Session 11 - CMOS Biochips and Bioelectronics

A 16×20 Electrochemical CMOS Biosensor Array with In-Pixel Averaging Using Polar Modulation

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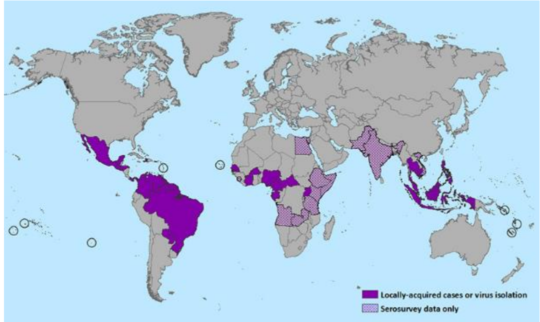
Point-of-care (POC) biosensors



Plus Analyzer, BD Veritor

iSTAT, Abbott Laboratories

HIV-1/HIV-2 Rapid Screen

- Brings molecular testing closer to patient for faster diagnosis
- Leads to earlier treatment in and outside clinical setting
- Designed for detection of single or small set of analytes

Time consuming and impractical for multi-analyte disease screening

Biosensor Arrays

GeneChip Scanner 3000, Affymetrix

NextSeq 550, Illumina

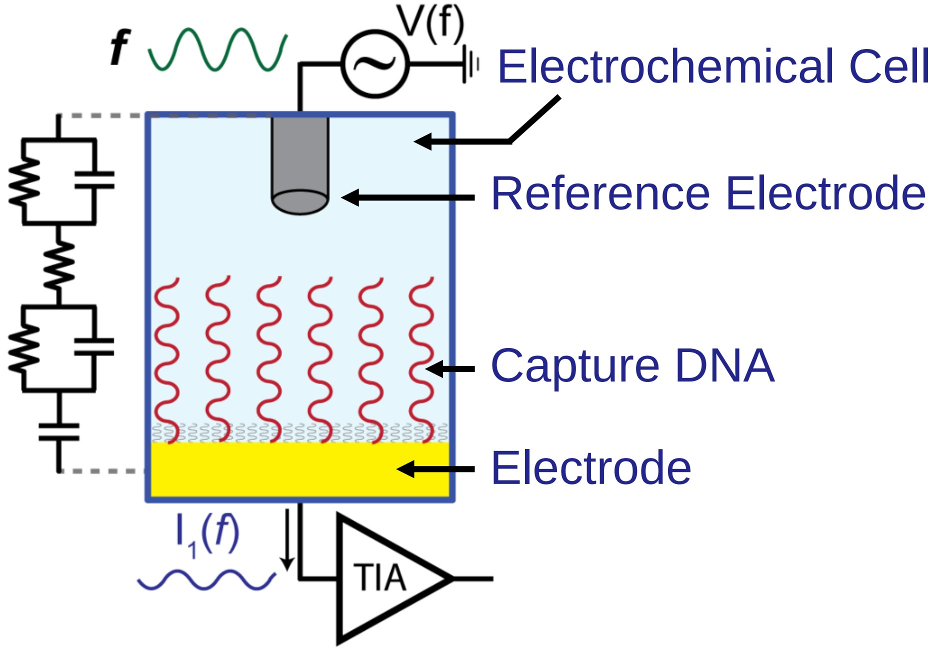
Agilent G2565CA

- Biosensor arrays offer parallelized multi-analyte detection
- Widely used arrays rely on expensive and bulky scanners
- ***Electrochemical Impedance Spectroscopy (EIS)***
  - Benefits from scalability of electrochemical sensors
  - Allows for both sensors and circuitry to be integrated together

EIS arrays are a promising technology for POC diagnostics

Impedance Spectroscopy Sensor

measure impedance
from 0.1 Hz to 100 kHz



Impedance Spectroscopy Sensor

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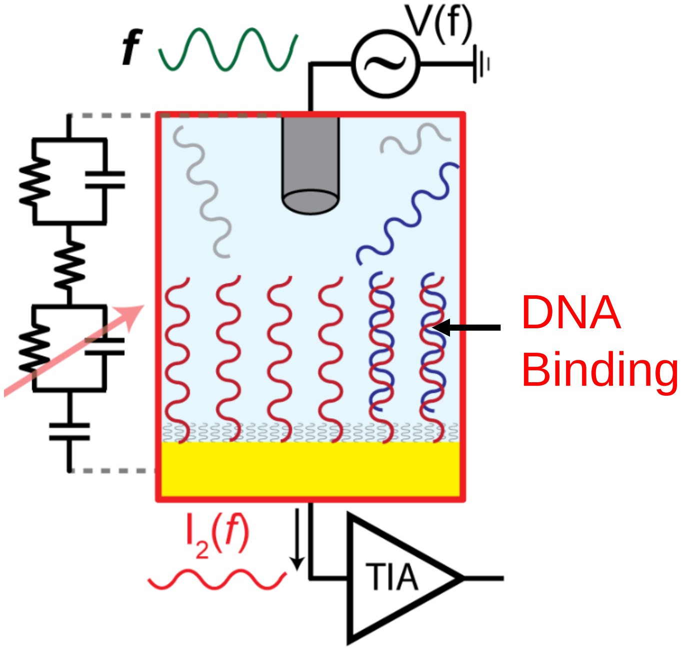
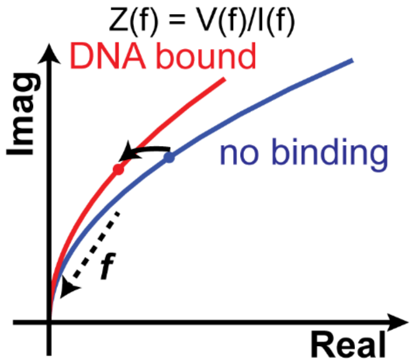


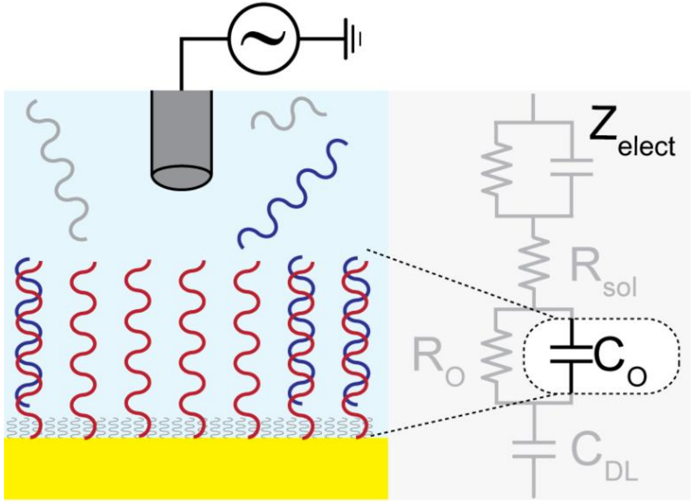


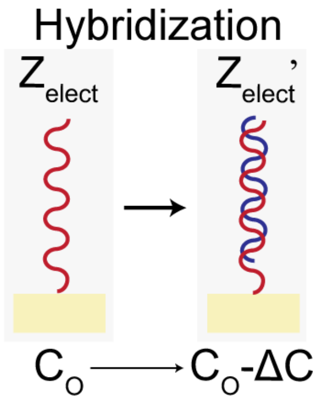
binding on surface
shifts impedance

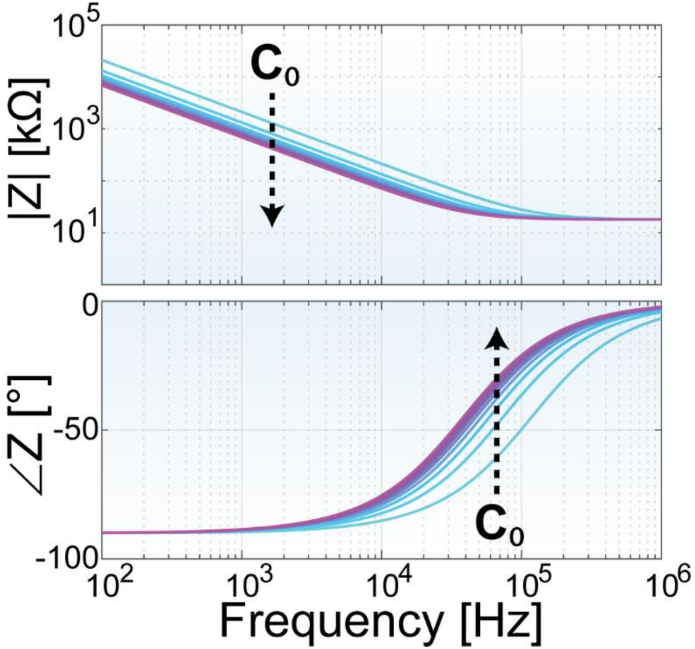
Standard EIS requires sensitive detection of both magnitude and phase

Biosensor Impedance Model

Only a single portion of impedance is modulated by binding



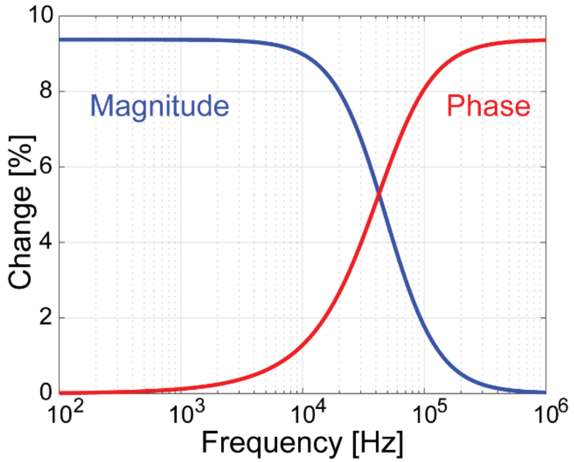




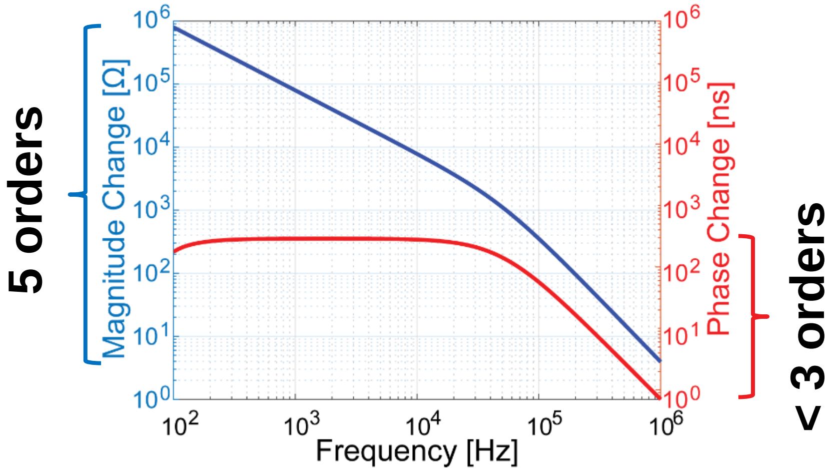
For biosensors, binding can be monitored by either magnitude or phase

Magnitude / Phase Measurement

Effect of 100 nF capacitance change in electrochemical cell



Capacitance change affects both magnitude and phase similarly

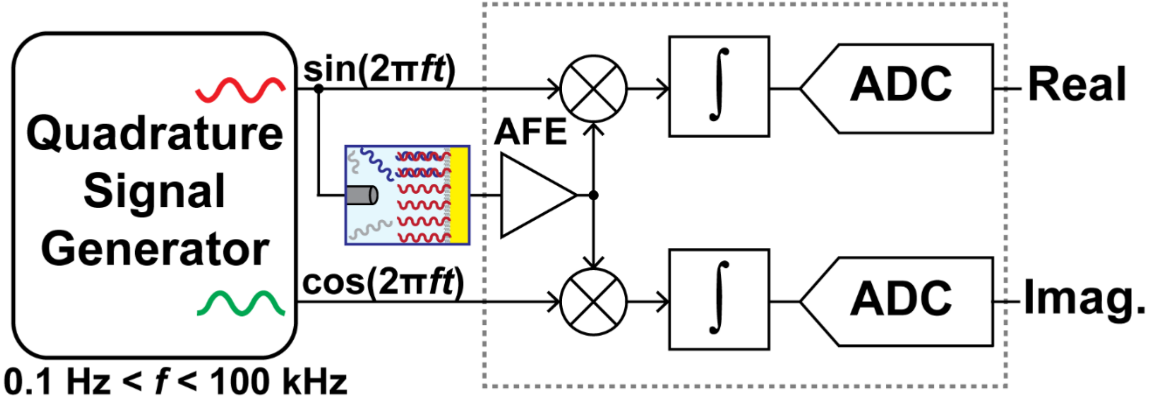


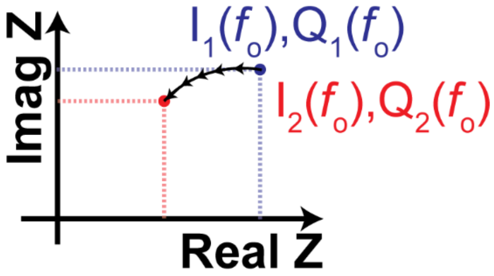
… but absolute magnitude spans a larger range

Requirements for phase less stringent than magnitude

Conventional EIS Measurement Circuitry

Real / Imaginary Based



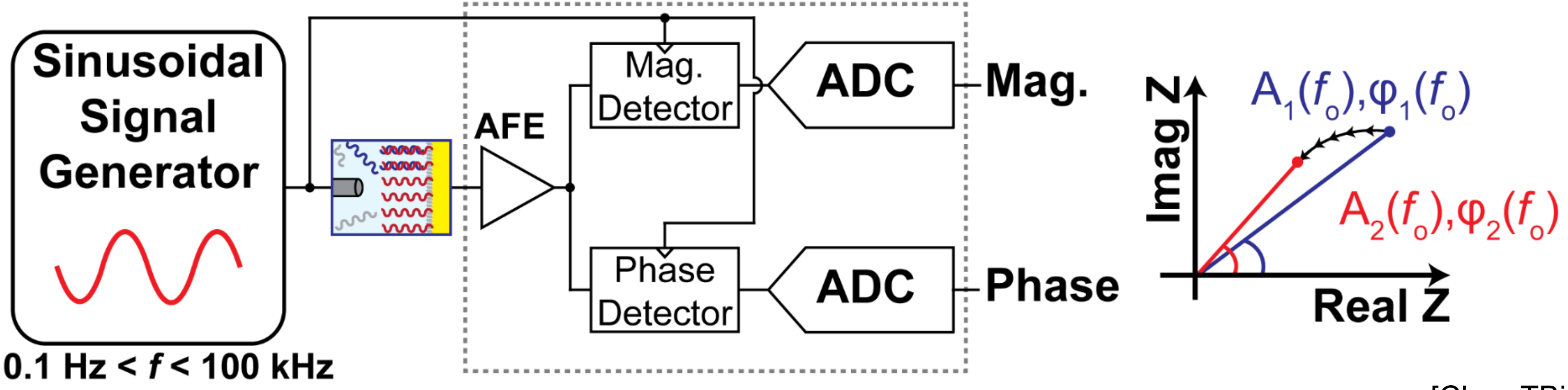


[Yang JSSC'09, Manickam ISSCC'10]

- ✘ Quadrature signal generation
- ✘ Lock-in amplifier/multipliers/integrators

Conventional EIS Measurement Circuitry

Magnitude / Phase Based

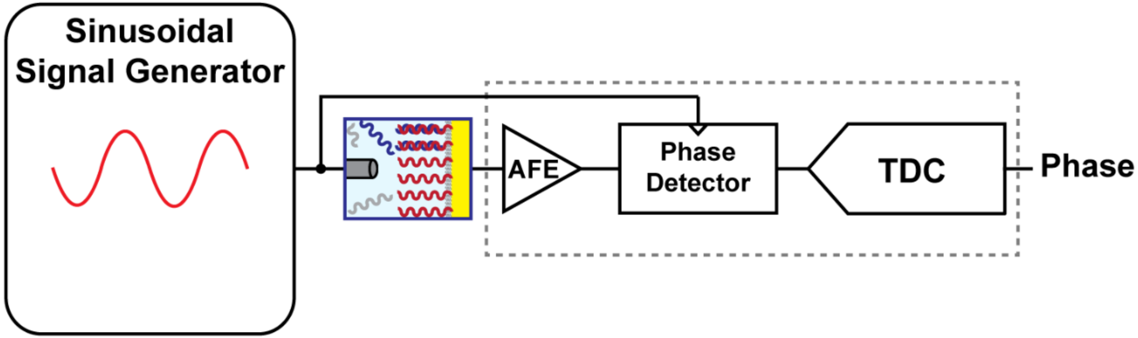


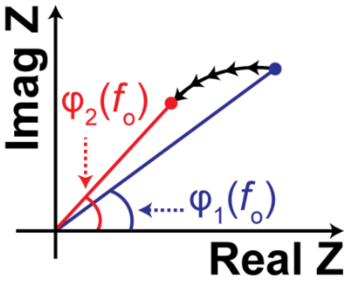
[Chen TBioCAS'17]

- ✔ Only single sinusoid generation
- ✘ Separate magnitude and phase blocks
- ✘ Magnitude spans several orders

Phase only detection can simplify and reduce measurement circuitry

Polar Phase Measurement

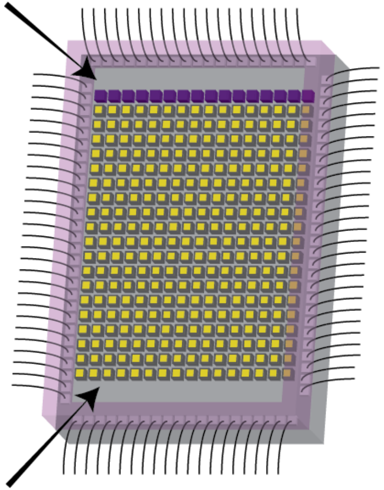


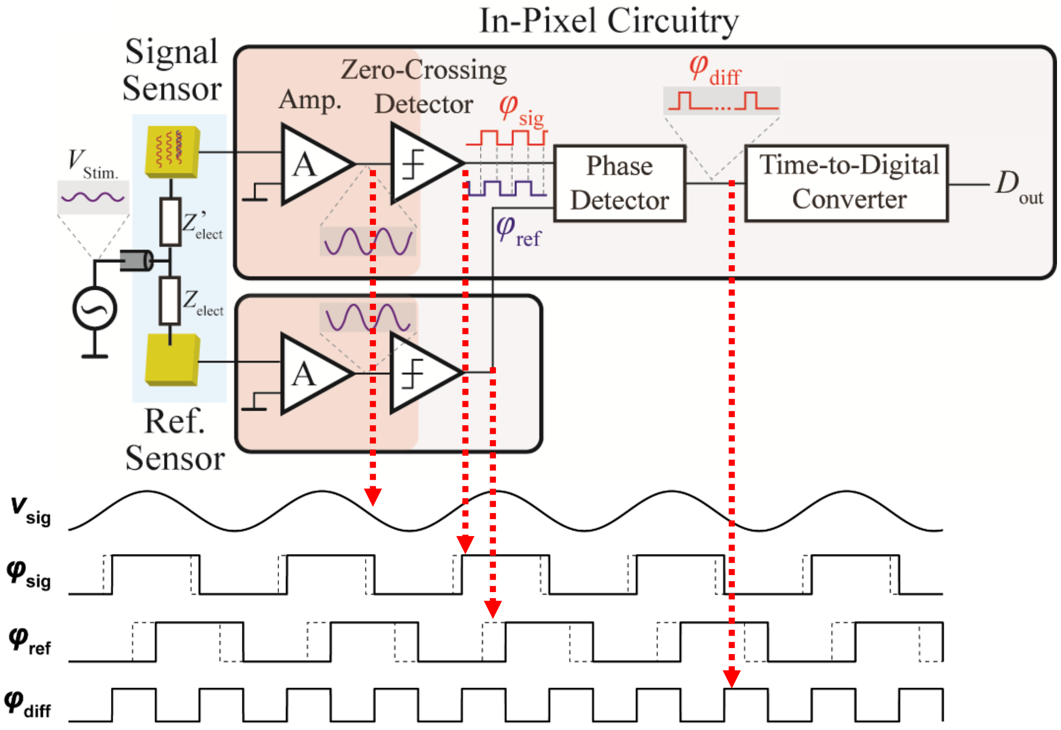


- ✔ Reduced measurement circuitry and area
- ✔ TDC footprint < ADC, allows for in-pixel digitization
- ✔ Topology enables in-pixel averaging for SNR improvement

Smaller in-pixel circuitry area for higher density arrays

CMOS Biosensor Array

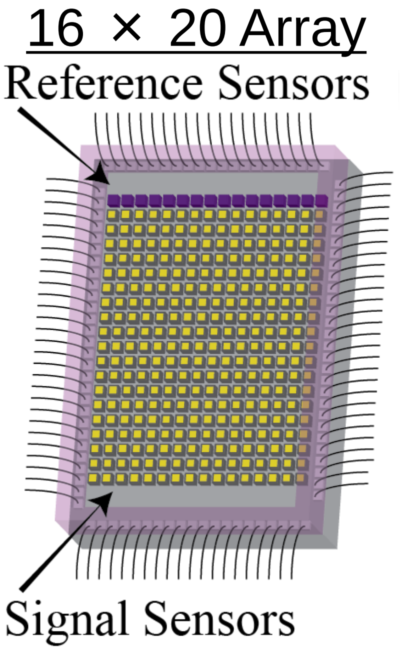


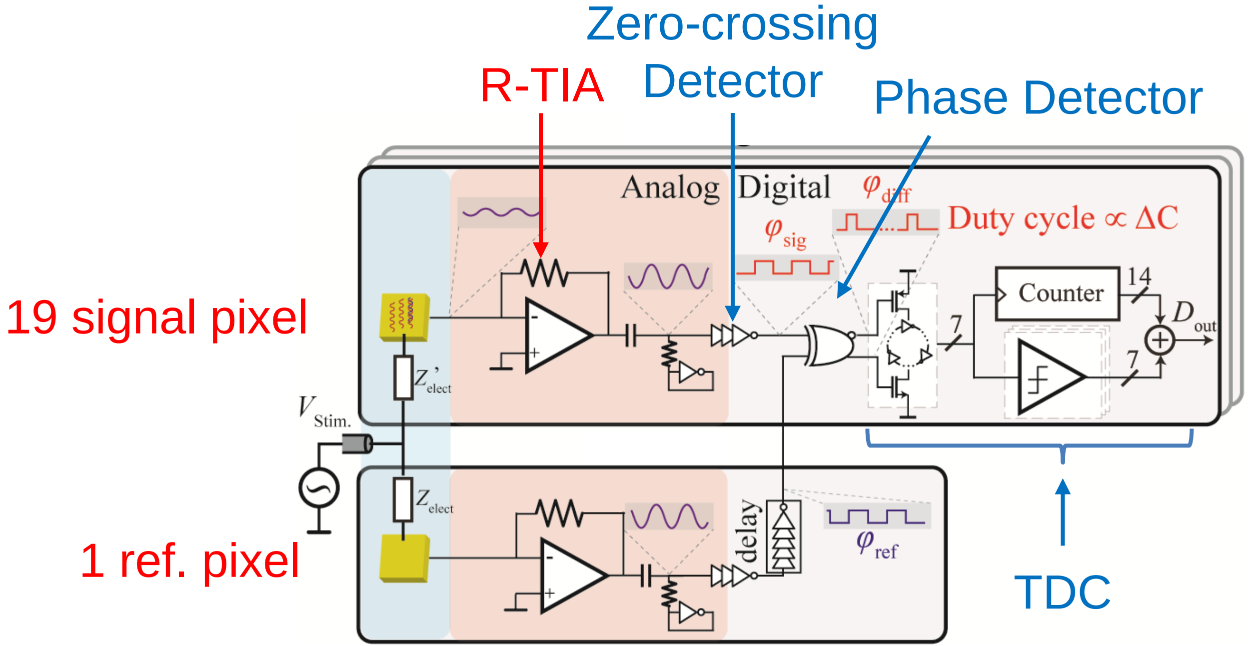


$\Delta\varphi_{diff} \propto D_{out}$

$\Delta C \propto \Delta\varphi_{diff}$

System Architecture

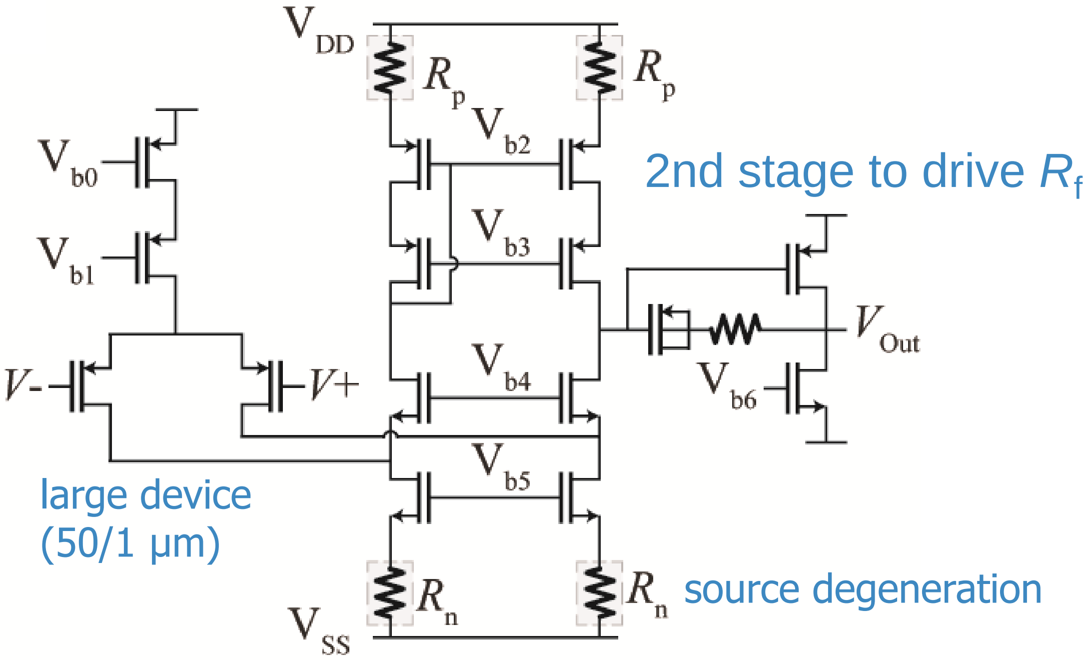




Mostly-digital circuitry reducing pixel area

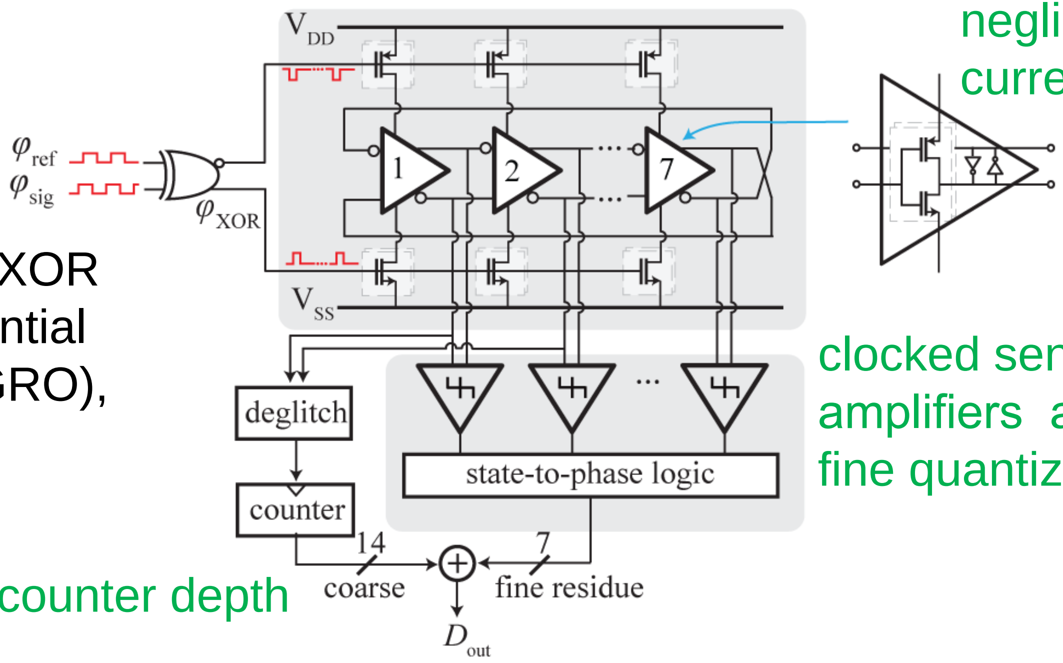
Resistive Feedback TIA

- 142 µW, 100 dB, & 36 MHz unity GBW
- Designed to minimize 1/f noise



Flicker noise corner less than 1 kHz and drives R_f = 100 kΩ

Phase-to-Digital Converter



GRO sized for negligible leakage current in off state

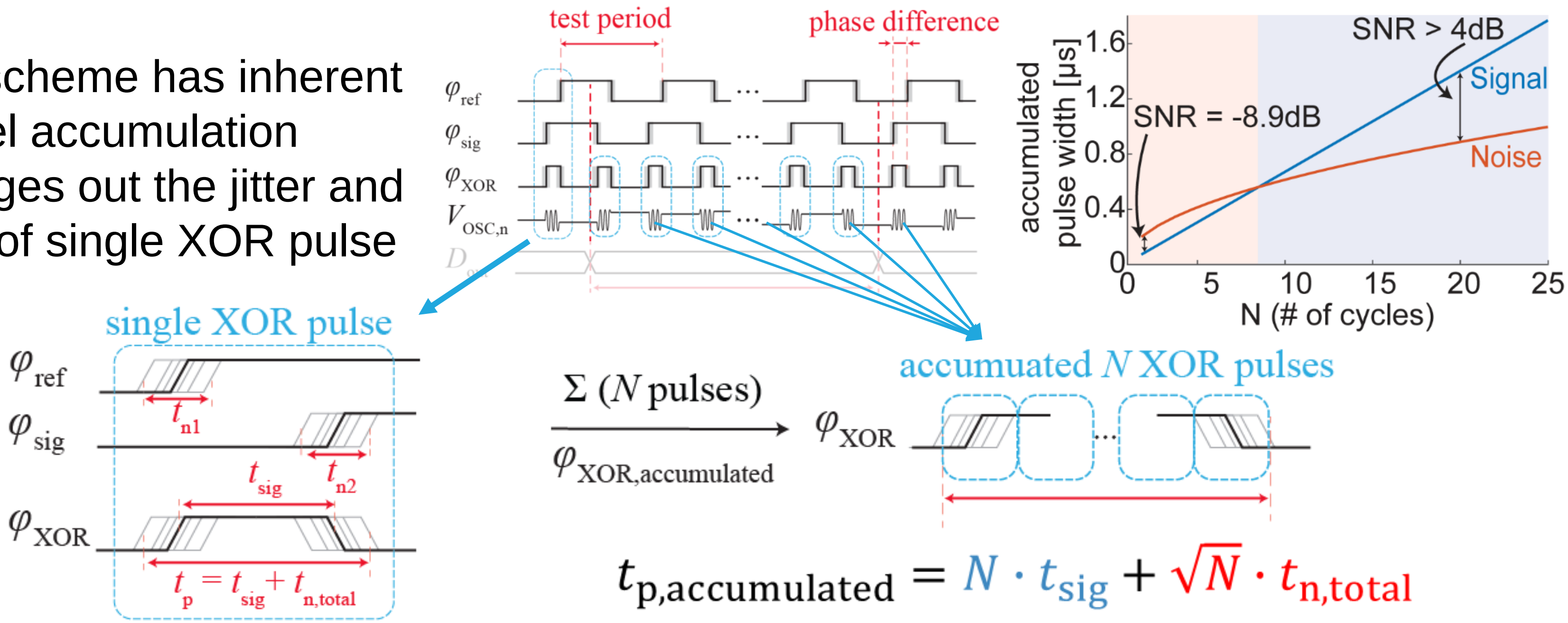
- Differential symmetric XOR
- 7-stage pseudo differential gated-ring oscillator (GRO), f_{osc} = 11 MHz

clocked sense amplifiers adds π/7 fine quantization levels

14-bit counter depth

TDC with In-pixel Averaging

- TDC scheme has inherent in-pixel accumulation
- Averages out the jitter and noise of single XOR pulse

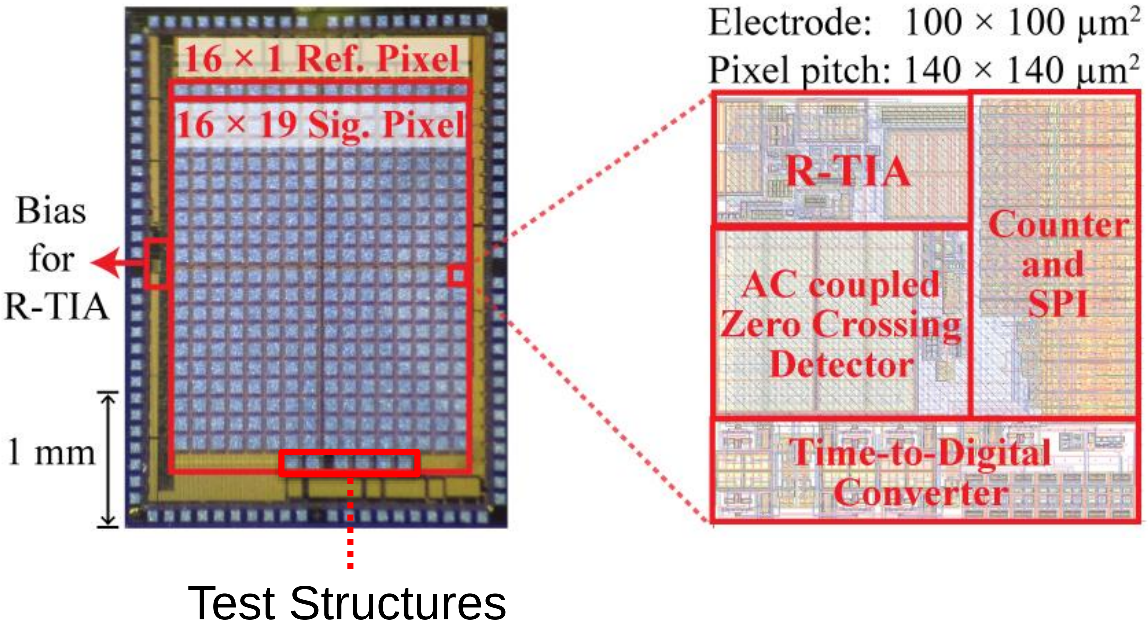


$$t_{p,accumulated} = N \cdot t_{sig} + \sqrt{N} \cdot t_{n,total}$$

Reduce jitter/phase noise by increasing measurement cycles

Chip Photo

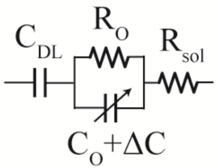
TSMC 0.18 μm CMOS



Characterization of In-Pixel Circuitry

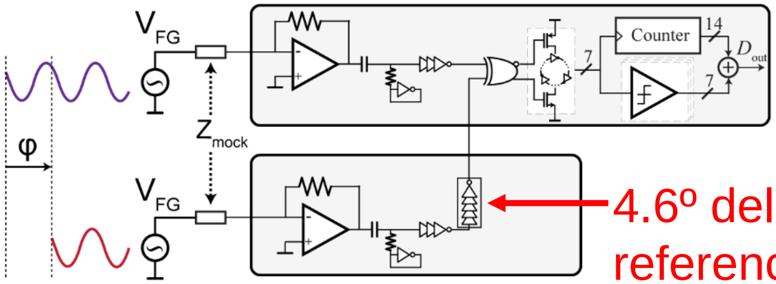
Setup

Mock electrochemical cell at inputs (sig & ref)

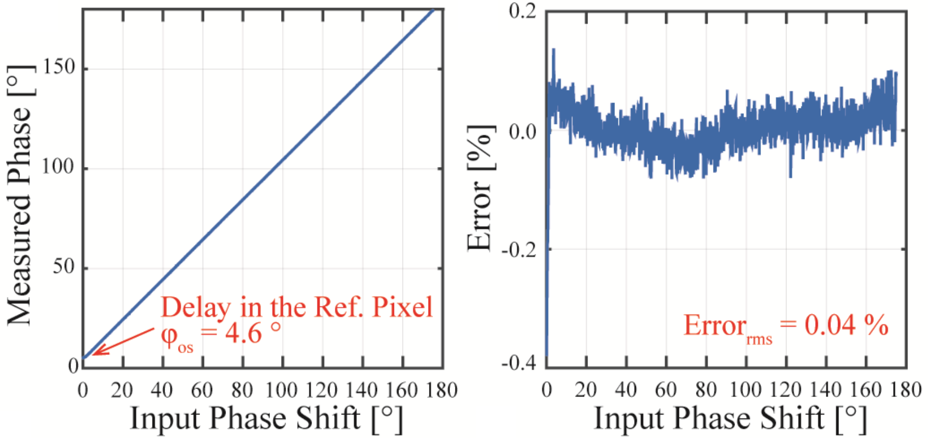


C_{DL}	R_O	R_{sol}	C_O
300pF	10GΩ	10kΩ	400pF

Linearity



4.6º delay in reference pixel

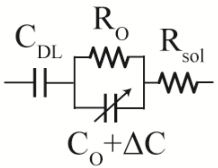


0.04% / 0.14° detectable phase shift.

Characterization of In-Pixel Circuitry

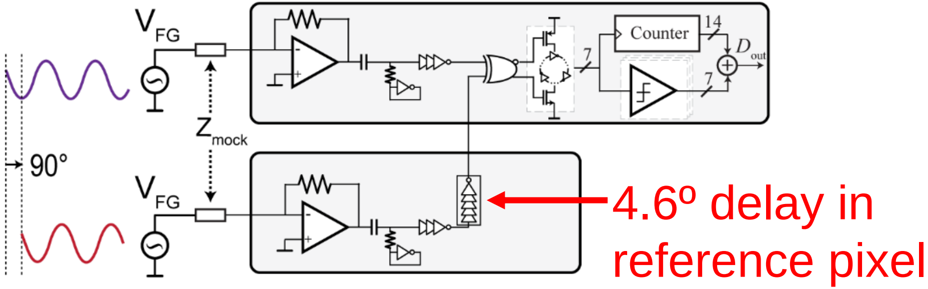
Setup

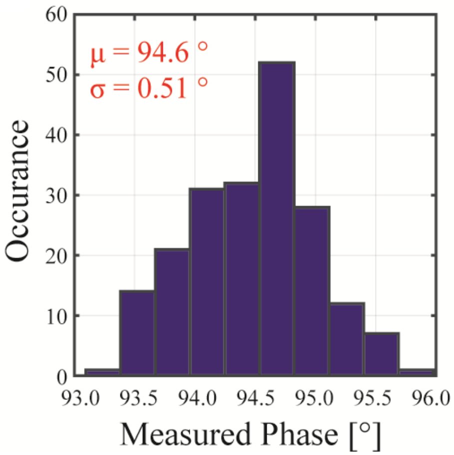
Mock electrochemical cell at inputs (sig & ref)

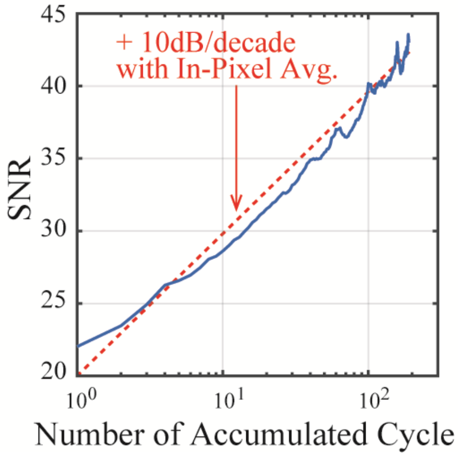


C_{DL}	R_O	R_{sol}	C_O
300pF	10GΩ	10kΩ	400pF

Noise



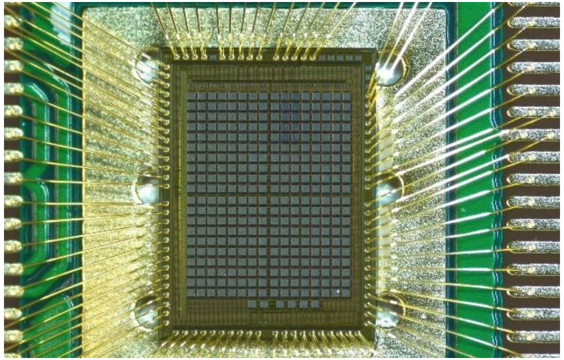




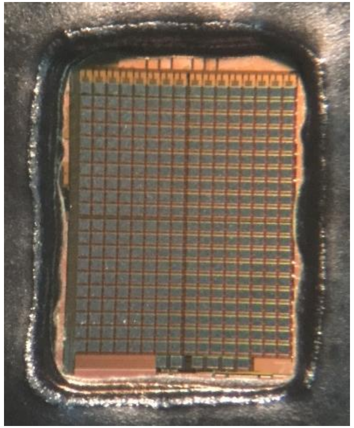
SNR is increased by +10dB with 10× in-pixel averaging cycles.

Packaging of CMOS Array

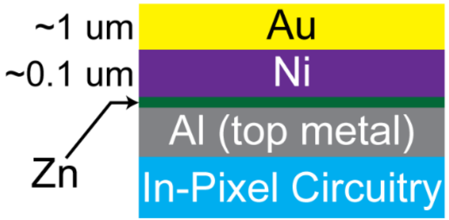
wire bonded to daughter board and mounted on motherboard

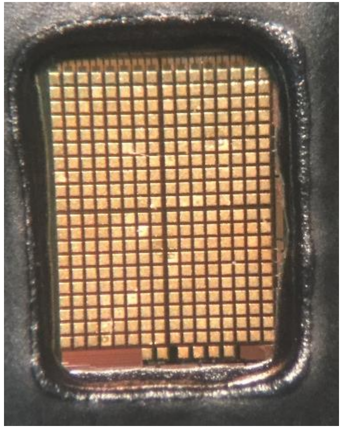


partial encapsulation with epoxy



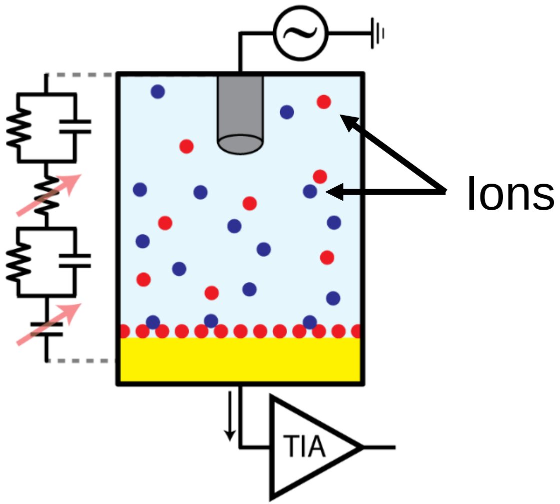
ENIG plating of electrodes

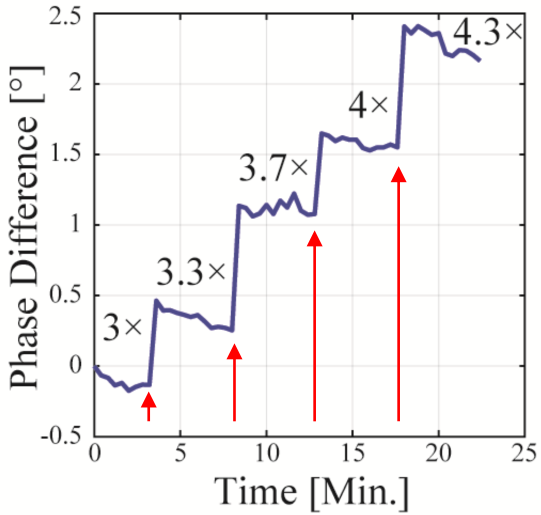




Electrochemical Measurements

- Measure varying buffer strengths as proxy for DNA binding
  - Ion concentration affects solution resistance and double-layer capacitance
  - Add 1 μL of 20×SSC (saline-sodium citrate) buffer repeatedly to 45 μL 3×SSC

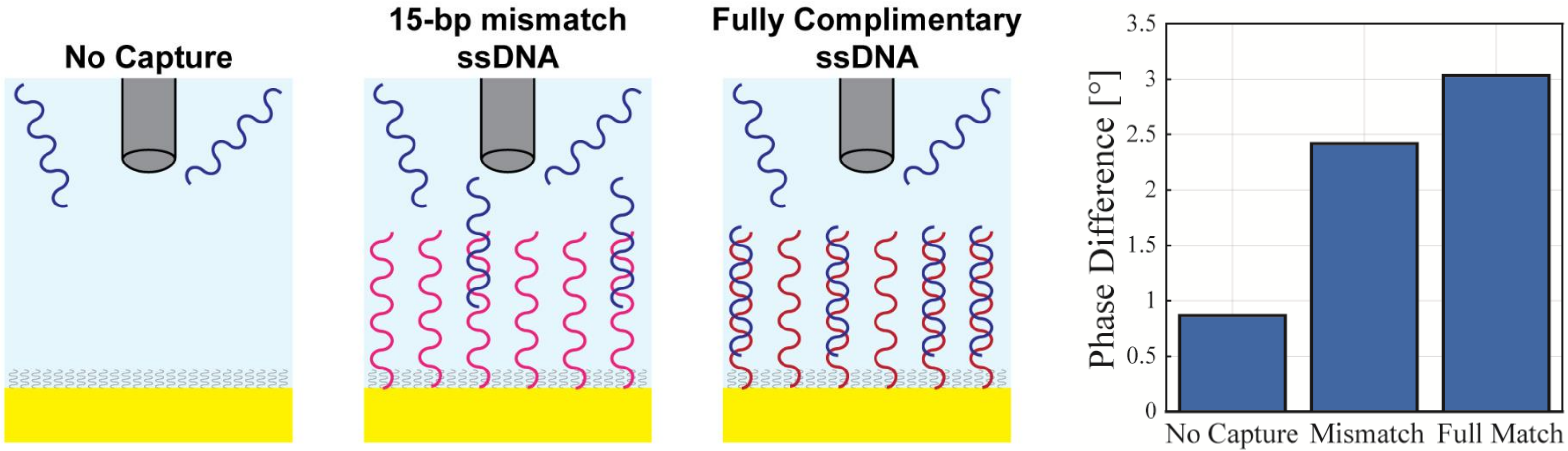




$\Delta\varphi_{diff} \propto$ Buffer Strength

Zika Assay Measurements

Functionalized with 30-nucleotide ssDNA associated with the Zika virus



Distinguish between complimentary and mismatched DNA

Comparison

	JSSC 2009	ISSCC 2010	TBCAS 2012	TBCAS 2017	This Work
Tech. [μm]	0.5	0.35	0.13	0.35	**0.18**
Power [mW]	0.006	84.5	0.35	0.32	**63**
On-Chip Electrodes	No	Yes	Yes	No	**Yes**
Num. Sensors	-	100	64	-	**320**
Num. Channels	1	100	16	1	**320**
Area/Ch. [μm²]	60,000	10,000*	60,000	70,000	**19,600**
Power/Ch. [μW]	6	845	5.57	320	**197**
ADC	On Chip	Off Chip	In Pixel	In Pixel	**In Pixel**
Output Format	8-bit	*Analog*	16-bit	10-bit	**21-bit**
Freq. [Hz]	$0.1 - 10^4$	$10^2 - 5\times10^7$	$0.1 - 10^4$	$10^{-4} - 10^5$	$\mathbf{5\times10^3 - 10^6}$
Quadrature Signal Req.	Yes	Yes	Yes	No	**No**
Magnitude Error	0.32% @10 Hz	-	-	0.28% @10 kHz	**N/A**
Phase Error	2.7% @1 kHz, 38 S/s	-	-	0.12% @10 Hz, 10 S/s	**0.04% @50 kHz, 24 S/s**

State-of-the-art rms phase error @ smallest area with in-pixel quantization

Conclusion

- High-density biosensor array for DNA hybridization
- Key challenges: **scalability** and **sensitivity**
- To address this, we:
  - Used a polar mode measurement scheme
  - Designed a mostly digital phase detector decreasing per pixel circuit area
  - Designed a TDC with in-pixel averaging to increase SNR
- Results:
  - Achieves state-of-the-art rms phase error of 0.04% / 0.14° at 50 kHz
  - Accumulation increases SNR 10 dB for every 10× readout time
  - Smallest area per channel with on-chip quantization
  - Successfully measured hybridization of Zika virus DNA