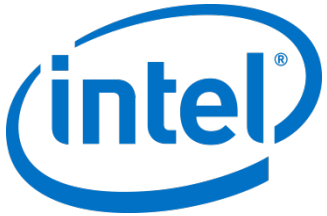


A Nanogap Transducer Array on 32 nm CMOS for Electrochemical DNA Sequencing

Drew A. Hall, Jonathan S. Daniels, Bibiche Geuskens, Noureddine Tayebi, Grace M. Credo, David J. Liu, Handong Li, Kai Wu, Xing Su, Madoo Varma, Oguz H. Elibol

Outline

- Background
- System Overview
- Circuit Architecture
- Transducer Integration
- Results
- Scalability
- Summary

Low Cost Sequencing Drives Applications

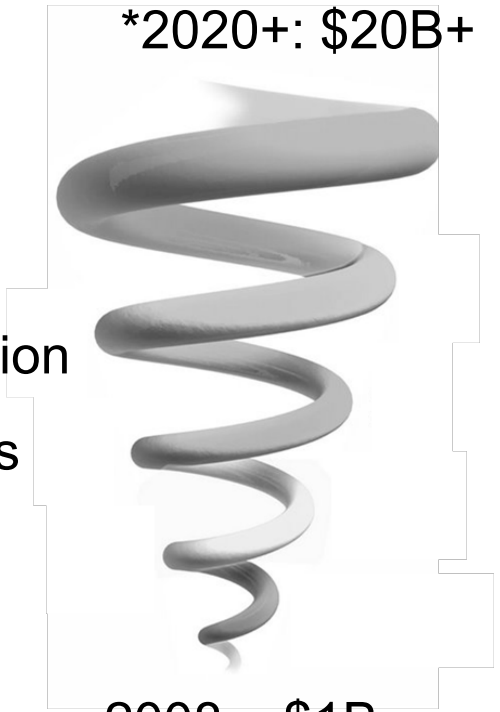
Services

Datasets

Computation

Algorithms

Silicon



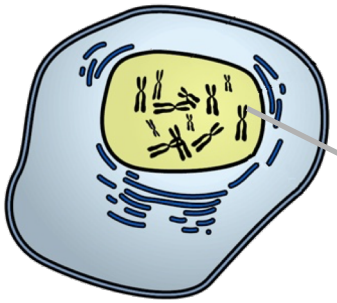
Targeted disease management
- Prevention, screening
- Clinical diagnostics
- Treatment, monitoring

Non-clinical industrial monitoring
- Environment/Ecology (metagenomics)
- Bio-defense; epidemiology
- Agriculture/food, beverages

Acceleration of drug development
- Disease association
- Compound screening
- Drug efficacy

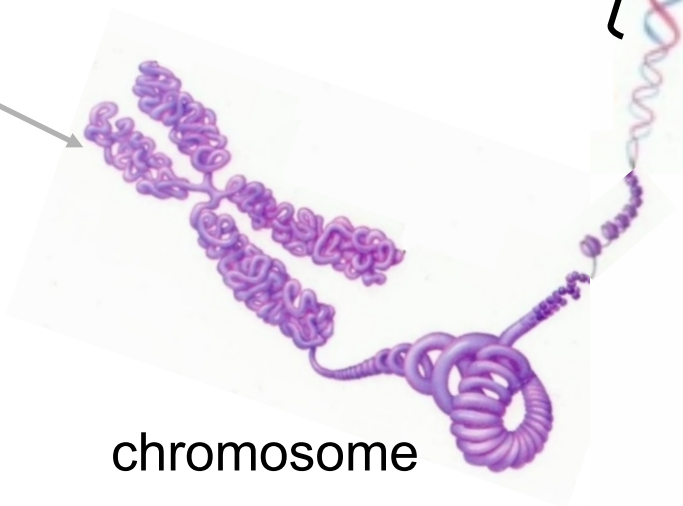
*http://www.forbes.com/sites/luketimmerman/2015/04/29/qa-with-jay-flatley-ceo-of-illumina-the-genomics-company-pursuing-a-20b-market/

DNA: The Blue Print of Life

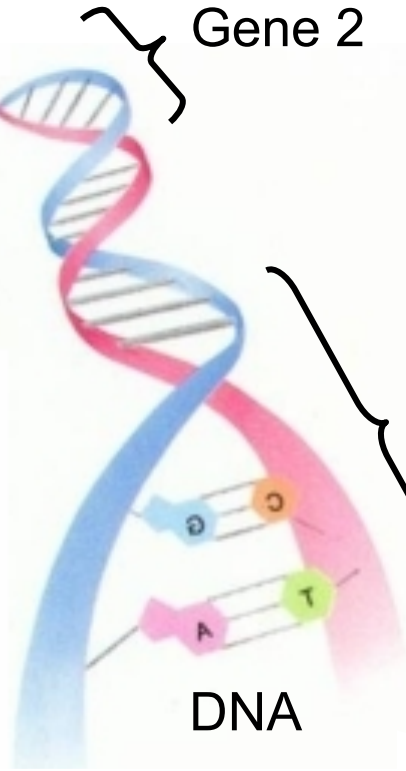


20-50 um

cell



chromosome



Humans: 10^{12} cells

23 pairs of chromosomes

3B bases

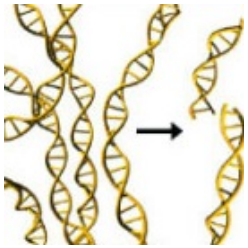
20K genes

A pairs with T

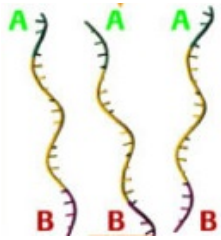
C pairs with G

DNA Sequencing Process Flow

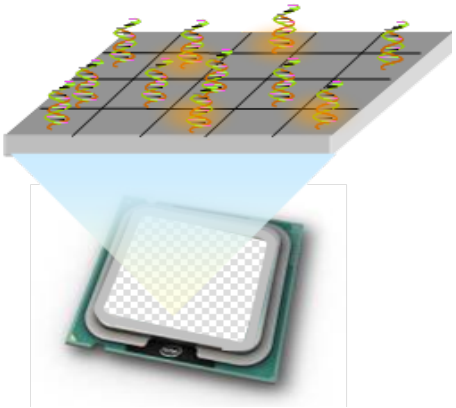
DNA Fragmentation



Library Preparation



Data Generation



Data Processing

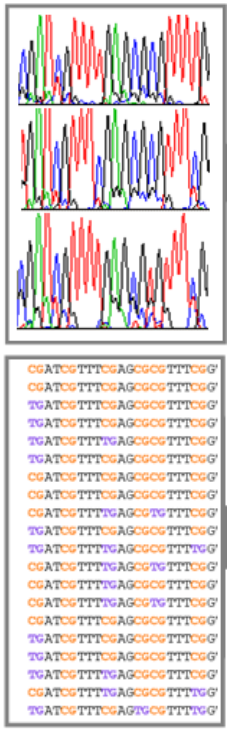
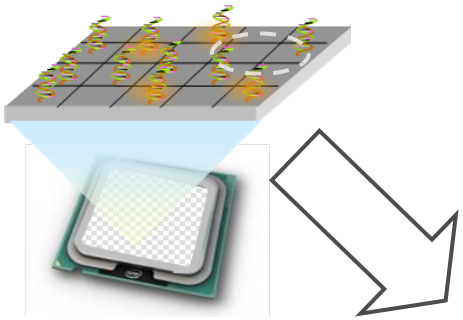
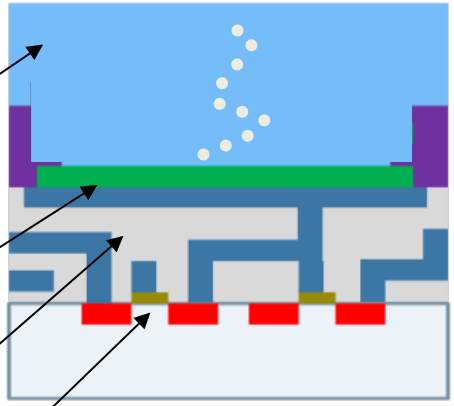


Image credits:
http://biochem.jacobs-university.de/BDPC/BISMA/manual_unique.php , http://www.454.com/products-solutions/how-it-works/index.asp, http://www.odec.ca/projects/2006/bach6k2/background.htm

System Overview



1- Chemical Signal Generation and Amplification



Post Processed

Standard CMOS

Reaction Fluid (Salt Water)

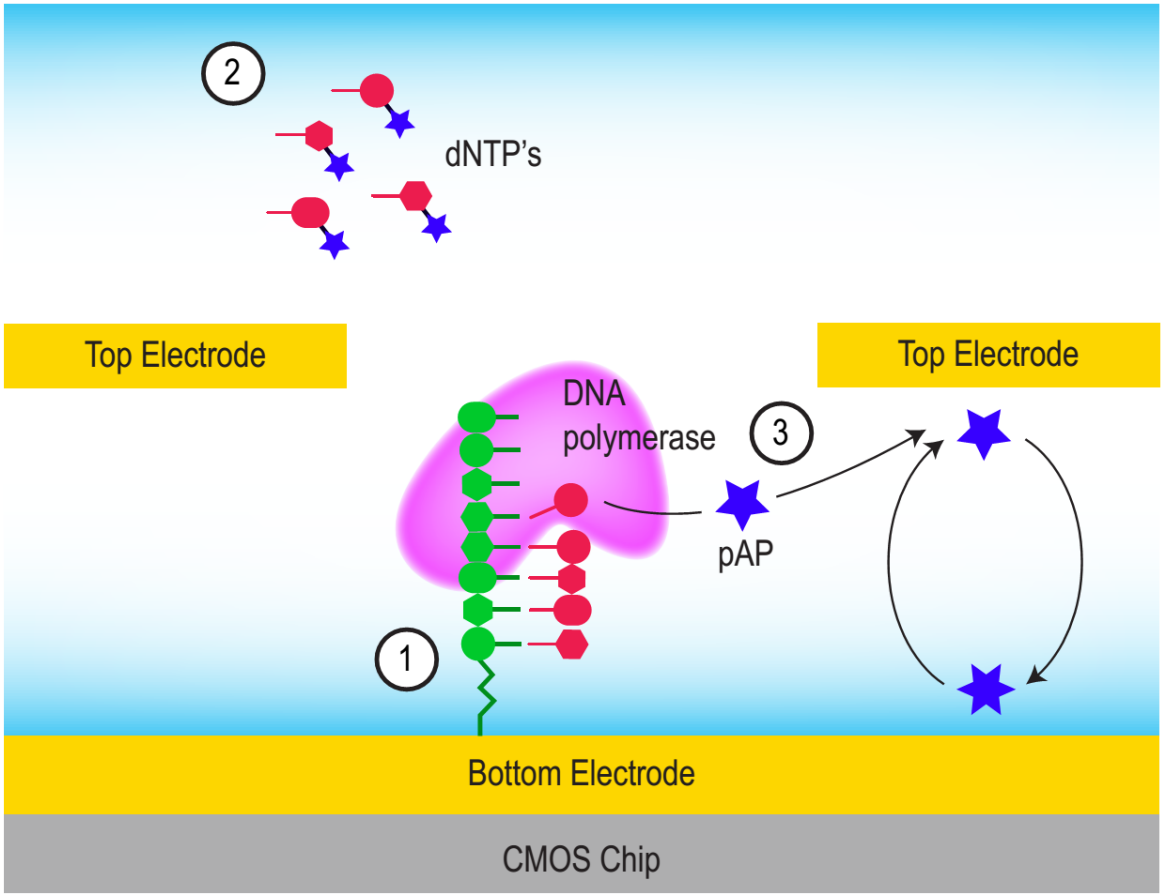
Transducer

Interconnect

Transistors

2- Electrical Signal Amplification and Detection

DNA Sequencing Flow - Pixel



1- A colony derived from a unique DNA strand is immobilized on each sensor

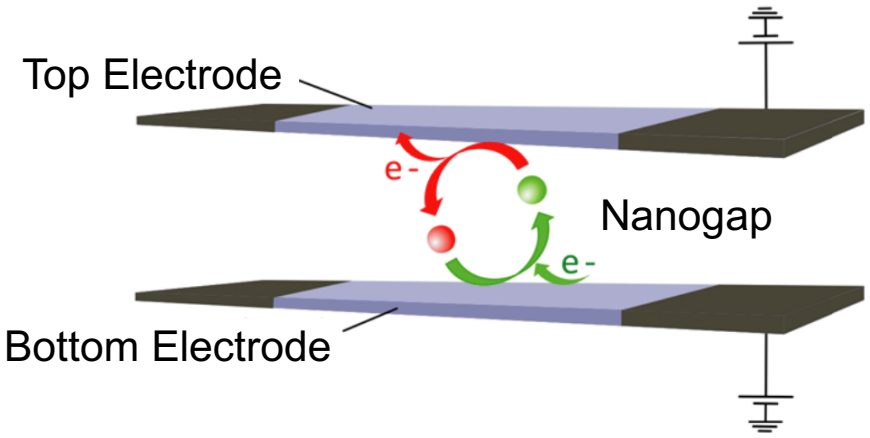
2- Each modified base is introduced sequentially through the solution (~min)

3- The electrochemical tag is released upon incorporation of the base and detected (after cleaving phosphate) (~sec)

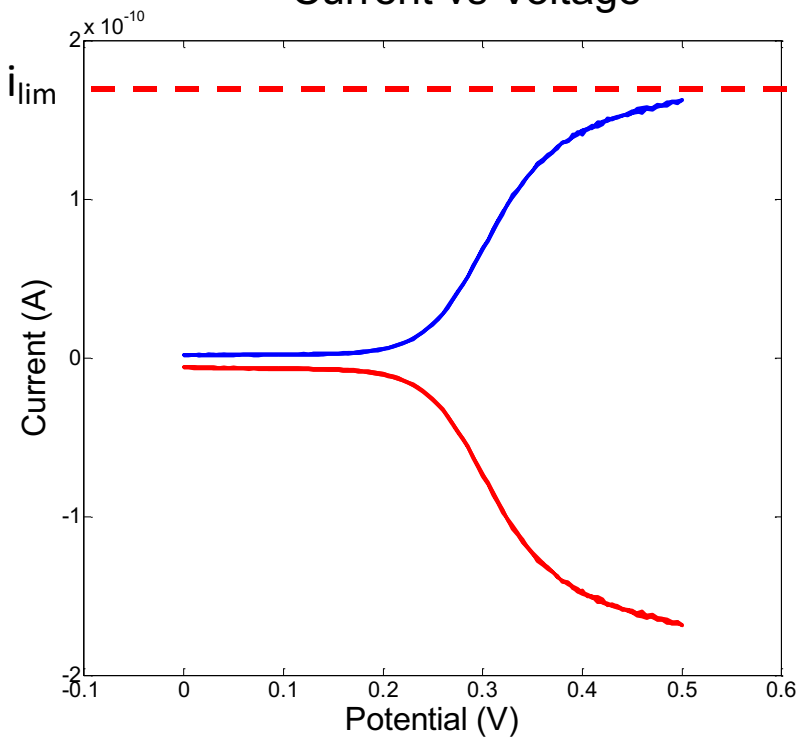
Presence of the tag is detected per pixel per base

Transduction Mechanism

Physical Model



Current vs Voltage



Redox Cycling

Average shuttling time ~ $\frac{z^2}{2D}$

z : gap size

D: diffusion coefficient of the molecule

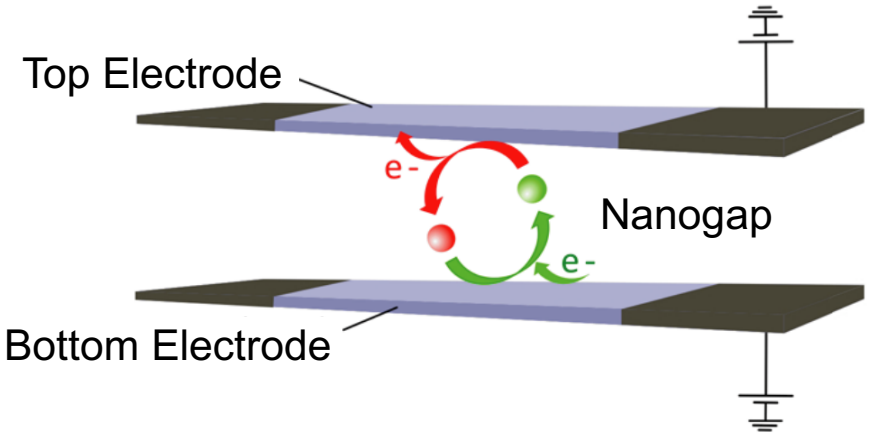
>50 fA current per molecule

independent of lateral dimensions

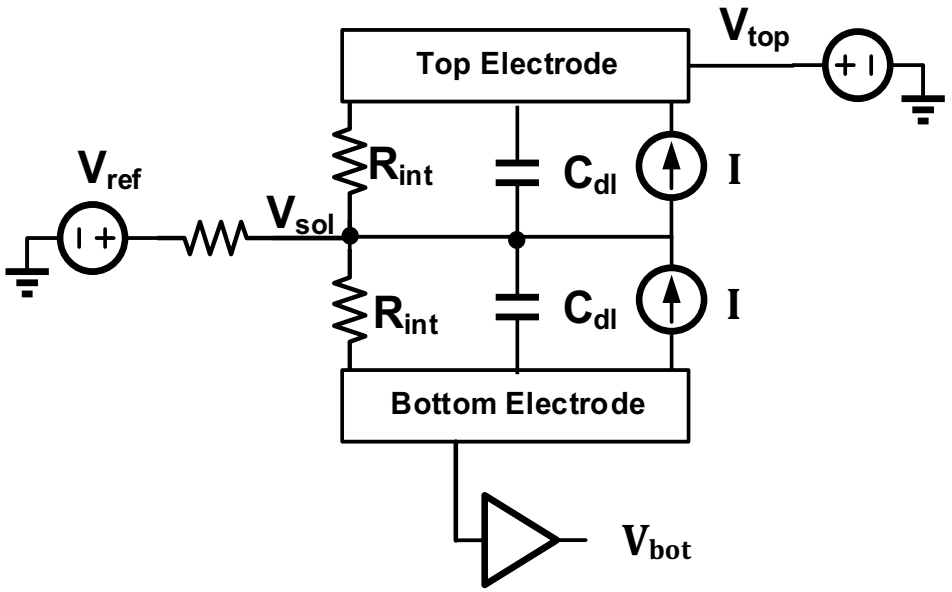
$$i_{lim} \propto \frac{\#\,\text{of molecules}}{\text{shuttling time}}$$

Transduction Mechanism

Physical Model



Electrical Model



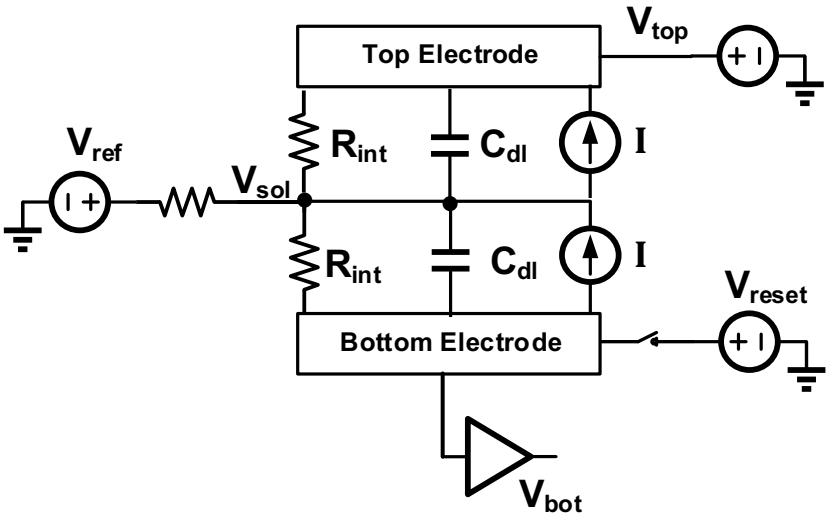
Average shuttling time ~ $z^2/2D$

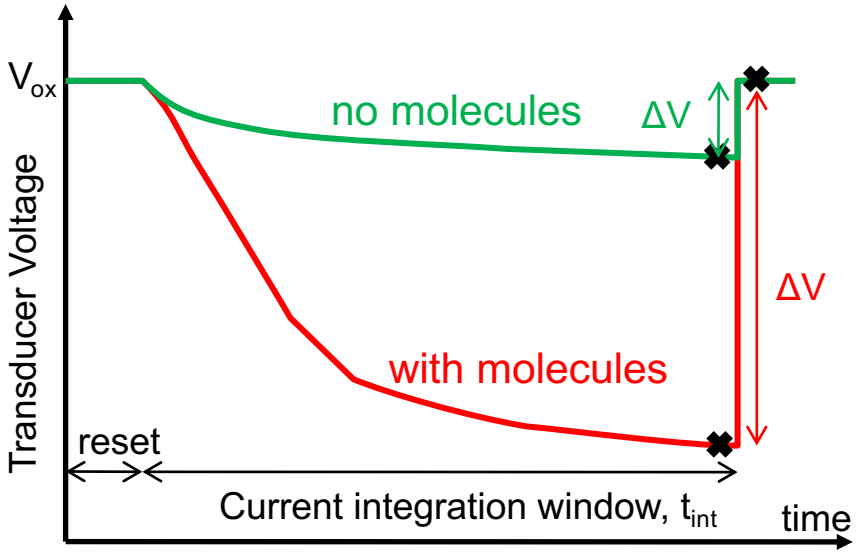
z : gap size

D: diffusion coefficient of the molecule

$$I \propto \frac{\#\,\text{of molecules}}{\text{shuttling time}}$$

Discharge Measurement

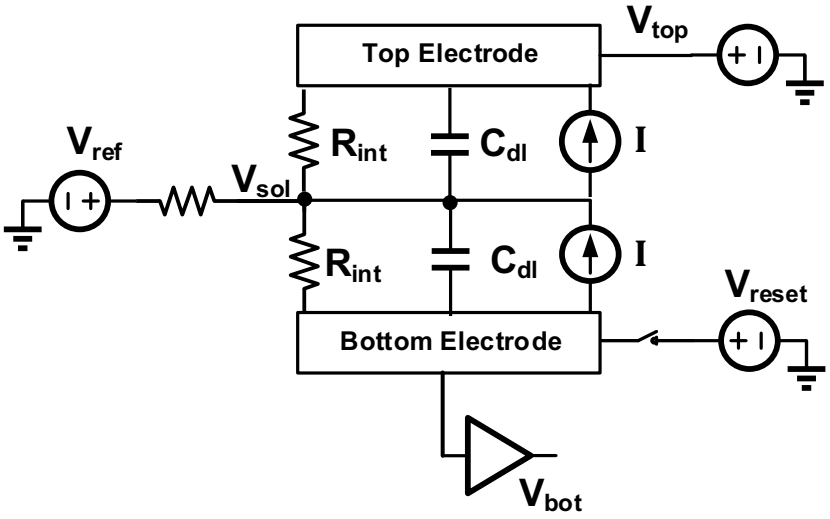


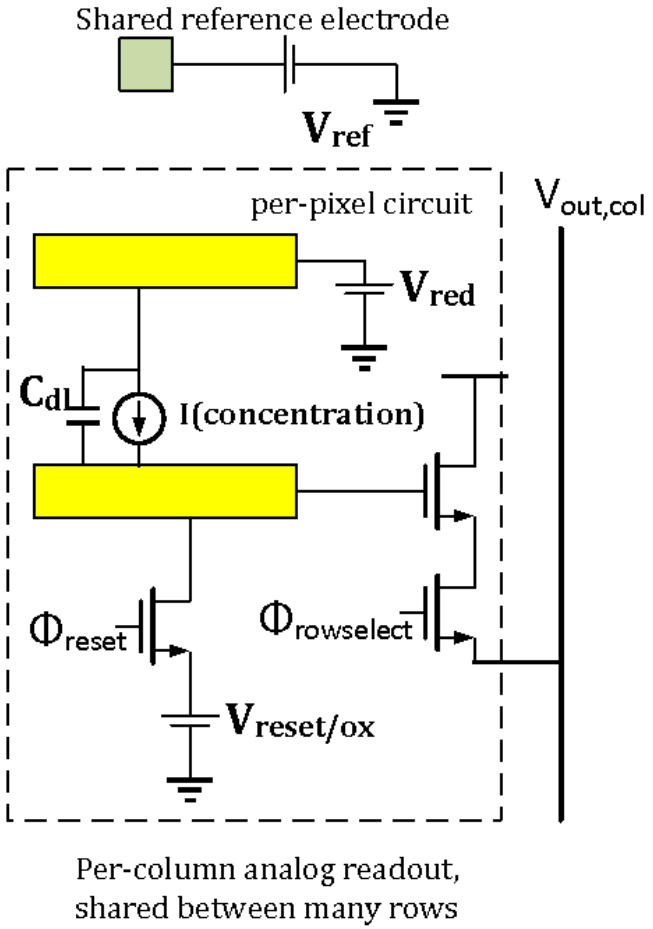


Voltage readout of the bottom electrode instead of current

Pixel Architecture

Model with Ideal Elements

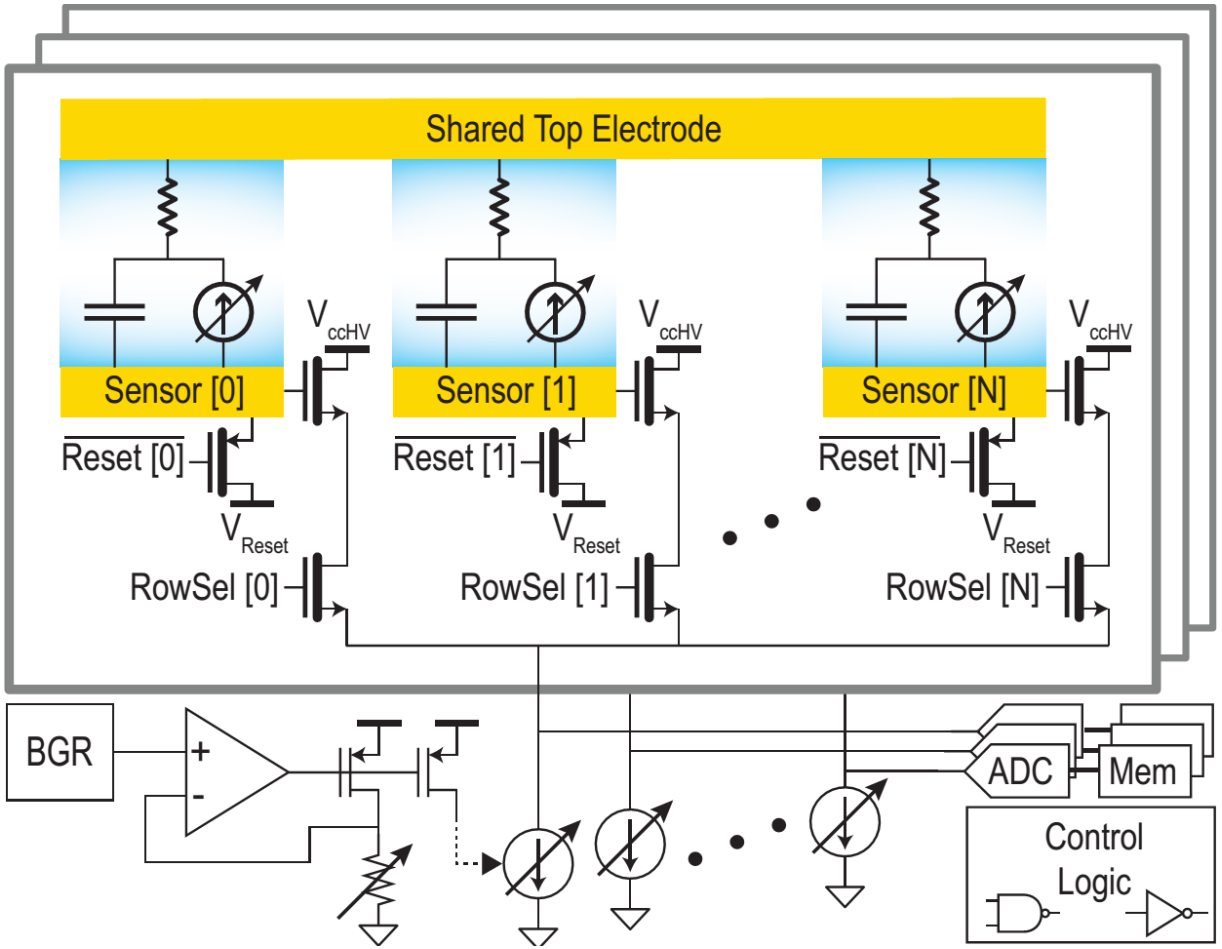




Per-column analog readout, shared between many rows

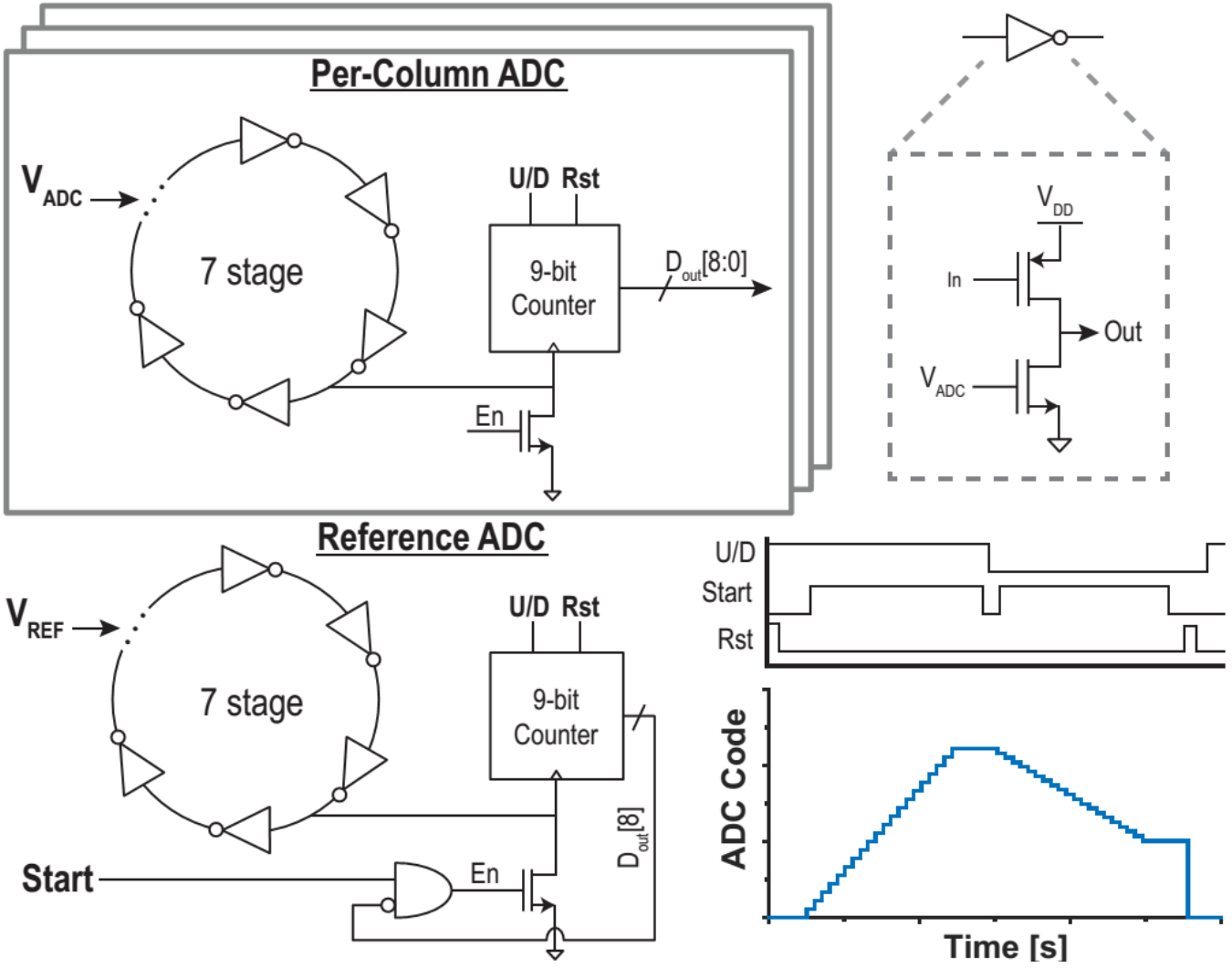
3 transistors per pixel: reset, follower, and row select

Chip Architecture

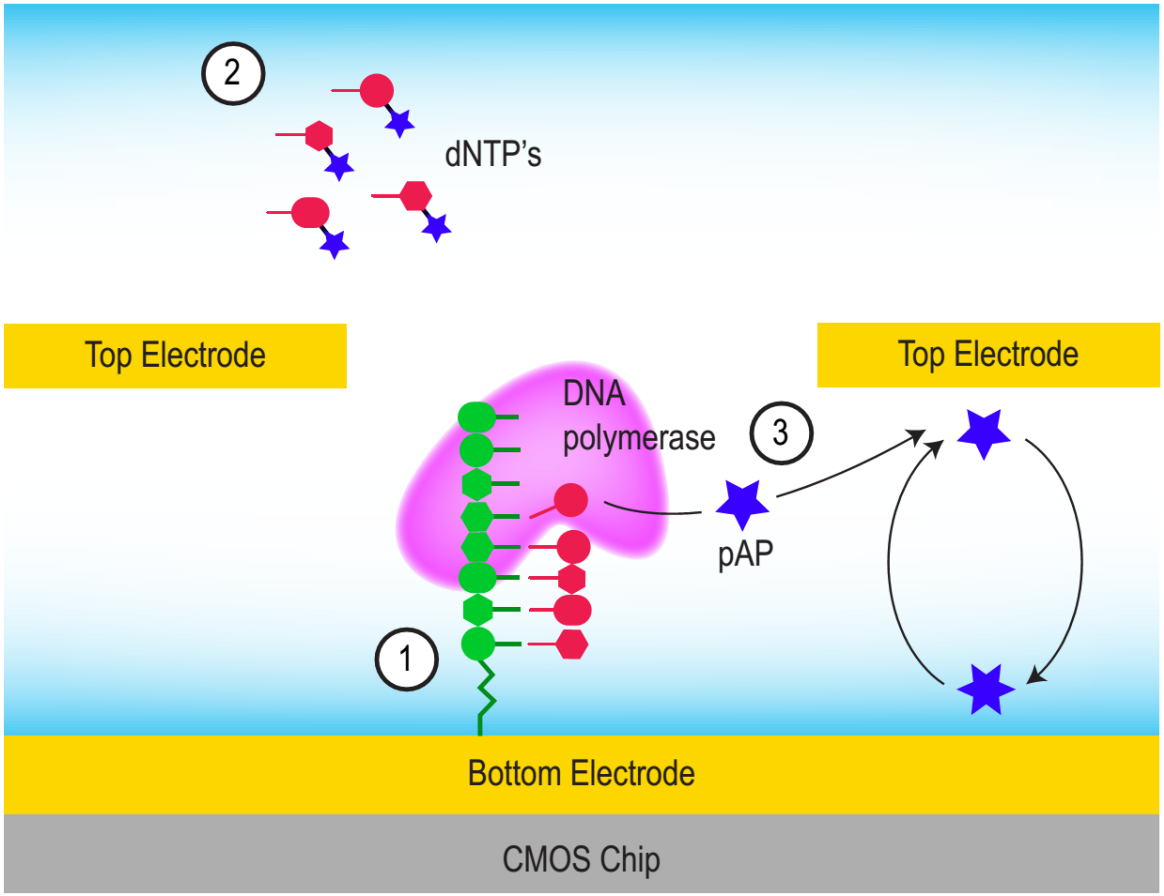


Column parallel readout, cycle through rows

VCO Based ADC



DNA Sequencing Flow - Pixel



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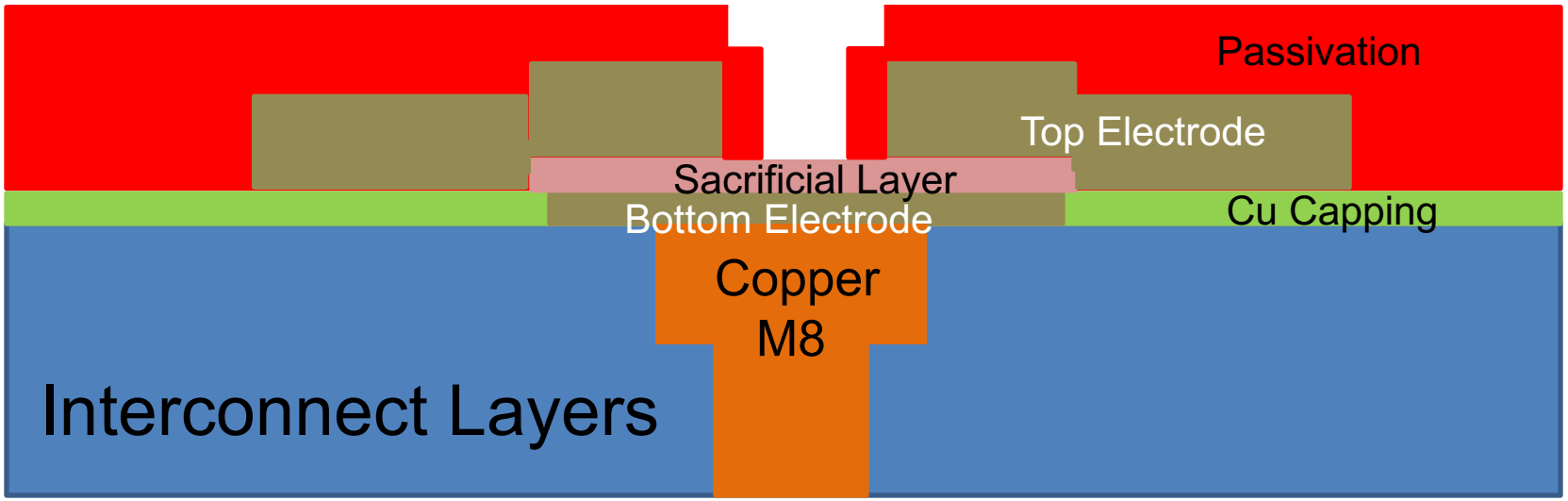
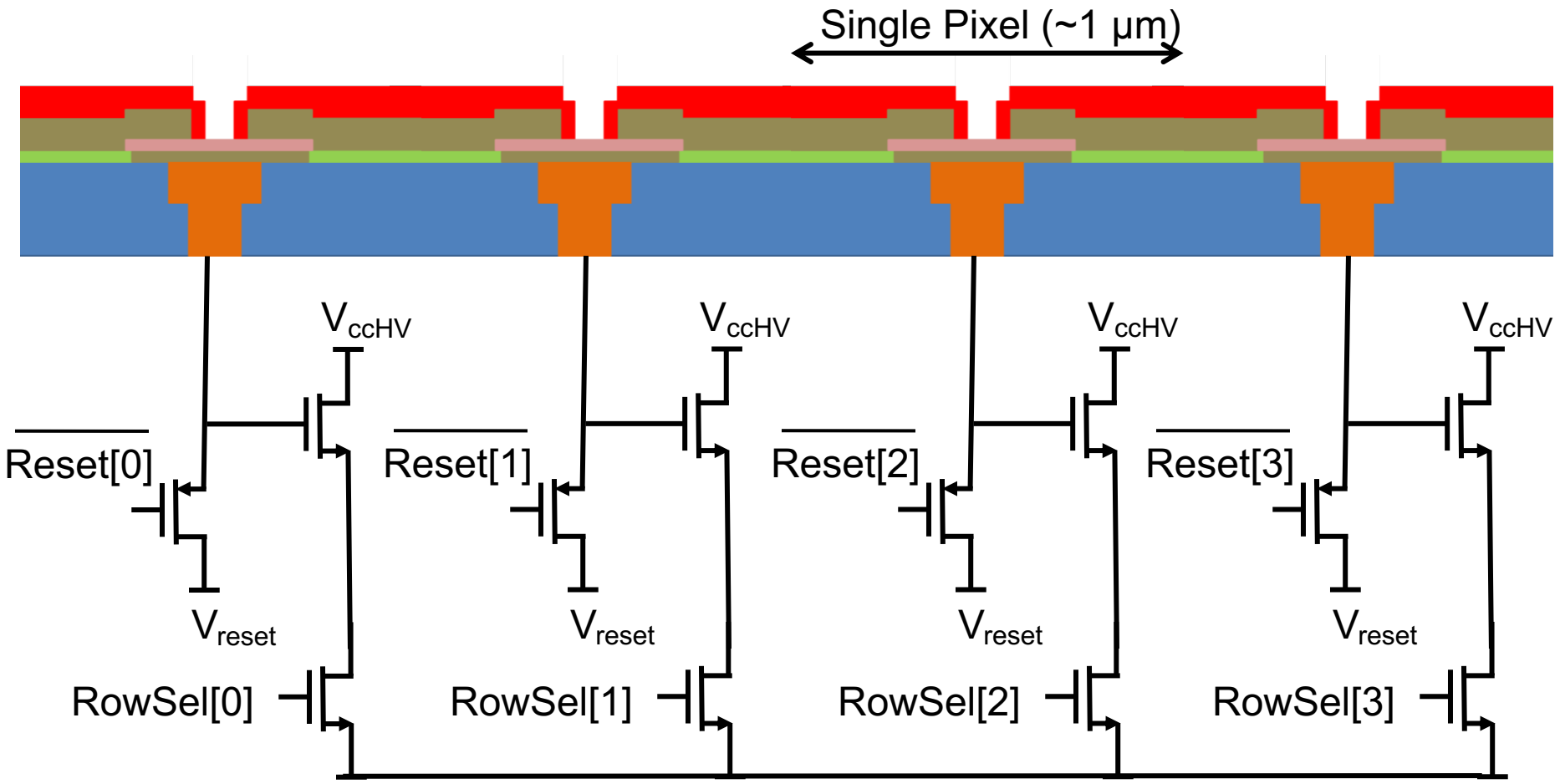
Transducer Integration

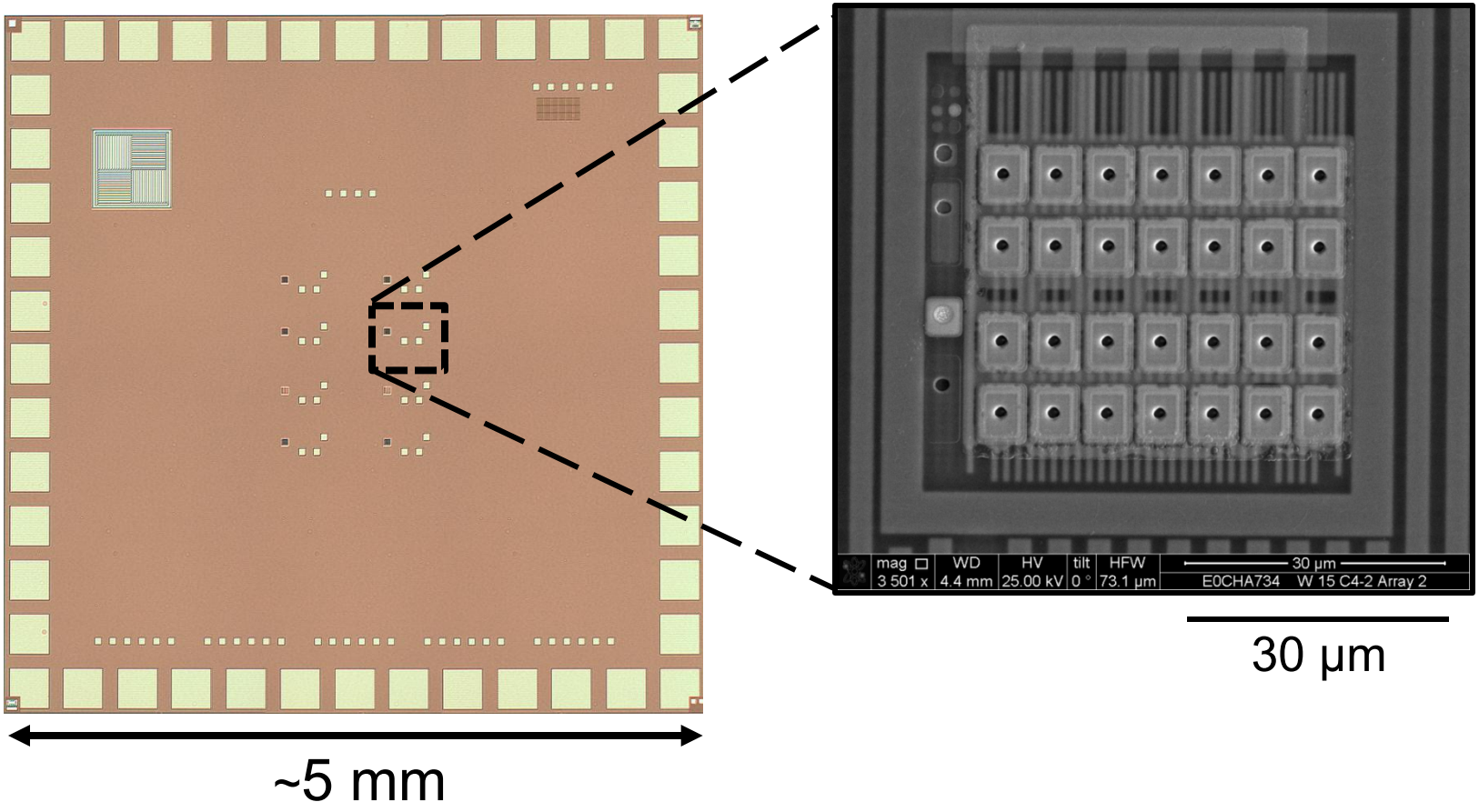


Post processing on standard CMOS wafer

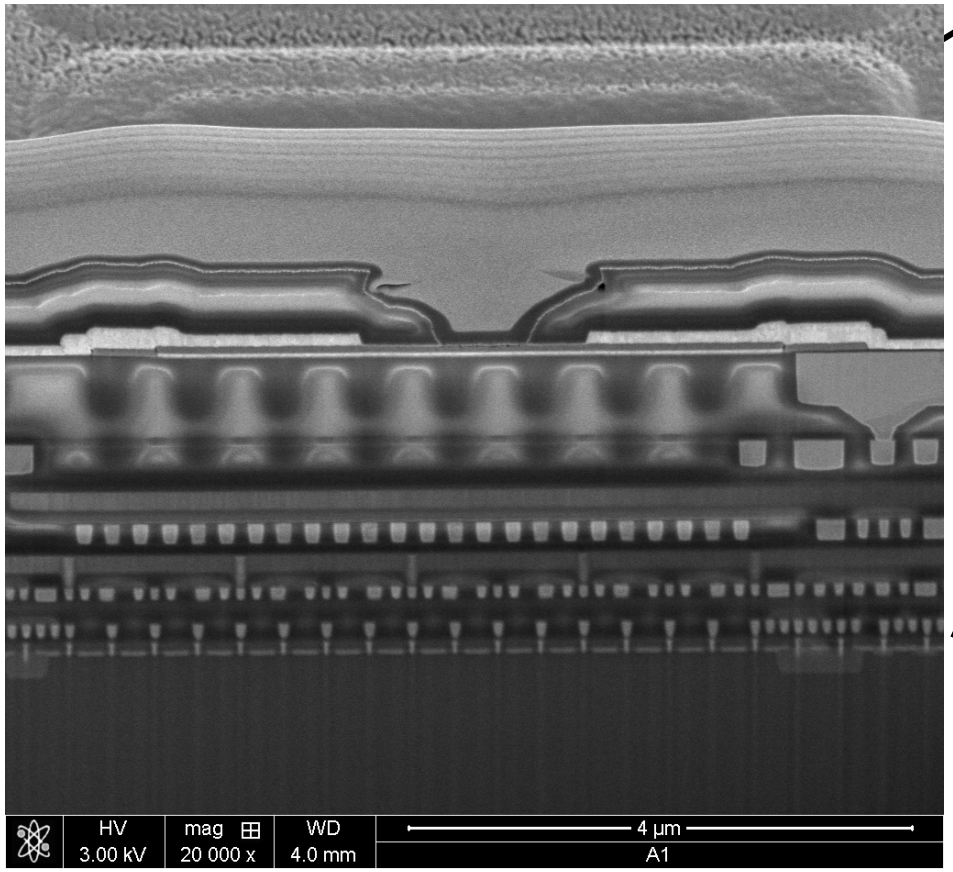
Transducer Integration



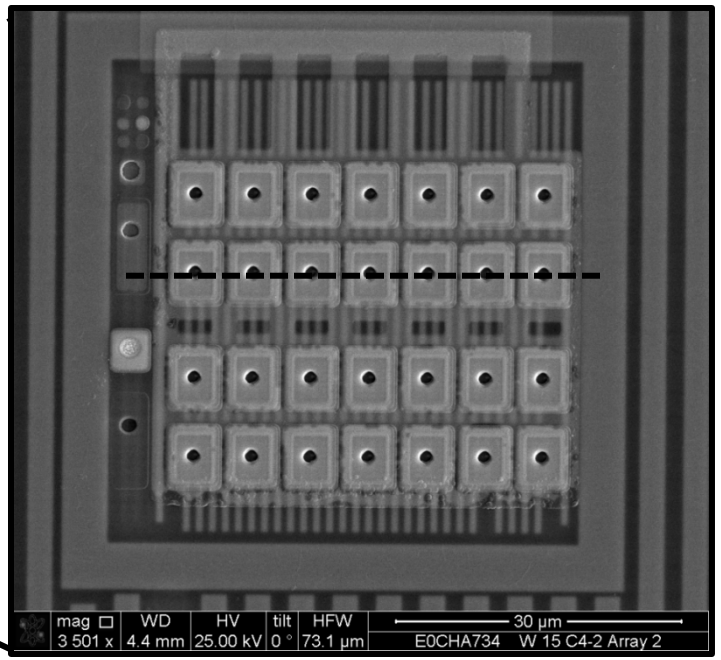
Transducer Integration



Transducer Integration

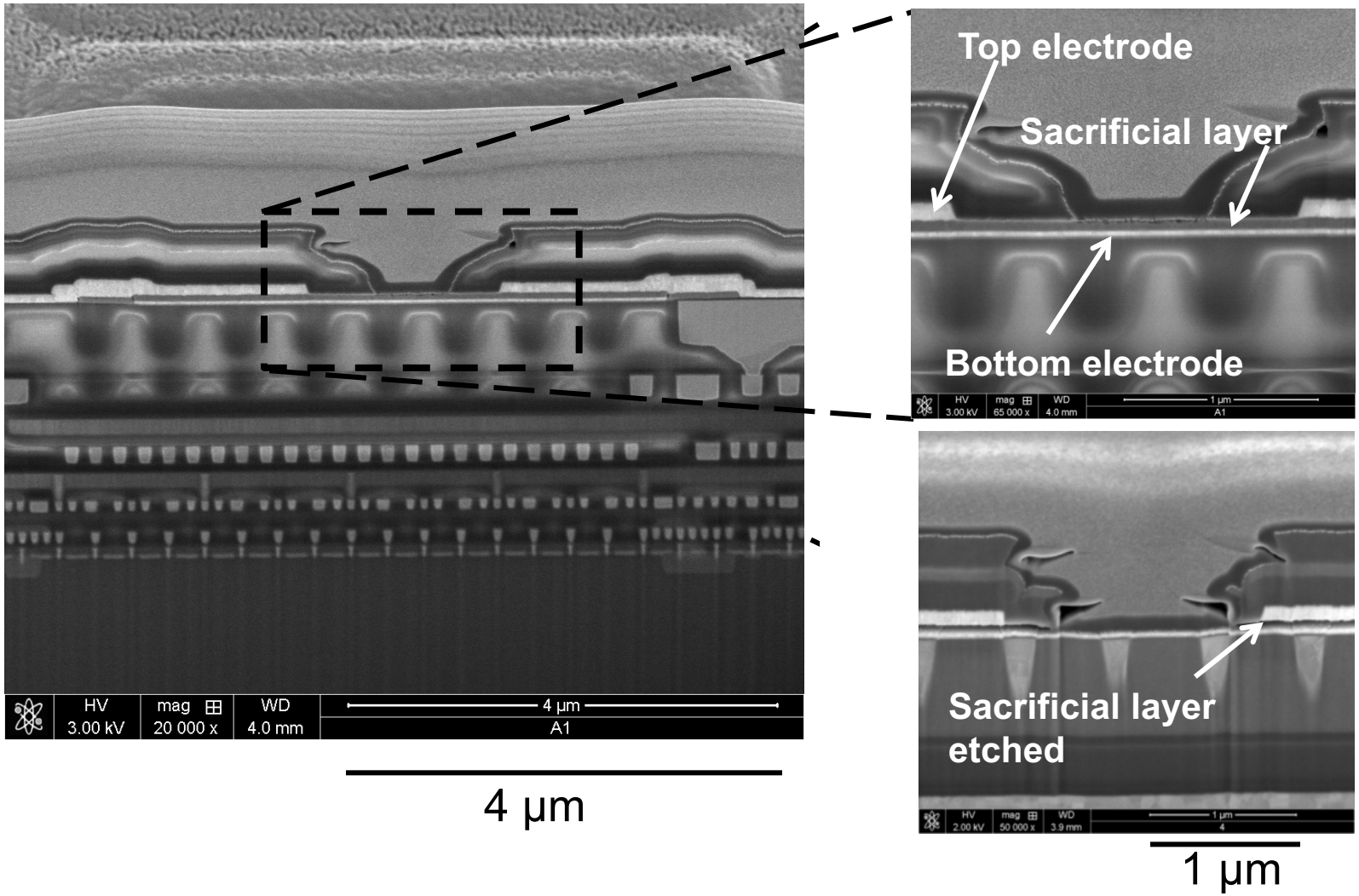


4 µm

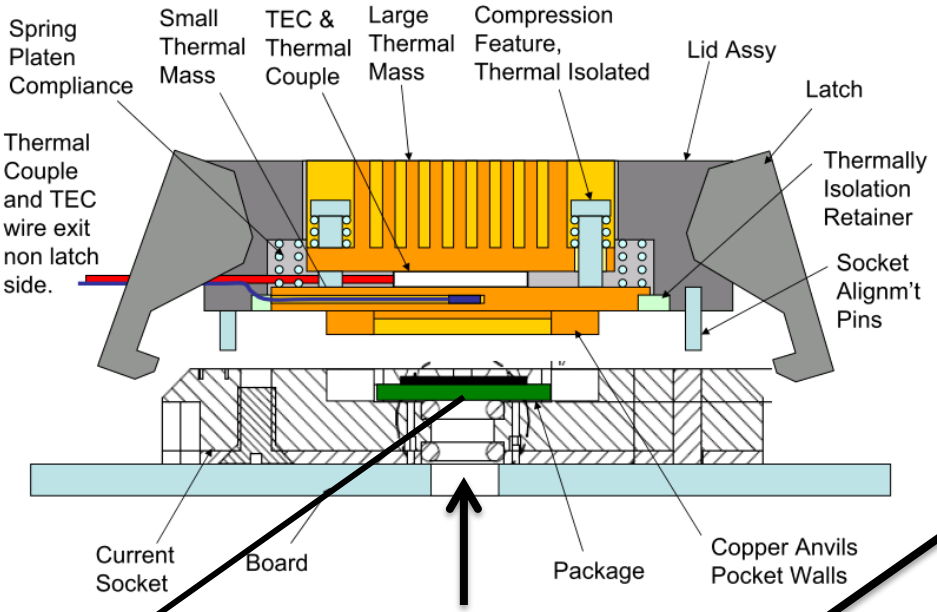


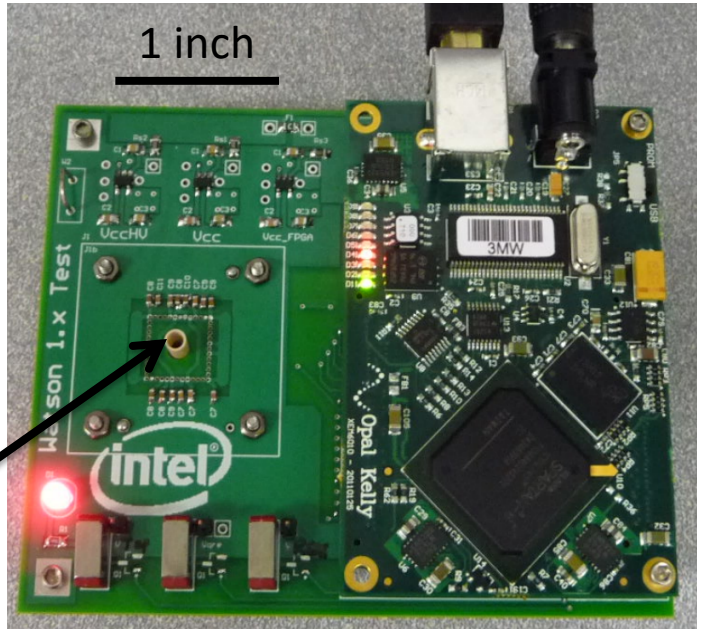
30 µm

Transducer Integration



Measurement System





Chip facing down

Fluid Inlet

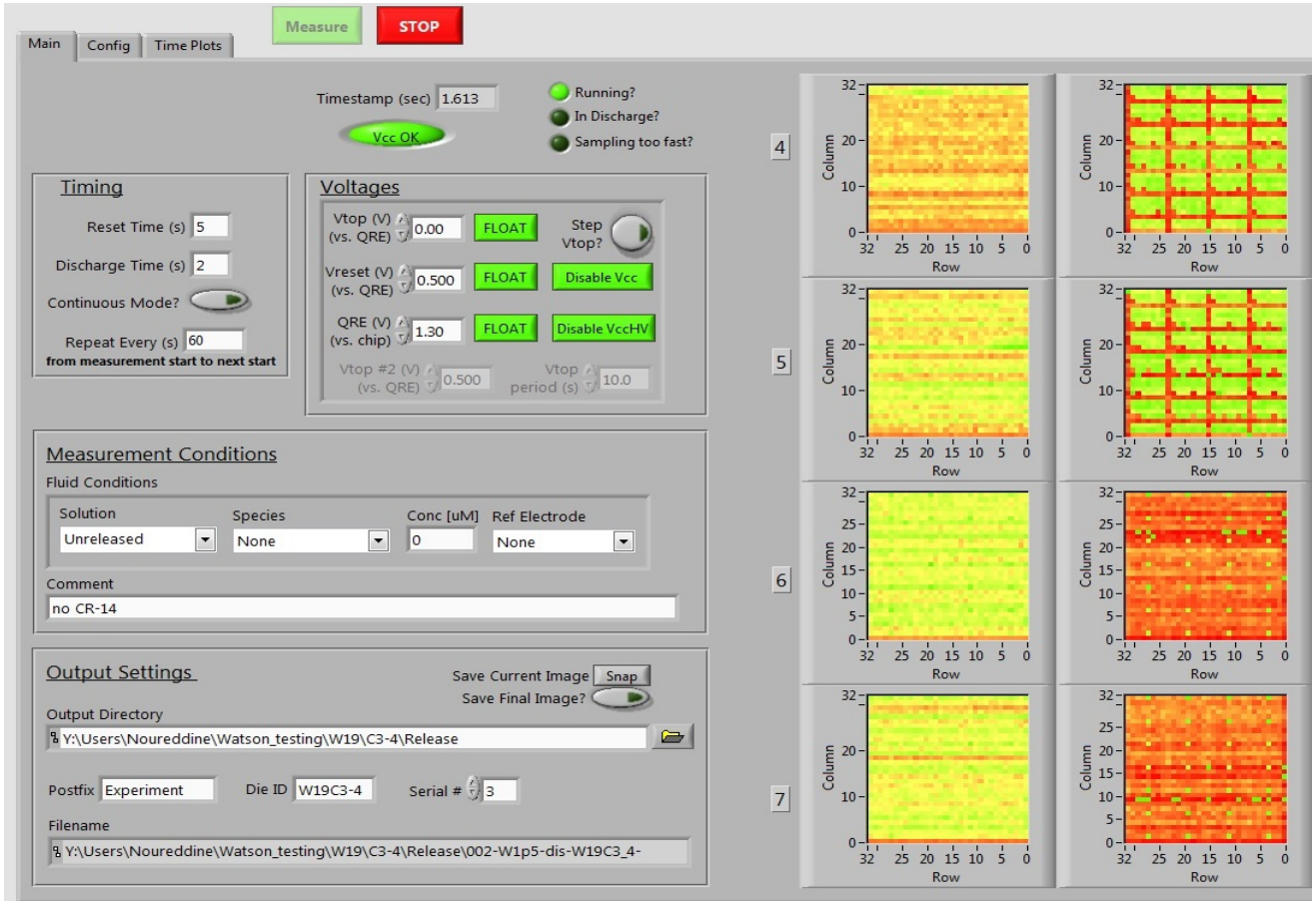
Bare chip electrical and fluidic interface

Custom board with FPGA connection

Data Collection

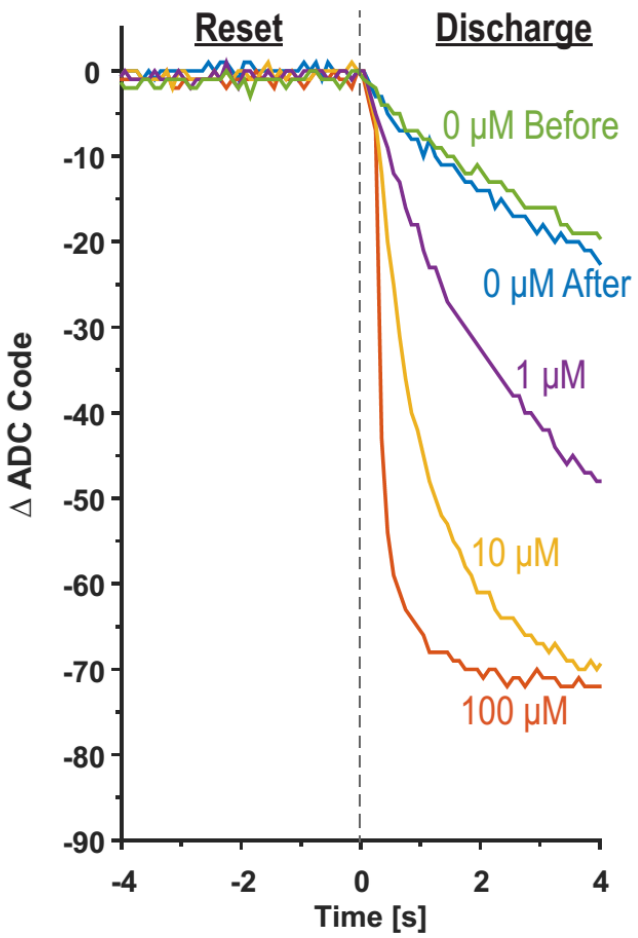
Control Panel

Data Display

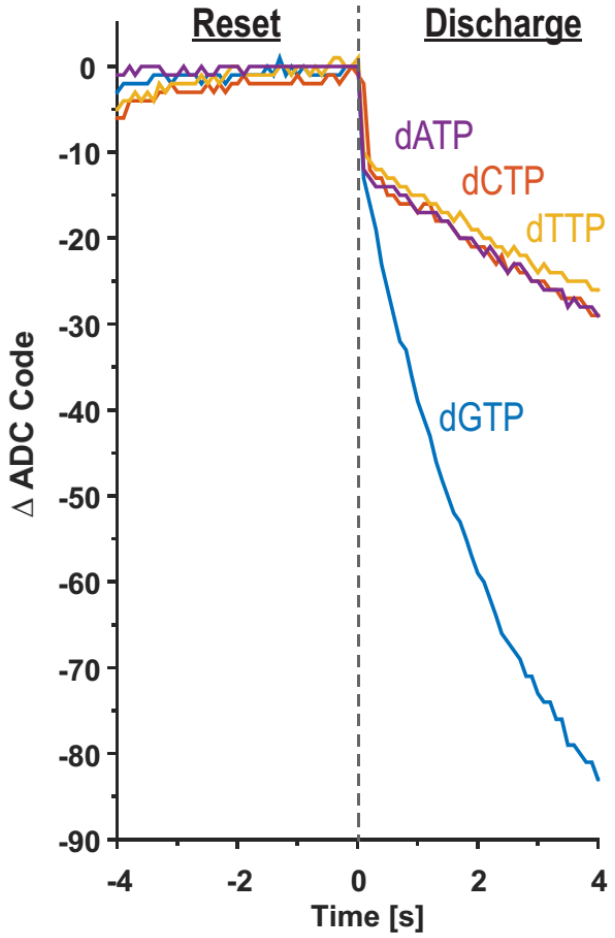


Measurement Results

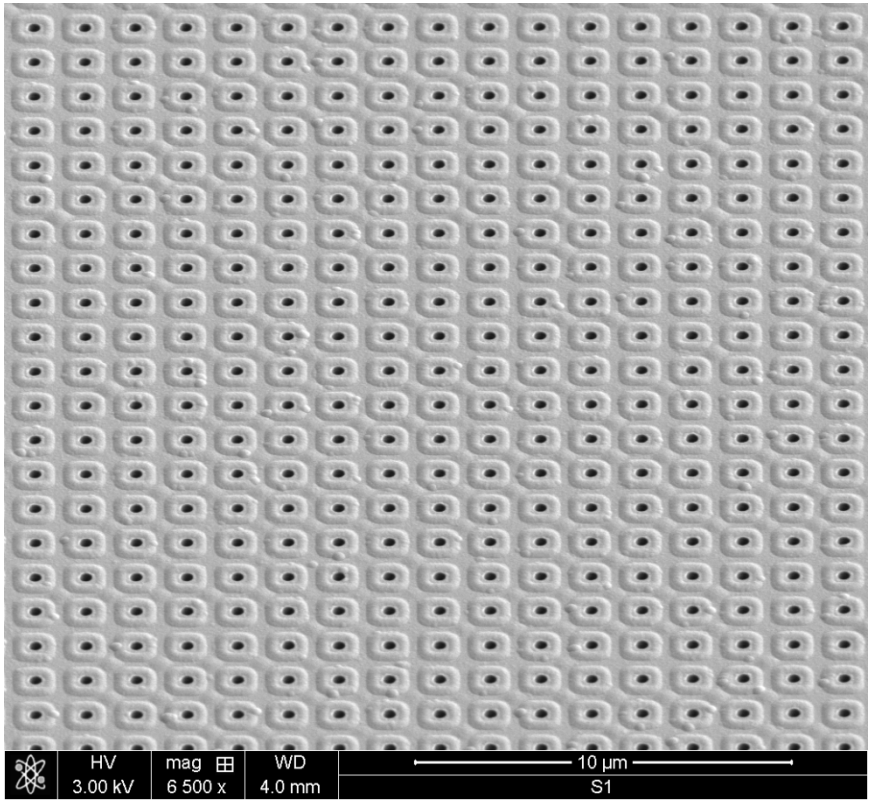
Electrochemical Tag Response and Recovery

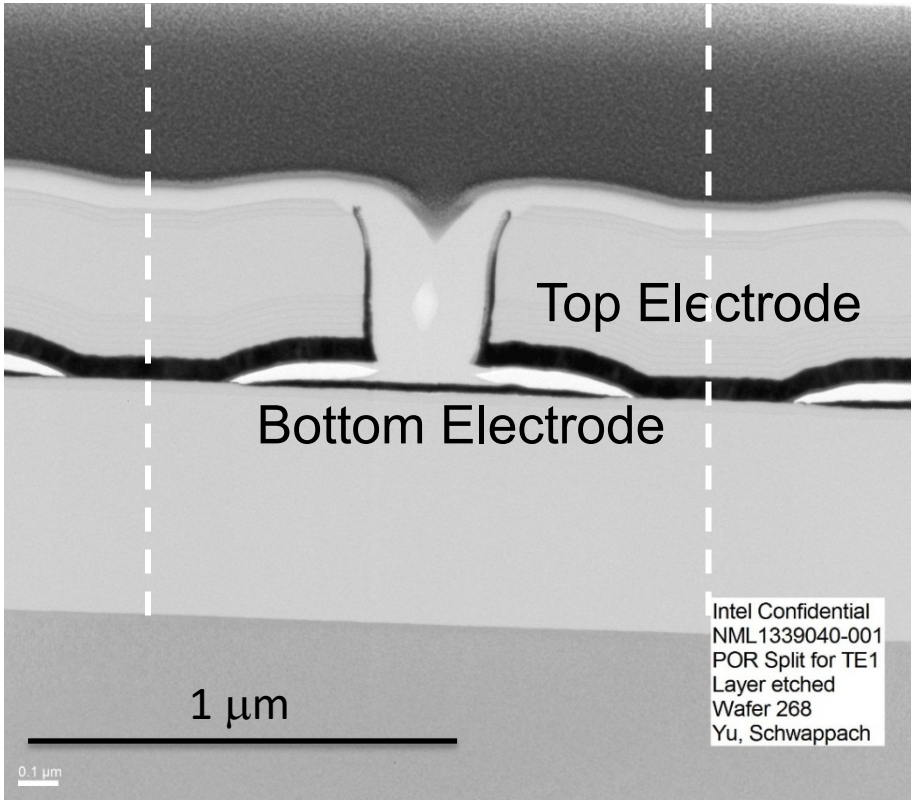


Sequencing Byproduct Detection



Transducer Scaling

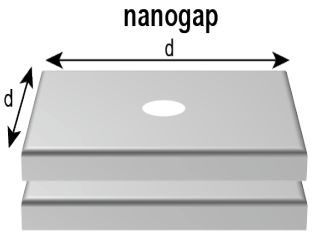




1M pixel array with 1.5 um pitch devices – Transducer Only

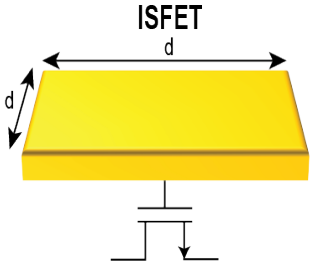
Scalability Comparison

Endpoint Detection



$$\text{Signal} \propto \frac{1}{\text{Capacitance}} \sim \frac{1}{d^2}$$

Continuous Monitoring



$$\text{Signal} \propto \frac{\text{Area}}{\text{Volume}} \sim \frac{1}{d}$$

- Relaxed requirements on frame rate
- Lateral dimension independent SNR

	ISFET	Nanogap
Frame Rate	>10 fps*	~1 fps
Noise Scaling	$1/d^2$	$1/d^2$
Signal Scaling	$1/d$	$1/d^2$
SNR	d	1

* Needed due to fast transient signal

Summary

System	
Technology	32 nm CMOS
Die size	5 mm x 5 mm
Number of pixels	8,192
Number of sensors	224
Power consumption	27.9 mW
Supply voltage	1.05 V / 1.8 V
Pixel	
Area	1 μm^2
Leakage	< 10 pA
Sensor	
Area	20 μm^2
Unit capacitance	1 $pF/\mu m^2$
Electrode spacing	60 nm
Signal/pAP molecule	50 fA
ADC	
FSR	700 mV
Conversion time	50 ns
Resolution	8-bit

- Scalable approach for electronic DNA sequencing on 32 nm process node
- Enabled by co-optimized circuits and transducers
- Demonstration of detection of nucleotide incorporation
- Sensitive and dense bio-sensing platforms can be realized in advanced process nodes

Acknowledgements

Group Members:

- Stephane Smith
- William Van Trump
- Tolga Acikalin
- Pradyumna Singh
- Ryan Field
- Hao Luo
- Mark Oldham
- Eric Nordman

Fabrication:

- Steven Cooperman
- Michael Lewis
- Elizabeth Lee
- Intel Fab Staff
- SNF Facility Staff

Characterization:

- Intel NML

Device Physics:

- Serge Lemay & Group