METITREE

BY MARIAN VAN OPSTAL

Powerful tool for identifying unknown metabolites

Contemporary metabolomics research is faced with great challenges. Individual metabolites in complex mixtures need to be analysed and identified. Liquid chromatography combined with multistage mass spectrometry (MS^n) appears to be a useful approach, especially since the availability of a promising tool for organising, processing, sharing, visualising and comparing MS^n data.

Multistage mass spectrometry involves re-fragmentation of former fragment ions. Repeating the process n times leads to a series of MS^n spectra in a so-called spectral tree. Each branch represents spectral data that provide pieces of the puzzle that describes the original structure of the investigated compound(s). "This approach is very suitable in metabolomics research," explains Theo Reijmers, analytical bioscientist at the Netherlands Metabolomics Centre (Leiden) and principle researcher engineer at NBIC-BioAssist. "Our goal is to unravel the whole metabolome, and that entails the analysis of thousands and thousands of compounds. Today, sophisticated platforms are available to get this job done. However, analysing the complex and abundant data seemed to become a major bottleneck," says Reijmers. Therefore, Netherlands Metabolomics Centre decided to start a cheminformatics project aimed at developing supporting computational tools. It ended up this summer with the launch of MetiTree, **Met**abolite **I**dentification **Tree**.

STEP BY STEP MetiTree integrates several different tools that have been developed in successive stages over the last five years. PhD student Miguel Rojas-Cherto focussed on data processing and comparison. He developed the so-called Multi-stage Elemental Formula (MEF) tool to enable the correct assignment of elemental composition to each ion. "In particular, the mass accuracy needed to generate one unique composition and the topology (width and depth) of the MS^n tree was addressed," explains Reijmers. Next, Miguel focussed on a novel approach for representing and calculating the similarity between high-resolution mass spectral fragmentation trees. He developed a tool that can be used to compare newly acquired MS^n data to data already stored in an internal library.

"Combining the two tools was an important step towards semi-automatic de novo identification of metabolites using MS^n data," Reijmers says. "Then we were challenged to turn the command line programs into a user-friendly tool. Michael van Vliet from the NMC Data Support Platform became involved to this end, and we asked NBIC's Bioinformatics Research Supports (BRS) group for assistance." These specialists succeeded in introducing an accessible user interface and in developing a dedicated spectral tree viewer allowing the simultaneous presentation of the spectral data, the fragmentation tree and the fragmentation reactions including chemical structures. "Finally, the step by step developed functionalities have been integrated in a web based application resulting in MetiTree, which will make the difficult task of identifying unknown metabolites much easier," concludes Reijmers. His group will continue to develop MetiTree by extending its features and expanding its reference library.

SUCCESSFUL APPLICATION "MetiTree has proved to fulfil needs in the metabolomics community and has received a great deal of interest," says Reijmers. "Its success was nicely illustrated in a recent publication by our colleagues at Leiden University*. They applied MetiTree in the so-called FinnDiane study to identify subtle changes in the urine metabolome of diabetes patients. It resulted in the discovery of early-stage biomarkers for diabetic kidney disease."

* Van der Kloet F.M. *et al.* (2012) *Metabolomics*, 9, 109-119.

MetiTree is available free
Open access: http://www.Metitree.nl
Source code: https://github/Netherlandsmetabolomicscentre/metitree/wki
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