CMOS Biochips: The Good, the Bad, and the Hype

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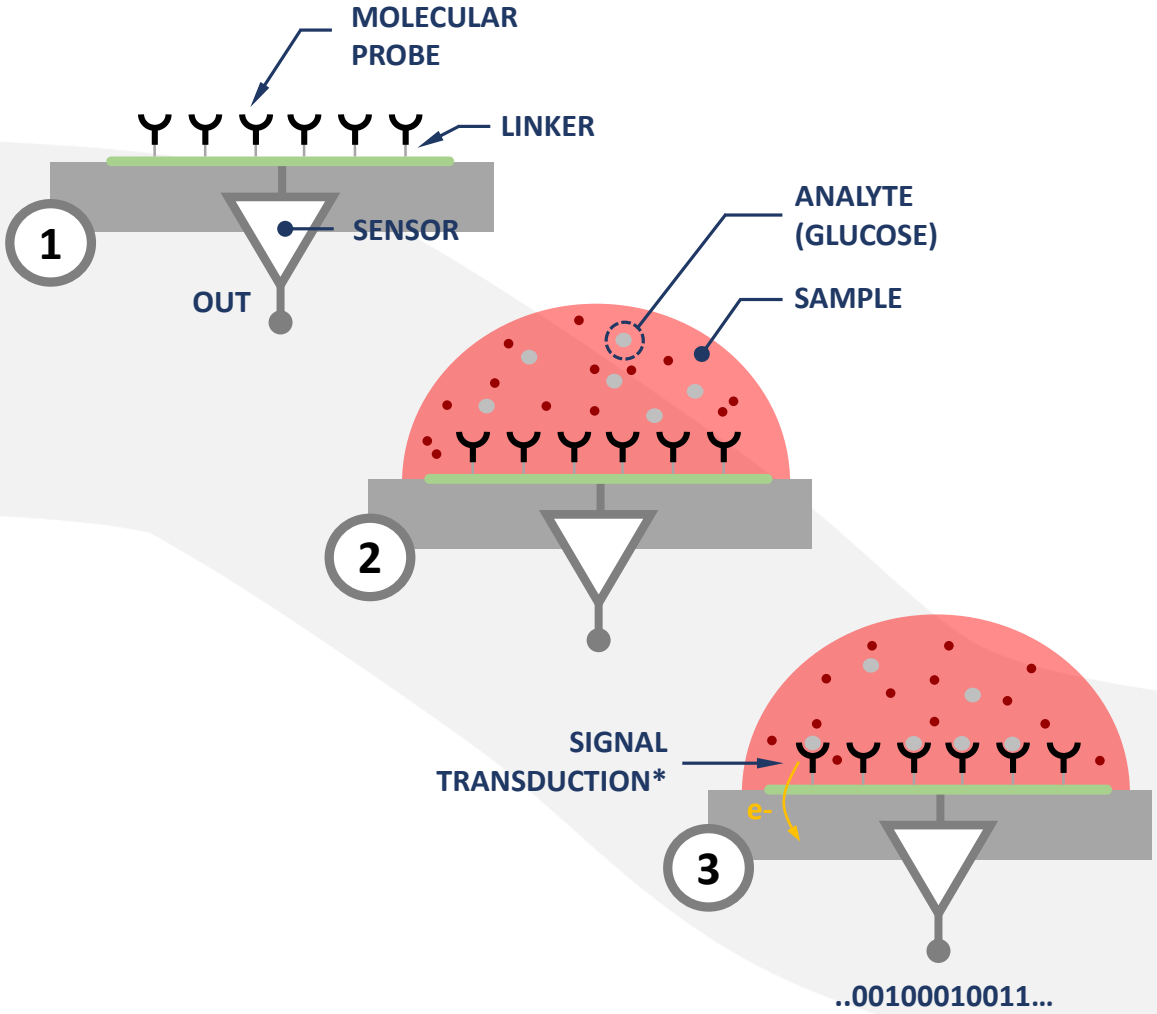
InSilixa

QUESTION 1:

What is a Biosensor?

Biosensors: Basic Concept

Detecting analytes in (aqueous) samples using “electronic” devices



* Transduction can be electronic, optical, mechanical, etc.

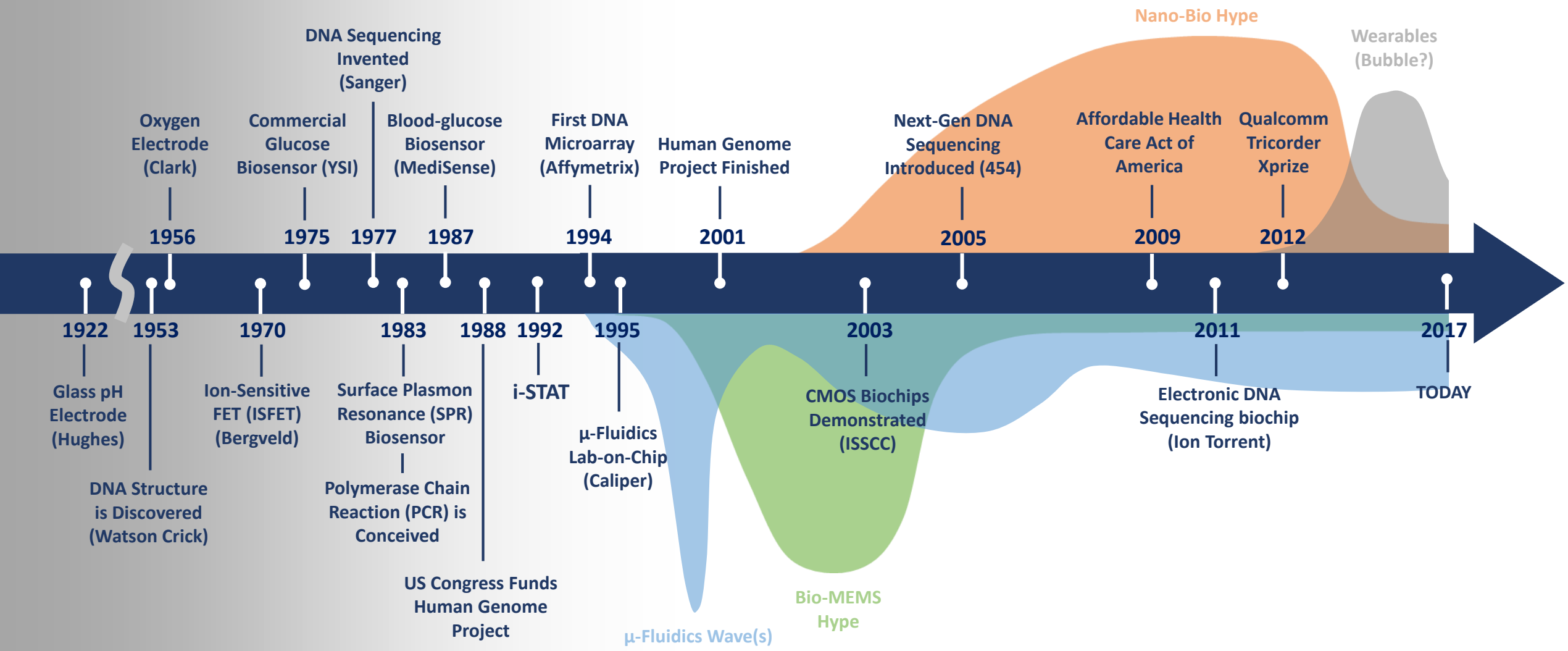
Biosensors: Analytes

Detecting analytes in (aqueous) samples using “electronic” devices

Examples	Concentration (Copies/ml)	Types/Strains*
Water	**3.3×10^{22}**	**-**
Glucose	10^{18}	1
Cholesterol	8×10^{17}	2
Antibodies/Hormones	10^{8}	> 10,000
DNA for Forensics	10^{7}	20
Upper Respiratory Viruses (*Flu A*, *Flu B*, *Rhinovirus*, etc.)	10^{4}	> 50
HIV Virus in Blood	4×10^{2}	> 50
***M. Tuberculosis* Bacteria**	10^{2}	> 300
Bacteria in Blood	10	> 1000
Food Poisoning Bacteria (*Salmonella*, *Listeria*, *E. Coli*)	1	> 50

* Including genotypes

History

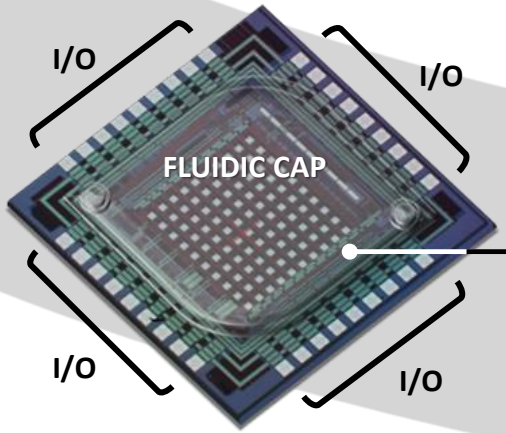

Nano-Bio Hype
Wearables (Bubble?)
DNA Sequencing Invented (Sanger)
Oxygen Electrode (Clark)
Commercial Glucose Biosensor (YSI)
Blood-glucose Biosensor (MediSense)
First DNA Microarray (Affymetrix)
Human Genome Project Finished
Next-Gen DNA Sequencing Introduced (454)
Affordable Health Care Act of America
Qualcomm Tricorder Xprize
1956
1975
1977
1987
1994
2001
2005
2009
2012
1922
1953
1970
1983
1988
1992
1995
2003
2011
2017
Glass pH Electrode (Hughes)
DNA Structure is Discovered (Watson Crick)
Ion-Sensitive FET (ISFET) (Bergveld)
Surface Plasmon Resonance (SPR) Biosensor
Polymerase Chain Reaction (PCR) is Conceived
US Congress Funds Human Genome Project
i-STAT
µ-Fluidics Lab-on-Chip (Caliper)
µ-Fluidics Wave(s)
CMOS Biochips Demonstrated (ISSCC)
Bio-MEMS Hype
Electronic DNA Sequencing biochip (Ion Torrent)
TODAY

QUESTION 2:

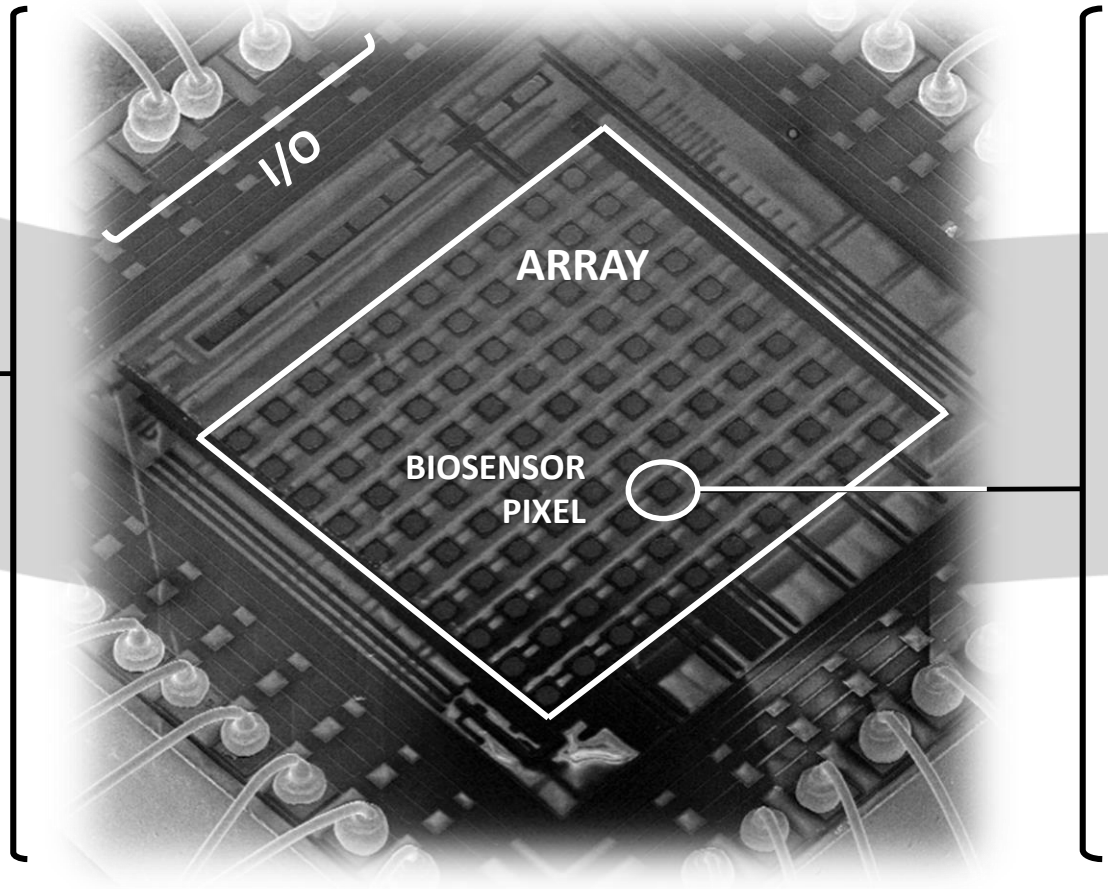
What is a CMOS biochip (biosensor)?

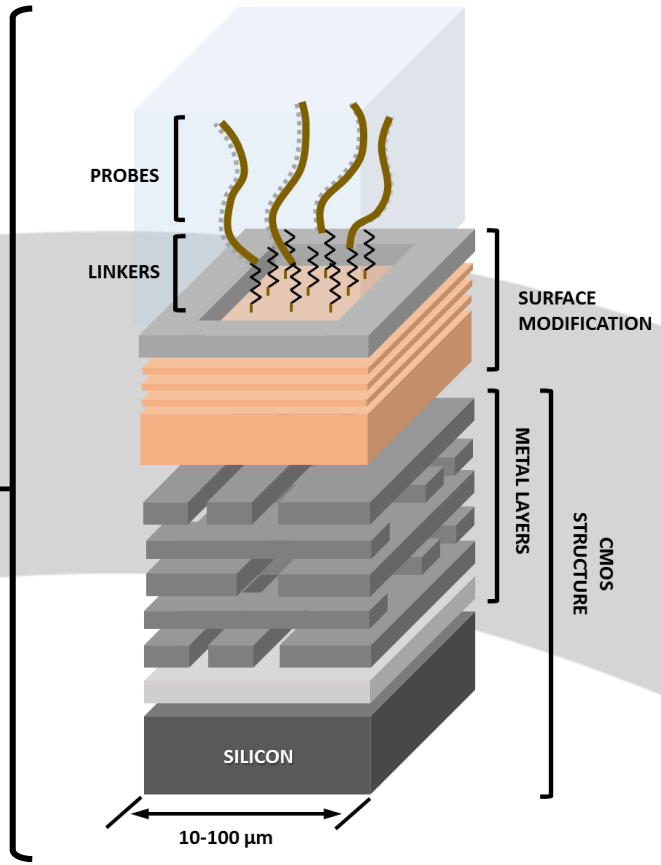
CMOS Biochip Anatomy

Modified CMOS chips capable of parallel biosensing



BIOCHIP MODULE

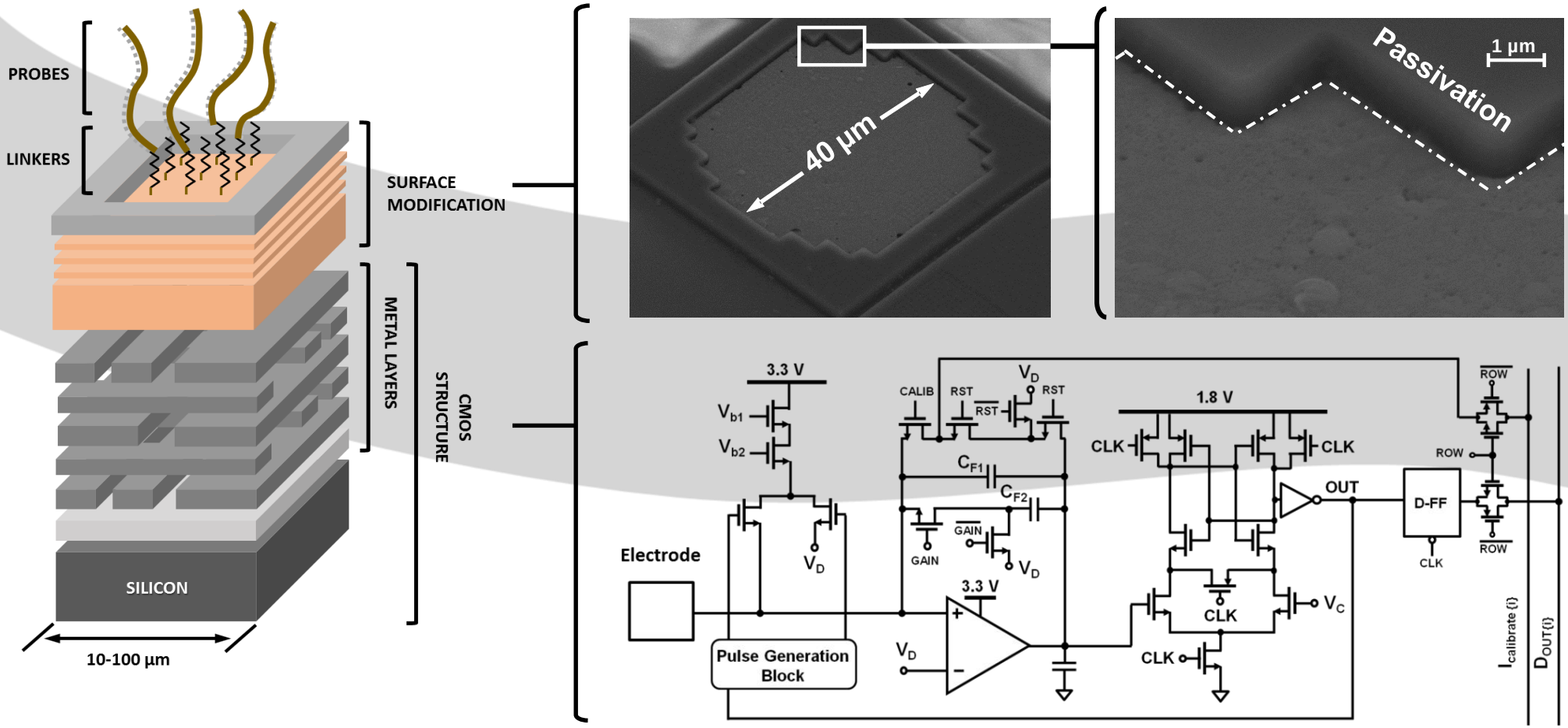




BIOSENSOR "PIXEL"

Biosensing “Pixel” Structure

“Pixels” include bio-recognition elements (probes), transducer, and CMOS-integrated sensor

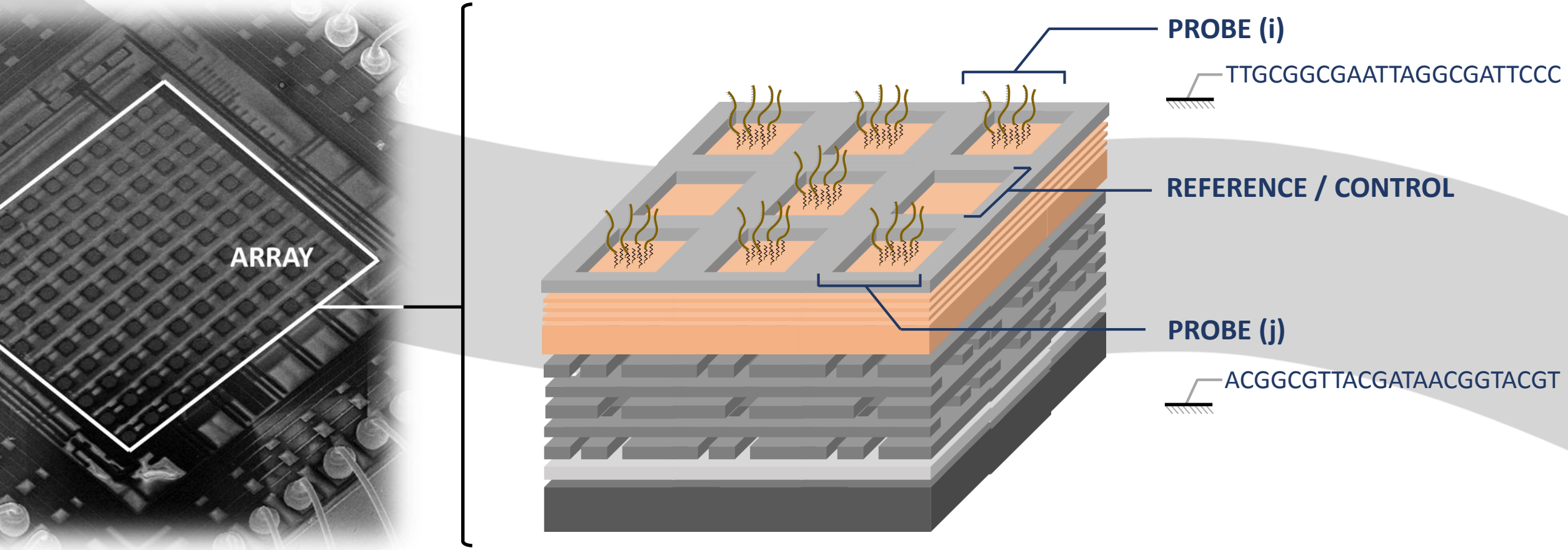


CMOS-COMPATIBLE TRANSDUCER

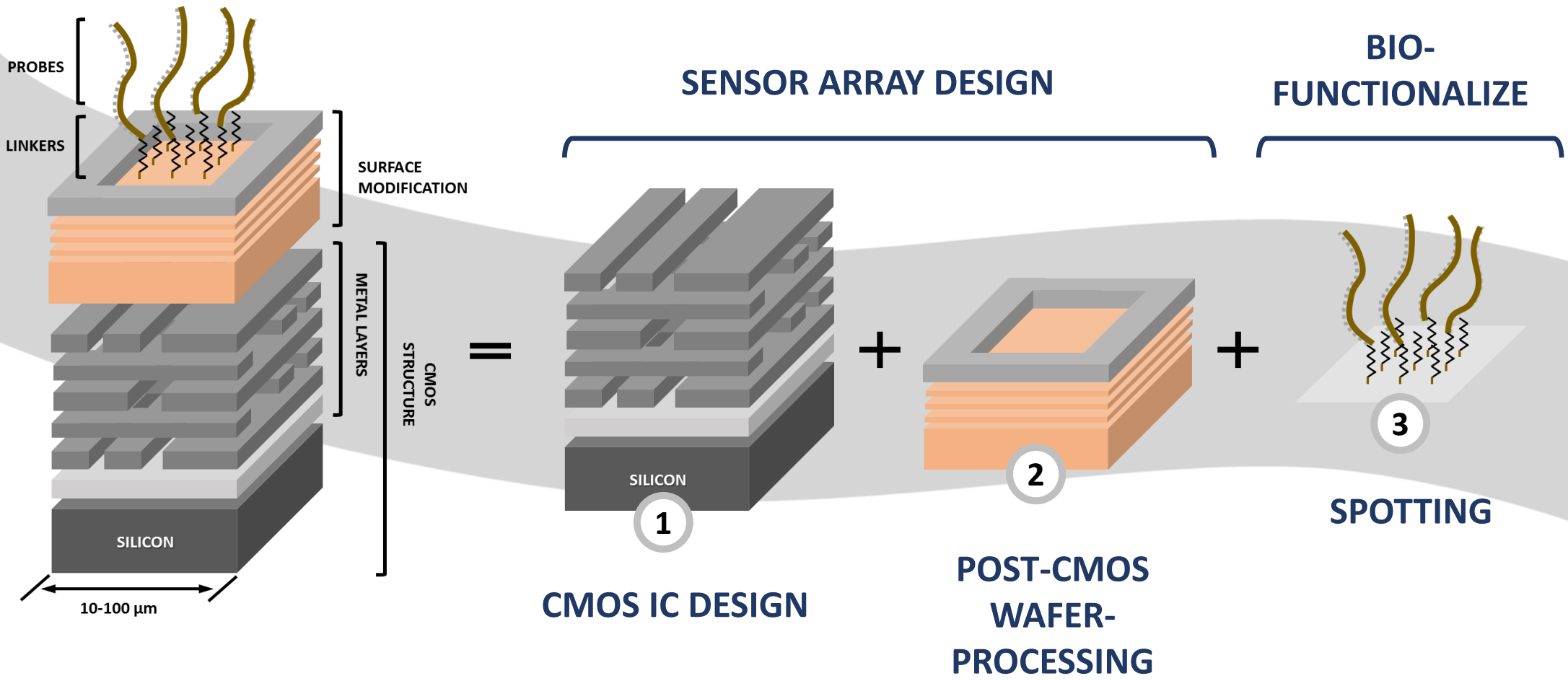
CMOS-INTEGRATED SENSOR

Parallel Detection: Multiplexing

Probes can define different molecular specificities at individual “pixels”

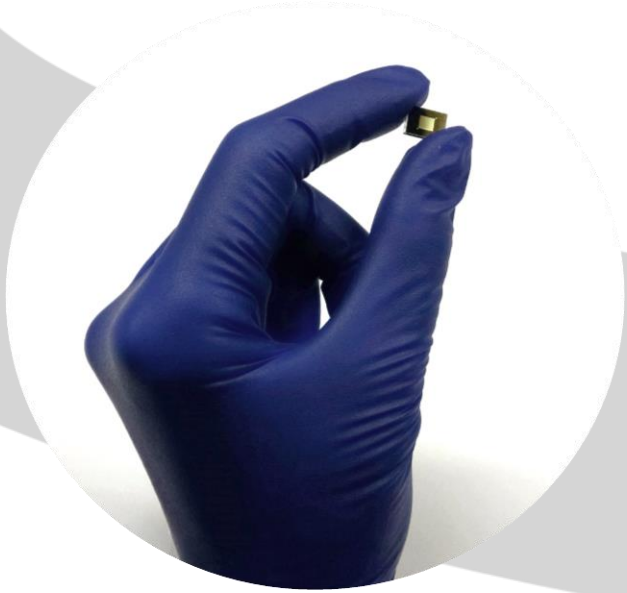


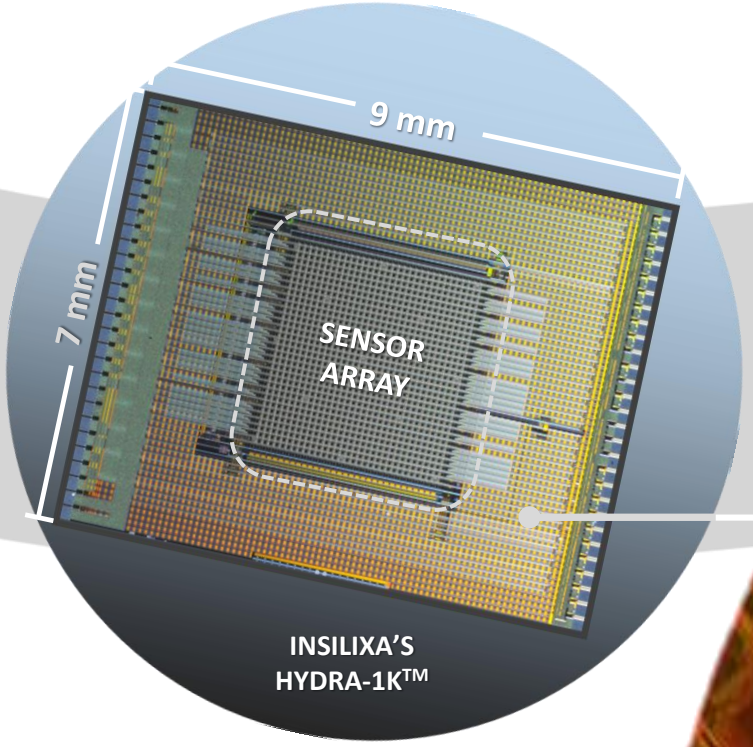
Creating CMOS Biochips

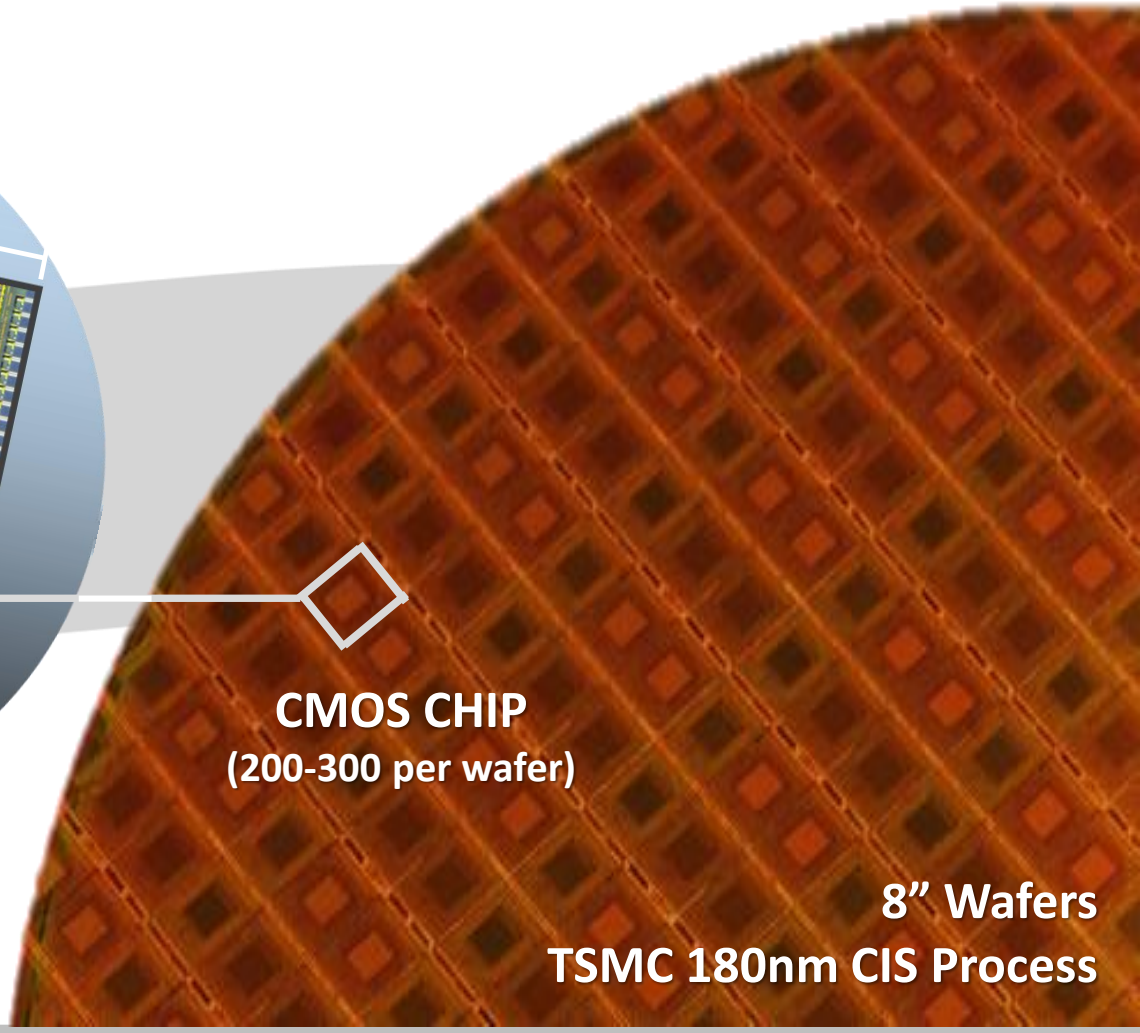


Manufacturing

CMOS chips are fabricated (steps 1 and 2) in semiconductor "eco-system"







CMOS CHIP
(200-300 per wafer)

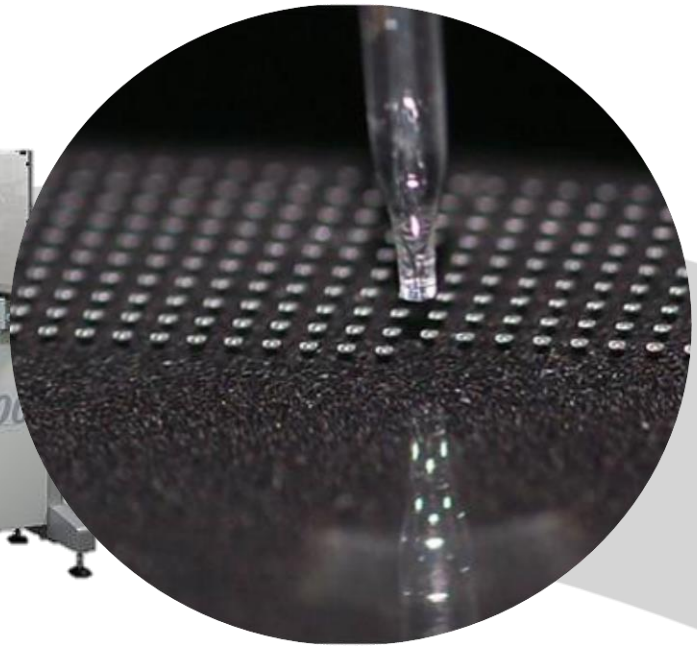
8" Wafers
TSMC 180nm CIS Process

Manufacturing

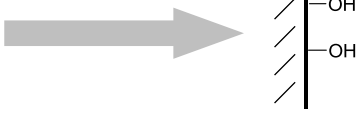
Bio-functionalization (step 3) is performed using automated assembly/spotting equipment

CVD SYSTEM

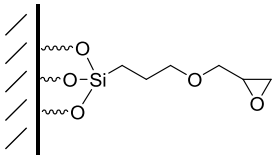
NON-CONTACT SPOTTING



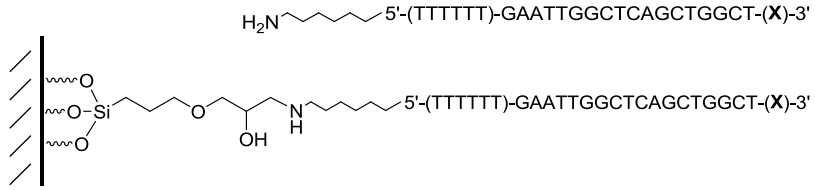
PLASMA TREATMENT



SILANATION



IMMOBILIZATION

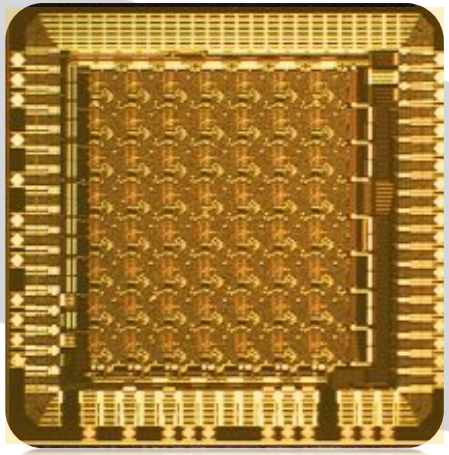
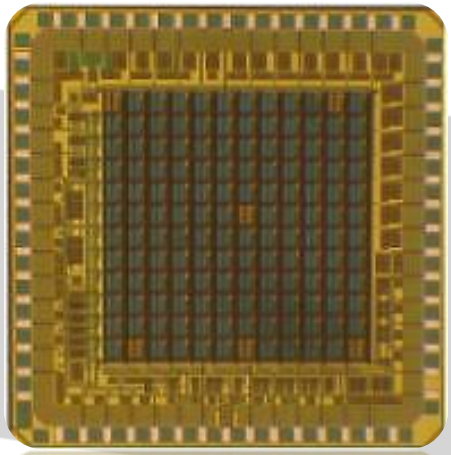
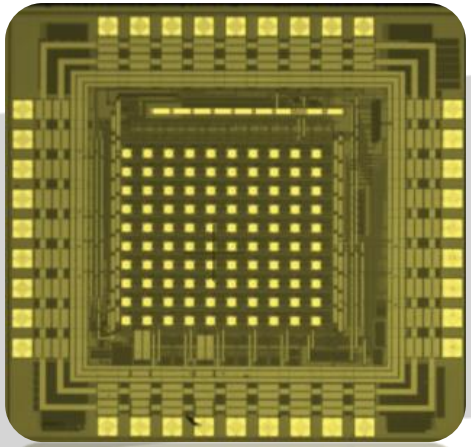
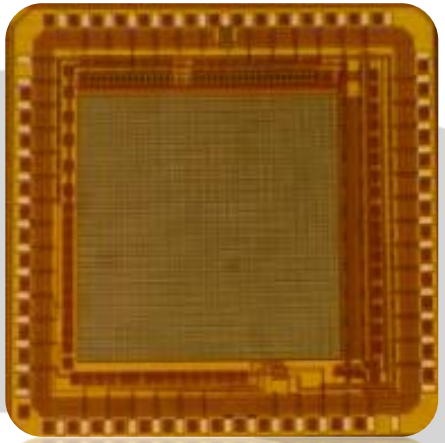


QUESTION 3:

Are biosensing detection modalities CMOS-compatible?

Versatility of CMOS

All relevant detection modalities are CMOS-compatible

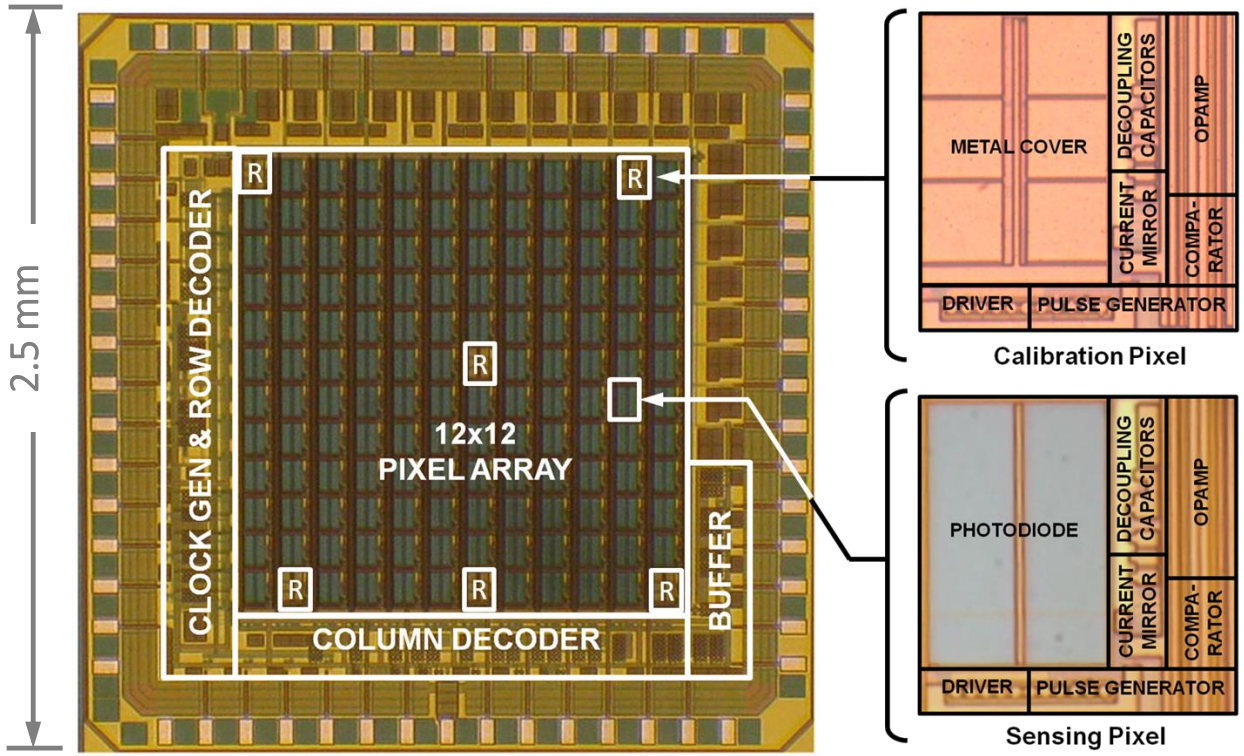
	FLUORESCENCE	BIOLUMINESCENCE	IMPEDANCE SPECTOSCOPY	CHARGE-BASED
				
YEAR	ISSCC 2009	VLSI 2011	ISSCC 2010	VLSI 2012
APPLICATION	Microarrays NAAT[1]	Immunoassays DNA Sequencing	Microarrays	DNA Sequencing

[1] Nucleic Acid Amplification Testing

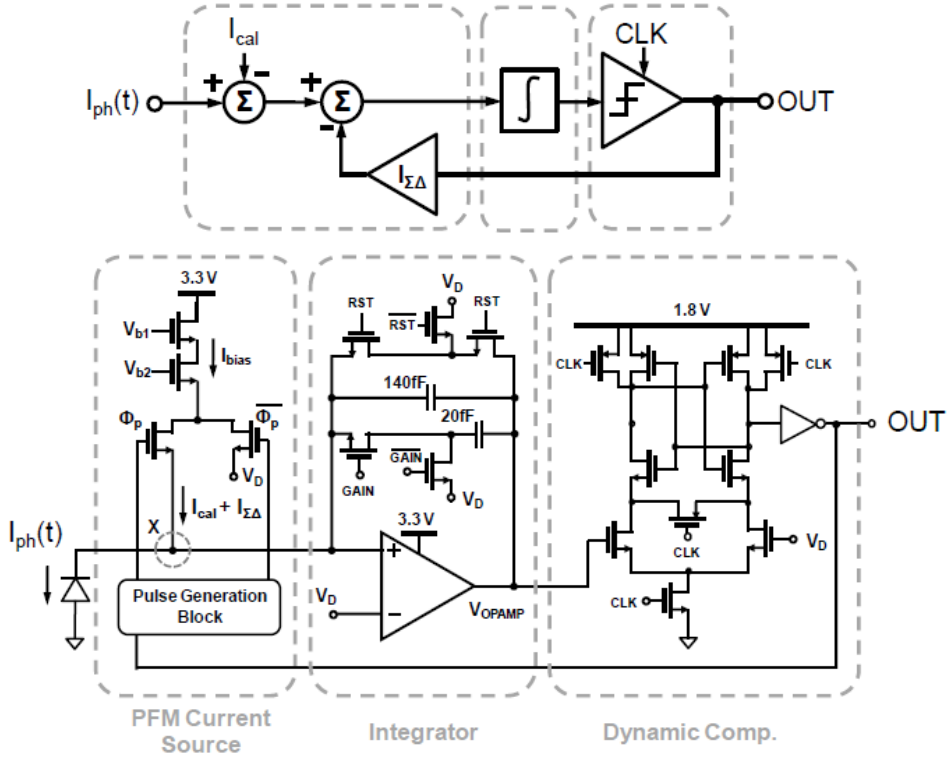
Example [1]

CMOS biochip tailored for high-dynamic range (HDR) bioluminescence detection

CMOS BIOCHIP



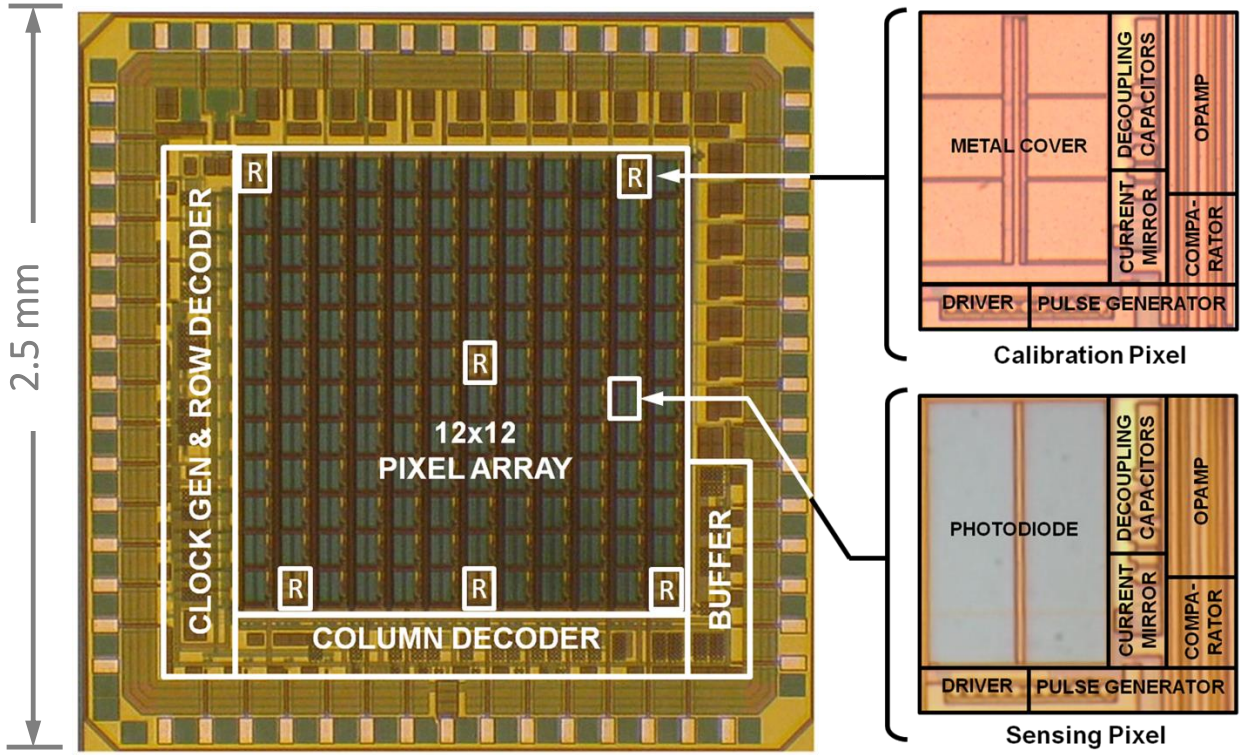
HDR ΔΣ Photosesnor



Example [1]

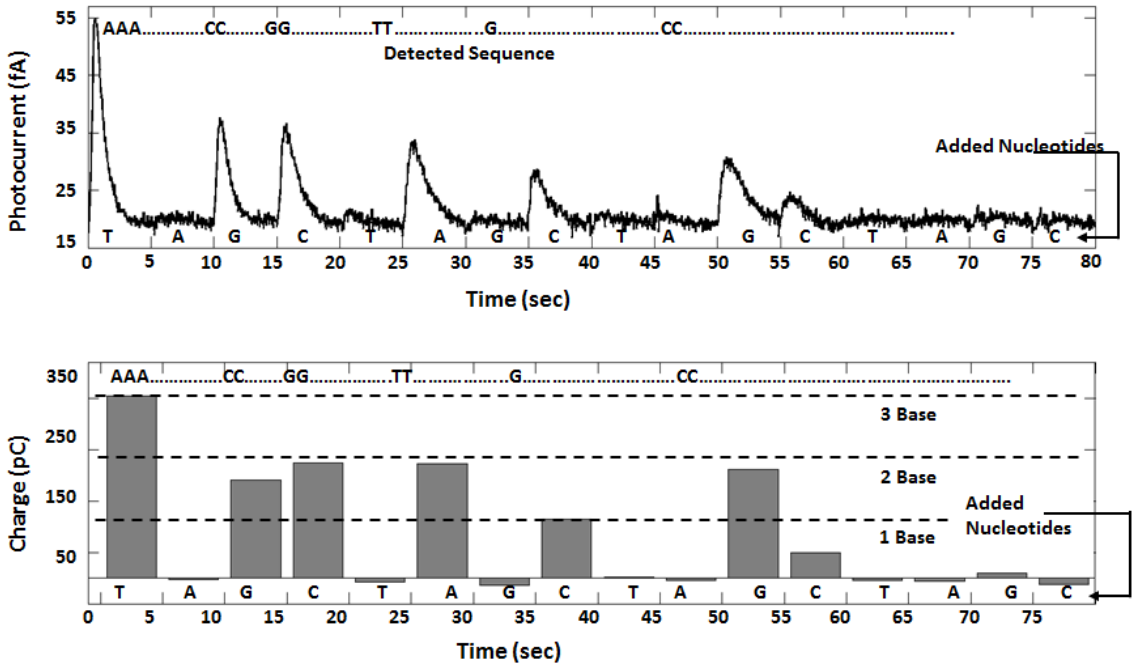
CMOS biochip tailored for high-dynamic range (HDR) bioluminescence detection

Micrograph



Bioluminescence DNA Sequencing

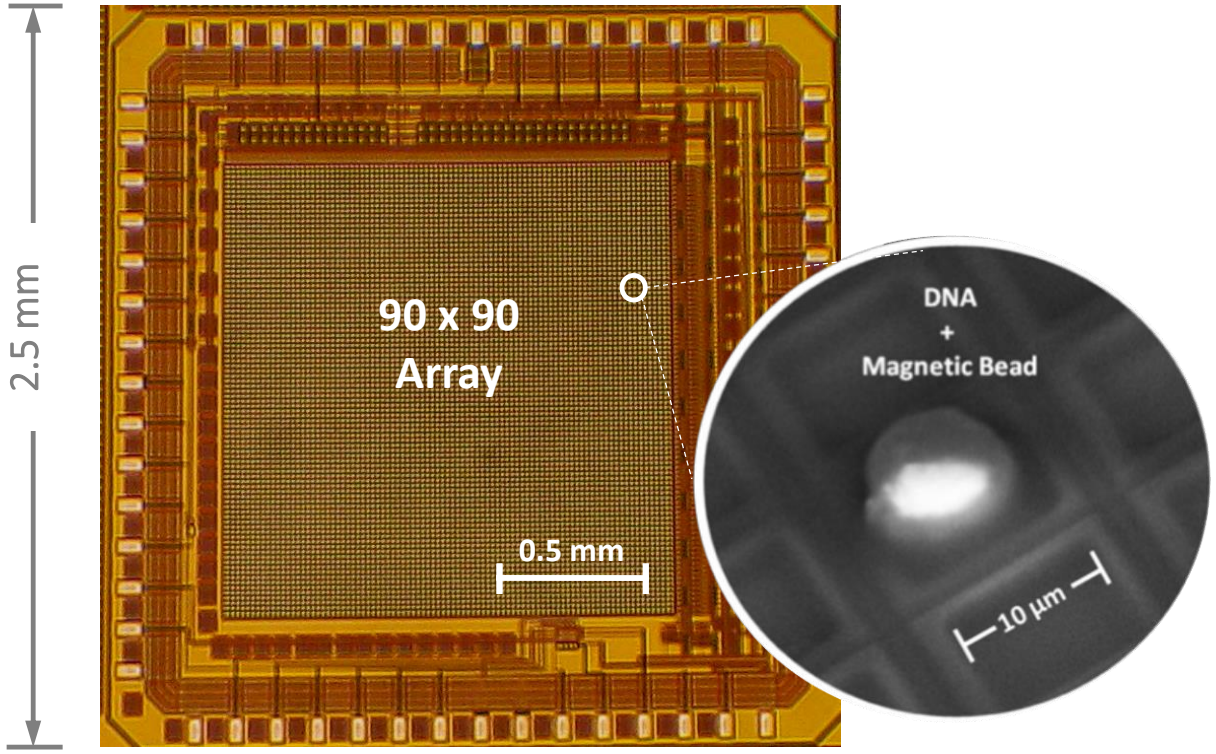
5'- CGTTGTAAAACGACGGC
3'- GCAACATTTTGCTGCCGAAACCGGTTGCC



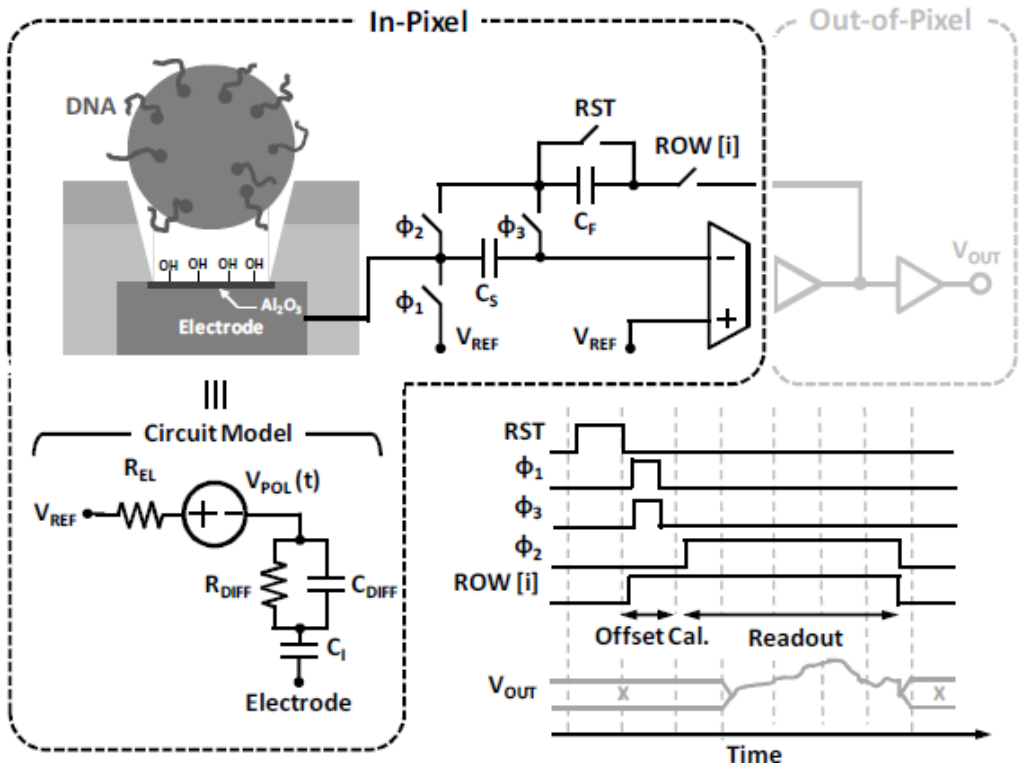
Example [2]

CMOS biochip with low noise charge sensor array

Micrograph



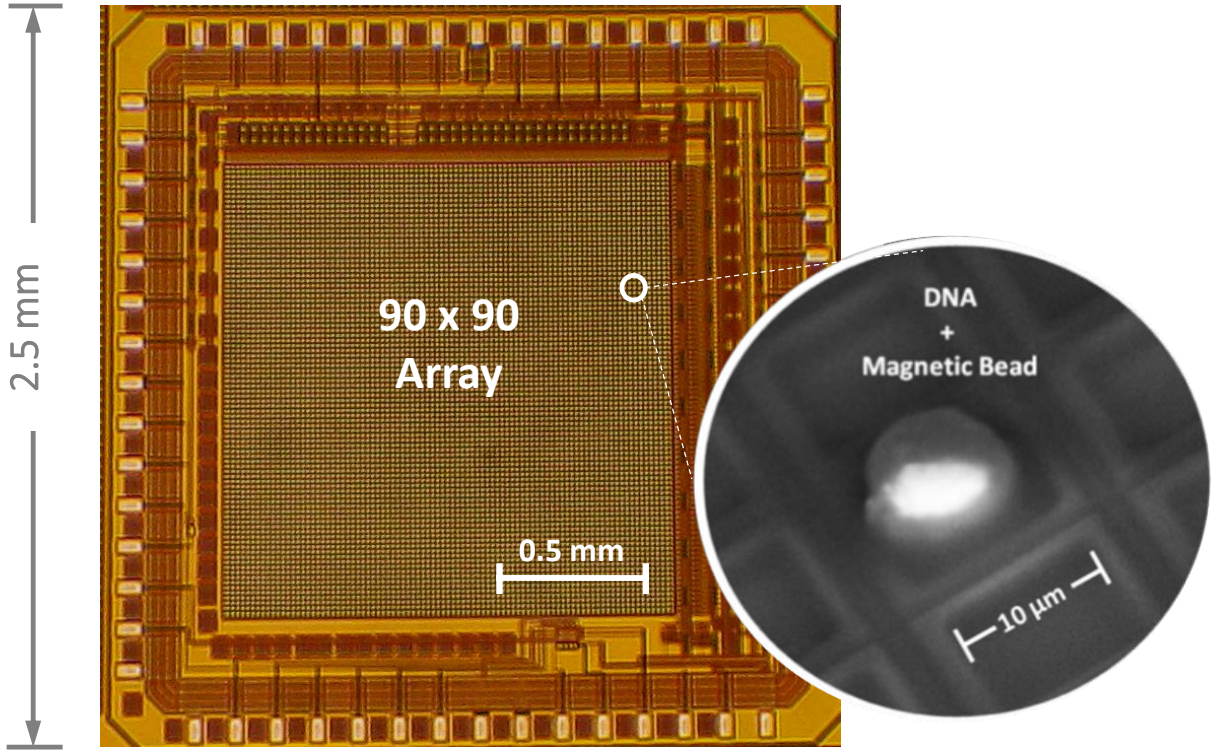
Switch-Capacitor Charge integrator w/ CDS



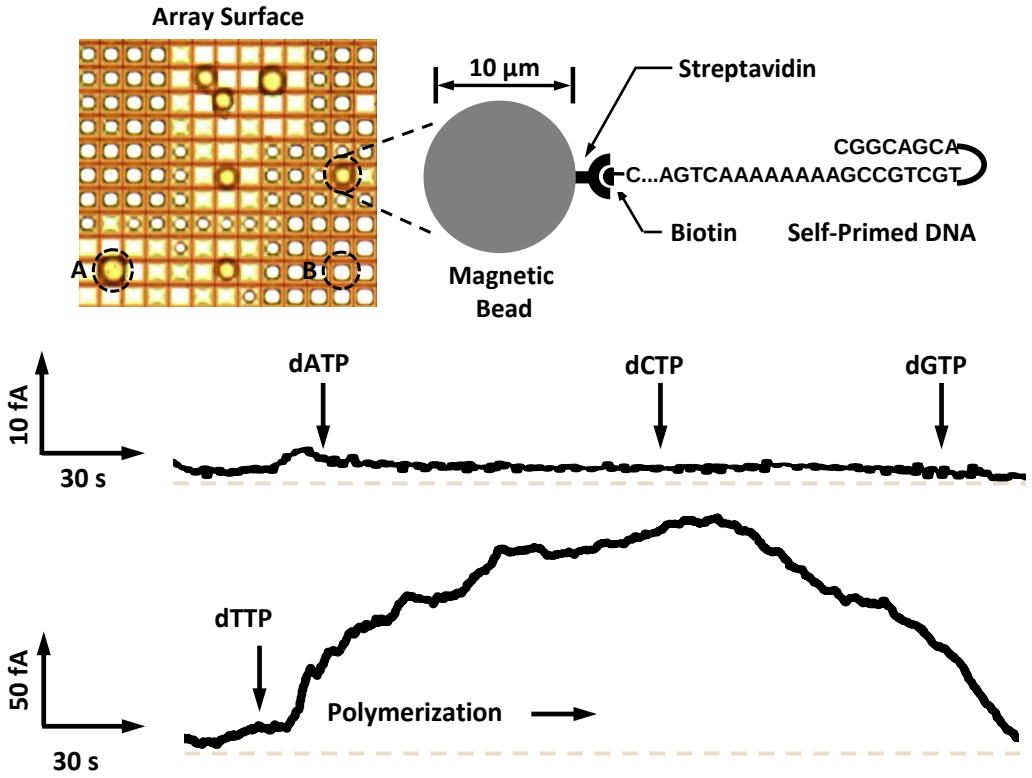
Example [2]

CMOS biochip with low noise charge sensor array

Micrograph



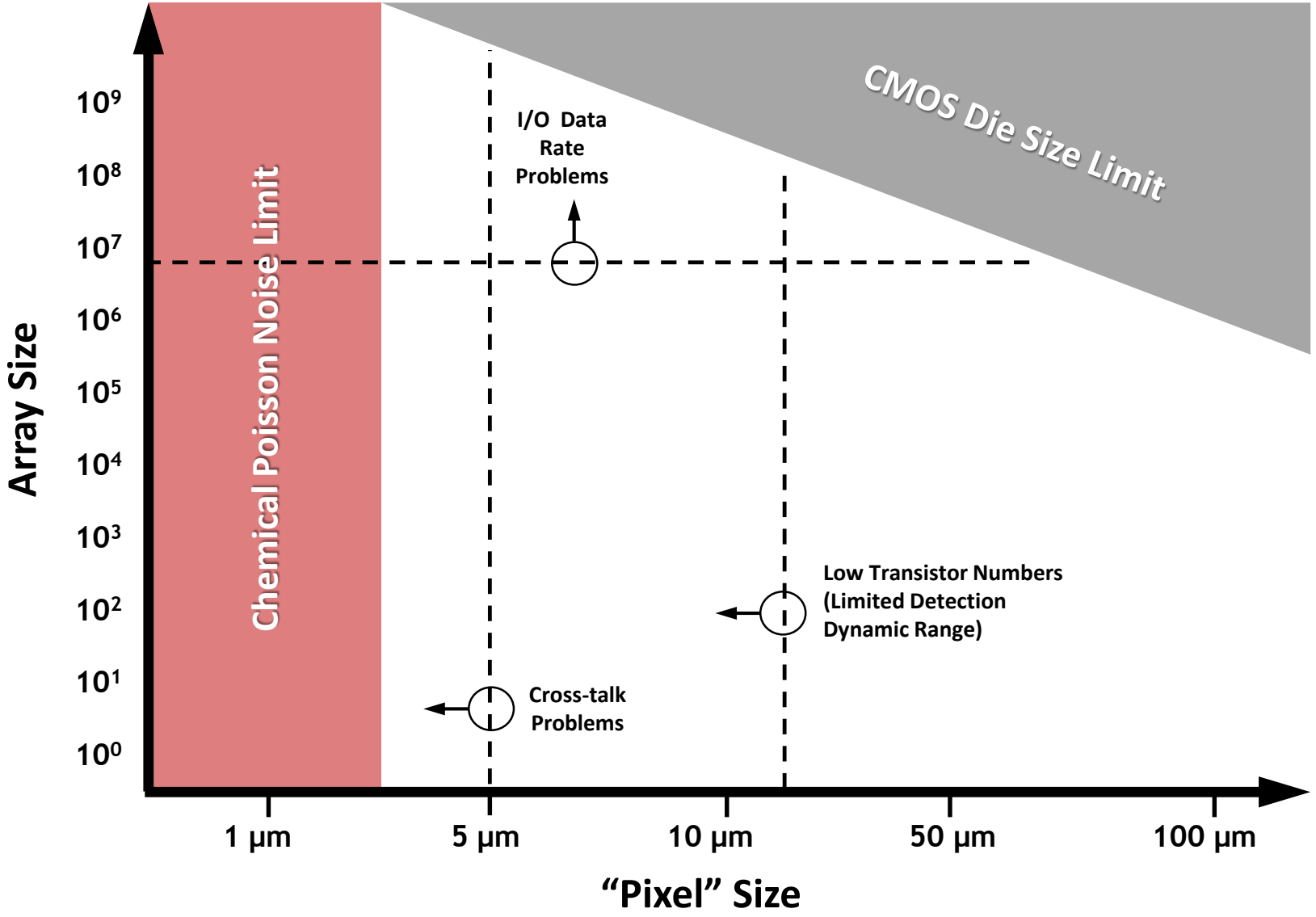
Charge-based DNA Sequencing



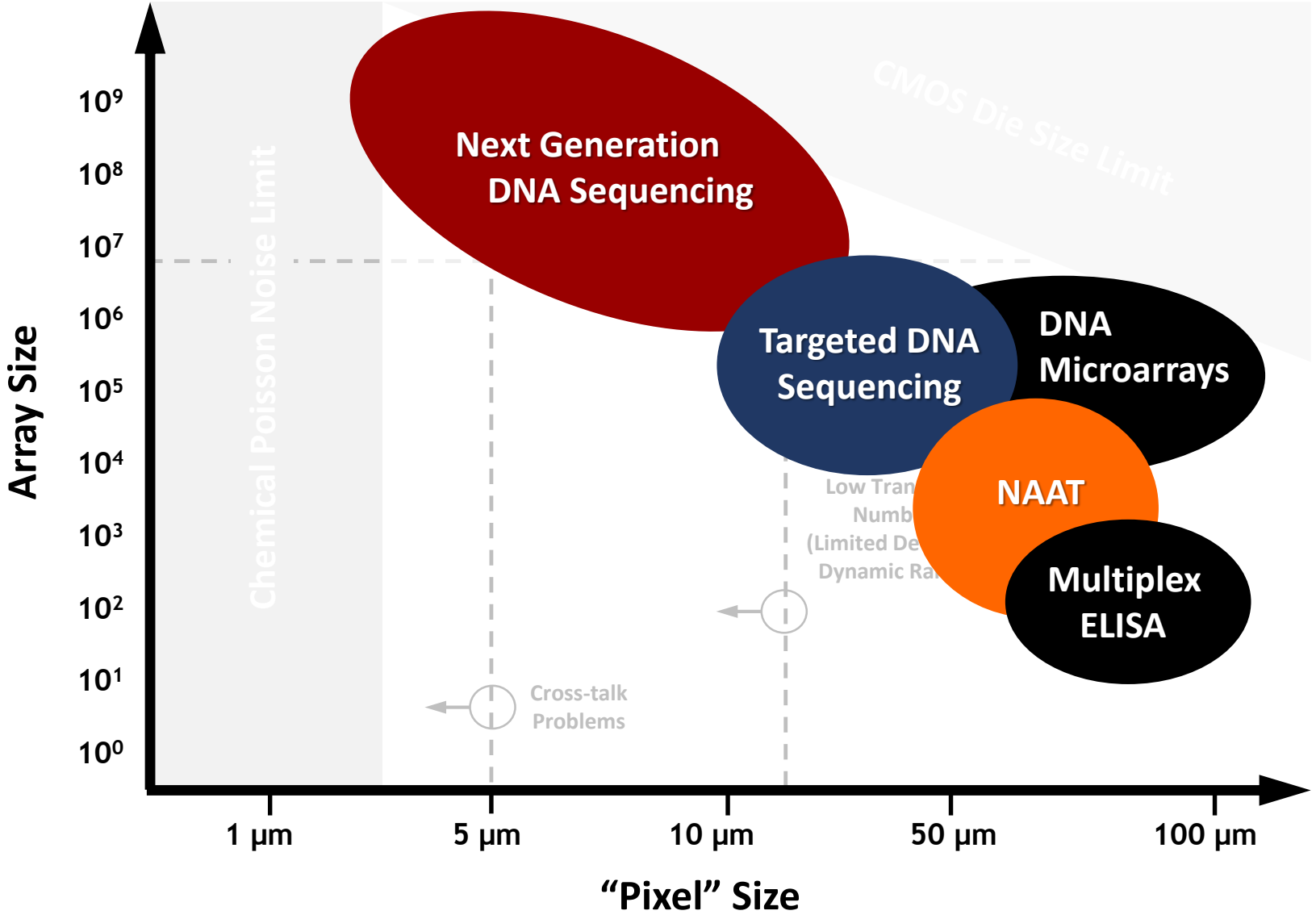
QUESTION 4:

What array densities and pixel sizes are required?
What are the implications on performance?

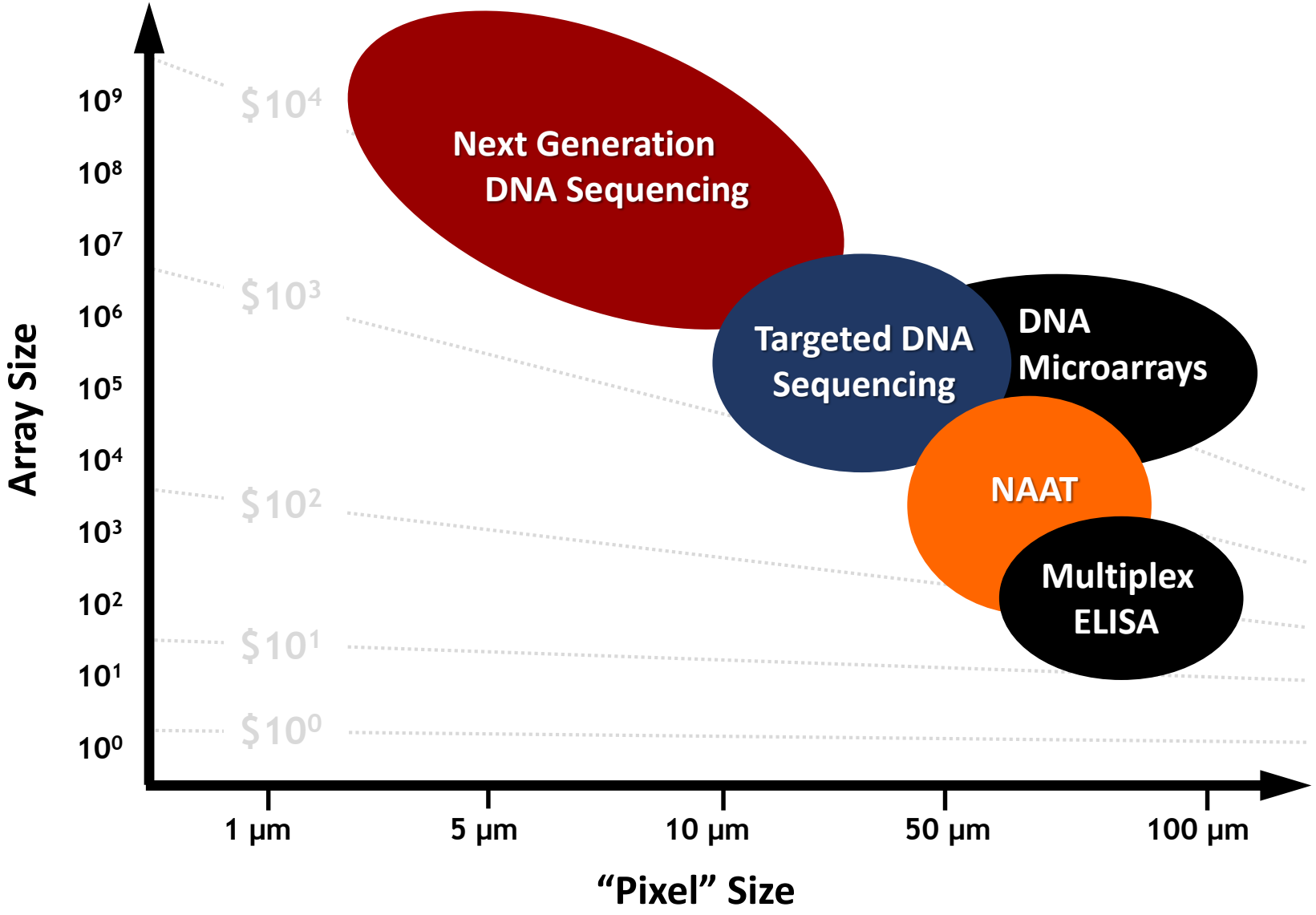
Fundamental Limits



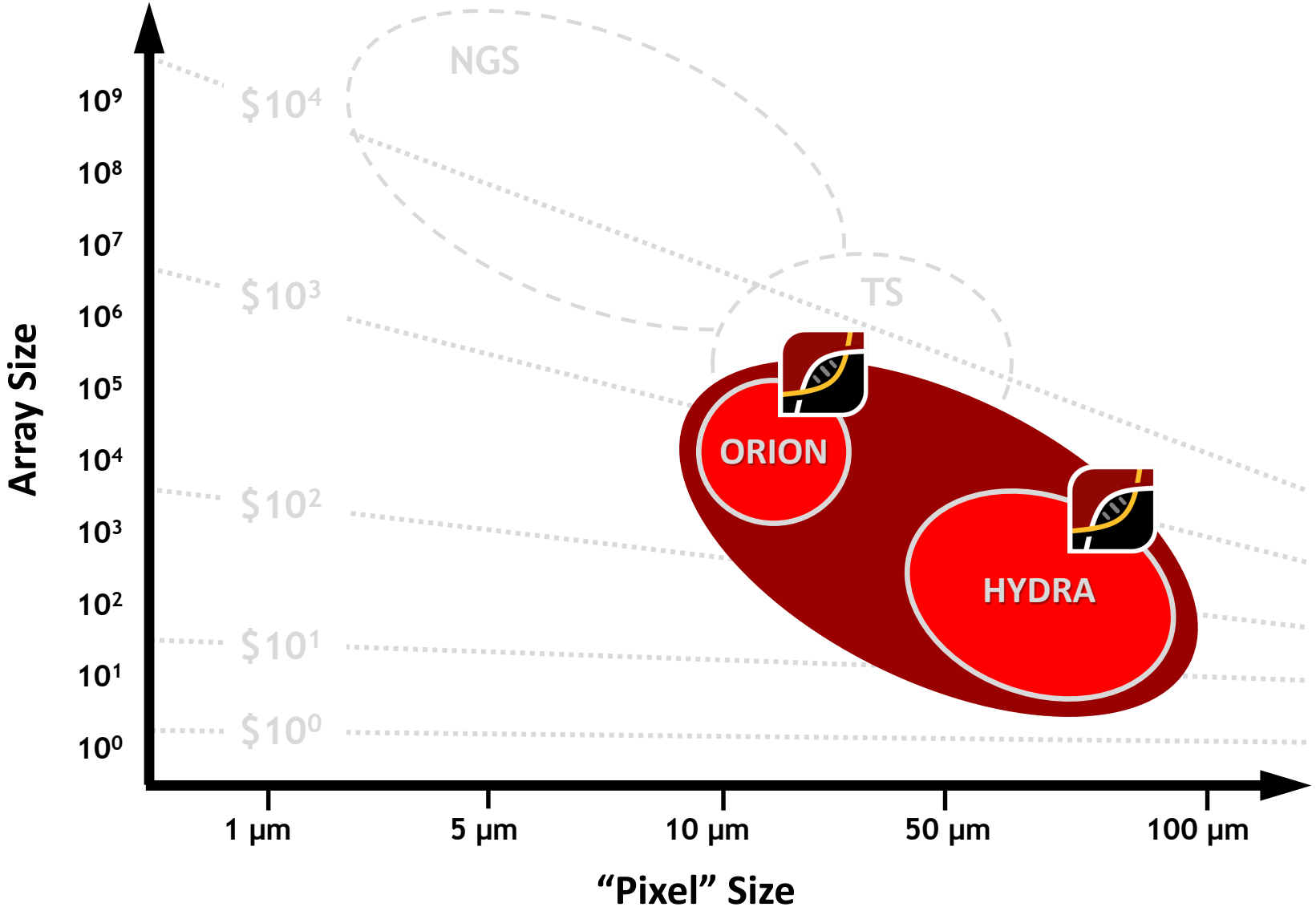
Application Overlay



Cost Overlay



Ideal Target Applications



QUESTION 5:

What is the HYDRA platform?

HYDRA Platform

Detection pathogens (viruses and bacteria) through DNA analysis

1 PATIENT SAMPLE

INSERTED IN THE TEST CARTRIDGE

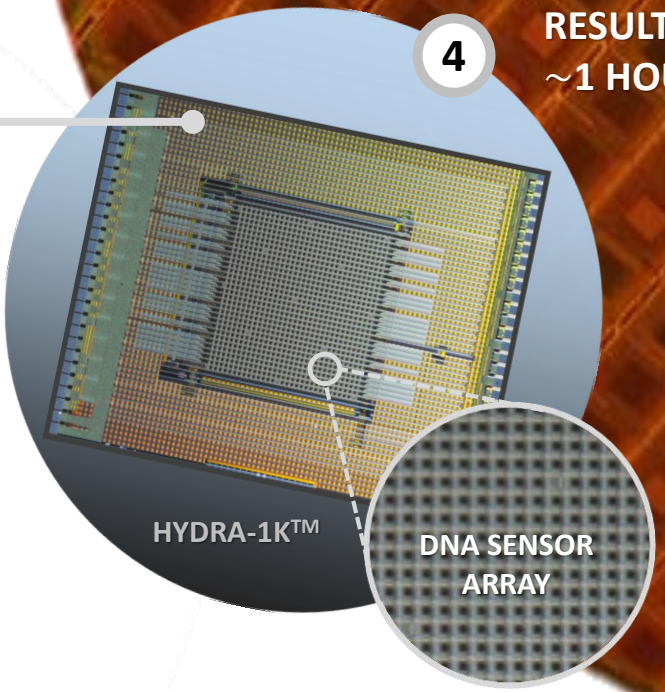
2

INSERTED IN THE READER

3

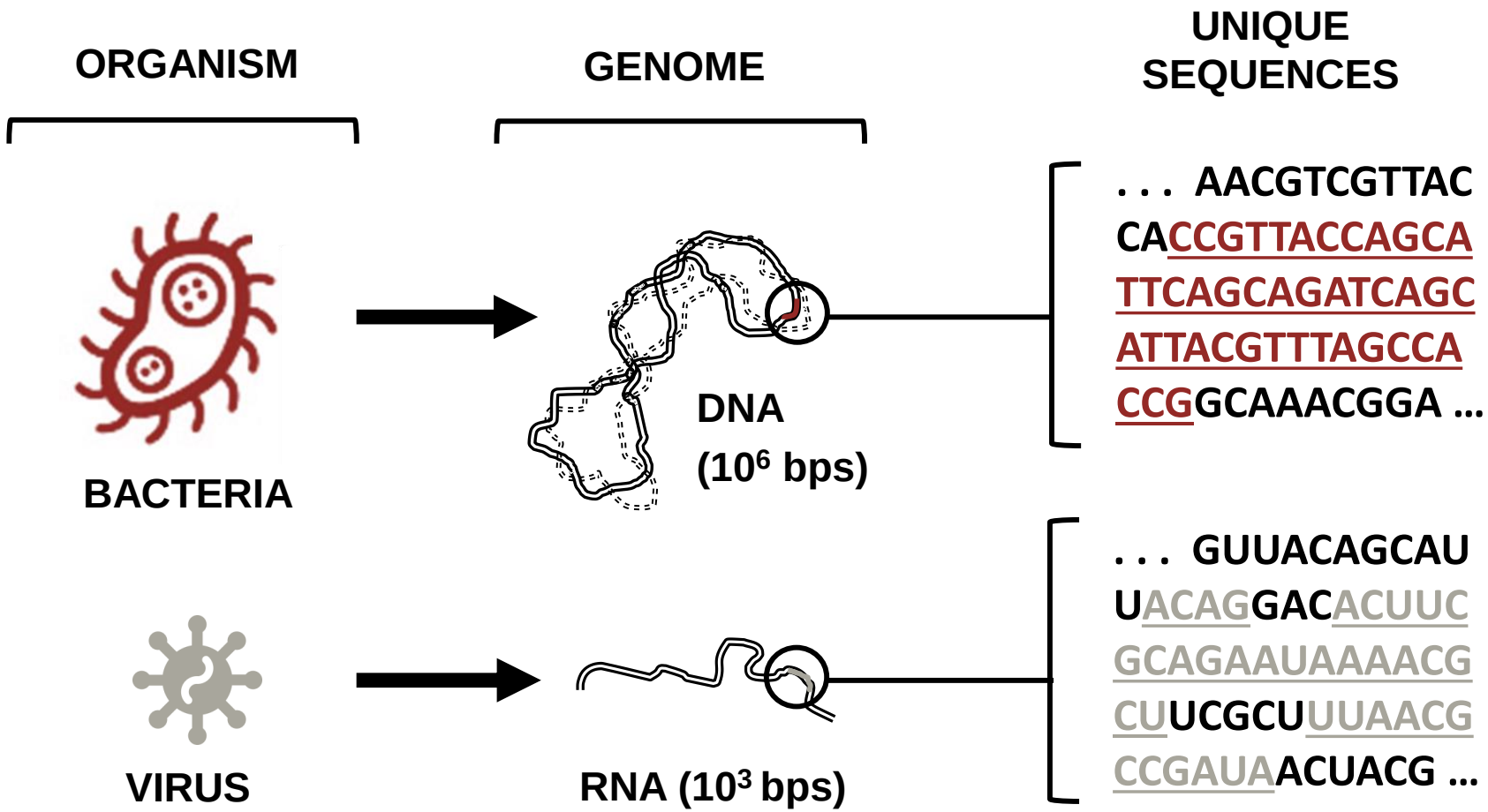
CMOS BIOCHIP

4 RESULTS IN ~1 HOUR



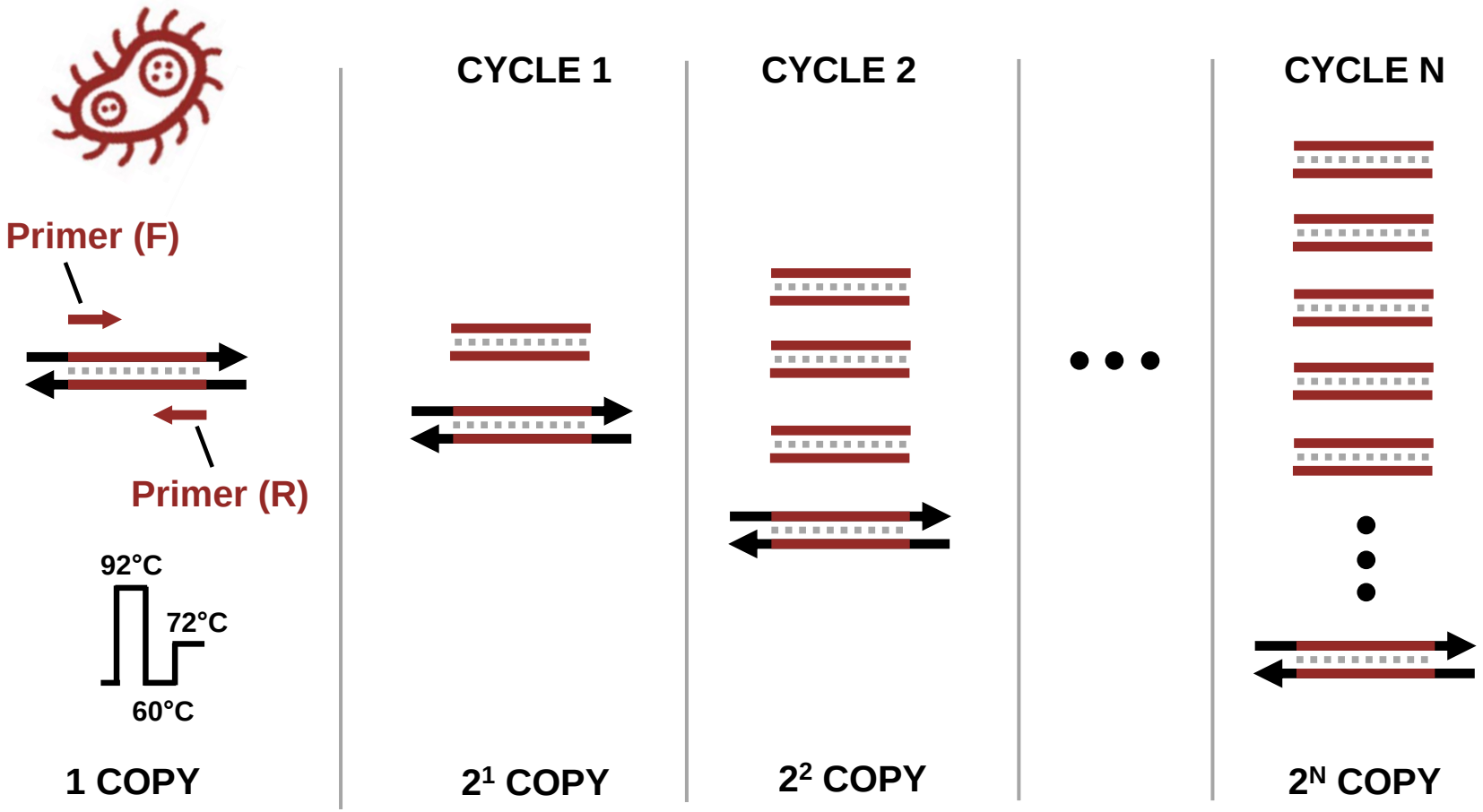
DNA SENSOR ARRAY

Identification Method



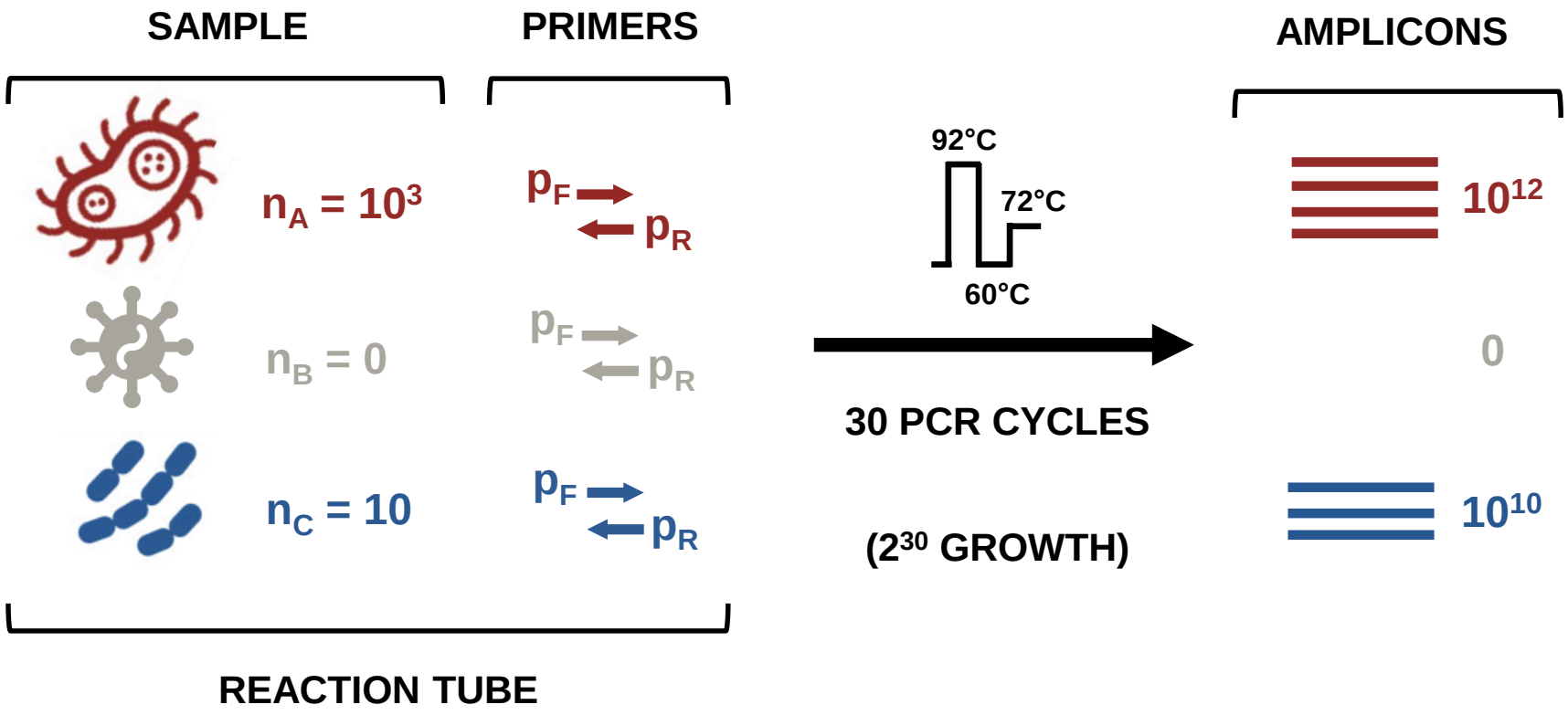
“Amplifying” the Signal Biochemically

Known DNA sequences can be exponentially replicated through PCR thermo-cycling processes



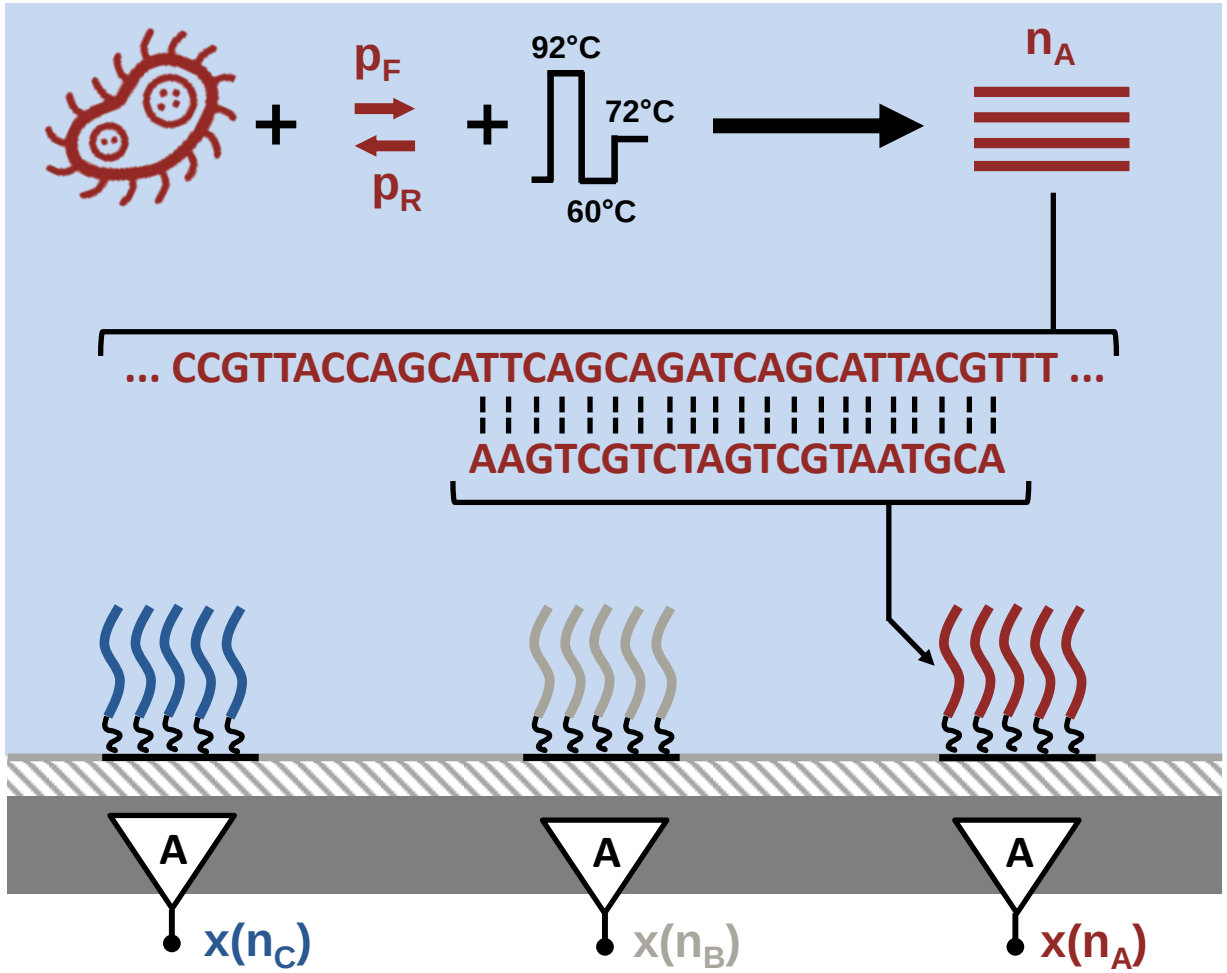
Parallel Detection (Multiplexing)

Multiple PCR reactions in a single chamber to identify multiple sequences (organisms)



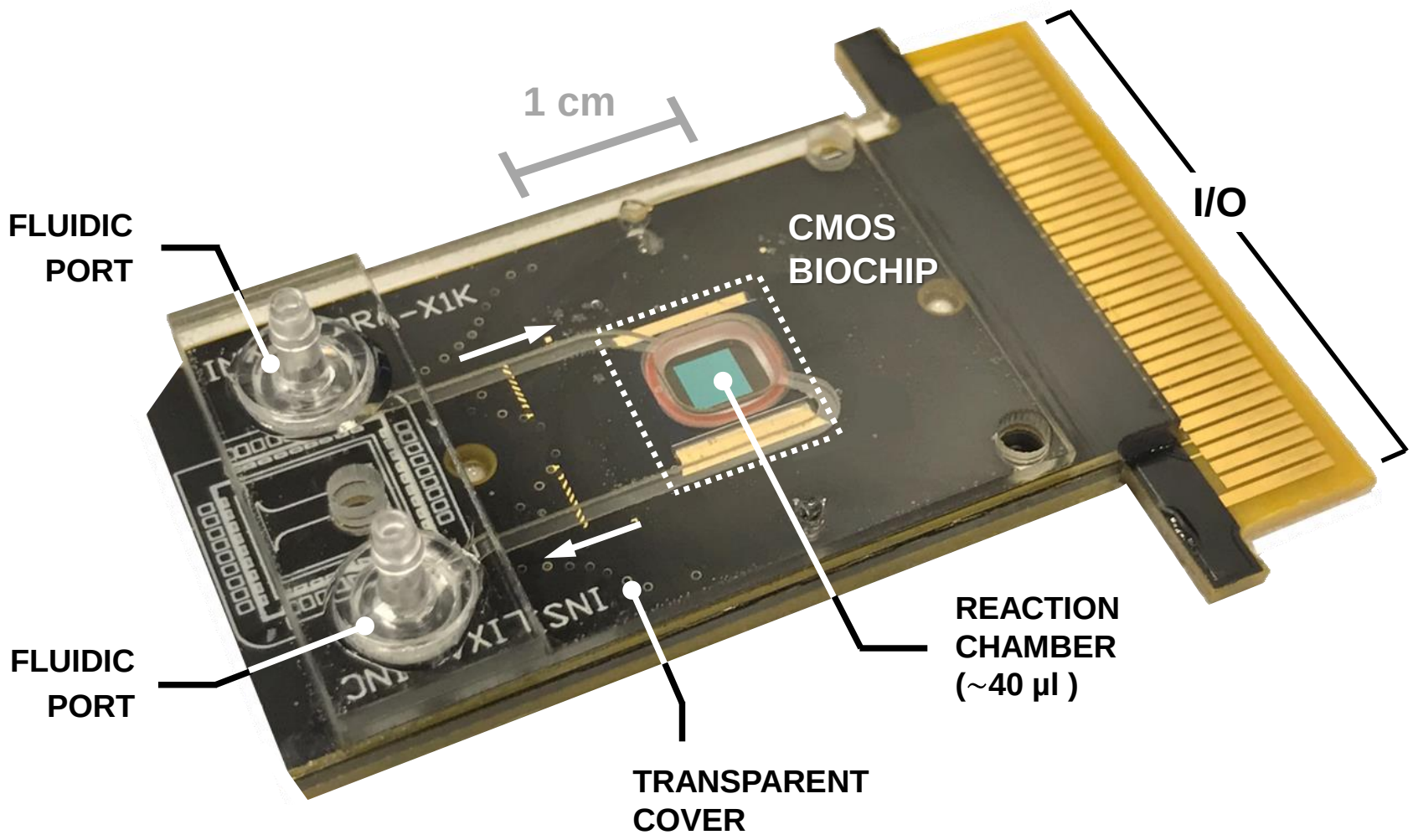
Biochip Concept

A biosensor array to detect all of the generated amplicons



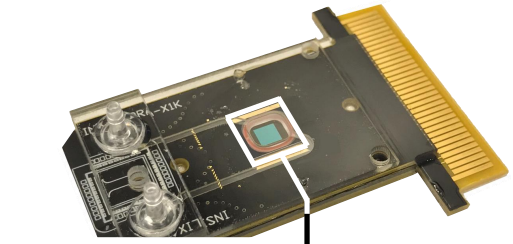
HYDRA-1K Biochip Module

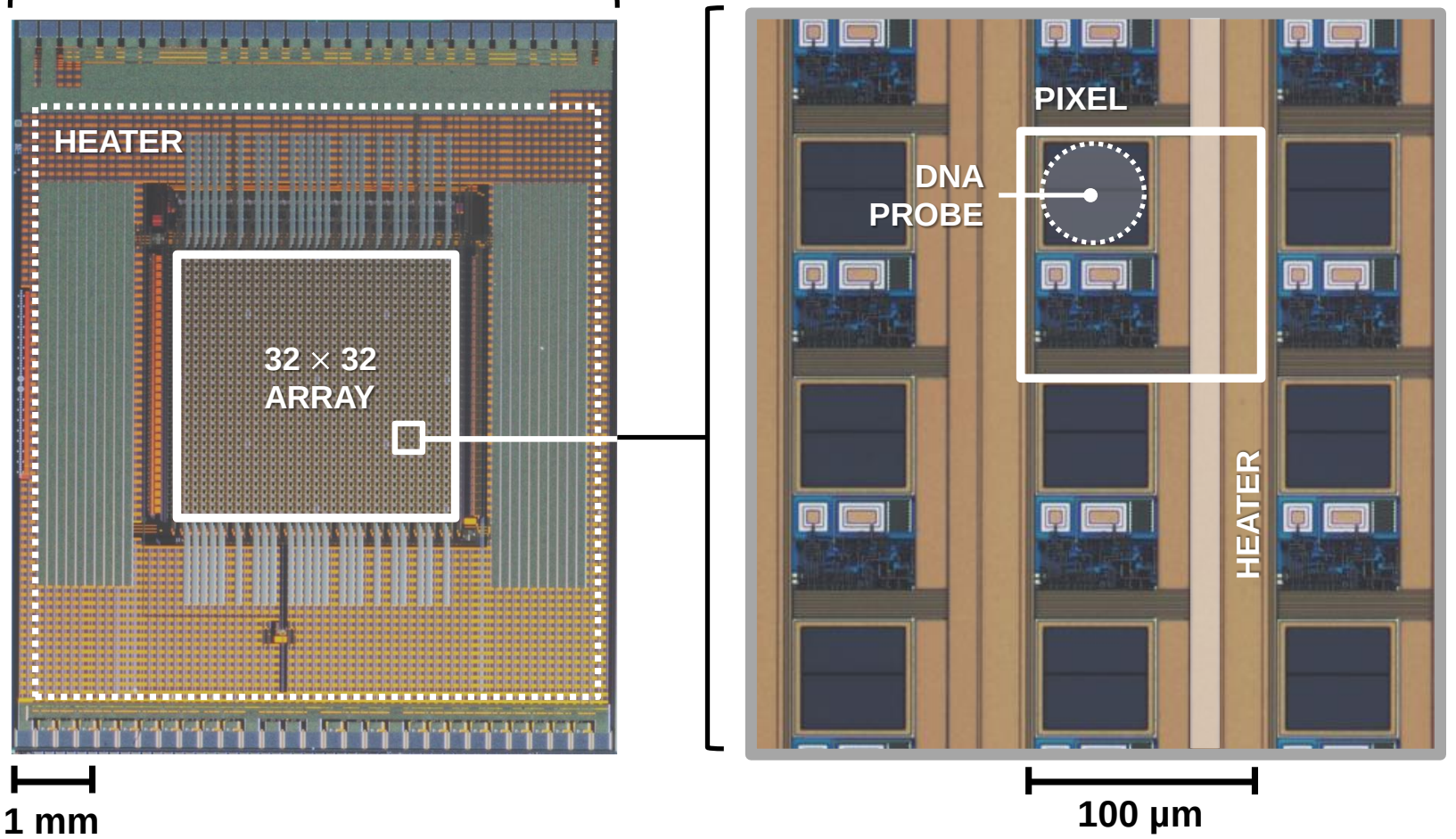
A disposable CMOS biochip module with flow-through fluidic system



CMOS IC

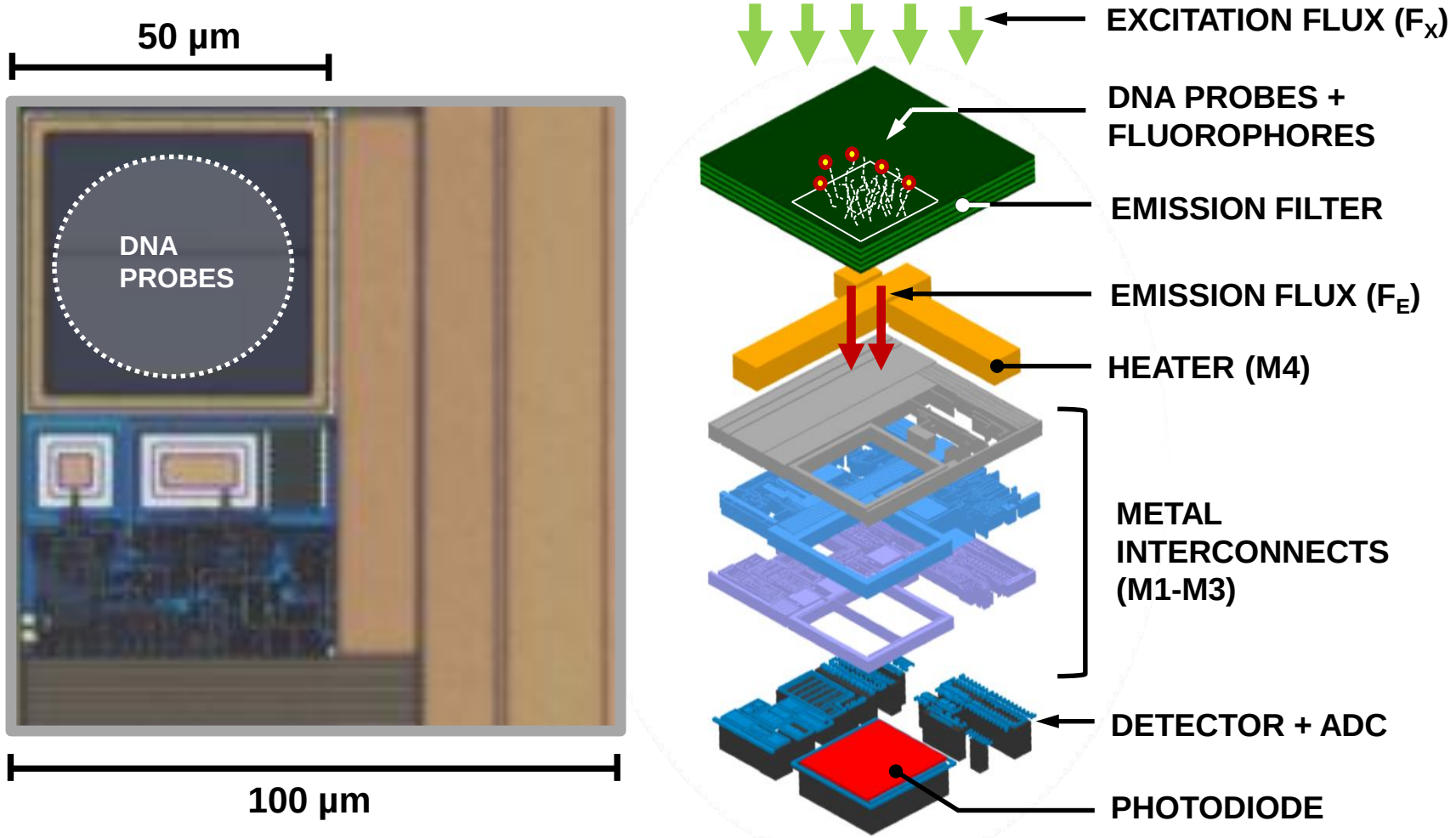
1024 integrated DNA biosensors with integrated heater





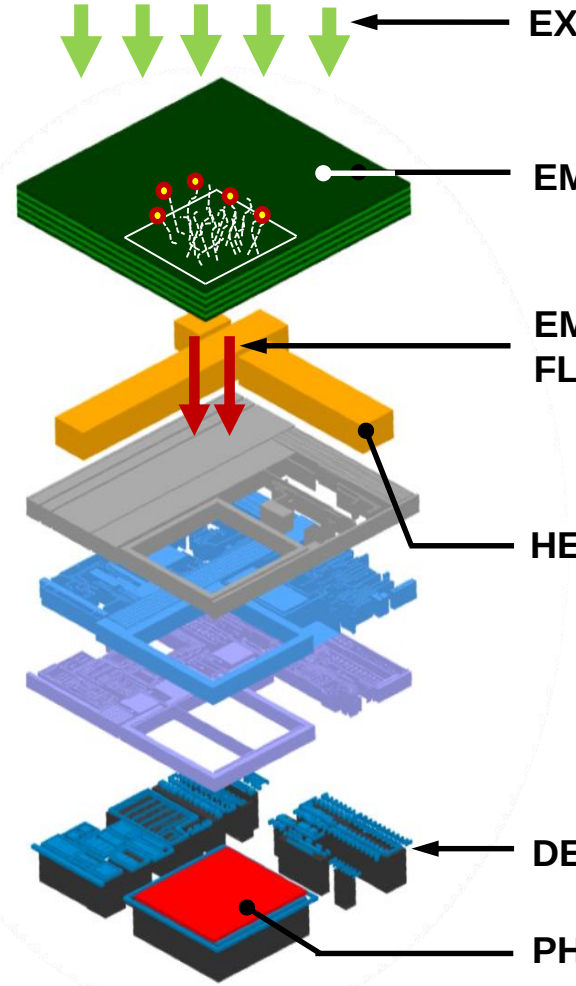
Pixel Structure

Continuous wave (CW) fluorescence detection for biosensing



Specifications

Fluorescence biosensing requires a high dynamic range detector



EXCITATION FLUX (F_X) ..... 10^{15}-10^{18} photons/cm^2/s

EMISSION FILTER ..... Optical Density (OD) > 3.5
Transition Band < 30 nm

EMISSION FLUX (F_E) ..... 10^{10}-10^{13} photons/cm^2/s

HEATER ..... 40°C – 95°C
Accuracy < 0.5°C
Rate = ±4°C/s

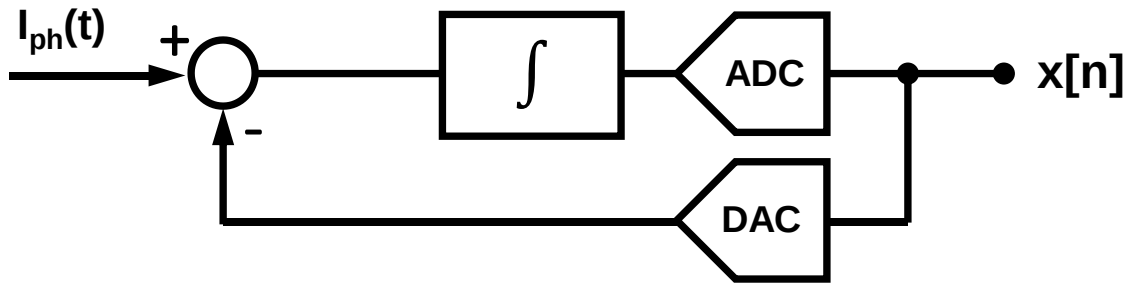
DETECTOR + ADC

PHOTODIODE ..... I_{sig} = 15 fA – 15 pA
I_{bg} = 200 fA – 200 pA

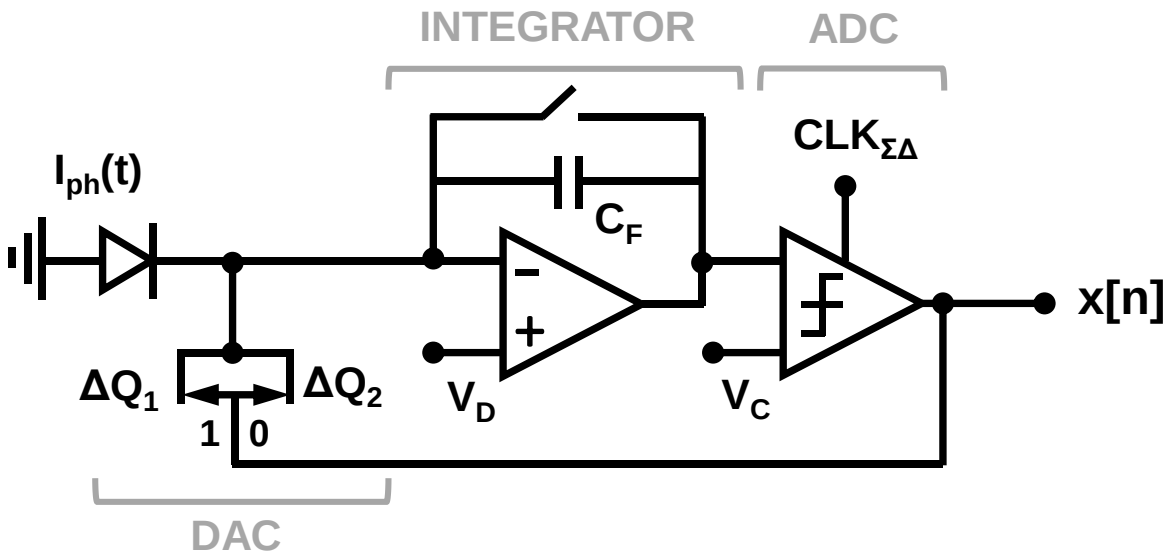
Pixel Architecture

Photocurrent (I_{ph}) detection using a 1st-order ΣΔ current sensor

BLOCK DIAGRAM

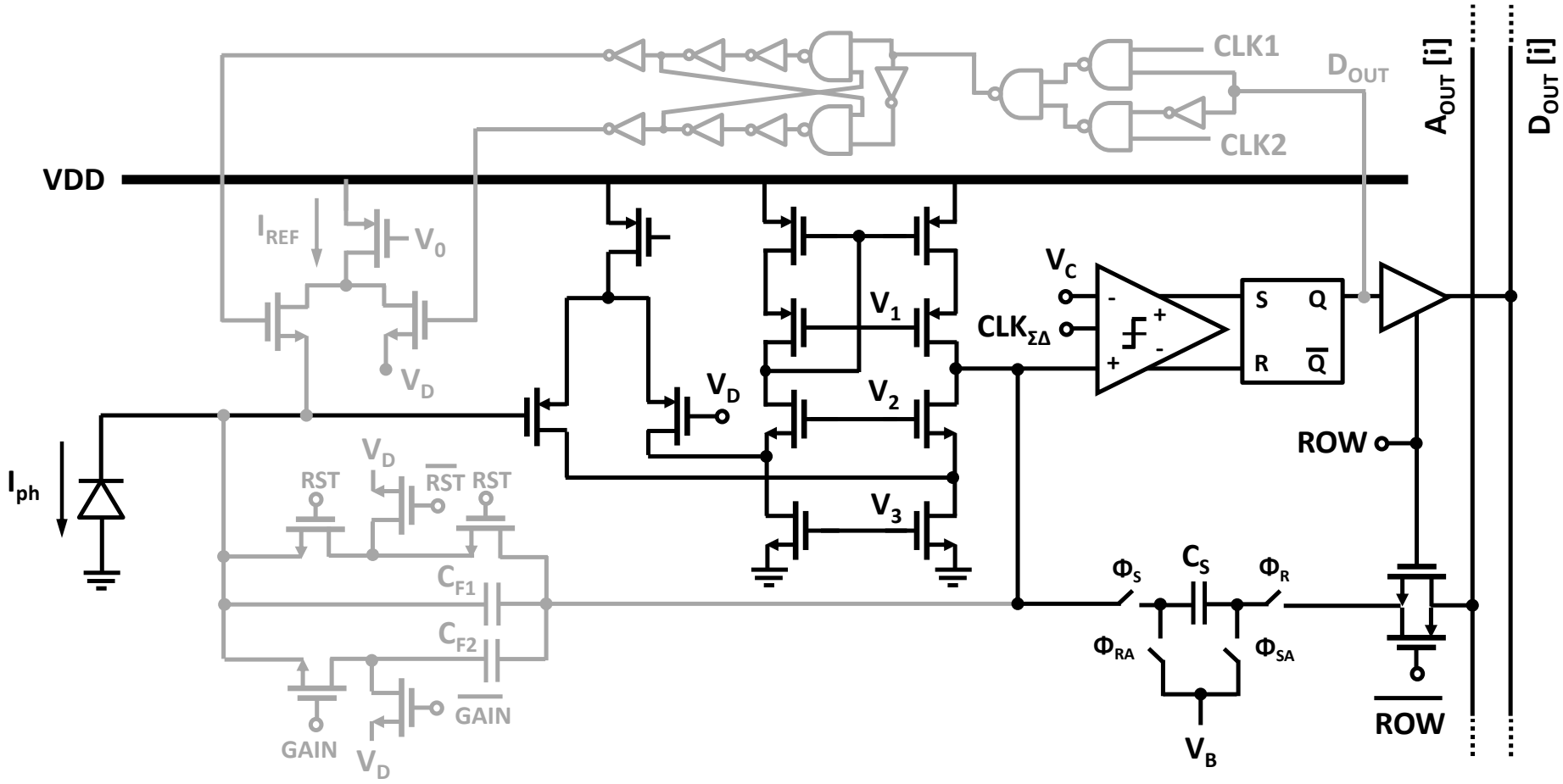


CIRCUIT TOPOLOGY

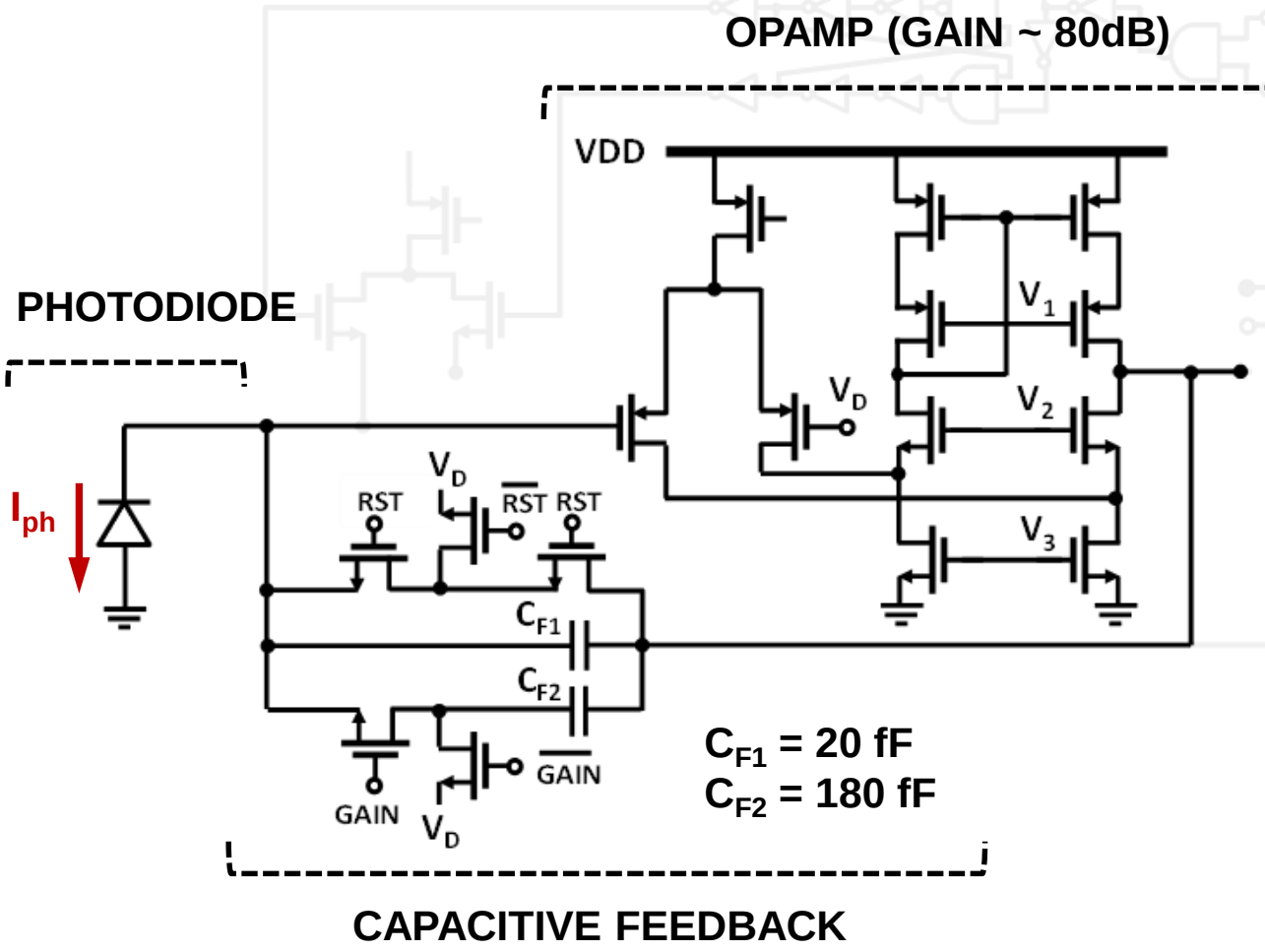


Pixel Circuitry

Forward path (—) and feedback path (—)

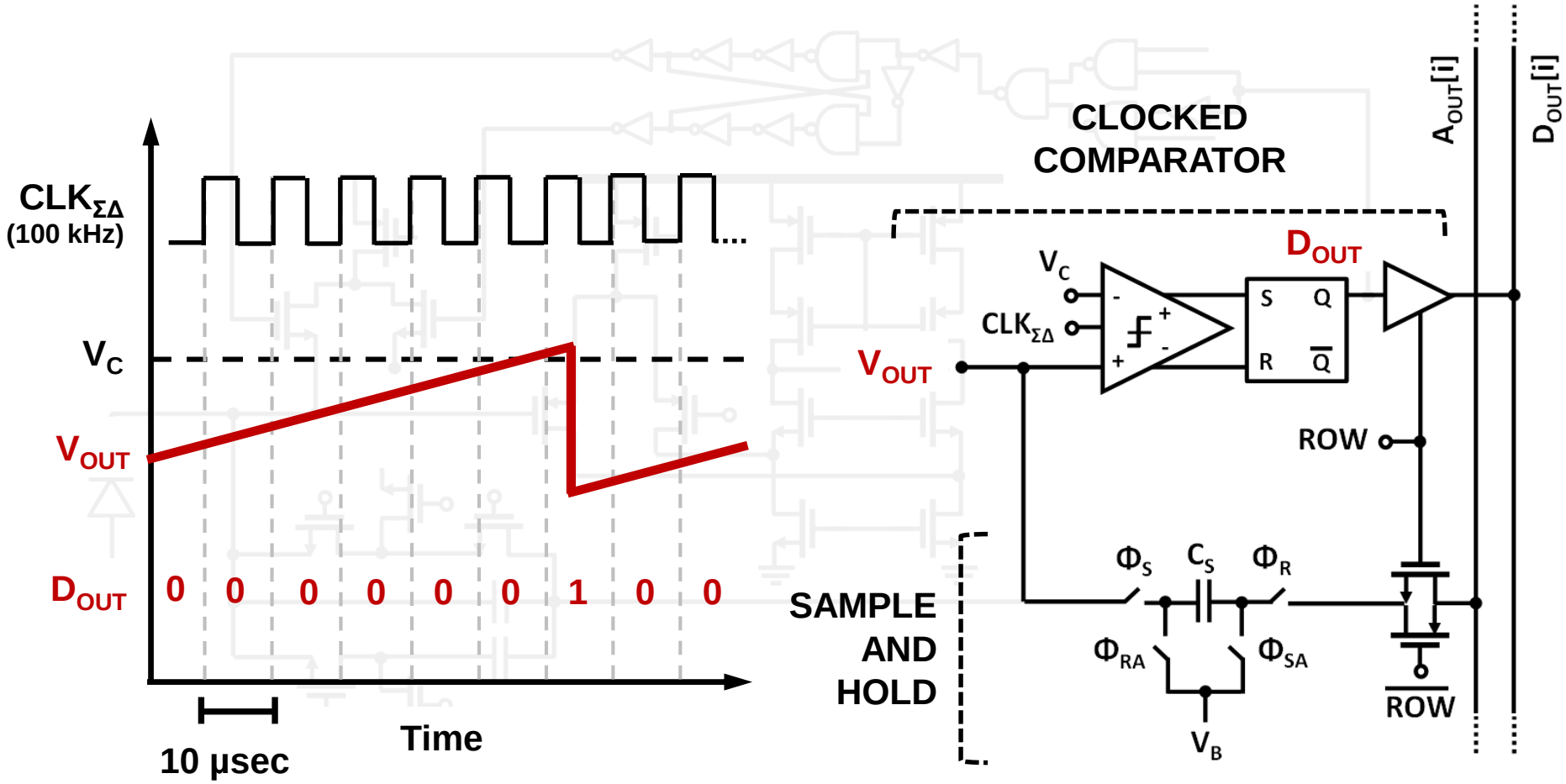


Pixel: Current Integrator

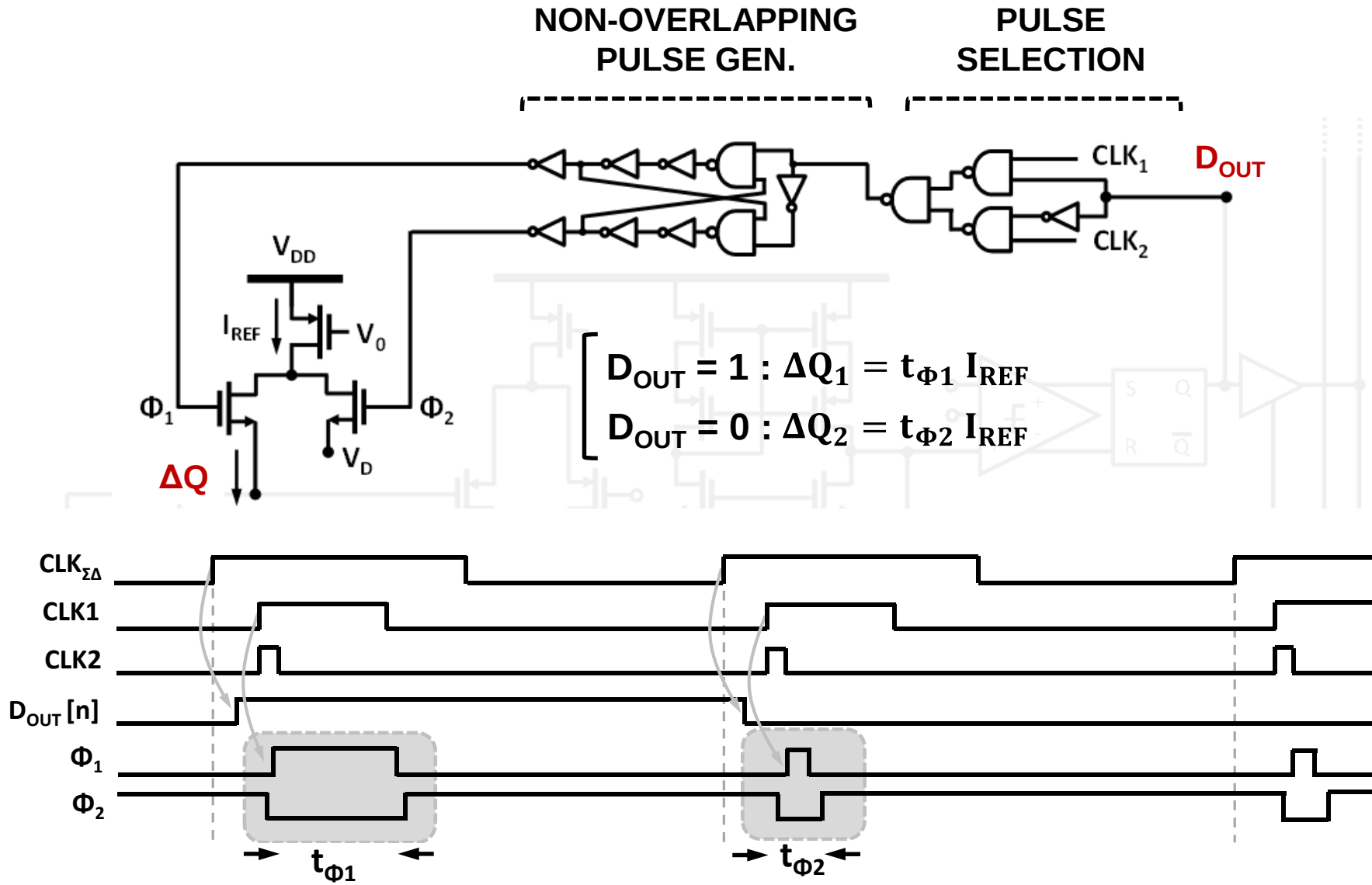


$$V_{OUT} = \int_{t_0}^{t} \frac{I_{ph}(\theta)}{C_F} d\theta$$

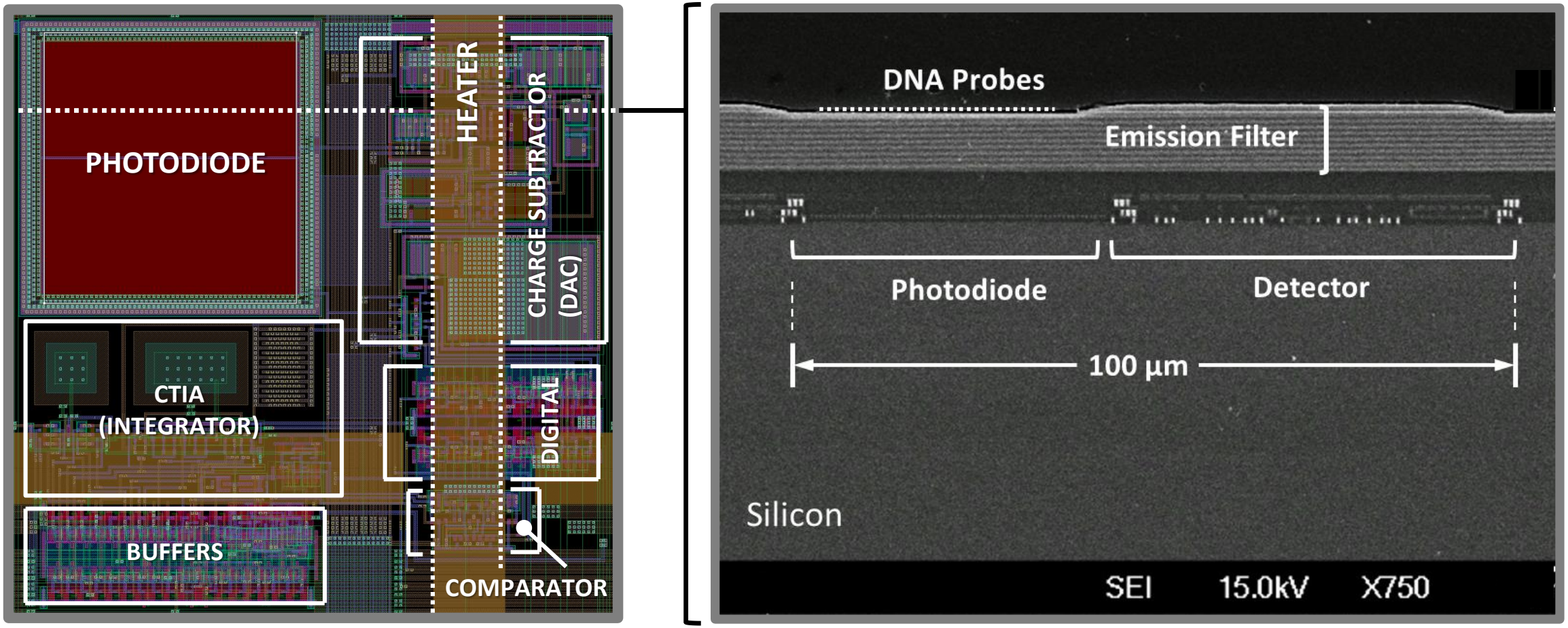
Pixel: Quantizer and S&H



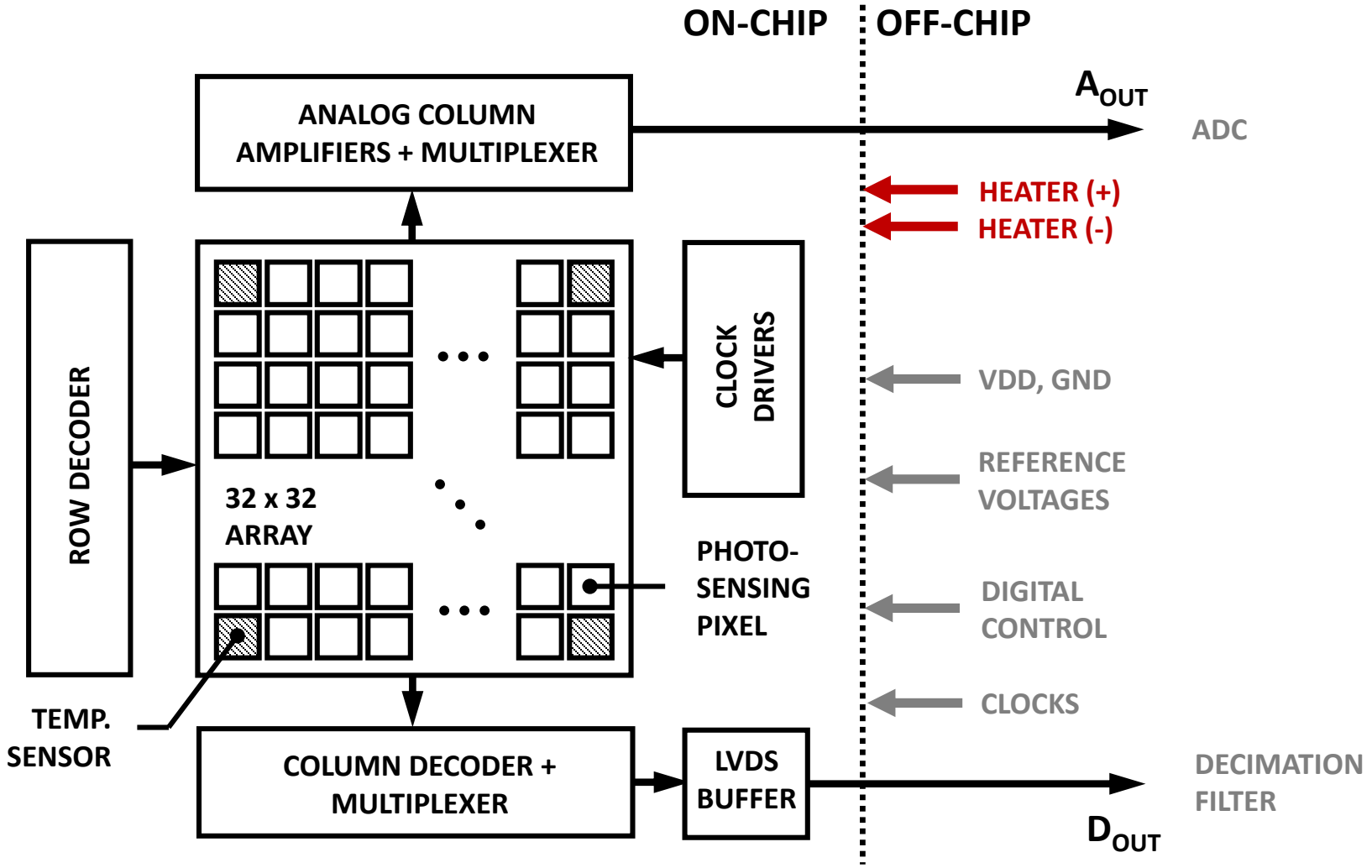
Pixel: DAC


NON-OVERLAPPING PULSE GEN.
PULSE SELECTION
CLK1
DOUT
CLK2
VDD
IREF
V0
Φ1
Φ2
VD
ΔQ
DOUT = 1 : ΔQ1 = tΦ1 IREF
DOUT = 0 : ΔQ2 = tΦ2 IREF
CLKΣΔ
CLK1
CLK2
DOUT [n]
Φ1
Φ2
tΦ1
tΦ2

Pixel: Layout and SEM Cross Section

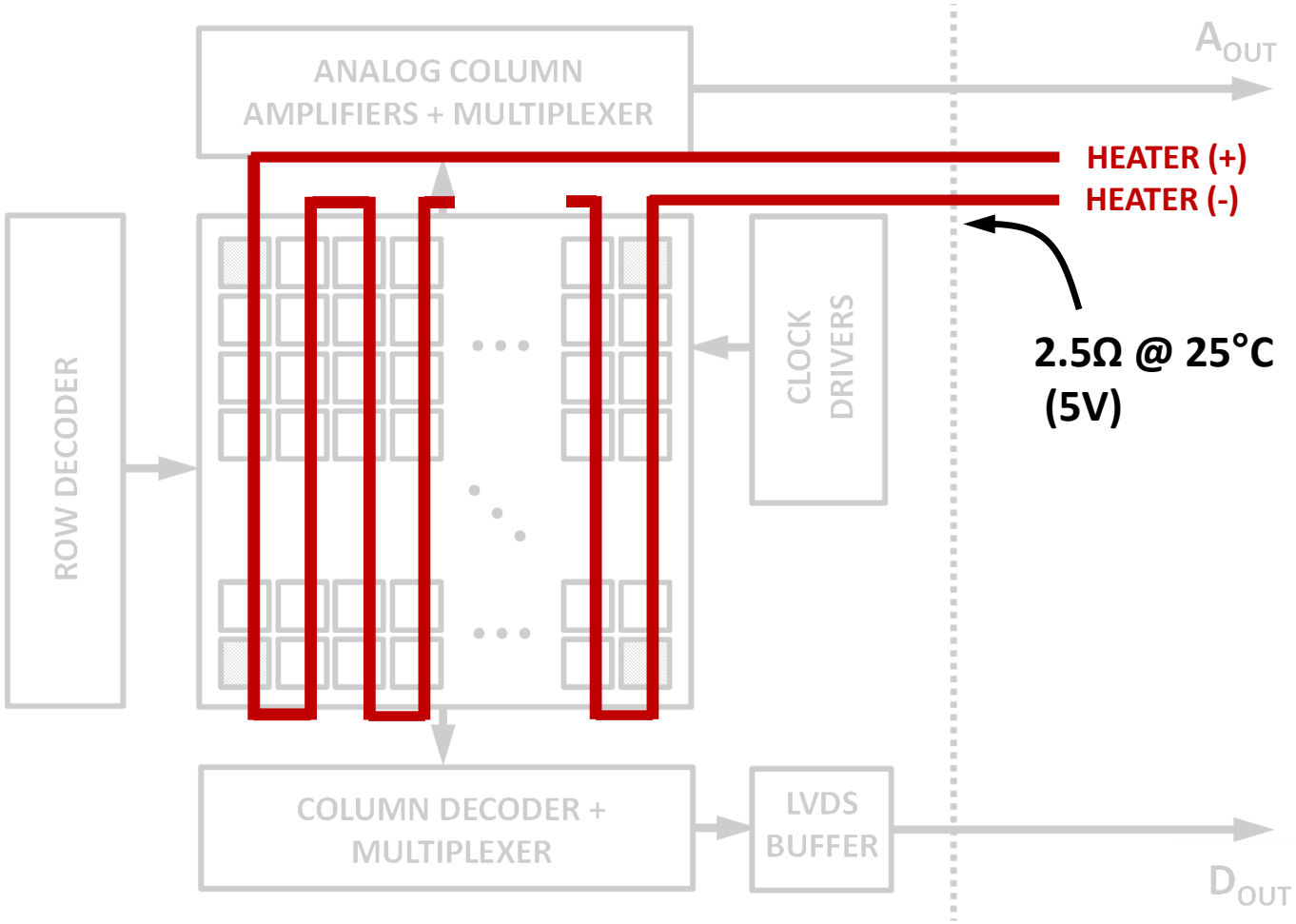


Array Architecture

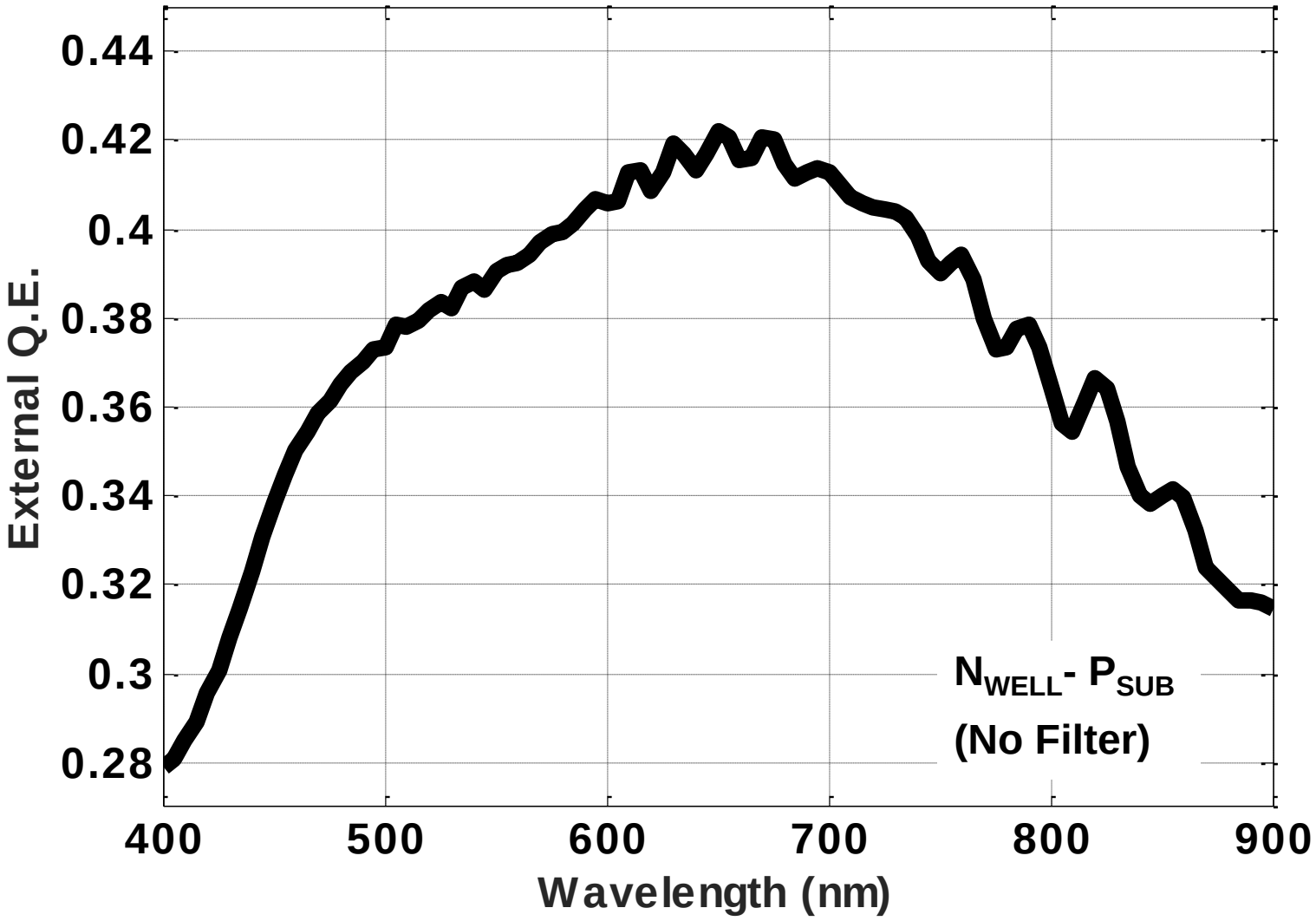


Temperature Sensor

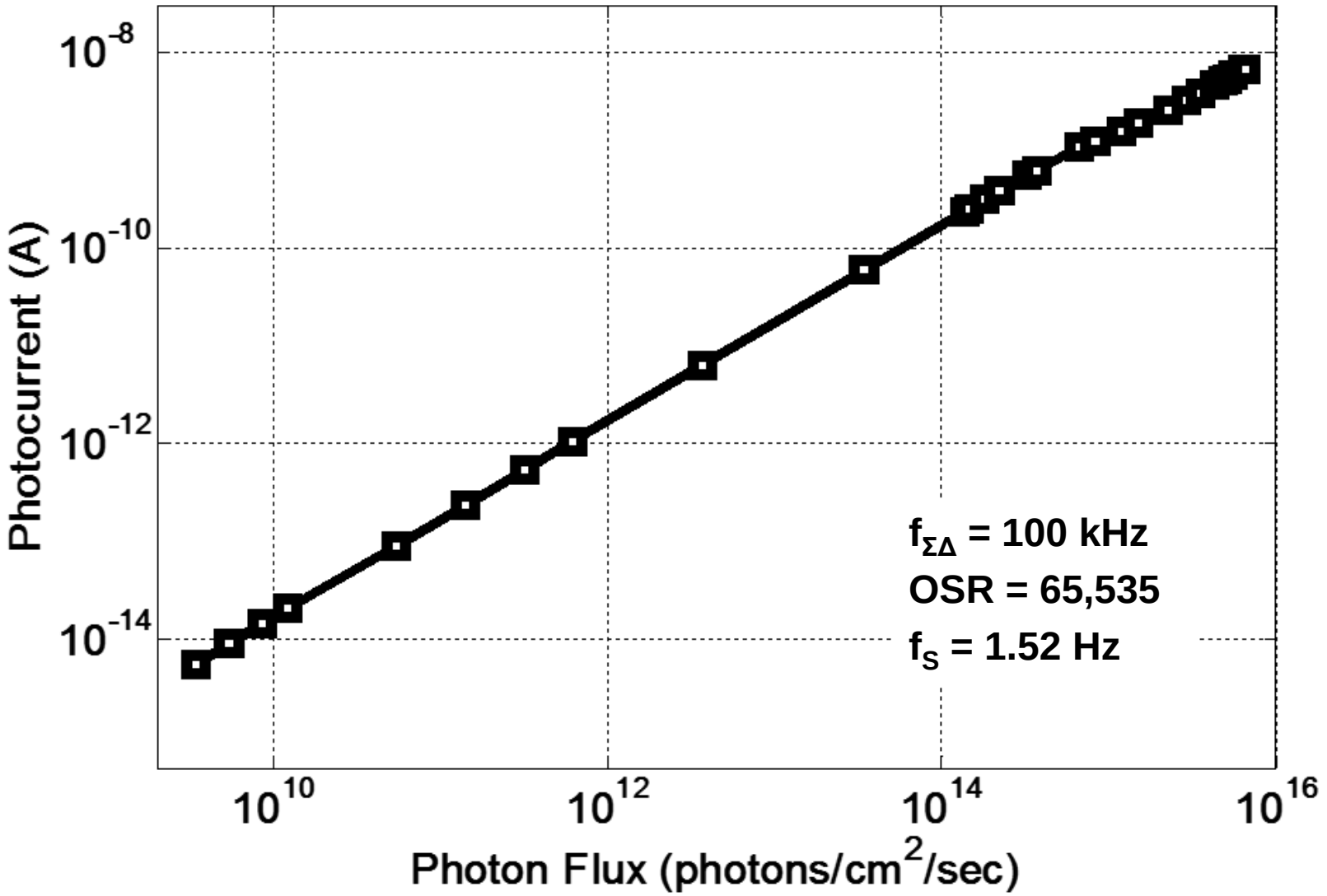
Resistive heater structure to uniformly heat the entire chip



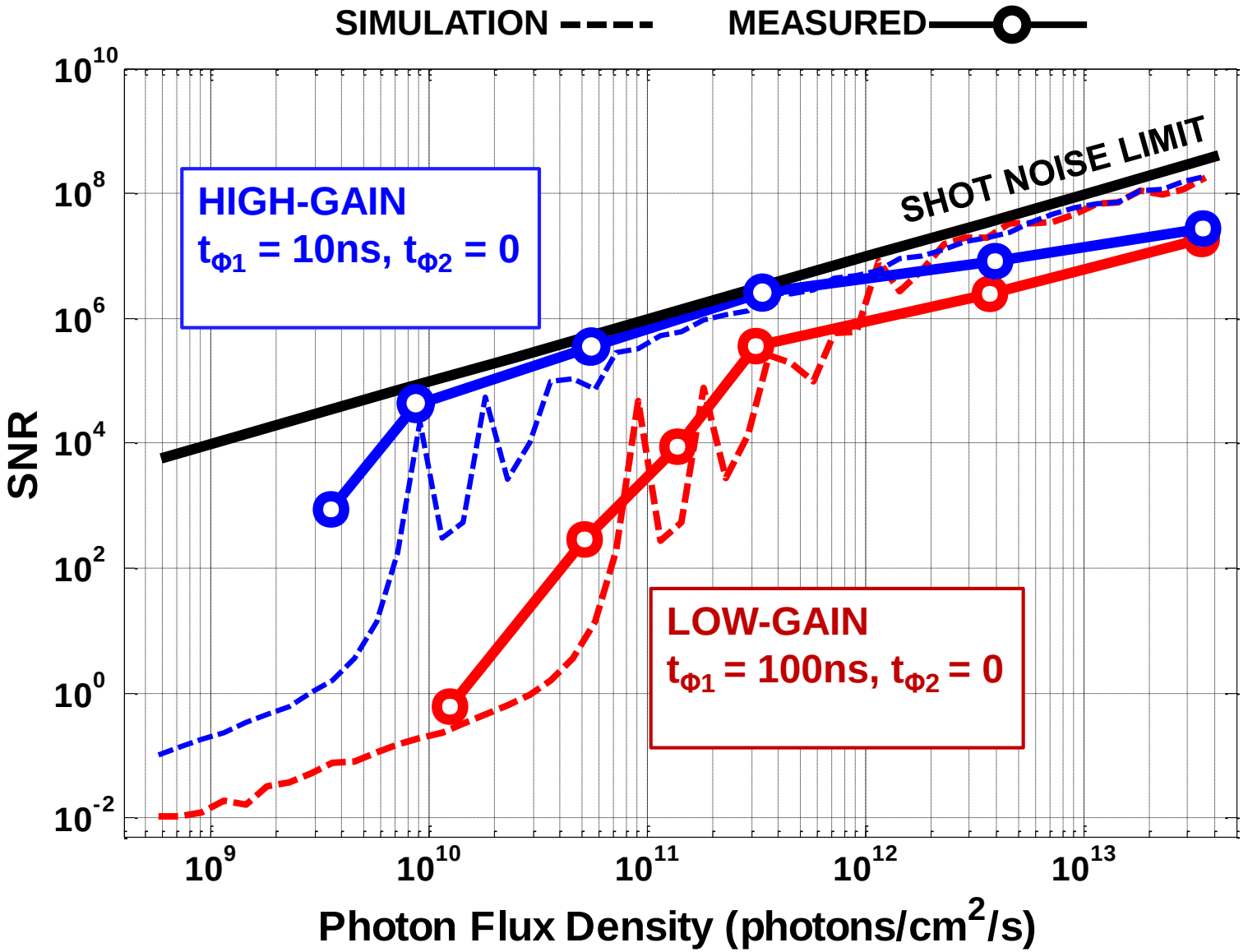
Photodiode Q.E.



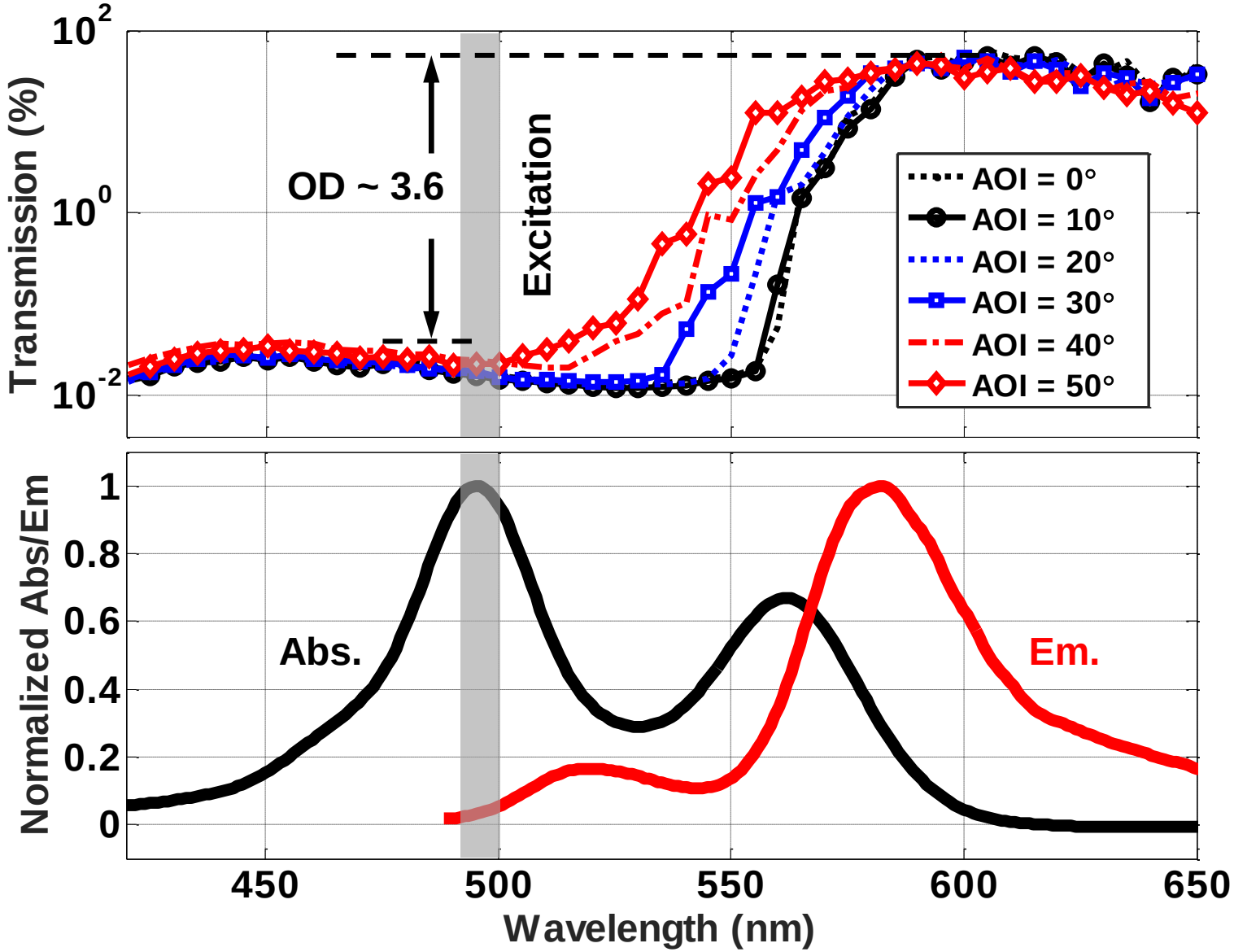
Linearity (λ_X = 495 nm)



SNR vs. Shot Noise



Filter Response



Experimental Setup

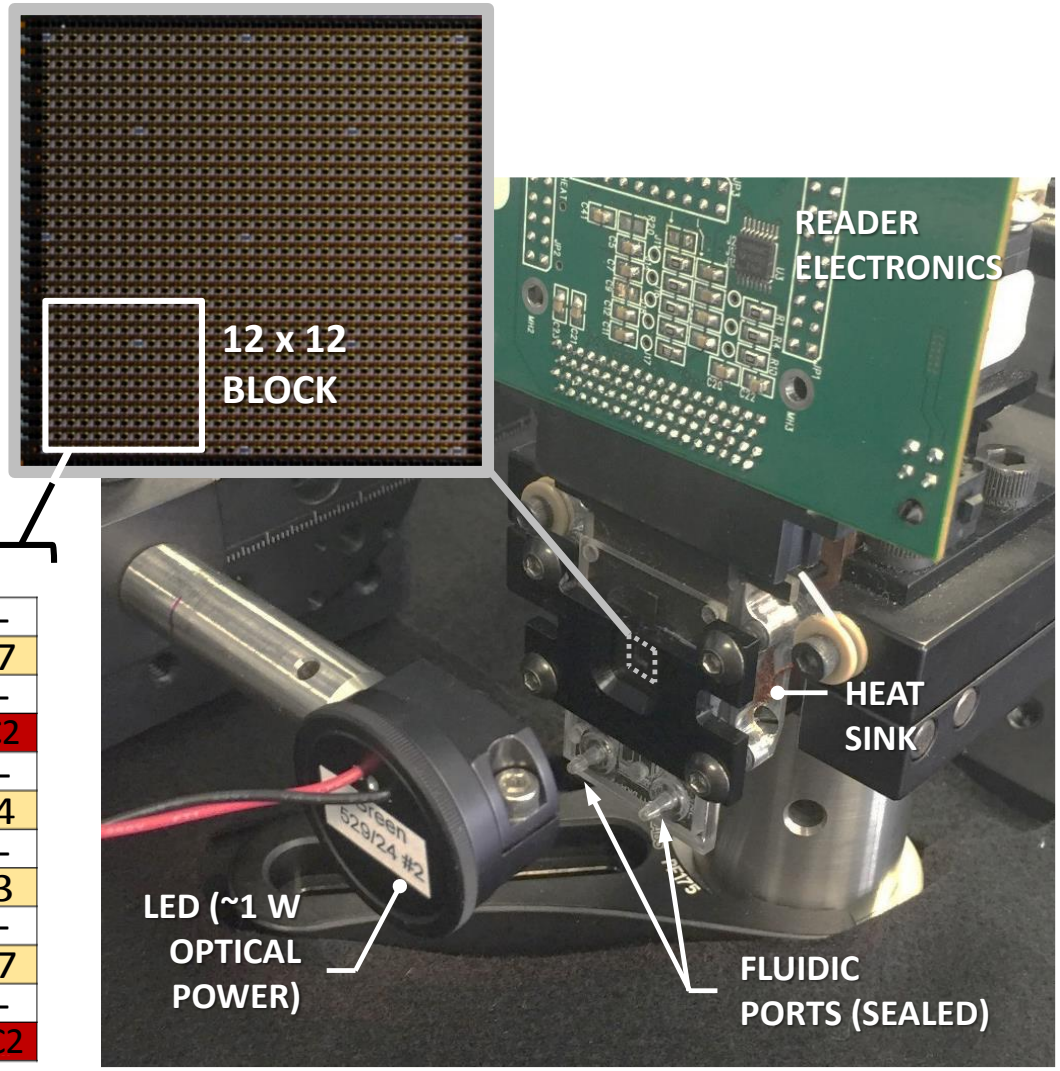
PROBES

1. Influenza A (FluA)
2. Influenza B (FluB)
3. Respiratory Syncytial Virus (RSV)
4. Parainfluenza virus (PIV)
5. Adenovirus C (AdVC)
6. Adenovirus E (AdVE)
7. Polio 1 (+ Control)

C1/C2: Manufacturing quality controls

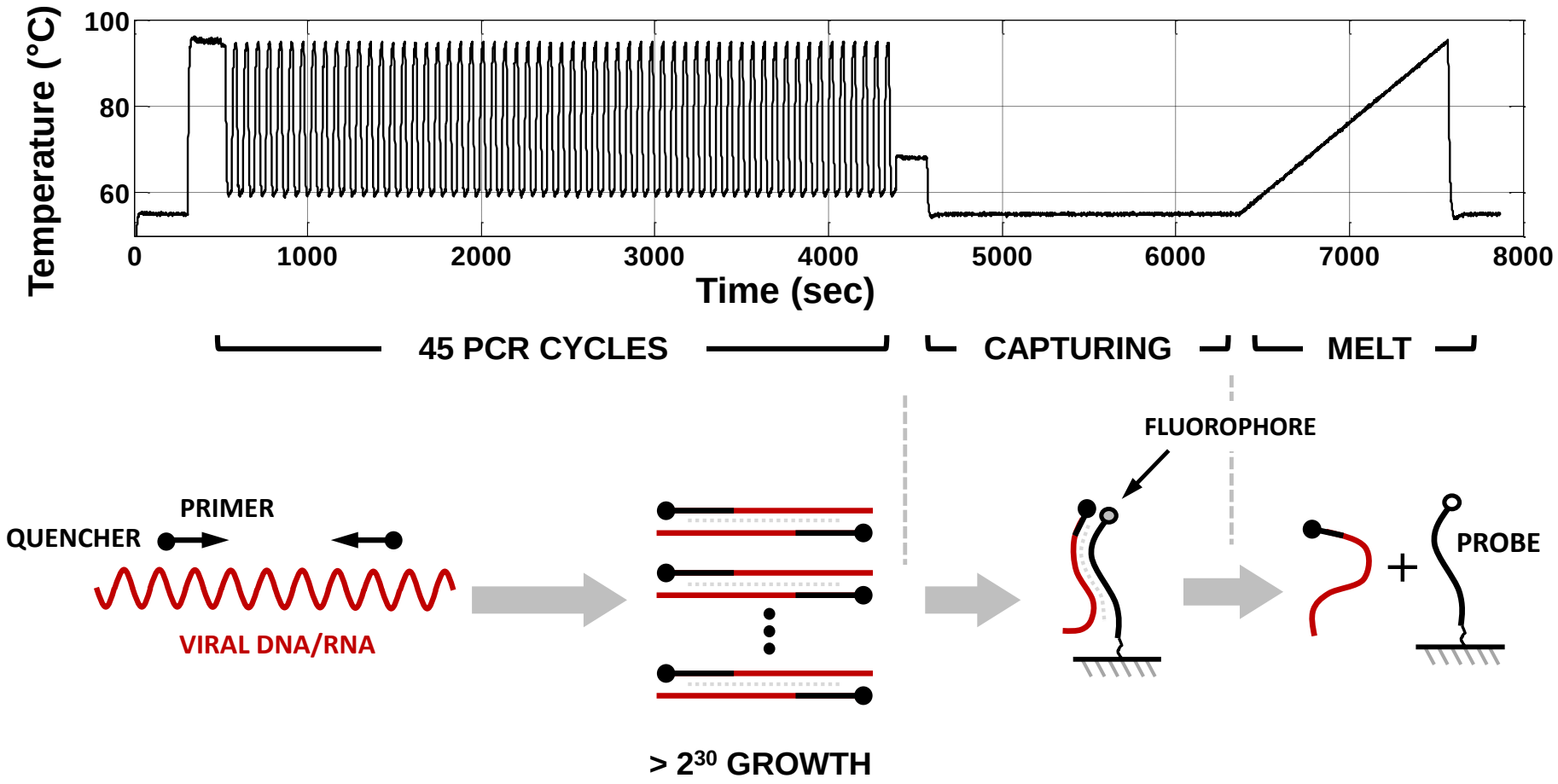
PROBES MAP

C1	-	-	-	-	-	-	-	-	-	-	-
3	3	4	4	6	6	5	5	5	6	C2	7
-	-	-	-	-	-	-	-	-	-	-	-
C2	C2	C2	1	1	2	3	3	4	4	7	C2
-	-	-	-	-	-	-	-	-	-	-	-
3	3	1	2	6	1	1	C2	2	3	3	4
-	-	-	-	-	-	-	-	-	-	-	-
C1	1	1	2	1	1	2	2	C1	4	4	3
-	-	-	-	-	-	-	-	-	-	-	-
5	5	5	C2	6	2	3	3	4	4	7	7
-	-	-	-	-	-	-	-	-	-	-	-
4	3	C1	1	1	4	4	3	3	1	2	C2



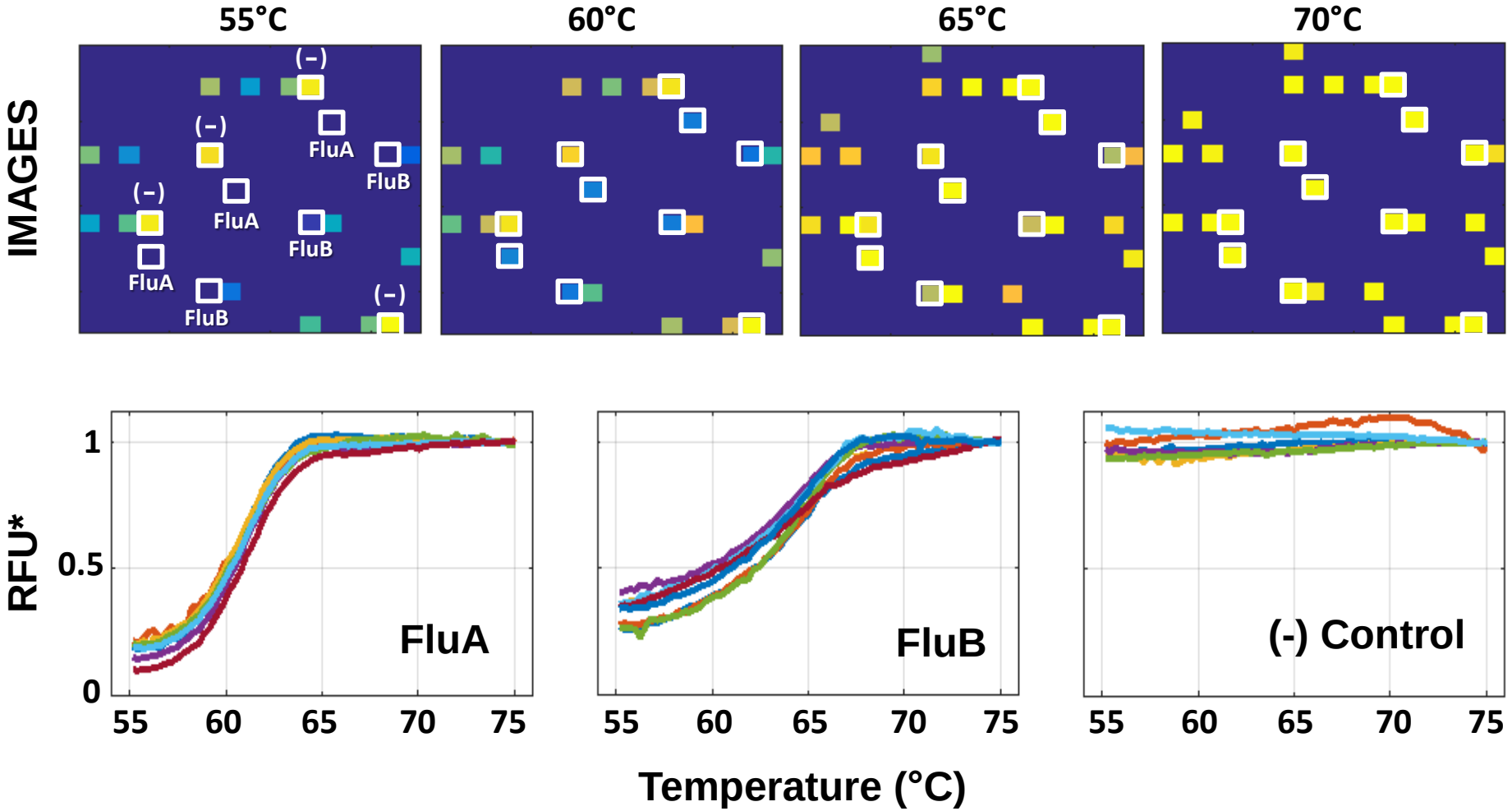
Multiplex PCR Setup

Multiplex PCR, capture and detection in ~2 hours



Melt Curve Results

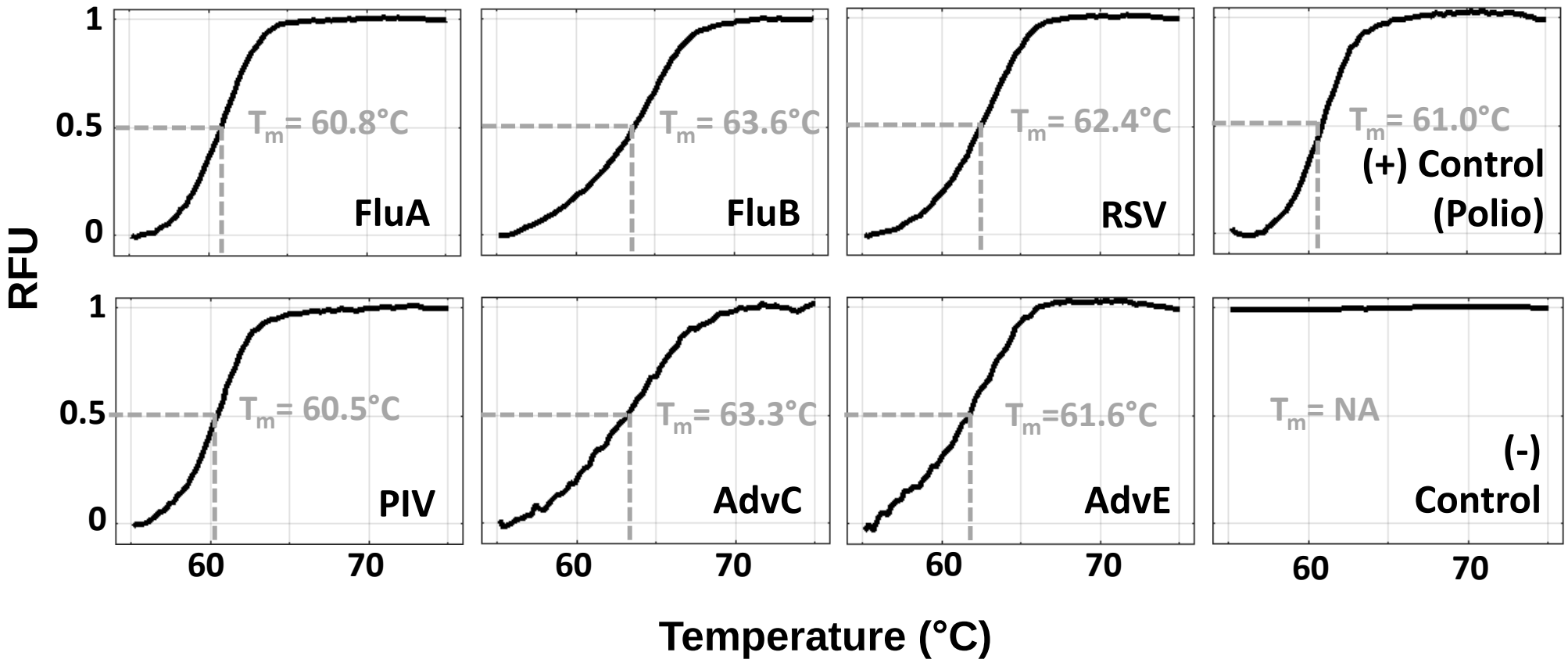
Melt results for ~100 copies/µl of FluA and FluB virus input



*Relative fluorescence unit

Viral Signatures

Measured melt signature for all inputs



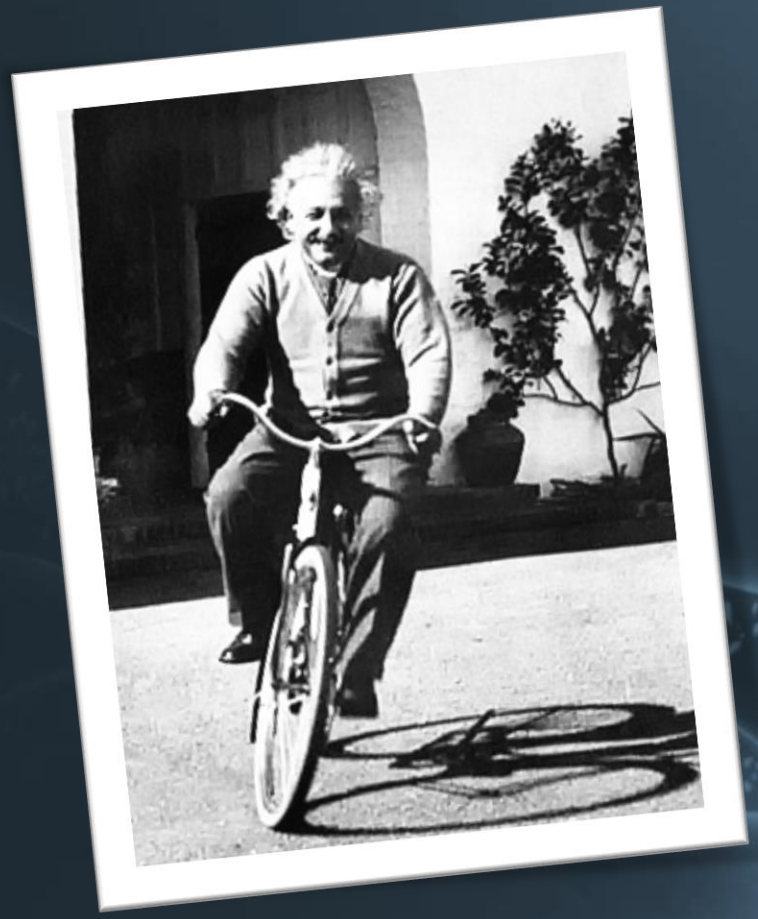
Conclusion

<u>The Good:</u> Ideal technology for point-of-care (PoC) and mass deployment molecular diagnostics?

<u>The Bad:</u> Complex and capital intensive manufacturing/assembly processes; requires convergence of multiple disciplines beyond engineering

<u>The Hype:</u> An overpromised field with lots of unproven technologies and failed projects, and limited successful commercial products

Small Differences Matter



Albert Einstein
(1879-1955)

–

Bobo the Chimp
(1995-Now)

= 1.5% DNA Difference

Biosensors: Random Numbers

Examples	Concentration (Copies/ml)	Types/Strains	Reimbursement (US)	Tests per Year (US) (Millions)	Consumer Application	"Electronic" Solution
Water	**3.3×10^{22}**	-	-	-	-	-
Glucose	10^{18}	1	**$10**	**700**	**+++**	
Cholesterol	8×10^{17}	2	**$15**	**> 500**	**+/-**	
Antibodies/Hormones	10^{8}	> 10,000	**$15 - $100**	**> 2000**	**++**	
DNA for Forensics	10^{7}	20	**$500**	**50**	**-**	
Upper Respiratory Viruses (*Flu A*, *Flu B*, *Rhinovirus*, etc.)	10^{4}	> 50	**$550**	**10**	**+++**	
HIV Virus in Blood	4×10^{2}	> 50	**> $100**	**25**	**+/-**	
***M. Tuberculosis* Bacteria**	10^{2}	> 300	**NA**	**0.2**	**+/-**	
Gram Negative Bacteria in Blood	10	> 1000	**> $200**	**50**	**-**	
Food Poisoning Bacteria (*Salmonella*, *Listeria*, *E. Coli*)	1	> 50	**> $100**	**100**	**++**	

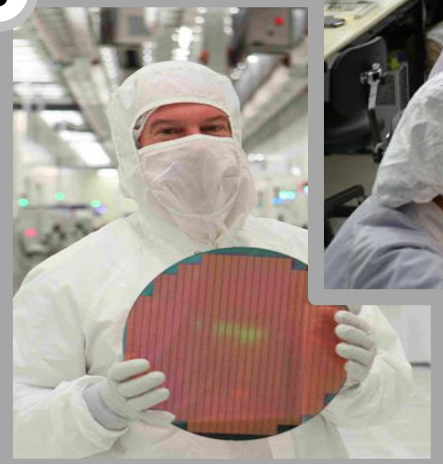
(Almost) Fabless Manufacturing

10 WEEKS

1 NEW DESIGN

2 MEGA FOUNDRIES

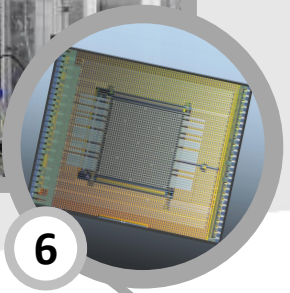
3 WAFER PROCESSING



4 ADVANCED PACKAGING

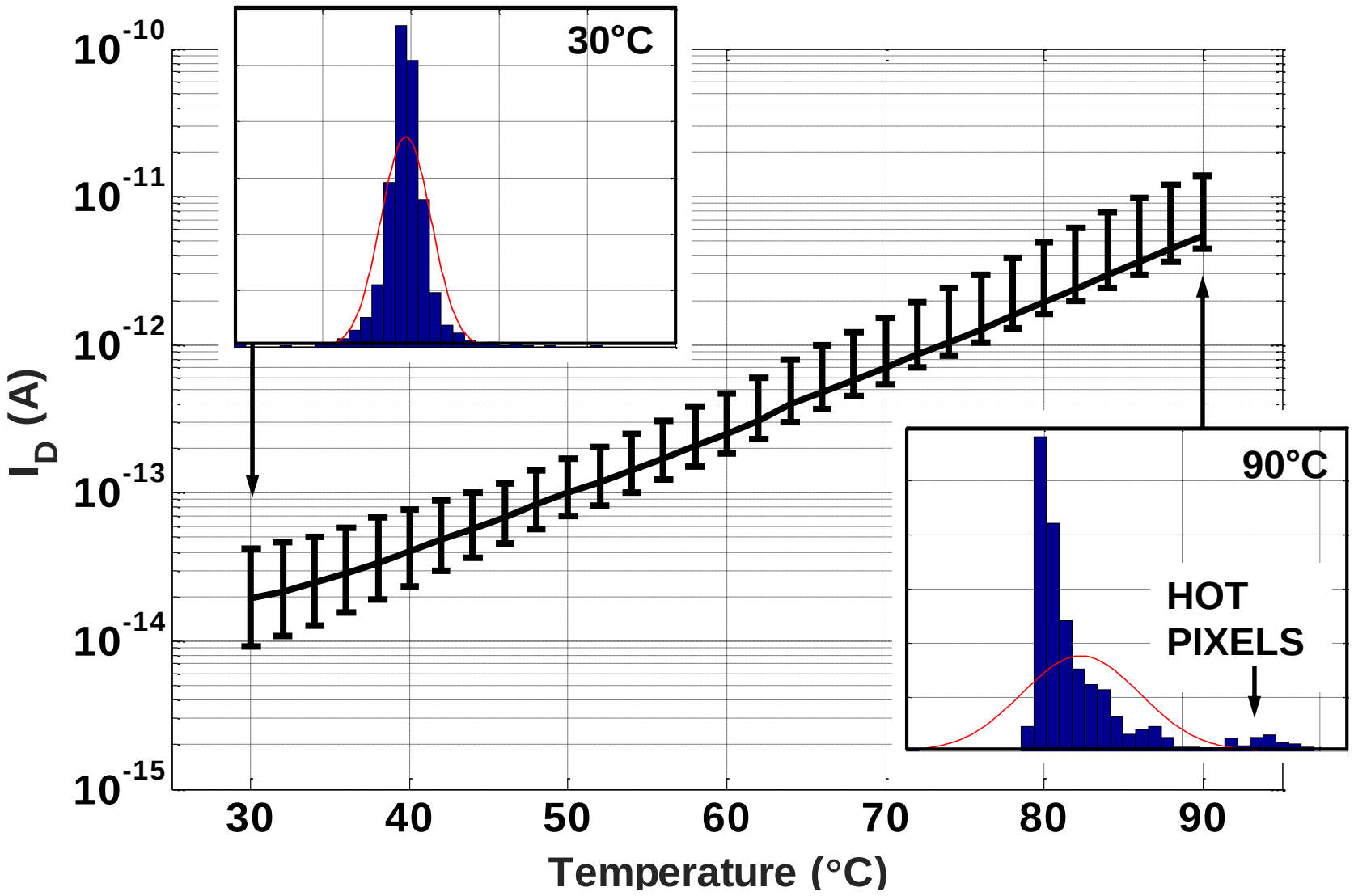
5 PROBE PRINTING

6 CMOS BIOCHIP



7 ASSEMBLY

Measured Dark Current (I_D)



Measurement Process

Correlated double sampling (CDS) to measure I_D and signal