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Single-molecule analysis with nanomechanical systems

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NEMS (nanoelectromechanical systems) now enable ultrasensitive measurement of the inertial mass of individual atoms and molecules [1]. We have employed NEMS devices to realize a new form of mass spectrometry (MS) enabling single-molecule analysis, and with it have analyzed individual large-mass biomolecular complexes, one-by-one, in real-time [2]. Recently, we developed an approach that enhances the previously-demonstrated capabilities of NEMS-MS by resolving the spatial mass distribution of the individual analytes - in real time with molecular-scale resolution - upon their adsorption onto the NEMS sensor [3]. This new approach, which we term inertial imaging, employs the ensemble of discrete time-correlated perturbations, resulting from each molecular adsorption event, to the multiplicity of modal frequencies of an individual NEMS sensor. From this ensemble of separately measured frequency shifts - all of which occur simultaneously upon the adsorption of each individual analyte - the spatial moments of the mass distribution can be deduced in real time for each analyte. The lowest moment yields the analyte's total mass; higher moments reveal its center-of-mass position of adsorption, the analyte's average diameter, and its spatial skew and kurtosis, etc. Together, the third and higher moments completely characterize the analyte's molecular shape. Once acquired, these moments can be employed to reconstruct the analyte's "inertial image". Unlike conventional imaging, the precision of inertial imaging is not set by wavelength-dependent diffraction phenomena; instead frequency fluctuation processes determine the ultimate limits of spatial resolution. Today's advanced NEMS devices are capable of resolving molecular-scale analytes. One of the most exciting current fields of application for this method focuses on the analysis of large proteins and biomolecular complexes - for example, membrane proteins, antibody isoforms, organelles, and viruses - in their native (unfragmented and non-denatured) state.

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