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
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

Giant Magnetoresistive Spin-Valves (GMR SV)

Passivation
Free Layer

<table>
<thead>
<tr>
<th>Oxide</th>
<th>[40 nm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoFe</td>
<td>[2 nm]</td>
</tr>
<tr>
<td>Cu</td>
<td>[2.3 nm]</td>
</tr>
</tbody>
</table>

Pinned Layer

<table>
<thead>
<tr>
<th>Ru</th>
<th>[0.85 nm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoFe</td>
<td>[2 nm]</td>
</tr>
<tr>
<td>PtMn</td>
<td>[15 nm]</td>
</tr>
</tbody>
</table>

Bias Point (90°)
Parallel (0°)
Antiparallel (180°)

\[
MR = \frac{R_{AP} - R_P}{R_P}
\]
The GMR SV as a Biosensor

Magnetic biochip

Sensor resistance changes from 1 → 2

Resistance

Time

1

net signal

2
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

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

S. Han, et al. ISSCC 2007
B. de Boer, et al. Biosens. and Bioelec. 2007
High Throughput Readout

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

Spectral Analysis

Spectrogram
Temperature Induced Signals

$\Delta T > 20^\circ C$

Carrier Tone

Uncorrected Side Tone

GMR SV Sensor

GMR SV Sensor
Temperature Correction

• Use the carrier tone to measure relative temperature change

• Corrected side tone

\[ \Delta ST = \kappa \cdot CT \]

• \( \kappa \) is a predetermined ratio of the \( TC_{MR}/TC_R \)
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System Architecture

Pseudo-differential analog front-end

Second order \( \Sigma \Delta \) modulator

Carrier Suppression

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

![Diagram showing carrier suppression and amplitude vs frequency]
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

<table>
<thead>
<tr>
<th>Entire Chip</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Technology:</strong></td>
<td>0.18 μm (2P / 6M)</td>
</tr>
<tr>
<td><strong>V\textsubscript{ddA} / V\textsubscript{dd} / V\textsubscript{ddD}:</strong></td>
<td>2.0 V / 2.1 V / 1.8 V</td>
</tr>
<tr>
<td><strong>Readout Columns:</strong></td>
<td>16</td>
</tr>
<tr>
<td><strong>Area:</strong></td>
<td>2.7 mm x 2.7 mm</td>
</tr>
<tr>
<td><strong>Power Consumption:</strong></td>
<td>55.8 mW</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Front-End</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gain:</strong></td>
<td>17.5 kΩ (84.9 dBΩ)</td>
</tr>
<tr>
<td><strong>Input Referred Spot Noise:</strong></td>
<td>120 pA/√Hz (58 nT/√Hz )</td>
</tr>
<tr>
<td><strong>w\textbackslash sensors:</strong></td>
<td>160 pA/√Hz (78 nT/√Hz )</td>
</tr>
<tr>
<td><strong>Power Consumption:</strong></td>
<td>19.8 mW (36 %)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>ADC</th>
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</thead>
<tbody>
<tr>
<td><strong>Sampling Frequency:</strong></td>
<td>10 MHz</td>
</tr>
<tr>
<td><strong>Oversampling Ratio:</strong></td>
<td>500</td>
</tr>
<tr>
<td><strong>Dynamic Range:</strong></td>
<td>84 dB</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sensors</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong># Sensors:</strong></td>
<td>256</td>
</tr>
<tr>
<td><strong>Readout Time:</strong></td>
<td>4 s</td>
</tr>
<tr>
<td><strong>Resistance / MR ratio:</strong></td>
<td>1.5 kΩ / 11 %</td>
</tr>
</tbody>
</table>
Temperature Correction

Uncorrected

$\Delta MR$ [PPM]

-45°C

-25°C

+25°C

-45°C

-25°C

Corrected

$\Delta MR$ [PPM]

0

0

0

0

0

Time [min]

Time [min]
Proteomic Measurement Results

Secretory leukocyte peptidase inhibitor (SLPI)

![Graph showing time vs. concentration with different concentration levels and R² = 0.996]

- ΔMR/ΔMR₀ [ppm]
- Concentration [pM]
- Time [min]
- 0 pM control + 2σ

ELISA LOD
Clinical Ovarian Cancer Data

ΔMR/MR₀ [ppm]

- B2M: p > 0.1
- SLPI: p > 0.1
- EGFR: p < 0.1
- CEA: p < 0.1
- FLT3LG: p < 0.0005
- EpCAM: p < 0.0001
- Trop2: p < 0.0001

Control
Ovarian Cancer
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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