ImaBiotech
Revealing Biological Secrets

An Image-Based Data-Driven Analysis of Metabolite Clusters Architecture in Heterogeneous Colorectal Cancer Tissues

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Reveal functional metabolomic heterogeneity in MSI samples with Uniform Manifold Approximation and Projection (UMAP).

Label free Mass Spectrometry Imaging (MSI) has been developed and used by ImaBiotech to detect and quantify metabolites in tissue for almost a decade. Although MSI provides a very rich information on the spatial distribution of biomolecular species in tissue section, the biggest challenge is to make sense of the large complex data set. Effective data visualization plays a role in exploring patterns/features in such big datasets Such insights are essential to facilitate data interpretation though context-guided visualization and help develop hypotheses on newly founded biological patterns.

- What are the metabolomic patterns within the phenotypic complexity of tissue of interest ?
- How tissue environment metabolite clustering drive the disease biology?

Clustering of metabolites within complex heterogeneous tissue

To overcome the challenge of a big and complex dataset, ImaBiotech's R&D team has developed a visualization workflow to overlay clustered metabolic patterns on tissue in order to identify system biological models for disease progression or therapy response assessment (Fig 1).

In this context, this study presents a workflow to project high dimensional spatial metabolic data on two-dimensional colorectal cancer tissue sections with different pathological stages of cancer (Fig 2).

This workflow allows to cluster metabolic components according to their biological function in the complexity of the tissue and can be applied to identify new metabolic signatures that correlate with disease prognostic or treatment prediction.

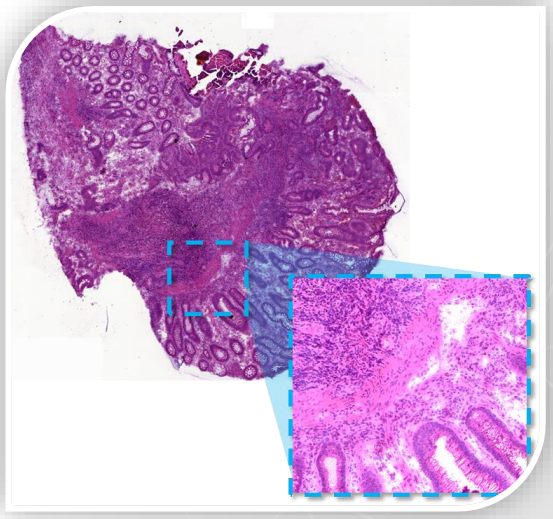


Fig 1. Example of a colorectal tissue section used for MSI analysis. The study includes three colorectal cancer samples representative of three pathological staging (Stage I to III).

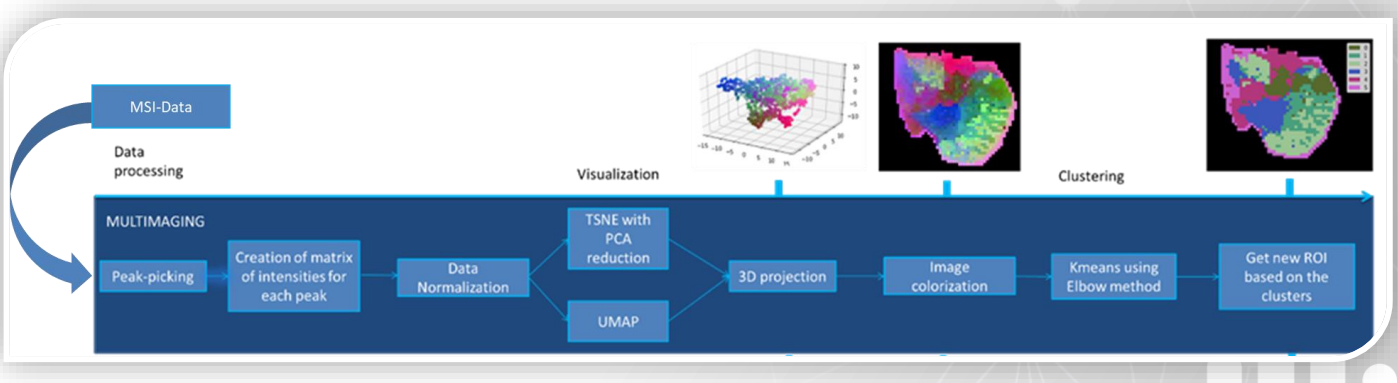


Figure 2. Presentation of the workflow for visualization of the metabolic data patterns in the complexity of the tissue.

Combination of MSI data and dimension reduction techniques

All QMSI data were normalized using L2 normalization. UMAP and T-SNE were used for dimensionality reduction to 3D projection of the data, then followed by a 2D transposition and image coloration.

As shown in Figure 3, the applied algorithms help to capture the heterogenous distribution patterns of the metabolites in the tissue. Comparing the performance of UMAP with T-SNE, we find that UMAP provides the fastest run times, and the most meaningful organization of metabolite clusters least affected by the outliers compared to T-SNE. This work highlights the use of UMAP for improved visualization and interpretation of MSI data.

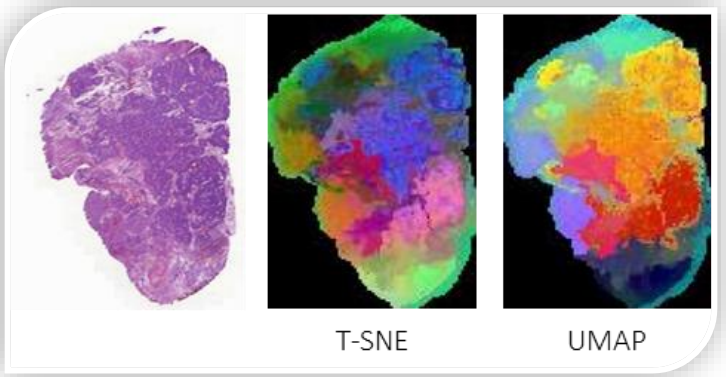
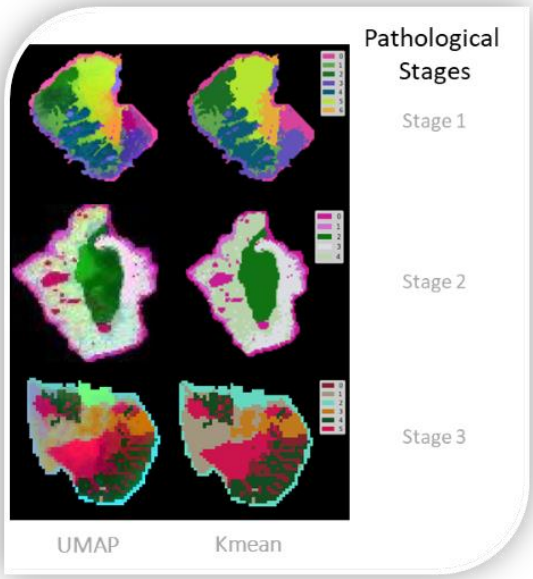


Figure 3. Visualization of differential expression metabolites related to their spatial distribution.

Clustering reveals differential metabolite pattern distributions according to disease progression



A downside of non-linear method however is their limited explicability. Although providing excellent and rapid insight into the major patterns presents in tissues, they do not reveal the statistical viability of these patterns. Kmean was then performed in order to qualify the patterns into real clusters that are used to classify tissue molecular heterogeneity.

The clustering patterns were different across the different pathological stages of the disease and the complexity of the metabolite patterns increased with disease extent. This shows that metabolite distribution is affected during disease progression and altered by the extent of the disease .

Figure 4. Classification of the metabolites according to pixel similarity

Conclusion

We present here a visualization tool to obtain insights regarding the heterogeneity of molecular patterns in this instance metabolites present in the tissue. This will help understand the underlying biological phenomena at play in the tissue.

We illustrated our approach on heterogeneous colorectal cancer tissue and were able to identify metabolites signatures that are differentially expressed along disease progression. The next step is to distinguish within each cluster the metabolites responsible for the disease progression signature. This tool is nonetheless a powerful tool in the search of disease mechanism or facilitate biomarker discovery

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