Unsupervised Omics Integration

Omics Integration and Systems Biology NBIS SciLifeLab course

Nikolay Oskolkov, Lund University, NBIS SciLifeLab, Sweden

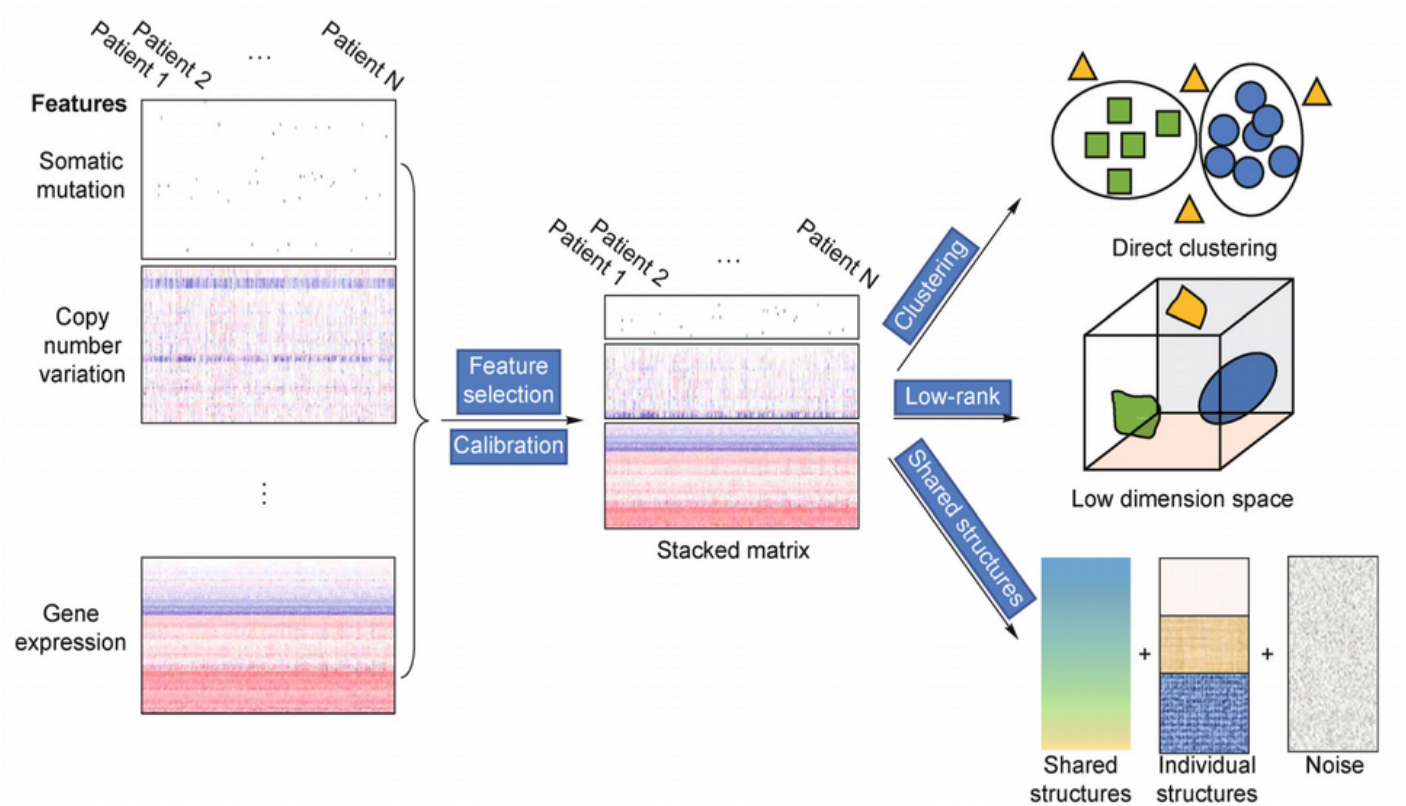
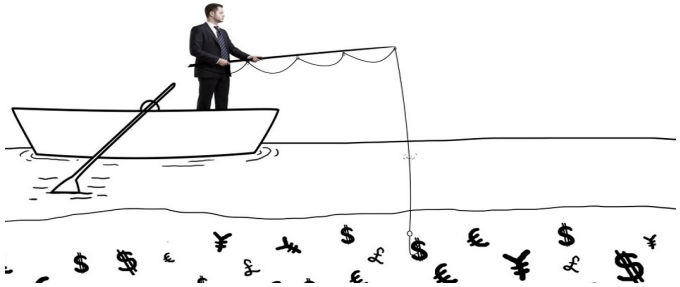


Image adapted from Wang et al., Quantitative Biology 4, p.58, 2016

Find me something in my data

Fishing expedition



- I do not understand your biological hypothesis

- I do not have any

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Editorial | Open Access | Published: 03 September 2020

A hypothesis is a liability

Itai Yanai & Martin Lercher

Genome Biology **21**, Article number: 231 (2020) | Cite this article

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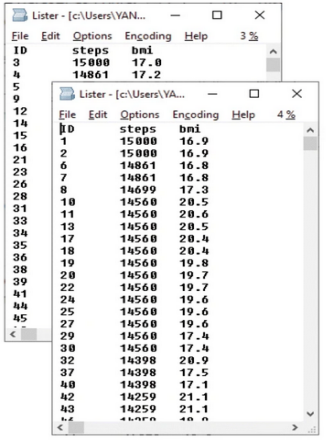
> " 'When someone seeks,' said Siddhartha, 'then it easily happens that his eyes see only the thing that he seeks, and he is able to find nothing, to take in nothing. [...] Seeking means: having a goal. But finding means: being free, being open, having no goal.' " Hermann Hesse

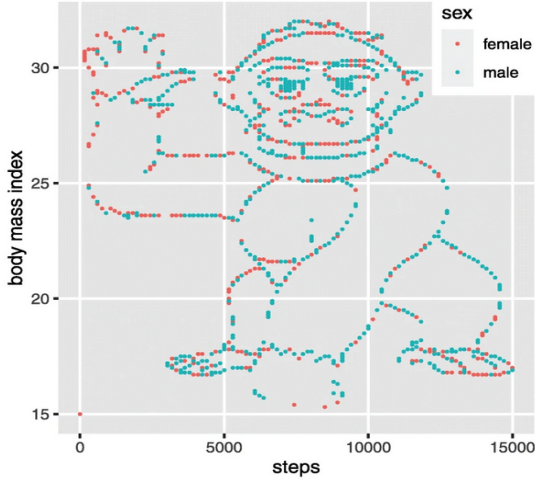
There is a hidden cost to having a hypothesis. It arises from the relationship between night science and day science, the two very distinct modes of activity in which scientific ideas are generated and tested, respectively [1, 2]. With a hypothesis in hand, the impressive strengths of day science are unleashed, guiding us in designing tests, estimating parameters, and throwing out the hypothesis if it fails the tests. But when we analyze the results of an experiment, our mental focus on a specific hypothesis can prevent us from exploring other aspects of the data, effectively blinding us to new ideas. A hypothesis then becomes a liability for any night science explorations. The corresponding limitations on our creativity, self-imposed in hypothesis-driven research, are of particular concern in the context of modern biological datasets, which are often vast and likely to contain hints at multiple distinct and potentially exciting discoveries. Night science has its own liability though, generating many spurious relationships and false hypotheses. Fortunately, these are exposed by the light of day science, emphasizing the complementarity of the two modes, where each overcomes the

a



ID	steps	bmi
1	15000	16.9
2	15000	16.9
6	14861	16.8
7	14861	16.8
8	14699	17.3
10	14560	20.5
11	14560	20.6
13	14560	20.5
17	14560	20.4
18	14560	20.4
19	14560	19.8
20	14560	19.7
22	14560	19.7
24	14560	19.6
25	14560	19.6
27	14560	19.6
29	14560	17.4
30	14560	17.4
32	14398	20.9
37	14398	17.5
40	14398	17.1
42	14259	21.1
43	14259	21.1

b



c

	Gorilla not discovered	Gorilla discovered
Hypothesis-focused	14	5
Hypothesis-free	5	9

a An artificial dataset given to students with and without explicit hypotheses on the relationship between BMI and the steps taken on a particular day, for men and women. **b** A plot of the dataset. **c** The contingency table for students in the two groups ("hypothesis-focused," "hypothesis-free") that discovered the gorilla or not [6]

MOFA (general) and MOFA+ (single cell)

Method

TRANSPARENT PROCESS OPEN ACCESS

molecular systems biology

Multi-Omics Factor Analysis—a framework for unsupervised integration of multi-omics data sets

Ricard Argelaguet[1,†], Britta Velten[2,†], Damien Arnol[1], Sascha Dietrich[3], Thorsten Zenz[3,4,5], John C Marioni[1,6,7], Florian Buettner[1,8,*], Wolfgang Huber[2,**] & Oliver Stegle[1,2,***]

Abstract

Multi-omics studies promise the improved characterization of biological processes across molecular layers. However, methods for the unsupervised integration of the resulting heterogeneous data sets are lacking. We present Multi-Omics Factor Analysis (MOFA), a computational method for discovering the principal sources of variation in multi-omics data sets. MOFA infers a set of (hidden) factors that capture biological and technical sources of variability. It disentangles axes of heterogeneity that are shared across multiple modalities and those specific to individual data modalities. The learnt factors enable a variety of downstream analyses, including identification of sample subgroups, data imputation and the detection of outlier samples. We applied MOFA to a cohort of 200 patient samples of chronic lymphocytic leukaemia, profiled for somatic mutations, RNA expression, DNA methylation and *ex vivo* drug responses. MOFA identified major dimensions of disease heterogeneity, including immunoglobulin heavy-chain variable region status, trisomy of chromosome 12 and previously underappreciated drivers, such as response to oxidative stress. In a second application, we used MOFA to analyse single-cell multi-omics data, identifying coordinated transcriptional and epigenetic changes along cell differentiation.

Keywords data integration; dimensionality reduction; multi-omics; personalized medicine; single-cell omics
Subject Categories Computational Biology; Genome-Scale & Integrative Biology; Methods & Resources
DOI 10.15252/msb.20178124 | Received 27 November 2017 | Revised 28 May 2018 | Accepted 29 May 2018
Mol Syst Biol. (2018) 14: e8124

Introduction

Technological advances increasingly enable multiple biological layers to be probed in parallel, ranging from genome, epigenome, transcriptome, proteome and metabolome to phenome profiling (Hasin *et al*, 2017). Integrative analyses that use information across these data modalities promise to deliver more comprehensive insights into the biological systems under study. Motivated by this, multi-omics profiling is increasingly applied across biological domains, including cancer biology (Gerstung *et al*, 2015; Iorio *et al*, 2016; Mertins *et al*, 2016; Cancer Genome Atlas Research Network, 2017), regulatory genomics (Chen *et al*, 2016), microbiology (Kim *et al*, 2016) or host-pathogen biology (Soderholm *et al*, 2016). Most recent technological advances have also enabled performing multi-omics analyses at the single-cell level (Macaulay *et al*, 2015; Angermueller *et al*, 2016; Guo *et al*, 2017; Clark *et al*, 2018; Colomé-Tatché & Theis, 2018). A common aim of such applications is to characterize heterogeneity between samples, as manifested in one or several of the data modalities (Ritchie *et al*, 2015). Multi-omics profiling is particularly appealing if the relevant axes of variation are not known *a priori*, and hence may be missed by studies that consider a single data modality or targeted approaches.

A basic strategy for the integration of omics data is testing for marginal associations between different data modalities. A prominent example is molecular quantitative trait locus mapping, where large numbers of association tests are performed between individual genetic variants and gene expression levels (GTEx Consortium, 2015) or epigenetic marks (Chen *et al*, 2016). While eminently useful for variant annotation, such association studies are inherently *local* and do not provide a coherent global map of the molecular differences between samples. A second strategy is the use of kernel- or graph-based methods to combine different

Method | Open Access | Published: 11 May 2020

MOFA+: a statistical framework for comprehensive integration of multi-modal single-cell data

Ricard Argelaguet, Damien Arnol, Danila Bredikhin, Yonatan Deloro, Britta Velten, John C. Marioni & Oliver Stegle

Genome Biology **21**, Article number: 111 (2020) | Cite this article
30k Accesses | **127** Citations | **119** Altmetric | Metrics

Abstract

Technological advances have enabled the profiling of multiple molecular layers at single-cell resolution, assaying cells from multiple samples or conditions. Consequently, there is a growing need for computational strategies to analyze data from complex experimental designs that include multiple data modalities and multiple groups of samples. We present Multi-Omics Factor Analysis v2 (MOFA+), a statistical framework for the comprehensive and scalable integration of single-cell multi-modal data. MOFA+ reconstructs a low-dimensional representation of the data using computationally efficient variational inference and supports flexible sparsity constraints, allowing to jointly model variation across multiple sample groups and data modalities.

Background

Single-cell methods have provided unprecedented opportunities to assay cellular heterogeneity. This is particularly important for studying complex biological processes, including the immune system, embryonic development, and cancer [1,2,3,4].

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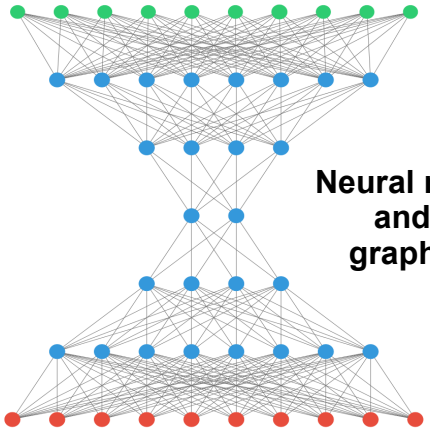
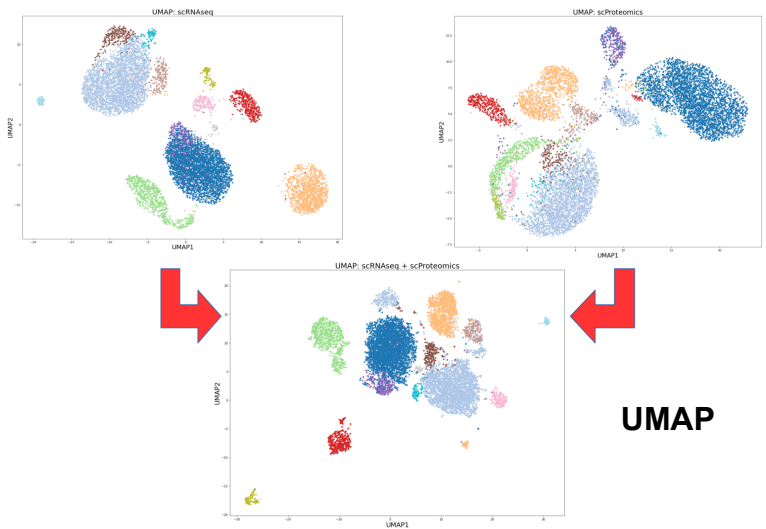
Sections | Figures | References

Overview of Integrative Methods

Convert to common space

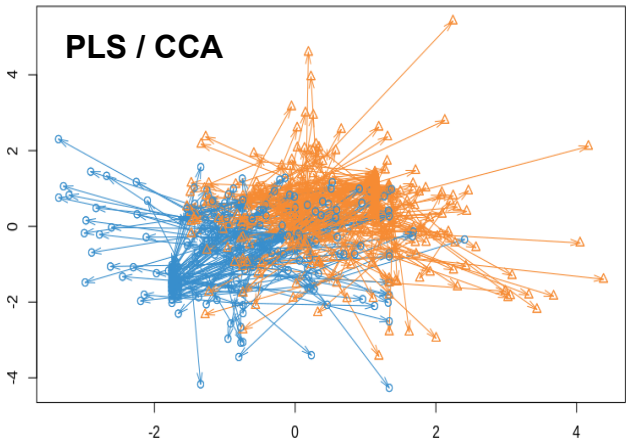


Neural nets and graphs

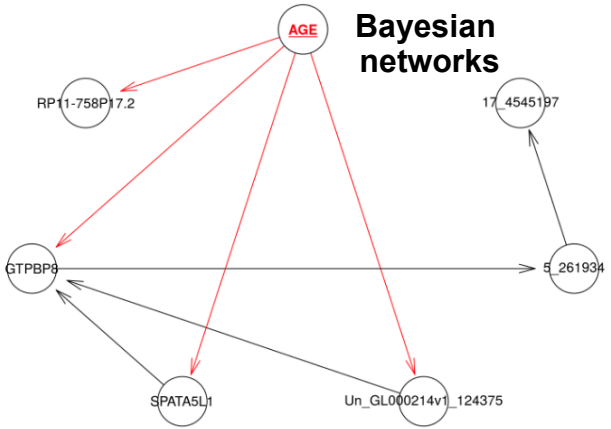


UMAP

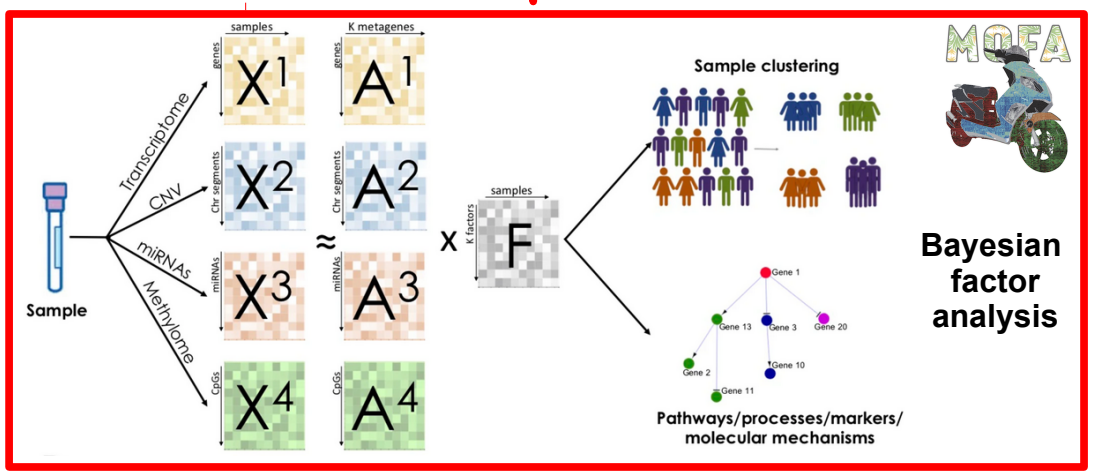
Extract common variation



Combine via Bayes rule

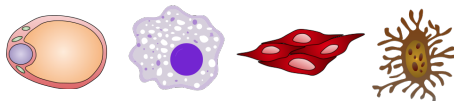


Bayesian networks

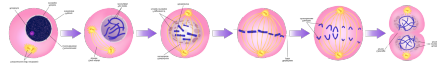


Bayesian factor analysis

Factor Analysis: Common Axes of Variation



CELL TYPE



CELL CYCLE

L_1

L_2

P_1

N

P_2

N

P_3

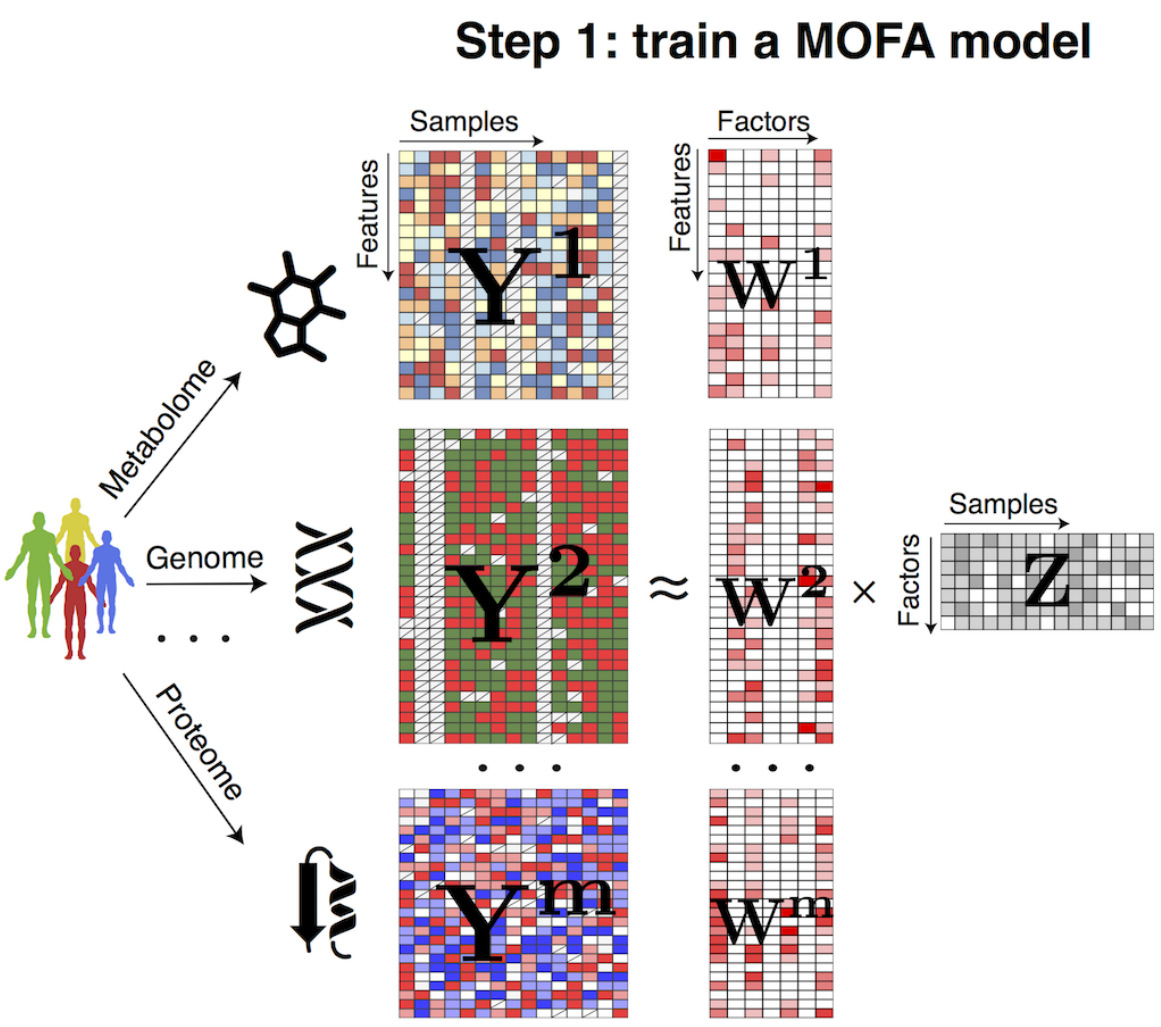
N

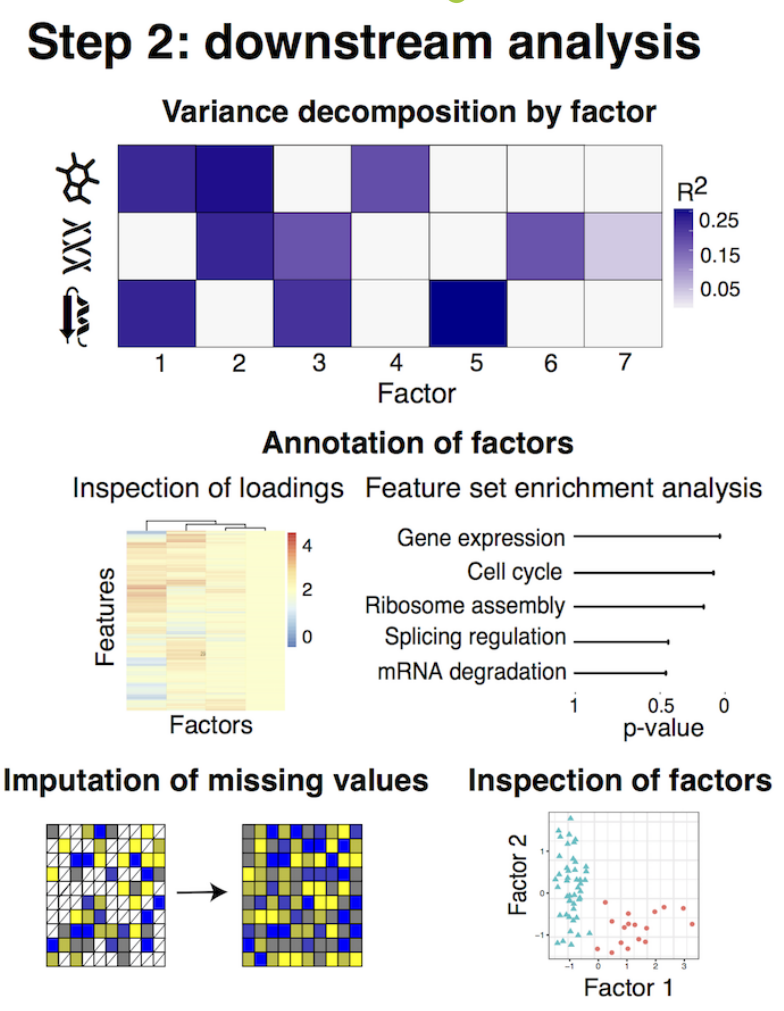
Gene expression

Methylation

Genetic mutation

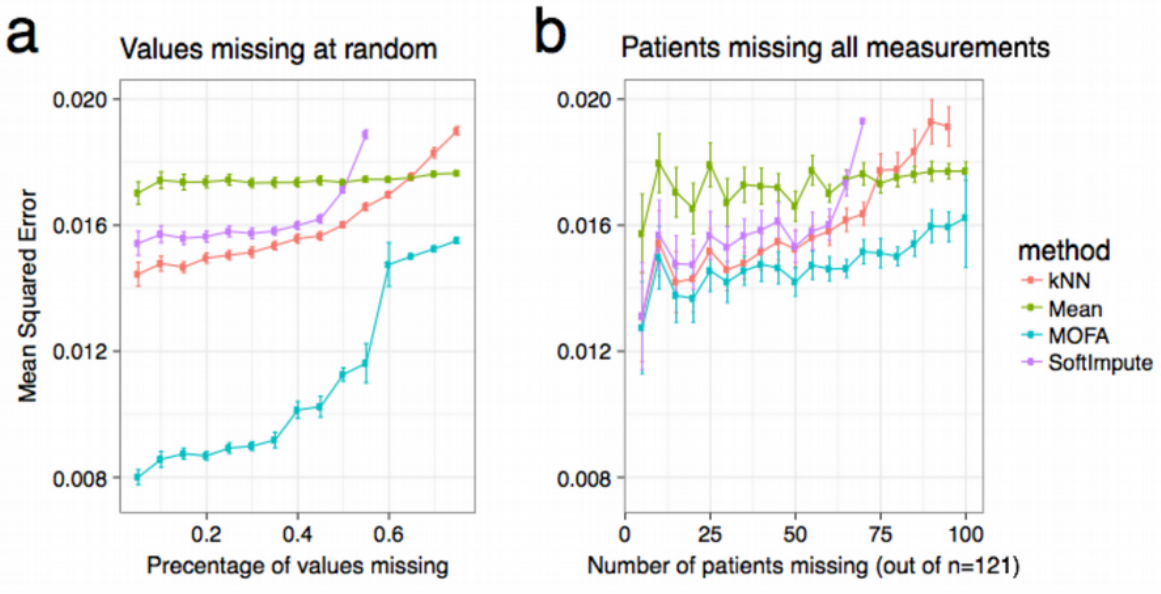
Multi-Omics Factor Analysis (MOFA)

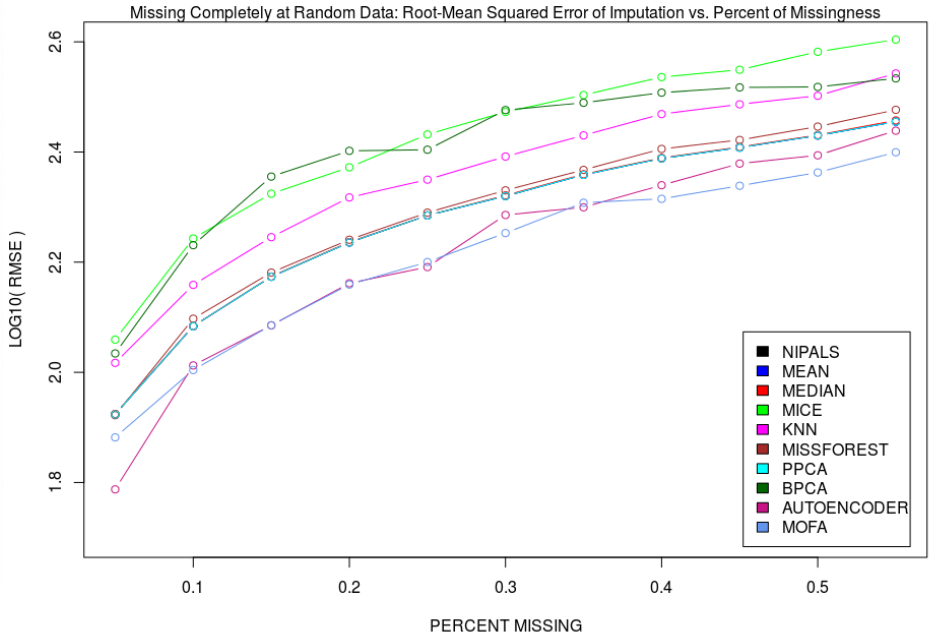




R. Argelaguet et al., Mol. Syst. Biol. 2018

MOFA: imputation of missing values





Bayesian framework is insensitive to missing data, priors compensate for the lack of data

MOFA: Bayesian Group Factor Analysis

Factor analysis models, also called latent variable models, are a probabilistic modelling approach which aim to reduce the dimensionality of a (big) dataset into a small set of variables which are easier to interpret and visualise. More formally, given a dataset $\mathbf{Y}$of N samples and D features, latent variable models attempt to explain dependencies between the features by means of a potentially smaller set of K unobserved (latent) factors. MOFA is a generalisation of traditional Factor Analysis where the input data consists of M matrices $\mathbf{Y}^m = [y^m_{nd}] \in \mathbb{R}^{N \times D_m}$ where each matrix m is called a view. Each view consists of non-overlapping features which usually, but not necessarily, represent different assays. The input data is then factorised as:

$$\mathbf{Y}^m = \mathbf{Z}\mathbf{W}^{mT} + \boldsymbol{\epsilon}^m, \tag{1}$$

where $\mathbf{Z} = [z_{nk}] \in \mathbb{R}^{N \times K}$ is a single matrix that contains the low-dimensional latent variables, $\mathbf{W}^m = [w^m_{dk}] \in \mathbb{R}^{D_m \times K}$ are loading matrices that relate the high-dimensional space to the low dimensional representation, and $\boldsymbol{\epsilon}^m = [\epsilon^m_d] \in \mathbb{R}^{D_m}$ denotes residual noise. We start by assuming Gaussian residuals $\boldsymbol{\epsilon}^m$, similar to standard (group) factor analysis models, while allowing for heteroscedasticity across features:

$$p(\epsilon^m_d) = \mathcal{N}\left(\epsilon^m_d \,|\, 0, 1/\tau^m_d\right). \tag{2}$$

This results in the following normal likelihood (for extensions to non-Gaussian settings see section 4):

$$p(y^m_{nd}) = \mathcal{N}\left(y^m_{nd} \,|\, \mathbf{z}_{n,:}\mathbf{w}^{mT}_{d,:}, 1/\tau^m_d\right), \tag{3}$$

where $\mathbf{w}^m_{d,:}$ denotes the d-th row of the loading matrix $\mathbf{W}^m$ and $\mathbf{z}_{n,:}$ the n-th row of the latent factor matrix $\mathbf{Z}$. For a fully probabilistic treatment we place prior distributions on the weights $\mathbf{W}^m$, the latent variables $\mathbf{Z}$ as well as on the precision of the noise $\boldsymbol{\tau}^m$. We use a standard Gaussian prior on the latent variables and a conjugate Gamma prior for the precision:

$$p(z_{n,k}) = \mathcal{N}\left(z_{n,k} \,|\, 0, 1\right), \tag{4}$$

$$p(\tau^m_d) = \mathcal{G}\left(\tau^m_d \,|\, a^\tau_0, b^\tau_0\right), \tag{5}$$

To ensure scalable inference we use a variational approach with a mean-field approximation [3]. Briefly, in variational inference the true intractable posterior distribution of the unobserved variables $p(\mathbf{X}|\mathbf{Y})$ is approximated by a simpler distribution of factorized form $q(\mathbf{X}) = \prod_i q(\mathbf{X}_i)$ that leads to an efficient inference scheme. Here, $\mathbf{X}$ denotes all the hidden variables (including parameters) and $\mathbf{Y}$ denotes all the observed variables.

Under this approximation, the true log marginal likelihood $\log p(\mathbf{Y})$ is lower bounded by:

$$\begin{aligned}\mathcal{L}(\mathbf{X}) &= \int q(\mathbf{X})\Big(\log \frac{p(\mathbf{X}|\mathbf{Y})}{q(\mathbf{X})} + \log p(\mathbf{Y})\Big) d\mathbf{X} \\ &= \log p(\mathbf{Y}) - \mathrm{KL}(q(\mathbf{X})||p(\mathbf{X}|\mathbf{Y})) \\ &\leq \log p(\mathbf{Y})\end{aligned} \tag{11}$$

$\mathcal{L}(\mathbf{X})$ is called the Evidence Lower Bound (ELBO), which is equal to the sum of the model evidence and the negative KL-divergence between the true posterior and the variational distribution. The key observation here is that increasing the ELBO is equivalent to decreasing the KL-divergence between the two distributions.

Variational learning involves optimising the functional $\mathcal{L}(\mathbf{X})$ with respect to the distribution $q(\mathbf{X})$. If we allow any possible choice of $q(\mathbf{X})$, then the maximum of the lower bound $\mathcal{L}(\mathbf{X})$ will occur when the KL-divergence vanishes, which occurs when $q(\mathbf{X})$ equals the true posterior distribution $p(\mathbf{X}|\mathbf{Y})$. Nevertheless, since the true posterior is intractable, this does not lead to any simplification of the problem. Instead, it is necessary to consider a restricted family of variational distributions that are tractable to compute and then seek the member of this family for which the KL divergence is minimised [2].

Mean-field approximation

The most common type of variational Bayes, known as mean-field approach, assumes that the variational distribution factorises over M disjoint groups of variables:

$$q(\mathbf{X}) = \prod_{i=1}^{M} q(\mathbf{x}_i)$$

Evidently, this family of distributions does not usually contain the true posterior because the unobserved variables have dependencies, but this assumption allows the derivation of an analytical inference scheme

R. Argelaguet et al., Mol. Syst. Biol. 2018

MOFA application for scNMTseq

nature COMMUNICATIONS

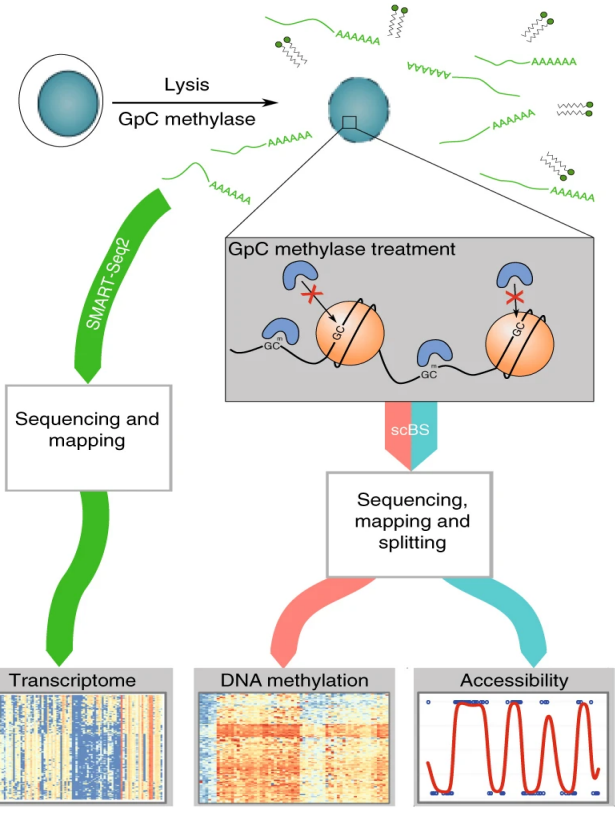
ARTICLE

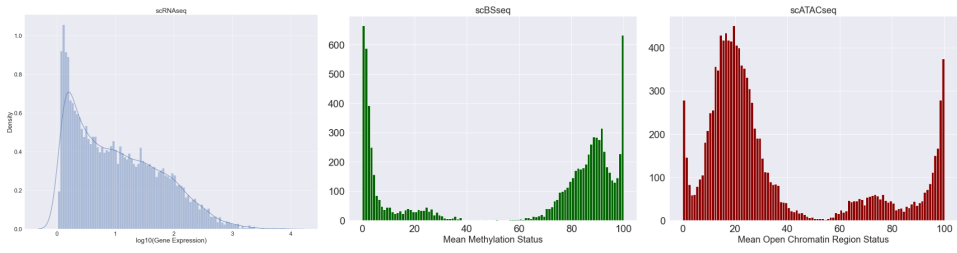
DOI: 10.1038/s41467-018-03149-4 OPEN

scNMT-seq enables joint profiling of chromatin accessibility DNA methylation and transcription in single cells

Stephen J. Clark[1], Ricard Argelaguet[2,3], ChantriolInt-Andreas Kapourani[4] Thomas M. Stubbs[1], Heather J. Lee[1,5,6], Celia Alda-Catalinas[1], Felix Krueger[7] Guido Sanguinetti[4], Gavin Kelsey[1,8] John C. Marioni[2,3,5] Oliver Stegle[2] Wolf Reik[1,5,8]

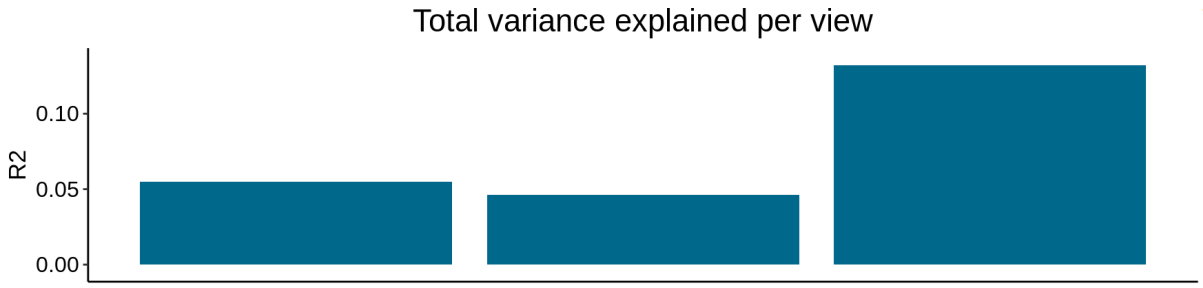
Parallel single-cell sequencing protocols represent powerful methods for investigating regulatory relationships, including epigenome-transcriptome interactions. Here, we report a single-cell method for parallel chromatin accessibility, DNA methylation and transcriptome profiling. scNMT-seq (single-cell nucleosome, methylation and transcription sequencing) uses a GpC methyltransferase to label open chromatin followed by bisulfite and RNA sequencing. We validate scNMT-seq by applying it to differentiating mouse embryonic stem cells, finding links between all three molecular layers and revealing dynamic coupling between epigenomic layers during differentiation.

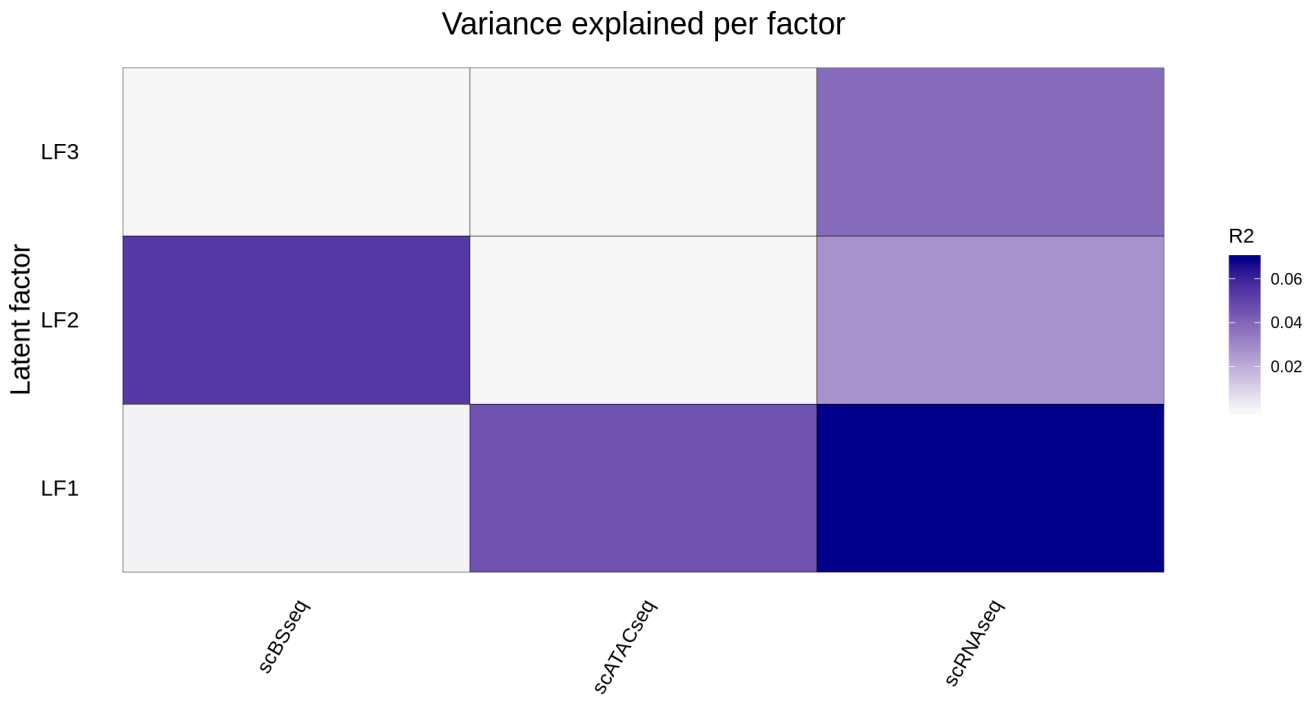


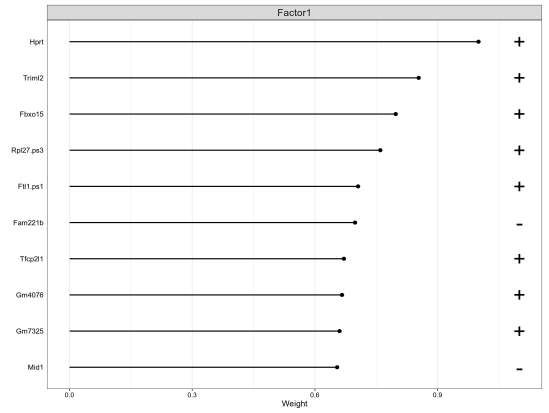


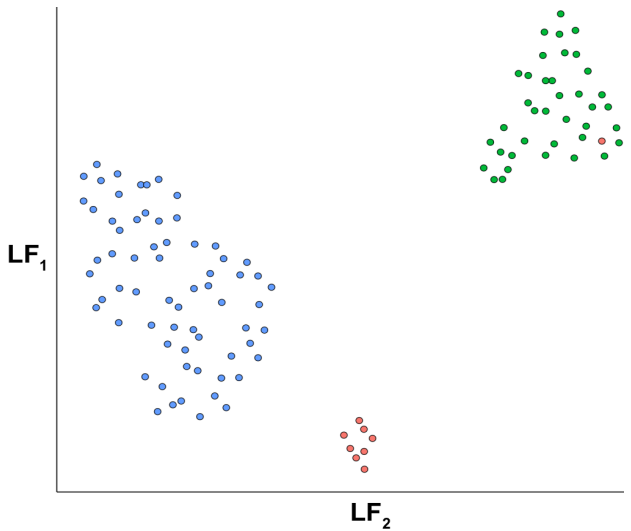
MOFA: Omics contributions to Latent Factors

$$R^2_{m,k} = 1 - \left(\sum_{n,d} y^m_{nd} - z_{nk} w^m_{kd} - \mu^m_d\right)^2 \Big/ \left(\sum_{n,d} y^m_{nd} - \mu^m_d\right)^2$$

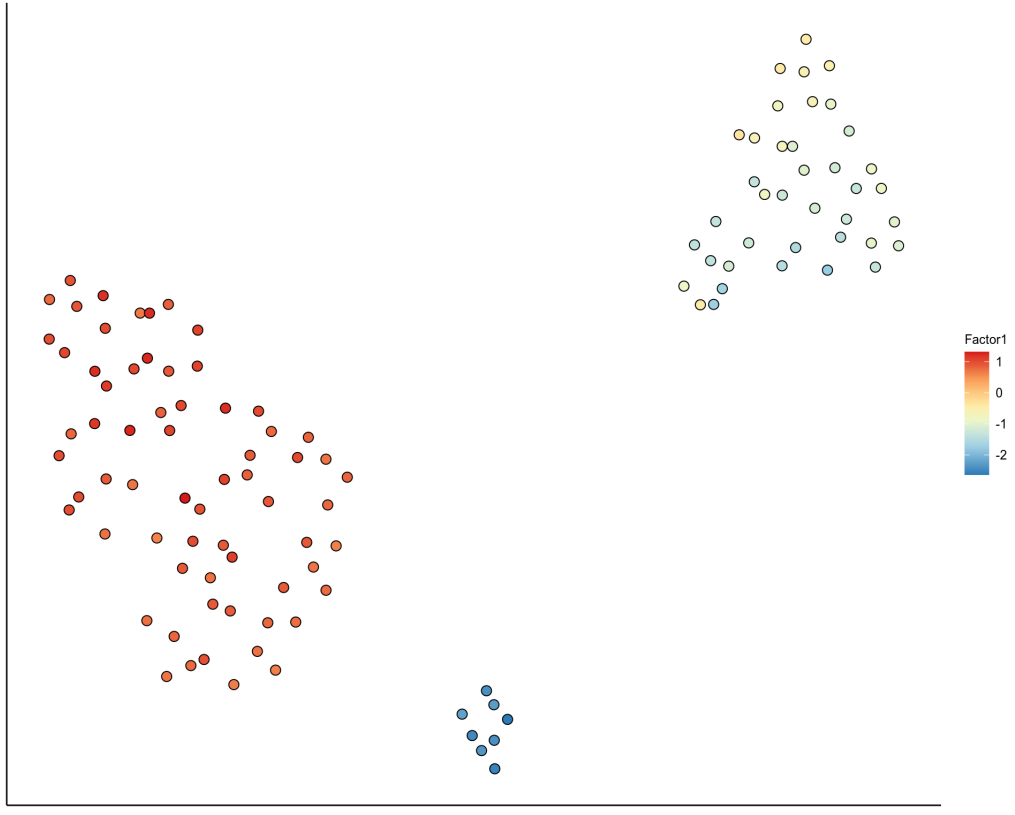


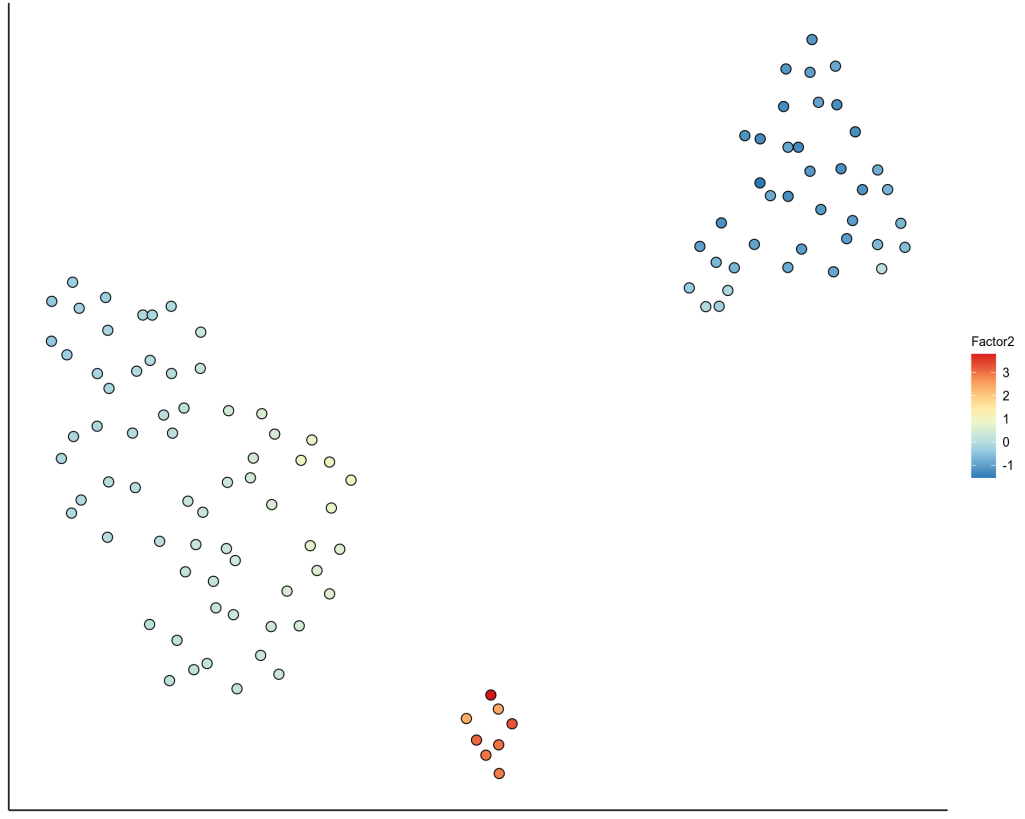






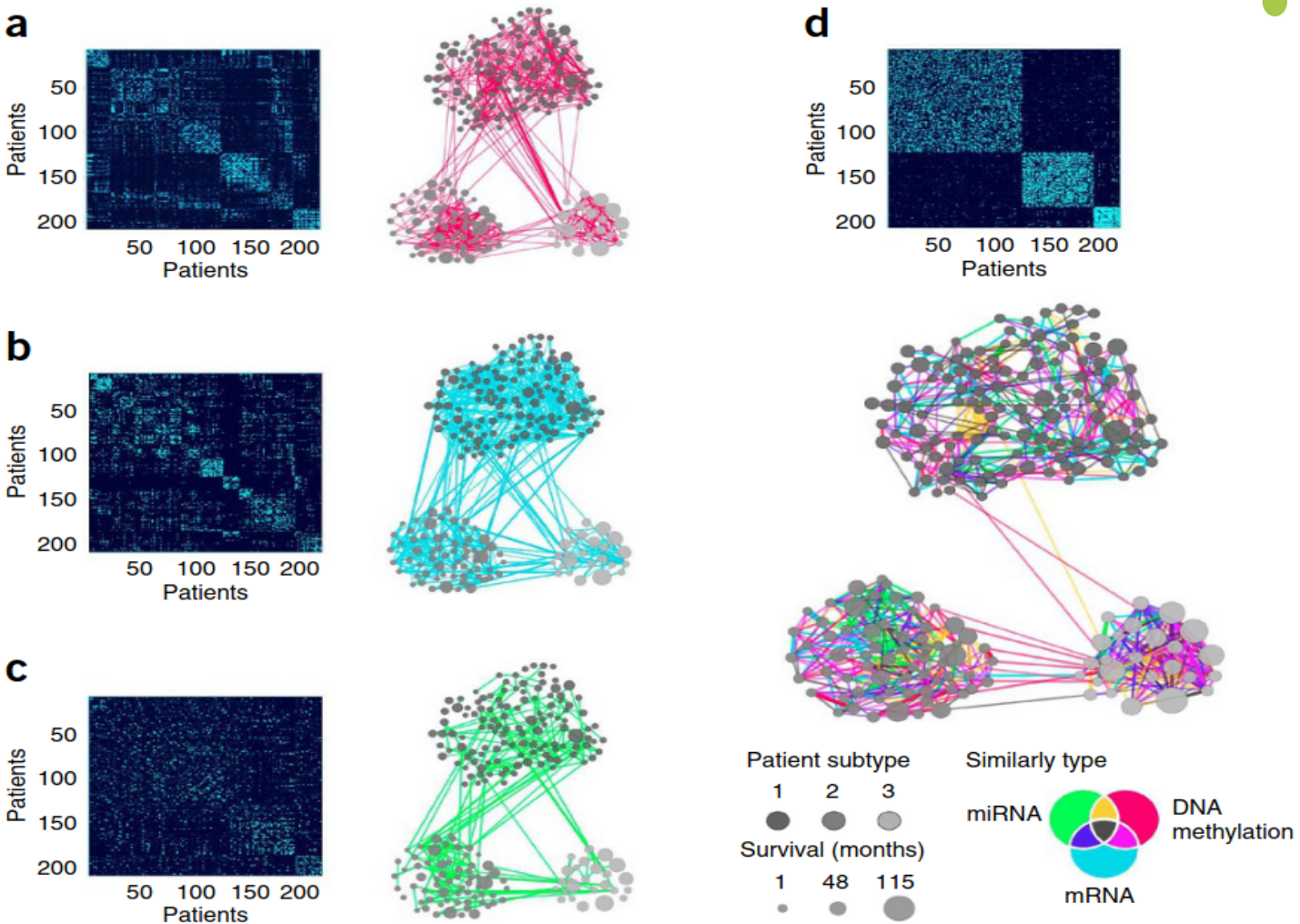
MOFA: Omics contributions to Clusters





Other unsupervised integrative Omics methods

Similarity Network Fusion (SNF)



Wang B., Mezlini A., Demir F. et al. Nat Methods 11, 333–337 (2014)

Clustering of Clusters (COC)

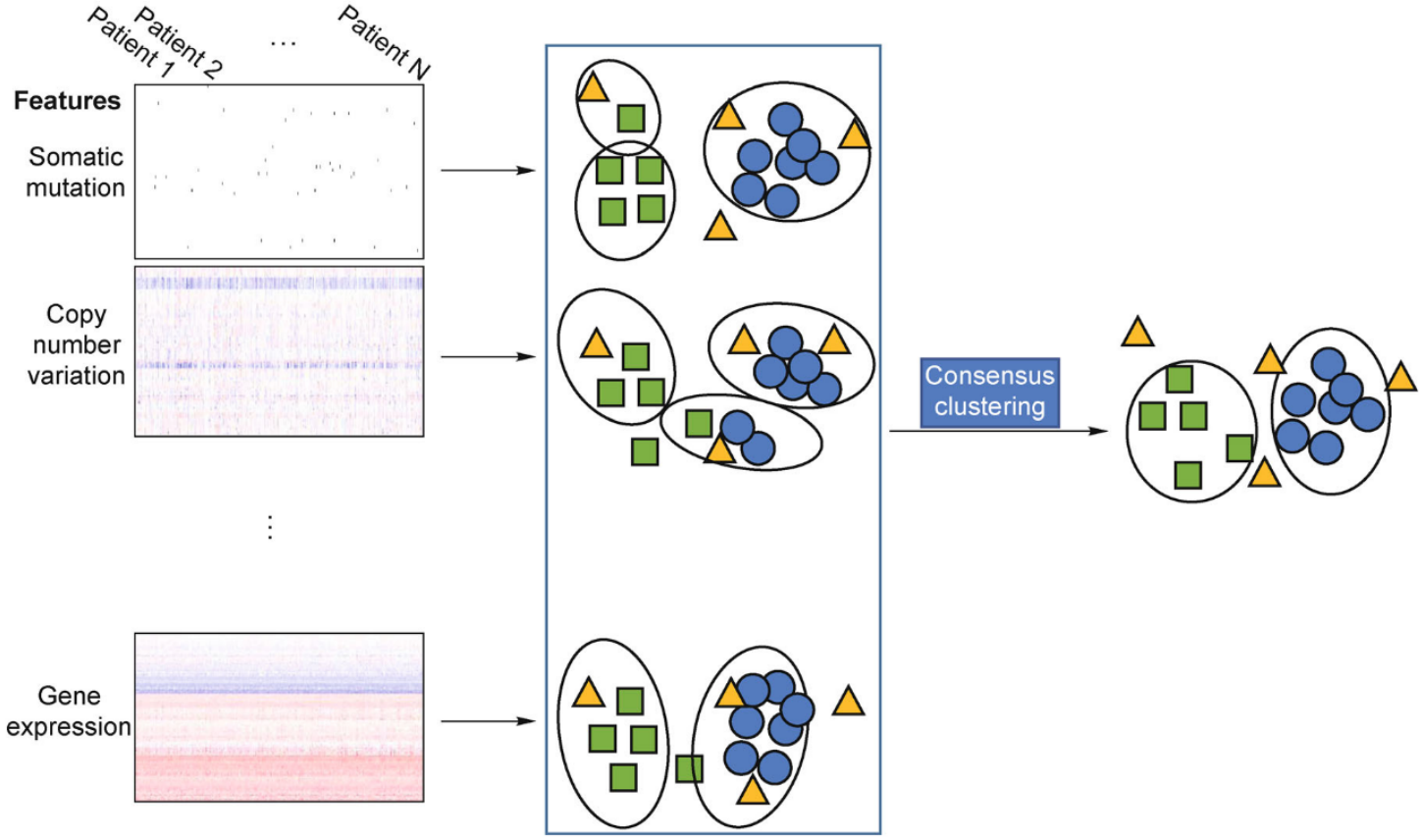
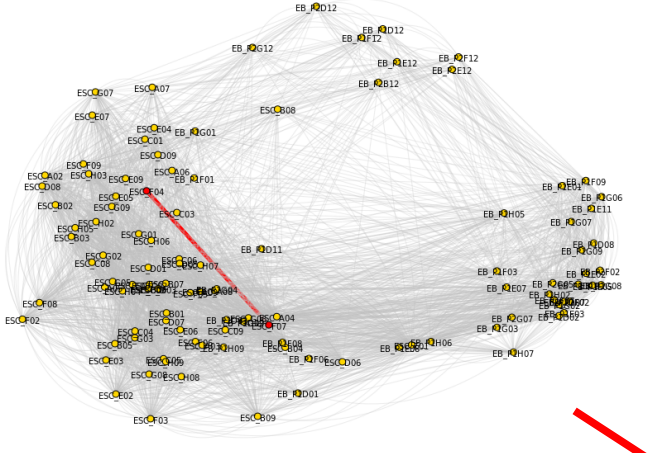


Figure 2. Clustering of clusters. This kind of methods first clusters in every single omics dataset and then integrates the primary clustering results into final cluster assignments.

Wang et al., Quantitative Biology 2016, 4(1): 58–67

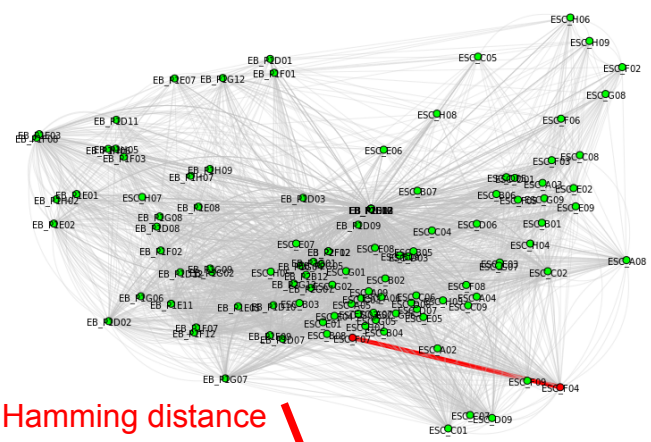
Graph Intersection Method

scRNAseq KNN Graph



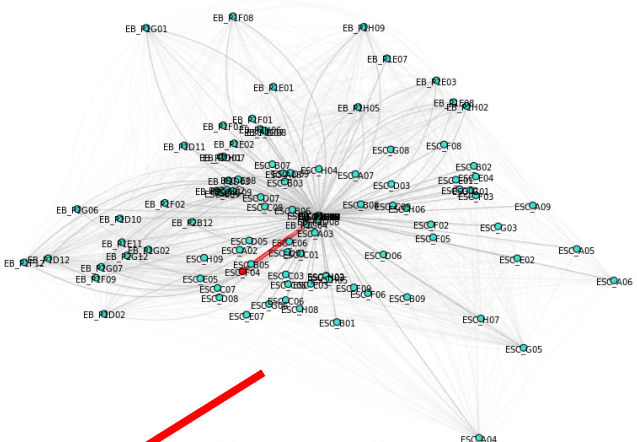
Euclidean distance

scBSseq KNN Graph



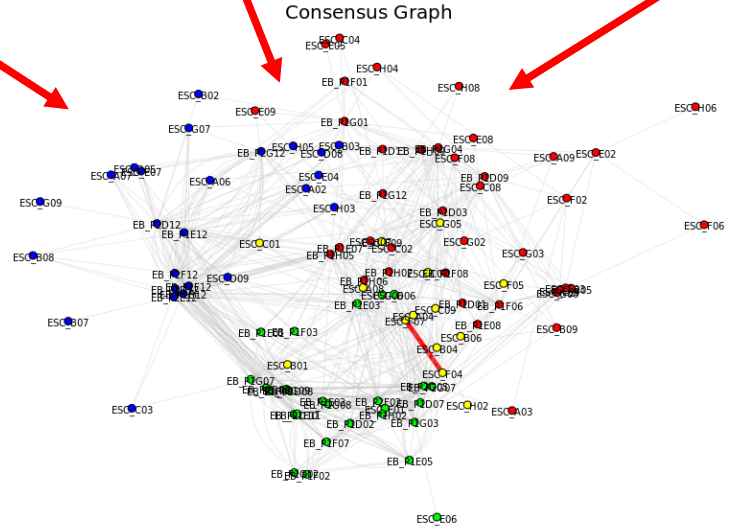
Hamming distance

scATACseq KNN Graph



Hamming distance

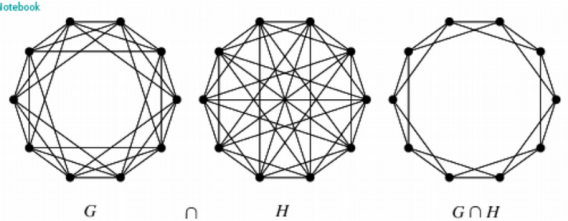
Consensus Graph



Keep edges consistently present across the Omics

Graph Intersection

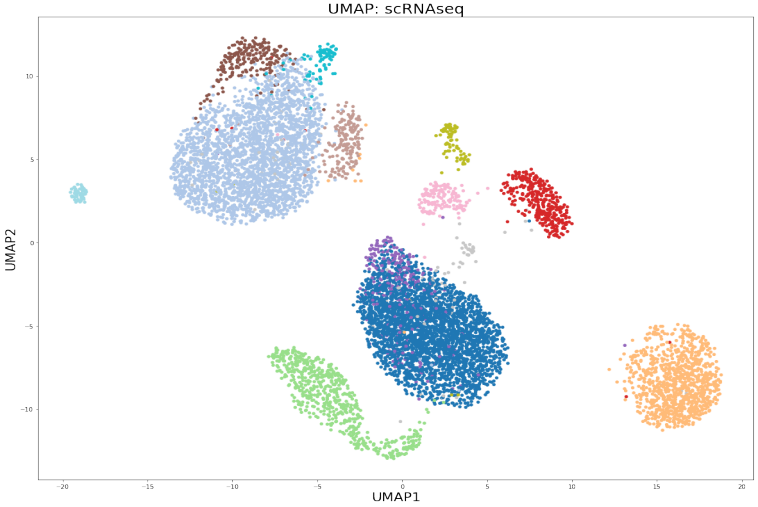
DOWNLOAD Wolfram Notebook

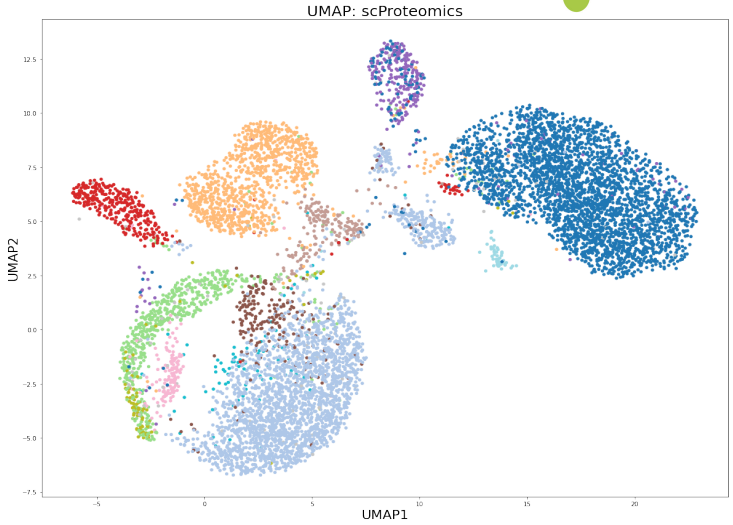


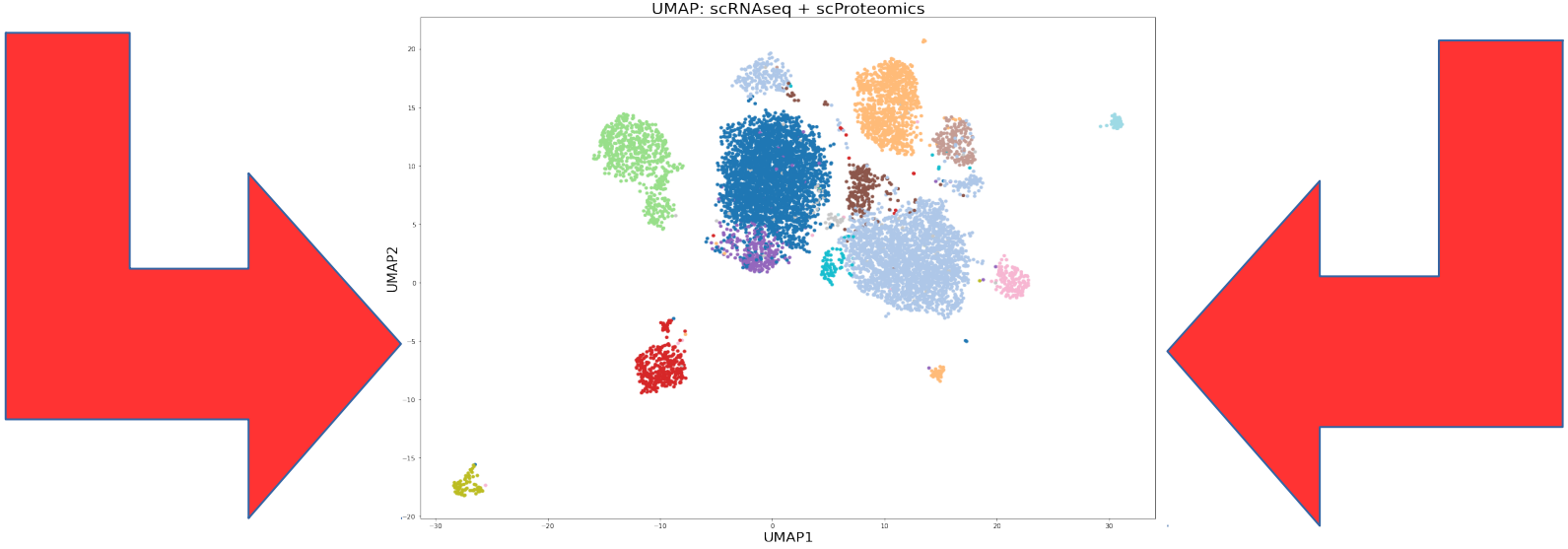
G ∩ H $G \cap H$

Let S be a set and $F = \{S_1, \ldots, S_p\}$ a nonempty family of distinct nonempty subsets of S whose union is $\bigcup_{i=1}^{p} S_i = S$. The intersection graph of F is denoted $\Omega(F)$ and defined by $V(\Omega(F)) = F$, with S_i and S_j adjacent whenever $i \neq j$ and $S_i \cap S_j \neq \emptyset$. Then a graph G is an intersection graph on S if there exists a family F of subsets for which G and $\Omega(F)$ are isomorphic graphs (Harary 1994, p. 19). Graph intersections can be computed in the Wolfram Language using `GraphIntersection[g, h]`.

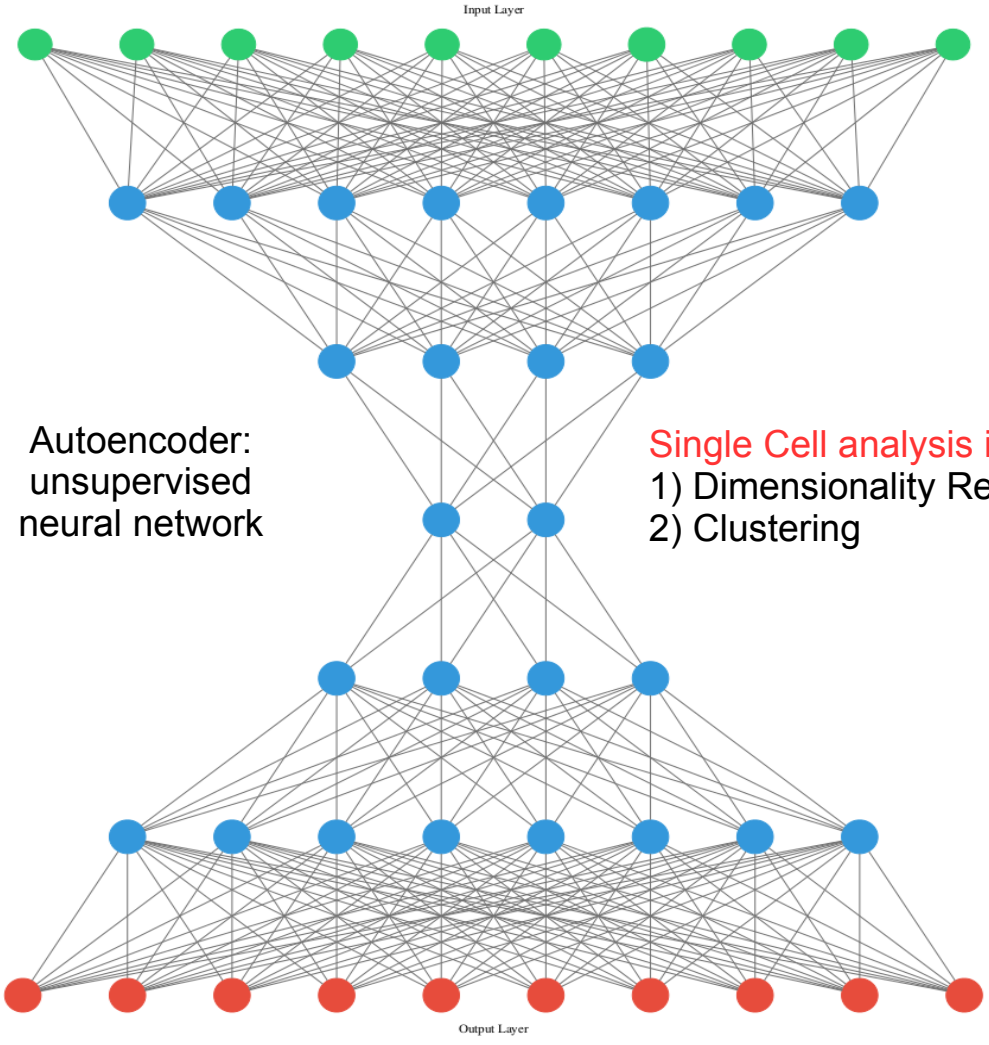
UMAP for data integration: CITEseq





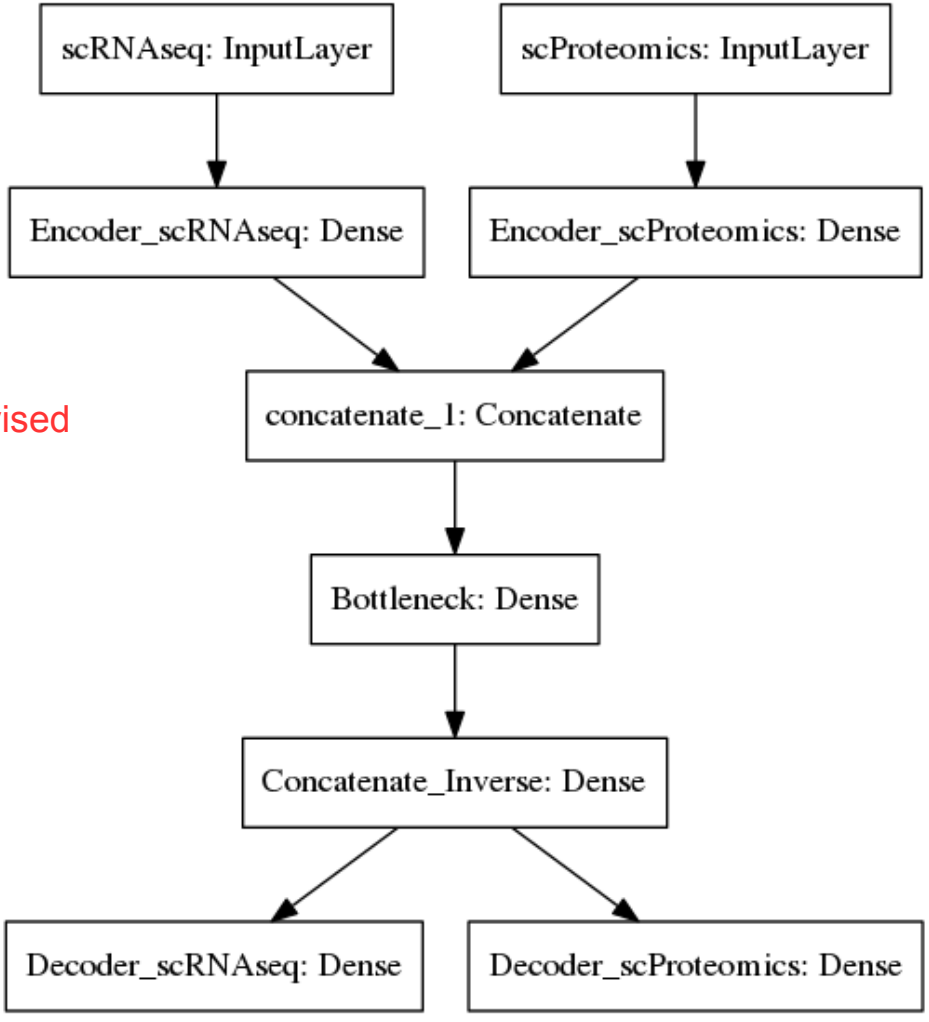


Autoencoder for data integration

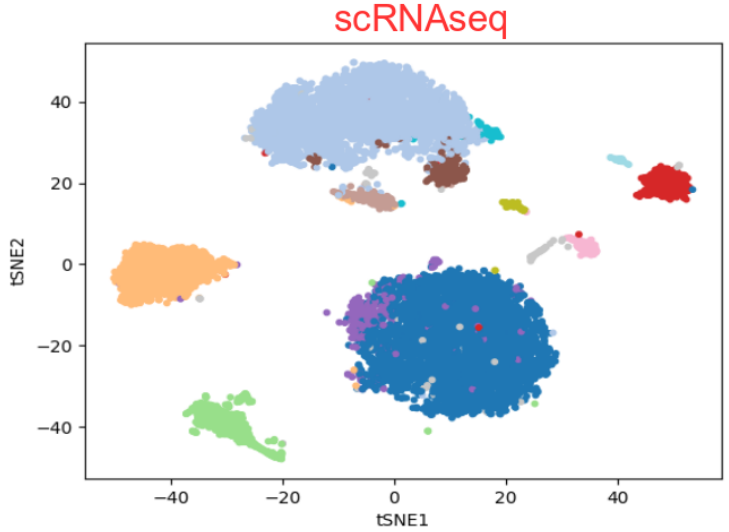


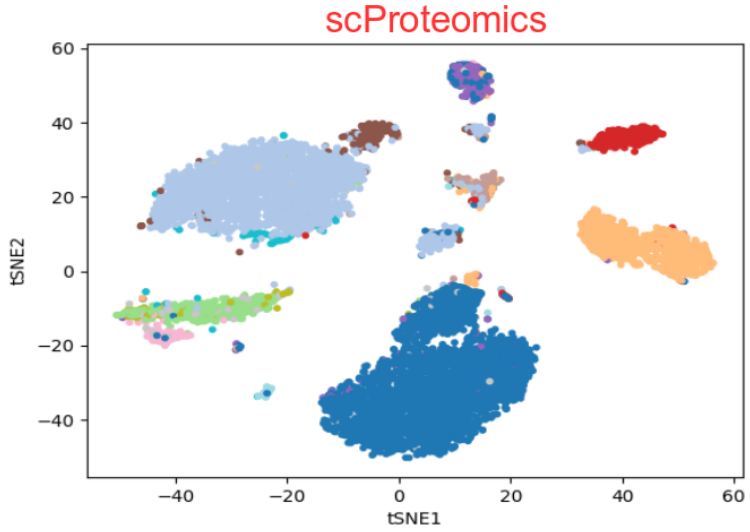
Autoencoder:
unsupervised
neural network

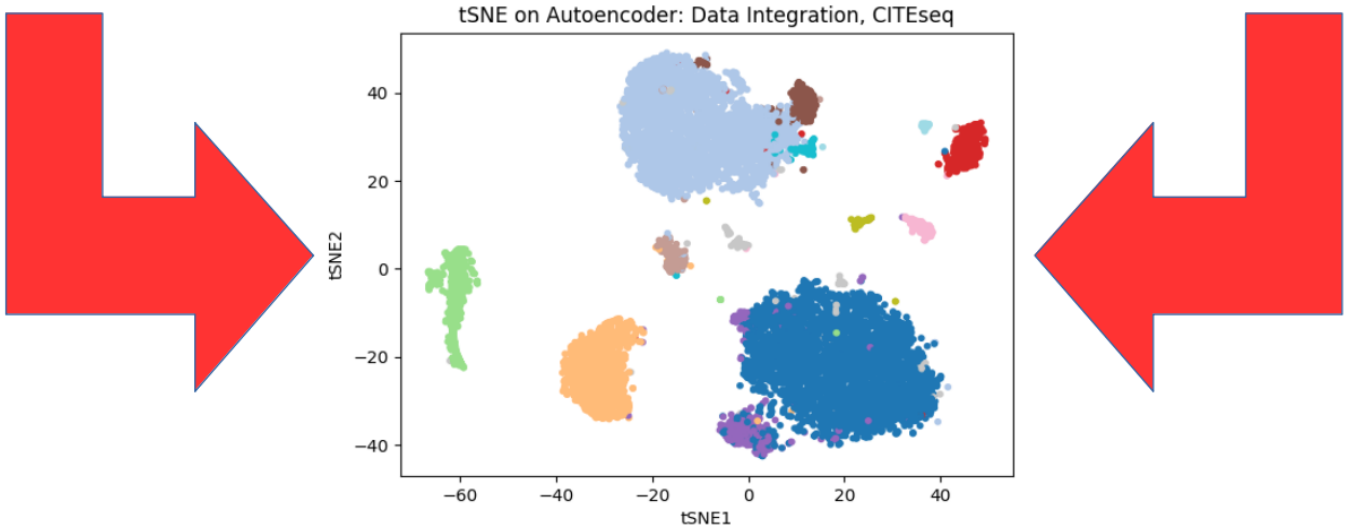
Single Cell analysis is unsupervised
1) Dimensionality Reduction
2) Clustering



Autoencoder for data integration: CITEseq







National Bioinformatics Infrastructure Sweden (NBIS)

Knut och Alice Wallenbergs Stiftelse

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