A 256 Channel Magnetoresistive Biosensor Microarray for Quantitative Proteomics

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Abstract

This work presents a high sensitivity biosensing platform for quantitative proteomics. Biomolecules labeled with magnetic nanoparticle (MNP) tags are quantitatively sensed by a high density array of 256 giant magnetoresistive spin-valve (GMR SV) sensors connected to a 0.18 μm CMOS sensor interface featuring 16 ΣΔ modulators with 84 dB dynamic range. The performance of the system is demonstrated through detection of a spiked tumor biomarker, epithelial cell adhesion molecule (EpCAM), at concentrations below 10 picomolar (pM).

Introduction

Microarrays are a vital tool to analyze large scale gene and protein expression changes in a single biological sample. To date, most microarrays have utilized optical labels and are only semi-quantitative (log-fold changes) in their readout. In contrast, we have realized a quantitative platform utilizing a magnetic immunoassay coupled with an array of 256 magnetic biosensors and an integrated data acquisition system. This platform boasts both high sensitivity and a large, high density sensor array enabling truly quantitative proteomic analysis.

The magnetic immunoassay is implemented as follows: a capture antibody, specific to a particular analyte (biomarker), is immobilized on the surface of the sensor. Upon introduction of a sample, which contains many different analytes, each capture antibody selectively binds to a targeted analyte. Subsequently, a matching detection antibody is added to the assay that also binds to the analyte. Magnetic nanoparticle (MNP) tags complete the magnetic immunoassay as shown in Fig. 1. The MNP tags are 50 nm in diameter and composed of several 10 nm superparamagnetic iron oxide cores embedded in dextran. The tethered MNP tags are detected by the underlying giant magnetoresistive spin-valve (GMR SV) sensors. Multiplex analyte detection is accomplished by immobilizing a different capture antibody on each of the individually addressable sensors.

GMR SV sensors exhibit giant magnetoresistance — a quantum mechanical effect wherein a change in magnetic flux is transduced into a change in electrical resistance through spin dependent scattering. Each MNP induces only a small resistance change, approximately 5 μΩ in a 2.5 kΩ sensor [1] due to their small size. To detect such minute resistance changes in the presence of the sensor's $1/f$ noise (with a typical 10 kHz noise corner), a modulation scheme is utilized where a time varying magnetic field (ω_f) and a time varying excitation voltage (ω_{c1-4}) are applied to the sensor [2]. This scheme spectrally separates the resistive and magnetoresistive components of the sensor (Fig. 2), modulating the signal induced by the MNP tags away from the high $1/f$ noise region of the sensor. The sensor array is composed of 4 sub-arrays in an 8x8 matrix for a total of 256 individually addressable sensors. Typically with such a large array, time-domain multiplexing is used to sequentially scan each sensor. To reduce the readout time, we also utilize frequency-domain multiplexing which is accomplished by simultaneously exciting multiple sensors in the array with different carrier frequencies and summing the resulting currents. For this current summing to work properly, the input of the sensor interface must be held at a fixed input potential. The signal from each sensor is then isolated after digitization though spectral analysis. Previous work has shown it is possible to integrate the GMR SV sensors and the sensor interface (without an ADC) on the same die [2]; however, the resulting sensors suffered in performance due to complications from the additional fabrication steps, negating many of
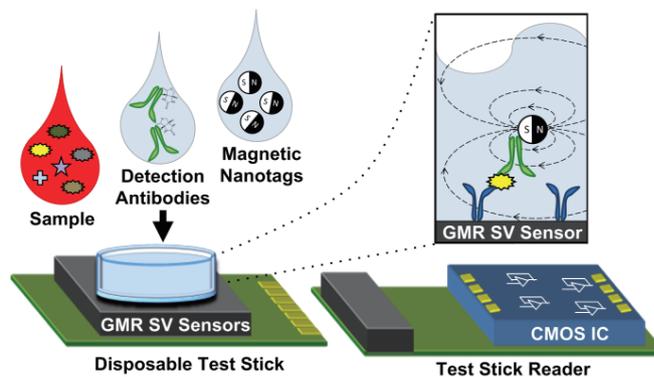

Fig. 1 Magnetic immunoassay on a GMR SV biosensor miroarray.

the benefits of integration. In this work, the sensors are off-chip in a one-time use test stick, thus simplifying its fabrication. However, this introduces an interfacing challenge due to the large interconnect capacitance which is addressed through circuit design.

Circuit Description

The interface and acquisition IC is arranged in a channelized format where each channel reads out 16 sensors. The block diagram for each of the 16 identical channels is shown in Fig. 3a and consists of two pseudo-differential transimpedance amplifiers (TIA) followed by a fully differential ADC driver and a ΣΔ modulator. The input architecture is highly constrained by the requirement to have a fixed input voltage. In the frequency band of interest (1 kHz to 10 kHz), a fully differential amplifier with a common mode input control [3] would add too much $1/f$ noise or alternatively require too much area to be an effective solution. Thus we opted for a pseudo-differential input stage to provide the virtual ground for the sensor. Each TIA is realized by a two-stage folded-cascode amplifier with gain boosting and resistive feedback (Fig. 3b). High loop gain is necessary to prevent the different sensor frequency components from mixing.

Since the magnetoresistance of the sensor is typically ≤10%, the current from the sensor is dominated by the sensor excitation signal. To attack this issue, we have employed a carrier suppression technique. A DAC at the input of the TIA injects a signal to suppress the excitation signal (ω_{c1-4}) by ~30 dB, thereby reducing the dynamic range requirement of the front-end. Each channel has 4 DACs corresponding to the 4 excitation signals and is implemented with a 6-bit R-2R ladder where the input excitation to the sensor is inverted and drives the DAC directly. The input code is adjusted to mimic the sensor resistance and injects a current that is 180° out of phase to the excitation signal. The DAC resolution is determined by the process spread (±20%) in the GMR SV sensor array.
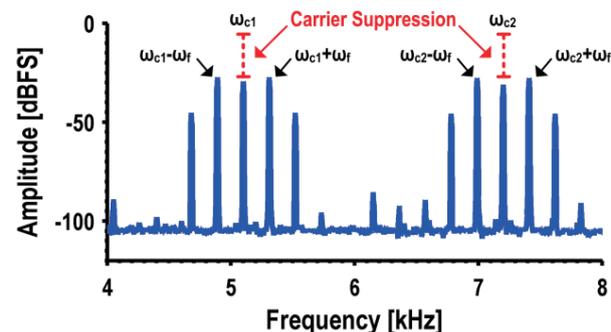

Fig. 2 Measured spectrum depicting modulation scheme with carrier suppression. Note that only two of the four carriers are shown for clarity.
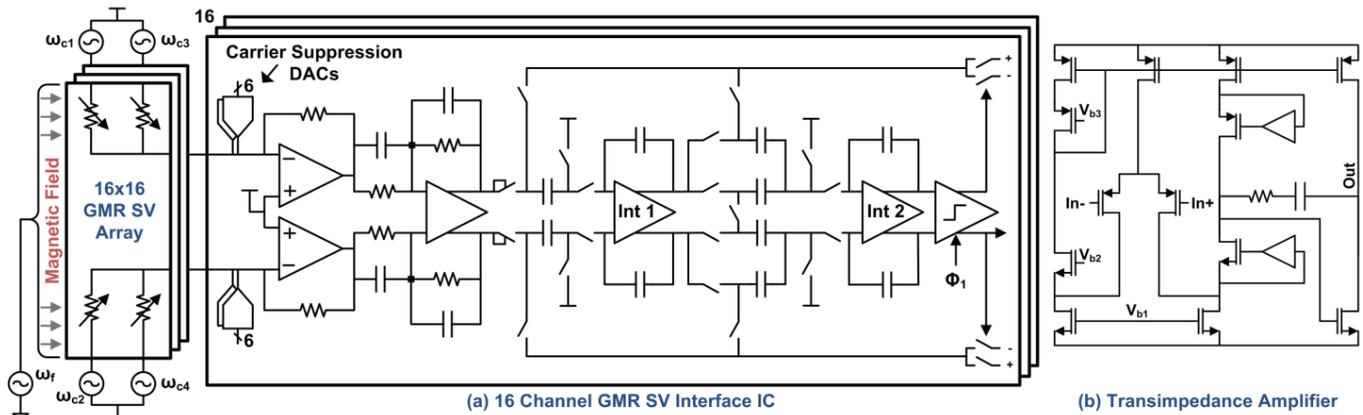
Fig. 3 a) Block diagram of one of the 16 identical signal paths. b) Schematic of the gain boosted transimpedance amplifier (biasing not shown).

The TIAs are followed by a two-stage amplifier which drives the ADC. Driving the ADC with the TIA itself would have been very power inefficient due to the large interconnect capacitance at the input (>10 pF). This architecture allows the TIA to have a low gain bandwidth (1 MHz) while the ADC driver is significantly faster (40 MHz) to allow for complete settling of the ADC sampling capacitors. The ADC is implemented with a switched capacitor, 2nd order, single bit, highly oversampled (OSR = 500) $\Sigma\Delta$ modulator running at 10 MHz and has a measured dynamic range (DR) of 84 dB. The size of each channel is 875 μm x 250 μm for a total die size of 2.7 mm x 2.7 mm with pads (Fig. 4). The interface and acquisition IC consumes a total of 55 mW with all channels operating.

Due to the large number of parallel signal paths, power was traded for area savings where possible. This was specifically addressed in the modulator using the following techniques. First, by using a high oversampling ratio, the sizes of the capacitors were scaled down proportionally. Second, the integrators were implemented with two-stage miller compensated amplifiers which allow for high output swing thereby further reducing the size of the capacitors. The architecture of the modulator was designed such that the sampling capacitors in the second stage are shared. Lastly, high density metal 1 to 5 comb capacitors were used to implement all capacitors. The size of the resulting modulator is only 250 μm x 215 μm (0.054 mm^2) and is one of the most compact implementations of a modulator with a data output rate >1 kHz and a DR >70 dB reported in the literature.

Measurement Results

To evaluate this system in a real biological testing environment, we measured spiked samples with epithelial cell adhesion molecule (EpCAM), a common tumor biomarker upregulated by almost all human carcinomas. Bovine serum albumin (BSA) coated sensors were used as a negative control to monitor non-specific binding. Fig. 5 shows both a real-time binding curve and a calibration curve for EpCAM, demonstrating detection above background down to 6 picomolar (pM) with a broad linear dynamic range. This system (6 pM protein, 256 sensors) compares very favorably to recently published integrated biosensor systems: S. Han et al. (10 nM DNA, 16 sensors) [2], Y. Liu et al. (4 nM protein, 8 sensors) [4], H. Wang et al. (1 nM DNA, 8 sensors) [5] and Y. Yazawa (50 pM DNA, 1 sensor) [6].

Conclusion

This work presents a novel sensor interface and acquisition system for a large array of giant magnetoresistive spin-valve biosensors with a focus on an area efficient design. Furthermore, we demonstrate state of the art biological protein detection with a limit of detection of 6 pM and a broad linear dynamic range (6 pM up to 2 nM). These characteristics make this platform very compelling and will enable large, quantitative proteomic studies to be performed in the future.

References

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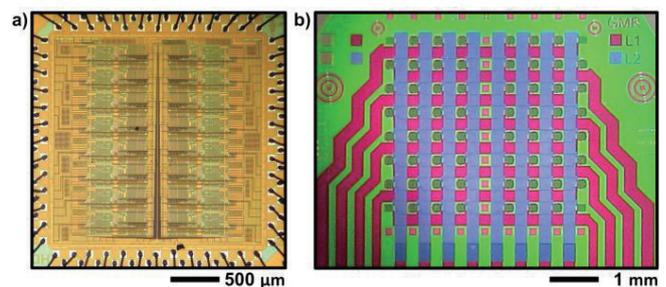[6] Y. Yazawa et al., "A wireless biosensing chip for DNA detection," *ISSCC,* 2005.

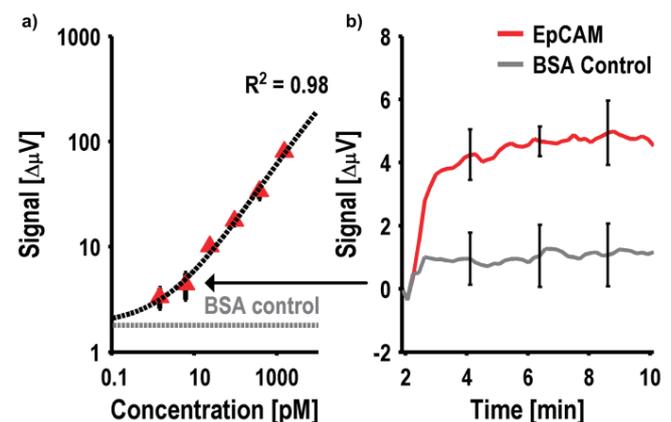Fig. 4 Die photos of (a) CMOS interface and acquisition IC and (b) GMR SV biosensor sub-array.

Fig. 5 a) Calibration curve for the EpCAM biomarker (n ≥ 8, error bars represent ±1σ). b) Real-time binding curve for 6 pM concentration.