Computational Approaches for Localization and Quantification of Compounds, Toxicants and their Metabolites

Study setup

Absolute quantitation in MALDI mass spectrometry imaging:
- Model A: Healthy mice exposed to chlordecone, 5 mg/kg, for 1 to 25 days
- Model B: Mice presenting liver necrosis were exposed to chlordecone, 8 mg/kg, for 10 days then CCl4 at 0.1 mg/kg.
- Control: Livers were from mice subjected to the same delivery, daily gavage with olive oil, but without chlordecone.

Quantitation of chlordecone:
- Different amounts of chlordecone (from 1 to 20 pmol/spot) were manually spotted on a control section mounted next to an exposed section.
- Labelled normalization in the normalization of the intensity of chlordecone hydrate detected at m/z 506.68 to the intensity of chlordecone hydrate detected at m/z 126.71 was then performed.

Calibration spots

Calibration curve (10 days)

Quantity of chlordecone for different time points:
- Accumulation profiles of chlordecone (5 mg/kg bw) in the mouse liver depending on days.
- Linearity of quantification results reflect good reproducibility.
- Limit of detection (LOD) and quantitation (LOQ) estimated at 1.2 µg/g and 3.9 µg/g.

Soft segmentation from LDA scores:
- Using annotated regions of necrotic area, a linear discriminant analysis (LDA) model was built with SCiLS Lab 2019b.
- Soft segmentation from LDA scores evaluate the probability for assignment to necrotic and healthy tissue.
- Quantitative evaluation is achieved by constructing Heatograms with kernel density estimate functions and receiver operating characteristic (ROC) curves.

Background

- Chlordecone is an organochlorine pesticide that was extensively used in the French West Indies to fight weevils in banana plantations from 1973 to 1993.
- This has led to a persistent pollution of the environment and to the contamination of the local population for several decades with effects demonstrated on human health.
- Chlordecone accumulates mainly in the liver where it is known to potentiate the action of hepatotoxic agents.

Summary

- Mass spectrometry imaging (MSI) is widely used in drug development and toxicology studies to gain information about absorption and distribution of parent compound and its metabolites as well as how the presence of these compounds impacts distribution of endogenous molecules.
- Previous work by Lagarigue et al. (Anal. Chem. 2014:86) presented an approach for quantitative mining MSI data of chlordecone toxicology study.
- The approach shown here includes methods for statistically expressing penetration in both qualitative and quantitative terms by soft segmentation, kernel density estimation, discriminant analysis, and quantitation of target molecules.

Highlights

- Quantitative of small molecules by MALDI imaging based on labelled normalization.
- MALDI imaging reveals in-situ localization of toxicant in pathological liver preserving information of localization.