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Single-beam multi-cantilever optical measurement head for cantilever array-based biosensors

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Abstract:
Here we present a homemade system for highly sensitive measurements of cantilever sensor arrays. Two unique techniques developed by our group are utilized. Firstly, the expanded beam deflection (EBD) method that allows truly simultaneous measurements of multiple cantilevers with a simple optical apparatus consisting of a single and stationary laser beam, while providing the same sensitivity as the original optical beam deflection (OBD) method. Secondly, the real-time Brownian noise extraction technique allows combined static-dynamic mode operation in gaseous or liquid environment with no need for external excitation of vibrations. Thus constructed measurement system allows highly sensitive simultaneous measurement of bending as well as flexural and torsional vibrations of up to 8 cantilevers.

Key words: cantilever sensor arrays, expanded beam deflection, Brownian noise, static mode, dynamic mode, static-dynamic mode

Cantilever sensors

Since invention of the atomic force microscope (AFM) by Binning et al. in 1986 [1] cantilever sensors are gaining increasing interest and wide applications, being constantly modified to perform new functions. In 1994 Gimzewski et al. employed a microcantilever as chemical reaction sensor, constructing first microcalorimeter [2]. The following years produced numerous publications on cantilever sensors and their various applications, summarized by Buchapudi et al. [3]. This yet young technology gained its recognition as a fast, versatile, and label-free analytical platform that can be applied to problems that other methods cannot solve or take too much effort, time, and money to solve.

Optical detection methods

The most sensitive method used to monitor motion of a micromechanical cantilever is the optical beam deflection (OBD) method, proposed by Meyer and Amer [4]. An optical beam is focused on the cantilever, reflected from its surface and directed onto a position sensitive detector. This method is used in the most of commercial and homemade AFM systems. It allows the cantilevers to be simpler and thinner than their piezoresistive counterparts allow and provides sensitivity equivalent to that of the interferometric method. It has been a challenge, though, to use this method on multicantilever arrays. Several approaches have been developed throughout recent years. They are schematically presented in Fig. 1.

Lang et al. [5] proposed using a time-multiplexed array of light sources in 1:1 projection onto the cantilever array and a single position sensitive detector. Álvarez et al. [6] proposed using a single light source to scan the cantilever array. The beam is reflected onto a single position sensitive detector and read out at previously determined intensity maxima. Both methods are quasi-simultaneous. A truly simultaneous readout system has been presented by Altmann et al. [7]. It consisted of two complete OBD setups aligned at an angle. It is, however, difficult to increase the number of cantilevers read out using this method.

Expanded beam deflection method

The EBD method, proposed by our group [8], allows simultaneous measurement of multiple cantilevers without time multiplexing and without multiplication of optical paths, while maintaining sensitivity of the OBD method. Its

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concept is shown in Fig. 1. The detector type depends on the mode of sensing. For dynamic mode operation, dedicated photodiode arrays are used to maximize sensitivity, while for static and combined static-dynamic mode operation, a specialized lateral-effect sensor arrays are used to ensure linear response characteristics.

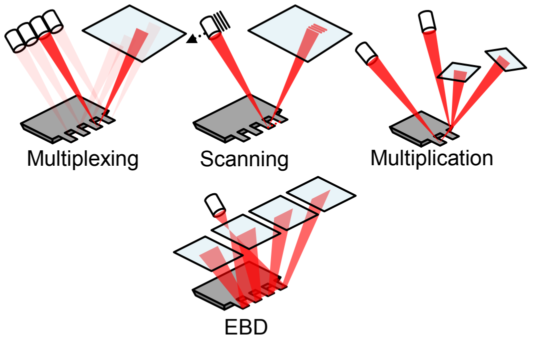

Fig. 1. Overview of multicantilever OBD technique implementations: multiplexing – multiple time-multiplexed light sources and a common detector; scanning – single, scanning light source and a single detector; multiplication – multiple complete OBD paths aligned at an angle; EBD – single, stationary light source and multiple detectors.

Brownian noise extraction technique

In dynamic mode sensing, no external excitation of vibrations is used. Instead, a real-time Brownian noise extraction technique is used [9]. A fast Fourier transform (FFT) is performed on the system's intrinsic noise and the spectra are averaged multiple times, revealing Brownian noise resonance peaks. The resonance frequencies and other parameters are extracted by fitting Lorentz curves to selected peaks using Levenberg-Marquardt algorithm.

MCAS system

Our Micro Cantilever Array Sensors measurement system (MCAS) consists of 7 distinctive parts, marked on a photography in Fig. 2. The laser module encompasses a constant-power laser controller, a radiator, a collimator, and a pair of cylindrical lenses. It is mounted in the optical head equipped with two tilting mirrors and two translation stages, which allow the laser beam to be positioned on the cantilever array and forwarded onto the detector.

The detector itself may have a form of a lateral-effect photodiode array or a classical photodiode array. For the former we use commercially available 16-element 1-D PSD array (1LA16-2,5_SU89, Sitek / Laser Components), while for the latter we have fabricated our own 8x2 photodiode arrays. The detector is connected with the module of 32 current-to-voltage converters. Converted signals are fed to the analog arithmetic circuits, which perform addition, subtraction, and division operations that depend on the actual detector configuration.

The base of the system forms the suspension for the flow cell. It allows easy replacement of flow cells and additional tilt correction as a compensation for varying refractive indices of used media. Finally, the flow cell made of polyether ether ketone (PEEK) is mounted in the suspension. It has a pair of ports for supplying gas or liquid, top and bottom window for optical access, and a removable cantilever holder. It has also one additional port for optional reference electrode, which allows electrochemical measurements. In such case, the cantilever serves as the working electrode and the counter electrode is integrated with the cantilever holder.

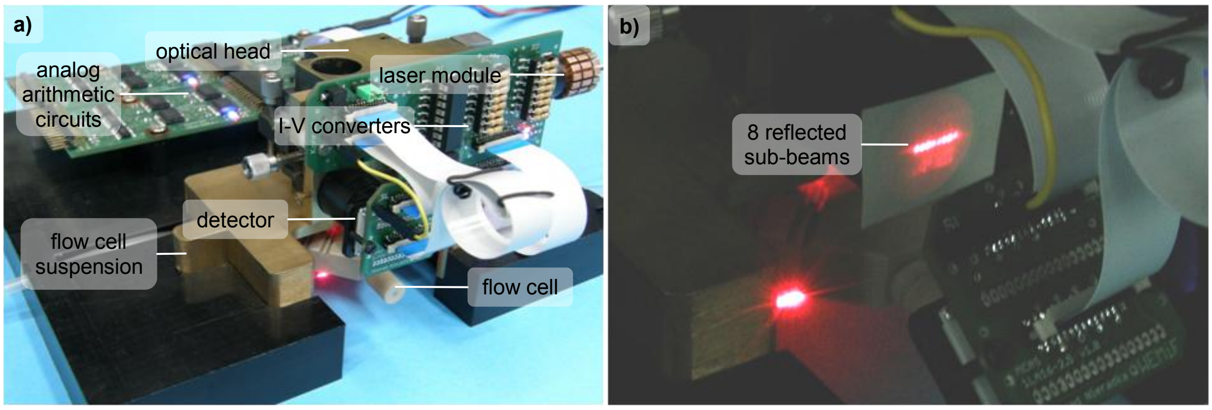

Fig. 2. Complete hardware photography: a) distinctive parts of the MCAS system; b) a paper sheet slid in place of the detector to reveal 8 sub-beams reflected from an 8-cantilever array (Octisensis, Micromotive Mikrotechnik). The intensity of reflected beams is reduced due to lack of gold coating on the cantilevers and their 1 μm thickness which make them almost transparent.

A paper sheet slid in place of the detector in Fig. 2b reveals 8 sub-beams reflected from 8-cantilever array.

Cantilever arrays

We have used three types of cantilever arrays for our experiments. We have fabricated our own 4-cantilever arrays (designated ITE). We have also used commercial 2-cantilever arrays (Arrow TL2Au, Nanoworld) and 8-cantilever arrays (Octisensis, Micromotive Mikrotechnik). In each case the length of the cantilevers was 500 µm, the width was 100 µm, and the pitch was 250 µm. ITE cantilevers were 2 µm thick and TL2Au and Octisensis were 1 µm thick. Top side of the ITE and TL2Au cantilevers was coated with gold.

Results and discussion

Fig. 3 shows acquired thermal noise spectra of ITE array. It demonstrates thermal noise resolution of the system even for stiffer cantilevers (1st eigenmode at 33.4 kHz). No crosstalk between resonance peaks is observed.

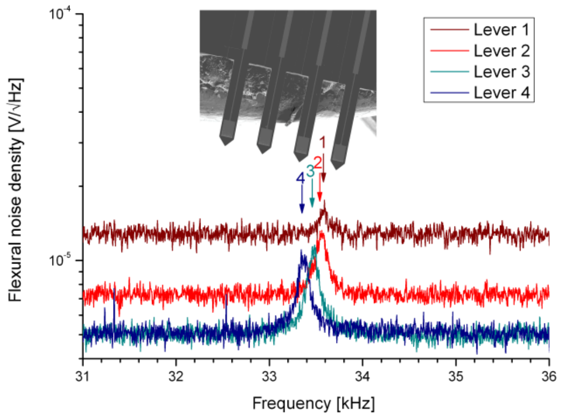

Fig. 3. Thermal noise of a microcantilever array measured in air in the MCAS system. Four ITE microcantilevers have been measured simultaneously using homemade 8x2-section photodiode. The photo-inset shows a SEM image of the cantilever array used.

In Fig. 4 we present similar measurement, though performed in water using softer TL2Au array and lateral effect photodiode array. The thermal noise resolution is also achieved, clearly revealing three first flexural modes. In the band between 2nd and 3rd flexural mode one may even see a minute geometrical cross-talk from 1st torsional mode.

Having thermal resolution combined with linear characteristic of lateral effect photodiode allows operating our sensors in combined static-dynamic mode.

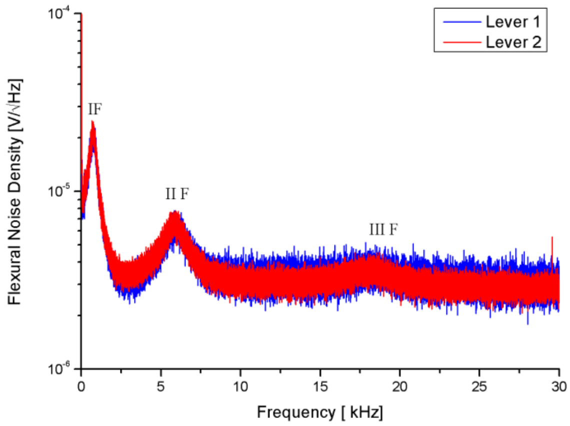

Fig. 4. Thermal noise of a microcantilever array measured in liquid in the MCAS system. Two TL2Au cantilevers have been measured simultaneously using lateral effect photodiode array. The three first flexural resonances shown in this plot overlap each other closely.

An example of measurement performed in such combined mode is shown in Fig. 5. TL2Au array has been differentially functionalized to respond differently for humidity. Left cantilever was made hydrophilic using 11-mercaptoundecanoic acid and right cantilever was made hydrophobic using 1-undecanethiol. Both cantilevers were measured simultaneously while different mixtures of dry and humid nitrogen were pumped through the flow cell.

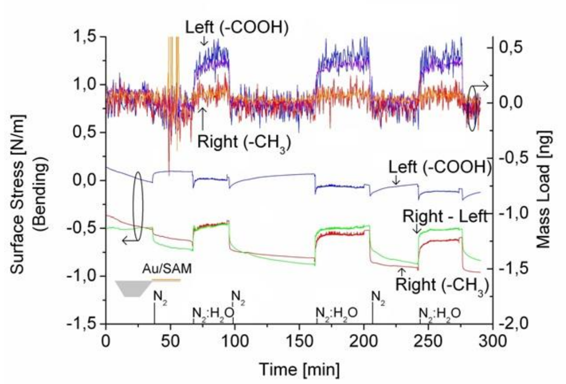

Fig. 5. Environmental factors measurement in combined static-dynamic mode using differentially functionalized TL2Au microcantilever array. The gold side of left cantilever has been coated with hydrophilic 11-mercaptoundecanoic acid SAM while that of right cantilever has been coated with hydrophobic 1-undecanethiol SAM. The native silicon oxide on the opposite side of the cantilevers was left unmodified, yielding minute hydrophilicity. The upper plots show added mass calculated from resonance frequency shift for the 1st and 2nd flexural mode. The lower plots show the bending of the microcantilevers and the differential signal.

The hydrophobic cantilever undergoes only slight mass loading (below 100 pg) in reaction to moisture due to minute hydrophilicity of the bottom silicon oxide side. The hydrophilic cantilever is loaded with almost 500 pg of water in response to humid nitrogen.

Since both sides of hydrophilic cantilever adsorb a layer of water, the differential surface stress is low. In the case of hydrophobic cantilever, we observe higher values of differential surface stress. After subtraction of static signals of both cantilevers, the initial thermal drift is compensated and signal with clear baseline is acquired, carrying information on the hydrophilic cantilevers gold side surface stress.

Conclusions

In our contribution, we have presented the design and operational characteristics of cantilever array optical measurement system along with comparison to other solutions present in the literature. The system is characterized by 250 fm/√Hz noise floor in all channels for photodiode array and thermal noise resolution for lateral-effect sensor arrays. We have shown preliminary measurements in gaseous and liquid environments using cantilevers functionalized with self-assembling monolayers (SAMs).

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