Gene networks: Inference, evaluation, usage, and beyond

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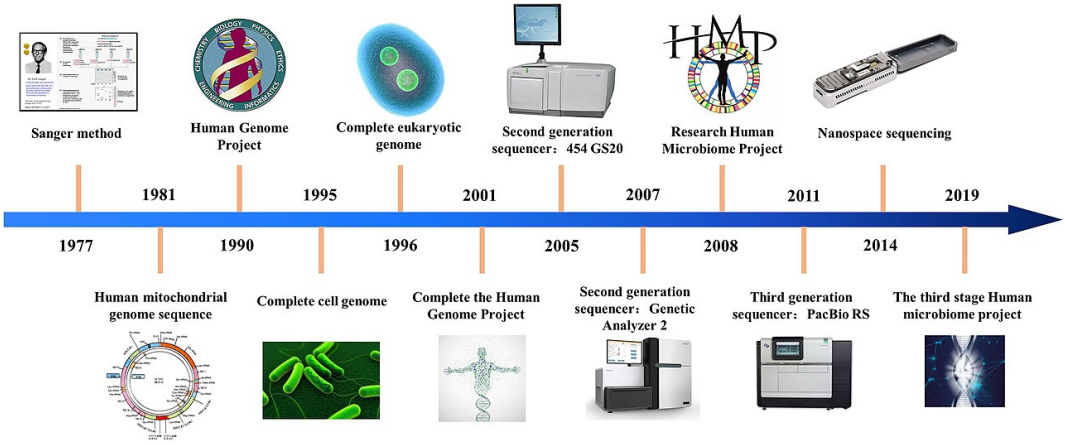
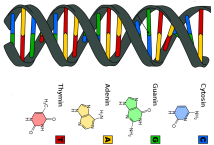
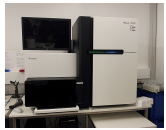
The revolution of "next Generation" sequencing technology



[Yang et al., 2020]

The revolution of “next Generation” sequencing technology





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+
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CNAGCTATCGCAACATGCCCATAGATTT
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TNCGTGTGTTCTCGTCTGGCATACTAAG
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TNCAGGACACGAAGACGACAAGTGTTAC
+
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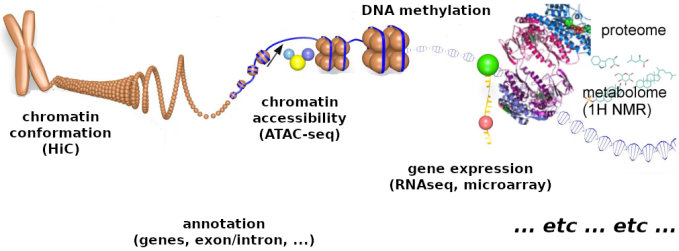
Collected data at genomic level are increasingly available



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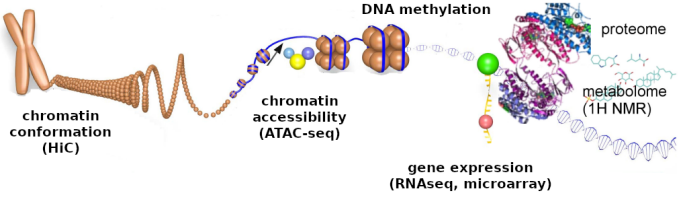
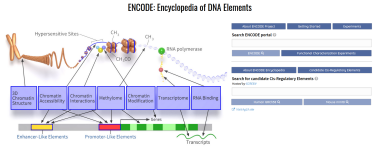




TCGA

GTExPortal

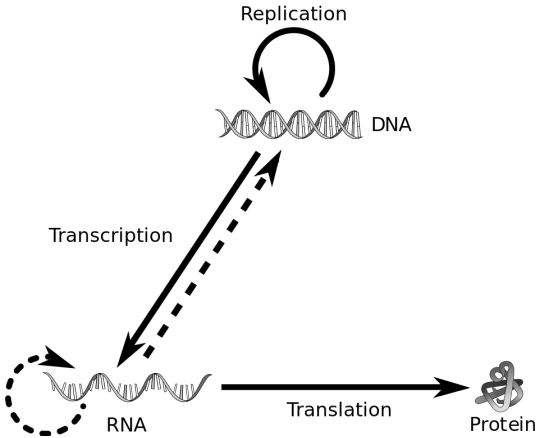
TARA OCEANS

FAANG
Functional Annotation of Animal Genomes

FR-AgENCODE

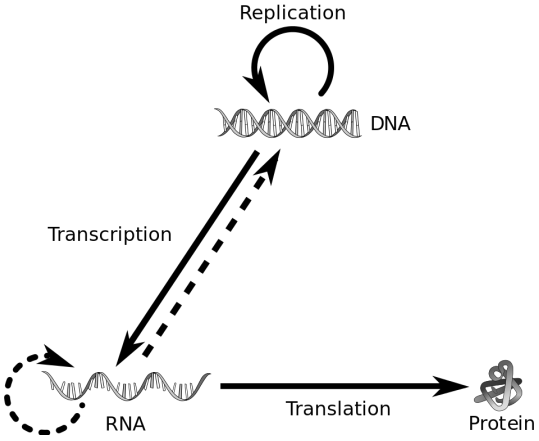
[Foissac et al., 2019]

Molecular biology dogma



[Barillot et al., 2012]

Molecular biology dogma... and beyond



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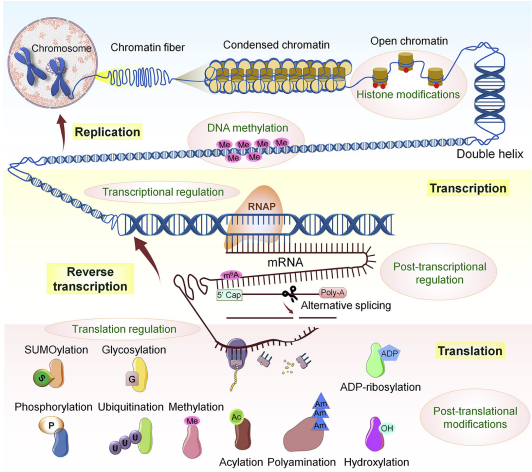
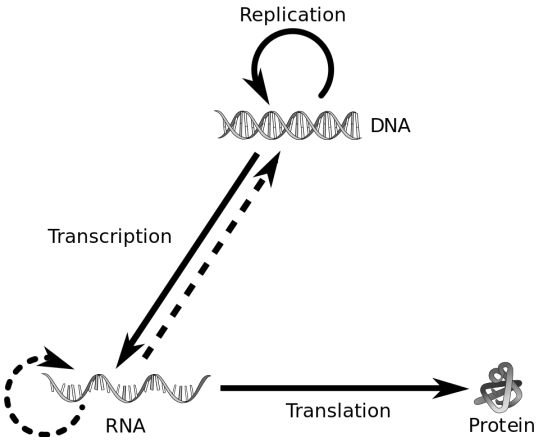


[Pramanik et al., 2021]

Molecular biology dogma... and beyond



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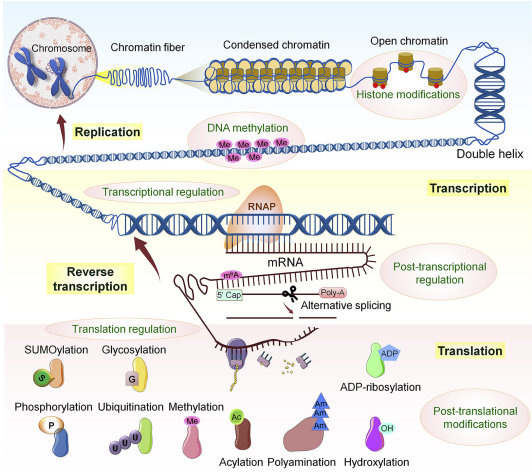
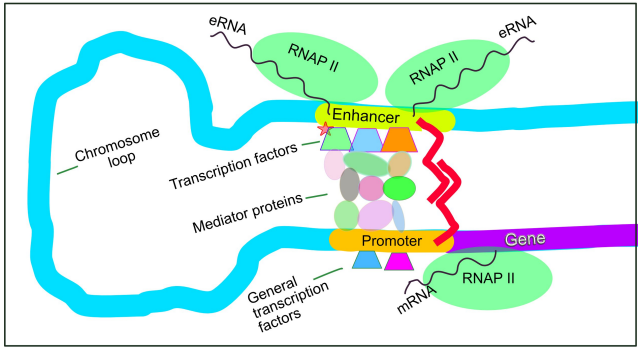


[Pramanik et al., 2021]

Main rule in biology: "There's no rule!"

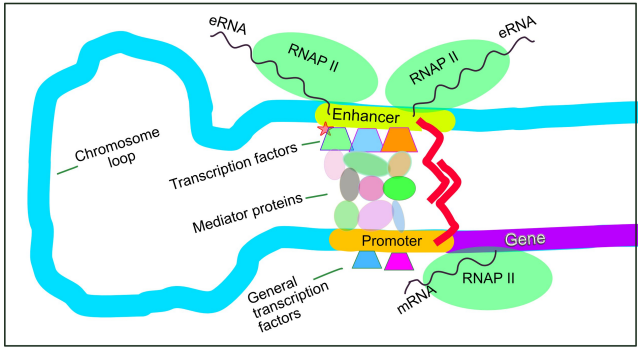
Interactions at a molecular levels: gene regulation(s)



What do we expect in the data?

Level of transcription (mRNA) of TF ↗ ⇒ mRNA of target gene ↗

Interactions at a molecular levels: gene regulation(s)



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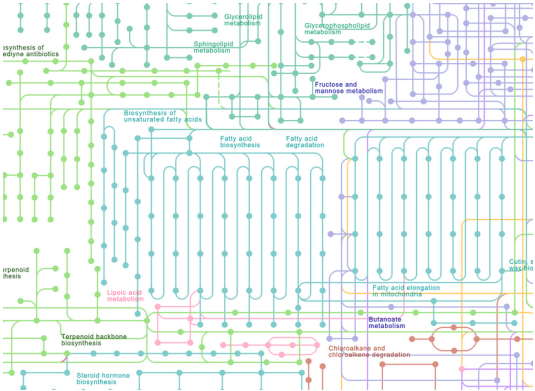
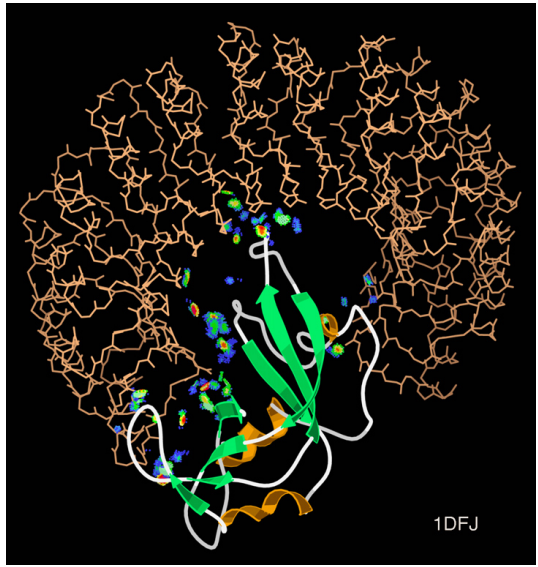
Network inference: Recover these dependency structures from gene expression

Other gene interaction networks: gene pathways, PPI

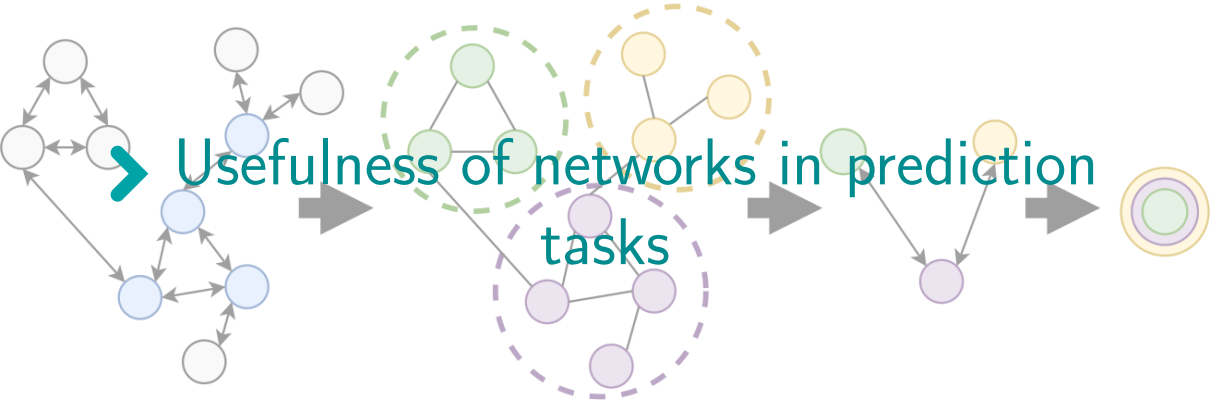




In this talk

- Can (and how) we use network information in predictive biology? Discussion on GNN

- What is the current quality of network inference methods in real-life situations?

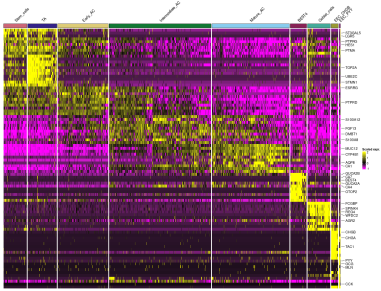


Usefulness of networks in prediction tasks

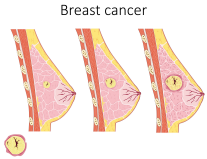
Predictive biology

Learn a classification / regression function:

$\underbrace{\mathbf{X}}_{n \times p}$ → $\underbrace{\mathbf{y}}_{n}$



gene expression



phenotype

Using the graph Laplacian in linear prediction models

Knowing a network, $\mathcal{G}$, with p nodes, $v_1, \ldots, v_p$:

$$\arg\min_{\beta \in \mathbb{R}^p} \sum_{i=1}^{n} \left(\beta^\top \mathbf{x}_i - \mathbf{y}_i \right)^2 + C \beta^\top L \beta \underbrace{+ C' \|\beta\|_1}_{\text{to enforce sparsity}}$$

- **[Li and Li, 2008]**: Y is time to death (Glioblastoma)
- $\Rightarrow$ implemented in R package **glmgraph** (not maintained, archived on CRAN) **[Chen et al., 2015]**

Similar idea using eigendecomposition of the Laplacian

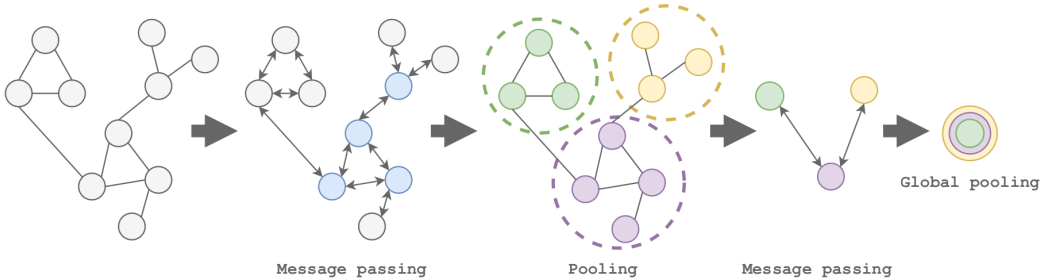
[Rapaport et al., 2007] (Y is irridiated / not irridiated)
L is symmetric and non-negative with $(\lambda_j)_{j=1,\dots,p}$ eigenvalues (in increasing order) and $(e_j)_{j=1,\dots,p}$ orthonormal eigenvectors

$$\arg\min_{\beta\in\mathbb{R}^p} \sum_{i=1}^{n} \left(\beta^\top \mathcal{S}(\mathbf{x}_i) - \mathbf{y}_i\right)^2 + C\|\beta\|_2^2 \qquad \text{with } \mathcal{S}(\mathbf{x}_i) = \sum_{j=1}^{p} \mathbf{x}_{ij}\phi(\lambda_j)e_j$$

Penalize non-smoothness of $\mathbf{x}_i$ over the network:

- low pass filter: $\phi(\lambda_j) = \lambda_j$ for $\lambda_j < \lambda^*$ and 0 otherwise
- attenuation of high frequencies $\phi(\lambda_j) = e^{-\beta\lambda_i}$

Alternative methods based on DL: Graph Neural Networks (GNN)



[Grattarola and Alippi, 2020]

Implemented in: Python libraries Spektral **[Grattarola and Alippi, 2020]** and PyTorch Geometric **[Fey and Lenssen, 2019]**

Message passing layers

- are the generalization of convolutional layers to graph data
- general concept introduced in **[Gilmer et al., 2017]**

Node features: $\mathbf{x}_j$ (for node v_j) $\longrightarrow$ Node latent representations: $h_j^t \in \mathbb{R}^K$ (computed iteratively for layers $t = 1, \ldots, T$)

$$h_j^{t+1} = F\left(h_j^t;\ \square_{j' \in \mathcal{N}(v_j)} \phi_t(h_j^t, h_{j'}^t)\right)$$

with

- $\square$: differential permutation invariant function (mean, sum...)
- ϕ_t: different possible shapes, involving weights learned during training phase

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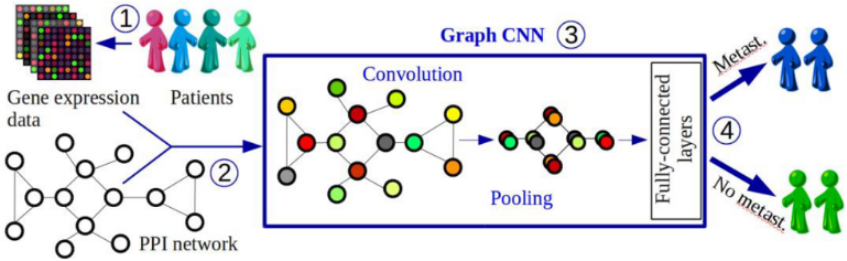
In particular: ChebNets **[Defferrard et al., 2016]** (based on Laplacian low band filtering)

Details

Several references show usefulness of GNN in predictive biology

[Chereda et al., 2019, Ramirez et al., 2020, McDermott et al., 2020, Chereda et al., 2021]



Replication study with negative control and simulated data



[Brouard et al., 2024]

Datasets:

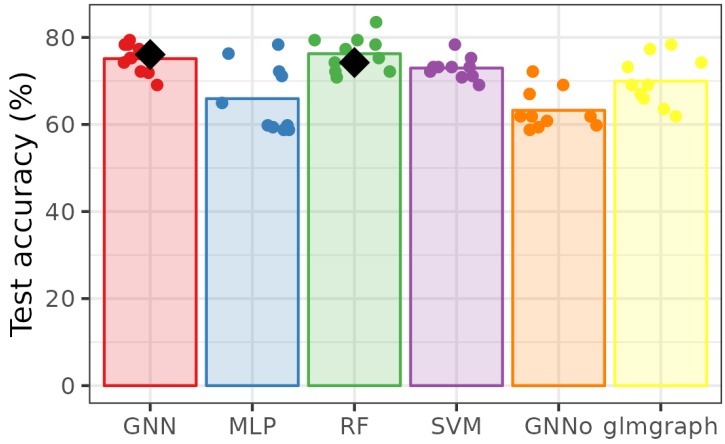
- **BreastCancer** **[Chereda et al., 2019, Chereda et al., 2021]**
  - 969 breast cancer patients belonging to 2 classes:
    - 393 with distant metastasis within the first five years
    - 576 without metastasis having the last follow-up between 5 and 10 years
  - graph : PPI network with 6888 nodes (main connected component)
- CancerType, F1000 ($\times 3$)
- + simulated data: with a mecanistic model and known gene regulatory network **sismonr** **[Angelin-Bonnet et al., 2020]** and DREAM5 dataset **[Marbach et al., 2012]**

Methodology of the replication study

- tested methods: GNN, RF, SVC, perceptron (with or without regularization), glmgraph (including a 5-fold CV to tune hyperparameters)
- with different networks (as negative control): PPI network, correlation network, random network, complete network
- methodology: 10-fold CV (same folds for all methods)

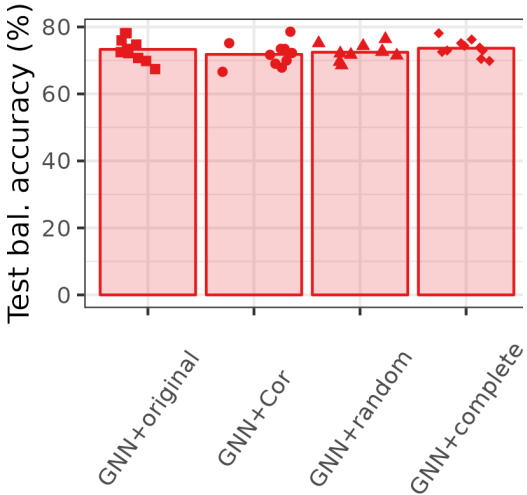
Take home messages from BreastCancer data [Chereda et al., 2021]

GNN results are reproducible but other (less computationnally demanding) methods are as good or better

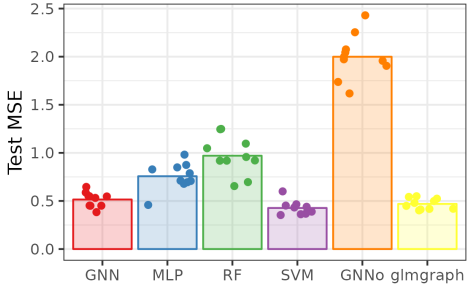


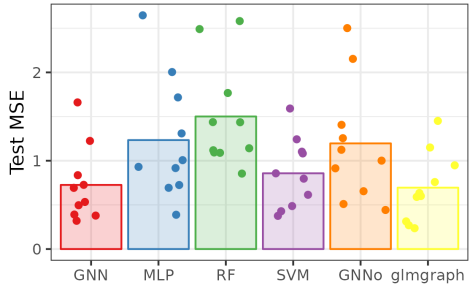
Take home messages from BreastCancer data [Chereda et al., 2021]

Provided network does not influence accuracy for GNN



What about simulated datasets?





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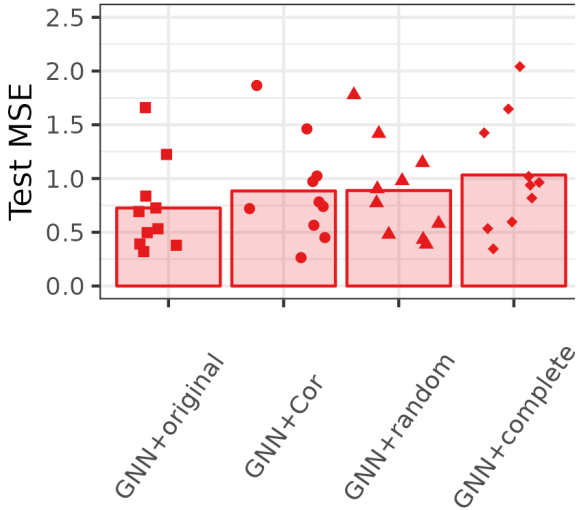


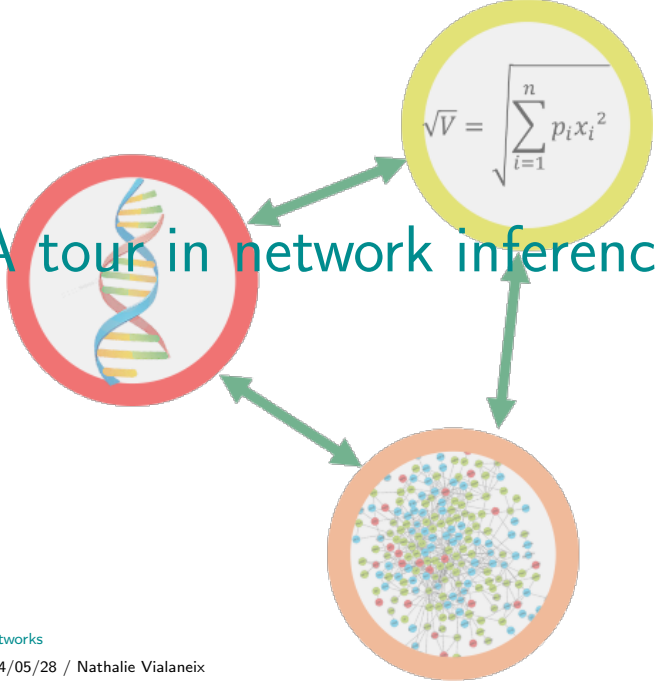
Take home messages

- Reproducibility / replication issues

- If knowing the regulation network can improve inference,
  - GNN are probably not the best candidate at the moment to use this information in an accurate way

  - knowledge on regulation network needs to be good

A tour in network inference



What is network inference?

$(n \times p)$ gene expression matrix $\mathbf{X}$

$\downarrow$

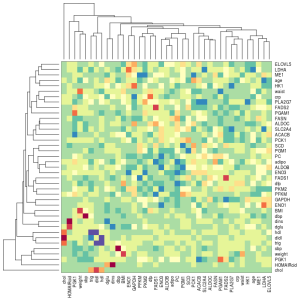
gene network (graph $\mathcal{G} = (V, E)$):

- nodes $V = \{1, \ldots, p\}$: genes
- edges $E \subset V \times V$: "dependency" between gene expressions

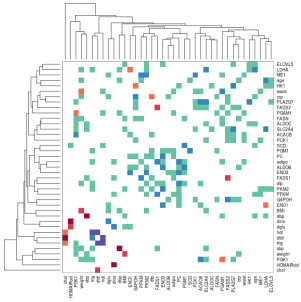
Usually: $n \ll p$

Main directions to address network inference

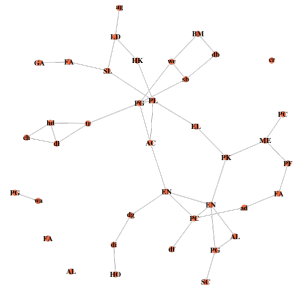
- Most used: "Relevance" network [**Butte and Kohane, 1999**, **Butte and Kohane, 2000**]: correlations (or MI) + threshold



"Correlations"



Thresholding



Network

Main directions to address network inference

- Most used: "Relevance" network **[Butte and Kohane, 1999, Butte and Kohane, 2000]**: correlations (or MI) + threshold

- GGM: Under $\mathbf{X}_i$ i.i.d. $\sim \mathcal{N}_p(0, \Sigma)$: edge between j and j' $\Leftrightarrow \mathbb{C}\mathrm{or}\left(X^j, X^{j'} | (X^k)_{k \neq j,j'}\right) \neq 0$
  - Edge between j and j' $\Leftrightarrow \left[\Sigma^{-1}\right]_{jj'} \neq 0$ **[Friedman et al., 2008]**
  - Edge between j and j' $\Leftrightarrow \beta_{jj'} \neq 0$ in

$$X^j = \sum_{j' \neq j} \beta_{jj'} X^{j'} + \epsilon_j$$

[Meinshausen and Bühlmann, 2006]

Many variants to account for discrete input data, design of the experiment, network structure, priors, ...

[Ambroise et al., 2009, Chiquet et al., 2011, Chiquet et al., 2016, Mohan et al., 2012, Gallopin et al., 2013, Villa-Vialaneix et al., 2014, Chiquet et al., 2021] ...

Main directions to address network inference

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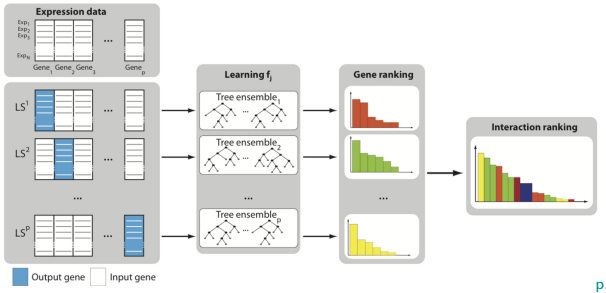
- Random forest: [**Huynh-Thu et al., 2010**] **GENIE3**

$$\forall j,\ X^j = F_j\left(\{X^{j'}\}_{j' \neq j}\right) + \epsilon_j$$

and many variants [**Aibar et al., 2017**, **Petralia et al., 2015**, **Cassan et al., 2023**]



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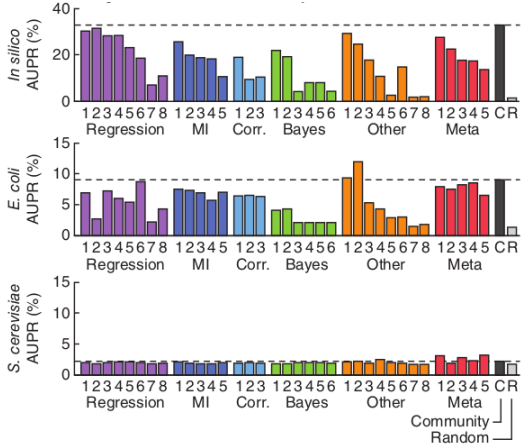
- Random forest: [**Huynh-Thu et al., 2010**] **GENIE3**
- Variational auto-encoder: [**Yu et al., 2019**, **Shu et al., 2021**] **DeepSEM** Details

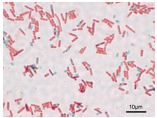
Method evaluation (DREAM4/5 challenges)



[Marbach et al., 2012]

- with known list of regulators, RF is often the best
- on higher organisms, no better than random guess

Insights into “methods / regulation mechanisms” relationships

Bacillus subtilis:

- $p \simeq 3,900$ genes / $n = 269$ experiments **[Nicolas et al., 2012]**
- regulation network **[Faria et al., 2016]**

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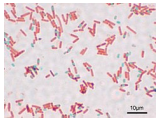

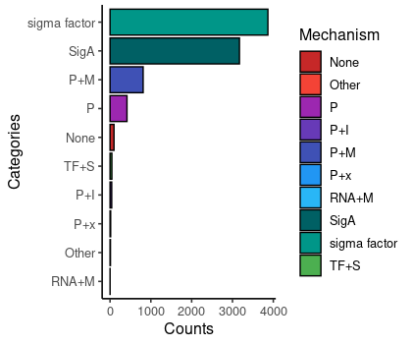

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- $p \simeq 3,900$ genes / $n = 269$ experiments **[Nicolas et al., 2012]**
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- direct regulations: σ factors or P/TF (transcription factor)
- indirect regulations: involving something outside product of gene expression

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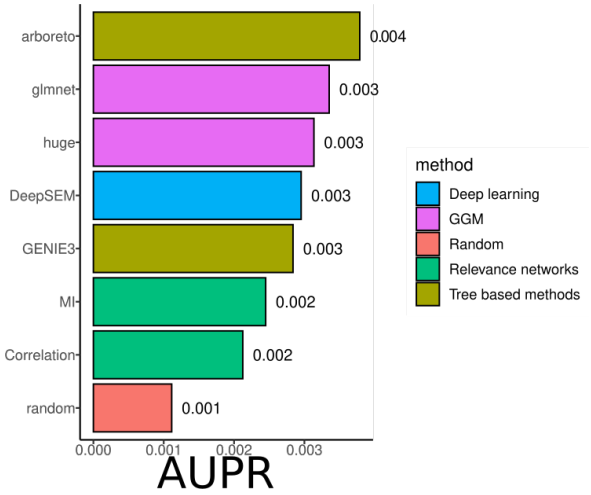

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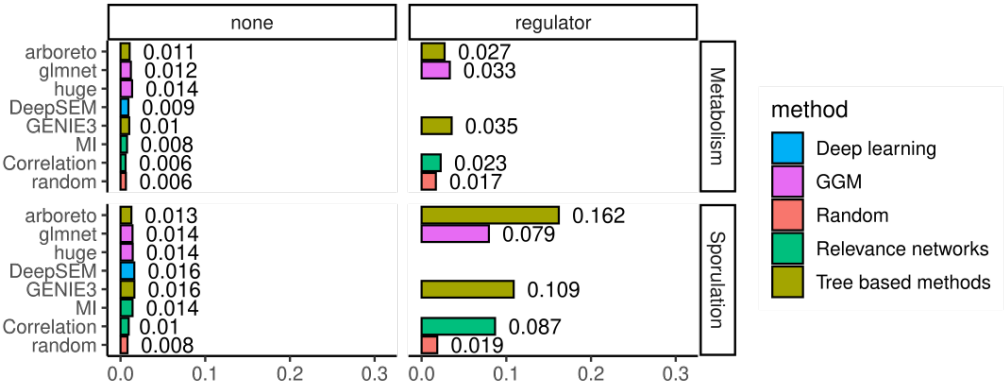
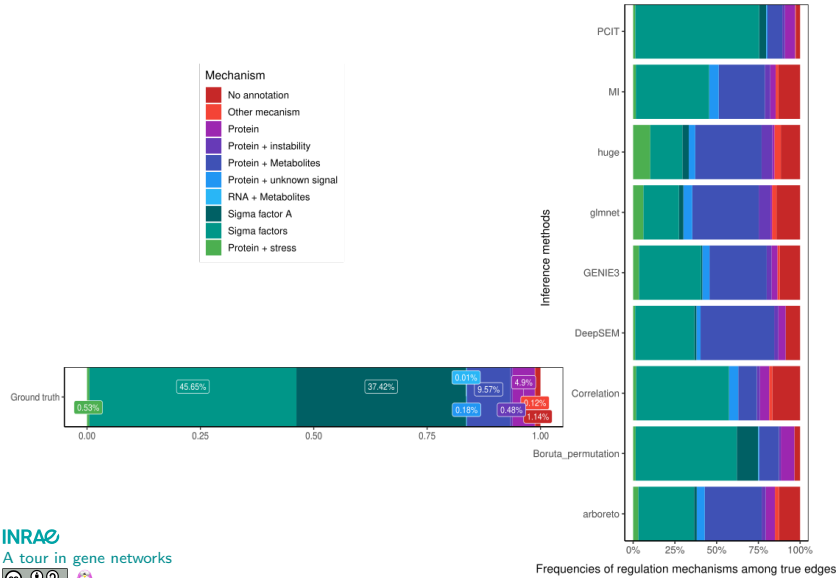


Insights into “methods / regulation mechanisms” relationships



Conclusion and possible ways to go...

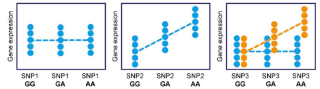
- When completely agnostic, network inference methods are not able to properly find gene-gene regulations ⇒ include other (experimental or knowledge) data **[Petralia et al., 2015, Cassan et al., 2023]**

- But, network clusters are biologically meaningfull

- Prediction beyond purely genetic is especially difficult ⇒ toward a more precise model of biological mechanisms? (hybrid statistical / deterministic models) **[Ventre et al., 2023]**

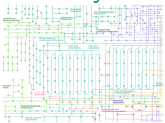
Thank you for your attention! More about omics?

Breeds/Ecotypes in GWAS



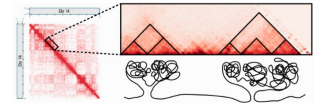
Jeong Hwan Ko "Données omiques" (10h20 today)

Pathway based metabolomics analysis



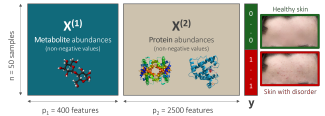
Camille Guilmineau "Multi-omique" (16h20 Thursday)

3D DNA structure



Élise Jorge "Données omiques" (11h05 today)

NMF for multi-omic integration



Aurélie Mercadié "Multi-omique" (15h35 Thursday)

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Credits

(unofficial) Beamer template made with the help of Thomas Schiex, Matthias Zytnicki and Andreea Dreau: https://forgemia.inra.fr/nathalie.villa-vialaneix/bainrae

- page 2: DNA image adapted from "double-stranded DNA" by MesserWoland, WikiMedia Commons and right arrow adapted from "Red short left arrow" from Ariel196, WikiMedia Commons
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- page 7: image from KEGG pathway is from https://www.genome.jp, image from Protein-Protein interaction (right) is from "RNAseInhibitor-RNAse complex" by Dcrjsr, Wikimedia Commons
- page 9: image of Breast Cancer is from "Breast cancer" by SMART-Servier Medical Art, part of Laboratoires Servier, Wikimedia Commons
- page 32: "microscopic image of the bacterial spore formation of Bacillus subtilis(ATCC 6633) Spore staining, magnification:1,000. (green) spores, (red) vegetatives" by Y tambe, WikiMedia Commons
- page 37: GWAS image from **[Quach and Quintana-Murci, 2017]** and 3D DNA image from **[Weinreb and Raphael, 2016]**

Architecture of the GCN used in Chereda et al., 2019, 2021

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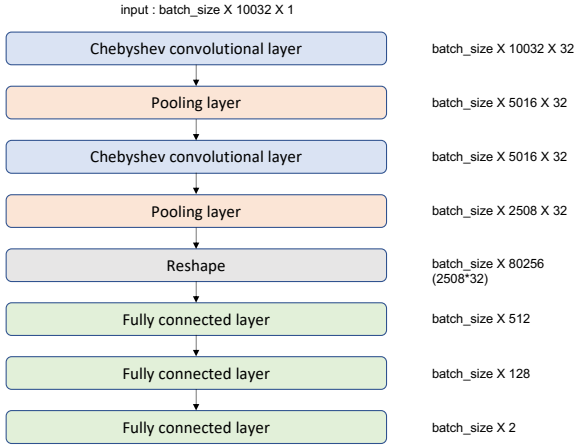

Convolutional layer

Back

- **Chebyshev convolutional layer**:
  - Spectral convolution on graph based on Laplacian low band filtering

$$y = \sum_{k=0}^{K} \theta_k T_k \left(\frac{2L}{\lambda_{max}} - I \right) x$$

where T_k are Chebyshev polynomials .

- **Graph convolutional layer**:
  - linear formulation wrt L by considering the case where $K = 1$
  - approximation by restraining the number of parameters

$$y = \theta \tilde{D}^{-1/2} \tilde{A} \tilde{D}^{-1/2} x, \quad \text{where } \tilde{A} = A + I$$

Graph coarsening [Defferrard et al., 2016]

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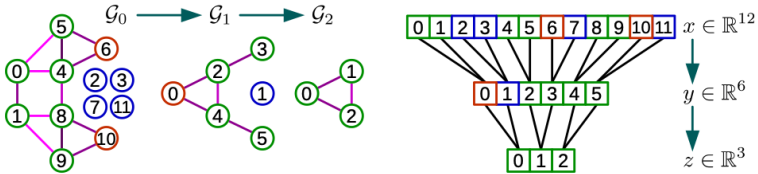

- Graclus algorithm: computes successive coarser versions of the graph
- clustering objective: normalized cut $W_{ij}\left(\frac{1}{d_i}+\frac{1}{d_j}\right)$
- Creation of a balanced binary tree: fake (disconnected) nodes are added to pair with singletons
- Vertices are then rearranged
  $\rightarrow$ pooling is analog to pooling a regular 1D signal

Implementation of the model of [Chereda et al., 2021] using Keras and Spektral

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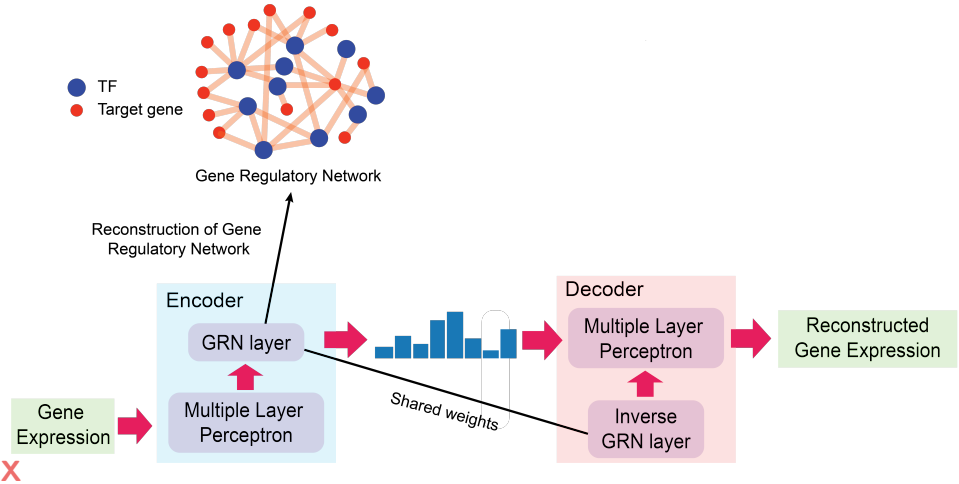
- Layers:
  - Convolutional layers: Spektral (ChebConv)
  - Pooling layers: the coarsening from [Defferrard et al., 2016] is computed in the preprocessing and then a max pooling of size 2 is used.
  - Fully connected layers: Keras (dense) with ℓ_2 regularization
- For creating mini-batches data, we use the mixed data mode of Spektral (single graph and different node attributes)
- The GNN model had to be adapted to take into account the different coarsened graphs

DeepSEM

Back

Variational auto-encoder: [Yu et al., 2019, Shu et al., 2021] DeepSEM



DeepSEM

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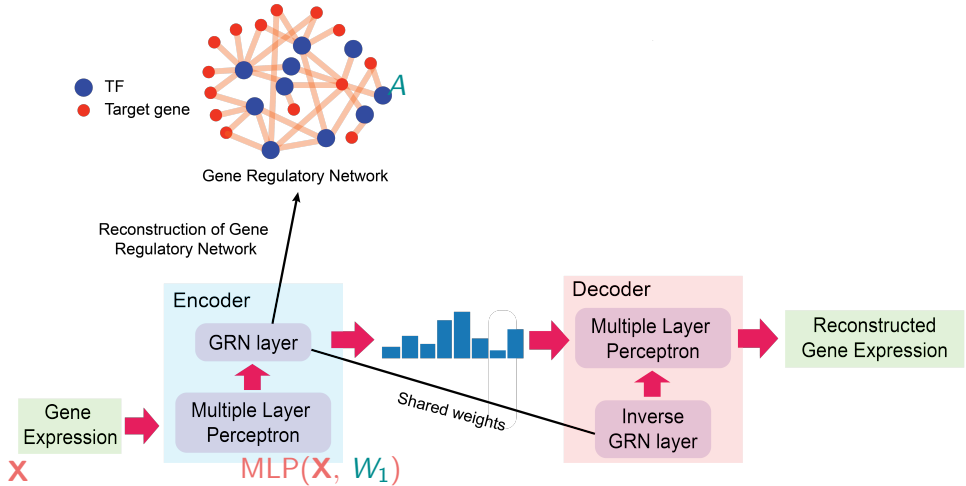
Variational auto-encoder: [Yu et al., 2019, Shu et al., 2021] DeepSEM



DeepSEM

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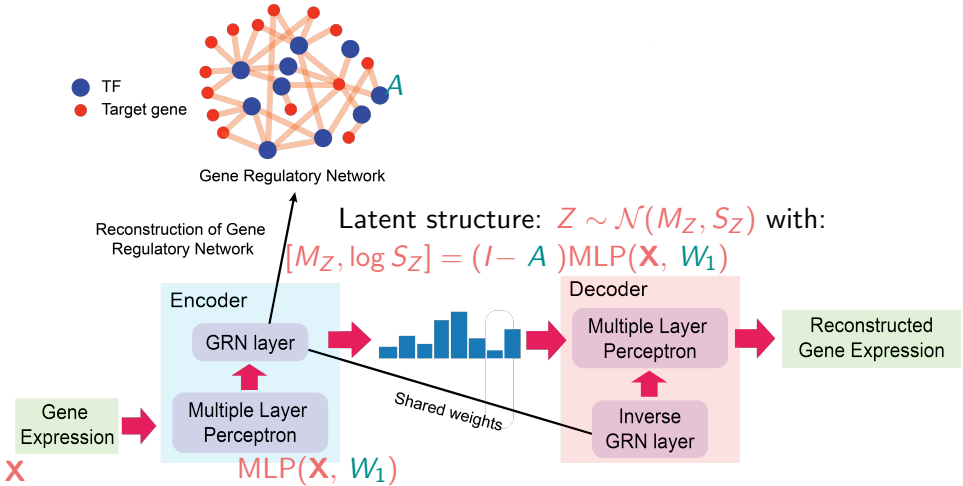
Variational auto-encoder: [Yu et al., 2019, Shu et al., 2021] DeepSEM



DeepSEM

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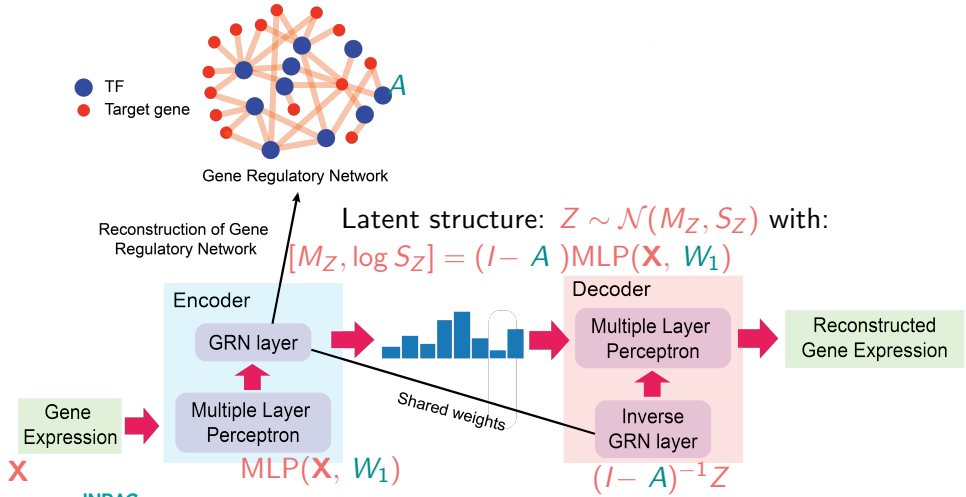
Variational auto-encoder: [Yu et al., 2019, Shu et al., 2021] DeepSEM



DeepSEM

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Variational auto-encoder: [Yu et al., 2019, Shu et al., 2021] DeepSEM