Statistical methods for data integration

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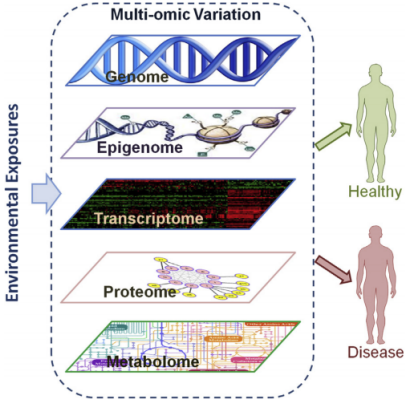
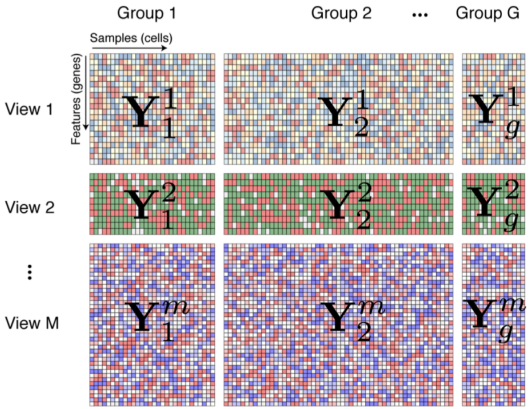
Why multi-omics?

The integrative analysis of diverse data modalities in a systems biology approach will capture better the molecular phenotypic varaition of biological systems

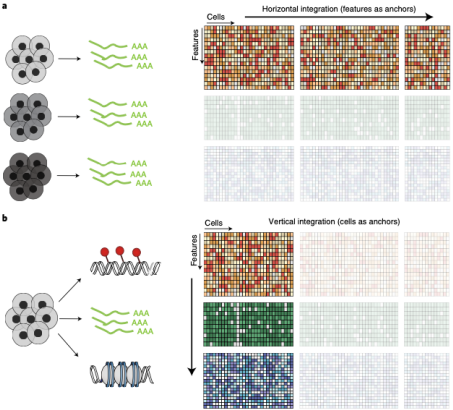


Abstraction of a multi-omics experimental design



Strategies for data integration

The first step is to choose the data dimension for the integration



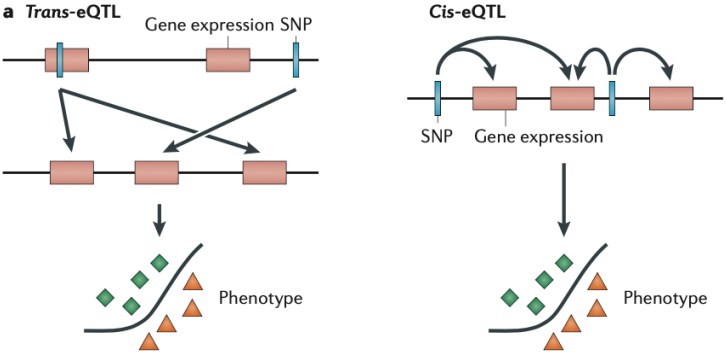
Strategies for vertical data integration

Two general strategies for vertical integration (multi-omics data derived from the same set of samples);

- **Local analysis**: test for marginal associations between features from different molecular layers. Typically supervised models.
- **Global analysis**: exploit the dependencies between the features to construct a mathematical representation of the data. Typically unsupervised models.

Local analysis

The most prominent examples of local analysis are quantitative trait loci mapping (GWAS and eQTLs)[1]:



[1] **Ritchie2015**.

eQTL: expression Quantiative Trait Loci

Local analysis

Local analysis is typically done using (generalised) linear models

phenotype

- GWAS
  trait or disease
- eQTL
  bulk gene
  expression

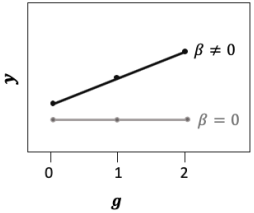
SNP effect

$$\underset{N}{\begin{bmatrix} \\ \boldsymbol{y} \\ \\ \end{bmatrix}} = \underset{N}{\begin{bmatrix} 0 \\ 1 \\ 2 \\ 0 \\ 0 \\ 1 \\ 0 \\ 2 \\ \\ \end{bmatrix}} \boldsymbol{g}\beta + \underset{N}{\begin{bmatrix} \\ \boldsymbol{\varepsilon} \\ \\ \end{bmatrix}}$$

SNP

noise

$$\boldsymbol{\varepsilon} \sim N(\mathbf{0}, \sigma_n{}^2 \boldsymbol{I})$$



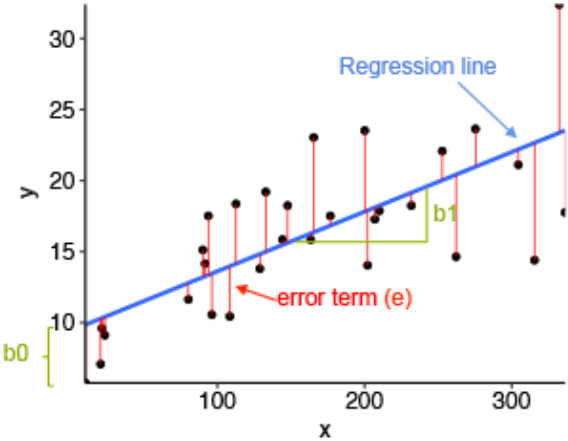
Test:

H0: $\beta = 0$

H1: $\beta \neq 0$

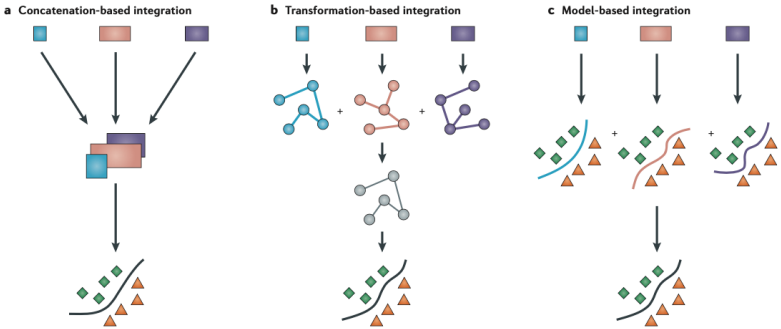
GWAS: Genome-Wide Association Study (GWAS)
eQTL: expression Quantiative Trait Loci

Local analysis



Global analysis

In global analysis the aim is to exploit the relationship between all features to create useful mathematical representations[2]



[2] Ritchie2015.

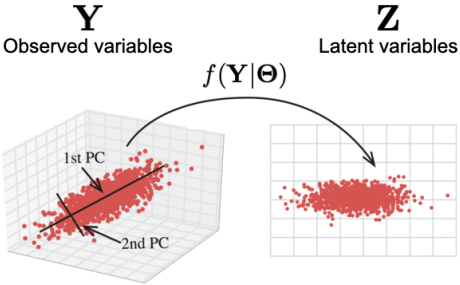
Global analysis

Challenges in (global) multi-omics data integration:

- Data collected using different techniques (i.e. data modalities) generally exhibit heterogeneous statistical properties
- Large amounts (and different patterns) of missing values
- Overfitting
- Undesired sources of heterogeneity
- Complexity of the data requires unsupervised interpretable approaches

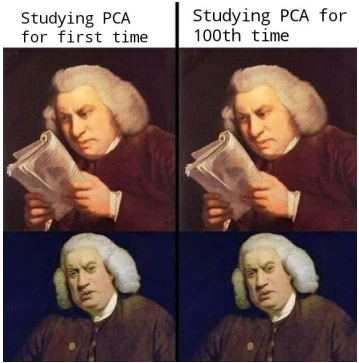
Latent variable models

Given a dataset $\mathbf{Y}$ of N samples and D features, latent variable models exploit the dependencies between the features to reduce the dimensionality of the data. The mapping from the high-dimensional to the low-dimensional space is performed via a function $f(\mathbf{Y}|\mathbf{\Theta})$:



Principal component analysis (PCA)

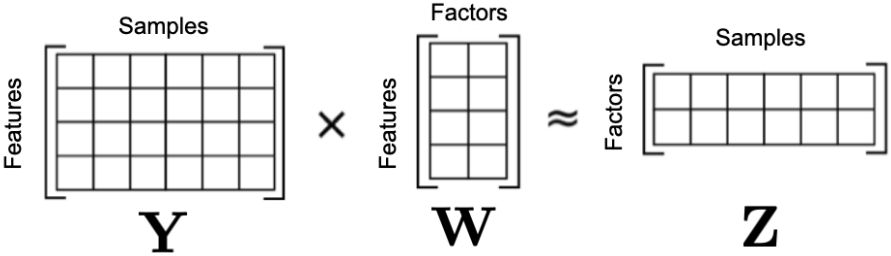
Principal Component Analysis (PCA) is the most popular technique for dimensionality reduction.



Credit to Raunak Joshi

Principal component analysis (PCA)

PCA defines $f(\mathbf{Y}|\mathbf{\Theta})$ to be a linear transformation via a matrix $\mathbf{W} \in \mathbb{R}^{D \times K}$ that maps the observations $\mathbf{Y} \in \mathbb{R}^{N \times D}$ onto the latent space $\mathbf{Z} \in \mathbb{R}^{N \times K}$.



Mathematical derivation of PCA: maximum variance formulation

The aim in PCA is to infer the matrix $\mathbf{W}$ such that the variance of $\mathbf{Z}$ (the projected data) is maximised. If we consider a single latent factor, the variance of the projected data is:

$$\begin{aligned}\sigma^2 &= \frac{1}{N}\sum_{n=1}^{N}(\mathbf{z}_n - \hat{\mathbf{z}})^2 \\ &= \frac{1}{N}\sum_{n=1}^{N}(\mathbf{y}_n^T\mathbf{w} - \hat{\mathbf{y}}^T\mathbf{w})^2\end{aligned}$$

where $\hat{\mathbf{y}}$ is a vector with the feature-wise means. If we center the data this simplifies to:

$$\sigma^2 = \frac{1}{N}\sum_{n=1}^{N}(\mathbf{y}_n^T\mathbf{w})^2$$

Mathematical derivation of PCA: maximum variance formulation

A bit of algebra allows us to define this equation in terms of the (centered) data covariance matrix: $\mathbf{S} = \frac{1}{N}\sum_{n=1}^{N} \mathbf{y}_n \mathbf{y}_n^T$:

$$
\begin{aligned}
\sigma^2 = \frac{1}{N}\sum_{n=1}^{N} (\mathbf{y}_n^T \mathbf{w})^T (\mathbf{y}_n^T \mathbf{w}) \\
= (\mathbf{w}^T \mathbf{y}_n)(\mathbf{y}_n^T \mathbf{w}) \\
= \mathbf{w}^T (\mathbf{y}_n \mathbf{y}_n^T) \mathbf{w} \\
= \mathbf{w}^T \mathbf{S} \mathbf{w}
\end{aligned}
$$

Mathematical derivation of PCA: maximum variance formulation

The optimisation problem to find the first latent variable could be defined as:

$$\hat{\mathbf{w}} = \arg\max_{\mathbf{w}} \mathbf{w}^T \mathbf{S} \mathbf{w}$$

(Q) Maximising this expression does not work, we need a constrain. Why?

Mathematical derivation of PCA: maximum variance formulation

The constrained optimisation problem can be defined as:

$$\hat{\mathbf{w}} = \underset{\|\mathbf{w}\|=1}{\arg\max}\, \mathbf{w}^T \mathbf{S} \mathbf{w}$$

It can be solved by introducing a Lagrange multiplier λ to enforce the constraint:

$$f(\mathbf{W}, \lambda) = \mathbf{w}^T \mathbf{S} \mathbf{w} + \lambda(1 - \mathbf{w}^T \mathbf{w})$$

By setting the derivative $\frac{\partial f(\mathbf{W},\lambda)}{\partial \mathbf{w}}$ to zero, we obtain the following equation:

$$\mathbf{S}\mathbf{w} = \lambda \mathbf{w}$$

which should be familiar (perhaps in this form $\mathbf{A}\mathbf{v} = \lambda \mathbf{v}$)?

Mathematical derivation of PCA: maximum variance formulation

Among all possible orthonormal basis, the one that maximises the projected variance corresponds to the basis defined by the eigenvectors of the covariance matrix $\mathbf{S}$. These vector basis are called the principal components.

The corresponding eigenvalue λ corresponds to the variance σ (proof in the appendix).

Generalisation to multiple principal components

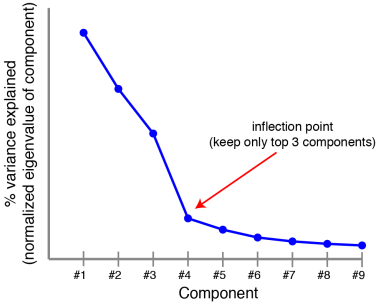
Most data can not be well-described by a single principal component. The k-th principal component can be found by subtracting from $\mathbf{Y}$ the reconstructed data by the previous $k-1$ principal components:

$$\hat{\mathbf{Y}} = \mathbf{Y} - \sum_{k=1}^{K} (\mathbf{z}_k \mathbf{w}_k^T)$$

and repeating the procedure above using the reconstructed covariance matrix $\hat{\mathbf{S}}$ as input

Finding the right number of Principal Components

Principal components are ranked by the amount of variance they capture in the original dataset, a scree plot can provide some sense of how many components are needed.



Problems of using PCA for multi-omics data integration

PCA is a great exploratory tool for single multivariate data sets, but it has important pitfalls in the analysis of multi-omics data:

- Does not generalise to an arbitrary number of data modalities.
- No natural way to combine different data modalities (binary data with continuous data).
- Cannot handle missing values.

Canonical correlation analysis

Canonical Correlation Analysis (CCA) is a simple extension of PCA to find linear components that capture correlations between **two** datasets[3].

Given two data matrices $\mathbf{Y}_1 \in \mathbb{R}^{N \times D_1}$ and $\mathbf{Y}_2 \in \mathbb{R}^{N \times D_2}$ CCA finds a set of linear combinations $\mathbf{U} \in \mathbb{R}^{D_1 \times K}$ and $\mathbf{V} \in \mathbb{R}^{D_2 \times K}$ with maximal cross-correlation.

For the first pair of canonical variables, the optimisation problem is:

$$(\hat{\mathbf{u}}_1, \hat{\mathbf{v}}_1) = \underset{\|\mathbf{u}_1\|=1, \|\mathbf{v}_1\|=1}{\arg\max} \; corr(\mathbf{u}_1^T \mathbf{Y}_1, \mathbf{v}_1^T \mathbf{Y}_2)$$

[3] **Hotteling1936**.