6.9 A CMOS 10kpixel Baseline-Free Magnetic Bead Detector with Column-Parallel Readout for Miniaturized Immunoassays

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The specific detection of anti-bodies or proteins in a point-of-care setting remains an unsolved technological challenge. While laboratory instruments rely on enzymatic labels and require complex, difficult-to-miniaturize optics, devices using super-paramagnetic labels have emerged as an attractive alternative for point-of-care systems [1]. The key challenge for all magnetic-bead detection systems [2-5] is the presence of a large measurement “baseline.” Since beads are paramagnetic, a polarization field must be applied in order to excite a magnetic response. This response is ~1000 times smaller than the polarization field, necessitating a combination of calibration, reference sensors [2], and temperature stabilization [5] to reject the polarization field. In addition to a low and stable baseline, a practical system should have low measurement time and large sensing area to reduce biological variations [6].

We demonstrate a detector that exploits label properties and circuit design to meet all the above constraints. The measurement baseline is reduced using the dynamics of magnetization in micro-beads (Neel relaxation) [4]. Since the bead signal decays with finite rate, it can be measured after the polarization field has been turned off, obtaining an ideally baseline-free measurement. In practice, residual polarization fields limit the reduction in baseline to 300× compared to conventional amplitude detection [2]. A sensing area of 0.64mm² reduces biological shot noise [6] below the statistical requirements of immuno-assays, while column-parallel readout ensures fast acquisition. The chosen CMOS-compatible Hall-effect platform allows integration of the whole system, comprising sensing elements, evaluation electronics, and magnetic polarization field generation on a single die enabling low cost and form factor when compared to GMR-based solutions.

Figure 6.9.1 shows a block diagram of the microsystem, which comprises 10,240 Hall-Effect sensors, subdivided into two main sub-arrays. Each sub-array is further organized into a left and a right bank consisting of 64 rows and 40 columns of sensors as well as wires for polarization field generation and address lines. A post-CMOS RIE etch is used to thin down the metal stack in the sensing area, improving sensitivity. After the etch, the Hall sensor is 3µm beneath the chip surface, and 1.2µm below the polarization wires. The sensors consist of 3µm-wide and 4µm-tall N-well diffusions and have a measured sensitivity of 50mV/T while drawing 1.1mA from a 2V supply. To reduce sensing time, rows are measured in parallel with 160 separate readout channels providing amplification and digitization. Figure 6.9.2 shows the architecture and timing diagram of a readout channel, consisting of a transconductance pre-amplifier (Gm) followed by a current-mode, 1st-order, continuous-time incremental ADC. The polarization wire carries a 1MHz 4-phase, 2mA bipolar excitation current, producing a positive and negative out-of-plane polarization field B⊥ during phases Φ1 and Φ2. During phase Φ4, the pre-amplifier is auto-zeroed by storing the amplifier and sensor offset, kT/C noise and charge-injection errors on Coffset. The Hall voltage is measured and amplified during phases Φ1' and Φ3'. The commutating switches invert the polarity of the signal during phase Φ4 and together with the inverted polarization field B⊥ eliminate low-frequency interference from the earth magnetic field and power line, as well as the errors stored in Φ4. The subtraction of the two samples in phases Φ2' and Φ3' occurs in the loop filter of the ADC after integration, lowering the sampling noise due to inherent 1st-order noise-shaping [7]. A counter decimates the ADC output to 1kHz, greatly reducing the off-chip communication bandwidth. To suppress low-frequency noise from the incremental ADC, the polarity of the polarization field in Φ4 and Φ2 is inverted after every decimated ADC sample is produced (Fig. 6.9.2) implementing a nested chopper with digital demodulation. To minimize the residual offset, the nested chopper switching occurs during a guard period while the ADC is being reset. Since the ADC processes its own offset, a full-scale much larger than the bead peak signal is employed to ensure accurate offset suppression in the digital domain.

The chip is fabricated in 2P6M 0.18µm CMOS (Fig. 6.9.7). The readout of the entire array takes 0.2 seconds and consumes 2.5J. Current consumption is 150mA from a 2V supply, dominated by the sensor bias (86mA), magnetic polarization field (32mA), and readout electronics (32mA). Readout electronics are pitch-matched to two columns and distributed along both the north and the south peripheries of the array. Each chain occupies 16×350µm² for the analog parts and another 16×400µm² for the on-chip decimation filters and serializers. Each sensor sub-tank occupies 320×500µm², for a total sensing area of 0.64mm². Figure 6.9.3 (top) shows the measured response of the chip to applied magnetic fields at the polarization frequency, corresponding to 410LSB/mT sensitivity. The measured baseline (bottom), remains below 5µT, limited by small residual polarization fields in Φ2 and Φ4. By comparison, amplitude measurement has an intrinsic offset greater than 2.5mT, larger than the readout electronics full scale. Since the average relaxation signal from a 4.5µm bead is approximately 5µT, the use of relaxation increases the signal-to-baseline ratio to >1 for 4.5µm beads compared to 0.03 in [2] and 10⁻⁵ in [5], greatly reducing sensitivity to drifts. The ultimate magnetic detection limit of the chip is set by long-term drift. Figure 6.9.4 shows the measured Allan Deviation both for amplitude and relaxation measurements. The relaxation technique reduces the random drift by 13× from 120 to 9nT. The measured system input-referred noise is 260nT/rt(Hz) and remains flat down to frequencies below 1mHz. This floor is low enough to detect a single 350nm diameter particle with unit volume susceptibility. In Fig. 6.9.5, the chip response to dried 2.8µm beads is shown as a function of optical bead count. The chip response is obtained by adding together the digitized outputs from all sensor elements. With an averaging time of 128ms/row, corresponding to an 8.2 second readout for the entire chip, the concentrations of 2.8µm M280 particles can be determined with an uncertainty (1σ) of 25 particles/sub array, or equivalently a 0.1% coverage of the sensing area. According to [8], this translates to an uncertainty in analyte concentration lower than 0.1ng/ml. The uncertainty increases to 200 particles/sub-array for 1µm particles. Employing longer measurement time, or in-pixel thresholding prior to summing can further reduce the error. Figure 6.9.6 compares this work to previous publications (bottom) and reports the results of an on-chip direct assay for human serum albumin (HSA). After the bondwires were encapsulated with epoxy, surface function-alization with different tiritations of HSA and incubation were performed. 5µL of fluid with anti-HSA magnetic beads was then placed directly in the package cavity. Washing of non-specifically bound beads was done with a permanent magnet. The current assay implementation successfully detects the target at 100ng/ml and is limited by the washing step.

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References:
Figure 6.9.1: Magnetic detector chip architecture.

Figure 6.9.2: Readout channel schematic and timing.

Figure 6.9.3: Chip transduction gain (top) and offset distribution averaged across rows (bottom).

Figure 6.9.4: Allan Deviation for relaxation measurement and amplitude detection measurement for a complete readout channel.

Figure 6.9.5: Measured chip response versus number of 2.8µm M280 Dynal Beads in the sensing area.

Figure 6.9.6: Results of direct HSA immunoassay performed on chip and summary table.
Figure 6.9.7: Annotated die photo.