VIB Hackathon on spatial omics tools and methods

Benjamin Rombaut[1,2,3], Lotte Pollaris[1,2,3], Chananchida Sang-aram[1,2,3], Michiel Ver Cruysse[1,3], Robrecht Cannoodt[5,1,2], Frank Vernaillen[4], Arne Defauw[4], Julien Mortier[4], Kresimir Bestak[6], Luuk Harbers[8], Miguel A. Ibarra-Arellano[6], Aroj Hada[6,7], Vladislav Vlasov[9], Michele Bortolomeazzi[10], Paul Kiessling[11], Alexander Sudy[12], Wouter-Michiel Vierdag[13], Miray Cetin[14], Lotte Van de Vreken[15], Quentin Blampey[16], Anastasiia Okhtienko[17], Daniel Dimitrov[6], Mayar Ali[18,19], Francesca Drummer[18, 20], Benedetta Manzato[21], Carlos Ariel Pulido-Vicuna[22,8], Susmita Mandal[23], Giovanni Palla[18], Laurens Lehner[18], Lorenzo Giordani[24], Claudio Novella-Rausell[21], Guillaume Sacchetti[22,8], Estella Yixing Dong[25], and Yvan Saeys[1,2,3]

1 Data Mining and Modelling for Biomedicine, VIB-UGent Center for Inflammation Research, Ghent, Belgium **2** Department of Applied Mathematics, Computer Science and Statistics, Ghent University, Ghent, Belgium **3** VIB Center for AI and Computational Biology, Ghent, Belgium **4** VIB Spatial Catalyst **5** Data Intuitive, Lebbeke, Belgium **6** Institute for Computational Biomedicine, Faculty of Medicine, Heidelberg University Hospital, Heidelberg, Germany **7** AI-Health Innovation Cluster, Heidelberg, Germany **8** VIB-KU Leuven Center for Cancer Biology, Leuven, Belgium **9** Brain and Systems Immunology Lab, Brussels Center for Immunology, Vrije Universiteit Brussel **10** ScOpen Lab, German Cancer Research Center (DKFZ), Heidelberg, Germany **11** RWTH Aachen, University Hospital **12** Center of Digital Health, Berlin Institute of Health at Charité – Universitätsmedizin Berlin, Germany **13** European Molecular Biology Laboratorium, Heidelberg, Germany **14** Systems Immunology and Single-Cell Biology, German Cancer Research Center (DKFZ), Heidelberg, Germany **15** VIB-UGent Center for Plant Systems Biology, Ghent, Belgium **16** MICS Laboratory, CentraleSupélec, Paris-Saclay University, Paris, France **17** Institute of Virology,Technical University of Munich, Munich, Germany **18** Institute of Computational Biology, Helmholtz Munich, Neuherberg, Germany **19** Institute for Tissue Engineering and Regenerative Medicine, Helmholtz Munich, Neuherberg, Germany **20** Institute for Stroke and Dementia Research, Klinikum Der Universität München, Ludwig-Maximilians-Universität, Munich, Germany **21** Department of Human Genetics, Leiden University Medical Center, Leiden 2333ZC, The Netherlands **22** Laboratory for Molecular Cancer Biology, Center for Cancer Biology, VIB, Leuven, Belgium; Department of Oncology, KU Leuven, Leuven, Belgium. **23** Institute of Pathology at Charité – Universitätsmedizin Berlin, Germany **24** Sorbonne Université, INSERM UMRS 974, Association Institut de Myologie, Centre de Recherche en Myologie, 75013 Paris, France. **25** Biomedical Data Science Center, Lausanne University Hospital; University of Lausanne, Lausanne, Switzerland.

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Introduction

During a three-day hackathon, work was performed on various topics within the field of spatial omics data analysis. The topics were organized in five workgroups and included benchmarking, pipelines, spatial transcriptomics, spatial proteomics, spatial multi-omics and cell-cell communication. Most tools and methods were considered in the context of the analysis ecosystem in Python for spatial (Marconato et al., 2024) and single-cell (Virshup et al., 2023) data analysis.

Results

Results were summarized in a final slide deck. A project board collected all task items and GitHub Issues. Here we give a brief overview for each of the five workgroups.

Workgroup pipelines

Nextflow During this hackathon, we have worked on and finished the template update for nf-core/molkart, an nf-core pipeline for processing Molecular Cartography data, allowing for the next expansion that will include spot-based segmentation options. Additionally, we have added Spotiflow, a spot-detection tool into the nf-core framework.

Isoquant Isoquant is a tool for the reconstruction and quantification of single-cell long-read RNA data (e.g. from PacBio and Oxford Nanopore). Currently, Isoquant is not optimized for spatial data and is limited to reconstructing and quantifying transcripts from a few thousand barcodes at most. While this is often sufficient for single-cell long-read RNA data, spatial data can scale to many more barcodes.

During this hackathon we identified the current bottlenecks in Isoquant and started on implementing a fix to circumvent this. From initial testing we can now perform reconstruction and quantification of transcripts on millions of barcodes efficiently. Currently we are performing further testing to ensure that results and downstream analyses are unaffected before submitting the fix as a pull request.

Infrastructure for pipelines

We merged support for incremental IO (partial read/write) in SpatialData (PR). Identified an issue for multiscale images. Discussed support for apply function on raster data in SpatialData (draft PR).

- Specific issues:
  - improve performance of isoquant for large spatial omics datasets
  - Build a computational benchmark for spatial omics data
    - identify datasets
    - identify first becnmarks
- Accessing remote datasets:
  - Upload spatial omics datasets to S3
  - Support for private remove object storage in SpatialData

Workgroup spatial transcriptomics

Napari plugin

Napari is a scalable interactive viewer for multi-dimensional data. It works natively in python. Within this hackathon, we worked on adding functionality to napari-spatialdata, a SpatialData plugin for napari. Firstly, we worked on reusing colors previously defined in the SpatialData object. Secondly, progress had been made to only visualize subsets of the cells. This would allow to plot a certain celltype colored by gene expression of gene x and another celltype colored by gene expression.
Thirdly, work on the annotation widget has been performed and checked. Lastly, it has been made possible for widgets to communicate with one another.

Annotation workflows

We discussed user stories for a workflow that entails drawing annotations interactively with Napari and using the annotations in downstream analysis steps. To this end, we identified the following tasks that would enable such workflow: - napari-spatialdata widget that would enable: 1. Drawing annotations on a specific image or coordinate system. 2. Rename the annotations, specifying various metadata to the annotation, such as the identity of the annotator, labels for the annotations and others. 3. Save the annotations back to the spatialdata object and on-disk. - Masked spatial graphs based on annotations: the annotations define specific areas of interest of the tissue. The analyst may wish to analyze the spatial structure enclosed in the annotations, or using the annotation as a "negative mask" in order to remove graph edges going across void regions of the tissue. - Calculating and plotting gene expression trends at

increasing distance to the annotation of interest (or within the boundaries of the annotations of interest). This is similar to the squidpy function `sq.tl.var_by_distance` but computing distances to polygon boundaries and not simply to the centroid of the polygon.

Visium HD on-the-fly rasterization

As mentionned in this SpatialData issue, Visium HD bins can't be rasterized in memory (i.e., converted to an image) as a single full-genome image. Indeed, the smallest bins are 2-microns-width squares with full-genome sequencing. Still, for visualization and analyses purposes, rasterization is needed. Therefore, we opened a new PR for bins rasterization, on which we support two modes: - rasterization of one or multiple channels (in-memory). It uses the indices of the sparse table in CSC format for efficiency. - lazy rasterization of the full data with dask (in particular, using map_blocks). The data is therefore rasterized when needed, for instance to display one or a few channels in napari-spatialdata.

Visium HD and Xenium Recently a dataset was published (https://www.biorxiv.org/content/10.1101/2024.06.04.597233v1) that applied multimodal spatial transcriptomics techniques on the same colorectal cancer samples on consecutive sections. Namely, Visium HD, Xenium as well as Visium v2 and scRNAseq was performed. Our goal was to compare the high resolution sequencing-based data from Visium HD with the imaging-based Xenium to show whether they can be used as validations for each other. To achieve this, we first converted the data of both modalities to spatialdata-objects and cropped and aligned the H&E image of the Visium HD assay to match the corresponding area of the Xenium HD chip by using the alignment functions of spatialdata. With the aligned dataset we were able to show that the marker gene for epithelial cells (*CEACAM6*) and a marker gene for crypt base columnar cells (*OLFM4*) are expressed in the same tissue regions. Finally, we were looking into further methods to analyze these datasets:

- Label transfer from scRNA-seq data to VisiumHD (RCTD speed-up verison) and Xenium (SingleR)
- Investigate the impact of different normalization methods on SVG detection, using Visium, VisiumHD, and Xenium replicates.
- Merging spatialdata objects of Xenium and VisiumHD
- Microenvironment detection using Banksy (https://github.com/prabhakarlab/Banksy_py)

Cellular niches Multiple unsupervised metrics have been added in this Squidpy PR to evaluate niches detection methods. Notably: - a niche continuity metric - a cross-slide homogeneity metric - DE tests to compare max gene expression across niches - ARI, NMI and Fowlkes-Mallows Index for niche result comparison (agreement)

Workgroup spatial proteomics

Group members had most experience with analysis of Miltenyi MACSima, Akoya Phenocycler, Lunaphore COMET and MIBI data.

Some common issues in spatial proteomics analysis were discussed. Reading in datasets in the SpatialData format still lacks for some platforms. Some interesting metadata is also included always included, such as physical pixel size, autofluorescence subtraction, imaging cycles and exposure time. The need in some datasets to detect misalignment and co-register the channel images, either all of them or specific ones. For segmentation, applying CLAHE and using cellpose was found to be sufficient for most cells. For exceptional cell shapes in tissues such as the heart and brain there is additional difficulty and need for fine-tuning the segmentation model with enough training data. This manual labeling is time-consuming and difficult to reproduce.

There was a lack of consensus on available normalization techniques and batch effect correction and their usefullness.

Four work items were selected:

1. Support for exporting cells in SpatialData and interactively annotating them using a classifier with Ilastik software (Berg et al., 2019).
2. Normalization facilitates the integration and comparison of data from different experiments, which is essential for large-scale studies and meta-analyses such as spatial omics data. Therefore, creation of an overview of normalization methods for downstream analysis of spatial proteomics datasets and a comparison between them is crucial. While evaluation & benchmarking would require a gold standard cell type dataset which is beyond the scope of this hackathon, a repository was created at https://github.com/SchapiroLabor/norm_methods/. that contains a summary of 9 methods adapted from published literature. All codes for each method are also available. A visualization of results obtained from these different methods on a MIBI dataset (not publicly available) is provided as well. Among the different methods, a visual qualitative comparison provides evidence that a combined method (Shaban et al. + Greenbaum et al.) may yield more promising results. We plan to extend the work from this hackathon with a quantitative comparison in the future.

3. An alternative to `spatialdata.to_polygons()` label vectorization function, which features improved performance, resolution of the invalid geometries, and `shapely.MultiPolygon` geom filtering based on the area.
4. Creating a new reader for MACSima datasets in spatialdata-io, with support for lazy loading, physical pixel size and imaging cycles.

Motivation for the polygon vectorization

Polygonal representation of cells is crucial for characterizing cellular morphologies and establishing spatial relationships between cells. This method is applicable when cells are located on different planes within tissue, as well as for calculating distances between various objects. However, there is a notable lack of tools that can take a `TIFF` file with cell labels and output a `GeoDataFrame` or `GeoJSON`. The developing branch of the `SpatialData` framework includes a `to_polygons()` vectorization function, but it lacks functionality for resolving invalid geometries and filtering multipolygons.

The following illustrates a practical example: when analyzing thick imaging samples without a z-stack, we observe different cell types located in different z-planes relative to each other. This is usually not an issue when masks come from mutually exclusive intensity channels. However, with more general markers, we may encounter incorrect and overlapping segmentation masks. Resolving these spatially overlapping segmentation masks through geometrical subtraction often results in fragmented multipolygons with small polygons and lines, affecting downstream applications.

We aim to address the problems of invalid geometries and multipolygon filtering and provide an easy-to-use function compatible with standard `NumPy` arrays (unlike `SpatialData`, which requires a `SpatialImage` instance to perform vectorization). Additionally, our approach improves (~2x increase) performance by avoiding chunking of the input array.

Workgroup spatial multi-omics

Spatial multi-omics are an emerging class of technologies that record two or more data modalities from biological samples in a spatial context. Modalities can among others include RNA, protein, epigenetic features like chromatin accesibility and pathohistological stains. True multi-omic datasets that reccord multiple modalities of the same cells are rare, which motivates our subproject on **multi-slice alignment** via image registration and integration algorithms. **Cell morphology** which is revealed by classical staining methods is a potential very informative source

Potential methods for morphology extraction:

- HEIP
- UNI
- Resnet50 example
- ScDino (Immuno fluorescence)

Spatial transcriptomics + Morphology:

- Visium HD Cancer Colon: Raw data, Nuclei Segmentation + Domains,Preprint
- Xenium Lung Cancer: Spatialdata,Raw data
- Xenium Breast Cancer: https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE243168
- Merfish RNA + IF How to dowload
- List of Visium, Xenium human cancer datasets: https://spatialdata.scverse.org/en/latest/tutorials/notebooks/datasets/README.html
- Morphology features tutorial squidpy (tensorflow) https://squidpy.readthedocs.io/en/stable/notebooks/tutorials/tutorial_tf.html **concept:** Correlate morphological features of tissue with corresponding genetic expression data. **Used Data:** Visium & Xenium Data **Procedure:** - extract morphological features from H&E image: Apply morph. feature model (Resnet, Alexnet, vision transformer...) per area corresponding to each visium/xenium bin - PCA + clustering of morphological features (k=6) - per-bin PCA + clustering of transcriptomic data - Correlate gene-expression clusters with morphological clusters - Extract DE genes corresponding to different morphological areas

Multi-omics datasets (same/different slides):

- SPOTS with the 10x Visium technology capturing whole transcriptomes and extracellular proteins https://doi.org/10.1038/s41587-022-01536-3, GSE198353. High-resolution images (https://figshare.com/account/home#/projects/143019)
- Stereo-CITE-seq spatial transcriptomics + proteomics (https://doi.org/10.1101/2023.04.28.538364)
- spatial transcriptomics + DVP proteomics (https://doi.org/10.1038/s41593-022-01097-3)
- Spatial-ATAC-RNA-seq (https://doi.org/10.1038/s41586-023-05795-1)
- Cite-seq, proteogenomics (https://doi.org/10.1016/j.cell.2021.12.018)
- spatial CITE-seq transcriptomics+proteomics (https://doi.org/10.1038/s41587-023-01676-0)
- Benchmark datasets for 3D mass spec imaging (=2D Mass spec imaging on adjacent sections) (https://academic.oup.com/gigascience/article/4/1/s13742-015-0059-4/2707545)
- https://doi.org/10.1038/s41467-023-43105-5 (suppl table 1, collection of publicly available datasets from different studies)
- spatial-ATAC and the spatial RNA-seq (MISAR-seq, https://doi.org/10.1038/s41592-023-01884-1)
- Mass spec imaging + spatial transcriptomics (Visium): https://www.nature.com/articles/s41587-023-01937-y (see data availability, e.g. https://data.mendeley.com/datasets/w7nw4km7xd/1, sma zip file)

Data integration

Challenges: - number of detected features (e.g. RNA-seq VS proteomics) - different feature counts, statistical distributions - differences in resolution (imaging-based) - image alignment/overlay (imaging-based) - batch effect - technical (heavy data)

Horizontal

merging the same omic across different datasets Reasons: - 3D maps - technical replicates, integrating batches - integrating across different technologies

not true multi-omics integration

Examples: - STAGATE (spatial transcriptomics, consecutive sections, adaptive graph attention auto-encoder, https://doi.org/10.1038/s41467-022-29439-6) - STAligner (spatial transcriptomics datasets, batch effect-corrected embeddings, 3D reconstruction, https://doi.org/10.1038/s43588-023-00543-x) - SpaGCN (spatial transcriptomics, graph convolutional network approach that integrates gene expression, spatial location and histology, https://doi.org/10.1038/s41592-021-01255-8) - PASTE (align and integrate ST data from multiple adjacent tissue sections) https://www.nature.com/articles/s41592-022-01459-6 - SpaceFlow (embedding is continuous both in space and time, Deep Graph Infomax (DGI) framework with spatial regularization, https://doi.org/10.1038/s41467-022-31739-w)

Vertical

merges data from different omics within the same set of samples (matched integration) Anchor - cell Examples: - archr (https://doi.org/10.1038/s41588-021-00790-6, https://doi.org/10.1073/pnas.211002511) - MaxFuse (fuzzy smoothed embedding for weaky-linked modalities, proteomics, transcriptomics and epigenomics at single-cell resolution on the same tissue section https://doi.org/10.1038/s41587-023-01935-0) - MultiMAP (nonlinear manifold learning algorithm that recovers a single manifold on which several datasets reside and then projects the data into a single low-dimensional space so as to preserve the manifold structure, https://doi.org/10.1186/s13059-021-02565-y) - Seurat5

Diagonal

Different cells/consecutive slides/different studies (unmatched integration) Examples:

- SpatialGlue (https://doi.org/10.1101/2023.04.26.538404)
  - graph neural network with dual-attention mechanism
  - 2 separate graphs to encode data into common embedding space: a spatial proximity graph and a feature graph
  - Spatial-epigenome-transcriptome, Stereo-CITE-seq, SPOTS, and 10x Visium (to be continued)
  - python script and a set of jupyter notebooks with examples
  - need all data in adata .h5ad format (using scanpy)
  - calling R from Python
- MEFISTO (https://doi.org/10.1038/s41592-021-01343-9)
  - factor analysis + flexible non-parametric framework of Gaussian processes
  - spatio-temporally informed dimensionality reduction, interpolation, and separation of smooth from non-smooth patterns of variation.
  - different omics, multiple sets of samples (different experimental conditions, species or individuals)
  - each sample is characterized by "view", "group", and by a continuous covariate such as a one-dimensional temporal or two-dimensional spatial coordinate
  - no examples of real spatial multi-omics integration
  - integrated into the MOFA framework (in R)
- SLAT (https://doi.org/10.1038/s41467-023-43105-5)
  - aligning heterogenous spatial data across distinct technologies and modalities (is it so?)
  - single-cell spatial datasets
  - graph adversarial matching
  - benchmarked on 10× Visium, MERFISH, and Stereo-seq
- Cross-modality mapping using image varifolds https://doi.org/10.1038/s41467-024-47883-4

For additional info see suppl file table1 General issue: gene-based, challenges with proteomics (and even more issues with metabolomics). Direct comparison of the tools is not possible due to different tasks and working principles. ### *In silico* datasets generation Experimental

design planning; sampling strategy; statistics; tools benchmarking - https://www.nature.com/articles/s41592-023-01766-6 - tissue scaffold: random-circle-packing algorithm to generate a planar graph - attributes on nodes represent cell type assignments - the labeling is based on two data-driven parameters (prior knowledge) for a tissue type: the proportions of the k unique cell types, and the pairwise probabilities of each possible cell type pair being adjacent (a k × k matrix) - by changing these 2 params one should be able to obtain simulations for different tissues and technologies - ! Quite buggy in installation & running - scDesign3 https://www.nature.com/articles/s41587-023-01772-1 - SRTsim (transcriptomics only) https://doi.org/10.1186/s13059-023-02879-z

Image Registration

Spatial landmark detection and tissue registration with deep learning. Paper: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11009106/ Code: https://github.com/ekvall93/ELD

Misc:

Data used in STalign paper: https://www.nature.com/articles/s41467-023-43915-7#data-availability

Data used in CAST. Link to data doesn't work.

Papers

- Integration of Multiple Spatial Omics Modalities Reveals Unique Insights into Molecular Heterogeneity of Prostate Cancer Spatial transcriptomics and Mass spec imaging were performed on adjacent sections, and registered via their respective H&E images. The datasets are not publically available.
- Search and Match across Spatial Omics Samples at Single-cell Resolution
- https://frontlinegenomics.com/a-guide-to-multi-omics-integration-strategies/

Workgroup cell-cell communication

The goal of the group was to run multiple spatial CCC methods, compare evaluations/visualizations and results. We selected the methods from Armingol et al. 2024. Table is on the github page of the group.

Results:

Methods were implemented and tested on a subset of the MERFISH whole mouse brain data (slice 80) from the Allen Brain Institute.

We obtained results for CCC for the following methods: COMMOT, SpatialDM, MEBOCOST, CellPhoneDB. SpatialDM, CellPhoneDB was run with LIANA+. We also ran SpaTalk but found no LR pairs, as the tool requires that the entire ligand-receptor-tf-target pathway is expressed for a LR pair to be considered, and this was likely not the case in a dataset with 1122 genes. For the other three tools we selected specific LR pairs to compare the results.

1. Comparision on cell type level

Q: Do the tools identify the same sender and receiver cells that participate at communication? A: LIANA+ (CellPhoneDB) and COMMOT find common ligand-receptor pairs, however, among the few cell-type source-target pairs we investigated, there was no consensus. The comparison was performed on a qualitative way rather than quantitative due to difference in output format and evaluation metrics used by the different tools. Because MEBOCOST does not use Ligand-Receptor interactions as the other tools but it calculates metabolic communication scores, we could not compare the results directly.

2. Comparison on spatial level

Where do the tools predict the communication to take place in tissue space? Do spatial methods benefit from the additional modality?

Discussion: - Comparison of results is difficult because i) there is no ground thruth regarding CCC, ii) output formats of methods vary, for example SpatialDM returns a $NxLR$ matrix with a score for each cell indicating the potential strength of a ligand or receptor and COMMOT returns a NxN matrix for each LR interaction, iii) different score metric - Different input databases on which communication analysis is based (metabolic vs ligand-receptor) but also within LR interactions it might use the CellPhoneDB or CellChat database

- (Cang et al., 2023)

Conclusions

This hackathon was attended by 37 participants from many institutes across Europe. It provided a usefull venue for the exchange of ideas and the development of new tools and methods for spatial omics data analysis. Status updates and results were summarized in a slide deck. A project board collected all task items and a Zulip stream was used for communication. Code to use the provided computational resources and some of the hackathon results are available in this git repository.

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