

Manufacturing Biology with Smart Silicon: Overcoming Analytical Bottlenecks in Advanced Therapy Production

Marcel Zevenbergen

Imec, the leading independent, not-for-profit R&D hub in nano-electronics and digital technologies

Founded in **1984**

Unique ecosystem, collaborating with **600+ industrial partners**

~ $4B invested in **leading-edge semiconductor fabs**

>6500 employees

Focus on **industry-relevant technology for compute & system technologies, datacom, connectivity, health, automotive and specialty markets**

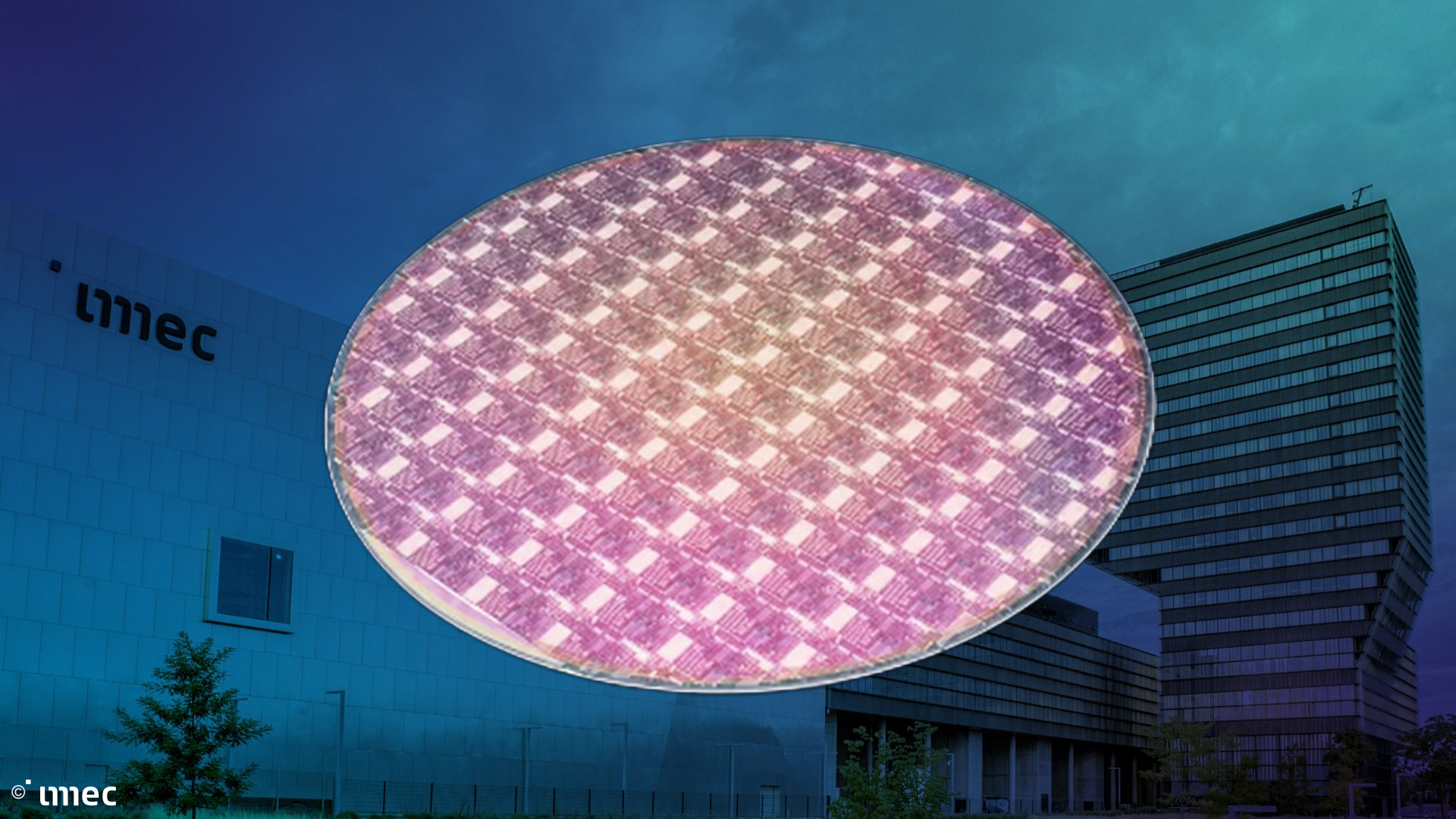
2024: €1B revenue, 187 patent applications, 2627 peer reviewed publications

imec

For 40 years, we have been pioneering the semiconductor roadmap.



imec


imec
© imec

The potential impact of microchips in Health is unprecedented



WE ARE HERE

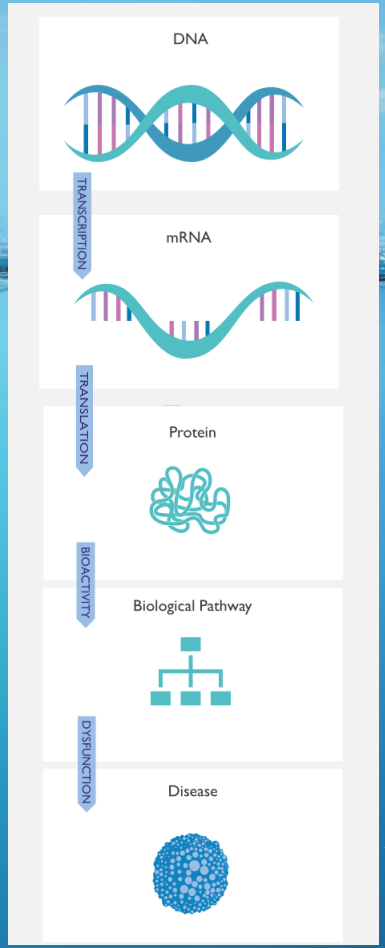
An estimated less than 1% of the biological data is accessible

Building **useful AI models** in **biology** will require **much more data**



imec

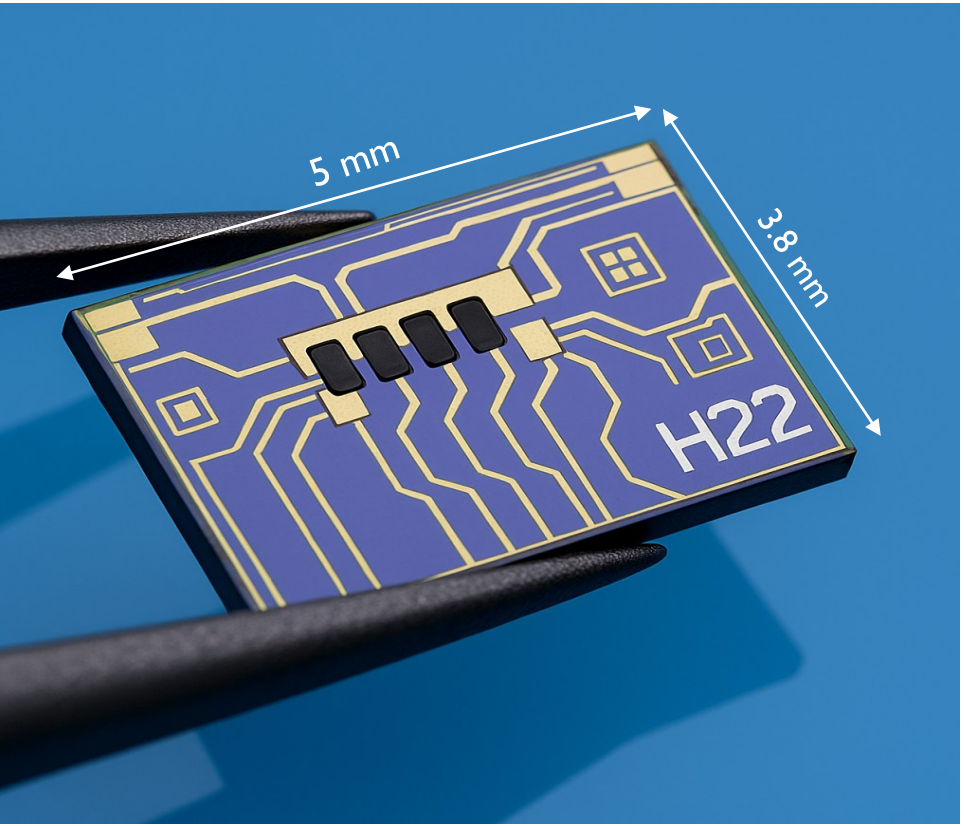
TO DIVE DEEPER INTO THE COMPLEXITY OF LIFE OUR TOOLSET NEEDS AN UPDATE



COMPLEXITY

imec

Advantages of chip technology

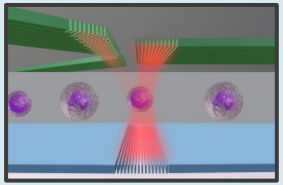


Miniaturization → multi-modal sensing

Microfluidics → µL sample volume, fast time to result

Our deeptech toolbox to enable real-time analytics

On chip flow cytometer



High-throughput cell sorting

- Rapid on-chip cell sorting
- 5000 cells/
- sec/channel achieved
- No moving parts: excellent durability

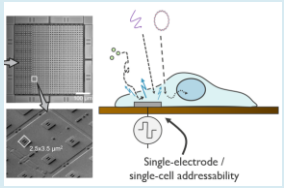
Label free cell phenotyping



Miniaturized microscope

- No optics
- No focusing, no mechanics
- Large field of view (20-500 mm^2)

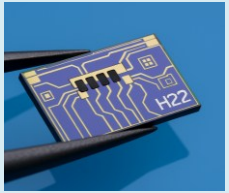
Electroporation



Payload delivery

- Payload delivery (CarT)
- Non viral-vector
- Single cell precision

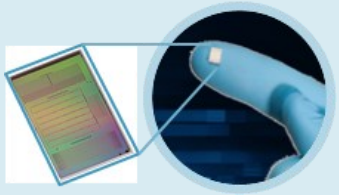
PATcube



Metabolite, ROS sensors

- Follow general organ cell health in situ
- Cell stress response upon perturbations

µELISA



Protein sensors

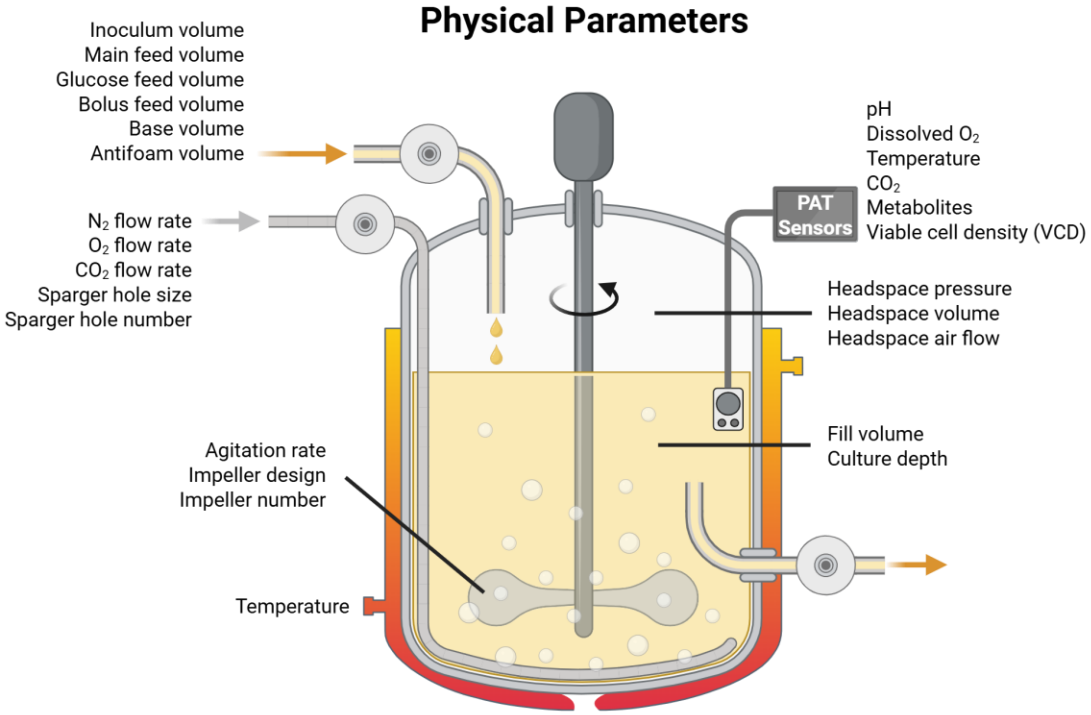
- Follow immune response/toxicity real-time
- Intermittent cytokine profiles (target: every 30 minutes)

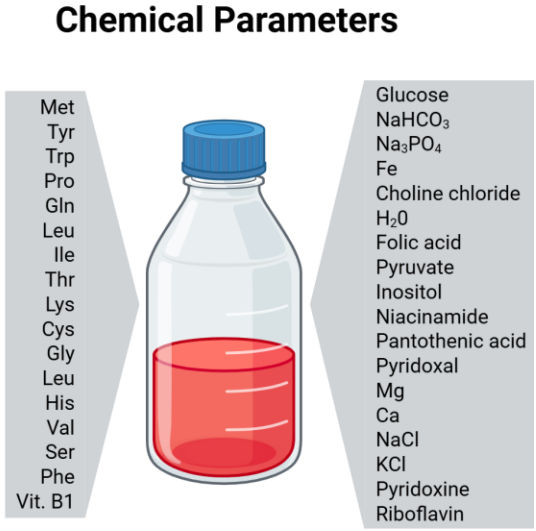
WHY?

imec

public

Massive parameter space In Bioprocessing

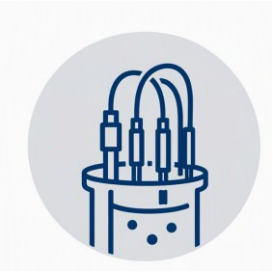




Content provided by Matteo Planchestainer, FHNW

High-throughput upstream screening & monitoring tools are critical for efficient parameter optimization

Conventional PAT Limits High-Throughput Bioprocess Monitoring



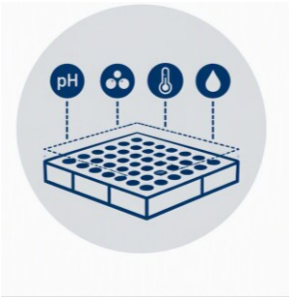
Multiple probes compete for limited space and can affect flow, headspace and reactor operation



Frequent offline sampling increases workload, sample consumption and contamination risk



Intermittent measurements make real-time process understanding and control difficult



High-throughput systems require seamless medium control and compact, multiparameter sensing integrated directly into the consumable

PATcube: a new generation of inline, multiparameter sensors

Enabling online monitoring for actionable insights

- ✓ Multiparameter sensor

  pH, DO, T°, glucose, lactate, ROS
  cell density, electrical conductivity (EC)

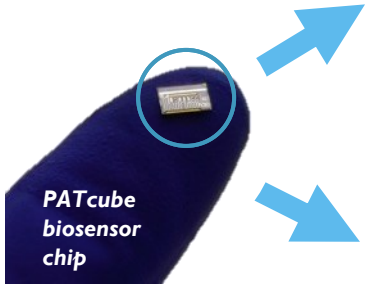
- ✓ Inline & real-time

- ✓ Single-use

- ✓ Expandable parameter selection

  Roadmap: ions, cell viability, proteins…

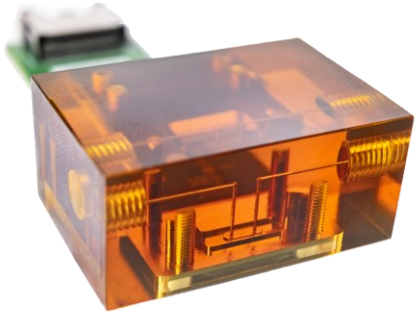
- ✓ Customizable form factor



Form factors achieved so far:



Probe: fits a standard PG 13.5 port



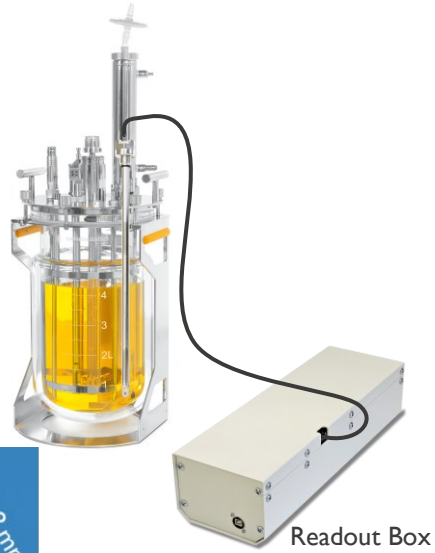
Microfluidic flow cell

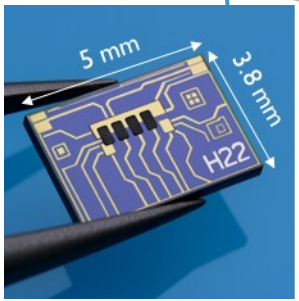
PATcube: quick glance into sensor performance

Technology demonstrators
tested including Readout Box

PATcube probe



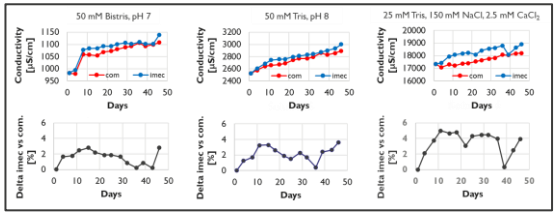




Readout Box

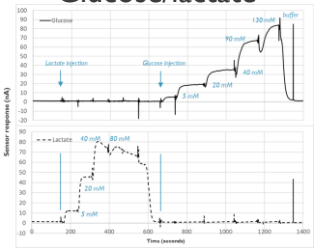
PATcube chip

Electrical conductivity



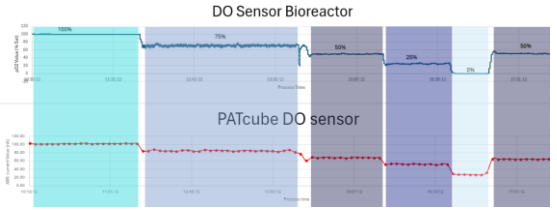
- Demonstrated sensor accuracy over 60 days, both in lab and bioreactor
- Absolute relative error compared to COTS sensor <5%

Glucose/lactate



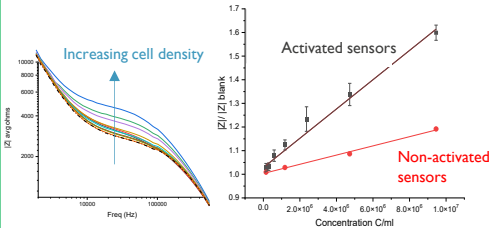
- No cross-sensitivity between glucose/lactate

Dissolved oxygen



- Demonstrated sensor accuracy over 30 days, both in lab and bioreactor
- No sensor degradation

Cell density (CHO Culture)

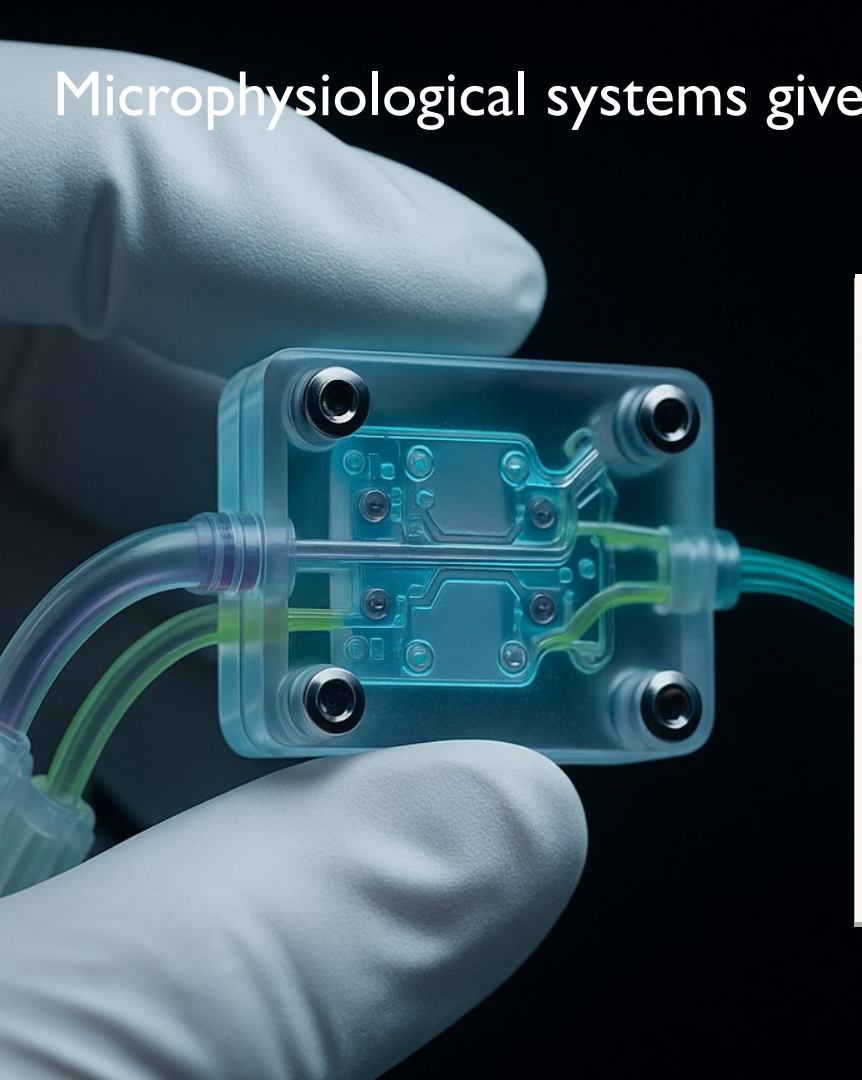


- Range: 10^5 - 2.5×10^7 (cells/mL)
- Work in progress: *viable* cell density

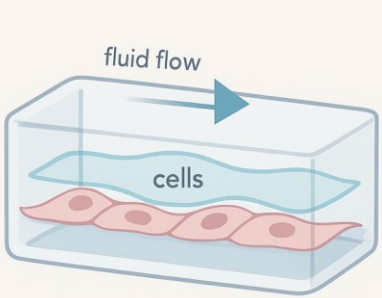
- Sterilizable & sterile insertion
- pH available as well (as separate die)
- Work in progress on ROS sensor

Microphysiological systems give us the body in miniature.

Sensors give it a voice.

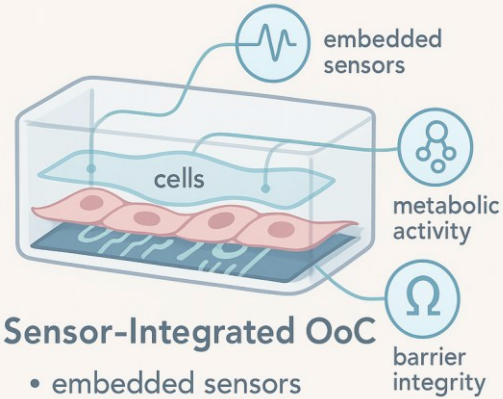


static snapshots vs. living data



Traditional OoC

- periodic measurements
- limited readouts
- end points only



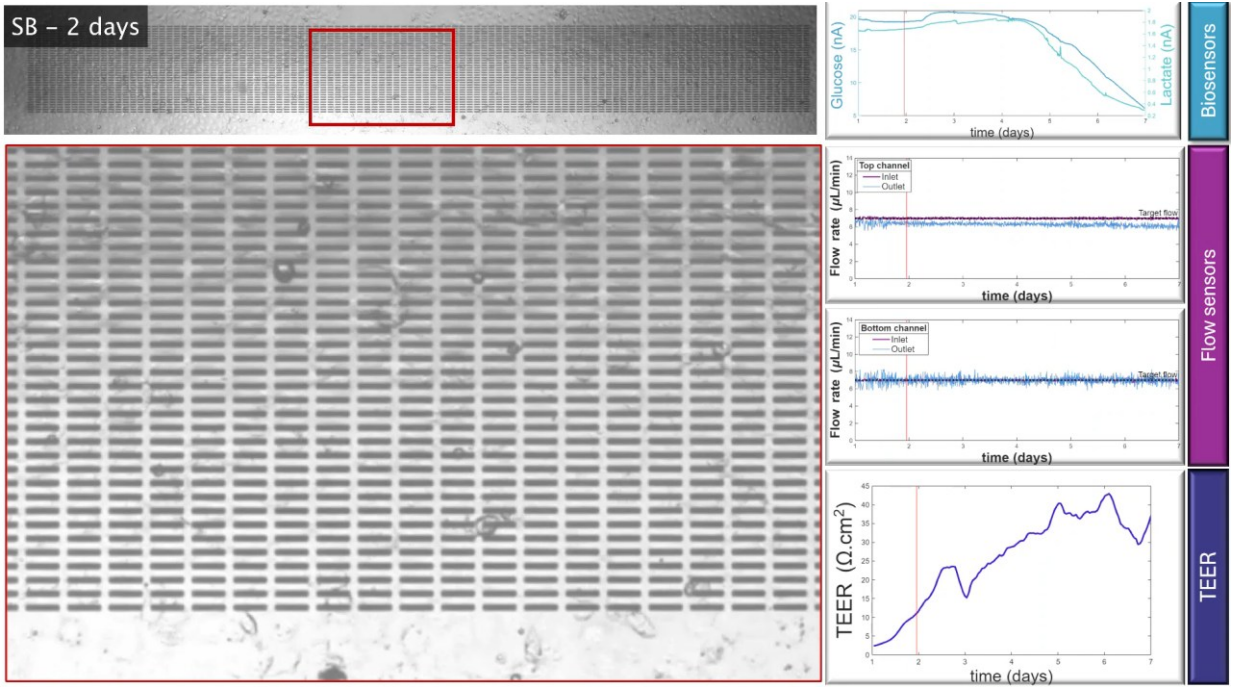
Sensor-Integrated OoC

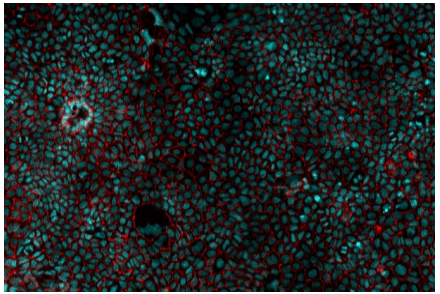
- embedded sensors
- continuous monitoring
- real-time insights

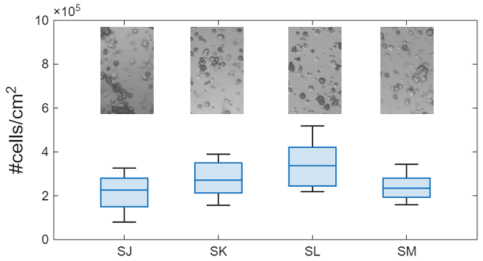
A platform that's not just a model — but a living data tracker

Showing our multi-model data capture appraoch

Insights beyond endpoint measurements: synchronized live imaging, flow rate, TEER, and metabolic sensing (biosensors for glucose, lactate and ROS measurements).







Automated cell seeding leading to **reproducible** and **robust monolayer** formation

public

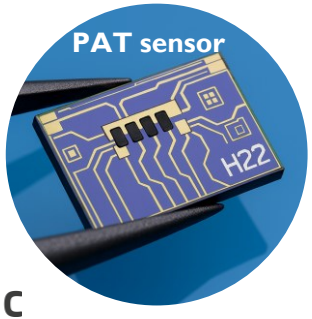
CSEM-IMEC Collaboration

Integration of PAT sensor into fluidic lid

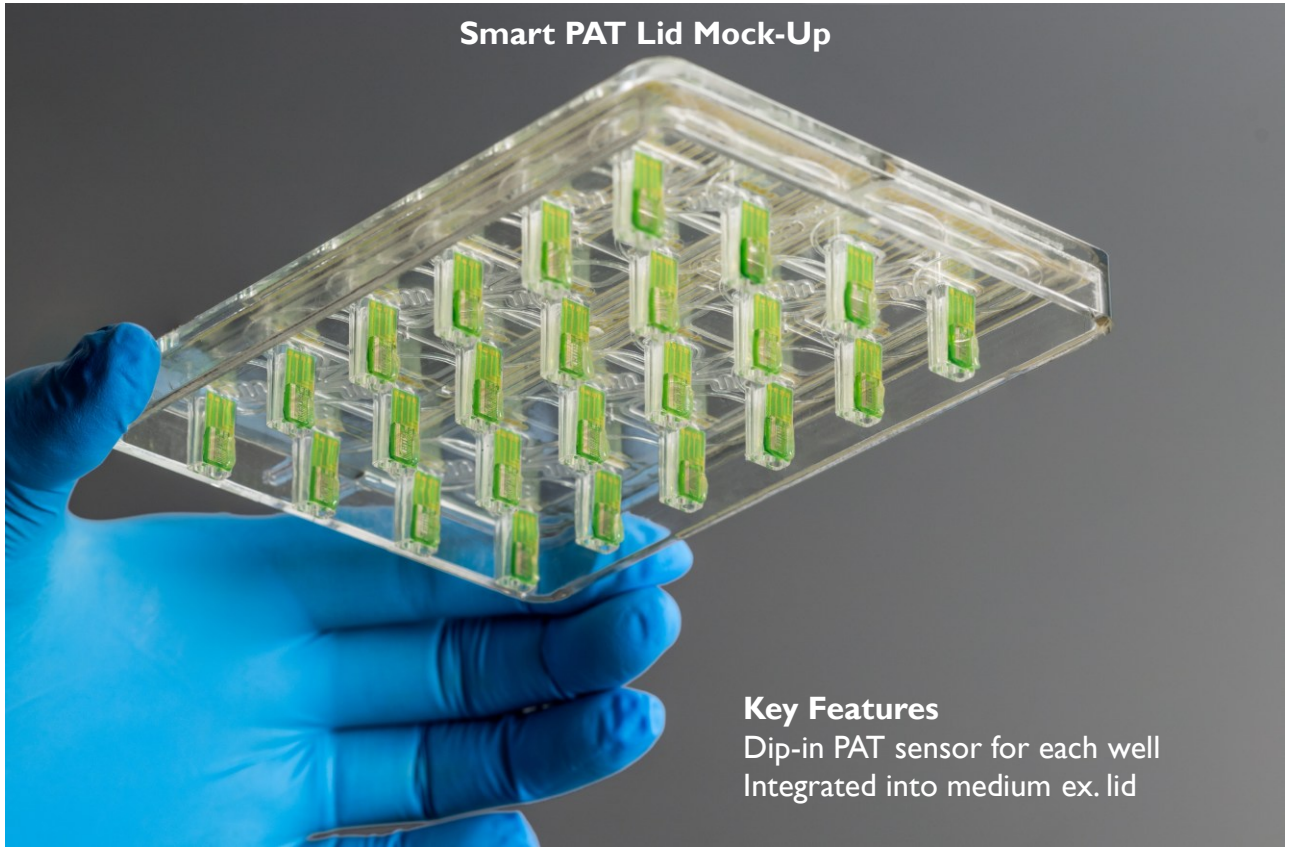


csem

imec



imec



public

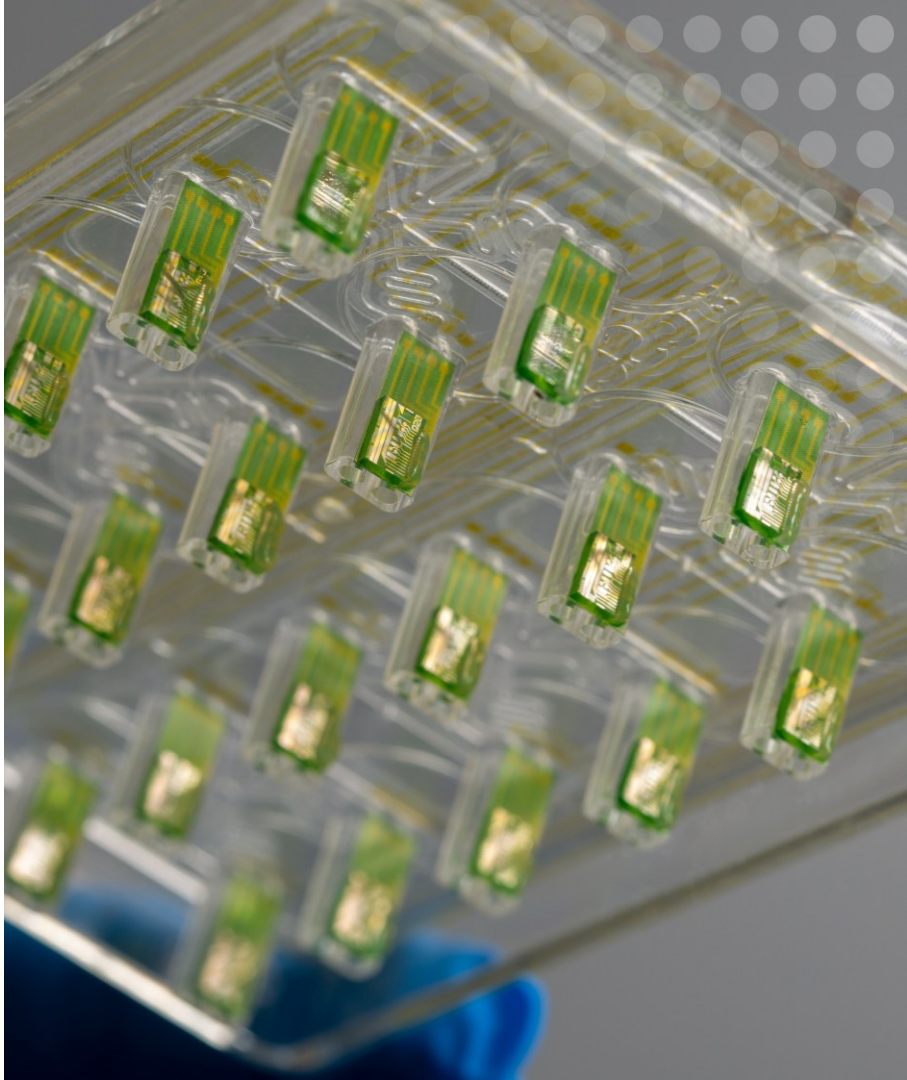
Broad range of applications

Long-term cell culture

- Adherent cells (e.g. neurons, MSCs)
- Suspension cells (e.g. CHO, HEK)
- Organoids

Bioprocessing upstream screening

- Clone selection
- Media formulation optimization
- Can be applied for fed-batch & perfusion



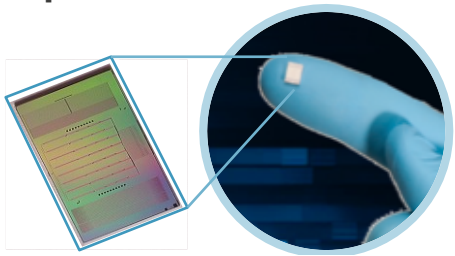
imec

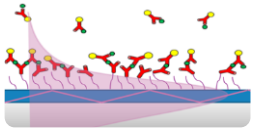
Product titers and contaminant control at-line

HCP & residual DNA

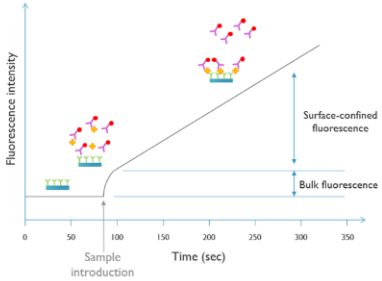
Application-specific components:
μELISA chip for HCP quantification

imec's μELISA



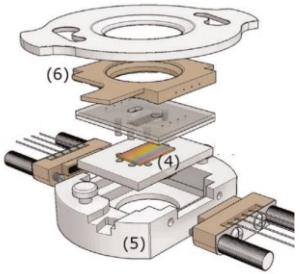


10 minutes, few μL sample
Fully microfluidics compatible
Ready for integration and automation



Integrated demonstrator for application:

First test instrument for testing
Design and fabrication of first proof-of-concept cartridge
Software and analytics package



Example of simple fluidic/chip and instrument set-up

imec

public



Marcel.Zevenbergen@Imec.nl