# LC-MS ANALYSIS

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# LC-MS ANALYSIS: MINI REVIEW FREQUENTLY USED OPEN SOURCE SOFTWARES

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***Abstract*— This paper provides information about open source softwares that most often used as a tool to analyze data generated from the Liquid chromatography-mass spectrometer (LC-MS) instrument and including a little discussion about how LC-MS works. LC-MS consists of Liquid Chromatography and Mass Spectrometer analytical instruments. This device extensively used in Metabolomics, because it provides more comprehensive information about the metabolites. It also shows the breadth of the diversity of chemical compounds in metabolites that make difficult and time-consuming to identification of metabolite's structures. This is an obstacle in efficient and accurate identification. So, many open source softwares developed to simplify and speed up the analysis and interpretation of LC-MS result. There are popular open source softwares. We compiling mini review of this open source softwares. The conclusion is open source softwares quite helpful in terms of data analysis and interpretation of compounds contained, but no one has provided a single interpretation, still need experts for reliable interpretation.**

***Keywords—LC-MS, Chromatography, LC-MS Software, Preprocessing data LC-MS***

## I. INTRODUCTION

Many medicinal plants are efficacious to cure diseases of mild to severe, such as cancer. However, the content of their chemical compounds not known yet. Many technologies were developed as tools to find out their compounds, although complex analysis is needed.

Analysis of data for metabolomics and identification of compounds progressed rapidly due to new applications and standardization of existing frameworks [1], [2]. Metabolomic data are obtained from at least three technologies which usually complement each other for analyzing metabolites, namely LCMS, GCMS, and NMR [3], [4], [5], [6]. Weber et al. provided information from international respondents that the percentage of technology utilized is LC-MS (83%), GC-MS (30%), NMR (26%), the rest use technology that is not very popular [7].

LC-MS is widely utilized because it allows the physical separation of thousands of metabolites, so it provides more comprehensive information about the tested metabolites [1], [4], [6]. This also shows the breadth of the diversity of chemical compounds in metabolites that make identification of structures, difficult and time-consuming [8]. This is an obstacle in efficient and accurate identification [1], [9], [10]. Therefore, to simplify and speed up the analysis and interpretation of LC-MS results, it is necessary to use computation and algorithms as software or application to extract meaningful information from existing active compounds [11]. There are already many stand-alone and web-based applications available and used to analyze the output of LC-MS, as summarized and published in [1], [5], [7], [12], [13].

Weber et al. [7] also provided information that the widely used open-source software was XCMS (70%), MZmine and MZmine2 (26%). Whereas according to [3], [13], [14] there are other software named MS-DIAL [3], [15], MAVEN and MetaboAnalyst [13] and agree that XCMS and mzMine software are commonly used. This software requires raw data from the instrument as an open format file. The open format file is needed because each instrument vendor provides a different closed format (proprietary) file. Open format file that is widely used is mzXML (70%) and mzML (41%) [7].

## II. BASIC PRINCIPLES OF LIQUID CHROMATOGRAPHY-MASS SPECTROMETER (LC-MS)

Chromatography is a method of separating components in a mixture in which the components to be separated are distributed selectively between two incompatible phases: the mobile phase through the stationary phase [16]. The mobile phase is described as "a fluid that seeps through or along with a pile of stationary phases in a definite direction." This can be liquid, gas, or supercritical fluid, while the stationary phase can be solid, gel, or liquid. If it is a liquid, the liquid can be

distributed to solids, which may not contribute to the separation process [17]. This technique is named as the mobile phase used, namely gas chromatography (GC), liquid chromatography (LC), or supercritical fluid chromatography (SFC) [16].

The chromatographic process occurs as a result of repeated absorption or release steps during the movement of the analyte throughout the stationary phase. This separation is caused by differences in the distribution coefficients of each analyte in the sample [16]; so it is said that Liquid chromatography uses the liquid as the mobile phase to transport sample molecules through stationary phase [11] which is the basic technique of separation in the fields of chemistry and related natural sciences.

Liquid chromatography is a universal technique used for the separation of compounds from mixtures [18] which safely separates various organic compounds, from small molecules drug metabolites to peptides and proteins [19]. Now modern liquid chromatography commonly utilizing high-performance liquid chromatography (HPLC) instruments [20]. HPLC facilitates analysis of chemical compounds with higher polarity and lower volatility in the broader mass range without derivatization [21].

It is challenging to ensure certain chemicals at a peak in Liquid Chromatography, even if the sample contains only a single chemical. Therefore it is necessary to add Mass Spectrometry, which will provide information about the mass of all chemicals in the peak, so it can be used to identify them [20].

Mass Spectrometry (MS) is based on the analysis of ions that move through a vacuum. The result is a mass spectrum, which provides valuable information about the molecular weight, structure, identity, number, and purity of the sample [20], [22]. The Mass Spectrometer usually consists of three main parts: ion source, mass analyzer, and detector. When the source ion converts the sample molecule into an ion, the mass analyzer resolves these ions both in a tube when flying or in an electromagnetic field before being measured by a detector. Several options are available for ion sources, namely Electrospray Ionization (ESI), Atmospheric Pressure Chemical Ionization (APCI), Atmospheric Pressure Photoionization (APPI), and Fast Atom Bombardment (FAB). Mass analyzers can be categorized as quadrupole, ion trap, Time-Of-Flight (TOF), orbit, and Fourier Transform Ion Cyclotron (FTICR) [23]. Quadrupole tends to be the simplest and cheapest mass analyzer [19].

Mass Spectrometry technology enables the development of flexible and reliable methods and simultaneous quantification of low and high analyte molecular weights in various concentrations [18]. In summary, Mass Spectrometry is used to measure mass to charge ratio of charged particles called mass-to-charge (m/z) ratio [20].

The combination of Liquid Chromatography with Mass Spectrometry (LC-MS) allows more definitive identification and facilitates the quantitative determination of compounds [17]. Figure 1 shows an overview diagram of the LC-MS device in general.

This device have four vacuum stage and allows filtering from the beginning, which is from the spray chamber where most solvents never enter the capillary. Only ions, gas dryers, and a small portion of solvents can passing through the capillary. At the exit of capillary, the skimmer do filtering. Heavier ions with greater momentum can pass through the skimmer apperture. The ions passing through the skimmer and move to the second stage of the vacuum system. In the second stage, the ions immediately focused to pass through on two vacuum stages using octopole. The ions can pass through the octopole because of the momentum that they receive from atmospheric pressure through capillary sampling. The ions coming out of this stage then pass through on two focusing lenses to fourth stage vacuum systems. In the fourth vacuum stage, a quadrupole mass analyzer separates ions from the mass ratio to the charge. The quadrupole has an electromagnetic field that determines the ratio of mass to charge that can pass through the filter at a certain time. The passing ions are focused on the detector [22]. The detector capture this data.

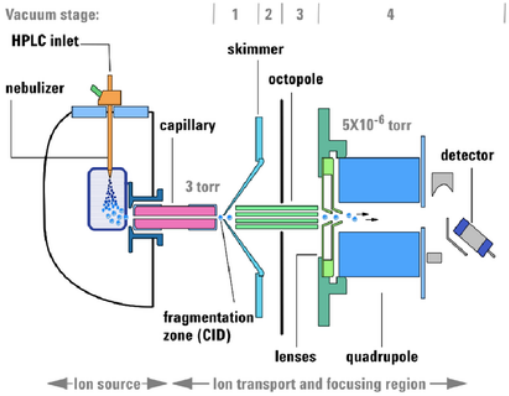


Fig. 1. Diagram of a quadrupole LCMS device for mass analysis [22]

The output of the LC-MS tool is 3D signals that are scattered with dimensions of intensity, m/z, and retention time for each detected feature (peak mass) [11] as shown in figure 2. In that figure, the height describes the exact intensity in a unit; the horizontal axis is m/z which is detected, while the other axis is the retention time in seconds.

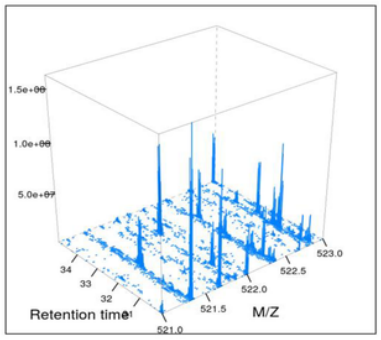


Fig. 2. Visualization of 3D LC-MS-generated data [24]

## III. FREQUENTLY USED OPEN SOURCE SOFTWARES

This chapter provides brief information about assistive software that is frequently used in processing LC-MS data based on Weber et al. [7].

### A. XCMS

This is the most often used tool in the first order, according to Weber et al. [7]. Clasquin et al. [26] stated that XCMS is a significant milestone in the development of metabolomics software. Its features are Noise filtering, peak detection, and alignment for LC-MS and GC-MS data [6]. XCMS focuses on preprocessing data to produce essential peaks visualization. XCMS developed into XCMS2; it adds a similarity search to identify with a connection to the METLIN database [27].

There are three essential things from XCMS, which are their advantages, namely design, availability, and flexibility because they are independent of machine vendors and are developed with R Language which is free [28].

The next development namely XCMS online, which is an online implementation of XCMS and complements existing shortcomings, such as providing several parameters for different instrument setups, PCA and univariate statistical analysis and direct links to METLIN databases for putative metabolite annotation [5].

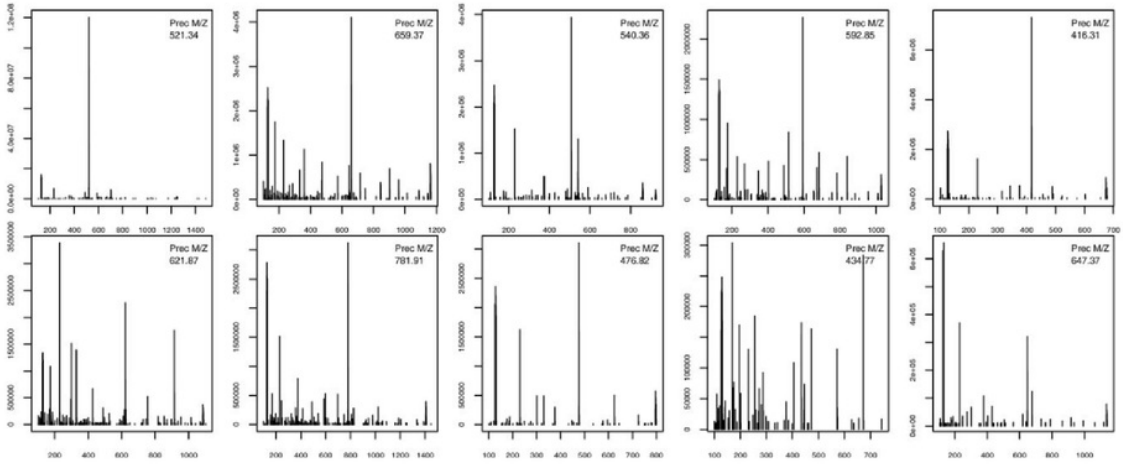


Fig. 3. 2D signal m/z vs. intensity of 3D LC-MS generated data [24]

```python
#!/usr/bin/env python2
# -*- coding: utf-8 -*-
"""
Created on Wed Apr 17 21:45:02 2019

@author: iwanbinanto

Program untuk ekstraksi data peak (m/z dg intensity) dari file raw mzXML
menjadi file .csv
"""
import numpy as np
import pyopenms
from mpl_toolkits.mplot3d import Axes3D
import matplotlib.pyplot as plt
from matplotlib import cm

exp = pyopenms.MSExperiment()
fig = plt.figure()
ax = fig.add_subplot(111, projection='3d')

#open file LC-MS sumber utk diekstrak setiap peak dalam setiap LC nya
pyopenms.FileHandler().loadExperiment("/Users/iwanbinanto/OneDrive - Bina Nusantara University/
                    Desertasi/Hasil LCMS_GCMS/convert-DataLCMS/D-BM 8-9_170818_10.mzXML", exp)

x=[]
y=[]
z=[]
for spectrum in exp:
    for peak in spectrum:
        #bikin array x,y,z untuk nantinya digambar scatter plot nya
        x.append(spectrum.getRT())
        y.append(peak.getMZ())
        z.append(peak.getIntensity())

#array yg ada harus dikonversi ke numpy array
ax.plot_trisurf(np.array(x), np.array(y), np.array(z), cmap=cm.coolwarm,linewidth=0, antialiased=False)

ax.set_xlabel('Retention Time')
ax.set_ylabel('m/z')
ax.set_zlabel('Intensity')

plt.title('Grafik D-BM 8-9_170818_10')

#simpan ke file dengan resolusi 800dpi
plt.savefig('coba3surf.png',dpi=800)
```

Fig. 4. Source code visualization of LC-MS data

To get 3D data and visualize it as in Figure 2 from raw data, can be done with Python programming using the pyOpenMS library [25], such as the source code in Figure 4. This 3D signal then converted into 2D signal to facilitate analysis and interpretation as seen on Figure 3. Commonly, they are m/z vs. intensity, although it does not close the possibility of m/z vs. retention time.

### B. *MZmine dan MZmine2*

MZmine was developed with Java and was first introduced in 2005 as open-source software for LC-MS data processing [29], [30]. Development of MZmine is motivated by the need software that facilitates mass spectrometry data processing and implementation of new normalization algorithms that can handle multiple spectra from the same sample and allows it to connect with a database [29]. Briefly, Pluskal et al. [30] said that MZmine provides workflow data analysis and implementation of a simple method for data processing and visualization. The open format file that is supported is netCDF, mzXML.

Together with its predecessor version, it is the second most frequently used tool, according to Weber et al. [7]. MZmine2 was also developed with Java and to overcome the shortcomings in the previous version, namely modularity. Without modularity, it will limit the development when new methods were developed by the scientific community. Therefore the MZmine2 software architecture was seen in Figure 4 [30].

MZmine2 is a tool for preprocessing LC-MS data even though it also includes the whole analysis workflow. Feature detection is available for high-resolution liquid chromatography-mass spectrometry (HRLC-MS) data using the GridMass algorithm [30] from Trevino et al. [31]. Postprocessing, metabolite identification, and statistical analysis have also been added [5].

Peak identification is done by searching in the existing database from the m/z value and retention times or can be done directly online because MZmine2 is already connected to an online database such as PubChem, KEGG, METLIN, or HMDB, and the interface has been provided. So it can be said that MZmine predicts the chemical compounds in a sample. It is just not mentioned what algorithm is used for the interpretation.

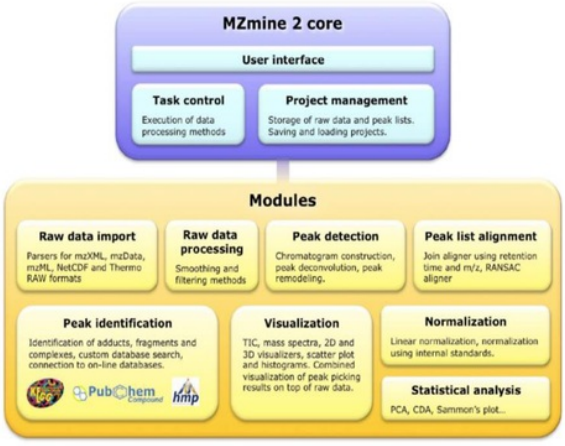


Fig. 5. software architecture and playing modules of MZmine2

MZmine2 supported file formats such as mzML (1.0 and 1.1), mzXML (2.0, 2.1 and 3.0), mzData (1.04 and 1.05), NetCDF, and the usual RAW format produced by Thermo Fisher Scientific instruments (requires the installation of Thermo Xcalibur) [30].

### C. *MS-DIAL*

Designed explicitly for preprocessing data with data deconvolution functions of untargeted MS/MS Data-Independent Acquisition (DIA) using the MS2Dec algorithm. Data-Independent Acquisition (DIA) in LC-MS/MS provides untargeted molecular data information comprehensively. MS-DIAL uses an algorithm based on Joint Aligner [5] from Pluskal et al. [30] for Peak Alignment, which is implemented on MZmine.

### D. *MAVEN*

It stands for Metabolomics Analysis and Visualization Engine, which was first introduced in 2010 by Melamud et al. [32]. MAVEN is built on the capabilities of existing opensource software, such as XCMS [26], [32]. MAVEN provides preprocessing, identification of different datasets. Peaks are selected, refined, and grouped, followed by retention time alignment. Peak quality scores are reported so that users can identify high-quality peaks [5]. Clasquin et al. [26] call MAVEN as Menu-driven, click-based navigation allows visualization of raw and analyzed data. The output of MAVEN is not yet a single prediction of a chemical compound; it is still a table that the expert will interpret but has been considered easily interpreted and reliable [26].

### E. *MetaboAnalyst*

MetaboAnalyst was developed with Java Server Faces as its web interface and the R language for its backend. Integration between Java and R uses the Reserve package. MetaboAnalyst is one of the applications that continue to be developed, starting from the initial version in 2009, which was later developed into version 2.0, version 3.0, version 4.0.

MetaboAnalyst 3.0 provides a collection of tools for analyzing metabolites from MS and NMR data with statistical focus, enrichment, and pathway analysis. It consists of eight independent analysis modules, which consist of three main categories, namely exploratory statistical analysis, functional analysis, and advanced methods for translational studies. XCMS algorithms are also used for peak picking, grouping, and retention time alignment, with additional parameters that are often used [5].

Consider the web version has limitations, the R package version was developed called MetaboAnalystR, and then MetaboAnalystR 2.0 [33] - [38].

## IV. CONCLUSION

There are many softwares that attempted facilitate biologists and chemists to interpret the compounds contained in a plant. Mostly, they developed based on existing one, especially on open source software.

However, no one can provide an interpretation of a single chemical compound contained in a plant as output. Therefore, needed developing software to accommodate it.

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# LC-MS ANALYSIS

PAGE 1

**Missing ","** You have a spelling or typing mistake that makes the sentence appear to have a com error.

**Article Error** You may need to use an article before this word.

**Wrong Form** You may have used the wrong form of this word.

**Missing ","** You may need to place a comma after this word.

**Wrong Article** You may have used the wrong article or pronoun. Proofread the sentence to mak sure that the article or pronoun agrees with the word it describes.

**Wrong Form** You may have used the wrong form of this word.

**Verb** This verb may be incorrect. Proofread the sentence to make sure you have used the correct fo of the verb.

**Article Error** You may need to use an article before this word. Consider using the article **a**.

**Wrong Form** You may have used the wrong form of this word.

**Article Error** You may need to use an article before this word.

**Missing ","** You may need to place a comma after this word.

**S/V** This subject and verb may not agree. Proofread the sentence to make sure the subject agrees v the verb.

**Article Error** You may need to use an article before this word. Consider using the article **the**.

**Proofread** This part of the sentence contains a grammatical error or misspelled word that makes y meaning unclear.

PAGE 2

**S/V** This subject and verb may not agree. Proofread the sentence to make sure the subject agrees v the verb.

**Article Error** You may need to use an article before this word. Consider using the article **the**.

**Article Error** You may need to use an article before this word. Consider using the article **the**.

**Article Error** You may need to use an article before this word.

**Article Error** You may need to remove this article.

**Missing ","** You may need to place a comma after this word.

**Missing ","** You may need to place a comma after this word.

**Article Error** You may need to remove this article.

**Article Error** You may need to use an article before this word.

**P/V** You have used the passive voice in this sentence. Depending upon what you wish to emphasize the sentence, you may want to revise it using the active voice.

**Prep.** You may be using the wrong preposition.

**Article Error** You may need to use an article before this word.

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**Article Error** You may need to use an article before this word.

**S/V** This subject and verb may not agree. Proofread the sentence to make sure the subject agrees w the verb.

**Verb** This verb may be incorrect. Proofread the sentence to make sure you have used the correct fo of the verb.



**Hyph.** You may need to add a hyphen between these two words.

**Sentence Cap.** Remember to capitalize the first word of each sentence.

**Missing ","** You may need to place a comma after this word.

**Proofread** This part of the sentence contains a grammatical error or misspelled word that makes y meaning unclear.



**Sentence Cap.** Remember to capitalize the first word of each sentence.

**Proper Noun** If this word is a proper noun, you need to capitalize it.

**Article Error** You may need to use an article before this word. Consider using the article **the**.

**Missing ","** You may need to place a comma after this word.

**Sentence Cap.** Remember to capitalize the first word of each sentence.

**Frag.** This sentence may be a fragment or may have incorrect punctuation. Proofread the sentence be sure that it has correct punctuation and that it has an independent clause with a complete subject and predicate.

**Missing ","** You may need to place a comma after this word.

**P/V** You have used the passive voice in this sentence. Depending upon what you wish to emphasize the sentence, you may want to revise it using the active voice.

**Sentence Cap.** Remember to capitalize the first word of each sentence.

**P/V** You have used the passive voice in this sentence. Depending upon what you wish to emphasize the sentence, you may want to revise it using the active voice.

**Missing "?"** Remember to use a question mark at the end of a question.

**Run-on** This sentence may be a run-on sentence. Proofread it to see if it contains too many independent clauses or contains independent clauses that have been combined without conjunctions or punctuation. Look at the "Writer's Handbook" for advice about correcting run-on sentences.

**P/V** You have used the passive voice in this sentence. Depending upon what you wish to emphasize the sentence, you may want to revise it using the active voice.

**Sentence Cap.** Remember to capitalize the first word of each sentence.

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**S/V** This subject and verb may not agree. Proofread the sentence to make sure the subject agrees v the verb.

**P/V** You have used the passive voice in this sentence. Depending upon what you wish to emphasize the sentence, you may want to revise it using the active voice.

**Run-on** This sentence may be a run-on sentence. Proofread it to see if it contains too many independent clauses or contains independent clauses that have been combined without conjunctions or punctuation. Look at the "Writer's Handbook" for advice about correcting run-on sentences.

**Confused** You have a spelling mistake near the word **an** that makes **an** appear to be a confused-v error.

**Article Error** You may need to use an article before this word. Consider using the article **a**.

**Proofread** This part of the sentence contains a grammatical error or misspelled word that makes y meaning unclear.

**Wrong Article** You may have used the wrong article or pronoun. Proofread the sentence to mak sure that the article or pronoun agrees with the word it describes.

**Sentence Cap.** Remember to capitalize the first word of each sentence.

**Wrong Form** You may have used the wrong form of this word.