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Mass spectrometry imaging: Facts and perspectives from a non-mass spectrometrist point of view

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ABSTRACT

Mass Spectrometry Imaging (MSI, also called Imaging Mass Spectrometry) can be used to map molecules according to their chemical abundance and spatial distribution. This technique is not widely used in mass spectrometry circles and is barely known by other scientists. In this review, a brief overview of the mass spectrometer hardware used in MSI and some of the possible applications of this powerful technique are discussed. I intend to call attention to MSI uses from cell biology to histopathology for biological scientists who have little background in mass spectrometry. MSI facts and perspectives are presented from a non-mass spectrometrist point of view.

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1. Introduction

Mass Spectrometry Imaging (MSI) is a technique that allows for 2D constructions of chemical abundance and has been used in biological and non-biological analyses of surfaces since the 60s. Molecule distributions in tissues and cells are predicted to be reconstructed and analyzed in 3D images very soon [1]. MSI is also referred to as Imaging Mass Spectrometry; however, in this review we will use the first denomination due to possible confusion with Ion Mobility Spectrometry (IMS), another technique in mass spectrometry (MS) used to distinguish molecules according to their mobility.

A search in Medline reveals thousands of published papers (original and reviews) using MSI and there are at least two well-known textbooks covering the biological applications of the technique [2,3]. Surprisingly, this powerful approach is not widely known even by top-level biological scientists not directly related to the MS field.

In this review, I present the MSI technique to scientists who are not familiar with it and may be able to use it to benefit their research. I do not expect to cover historical aspects of this technique or to provide an extensive review of the knowledge in the field. I will start with basic mass spectrometer anatomy and then present actual applications, problems and perspectives of MSI from a non-mass spectrometrist point of view.

2. A general view of the mass spectrometer's anatomy

The invention of the mass spectrometer is attributed to Sir Joseph John Thomson, who received the Nobel Prize in 1906. Mass spectrometrists, originally physicists and analytical chemists, love acronyms. Starting in the field can be as difficult as the first neuroanatomy class is to a freshman. Here, I am going to try to help the reader, as much as I can, in the scary world of the different mass spectrometers and the hyphenated techniques.

The mass spectrometer measures the mass-to-charge ratio (m/z) and is composed of three major parts (Fig. 1). Knowing these parts is mandatory to understanding what a designated mass spectrometer can do, as selecting the appropriate ionization source for an experiment and choosing the right mass analyzer are essential decisions for experimental success. For a more detailed discussion, I recommend reviews by Becker et al., (2010), Rubakhin and Sweedler (2010) and Vickerman (2011) [4–6].

2.1. The ion source

The ion source is the component responsible for applying charge to the molecules to produce ionization. The most well-known ion sources among non-mass spectrometrists are Electro-Spray Ionization (ESI) and Matrix-Assisted-Laser-Desorption/Ionization (MALDI). The desorption/ionization methods currently

Abbreviations: FTMS or FTICRMS, Fourier Transform Ion Cyclotron Resonance Mass Spectrometry; fMRI, functional Magnetic Resonance Imaging; ICR, Ion Cyclotron Resonance; IMS, Ion Mobility Spectrometry (ion mobility mass spectrometry); GC, Gas Chromatography; LA-ICP, Laser Ablation Inductively Coupled Plasma; MS, Mass Spectrometry; MSI, Mass Spectrometry Imaging; NTA, Non-Target Analysis; PET, Positron Emission Tomography; Q, Quadrupole; QT, Quadrupole Ion Trap; S/N, Signal-to-Noise ratio; TOF, Time of Flight; TQ, Tandem quadrupole.

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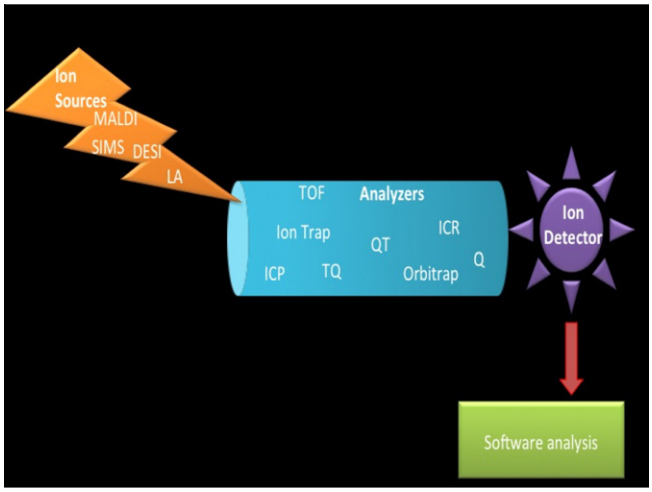

Fig. 1. The anatomy of a hypothetical mass spectrometer. Some of the possible ion sources and mass analyzers are shown together with both the detector and computer. This hypothetical mass spectrometer is in line with an event flow.

most used for MSI are secondary ion mass spectrometry (SIMS), desorption electrospray ionization (DESI), laser ablation (LA) with post-ionization and MALDI. Different imaging methods for MSI can be used in multi-approach imaging studies [7].

Light sources are used to vaporize and ionize molecules. LA is generally coupled to inductively coupled plasma (ICP), allowing for investigation of inorganic molecules. The LA-ICP-MSI technique has yielded important information about metal distributions in various tissues from a variety of species.

DESI uses charged solvents or droplets to bombard molecules, causing desorption and ionization of analytes in an electric field. Because DESI does not require sample preparation and can be used with different surfaces, its use in biological samples is increasing. SIMS uses a beam of accelerated ions, such as Au^+, Ar^+, Xe^+, O^-, O_2^+, Ga^+, and Cs^+, that targets the sample to promote desorption and ionization with higher spatial resolution (<μm) than MALDI [8], thus providing a clear advantage for analyses of biological samples. SIMS has been used to study endogenous and xenobiotic compounds, permitting the tracking of precursor ions and metabolite distribution in tissue. The high resolution of SIMS allows for studying the uptake and subcellular distribution of metals in cryogenically prepared tumoral cells [9]. New equipment capable of improving SIMS by creating 3D images of biological samples has been described [10]. This approach may be useful for understanding the chemical speciation of metals used in cancer therapeutics. Due to the difficulty in ion desorption with high m/z values by SIMS, MALDI remains the most cited source for MSI for biological applications [11].

MALDI desorbs and ionizes molecules by firing a laser over a sample co-crystallized with a matrix (generally 2,5-dihydroxybenzoic acid – DHB and alpha-cyanocinnamic acid – CHCA) for further analysis. MALDI frequently generates ions with a single charge, facilitating data processing and analysis. The spatial resolution of MALDI is low for investigation at cellular and subcellular levels (20–50 μm). Thinking as a biochemist (and sometimes as a cell biologist), I suspect that the biggest challenges for equipment development are going to be in increasing the spatial resolution. There are some problems with trying to understand a cell from a 2D/3D point of view: 1) the laser energy requirement for desorption/ionization is high and the diameter of the laser beam used to fire samples is still wide. Decreasing the beam would promote spatial resolution; however, the problem lies in the relationship between the laser diameter and the number of molecules to be detected; and 2) to reconstruct the cellular architecture, cellular compartmentalization must be respected. As we know from confocal microscopy, it is very important to determine and control the beam penetration. Thus, it is difficult to use MSI because the beam enters the tissue, burning all the way down. Desorption/ionization can burn adjacent areas, thus decreasing spatial specificity even with a very precise stepping motor. I expect that alternative approaches for collecting samples and promoting further ionization will be developed in the future.

2.2. The mass analyzer

After ionization, the ions are sent to the mass analyzer, which is the part of the mass spectrometer responsible for separating the generated ions. Ions are selected according to their mass, charge and shape. The mass analyzer plays an important role in sending and selecting ion packages to the detector, improving sensitivity. Some high-end instruments use the analyzer to throw away undesirable molecules, thus decreasing the noise and improving the signal-to-noise ratio (S/N) and detection limits.

Different analyzers are commercially available and use a variety of physical strategies to separate ions, including the possibility of ion fragmentation for further analysis. Pulsed analyzers are generally used for ion identification with high mass resolution. Time-Of-Flight (TOF), ion trap, Orbitrap and Ion Cyclotron Resonance (ICR) are frequently used in MSI. This approach is often used either to identify a desirable molecule or to compare different states using Non-Target Analysis (NTA). The quadrupole single (Q), tandem (TQ) and hybrid ion trap (QT) are usually used for quantification processes for a particular m/z value. Companies are using the properties of different analyzers to build hybrid machines to amplify the range of use and to decrease the relative experimental cost.

2.3. The mass detector

The detector is the end of a mass spectrometer. It is responsible for quantification of ions after separation by the analyzer. Detectors receive the signals and send them to the mass detector, building the mass spectrum. The different spectra are analyzed using software produced and optimized by the manufacturer. Signal detection and analysis are always related to the S/N ratio, especially with MSI.

2.4. The computer

I began by saying that a mass spectrometer is composed of three major parts. Indeed, due to the large number of spectra generated (one for each xy coordinate), many gigabytes of data can be produced during a MSI experiment, requiring data storage. Image treatment requires fast processing, so the computer hardware and software can be rate-limiting factors. For MSI especially, the software and computer configuration dedicated to the mass spectrometer are extremely important.

3. MSI applications in biological sciences: from tissues to cells

MSI has been used to solve several biological questions. I will discuss some of the important MSI uses (including non-biological applications) to give different perspectives of the technique. I am positive that what we learn from non-biological applications of MSI can be adapted to reveal new possibilities for biological research. For example the understanding of the composition of layers of paint in the study of ancient pictures can help us to elucidate paleontological issues as well as tissue aging, separating out the information from the biological sample and the environmental

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