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REVIEW ON MALDI MASS SPECTROMETRY AND ITS APPLICATION IN CLINICAL RESEARCH

Oluwatosin Ogundairo¹, Oluwatoyin Ayo-Farai², Chinedu Paschal Maduka³,
Chiamaka Chinaemelum Okongwu⁴, Abdulraheem Olaide Babarinde⁵, &
Olamide Tolulope Sodamade⁶

¹Independent Researcher, Louisiana, USA.

²Jiann-Ping Hsu College of Public Health, Georgia Southern University, USA

³Institute of Human Virology, Nigeria

⁴Faculty of Community Health and Primary Care, Department of Public Health,
University of Lagos, Nigeria

⁵The Heller School for Social Policy and Management, Brandeis University, Waltham
Massachusetts, USA

⁶Africa Voices HQ, Nigeria

Corresponding Author: Oluwatosin Ogundairo

Corresponding Author Email: jokedairo@gmail.com

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ABSTRACT

Mass spectrometry has emerged as a powerful analytical tool in various scientific disciplines, and Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry (MALDI-MS) has gained significant prominence, particularly in the field of clinical research. This review provides a comprehensive overview of MALDI-MS, its principles, and its applications in clinical research settings. This study delves into the technical aspects of MALDI-MS, discussing key components such as the matrix, sample preparation methods, and mass analyzers. It highlights recent advancements and innovations in MALDI-MS technology, showcasing its evolution and adaptation to meet the increasing demands of clinical applications. MALDI-MS involves the use of laser energy to desorb and ionize molecules from a solid-phase matrix, enabling the

analysis of a wide range of biomolecules, including proteins, peptides, lipids, and metabolites. The technique's ability to analyze complex biological samples with high sensitivity and specificity has made it invaluable in clinical research. In the realm of clinical research, MALDI-MS has found applications in disease diagnosis, biomarker discovery, and therapeutic monitoring. The review explores specific examples of MALDI-MS applications in various clinical areas, including oncology, infectious diseases, and metabolic disorders. Case studies and experimental findings are presented to underscore the practical utility of MALDI-MS in these contexts. Moreover, the review discusses the challenges and limitations associated with MALDI-MS in clinical research, such as standardization of protocols, reproducibility, and sample heterogeneity. Strategies to overcome these challenges are addressed, emphasizing ongoing efforts to enhance the reliability and robustness of MALDI-MS-based analyses in clinical settings. MALDI-MS has proven to be a transformative technology in clinical research, offering unique insights into the molecular landscape of diseases and paving the way for personalized medicine. As MALDI-MS continues to evolve, its integration into routine clinical workflows holds the potential to revolutionize diagnostics and improve patient outcomes. This review serves as a valuable resource for researchers, clinicians, and industry professionals seeking a comprehensive understanding of MALDI-MS and its myriad applications in the field of clinical research.

Keywords: MALDI-MS, Clinical Research, Review, Ionization Mass Spectrometry.

INTRODUCTION

Matrix-assisted laser desorption/ionization (MALDI) mass spectrometry (MS) has emerged as a powerful tool in clinical research, offering a versatile and sensitive approach for analyzing a wide range of biomolecules, including proteins, peptides, lipids, and nucleic acids (Borisov, Matveeva, and Zaikin, 2023, Williams-Pavlangos, et al., 2023). Its ability to rapidly provide high-resolution mass spectra without the need for extensive sample preparation has made it a valuable tool for various clinical applications, including biomarker discovery, disease diagnosis, and therapeutic development (Harvey, 2023).

MALDI-MS has gained significant traction in biomarker discovery, enabling the identification of unique molecular signatures associated with specific diseases or conditions (Neagu et al., 2023). By analyzing biological samples, such as blood, serum, or tissue, researchers can detect and characterize potential biomarkers that can serve as early indicators of disease progression or treatment response (Jalaludin, Lubman, and Kim, 2023). This information can aid in developing diagnostic tools and personalized treatment strategies.

MALDI-MS is increasingly being applied to disease diagnosis, particularly in areas where traditional diagnostic methods are limited or unreliable. For instance, MALDI-MS has demonstrated effectiveness in identifying and differentiating bacterial strains, contributing to rapid and accurate diagnosis of infectious diseases. Additionally, MALDI-MS is being explored for diagnosing cancer and other complex diseases by analyzing tumor biopsies or blood samples.

MALDI-MS plays a crucial role in therapeutic development, particularly in the areas of drug discovery and pharmacodynamics. By analyzing drug-protein interactions and monitoring drug distribution in tissues, researchers can assess drug efficacy and optimize drug design (He et al.,

2021). Additionally, MALDI-MS can be used to monitor drug metabolism and identify potential drug metabolites, aiding in pharmacokinetic studies and personalized medicine approaches (Castellino, Groseclose, and Wagner, 2011, Greco et al., 2018).

MALDI-MS offers several advantages that make it a valuable tool in clinical research. MALDI-MS can detect and quantify minute amounts of biomolecules, making it ideal for analyzing low-abundance proteins or peptides (Novaconi et al., 2023). MALDI-MS offers rapid sample analysis, providing results within minutes, allowing for timely decision-making in clinical settings. MALDI-MS can analyze a wide range of biomolecules, including proteins, peptides, lipids, and nucleic acids, making it a versatile tool for various clinical applications. MALDI-MS requires minimal sample preparation, reducing the risk of sample degradation and preserving the integrity of biomolecules (Wang, Shunxiang, and Qian, 2023, Wei, Luo, and Zhan, 2023). MALDI-MS provides reproducible results, ensuring the reliability and consistency of data generated as MALDI-MS technology continues to advance, its role in clinical research is expected to expand further. With its ability to provide rapid, sensitive, and versatile analysis of biomolecules, MALDI-MS holds immense potential for biomarker discovery, disease diagnosis, and therapeutic development, contributing to improved patient care and outcomes. This study delves into the technical aspects of MALDI-MS, discussing key components such as the matrix, sample preparation methods, and mass analyzers. It highlights recent advancements and innovations in MALDI-MS technology, showcasing its evolution and adaptation to meet the increasing demands of clinical applications.

MALDI MASS SPECTROMETRY IN CLINICAL RESEARCH.

Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry (MALDI-MS) has emerged as a transformative technology in clinical research, providing a versatile platform for molecular analysis. This abstract explores the applications, recent advancements, and significance of MALDI-MS in the context of clinical research.

MALDI-MS finds widespread applications in clinical research, notably in disease diagnosis, biomarker discovery, drug development, and microbial identification. It enables the rapid and accurate identification of disease-specific biomarkers, aiding in early diagnosis and subtyping of various medical conditions. The technique also contributes to understanding drug metabolism and pharmacokinetics, facilitating drug development and personalized medicine. In microbial identification, MALDI-MS offers a rapid and precise method for pathogen detection and assessment of antibiotic resistance, crucial for guiding treatment strategies.

Recent advancements in MALDI-MS technology have expanded its capabilities. High-resolution MALDI imaging allows detailed spatial mapping of molecular distributions within tissues, providing insights into disease progression and treatment response. Integration with liquid chromatography (LC-MALDI) enhances peak resolution and sensitivity, particularly in complex proteomic studies. Tandem mass spectrometry (MALDI-MS/MS) provides improved structural information, enhancing identification accuracy. Automation and high-throughput analysis have accelerated data generation, making MALDI-MS applicable in large-scale clinical studies.

The significance of MALDI-MS in clinical research is profound. It supports precision medicine by providing molecular information for tailored treatment strategies, contributes to early disease detection, and advances therapeutic monitoring. The technology bridges the gap between research and clinical practice, translating molecular discoveries into diagnostic and therapeutic

applications. MALDI-MS has become integral to patient-specific profiling, enabling more effective and personalized healthcare.

MALDI-MS stands as a cornerstone technology in clinical research, offering a comprehensive and powerful tool for molecular analysis. Its applications in disease diagnosis, biomarker discovery, drug development, and microbial identification, coupled with recent advancements, underscore its significance in advancing clinical research. As MALDI-MS continues to evolve, its transformative impact on diagnostics, treatment strategies, and disease understanding positions it as a pivotal player in shaping the future of personalized medicine and clinical practice.

Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry (MALDI-MS) has evolved into a transformative tool in clinical research, offering unprecedented capabilities for molecular analysis. This review explores the applications and recent advancements of MALDI-MS, emphasizing its significance in the medical field.

Applications in Clinical Research: MALDI-MS enables the rapid and accurate identification of disease-specific biomarkers, aiding in the diagnosis and subtyping of various medical conditions. Differentiation of cancer subtypes, microbial identification, and characterization of neurological disorders. MALDI-MS facilitates the discovery and validation of biomarkers associated with diseases, enabling early detection and personalized treatment strategies. Identification of serum, tissue, or urine biomarkers for conditions such as cancer, diabetes, and neurodegenerative disorders.

Applications of MALDI-MS in Clinical Research: Disease Diagnosis and Subtyping: Biomarker Discovery and Validation

MALDI-MS has emerged as a powerful tool for disease diagnosis and subtyping, particularly in the area of biomarker discovery and validation. Biomarkers are molecules that can serve as indicators of disease presence, progression, or treatment response. MALDI-MS offers several advantages for biomarker research, including its ability to:

Identify unique molecular signatures: MALDI-MS can detect and characterize a wide range of biomolecules, including proteins, peptides, lipids, and nucleic acids. By analyzing these biomolecules in biological samples, such as blood, serum, or tissue, researchers can identify unique molecular patterns associated with specific diseases. **Provide high sensitivity:** MALDI-MS can detect low-abundance biomolecules, making it suitable for identifying biomarkers that may be present in small amounts. MALDI-MS can provide results within minutes, enabling researchers to quickly screen for potential biomarkers and assess their diagnostic potential.

The process of biomarker discovery and validation using MALDI-MS typically involves the following steps. **Sample Collection and Preparation:** Biological samples are collected from patients with and without the disease of interest. Samples are then prepared for MALDI-MS analysis, which may involve steps such as protein extraction, purification, and digestion. **MALDI-MS Analysis:** MALDI-MS is used to analyze the prepared samples, generating mass spectra that represent the molecular profiles of the samples. Statistical analysis and machine learning algorithms are used to compare the mass spectra of cases and controls, identifying potential biomarkers that show significant differences in abundance or pattern between the two groups. Further studies are conducted to validate the identified biomarkers, assessing their sensitivity, specificity, and reproducibility in larger patient cohorts.

MALDI-MS has been successfully applied to biomarker discovery and validation for various diseases. MALDI-MS has been used to identify protein and peptide biomarkers for various cancers, including breast cancer, lung cancer, and colorectal cancer. These biomarkers can aid in early diagnosis, cancer subtype classification, and treatment selection. MALDI-MS has been used to identify bacterial and viral biomarkers, enabling rapid and accurate diagnosis of infectious diseases. This is particularly valuable for diseases where traditional diagnostic methods may be limited or unreliable. MALDI-MS has been used to identify protein and peptide biomarkers for neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease. These biomarkers can aid in early diagnosis, disease monitoring, and drug development.

The ability of MALDI-MS to identify and validate biomarkers is revolutionizing the field of clinical research, leading to improved diagnostic tools, personalized treatment strategies, and better patient outcomes. As MALDI-MS technology continues to advance, its role in biomarker discovery and validation is expected to expand further, paving the way for more effective and individualized healthcare.

Drug Metabolism and Pharmacokinetics: MALDI-MS contributes to understanding drug metabolism and pharmacokinetics, aiding in drug development and personalized medicine. Monitoring drug metabolites, assessing drug distribution in tissues, and optimizing drug formulations. MALDI-MS facilitates rapid and accurate identification of microbial species and determination of antibiotic resistance profiles. Identification of pathogens in clinical samples, assessment of antibiotic susceptibility, and epidemiological studies.

Proteomic Profiling of Clinical Samples: MALDI-MS allows high-throughput proteomic profiling, providing insights into the molecular signatures of diseases. Comparative proteomics of tissues, serum, or urine to discover disease-specific protein markers. Improved spatial resolution in MALDI imaging allows for detailed mapping of molecular distributions within tissues. Enhanced resolution enables the identification of subtle molecular changes in disease progression and treatment response.

Integration with Liquid Chromatography (LC-MALDI): Integration of MALDI with liquid chromatography enhances the separation of complex biological samples. Improved peak resolution and sensitivity, particularly in proteomic studies.

Recent Advancements in MALDI-MS: High-Resolution MALDI Imaging and Integration with Liquid Chromatography (LC-MALDI)

Matrix-assisted laser desorption/ionization (MALDI) mass spectrometry (MS) has undergone significant advancements in recent years, expanding its capabilities and applications in various fields, particularly in biomedical research, drug discovery, and clinical diagnostics. These advancements have led to increased sensitivity, specificity, and resolution, enabling the analysis of a wider range of biomolecules and providing more detailed information about their structure and function.

High-Resolution MALDI Imaging, Integration with Liquid Chromatography, Machine Learning and Artificial Intelligence (AI) Applications, Automation and High-Throughput Analysis, Tandem Mass Spectrometry are some of the key recent advancements in MALDI-MS (Kernalléguen et al., 2023, Wang et al., 2023, Dueñas et al., 2023). MALDI-IMS has emerged as a powerful tool for visualizing the spatial distribution of biomolecules within tissues and organs. By combining MALDI-MS with high-resolution imaging techniques, such as MALDI-

FTICR MS and MALDI-TOF MS with improved resolution, researchers can generate detailed molecular maps of tissues, revealing the localization of specific proteins, peptides, lipids, and other biomolecules. This information has valuable applications in drug discovery, disease diagnosis, and biomarker research. The integration of MALDI-MS with liquid chromatography (LC) has significantly expanded the range of analytes that can be analyzed by MALDI-MS. LC-MALDI coupling allows for the separation of complex mixtures of biomolecules prior to analysis by MALDI-MS, enabling the identification and quantitation of individual components, even those present in low abundance. This technique is particularly valuable for analyzing biological fluids, tissue extracts, and pharmacokinetic studies. Tandem mass spectrometry (MS/MS) techniques, such as MALDI-TOF/TOF MS and MALDI-QTOF MS, have been incorporated into MALDI-MS instruments, providing enhanced structural characterization of biomolecules. MALDI-MS/MS can fragment biomolecules, generating sequence-specific fragment ions that provide detailed structural information. This information is crucial for identifying and characterizing proteins, peptides, and other biomolecules, aiding in drug discovery, biomarker research, and proteomics studies.

Also, Automation and high-throughput analysis capabilities have been incorporated into MALDI-MS instruments, streamlining data acquisition and analysis, particularly for large-scale studies. Automated sample preparation, data acquisition, and analysis software have significantly reduced the time and labor required for MALDI-MS experiments, enabling researchers to process large numbers of samples efficiently. Machine learning and AI are being applied to MALDI-MS data analysis, enabling the development of automated data interpretation tools and improving the accuracy of biomarker identification and disease classification. AI algorithms can analyze complex MALDI-MS data sets, identifying patterns and relationships that may be difficult for humans to detect.

These recent advancements have significantly enhanced the capabilities of MALDI-MS, expanded its applications and providing new insights into biological processes. As MALDI-MS technology continues to evolve, it is expected to play an increasingly important role in biomedical research, drug discovery, clinical diagnostics, and personalized medicine.

MALDI-MS has undergone significant advancements in recent years, expanding its capabilities and applications in various fields. Two notable advancements are high-resolution MALDI imaging and integration with liquid chromatography (LC-MALDI).

High-resolution MALDI imaging (MALDI-IMS) has emerged as a powerful tool for visualizing the spatial distribution of biomolecules within tissues and organs. By combining MALDI-MS with high-resolution imaging techniques, such as MALDI-FTICR MS and MALDI-TOF MS with improved resolution, researchers can generate detailed molecular maps of tissues, revealing the localization of specific proteins, peptides, lipids, and other biomolecules. High-resolution MALDI imaging has found valuable applications in various areas as shown in the figure 1.

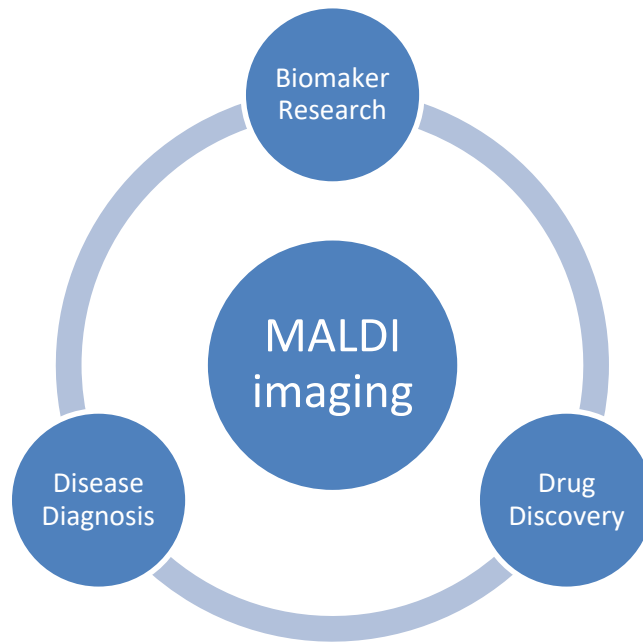


Figure 1. Area of application of High-resolution MALDI imaging

MALDI-IMS can help identify and localize drug targets within tissues, facilitating drug development and optimizing drug delivery strategies. Disease Diagnosis: MALDI-IMS can aid in disease diagnosis by revealing the distribution of disease-associated biomarkers within tissues, providing insights into disease progression and treatment response. MALDI-IMS can facilitate biomarker discovery and validation by identifying biomolecules that show distinct localization patterns in different disease states.

The integration of MALDI-MS with liquid chromatography (LC) has significantly expanded the range of analytes that can be analyzed by MALDI-MS. LC-MALDI coupling allows for the separation of complex mixtures of biomolecules prior to analysis by MALDI-MS, enabling the identification and quantitation of individual components, even those present in low abundance. liquid chromatography technique is particularly valuable for analyzing the three items shown in figure 2.

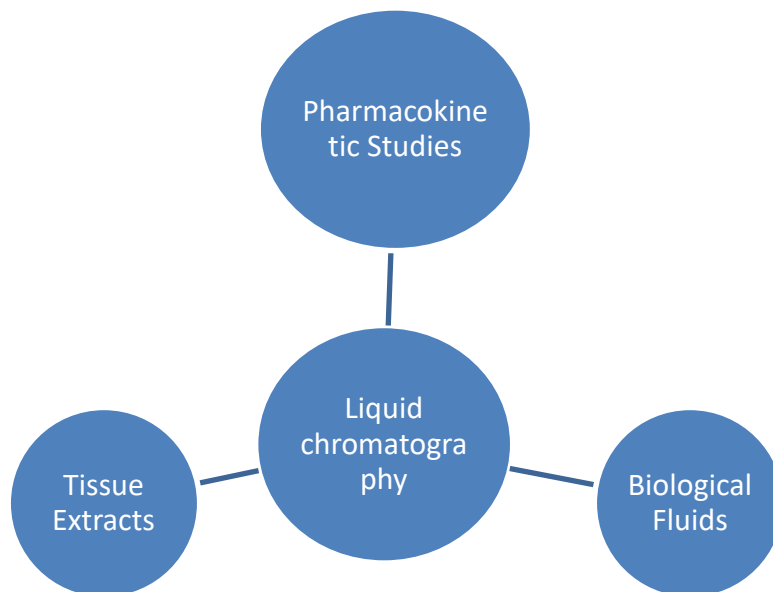


Figure 2. Liquid chromatography technique areas of analysis

LC-MALDI can effectively analyze complex biological fluids, such as blood serum or plasma, which contain a wide range of biomolecules with varying concentrations. LC-MALDI can be used to analyze tissue extracts, separating complex mixtures of proteins, peptides, and lipids for detailed characterization. LC-MALDI can monitor drug distribution and metabolism in biological fluids, providing valuable insights into drug efficacy and pharmacokinetics.

These advancements in MALDI-MS have significantly enhanced its capabilities, expanding its applications and providing new insights into biological processes. High-resolution MALDI imaging offers a detailed view of molecular distribution within tissues, while LC-MALDI expands the range of analyzable biomolecules. As MALDI-MS technology continues to evolve, it is expected to play an increasingly important role in biomedical research, drug discovery, and clinical diagnostics.

MALDI-MS/MS provides enhanced structural information through tandem mass spectrometry. Improved identification accuracy, particularly for complex samples and post-translational modifications. Automation of sample preparation and data acquisition enables high-throughput analysis. Accelerated data generation, making MALDI-MS more applicable in large-scale clinical studies.

Significance of MALDI-MS in the Medical Field: Precision Medicine Implementation

MALDI-MS has emerged as a transformative tool in the medical field, playing a pivotal role in the implementation of precision medicine. Precision medicine aims to tailor medical treatments to individual patients based on their unique genetic, molecular, and lifestyle characteristics. MALDI-MS contributes to precision medicine in several ways as shown in figure 3.

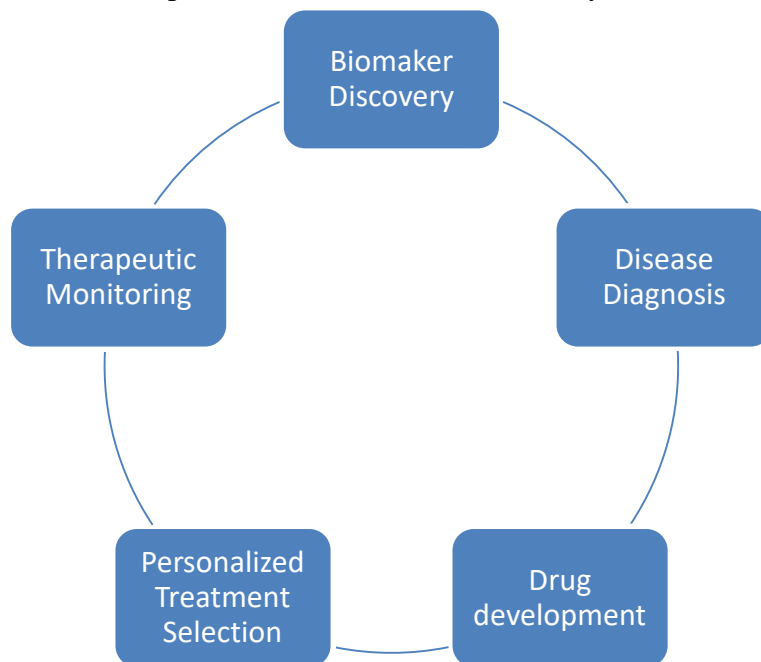


Figure 3. Areas of MALDI-MS contribution to precision medicine

MALDI-MS enables the identification of unique molecular signatures associated with specific diseases or conditions. These biomarkers can serve as indicators of disease presence, progression, or treatment response, guiding personalized treatment decisions. MALDI-MS facilitates rapid and accurate diagnosis of various diseases, including infectious diseases, cancer, and neurodegenerative diseases. This information enables early intervention and personalized treatment strategies. MALDI-MS provides insights into drug-protein interactions,

drug distribution, and drug metabolism, aiding in drug discovery and optimization. By understanding how drugs interact with the body, researchers can design more effective and safer therapies. MALDI-MS can monitor drug levels and metabolites in biological fluids, enabling personalized dosage adjustments and optimizing therapeutic efficacy while minimizing side effects. MALDI-MS can help predict a patient's response to specific treatments, enabling the selection of the most effective therapy for each individual patient. This personalized approach maximizes treatment outcomes and reduces unnecessary interventions.

Examples of MALDI-MS applications in precision medicine include; Cancer Treatment, Neurological Disorders, and Infectious Disease Management. MALDI-MS can identify tumor-specific biomarkers, enabling the selection of targeted therapies that specifically target the cancer cells, minimizing harm to healthy cells. MALDI-MS can identify protein and peptide biomarkers for neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, aiding in early diagnosis and personalized treatment strategies. MALDI-MS can rapidly identify and characterize bacteria, fungi, and viruses, enabling effective antibiotic or antiviral treatment selection.

MALDI-MS is revolutionizing the way we approach healthcare, moving towards a more personalized and effective model of treatment. As MALDI-MS technology continues to advance, its impact on precision medicine is expected to expand further, leading to improved patient care and outcomes.

Precision Medicine Implementation: MALDI-MS supports the principles of precision medicine by providing molecular information for tailored treatment approaches. Patient-specific profiling contributes to more effective and personalized therapeutic strategies. MALDI-MS enables the identification of early molecular changes associated with diseases (Piras and Cramer, 2023). Early detection allows for timely intervention and improved outcomes in conditions like cancer and neurodegenerative disorders (Chiang, and Hsiao, 2023). MALDI-MS aids in monitoring treatment responses and drug efficacy. Real-time monitoring enhances the ability to adjust treatment regimens for optimal patient outcomes.

Bridging the Gap Between Research and Clinical Practice: The advancements in MALDI-MS technologies contribute to bridging the gap between research findings and clinical applications. Translation of molecular discoveries into clinical diagnostics and decision-making.

MALDI-MS has emerged as a cornerstone technology in clinical research, with diverse applications ranging from disease diagnosis to drug development (Shah et al., 2023, MALDI-TOF, and Dikler, 2023). Recent advancements in resolution, integration with other techniques, and automation have further elevated its significance in the medical field. As MALDI-MS continues to evolve, its potential to revolutionize diagnostics, treatment strategies, and our understanding of diseases makes it a key player in shaping the future of clinical research and personalized medicine.

Fundamentals of MALDI-MS: Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry (MALDI-MS) represents a powerful analytical technique widely applied in various scientific disciplines. This section delves into the core principles, instrumentation, and essential sample preparation techniques that constitute the fundamentals of MALDI-MS.

MALDI-MS is a mass spectrometric technique known for its ability to ionize large biomolecules, providing detailed molecular information (Williams-Pavlantos, and

Wesdemiotis, 2023). It explores the foundational principles of ionization and mass spectrometry within the context of MALDI. The matrix serves a crucial role in facilitating the ionization process. It unpacks the intricate process of laser-induced desorption and ionization within the MALDI context.

Mass Spectrometry Instrumentation Overview: Mass spectrometry (MS) is an analytical technique that measures the mass-to-charge ratio of ions to identify and quantify molecules in simple and complex mixtures (Lai and Wang, 2023). MS has become invaluable across a broad range of fields and applications, including proteomics (Babele and Yadav, 2023). The development of high-throughput and quantitative MS proteomics workflows within the last two decades has expanded the scope of what we know about protein structure, function, modification, and global protein dynamics. This overview outlines the role of mass spectrometry in the field of proteomics, reviews MS methodology and instrumentation, and touches on sample preparation and liquid chromatography–based separation prior to MS analysis. Figure 4 shows the working operation

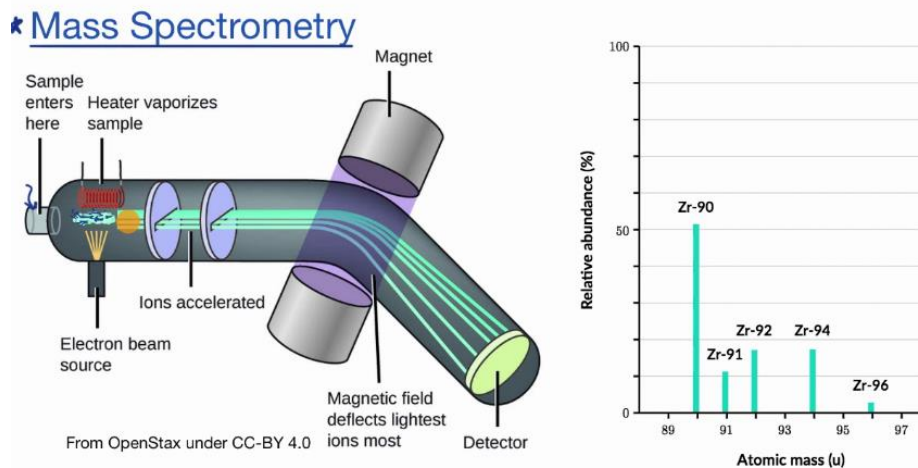


Figure 4. Working operation of Mass spectrometry (libry.tv)

Mass Spectrometer Components: the key components of the mass spectrometer are presented in figure 5.

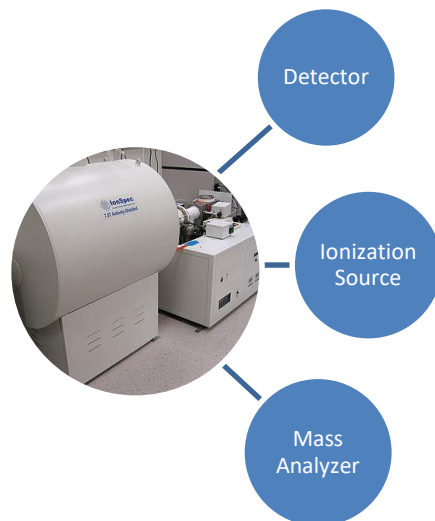


Figure 5. Key Components of Mass Spectrometer

The ionization source provides an overview of the ionization source specific to MALDI-MS. The mass analyzer discusses the types of mass analyzers employed in MALDI-MS. Detector describes the detector system capturing ions after the ionization process.

Time-of-flight mass spectrometry (TOFMS) is a method of mass spectrometry in which an ion's mass-to-charge ratio is determined by a time-of-flight measurement (Hegen et al., 2023). Ions are accelerated by an electric field of known strength, which results in an ion having the same kinetic energy as any other ion that has the same charge. This acceleration results in the ions having different velocities, which are measured by the time it takes for the ions to reach a detector. The mass-to-charge ratio of the ions is then calculated from the time-of-flight data. TOFMS is a versatile analytical technique used to detect and characterize mixtures of organic molecules.

In the context of matrix-assisted laser desorption/ionization (MALDI) mass spectrometry (MS), TOFMS is a popular choice due to its high sensitivity, high resolution, and wide mass range. TOFMS is also capable of analyzing complex mixtures of molecules, making it a valuable tool in proteomics research. One of the limitations of TOFMS is its susceptibility to matrix interferences, which can lead to poor signal-to-noise ratios and decreased sensitivity. Additionally, TOFMS is not as effective as other mass spectrometry techniques for the analysis of large molecules such as proteins and peptides.

Sample Preparation Techniques: In MALDI-MS, the matrix plays a crucial role in the ionization process. It is responsible for absorbing the laser energy and transferring it to the analyte molecules, resulting in the formation of ions (Sivanesan et al., 2023). The following are some criteria that guide the selection of an appropriate matrix; the matrix should have a strong optical absorption in either the ultraviolet or infrared range to efficiently absorb the laser irradiation (Gu et al., 2021). The matrix should contain polar groups, which allow them to be used in aqueous solutions (Schulthess et al., 2014). The matrix should have a low volatility to prevent sublimation during the MALDI process (Fonville et al., 2012). The matrix should have a minimal spectral overlap with the analyte of interest to avoid interference with the detection of the analyte ions (Gemperline, Rawson, and Li, 2014). Common techniques for preparing matrices in MALDI-MS include the dried droplet method, the sandwich method, and the sublimation method (Li, 2009). The dried droplet method is the most commonly used technique and involves mixing the matrix and analyte in a volatile solvent, followed by drying the mixture on a MALDI target plate. The sandwich method involves placing the matrix and analyte between two layers of matrix, while the sublimation method involves depositing the matrix onto the MALDI target plate by sublimation (Wiangnon, and Cramer, 2015).

In MALDI-MS, sample preparation is a crucial step that can significantly impact the quality of the results. The following are some considerations for different sample states (Kussmann, and Roepstorff, 2000). Solid samples can be directly analyzed by MALDI-MS. However, the presence of impurities and contaminants can interfere with the analysis. Therefore, it is essential to clean the sample surface before analysis (Dewi et al., 2023). Liquid samples can be analyzed by MALDI-MS using the dried droplet method. In this method, the sample is mixed with the matrix and deposited on the MALDI target plate. The solvent is then allowed to evaporate, leaving behind a dried droplet of the sample-matrix mixture. Gas samples can be analyzed by MALDI-MS using the desorption/ionization on silicon (DIOS) method. In this method, the gas

sample is adsorbed onto a silicon wafer, which is then coated with a matrix. The matrix is then irradiated with a laser, resulting in the desorption and ionization of the gas molecules.

Pre-treatment procedures are essential for removing impurities and contaminants from the sample (Kanik, Kuligiewicz, and Cullen, 2024). Common pre-treatment procedures include washing the sample with solvents, filtering the sample, and centrifugation. Co-crystallization techniques are used to co-crystallize the matrix and the sample, which can improve the sensitivity and reproducibility of the analysis. Common co-crystallization techniques include the dried droplet method, the sandwich method, and the sublimation method.

MALDI-MS Imaging Sample Preparation: MALDI-MS imaging is a powerful technique that allows for the spatially resolved analysis of biological samples (van de Van et al., 2016). MALDI-MS imaging is a spatially resolved analysis technique that allows for the visualization of the spatial distribution of molecules in biological samples (Calligaris et al., 2013). MALDI-MS imaging has a wide range of applications in biomedical research, including the identification of biomarkers, the characterization of drug distribution in tissues, and the study of metabolic pathways.

Drug Development and Pharmacokinetics: Drug development and pharmacokinetics are closely intertwined disciplines that play a critical role in the discovery, development, and optimization of safe and effective medications. Pharmacokinetics, the study of how the body absorbs, distributes, metabolizes, and eliminates drugs, provides essential information throughout the drug development process, guiding decisions on drug formulation, dosage, and administration.

In the early stages of drug discovery, pharmacokinetics plays a pivotal role in identifying and selecting promising drug candidates. By evaluating the pharmacokinetic properties of potential drugs, researchers can assess their absorption, distribution, metabolism, and elimination (ADME) profiles, ensuring that drugs reach their intended targets and are eliminated from the body at an appropriate rate.

Throughout the drug development process, pharmacokinetics provides valuable insights into drug behavior and helps ensure that drugs are safe and effective. Pharmacokinetic studies are conducted at various stages, including; Preclinical Studies, Phase I Clinical Trials, and Phase II and III Clinical Trials. In preclinical studies, pharmacokinetics is used to evaluate drug absorption, distribution, metabolism, and elimination in animal models. This information is crucial for predicting how the drug will behave in humans and informing decisions on dosage, formulation, and route of administration. In Phase I clinical trials, pharmacokinetics is used to evaluate the drug's safety and tolerability in small groups of healthy volunteers. This information helps determine the appropriate dosage for further clinical trials and assess the drug's potential for adverse effects. In Phase II and III clinical trials, pharmacokinetics is used to evaluate the drug's efficacy and safety in larger patient populations. This information provides the basis for regulatory approval and helps determine the optimal dosage and administration schedule for the drug.

Even after a drug has received regulatory approval and is marketed, pharmacokinetics continues to play a crucial role in ensuring its safety and effectiveness. Post-market surveillance studies monitor the drug's pharmacokinetic behavior in real-world settings, identifying any potential interactions with other drugs or effects in specific patient populations.

Pharmacokinetic modeling and simulation (PK/PD) are powerful tools that can be used to predict drug behavior and inform drug development decisions. PK models describe the pharmacokinetic properties of a drug, while PD models describe the relationship between drug concentration and pharmacological effect. By combining PK and PD models, researchers can simulate the drug's behavior in various scenarios, predicting its efficacy, safety, and potential for drug interactions.

Pharmacokinetics is a rapidly evolving field, with new technologies and approaches emerging continuously. These advancements are expected to further enhance the role of pharmacokinetics in drug development, leading to safer, more effective, and personalized medications.

Drug development and pharmacokinetics are inseparable partners in the quest for effective and safe medications. Pharmacokinetic insights guide decisions throughout the drug development process, from initial discovery to post-market surveillance, ensuring that drugs are tailored to the human body and provide optimal therapeutic benefits.

Microbial Identification and Antibiotic Resistance: Microbial identification and antibiotic resistance are crucial aspects of clinical microbiology, providing essential information for diagnosing infections, selecting appropriate antibiotic therapies, and monitoring the spread of antibiotic-resistant pathogens. Rapid and accurate microbial identification and assessment of antibiotic susceptibility are necessary for effective patient management and infection control practices.

Rapid pathogen detection methods are essential for timely diagnosis and treatment of infections. Traditional methods, such as culture and microscopy, can be time-consuming and labor-intensive, delaying appropriate antibiotic therapy. Molecular techniques, such as polymerase chain reaction (PCR) and nucleic acid hybridization, offer rapid and accurate pathogen identification, enabling clinicians to initiate treatment sooner and improve patient outcomes.

Antibiotic susceptibility testing (AST) is critical for determining the effectiveness of different antibiotics against specific pathogens. Traditional AST methods, such as agar diffusion and broth dilution, are also time-consuming and require several days to complete. Rapid AST methods, such as automated broth microdilution and phenotypic resistance testing, offer quicker results, allowing for more timely and targeted antibiotic therapy.

Microbial identification and antibiotic resistance data are crucial for epidemiological studies, providing valuable insights into the spread of infectious diseases and antibiotic resistance patterns. This data can be used to develop effective prevention and control strategies, track the emergence of new antibiotic-resistant strains, and inform public health policy decisions.

Technologies for Microbial Identification and Antibiotic Resistance: Numerous technologies are employed for microbial identification and antibiotic resistance testing, including: Molecular Methods, Automated AST Systems, Mass Spectrometry. In molecular methods which uses PCR, nucleic acid hybridization, sequencing technologies, Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry, Automated AST Systems; Automated broth microdilution, phenotypic resistance testing, and Electrochemical biosensors, microfluidic devices

Challenges and Future Directions: Despite significant advancements, challenges remain in microbial identification and antibiotic resistance testing. These include emergence of new and resistant pathogens. Continuous surveillance and research are needed to identify and characterize new pathogens and emerging resistance mechanisms. Development of rapid and

accurate diagnostic tests. Ongoing efforts are focused on developing faster and more reliable diagnostic tools for both pathogen identification and antibiotic susceptibility testing. Improved data integration and sharing: Effective data management and sharing platforms are essential for tracking antibiotic resistance patterns and informing public health interventions.

Microbial identification and antibiotic resistance are critical areas in clinical microbiology, providing essential information for patient care, infection control, and public health measures. Advances in molecular techniques, automated systems, and biosensors are transforming the field, enabling rapid and accurate diagnosis of infections, personalized antibiotic therapy, and effective surveillance of antibiotic resistance patterns. Continuous research and development are crucial to address emerging challenges and ensure that effective tools are available to combat infectious diseases and the spread of antibiotic resistance.

Recent Technological Advancements in MALDI-MS: Matrix-assisted laser desorption/ionization (MALDI) mass spectrometry (MS) has emerged as a powerful tool in various fields, including biomedicine, forensics, and environmental analysis. Recent technological advancements have further enhanced the capabilities of MALDI-MS, expanding its applications and providing new insights into biological processes.

High-resolution MALDI imaging (MALDI-IMS) offers a unique approach for visualizing the spatial distribution of biomolecules within tissues and organs. By combining MALDI-MS with high-resolution imaging techniques, such as MALDI-FTICR MS and MALDI-TOF MS with improved resolution, researchers can generate detailed molecular maps of tissues, revealing the localization of specific proteins, peptides, lipids, and other biomolecules. This information has applications in drug discovery, disease diagnosis, and biomarker research.

The integration of MALDI-MS with liquid chromatography (LC) has significantly expanded the range of analytes that can be analyzed by MALDI-MS. LC-MALDI coupling allows for the separation of complex mixtures of biomolecules prior to analysis by MALDI-MS, enabling the identification and quantitation of individual components, even those present in low abundance. This technique is particularly valuable for analyzing biological fluids and tissue extracts, where a wide range of biomolecules may be present.

Tandem mass spectrometry (MS/MS) techniques, such as MALDI-TOF/TOF MS and MALDI-QTOF MS, have been incorporated into MALDI-MS instruments, providing enhanced structural characterization of biomolecules. MALDI-MS/MS can fragment biomolecules, generating sequence-specific fragment ions that provide detailed structural information. This information is crucial for identifying and characterizing proteins, peptides, and other biomolecules, aiding in drug discovery, biomarker research, and proteomics studies.

Automation and high-throughput analysis capabilities have been incorporated into MALDI-MS instruments, streamlining data acquisition and analysis, particularly for large-scale studies. Automated sample preparation, data acquisition, and analysis software have significantly reduced the time and labor required for MALDI-MS experiments, enabling researchers to process large numbers of samples efficiently. These advancements have facilitated large-scale proteomics studies, biomarker discovery, and clinical research applications.

Recent technological advancements in MALDI-MS have transformed the technique into a versatile and powerful tool for analyzing a wide range of biomolecules in various fields. High-resolution MALDI imaging, integration with LC, tandem MS capabilities, and automation have expanded the applications of MALDI-MS and provided new insights into biological processes.

As MALDI-MS technology continues to evolve, it is expected to play an increasingly significant role in biomedical research, drug discovery, clinical diagnosis, and environmental analysis.

Significance in Clinical Practice: MALDI-MS has emerged as a transformative tool in clinical practice, offering significant advancements in precision medicine, early disease detection, therapeutic monitoring, and clinical diagnostics.

MALDI-MS plays a pivotal role in implementing precision medicine by enabling the identification of unique molecular signatures associated with specific diseases or conditions. This information allows clinicians to tailor treatments to individual patients based on their specific molecular profiles, maximizing treatment efficacy and minimizing side effects. For instance, MALDI-MS can be used to identify biomarkers for cancer, enabling personalized cancer therapies.

The ability of MALDI-MS to detect and characterize biomolecules at low concentrations makes it a valuable tool for early disease detection. By analyzing biomolecules in biological samples, such as blood, serum, or tissue, MALDI-MS can identify early signs of disease, enabling timely intervention and improved patient outcomes. For example, MALDI-MS can be used to detect potential biomarkers for Alzheimer's disease, allowing for early diagnosis and potential treatment strategies.

MALDI-MS can be used to monitor drug distribution, metabolism, and efficacy in patients, providing valuable information for optimizing therapeutic strategies. By measuring drug levels and metabolites in biological fluids, clinicians can adjust drug dosages and regimens to ensure optimal therapeutic effects while minimizing adverse reactions. This personalized approach to therapeutic monitoring has significant implications for improving patient outcomes and reducing healthcare costs.

MALDI-MS is rapidly translating into clinical practice, offering new diagnostic tools and approaches for various diseases. In clinical microbiology, MALDI-MS can be used for rapid and accurate identification of bacteria, fungi, and viruses, enabling timely treatment of infectious diseases. In cancer diagnosis, MALDI-MS can be used to identify tumor-specific proteins and peptides, aiding in cancer classification and treatment selection.

MALDI-MS has revolutionized clinical practice, providing a powerful tool for precision medicine, early disease detection, therapeutic monitoring, and clinical diagnostics. Its ability to analyze biomolecules with high sensitivity and specificity has led to the development of novel diagnostic tools, personalized treatment strategies, and improved patient outcomes. As MALDI-MS technology continues to advance, its impact on clinical practice is expected to expand further, transforming the way we diagnose, treat, and monitor diseases.

MALDI-MS: Challenges and Future Directions: Despite its remarkable progress and transformative impact on various fields, MALDI-MS still faces certain challenges that need to be addressed, while also holding immense potential for future technological developments and clinical applications.

Addressing Current Challenges: MALDI-MS requires sample preparation to convert biomolecules into ionization-ready forms. This can be a complex and time-consuming process, especially for certain types of samples, such as tissues or complex biological fluids. The ionization efficiency of different biomolecules can vary significantly, leading to potential biases in the analysis. Developing strategies to enhance the ionization of low-abundance biomolecules

is crucial for comprehensive analysis. MALDI-MS generates complex datasets that require sophisticated data analysis and interpretation tools. Developing user-friendly and robust software tools is essential for making MALDI-MS more accessible to researchers and clinicians.

Future Technological Developments: Improved Ionization Sources by developing new ionization sources that can effectively ionize a wider range of biomolecules with enhanced sensitivity and ionization efficiency is crucial for expanding the applicability of MALDI-MS. High-Resolution Ion Detection by enhancing the mass resolution and accuracy of MALDI-MS instruments will enable the detection and characterization of closely related biomolecules, such as isoforms and post-translationally modified proteins. Integration with Other Imaging Techniques by combining MALDI-MS with other imaging modalities, such as optical microscopy or electron microscopy, will provide a more comprehensive understanding of the spatial distribution of biomolecules within tissues and cells. Automated Sample Preparation and Data Analysis by developing automated sample preparation and data analysis pipelines will streamline MALDI-MS workflows and make the technique more accessible to a wider range of users.

Potential Clinical Applications: Biomarker Discovery and Disease Diagnosis. MALDI-MS has the potential to revolutionize disease diagnosis by enabling the identification of unique molecular signatures associated with specific diseases. This information can lead to the development of early diagnostic tools and personalized treatment strategies. Drug Discovery and Development. MALDI-MS can be used to evaluate drug interactions, monitor drug metabolism, and assess drug efficacy, providing valuable insights for drug discovery and development processes. MALDI-MS can facilitate precision medicine by tailoring treatments to individual patients based on their unique molecular profiles, maximizing treatment efficacy and minimizing side effects. Developing portable and user-friendly MALDI-MS instruments has the potential to bring the power of MALDI-MS to point-of-care settings, enabling rapid and accurate diagnosis at the patient's bedside.

MALDI-MS has emerged as a powerful tool with immense potential for future technological advancements and clinical applications. Addressing current challenges and pursuing these future directions will further expand the capabilities of MALDI-MS, leading to significant breakthroughs in various fields, including biomedicine, drug discovery, and clinical diagnostics.

Future Prospects and Role of MALDI-MS in Personalized Medicine

As MALDI-MS technology continues to advance, its impact on personalized medicine is expected to expand further. Portable MALDI-MS instruments could enable rapid and accurate diagnosis at the point-of-care, facilitating personalized treatment decisions in real-time settings. Integration of MALDI-MS with AI and Machine Learning: Combining MALDI-MS data with AI and machine learning algorithms could enhance biomarker discovery, improve disease diagnosis, and optimize treatment selection for individual patients. MALDI-MS could play a pivotal role in personalized drug development by enabling the identification of drug targets and tailoring drug therapies to specific patient populations based on their genetic and molecular profiles. MALDI-MS could be used to monitor treatment response and disease progression in real-time, enabling timely adjustments to treatment plans and improved patient outcomes.

CONCLUSION

MALDI-MS has revolutionized the field of bioanalysis, offering a versatile and powerful tool for analyzing a wide range of biomolecules, including proteins, peptides, lipids, and nucleic acids. Its ability to provide rapid, sensitive, and high-throughput analysis has made it an indispensable tool in various fields, particularly in biomedical research, drug discovery, and clinical diagnostics.

MALDI-MS has significantly impacted clinical research, providing researchers with a powerful tool to address critical questions in disease diagnosis, biomarker discovery, therapeutic development, and personalized medicine. MALDI-MS is increasingly being used for rapid and accurate diagnosis of infectious diseases, cancer, and other conditions. Its ability to identify and characterize biomolecules with high specificity enables the development of novel diagnostic tools and approaches. MALDI-MS plays a crucial role in biomarker discovery, facilitating the identification of unique molecular signatures associated with specific diseases or conditions. These biomarkers can serve as early indicators of disease progression, treatment response, or disease recurrence, aiding in clinical decision-making and patient management. MALDI-MS is valuable in therapeutic development, providing insights into drug-protein interactions, drug distribution, and drug metabolism. This information guides drug design, optimizes dosage regimens, and assesses drug efficacy, contributing to the development of safer and more effective therapies. MALDI-MS facilitates the implementation of personalized medicine by enabling the tailoring of treatments to individual patients based on their unique molecular profiles. This approach maximizes treatment efficacy, minimizes side effects, and improves patient outcomes.

MALDI-MS has emerged as a transformative tool in clinical research and holds immense potential for further advancements in personalized medicine. As its capabilities expand and its applications broaden, MALDI-MS is poised to revolutionize the way we diagnose, treat, and monitor diseases, leading to a more personalized and effective approach to healthcare.

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