Whitepaper

From materials to microorganisms: The emergence of MALDI-TOF as a tool for clinical diagnostics

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Introduction

Within the last 30 years, matrix-assisted laser desorption/ionization (MALDI), in conjunction with time-of-flight mass spectrometry (TOF MS), has emerged as a powerful technology for determining structures of macromolecules such as proteins, and more importantly, for identifying microorganisms to species level through their proteomic 'fingerprints'.

This whitepaper looks back at the history of MALDI-TOF, the early role of Bruker's scientists in producing the first commercial MALDI-TOF system, and their resulting influence on the technique's widespread adoption. It considers the expansion of its applications, from materials and pharmaceuticals to the biomolecular field, driven by improvements in the instrumentation, the launch of the Bruker MALDI Biotyper®, the software, and the mass-spectral reference libraries used to identify unknown microorganism samples.

Finally, it explores the ongoing evolution of MALDI Biotyper applications, further advancing today's patient care through fast, easy and cost-effective microorganism identification in a hospital setting.

The origins and early history of MALDI

Like many scientific advances, MALDI had its origins in a sequence of unexpected discoveries and insights. In the mid-1980s, various groups around the globe – including Koichi Tanaka in Japan, and Michael Karas, Doris Bachmann and Franz Hillenkamp in Germany – were carrying out research using laser desorption. The latter group, based at the University of Frankfurt and Muenster, were having trouble with background signals during laser desorption of Ca^{2+} ions,[1] and they suspected that the background was derived from the polymer matrix. This led to a proposal that laser desorption could also be used to generate ions of organic molecules – and so the concept of MALDI was born.

Bruker's involvement in this research quest – to ionize organic macromolecules in order to analyze them using mass spectrometry (MS) – took place in the mid-1980s, and was carried out at Bremen, Germany, within the company Bruker Franzen Analytik GmbH. The work was led by the late Dr. Jochen Franzen, who had found some success with resonance-enhanced multiphoton ionization (REMPI).

Bruker's first commercial MALDI-TOF instrument

Bruker realized that, should MALDI become a viable prospect, there was opportunity to couple it to their existing TOF technology (Bruker TOF-1), which had been available on the market since 1988. This realization hinged on the fact that MALDI generates packets of ions as a consequence of needing to pulse the laser. These ion packets couldn't be analyzed by scanning MS instruments such as quadrupoles, but were perfect for coupling to TOF instruments, which at the time were not so well-known in the analytical community.

The commercial landscape changed in 1991, when the publication of a detailed paper on MALDI by Hillenkamp made the details of the technology public and eliminated any possibility of a patent being granted. As a result, Bruker moved quickly to develop a MALDI-based ion source that could be used in conjunction with its existing TOF system. A fully functional prototype of the resulting MALDI-TOF system – known as Reflex MALDI-TOF – was presented the same year at the International Mass Spectrometry Conference, and this was followed in 1992 by a full commercial roll-out.

Early applications of MALDI-TOF

Bruker's first Reflex MALDI-TOF system could accommodate a single sample, but the need for higher throughput meant that this was soon extended, with subsequent models offering capacity for up to 10 samples (1993), 26 samples (1994) and 384 samples (1998), the latter in a microtiter plate format. Importantly, all these systems offered linear MALDI-TOF as well as reflectron MALDI-TOF operation, which increases mass accuracy and mass resolution – a capability that is still used today.

A further key for success in the early years was Bruker's introduction of pulsed ion extraction (PIE) in 1996, which improved mass resolution by compensating for the energy distribution of molecular ions. This capability also proved popular, and is marketed today as 'panoramic mass resolution' (PAN™).

Despite these advantages, this early instrumentation and software required considerable expertise to operate, meaning that at first it was largely used for academic research. But as the benefits of MALDI-TOF for analyzing larger molecules became clear, an increasing number of real-world applications opened up, especially relating to quality control.

One such application was in materials science, specifically to determine the chain length of polymers.[3] Previous technologies had a lack of precision and took a long time to generate results. By being able to determine the mass distribution of large polymer molecules very quickly and much more precisely, MALDI-TOF presented an appealing alternative. This had immediate use in a number of applications – for example, in processing car parts, where knowing the length of the polymer chain helps to ensure that the polymer product is both stable and flexible.

2017 25 Years of MALDI

In 2017, we celebrate MALDI — the breakthroughs, the insights made and those to come. Over the decades, we have built knowledge to evolve the technology, we pushed boundaries in its application, and we created a world-class family of instruments.

2015 rapifleX with 10kHz Laser

Bruker introduces 10kHz scanning SmartBeam 3D Laser technology that delivers true pixel fidelity using aspherical optics for ultra-high speed MALDI MS applications.

2013 solariX XR MALDI

Bruker introduces the solariX MALDI FTMS System with e**X**treme **R**esolution

2007 MALDI Biotyper

Bruker introduces bench-top MALDI Biotyper MS system for microbiology applications.

2005 SmartBeam Laser

The Bruker-patented SmartBeam Laser technology is introduced. This innovation optimizes UV laser focus profiles for improved MALDI performance. Bruker is the world's only Mass Spec manufacturer developing and producing their own laser technology.

Holle et. al. J.Mass Spectrom. 2006; 41: 705-716

2004 autoflex TOF/TOF microflex LRF & LT

microflex LRF is introduced as benchtop system for routine applications e.g. polymer analytic and high molecular mass conformation.

autoflex TOF/TOF is used as "workhorse" for various analytical workflows incorporating the established TOF/TOF technology.

2002 Nobel Prize for MALDI

Koichi Tanaka shares Nobel Prize in Chemistry with John B. Fenn and Kurt Wüthrich for the development of methods for identification and structural analysis of biological macromolecules.

2001 ultrafleX TOF/TOF

Expansion of Bruker's fleX series modular design with the ultrafleX TOF and TOF/TOF. The new fragmentation technology TOF/TOF is established in research instruments to gain structural information of biomolecules.

2000 autoflex TOF

Bruker introduces the worlds first MALDI-TOF system dedicated for automation and robotic supported workflows. By combining the autoflex with an automated universal microplate handler, the system enabled high-sample throughput for up to 30,000 samples.

1997 First publication MALDI Imaging

Molecular imaging of biological samples: localization of peptides and proteins using MALDI-TOF MS.

Caprioli RM, Farmer TB, Gile, J.
Anal Chem. 1997 Dec 1;69(23):4751-60.

1996 Pulsed Ion Extraction

Bruker introduces pulsed ion extraction (PIE), improving the MS resolution by orders of magnitude showing isotopic distribution of biomolecules.

1992 REFLEX MALDI-TOF

Bruker introduces its first commercially available MALDI-TOF system using patented gridless ion-reflectron for simultaneous time and spatial ion focusing.

Timeline created in 2017, at the occasion of celebrating 25 years of MALDI at Bruker.

Another practical application in the early days of Reflex MALDI-TOF was in the pharmaceutical industry. The inherent sensitivity of MALDI-TOF made it highly suited to detecting and identifying trace levels of contaminants in drug development and production – improving the speed, accuracy, reliability and limits of detection compared to existing methods.

The Reflex MALDI-TOF also found application in biomolecular research, with early work at the University of Michigan showing how MALDI-TOF could be used to identify pre-sonicated bacterial suspensions based on their protein profiles.[4] Less than two years later, a flurry of papers from researchers at Manchester Metropolitan University,[5] the National Center for Toxicological Research[6] and Edgewood Research[7] extended this concept to the analysis of *intact* gram-positive and gram-negative bacteria using their 'spectral fingerprints'. From these and other studies, it became clear to the scientists at Bruker that MALDI-TOF had great potential for identifying bacteria – a concept that we can now recognize as laying the groundwork for the modern implementation of this technique in clinical diagnostics.

Improvements in MALDI-TOF system useability

Alongside continued research advances in the late 1990s – including an increase in accessible molecular mass and the development of algorithms for spectral comparison[9] – came a recognition by Bruker that improvements in system usability were needed to break into new markets. It was no longer sufficient to have a system that was technically outstanding; it needed to be easy to use too.

This required a change in mindset to not only focus on the hardware, but also making the technology more accessible by an easy to use and intuitive software. Alongside these developments came consumables, automation tools, modules for tailored workflow and standard operating procedures.

Unlike other manufacturers, Bruker implemented many of these product changes using in-house expertise rather than by outsourcing. This made it much easier to uphold product quality, and helped cement its reputation as a leader in the field.

The MALDI Biotyper: launch and product evolution

The improvements in system useability allowed Bruker to greatly expand its presence in the field of microorganism identification and clinical diagnostics. Following the early studies, Bruker had been working on the development of these applications, leading to the launch of the MALDI Biotyper in 2007.[10] This instrument delivered vast improvements for microbial identification compared to traditional metabolite-derived biochemical techniques in terms of accuracy, speed, species coverage, ease of use and cost-effectiveness.

Within a few years, the MALDI Biotyper had gained a global reputation for microbial identification in a clinical setting, supported by the creation of the Microbiology and Diagnostics business within Bruker and the release of the IVD-CE certified model in 2009. As an illustration of this, early studies described the identification of a range of microorganisms, including bacteria,[11,12,13,14,15] yeasts[16] and fungi.[17,18]

Today, applications of the MALDI Biotyper include:

- **Clinical diagnostics:** The identification of microorganisms to the species level is a key focus of microbiological laboratories across the globe. The MALDI Biotyper is used to identify microbe species accurately and rapidly, to help in finding the appropriate therapy and improve patient care.

- **Pharmaceuticals:** Drugs and vaccines must be free from microorganism contamination, and the MALDI Biotyper is used to identify contaminating strains so that the source can be located and contained.

- **Veterinary labs:** A critical task in veterinary microbiology is securing identification of veterinary pathogens. The MALDI Biotyper allows this to be done in a timely manner, to control the incidence and spread of pathogens.

- **Water testing:** To test for waterborne microbes, many test laboratories still rely on time-consuming techniques involving subculturing of 'presumptive colonies'. The MALDI Biotyper eliminates the need for this step, speeding up water testing.

- **Foods and beverages:** Accurate microbiological testing is vital for the detection of foodborne pathogens, possible food spoilage organisms and technological strains. Using the MALDI Biotyper, laboratories can rapidly identify and confirm the species involved, enabling food and beverage manufacturers to make fast decisions.

The expansion of the spectral library has been central to all this success. In the early days of the MALDI Biotyper, Bruker microbiologists were well aware that its applications depended crucially on being able to match the mass spectrum of an unknown organism against a reference library. From the outset, Bruker therefore worked internally, with its customers and multiple national strain collection reference centers, to obtain a broad species coverage. The resulting spectral libraries are comprehensive and continue to be updated annually, meaning that today, the MALDI Biotyper can identify close to 4,700 species (library versions 2022).

Current microbiological and diagnostic applications

In the last 10 years, the applications of the MALDI Biotyper in microbiology and clinical diagnostics have expanded enormously. To illustrate some of this diversity, this section cites a selection of papers that show how the applications of the MALDI Biotyper are evolving.[19]

As an example, the direct identification from positive blood culture by using Bruker's MBT Sepsityper® IVD Kit needs to be mentioned. Sepsis is a life-threatening condition that reportedly affects more than 30 million people worldwide each year. Early identification of the causative pathogen significantly improves patient outcomes in terms of morbidity and mortality, and has a positive impact on the healthcare economy.[20]

Another approach with widespread applicability is phenotypic resistance testing, in which the MALDI Biotyper is used to detect certain proteins involved in resistance to antibiotics of a particular structural class. A good example is the identification of ß-lactamases,[21] with the MBT STAR-Carba kit being launched in 2017 for the detection of carbapenemase activity.

Other approaches offer the option for more broad-based resistance/susceptibility testing, and include the use of isotope-labeled amino acids to cause a diagnostic peak shift in newly synthesized proteins.[22] A further recent advance – implemented in the ASTRA assay – provides a measure of susceptibility, by acquiring mass spectra both with and without antibiotic.[23,24]

Although the MALDI Biotyper is typically used to determine organisms to species level, in many cases there are signals that enable the determination of certain biomarkers, and this offers an alternative approach to phenotypic resistance testing. This has the potential to be useful for particularly virulent or resistant strains, as demonstrated for *Bacteroides fragilis*,[25] *Streptococcus agalactiae*,[26] *Klebsiella pneumoniae*,[27] and phylogroups of *Escherichia coli*.[28,29] A potential marker for methicillin-resistant *Staphylococcus aureus* has also been identified.[30]

These advances in diagnostics are complemented by improvements to sample preparation workflows, driven by the ever-growing need for faster turnaround times, and exemplified by a modified assay for resistance detection performed directly on the MALDI target plate.[31] Extending the workflow concept further is the incorporation of the MALDI Biotyper into a total laboratory automation approach, which has been shown to result in significant improvements in sample throughput.[32]

MALDI Biotyper® sirius & MALDI Biotyper® sirius one

Conclusion

Within a remarkably short space of time, MALDI-TOF has been transformed from a research laboratory application to a technique that is used every day in thousands of microbiology laboratories worldwide; approximately 180 million identifications are performed globally on an annual base, using the MALDI Biotyper (2022). This transformation is due in large part to the product innovation spearheaded by scientists at Bruker, who have strived to make the technology not only powerful but easy to use by the non-specialist.

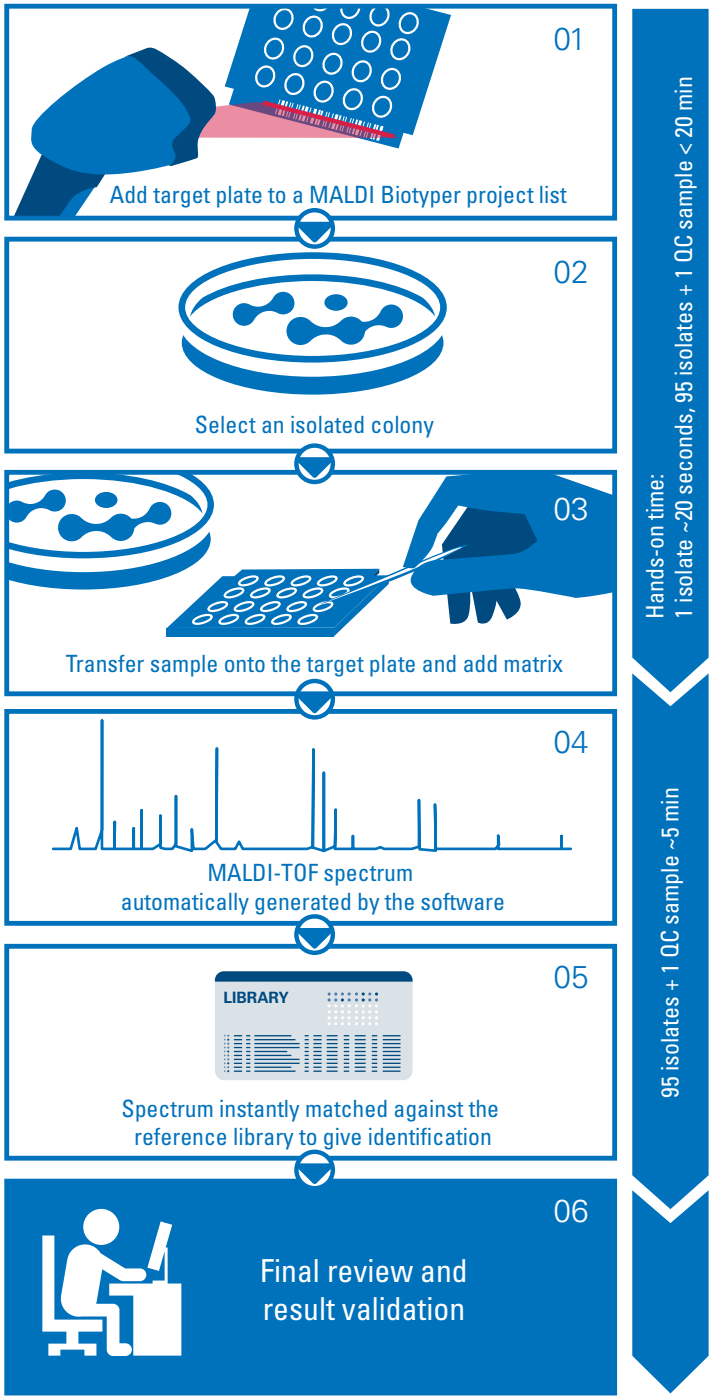
Today, within the clinical sector, Bruker's MALDI Biotyper is routinely employed across a wide range of applications, with rapid workflows helping contribute towards faster diagnosis of microbial infections. This leads to more timely therapeutic interventions that, ultimately, help save patients' lives.

About the MALDI Biotyper

The MALDI Biotyper is an easy-to-use microorganism identification system based on MALDI-TOF MS. It determines the unique proteomic fingerprint of a microorganism and matches characteristic patterns with an extensive reference library to determine the organism's identity. Continuous expansion of the reference library ensures that a broad range of microorganisms can be identified easily and reliably.

The MALDI Biotyper provides results quickly, allowing unbiased identification of cultured bacteria, yeasts and fungi to species level within a few minutes. Its broad applicability and low sample processing costs make the instrument ideal for identifying microorganisms in a clinical or industrial setting.

The MALDI Biotyper workflow is streamlined and simple, and no experience with mass spectrometry is needed. Workflows are fully traceable, and analysis of a full 96-spot MALDI target plate on the latest generation of MALDI Biotyper systems takes only about 5 minutes.



Click here for more information about the MALDI Biotyper.

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