

# High Resolution Mass Spectroscopy for Single Cell Analysis

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## ABSTRACT

Mass spectroscopy is an important analytical tool that has found pervasive use in numerous fields. This review tries to look at the recent advances in high resolution mass spectroscopy for single cell analysis covering the developments that contribute to improvement of the resolution of mass spectroscopy. These advances have been able to foment further challenges which require further research. This paper attempts to highlight these challenges and alludes to possible solutions for these challenges.

**Keywords:** Single Cell; Mass Spectroscopy; Mald; Nanophotonic; Laser Ablation; High Resolution

## Introduction

The importance of single cell analysis cannot be overstated as it is an analysis of a fundamental unit of biology which holds transcribed in itself the architectural print of genome and which is the biological manifestation of it. Single cell mass spectroscopy is a new and an increasingly important field of study with increasingly numerous applications. These applications of single cell mass spectrometry include, but are not restricted to Transcriptomics [1,2], Metabolomics [3], and Proteomics [4,5]. Single cell mass spectroscopy enables mapping of distribution of biomolecules at the subcellular resolution. The single cell analysis has been so instrumental in bringing about promising breakthroughs. It furnishes us with uniquely important insights into the variability of diseases and their treatments, highlighting the differences, and more importantly the causes of those differences [6]. The achievements of single cell analysis include analysis of mutations leading to brain cancer [7,8], understanding neuropathic pains [9], the profiles of transcription from the embryo of the hippocampus of the mouse and its neocortical neurons [10,11]. Chemical characterization of the single cell is an area of immense importance. Researchers over the years have developed various methods for such an analysis. Mass spectrometry has come to become a standard operational procedure for most of these technique from metabolomics to proteomics to genomics.

Given the prevalent importance of the single cell analysis, various researchers have devised many different methods to carry out Mass Spectroscopy for single cell analysis. This paper seeks to outline some of the important contributions made in this field, giving due importance to the methods adopted for each of those contributions.

## Discussion

Various techniques have been developed by researchers for the purpose of mass spectrometry. Each of these methods have its own advantages and disadvantages. Among these dozens of techniques three of the most commonly used techniques are Matrix-Assisted Laser Desorption Ionization (MALDI) [12], Secondary Ion Mass Spectrometry (SIMS) [13] and Desorption Electrospray Ionization (DESI) [14-16]. According to Petras et al. the figures of merits (lateral / spatial resolution, mass resolution, and duty cycle) of each of these techniques are defined by ionization source and mass analyzer [17]. The development of MS methods can be classified into two different categories based on the ionization method employed. Soft ionization methods are those methods that cause only limited or no fragmentation of the sample molecules, making them more desirable. This is achieved by allowing only limited increase in the internal energy of the molecule during the process

of ionization. These techniques suffer from lower mass limit of the produced ions such that the energy produced was not enough to ionize protein molecules. The hard ionization techniques, on the other hand, introduced very high fragmentation, but could ionize the proteins. This changed with the advent of MALDI [18,19].

MALDI improves the ionization mass many folds by the addition of matrix elements (cobalt nanoparticles and glycerol) while ionization was carried out using a laser [12,20,21]. But this many fold increase in the ionization comes at a cost of heavy noise from the matrix elements. Restricting the observable molecules among the sample, more importantly making the analysis of smaller molecules difficult [21]. Further development of MALDI, removing the overheads introduced by the steps of sample preparation and vacuum creation. These methods are known as Atmospheric Pressure Mass Spectrometry (AP-MS). In atmospheric pressure mass spectrometry, the sample is placed at atmospheric pressure rather than in a vacuum and with minimum or no sample preparation steps required for the analyte [22]. The advent of MALDI encouraged research in Laser Desorption and Ionization (LDI) based methods, but without the disadvantage of matrix noise. These LDI based variants of MALDI include use of graphite based matrix surface for ionization enhancement often called SALDI [23,24], use of gold nanowires [25,26], use of silver nanowires [27], use of Germanium nanodots [28,29], Platinum nanoflowers [30], Graphite Assisted Laser Desorption Ionization (GALDI) [31], silicon nanowires [32, 33], and nano-structured silicon surfaces [34-36]. One of the influential techniques was Nano Post Array (NAPA) [37].

Bennet Walker created Nano posts on the silicon substrate, in order to enhance the ion production of the system. The silicon nanopost array based ionization was used along with curved field reflectron time-of-flight (ToF) mass spectrometer and an ultraviolet nitrogen laser. The method was able to achieve mass range of 50 and 1500 Da with the limit of detection being 800zmol and 20zmol. The method proved useful for a lot of small molecules including pharmaceuticals, natural products, explosives, and metabolites with the additional advantage of no background due to absence of matrix in the analyte composition, unlike MALDI [38]. In a later work, NAPA was combined with Laser Desorption and Ionization (LDI) to produce NAPA-LDI-MS by Andrew Korte and his colleagues [39]. They were able to show that the combination of NAPA with LDI is potent for the detection of small molecules which is of immense importance for metabolite analysis and furthering the understanding of chemistry of metabolic reactions. The technique is able to detect large metabolic molecules as well as small molecules, thus widening the range of observable molecules. The technique was found to be useful for the detection of many classes of molecules including nucleotides, amino acids, xenobiotics, carbohydrates, lipids, etc., when tested on extracted samples of human serum. The samples were extracted from both aqueous and organic extracts.

After the production of Ion, the next important step is to get these Ions into the spectroscopic chamber. This is where Ion Mobility Separation (IMS) plays a role. It is a quick method for separating ions of different chemicals using collision cross-section with buffer gas. This interaction with buffer gas, which is an inert gas, takes place in a cell under electric field [40]. LAESI-IMS-MS was created out by combining traditional LAESI with IMS in order to conduct direct analysis of proteins mixtures from sections of mouse brain and various other biological samples. LAESI-IMS-MS improves the throughput rate of molecular detection, enabling LAESI to differentiate between analytes with similar mass to charge ratios through the separation of isobaric or other ions creating interference. The combination of LAESI and IMS drastically improves the reliability of molecular identification [41]. Laser radiation has become a preferred source of ion production because when in interaction with nanostructures results in unique processes [21]. The nature of the phenomenon that will ensue depends on various factors such as structural dimensions, material properties and the characteristics of the laser pulse employed for the experiment. In MALDI, the ionization is ensued due to rapid phase transition that would release the biomolecule from the matrix, and it will then be ionized by the plume [42-46].

As is evident from the nature of these methods, the generation of ions from biological substances is of crucial importance. The type of ions produced from these methods, variety of molecules produced from such a mass spectrometric method and their abundance depends on the nature of ionization process employed [21] Resolution is one of the most important elements among the figures of merit for a mass spectrometric system. A lot of effort has been directed towards achieving higher resolution from the spectroscopy. Resolution is considered in three ways; Lateral resolution, depth resolution and mass resolution. Lateral resolution is the minimum distance between two distinct objects that can be resolved on a given surface [47]. Depth resolution gives the thickness of the layer of material which is removed from a sample at each analysis. Techniques such as laser ablation electrospray ionization (LAESI) and secondary ion mass spectrometry (SIMS) make the resampling of a given sample possible, which can get information of successive layers of the sample through re-scanning. Through such operations, a sample can be analyzed layer by layer and its three-dimensional image can be generated. On the other hand, dividing the sample into thin slices and imaging each slice can be used to obtain three-dimensional information using MALDI and DESI [48]. Lastly, mass resolution is the ability of the mass analyzer to differentiate between two different masses.

The resolving power of a mass analyzer can thus be obtained by dividing mass of the sample by the peak width necessary for separation at a given mass. With the resolving power of 1000, it is difficult to differentiate between two isotopes. On the other hand, if the resolving power of the mass analyzer is 5000, the differentiation

between two isotopes is possible [49,50]. The mass resolution of a mass analyzer is an important feature of the system, but it is not the problem that will be addressed in this work. This work is focused on the lateral resolution and the depth resolution of the samples. "It should be noted that a higher lateral resolution results in smaller amount of material that is available for MS analysis. Thus, the smallest crater size that provides the best lateral resolution may lead to an inability to obtain MS signals." [51] The resolution of the system is thus based on the ability of the system to better ionize and detect larger as well as smaller molecules. The better ability to focus the laser and the ability to achieve a better depth of focus seem to be hinged in a trade-off. The earlier works have used many mechanisms of focusing the light, but these mechanisms juggle a trade-off between sharpness of the spot size and the penetration depth of the laser beam. A small spot-size leads to lower depth of focus and therefore lower penetration of the beam [52]. On the other hand, in case an ordinary focusing method is used, as is the case in most of the works of Vertes, this leads to fragmentation of the biological molecules.

The presence of ablating laser and the mass spectrometer on the same side of the sample can also be a hindrance in their ability to achieve better results. Calling this topology as reflection geometry (rg), a lot of works were conducted to achieve similar or better results from transmission geometry (tg). The transmission geometry has laser source below the sample, the ablated plumes travels along the direction of the laser, with the spectrometer right above it [53-56]. Transmission geometry has been adopted for various methods by different research groups producing among other methods tg-MALDI. This was used by Zavalin et. al. in order to obtain sub-cellular spatial resolution by focusing the laser beam on the dimensions less than 1 $\mu$ m. This enables the direct imaging of heterogeneous tissue sections, single cells and single cell lipid imaging with sub-cellular resolution [57]. The Desorption Electrospray Ionization has also been modified into transmission geometry to produce tg-DESI [58]. The system was tested on Nicotine and Bradykinin for both dry as well as well samples. The limit of detection for both Nicotine and Bradykinin samples was found to be 1.0pg and 0.3pg respectively for dry samples whereas in case of wet samples the limits of detection was 0.5pg and 0.3pg respectively. These results suggest that the sensitivity of the system in transmission geometry is comparable with the sensitivity of the results obtained from a system set up in reflection geometry.

In a similar work, Jacobson et al. conducted an In-Situ analysis of mammalian cells through tg-LAESI without any sample preparation. They introduced a 40x reflective objective as well along the path of laser to make the spot size smaller to about 10-40 $\mu$ m, this offered a tenfold improvement in Numerical Aperture compared to plano-convex lens used in rg-LAESI systems [59]. The system resulted in a limit of detection for rhodamine 6G, leucine enkephalin, and glutathione to be 300amol, 170fmol and 100fmol respectively. All these results were obtained through the

use of transmission geometry instead of reflection geometry and did not show any significant improvement when compared to their counterparts using reflection geometry. Most of the results obtained through these works show that transmission geometry and reflection geometry are at best comparable.

## Conclusion

In light of the above given discussion and analysis, it can be safely concluded that AP-MALDI is a good method to do mass spectroscopy, but it suffers from noise due to presence of matrix. Among other methods, SALDI and its variants provide a promising alternative because the improved ionization produced. Interesting improvisation in ionization method came with introduction of NAPA. Which increases the ionization many fold?

All these methods have their own shortcomings when depth resolution is used as a figure of merit. All of the methods which enable us to obtain resolution to the level of a single cell make the spatial information about those cells either very difficult to obtain or make it totally unavailable. The focusing mechanisms available to us at the moment can afford limited depth of focus for the focused light. It seems that unless we are able to improve the depth of focus of our instruments, we would not be able to improve the depth of focus of our analysis. In this regard, one of the possible routes is to employ metamaterial structures in order to create a deeper depth of focus. This is because, if it is possible to generate a beam of light which can stay focused for a longer distance in the transverse direction, it can potentially improve the resolution and the depth of focus of the spectroscopy. This can be potentially achieved by two methods. The first method can be, to use Super Oscillation of the light waves in order to improve the depth of focus [60] or the use a recently developed method of 'flying focus' in order to achieve focus at arbitrary depth [61].

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