Mathematical Frameworks for Integrative Analysis of Multi-omics Biological Data

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Abstract

Introduction to single cell and imaging multi-omics

Current multi-omic technologies

Challenges for interpretation

Interpretation requires a good understanding of the methods (no black boxes, a common language)

Communicating within the field: what approaches are we talking about?

Interpretation of the output from the analyses of the data is facilitated by the incorporation of contiguous information.

Redundant biological knowledge and incorporation of information from databases are important in the process. Biological Interpretations: bridges to data bases such as KEGG, Gene Ontology, HCA. Validation through complementary data.

Visualization tools for interpretation and communication

Examples: Brushing UMAP.

Explaining results to biologists through generative models and simulations (ex: Factor Analysis).

Issues of over-discretization, over-simplification

Example 1: The notion of cell-type is insufficient (Communication challenge with biologists about tradeoffs between focusing on rare cell types vs. more “continuous” view on cell types).

Problem with loss of information in the desire to simplify.

Counterexamples

Case studies

scNMT-seq as a case-study for epigenetic regulation

Overview and biological question

Computational challenges

- Identification of multi-omics signatures that characterize lineage, stage or both.

- Handling missing values
- Do epigenetic changes in some genomic contexts affect cell fate decision more than others? If so, how?

Methods for stats/math analyses and results summary

scRNA-seq + FISH as a case study for spatial transcriptomics

Overview and biological question

Computational challenges

- Can scRNA-seq data be overlaid onto seqFISH for resolution enhancement
- What is the minimal number of genes needed for data integration?
- Are there signatures of cellular co-localization or spatial coordinates in the non-spatial scRNA-seq data?

Methods for stats/math analyses and results summary

Spatial proteomics and cross-study analysis

Overview and biological question

Computational challenges

- Integrating partially-overlapping proteomic data collected on different patients with similar phenotypes
- Integration of spatial x-y coordinate co-location and co-expression
- Integration with other 'omics datasets (e.g., scRNA-seq) to support the results of these proteomic analyses
- Can we predict the spatial expression patterns of proteins measured on mass-tag but not measured in the MIBI-TOF data?
- What additional information can we learn about the different macrophage and immune populations in breast cancer by conducting integrated analyses of these datasets?

Methods for stats/math analyses and results summary

Overview of common analytical methods spanning technologies / case studies

- matrix factorization
- neural network / autoencoders

Software strategies to enable analyses of multimodal single cell experiments

Key questions

- How should multimodal single cell data be managed for interactive and batch analyses?
- What methods will help software developers create scalable solutions for multimodal single cell analysis?

- How can we ensure that visualization methods that are central to multimodal single cell analysis are usable by researchers with visual impairments?

Data management strategies

- Abstract data type: “multiassay experiment”. This reflects the idea that each mode will be characterized by a different collection of features on possibly non-overlapping collections of samples. The metadata on features should be clearly and conventionally defined. For example, genes and transcripts are enumerated using Ensembl catalog identifiers; regions of accessibility are defined using genomic coordinates in a clearly specified reference build. Metadata on samples must include all relevant information on experimental conditions such as treatment, protocol, and date of technical processing.

(More fodder-AS)

Key points: 1) What do we want to store and share? Data object vs analysis object. How would the design change based on what is stored? 2) Do we need a flexible, universal framework (e.g. MAE) or an experiment class for every possible combination of modalities or technologies? 3) Do we have adequate data representation for all “assays”?

- Multi-modal single cell data may consist of multi-assay measurements from the same cell (e.g. citeSeq, sci-CAR) or integration of multi-assay measurements from distinct cells from the same or distinct starting samples. A sample here refers to the biological specimen of origin (tissue A from individual X). A data container for a multi assay analysis must hold

1. Assay slots containing variables or features from multiple modalities (e.g. gene expression units from sc-RNAseq and protein units from sc-proteomics). In some cases, the feature may be multidimensional (e.g. spatial coordinates, locations of eQTLs).
2. Observations or cell identities
3. Metadata for sample of origin for the individual cells, e.g. study, center, phenotype, perturbation.
4. A map between the different assays to enable analysis

- The MAE is such a Bioconductor container for overlapping observations, and may serve as a starting point for further expansion. Besides the primary data elements for storing “data objects”, the summarizedExperiment class offers attributes and Methods for storing results of analysis, as an “analysis object”.
  - While common assays such as RNAseq and ATACseq have well-defined data representations (e.g. transcript names), data representation need to be defined newer assays, which may need multiple dimensions for adequate definition (e.g. x, y, z coordinates for images).
  - The observations of different modalities may not be directly comparable (e.g. RNA may be measured from individual cells but spatial transcriptomics may cover a few cells in the matched area).
  - In the absence of universal standards, the metadata may vary from analysis to analysis.

(Note, standard BioC container/class terms may not be correctly used. End of fodder - AS)

- Serializations and data access methods for
  - spatial transcriptomics
  - scNMT-seq …

Scalability strategies

Reducing barriers to interpretable visualizations

[An overview of the issues with impaired color perception]

[US Government tools for accessibility]

Details of working components

Type	Brief name	Description	URL	Author email
R data class	MultiAssayExperiment	unify multiple experiments	bioconductor.org	many
R package	Giotto	Spatial transcriptomics	...	...
python library	PyTorch	deep learning	...	...

Techniques and challenges for benchmarking methods

Outline:

- We must first define what we are benchmarking
  - recovery of cell types / clusters
  - discovery of relationships between data modalities, e.g. gene regulatory relationships observed between chromatin accessibility and gene expression
  - ...
- Strategies for benchmarking
  - simulation (and we can discuss the difficulties with simulating covariance structure across features and data modalities)
  - benchmarking datasets
  - cross-validation within study (and we can discuss issues in matching dimensions of latent space across folds). For this Mike has a lot of literature in Google Doc to include on papers that have performed either permutation or cross-validation to assess model performance.
  - cross-study validation (are relationships discovered in one dataset present in other datasets, potentially looking across single cell and bulk)

Discussion

Emerging analytical methods and technologies

Community needs for data structures, analysis methods, etc

Glossary

Consensus term	Synonyms	Description
Network	Graph	A set of *nodes*, representing objects of interest, linked by *edges*, representing specific relationships between nodes.

Consensus term	Synonyms	Description
Node	Vertex	Element of interest in a network and linked to other nodes. For example: people, cells, proteins or genes. Nodes can have several properties called *attributes* like cell type or position.
Edge	Link	The relationship between 2 nodes in a network. For example: friendship in social networks, cells in contact in a spatial network, or gene-gene interactions in a gene regulatory network.

References