Ion based DNA Sequencing using CMOS ISFET

Lab-on-a-chip pH sensing method:
- Detect $H^+$ (or pH) released from incorporated nucleotides during DNA sequencing by CMOS ISFET sensor
- Low cost with on-chip detection

1. Cut DNA single strand into slices & amplify onto microbead
2. Distribute into microwell array above ISFET sensor
3. Sequentially flush ATCG & Measure the proportional pH variation.

[Ref: Ion Torrent]
Challenges of pH Sensing for DNA Sequencing

1. The measured pH response has no correlation with the physical locations that contain microbeads. Crosstalk from neighbouring microbeads will lead to false pH detection.

2. pH variation of large-arrayed ISFET sensor exists due to pixel-to-pixel threshold voltage $V_T$ mismatch, or fixed pattern noise (FPN), which can significantly degrade pH detection accuracy.

- The previous approach by one sensing domain (pH) is difficult to improve the accuracy and throughput for large-arrayed DNA sequencing.

Literature works from Imperial College, U. Glasgow, Ion Torrent
Our Solution: **Dual-mode CMOS Ion-Image Sensor**

- **Microbeads with DNA slices**
- **Dual-mode CMOS Sensor**
  - **Ion Sensing**
  - **Contact Imaging**
- **pH Changes**
- **Microbead Locations**
- **Correlated pH Sensing Data**

**CIS based Contact Imaging + ISFET based Ion Sensing**
Dual-mode Low FPN CDS Readout

\[ V_{\text{OUT1}} = V_{\text{OUTP}} - V_{\text{OUTN}} = \alpha \cdot \left( \frac{C_S}{C_F} \right) \cdot (V_{\text{RST}} - V_{\text{CM}} + V_T) \]

\[ V_{\text{OUT2}} = V_{\text{OUTP}} - V_{\text{OUTN}} = \alpha \cdot \left( \frac{C_S}{C_F} \right) \cdot (V_{\text{REF}} - V_{\text{CM}} + V_T - dV) \]

\[ V_{\text{OUT1}} - V_{\text{OUT2}} = \alpha \cdot \left( \frac{C_S}{C_F} \right) \cdot (V_{\text{RST}} - V_{\text{CM}} + V_T + dV) \]

- **Objective**: Remove pixel-wise \( V_T \) mismatch

  \[ \downarrow \]

- **Before loading solution**:
  \[ V_{\text{OUT1}} = V_{\text{OUTP}} - V_{\text{OUTN}} = \alpha \cdot \left( \frac{C_S}{C_F} \right) \cdot (V_{\text{RST}} - V_{\text{CM}} + V_T) \]
  \( \alpha \): source follower gain

  \[ \downarrow \]

- **After loading solution**:
  \[ V_{\text{OUT2}} = V_{\text{OUTP}} - V_{\text{OUTN}} = \alpha \cdot \left( \frac{C_S}{C_F} \right) \cdot (V_{\text{REF}} - V_{\text{CM}} + V_T - dV) \]
  \( dV \): desired voltage signal caused by \( H^+ \)

  \[ \downarrow \]

- **Difference correlated sampling**:
  \[ V_{\text{OUT1}} - V_{\text{OUT2}} = \alpha \cdot \left( \frac{C_S}{C_F} \right) \cdot (V_{\text{RST}} - V_{\text{REF}} + dV) \]

  \[ \downarrow \]

- **\( V_T \) mismatch removed**
64x64 Dual-mode Sensor Testing Setup

**Parameters** | **Specifications**
--- | ---
Process | Standard TSMC 0.18μm CIS
Pixel Type | Dual-Mode (Image and Chemical)
Pixel Size | 10μm×10μm
Pixel Optical Sensing Area | 20.1μm²
Pixel Chemical Sensing Area | 22.3μm²
Array Size | 64×64
Die Area | 2.5mm×5mm
ADC ENOB | 11.4 bits
ADC SNDR | 70.35dB
FPN | 0.3%
Frame Rate | 1200fps
Total Power Consumption | 32mA @ 3.3V
Measurement Results

Correlation of contact image and pH map

Characterization of sensitivity and pH accuracy

Comparison with State-of-the-art ISFET Sensors

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