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Machine Learning for Human Microbiome

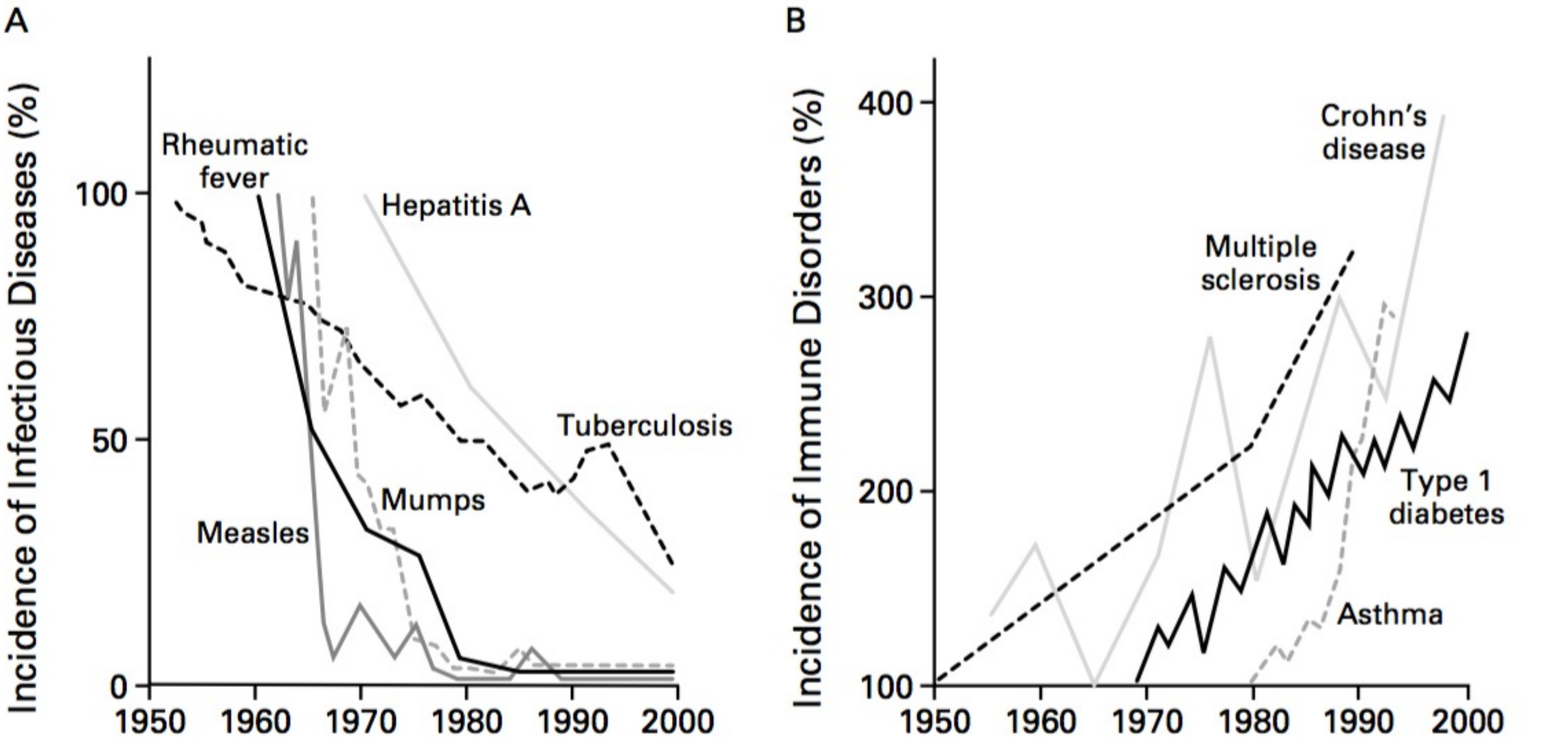
State of the art and Open Challenges

MetaGenoPolis

Centre de recherche INRAE de Jouy-en-Josas
Domaine de Vilvert, Bât.325
78 350 Jouy-en-Josas France

Huge diversity of the gut microbiota

A major role in health and diseases



Bach JF, N Eng J Med 2

Applications in nutrition, health and well-being

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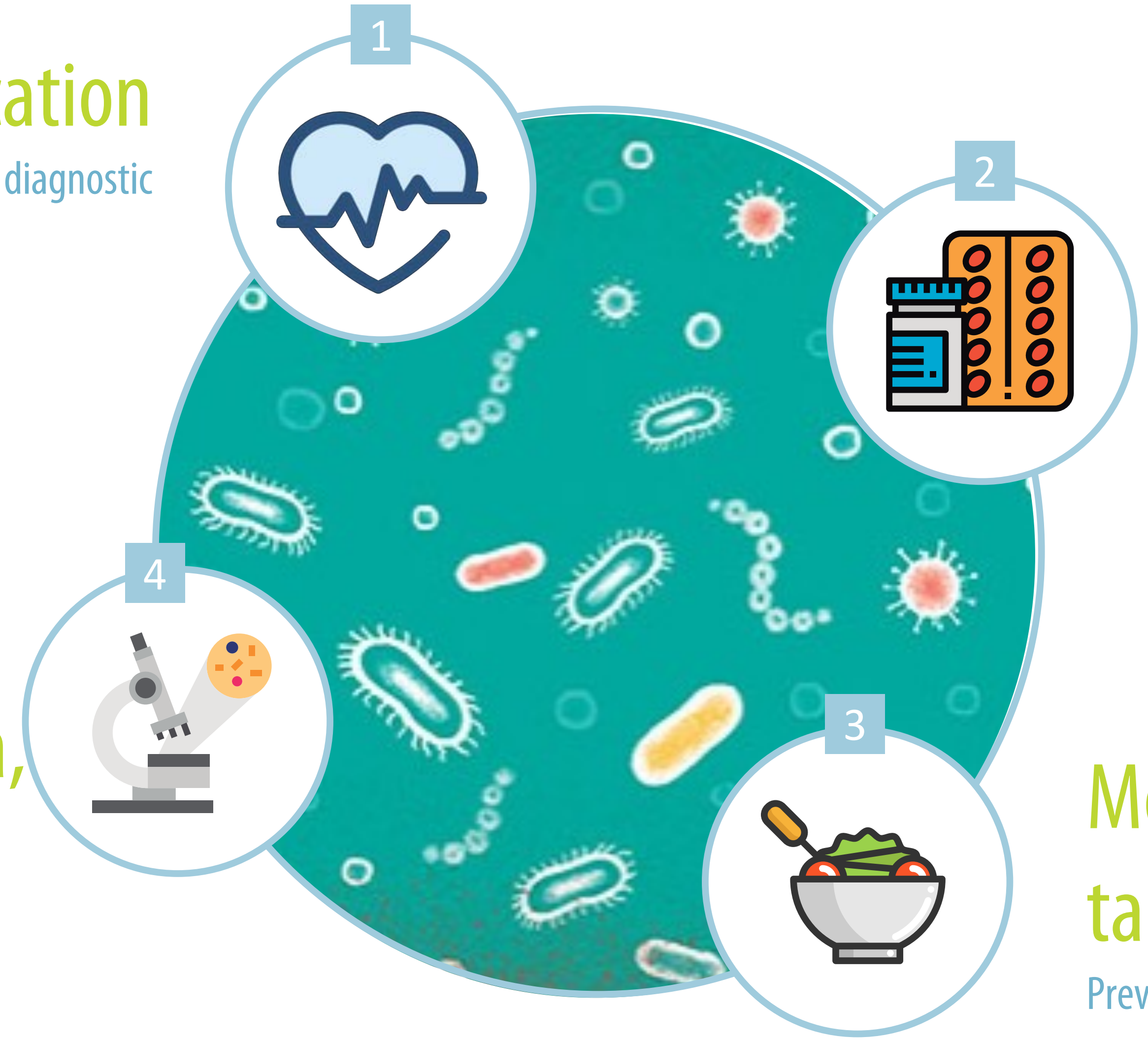


Stratification
Personalization for diagnostic

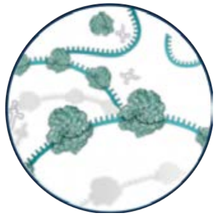
New treatments
New therapeutic targets

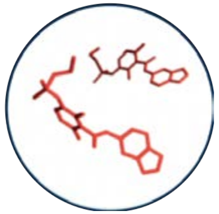
Modulation target
Preventive or curative

The microbiota, saviour organ
Microbiome transplantation

The study of « Meta-omics »

Metagenomics		Metatranscriptomics	Metaproteomics	Metabolomics





16S sequencing	Shotgun sequencing	RNA sequencing	Mass spectrometry (MS)	MS or Nuclear Magnetic Resonance (NMR)
Who is here?	What can they do?	What are they doing?	What are the proteins operating in the system?	What are the chemical fingerprints that cellular processes leave behind?

Taxonomic and functional composition

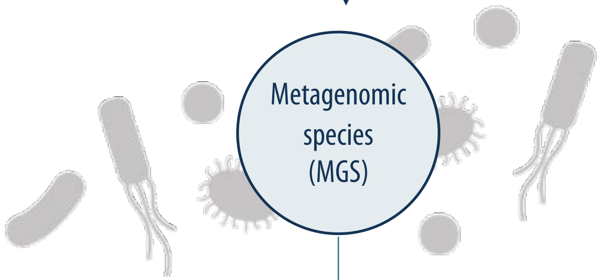
10.4 M gene catalogue for human gut microbiome

▼

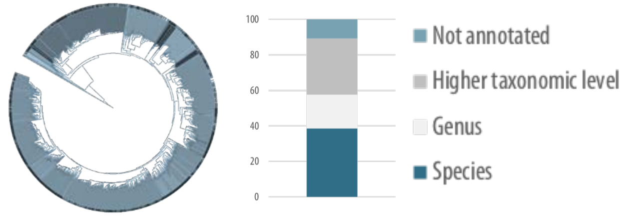
MSPminer clustering

▼

Metagenomic species (MGS)



MGS taxonomy annotation



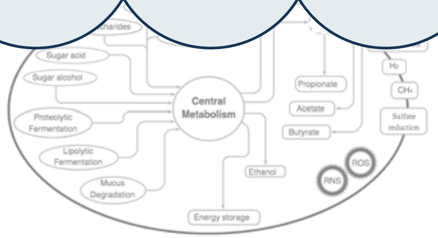
Plaza Oñate, Florian, et al. Bioinformatics 35.9 (2019): 1544-1552.

Who is here?

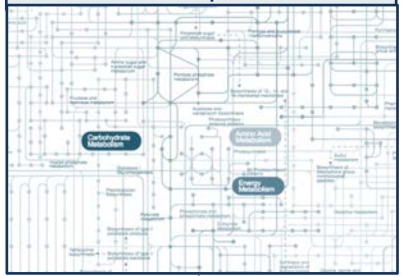
▶ KEGG functional annotation

▼

KEGG Modules | Gut Metabolic Modules | Gut-Brain Modules



Module exploration



What can they do?

Exploratory statistical analyses

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What is the diversity of the sample?

Metagenomic species (MGS)

Metabolic Modules

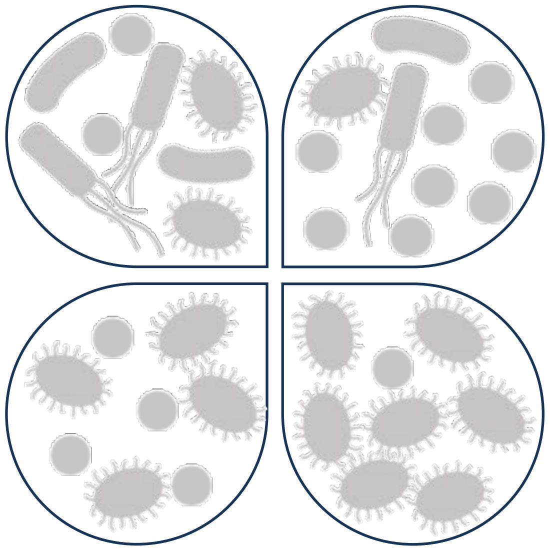
How it compares with others?

Exploratory statistical analyses

- Alpha Diversity
- Beta Diversity
- Gamma Diversity

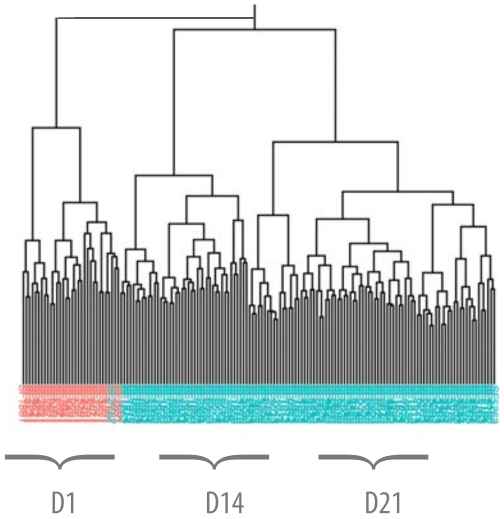
Rich and even

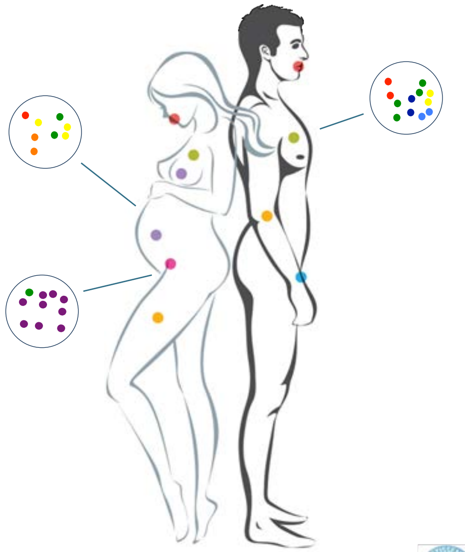
Rich and uneven



Poor and even

Poor and uneven



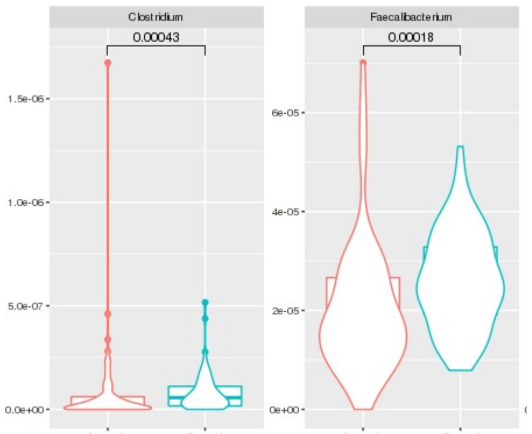


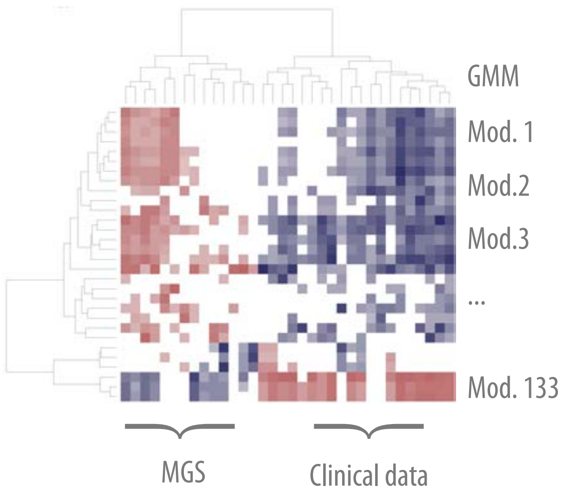
Data integration and machine learning

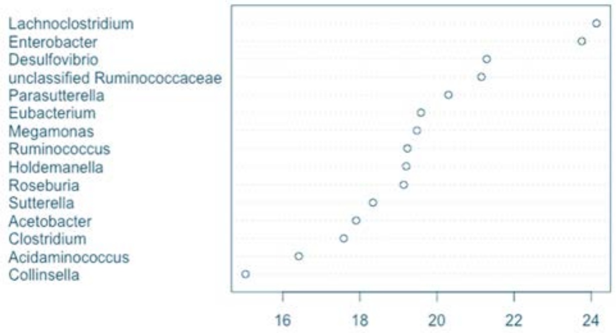
Metadata | MGS | MM | Omics

Integrative data analysis

- Identifying the changes in the microbiota
- Correlation analysis
- Network inference
- Variable selection and modelling



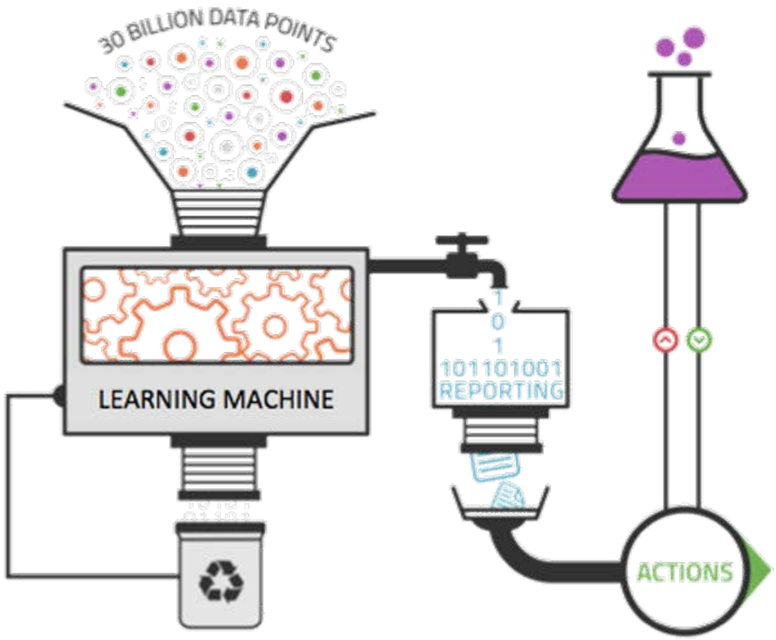




Machine Learning for microbiome analysis

Machine Learning

Set of methods based on **algorithms** that use **mathematical procedures** to analyze data structuring



Machine learning algorithms 'learn' from data and can improve

Advantages

- Less demanding to build (data-driven learning)
- Less difficult to encode (rules established by the process)
- More flexible (integration of new data)

Limitations

- More difficult to interpret (especially deep learning)

"Machine learning is the field of study that gives computers the ability to learn without being explicitly programmed"

— Arthur L. Samuel, AI pioneer, 1959

The Three Types of Machine Learning Algorithms

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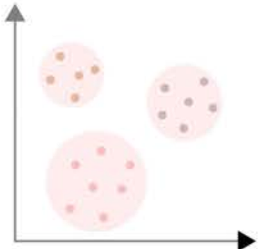


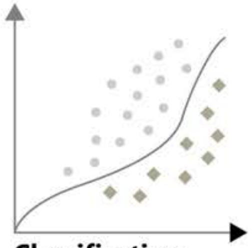


image by Moreno-Indias, Isabel, et al. Frontiers in Microbiology 12 (2021): 277.

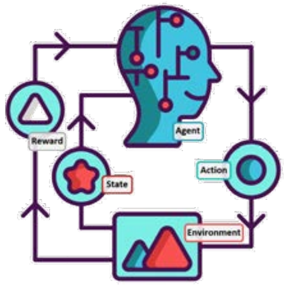
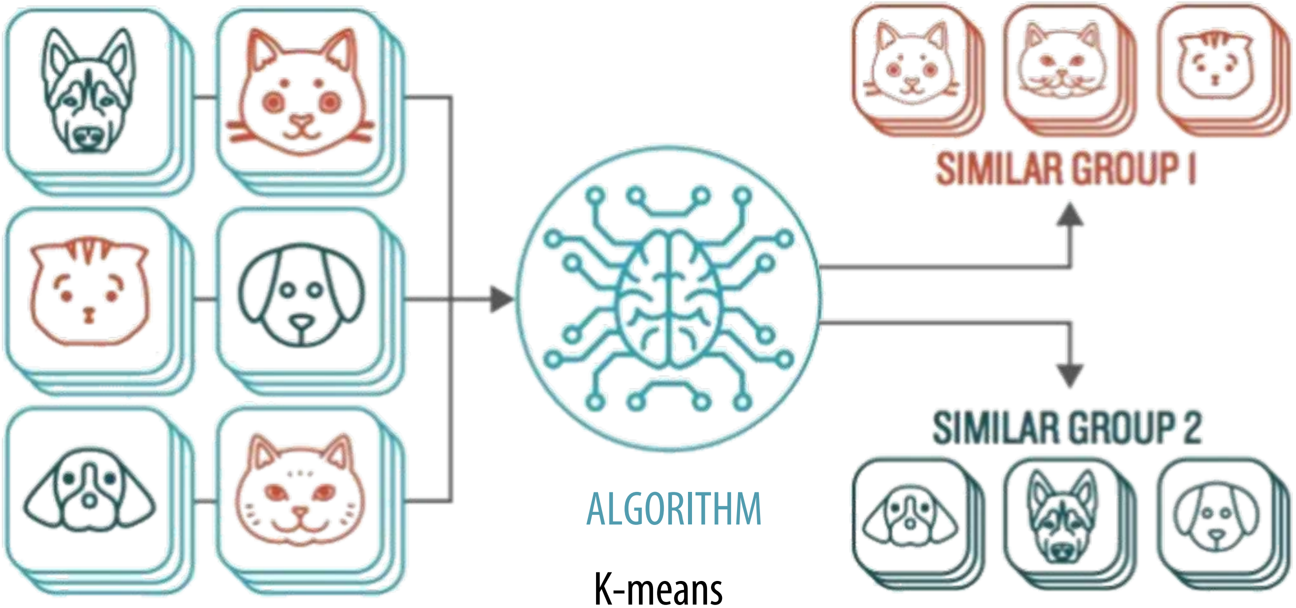


image by Flat-Icons on IconScout under license to Chris Mahoney

How unsupervised learning works

STEP 1

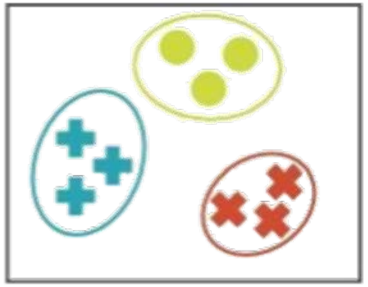
STEP 2



K-means
Hierarchical Clustering
Gaussian Mixte Model
Principal Component Analyses
Multidimensional scaling (MDS)
. . .

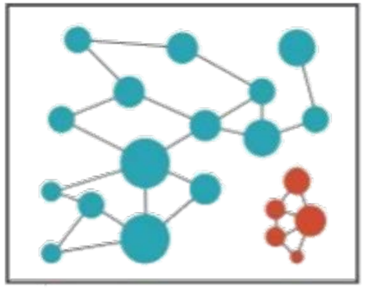
Source: adapted from Booz Allen Hamilton

TYPES OF PROBLEMS



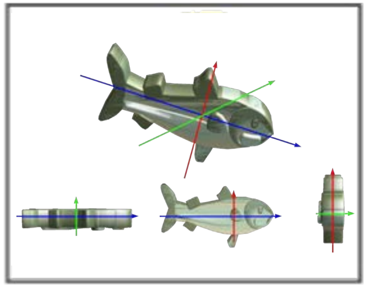
CLUSTERING

Identifying similarities in groups



ANOMALY DETECTION

Identifying abnormalities in data

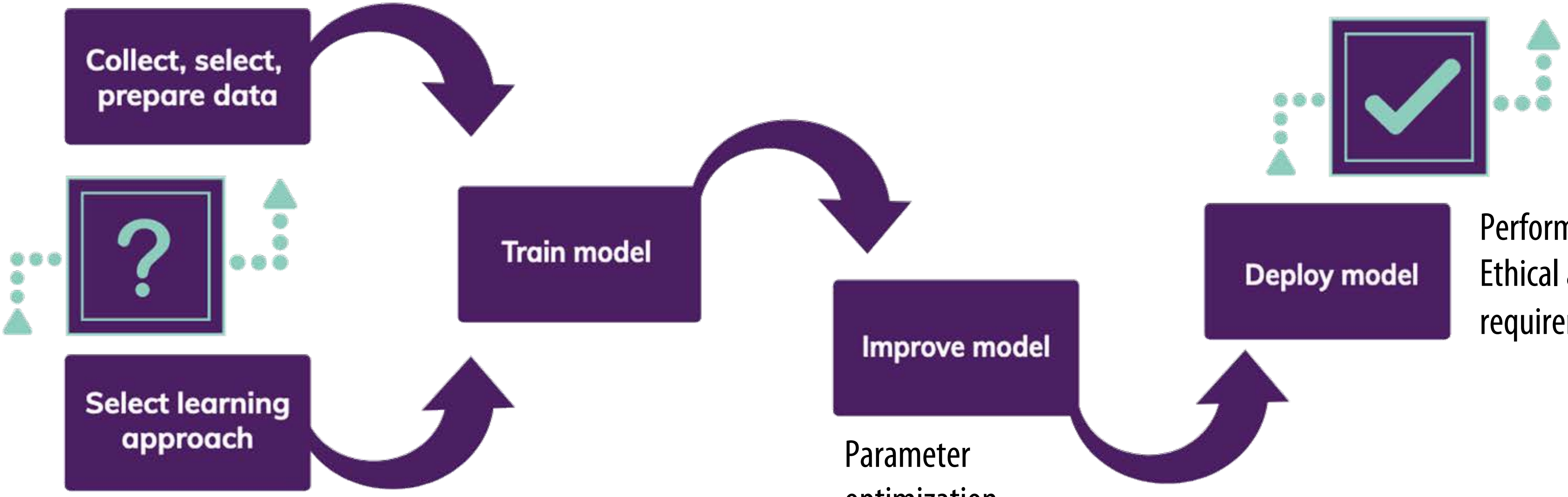


DIMENSIONALITY REDUCTION

Concise input for supervised learning

Building a supervised learning model

Data organization
and preparation



Lasso
Random forest
SVM
…

Parameter
optimization

Performance criteria
Ethical and regulatory
requirements

[Artificial intelligence for genomic medicine Report]

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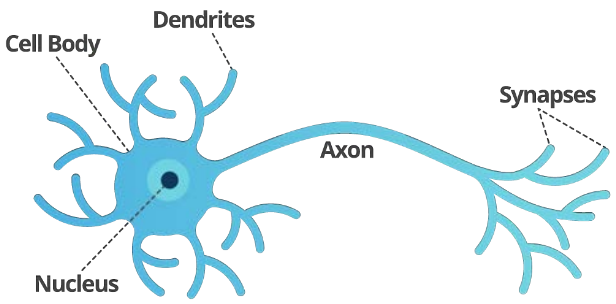
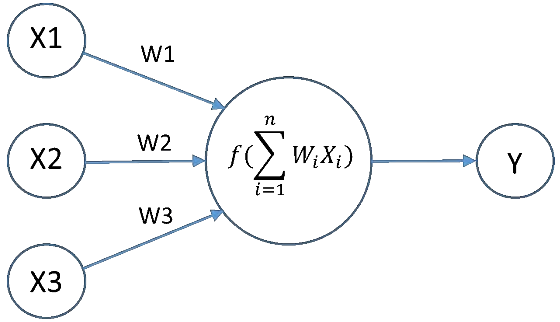
Artificial neural network

Collection of **connected units** (artificial neurons) whose functioning is inspired by **neurons** in the brain.





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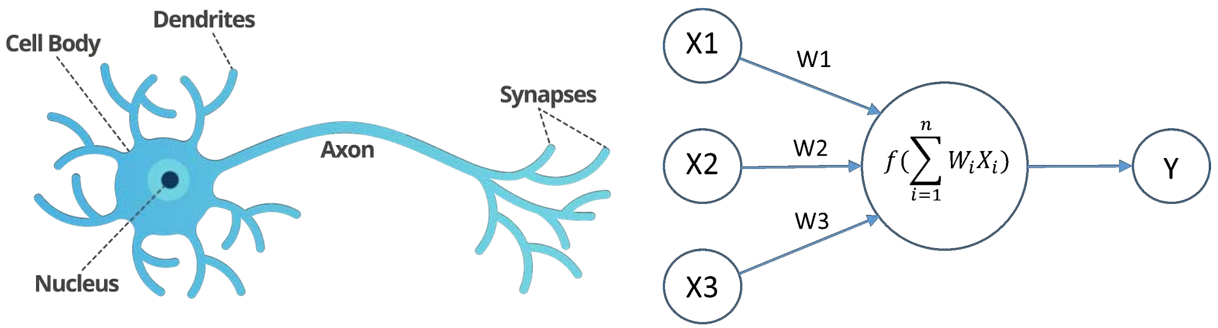
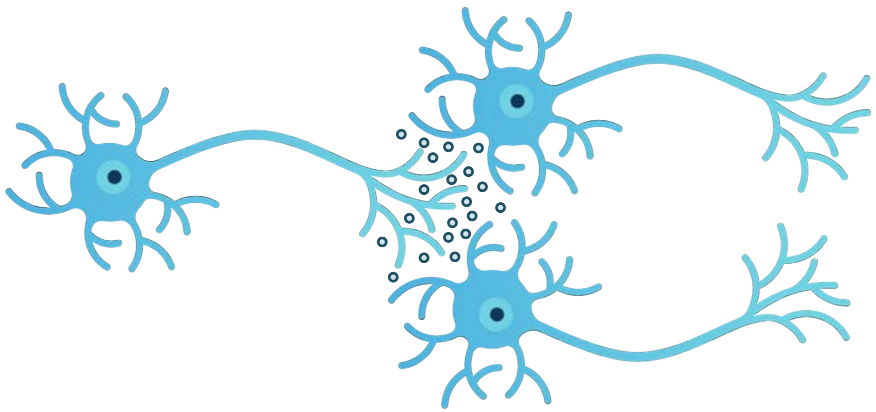
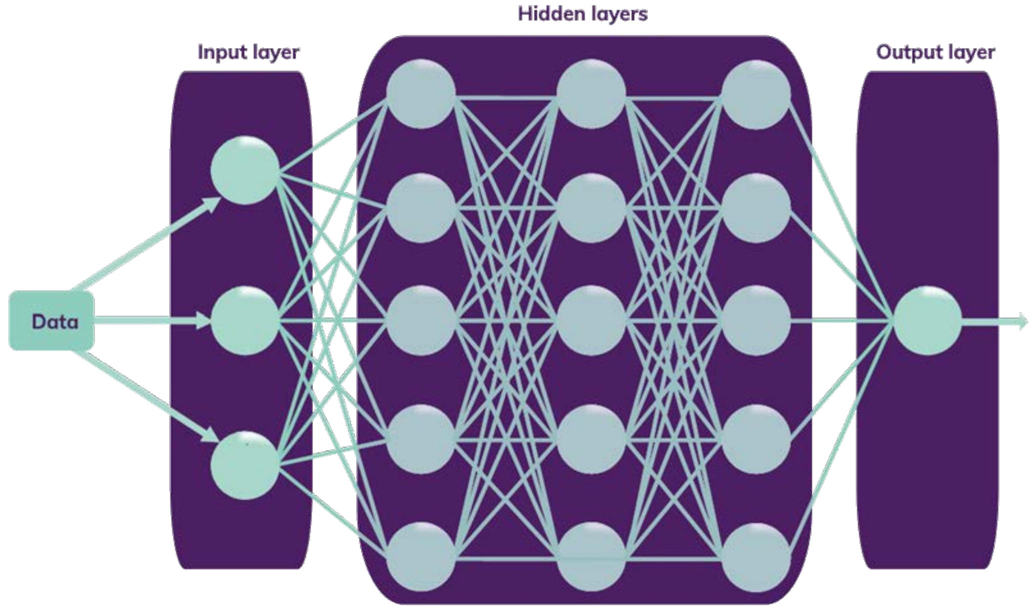


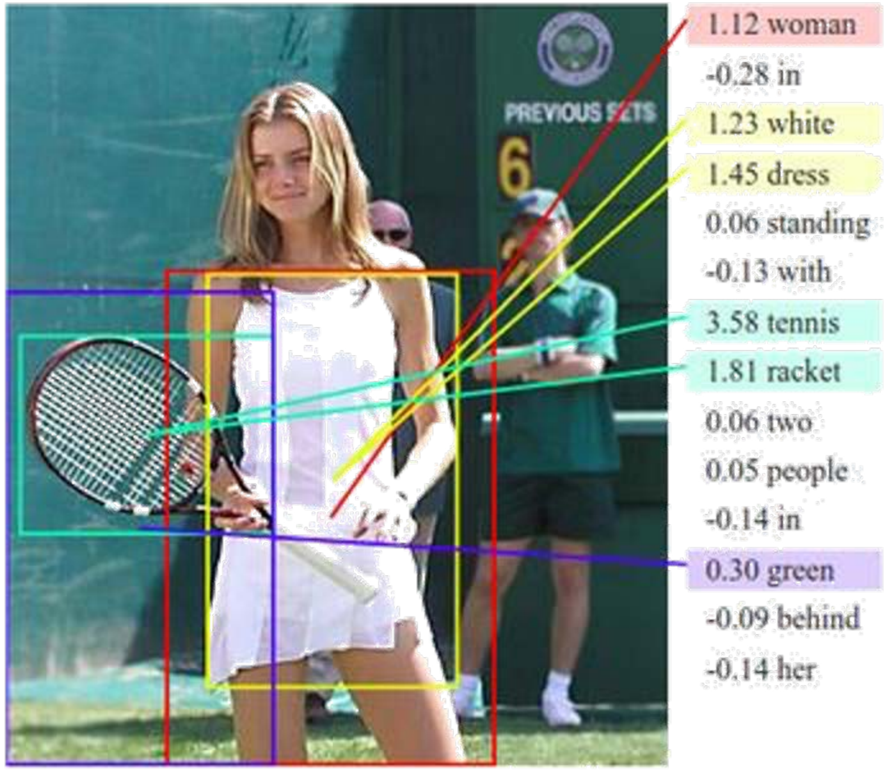
Deep Learning
Learning process based on **large artificial neural networks** (many hidden layers)





[Artificial intelligence for genomic medicine Report]

Deep Learning

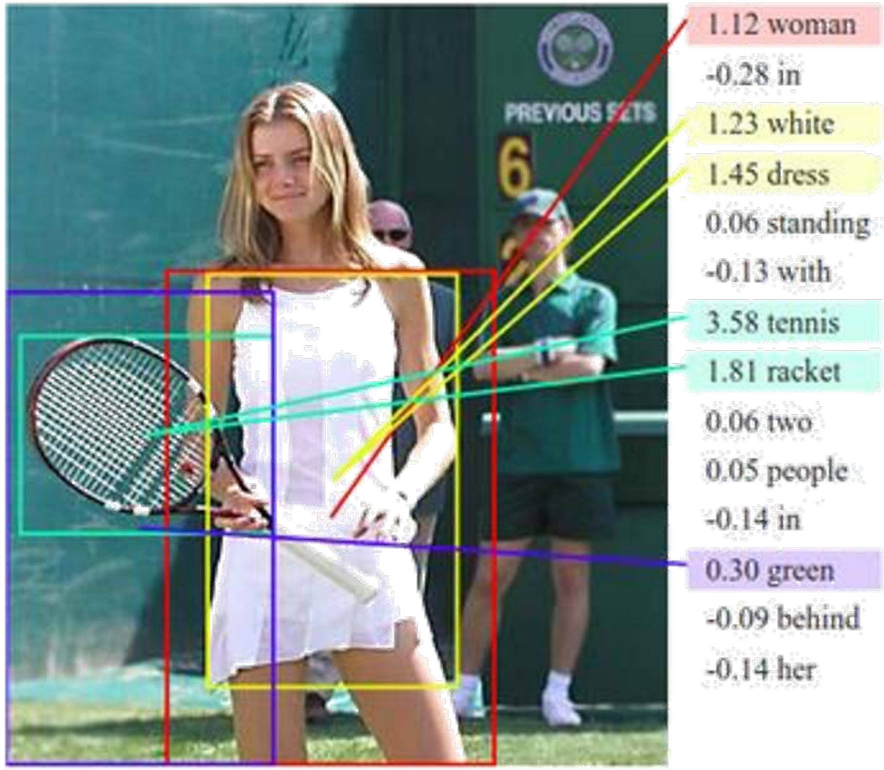


https://cs.stanford.edu/people/karpathy/deepimagesent/

Main applications

- Image recognition,
  facial recognition and object detection
- Natural language processing

Deep Learning



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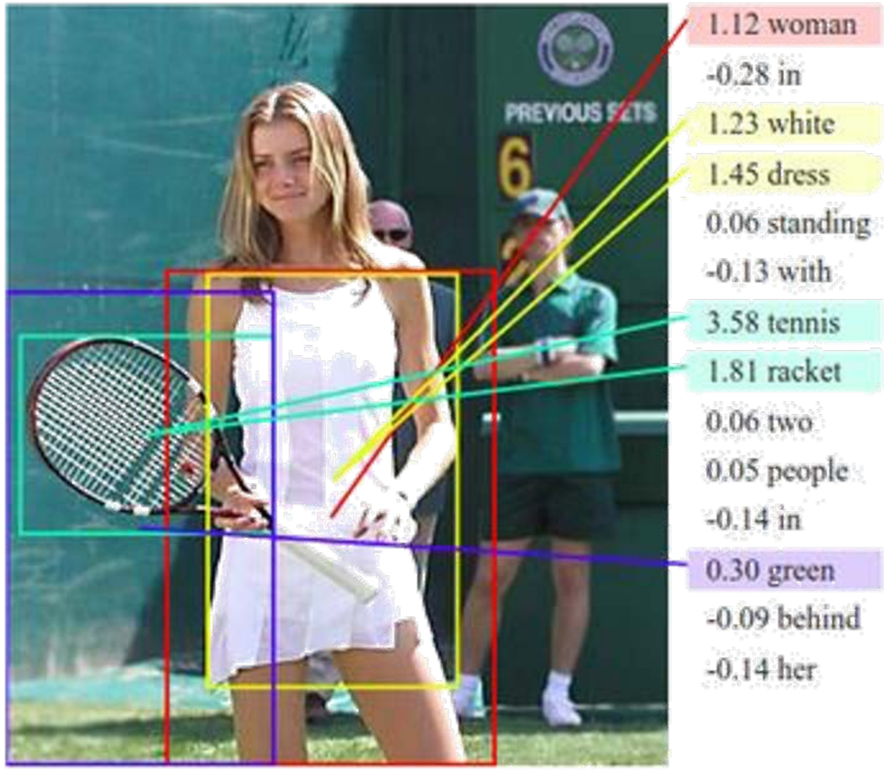
Advantages

- More flexible (modeling very complex relationships)
- Less dependent on prior knowledge of the field

Limitations

- Require huge amount of data
- May be subject to overfitting (generalization to other data)
- Costly calculation (large number of operations)
- Difficult to interpret (extraction of biological knowledge)

Deep Learning



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a) Husky classified as wolf (b) Explanation

"The question of whether a computer can think is no more interesting than the question of whether a submarine can swim."

– Edsger W. Dijkstra

Application of Deep Learning for microbiome?

What works in other domains

- **Nature of the data**

  - Images (well known modelling)

  ***Challenge**: microbiome data are not deeply understood*

  - Large datasets (ImageNet: 14+ M images)
  - Transfer learning : it is possible to train a neural network on one image category to transfer it to another

  ***Challenge**: much less data available, large heterogeneity*

- **Nature of the *question***
  - Humans can solve the problem

  ***Challenge**: humans can't solve the problem*

from Chloé-Agathe Azencott

Examples of application to microbiome data

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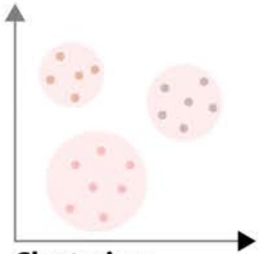
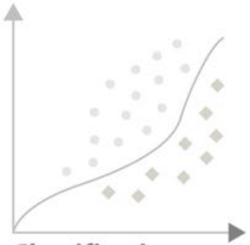
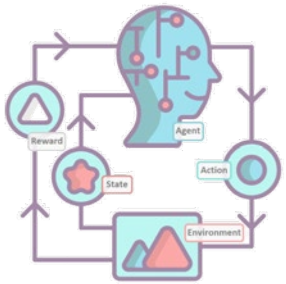
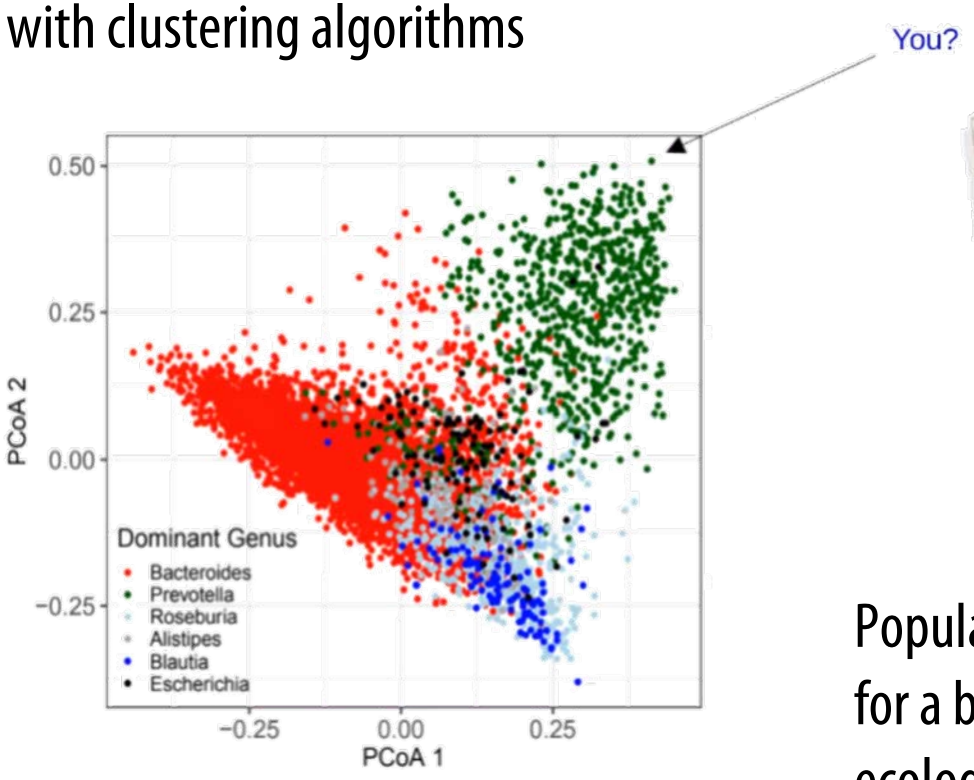


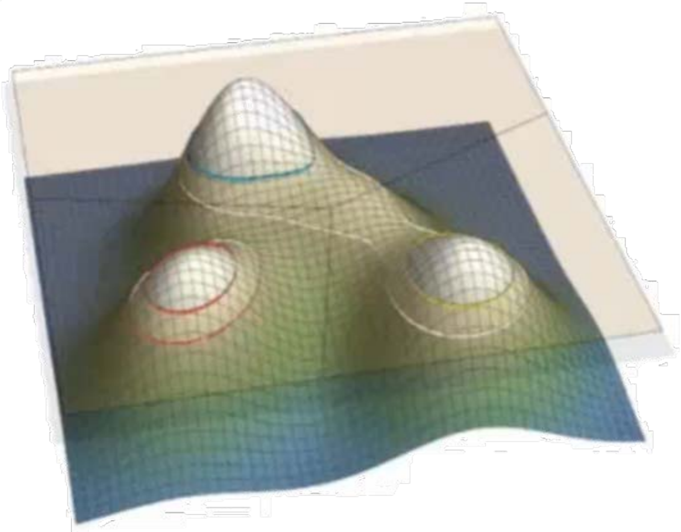




Unsupervised learning: enterotypes

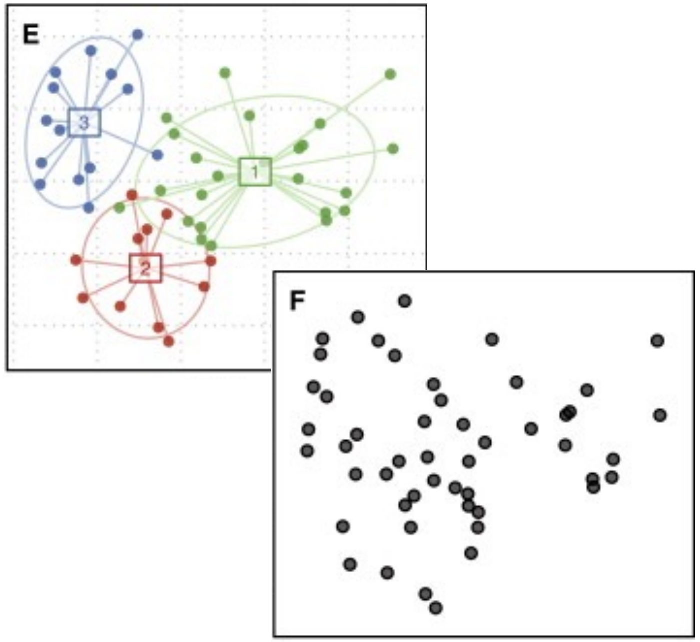
Identification of microbiome enterotypes with clustering algorithms





Population stratification is a useful approach for a better understanding of functional, ecological and medical information.

Certain visualizations can cause the eye to perceive discrete clusters to be stronger than they are



Salosensaari, Aaro, et al. Nature communications 12.1 (2021): 1-8.

Costea, Paul I., et al. Nature microbiology 3.1 (2018): 8-16

Knights, Dan, et al. Cell host & microbe 16.4 (2014): 433-437.

Unsupervised learning: microbial networks

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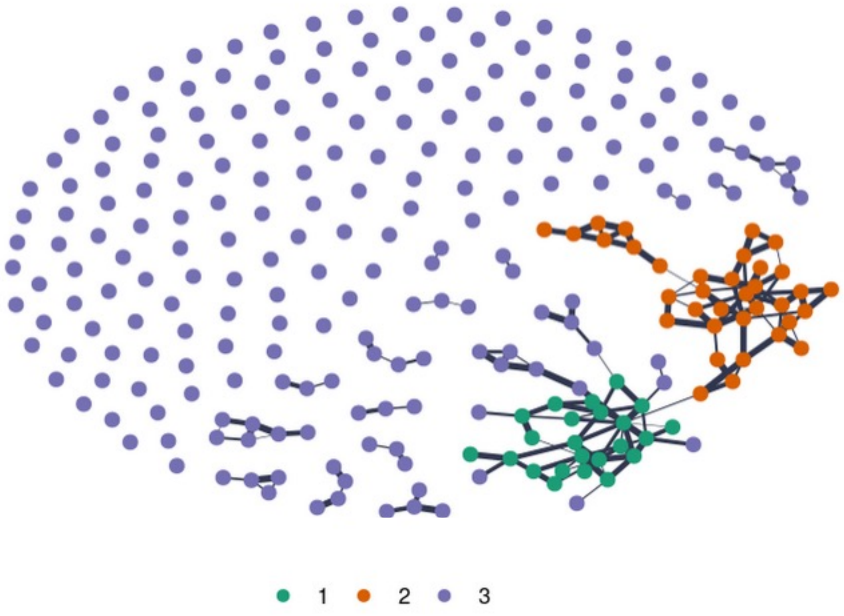
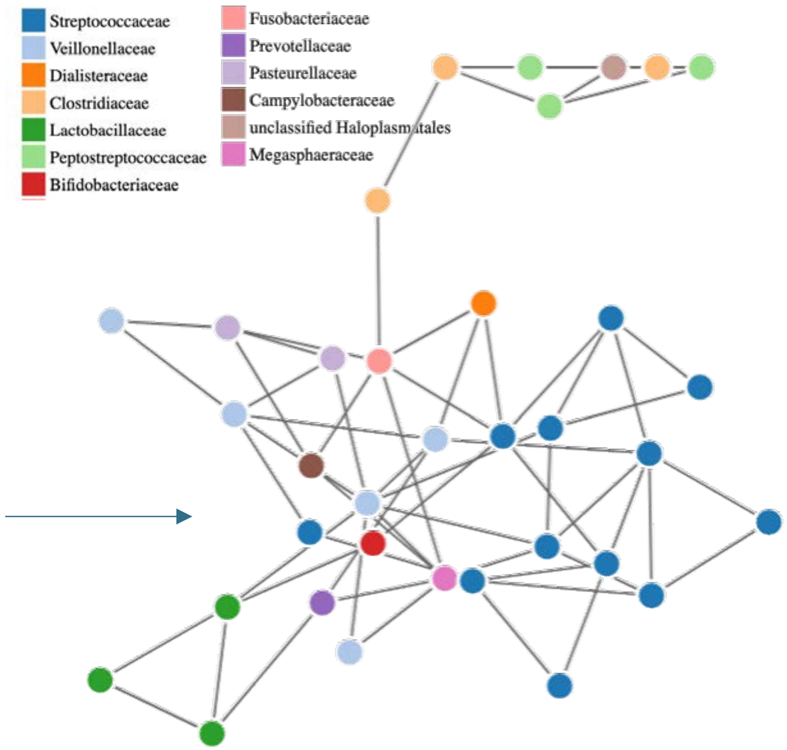
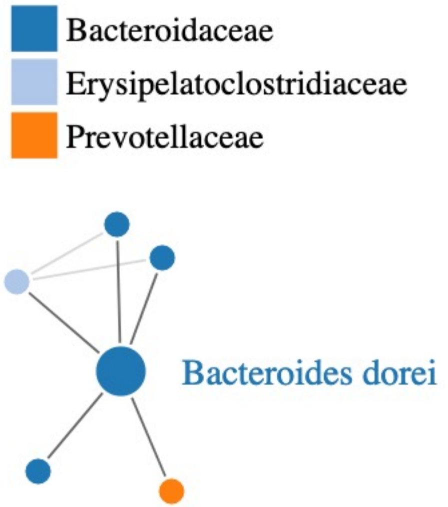
Microbial network construction is a popular explorative data analysis technique…







… to identify taxa sharing a common role in an ecosystem

Faust, Karoline. "Open challenges for microbial network construction and analysis." The ISME Journal (2021): 1-8.

Raphaëlle Momal

Camille Champion

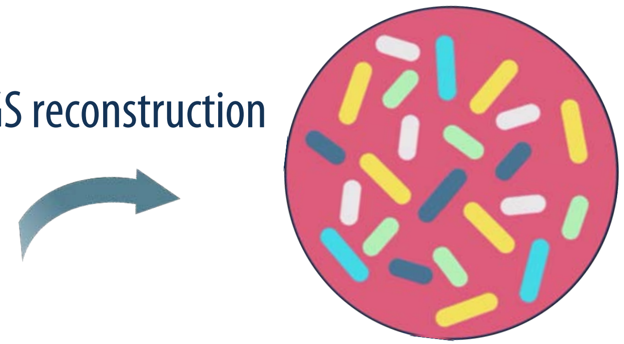
Unsupervised learning: dimensionality reduction

~10 million genes

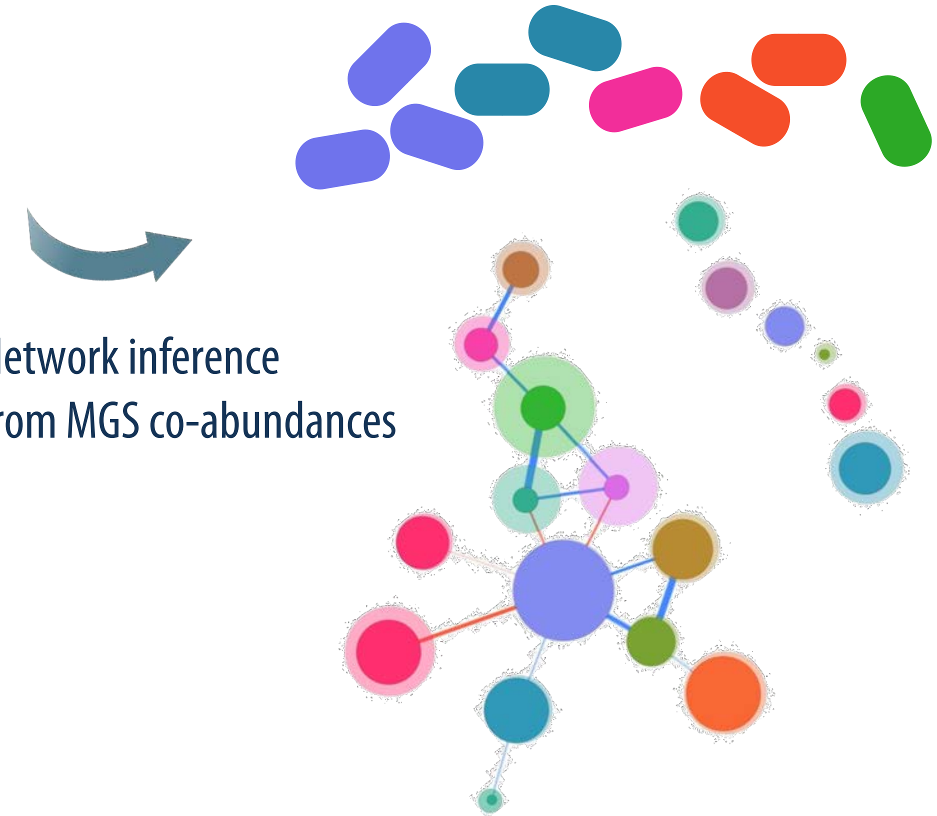
~2 000 MGS

~20 guilds

MGS reconstruction



Network inference
from MGS co-abundances



Genes co-varying in abundance
as encoded on the same genome

Plaza Oñate, Florian, et al. Bioinformatics
35.9 (2019): 1544-1552.

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Unsupervised Learning

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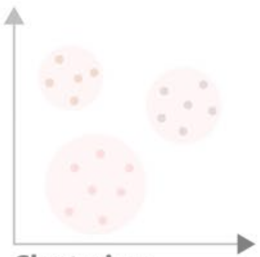
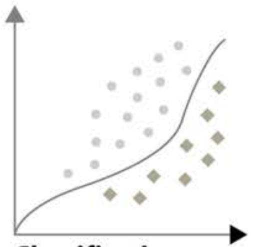
- No feedback
- Find an underlying structure in the data



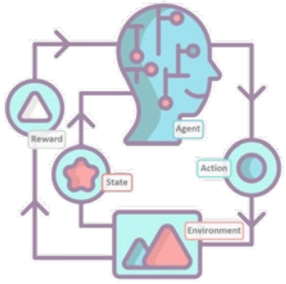
Supervised Learning

- Labelled data
- Direct feedback
- Prediction of an output



Reinforcement Learning

- A set of rules / No labels
- Reward system
- Iterative self-teaching



Supervised learning: diagnostic or prognostic

Common algorithms used for disease-prediction tasks :

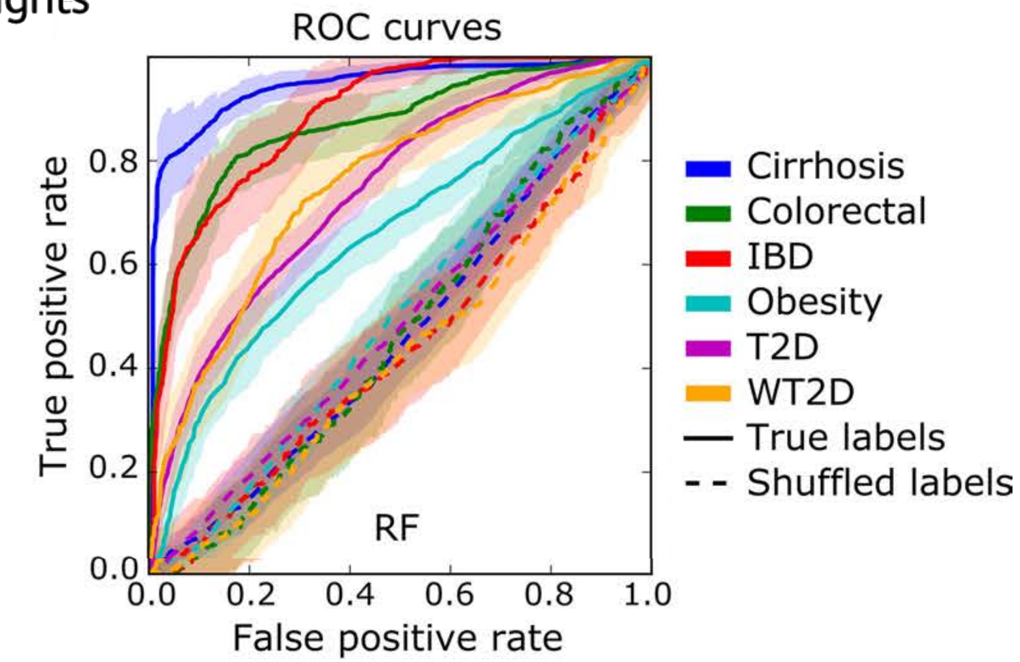
- Random forest (RF) / decision trees
- Support vector machines (SVM)
- Gradient boosting
- LASSO / ridge / elastic net regression
- Partial Least square regression (PLS)
- Neural networks
- K-nearest neighbors (KNN)
- …

Marcos-Zambrano, Laura Judith, et al. Frontiers in microbiology 12 (2021): 313

Moreno-Indias, Isabel, et al. Frontiers in Microbiology 12 (2021): 277.

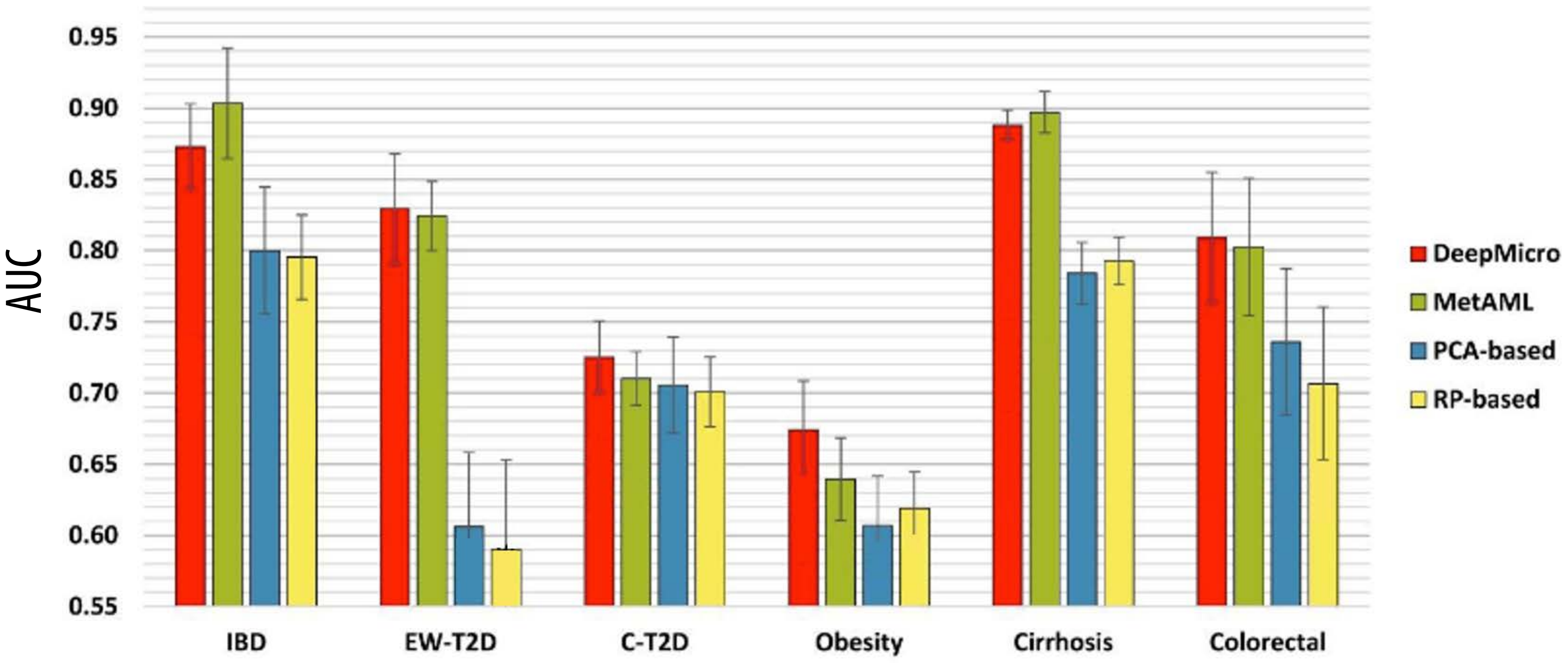
Some popular Machine Learning tools

Machine Learning Meta-analysis of Large Metagenomic Datasets: Tools and Biological Insights



Pasolli, Edoardo, et al. PLoS computational biology 12.7 (2016): e1004977.

Deep learning for microbiome data



Disease prediction performance for abundance profiles-based models

"Considerable effort has gone into increasingly powerful deep learning algorithms, but with only minor improvements in performance and modest changes in the ranking of the importance of features."

Oh, Min, and Liqing Zhang.
Scientific reports 10.1 (2020): 1-9.

LaPierre, Nathan, et al.
Methods 166 (2019): 74-82.

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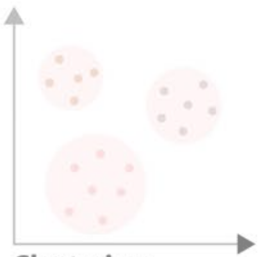

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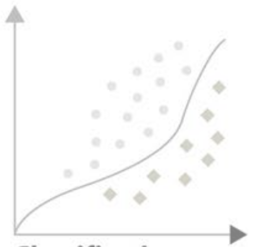
- ▷ Direct feedback
- ▷ Prediction of an output



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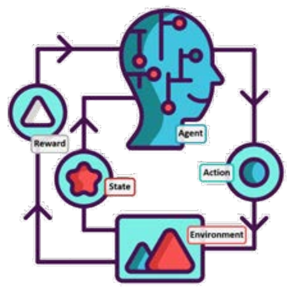

Generative Adversarial Networks to Boost the Performance of Machine Learning in Microbiome

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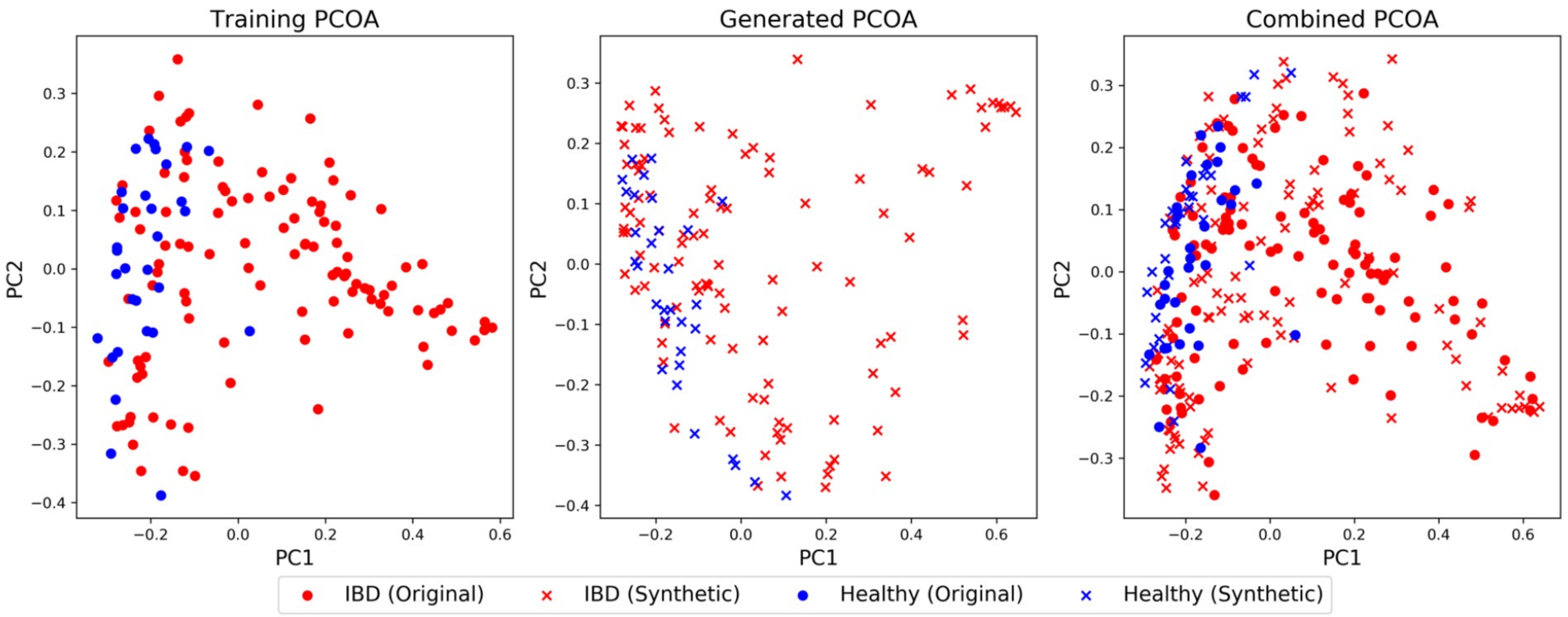
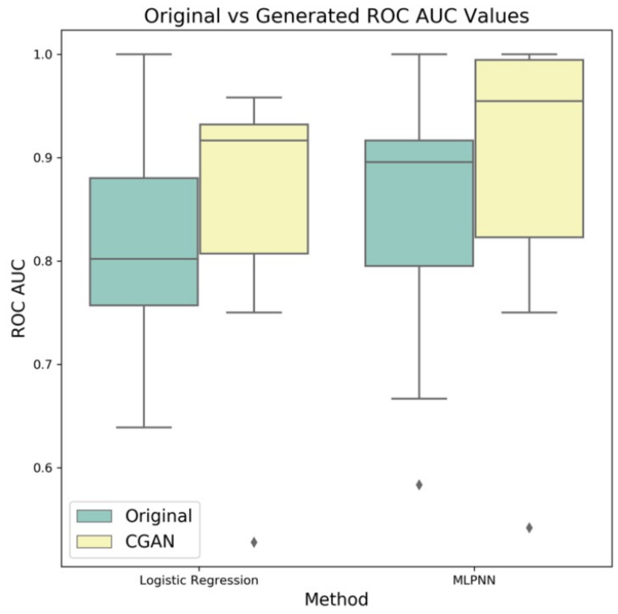
Data-driven simulation of microbiome data using a conditional generative adversarial network





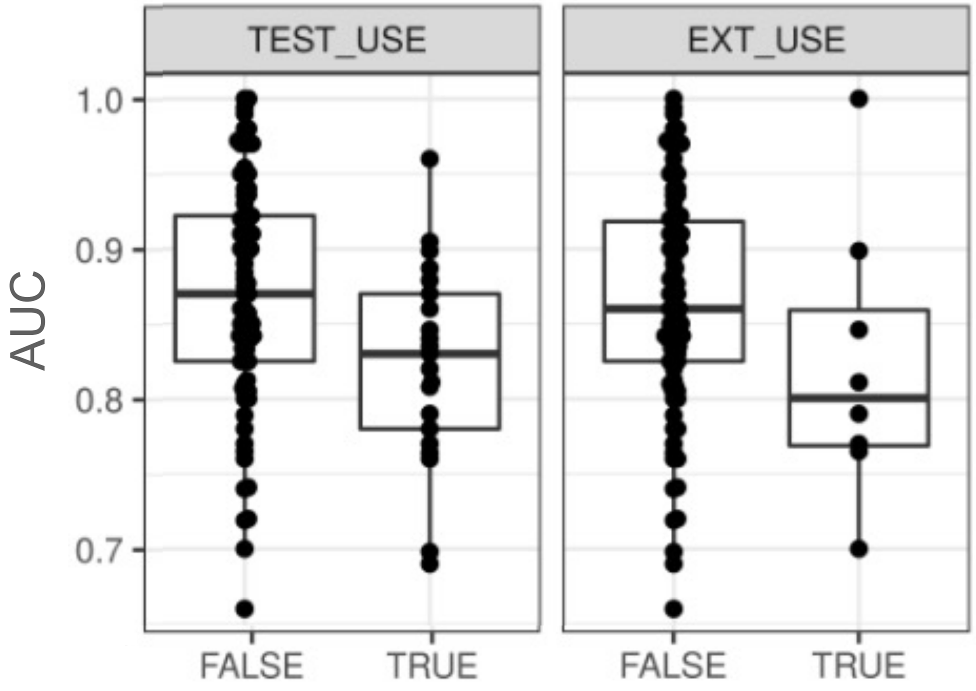
Synthetic samples generated can boost disease prediction

Reiman, Derek, and Yang Dai. "Using Conditional Generative Adversarial Networks to Boost the Performance of Machine Learning in Microbiome Datasets." bioRxiv (2020).

Open challenges for microbiome data analysis

Misuse of machine learning models

Failures in model verification make it impossible to know whether or not a trained model is fit for purpose



Among 102 articles **88% of the published AUCs** cannot be trusted at face value.

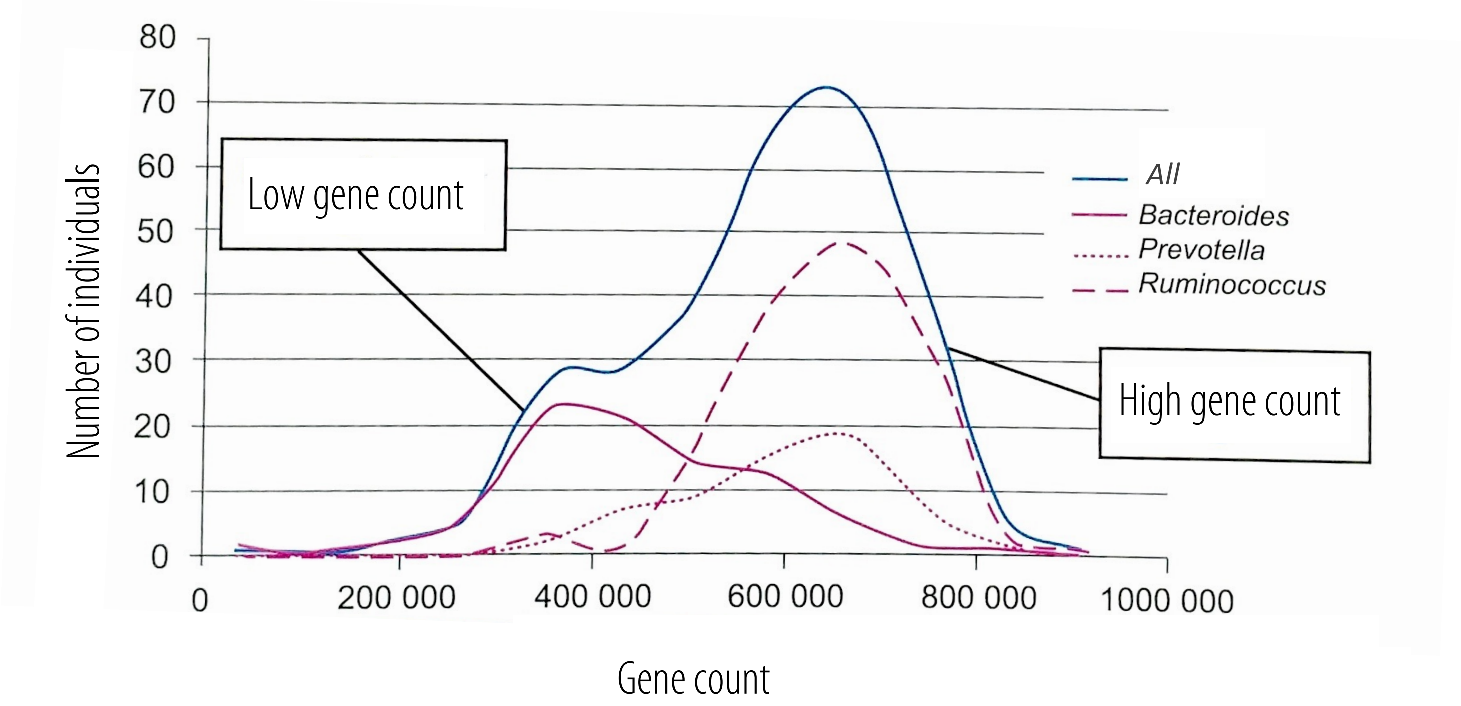
"These findings cast serious doubt on the general validity of research claiming that the gut microbiome has high diagnostic or prognostic potential in human disease."

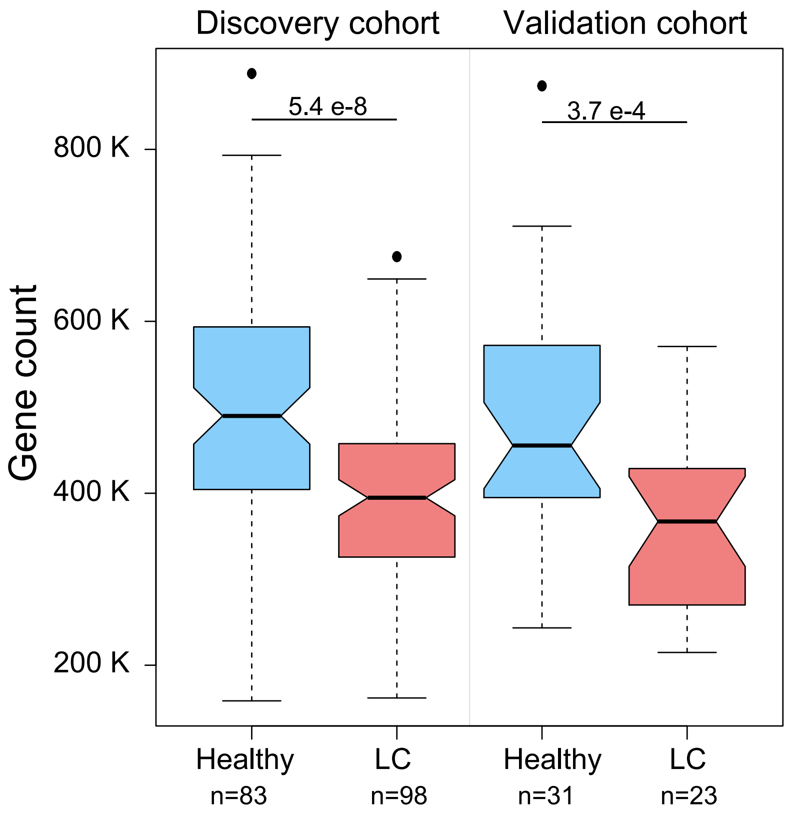
Quinn, Thomas P. "A Systematic Review of Human Gut Microbiome Research Suggests Widespread Misuse of Machine Learning." arXiv preprint arXiv:2107.03611 (2021).

Inter-individual variability

High inter-individual variability

& limited data available





Marteau, Philippe, and Joël Doré. Ed John Libbey (2017).

Qin, Nan, et al. Nature 513.7516 (2014): 59-64.

Integration of French gut in an international project
(MMHP : Million Microbiomes from Humans Project)

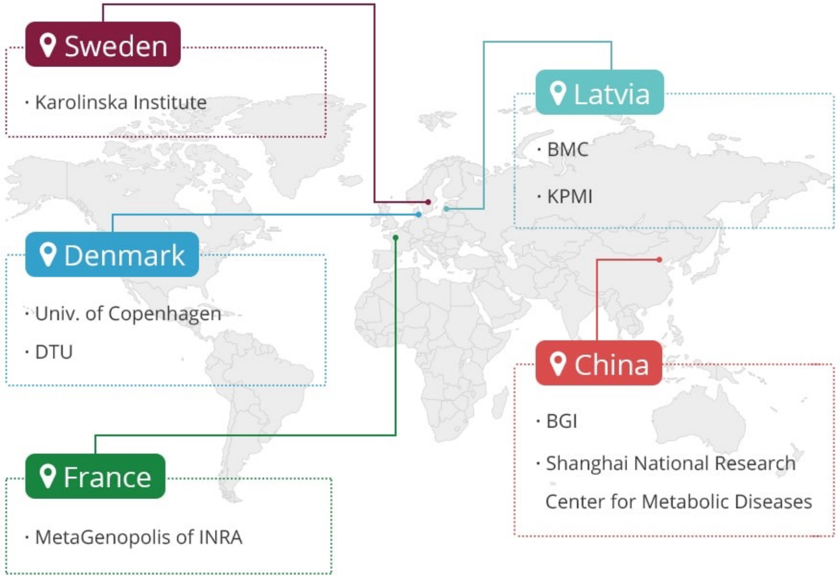
Vision and mission of MMHP

- Analyze 1 million microbial samples from intestines, mouth, skin, reproductive tract…
- Build the world's largest database of human microbiome
- Create solid data foundation for microbiome research
- Draw a microbiome map of the human body

MGP is a founding member of MMHP, officially launched on October 26th, 2019 at the 14th International Conference on Genomics (ICG-14)

MGP participates to MMHP by bringing 100,000 French gut metagenomes

Founding members of the project



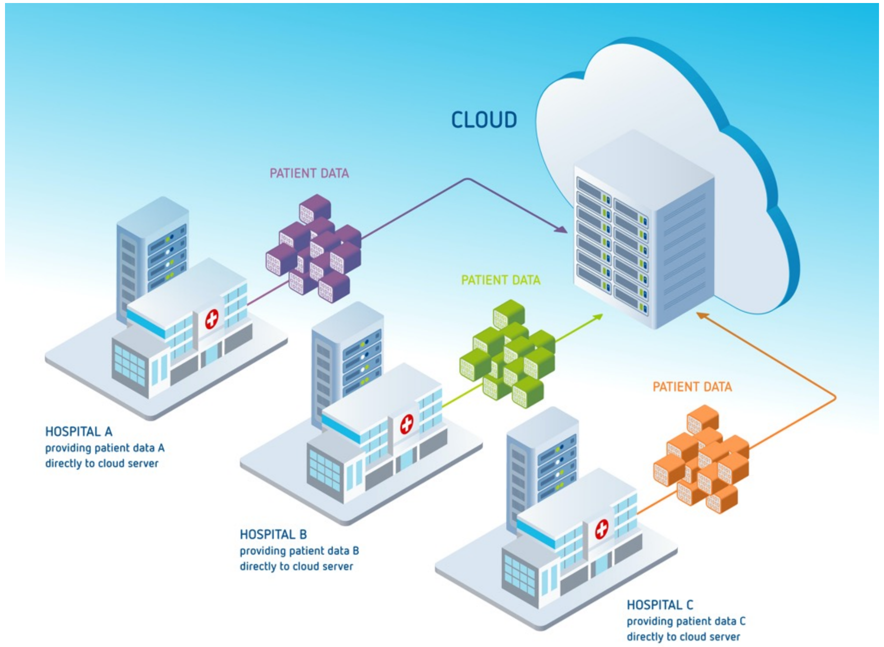
https://db.cngb.org/mmhp/

With Partners (Open for collaboration) :
Germany , Italy, The Netherlands, Spain….

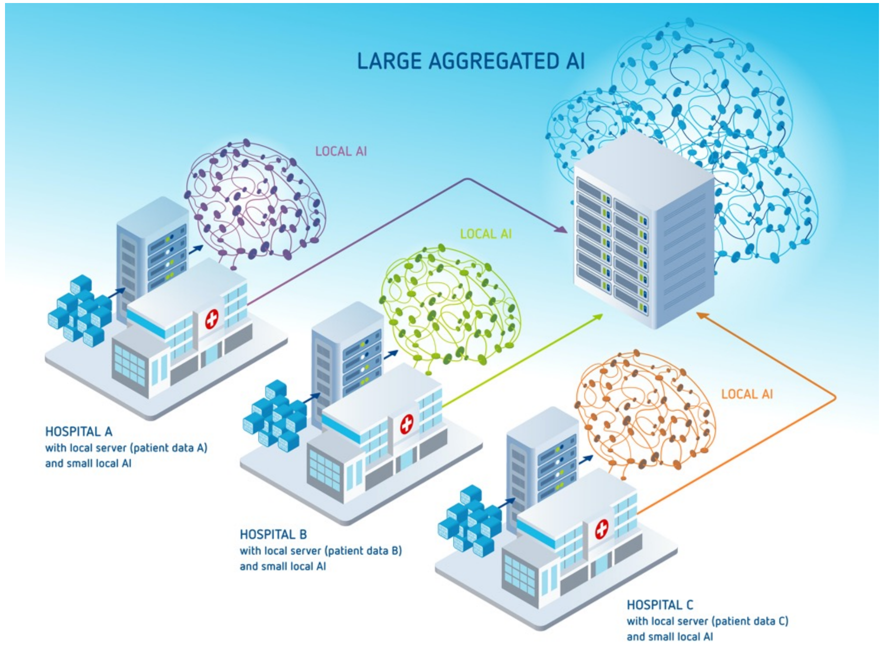
Learning from multiple datasets

Federated learning / differential privacy / domain adaptation

Current general approach to machine learning in medicine



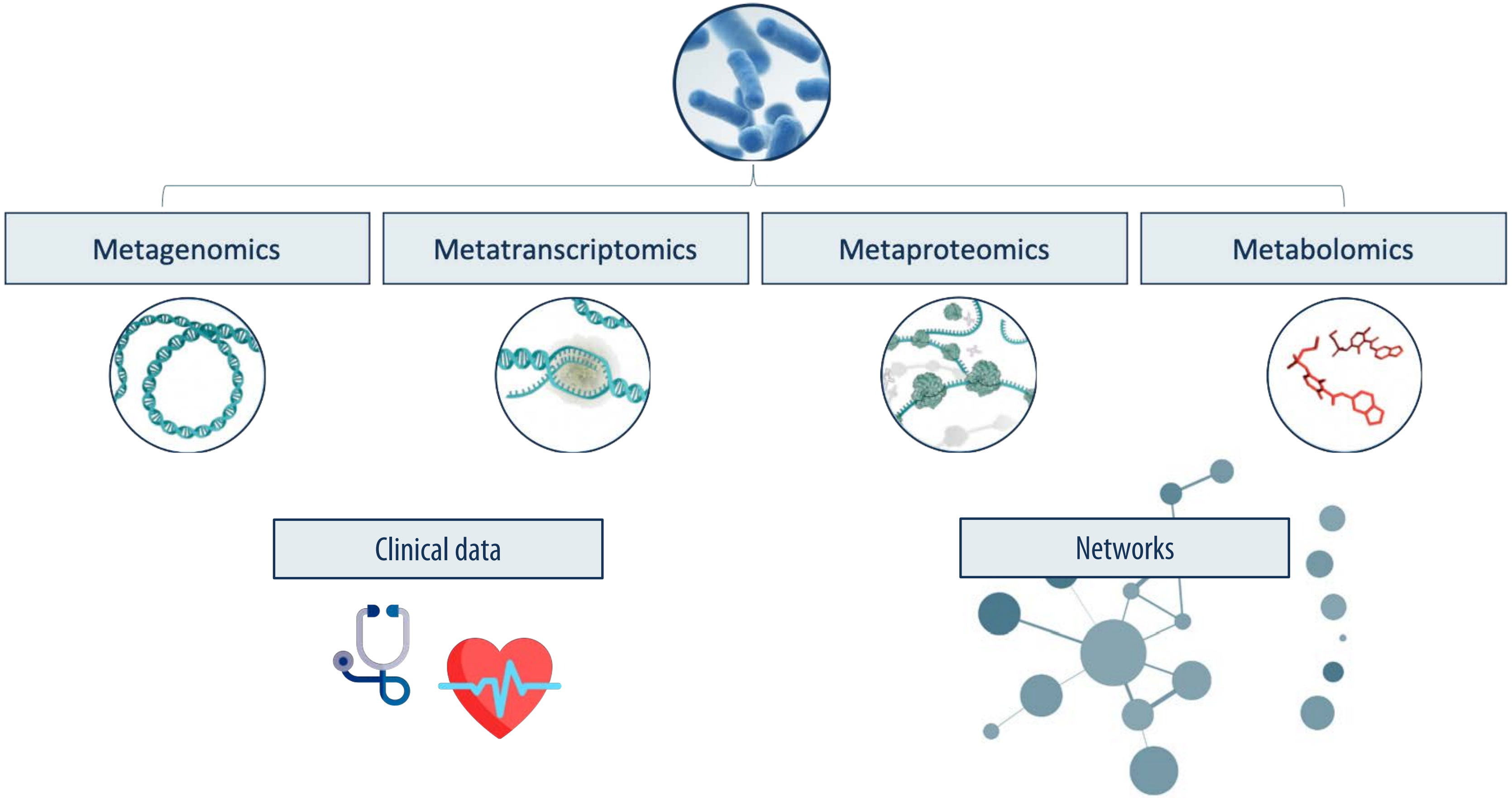
Federated approach to machine learning in medicine



https://featurecloud.eu

Integration: learning from heterogeneous data sets

multi-view learning



Take home messages

- **Methods for data exploration** include taxonomic and functional composition, diversity analyses, data integration and machine learning
- **Statistical specificities of microbiome data** limit the methods available and the design of new methods is an active research area
- **Unsupervised**, **Supervised** and **Reinforcement learning** are the three types of ML algorithms successfully applied to microbiome data
- The **current challenges and active research areas** are the misuse of ML models, high inter-individual variability, federated learning and data integration

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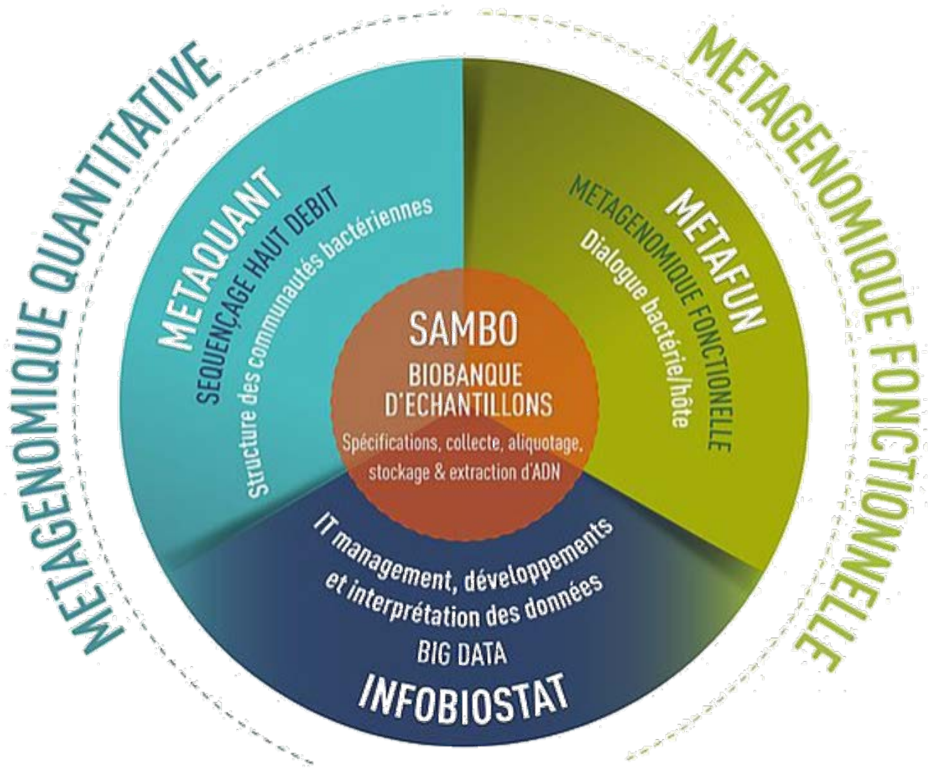
metagenopolis mgps.eu



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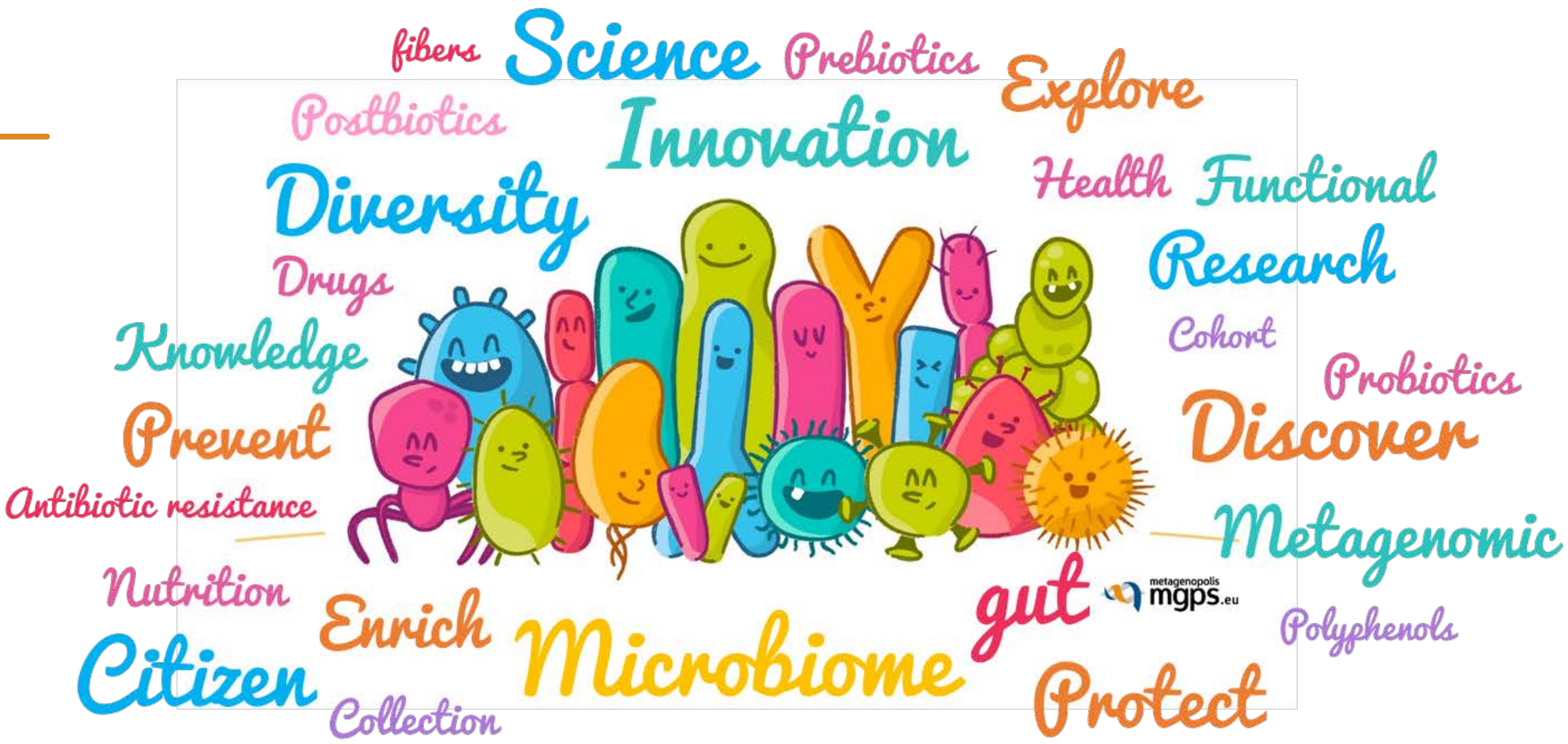
Thanks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