Comparison of network inference packages and methods for multiple networks inference

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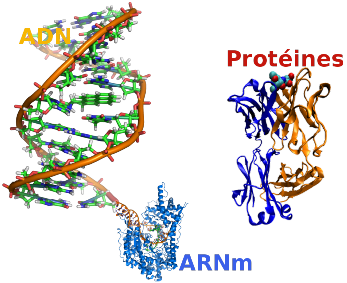
Joint work with **Nicolas Edwards**, **Laurence Liaubet**, **Nathalie Viguerie** & **Magali SanCristobal**

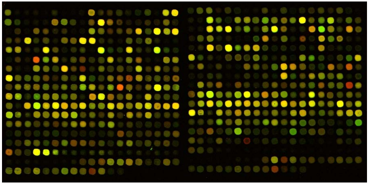
Plan

1. From transcriptomic data to network
2. Network inference and multiple networks inference using R
3. Simulations

Transcriptome

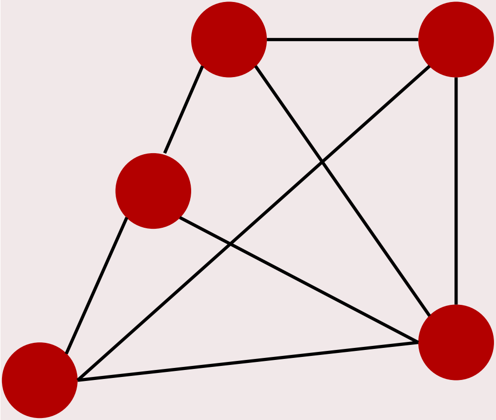
- **DNA** contains the genetic instructions used in the development and functioning of living organims
- Molecular unit of the DNA, **genes**, are not all identically **expressed** in a given cell: it is assessed by means of the quantity of the corresponding mRNA
- Genes expression can be measured by microarray, RT PCR...: **transcriptomic data**





Modelling multiple interactions between genes with a network

Co-expression networks



- **nodes**: genes
- **edges**: “direct” co-expression between two genes

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Co-expression networks

- **nodes**: genes
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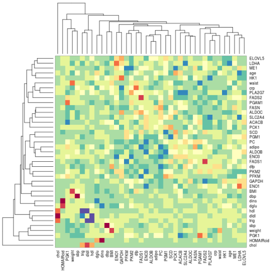
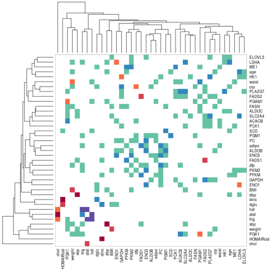
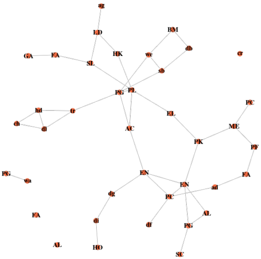
Method:



“Correlations”



Thresholding



Graph

Multiple networks inference

Transcriptomic data coming from several different conditions.

Examples:

- genes expression from pig muscle in **Landrace** and **Large white** breeds;
- genes expression from obese humans **after** and **before** a diet.

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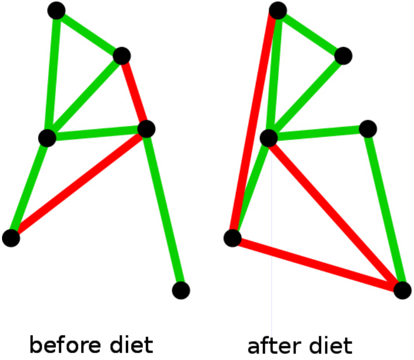

before diet

after diet

- **Assumption**: A common functioning exists regardless the condition;
- Which genes are correlated **independently from/depending on** the condition?

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Theoretical framework

Gaussian Graphical Models (GGM) $X \sim \mathcal{N}(0, \Sigma)$ Seminal work **[Schäfer and Strimmer, 2005]**, **GeneNet**: estimation of the **partial correlations**

$$\pi_{jj'} = \mathrm{Cor}(X^j, X^{j'} | X^k, k \neq j, j')$$

(by using the inverse of $\widehat{\Sigma} + \lambda\mathbb{I}$) and edges selection by a Bayesian test based on a mixture model.

Theoretical framework

Gaussian Graphical Models (GGM) $X \sim \mathcal{N}(0, \Sigma)$ Edges selection by sparse penalty: **graphical LASSO** **[Meinshausen and Bühlmann, 2006, Friedman et al., 2008]**, **glasso**:

$$X^j = \sum_{k \neq j} \beta_{jk} X^k + \epsilon.$$

where $(\beta_{jk})_{jk}$ are estimated by

$$\max_{(\beta_{jk})_{k \neq j}} \left(\log \mathrm{ML}_j - \lambda \sum_{k \neq j} |\beta_{jk}| \right).$$

β_{jk} is related to $S = \Sigma^{-1}$ by $\beta_{jk} = -\frac{S_{jk}}{S_{jj}}$.

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Other related packages: **parcor** (different regularization methods for GGM, CV selection), **GGMselect** (network selection among a family): not used here

Multiple networks

Independent estimations: if $c = 1, \ldots, C$ are different samples (or "conditions", e.g., breeds or before/after diet...)

$$\max_{(\beta_{jk}^c)_{k\neq j, c=1,\ldots,C}} \sum_c \left(\log \mathrm{ML}_j^c - \lambda \sum_{k\neq j} |\beta_{jk}^c| \right).$$

Multiple networks

Independent estimations: if $c = 1, \ldots, C$ are different samples (or "conditions", e.g., breeds or before/after diet...)

$$\max_{(\beta^c_{jk})_{k\neq j, c=1,\ldots,C}} \sum_c \left(\log \mathrm{ML}^c_j - \lambda \sum_{k\neq j} |\beta^c_{jk}| \right).$$

Joint estimations:

Implemented in the package **simone**, **[Chiquet et al., 2011]**

GroupLasso Consensual network between conditions (enforces identical edges by a group LASSO penalty)

CoopLasso Sign-coherent network between conditions (prevents edges that corresponds to partial correlations having different signs; thus allows one to obtain a few differences between the conditions)

Intertwined In GLasso replace $\widehat{\Sigma}^c$ by $1/2\widehat{\Sigma}^c + 1/2\overline{\Sigma}$ where $\overline{\Sigma} = \frac{1}{C}\sum_c \widehat{\Sigma}^c$

Multiple networks

Independent estimations: if $c = 1, \dots, C$ are different samples (or "conditions", e.g., breeds or before/after diet...)

$$\max_{(\beta_{jk}^c)_{k \neq j, c=1,\dots,C}} \sum_c \left(\log \mathrm{ML}_j^c - \lambda \sum_{k \neq j} |\beta_{jk}^c| \right).$$

Joint estimations: Additional tested approaches:

- Use the fact that individuals are paired (if concerned) to compute the partial correlations: $\widehat{\mathbf{X}}_i^c = 1/2\mathbf{X}_i^c + 1/2\overline{\mathbf{X}_i}$ with $\overline{\mathbf{X}_i} = \sum_c \widehat{\mathbf{X}}_i^c$ (implemented with **GeneNet** and **simone**)
- Combine the partial correlations instead of the correlations as in **Intertwined** (implemented from independent estimations obtained using **simone**, called "therese")

Tested packages and features

	Indep.	Joint	Selection?	Inputs	Outputs
GeneNet	[1]	No	confidence threshold	X	$(\pi_{ij})_{ij}$
glasso	[2,3]	No	none (but LASSO path is available)	$\widehat{\Sigma}$	$(S_{ij})_{ij}$
simone	[2,3]	Yes	number of edges AIC, BIC (LASSO path)	X	$(S_{ij})_{ij}$

with

[1] **[Schäfer and Strimmer, 2005]**

[2] **[Meinshausen and Bühlmann, 2006]**

[3] **[Friedman et al., 2008]**

not shown: CV selection is not included in **glasso** and **simone**, but it can be implemented (be careful to the internal scaling and to the outputs)

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Data

Datasets coming from

The ANR project “DéLiSus” (“caractérisations génétique et phénotypique fines de populations porcines françaises”, genetic and phenotypic variability of French pigs)

The pan-European project “DiOGenes” (Diet, Obesity and Genes: new insight on obesity problems and routes to prevention)

Datasets description

Real datasets

“DiOGenes” dataset:

- **variables**: 39 variables (genes expressions and clinical variables)
- **conditions**: before/after a diet (paired individuals: 204 obese women)

“DeLiSus” dataset:

- **variables**: expression of 123 genes
- **conditions**: two breeds (33 “Landrace” and 51 “Large white”)

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Real datasets

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- **variables**: expression of 123 genes
- **conditions**: two breeds (33 "Landrace" and 51 "Large white")

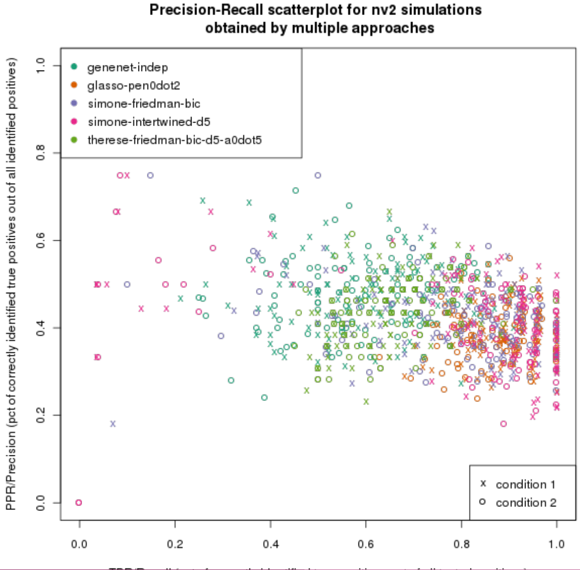
Simulated dataset

To compare methods, a dataset was simulated from a GGM (with **simone**):

- **underlying network**: 39 variables with 5 groups of preferential attachment and a density equal to approximatly 3-4%.
- **children networks**: two networks obtained by randomly permuting 10% of the edges;
- **variables**: 2 × 204 observations of a GGM coming from these networks (observations are not pairwise).

Simulation results and conclusions

All methods



$$\textbf{Precision} = \frac{\text{tp}}{\text{p}}$$

$$\textbf{Recall} = \frac{\text{tp}}{\text{tp}+\text{fn}}$$

Simulation results and conclusions

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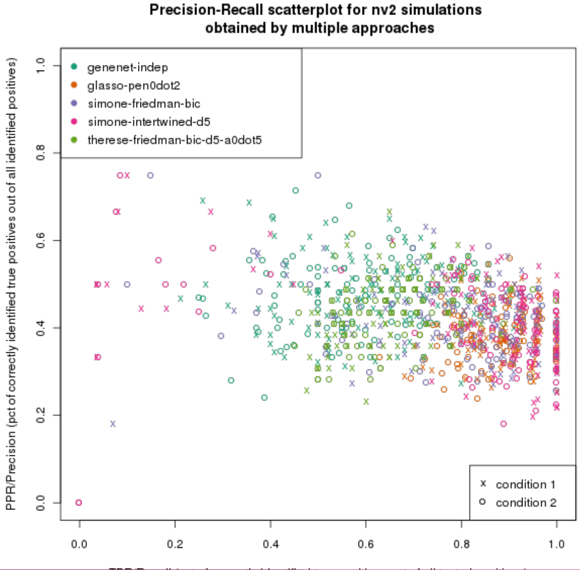

Precision$= \frac{\text{tp}}{\text{p}}$

Recall$= \frac{\text{tp}}{\text{tp}+\text{fn}}$

- **glasso** performs well (with very low variability) but no real solution for tuning;
- **simone** performs well (especially joint methods), with an automatic tuning but large variability;
- "therese" has a low variability but no real solution for tuning;
- **GeneNet** has a low recall and a low variability.

Simulation results and conclusions

Numerical performances

Graph densities

True density: 3.57% (on average)

- **GeneNet** (automatic): 4.38%
- **glasso** (manual): 8.14%
- **simone** (indep, BIC): 6.65% and **simone** (joint, BIC): 5.87%
- “therese” (semi manual): 5.26%

Simulation results and conclusions

Numerical performances

Graph densities

True density: 3.57% (on average)

- **GeneNet** (automatic): 4.38%
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Shared edges between conditions

Truth: 20.28% (on average)

- **GeneNet** (automatic): 15.95%
- **glasso** (manual): 32.74%
- **simone** (indep, BIC): 26.69% and **simone** (joint, BIC): 31.15%
- "therese" (semi manual): 30.92%

“DiOGenes” dataset (39 variables, 204 obese women, fixed density 5%)

	Density	Transitivity	% shared
[1] **GeneNet**	0.06	0.22	0.68
[2] **GeneNet** (paired)	0.09	0.24	0.84
[3] **simone** (indep., Fried.)	0.05	0.52	0.76
[4] **simone**, CoopLasso	0.06	0.30	1.00
[5] **simone**, GroupLasso	0.06	0.30	1.00
[6] **simone**, intertwined	0.05	0.37	0.97
[7] **simone**, paired	0.04	0.52	0.94
[8] “therese”	0.05	0.46	0.82

	[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]
[1]	1.00	0.98	0.45	0.61	0.61	0.53	0.42	0.42
[2]		1.00	0.58	0.66	0.66	0.66	0.55	0.58
[3]			1.00	0.79	0.79	0.84	1.00	0.92
[4]				1.00	1.00	0.95	0.76	0.76
[5]					1.00	0.95	0.76	0.76
[6]						1.00	0.82	0.79
[7]							1.00	0.97
[8]								1.00

“DeLiSus” dataset (restricted dataset with 84 genes (51 pigs))

	Density	Transitivity	% shared
[1] **GeneNet**	0.00	0.71	0.46
[2] **simone**, MB-AND	0.05	0.08	0.17
[3] **simone**, Fried.	0.05	0.19	0.22
[4] **simone**, intertwined	0.05	0.09	0.52
[5] **simone**, CoopLasso	0.06	0.09	0.88
[6] **simone**, GroupLasso	0.04	0.07	0.99
[7] “therese”	0.05	0.17	0.66

	[1]	[2]	[3]	[4]	[5]	[6]	[7]
[1]	1.00	0.00	0.00	0.00	0.00	0.00	0.00
[2]		1.00	0.71	0.76	0.64	0.56	0.57
[3]			1.00	0.67	0.55	0.53	0.78
[4]				1.00	0.80	0.67	0.58
[5]					1.00	0.84	0.60
[6]						1.00	0.74
[7]							1.00

Conclusion

- **simulations**: BIC is not always relevant ⇒ target density, CV, **GGMselect**...? Joined methods produce more shared edges between conditions

Conclusion

- **simulations**: BIC is not always relevant ⇒ target density, CV, **GGMselect**...? Joined methods produce more shared edges between conditions
- **real life datasets**
  - **low dimension case**: large consensus between methods; joined methods are too similar (except maybe paired **GeneNet** and "therese")
  - **larger dimension case**: methods are less consensual; GroupLasso and CoopLasso still produce too much shared edges
  - **very large dimension** *(not shown)*: 464 gene expressions for $51 + 33$ pigs gave very bad performances: on real dataset, some methods were unable to produce results (and BIC selected graphs with no edge); hence, on simulated datasets with the same sample size and dimension, the recall was always very low.

Collaboration

Any questions?...

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Chiquet, J., Grandvalet, Y., and Ambroise, C. (2011).
Inferring multiple graphical structures.
Statistics and Computing, 21(4):537–553.

Friedman, J., Hastie, T., and Tibshirani, R. (2008).
Sparse inverse covariance estimation with the graphical lasso.
Biostatistics, 9(3):432–441.

Meinshausen, N. and Bühlmann, P. (2006).
High dimensional graphs and variable selection with the lasso.
Annals of Statistic, 34(3):1436–1462.

Schäfer, J. and Strimmer, K. (2005).
An empirical bayes approach to inferring large-scale gene association networks.
Bioinformatics, 21(6):754–764.