wide Expression Profiling of Individual Cells Using Nanoliter Droplets. *Cell*. 2015;161(5):1202-1214. doi:10.1016/j.cell.2015.05.002

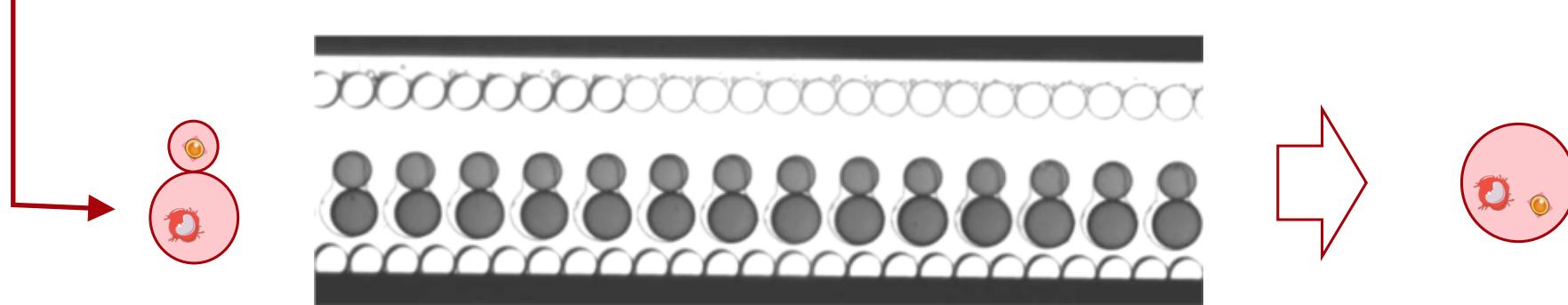
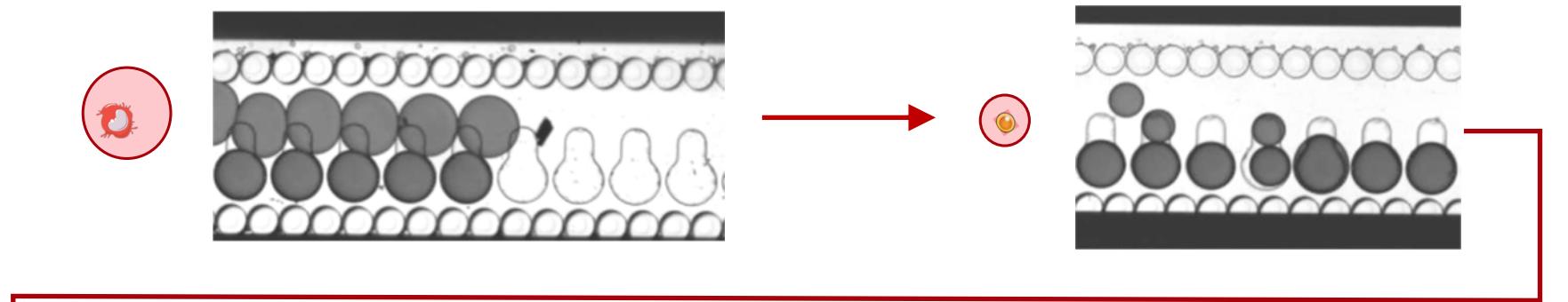
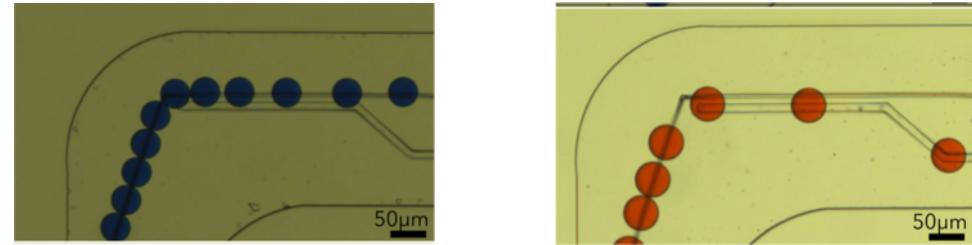
# Droplet “machine”

- Place one cell into one droplet



# Droplet “machine”

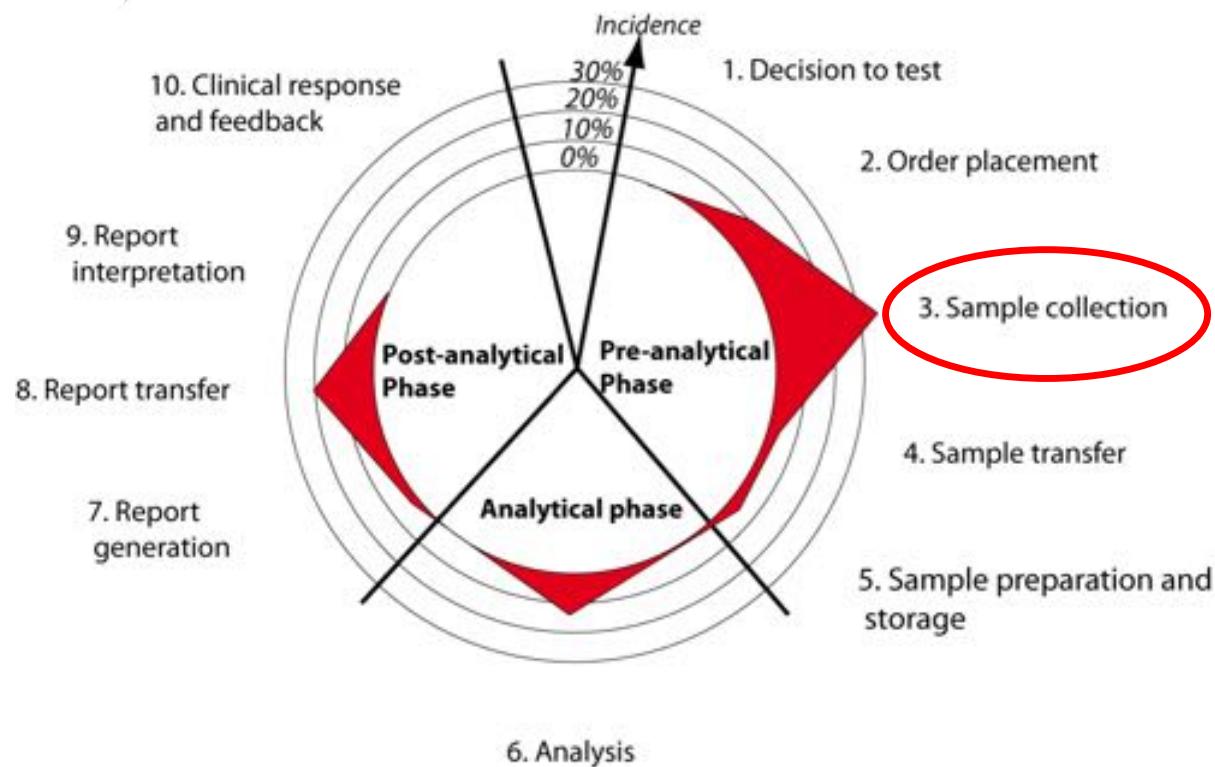
- Merge two cell loaded droplets



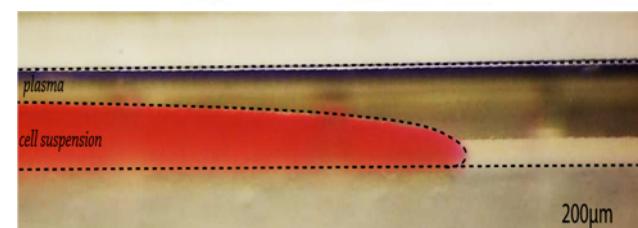
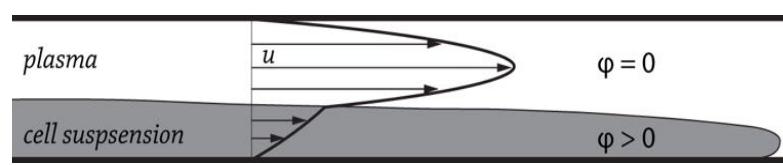
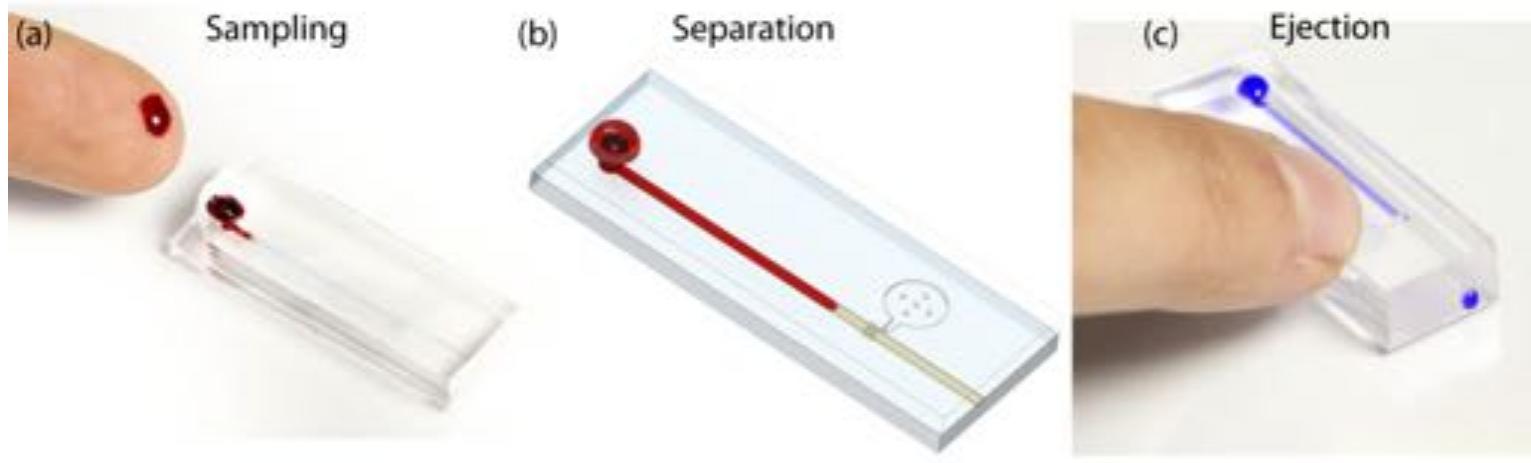
# Challenges in bio-analytics

- High sensitivity and selectivity sensors are missing (e.g. MS)
- Sample preparation challenge

# Source of errors in biosensing



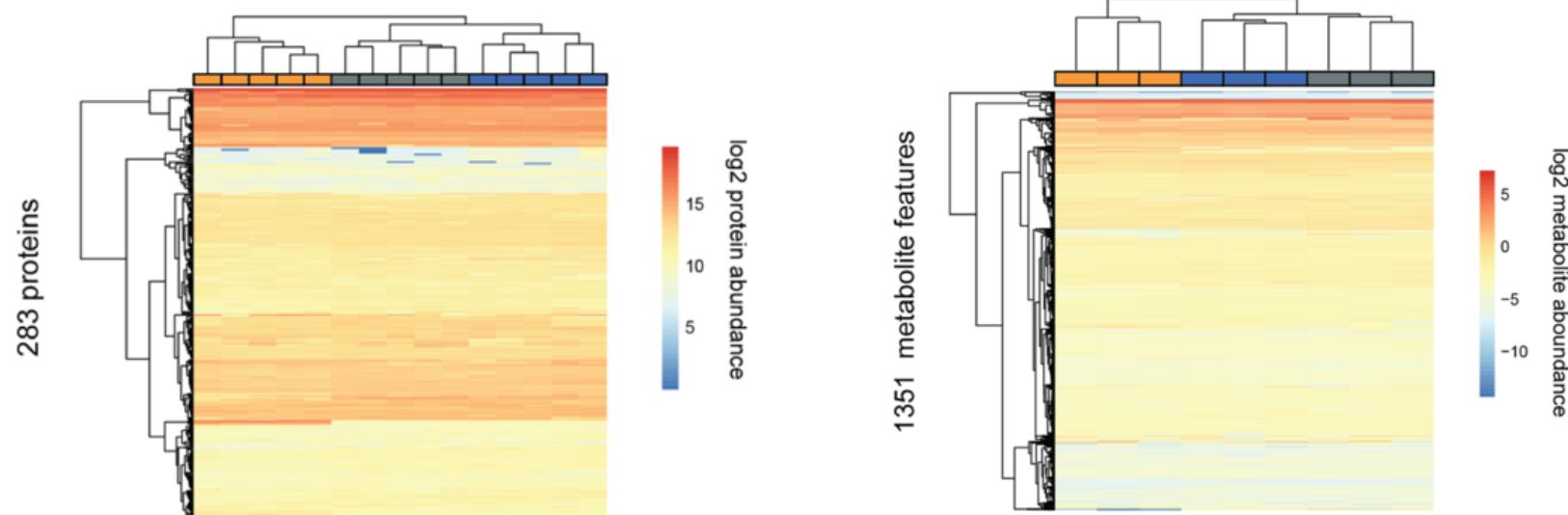
# Blood sampling



A. Thomas, CHUV, J. Deglon HUG

Forchelet, D., Béguin, S., Sajic, T. et al. Separation of blood microsamples by exploiting sedimentation at the microscale. *Sci Rep* 8, 14101 (2018).

# Blood sampling



A. Thomas, CHUV, J. Deglon HUG

Forchelet, D., Béguin, S., Sajic, T. et al. Separation of blood microsamples by exploiting sedimentation at the microscale. *Sci Rep* 8, 14101 (2018).

# What to conclude ???

- Lab-on-Chip “dream” triggered innovation
  - ... opened unexpected applications, beyond analytics
- Technologies are simple. The challenges are in the applications

**“find the right technology for the right need”**

## Acknowledgements

- All current and past PhD students, postdocs and scientists at the Microsystems Laboratory
- All our friendly collaborators over many years
- EPFL and grants from SNSF, EU, Innosuisse and various programs and foundations
- Super EPFL platforms: CMi, BIOP, CTV, ...



Micro 3D printing of ice  
(© Ludovic Serex, LMIS4)

# Thank you

Prof. Philippe Renaud  
Microsystems Laboratory