FLUIDFM: COMBINING AFM AND NANOFLUIDICS IN A NOVEL TOOL FOR SINGLE-CELL EXPERIMENTS AND BEYOND

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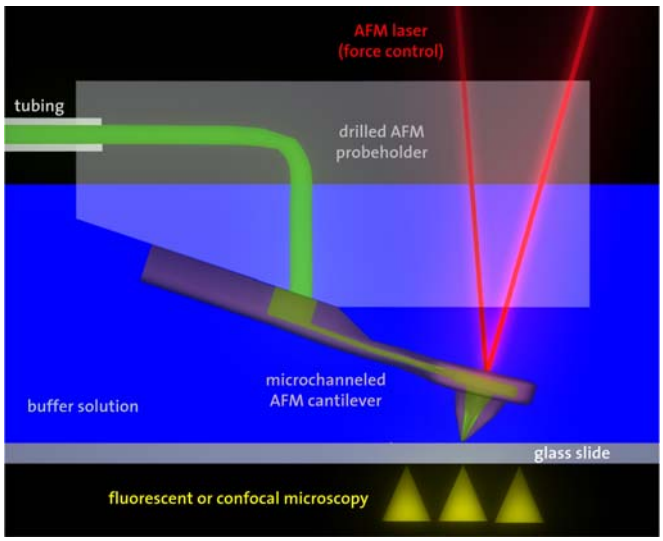
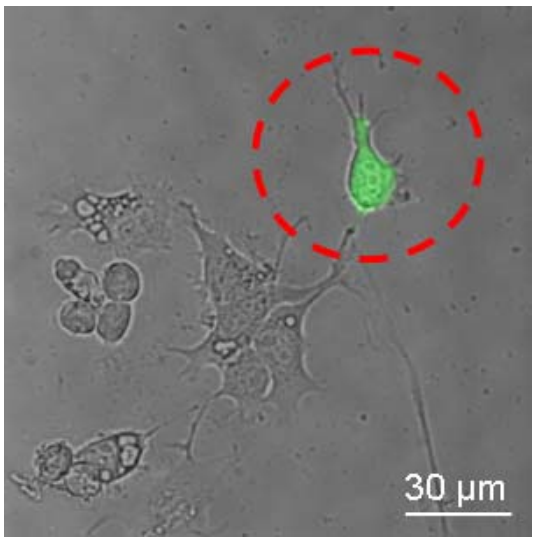
In this lecture, we describe the invention of a new type of atomic force microscope (AFM) including a nanofluidic circuit. This system is the result of a collaboration with **CSEM SA** (Neuchâtel, Switzerland). We call it the "fluidFM" [1] and can be used to dispense ultra small quantities of a solution from the AFM tip onto a sample in liquid or gaseous environment. A standard optical-beam detection and feedback system allows the forces between AFM tip and sample to be controlled to within a picoNewton resolution.

The instrument is composed of custom made AFM cantilevers encompassing an integrated microfluidics channel which are fabricated at CSEM [2]. The micro-channel ends at a well defined aperture located at or in the vicinity of the apex of the AFM probe tip while the other end is connected to a reservoir etched in the upper face of the cantilever chip. The cantilever chip is then fixed against an AFM probe holder so that the reservoir coincides with a macroscopic channel drilled in the AFM probeholder and terminating with a tube connector. In this way, a continuous and "closed" fluidic channel is thus created from the tube to the tip aperture that can be filled with whatever solution and the can be immersed in whatever liquid environment.





We show that biological molecules can be dispensed in their native aqueous environment highly locally, thanks to a gentle but close contact between the dispensing tip and a surface.
To date, AFM-based methods of transporting material have been of limited use in biomedical applications: dip-pen and similar methods allow liquid and water-soluble molecules to be patterned at high resolution but only in air; transport of molecules grafted to the AFM tip only allows the delivery of small quantities of a limited range of molecules.
In contrast, the fluidFM is flexible and versatile: an almost unlimited range of liquids and soluble molecules can be delivered either in air or in a physiological buffer, while force feed-back allows precise work with delicate samples in a variety of different experimental configurations.

As proof of principle, we also demonstrate the use of the fluidFM by injecting arbitrary substances into individual living cells or subcellular structures of living cells. In this model experiment we used a simple fluorescent dye to demonstrate the capabilities of our technique. Thanks to the precise AFM force feedback, we could reliably discriminate between staining by gentle contact on the membrane or by injection upon cell perforation.
We strongly believe that the fluidFM will have an important impact in bionanotechnology both opening a new chapter of biological experiments towards precise single-cell infection with time resolution and, on the other hand, enabling a new generation of analytical methods involving in situ femtoliter sampling and analysis. Moreover, its versatility will surely stimulate innovative experiments from physics to materials science, chemistry and molecular electronics.

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[1] A. Meister, M. Gabi, P. Behr, P. Studer, J. Vörös, P. Niedermann, J. Bitterli, J. Polesel-Maris, M. Liley, H. Heinzelmann, T. Zambelli, *Nano Letters* (2009) doi:10.1021/nl901384x.

[2] A. Meister, J. Przybylska, P. Niedermann, C. Santschi, H. Heinzelmann, *NSTI-Nanotech 2008* **3** (2008) 273.