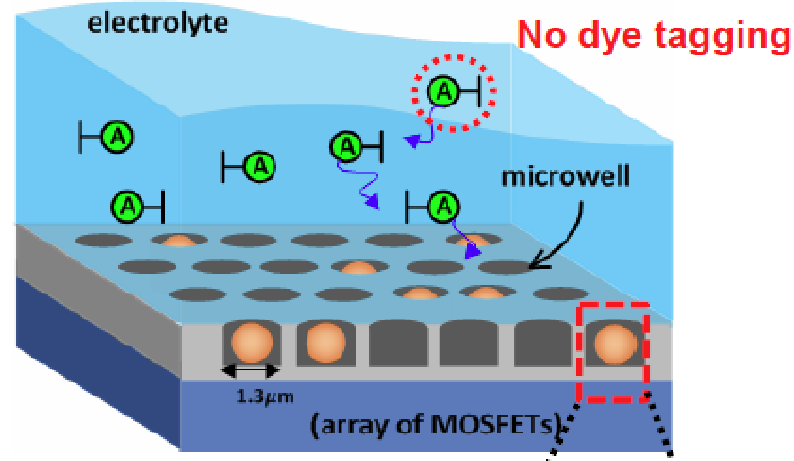
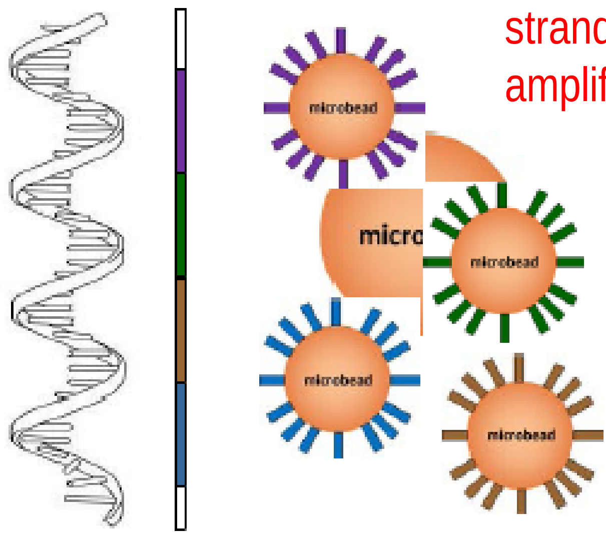
Ion based DNA Sequencing using CMOS ISFET

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

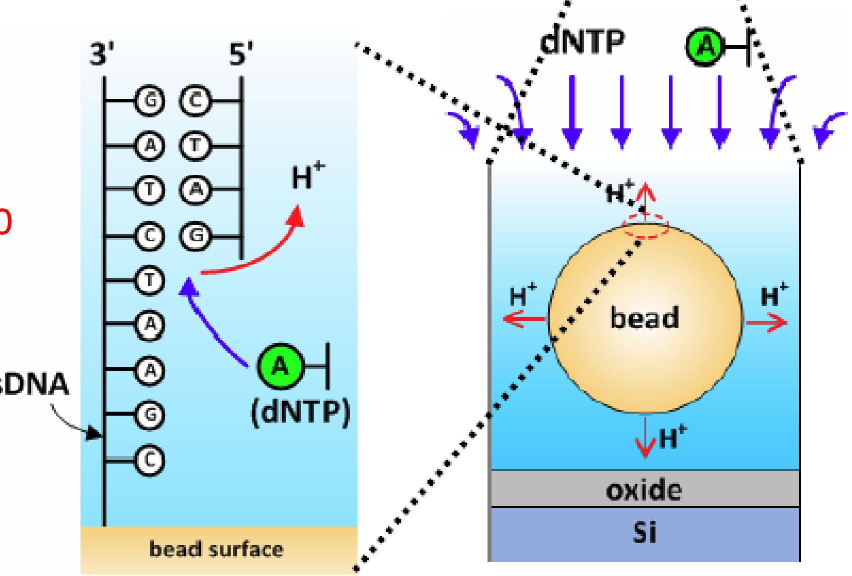




1. Cut DNA single strand into slices & amplify onto microbead

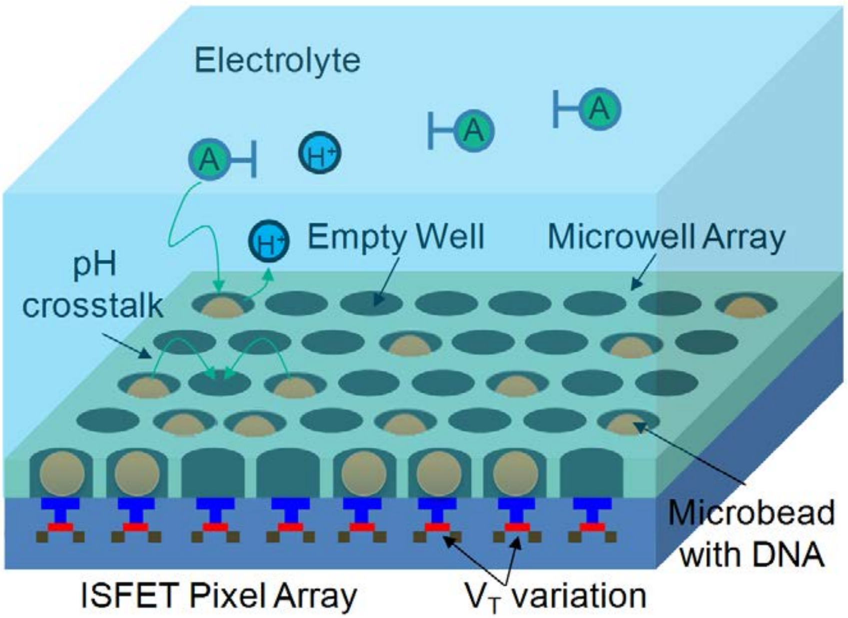
2. Distribute into microwell array above ISFET sensor

3. Sequentially flush ATCG & Measure the proportional pH variation.



[Ref: Ion Torrent]

Challenges of pH Sensing for DNA Sequencing

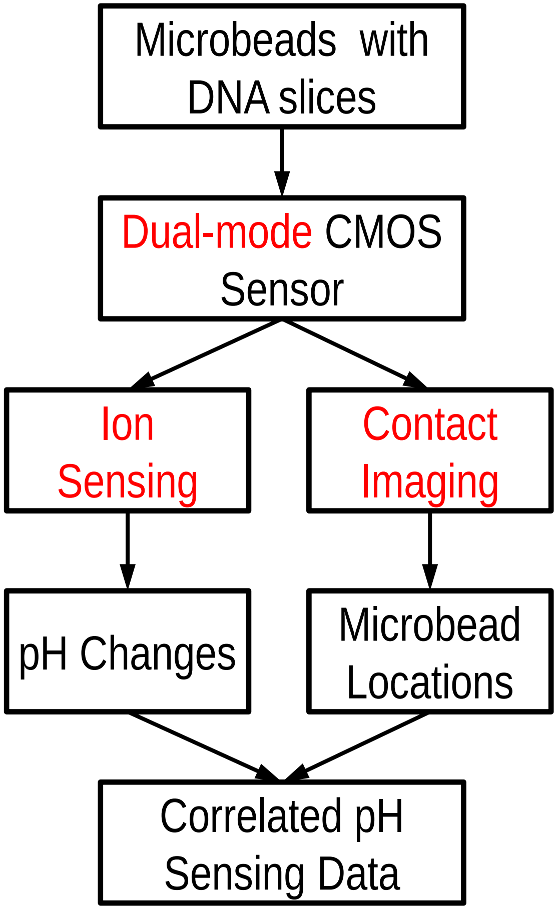


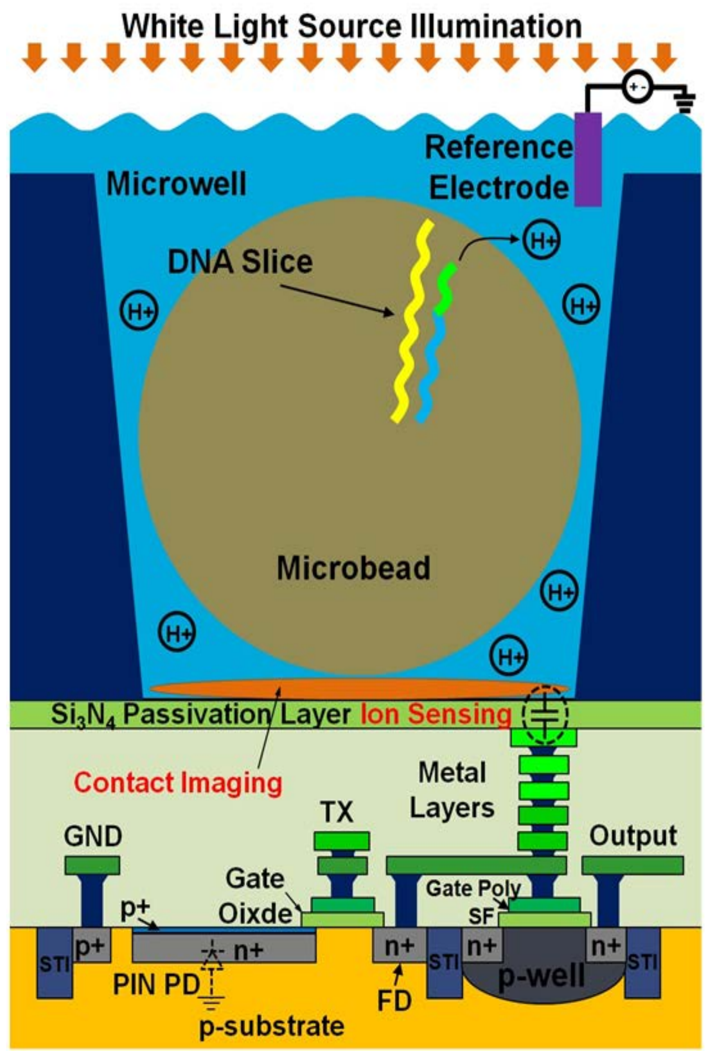
1. The measured pH response has no correlation with the physical locations that contain microbeads. Crosstalk from neighbouring microbeads will lead to false pH detection.
2. pH variation of large-arrayed ISFET sensor exists due to pixel-to-pixel threshold voltage V_T mismatch, or fixed pattern noise (FPN), which can significantly degrade pH detection accuracy.

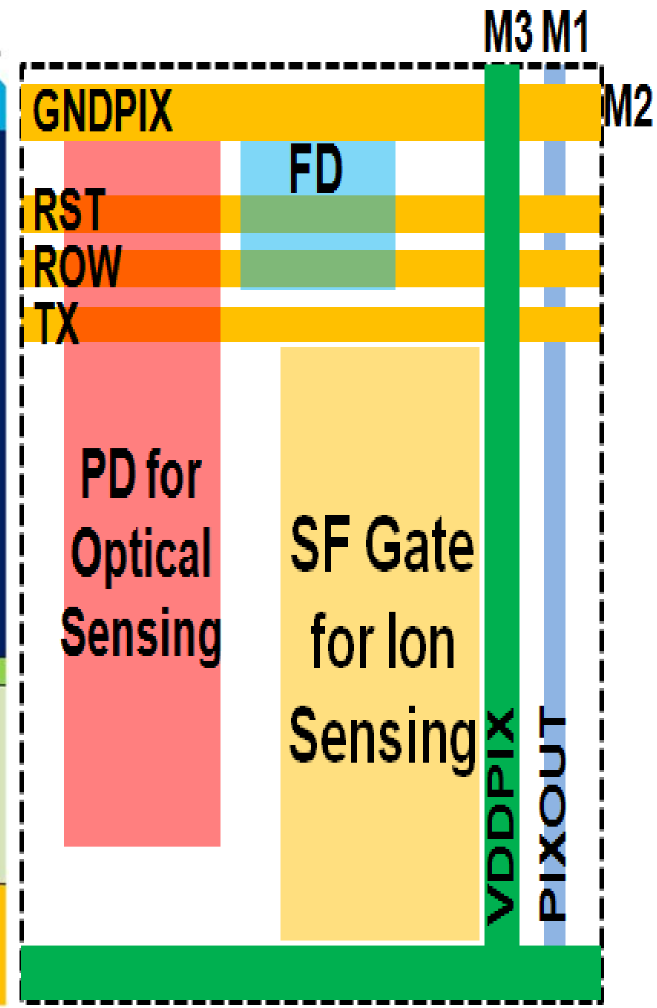
- ➢ The previous approach by one sensing domain (pH) is difficult to improve the accuracy and throughput for large-arrayed DNA sequencing.

Literature works from Imperial College, U. Glasgow, Ion Torrent

Our Solution: Dual-mode CMOS Ion-Image Sensor

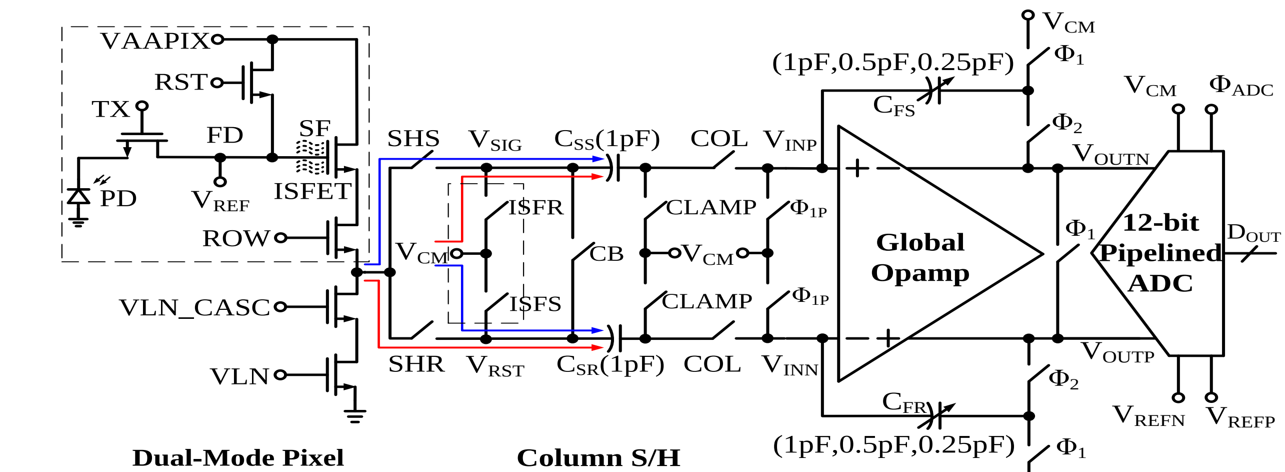


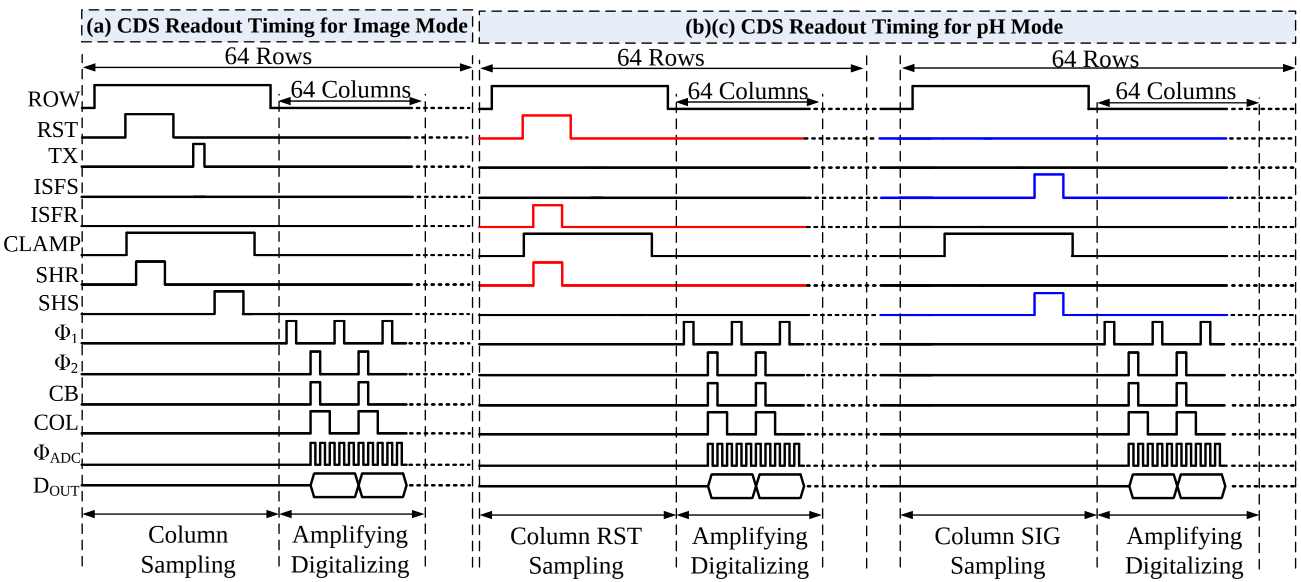




CIS based Contact Imaging + ISFET based Ion Sensing

Dual-mode Low FPN CDS Readout





(a) Capture Contact Image **(b) Before Loading Solution** **(c) After Loading Solution**

- **Objective**: Remove pixel-wise V_T mismatch

- **Before loading solution**:

$V_{OUT1} = V_{OUTP} - V_{OUTN}$
$= \alpha \cdot (C_S/C_F) \cdot (V_{RST} - V_{CM} + V_T)$

α: source follower gain

- **After loading solution**:

$V_{OUT2} = V_{OUTP} - V_{OUTN}$
$= \alpha \cdot (C_S/C_F) \cdot (V_{REF} - V_{CM} + V_T - dV)$

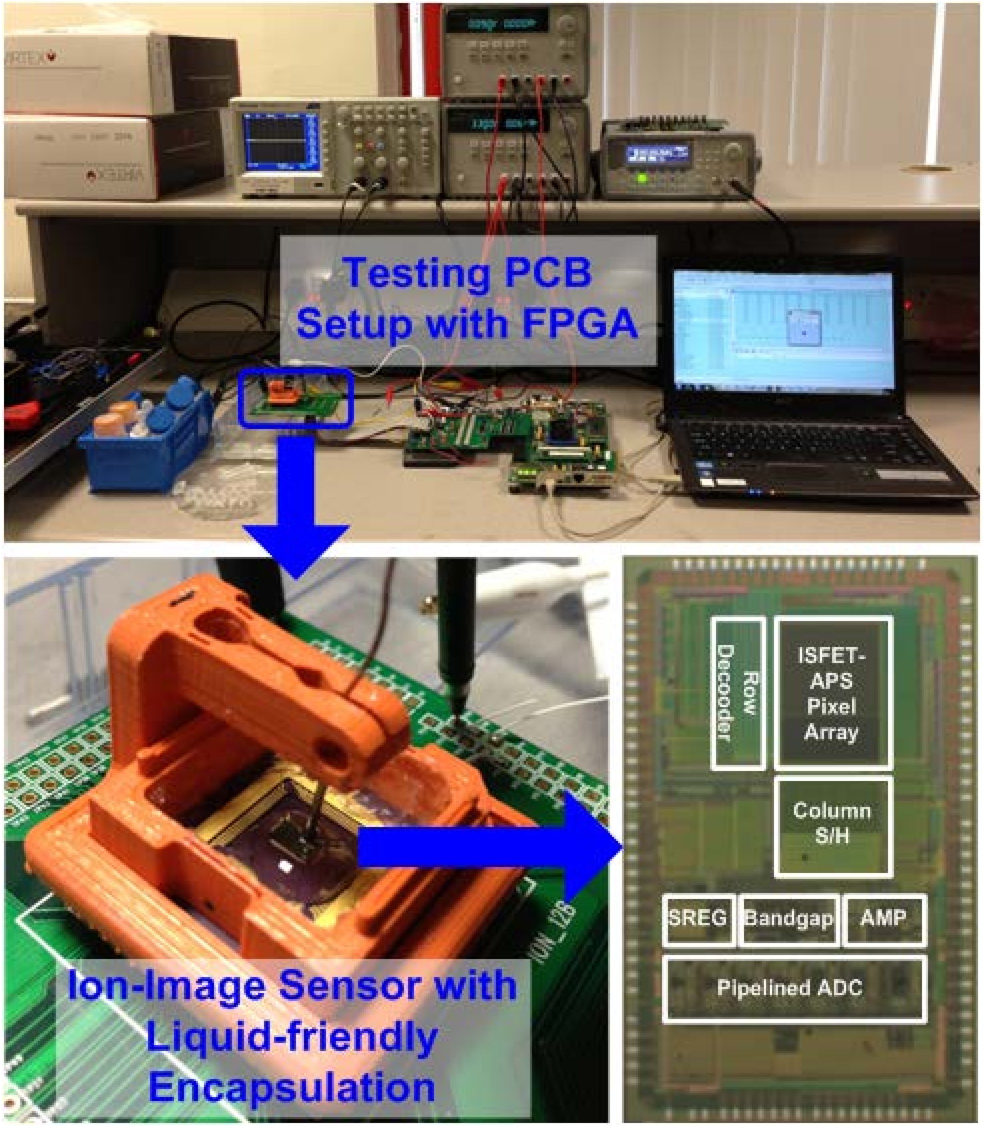
dV: desired voltage signal caused by H^+

- **Difference correlated sampling:**

$V_{OUT1} - V_{OUT2} =$
$\alpha \cdot (C_S/C_F) \cdot (V_{RST} - V_{REF} + dV)$

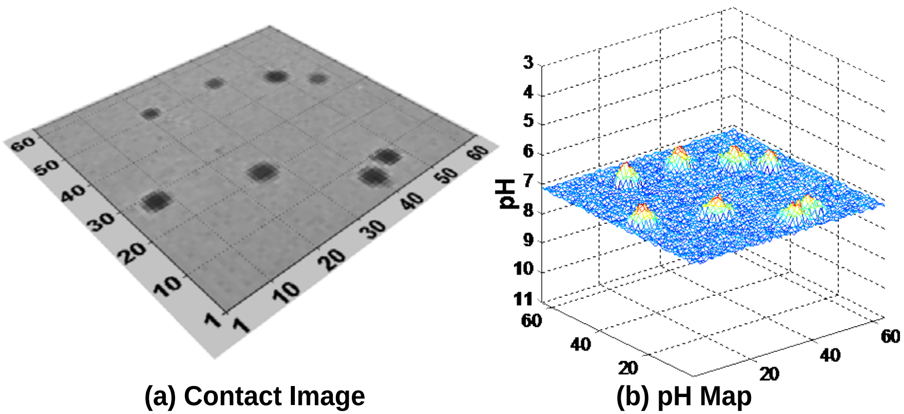
- **V_T mismatch removed**

64x64 Dual-mode Sensor Testing Setup

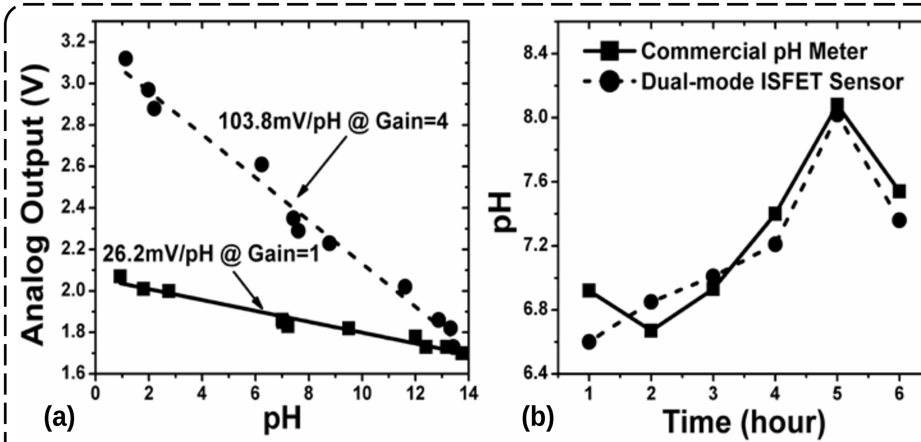


Parameters	Specifications
Process	Standard TSMC 0.18µm CIS
Pixel Type	Dual-Mode (Image and Chemical)
Pixel Size	10µm×10µm
Pixel Optical Sensing Area	20.1µm^2
Pixel Chemical Sensing Area	22.3µm^2
Array Size	64×64
Die Area	2.5mm×5mm
ADC ENOB	11.4 bits
ADC SNDR	70.35dB
FPN	0.3%
Frame Rate	1200fps
Total Power Consumption	32mA @ 3.3V

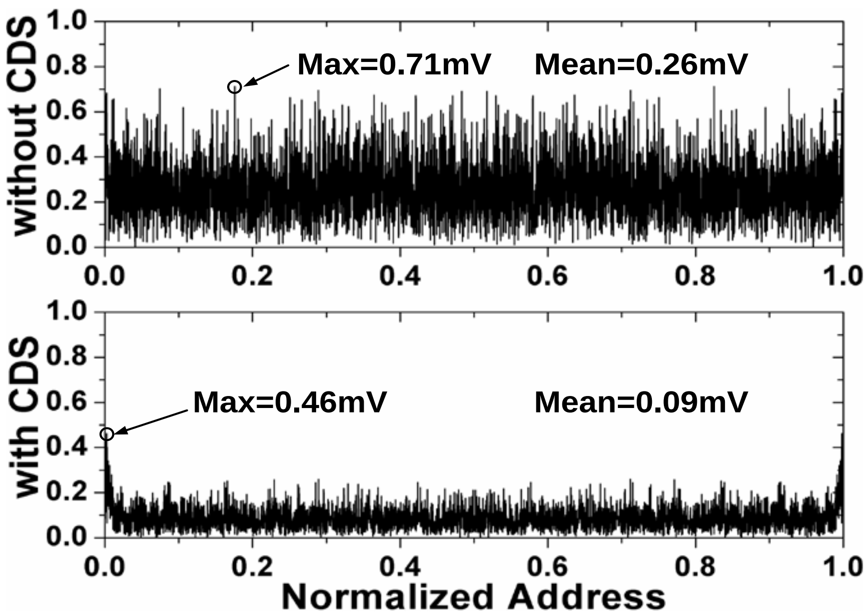
Measurement Results



Correlation of contact image and pH map



Characterization of sensitivity and pH accuracy



Noise reduction with CDS readout

	[7]	[8]	[9]	[10]	[11]	This Work
Process	5μm Non-CMOS	0.35μm Modified CMOS	0.35μm Standard CMOS	0.18μm Standard CMOS	0.35μm Standard CMOS	**0.18μm** Standard CMOS
Pixel Size	200μm × 200μm	12.8μm × 12.8μm	10.2μm × 10.2μm	20μm × 2μm	150μm× 150μm	**10μm × 10μm**
Array Size	10 × 10	16 × 16	64 × 64	8 × 8	8×8	64 × 64
Frame Rate	30fps	-	100fps	-	6fps	1200fps
Sensitivity (mV/pH)	229	46	20	37	57	26.2 (gain=1) 103.8 (gain=4)
Dual-Mode	No	No	No	No	Yes	Yes

Comparison with State-of-the-art ISFET Sensors