

Inferring mutual information networks using the *minet* package

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1 Introduction

The *minet* package provides a set of functions to infer mutual information networks from a dataset [10]. If fed with microarray data, the package returns a network where nodes denote genes and edges model statistical dependencies between genes. The weight of an edge provides evidence about the existence of a specific (e.g transcriptional) gene to gene interaction.

The inference proceeds in two steps. First, the Mutual Information Matrix (*MIM*) is computed, a square matrix whose MIM_{ij} term is the mutual information between gene X_i and X_j . Secondly, an inference algorithm takes the *MIM* matrix as input and attributes a score to each edge connecting a pair of nodes. Different entropy estimators are implemented in this package as well as different inference methods, namely **aracne**, **clr** and **mrnet** [1, 6, 9]. Also, the package integrates accuracy assessment tools, like PR-curves and ROC-curves, to compare the inferred network with a reference one.

This vignette guides the package user in :

1. Estimating the mutual information matrix.
2. Inferring a network modeling the interactions between the dataset's variables.
3. Comparing the inferred network to a network of known interactions in order to compute F_β - scores.
4. Plotting precision-recall and receiver operating characteristic curves.
5. Plotting the inferred network using the *Rgraphviz* package.

The data used in the following examples was generated using the *SynTReN* simulator [4]. This data generator uses a known network of interacting genes in order to generate gene expression levels for all the genes included in the network. Once the network is inferred from the generated data, it can be compared to the true underlying network in order to validate the inference algorithm.

2 Mutual Information Estimation

Mutual information networks are a subcategory of network inference methods. These methods set a link between two nodes if it exhibits a high score based on the mutual information between the nodes.

Mutual information networks rely on the computation of the mutual information matrix (MIM), a square matrix whose element

$$MIM_{ij} = I(X_i; X_j) = \sum_{x_i \in \mathcal{X}_i} \sum_{x_j \in \mathcal{X}_j} p(x_i, x_j) \log p(x_i) p(x_j)$$

is the mutual information between X_i and X_j , where $X_i \in \mathcal{X}, i = 1, \dots, n$, is a discrete random variable denoting the expression level of the i th gene.

2.1 Obtaining The Mutual Information Matrix

```
> library(minet)
> data(syn.data)
> estimator = "spearman"
> mim <- build.mim(syn.data, estimator)
> mim[1:5, 1:5]
```

	CDC11	SWI4	CDC10	SPT16	SWI4_SWI6
CDC11	0.0000000	6.9077553	6.9077553	0.2576434	2.409649
SWI4	6.9077553	0.0000000	6.9077553	0.2576434	2.409649
CDC10	6.9077553	6.9077553	0.0000000	0.2576434	2.409649
SPT16	0.2576434	0.2576434	0.2576434	0.0000000	0.219135
SWI4_SWI6	2.4096490	2.4096490	2.4096490	0.2191350	0.000000

In the above code, the mutual information matrix is built using the function `build.mim`. This function takes the dataset and one of the mutual information estimator explained in this section as input. All the estimators require discrete data values. The `discretize` function allows the user to choose between two binning algorithms.

3 Network Inference

Three network inference methods are available in the package : `aracne`, `clr` and `mrnet`. These receive as input the mutual information matrix and return the weighted adjacency matrix of the network. The network can be directly inferred from the dataset by using the `minet` function. This function takes as input the dataset, the name of the estimator and the name of the discretization method to be used as well as the number of bins to be used.

3.1 Obtaining The Network

In the following code, the `mrnet` algorithm is applied to the mutual information matrix estimated in the previous section:

```
> net <- mrnet(mim)
> net[1:5, 1:5]
```

	CDC11	SWI4	CDC10	SPT16	SWI4_SWI6
CDC11	0.000000	6.9077553	6.9077553	0	2.4096490
SWI4	6.907755	0.0000000	0.0000000	0	0.5476285
CDC10	6.907755	0.0000000	0.0000000	0	0.5476285
SPT16	0.000000	0.0000000	0.0000000	0	0.0000000
SWI4_SWI6	2.409649	0.5476285	0.5476285	0	0.0000000

The returned value is the weighted adjacency matrix of the network.

3.2 MRNET

The MRNET approach [9] consists in repeating a MRMR feature selection procedure for each variable of the dataset. The MRMR method [13] starts by selecting the variable X_i having the highest mutual information with the target Y . In the following steps, given a set \mathcal{S} of selected variables, the criterion updates \mathcal{S} by choosing the variable X_k that maximizes $I(X_k; Y) - \frac{1}{|\mathcal{S}|} \sum_{X_i \in \mathcal{S}} I(X_k; X_i)$. The weight of each pair X_i, X_j will be the maximum score between the one computed when X_i is the target and the one computed when X_j is the target.

3.3 CLR

The CLR algorithm [6] considers the MIM as the weighted adjacency matrix of the network but instead of using the information $I(X_i; X_j)$ as the weight of the link between features X_i and X_j , it takes into account the score $\sqrt{z_i^2 + z_j^2}$, where

$$z_i = \max \left\{ 0, \frac{I(X_i; X_j) - \mu_i}{\sigma_i} \right\}$$

and μ_i and σ_i are, respectively, the mean and the standard deviation of the empirical distribution of the mutual information values $I(X_i; X_k)$, $k = 1, \dots, n$.

3.4 ARACNE

The ARACNE algorithm [1] is based on the Data Processing Inequality. This inequality states that, if gene X_1 interacts with gene X_3 through gene X_2 , then

$$I(X_1; X_3) \leq \min(I(X_1; X_2), I(X_2; X_3))$$

The ARACNE procedure starts by assigning to each pair of nodes a weight equal to the mutual information. Then the weakest edge of each triplet is interpreted

EDGE	Infered	Not Infered
Exists	TP	FN
Doesn't Exist	FP	TN

Table 1: Confusion matrix

as an indirect interaction and is removed if the difference between the two lowest weights is above a threshold W_0 . The function `aracne` has an extra argument `eps` which is the numerical value of W_0 .

3.5 The minet function

The `minet` function infers directly the mutual information network from the input dataset. Besides the dataset, this function's arguments are the mutual information estimator, the inference method, the binning algorithm and the number of bins to be used. All the instructions used until now can then be summarized with the following call to `minet`:

```
> library(minet)
> data(syn.data)
> net <- minet(syn.data, method = "mrnet")
> net[1:5, 1:5]
```

	CDC11	SWI4	CDC10	SPT16	SWI4_SWI6
CDC11	0.0000000	1.00000000	1.00000000	0	0.34883242
SWI4	1.0000000	0.00000000	0.00000000	0	0.07927735
CDC10	1.0000000	0.00000000	0.00000000	0	0.07927735
SPT16	0.0000000	0.00000000	0.00000000	0	0.00000000
SWI4_SWI6	0.3488324	0.07927735	0.07927735	0	0.00000000

Note that in this case the returned object is the *normalized* weighted adjacency matrix of the network (i.e. the values range from 0 to 1).

4 Validation

4.1 Obtaining Confusion Matrices

The networks inferred using this package are weighted but many low weighted edges can be removed by using a threshold value. By setting to 0 all edges whose weight are lower than the threshold and to 1 the other edges weight, the network inference problem can be seen as a binary decision problem. The decision made by the algorithm can be summarized by a confusion matrix (see table 4.1).

In our case, the threshold value can be seen as the minimal edge weight required for the edge to be inferred : edges whose weight are strictly below the threshold are removed from the network. Then, a different confusion matrix

is obtained for each different threshold. The table returned by the `validate` function contains all the confusion matrices obtained with `steps` thresholds ranging from the lowest to the highest value of the edges weight.

```
> library(minet)
> data(syn.data)
> data(syn.net)
> net <- minet(syn.data)
> table <- validate(net, syn.net, steps = 20)
> table[1:10, ]
```

	thrsh	tp	fp	tn	fn
1	0.00	130	2370	0	0
2	0.05	52	126	2244	78
3	0.10	48	76	2294	82
4	0.15	48	70	2300	82
5	0.20	44	62	2308	86
6	0.25	44	48	2322	86
7	0.30	44	44	2326	86
8	0.35	40	26	2344	90
9	0.40	40	26	2344	90
10	0.45	40	26	2344	90

In the above code, the `validate` function compares the inferred network `net` to `syn.net`, the network underlying `syn.data`. Note that the true underlying network has to be a matrix containing values 1 (presence of the edge) or 0 (absence of the edge).

Each line of the returned table contains the threshold used and the confusion matrix obtained by comparing `syn.net` to the inferred network.

Note that the `validate` function distinguishes the following cases:

- Both networks are oriented
- Both networks are unoriented
- One of the network is oriented and the other unoriented

In the third case, the oriented network will be considered unoriented.

4.2 Using the Confusion Matrices

The confusion matrix summarizes the decisions made by the algorithm. Thus in order to compare inference algorithms, we compare their confusion matrix, more precisely, we compare several criteras that are derived from that matrix [3]:

- Precision: $p = \frac{TP}{TP+FP}$
- Recall: $r = \frac{TP}{TP+FN}$

- True Positive Rate: $tpr = \frac{TP}{TP+TN}$
- False Positive Rate: $fpr = \frac{FP}{FP+FN}$
- F_β -score: $F_\beta = (1 + \beta) \frac{pr}{\beta p + r}$

These scores are returned by the functions `rates`, `pr` and `fscores`. The functions `show.pr` and `show.roc` can be used to visualize precision-recall curves and receiver operating characteristic curves respectively. The `show.pr` function uses the precisions and recalls computed by the function `pr` and the `show.roc` relies on the rates returned by the `rates` function in order to plot receiver operating characteristic curves. All these functions take as input the data.frame returned by the `validate` function:

```
> library(minet)
> data(syn.data)
> data(syn.net)
> net1 <- minet(syn.data, method = "mrnet")
> net2 <- minet(syn.data, method = "clr")
> table1 <- validate(net1, syn.net, steps = 50)
> table2 <- validate(net2, syn.net, steps = 50)
```

Once the data.frames `table1` and `table2` are computed, we can use the function

- `pr(table)` to obtain precisions and recalls.
- `rates(table)` to obtain true positive rates and false positive rates.
- `fscores(table,beta)` to obtain F_β - scores.

Both functions `show.pr` and `show.roc` return the device associated to the plotting window used. This allows the user to plot several curves on the same figure. The following code generates the curves.

```
> dev <- show.pr(table1, pch = 2, type = "b", col = "green")
> show.pr(table2, device = dev, pch = 1, type = "b", col = "blue")
```

pdf
2

```
> dev <- show.roc(table1, type = "b", col = "green")
> show.roc(table2, device = dev, type = "b", col = "blue")
```

pdf
3

References

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