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Toward Single-Molecule Nanomechanical Mass Spectrometry¹

MICHAEL ROUKES, California Institute of Technology

Mass spectrometry (MS) has become a preeminent methodology of proteomics since it provides rapid and quantitative identification of protein species with relatively low sample consumption. Yet with the trend toward biological analysis at increasingly smaller scales, ultimately down to the volume of an individual cell, MS with few-to-single molecule resolution will be required. We report the first realization of MS based on single-biological-molecule detection with nanoelectromechanical systems (NEMS). NEMS provide unparalleled mass resolution, now sufficient for detection of individual molecular species in real time. However, high sensitivity is only one of several components required for MS. We demonstrate a first complete prototype NEMS-MS system for single-molecule mass spectrometry providing proof-of-principle for this new technique. Nanoparticles and protein species are introduced by electrospray injection from the fluid phase in ambient conditions into vacuum and subsequently delivered to the NEMS detector by hexapole ion optics. Mass measurements are then recorded in real-time as analytes adsorb, one-by-one, onto a phase-locked, ultrahigh frequency (UHF) NEMS resonator. These first NEMS-MS spectra, obtained with modest resolution from only several hundred mass adsorption events, presage the future capabilities of this methodology. We outline the substantial improvements feasible in near term, through recent advances and technological avenues that are unique to NEMS-MS.

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