25.6 A Frequency-Shift CMOS Magnetic Biosensor Array with Single-Bead Sensitivity and No External Magnet

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Future Point-of-Care (PoC) molecular-level diagnosis requires advanced biosensing systems that can achieve high sensitivity and portability at low power consumption levels, all within a low price-tag for a variety of applications such as in-field medical diagnostics, epidemic disease control, biohazard detection, and forensic analysis. Magnetically labeled biosensors are proposed as a promising candidate to potentially eliminate or augment the optical instruments used by conventional fluorescence-based sensors. However, magnetic biosensors developed thus far require externally generated magnetic biasing fields [1-4] and/or exotic post-fabrication processes [1,2]. This limits the ultimate form-factor of the system, total power consumption, and cost. To address these impediments, we present a low-power scalable frequency-shift magnetic particle biosensor array in bulk CMOS, which provides single-bead detection sensitivity without any (electrical or permanent) external magnets.

The core of the sensing scheme is based on high-stability integrated oscillators with on-chip LC resonators. An AC electrical current through the on-chip inductor generates a magnetic field and polarizes the magnetic particles present in its vicinity. This increases the total stored magnetic energy in the space and thereby the effective inductance of the inductor. The oscillation frequency of \( f_0 = 1/(2\pi\sqrt{LC}) \), then down-shifts due to the increase in inductance, as shown in Fig. 25.6.1. This frequency-shift sensing scheme therefore needs no external magnetic field biasing and can be completely implemented in a planar process, such as CMOS to ensure a small form-factor, low power and low cost. Moreover, the sensor scheme can be easily scaled to an array on the same CMOS chip for parallel detection. This allows testing of different analytes or biosamples by different molecular capturing probes to promote throughput.

The biosensor array contains 8 parallel sensor cells, which can be addressed independently by a digitally controlled multiplexer (Fig. 25.6.2). Each biosensor cell is composed of a pair of differential sensor oscillators, one as the active sensor and the other as the reference, sharing the same supply, bias and local on-chip temperature controller. The frequency shift due to a single micron-size magnetic bead is typically a few parts per million (ppm) of the resonant frequency. To facilitate accurate detection of such a small frequency shift, a 2-step downconversion architecture is used to shift the frequency center tone of 1GHz to below 10kHz. Unlike direct downconversion, this architecture guarantees that neither of the LO signals are close to the sensor free-running frequency and hence prevents oscillator pulling or injection locking. By using a baseband 15b frequency counter, a frequency counting resolution of better than 0.3Hz (3×10^4ppm) is achieved.

In terms of the sensor cell design, the key challenge is to achieve stable long-term frequency behavior, i.e., low phase noise at small offset frequencies (below kHz), to guarantee a sub-ppm frequency resolution. This phase noise behavior is generally dictated by the active device flicker noise, on-chip temperature variations, and the supply/biasing noise, which are addressed by 3 design techniques as follows.

In this design, complementary cross-coupled pairs are used as the oscillator core. To suppress the flicker noise upconversion from the tail current source, the NMOS and PMOS pairs are scaled and implemented with a symmetrical layout. This improves the intrinsic oscillator frequency stability and the robustness against process gradient. Consuming 4mA from a 1.2V supply, the oscillator achieves a phase noise of -135dBc/Hz and -58dBc/Hz at the offset frequencies of 1MHz and 1kHz, respectively.

To stabilize the long-term frequency behavior against ambient temperature change, an on-chip temperature controller is implemented using a PTAT voltage generator as the temperature sensor, a power PMOS array as the heater/actuator, and a bandgap voltage as a temperature-independent reference (Fig. 25.6.3). The bandgap core is placed in close proximity of the oscillator active devices for accurate temperature sensing, while the power PMOS array surrounds the oscillator cores to minimize the spatial temperature difference within the controller. This setup forms an overall 1st-order electrical-thermal feedback loop which has a typical DC gain of 20.5dB and is compensated by a dominant pole in the kHz range to guarantee stability.

To further suppress any low-frequency perturbations, such as supply noise, substrate interference and residual thermal variation, a differential sensing scheme is implemented. Each differential sensor pair contains a sensing and a reference oscillator, sharing the same supply/bias and on-chip temperature regulator. By alternating between the oscillators within a short time window (e.g., 100ms or less) and measuring their oscillation frequency, the common-mode frequency drift can be subtracted to achieve a differential frequency standard deviation of less than 0.13ppm. Moreover, alternating the oscillators also eliminates the possibility of mutual injection locking of these two oscillators that operate at very close frequencies.

The sensor is tested with magnetic beads of diameter 4.5µm, 2.4µm, and 1µm. Typical sensor responses are plotted in Fig. 25.6.4. As can be seen, a single magnetic bead (D=2.4µm) results in a frequency shift of 2.6ppm, which can be readily detected. In a separate experiment, a single carbonxylic magnetic bead (D=1µm) results in a frequency shift of 0.25ppm, still detectable by the system. A long measurement of 90s is performed to verify the repeatability and stability of this result. This sensor achieves a better sensitivity compared with previously published schemes [1,4], which also require external magnetic-field biasing and/or complex post-fabrication processes. As the control experiment, we also test non-magnetic beads made only of polystyrene that is used for structuring magnetic beads. The measurement verifies that the sensor frequency shift is mainly due to the inductance increase as opposed to the capacitance change by the presence of magnetic beads. The measured sensor sensitivity results are summarized in Fig. 25.6.6.

To form a complete handheld magnetic-particle-sensing system, a low-cost polydimethylsiloxane (PDMS) microfluidic structure is fabricated and bonded to the CMOS sensor chip, as shown in Fig. 25.6.7. The microfluidic structure supports eight pairs of independent differential-sensing chambers with individual volume of less than 0.2nL. The achievable microfluidic channel width/separation of the PDMS fabrication facilities limits the minimum spacing of adjacent inductors to 250µm, which can be substantially reduced by a more advanced microfluidics process.

To verify the actual biomolecular sensing functionality, an experiment on physical DNA samples is performed. Neutravidin molecules first immobilize the biotin-labeled DNA probes to the biotin modified PDMS bottom surface [5], while \( \beta-\text{D}-\text{dodecyl-N}-\text{maltoside} \) (DM) molecules are used to prevent nonspecific binding between neutravidin and PDMS surface. At the presence of the digoxigenin (dig) modified target complementary DNA strands, the antigold-labeled magnetic nanoparticles (D=50nm) are captured onto the sensor surface by the dig-antidig link. For 1nM DNA samples (1k base pairs in length), the sensor reliably registers a 2.8ppm frequency-shift, as illustrated in Fig. 25.6.5. A control experiment using fluorescent imaging of DyLight 488-labeled magnetic nano-particles with and without complementary DNA is used to verify the actual binding of the magnetic nanoparticles to the strand demonstrating the viability of this approach.

The sensor array system consumes a total power of 165mW and occupies 2.95×2.56mm^2 in a 0.13µm CMOS process.

Acknowledgments:
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Reference:
**Figure 25.6.1**: Frequency-shift magnetic sensor sensing mechanism.

**Figure 25.6.2**: Sensor system block diagram.

**Figure 25.6.3**: On-chip temperature regulator schematic.

**Figure 25.6.4**: Typical sensor response to a single magnetic bead.

**Figure 25.6.5**: Sensor response to 1n molar DNA sample labeled by magnetic nanoparticles (D=50nm).

**Figure 25.6.6**: Sensitivity summary on magnetic bead sensing.

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### Sensor Performance on Magnetic Bead Sensing

<table>
<thead>
<tr>
<th>Bead Type</th>
<th>Bead Size (Diameter)</th>
<th>Averaged ΔDiff per Beads</th>
<th>Sensitivity (# of Beads)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnetic Bead (Type 1)</td>
<td>4.5μm</td>
<td>9.6ppm</td>
<td>1</td>
</tr>
<tr>
<td>Magnetic Bead (Type 2)</td>
<td>2.4μm</td>
<td>2.6ppm</td>
<td>1</td>
</tr>
<tr>
<td>Magnetic Bead (Type 3)</td>
<td>1μm</td>
<td>0.23ppm</td>
<td>1</td>
</tr>
<tr>
<td>Polystyrene Bead (Non-Magnetic)</td>
<td>1μm</td>
<td>0.0035ppm</td>
<td>80</td>
</tr>
</tbody>
</table>
Figure 25.6.7: Die micrograph for CMOS frequency-shift-based magnetic sensor array with integrated microfluidic structures. The zoom-in view of one differential sensing pair is provided on the right.