

Fast Chemical Imaging at High Spatial Resolution by Laser Ablation Inductively Coupled Plasma Mass Spectrometry

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ABSTRACT

In recent years, chemical imaging was prognosticated to become one of the key analytical applications for Laser Ablation Inductively Coupled Plasma Mass Spectrometry (LA-ICP-MS). However, moderate spatial resolution and the associated measurement time required for a larger sampling area, have restricted this versatile, high sensitivity technique from being routinely used in two-dimensional chemical imaging. This work describes the development and investigation of a low dispersion sample chamber (tube cell) which allows improving the imaging capabilities by reducing a single LA shot duration to 30 ms (full width at 1% maximum). The new tube cell is based on a constant laminar flow and a well-controlled delivery of the laser ablated aerosol into the transport system, leading to minimized tailing of the aerosol washout and helping to separate the signals even at repetition rates as high as 20-30 Hz. To demonstrate the improved imaging capabilities, micro-structured metallic thin film patterns were analyzed at a spatial resolution of a few micrometers. The LA-ICP-MS results obtained were comparable to Synchrotron-based micro X-ray Fluorescence (SR-microXRF). The suitability of the newly designed cell for multielement acquisitions was demonstrated using a simultaneous ICP-Mattauch-Herzog-MS. Finally, the novel laser ablation cell was applied to image the distribution of metal-tagged biomarker in a thin section of breast cancer tissue. This application demonstrates that the technique is capable to produce sub-cellular ($\sim 1 \mu\text{m}$) spatial resolution, which is crucial for morphological assessment in cancer diagnostics.

KEYWORDS

LA-ICP-MS, chemical imaging, fast washout, laser ablation cell, SR-microXRF, sub-cellular resolution, tissue imaging, Mattauch-Herzog MS, breast cancer

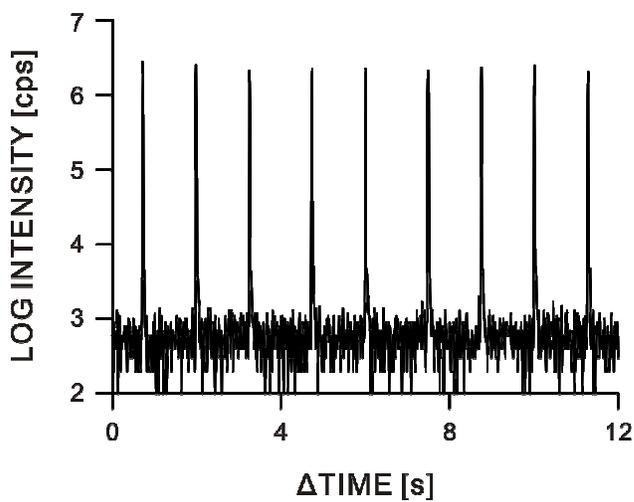
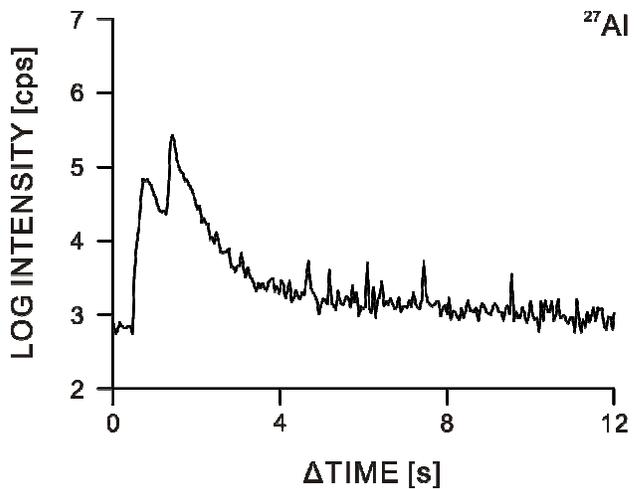


Figure S-1. Conventional circular LA cell¹ performance (1 shot, 50ms dwell time) comparing to tube cell performance (9 shots, 10ms dwell time), demonstrated by single LA shot of a 10 μm spot on NIST610 SRM. Y axes indicate the order of magnitude.

LOD comparison between the tube cell and the conventional setup. In the conventional laser ablation setup, a normal circular LA cell was routinely utilized.¹ The single laser ablation shot ²⁷Al signal using the circular LA cell has been shown in Figure S-1, top panel, which is approximately one order of magnitude lower peak height sensitivity comparing to that of the tube cell (Figure S-1, bottom panel). These two measurements were acquired based on a similar performance of the background signal. Therefore, the single shot LOD calculation is solely depending on the sensitivity (peak height) of the single shot LA signal.² In the current comparison, a 10 fold improved LOD has been achieved using tube cell.

Detailed LIFT method for micro-structured metallic thin film patterns preparation.

The samples used for demonstrating imaging capabilities were produced by a laser-induced forward transfer (LIFT) method, which is extensively explained elsewhere.^{3,4} For the preparation of the donor substrate, a high quality fused silica substrate was covered with a UV-absorbing triazene polymer (TP) layer as a sacrificial dynamic release layer (DRL), on which different thin film materials were deposited. In the transfer procedure, a 308 nm XeCl excimer laser beam was shaped using an 'ETH' [Eidgenössische Technische Hochschule] (or 'PSI' [Paul Scherrer Institute]) hollow mask, then imaged with a 4 fold demagnification before onto the TP layer through the silica substrate (the 'back side' of the donor substrate). The TP-DRL was ablated and the generated shockwave propelled the thin film towards a glass receiver substrate coated with PEDOT:PSS (poly(3,4-ethylenedioxythiophene) blended with poly(styrenesulfonate)), a typical polymeric blend used in organic electronics. The donor and receiver substrates were separated using a 10 µm spacer, and contained in a vacuum chamber at a reduced pressure of 1 mbar.

Instrumentation and operating conditions for imaging of micro-structured thin film pattern with Al/Ag. Prior to laser ablation, the sample was imaged using the lab-based XRF. The ORBIS system as previously employed was operated at 40 kV and 500 mA. An X-ray beam size ($\phi=30\ \mu\text{m}$) was selected. The whole sample area was mapped with a pixel size of $10 \times 8\ \mu\text{m}^2$ in about 2.5 hours. Each pixel was integrated for 2 s. The sample chamber was under vacuum and no filter was applied to the incident X-ray beam.

LA-ICPMS imaging on this metallic thin film pattern was also imaged using an ArF excimer laser system coupled to a prototype ICP-Mattauch-Herzog Mass Spectrometer (ICP-MH-MS, 3rd generation, SPECTRO Analytical Instruments GmbH), which allows simultaneous detection of the entire atomic mass spectrum. A pair of quartz glass attenuators was inserted into the beam path of the laser to reduce the fluence to $6.8\ \text{J}/\text{cm}^2$. The sample was automatically scanned line by line in the same direction (raster) at a laser frequency of 10 Hz. Image pixel size was $6 \times 6\ \mu\text{m}^2$, which was slightly larger than the laser spot size of $5\ \mu\text{m}$. The total image size was 148×61 pixels. The operating conditions of the ICP-MH-MS were optimized for maximum sensitivity of the masses of interest. The fast transient signals were collected in counting mode. The isotopes ^{27}Al , ^{107}Ag , and ^{109}Ag were acquired at a frequency of 10 Hz and the corresponding regions of interest (ROI) in the mass spectrum were integrated simultaneously and background corrected. Since the MH-MS employed did not allow a dwell time less than 100 ms when acquiring transient signals, an assumption has to be made for the fast 10 Hz raster scan that each single shot signal falls in to one dwell time duration. This assumption is to some extent valid based on the short pulse duration discussed in the main text. However the spatial resolution might be deteriorated if the switching between two dwell periods is on a single shot signal peak instead of in between two peaks. In order to overcome this uncertainty, a MH-MS with faster detector responses or a high temporal resolution TOF-MS is of advantage.

Fast imaging of micro-structured thin film pattern of Al and Ag using a simultaneous Mattauch-Herzog mass spectrometer. As described in the main text, a potential restriction of this LA-ICP-MS imaging system is the number of isotopes which can be imaged in one laser shot. This limitation is caused by the sequential nature of data collection employed by the quadrupole or single collector sector field types of mass analyzers readily available and usually used. In order to record multiple isotopes simultaneously, mass analyzers such as a Mattauch-Herzog MS (MH-MS) or Time-of-Flight-MS (TOF-MS) would be most usefully utilized.

Figure S-2 compares the microscopic elemental images acquired using a LA-ICP-MH-MS to the optical microscope, and a lab-based micro-XRF system. The LA-ICP-MH-MS generated images reveal sharp pattern boundaries and characteristic microscopic features (indicated by white arrows in Figure S-2 a and b). However, due to the larger laser spot size required to obtain the sensitivity and the associated step size employed, the ICP-MH-MS images were not as detailed as the ICP-Q-MS images shown in Figure 5c and d. In contrast to Q-MS images, the top limits of the color bar in the MH images were scaled close to the maximum intensities, however they still showed a nearly homogeneous signal distribution in the pattern region. Therefore, a better representation of the real sample composition (no aliasing artifact) was obtained. One of the major advantages of the simultaneous mass spectrometer is the capability of measuring isotope ratios on every data point, which is not possible when using an ICP-Q-MS instrument.

In the present study, Figure S-3 a and b compares chemical images based on two naturally occurring Ag-isotopes present in the 'PSI' metallic Ag thin film pattern. Images were acquired using a LA-ICP-MH-MS. Both ^{107}Ag and ^{109}Ag isotopes showed highly correlated images. Within a short single shot signal pulse (compare also to Figure 3), such a high correlation can only be established if the two isotopes are acquired at the same time.

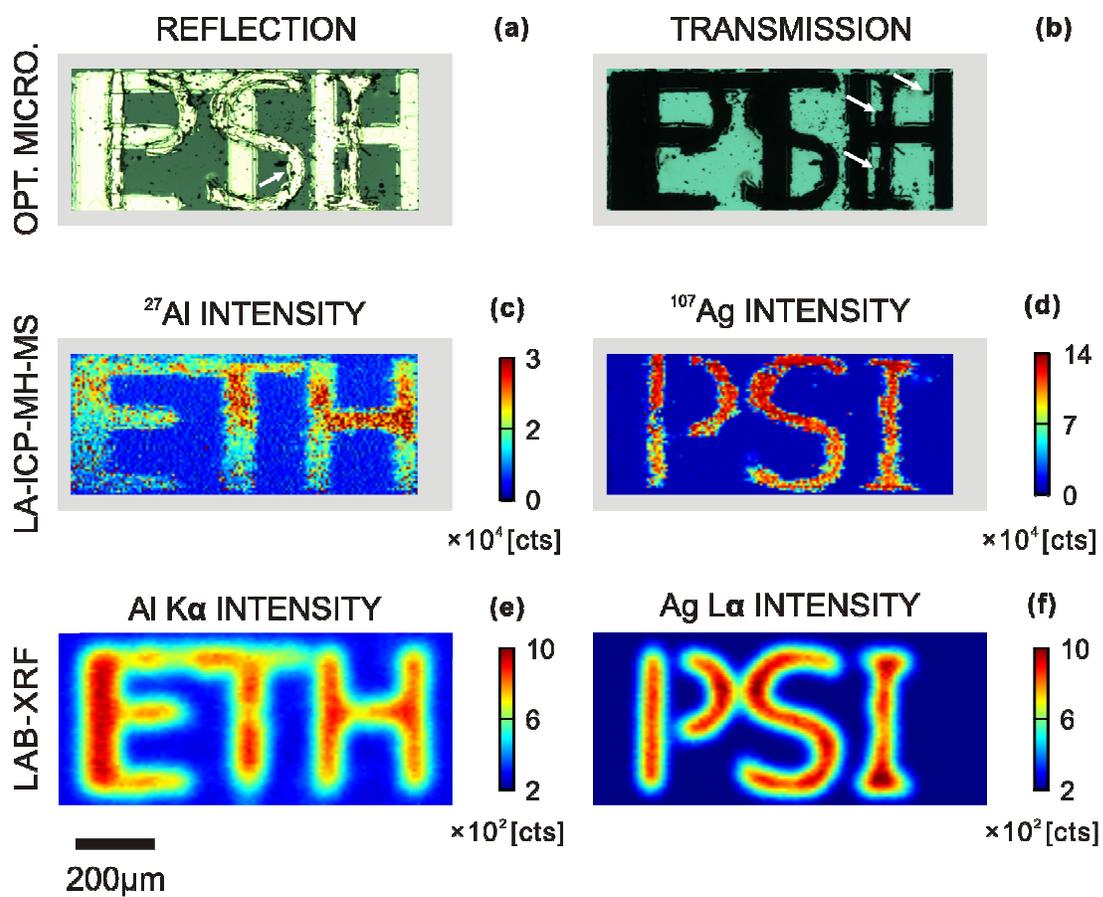


Figure S-2. Micro-structure metallic thin film pattern with Al ‘ETH’ thin film on bottom and Ag ‘PSI’ thin film on top was imaged by (a) and (b) optical microscopy; (c) and (d) tube cell equipped simultaneous acquisition LA-ICP-Mattauch-Herzog-MS; (g) and (h) lab based microXRF.

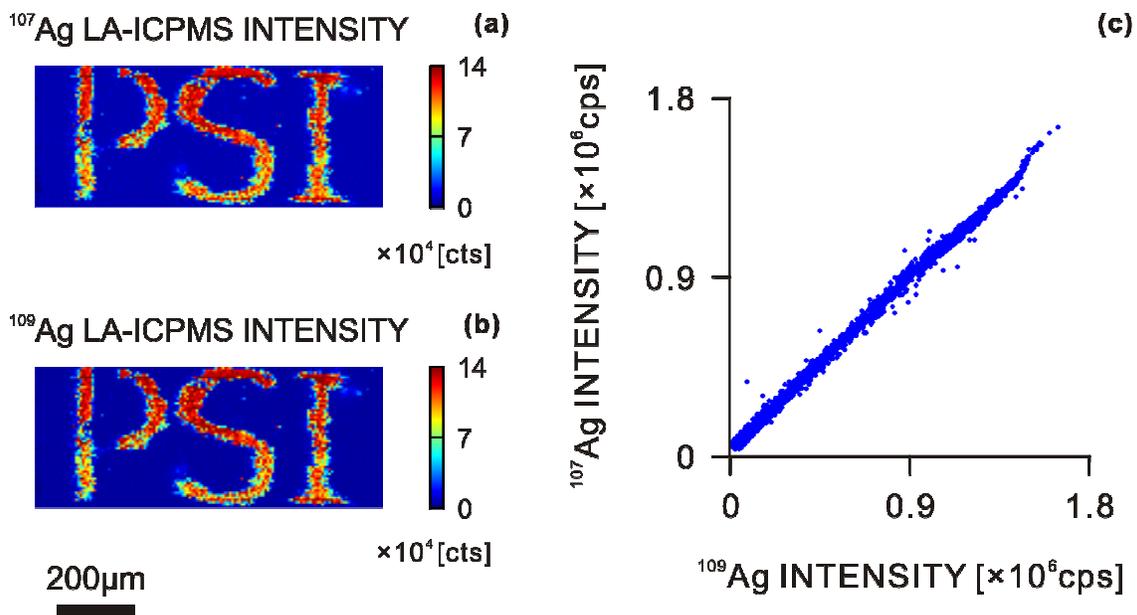


Figure S-3. Simultaneous acquisition of the two Ag isotopes (a) ^{107}Ag and (b) ^{109}Ag during micro-structure metallic thin film pattern with Al/Ag imaging by ICP-Mattauch-Herzog-MS. (c) correlation of the two Ag isotopes.

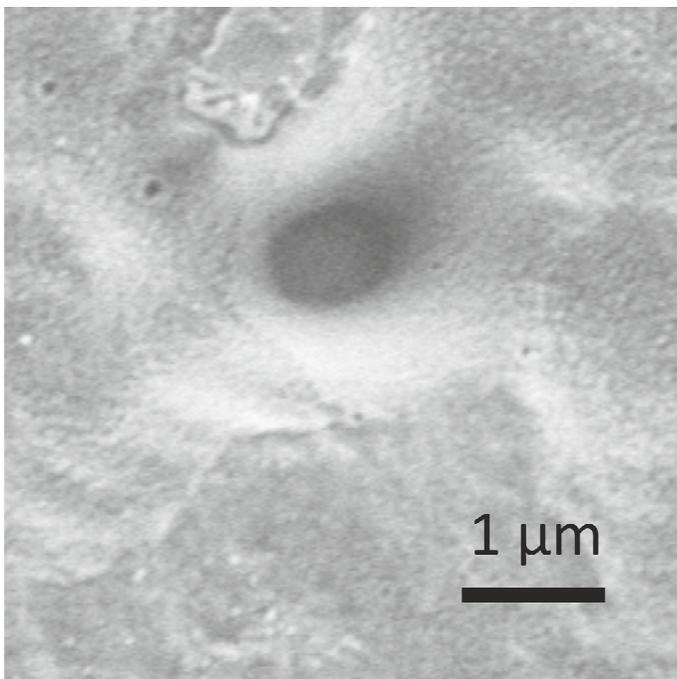


Figure S-4. Scanning electron microscope image of a single laser shot crater on the breast cancer tissue thin section.

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