Single-particle mass spectrometry with arrays of frequency-addressed nanomechanical resonators

Eric Sage¹, Marc Sansa¹, Shawn Fostner¹, Martial Defoort¹, Marc Gély¹, Akshay K. Naik², Robert Morel³, Laurent Duraffourg¹, Michael L. Roukes⁴, Thomas Alava¹, Guillaume Jourdan¹, Eric Colinet¹,⁸, Christophe Masselon⁵,⁶,⁷, Ariel Brenac³ & Sébastien Hentz¹

One of the main challenges to overcome to perform nanomechanical mass spectrometry analysis in a practical time frame stems from the size mismatch between the analyte beam and the small nanomechanical detector area. We report here the demonstration of mass spectrometry with arrays of 20 multiplexed nanomechanical resonators; each resonator is designed with a distinct resonance frequency which becomes its individual address. Mass spectra of metallic aggregates in the MDa range are acquired with more than one order of magnitude improvement in analysis time compared to individual resonators. A 20 NEMS array is probed in 150 ms with the same mass limit of detection as a single resonator. Spectra acquired with a conventional time-of-flight mass spectrometer in the same system show excellent agreement. We also demonstrate how mass spectrometry imaging at the single-particle level becomes possible by mapping a 4-cm-particle beam in the MDa range and above.

¹Univ. Grenoble Alpes, CEA, LETI, 38000 Grenoble, France. ²Centre for Nano Science and Engineering, Indian Institute of Science, Bangalore 560012, India. ³Univ. Grenoble Alpes, CEA, CNRS, Grenoble INP, INAC-Spintec, 38000 Grenoble, France. ⁴Kavli Nanoscience Institute and Departments of Physics, Applied Physics, and Bioengineering, California Institute of Technology, MC 149-33, Pasadena, CA 91125, USA. ⁵Université Grenoble-Alpes, 38000 Grenoble, France. ⁶CEA, BIG, Biologie à Grande Echelle, 38054 Grenoble, France. ⁷Inserm, Unité 1038, 38054 Grenoble, France. ⁸Present address: APIX Analytics, 7 parvis Louis Néel – CS20050, 38040 Grenoble, France. Correspondence and requests for materials should be addressed to S.H. (email: sebastien.hentz@cea.fr)
Mass spectrometry (MS) has been one of the fastest-growing analytical techniques over the past two decades and has become an essential tool in a broad variety of fields. MS is particularly well suited to the analysis of light molecules: it is based on ionization, which raises issues for high-mass species. Routine use of MS in the MDa (\(10^{-5}\) kg) range has become an essential tool in a broad variety of fields and has become an essential tool in a broad variety of fields. MS is particularly well suited to the analysis of light molecules: it is based on ionization, which raises issues for high-mass species. Routine use of MS in the MDa (\(10^{-5}\) kg) range has become an essential tool in a broad variety of fields and has become an essential tool in a broad variety of fields. MS is particularly well suited to the analysis of light molecules: it is based on ionization, which raises issues for high-mass species. 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Fig. 1 Array of nanomechanical resonators. SEM images of 5×4 NEMS array used for nanomechanical mass spectrometry. Typical horizontal and vertical pitches are 20 and 55 µm respectively. a General view of the array, b zoom on two resonators (silicon is false-colored in deep blue), and their metal interconnects (AlSi). c, d zoom-in on interconnects and via. The first metal level is colored in deep yellow, the second one in light yellow. e Typical doubly clamped in-plane resonator used in this study. The beams are designed to resonate around 30 MHz for mode 1 and 80 MHz for mode 2. Typical dimensions for the resonant beam are: 160 nm (thickness), 300 nm (width), and 5–10 µm (length). In-plane motion transduction is performed using piezoresistive nanogauges in a bridge configuration to allow background cancellation. Electrodes are specifically patterned for efficient mode 1 and mode 2 actuation. For a resonance frequency \( f_0 \), bias voltages at \( f_0 + \Delta f \) are applied to both nanogauges (with 180° dephasing). Tension/compression in the gauges mix their resistance change to obtain a downmixed differential output voltage at \( \Delta f \), typically around a few 10's of kHz. f Schematic of the interconnect layout. Each resonator has a unique beam length, hence a unique resonance frequency.

Fig. 2 Frequency-addressing technique. a An open loop response of an array of 20 NEMS is recorded for mode 1 and mode 2 (inset). Each peak corresponds to the resonance of a single NEMS resonator for which resonance frequency and phase reference can be used as an address. We are showing here an example with only 19 resonance peaks: one resonator in the array failed after a long period of operation, as confirmed by scanning electron microscopy (SEM) observation. Yet, the array as a whole could still be operated without performance degradation, demonstrating the robustness of the parallel architecture. b The resonance frequency of every single resonator in the array is sequentially monitored over time: a PLL locks onto a given resonator, registers its current resonance frequency after a given idling time \( \tau_{PLL} \) (here 8 ms) and then switches to the next resonator. The duty cycle of a whole array is then \( N\tau_{PLL} \) (here 152 ms with \( N = 19 \) NEMS). From the recorded data points, individual frequency time traces can be extracted, and their frequency stability calculated. c Frequency stabilities obtained using a single individual resonator (not in array, green), a resonator of strictly identical dimensions within an array without frequency addressing (yellow) and the same resonator with frequency addressing (red). See “Frequency stability measurements” in the “Methods” for details on the selected frequency stability estimator. The three plots appeared identical within measurement uncertainty: the parallel architecture of our arrays along with the frequency-addressing technique allows reaching the regime where frequency fluctuations set the frequency stability limit of our resonators, down to similar values as single resonators.
Frequency stability of the arrays of nanomechanical resonators.

Frequency stability is a key parameter to the performance of nanoresonators for mass sensing. In a regime where additive white noise is dominant, based on the simple dynamic range equation, the frequency stability can be expressed in the voltage domain as\(^1\):

\[
\frac{\delta f}{f_0} \approx \frac{1}{2Q} \frac{S_n}{V_{\text{out}}} \sqrt{BW}
\]

(1)

where \(Q\) is the resonator’s quality factor, \(V_{\text{out}}\) the output signal amplitude at any given NEMS resonance frequency (in V), \(S_n\) the noise spectral density at the output (in \(V\ Hz^{-1/2}\)), and \(BW\) the measurement bandwidth (in Hz). As mentioned above, the output signal of an individual resonator in array configuration scales like the inverse of the number of devices, \(V_{\text{out}} \propto \frac{1}{\sqrt{N}}\). In our case, \(S_n\) is the sum of lock-in input noise (constant, typically less than \(10 \text{ nV Hz}^{-1/2}\)), of Johnson noise due to the piezoresistive gauges and of thermomechanical noise. All piezoresistances being connected in parallel, Johnson noise scales like \(\frac{1}{\sqrt{N}}\). Since Johnson noise for a single device is typically in the same order of magnitude as the lock-in input noise, it becomes negligible for an array. Thermomechanical noise for a single resonator is typically in the same order as Johnson noise or the lock-in input noise. Like output signal, it scales in the voltage domain like \(\frac{1}{\sqrt{N}}\) and becomes negligible for an array. Finally \(S_n\) is dominated by the lock-in input noise, which does not scale with the number of resonators in the array, while the output voltage \(V_{\text{out}}\) is inversely proportional to the latter. In a regime where additive white noise is dominant, the frequency stability of resonators within our arrays is expected to degrade proportionally with the number of resonators \(\left(\frac{1}{\sqrt{N}}\right) \propto (N-1)\).

From the individual time frequency traces measured with our sequential closed-loop scheme, the frequency stability of every resonator within the array can be plotted. Figure 2c compares three different cases: the first is the frequency stability of a single resonator (not in an array) with a usual down-mixing scheme. The second is the frequency stability of a resonator of identical dimensions within an array, but operated with the same readout scheme (no frequency addressing). Finally, the third case corresponds to the same resonator within an array with frequency addressing. The three plots are similar within measurement uncertainty. Yet, in the case of additive white noise, we could expect a factor 20 between the two first cases. We attribute this discrepancy to the presence of resonance frequency fluctuations in the mechanical domain: we have recently shown that the frequency stability of similar silicon single resonators is limited by frequency fluctuations rather than additive white noise\(^7\), more than two orders of magnitude above what is expected from Eq. (1). The physical origin of these frequency fluctuations is still under investigation: we have discarded instrument noise, temperature fluctuations, charge fluctuations, non-linearities, adsorption–desorption noise, molecule diffusion, as well as defect motion in the crystalline lattice. Several mechanisms remain to be studied, among which surface effects. In this regime, the frequency stability does not depend on signal level and depends very weakly on integration time. We find the same behavior with our arrays and using the frequency-addressing technique. It should also be noted that frequency stabilities of all resonators within the array are of very similar levels (Supplementary Figure 4). Finally, the frequency-addressing technique does not degrade the frequency stability of our nanoresonators and the limits of detection in mass of single and arrayed resonators are similar.

Single-particle mass spectrometry with arrays of nanomechanical resonators. We subsequently perform single-particle mass spectrometry with our arrays of nanomechanical resonators in a custom setup described in detail elsewhere\(^6,18\). The system consists of four main vacuum chambers (Fig. 3a): a metallic nanocluster source, an intermediate chamber, a deposition chamber and an in-line TOF mass spectrometer. Metallic nanoclusters are generated using a sputtering gas-aggregation technique with tunable size and deposition rate. Nanoclusters are then expelled into the vacuum deposition chamber (\(10^{-5}\) Torr) through a differential pumping stage. The deposition rate is measured using a quartz crystal microbalance (QCM) placed on a translational stage. Upon retraction of this stage, the array of resonators is exposed to the cluster flux. When both NEMS and QCM are retracted, the particle flux enters the acceleration region of the in-line TOF mass spectrometer, where the mass-to-charge distribution of charged particles is measured. The configuration of the deposition chamber allows QCM, TOF-MS, and NEMS-MS measurements sequentially on the same cluster population.

As previously described\(^6\), we selected tantalum as the analyte as it is both dense (16.6 g cm\(^{-3}\)) and readily condenses into large clusters. The TOF and NEMS-MS mass spectra acquired for various populations are compared. An example of frequency traces in simultaneous two-mode operation acquired using the frequency-addressing technique during the exposition to cluster beam is shown Fig. 3b. Frequency jumps larger than the frequency stability \(3\sigma\) are considered as actual particle landing events and converted into a mass probability distribution\(^6\) (the stiffness of the particles is neglected due to their very small size, the in-plane motion of the resonator and its width-to-thickness ratio\(^{14}\)). The mass sensitivity of each NEMS is measured by comparing its frequency response to uniform mass deposition with that of a QCM as detailed elsewhere\(^6\). This is performed for the 19 resonators simultaneously with the frequency-addressing technique (Supplementary Figure 5). Extracted mass sensitivities range from 15.3 to 32.5 Hz/ag for mode 1 and 42.9 to 87.8 Hz/ag for mode 2, which is consistent with the range of the resonator lengths. Monitoring the first two modes of all NEMS is achieved with a PLL response time of 8 ms, yielding a total array response time of 152 ms. Tuning of the nanocluster source parameters and use of a mechanical chopper (Fig. 3a) yield particle adsorption event rates per resonator in the order of one event every few seconds, making the landing of several particles within the duty cycle very unlikely. The mass probability distributions obtained for each event are added for each resonator to build individual mass spectra; the same operation can be performed for all resonators to build the overall array mass spectrum. Mass spectra of three different nanocluster populations acquired by both NEMS-MS and TOF-MS technique are displayed in Fig. 3c. Just like individual nanomechanical resonators\(^6\), NEMS-MS performed with arrays directly provide the cluster mass distribution independently of the particles charge state. Conversely, TOF-MS provide mass-to-charge ratio distributions corresponding to multiple charge states of the measured clusters, making spectra interpretation less straightforward. Each NEMS-MS spectrum is acquired in only 4 min and yielded \(~1000\) events. Each resonator detect a similar number of events during this amount of time (~50 events per resonator), demonstrating the 19-fold improvement in capture efficiency due to the use of the array. The overall spectrum provide an accurate mean mass of the cluster populations over a large mass range (530–2400 kDa), with a broader distribution than the TOF spectrometer. As a matter of fact, these experiments are performed in a mass range compatible with operation of the TOF mass spectrometer, i.e., just above the resonator’s mass limit of detection. Over a few MDa, ions are not sufficiently accelerated in order for the ion detector to provide a
signal and the TOF spectrometer becomes unable to perform a correct analysis (Supplementary Figure 6). Conversely, the NEMS limit of detection remaining constant with mass, its resolving power (ratio of analyzed mass to mass resolution) improves with increasing mass (Supplementary Figure 7). For a given cluster population, however, arrays yield slightly broader peaks than those of a single resonator. We attribute this to the heterogeneity in both mass sensitivities and mass resolutions of individual NEMS across the array (Supplementary Figures 8 and 9). This effect will become negligible at masses far from this limit of detection, where mass resolution will become negligible compared to measured mass. Nonetheless, our results demonstrate that such frequency-addressed arrays multiply the capture efficiency by the number of individual resonators in the array, in our case, by more than an order of magnitude.

**NEMS mass spectrometry imaging at the single-particle level.**

The frequency-addressing scheme also provide access to individual information of each resonator. This can be put to use, for example, to obtain a spatial mapping of the particle beam. For this purpose, the 100 µm x 250 µm NEMS array is moved to scan the 4-cm-diameter particle beam. Figure 4 shows maps of event number within the array in a given measurement time (here, 4 min), as well as individual spectra obtained with each resonator. These results are presented for two different array locations within the particle beam: close to its center, where the event rate is very homogeneous throughout the array and at the edge of the beam, where there is a clear asymmetry between resonators situated well within the particle beam and the resonators outside of it. The cluster source in our system displays slow drift and day to day variability. As a consequence, we could perform mass analysis at only two different positions in the beam within the time frame available for a stable enough cluster source and for a reasonable number of events on each resonator.

**Discussion**

In conclusion, we demonstrate here single-particle nanomechanical mass spectrometry with arrays of NEMS operated with a frequency-addressing scheme. These arrays can comprise several tens of nanoresonators, increasing the total capture cross-section by the same factor. Detection efficiency is today the main limitation of NEMS-based mass spectrometry with analysis time up to several hours. This time can be reduced by more than an order of magnitude with the frequency-addressing technique, while keeping the same mass limit of detection: frequency stability of the silicon nanoresonators used here being limited by frequency fluctuations, it is not degraded by the frequency-addressing technique. The number of resonators in the array could be further increased, with the caveat that both total input impedance of the array and output voltage would decrease accordingly. Additive white noise would eventually dominate and the frequency stability would degrade. We estimate that this may not be the case for arrays including up to between 50 to 100 nanoresonators. The main price to pay for the frequency-addressing technique is an
Towards better resolution imagers as well as high-mass cap-
images with one single shot and efforts in the

Fig. 4 NEMS-MS beam imaging. The NEMS array is placed at the center of the particle beam (a) or at the edge (b). The event number is measured for each NEMS and plotted on interpolated surface maps for each case. Mass spectra obtained with each individual resonator for a 4 min acquisition are shown. A mechanical chopper is used to adapt the particle adsorption event rate to the array response time. The spectra are displayed as a matrix pattern reproducing the device physical layout (5×4). Each individual plot shows the intensity (a.u.) versus mass (kDa).

increase in duty cycle: an array comprising 100 resonators could be sampled in a few 100 ms. This is not very relevant for today’s low-efficiency NEMS-MS systems, where the probability of multiple events within a duty cycle is very low. In the future, however, as system particle transfer efficiencies improve, this probability will certainly increase. To circumvent such problem, several arrays with frequency addressing could eventually be operated simultaneously in parallel with multiple-channel electronics.

We also demonstrate here how the frequency-addressing scheme can provide individual resonator information: the array becomes a sort of particle imager, each resonator acting as a pixel. With this technique, mass spectrometry imaging (MSI) at the single-particle level becomes possible. MSI generally relies on the analysis of localized desorption events sequentially in time and has already proven its great potential for clinical applications and cancer research. More recent techniques perform multi-pixel images with one single shot and efforts in the field are pushing towards better resolution imagers as well as high-mass capability. NEMS-MS imaging with frequency-addressed arrays has this potential. Ultimately, arrays of nanoresonators with µm-sized pixels covering large areas could be fabricated with CMOS co-integration. Many frequency-addressed arrays could thus be operated simultaneously with an integrated electronics, like a CMOS imager. MS analysis of massive biological species could then be performed with NEMS-MS systems using gas-phase transfer techniques like electrospray ionization or surface acoustic wave nebulization, leading to limit of detection and efficiency similar to conventional MS. Moreover, the mass resolution of an array of NEMS does not theoretically depend on particle mass (in the same experimental conditions), improving the relative precision at higher mass. Beside biological research and biomedical applications, NEMS-MS imaging could be of great interest for the characterization of ionization sources efficiency, as well as the characterization of sampler performance in aerosol science.

Methods

Array fabrication. The NEMS arrays employed in this work are fabricated from CMOS-compatible materials and VLSI processes. They are fabricated from a 200-nm SOI wafer with 160-nm-thick silicon layer. The top silicon layer is implanted with boron ions (p-type, ~10^{19}cm^{-3}) resulting in silicon resistivity of a few
A hybrid e-beam/DUV lithography technique is used and the top silicon layer is subsequently etched by anisotropic reactive ion etching (RIE). A silicon oxide layer is deposited and patterned to open the contact area between silicon and metal. A first AlSi layer is deposited and patterned to define metal leads. A second silicon oxide layer is deposited, planarized by chemical mechanical polishing and patterned to open the via holes for electrical contact between the first and second metal levels. The second AlSi layer is then deposited and patterned to define the top level electrical leads and wire-bonding pads. Finally, the devices are released by vapor HF isotropic etching.

**Mass and position calculation.** When a particle of mass $m$ lands on a resonator at the position $x$, a frequency shift $\Delta f_n$ of the mode $n$ occurs:

$$\Delta f_n = 2M \frac{\alpha_n}{f_n} \frac{a_n}{a} \rho(x)^2$$

with $f_n$ and $\rho(x)^2$ being respectively the nominal frequency and the position dependent normalized mode shape of the mode $n$. Using the two modes of the NEMS, we obtain:

$$\rho_1(x)^2 = \frac{a_1}{a} \frac{\alpha_1}{f_1}$$

$$\rho_2(x)^2 = \frac{a_2}{a} \frac{\alpha_2}{f_2}$$

The function $g(x) = \frac{\rho(x)^2}{\rho_1(x)^2}$ is invertible only on half of the beam $x \in [0; 0.5]$ or $x \in [0.5; 1]$, but as a doubled clamped beam as used here is symmetric, we can solve the position in only one of those two halves:

$$x = g^{-1} \left( \frac{a_1}{a} \frac{\alpha_1}{f_1} \right) \in [0; 0.5]$$

Then the mass of the landed particle can be calculated:

$$\Delta m = 2M \frac{\alpha_1}{f_1} \frac{a_1}{a} = 2M \frac{\alpha_2}{f_2} \frac{a_2}{a}$$

**Frequency stability measurements.** In Fig. 2c, frequency stabilities are compared for three different cases. In each case, bias and drive voltages are increased until the frequency stability stopped improving (meaning the limiting source of noise is intrinsic to the resonator itself). This “limit” frequency stability is the one plotted for each case. It is obtained with 0.3 to 0.4 V drive voltage for both single and array resonators, 1.25 V bias voltage for a single resonator and 3.5 V bias voltage for the array.

Importantly, it should be noted that the standard Allan deviation cannot be used in the case of frequency addressing as there is dead time in between each measurement time for each sample is then obtained. This estimator is useful for comparison purposes, but should not be mistaken with rigorous Allan deviation measurements. This estimator also has the advantage of being less sensitive to the drift of the measurement.

**Mass sensitivity calibration.** Calibration of the NEMS sensitivity is essential for a correct comparison between TOF-MS and NEMS-MS. The NEMS frequency response to uniform mass deposition is compared to mass deposition rates provided by a QCM. This procedure is all the more relevant with arrays as all resonators are used in the case of frequency addressing as there is dead time in between each measurement.

**Data availability.** The data that support the findings in this study are available from the corresponding author upon reasonable request.

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**Acknowledgements**

We acknowledge support from the LETI Carnot Institute NEMS-MS project, as well as from the European Union through the ERC Enlightened project (616251) and the Marie-Curie Eurotalents incoming (M.S.) fellowship.
Author contributions
All authors contributed to this work. M.G. supervised the fabrication of arrays.

Additional information
Supplementary Information accompanies this paper at https://doi.org/10.1038/s41467-018-05783-4.

Competing interests: The authors declare no competing interests.

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