Single-Molecule Analysis with Nanomechanical Systems

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Nanoelectromechanical systems (NEMS) offer exciting prospects for research in the life sciences and medicine. Throughout this talk, while presenting the technological underpinnings of our efforts, I will focus on new applications that become possible – including the analysis of intact protein complexes (such as membrane proteins, antibody isoforms, organelles, and viruses) and the unprecedented potential for *deep proteomic profiling of individual cells*.

NEMS uniquely enable ultrasensitive measurement of the inertial mass of *individual* atoms and molecules [1] and, thereby, permit realization of a new form of mass spectrometry (MS) with single-molecule resolution. We have used this to analyze individual large-mass biomolecular complexes, one-by-one, in real-time [2]. More recently, we've developed an approach that permits resolving the *spatial mass distribution* of the individual analytes – in real time, with molecular-scale resolution [3]. We term this approach *inertial imaging*; it employs the discrete time-correlated perturbations to multiple vibrational modes – resulting from each individual molecular adsorption event – to yield the spatial moments of the mass distribution for each analyte in real time. 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.* Once acquired, these moments permit reconstruction of each analyte's image. However, unlike conventional imaging, precision here is not set by wavelength-dependent diffraction phenomena; instead frequency fluctuation processes determine the ultimate spatial resolution limits. Today's advanced NEMS devices are already capable of resolving molecular-scale analytes. In our current efforts, we are both upscaling measurement throughput [4] and harnessing cavity optomechanics to multiplex arrays of NEMS sensors to superconducting microwave resonators. I will provide a description of these advances, and then outline the potential mass sensitivity down at the quantum limit, why they are special in enabling ultrasensitive measurements with minimal backaction, and how such a "quantum" approach could ultimately be transformational for molecular analysis.

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[2] Hanay, M. S., Kelber, S. I., Naik, A. K., Chi, D., Hentz, S., Bullard, E. C., Colinet, E., Duraffoug, L. & Roukes, M. L., *Single-protein Nanomechanical Mass Spectrometry in Real Time.* Nature Nanotechnology, **7**, 602-608 (2012).
[3] Hanay, M. S., Kelber, S. I., O'Connell, C. D., Mulvaney, P., Sader, J. E. & Roukes, M. L., *Inertial Imaging with Nanomechanical Systems.* Nature Nanotechnology **10**, 339-344 (2015).
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Michael Roukes is the Frank J. Roshek Professor of Physics, Applied Physics, and Bioengineering at the California Institute of Technology. His scientific interests range from quantum measurement to applied biotechnology – with a unifying theme of the development, very-large-scale integration and application of complex nanosystems to precision measurements in physics, the life sciences and medicine. Roukes was the founding Director of Caltech's *Kavli Nanoscience Institute* (KNI) from 2003-2006. In 2007, he co-founded the *Alliance for Nanosystems VLSI* (very-large-scale integration) with scientists and engineers at CEA/LETI in Grenoble, which maintains a $B-scale microelectronics research foundry. He then continued as co-director of Caltech's KNI from 2008 until 2013. Since then he has returned to full-time pursuit of research efforts with his group and collaborators. Concurrent with his Caltech appointment, held a *Chaire d'Excellence* in nanoscience in Grenoble, France from 2008-2016. Among his honors, Roukes is a recipient of the NIH Director's Pioneer Award and has been awarded *Chevalier* (Knight) *dans l'Ordre des Palmes Academiques* by the Republic of France.