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A Review on Mass Spectrometry: Technique and Tools

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ABSTRACT
Protein structure prediction has gain important in area of life sciences, because of its complex structure. The protein-protein interaction is necessary to study the behavior of protein in a specific environment, and study molecular relationship in living systems. Therefore, large scale proteomics technologies are required to measure physical connection of proteins in living organisms. Mass Spectrometry uses the technique to measure mass-to-charge ratio of ion. It's an evolving technique for characterization of proteins. A Mass Spectrometer can be more sensitive and specific, also complement with other LC detectors. Liquid Chromatography, unlike gas chromatography is a separation technique which helps to separate wide range of organic compounds from small molecular metabolites to peptides and proteins. This paper addresses the study of data analysis using mass Spectrometry. It also includes the study of various methods of Mass Spectrometry data analysis, the tools and various applications of Mass Spectrometry.This review briefs on Mass Spectrometry technique, its application, usage, and tools used by Mass Spectrometry.

Keywords **–** complex, LC (Liquid chromatography) detectors, Mass Spectrometry, mass-to-charge ratio, Protein-protein interaction.

I. INTRODUCTION

Bioinformatics is a novel approach in recent investigations on sequence analysis and structure prediction of proteins. The central challenge for Bioinformatics is not only to store and retrieve data but also to develop tools for data analysis. A number of tools are also available for protein characterization, structure identification, and visualization.

Mass Spectrometer is a quantitative tool used to measure the mass-to-charge ratio of ions. An ion is atom or group of atoms which have gained or lost one or more electrons making them negatively or positively charged. The two primary methods for ionization of whole proteins are electrospray ionization (ESI-which turns the sample proteins into ions) and matrix-assisted laser desorption/ionization (MALDI- It uses laser to ionize the sample proteins and then push the proteins into the analyzer to produce a Mass Spectrum.). As it is an essential tool in proteomics, it is necessary to understand the results and the principles of Mass Spectrometer. The various steps in mass spectrometry can be performed on a single sample by some mass spectrometer. They prefer the modularity method i.e.to generate the spectrum for a single ion, then fragmenting the ion and getting the spectrum. So it can work with complex molecules piece by piece until its structure is determined.

A typical Mass Spectrometer consists of three parts: a mass analyzer, a detector and an ion source. The ion source produces ions from the sample. The Mass Analyzer separates ions with different mass-to-charge ratios, these different ions are detected by detector. Finally, the mass spectrum is generated after all the data have been collected. **Fig.1** is a scheme graph of the Mass Spectrometer [1].

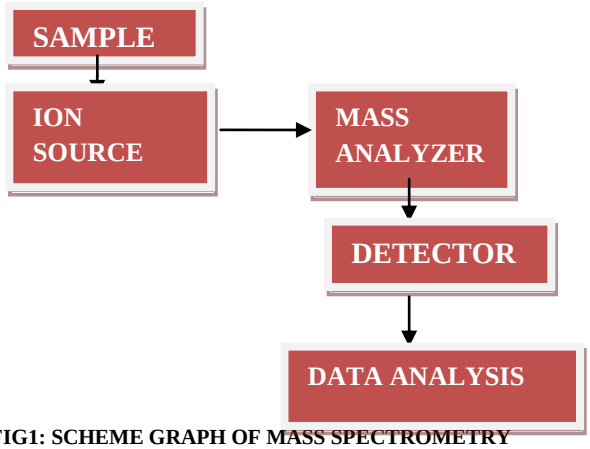

FIG1: SCHEME GRAPH OF MASS SPECTROMETRY

II. Various tools available for Protein Prediction using Mass Spectrometry

Peptide identification algorithms fall into two broad classes: database search and *de novo* search. The first search takes place against a database containing all amino acid whereas the latter deduce peptide sequences without knowledge of genomic data. At present, database search is more reliable and considered to produce higher quality results for most uses. With advancement in

instrument precision, the *de novo* search may become increasingly captivating.

2.1 Database Search Algorithms

2.1.1. SEQUEST

SEQUEST [2] is a patented tandem mass spectrometry data analysis program. It was developed by John Yates and Jimmy Eng in 1994. The algorithm used by this program is covered by several US and European software copyrights. SEQUEST identifies collections of tandem mass spectra to peptide sequences that have been evolved from databases of protein sequences. SEQUEST, like many engines, learns each tandem mass spectrum one by one. The software evaluates protein sequences from a database to calculate the list of peptides. The peptide's intact mass is known from the mass spectrum, and SEQUEST uses this information to find the group of candidate peptides sequences that could be compared to the spectrum by including only those which are equally near the mass of the observed peptide ion.

2.1.2 Mascot

Mascot [3] is a proprietary identification program readily available from Matrix Science. Instead of using the cross correlation method, it carries out mass spectrometry data analysis through statistical comparisons of matches between projected and observed peptide fragments. In addition to the identification features, support for peptide quantization methods is provided, as per version 2.2.

2.1.3. PEAKS DB

PEAKS DB [4] is a proprietary database search engine, run in cohesion with de novo sequencing to automatically formalize the search results, allowing for a higher number of searched sequences for the available false search rate. In addition to providing an independent database search, results can be integrated as part of the software's multi-engine (Sequest, Mascot, X!Tandem, OMSSA, PEAKS DB) consensus reporting tool, in Chorus. The tool also provides a list of sequences identified exclusively by de novo sequencing.

2.2 De novo Sequencing Algorithms

DeNovoX performs *de novo* sequencing [5] on CID spectra obtained with ion trap mass spectrometers. The software was launched by Thermo Fisher Scientific in 2002, was the first commercial software for low-resolution data. DeNovoX presents complete and/or partial peptide sequences. Each output sequence comes with the probable symptoms of how likely it is for the sequence to be obtained. Probabilistic results are used while implementing the software.

2.2.1 DeNoS

DeNoS [6] is part of the software tool Protein matching Analysis Software (PAS) which is part of the software package; Medicwave Bioinformatics Suite (MBS).DeNoS performs sequencing of peptides by gathering the data from CAD and ECD spectra with high reliability. Hierarchal algorithm is used by DeNoS. In the initial step fragments that are confirmed in both CAD and ECD (so called Golden Complementary Pairs) along with fragments that are only found in CAD (so called Complementary Pairs) are used. After that, one-by-one fragments with less assurance are used. Ultimately, if the peptide is still not fully sequenced, the software uses a crucial application from the graph theory to sequence the left out peptide parts with "unreliable" fragments.

2.2.2 PEAKS

PEAKS[7] de novo automatically provides a confidence scores on individual amino acid assignments, a complete sequence for individual peptide, greater knowledge for scientifically sensitive, in-depth investigations simple reporting and greater knowledge for scientifically sensitive, in-depth investigations for high-throughput analysis,. A de novo, manually assisted mode, is present for users who wish to idealize their results further. Automated de novo sequencing on full LC run processed data faster than 1 spectrum per second.

2.2.3 Lutefisk

For the de novo interpretation of peptide spectrum Lutefisk software is available [8].

2.3 *MS/MS peptide quantification*

2.3.1 OpenMS / TOPP

OpenMS [9] is a software C++ library for LC-MS/MS data management and analysis; it offers an infrastructure for the development of softwares related to mass spectrometry. It is free software available under the 2-clause BSD license (previously under the LGPL).TOPP - The Opens Proteomics Pipeline - is a set of small applications that can be sequenced to create analysis pipelines tailored for a particular problem. TOPP is developed using the structures and algorithms provided by OpenMS. TOPPView is viewer software that visualization of mass spectrometric data on MS1 and MS2 level as well as in 3D; additionally it also displays chromatographic data from SRM experiments (in version 1.10). OpenMS and TOPP is a collaboration project of the Algorithmic Bioinformatics group at the Free University of Berlin and the Applied Bioinformatics group at Tubingen University.

2.3.2. MaxQuant

MaxQuant is a proprietary software for numerical proteomics developed by Jorgen Cox and others at the Max Planck Institute of Biochemistry in Martinsried, Germany.[10] The software is released

as freeware under the "MaxQuant" Freeware Software License Agreement" and written in C#. The software provides its own search engine called Andromeda, and also accepts the analysis of label free and SILAC based proteomics experiments.

2.4 Other Softwares

2.4.1 AnalyzerPro

AnalyzerPro is proprietary software by SpectralWorks Limited. It is a software application for processing mass spectrometry data and is vendor independent. Using proprietary algorithms, AnalyzerPro can process data by both GC-MS and LC-MS using both qualitative and quantitative processing. On large scale, it is used for metabolomics data processing using MatrixAnalyzer for the comparison of multiple data sets.

2.4.2 Analyst

Analyst is licensed software by AB Scitex, a division of The Danaher Corporation.

2.4.3 RemoteAnalyzer

RemoteAnalyzer is proprietary software by Spectral Works Limited. It is a vendor independent 'Open Access' client/server based solution to provide a walk-up and use LC-MS and GC-MS data system. Data processing support and Instrument control for multiple vendors' hardware is provided. massXpert [11] is another tools used in Mass spectrometry.

2.4.4 ESIprot 1.0 / ESIprot Online

Electrospray ionization (ESI) mass spectrometry (MS) devices with relatively low resolution are widely used for metabolomics and proteomics. Ion trap devices like the Agilent MSD/XCT ultra or the Bruker HCT ultra are typical representatives. The ESI-MS data of most of the naturally occurring proteins can be computed, the availability of data evaluation software for such ESI protein spectra with low resolution is quite moderate. ESIprot 1.0 allows the charge state determination and molecular weight calculation for low resolution electrospray ionization (ESI) mass spectrometry (MS) data of proteins. Whereas ESIprot 1.0 is written in Python (GPL v3 License), the online freely available PHP web application is ESIprot.

III. MASS SPECTROMETRY DATA ANALYSIS

Key to making this paradigm shift possible has been the development of bioinformatics software that allows one to correlate bimolecular MS data directly with protein sequence databases [12]. Two kinds of MS bioinformatics software exist:

(1) Software for identifying proteins from peptide mass fingerprints and

(2) Software for identifying peptides or proteins directly from uninterrupted tandem (MS/MS) mass spectra.

Peptide mass fingerprinting was developed in the early 1990s to identify proteins from proteolysis fragments (Pappies al., 1993; Yates al., 1993; MANNet al., 1993). Specifically, if a pure protein is digested with a protease that cuts at predictable locations (say trypsin), the result will be a peptide mixture containing a unique collection of between 10–50 different peptides, each with a different or characteristic mass. Running this mixture on a modern ESI or MALDI instrument will lead to an MS spectrum with dozens of peaks corresponding to the masses of each of these peptides. Because no two proteins are likely to share the same set of constituent peptides, this mixture is called a peptide mass fingerprint. By comparing the observed masses of the mixture with predicted peptide masses derived from all known protein sequences it is theoretically possible to identify the protein of interest (providing the protein has been previously sequenced). Specifically, in the course of performing a mass fingerprint search, database sequences are theoretically "cleaved" using known protease cutting rules, the resulting hypothetical peptide masses are calculated and the whole protein is ranked according to the number of exact (or near exact) cleavage fragment matches made to the observed set of peptide masses. The sequence with the highest number and quality of matches is usually selected as the most attractive candidate. Most of the mass finger printing softwares are freely available while some are sold as commercial products. When peptide masses are read from the protein databases, it must be taking into notice that mono-isotopic masses from500-3000mz^{-1} is accurately readable or restricting the size of database is also a wise decision.

Because of the inclusion of noise the search for peptide mass fingerprinting is not an easy task. The common complications included in it are as follows [4]:

(1) disappearance of key peaks due to nonspecific ion suppression,
(2) appearance of extra peaks from protease autolysis,
(3) appearance of peaks from post-translational or artifactual chemical modification,
(4) appearance of peaks from non-specific cleavage, or from contaminating proteases, and
(5) appearance of peaks from contaminating impurities, contaminating homologs, or splice variants.

Due to such complications the reliability and performance of search gets reduced. The secondary searches are called "orphan" masses are made readily available. It also allows comparing the results with other search algorithms as SEARCH. But the best way is to apply various methods of mass fingerprinting and combining the result, called 'Single Averaging'. The programs works typically by scanning the databases and probability of a protein

matching increases with maximum matched sequence.

3.1 Data representations

Mass spectrometry produces different types of data. The most common visualization technique is the mass spectrum i.e. Graphical Representation. Various types of mass spectrometry data are best represented as a mass chromatogram. Types of chromatograms include total ion current (TIC), selected ion monitoring (SIM), and selected reaction monitoring (SRM), among many others. Other types of mass spectrometry data are well represented as a three-dimensional map. In this form, intensity the y-axis, the mass-to-charge, m/z is on the x-axis, and an additional parameter, is plotted on the z-axis.

3.2 Data analysis

Mass spectrometry data analysis particular to the type of experiment producing the data. Fundamental divisions of data are general in understanding any data. Many mass spectrometers work in either electron mode or positive ion mode. Sometimes it is very necessary to know whether the obtained ions are negatively or positively charged. It is often essential in determining the neutral mass but it also symbolizes something about the nature of the molecules.

Various ion source results in arrays of fragments obtained from the fundamental molecules. The ionization source creates many fragments and mostly single-charged (1-) radicals (odd number of electrons), whereas non-radical quasimolecular ions, an electrospray source usually produces that are frequently multiply charged. Tandem mass spectrometry produces fragment ions post-source and can change the kind of data obtained by an experiment.

A strongly prepared biological sample will probably contain a specific amount of salt, adducts get formed with the analyte molecules in various analyses Knowledge of the initial sample can provide insight into the component molecules of the sample and their peptides(protein in form of fragments). A sample from this synthesis/manufacturing process will probably consist of impurities chemically related to the target component.

Results can also depend heavily on sample preparation and how it was introduced. Much of the energetics of the desorption/ionization event is controlled by the matrix rather than the laser power. Mass spectrometry can measure sample purity, molecular structure and molar mass. Each of these queries requires a different experimental procedure; so adequate definition of the experimental goal is an early requirement for collecting the proper data and evolving the data.

3.3 Interpretation of mass spectra

Since the specific structure or peptide sequence of a molecule is decrypted through the set of fragment of masses, the combined usage of various techniques helps in the interpretation of mass spectra. The first way of identifying an unknown compound is to compare its experimental mass spectrum against databases of mass spectrum. The software assisted interpretation or manual interpretation [15] of mass spectra must be performed if match in spectral database in not found. Computer simulation of ionization and fragmentation processes occurring in mass spectrometer is the fundamental tool for assigning structure or peptide sequence to a molecule. Such simulation is often supported by a fragmentation library [16] that contains published patterns of known decomposition reactions. Software developed on this idea has been developed for both small molecules and proteins.

3.4 Analysis of mass spectra

It can also be spectra with accurate mass. A mass-to-charge ratio value (m/z) with only integer precision can represent an immense number of theoretically possible ion structures; so specific mass figures mainly reduce the number of candidate in molecular formulas. All molecular formulas that theoretically fit a given mass with specified tolerance can be calculated by the computer algorithm called as formula generator. The precursor ion fingerprinting, technique used for structure prediction identifies individual pieces of structural information by carrying a search of the tandem spectra of the molecule under investigation against a library of the product-ion spectra of structurally characterized precursor ions. Mass spectrometry can measure, sample purity, molecular structure and molar mass. These queries require a different experimental procedure; so an adequate definition of the experimental goal is an early requirement for collecting the proper data and successfully interpreting it.

IV. R PACKAGES FOR MASS SPECTROMETRY DATA ANALYSIS

R language is generally used by the life sciences people for evaluating the results obtained. It is useful for analysing the data. R packages in combination with Bioconductor packages also help to analyse the proteomics data. The various R packages available are as follows:

4.1 The mzR Package

The mzR package [19] provides a unified interface to various mass spectrometry open formats. This code chunk, taken mainly from the openMSfile documentation illustrated how to open a connection to the raw data file. mzR package is also applicable to an mzXML, mzData or netCDF file. mzR is used by other packages, like MSnbase [14], TargetSearch

[15] and xcms that provide a higher level abstraction to the data.

4.2 MSnbase

MSnbase provides base functions and classes for MS-based proteomics that allow facile data and meta-data processing, manipulation and plotting [13] [14].

4.3 The MALDIquant package

MALDIquant gives a combined analysis pipeline for MALDI-TOF and other mass spectrometry data. Differentiating features include baseline subtraction methods such as SNIP TopHat or TopHat, peak alignment using warping functions used for handling of replicated measurements and also allowing spectra with different resolutions.
The MALDIquant package contains of two main R packages:

- MALDIquant consist of the base functionality for accessing mass spectrometry data.
- MALDIquantForeign contains interface for importing and exporting data.

4.4 The isobar package

The isobar package [15] provides methods for the statistical analysis of isobarically tagged MS2 experiments.

4.5 The synapter package

The synapter package comes with a detailed vignette that describes how to prepare the MSE data and then process it in R. Several interfaces are available provided the user with easy batch processing capabilities, or a graphical user interface and maximum control. The conversion into MSnSet instances and filter and combination thereof as well as statistical analysis are also described.

4.6 digeR16

This is available on CRAN but not listed in the Chemometrics and Computational Physics Task View, provides a GUI interface for analysing 2D DIGE data. (http://cran.r-project.org/web/packages/digeR/index.html) using R and Bioconductor for Proteomics Data Analysis. It allows performing score plot, feature selection, correlation analysis, classification and power analysis for 2D DIGE experiment data.

V. ADVANTAGES AND DISADVANTAGES OF MASS SPECTROMETRY

5.1 Advantages

i) High Sensitivity– ability to detect very small amounts)
ii) High Selectivity– Ability to tell molecules apart in a mixture
iii) High Time Resolution
iv) Low Cost
v) small sample size
vi) fast
vii) differentiates isotopes
viii) can be combined with GC and LC to run mixtures, or can also be run in tandem for proteins or peptides etc.

5.2 Disadvantages

i) doesn't directly give structural information (although we can often figure it out)
ii) Needs pure compounds.
iii) Difficult with non-volatile compounds.

VI. APPLICATIONS OF MASS SPECTROMETRY

Mass Spectrometry consists of determining the isotopic composition of elements in a molecule, identifying unknown compounds, and determining the structure of a compound by understanding its fragmentation. Other uses include evaluating the amount of a compound in a sample or studying the fundamentals of gas phase in chemistry MS is now in very common use in analytical laboratories that study chemical, physical, or biological properties of a great variety of compounds.

6.1 Isotope ratio MS: isotope dating and tracking

Mass spectrometry is also used to determine the composition of elements in a sample. Variations in mass among isotopes of an element are very less, and the less abundant isotopes of an element are typically very rare, so a very sensitive instrument is requirement of Mass Spectrometry. These instruments, sometimes allude to as isotope ratio mass spectrometers (IR-MS), it uses a single magnet to bend a beam of ionized particles towards a series of Faraday cups which convert particle impacts to electric current. Isotope ratios are important markers of a variety of processes. The age of materials for example as in carbon dating is determined by isotopes ratios. Marking with isotopes which are stable are also used for protein quantification.

6.2 *Protein* characterization

Mass spectrometry is an important method for the characterization and sequence prediction of proteins. Fundamentally, the two methods for ionization of whole proteins are electrospray ionization (ESI) and matrix-assisted laser desorption/ ionization (MALDI). For characterizing Proteins two approaches are used. In the first, intact proteins are ionized by either of the two techniques described, and then introduced to a mass analyzer. This approach of Protein analysis is referred to as "top-down" strategy. In the other approach, proteins are enzymatically digested into smaller peptides using proteases.

The mass analyzer gets introduced from the collection of peptide. When the characteristic pattern of peptides is used for the identification of the protein the method is called peptide mass fingerprinting (PMF), if the identification is performed using the sequence data determined

in tandem MS analysis, called as de novo sequencing. This is called as "bottom-up approach.

6.3 Space exploration

Mass Spectrometry has also reached to other planets and moons, as a standard method for analysis. In early 2005 the Cassini–Huygens mission delivered a specialized GC-MS instrument aboard. It is the Huygens probe through the atmosphere of the largest moon of the planet Saturn, Titan, This instrument analyzed atmospheric samples, once the probe had landed, along its descent ,trajectory and was able to vaporize and analyze samples of Titan's frozen, hydrocarbon covered surface. These measurements compare the abundance of isotope(s) of each particle comparatively to earth's natural abundance.[17] Also on board the Cassini–Huygens spacecraft is an ion and neutral mass spectrometer which has been taking measurements of Titan's atmospheric composition .A Thermal and Evolved Gas Analyzer mass spectrometer was carried by the Mars Phoenix Lander launched in 2007[18]. Mass spectrometers are also widely used in space missions to measure the composition of plasmas.

6.4 Respired gas monitor

Mass spectrometers were used in hospitals for respiratory gas analysis beginning around 1975 through the end of the century. Found mostly in the operating room, a part of a complex system, which consist of respired gas samples from patients undergoing anaesthesia were drawn into the instrument through a valve mechanism. The instrument is designed to sequentially connect up to 32 rooms to the mass spectrometer. All operations of the system are directed by the computers. The anaesthesiologist uses the data collected from the mass spectrometer was delivered to the individual rooms.

VII. CONCLUSION

The data originated in the field of Proteomics is very large .It's the need of the day that these huge amount of data need to be managed and analysed. Various tools and techniques are available for the protein prediction. Mass Spectrometry is an analytical method for data analysis which originated in large amount. We have seen the various aspects of Mass Spectrometry. The mass Spectrometry tools and databases available. Also we have seen the advantages and disadvantages of the method and various application of it.

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