

# Machine Learning View of OMICs Integration

ISMB / ECCB 2021

Tutorial 4: A practical introduction to multi-omics integration and network analysis

Nikolay Oskolkov, NBIS SciLifeLab, 22.07.2021

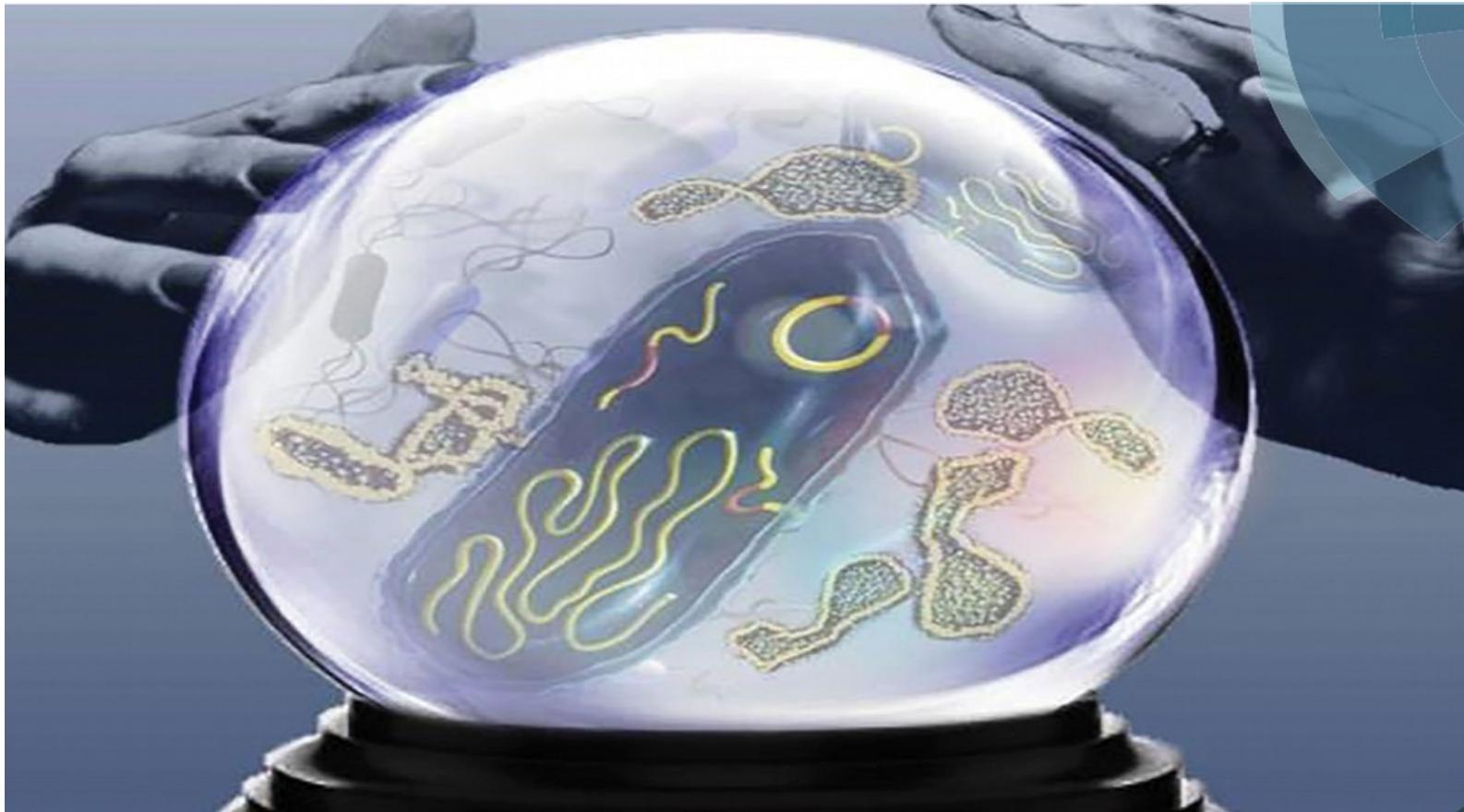
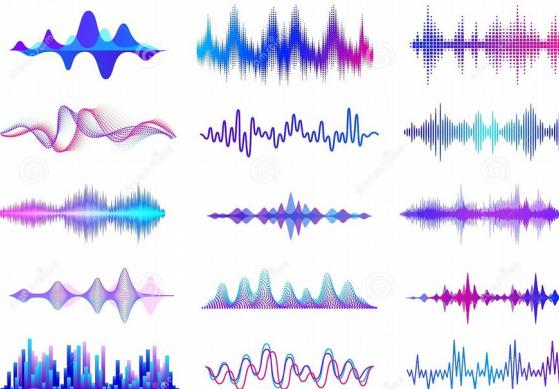


Image adapted from Molecular Omics, Issue 1, 2018

## Tabular

Data	AERMOD Total	Yr	Mon	Day	DataTime	DataSource	DatabaseTable
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End Date	1/1/2008	1	1	1	1	24:00	0.0000
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4	4	0	1	1	1	00:00	-0.0000
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6	6	0	1	1	1	00:00	-0.0000
7	6	0	1	1	1	00:00	-0.0000
8	8	0	1	1	1	00:00	-0.0000
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10	10	0	1	1	1	00:00	-0.0000
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12	12	0	1	1	1	00:00	-0.0000
13	13	0	1	1	1	00:00	-0.0000
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23	23	0	1	1	1	00:00	-0.0000
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34	34	0	1	1	1	00:00	-0.0000
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36	36	0	1	1	1	00:00	-0.0000
37	37	0	1	1	1	00:00	-0.0000
38	38	0	1	1	1	00:00	-0.0000
39	39	0	1	1	1	00:00	-0.0000
40	40	x	1	1	1	00:00	-0.0000

## Sound



© dreamstime.com

ID 142115245 © Spicytruffle

## Text

Editing Wikipedia articles on  
Medicine



**Engage with editors**  
Part of the Wikipedia experience is receiving responses to feedback from other editors. Do you submit your content on the last day, then leave? Wikipedia! Real human volunteers from the Wikipedia community will likely read and respond to it, and it would be polite for you to acknowledge the time they volunteer to polish your work! Everything submitted to Wikipedia is reviewed by multiple, real humans! You may not get a comment, but if you do, please acknowledge it.

### Be accurate

You're editing a resource millions of people use to make medical decisions, so it's vitally important to be accurate. Wikipedia is used more for medical information than the websites for WebMD, NIH, and the WHO. But with great power comes great responsibility!

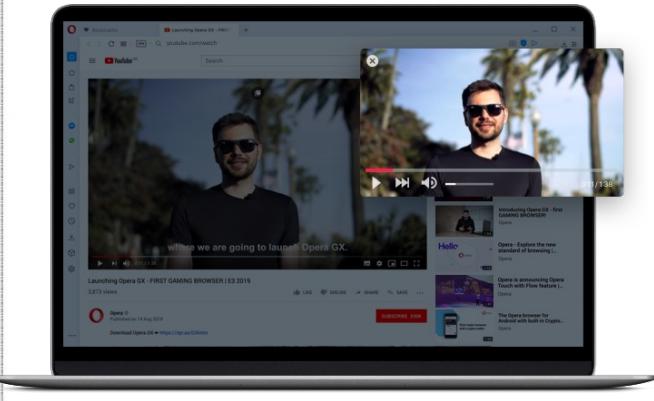
### Understand the guidelines

Wikipedia editors in the medicine area have developed additional guidelines to ensure that the content on Wikipedia is medically sound. Take extra time to read and understand these guidelines. When you edit an article, ensure you're meeting all the editorial requirements. If not, your work is likely to be undone by other editors as they clean up after you. That takes valuable volunteer time away from creating content. If you're not comfortable working under these guidelines, talk to your instructor about an alternative off-wiki assignment.

**Scared? Don't be!**  
Everybody on Wikipedia wants to make the best encyclopedia they can. Take the time to understand the rules, and soon you'll be contributing to a valuable resource you use on a daily basis!

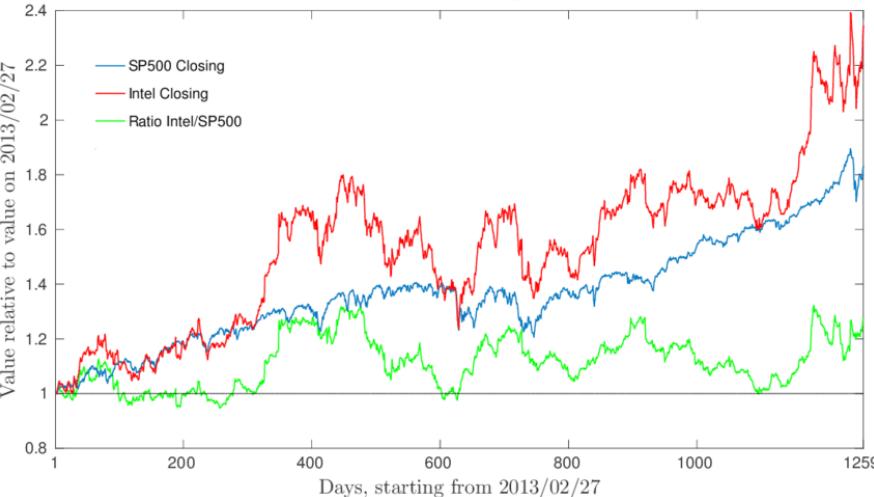
# DATA

## Video



## Time Series

Normalized Financial Time Series and Ratio



Days, starting from 2013/02/27

$$N = \begin{pmatrix} 0 & 3 & 1 & 0 & 2 & 3 & 8 & 1 & 1 & 3 \\ 1 & 1 & 0 & 0 & 7 & 1 & 2 & 2 & 3 & 3 \\ 1 & 2 & 2 & 0 & 0 & 6 & 7 & 1 & 2 & 2 \\ 1 & 2 & 3 & 10 & 0 & 4 & 6 & 1 & 0 & 5 \\ 3 & 2 & 2 & 1 & 4 & 3 & 2 & 1 & 6 & 0 \\ 7 & 4 & 4 & 5 & 3 & 9 & 6 & 1 & 6 & 1 \\ 7 & 1 & 1 & 5 & 2 & 8 & 9 & 1 & 3 & 6 \\ 5 & 0 & 1 & 6 & 2 & 0 & 0 & 0 & 1 & 5 \\ 1 & 6 & 3 & 3 & 4 & 6 & 2 & 0 & 1 & 1 \\ 1 & 2 & 2 & 4 & 1 & 1 & 3 & 0 & 8 & 2 \end{pmatrix}$$

# OMIC1

P <sub>2</sub>	0	3	1	0	2	3	8	1	1	3
N	1	1	0	0	7	1	2	2	3	3
	1	2	2	0	0	6	7	1	2	2
	1	2	3	10	0	4	6	1	0	5
	3	2	2	1	4	3	2	1	6	0
	7	4	4	5	3	9	6	1	6	1
	7	1	1	5	2	8	9	1	3	6
	5	0	1	6	2	0	0	0	1	5
	1	6	3	3	4	6	2	0	1	1
	1	2	2	4	1	1	3	0	8	2

OMIC2

P <sub>3</sub>									
N	0	3	1	0	2	3	8	1	1
	1	1	0	0	7	1	2	2	3
	1	2	2	0	0	6	7	1	2
	1	2	3	10	0	4	6	1	0
	3	2	2	1	4	3	2	1	6
	7	4	4	5	3	9	6	1	6
	7	1	1	5	2	8	9	1	3
	5	0	1	6	2	0	0	0	1
	1	6	3	3	4	6	2	0	1
	1	2	2	4	1	1	3	0	8

OMIC3

$$\begin{pmatrix} 0 & 1 & 0 & 1 \\ 1 & 0 & 1 & 1 \\ 1 & 1 & 0 & 1 \\ 1 & 0 & 1 & 1 \end{pmatrix} \quad \text{Metabolomics} \\ \text{N} \approx \text{P}$$

# Metabolomics

## N ≈ P

$$\begin{pmatrix} 0 & 1 & 0 & 1 \\ 1 & 0 & 1 & 1 \\ 1 & 1 & 0 & 1 \\ 1 & 0 & 1 & 1 \end{pmatrix} \quad \text{Proteomics} \quad N \approx P$$

# Proteomics N ≈ P

- manageable

$$\begin{pmatrix} 0 & 1 & 0 & 1 & 0 & 1 & 0 & 1 & 0 & 1 & 0 & 1 & 0 & 1 & 0 & 1 \\ 1 & 0 & 1 & 1 & 1 & 0 & 1 & 1 & 1 & 0 & 1 & 1 & 1 & 0 & 1 & 1 \\ 1 & 1 & 0 & 1 & 1 & 1 & 0 & 1 & 1 & 1 & 0 & 1 & 1 & 1 & 0 & 1 \\ 1 & 0 & 1 & 1 & 1 & 0 & 1 & 1 & 1 & 0 & 1 & 1 & 1 & 0 & 1 & 1 \end{pmatrix}$$

# Transcriptomics

N << P  
(Single cell: N  $\leq$  P)

# impossible

# Genomics N <<< P

# Methylomics

## N <<< P

# The Curse of Dimensionality complicates OMICs Integration

P is the number of features (genes, proteins, genetic variants etc.)  
 N is the number of observations (samples, cells, nucleotides etc.)

## Biomedicine

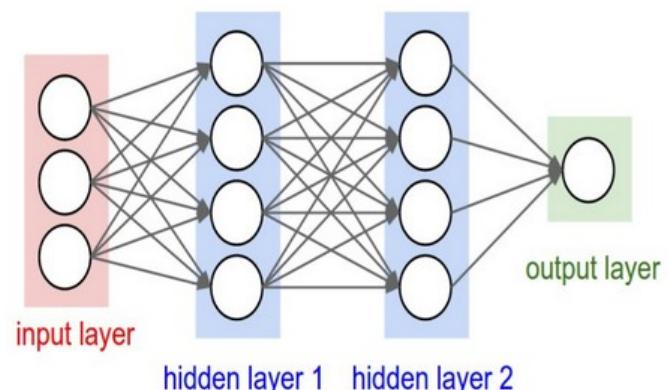
## Bayesianism

 $P \gg N$ 

## Frequentism

 $P \sim N$ 

## Deep Learning

 $P \ll N$ 

## Amount of Data

Ex.1

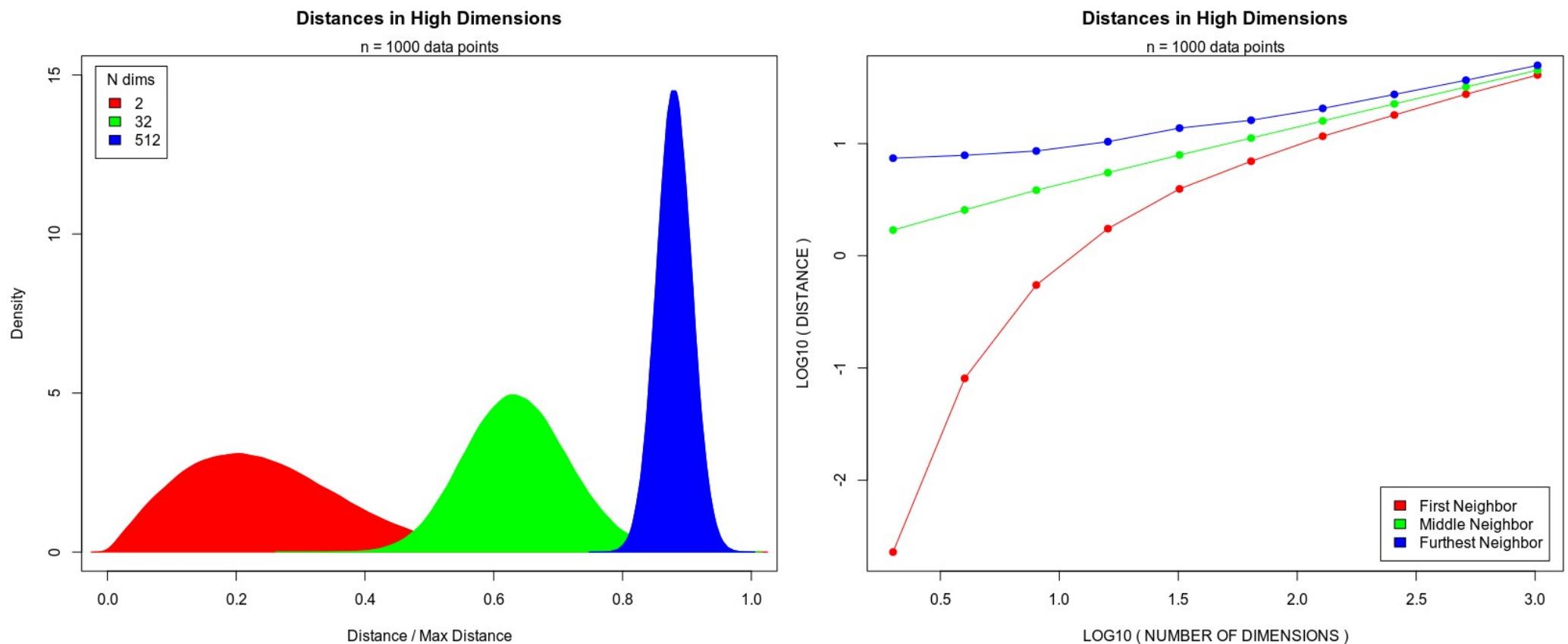
$$Y = \alpha + \beta X$$

$$\beta = (X^T X)^{-1} X^T Y$$

$$(X^T X)^{-1} \sim \frac{1}{\det(X^T X)} \dots \rightarrow \infty, \quad n \ll p$$

$$\text{Ex.2} \quad E[\hat{\sigma}^2] = \frac{n-p}{n} \sigma^2$$

Biased ML variance estimator in HD-space



Data points become far from each other and equidistant from each other in high dimensions

The differences between closest and furthest data point neighbours disappears in high-dimensional spaces – can't cluster

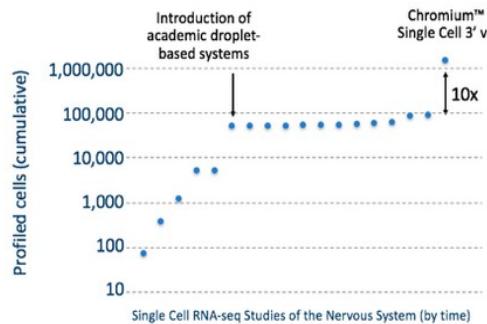
In high-dimensional space we can not separate cases and controls any more

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Our 1.3 million single cell dataset is ready 0 KUDOS



POSTED BY: grace-10x, on Feb 21, 2017 at 2:28 PM

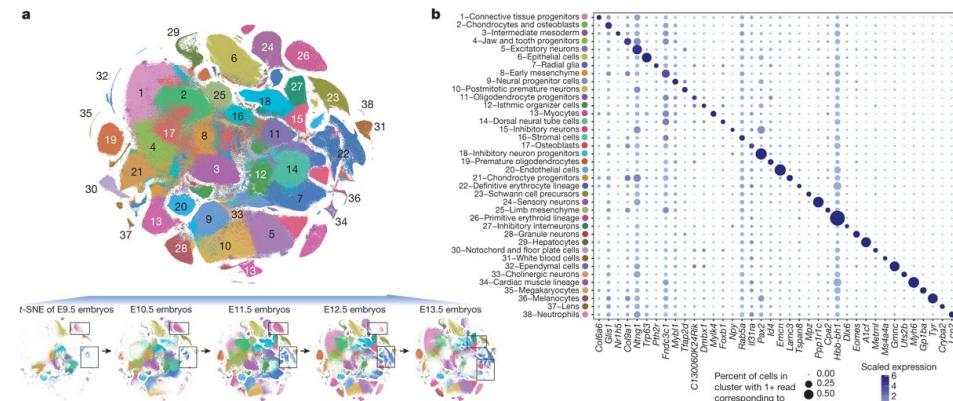
At ASHG last year, we announced our 1.3 Million Brain Cell Dataset, which is, to date, the largest dataset published in the single cell RNA-sequencing (scRNA-seq) field. Using the Chromium™ Single Cell 3' Solution (v2 Chemistry), we were able to sequence and profile 1,308,421 individual cells from embryonic mice brains. Read more in our application note [Transcriptional Profiling of 1.3 Million Brain Cells with the Chromium™ Single Cell 3' Solution](#).

**Watch out Underfitting!  
Paradise for Deep Learning!**

MENU nature

Fig. 2: Identifying the major cell types of mouse organogenesis.

From: [The single-cell transcriptional landscape of mammalian organogenesis](#)



Solutions Resources

Explore 4,000,000 CELLS at ease with BIOTURING BROWSER

EXPLORER NOW

A next-generation platform to re-analyze published single-cell sequencing data

Single Cell Analysis

5,500,000 cells will be indexed into BioTuring Single-cell Data Repository this September

Search

by biomembers • August 30, 2019

Human Cell Atlas, single-cell data

We are glad to announce that we will upsize the current single-cell database in BioTuring Single-cell Browser to 5,500,000 cells this September. With this release, we will double the current number of publications indexed in BioTuring Single-cell Browser, and cross the number of cells hosted on available public single-cell data repositories like [Human Cell Atlas \(HCA\)](#) and [Broad Institute's Single-cell Portal](#).

A new tool to interactively visualize single-cell objects (Seurat, Scanpy, SingleCellExperiments, ...)  
September 26, 2019

5,500,000 cells will be indexed into BioTuring Single-cell Data Repository this September  
August 30, 2019

# How to define and evaluate OMICs Integration?



Exploration and  
Integration of  
Omics datasets

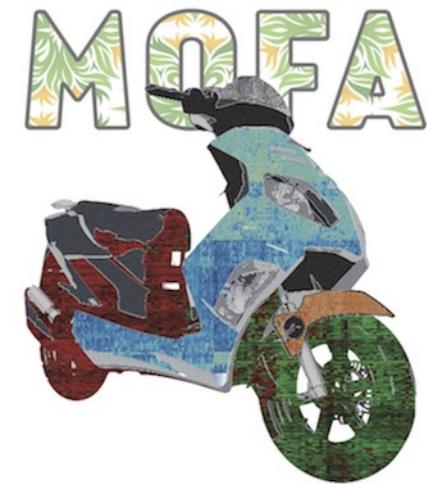
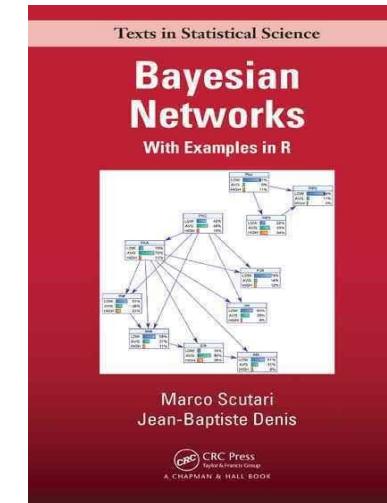
## Clustering of Clusters



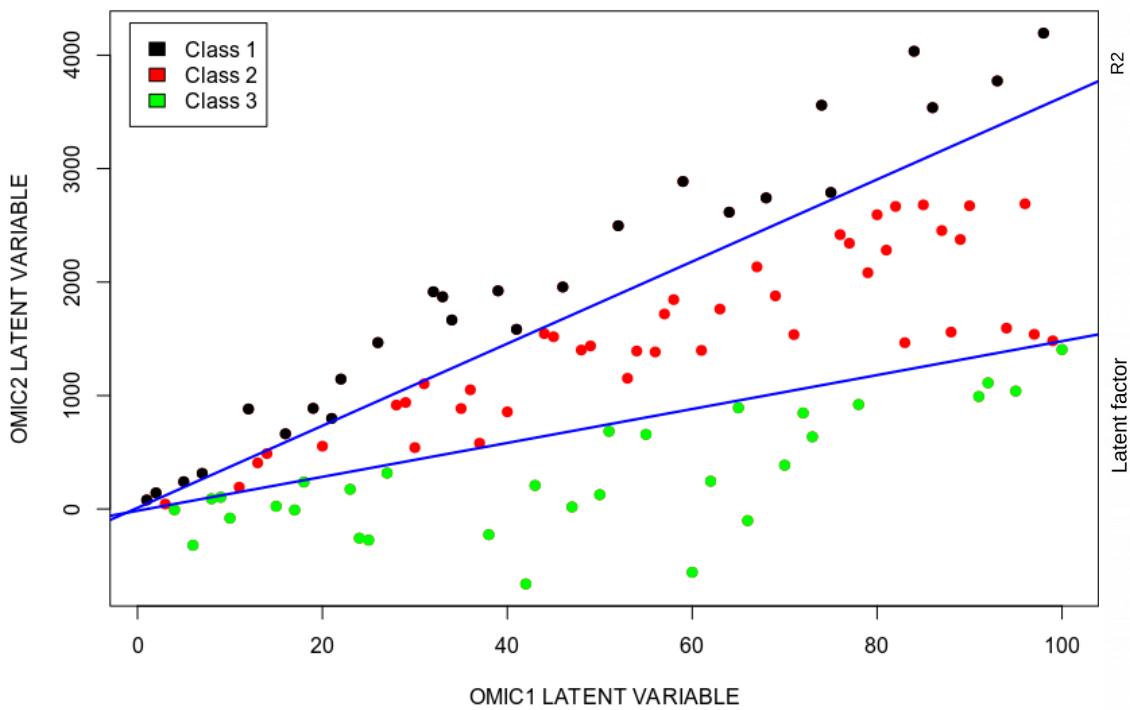
OnPLS

JIVE

DISCO

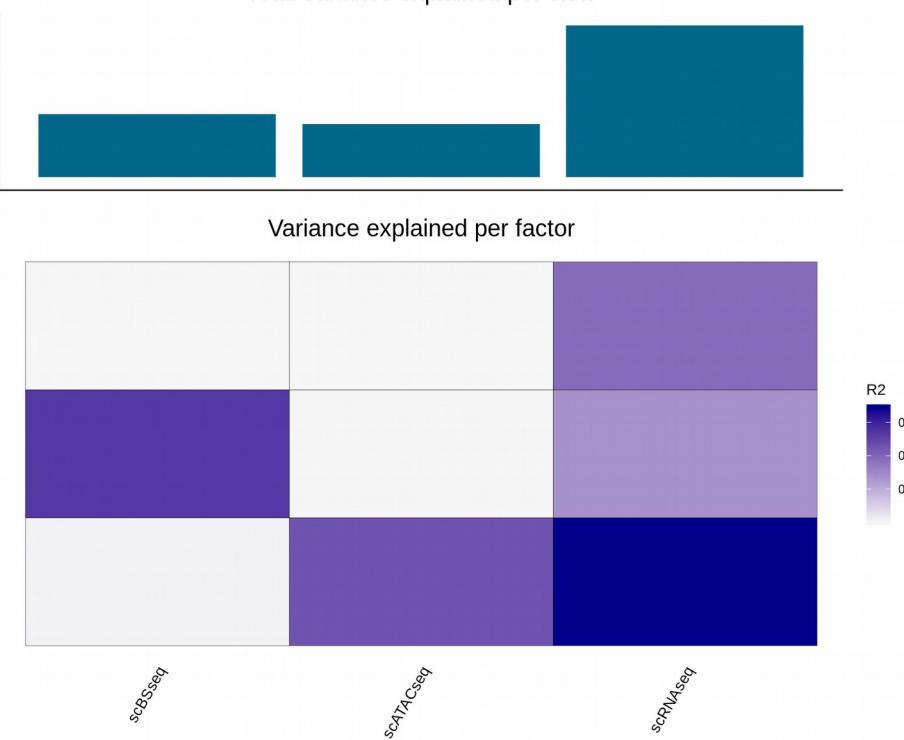


## Idea Behind OMICs Integration: See Patterns Hidden in Individual OMICS



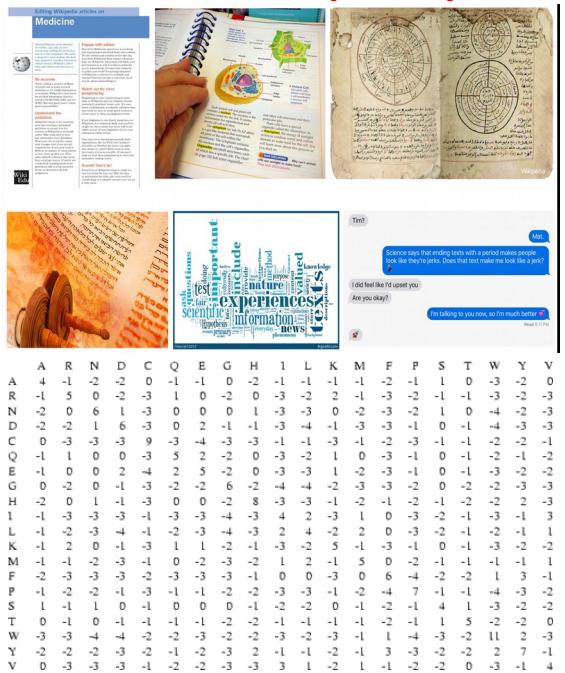
Total variance explained per view

Variance explained per factor



# How I Evaluate OMICs Integration, Data Science: Boost in Prediction

**TEXT (78%)**

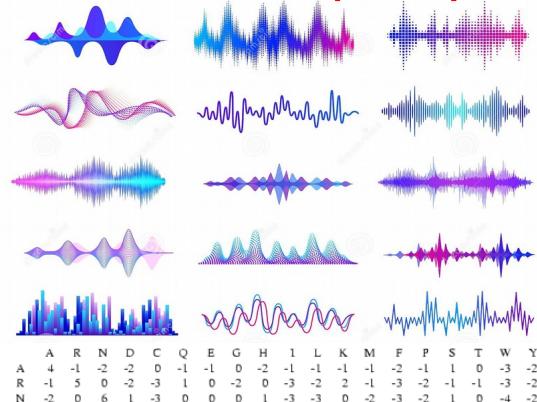


**IMAGE (83%)**



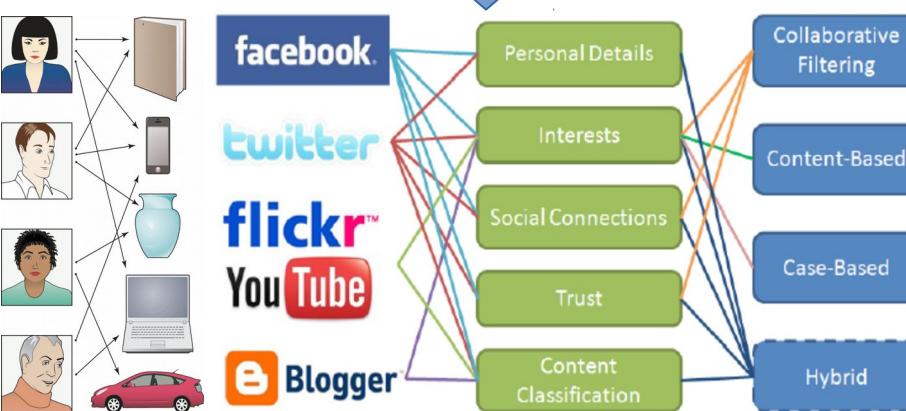
A	R	N	D	C	Q	E	G	H	I	L	K	M	F	P	S	T	W	Y	V
A	4	-1	-2	-2	0	-1	-1	-2	-1	-1	-1	-1	-2	-1	1	0	-3	-2	0
R	-1	5	0	-2	-3	1	0	-2	0	-3	-2	2	-1	-3	-1	-3	-2	-1	-3
N	-2	0	6	1	-3	0	0	-2	0	-3	-2	1	0	-4	-2	-3	0	-4	-2
D	-2	-2	1	6	-3	0	0	-1	-3	-4	-1	-3	-3	0	-1	-3	-1	0	-3
C	0	-3	-3	-3	9	-3	-4	-3	-1	-3	-1	-2	-3	-1	-1	-2	-2	-1	-2
Q	-1	1	0	0	-3	5	2	-2	0	-3	-2	1	0	-3	1	0	-1	-2	-1
E	-1	0	0	2	4	2	5	-2	0	-3	-3	-1	-2	-3	0	-1	-3	-2	-2
G	0	-2	0	-1	-3	-2	6	-2	-4	-4	-2	-3	-2	0	-2	-2	-3	-3	-3
H	-2	0	1	-1	-3	0	0	-2	8	-3	-3	-1	-2	-1	-2	-2	2	-3	-3
I	-1	-3	-3	-3	-1	-3	-3	-4	-3	4	2	-3	1	0	-3	-2	-1	-3	-1
L	-1	-2	-3	-4	-1	-2	-3	-4	-3	-2	-2	2	0	-3	-2	-1	-2	-1	-1
K	-1	2	0	-1	-3	1	1	-2	-1	-3	-2	5	-1	-3	1	0	-1	-3	-2
M	-1	-1	-2	-3	-1	0	-2	-3	-2	1	2	-1	5	0	-2	-1	-1	-1	1
F	-2	-3	-3	-3	-2	-3	-3	-3	-1	0	0	-3	0	6	-4	-2	1	3	-1
P	-1	-2	-2	-1	-3	-1	-1	-2	-2	-3	-1	-2	-4	7	-1	-4	-3	-2	-2
S	1	-1	1	0	-1	0	0	-1	-2	-2	0	-1	-2	-1	4	1	-3	-2	-2
T	0	-1	0	-1	-1	-1	-1	-2	-2	-1	-1	-1	-2	-1	1	5	-2	-2	0
W	-3	-3	-4	-4	-2	-2	-3	-2	-2	-3	-2	-3	-1	1	-4	-3	11	2	-3
Y	-2	-2	-3	-3	-2	-1	-2	-3	-2	-1	-1	-2	-3	-2	-2	2	7	-1	4
V	0	-3	-3	-3	-3	-1	-2	-3	-3	3	1	-2	1	-1	-2	0	-3	-1	4

**SOUND (75%)**



A	R	N	D	C	Q	E	G	H	I	L	K	M	F	P	S	T	W	Y	V
A	4	-1	-2	-2	0	-1	-1	-2	-1	-1	-1	-1	-2	-1	1	0	-3	-2	0
R	-1	5	0	-2	-3	1	0	-2	0	-3	-2	2	-1	-3	-1	0	-4	-2	-3
N	-2	0	6	1	-3	0	0	0	1	-3	-3	0	-2	-3	1	0	-4	-2	-3
D	-2	-2	1	6	-3	0	0	-2	-3	-2	2	-1	-3	-1	-3	1	0	-4	-2
C	0	-3	-3	-3	9	-3	-4	-3	-1	-3	-1	-2	-3	-1	-1	-2	-2	-1	-2
Q	-1	1	0	0	-3	5	2	-2	0	-3	-2	1	0	-3	1	0	-1	-2	-1
E	-1	0	0	2	4	2	5	-2	0	-3	-3	-1	-2	-3	0	-1	-3	-2	-2
G	0	-2	0	-1	-3	-2	6	-2	-4	-4	-2	-3	-3	0	-2	-2	-3	-2	-3
H	-2	0	1	-1	-3	0	0	-2	8	-3	-3	-1	-2	-1	-2	-2	2	-3	-3
I	-1	-3	-3	-3	-1	-3	-3	-4	-3	4	2	-3	1	0	-3	-2	-1	-3	-1
L	-1	-2	-3	-4	-1	-1	-2	-3	-4	-3	2	4	-2	2	0	-3	-2	-1	-1
K	-1	2	0	-1	-3	1	1	-2	-1	-3	-2	5	-1	-3	1	0	-1	-3	-2
M	-1	-1	-2	-3	-1	0	-2	-3	-2	1	2	-1	5	0	-2	-1	-1	-1	1
F	-2	-3	-3	-3	-2	-3	-3	-3	-1	0	0	-3	0	6	-4	-2	1	3	-1
P	-1	-2	-2	-1	-3	-1	-1	-2	-2	-3	-1	-2	-4	7	-1	-1	-4	-3	-2
S	1	-1	1	0	-1	0	0	-1	-2	-2	0	-1	-2	-1	4	1	-3	-2	-2
T	0	-1	0	-1	-1	-1	-1	-2	-2	-1	-1	-1	-2	-1	-1	-1	-1	1	0
W	-3	-3	-4	-4	-2	-2	-3	-2	-2	-3	-2	-3	-1	1	-4	-3	11	2	-3
Y	-2	-2	-3	-3	-2	-1	-2	-3	-2	-1	-1	-2	-3	-2	-2	2	7	-1	4
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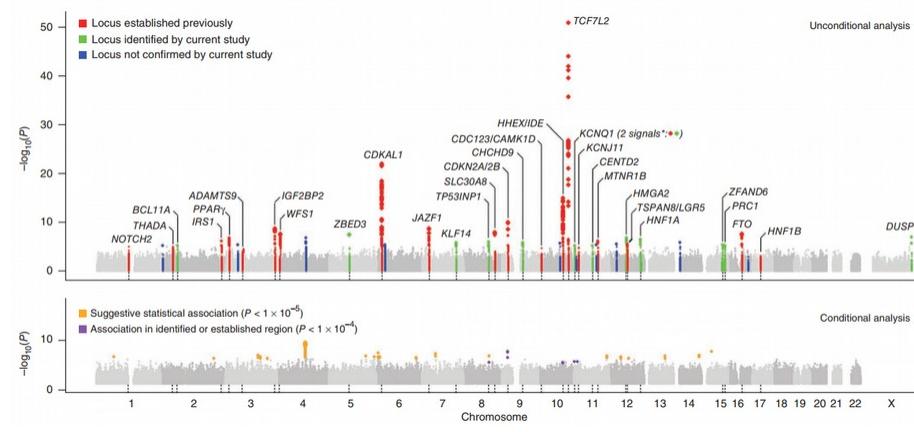
**Predict Facebook user interests**



**Data Integration Accuracy: 96%**

# Prediction is an Ultimate Criterion of Successful OMICS Integration

## Statistics searches for candidates



Consequence



NEWS FEATURE PERSONAL GENOMES NATURE/Vol 456/5 November 2008



The case of the missing heritability

B. Maher, Nature 456, 18-21 (2008)

## Machine Learning optimizes prediction



A clinically applicable approach to continuous prediction of future acute kidney injury

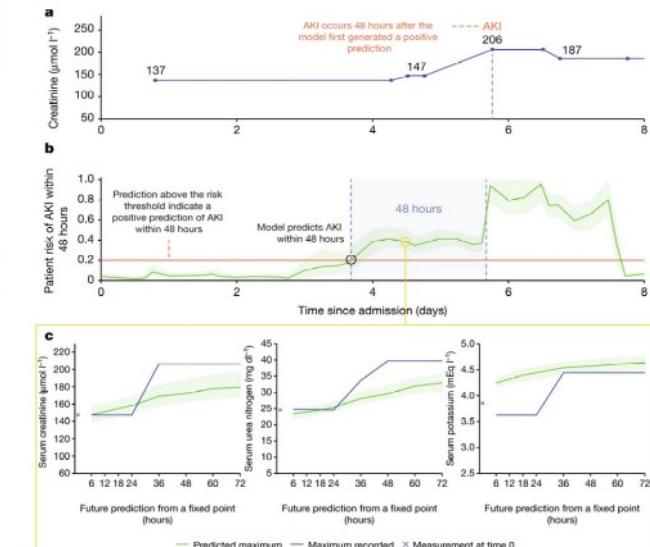
Nenad Tomasev, Xavier Glorot, [...] Shair Mohamed

Nature 572, 110-119 (2019) Download Citation ↗

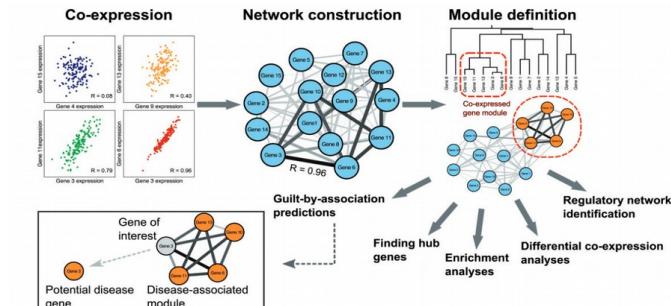
### Abstract

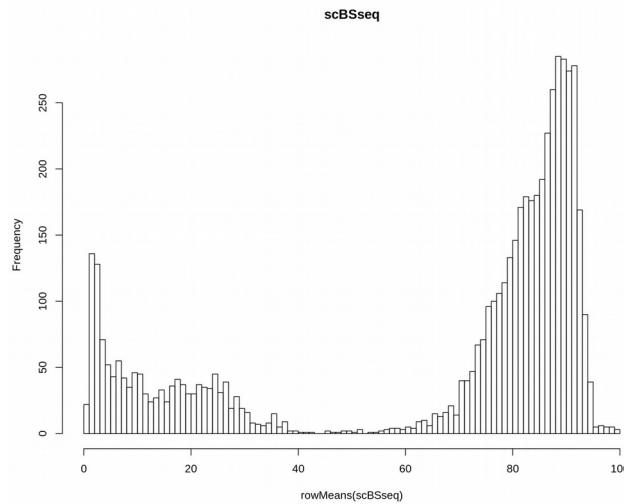
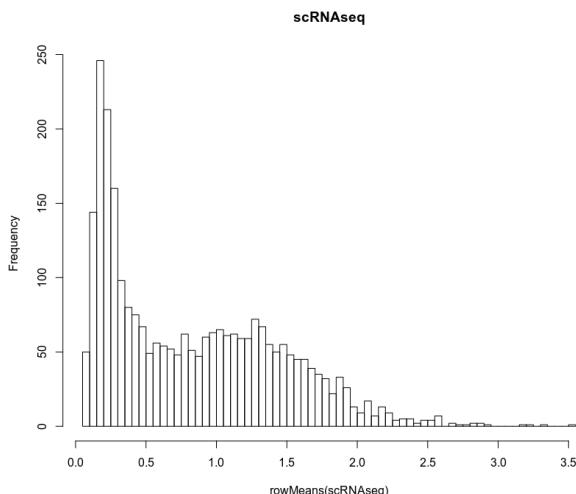
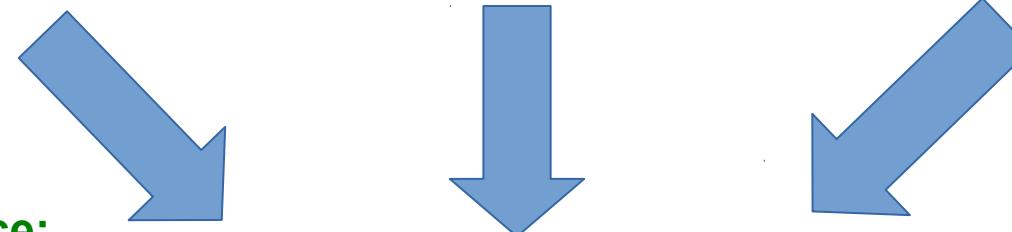
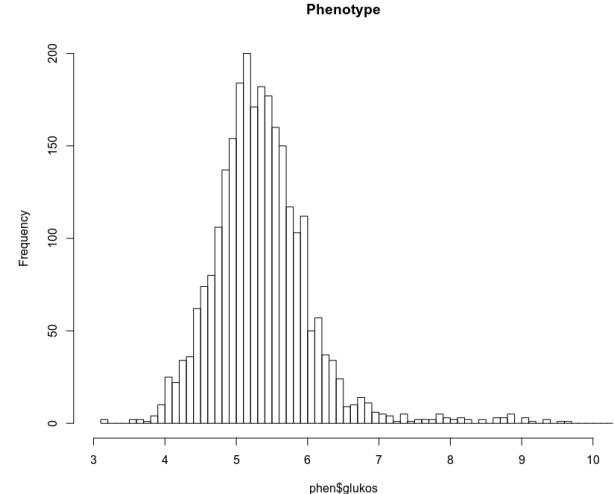
The early prediction of deterioration could have an important role in supporting healthcare professionals, as an estimated 11% of deaths in hospital follow a failure to promptly recognize and treat deteriorating patients<sup>1</sup>. To achieve this goal requires predictions of patient risk that are continuously updated and accurate, and delivered at an individual level with sufficient context and enough time to act. Here we develop a deep learning approach for the continuous risk prediction of future deterioration in patients, building on recent work that models adverse events from electronic health records<sup>2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17</sup> and using acute kidney injury—a common and potentially life-threatening condition<sup>18</sup>—as an exemplar. Our model was developed on a large, longitudinal dataset of electronic health records that cover diverse

From: A clinically applicable approach to continuous prediction of future acute kidney injury



Consequence

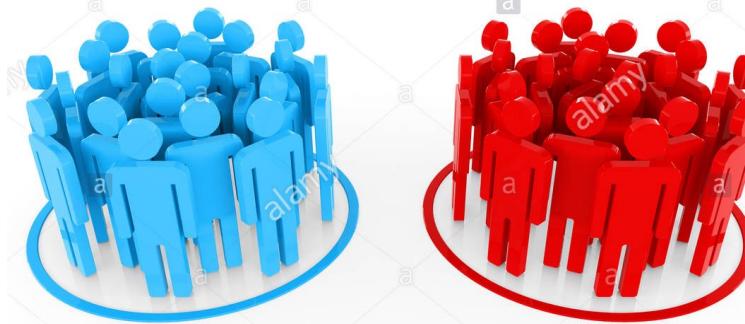


**Methylation (78%)****Gene Expression (83%)****Phenotype (75%)**

**1) Convert to common space:**  
Neural Networks, SNF, UMAP

**2) Explicitly model distributions:**  
MOFA, Bayesian Networks

**3) Extract common variation:**  
PLS, CCA, Factor Analysis



**HEALTHY**

**SICK**

**Data Integration  
Accuracy: 96%**



# National Bioinformatics Infrastructure Sweden (NBIS)

SciLifeLab



*Knut och Alice  
Wallenbergs  
Stiftelse*



LUNDS  
UNIVERSITET