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## Piezoresistive cantilever array for life sciences applications

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**Abstract.** Atomic Force Microscopy (AFM) techniques are used with one- or two-dimensional arrays of piezoresistive probes for parallel imaging. We present a newly designed AFM platform to drive these passivated piezoresistive cantilever arrays in air and liquid environments. Large area imaging in liquid as well as qualitative and quantitative analysis of biological cells are demonstrated by the means of piezoresistive cantilever for the first time to our knowledge. Noise limitations in topography and force resolutions of these piezolevers are quantified.

### 1. Introduction

Microcantilevers used in AFM allow to measure surface properties e.g. topography and chemical forces with sub-Angström and piconewton resolution. Moreover, the ability to explore biological samples in air and liquid environments with molecular precision shows an increasing interest in the biologist community [1].

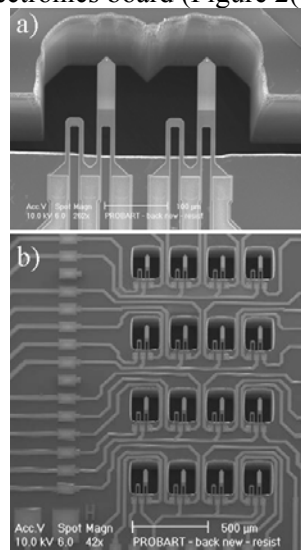
Highly parallel operation of large arrays of sensors allows a faster throughput, important e.g. to increase statistics in quantitative measurements. It guarantees also an increased speed over techniques based on an individually operated Scanning Probe Microscope (SPM), without sacrificing the sensitivity of the individual sensors [2, 3]. The use of self-sensing cantilevers with built-in deflection detection skims simplifies the operation of the parallel system compared to a parallelized optical read-out scheme, because it avoids optical alignments otherwise required for operation. The main fields of application foreseen for such arrays are high resolution microscopy, data storage [4,5] and life science [6].

In this work, we present the development and applications of piezoresistive [7] probe array technology in microscopy and life science. With appropriated passivation, this integrated system can be operated in air and liquid environments. The capabilities of these new passivated piezoresistive cantilevers are demonstrated with qualitative and quantitative measurements. For the first time to our knowledge, the imaging of biological cells in a buffered solution by means of piezoresistive scanning probes is demonstrated.

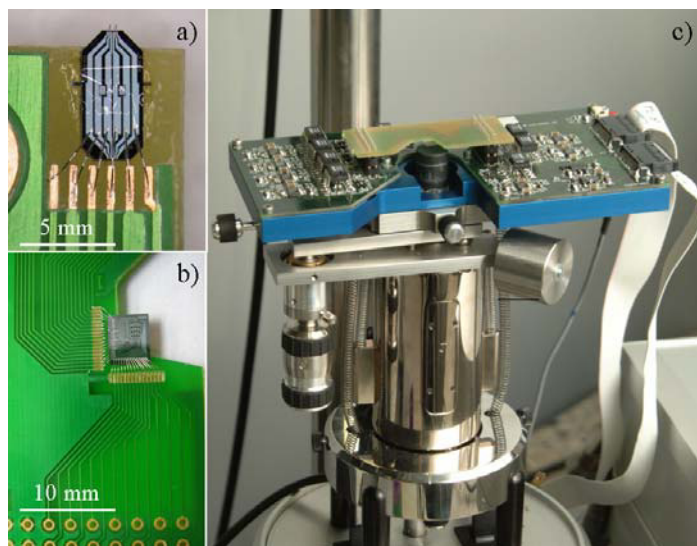
## 2. Experimental device

The principle of piezoresistive cantilever deflection readout is based on the measurement of the electrical resistance of the piezoresistive cantilever. The change of the piezoresistance is proportional to its strain, induced by the deflection of the cantilever.

The microlevers are elaborated in single crystalline silicon following different steps of microfabrication [8]. The two important steps of the process are the boron ion implantation to create the piezoresistive layer in the lever and the deposition of a passivation layer onto the array in order to seal the electrical connections from the liquid environment. A 2x1 and a 4x4 cantilever array are shown in Figure 1(a) and 1(b) respectively. Each piezoresistive cantilever is associated with a reference piezoresistance in order to compensate thermal drift. Specially designed Printed Circuit Boards (PCBs) are used for the mechanical and electrical connections of the probe arrays (Figures 2(a) and 2(b)) with the electronics board (Figure 2(c)).



**Figure 1.** Scanning electron microscope images of a (a) 2x1 and a (b) 4x4 cantilevers arrays. Each piezoresistive cantilever is associated to a reference piezoresistance.



**Figure 2.** (a) 2x1 and (b) 4x4 cantilever array fixed and wire-bonded on especially designed PCBs. The electrical contacts are sealed by the means of Cementit glue. (c) Implementation of the special AFM head to treat all electrical signals from the array in parallel. It is mounted on top of the scanner of a Digital Instruments microscope [9]. Above the electronics board, a PCB with a 4x4 cantilever array is mechanically and electrically clipped. A specially designed tilt stage is placed below the electronic board in order to set the alignment of the probes in front of the sample.

A special AFM head (Figure 2(c)) has been designed to treat all electrical signals from the array in parallel. To be usable by the acquisition card of the commercial microscope [9], the values of the cantilever and the reference resistances are converted into voltages thanks to two independent constant current sources. Then, these voltages are compared in differential amplifiers also located on the AFM

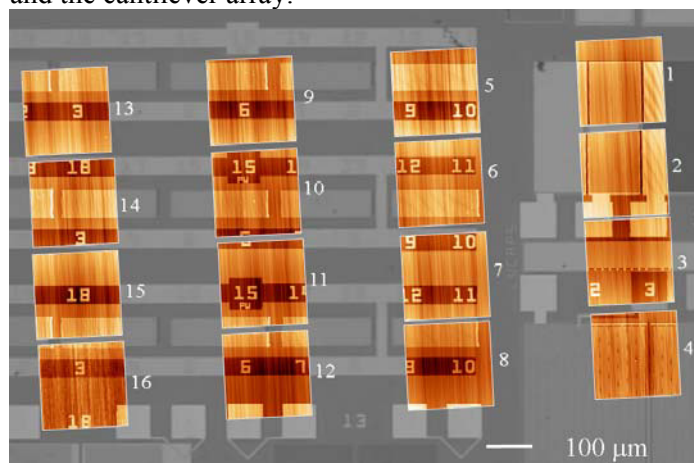
head (Figure 2(c)). The electronics board contains sixteen similar circuits to treat in parallel the electrical signals of sixteen levers.

Commercially available piezo-tube scanner and software [9] have been used to perform the scanning of the sample and the image acquisition. All the measurements are performed in contact (DC) mode. Arrays of 2x1 and 4x4 piezolevers have been used in constant height mode. One lever of the 2x1 array has been used in constant force mode with feedback regulation in distance.

### 3. Results and discussion

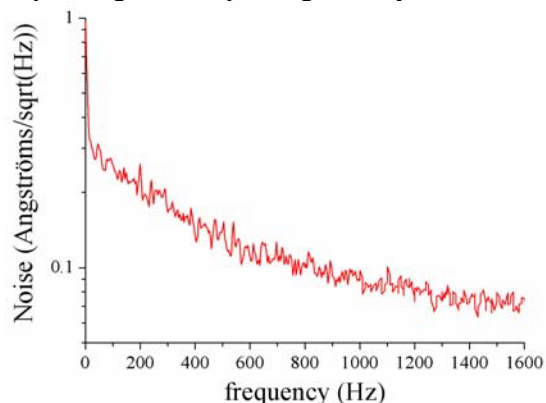
The cantilevers' electrical resistances show a mean value of 7 kohms ( $\pm 1$  kohm). The characterization of the mechanical properties of the cantilevers, in the 2x1 and 4x4 arrays, gives a resonance frequency between 30 to 60 kHz and a spring constant of 0.06 to 0.5 N/m.

To demonstrate the performances of the system, hard and soft samples have been imaged in air and liquid environment. Liquid operations have been done in Phosphate Buffered Saline (PBS) solution with a concentration of 0.01 M. A droplet of this conductive solution is trapped between the sample and the cantilever array.



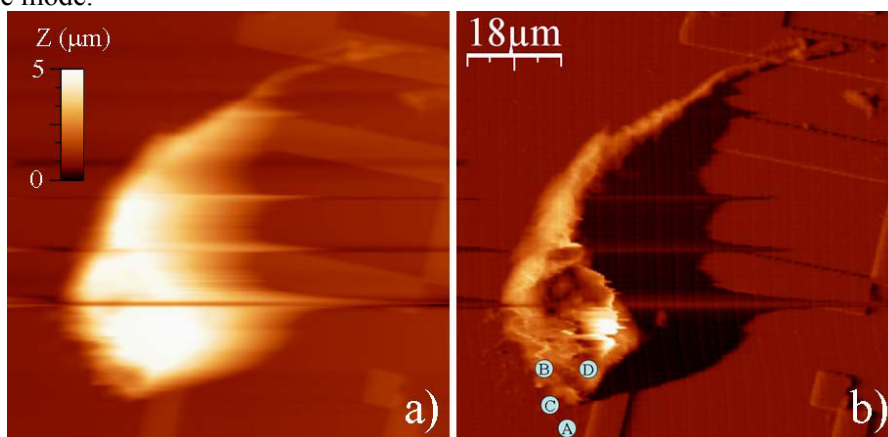
**Figure 3.** Sixteen AFM images (colored in orange) obtained in parallel in buffer solution (PBS 0.01M) with a 4x4 array of cantilevers. The probe array was operated in constant height mode on a micro-structured silicon substrate. In the background, the optical microscope image of the sample is shown. The same result has been achieved in air (not shown here).

Figure 3 shows AFM images acquired in parallel by a 4x4 cantilever array. In the time of one image, the probe array has scanned over sixteen images in the same time allowing to rapidly image hundreds of micrometers square surface. The sensitivity of the integrated system allows a resolution of 2.6 nm (peak-to-peak) in the vertical direction in the bandwidth of 8 kHz of the electronics. The limitation of the minimal detectable deflection is mainly due to the  $1/f$  noise of the sensor as shown in Figure 4. Over a bandwidth from 10Hz to 1 kHz, it is equal to 4.8 Angströms<sub>rms</sub>. The lateral resolution, depending of the tip-end geometry, was on the order of 20 nm.



**Figure 4.** Noise spectrum in air of one lever of a 4x4 array with a stiffness of 0.08 N/m. The bias current is set to 235 microAmperes. The minimal detectable deflection in the bandwidth from 10Hz to 1kHz is equal to 4.8 Angströms<sub>rms</sub>.

In order to extend our investigations to life science applications, the potential of piezoresistive cantilevers to image and to characterize biological samples in liquid has been evaluated. Figure 5 demonstrates the capability of a single piezolever to image biological cells in buffer solution in constant force mode.



**Figure 5.** (a) Topography and (b) deflection AFM images in constant force mode of a fibroblast cell on a silicon surface in a buffer solution (PBS 0.01M) obtained with one piezoresistive lever. The dots indicate the locations of four spots of the probe where force curves were acquired, above the substrate (A) and above the cell (B), (C), (D).

Additionally, force spectroscopy measurements of the cell membrane by the cantilever probe could also be successfully achieved. Figure 6 shows force curves performed on different points of the cell with resolution better than 160 pN (peak-to-peak). The curvature in the repulsive regime gives information about the elastic modulus of the cell. Sudden jumps in the curves are related to snapping in the tip-cell interaction. Such quantitative results are utmost promising for parallel characterization of cell mechanical properties and cell adhesion onto the surface [10] by the means of piezoresistive cantilever arrays.

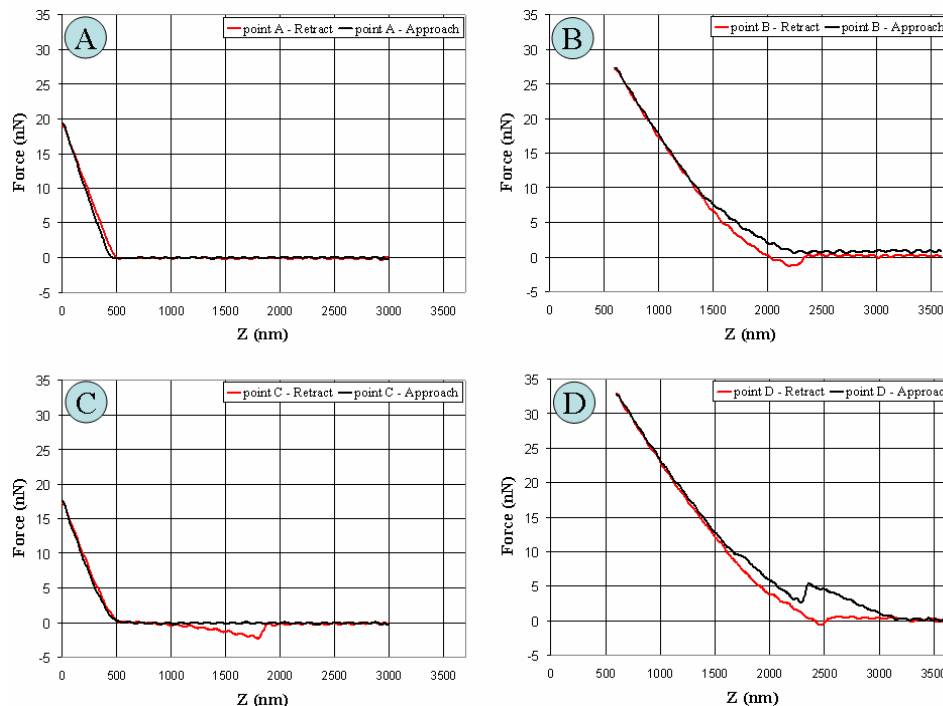
#### 4. Conclusion

The operation of passivated piezoresistive probe arrays in both air and liquid environment has been demonstrated. In liquid, fast parallel large area imaging with nanometer resolution has been achieved. Such piezoresistive probes enabled to image biological cells in buffer solution. Moreover, complementary force spectroscopy investigations can give valuable insights into the mechanical and adhesion properties of the cells.

In a near future, such 2D-arrays of passivated piezoresistive levers are expected to find promising applications in statistical measurements for biology and chemistry (mechanical properties of cells, force spectroscopy of proteins binding, chemical nose [11]).

#### Acknowledgements

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**Figure 6.** Force curves obtained on the four dots indicated on Figure 5(b) above the sample.

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