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

Chung-Lun Hsu*, Alexander Sun*, Yunting Zhao*, Eliah Aronoff-Spencer† and Drew Hall*

*Department of Electrical and Computer Engineering, University of California, San Diego, USA
†School of Medicine, University of California, San Diego, USA
Point-of-care (POC) biosensors

• 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

- 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

measure impedance from 0.1 Hz to 100 kHz

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

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

[Yang JSSC'09, Manickam ISSCC'10]
Conventional EIS Measurement Circuitry

Magnitude / Phase Based

- Sinusoidal Signal Generator
  - 0.1 Hz < f < 100 kHz

- AFE
  - Mag. Detector
  - Phase Detector

- ADC

- Mag.
- Phase

- Imag Z
- Real Z

- $A_1(f_0), \phi_1(f_0)$
- $A_2(f_0), \phi_2(f_0)$

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

Phase only detection can simplify and reduce measurement circuitry

[Chen TBioCAS’17]
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

\[ \Delta \varphi_{\text{diff}} \propto D_{\text{out}} \]

\[ \Delta C \propto \Delta \varphi_{\text{diff}} \]
System Architecture

- **16 x 20 Array Reference Sensors**
- **19 signal pixel**
- **1 ref. pixel**
- **Mostly-digital circuitry reducing pixel area**

Diagram:
- **R-TIA**
- **Zero-crossing Detector**
- **Phase Detector**
- **TDC**
- **Analog**
- **Digital**
- **Duty cycle \( \propto \Delta C \)**
- **Counter**
- **Delay**

**IEEE SSAGS**

**CICC 2018 San Diego, CA**
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

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

GRO sized for negligible leakage current in off state

Clocked sense amplifiers adds $\pi/7$ 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

\[
\Sigma (N \text{ pulses}) \rightarrow \varphi_{\text{XOR, accumulated}}
\]

\[
t_p,\text{accumulated} = N \cdot t_{\text{sig}} + \sqrt{N} \cdot t_{n,\text{total}}
\]

Reduce jitter/phase noise by increasing measurement cycles
Chip Photo

TSMC 0.18 μm CMOS

16 x 1 Ref. Pixel
16 x 19 Sig. Pixel

Electrode: 100 x 100 μm²
Pixel pitch: 140 x 140 μm²

Bias for R-TIA

1 mm

Test Structures
Characterization of In-Pixel Circuitry

Setup
Mock electrochemical cell at inputs (sig & ref)

Linearity

4.6° delay in reference pixel

0.04% / 0.14° detectable phase shift.
Characterization of In-Pixel Circuitry

Setup
Mock electrochemical cell at inputs (sig & ref)

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

\[ \Delta \varphi_{\text{diff}} \propto \text{Buffer Strength} \]
Zika Assay Measurements

Functionalized with 30-nucleotide ssDNA associated with the Zika virus

Distinguish between complimentary and mismatched DNA
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<th></th>
<th>JSSC 2009</th>
<th>ISSCC 2010</th>
<th>TBCAS 2012</th>
<th>TBCAS 2017</th>
<th>This Work</th>
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<td>Tech. [µm]</td>
<td>0.5</td>
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<td>Num. Sensors</td>
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<td>Num. Channels</td>
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<td>Area/Ch. [µm²]</td>
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<td>10,000*</td>
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<td>Power/Ch. [µW]</td>
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<td>ADC</td>
<td>On Chip</td>
<td>Off Chip</td>
<td>In Pixel</td>
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<td>Output Format</td>
<td>8-bit</td>
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<td>16-bit</td>
<td>10-bit</td>
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<td>Freq. [Hz]</td>
<td>0.1 - 10⁴</td>
<td>10² - 5×10⁷</td>
<td>0.1 - 10⁴</td>
<td>10⁻⁴ - 10⁵</td>
<td>5×10³ - 10⁶</td>
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<td>Quadrature Signal Req.</td>
<td>Yes</td>
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<td>No</td>
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<td>Magnitude Error</td>
<td>0.32% @10 Hz</td>
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<td>Phase Error</td>
<td>2.7% @1 kHz, 38 S/s</td>
<td>-</td>
<td>-</td>
<td>0.12% @10 Hz, 10 S/s</td>
<td>0.04% @50 kHz, 24 S/s</td>
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</table>
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