Design of a cantilever-based system for genomic applications
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Abstract

In this work we present the development of a system intended for DNA label free detection, based on piezoresistive microcantilever arrays and dedicated readout ASIC. Detector design and microfabrication technologies have been optimised for detection sensitivity, providing an efficient direct electrical measurement of DNA hybridisation. Three technological approaches were investigated and optimised by using analytical and finite element analysis: single crystal Si beams with implanted piezoresistors, SiO$_2$ cantilever with poly-Si piezoresistors and polymeric beams with gold strain gauges. According to results, the most performing technological approach is based on Silicon-On-Insulator (SOI) wafers, allowing the realisation of low thickness beams (340 nm silicon layer) with n-type resistors. Readout ASIC has been implemented in a separate chip using a 0.35μm CMOS technology to provide a high resolution and low noise readout of the sensors, by also providing the compensation of large offset in the detector response.

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1. Introduction

For Point-of-Care analyses, where small number of DNA sequences need to be detected and reagent storage cannot be guaranteed, non-labelled methods with direct electronic readout can be an interesting alternative to labelled methods for DNA detection and typing commonly used in genomics laboratories. Among different options, cantilever micro-mechanical structures are one of the most promising MEMS label free detectors [1]. Most cantilever-based DNA sensors work in static mode, in which the surface of the thin cantilevers is coated with a self-assembled monolayer (SAM) of ss-DNA probes and a surface stress is generated when the complementary DNA hybridises onto the surface [1-2]. The nanomechanical effects resulting in the beam deflection upon hybridization involve a complex mix of phenomena, ranging from electrical interaction of built-in charge in DNA phosphate backbone to steric hindrance of probes. Thus, device response is very sensitive to probe length, density of surface coating and experimental conditions such as ionic strength of hybridisation buffer [2].
Several methods are available for cantilever readout, among which optical lever setups are the most used due to the high resolution they can provide [1], but other approaches such as piezoresistive readout can provide advantages in terms of setup complexity, direct electrical measurement and the possibility to integrate large arrays also with on-chip electronics. On the other hand, when using piezoresistive cantilevers, devices must be optimized for high performances and a tailored readout circuit must be implemented, able to measure the small variation of resistance or potential expected from microcantilevers.

In this paper, using analytical and numerical methods, we evaluate and compare the performances of different technologies for resistive cantilever DNA sensors, in particular single-crystal Si beams with implanted resistors, SiO₂ beams with poly-Si resistors and polymeric beams with gold strain gauges in order to select the best technological approach. The design of devices has been implemented and optimised using FE simulations, also providing an estimation of detector performances in operative conditions. A dedicated ASIC has been implemented for the readout of low signals from the Wheatstone bridge of the detectors.

### 2. Technology selection

In static cantilever, generated surface stress can be modelled as a uniform bi-axial stress on the surface, thus resulting in a circular deformed shape of an ideal “infinite” beam. In real devices, root region is constrained by the substrate and therefore stress distribution in that region is modified. The piezoresistive response arising from deformation is linearly dependent on beam curvature, and can be optimised by using materials with low stiffness and thin structures. A simple analytical model of mechanical structures of the beam, based on laminate theory, has been set up, as described in [3]. In order to evaluate the performances of different technologies in realistic conditions, a mechanical load \((\sigma_F t_F) = 2 \times 10^{-3} \text{ [Pa m]}\) has been applied on the device surface. This value was calculated from data in [4] and equivalent to the differential momentum arising from hybridisation of DNA with SNPs at 400nM concentration on probes 12 base pairs long. In order to check the accuracy of the model, results from literature [5] have been successfully reproduced [6].

Different technologies for detector realisation have been compared by using this model, starting from a set of three technological approaches: monocristalline Si beams with implanted piezoresistors, thin film cantilever with poly-Si piezoresistors and polymeric beams with metallic strain gauges. Polymeric materials have been evaluated because of their low Young’s modulus, allowing a reduction of beam stiffness, and thus an increase of sensitivity. As regards the integration of the overall detection system, implanted resistors on single-crystal silicon and polysi-lcon elements are fully compatible and easily implemented in CMOS processes and provide the best sensitivity of piezoresistors, while polymeric devices have low realisation costs but also low CMOS compatibility [7]. The thickness of structural layers has been optimised for each technology using analytical models of the structures and an applied surface stress equivalent to DNA interaction. An optimisation of mechanical properties of each technology has been performed in terms of detector response by taking into account technical constraint and device suitability. Evaluated structures and optimised thicknesses are:

- single crystal beams with implanted resistors (“SOI” technology; thicknesses: Si 340nm, SiO₂ 200nm, Au 20nm, junction depth: 100nm)
- SiO₂ beams with poly-silicon piezoresistors (“SiO₂-poly-Si” technology; thickness SiO₂ 400nm, poly-Si 100nm, SiO₂ 200nm, Au 20nm)
- SU-8 beams with strain gauges: SU-8 800nm, Au strain gauge (100nm), SU-8 200nm, Au 20nm

Table 1: Analytical evaluation of response to SNP achievable with different technologies.

<table>
<thead>
<tr>
<th>Device type</th>
<th>Structural material and typ. Young’s modulus</th>
<th>readout sensitivity ([\Delta R/R \sigma^{-1}, 10^{-11} \text{Pa}^{-1}])</th>
<th>(\Delta R/R @ 400\text{nM [ppm]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOI – n resistors</td>
<td>single crystal Si, 169 GPa</td>
<td>(K_{L}=-31) (K_{T}=-18)</td>
<td>5.2</td>
</tr>
<tr>
<td>SiO₂ – poly-Si</td>
<td>poly-Si, 150 GPa</td>
<td>(K_{L}=51) (K_{T}=-18)</td>
<td>3.8</td>
</tr>
<tr>
<td>SU8 – strain gauges</td>
<td>SU8, 4 GPa</td>
<td>(K_{L}=2) (K_{T}=-2)</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Comparing the obtained results (Table 1), single crystal devices provide higher performances than poly-Si piezoresistors, as expected from the piezoresistive coefficients. Despite the low Young’s modulus, polymeric beams
show the lowest response, because the high stiffness of strain gauges in comparison with the polymer’s, resulting in a shift of the neutral axis of deflection toward the resistor and therefore a low stress on the sensing element. Then, a higher thickness of polymer is needed to provide sufficient mechanical efficiency of the beam. The shift of the neutral axis, in addition to the poor stress sensitivity of strain gauges, makes the polymeric approach less appealing. The selection of a different sensitive layer, with higher sensitivity and lower stiffness, is then the key point in order to get better performances from these devices. In conclusion, among available technologies, the approach based on Silicon-On-Insulator (SOI) wafers has been selected for the fabrication of microcantilevers, allowing the realisation of low thickness beams (340 nm silicon layer).

3. Design optimisation

In order to optimise the design and implementation of devices, different doping types and resistor orientations has been considered and evaluated using FE simulation of mechanical structures. For bending mode, p-type resistors have very low performance with respect to n-type, especially for long beams, where stress distribution is almost biaxial. p-type resistors become competitive in root region due to the mechanical constraint of the support, although still with lower response than n-type <100>.

As shown in FE analysis results (Figure 1), orientation of resistors with respect to crystallographic planes is not influent for “long beams”, while in the root region n-type <100> orientation provide an advantage in terms of sensitivity. <100> n-Si can provide a response with integral average $\Delta R/R=8.1$ppm over the region with length L=W=200μm, which represent a 1.47 increase of the response with respect to “long beam” region. Unfortunately, this orientation makes the device incompatible with TMAH wet etching release from back, because of crystalline planes orientation and then cannot be easily realised.

Figure 1: Simulated response of piezoresistive element to SNP mismatch at 400nM concentration, as a function of position along the beam.

Figure 2: Design of microcantilever array. In the inset, detail of the Wheatstone bridge configuration and resistor design.
As discussed in the previous section, detection of Single Nucleotide Polymorphisms (SNPs) needs the measurement of resistance variation in the 1-10 ppm range, while larger mismatches can provide signals with up to one order of magnitude more. Under these conditions, the use of a 4 terminal Wheatstone bridge readout is needed, using 2 bulk resistors to reject thermal effects on the measurement and a reference beam to reject all non-specific interaction of beams with the sample. A 16 element array has been designed (Figure 2) with n-type resistors covering the whole beam surface to minimise the electrical noise of resistors. The technological spread of implanted resistances is typically a few %, thus leading to a relatively high initial unbalance of bridge. An appropriate calibration procedure is needed to preserve the measurement sensitivity and range.

4. ASIC design

Since the variation of cantilever resistance due to the DNA hybridization is expected in the range of few ppm, with a 3.3V power supply an equivalent voltage variation between the two inputs is expected in the order of few μV. In order to be able to detect such a weak signal over a quite wide spread of offset values, a dedicated readout ASIC has been implemented. The readout channel converts the input voltage difference in a proportional current and, after two calibration stages, integrates the resulting current on a capacitor for a proper integration time (Figure 3). As a result, the programmable circuitry allows a fine tuning of the chip in order to compensate the expected maximum variation of ±100mV at 3.3V of voltage supply and maximize the remaining dynamic range for the useful signal caused by the hybridization process. Details of circuit design are reported in [8]. The circuit, realized using a 0.35μm CMOS technology, occupies an area of about 1300x800 μm², pad excluded, with an estimated power consumption of about 35mW.

![Figure 3: Simplified schematic of the readout channel.](image)

5. Conclusions

FE and analytical modelling has been implemented to evaluate the performances of different technologies, showing that thin single crystal beams outperform SiO₂ and polymeric beams. n- and p-type resistors with different orientation has been considered in order to optimise the design of devices. A differential readout has been implemented, using four resistances in a Wheatstone configuration where two bulk resistances are coupled with two cantilevers used respectively for detection and reference. A new ASIC architecture has been also designed to read the cantilever signals. The proposed readout circuit consists of a single analog channel able to provide an analog output proportional to the input difference, including a two steps calibration for offset compensation.

References