Magnetoresistive Biosensors for Quantitative Proteomics

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Applications of Biosensors

Clinical Diagnostics

- Disease detection
  - HIV/AIDS
  - Cancer
  - Cardiovascular (heart) disease
- Therapy progression

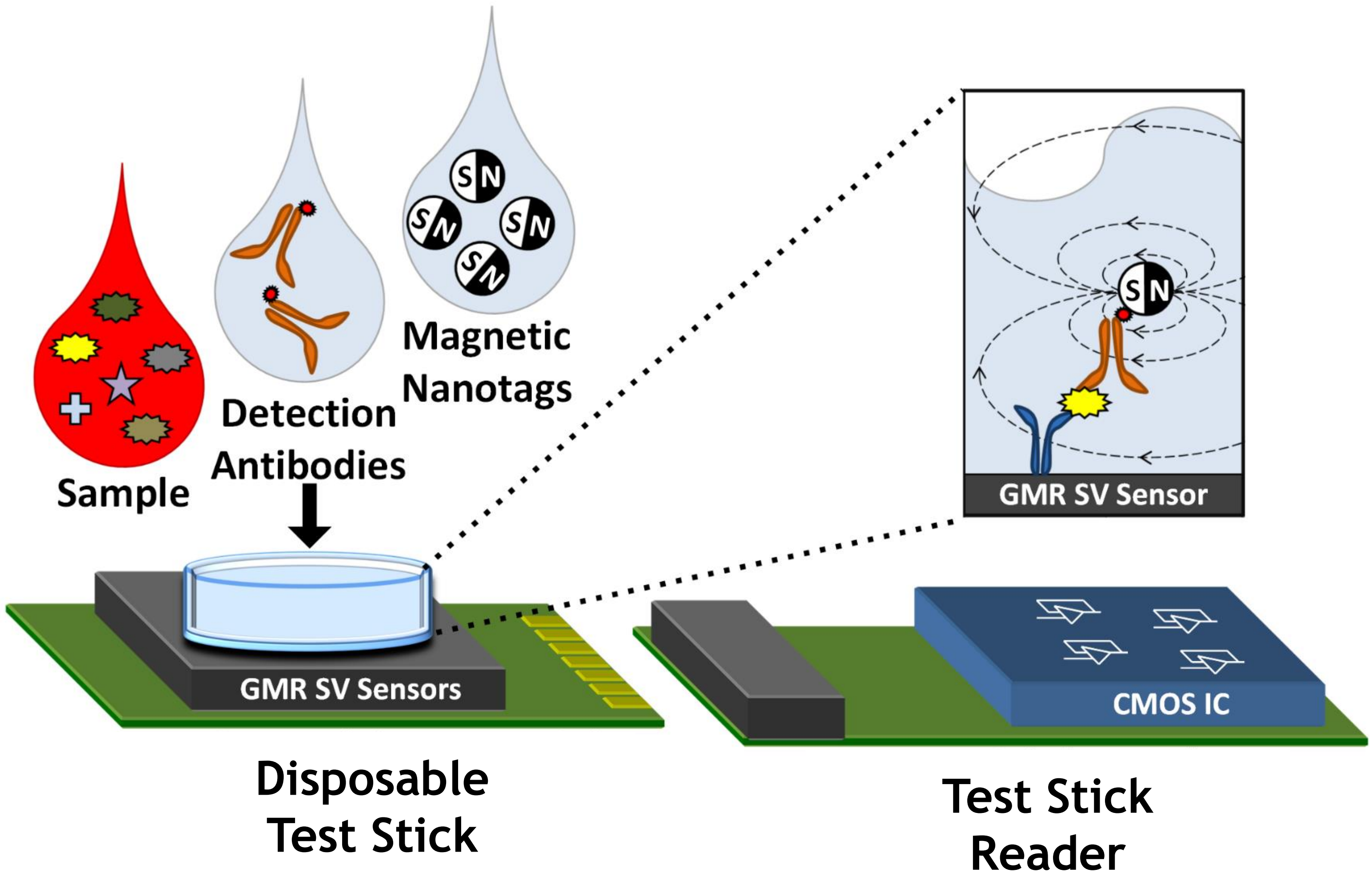
Biomedical Research

- Drug discovery
- Kinetics of protein interactions

Environmental Testing

- Water pollution
- Food contamination
- Toxins

Concept



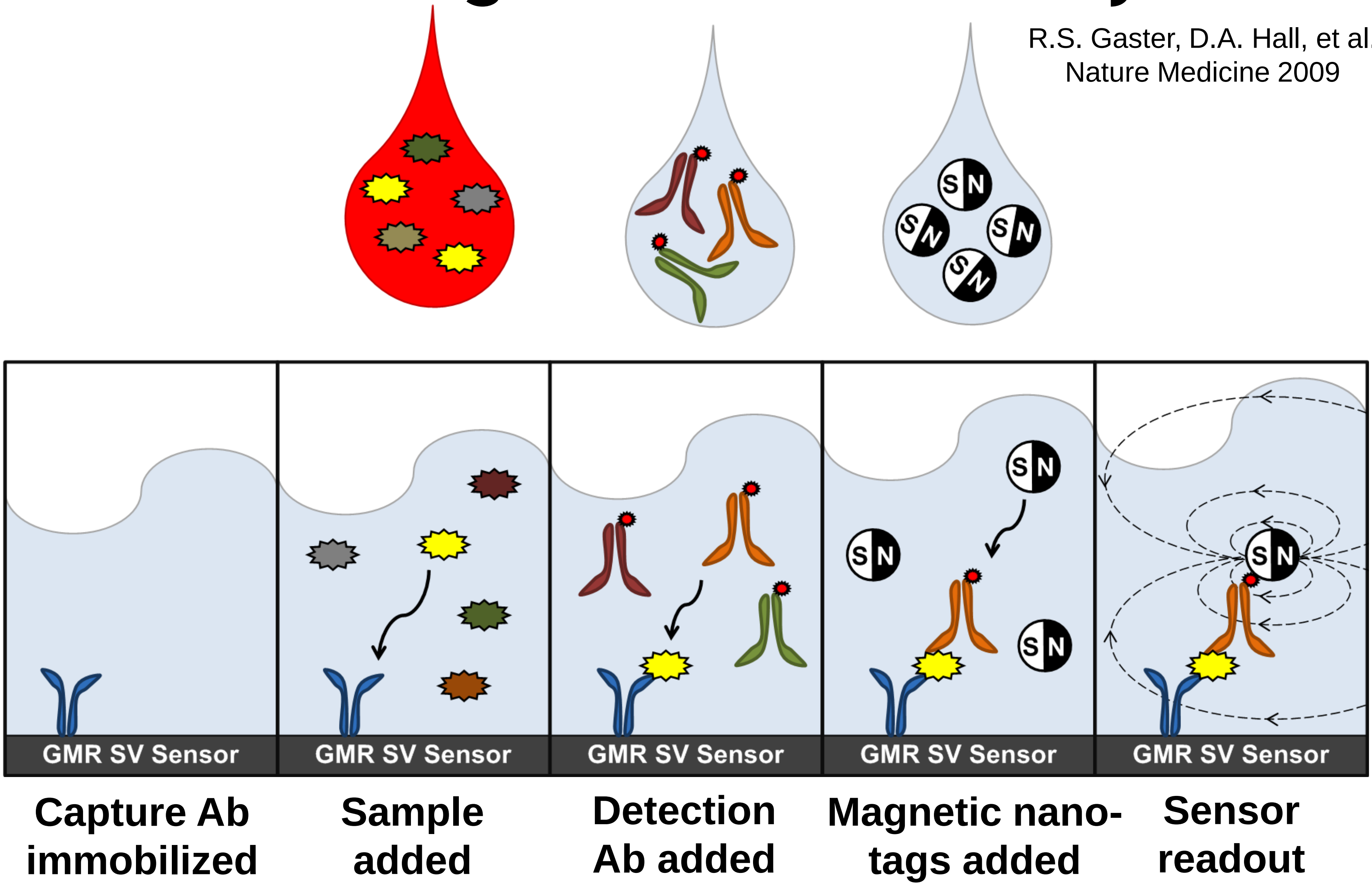
Magnetic
Nanotags
Detection
Antibodies
Sample
GMR SV Sensor
GMR SV Sensors
CMOS IC
Disposable
Test Stick
Test Stick
Reader

Outline

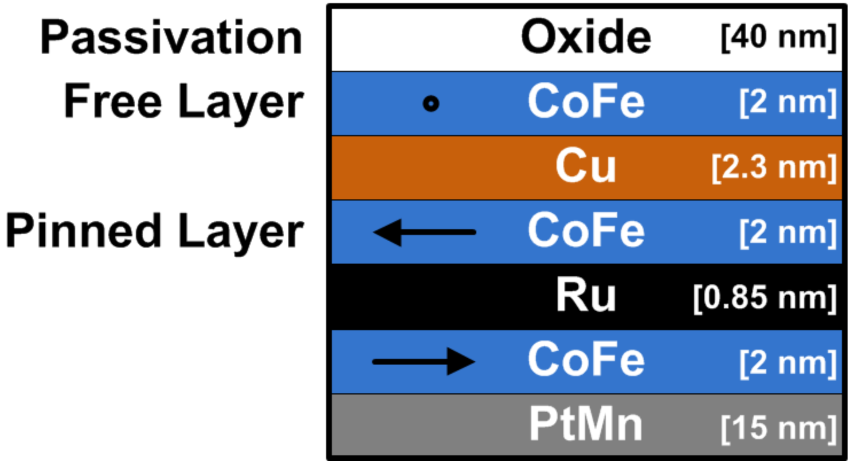
- Motivation and Applications
- **Magnetic Biosensing**
  - Background
  - High throughput readout
  - Temperature correction technique
- CMOS Biosensor Microarray
  - Circuit and system design
  - Measurement results
- Conclusion

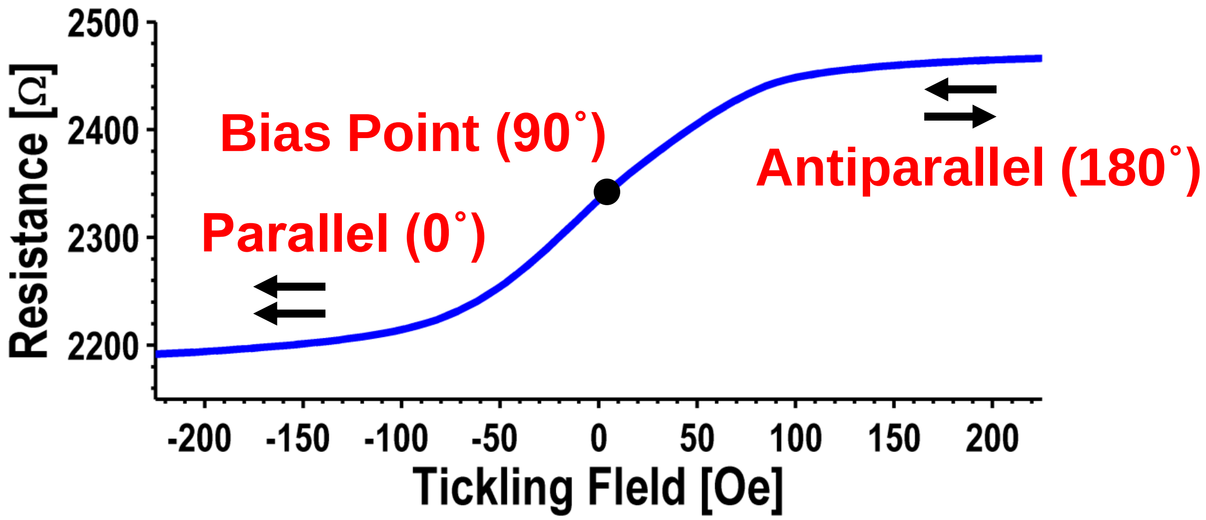
The Magnetic Immunoassay

R.S. Gaster, D.A. Hall, et al.
Nature Medicine 2009



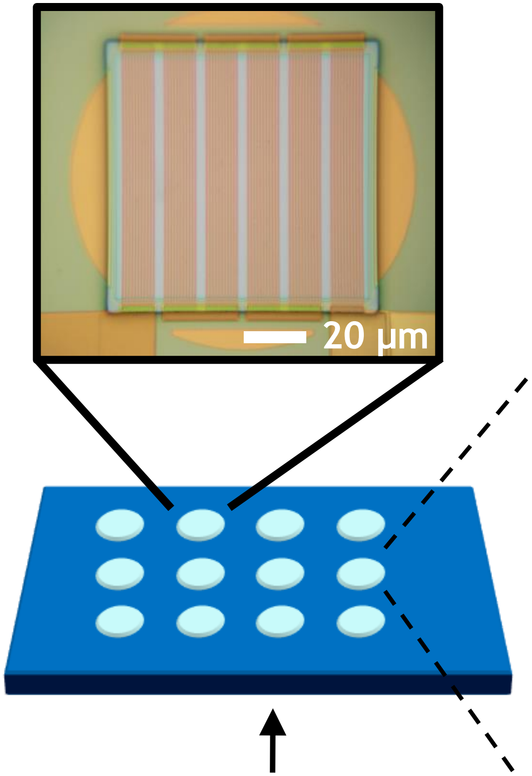
Giant Magnetoresistive Spin-Valves (GMR SV)

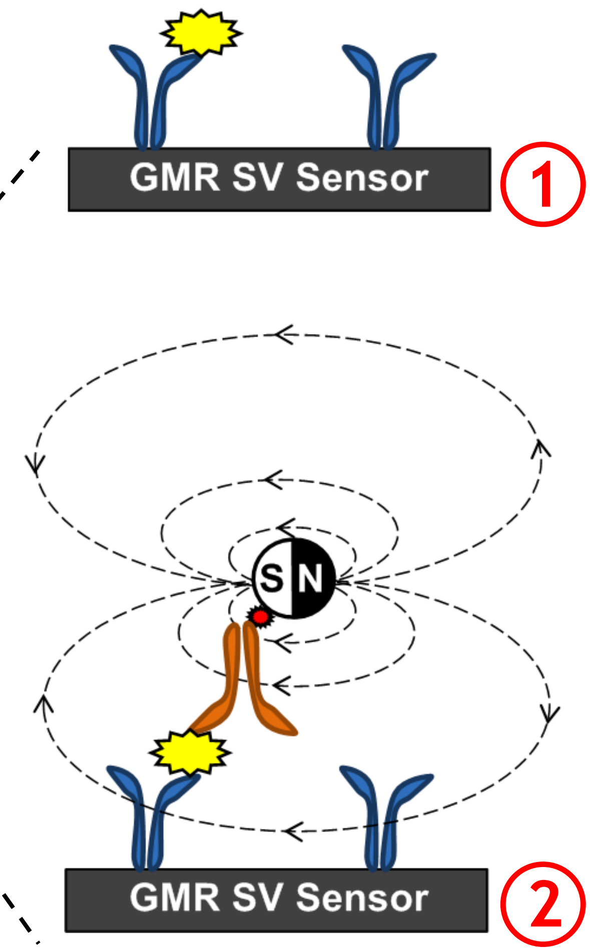




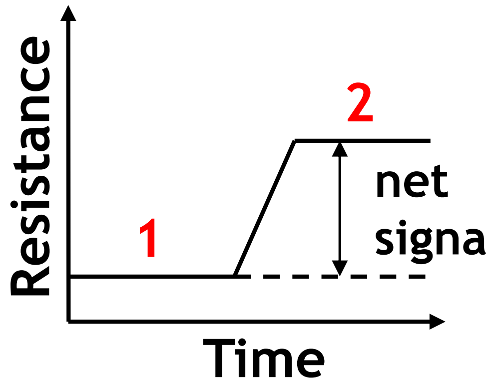
$$MR = \frac{R_{AP} - R_P}{R_P}$$

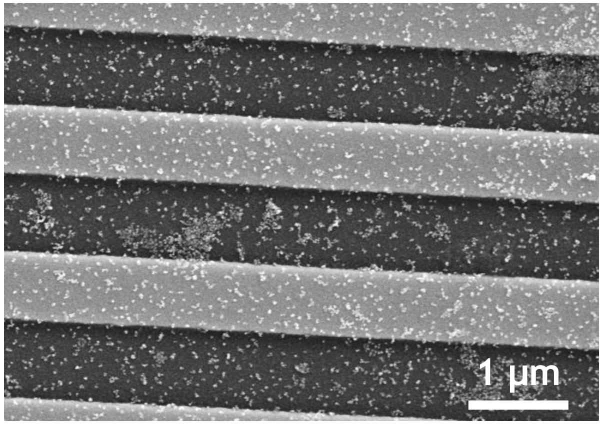
The GMR SV as a Biosensor



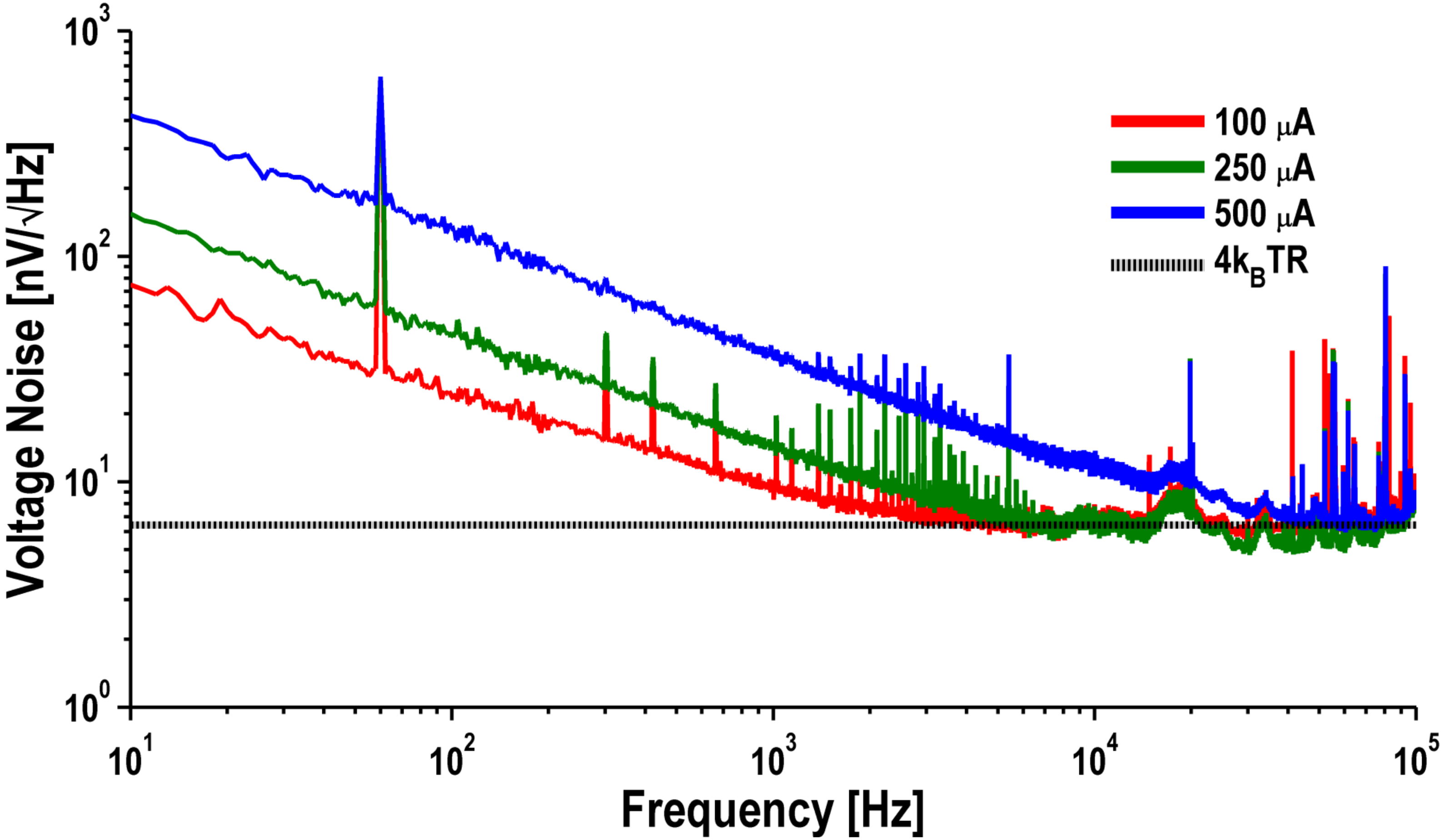


Sensor resistance changes from 1 → 2





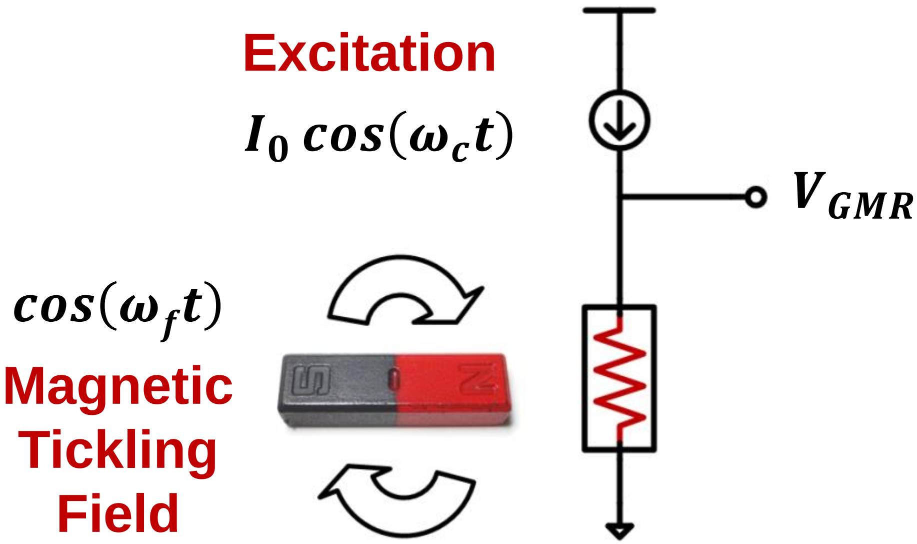
Sensor Noise Spectrum



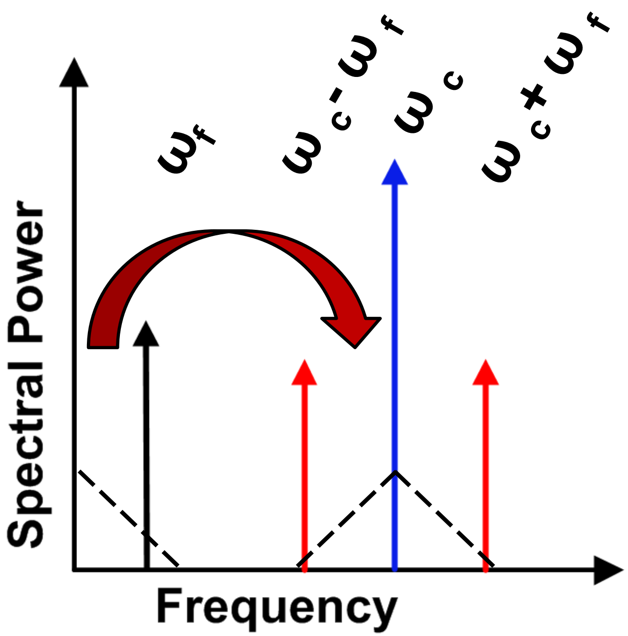
D.A. Hall, R.S. Gaster, et al. - Biosensors and Bioelectronics 2010

Signal Modulation Scheme

- Modulate the signal from magnetic nanotags away from $1/f$ noise of sensor and interface electronics
- Electrical excitation and magnetic field modulated



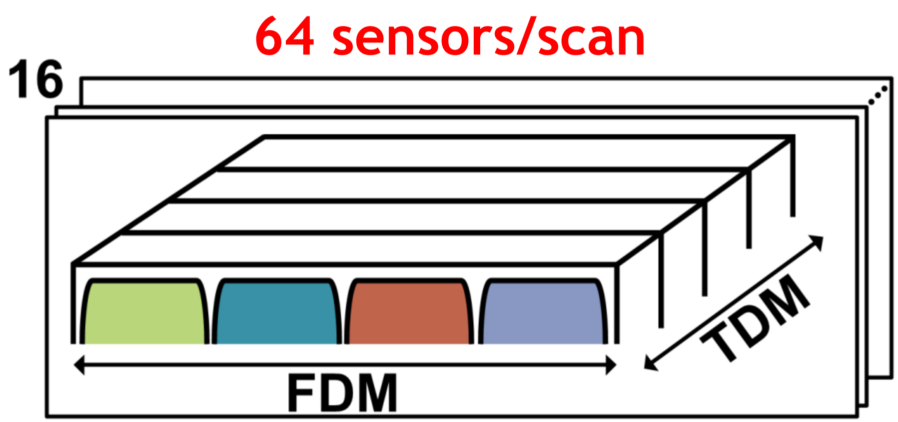
$$V_{GMR}(t) = I_0 R_0 \cos(\omega_c t) + \frac{I_0 \Delta R_0}{2} \cos\left((\omega_c \pm \omega_f) t\right)$$



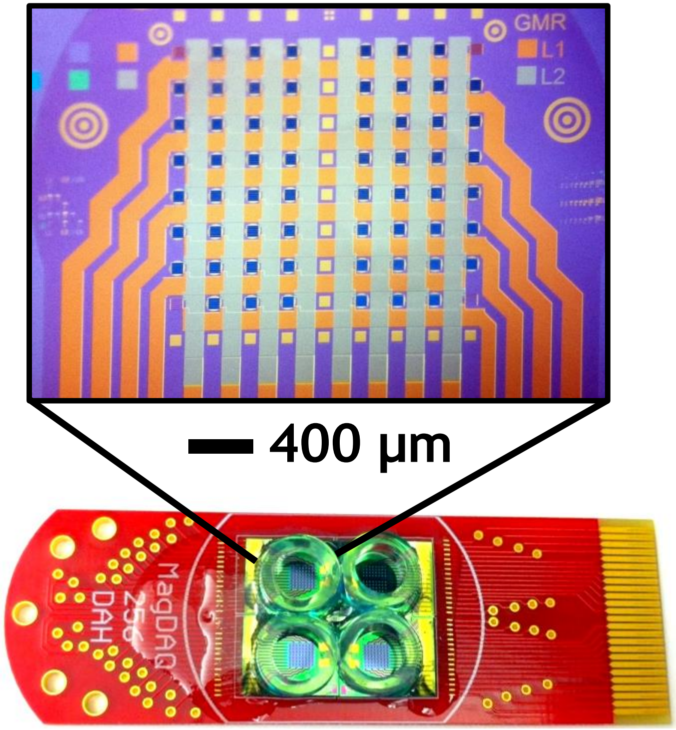
S. Han, et al. ISSCC 2007
B. de Boer, et al. Biosens. and Bioelec. 2007
Aytur, et al. Actuator and Microsystems 2002

High Throughput Readout

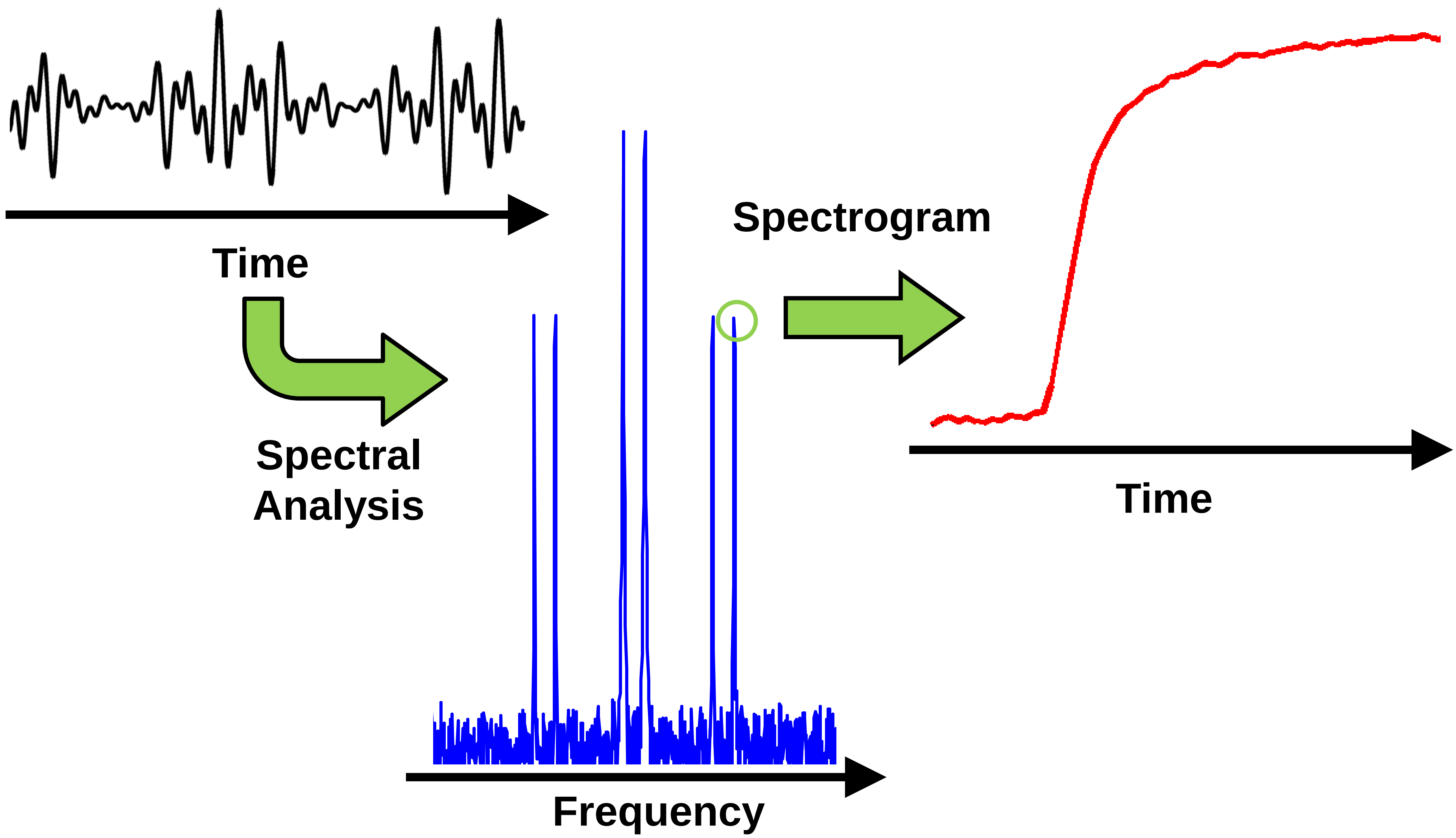
- Techniques used to reduce readout time
  - Parallelized “column” readout
  - Frequency division multiplexing (FDM)
  - Time division multiplexing (TDM)



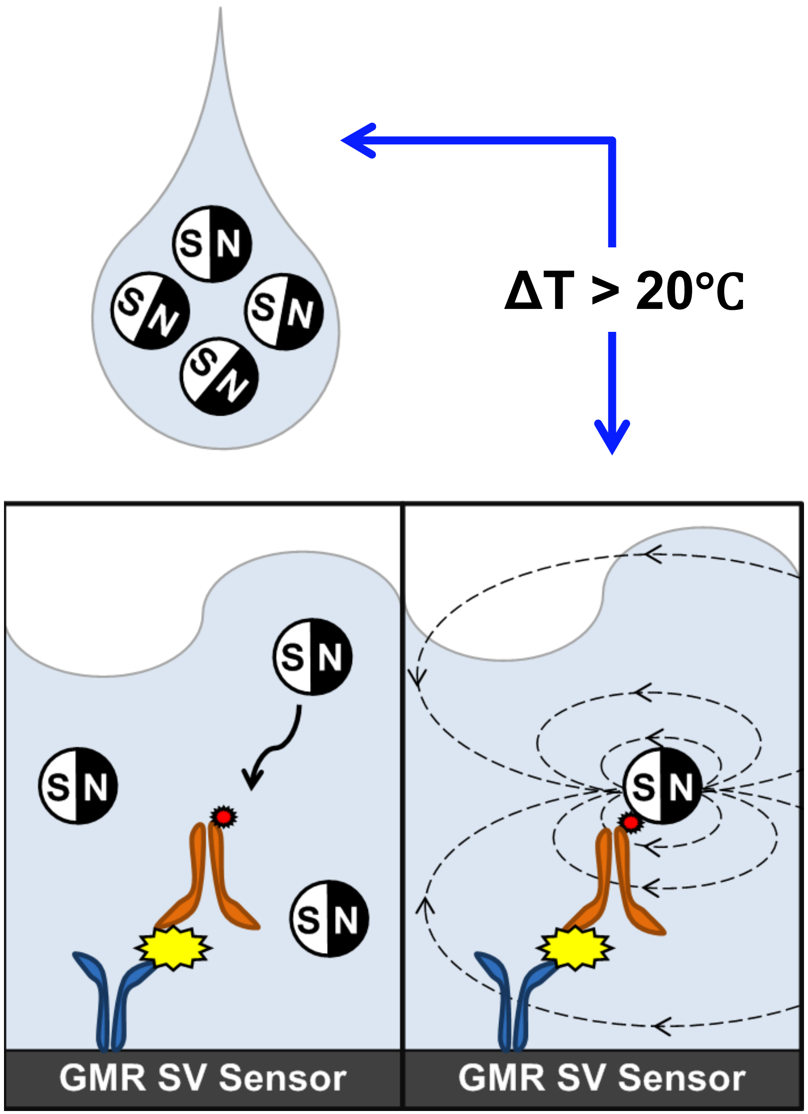
4x8x8 GMR SV Array

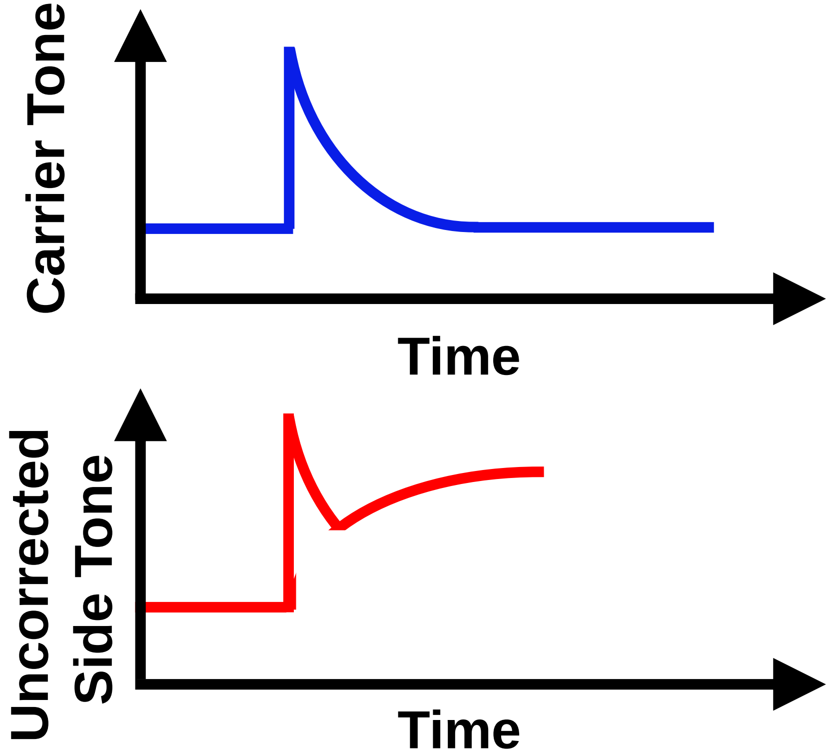


Two Tone Example



Temperature Induced Signals





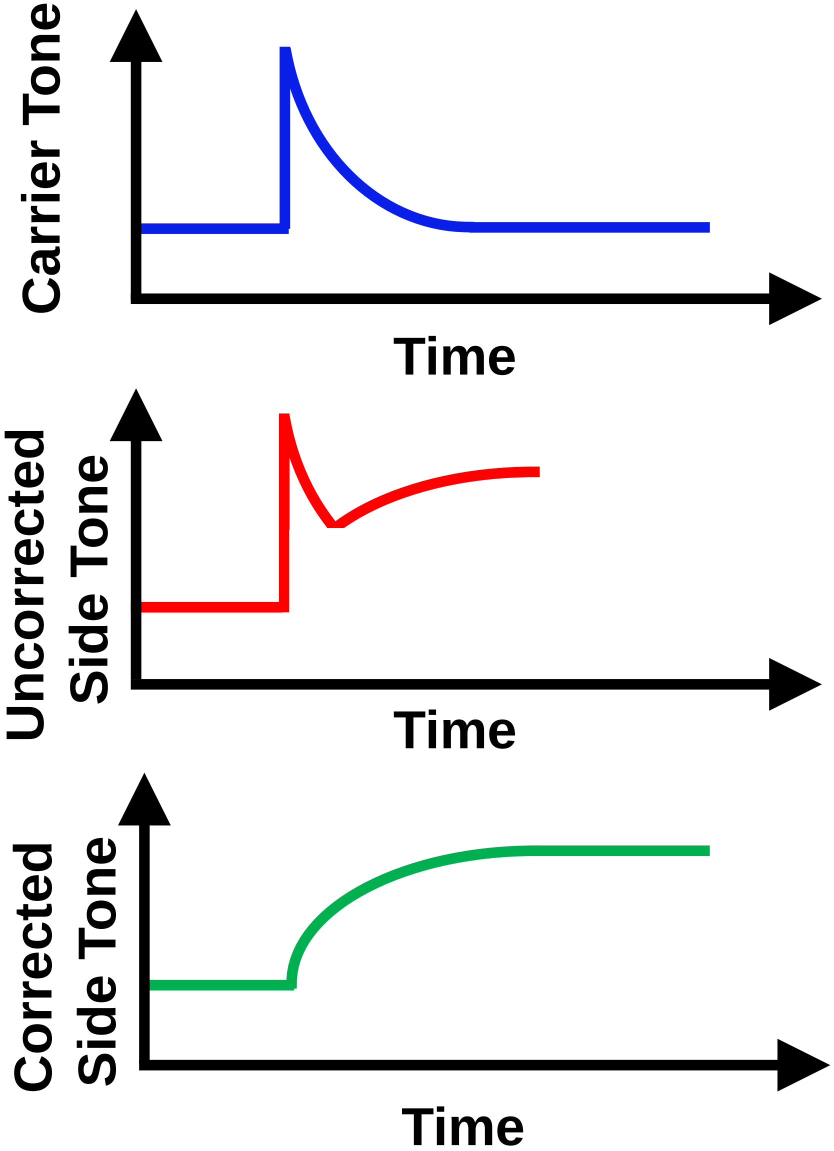
Temperature Correction

- Use the carrier tone to measure relative temperature change

- Corrected side tone

$$\Delta ST - \kappa \cdot CT$$

- κ is a predetermined ratio of the TC_{MR}/TC_R



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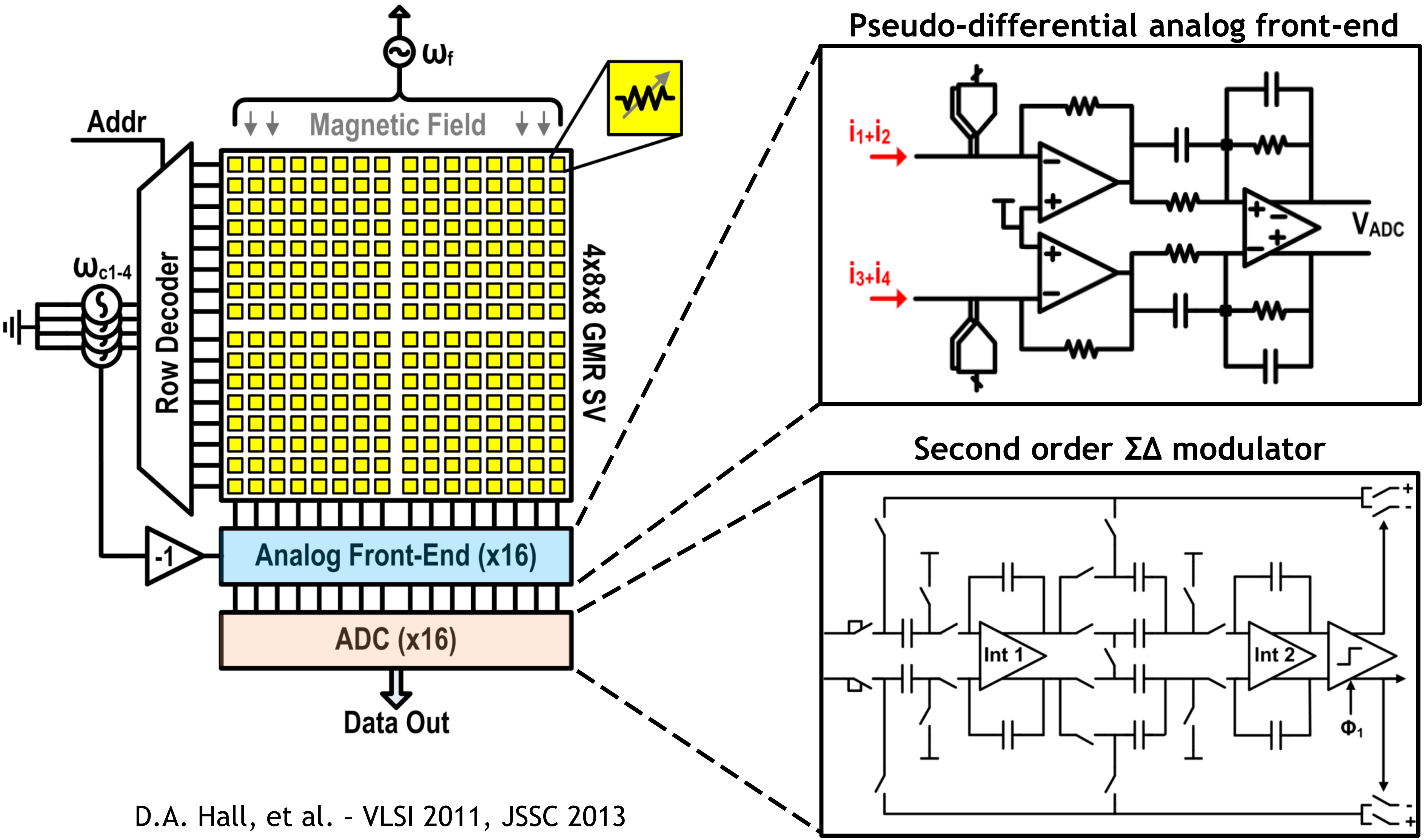
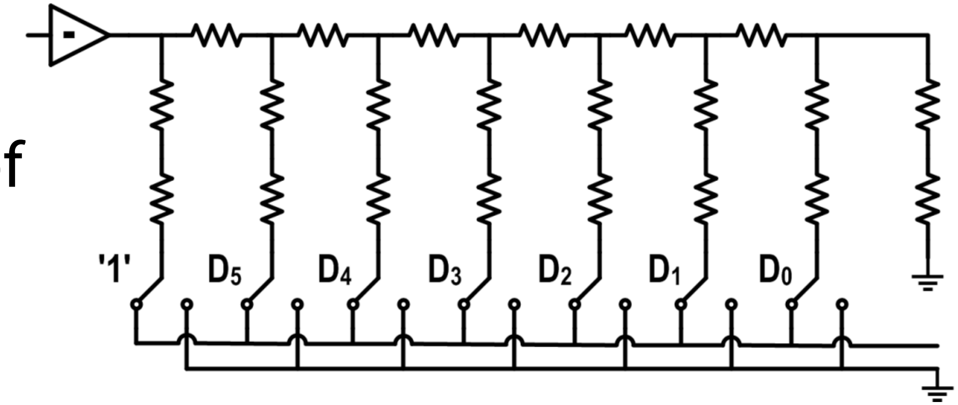
System Architecture

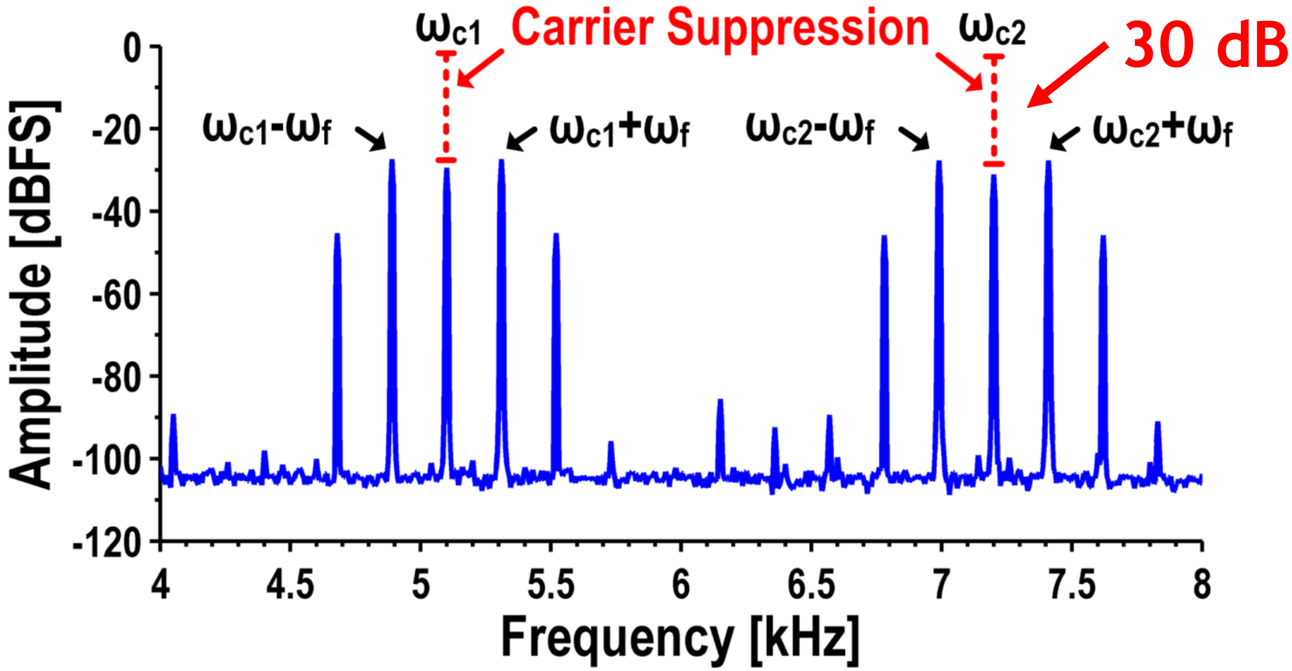


D.A. Hall, et al. – VLSI 2011, JSSC 2013

Carrier Suppression

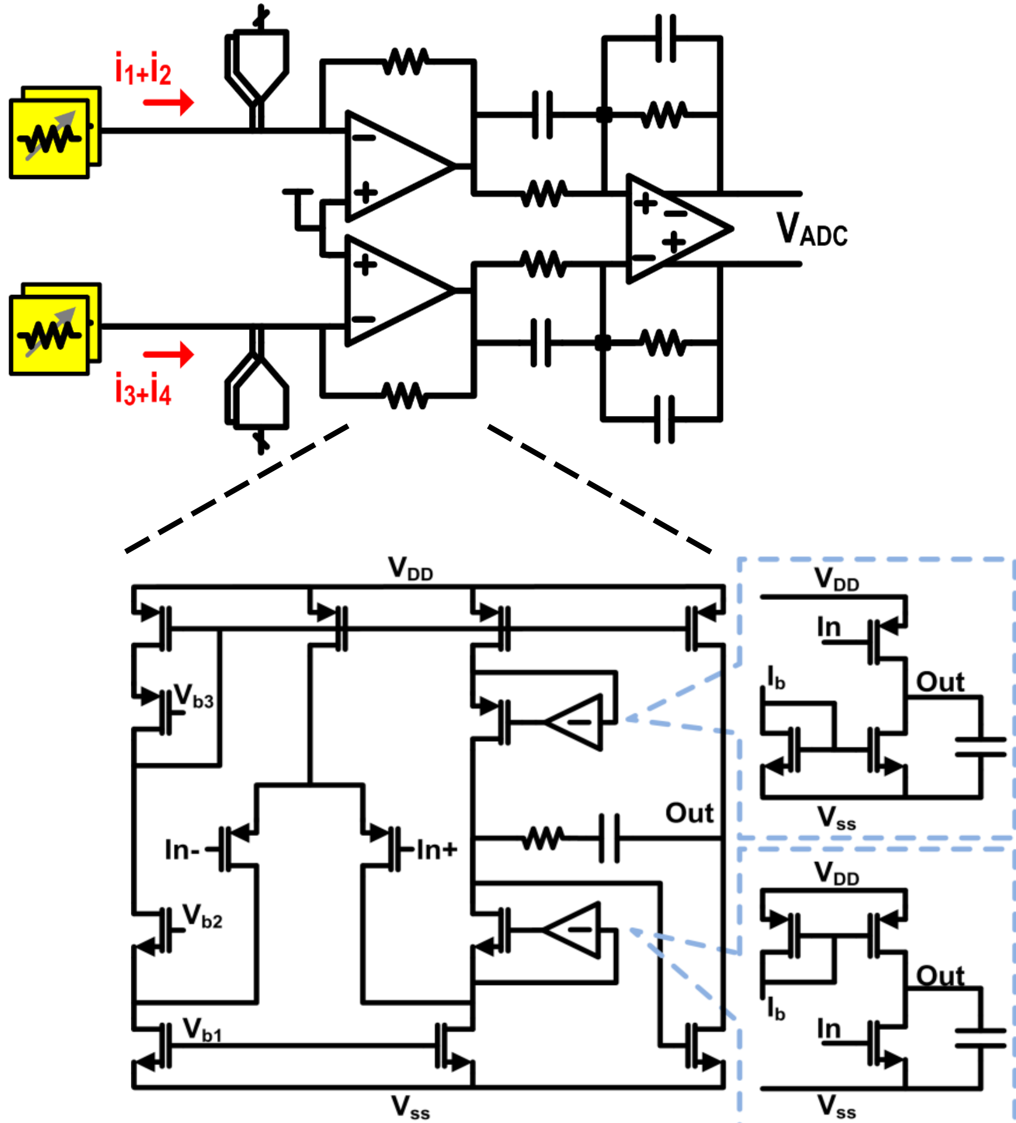
- Resistive DAC (RDAC)
  - Injects current 180° out of phase to suppress carrier
  - 6+1 bit R-2R ladder





Analog Front-End

- Sensor interface requirements
  - Single ended input
  - Fixed input potential
  - High linearity
  - Isolation from ADC kickback

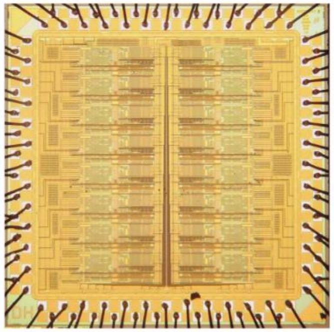


D.A. Hall, et al. – JSSC 2013

Performance Summary

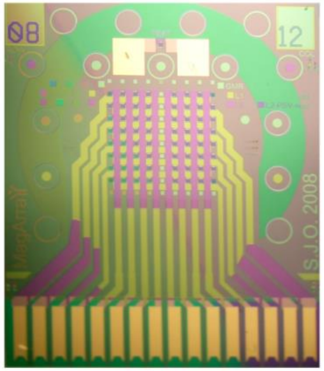
Entire Chip	Technology:	0.18 µm (2P / 6M)
	V_{ddA} / V_{dd} / V_{ddD}:	2.0 V / 2.1 V / 1.8 V
	Readout Columns:	16
	Area:	2.7 mm x 2.7 mm
	Power Consumption:	55.8 mW
Front-End	Gain:	17.5 kΩ (84.9 dBΩ)
	Input Referred Spot Noise:	120 pA/√Hz (58 nT/√Hz)
	w\ sensors:	**160 pA/√Hz (78 nT/√Hz)**
	Power Consumption:	19.8 mW (36 %)
ADC	Sampling Frequency:	10 MHz
	Oversampling Ratio:	500
	Dynamic Range:	84 dB
Sensors	# Sensors:	256
	Readout Time:	4 s
	Resistance / MR ratio:	1.5 kΩ / 11 %

Readout IC



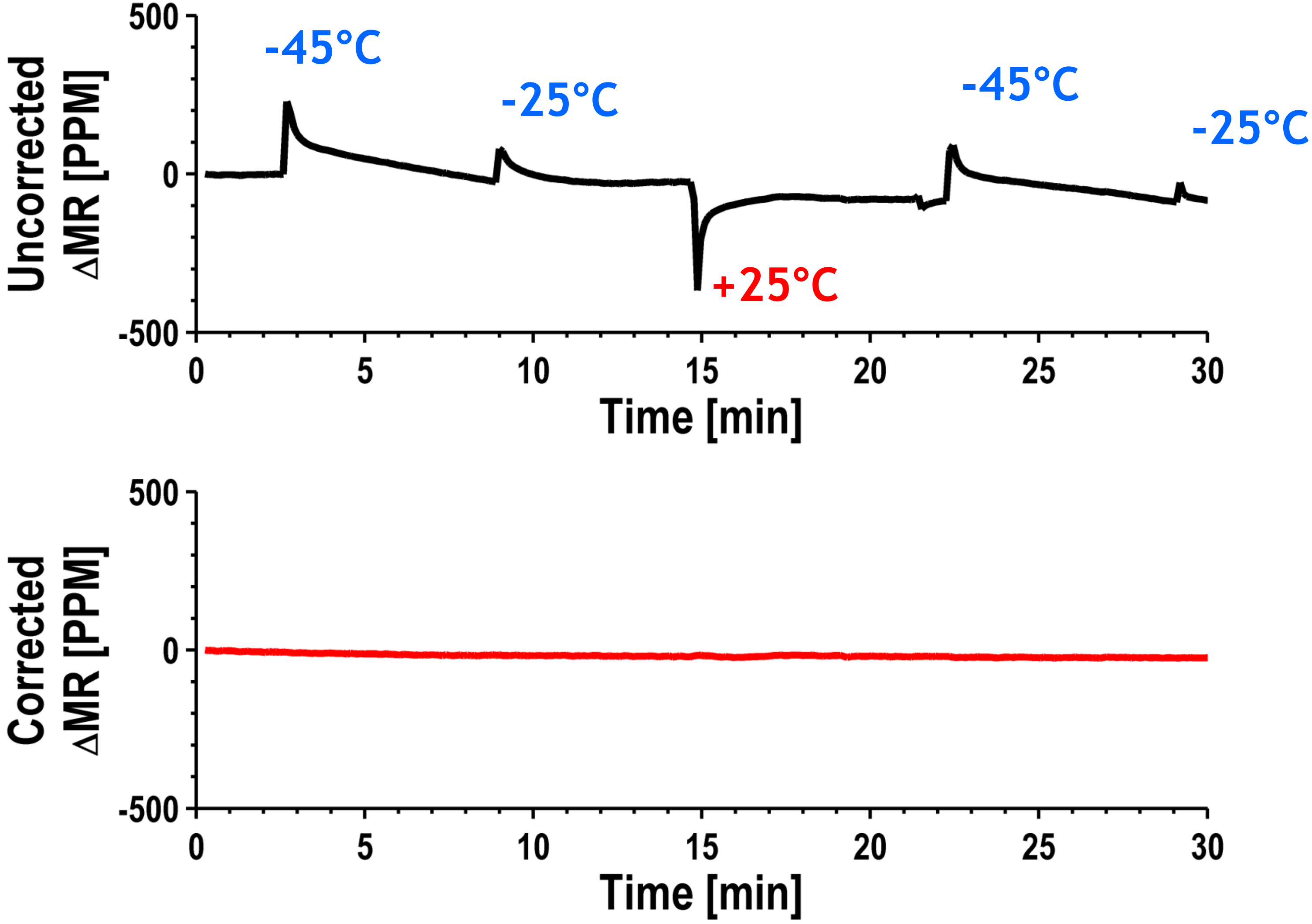
500 µm

Sensor Die

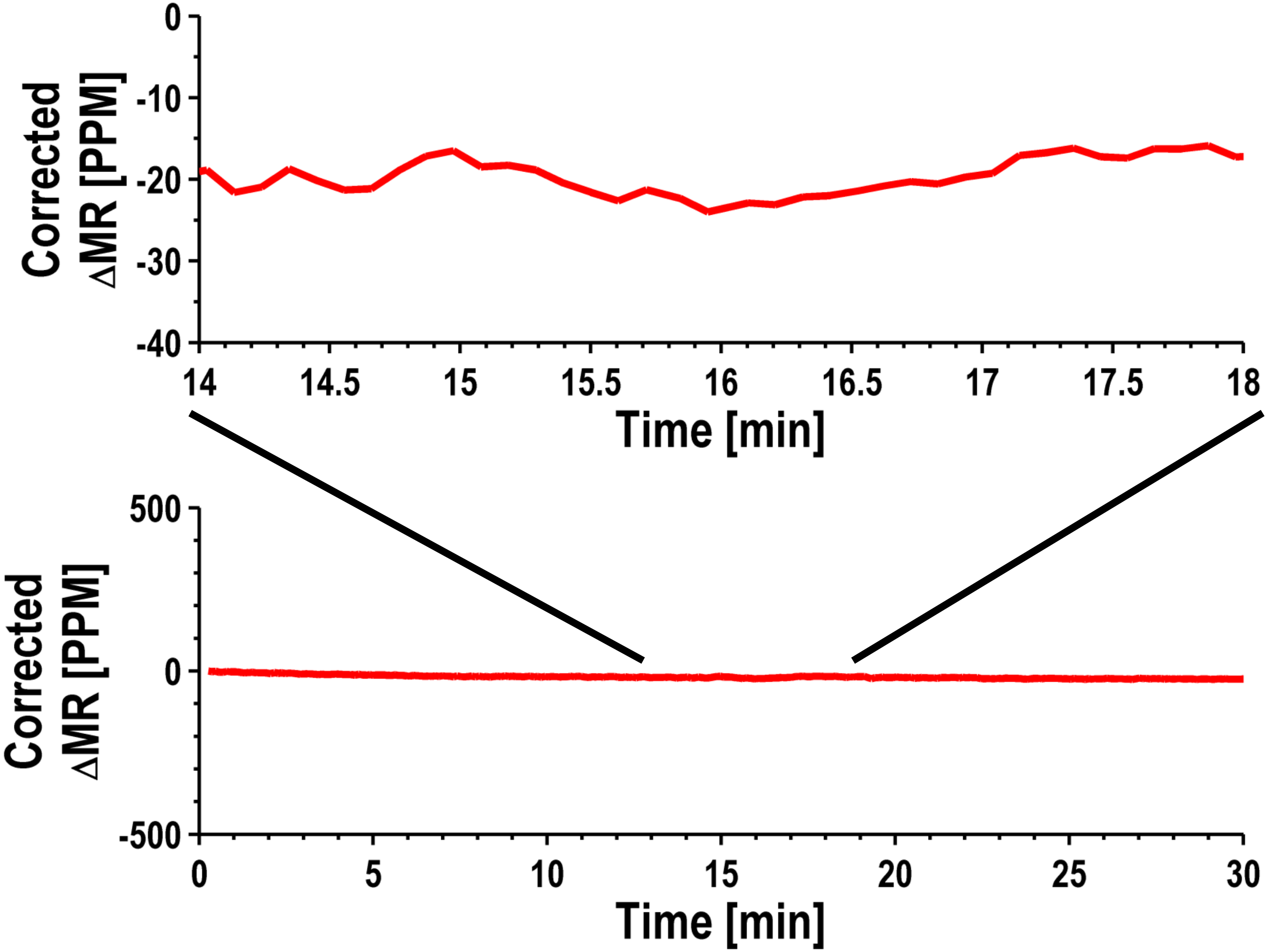


2 mm

Temperature Correction

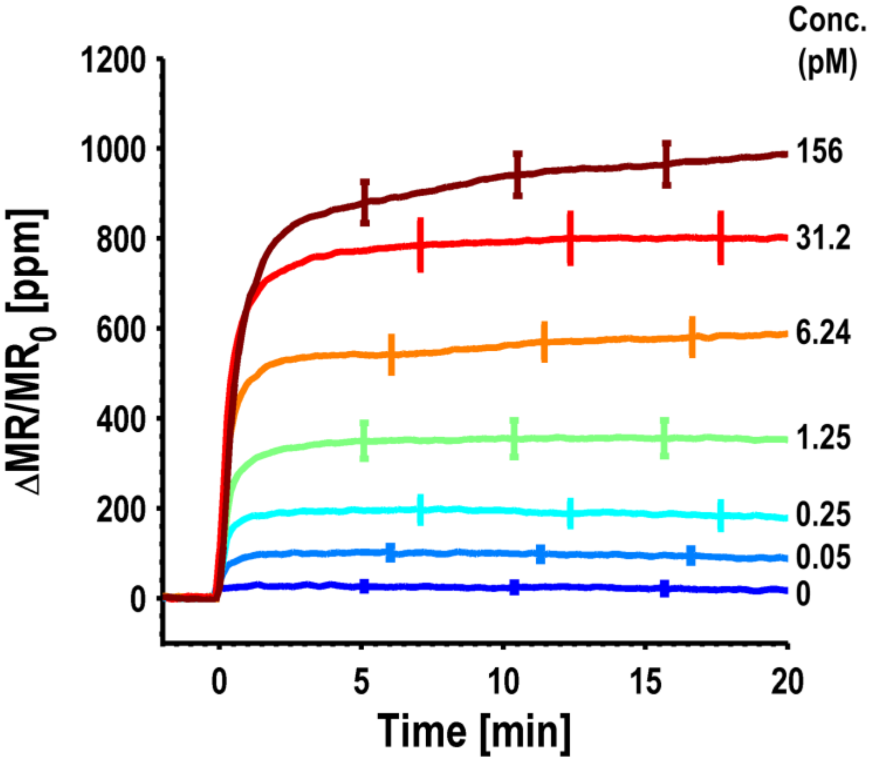


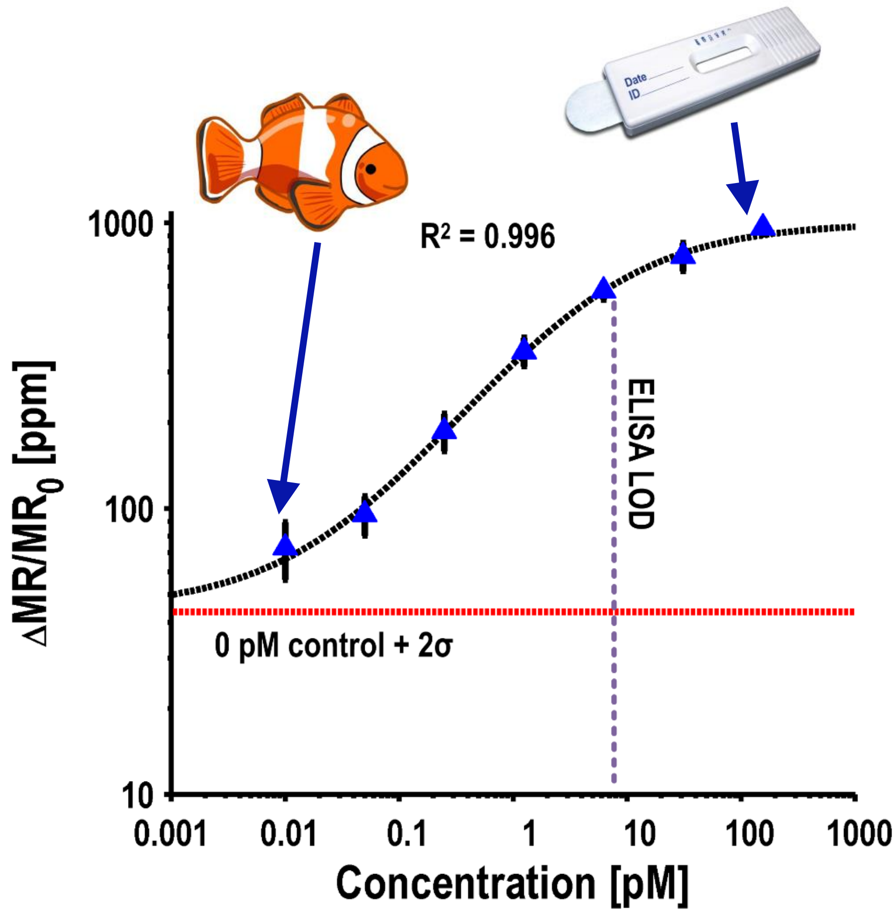
Temperature Correction



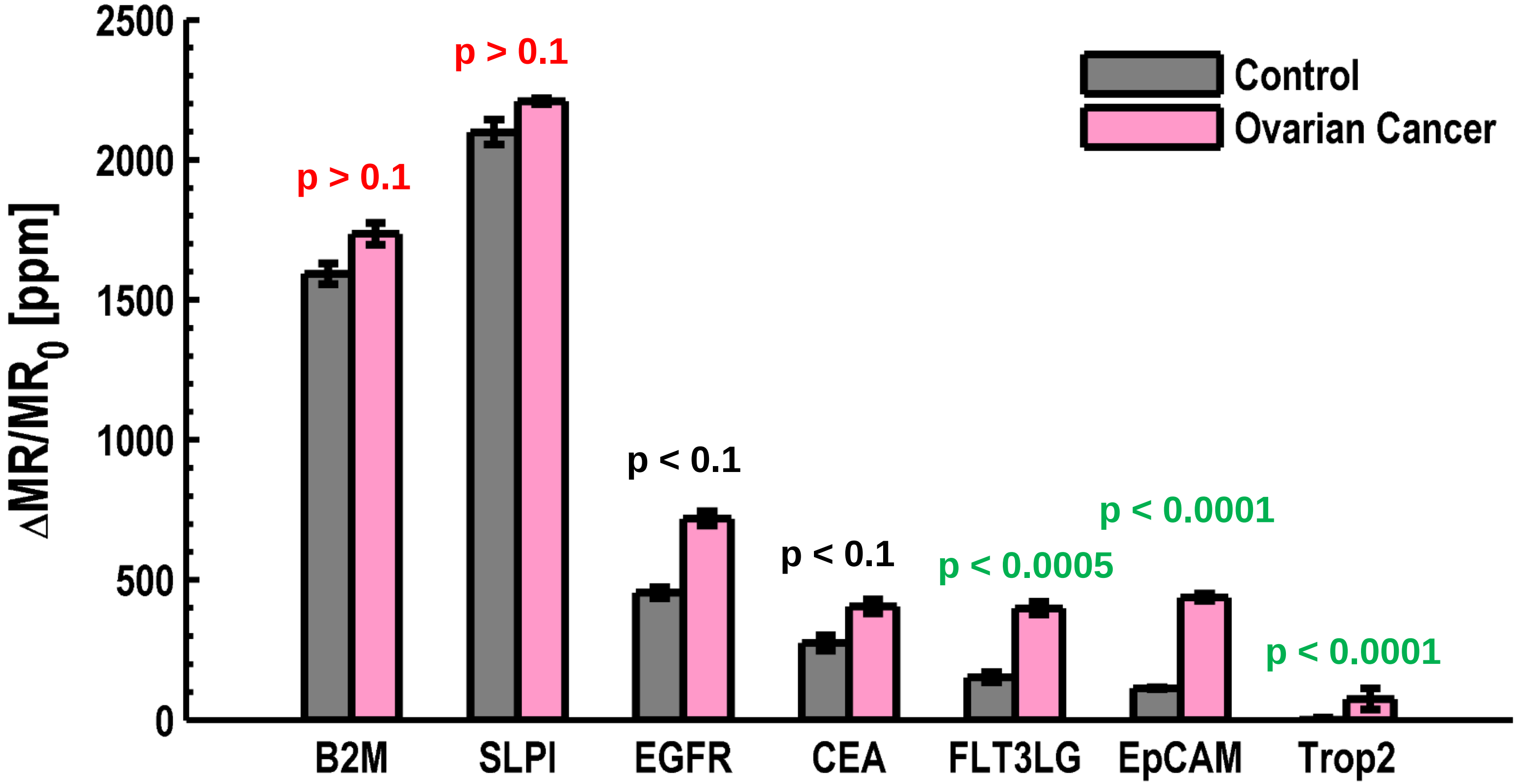
Proteomic Measurement Results

Secretory leukocyte peptidase inhibitor (SLPI)





Clinical Ovarian Cancer Data



Summary

- Demonstrated a scalable CMOS integrated biosensing platform based on GMR SV sensors and magnetic nanotags
  - Fully quantitative and highly sensitive
  - Large sensor array with multiplex detection
  - Rapid real-time readout
  - Carrier referenced temperature correction scheme

Acknowledgements

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