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Nanomechanical membrane sensors for non-invasive analysis of exhaled breath samples from cancer patients

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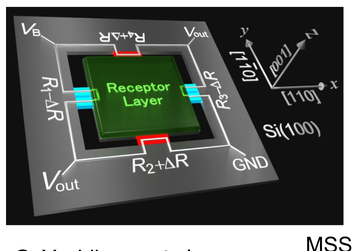
1.Motivation and Introduction

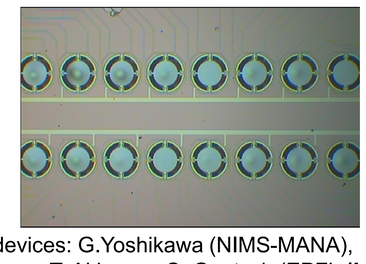
For many diseases, in which a particular organ of the body is affected, chemical by-products are found in the patient's exhaled breath, e.g. acetone for diabetes. While analysis of breath is often done using gas chromatography and mass spectrometry methods, measurement of data and interpretation of results are very time-consuming. We performed characterization of patients' exhaled breath samples by an electronic nose technique based on an array of nanomechanical sensors, which yields results in a simpler workflow.

2. Measurement device

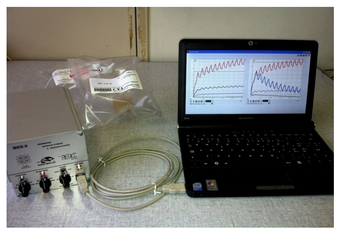
We use arrays of piezoresistive membrane surface stress sensors (MSS), which are read out electrically. In comparison to the cantilever geometry, the four piezoresistive bridges holding the membrane produce a four times higher signal. The measurement chamber with the sensor array, the piezo-actuated micropumps for delivery of gaseous samples and the data acquisition board are housed in a case (10cm x 10cm x 16cm). The measurement setup is powered via the USB port of a netbook computer.



G. Yoshikawa et al, Nano Lett. **11**, 1044 (2011).



MSS devices: G.Yoshikawa (NIMS-MANA), F. Loizeau, T. Akiyama, S. Gautsch (EPFL-IMT-SAMLAB)



Compact measurement setup H.P. Lang, A. Tonin (2012).

3. Sensor functionalization and measurement principle

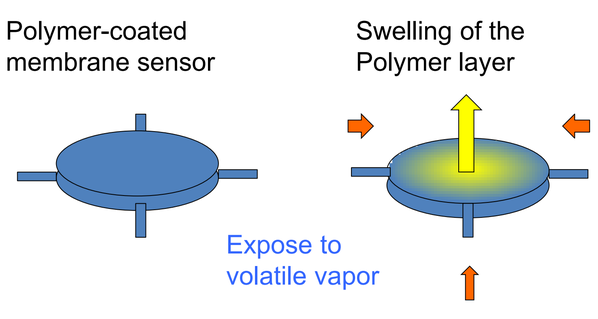
Each sensor of the array is coated with a different polymer layer. By pumping the exhaled air sample into the measurement chamber, volatile organic compounds present in patients' breath diffuse into the polymer layers and deform the sensors due to a change in surface stress. The deflection pattern of the sensors in the array provides information to characterize the condition of the patient.

Polymer coating by inkjet spotting

Total dispensed amount per MSS: 6 nL polymer solution in water (1mg polymer/mL)

Polymers:
CMC, PEO, PEGMEMA, HPC, PAA-AA, PVPy, PIB, PEI

Principle of Measurement



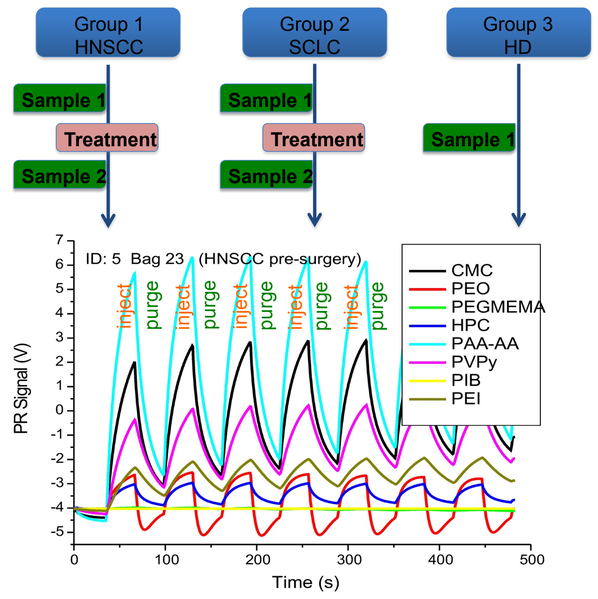
- On exposure to volatile organic compounds (VOCs), the polymer layer swells, producing surface stress and bulging of the membrane
- The presence of VOCs is detected via piezoresistive response of the membrane.

4. Clinical study (CHUV Lausanne)

In a clinical study, we investigated breath samples before and after treatment (surgery) from head & neck cancer patients (head and neck squamous cell carcinoma, HNSCC), lung cancer patients (squamous cell lung carcinoma, SCLC) and healthy donors (smokers) in a double blind trial. The patient inclusion criteria are based on histologically confirmed squamous cell carcinoma at a comparable stage. The patients are in the same age groups. Each breath sample has been measured six times and is evaluated using principal component analysis (PCA).

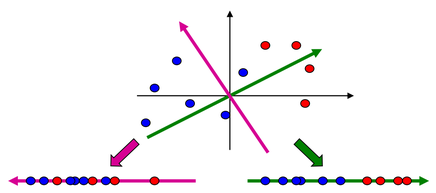
Ash tray at the entrance of the CHUV hospital

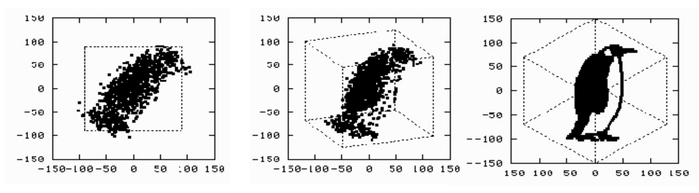
Tedlar breath sample bag.



Measured raw data for seven consecutive inject-purge cycles. The colors correspond to the responses of the individual MSS sensors, each of them coated with a different polymer.

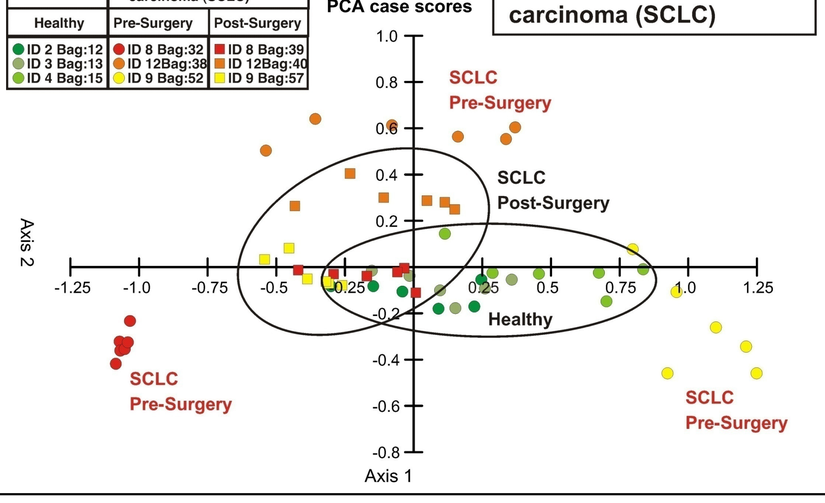
5. Principal Component Analysis (PCA)





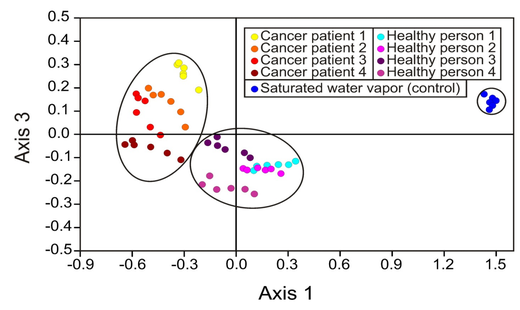
6. Results: Squamous Cell Lung Carcinoma

Control	Squamous cell lung carcinoma (SCLC)	
Healthy	Pre-Surgery	Post-Surgery
ID 2 Bag:12	ID 8 Bag:32	ID 8 Bag:39
ID 3 Bag:13	ID 12Bag:38	ID 12Bag:40
ID 4 Bag:15	ID 9 Bag:52	ID 9 Bag:57



In contrast to Head & Neck Squamous Cell Carcinoma, there are different types of Squamous Cell Lung Carcinoma, i.e. epidermoid carcinoma and adenocarcinoma. Patient ID 8 and 12 have been diagnosed to suffer from epidermoid carcinoma.

7. Results: Identification of Head & Neck Cancer Patients

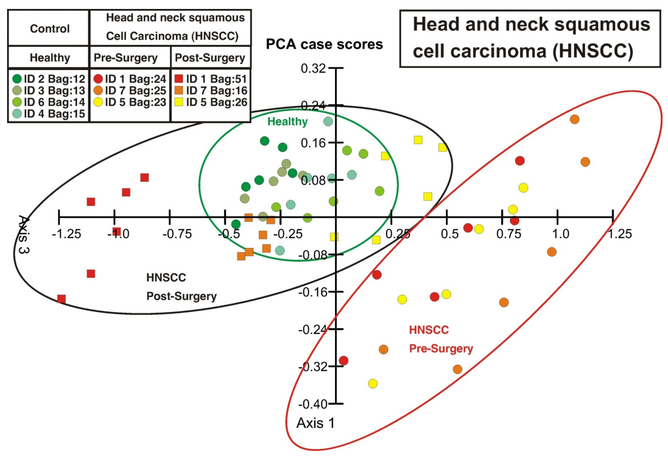


PCA showed clear distinction of patients suffering from head & neck cancer and healthy persons.

A control sample containing saturated water vapor is found to be very different from the breath samples.

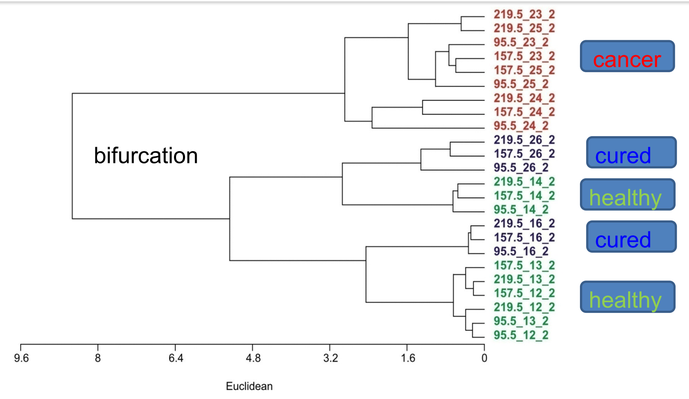
8. Results: Head & Neck Squamous Cell Carcinoma

Control	Head and neck squamous Cell Carcinoma (HNSCC)	
Healthy	Pre-Surgery	Post-Surgery
ID 2 Bag:12	ID 1 Bag:24	ID 1 Bag:51
ID 3 Bag:13	ID 7 Bag:25	ID 7 Bag:16
ID 6 Bag:14	ID 5 Bag:23	ID 5 Bag:26
ID 4 Bag:15		

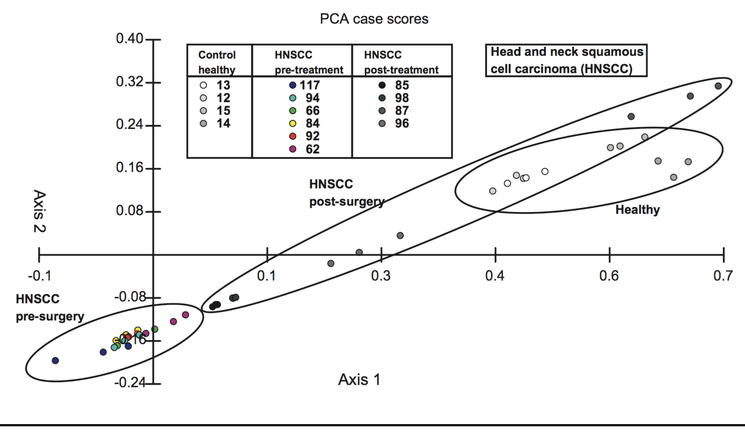


Treatment of head & neck cancer is performed by surgery, i.e. complete removal of the tumor. Breath samples before and after surgery are compared and are found to be clearly distinct from each other.
The technique is completely non-invasive, since only patients' breath samples are required.

Cluster Analysis (Unweighted Pair Group Method with Arithmethic Mean, UPGMA)



UPGMA is a hierarchical clustering method for the classification of measurements based on their pairwise similarities. The tree diagram (dendrogram) shows bifurcations for distinct distances between pairs of measurements.



Additional PCA result for more patient breath samples also showing clear distinction between condition before and after surgery (complete removal of the tumor).

The clinical study is still in progress.