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DEVELOPMENT OF ADVANCED PROCESSING WORKFLOW FOR UNTARGETED VOLATILOMICS BY GC×GC-TOFMS

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Introduction

With the growing interest of breath and volatile molecules based diagnosis development, there is a need for integrated solutions allowing to robustly screen sample volatilome. The understanding of the metabolic pathways involved in volatile markers production could open new therapeutic routes for high variety of inflammatory or infectious diseases. Over the years, comprehensive two-dimensional gas chromatography (GC×GC) has become a method of choice for complex mixture characterization. The two chromatographic dimension and the possibility to hyphen high-speed high-resolution time-of-flight mass

spectrometers (HRTOFMS) locates GC×GC as a method of choice for untargeted metabolomics. However, this development comes with a complexification of the data generated, requiring the development of computing tools for automated data processing.

Methods

In this study, different types of in vitro and ex vivo samples were analyzed by solid phase microextraction (SPME) coupled to GC×GC-TOFMS. Bronchoalveolar lavage fluids (BALF) and cell culture headspace were analyzed as part of a discovery study for lung inflammation mechanisms characterization. In practice, a central composite design was created for optimal fiber selections and analytical conditions optimization. Automatic image processing was used for chromatogram alignment and mass spectra matching. 70 eV electron ionization was used to generate specific fragmentogram. Scripting on the mass spectra were developed in order to rapidly identify contaminants in the complex data set generated. Different approaches for data normalization and features selection based on machine learning algorithms were compared.

Preliminary Data

A QC mixture was designed by pooling an aliquot of the different liquid samples and spiking internal standards. Central composite design is a method of choice to establish optimal analytical conditions. For SPME, the peak intensity was used as a quality metric versus the fiber type, incubation time and temperature as variable parameters. For the GC×GC-TOFMS, there is no defined quality metric for multidimensional techniques. Peak dispersion and chromatographic space occupation was then used versus the temperature ramp and the carrier gas flow. Based on this optimal conditions, the different sample types were injected. Different mass spectra screening scripts were developed in order to

automatically removed contaminants, such as plasticizers and siloxanes emitted by the SPME fiber and the column. Next, different normalization methods were compared. Indeed, untargeted screening relies on the relative quantification. A proper normalization is required prior to any data mining. Z-score and probabilistic quotient normalization were the two best performing approaches depending on the sampling methods. On one side, Z-score required control analytical conditions from sampling to detection. On the other side, probabilistic quotient normalization is best performing for uncontroled sampling, as in the clinical context. Pearson and Spearman correlation, as well as unsupervised principal component analysis, were used to evaluated the normalization efficiency. Finally, different approaches were compared for feature selection and information extraction. The first is based on Fisher Ratio calculation. This univariate method is based on the ratio between variances, as for an ANOVA. This approach is widely used in the field, so it was used as a reference for method comparison. Second, we compared different machine learning techniques, namely: Random Forest, Support Vector Machine, and Partial Least Squares. Finally, sample clustering was used to evaluate the efficiency of the different approaches.

Novel Aspect

The development of integrated processing solutions for GC×GC-TOFMS open the doors of high-throughput untargeted volatilomics.

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