

## **NANOMECHANICAL DEVICES: ULTRASENSITIVE SENSORS OF MOLECULAR RECOGNITION AND CONFORMATIONAL CHANGES OF BIOMOLECULES.**

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In the last years, a large variety of ultrasensitive nanomechanical sensors that have been developed and used as biological sensors. The results demonstrate that rapid detection of biomolecules with high sensitivity and specificity without need of sample pre-treatment and labeling with fluorescent dyes. The applications range from protein and DNA detection to detection of single pathogens. This technology has the potential to revolutionize the fields of molecular biology and preventive medicine. However, it is still needed a major multidisciplinary convergence and development of nanofabrication techniques, measurement schemes, theory, large scale integration of nanodevices, optical and electrical components & microfluidics. In addition, all of these high cost developments must lead to a final technology suitable for mass production at low cost. Here, we present results in several of the battle fronts described above faced in collaboration with several multidisciplinary scientific and industrial partners. The results can be split into dynamic and static modes nanomechanical sensors. In the dynamic mode, the nanomechanical structure resonates at its natural frequency, which sensitively changes when the resonator interacts with the biomolecules present in the sample [1,2]. In the static mode, it is monitored the deflection of a cantilever which changes as a consequence of the surface stress originated from molecular adsorption.

### **Dynamic Nanomechanical Biosensors**

In order to develop nanomechanical devices for ultrasensitive pathogen detection, we have measured the effect of the bacteria adsorption on the resonant frequency of microcantilevers as a function of the adsorption position and vibration mode [3,4]. The resonant frequencies were measured from the Brownian fluctuations of the cantilever tip. We found that the sign and amount of the resonant frequency change is determined by the position and extent of the adsorption on the cantilever with regard to the shape of the vibration mode [5,6]. To explain these results, a theoretical one-dimensional model is proposed. We obtain analytical expressions for the resonant frequency that accurately fits the data obtained by the finite element method. More importantly, the theory data shows a good agreement with the experiments. Our results indicate that there exist two opposite mechanisms that can produce a significant resonant frequency shift: the stiffness and the mass of the bacterial cells. The combination of high vibration modes and the confinement of the adsorption to defined regions of the cantilever allow detection of single bacterial cells by only measuring the Brownian fluctuations, i.e., without any use of external energy. These results are relevant in order to obtain reproducible and sensitive nanomechanical sensors. The results of this study have been applied for a new design of arrays of nanomechanical resonators, with a volume of about  $10^4$  times smaller for ultrasensitive detection of nucleic acids. The fabricated arrays have alternate nanomechanical resonators with different sensitized regions to obtain a double signature of the target based on the mass and stiffness of the molecule. We have been able to detect DNA hybridization at the level of few femtograms in air and without any external excitation, which implies one of the highest sensitivities obtained in these conditions.

## **Static Nanomechanical Biosensors**

We show two relevant applications of nanomechanical biosensors: functional genomics and bionanomachines. In the first case, we show that adsorption of water on highly-packed self-assembled monolayers of single stranded (ss) DNA has an extraordinary effect on the intermolecular interactions. We have followed the process by measuring the nano-scale bending that a silicon microcantilever, on which the ssDNA monolayer is attached, experiences under controlled relative humidity. More importantly, the hydration-induced tension undergoes dramatic changes when the monolayer interacts with either complementary or single mismatched ssDNA targets. The analysis of the results suggests that the tension of the nucleic acid films is mainly governed by the hydration forces originated in the intermolecular channels. The discovered phenomena open the door for the development of a novel label-free DNA biosensor with specificity to single mutations and a sensitivity of at least ten times higher than the label-dependent DNA microarrays [7]. In the second case, bionanomachines such as chaperonins are immobilized on the cantilever. The conformational changes driven by the ATP hydrolysis lead to measurable cantilever fluctuations. This technique can provide new insight about the dynamics of molecular motors that have been elusive so far.

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