

Information-Theoretic Network Inference

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CIL contact day

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Example: Gene Network

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Gene interaction:

- Biological dogma: gene \rightarrow RNA \rightarrow protein
- A protein can block or activate another gene

Network:

- Each node of the network is gene (a variable).
- There is a link between two nodes if there is a direct interaction between them.

Interests:

- Knowledge representation
- Reverse engineering
- Drug discovery

Principle of Network Inference

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- input: Data, $m \times n$ matrix, where $DATA_{ij}$ is the RNA-concentration of G_i at experiment Exp_j (microarray)
- output: Network, $n \times n$ symmetric matrix, where NET_{ij} is the probability of a direct interaction between G_i and G_j

DATA	G_1	G_2	...	G_n
Exp 1	0.1	0.9	...	0.5
Exp 2	0.4	0.7	...	0.1
Exp 3	0.6	0.2	...	0.7
...
Exp m	0.2	0.3	...	0.8



NET	G_1	G_2	...	G_n
G_1	-	0.3	...	0.8
G_2	0.3	-	...	0.6
...	-	...
G_n	0.8	0.6	...	-

Known methods

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- Boolean Networks
- Bayesian Networks
- Differential Equation Networks
- Association Networks
 - Partial Correlation
 - Mutual Information (Information-Theoretic Networks)

Relevance Network

Definition (Mutual Information)

The *mutual information* between two random variables X_i and X_j is defined as,

$$I(X_i; X_j) = \sum_{x_i \in \mathcal{X}} \sum_{x_j \in \mathcal{X}} p(x_i, x_j) \log \left(\frac{p(x_i, x_j)}{p(x_i)p(x_j)} \right) \quad (1)$$

Discretize data + compute MI for all couples of genes

MIM	G_1	G_2	...	G_n
G_1	-	$I(G_1; G_2)$...	$I(G_1; G_n)$
G_2	$I(G_1; G_2)$	-	...	$I(G_2; G_n)$
...	-	...
G_n	$I(G_1; G_n)$	$I(G_2; G_n)$...	-

RELNET: False Positive Trends

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- Normalize the matrix (MIM) and consider it as the inferred network [Butte and Kohane, 2000]
- The method is $O(m \times n^2)$
- False Positive Trends:
Assume G_1 influence G_3 through G_2

$$G_1 \rightarrow G_2 \rightarrow G_3$$

Then $I(G_1; G_2)$ and $I(G_2; G_3)$ will be high
but also $I(G_1; G_3) \rightarrow$ add false link between G_1 and G_3

Algorithm for the Reconstruction of Accurate Cellular Network [Margolin et al., 2006]

There are three cases of indirect interaction with three variables:

- $G_1 \rightarrow G_2 \rightarrow G_3$
- $G_1 \leftarrow G_2 \rightarrow G_3$
- $G_1 \rightarrow G_2 \leftarrow G_3$

Whatever the case, $I(G_1; G_3) < I(G_1; G_2)$ and $I(G_1; G_3) < I(G_2; G_3)$ by the data processing inequality

- For all triples of genes suppress the weakest link among them.

ARACNE: False Negative Trends

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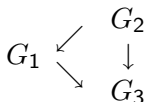
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- Aracne is $O(m \times n^2 + n^3)$
- False Negative Trends:
Assume a triple interaction



The algorithm will suppress a good link

Minimum Redundancy - Maximum Relevance

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The minimum redundancy - maximum relevance (MRMR) criterion [Peng and Long, 2004] consists in

- selecting the variable that maximizes u_i , the relevance to the output Y ,

$$u_i = I(X_i; Y) \quad (2)$$

- and that minimizes the mean redundancy z_i with the already selected variable,

$$z_i = \frac{1}{d} \sum_{X_j \in X_S} I(X_i; X_j) \quad (3)$$

$$X_{MRMR} = \arg \max_{X_i \in X_{-S}} \{u_i - z_i\} \quad (4)$$

Mrmr Example

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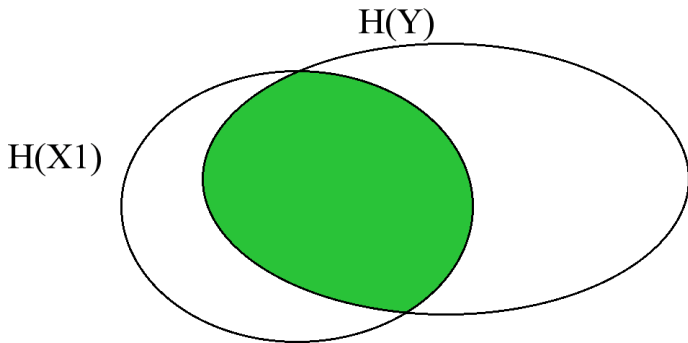
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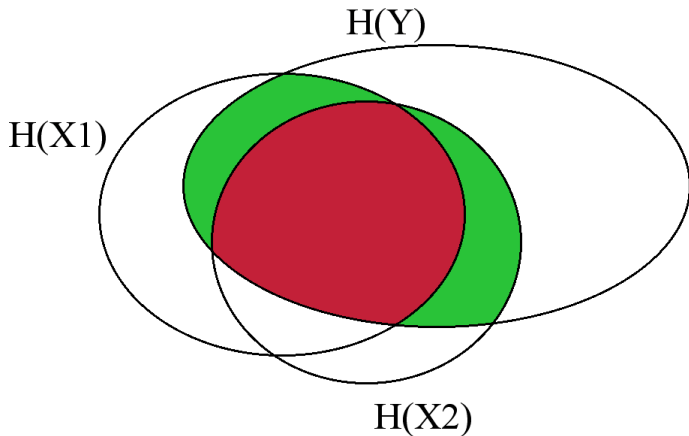
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Mrmr Example



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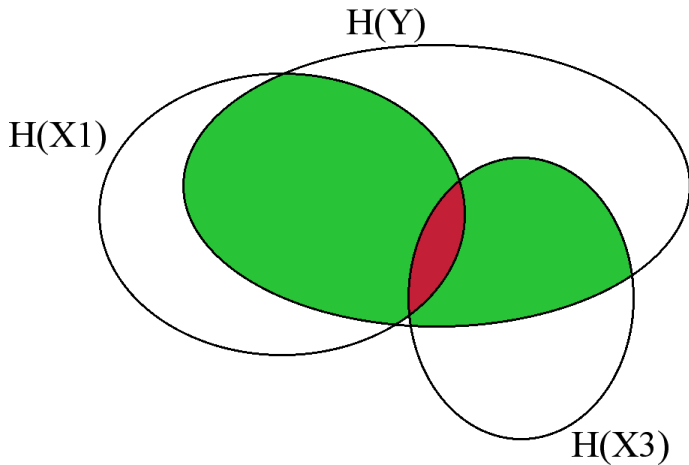
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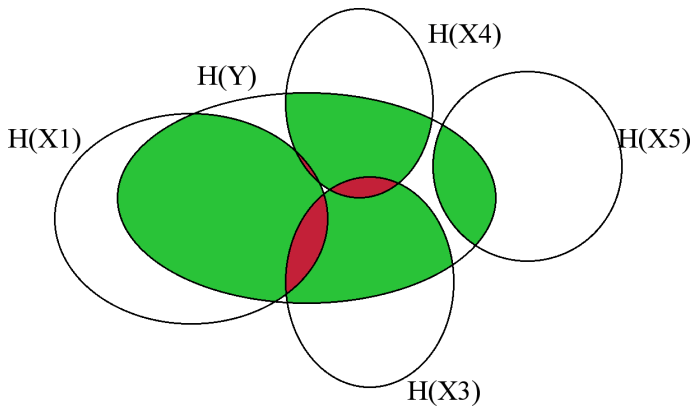
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Minimum Redundancy - Maximum Relevance

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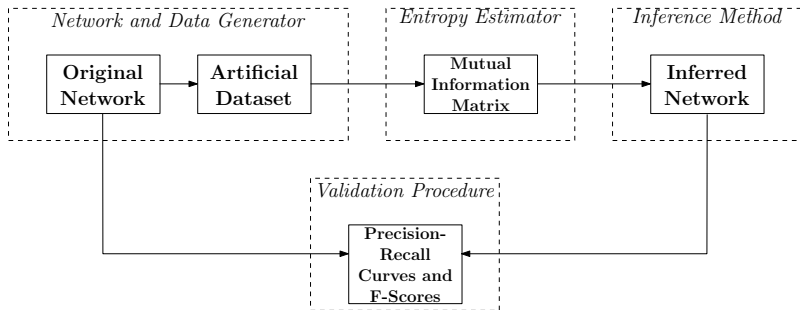
- Greedy approach selecting the variable with best trade-off relevance-redundancy
- Selection of a subset of variables (composed of the most independent ones)

Network Inference Algorithm :

- Compute the MIM, $O(m \times n^2)$
- For variable X_1 , compute the MRMR score of all the other variables, $O(n^2)$
- Repeat the operation for all variables, $O(n^3)$
- Normalize the score matrix, $O(n^2)$
- The method is $O(m \times n^2 + n^3)$

Experimental Framework

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Validation

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Table: Confusion matrix.

edge	actual positive	actual negative
inferred positive	TP	FP
inferred negative	FN	TN

Precision and Recall:

$$p = \frac{TP}{TP + FP}, \quad r = \frac{TP}{TP + FN}$$

F-Scores:

$$F_{\beta} = (1 + \beta^2) \frac{pr}{r + \beta^2 p},$$

A weighted harmonic average of precision and recall.

Datasets

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Table: The six artificial datasets generated, where n is the number of genes and m is the number of samples.

Dataset	Generator	Topology	n	m
dR1	sRogers	power-law tail	2000	1000
dR2	sRogers	power-law tail	1000	750
dR3	sRogers	power-law tail	600	600
dS1	SynTReN	<i>E. coli</i>	500	500
dS2	SynTReN	<i>E. coli</i>	300	300
dS3	SynTReN	<i>E. coli</i>	50	500

F-Scores

F-scores with $\beta = 1$ (precision as important as recall). The best score for each dataset is in boldface.

Dataset	RelNet	ARACNE	MRNet
1	0.24	0.28	0.26
2	0.25	0.36	0.29
3	0.25	0.45	0.45
4	0.09	0.06	0.10
5	0.16	0.12	0.19
6	0.18	0.11	0.24

F-Scores

F-scores with $\beta = 0.5$ (precision more important than recall).
The best score for each dataset is in boldface.

Dataset	RelNet	ARACNE	MRNet
1	0.29	0.37	0.38
2	0.31	0.38	0.39
3	0.32	0.49	0.52
4	0.07	0.08	0.13
5	0.13	0.14	0.15
6	0.13	0.15	0.20

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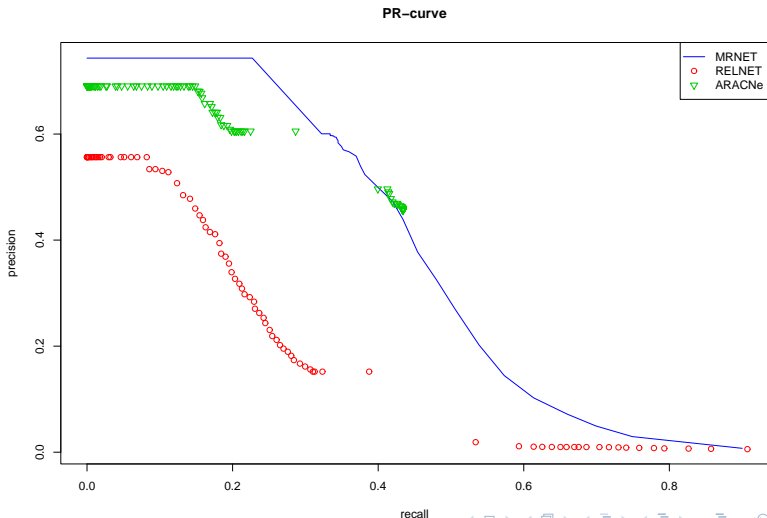
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Curves: DR3 (600,600)



Conclusions and Future Works

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Further work will focus on:

- the significativity of performances
- the robustness of the inference to noise and to the mutual information estimator
- analyzing real biological datasets

Bibliography

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