

MP 12.3

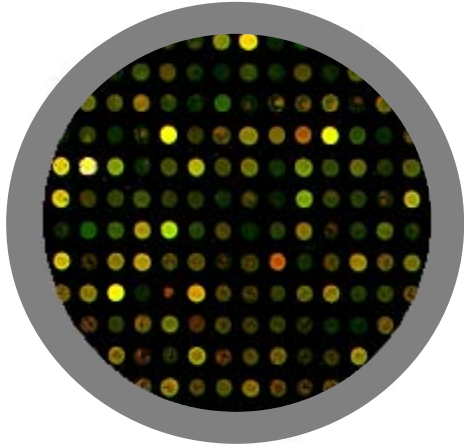
**A 0.18mm CMOS 10^{-6} lux
Bioluminescence Detection
System-on-Chip**

H. Eltoukhy, K. Salama, A. El Gamal,

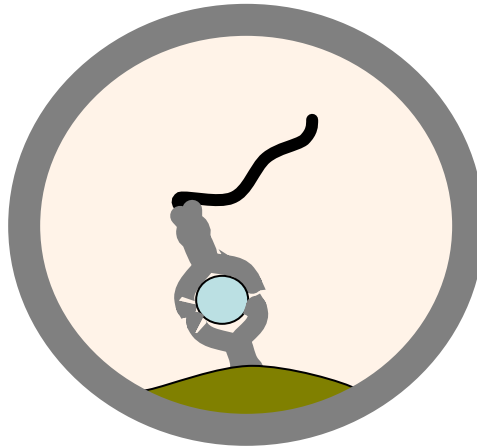
M. Ronaghi, R. Davis

Stanford University

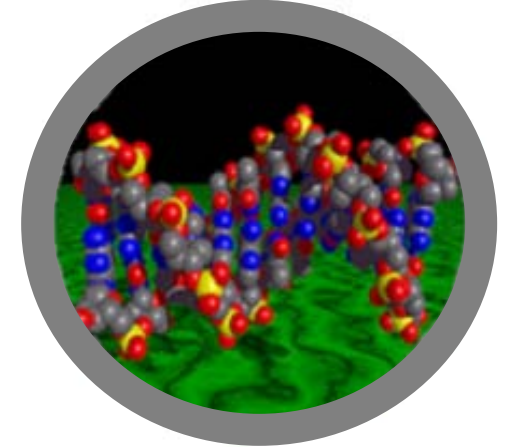
Bio-sensor Applications



Gene Expression



Immunoassay

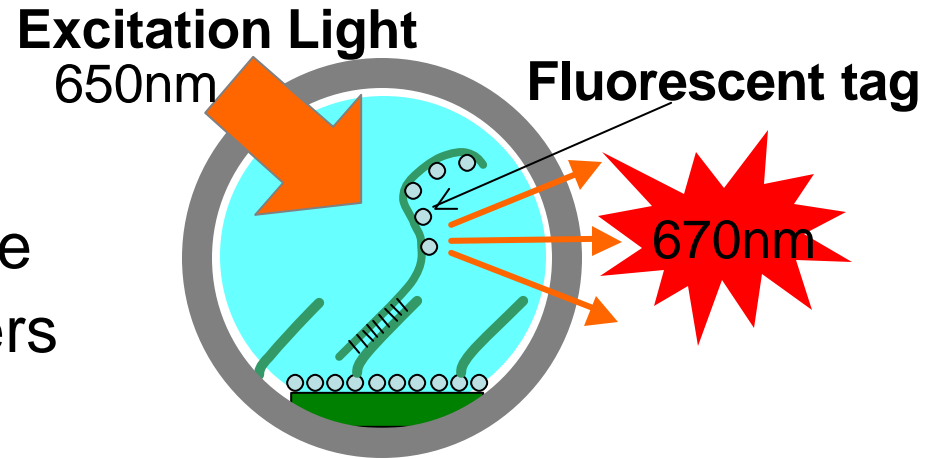


DNA Sequencing

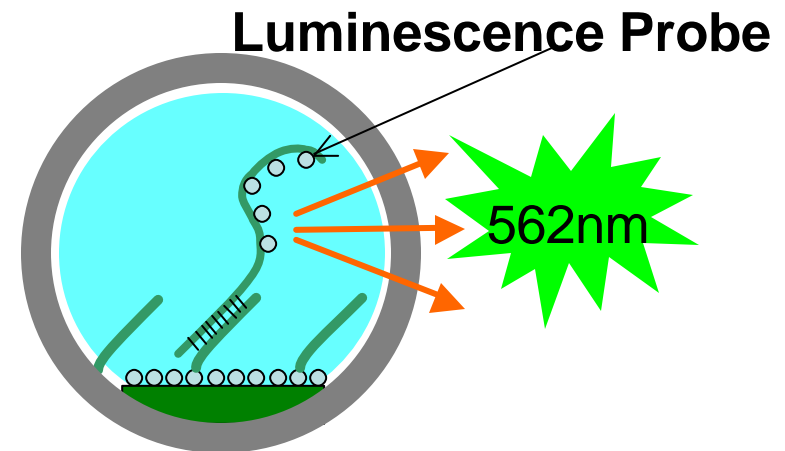
- Medical diagnostics
- Biohazard detection and Biodefense
- Pharmaceutical and drug discovery

Photoemissive Assay Methods

- **Fluorescence:**
 - Widely used, but
 - Need excitation source
 - Need interference filters
 - Photobleaching
 - Difficult to integrate

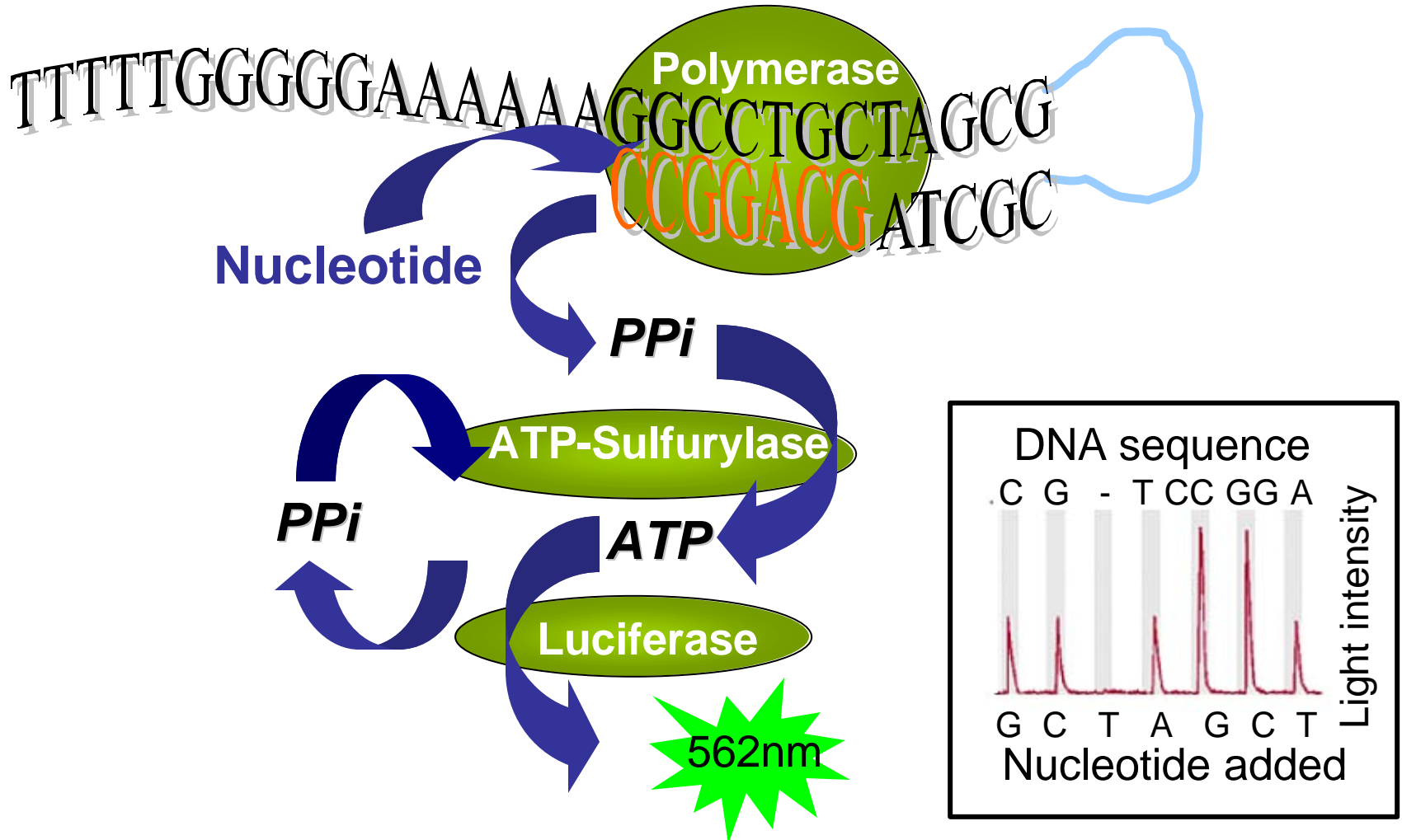


- **Luminescence**
 - Lower background
 - High sensitivity
 - Long emission time
 - Suited for lab-on-chip



Pyrosequencing

Real time DNA sequencing through synthesis (Ronaghi '96)



Current Detection Systems

- Use cooled CCD/PMT-based systems:
 - Bulky
 - Slow
 - Need large amounts of reagents
 - High loss in optical path
 - Need a computer for processing

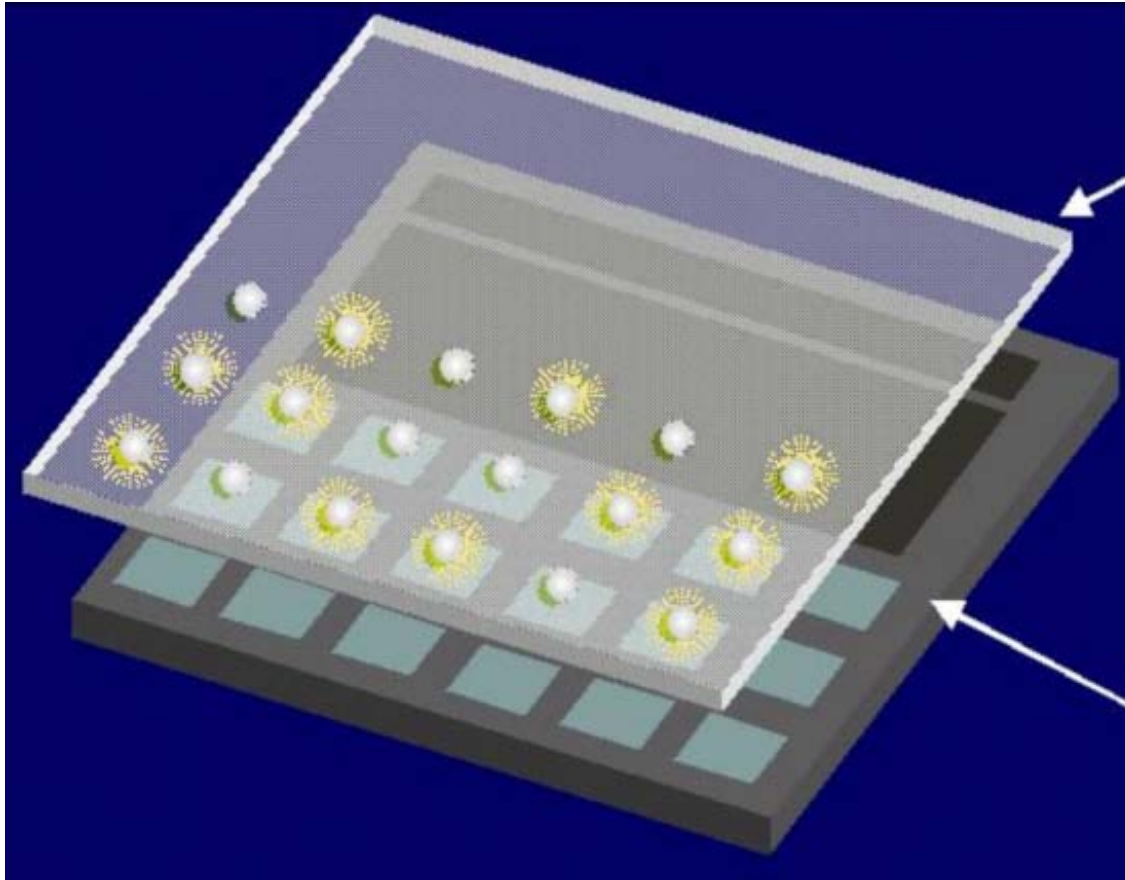


**Need inexpensive, hand-held detection systems
for point of care/on site applications**

Application Characteristics

- Small array size (1-1000 spots)
- Large spots ($\approx 150\mu\text{m} \times 150\mu\text{m}$)
- Long integration times (1s to 3min)
- **Challenge:** Detect below 10^{-6} lux over 30sec @ room temperature
- Off-the-shelf CCD&CMOS sensors are not suited
 - Small pixels: High leakage, low sensitivity
 - Off-chip ADC and processing
 - CCDs: Slow, destructive reads

Luminescence Detection System



Transparent slide with immobilized luminescent reporters/probes

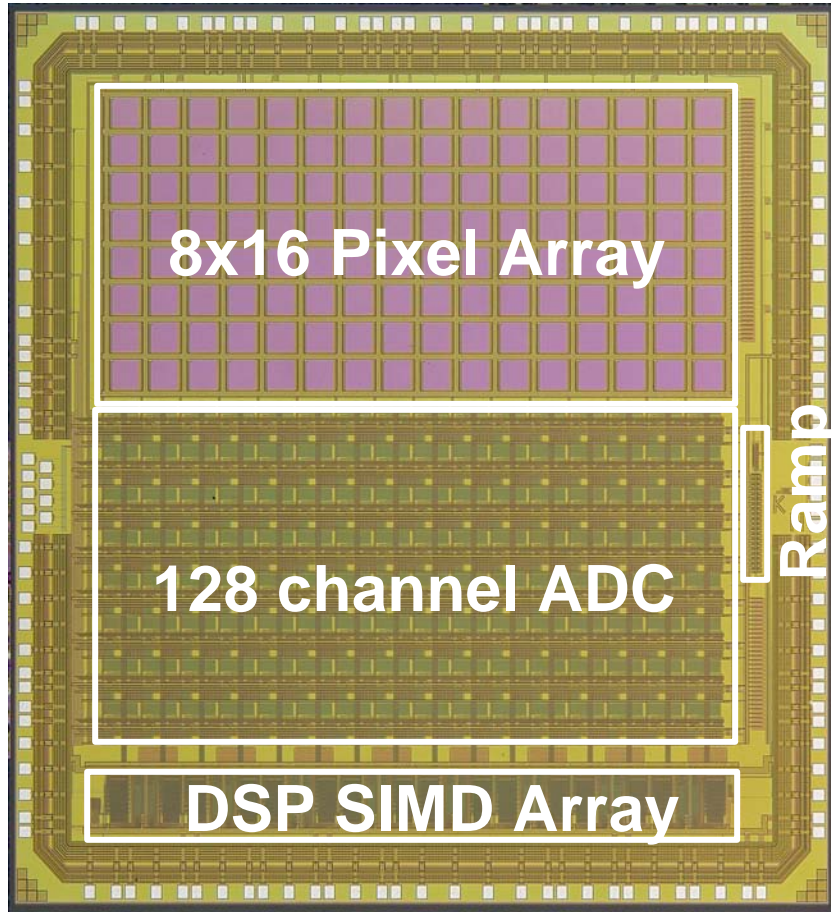
Optical detection and analysis CMOS chip

Joint work with Stanford Genome Technology Center and Stanford Nano-Fabrication Group

Outline

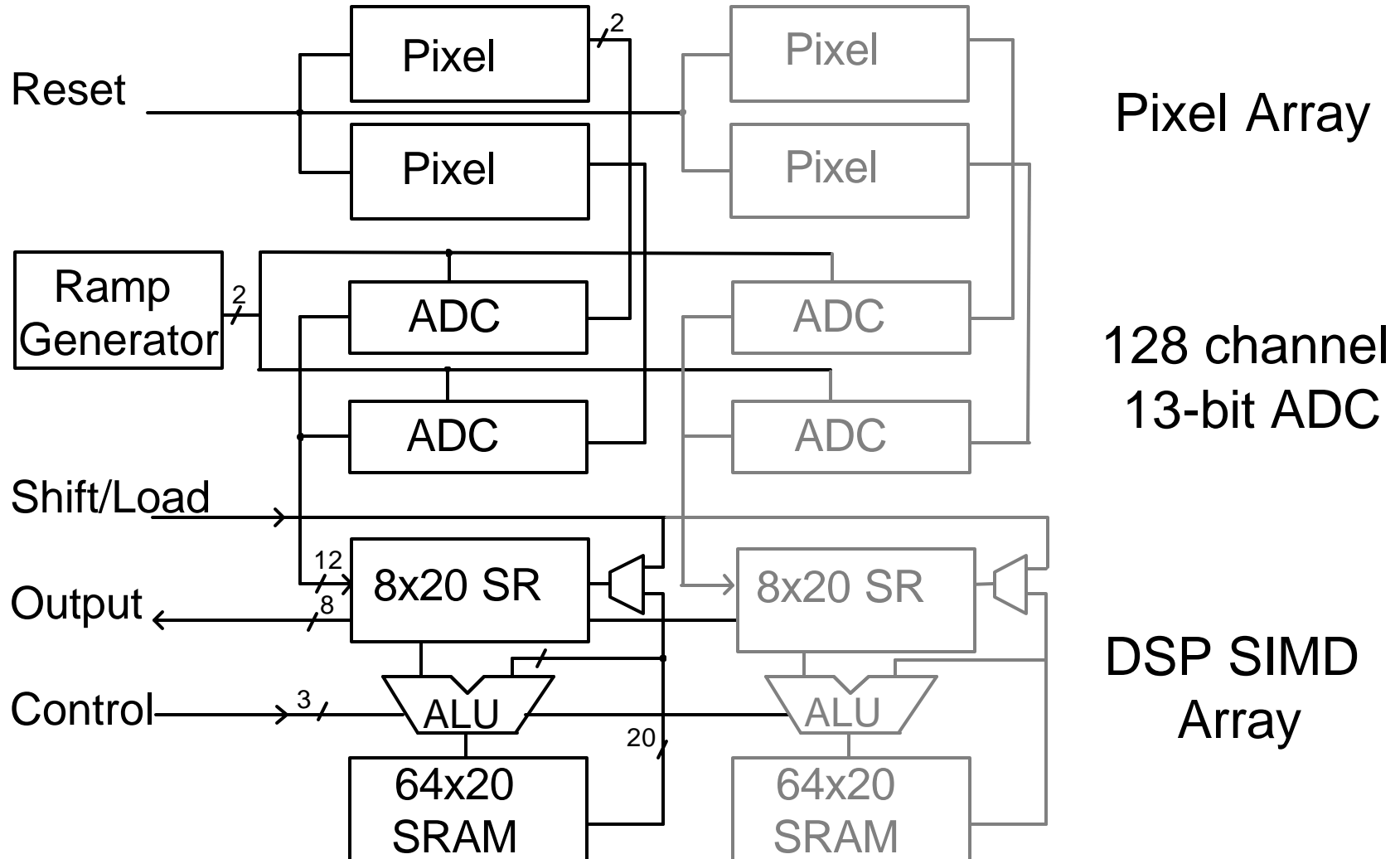
- Chip block diagram
- Circuit schematics and measurements
- Measured performance:
 - Optical characteristics
 - ADC characteristics
- Achieving low light detection
- Conclusion

Chip Characteristics

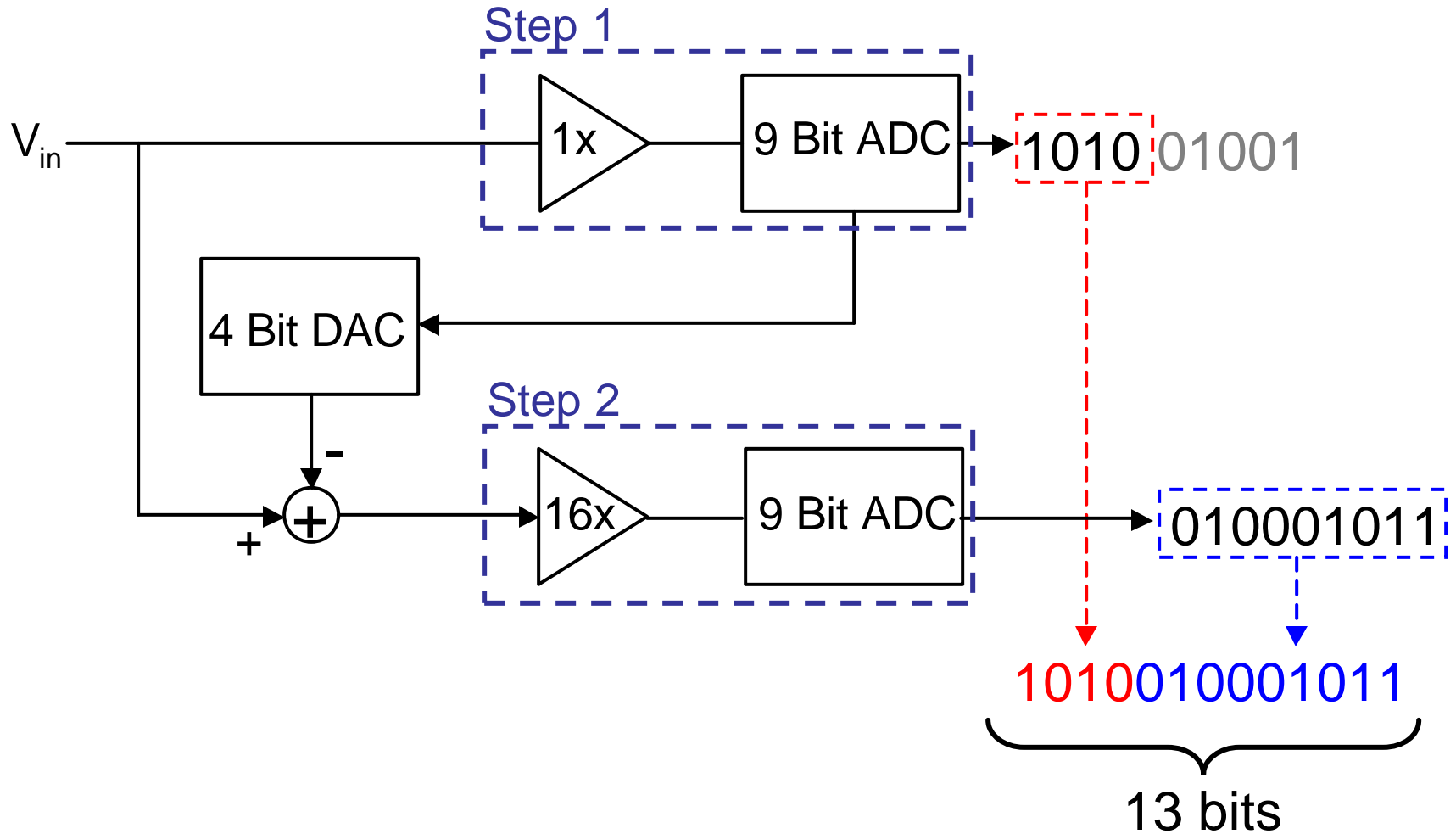


- 0.18 μm CMOS (CIS) process
- 5mm x 5mm (492K transistors)
- 8 x 16 pixel array (230 μm sq.)
- P+/N/Psub photodiode
- Pseudo-differential pixel
- Per-pixel 2-step 13-bit ADC
- Integrated ramp generator
- Per-column DSP
- 320 Mbits/s readout rate
- Static power: 26mW

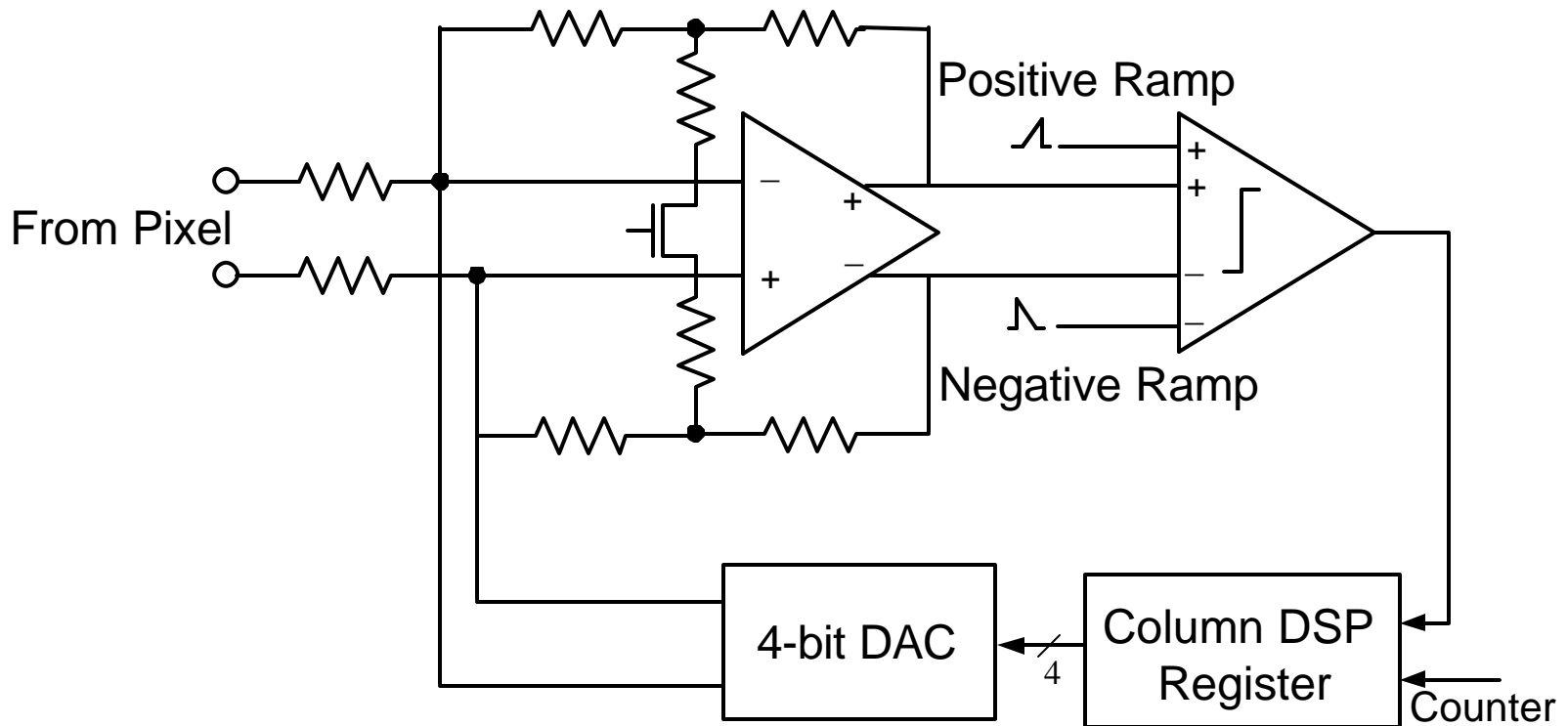
Chip Block Diagram



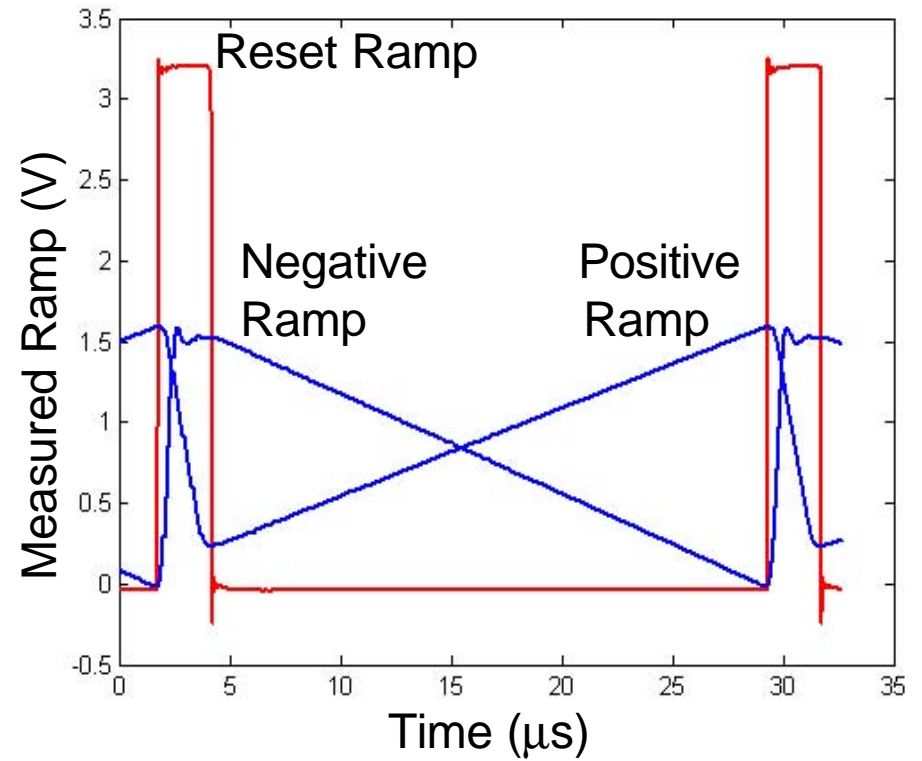
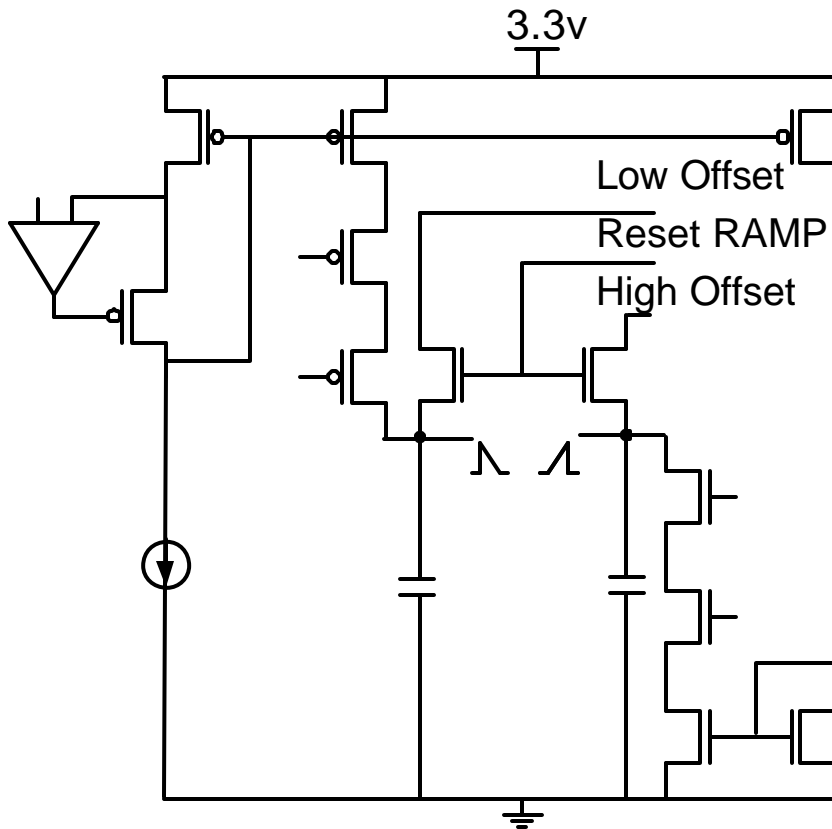
13-bit 2-step ADC



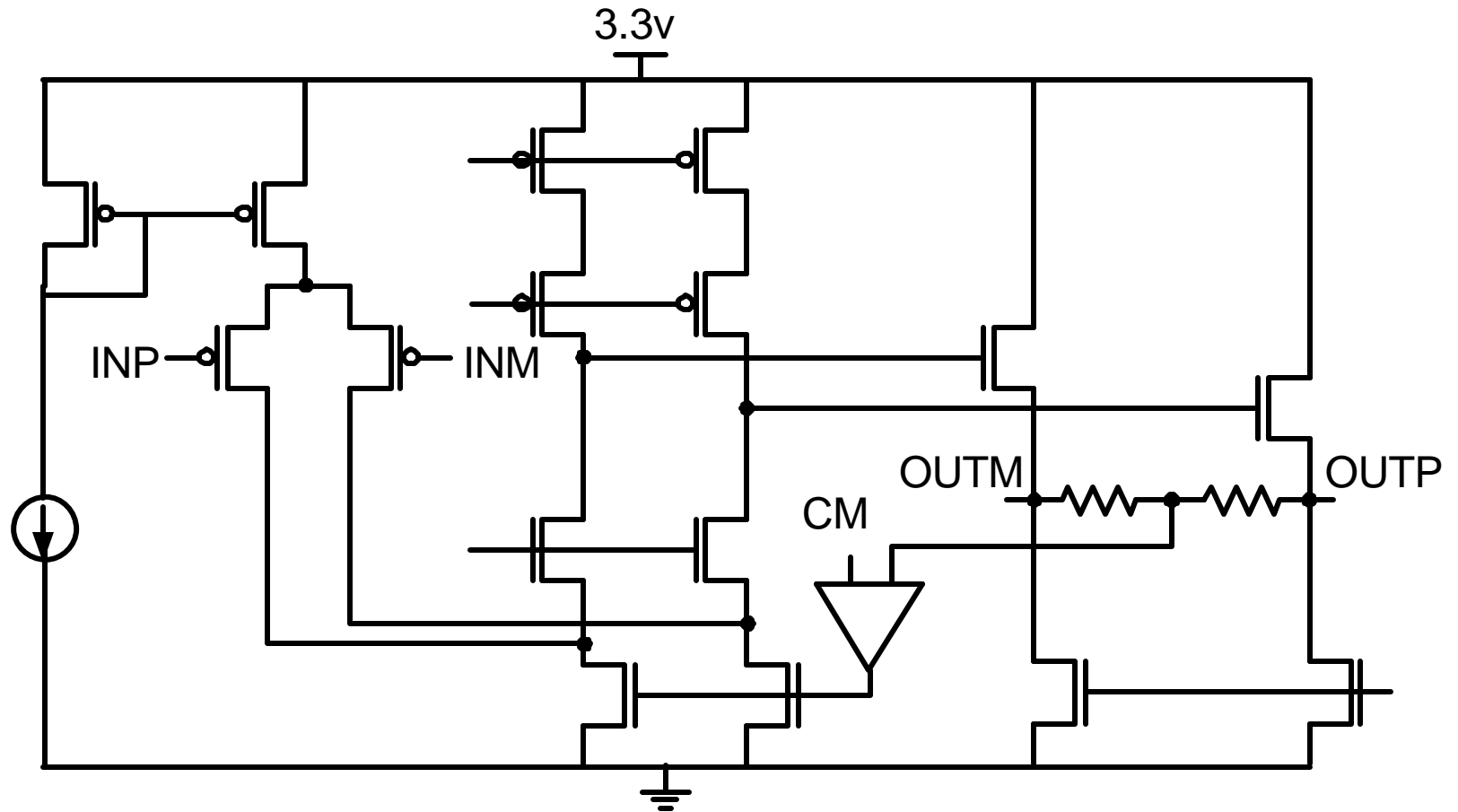
ADC Implementation



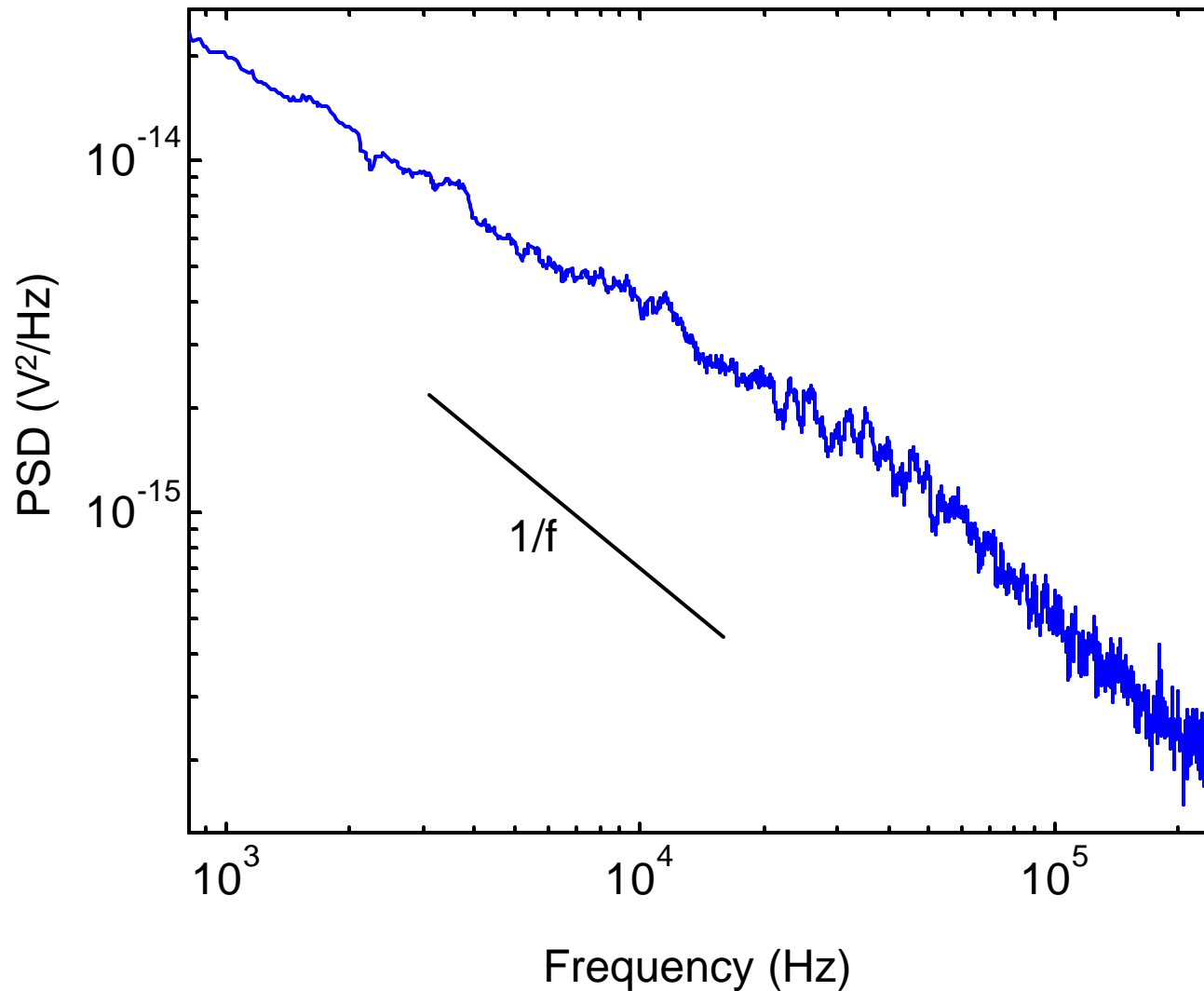
Differential Ramp Circuit



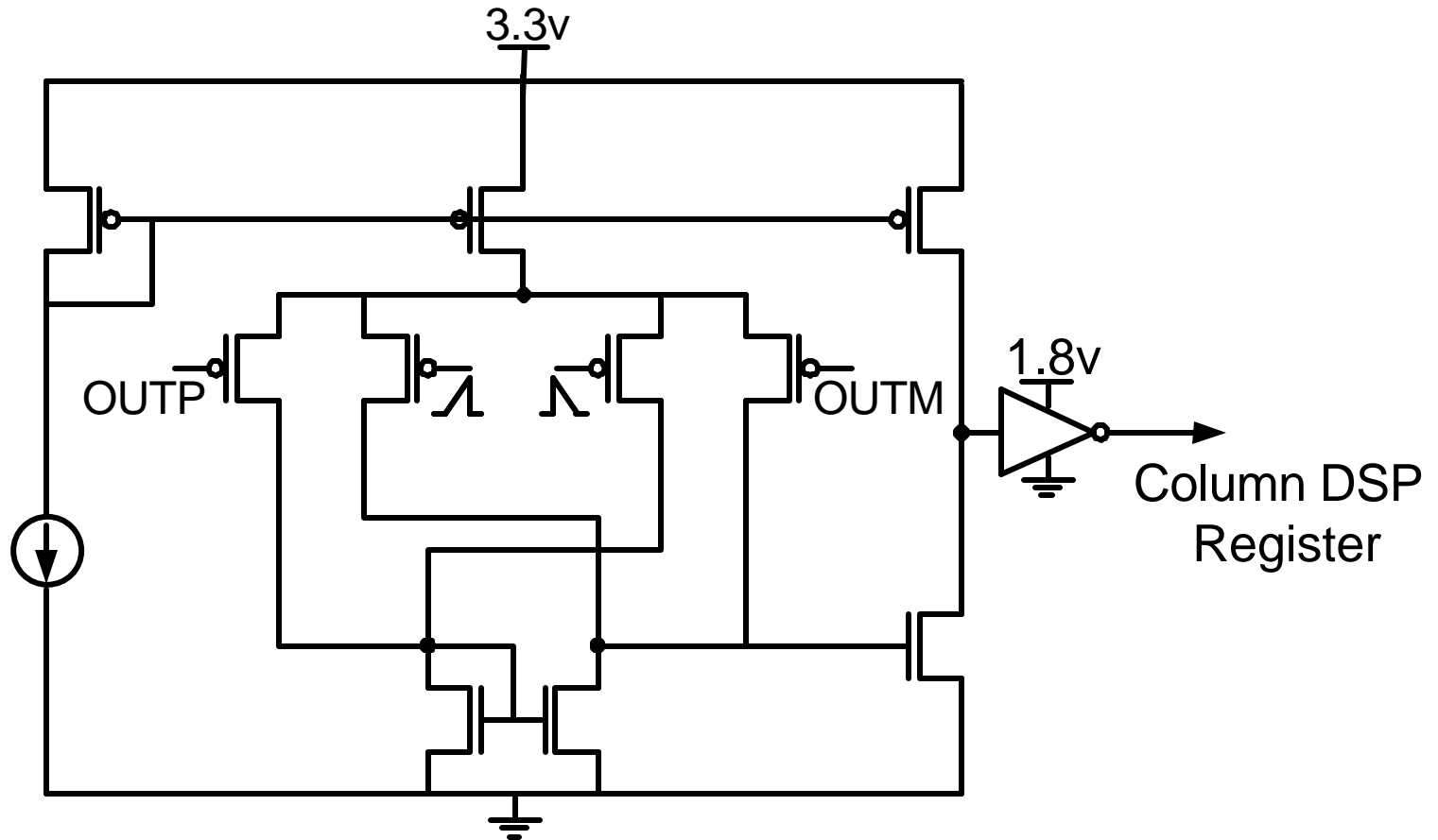
Differential Amplifier



Measured VGA Noise PSD



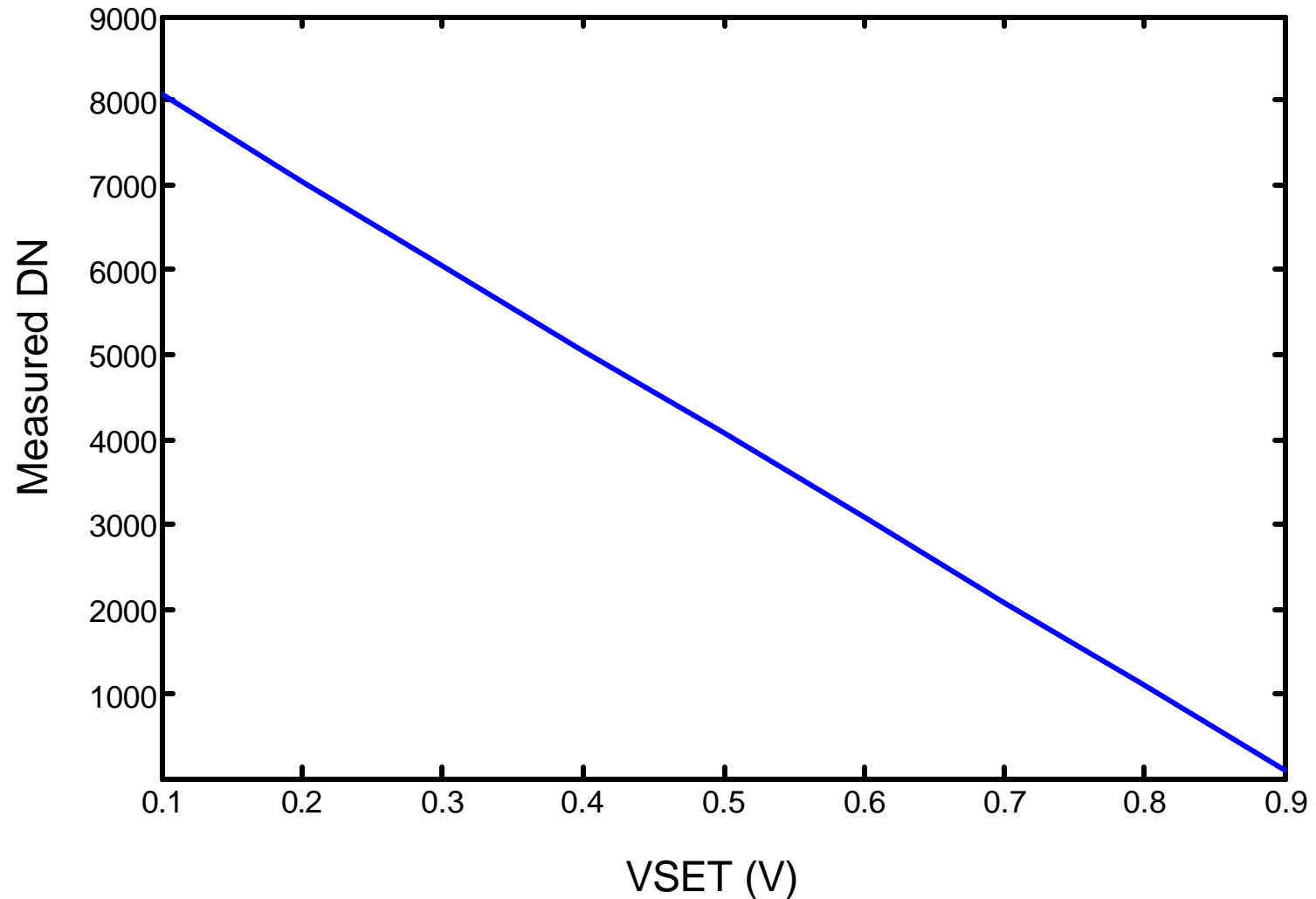
Differential Difference Comparator



Measured Optical Characteristics

Array Size	8x16 pixels
Pixel size	230 μ m x 230 μ m
Photodetector	P+/N/Psub 150 μ m x 150 μ m
Voltage Range	0.1-0.9 V
Dark Signal	2.6 mV/s
QE @ 560nm	0.4
Sensitivity	160 V/lux.sec
Follower non-linearity	< 0.1%
Dynamic Range	61 dB

2-Step Full ADC



Measured ADC Characteristics

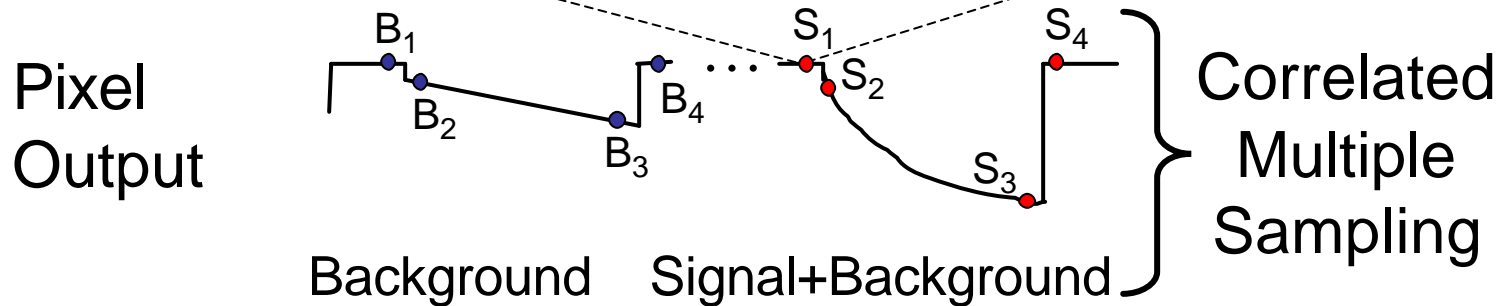
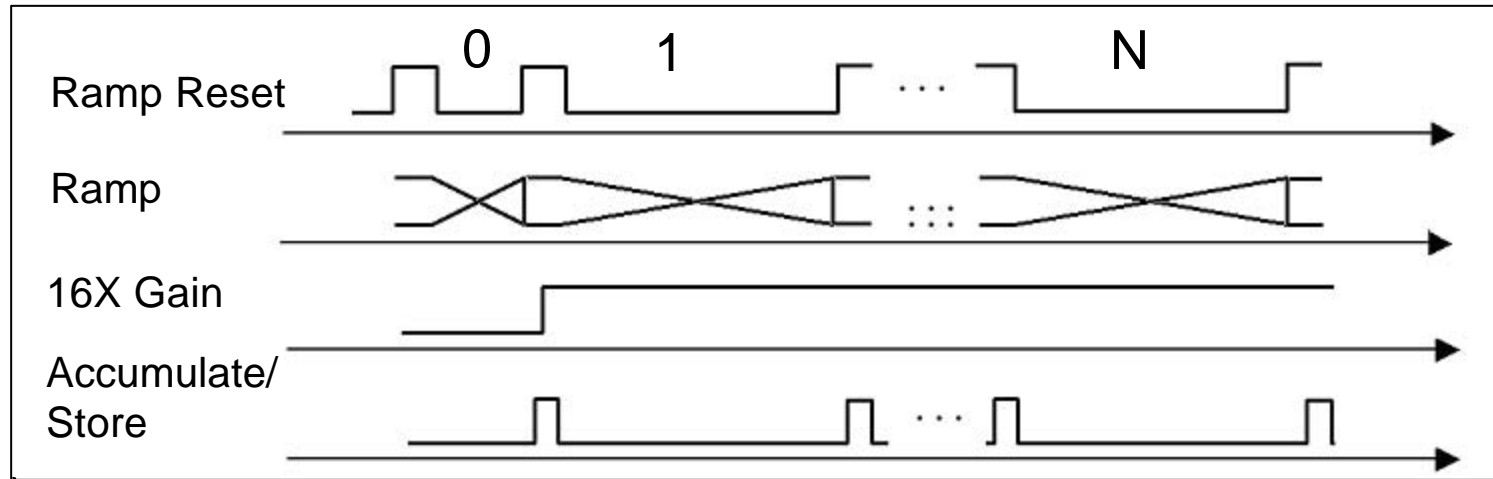
Architecture	128 channel 2-step
Resolution	13-bit
Area	7mm ²
Conversion Rate	7.1Msample/sec
INL	0.033%
DNL	50μV (0.5LSB)
FOM=Power/(2 ^{b+1} BW)	1.2pJ

b : Effective number of bits

Achieving Low Light Detection

- Direct optical coupling (Eggers '94)
- Detector and luminescent assay matching
- Low noise design
- High ADC resolution
- Background subtraction
- Averaging for read noise reduction
- Correlated Multiple Sampling (Fowler '91)

System Operation

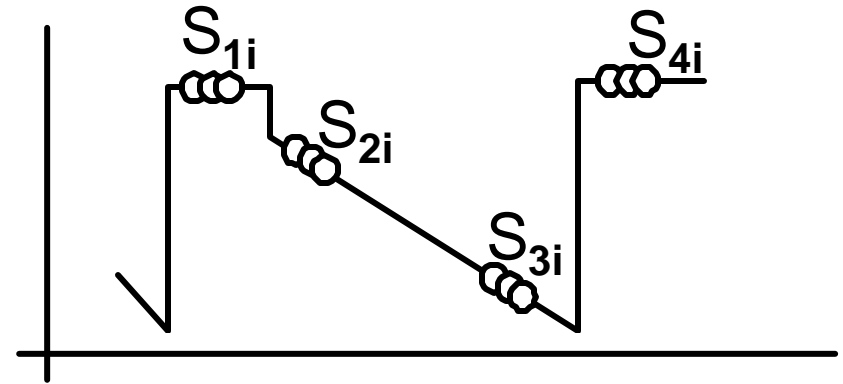


$$S = (\bar{S}_3 - \bar{S}_2) - (\bar{S}_4 - \bar{S}_1) - (\bar{B}_3 - \bar{B}_2) + (\bar{B}_4 - \bar{B}_1)$$

Comparing Sampling Techniques

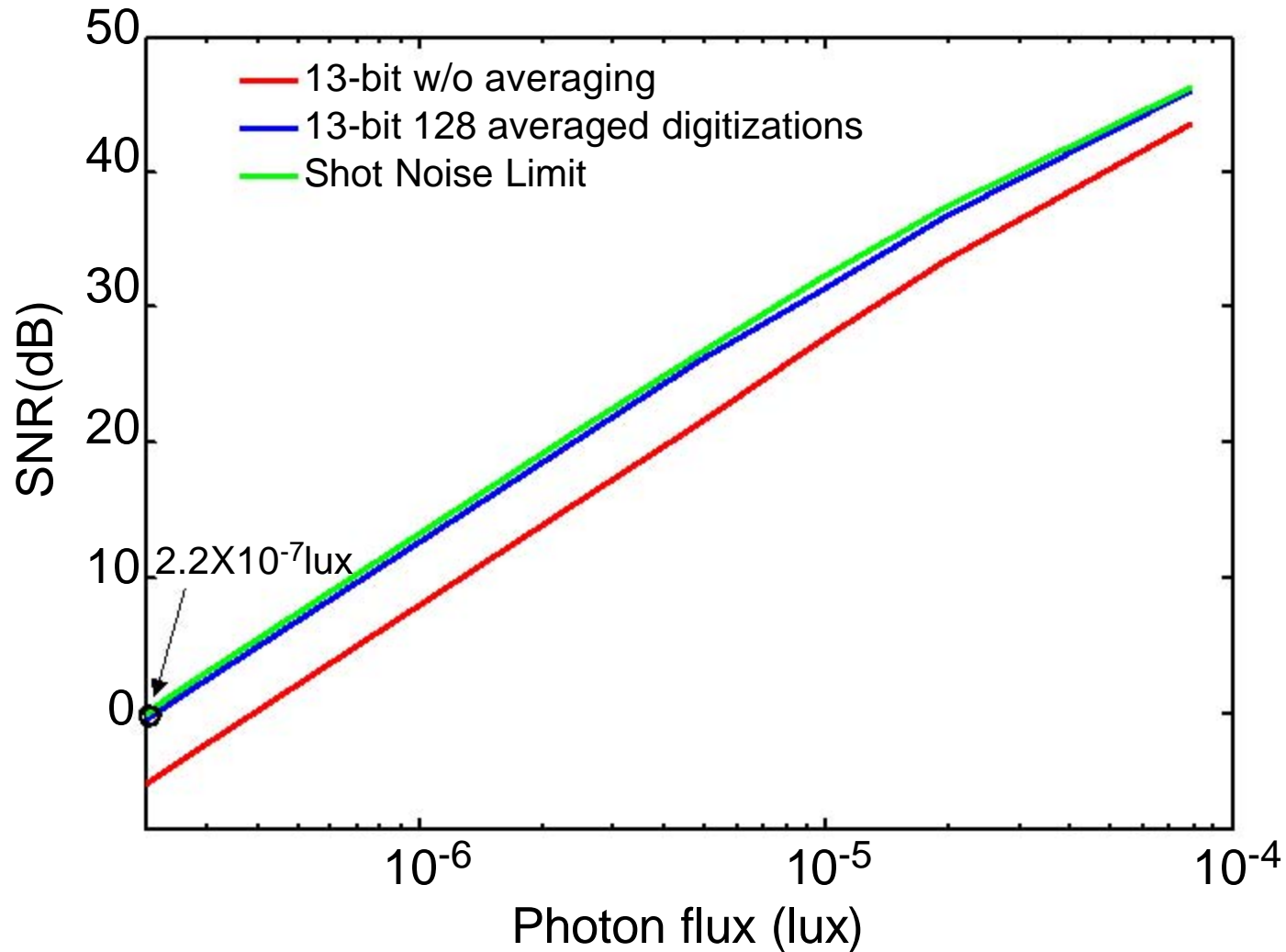
Experiment:

Frames = 50
 T_{int} = 80sec
 N = 16
 ΔT_i = 25 μ s

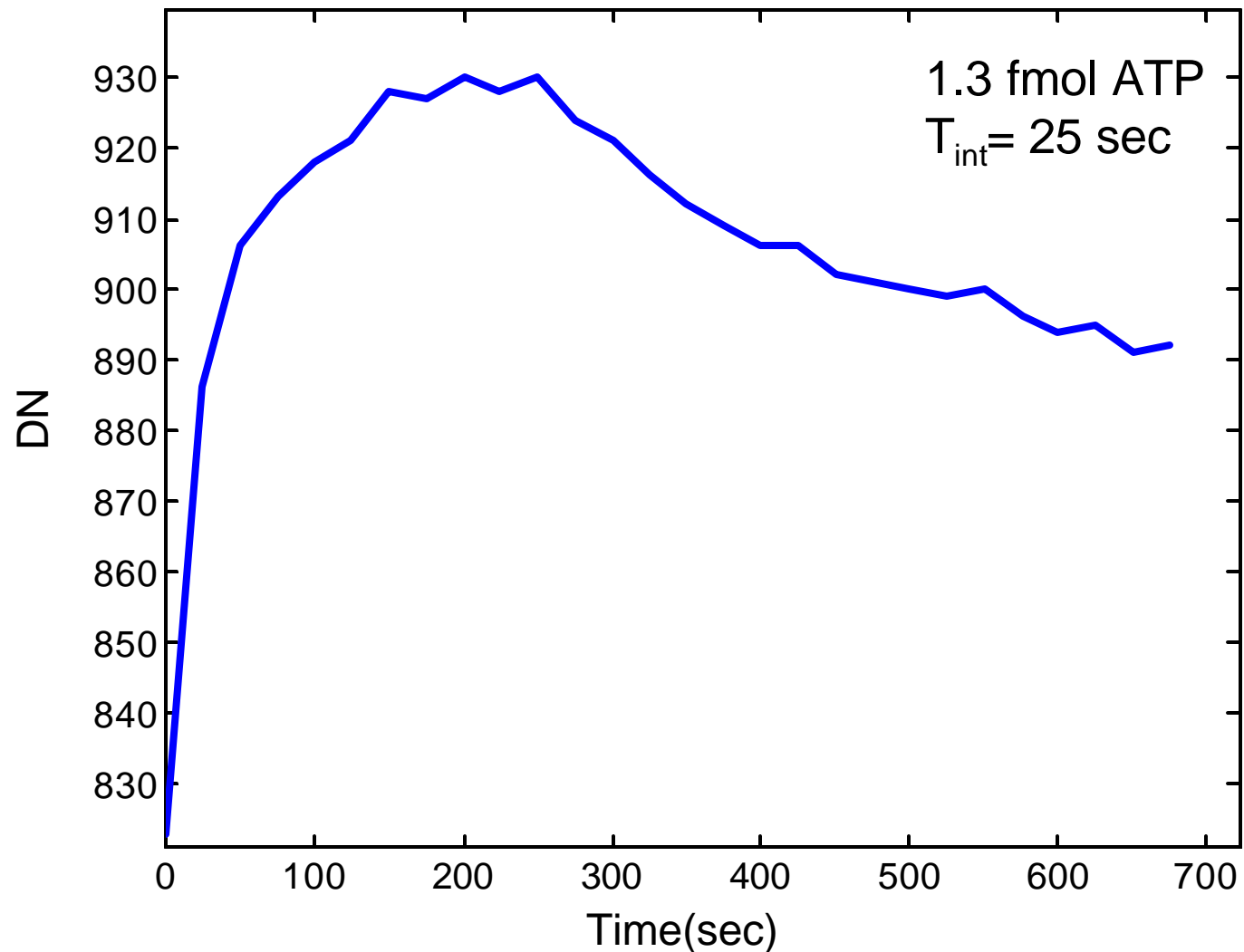


Technique	Offset	Reset	1/f	Read	Loss
$S = (S_3 - S_4)$	✓		✓	2X	-15.44dB
$S = (S_3 - S_2)$	✓	✓		2X	-6.94dB
$S = (S_3 - S_2) - (S_4 - S_1)$	✓		✓	4X	-9.42dB
$S = (\bar{S}_3 - \bar{S}_2)$	✓	✓		2X/N	-2.05dB
$S = (\bar{S}_3 - \bar{S}_2) - (\bar{S}_4 - \bar{S}_1)$	✓	✓	✓	4X/N	-1.12dB

System Detection Limit



Measured Pyrosequencing Reaction



Conclusion

- There is need for hand-held luminescence detection systems
- Described a 0.18 μm detection SoC:
 - 8x16 pseudo-differential pixel array
 - Per-pixel 13-bit 2-step ADC
 - Per-column SIMD DSP
- Detects 10^{-6} lux over 30sec integration time:
 - Direct optical coupling and array customization
 - High ADC resolution and averaging
 - Correlated multiple sampling