RASECAN–Parallel AFM for Rapid Cancer Diagnosis

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Changes in cell stiffness (and extracellular matrix) are characteristic of breast cancer cells and affect disease prognosis. Indentation atomic force microscope (AFM) on biopsy samples of living breast tissues shows different stiffness profiles for benign and malignant tissues. CSEM is developing a new parallel AFM diagnostic tool using parallelized mechanical sensors to analyze breast tissues within fifteen minutes, for hospital use.

Cancer initiation and progression are accompanied at the molecular level by complex structural changes in both cells and extracellular matrix[1]. The histological analysis of breast cancer biopsies is currently a slow and qualitative process taking several days and requiring an expert visual evaluation of the samples. However, recent scientific work has demonstrated an alternative approach to histological analysis: the use of atomic force microscopy (AFM) to measure the local mechanical properties of the breast biopsy samples. Typical stiffness profiles have been correlated to histopathological analysis of healthy and malignant human breast tissues (Figure 1) demonstrating a correspondence of the two approaches. These distinct nanomechanical signatures of breast cancer can be used as a diagnostic tool.

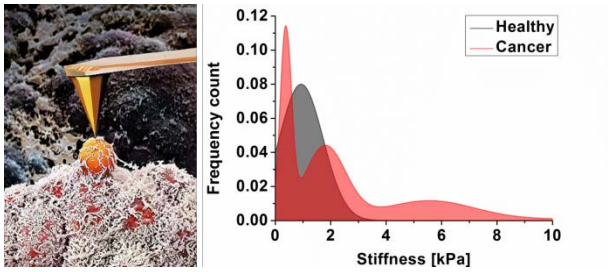

Figure 1: Nanometer-scale palpation of breast tissue (left) and (right) typical mechanical profiles of healthy (single peak in grey) and cancerous (multiple peaks in red) tissues.

AFM is the ideal tool to reliably and quantitatively investigate the mechanical properties of breast biopsies. However, it is slow. AFM analysis of a single biopsy sample requires the acquisition of around 15'000 individual force displacement curves since a large number of measurements are required for a statistically meaningful set of data. This is a significant limitation because one of the major obstacles for a routine use of AFM analysis in hospitals is the diagnostic time which currently takes several hours.

CSEM is addressing the need for reduced analysis time by developing a new AFM diagnostic tool using parallelized mechanical sensors. The objective is to reduce data acquisition time from hours to minutes. This new instrument is based on an existing commercial AFM-based diagnostic tool called ARTIDIS® (Automated and Reliable Tissue DIagnosticS) from Nuomedis/Nanosurf that performs highly automated but serial measurements. The standard procedure starts with a breast biopsy of the suspicious lesion under ultrasound imaging guidance. Multiple stiffness maps are then acquired across the entire biopsy using one AFM cantilever. The replacement of this single cantilever by a 1D array of cantilevers - eight cantilevers operating in parallel – involves an innovative parallel read-out of the probes. Compared to the current state of the art where only one probe is used, these arrays will reduce the data acquisition time by a factor of eight.

The strategy consists of reading the 1D cantilever array by eight semiconductor lasers (VCSELs, Vertical Cavity Surface Emitting Laser). Each laser beam is focused on the end of one of the cantilevers (Figure 2), with the reflection monitored by a position sensitive photodetector. A major technical challenge of the project is the implementation of a simple system for the alignment of VCSELs, optical systems, cantilevers and sample.

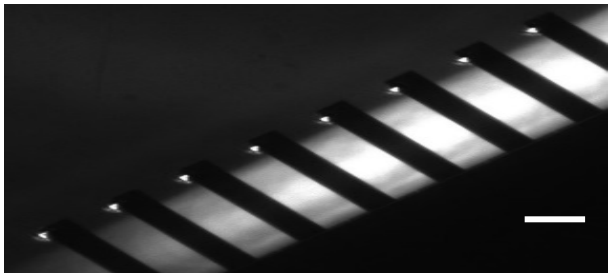

Figure 2: Optical image of a 1D array probe composed of eight cantilevers and their lasers during alignment (scale bar 250 µm).

The first phase of the project yielded the proof-of-principle with ultrafast readout of a 1D cantilever array and parallel force spectroscopy demonstrated on hydrogels of similar stiffness to living tissues. Currently, the second phase is approaching a working prototype (Figure 3). An easy-to-use alignment system has been miniaturized and integrated in the ARTIDIS instrument, while packaging and drivers for the VCSEL arrays have been implemented. The first force displacement curves have been acquired in parallel on hydrogels. Throughout testing and validation of the prototype, it was observed that reduction of biopsy roughness might be required to facilitate the parallel measurements.

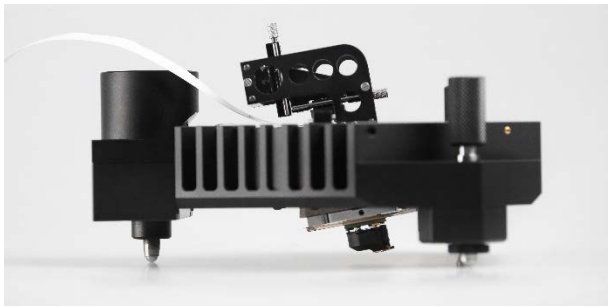

Figure 3: The parallel AFM prototype, with the mechanical laser alignment (top) and the probe array holder (bottom).

This work is partially funded by the Swiss research program Nano-Tera.

[1] M. Plodinec, *et al.*, "The nanomechanical signature of breast cancer", Nature Nanotechnology, 7, 2012, 757-765.