PhD projects R3-5 and R3-8

Statistical Procedures and Numerical Algorithms for Analyzing MALDI Data
Two-Sample Testing for the Comparison of MALDI Spectra

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RTG 2224

Statistical Analysis of MALDI Data

- Spectra obtained using Matrix-Assisted Laser Desorption/Ionization (MALDI) imaging
- Observations $x \in \mathbb{R}^d$ with d between 2.000 and 100.000
- Each entry x_i is proportional to the number of ions detected at a specific m/z (mass-to-charge) ratio.

Statistical Analysis of MALDI Data - Modelling

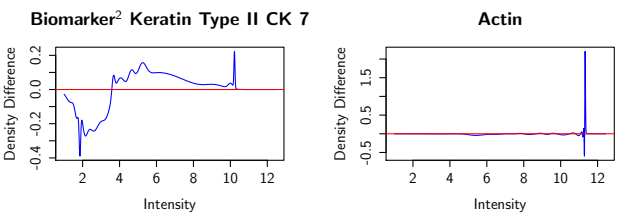
- Total number of ions is large[1] ($\approx 10^9$)
- Number of ions correlated with concentration of analyte[1]

Marginal approximation of the log-likelihood

$$\sum_{i=1}^{n} \log \left(\sum_{k=1}^{K} p_{j,k} \cdot \underbrace{\phi\left(x_j^{(i)} \,|a_i\mu_{j,k}, a_i\sigma_{j,k}^2\right)}_{\textbf{Gaussian approximation}} \right) + \underbrace{\log R(\sigma_j)}_{\textbf{Regularization}} \tag{1}$$

$x^{(1)}, \ldots, x^{(n)}$ independent observations, $a_i := \left\|x^{(i)}\right\|_1$ and **penalty** R is an inverse gamma prior on the variance

- Observations not identically distributed
- ML estimates for $p_j, \mu_j, \sigma_j \in \mathbb{R}^K$ can be obtained by applying Expectation-Maximization to (1).
- **Vectorized implementation** on the GPU



Statistical Analysis of MALDI Data - Feature Selection

Goal: Find m/z values that differ between samples
↪ Potential biomarkers

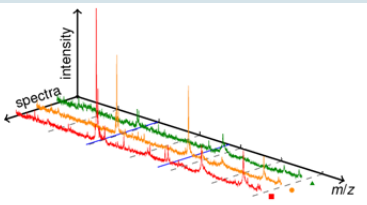
Developed Approach[3] (FDR-controlling Feature Selection)

1. Normalize variance trend
2. Subsampling bootstrap of test statistic[4] (or of AUC)
3. FDR control (BY) to determine number of features

Supervised learning (cross-validated accuracy reported)

Method/Data set	Leuschner et al. (2018)	Task ADSQ (Spot) of Behrmann et al. (2017)
IsotopeNet[5]		0.845
Flog_int (60 Features)[6]	0.899	
FDR-controlling FS[3] + RF	**0.926**	**0.866**

2-sample testing for the comparison of MALDI spectra



- Compute effective numbers of tests for two-sample or k-sample comparison problems in the context of MALDI.[7]
- Multiplicity- and dependency-adjustment method (MADAM) for control of the family-wise error rate [8]
- Supervised classification
- Feature Selection
- Arbitrary dependence structure
- Copula-based methods
- Resampling-based methods
- Multiple type I error rates
  - Family-wise error rate [9]
  - False discovery rate [10]
  - False discovery exceedance
- Likelihood-Ratio test based on (1)

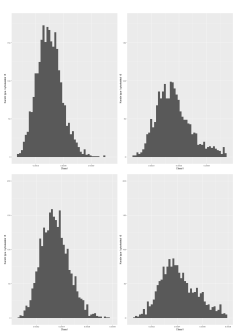
Elements of the project

An effective number of test of order i, given by
$M_{eff}^{(i)} \equiv M_{eff}^{(i)}(\alpha_{loc}, \mathbf{T}) = 1 + \epsilon(i) + \sum_{j=i\vee 2}^{M} \kappa_j^{(i)}$

The $MADAM_i$ transforms the values of the test statistics $T_1, T_2, \cdots, T_M$ into one of the following multiplicity- and dependency-adjusted p-values.

$$p_{\Sigma,j}^{MADAM_i}(x) = b^{(i)}(\mathbb{P}, t_j)$$
$$p_{\prod,j}^{MADAM_i}(x) = 1 - \beta^{(i)}(\mathbb{P}, t_j)$$

where the order of *i* can be considered as a tuning parameter of the MADAM approach.



Do the distributions between classes differ?

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