MetiTTree: a web application to organize and process high-resolution multi-stage mass spectrometry metabolomics data

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ABSTRACT

Identification of metabolites using high-resolution multi-stage mass spectrometry (MS²) data is a significant challenge when dealing with metabolomics data. MetiTTree is a user-friendly, web application dedicated to organize, process, share, visualize and compare MS² data. It integrates several features to export and visualize complex MS² data, facilitating the exploration and interpretation of metabolomics experiments. A dedicated spectral tree viewer allows the simultaneous presentation of three related types of MS² data, namely, the spectral data, the fragmentation tree and the fragmentation reactions. MetiTTree stores the data in an internal database to enable searching for similar fragmentation trees and matching against other MS² data. As such MetiTTree contains much functionality that will make the difficult task of identifying unknown metabolites much easier.


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1 INTRODUCTION

Metabolite identification is a challenging but essential step for the interpretation and understanding of many biological processes for an increasing number of applications such as biomarker discovery, drug discovery or nutritional studies. The feasibility of using multi-stage mass spectrometry (MS²) for identification of metabolites has been shown before (Sheldon et al., 2009). The complexity of the data generated demands new computational infrastructures to organize the data and to extract relevant information. Recently, databases have been set up for storing fragmentation spectra such as MS² data (e.g. MassBank; Horai et al., 2010), and tools have been developed to process MS² data (e.g. the MEF tool; Rojas-Chertó et al., 2011), or to compare MS² data (e.g. Mass Frontier; Thermo Fisher Scientific). In this article we present a web application called MetiTTree with the novelty that it combines the processing of high-resolution MS² data with a personal local library to organize the fragmentation data. Furthermore, it allows the comparison of MS² data to help the researcher with the identification of metabolites. MetiTTree is available at http://www.MetiTree.nl together with some test MS² data.

2 METHODS

2.1 Web application

MetiTTree (Metabolite Identification Tree) is a web application intended to aid in the metabolite identification process. Currently, MetiTTree offers the possibility to organize, process, share, visualize and search for similar high-resolution MS² data. MetiTTree’s web interface is accessed through a web browser and it was created using the Grails (http://grails.org) framework.

2.2 Data processing and comparison

In order to process MS² data, MetiTTree integrates the MEF tool (Rojas-Chertó et al., 2011), which extracts chemical information from the fragments assigning the elemental composition to the ions and neutral losses. MetiTTree also allows the comparison of newly acquired MS² data to data that are already stored in an internal library (Rojas-Chertó et al., 2012).

2.3 Data visualization

MetiTTree incorporates a JavaScript spectral tree viewer developed to visualize MS² data (https://trac.ncbi.nlm.nih.gov/trac/browser201017/), in order to facilitate the exploration, interpretation and validation of the results. This viewer interconnects three MS² items: the spectrum, which contains mass peaks, the fragmentation tree, which contains fragment nodes/elemental compositions, and the fragmentation reactions, which contain structures.

3 USAGE EXAMPLE

MS² data previously published by our group (Rojas-Chertó et al., 2011, 2012) are used to demonstrate how metabolites
can be identified using the MetiTree web application. These data are freely accessible as test data in MetiTree.

3.1 Data processing
The required input to process MS^n data is mzXML files and the settings of the processing parameters. Processing parameters are grouped into those to extract the mass spectrometry information (m/z, intensity and retention time) and those to enrich the MS data with chemical information (elements and number of atoms). MetiTree allows individual file as well as batch processing. Furthermore, the same mzXML file can be processed several times with different sets of parameters. The results and parameters’ information are stored to allow for posterior revision.

3.2 Data visualization
Once the data are processed, it can be displayed using the spectral tree viewer (Fig. 1A). When the node (a fragment) is selected, the corresponding spectrum is displayed together with the concatenated reactions that connect the parent ion with the selected fragment. The structure of the fragment can only be displayed if it has been previously assigned. The results generated by MetiTree can be exported to different formats (CSV, CML; Murray-Rust and Rzepa, 1999) and PDF for further analysis or for presenting results in reports and publications.

3.3 Library storage
MetiTree creates directories for grouping mzXML files, assisting with the organization of the data according projects or topics. Processed MS^n data can be stored in one or multiple internal databases (Fig. 1B). Because the users are organized in groups, they can share files and libraries with other group members. All MS^n data can be labeled with an InChI identifier of the compound, which is automatically cross-referenced with PubChem and ChemSpider databases.

3.4 Data search
MetiTree integrates the functionality to query for similar MS^n data (Rojas-Cherto et al., 2012) stored in the library. The results are presented in a list showing the chemical structures of the most similar MS^n data and the corresponding similarity values. A value near 100 indicates that MS^n data are highly similar, while a value close to 0 illustrates that they are very different. If a fragmentation tree of the same compound is present in the library, complete identification is possible (identity search). If similar fragmentation data are found (similarity search), this substructure information can be used to generate candidate structures of the unknown compound (partial identification).

3.5 Future
In the near future this new web application will also accept the uploading of other types of MS^n files (e.g. cml, mzML) and manual annotation of MS^n data with chemical structural information (assigning substructures to the nodes of the fragmentation trees) will also be possible.

4 CONCLUSION
The growing interest in metabolite identification has increased the need to create computational and visual tools for MS^n analysis. MetiTree, which gathers several in-house developed tools, is an easy-to-use web application that combines processing, sharing, visualizing and querying MS^n data to help researchers to identify metabolites of interest and decrease the time-consuming task of identifying metabolites.

Fig. 1. Overview of the MetiTree process flow. After the user submits MS^n spectra, MetiTree will process these according to a set of parameters. Afterwards, the processed data can be stored in an internal library and labeled as a reference compound using the InChI identifier. The results are presented in different formats and viewers, which facilitates the exporting of text and figures for their use in reports and publications (A). Finally, MS^n data can be queried to find similar MS^n data in the library (B) and the query results are presented in a list.
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