Toward direct application of multivariate statistical analysis to MRS Datasets

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MESTRELAB RESEARCH
NMR Solutions

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Introduction

In the past decade 3T MRI started to be routinely used for clinical examinations because, compared to the first 1.5T MRI spectrometers, it results in enhanced SNR and faster acquisitions. Nowadays, high field MRI spectrometers (3 to 7T and above) are used in many centres, mostly for research purposes. Higher magnetic field lead to better spatial resolution, while also increasing the separation of chemically distinct peaks, making it easier to attempt spectra profiling for metabolite identification. Despite this increase in spectral resolution, investigators and physicians hardly ever analyze the whole fingerprint of the spectrum which limits peak identification and quantification.

In this work we investigate the possibility to perform chemometric analysis on MRS datasets. To do so we have collected and analyzed localized spectroscopy, performed on patients diagnosed with various grades of glioma. Gliomas account for about 40% of total primitive brain tumours, and a discrimination between high and low glioma grades remains a vital diagnostic decision, determining the most effective treatment and having an important impact on the patient management and its outcome. We discuss the application of the Global Spectrum Deconvolution algorithm (GSD) on MRS data, followed by the generation of synthetic spectra to be used to generate the matrix used in subsequent statistical evaluation. GSD, made available in the Mnova software package of Mestrelab, is capable of identifying even poorly resolved spectral peaks and of fitting all recognizable peaks even in a very complex 1D spectrum in a surprisingly short time (typically a dozen seconds for up to 1000 peaks). It is fully automatic and objective (no human intervention is required) and produces a table of all detectable spectral peaks and their parameters. Such a table can be then used for various purposes like generation of artifact-free synthetic spectra (with or without resolution enhancement), stick spectra, artefact-free integrals, as well as accurate binning void of any bin-crossover problems due to the overlapping wings of spectral peaks.

OPENING SPECTRA UNDER MNOVA 8.1.1.
It is already possible to open different file format such as Philips, Siemens, LCModel ASCII, Bruker or Varian.
Spectra can be easily stacked and processed all at the same time: phase correction, baseline correction, windows functions, etc...
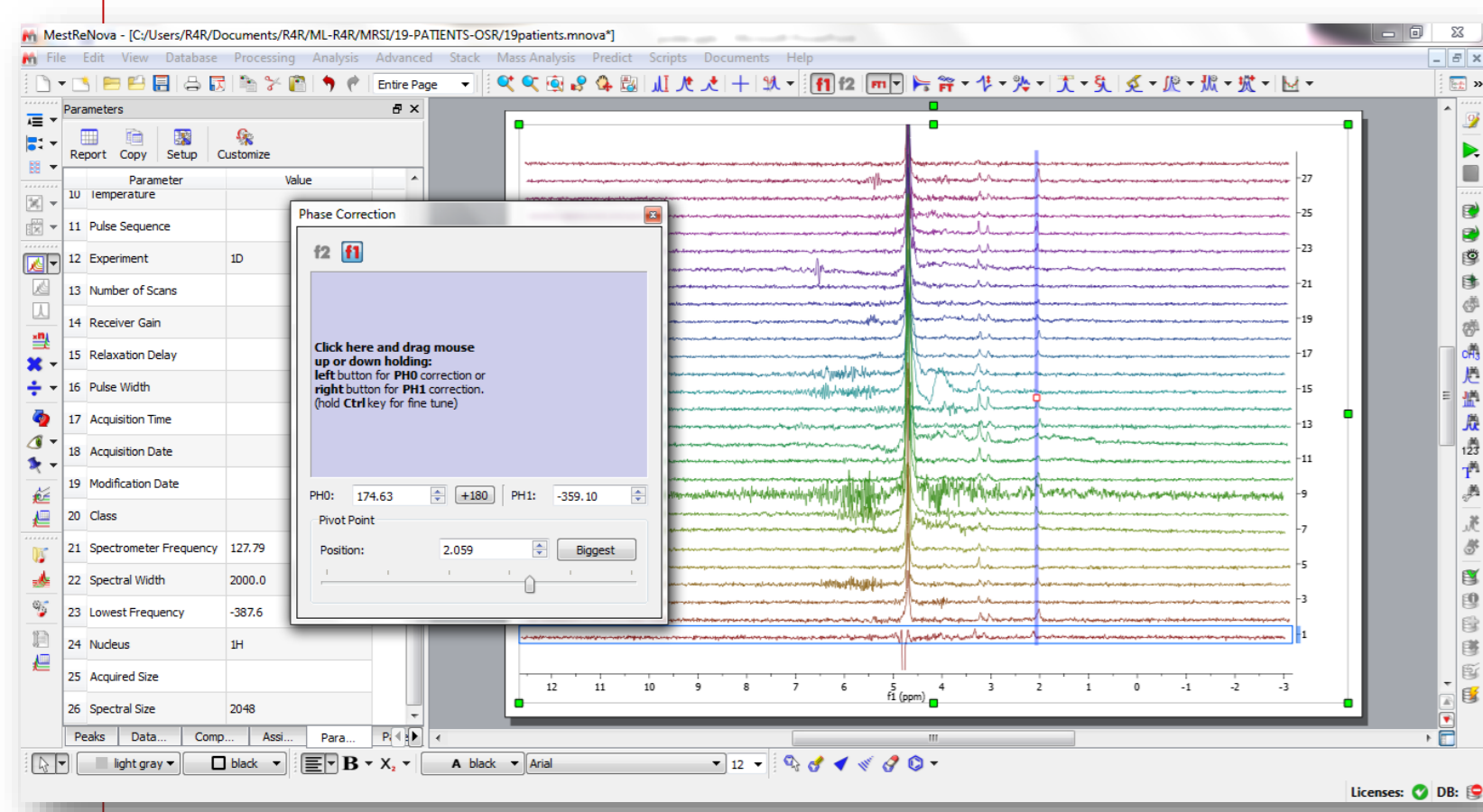
**Spectra processing and manipulation**
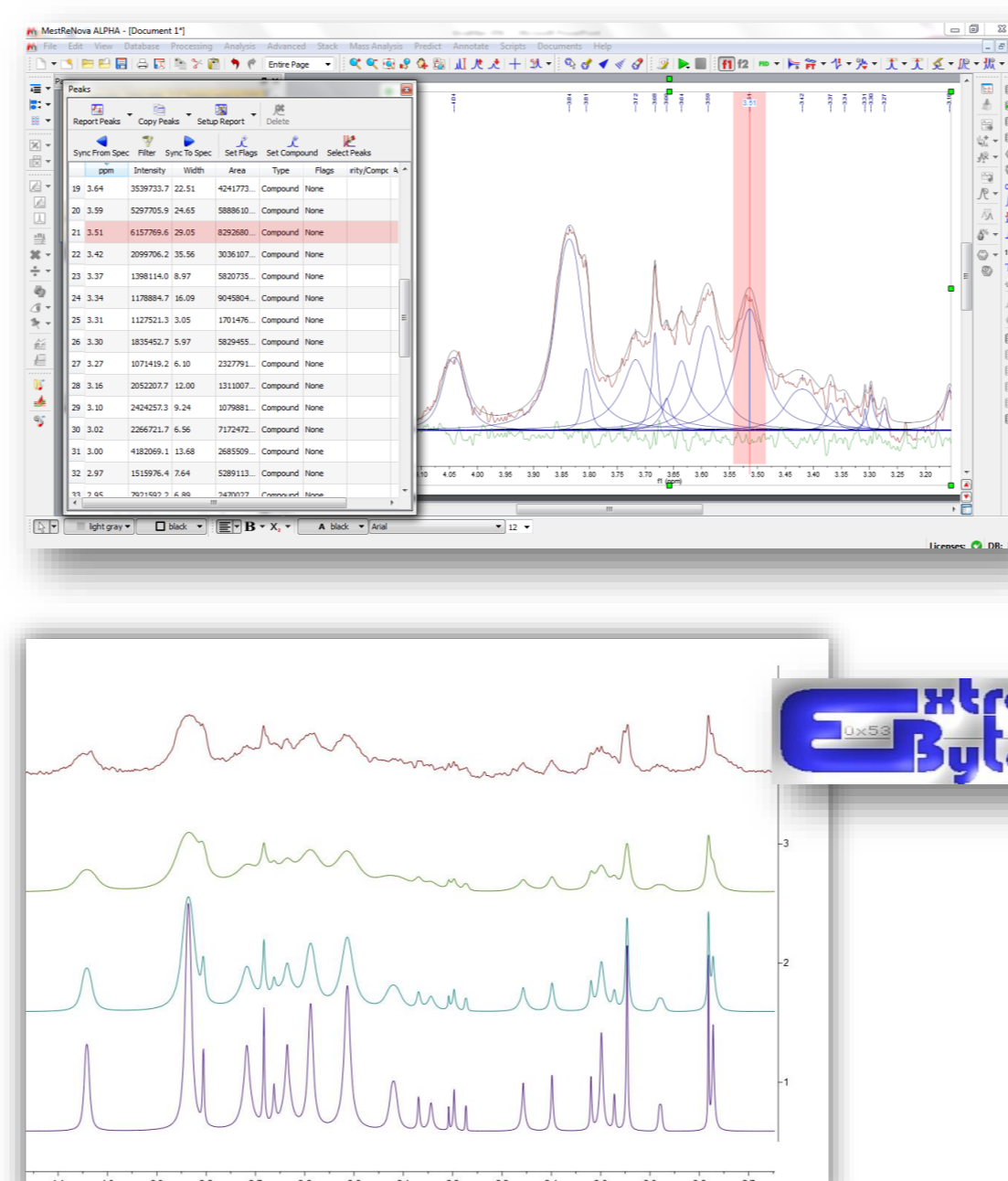
GSD (Global Spectral Deconvolution)

There are several advantages passing a spectrum through the GSD procedure and reducing it to an equivalent and clean list of peaks:

• Integrals are replaced by summing peak areas with a total exclusion of peak overlap errors. This leads to a general resolution enhancement and open the possibility to quantify easily buried spectral regions.

• As consequence of the deconvolution baseline is automatically corrected even for those problematic spectra.

• Peaks List generated by GSD, rather than the spectrum, becomes The Input to further editing and analyses such as multivariate analysis.

[www.ebyte.it/stan/Poster_GSD.html]
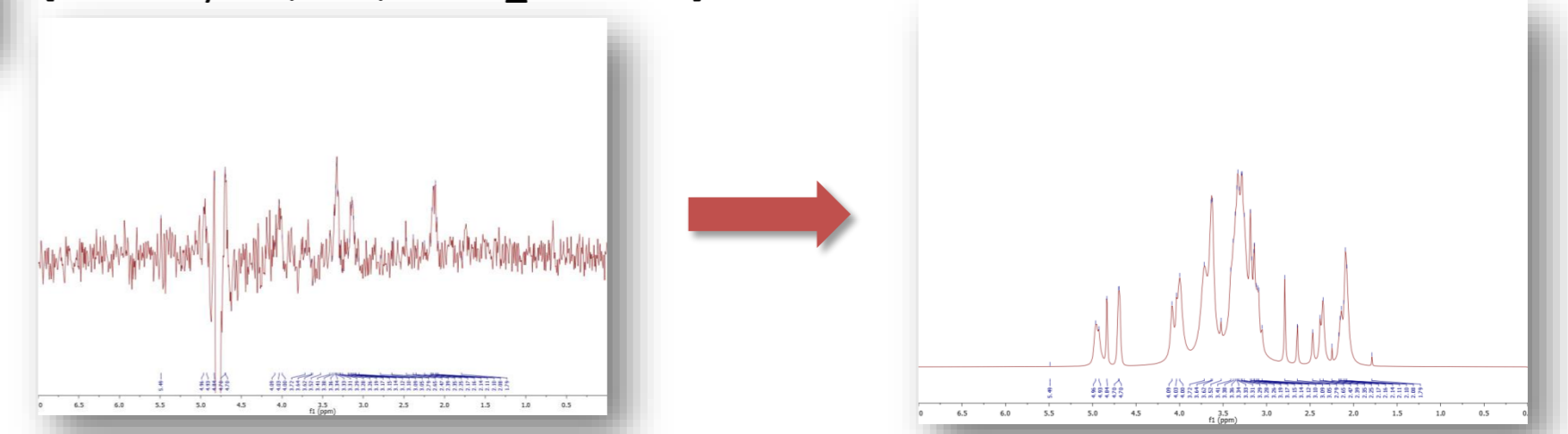

Peak overlap and deconvolution
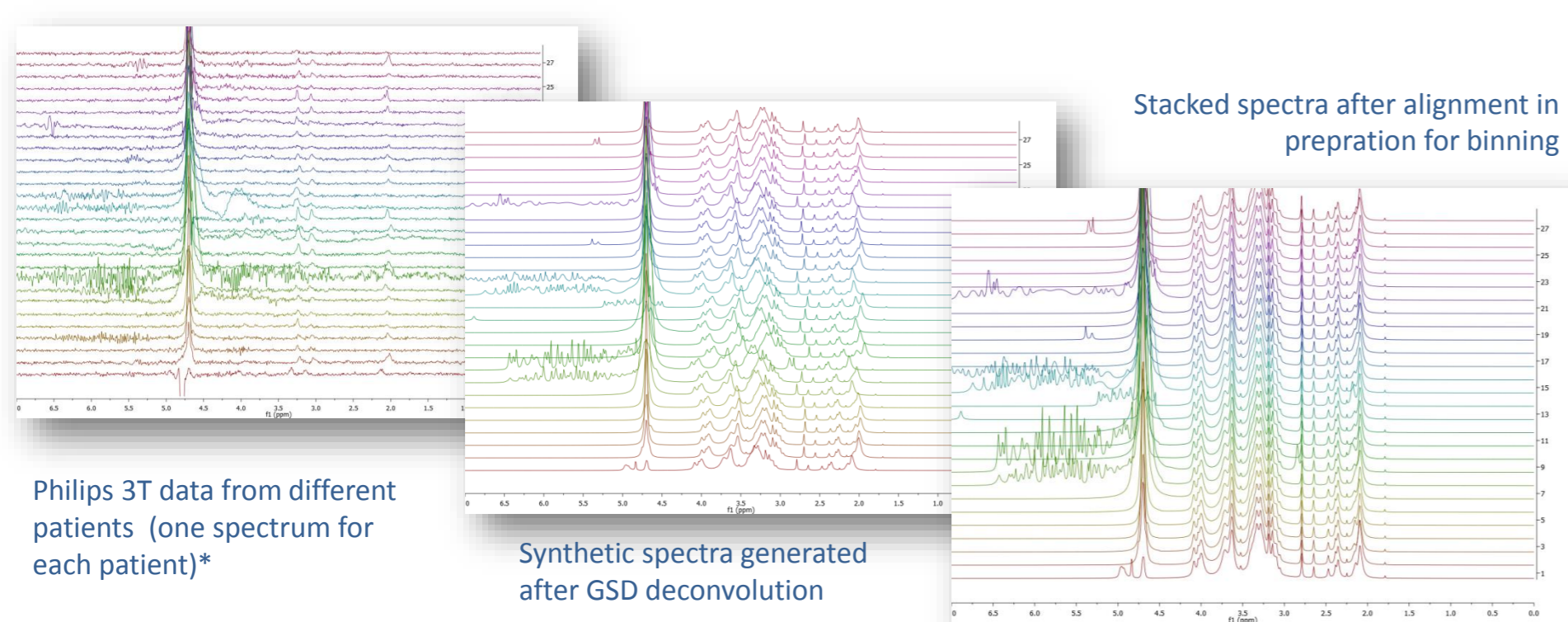
Philips 3T data from different patients (one spectrum for each patient)*

Synthetic spectra generated after GSD deconvolution

Stacked spectra after alignment in prepration for binning

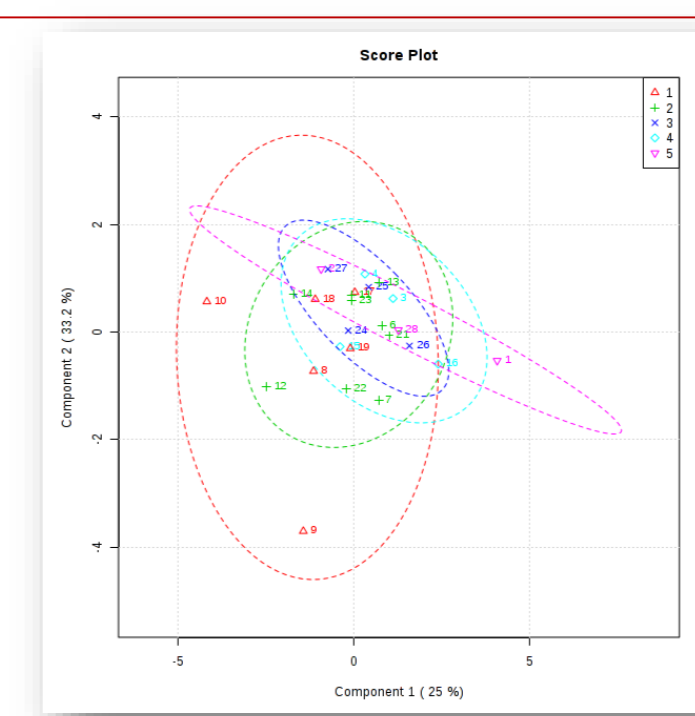*Data courtesy from HSR Hospital (Milan, IT)– Neuroimaging Unit

Binning. Regular Binning with 0.025ppm bin width, and binned spectral window from 0.025ppm to 4.2 ppm
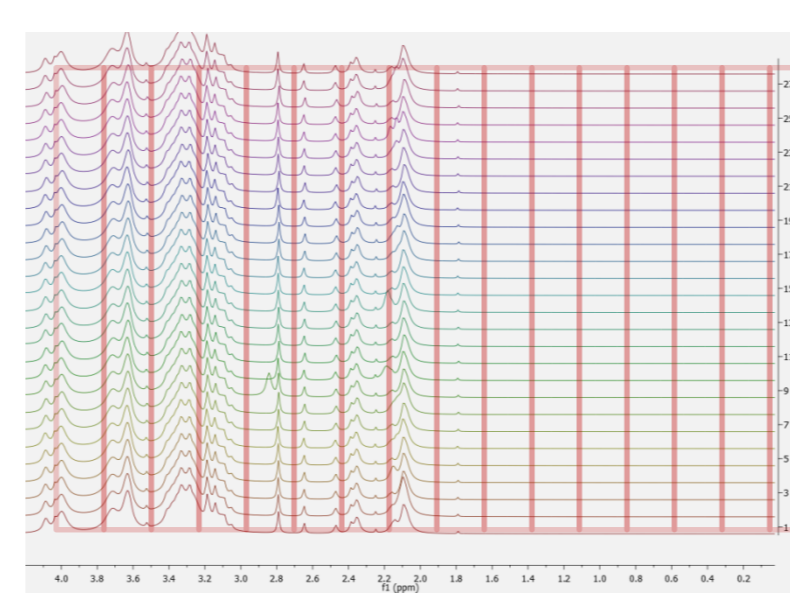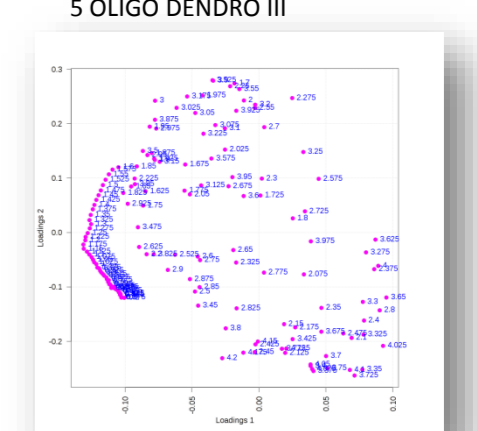
Bins exported as CSV Matrix

CSV Matrix upload to Metaboanalyst web server (www.metaboanalyst.ca)

Analysis
Data Transformation: cube root;
Data Scaling: range;
PLS-DA Analysis

Score Plot

Classes according to further biopsy:
1 DNET
2 ASTRO II
3 OLIGO ASTRO II
4 OLIGO DENDRO II
5 OLIGO DENDRO III

*Data courtesy from HSR Hospital (Milan, IT)– Neuroimaging Unit

Spectra Binning and Analysis

Moreover, with the aim to identify metabolite peaks in an MRS spectrum using freely available metabolite databases (e.g.HMDB), we introduce the spin system definition for each standard metabolite. This allows us to take advantage of the spin simulation tool available under the used software to simulate the spin system at any desired magnetic field and nearly spin system size independently. The resulting simulated spectra are then employed to assign selected peaks in the MRS spectrum of interest.
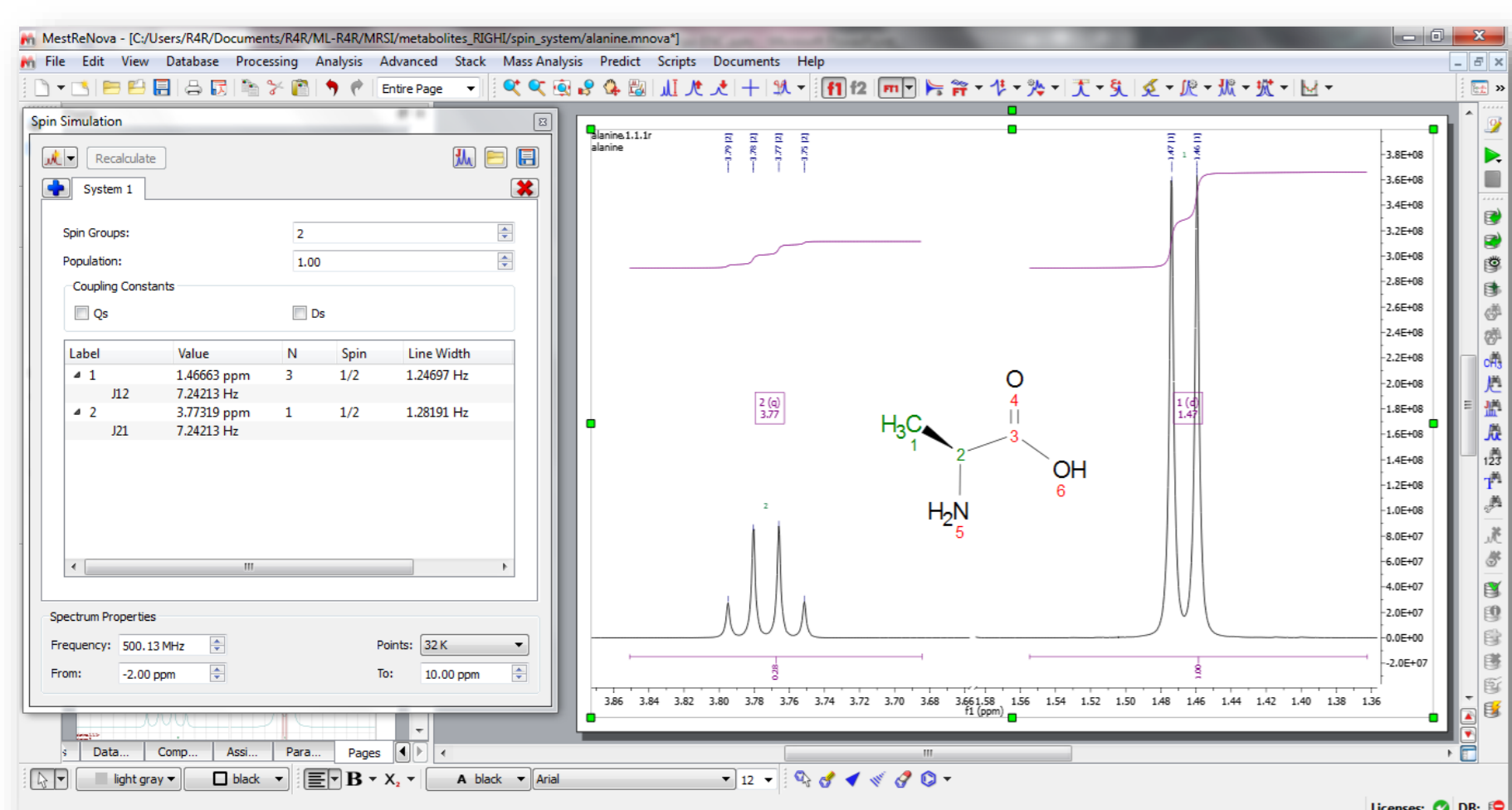

1H spectrum of alanine at 500MHz , and relative structure. Starting from multiplets detection and definition, 1H spectrum is then fully assigned. Using Spin Simulation Tool under Mnova it is possible to create and save alanine spin system for further use.

ALANINE SYNTHETIC 1H-NMR spectrum simulated at 3T (128.7MHz)

ALANINE 1H-NMR spectrum at 500MHz
Bruker spectrometer

ALANINE PHANTOM 1H-NMR spectrum at 3T
Philips spectrometer
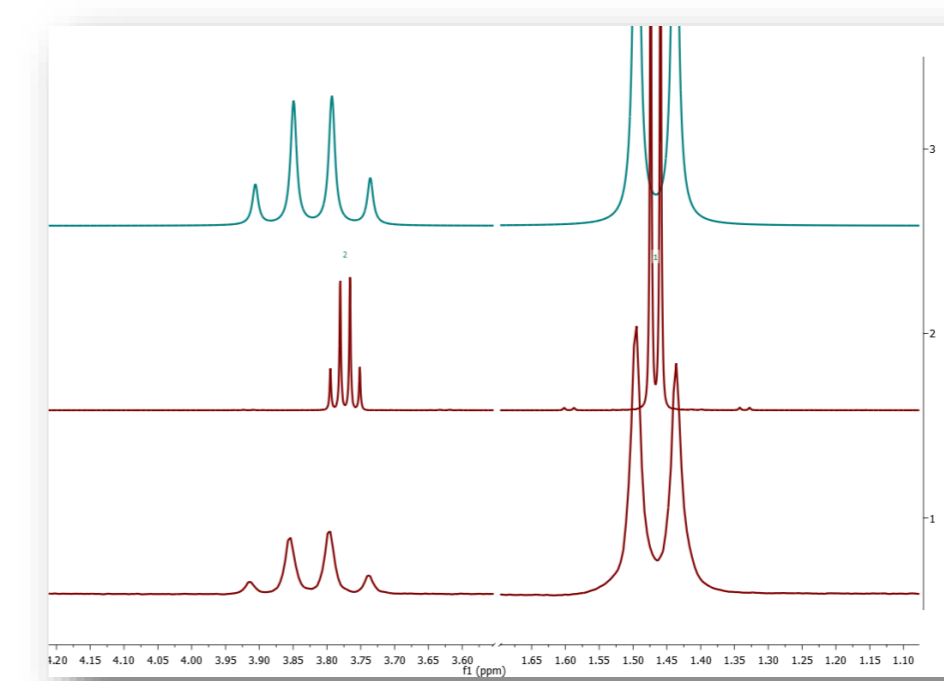
Traditionally Spin Simulation algorithm were limited to 11-12 magnetic unequivalent coupled particles. However, this is completely insufficient to tackle the 'small molecules' of today. Simulation nowadays calls for brand new approximate algorithms involving, for example, fragmentation techniques. Mnova SpinSimulation toolkit includes such sophisticated fragmentation algorithm which makes it possible the simulation of any spin system regardless of its size.

Choline peak identification of MRSI spectrum [choline spectrum downloaded from HMDB]

original MRSI spectrum
synthetic MRSI spectrum
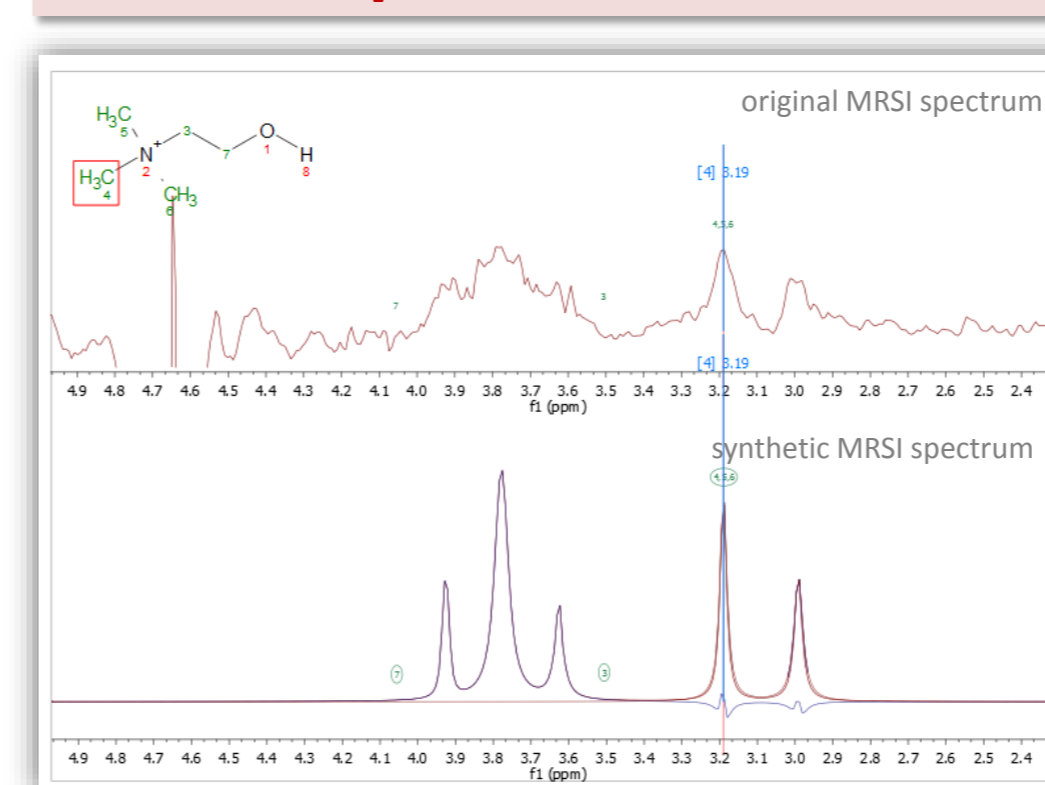
Auto-classification of lactate in one click