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PATLiSci II RTD 2013

FNSNF

Towards rapid sensing of cancer with nanomechanical cantilevers

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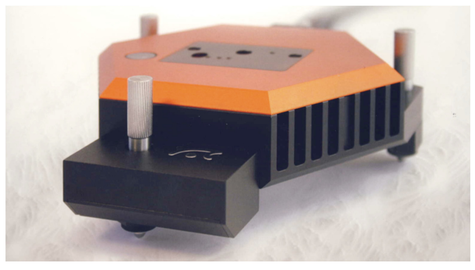
SNI SWISS NANOSCIENCE INSTITUTE
EINE INITIATIVE DER UNIVERSITÄT BASEL UND DES KANTONS AARGAU

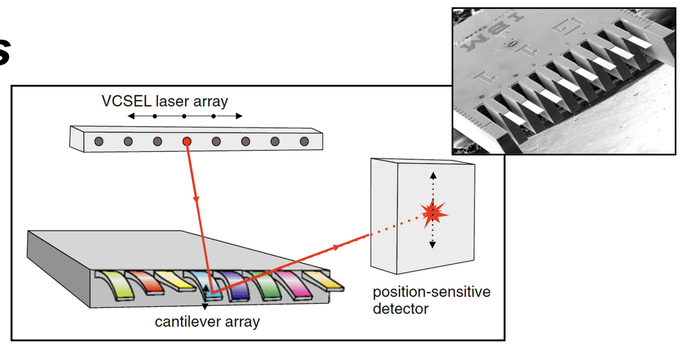
1. Motivation and Introduction

The goal of this project is to develop and apply nanomechanical tools for diagnosis of **breast cancer** and **melanoma** with increased throughput compared to existing technology. As the **elasticity of breast cancer cells and healthy breast tissue cells differs significantly**, breast cancer can be diagnosed using an atomic force microscope (AFM) and acquiring an elasticity histogram (force vs. distance curve mapping). An array of cantilevers with tips will be applied to increase the number of acquired curves through **parallelization**. As complementary information and as a control we will use an array of AFM cantilevers as **nanomechanical sensors for detection of cancer markers** by evaluation of the bending response due to surface stress changes on the surface of functionalized cantilevers.

2. Existing Platforms

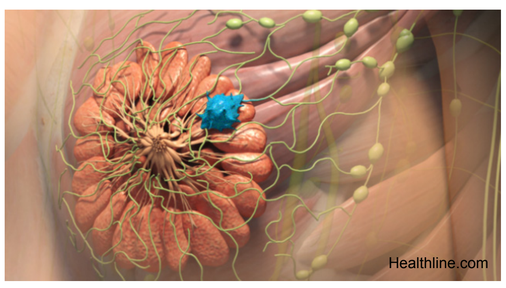


Nanosurf® **FlexAFM** research atomic force microscopy head – a versatile instrument for imaging and **force vs. distance curves.**



Nanomechanical cantilever array sensors for surface stress change measurements during adsorption of molecules. An array of eight VCSEL light sources is used to determine the deflection of the eight cantilevers in an array.

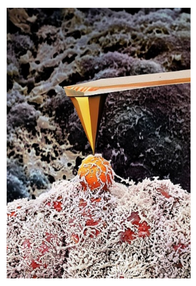
3. Breast Cancer



- 2nd most frequent cause of death for women world-wide
- 1 million new incidences per year (WHO)
- Histopathological diagnosis takes several days and combinations with histochemical methods are needed to avoid high error rates with purely cytomorphological diagnosis

Palpation on the macroscale

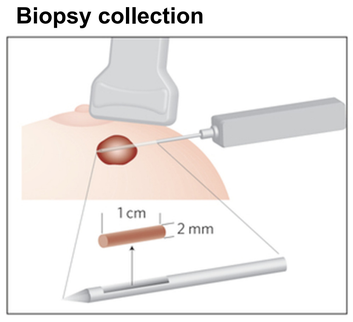
The examiner touches and feels the patient's body

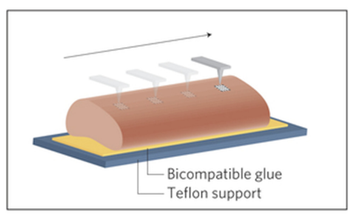


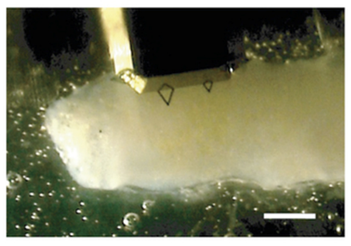
Indentation on the nanoscale

The tip touches and feels the molecular structures

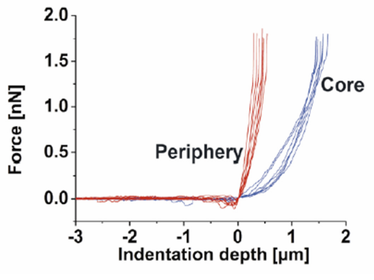
Biopsy collection

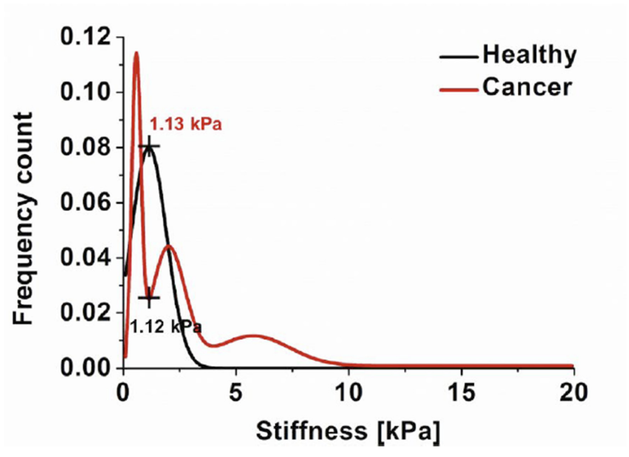






AFM cantilevers probing the surface of a biopsy by acquiring **force distance indentation curves**

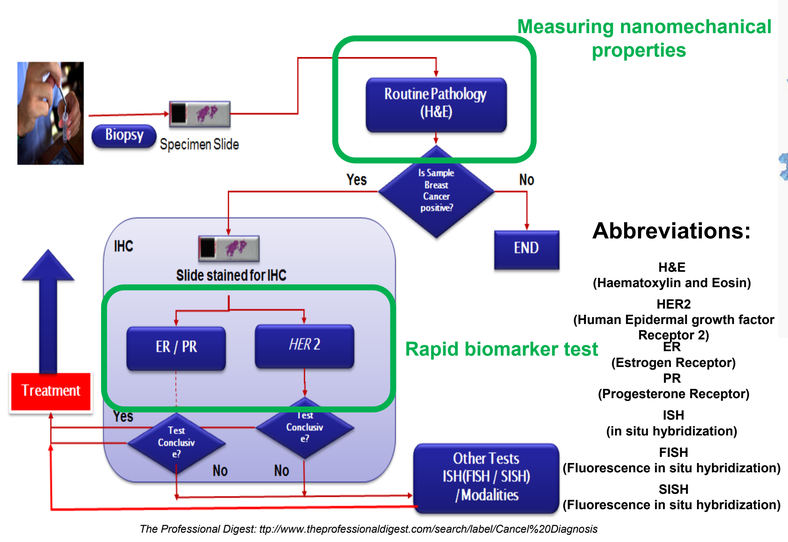




Healthy and **cancerous** breast tissue cells show **very different elastic properties** in a **histogram** of force distance curves,

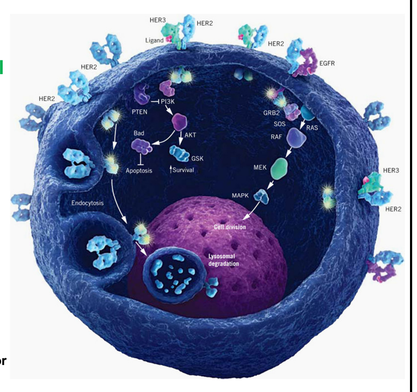
Marija Plodinec et al, Nature Nanotechnology **7**, 757 (2012)

4. Cancer Detection Workflow



Abbreviations:

H&E (Haematoxylin and Eosin)
HER2 (Human Epidermal growth factor Receptor 2)
ER (Estrogen Receptor)
PR (Progesterone Receptor)
ISH (in situ hybridization)
FISH (Fluorescence in situ hybridization)
SISH (Fluorescence in situ hybridization)

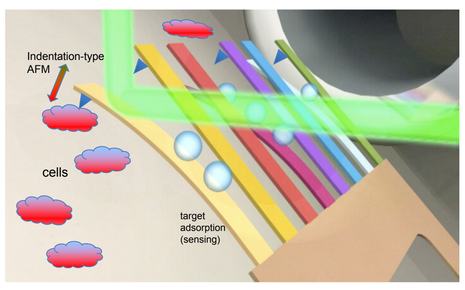


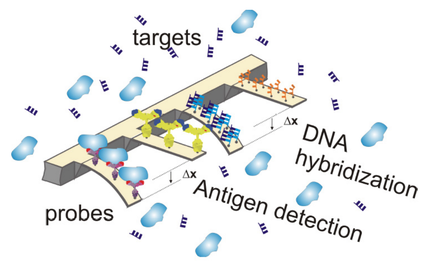
HER-2: Human Epithermal Growth Factor Receptor 2

Important test in immunohisto-chemistry, but expensive therapy (42 k€)

Monitoring important

5. Biomarker Test with Nanomechanical Cantilevers





- **Local biomarker tests** of biopsy samples with pre-functionalized cantilever arrays to **complement the tumor diagnosis**
- Main focus will be on the detection of the **HER2** gene and its proteins providing information about the character and progression of the tumor
- Biomarker detection is also applicable to other tumors, e.g. **melanoma**:

A single point mutation in a gene (*BRAF*) involved in cell growth, called BRAF V600E, is responsible for unregulated cell growth.
A drug is on the market, called femurafenib, inhibits the activity of the mutated protein, improves treatment efficacy at later stages of melanoma.
Presence of this mutation determines eligibility to BRAF inhibitor treatment. The mutation (T-A transversion) is detected using cantilever arrays

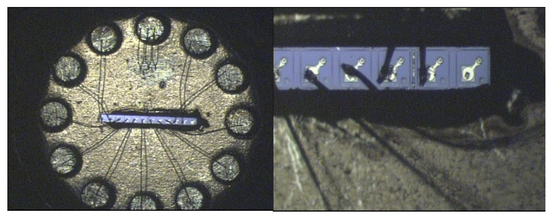
Melanoma

François Huber et al., Nature Nanotechnology **8**, 126 (2013)

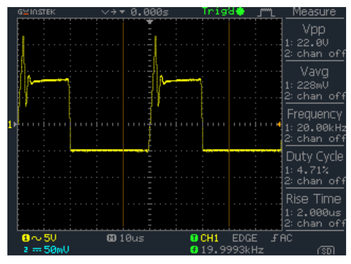
6. From Single AFM Cantilevers to Arrays

Acquisition of force distance curves requires a data rate of 20 kHz when operating **eight** cantilevers instead of **one**. Using optical beam deflection for cantilever bending readout requires to switch the light source between the eight cantilevers.

Option 1: Vertical Cavity Surface Emitting Lasers (VCSELs)



Replace single laser and optics in the Nanosurf® FlexAFM head **by a VCSEL array** for multiplexed readout of the cantilever array.

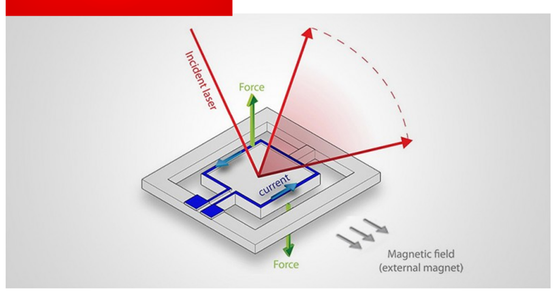


Performance of VCSEL switching (on/off) at 20 kHz using a position sensitive detector and dedicated electronics

Square-wave actuation of VCSEL using a function generator.

Option 2: MEMS scanning mirrors

Lemoptix



Keep single laser and optics in the Nanosurf® FlexAFM head and **use a MEMS mirror** for multiplexed readout of the cantilever array.

MAGNETIC ACTUATION PRINCIPLE
•Mirror made of Si
•a current flowing on the mirror coil, under a magnetic field, induces mechanical displacement of the reflective area.
•Actuation voltage < 5 V
•Linearity of mech. motion vs. actuation signal
•No motion hysteresis