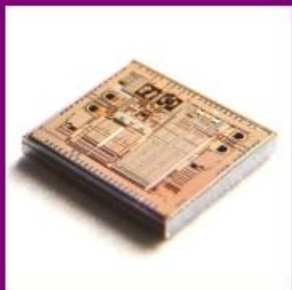
ENABLING POINT OF CARE DIAGNOSTICS WITH SEMICONDUCTOR TECHNOLOGIES

MARCH 6TH, 2013
SENSORS IN MEDICINE CONFERENCE

PARU DESHPANDE
PROGRAM DIRECTOR
LIFE SCIENCE TECHNOLOGIES, IMEC

IMEC RESEARCH PROGRAMS



Green Radio

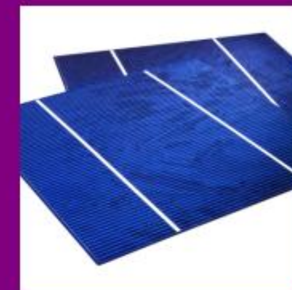
Low power wireless communication

Human++

BAN
Life sciences

NVision

Imaging
3D visualization



Energy

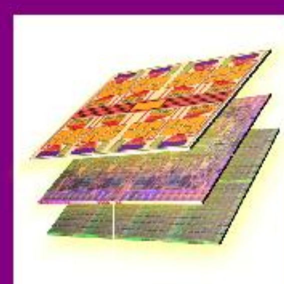
Photovoltaics
Power devices

Core CMOS

Lithography

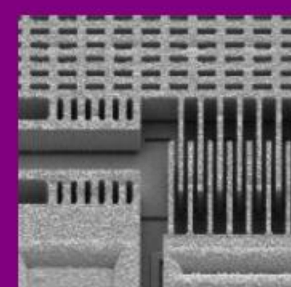
Devices

Interconnects



CMORE

MEMS, Sensors
Photonics



Organic electronics

LIFE SCIENCES @ IMEC

Process integration
Process technology
Fab operations

Joint teams
Concept development

Cell biology
Molecular biology
Surface chemistry
Assay development

>100 people work on life science projects at imec today

THE HEALTHCARE CHALLENGE

350M
Living with diabetes

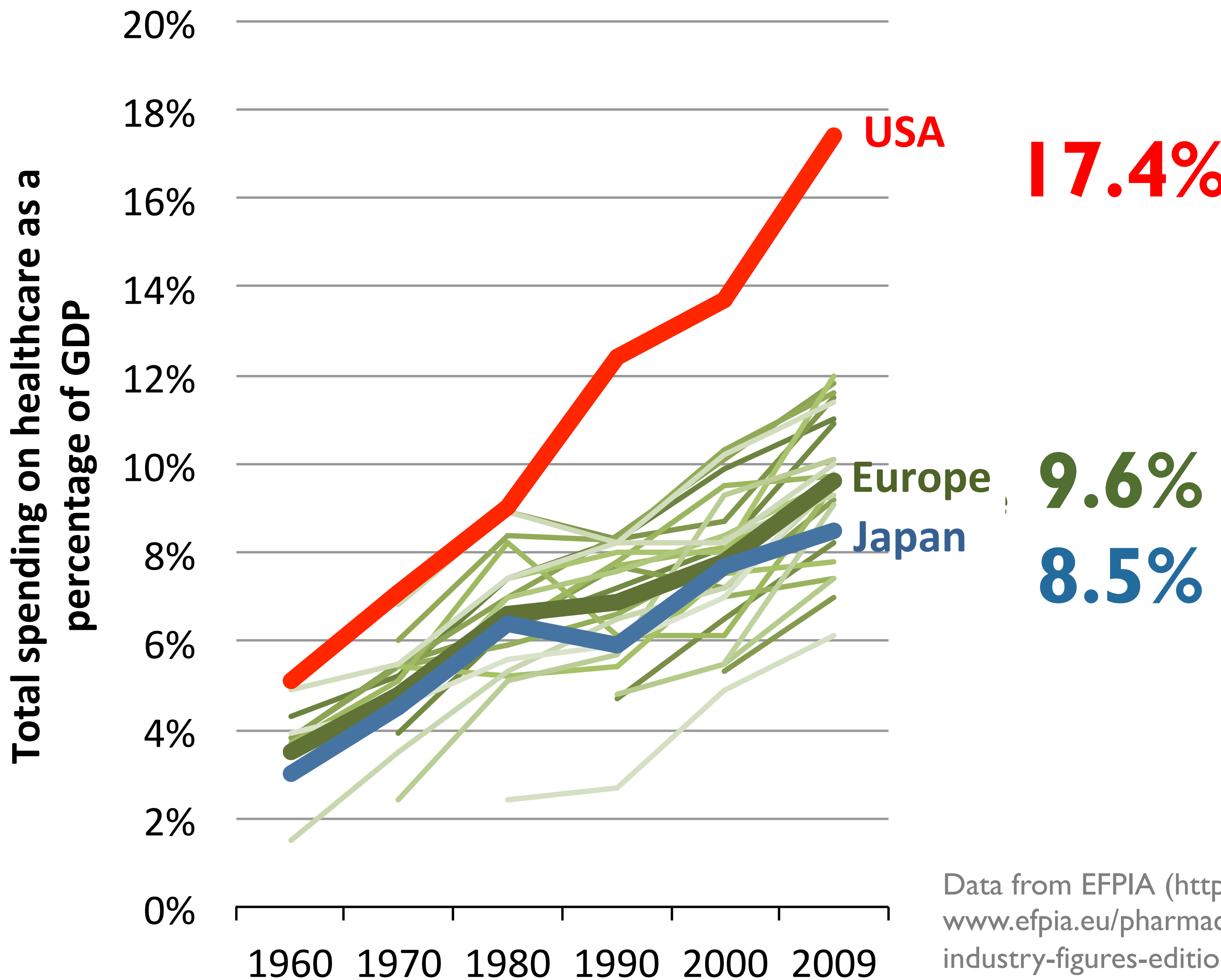
12M
new cancer patients each year

36M
Living with Alzheimer's

17M
deaths from heart disease each year

132M
Newborn babies this year

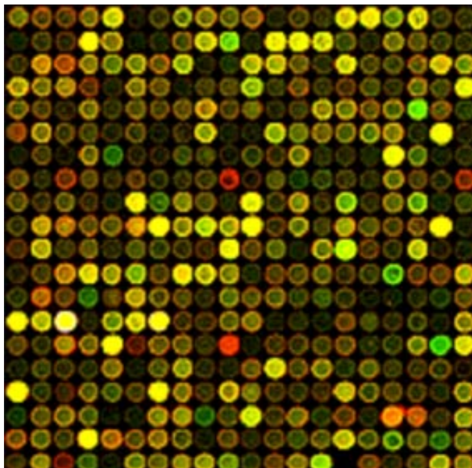
THE HEALTHCARE CHALLENGE

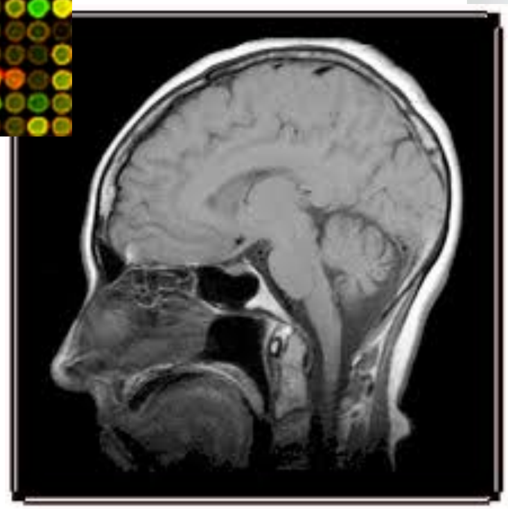


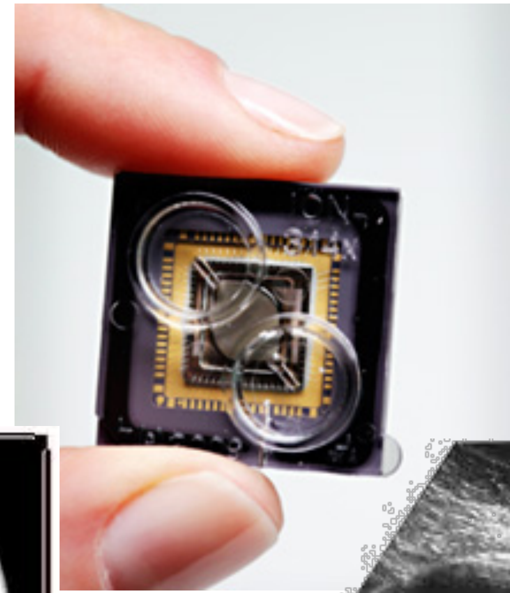
Data from EFPIA (http://www.efpia.eu/pharmaceutical-industry-figures-edition-2012)

TECHNOLOGY IN HEALTHCARE

New tools enable earlier diagnosis, detailed understanding and targeted treatment.



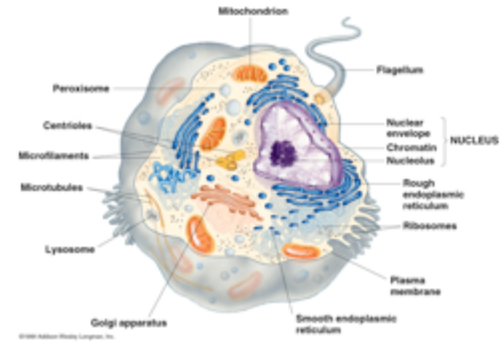




Technology can enable a new healthcare toolbox.

IMEC LIFE SCIENCES

Molecules
DNA, RNA, proteins, metabolites



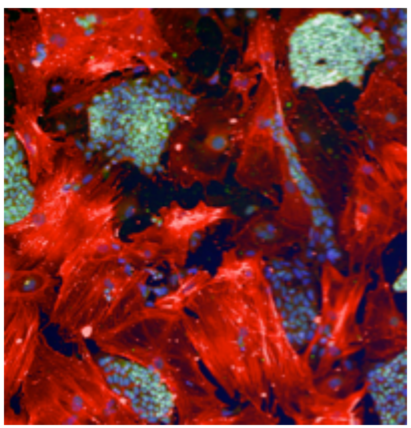
Cells

Molecular diagnostics

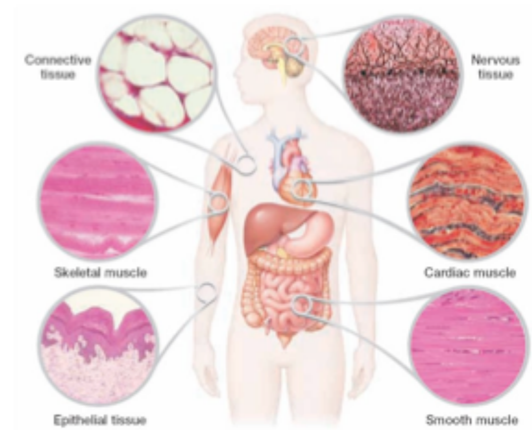
Cell-based analysis

In vitro systems

In vivo probes



Cell cultures

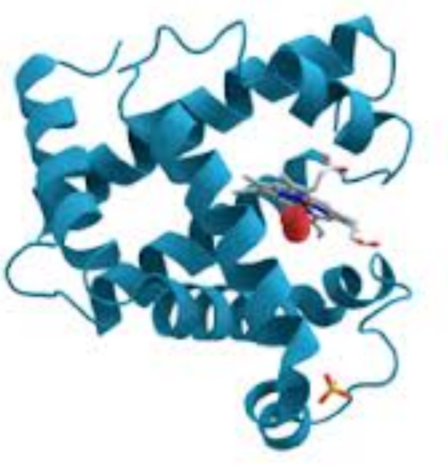


Tissue

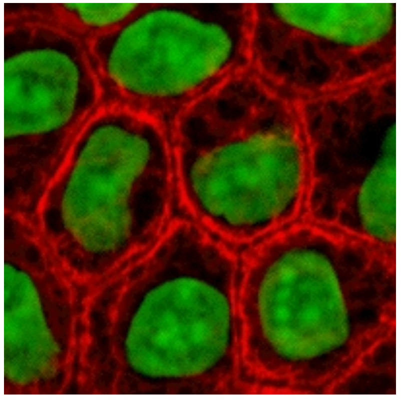
MOLECULAR TOOLS – UNDERSTANDING BIOLOGY AT ITS NATIVE SCALE

Biology is enormously complex down to the smallest length scales – need new tools to decipher biology at its native scale.

DNA – 2nm



Protein (<10nm)



Cells (<100 um)

biology • • • • • • microsystem

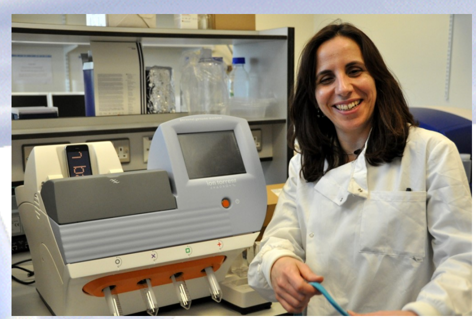
DNA SEQUENCING: A LESSON IN INTEGRATION

1951 – X-Ray diffraction used to determine the structure of DNA

> "This structure has novel features which are of considerable biological interest."

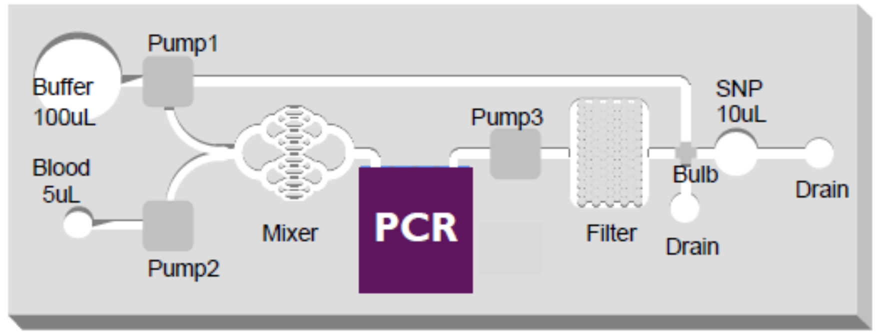
2000 – First working draft of human genome sequence

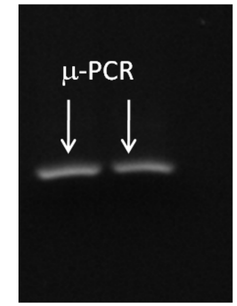
2013 – Lots of players in sequencing market (PacBio, Life Tech, Illumina, 454, Oxford Nanopore, …)
Cost for whole genome sequencing less than $5000 and can be done in days

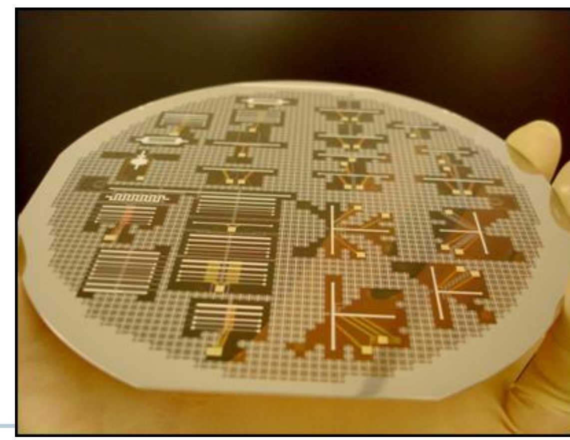


imec

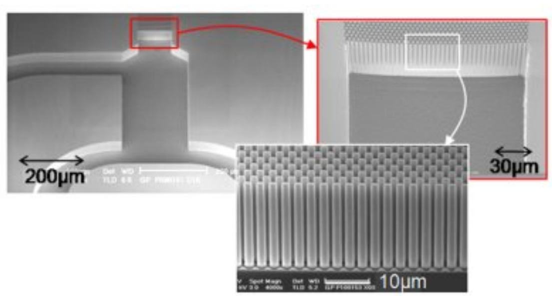
MICRO-PCR FOR RAPID SNP DETECTION

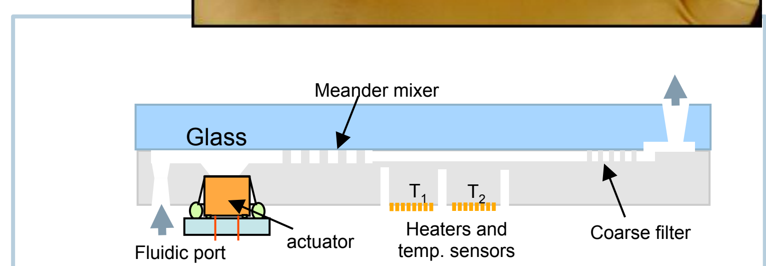






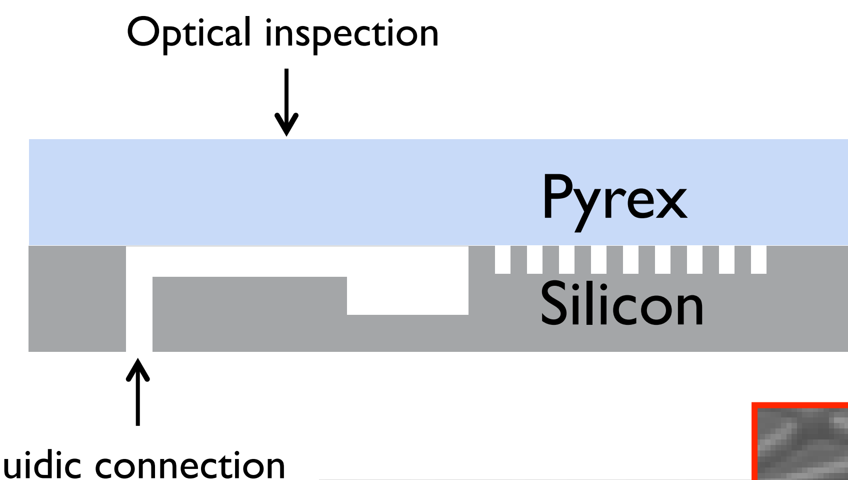
- **Multiplex** detection of SNP's
- **Rapid** amplification because of faster thermal cycling
- Direct detection from **blood**
- **Small form factor**



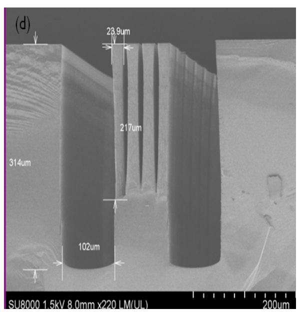


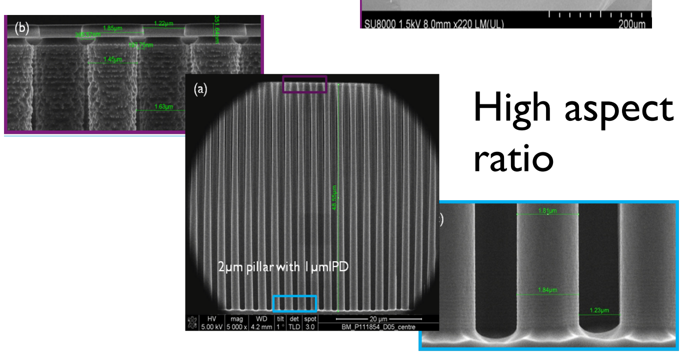
SILICON MICROFLUIDIC PLATFORM

- Based on silicon – Pyrex
- Design flexibility achieved by combining on the same chip
  - Coarse structures (critical dimensions 500um-3um)
  - Fine structures (critical dimensions 3um-0.5um)
- Aspect ratio up to 40



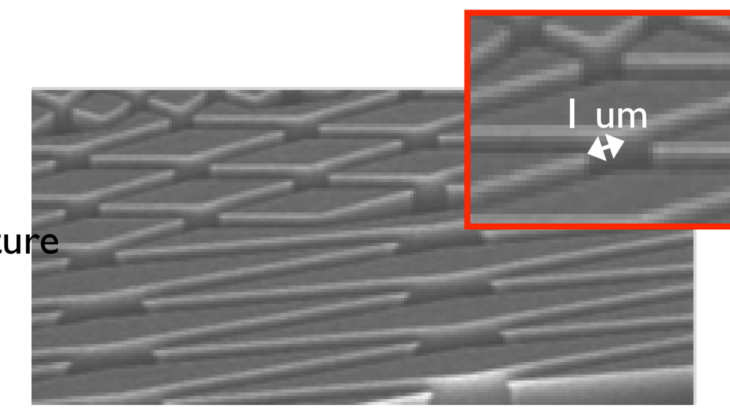
Coarse structures





High aspect ratio

Fine structure

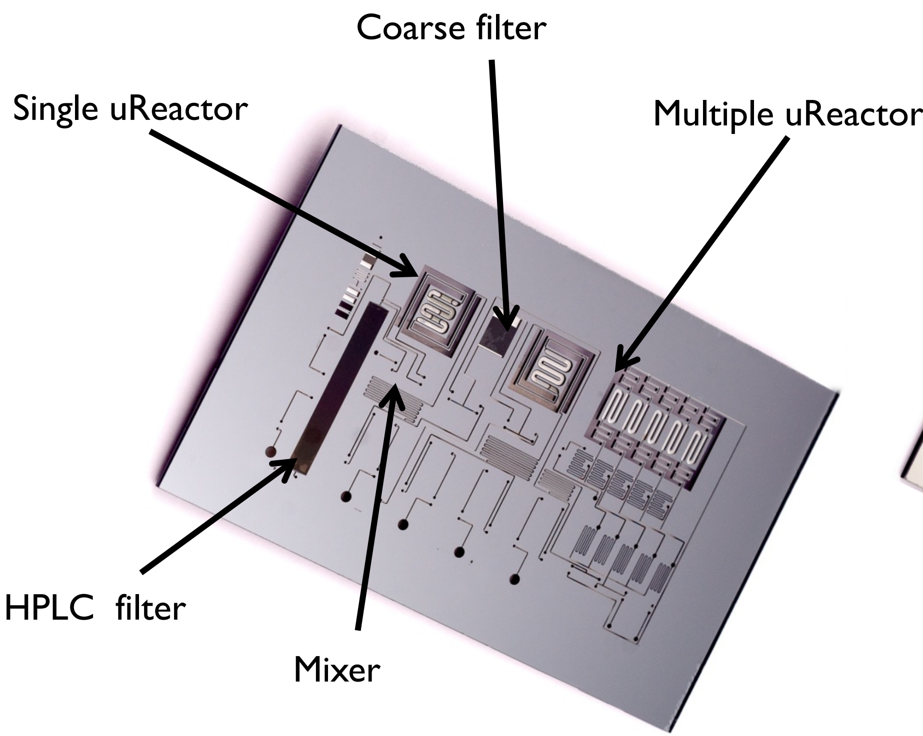


SILICON MICROFLUIDIC PLATFORM

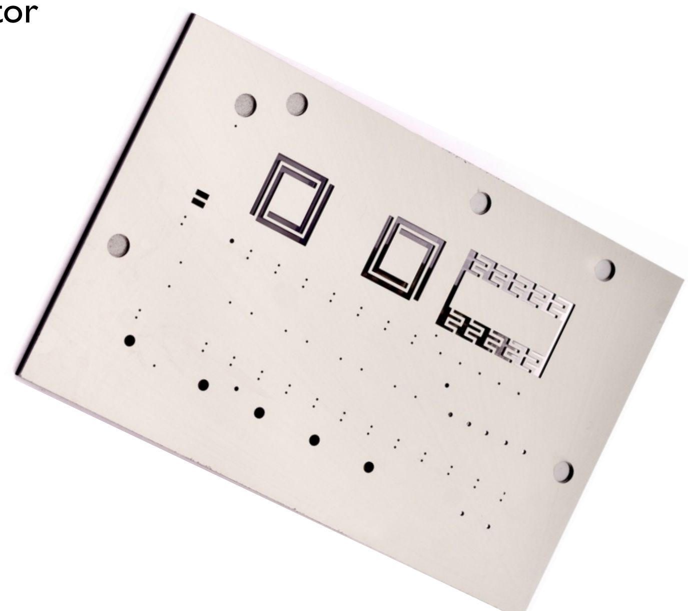
Key aspect of the process:

•Co-fabrication of coarse and fine structures on the same wafer.

•Requires protection of etched coarse structures during definition of fine structures.

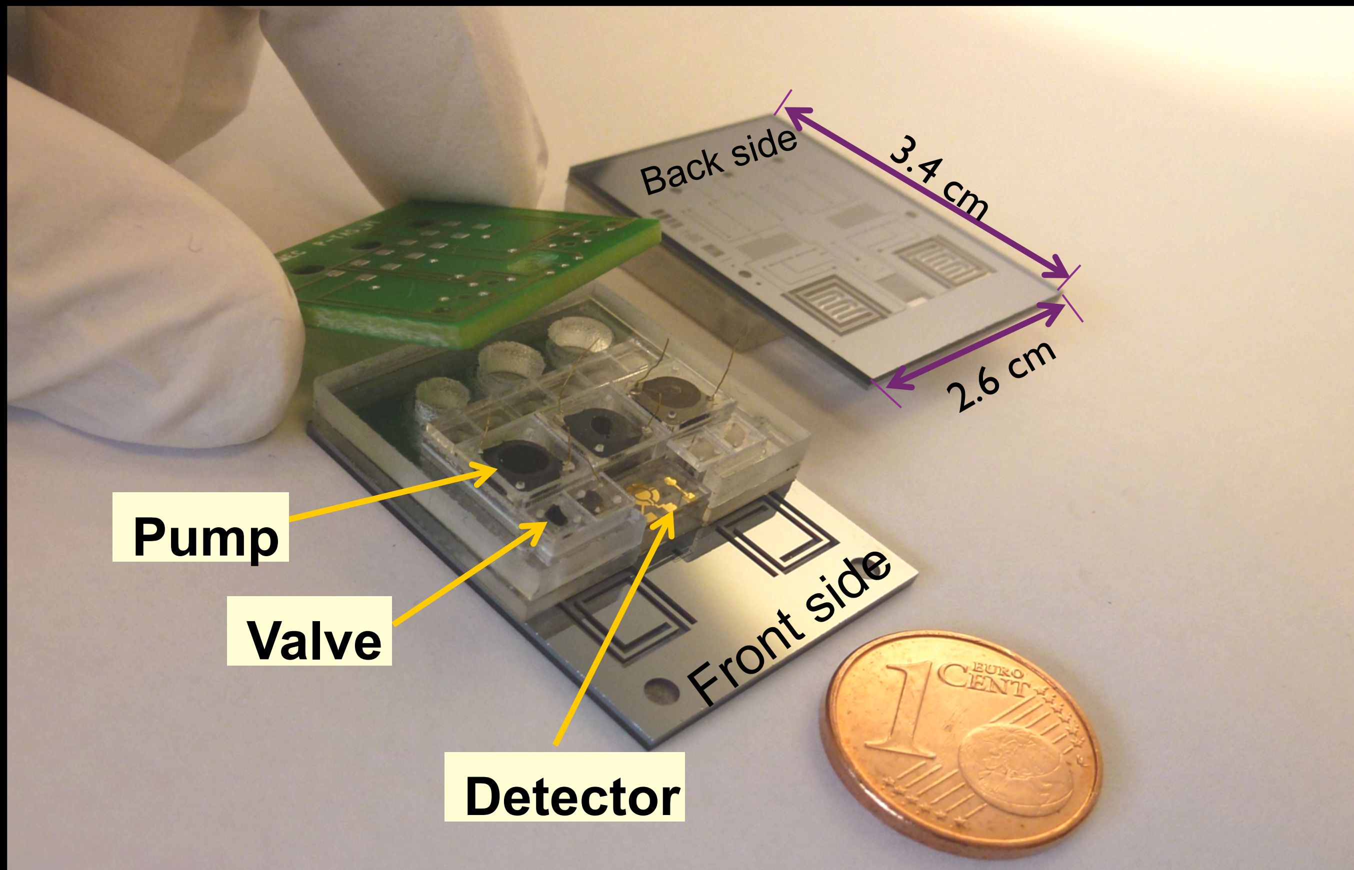


Front side



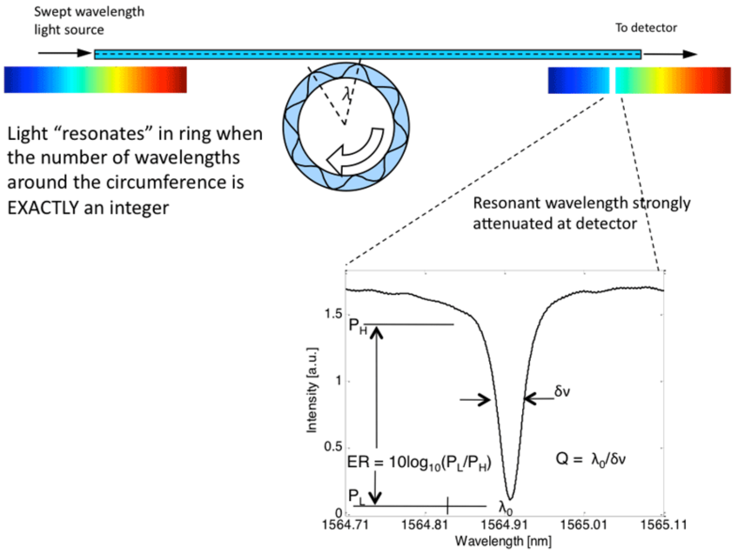
Back side

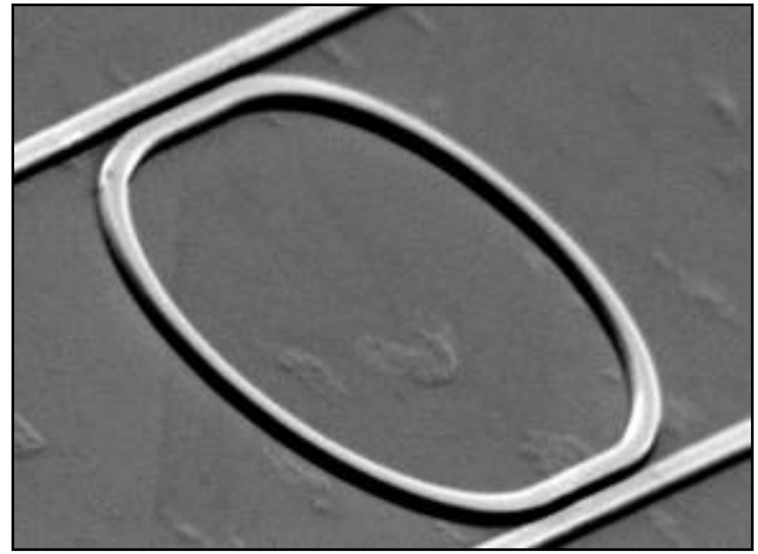
SNP DETECTION SYSTEM



GENALYTE BIOSENSOR

SILICON PHOTONICS

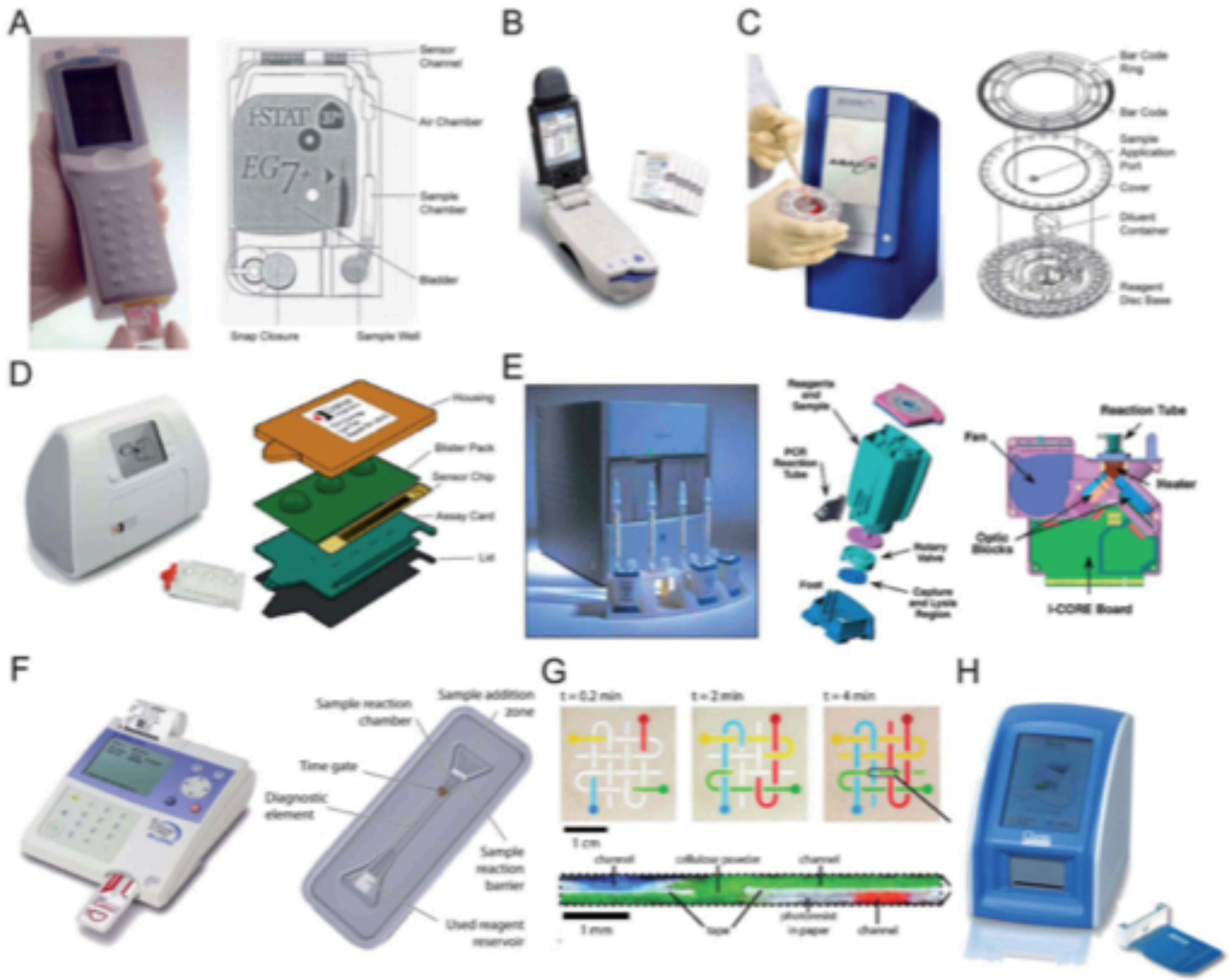




source www.genalyte.com

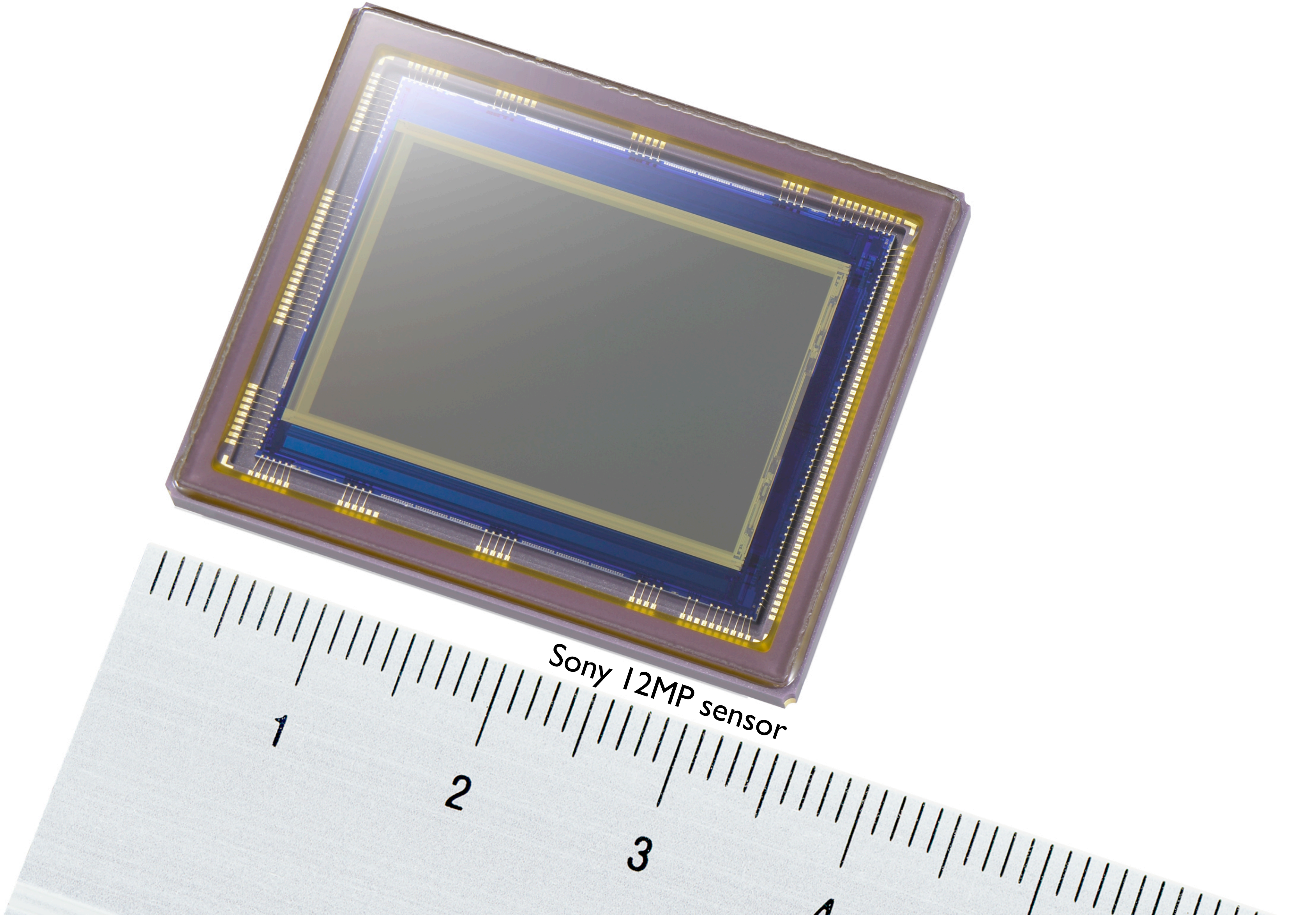
Genalyte leverages imec silicon photonics platform to develop and manufacture (low-volume production) its disposable bio-sensor chips.

NEED TO SIMPLIFY INSTRUMENT ZOO



Chin, et al., Lab on Chip, 2012, **12**, 2118-2134

SEMICONDUCTOR TECHNOLOGY IS AN IDEAL PLATFORM FOR HIGH CONTENT 'INSTRUMENTATION'



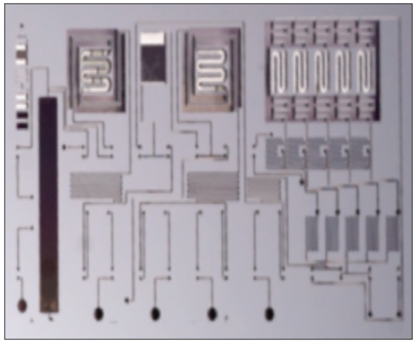
Sony 12MP sensor

EXTREMELY PERSONAL D_X

- Use most ubiquitous computing and networking platform: the **smartphone**

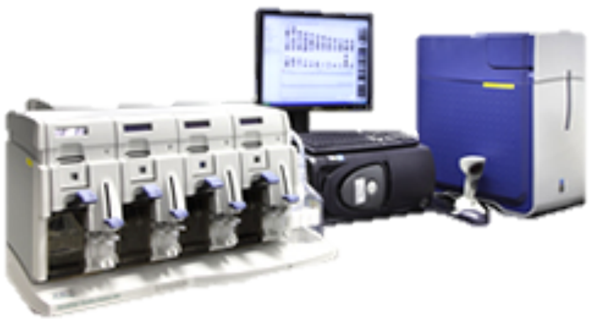
- Disposable tests (wetware and detection)
  - Possible assays: DNA/RNA (PCR based, electrochemical or optical detection), protein (affinity based, optical detection), metabolites/gases (electrochemical detection)
  - Fluid actuation built into chip (e.g. capillary force)

- Truly personal health management
  - Equipment-free and user friendly
  - Sensitive/specific/rapid (Si microfluidics)
  - Data processing, visualization and communication is already built-in



FUTURE DIRECTION FOR MOLECULAR ANALYSES

- Well-serviced
- Solutions exist



No compelling solutions on the market yet

Type	Benchtop	Portable	Smartphone
Where?	Clinical lab	Clinical lab or Dr's office	Home or Dr's office
What?	Expensive and dedicated instrument, low-cost disposable	Lower cost dedicated instrument, low-cost disposable	**No instrument**. More functions integrated into disposable. Data processing in smartphone or cloud.
Instrument cost	$10-100k	$1-5K	$0 or <$0.5k
Disposable cost	$1-10	$1-10	$1-10

BUT WE NEED A NEW TOOL-SET

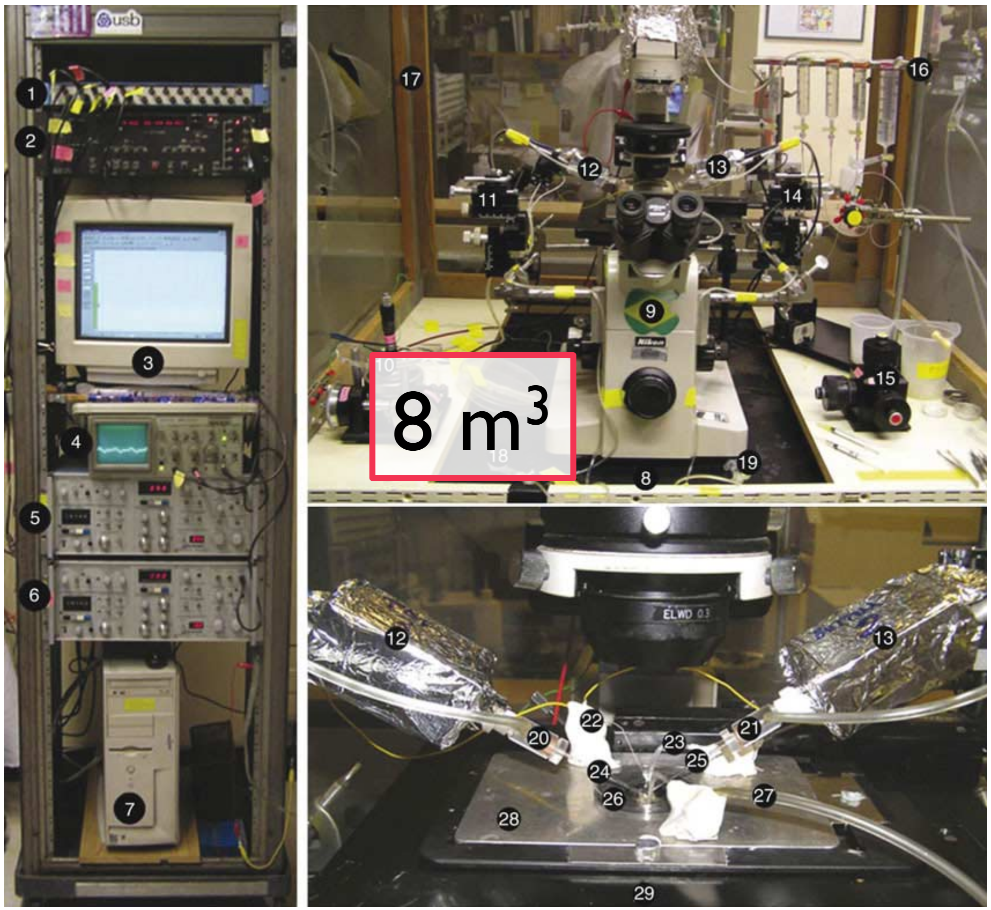
Eliminating the 'instrument' doesn't mean we need to give up on functionality

In the same way we reach for a pump or camera or valve we need a chip-based tool-box to work with.

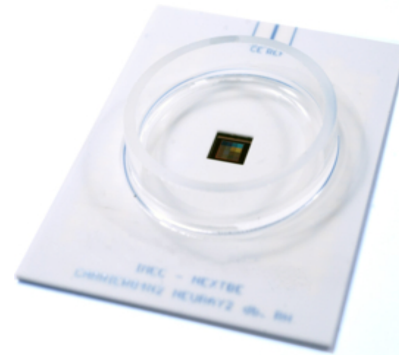
For diagnostics, we need to leverage advances in semiconductors but also drive the roadmaps.

SMALLER TECHNOLOGY, SMALLER FOOTPRINT

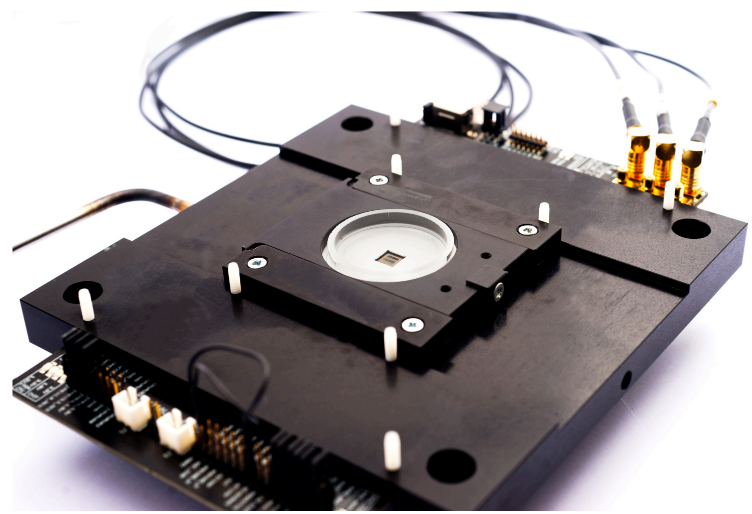
Classic patch clamp setup



CMOS chip setup

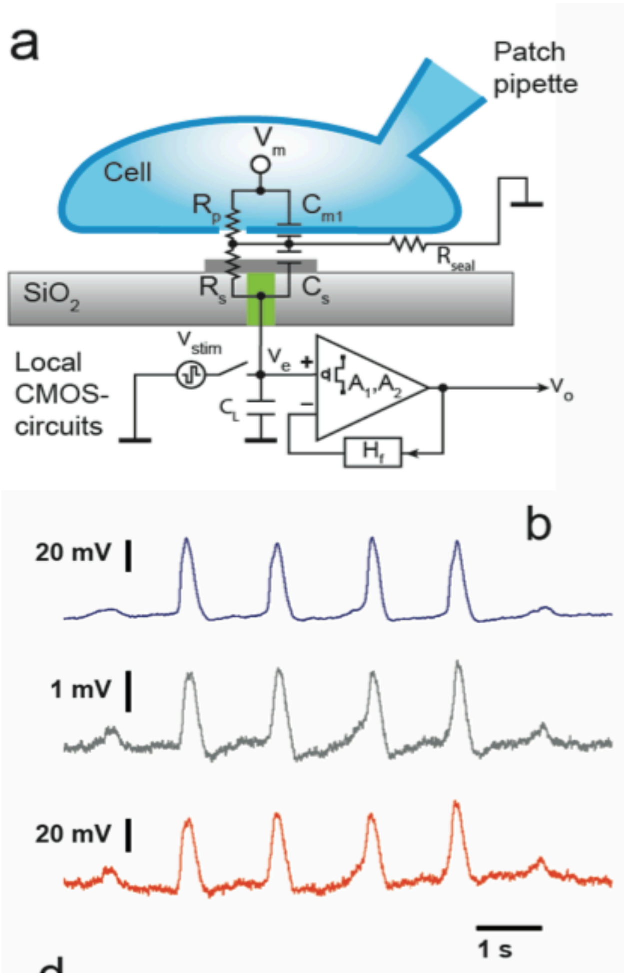


200 cm^3

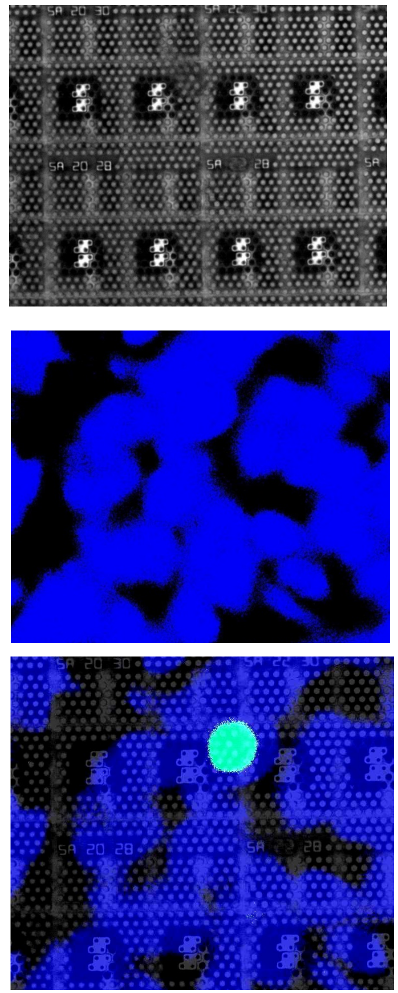


SINGLE CELL ANALYSIS

Single cell patch clamp



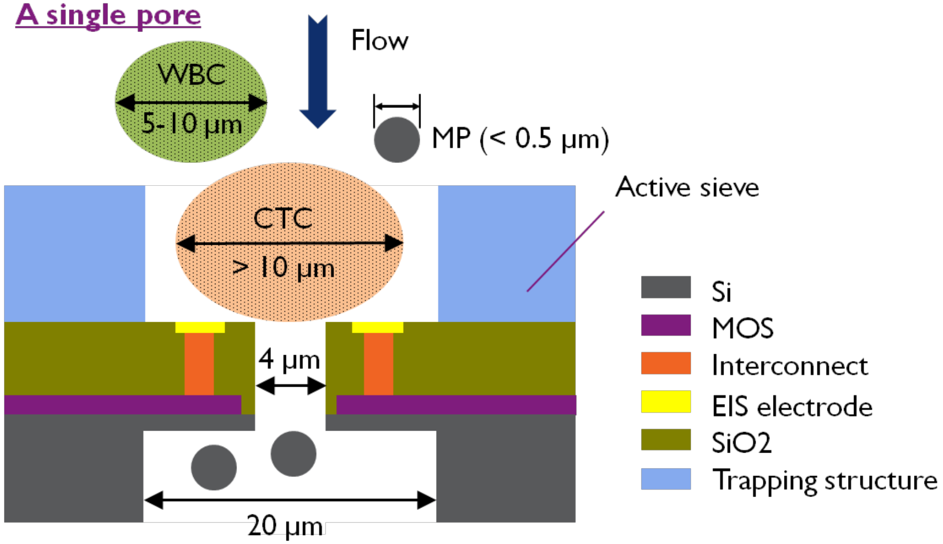
Single cell transfection

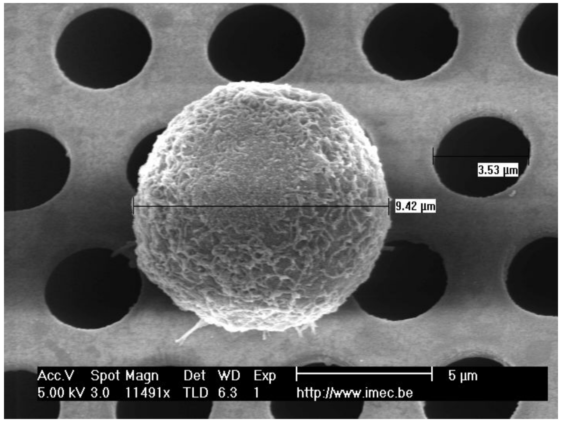


- 16,384 electrode array on active electronics
- Biocompatible for most demanding cell cultures (including stem cells)
- Parallel single-cell recording of neurons and cardiac cells
- Parallel single-cell patch clamp
- Addressable single-cell transfection
- Compatible with current workflow (microscope and incubator)

Single cell *analysis of cancer cells*

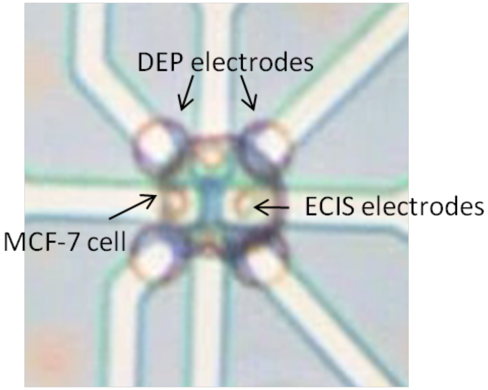
1) **Arrays of pores** to enrich potential cancer cells from blood

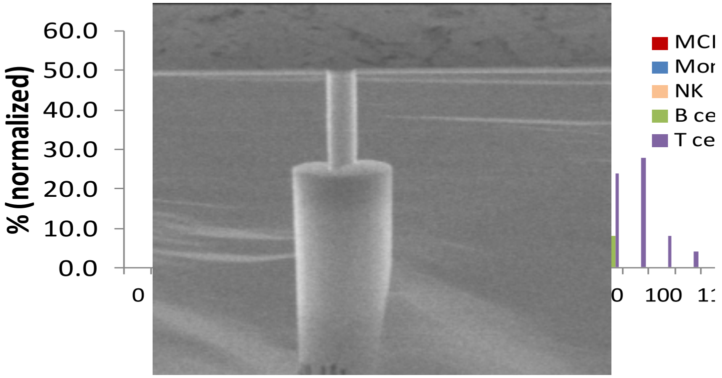




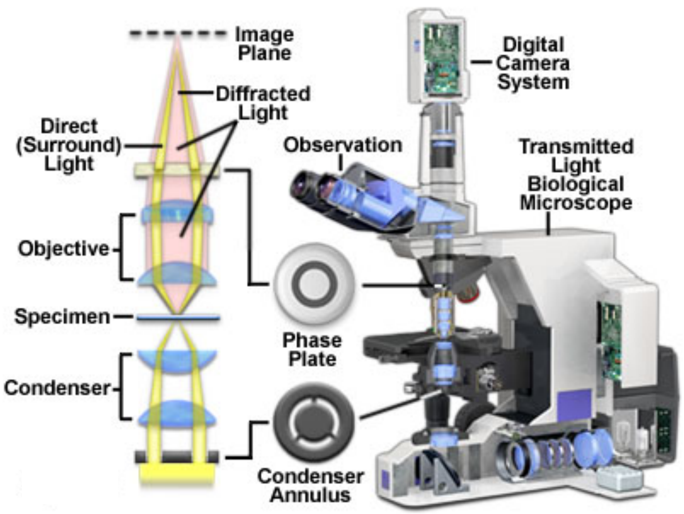
2) Identification of individual cancer cells by **single cell impedance sensing**

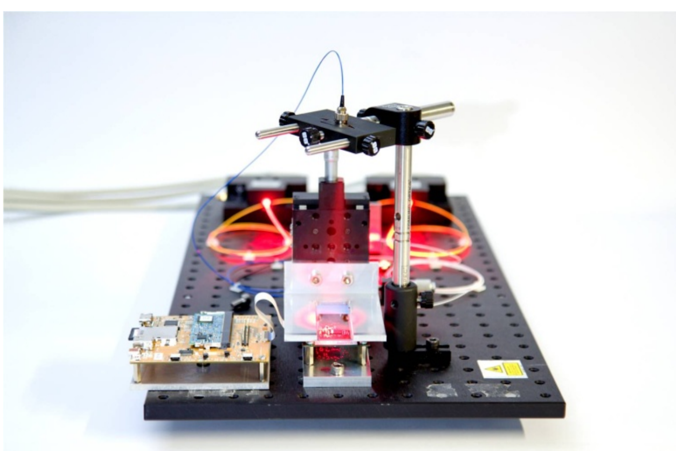
3) Molecular content to be extracted using backside **fluidic access**





LENS-FREE MICROSCOPY
COMPACT, LOW COST AND SCALABLE !





<u>Traditional optical microscope:</u>

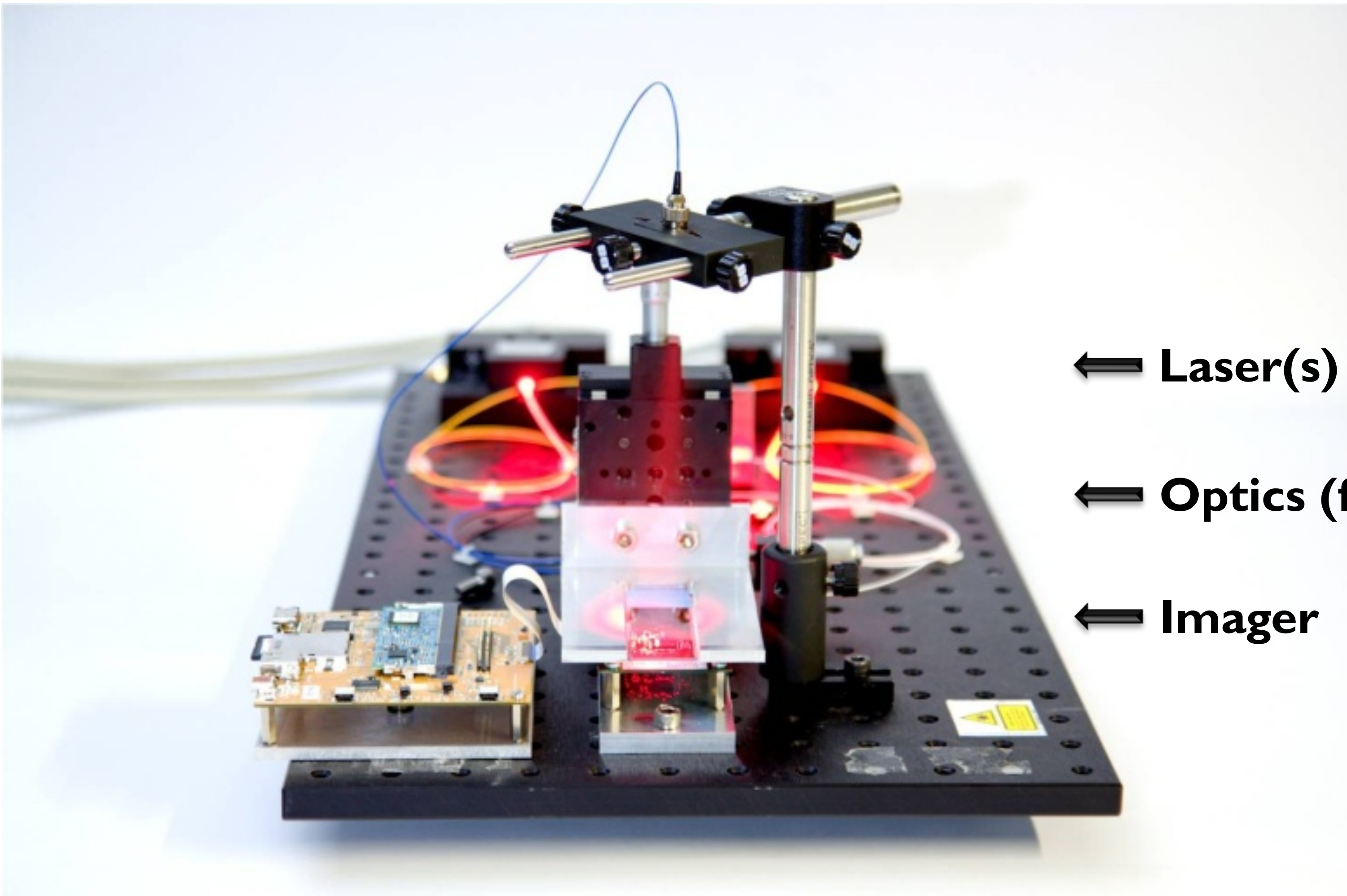
- Bulky, mechanically complex
- Focusing by <u>*mechanical*</u> movement of optical elements
- High quality lenses (does not scale well)
- Limited field of view (0.2 ~ 2 mm^2)

→ example = phase contrast microscope

<u>Lens-Free Microscope:</u>

- Compact, customizable, scalable → match with application!
- Focusing is part of post-processing in software
- No lenses (minimal optical and mech. components)
- Large field-of-view (FOV > 20mm^2)
- High resolution (e.g. < 2µm, can be tuned)

LENS-FREE MICROSCOPY: THE PROTOTYPE



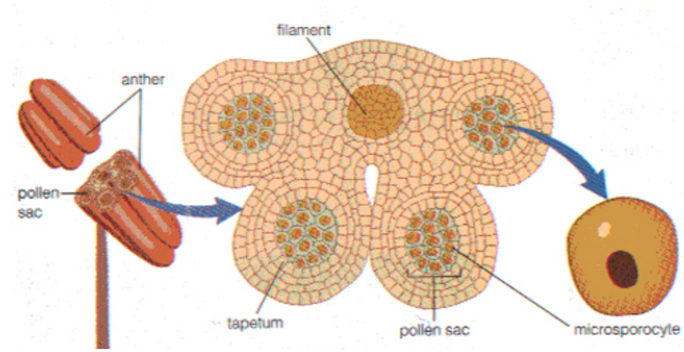
⟸ Laser(s)

⟸ Optics (fibers)

⟸ Imager

(Optionally) reflective collimator

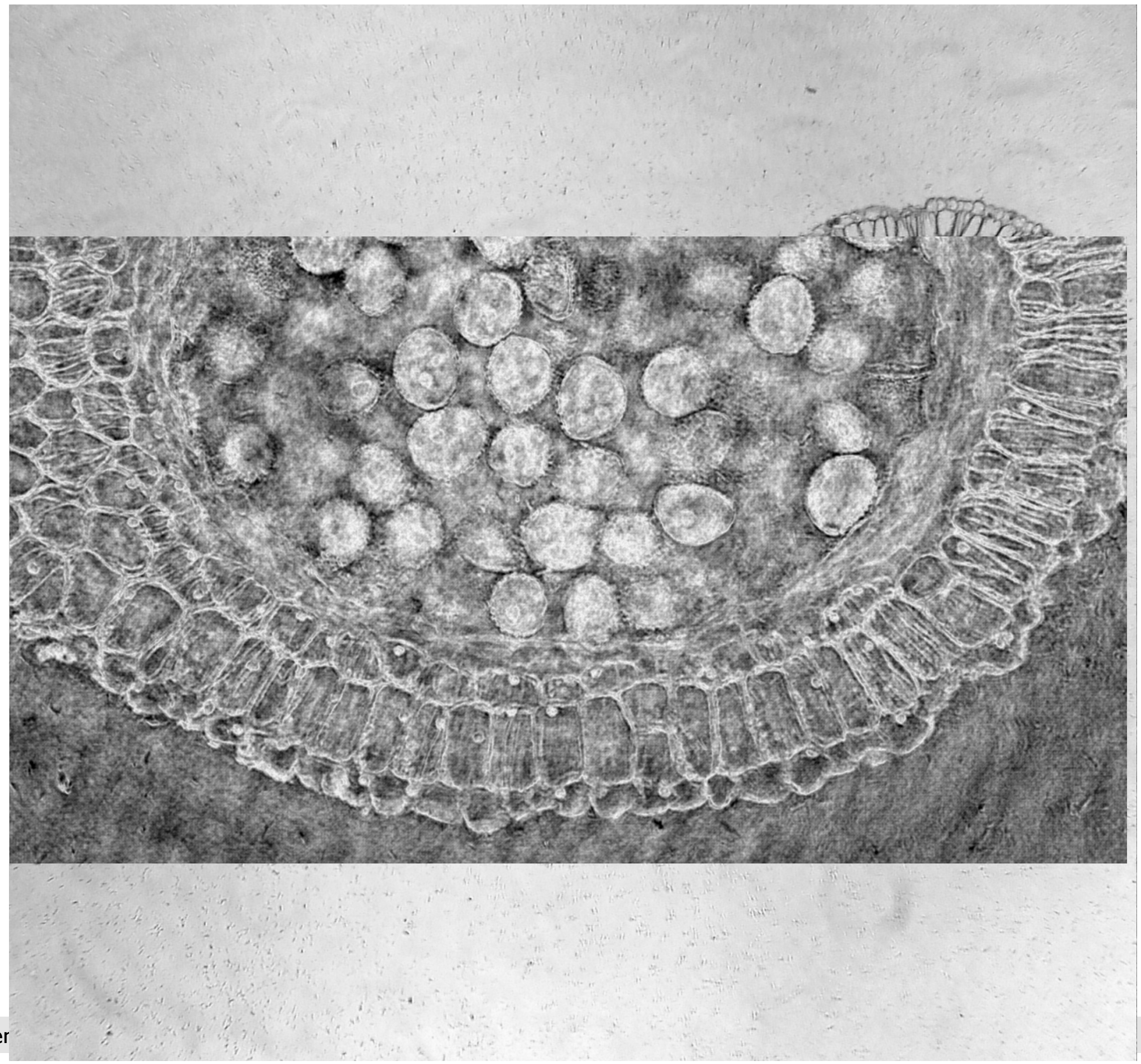
EXAMPLE: LILY ANTHER
LENS-FREE VS. PHASE CONTRAST



Raw imager output

Reconstructed lens-free image

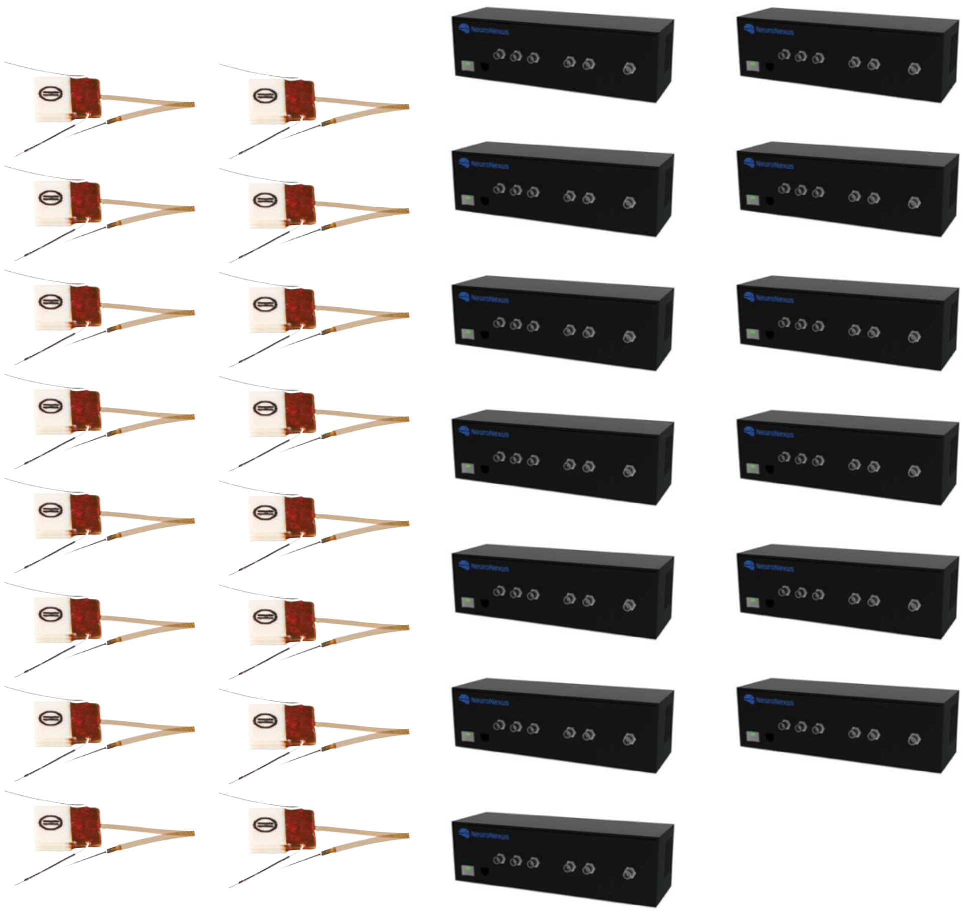
Reference Phase-contrast

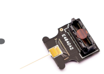


COMPLEX INTEGRATION IS KEY

28
16-electrode probes

13
4-channel preamp+ADC

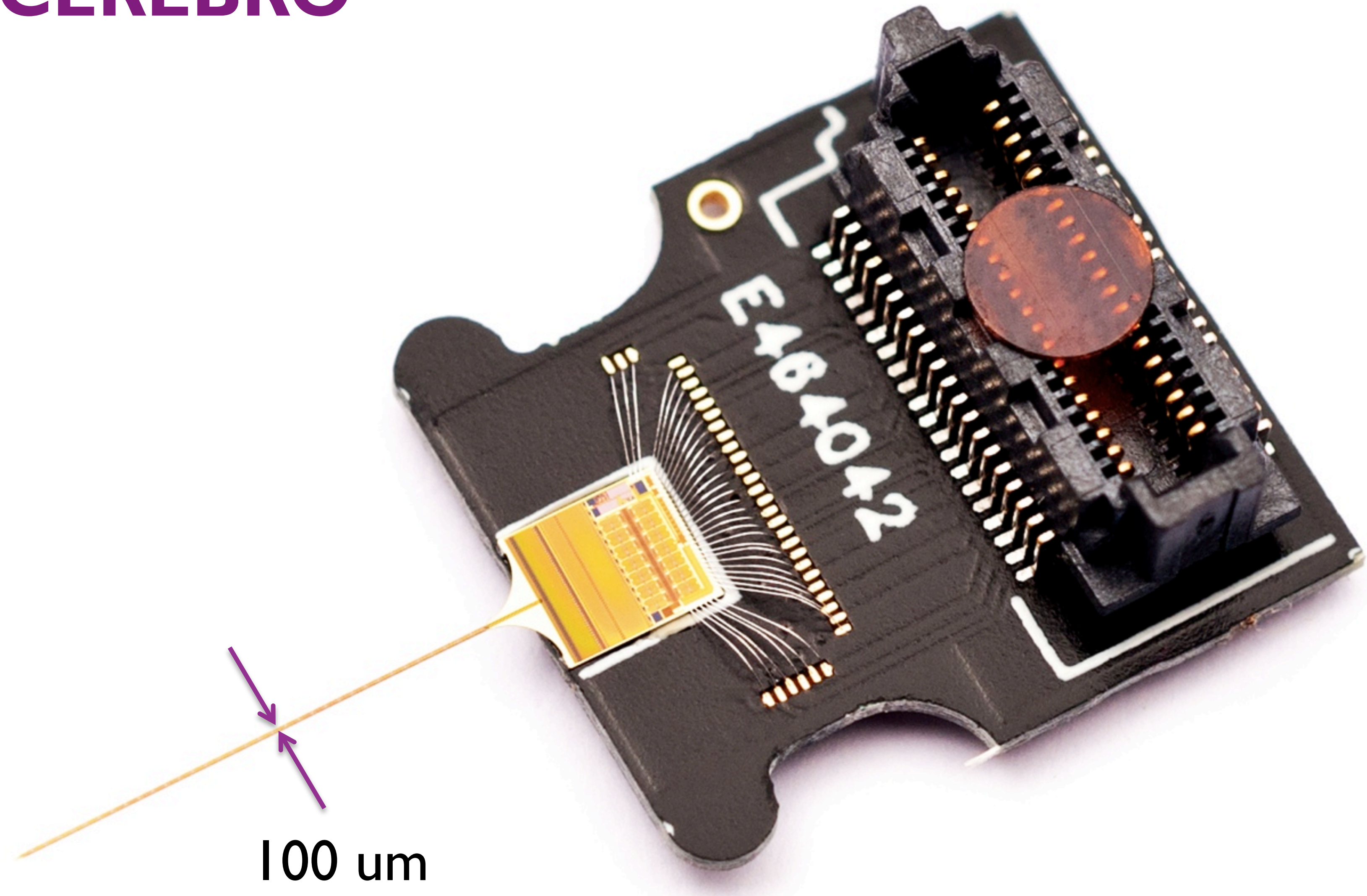




CEREBRO

- 456 electrodes
- On-chip amplification, filters, analog-to-digital conversion for 52 channels
- Very-low-noise: 4 µVrms
- Recording + stimulation

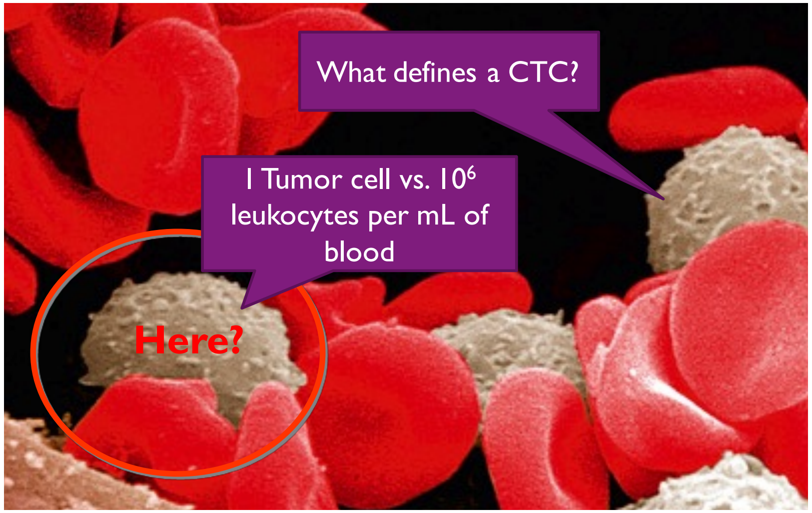
CEREBRO



GRAND CHALLENGE IN CANCER DETECTION

- **90% of cancer patients die from metastasis**
- Metastasis correlates with the number of **circulating cancer cells** that may spread the disease
- **CTC isolation is very challenging!**

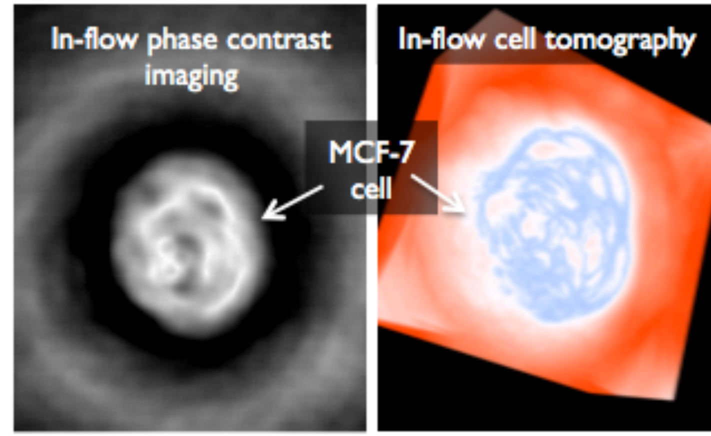
  1 mL of blood contains:
  - 10^9 blood cells
  - 10^6 white blood cells (WBCs)
  - 1 CTC
- Molecular characterization is inhibited by WBC background
  - **Need for single cell characterization and fluidic access!**



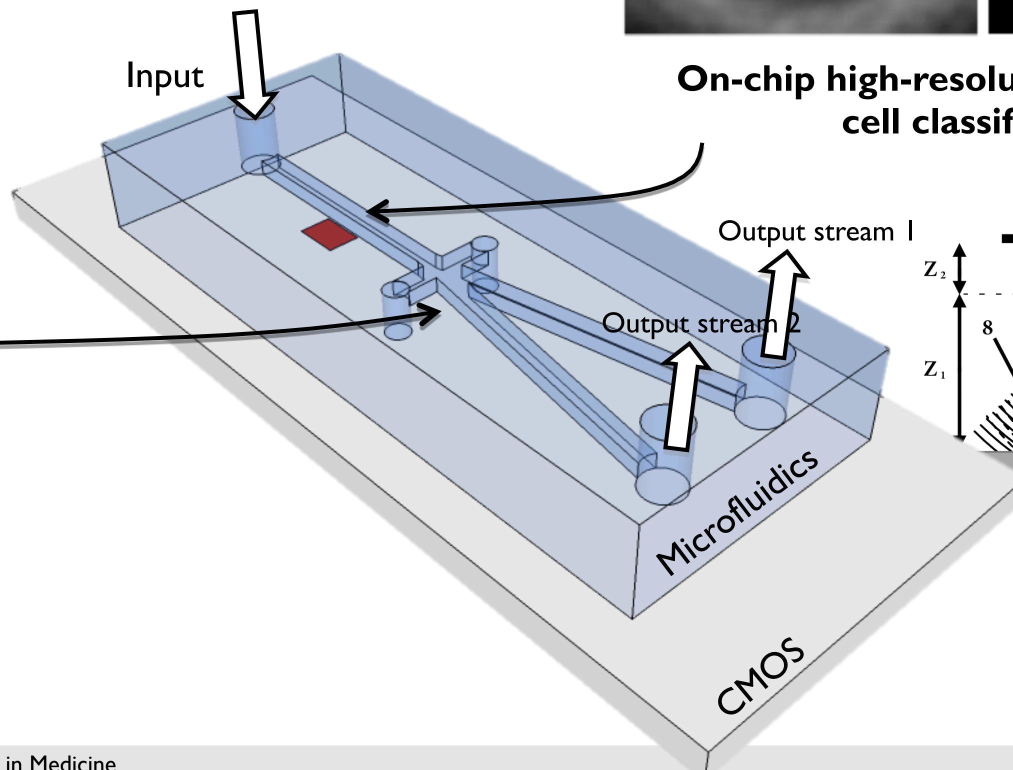
HIGH-THROUGHPUT IMAGING FLOW CYTOMETER

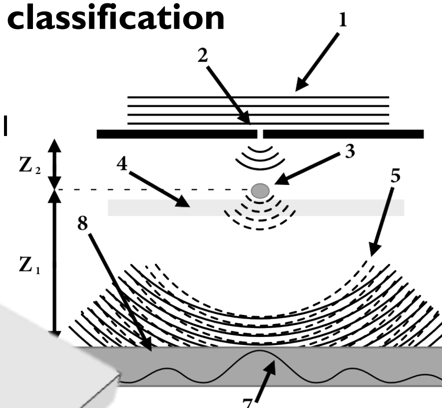
Scalable to 20,000,000 cells/s

>1000-fold improvement over current systems

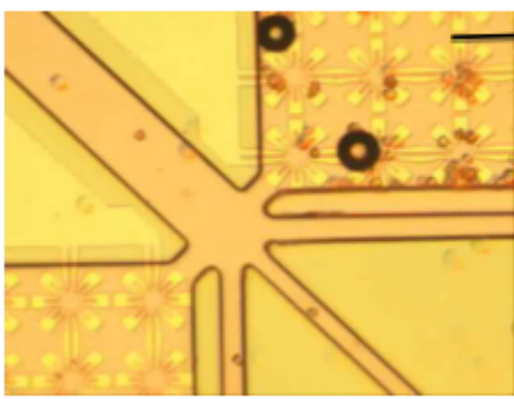


On-chip high-resolution imaging for cell classification





Fast microfluidic bubble-jet cell routing



IN SUMMARY

There are a lot of instruments in the market, probably too many.

There is clear desire to implement functionality onto the disposable but this requires complex integration.

Semiconductor technology is a key enabling platform but the diagnostics industry needs a ‘tool-box’ to work with.

ASPIRE
INVENT
ACHIEVE

Thank you!