Causal Computational Models for Gene Regulatory Networks

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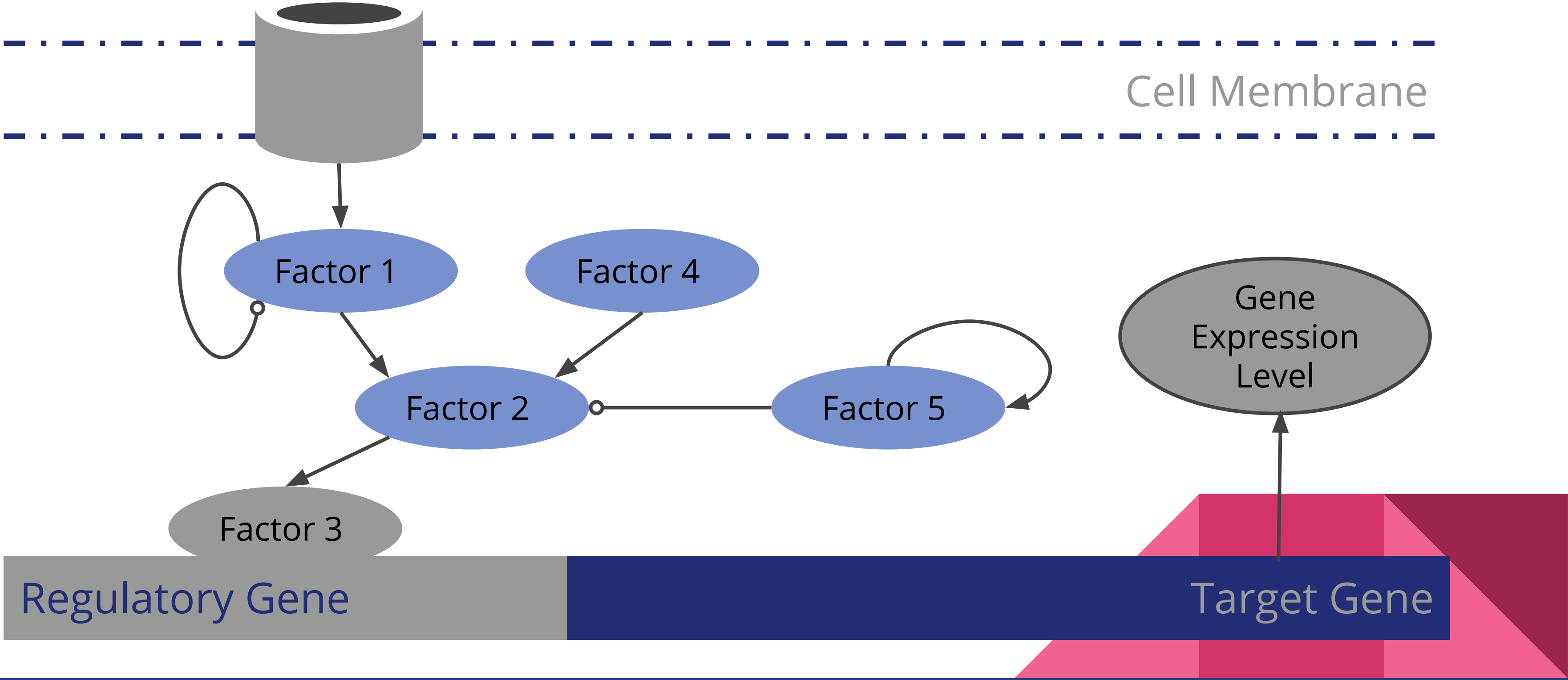
Gene Regulatory Networks



Problem Statement

To create computational models of GRNs,

which capture causal interactions between the genes ,

with emphasis on reducing dimensionality of the problem,

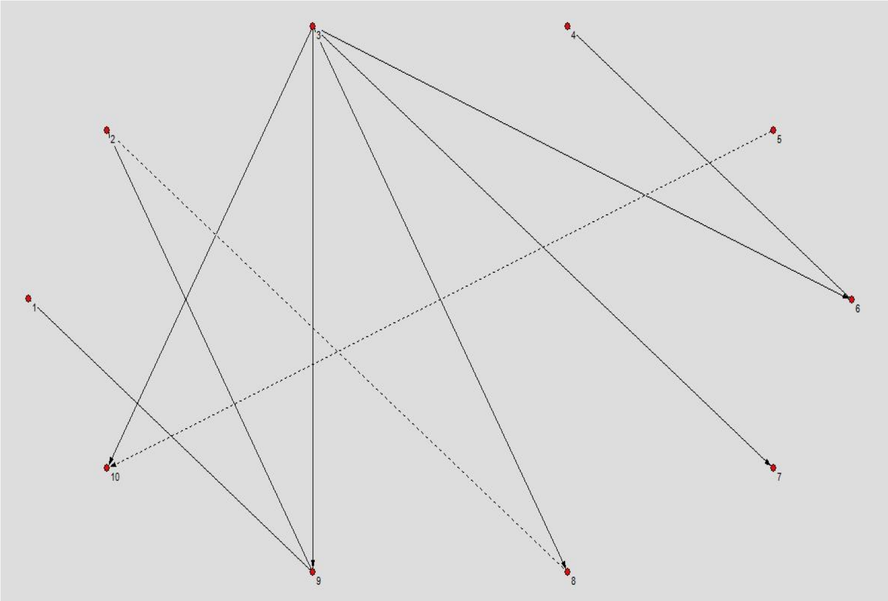
to allow wet lab work for in/validation for disease networks.

Data

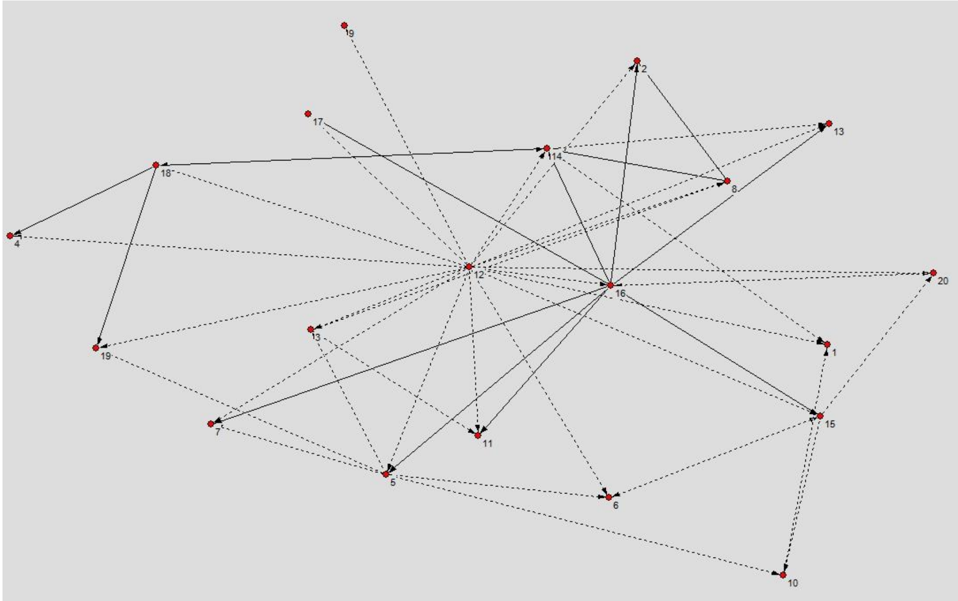
- ➢ SysGenSIM software for synthetic data
- ➢ Scale free networks of some average node degree
- ➢ Networks of size 10, 20, 50 and 100
- ➢ Both 500 and 1000 timesteps for ever network size

$$\frac{\mathrm{d}\,G_g}{\mathrm{d}\,t} = Z_g^c \cdot V_g \cdot \theta_g^{syn} \cdot \prod_k \left(1 + A_{k,g} \frac{G_k^{h_{k,g}}}{G_k^{h_{k,g}} + (K_{k,g}/Z_k^t)^{h_{k,g}}}\right) - \lambda_g \cdot \theta_g^{deg} \cdot G_g$$

Networks

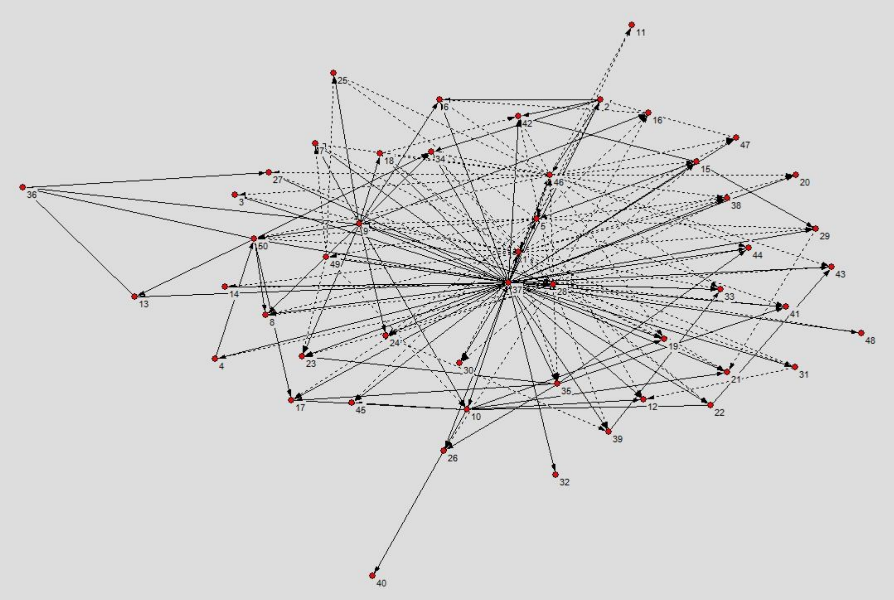


Network Size 10

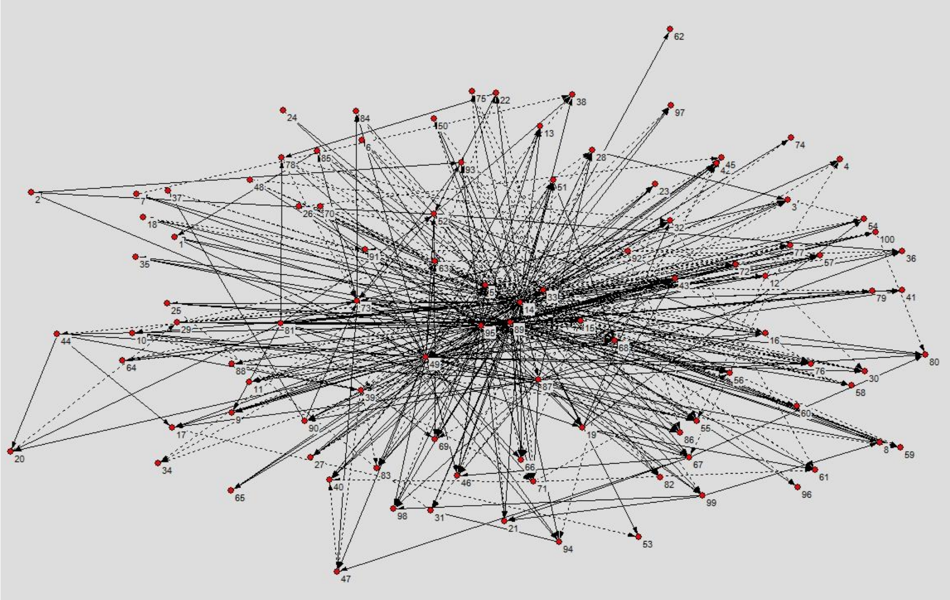


Network Size 20

Networks

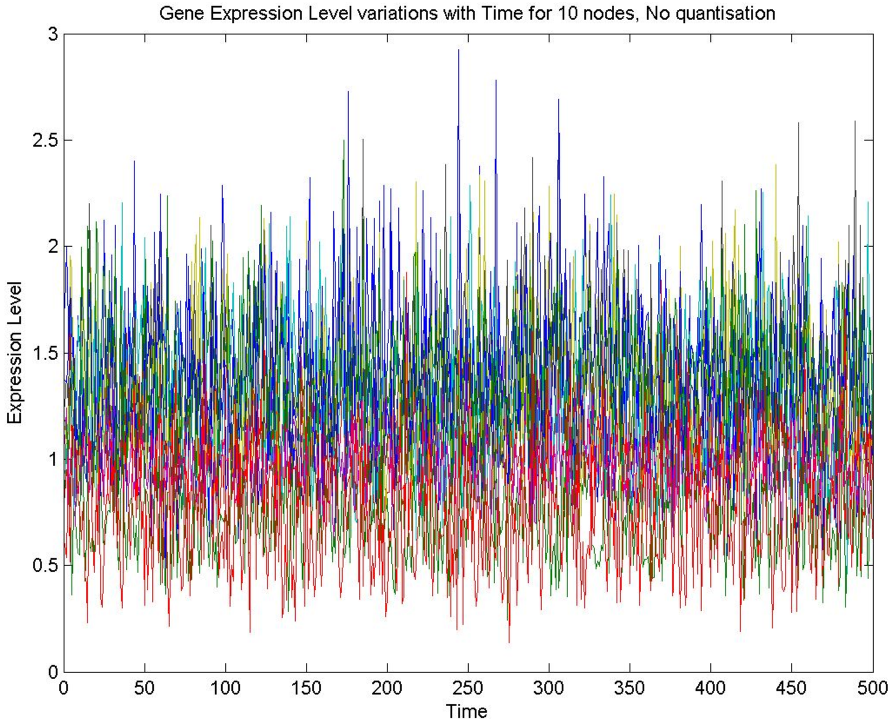


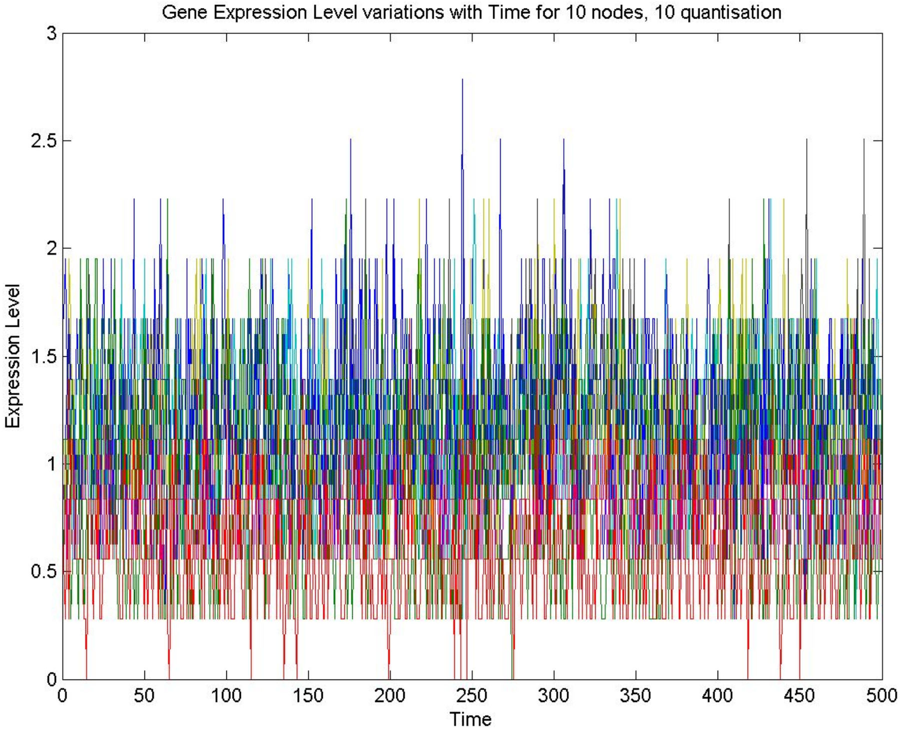
Network Size 50



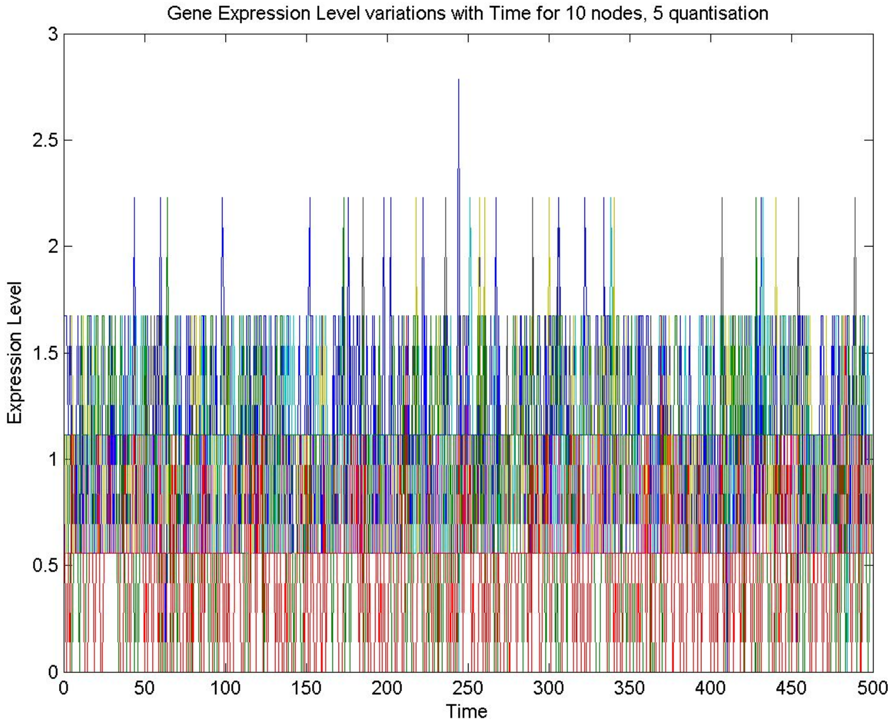
Network Size 100

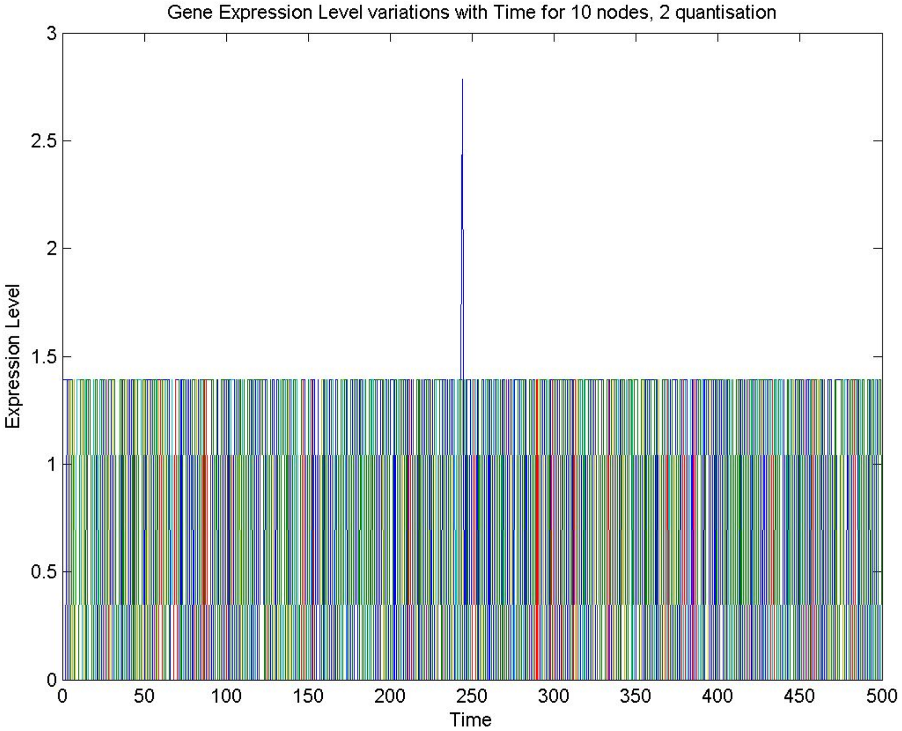
Data Quantisation





Data Quantisation





Techniques

- ➢ **Correlation** - lagged correlation coefficient for time series data, along with lag value to infer directionality
- ➢ **Granger Causality** - X causes Y iff prediction of Y is significantly better, given past X and Y, as compared to with Y alone
    - Regression residue analysis
    - F-statistic
- ➢ **Mutual Information** - measure of mutual dependence between X and Y
- ➢ **Transfer Entropy** - X causes Y iff prediction of Y is significantly better, given past X and Y, as compared to with Y alone
    - Probabilistic prediction analysis

Techniques In a Nutshell

	Linear	Non Linear
Non Predictive	Correlation	Mutual Information
Predictive	Granger Causality	Transfer Entropy

Parameters

- Size
- Quantisation Levels
- Time Series Length
  - Time Lag
- Techniques
  - Smoothing

Parameters

- Size [10, 20, 50, 100]
- Quantisation Levels [2, 5, 10, 20]
- Time Series Length [500, 1000]
  - Time Lag
- Techniques [ra, co, gc, mi, te]
  - Smoothing
- > 150 experiment runs

Parameters - Time Lag

- Model Selection using Bayesian Information Criterion, for Granger Causality

$$BIC = -2 \log(L) + k \log(n)$$

- Maximum possible information transfer, for others (max_lag = 5)

Results - Correlation

Size : 10

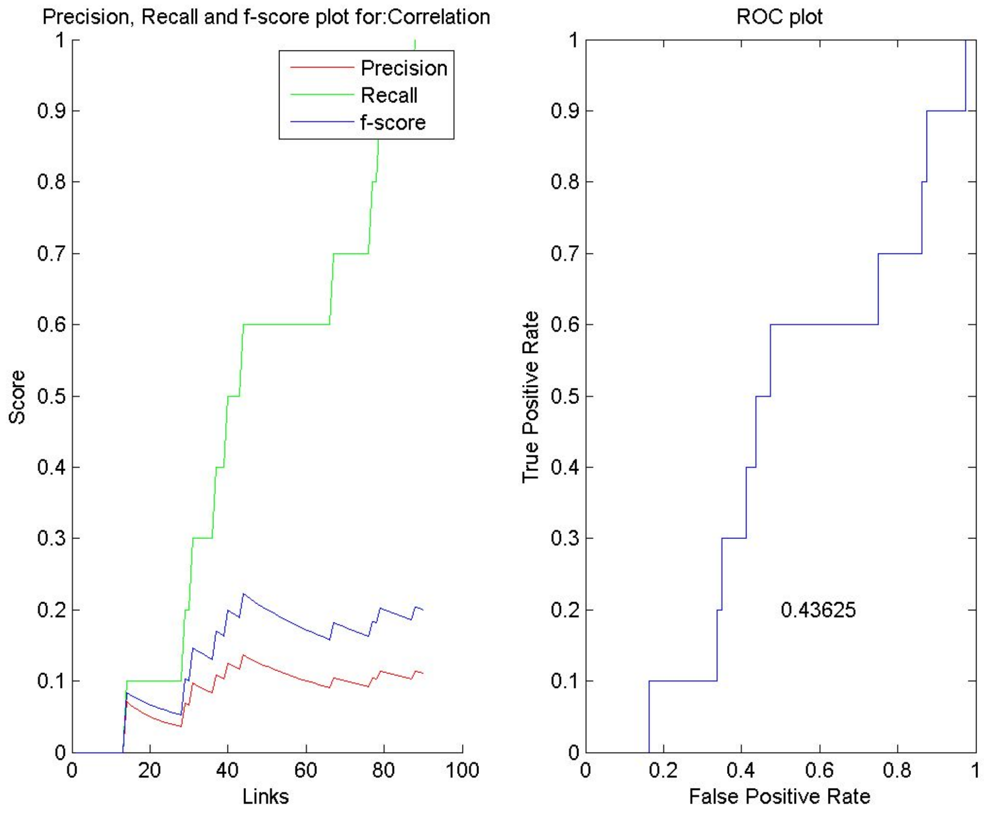
Type : Scale free

Average Degree : 3

Linearity : Non linear

Data points : 500

Bins : 2



Results - Correlation

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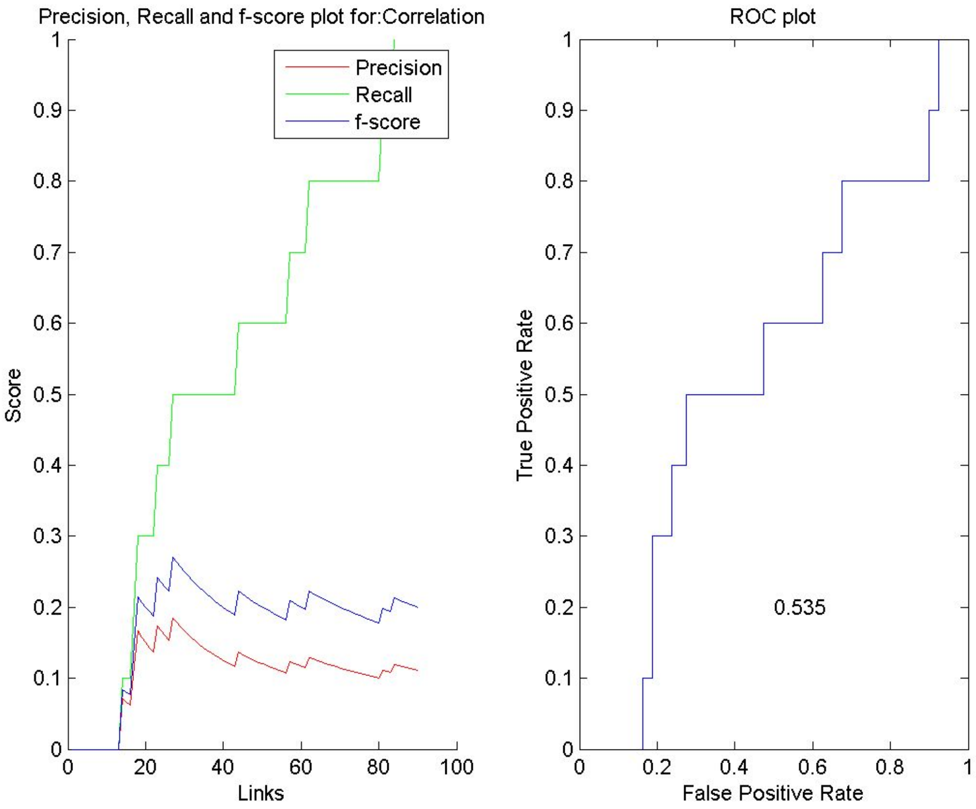


Results - Correlation

Size : 20

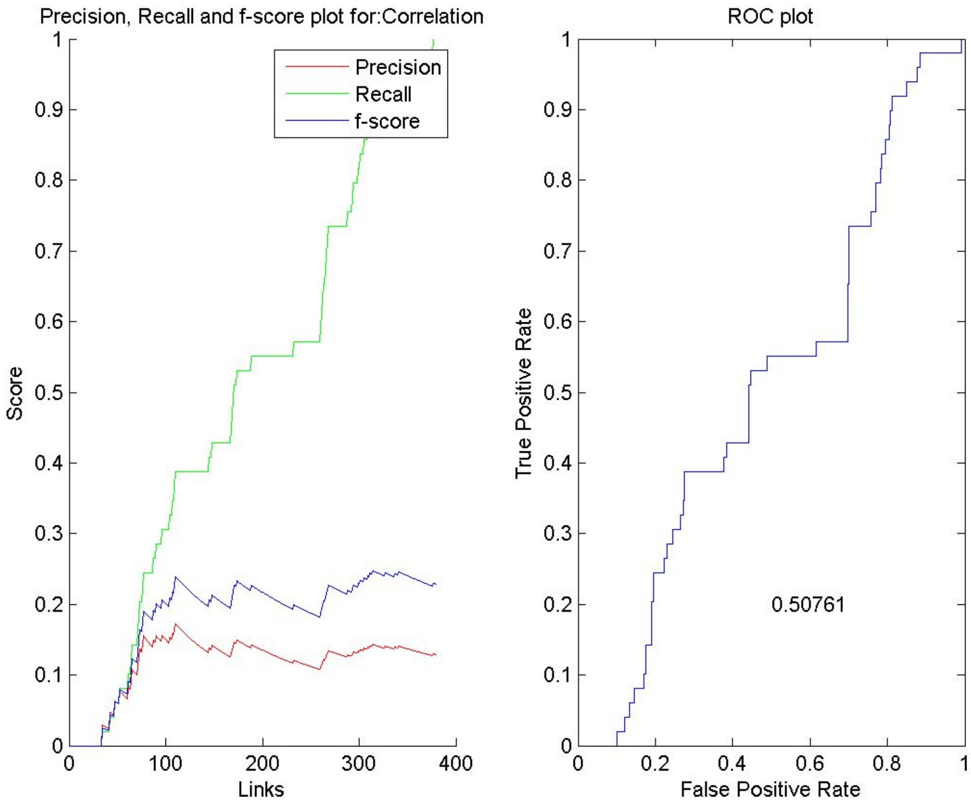
Type : Scale free

Average Degree : 4

Linearity : Non linear

Data points : 500

Bins : 2



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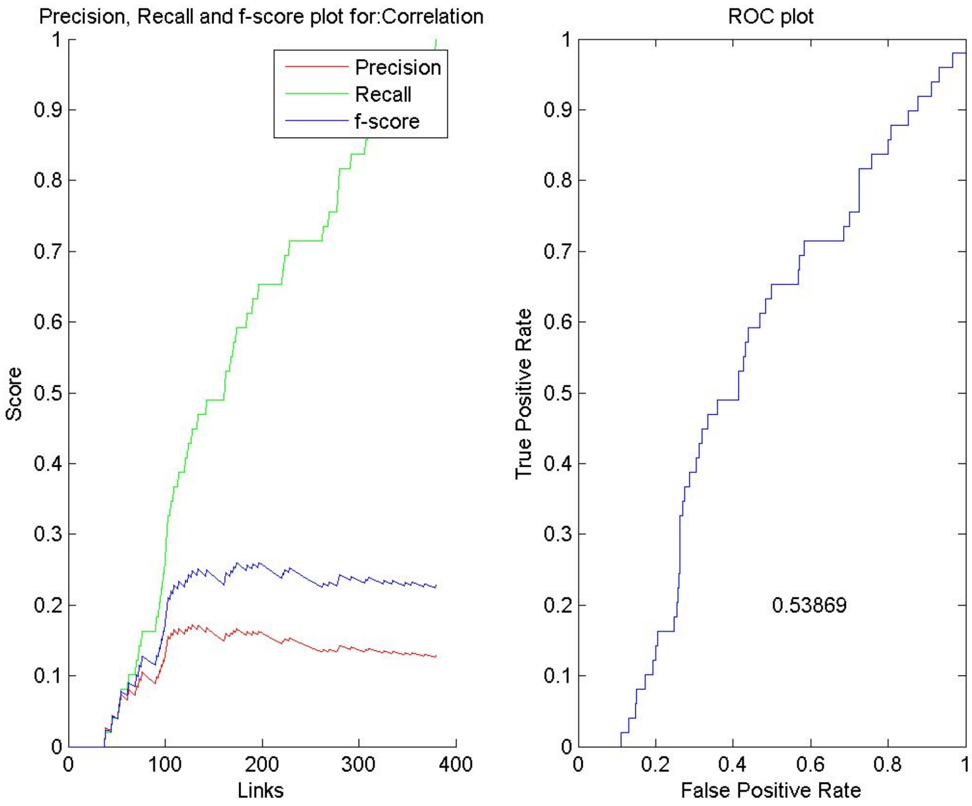


Explanation - Correlation

Correlation --/--> Causality

- ➢ Strong correlation between independent genes with common ancestors, especially if they are siblings
- ➢ Scaling of correlation to [0, 1] as correlation coefficient reduces difference

Results - Pairwise Granger Causality

Size : 10

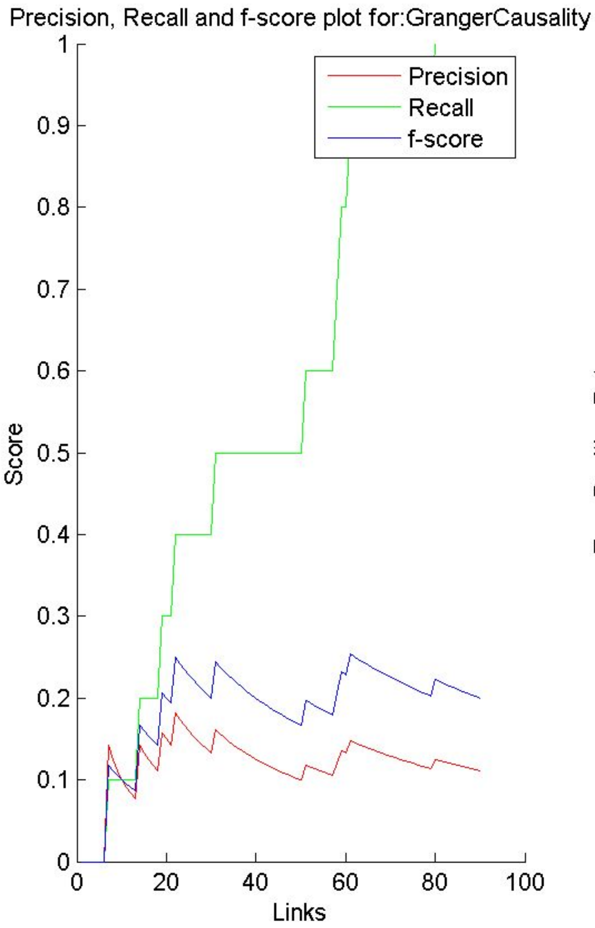
Type : Scale free

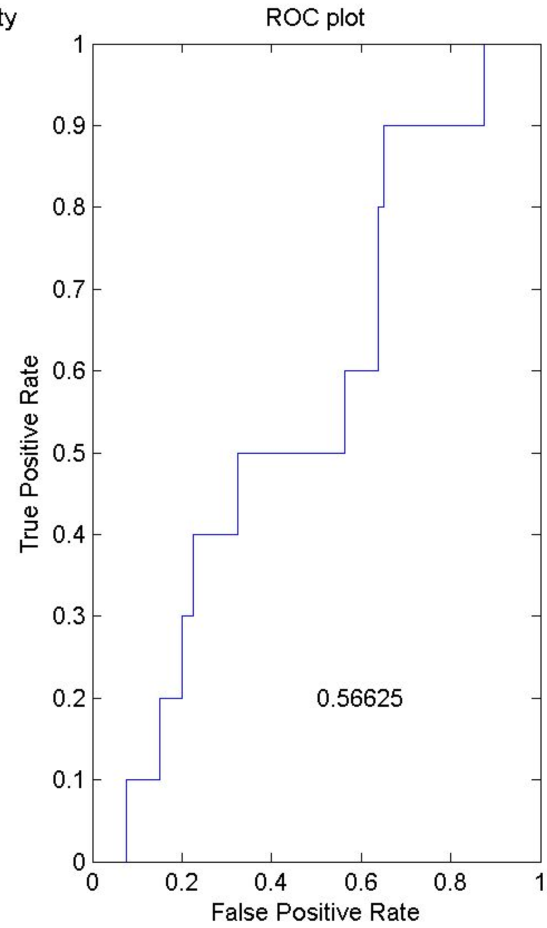
Average Degree : 3

Linearity : Non linear

Data points : 500

Bins : 2





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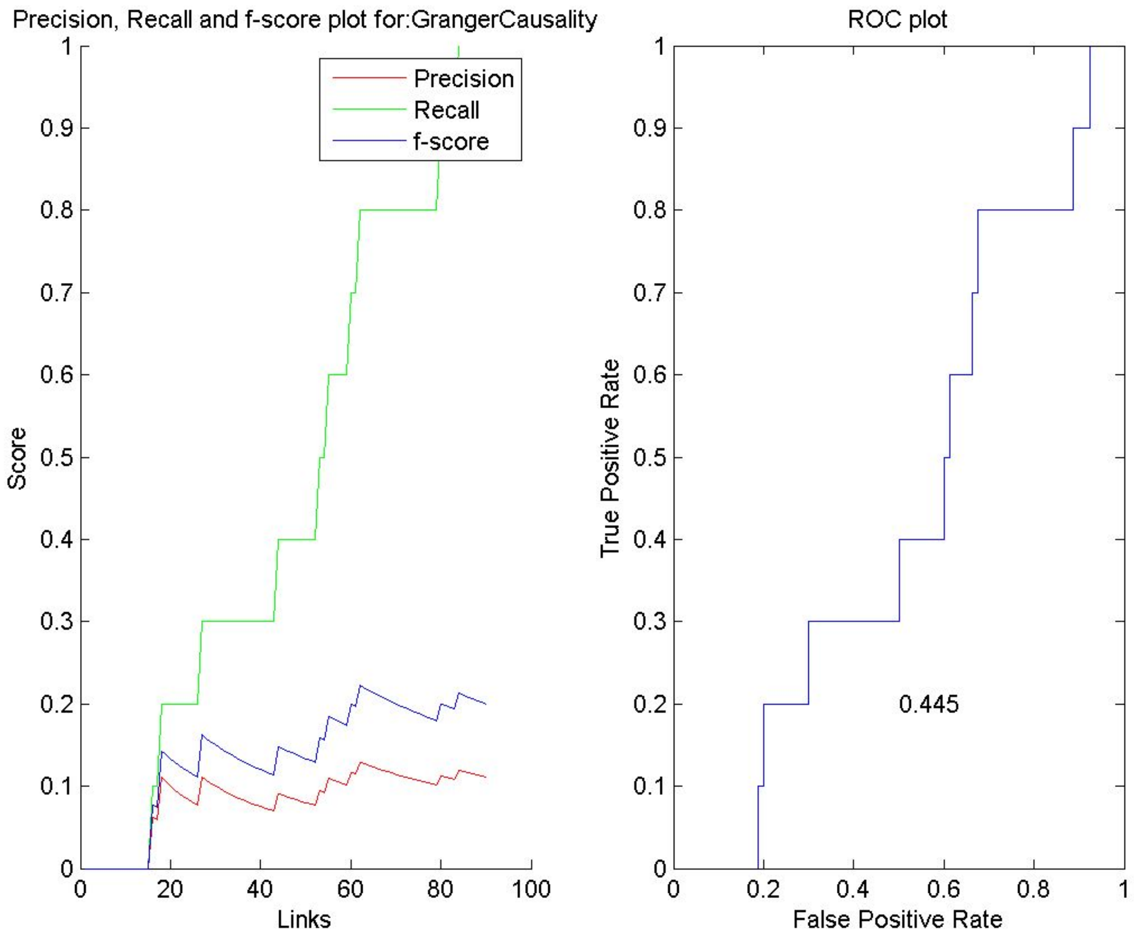

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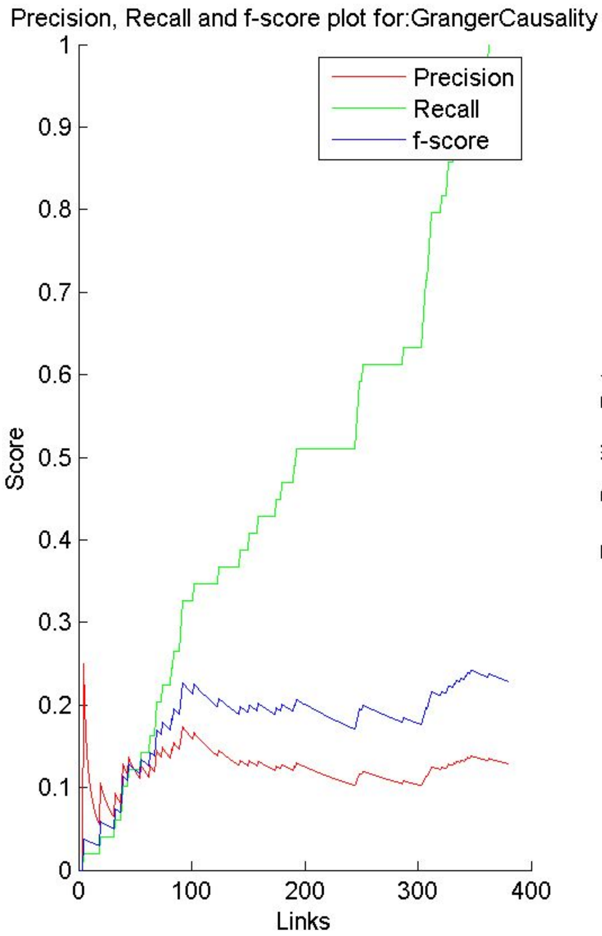

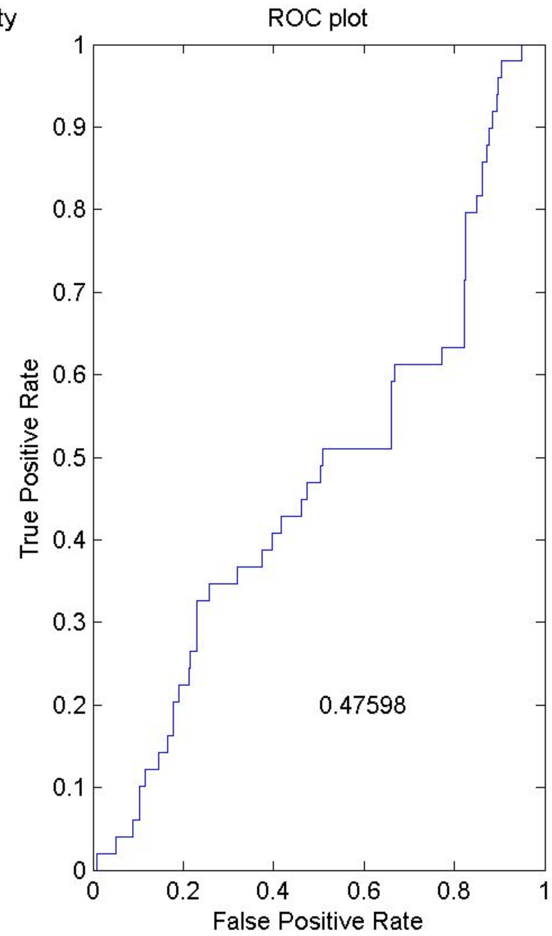

Results - Pairwise Granger Causality

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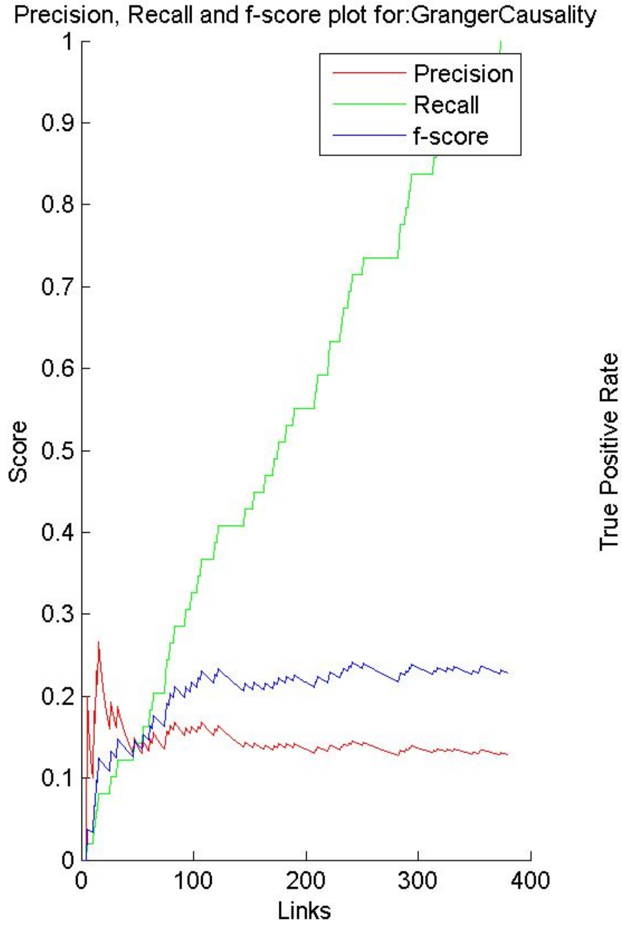
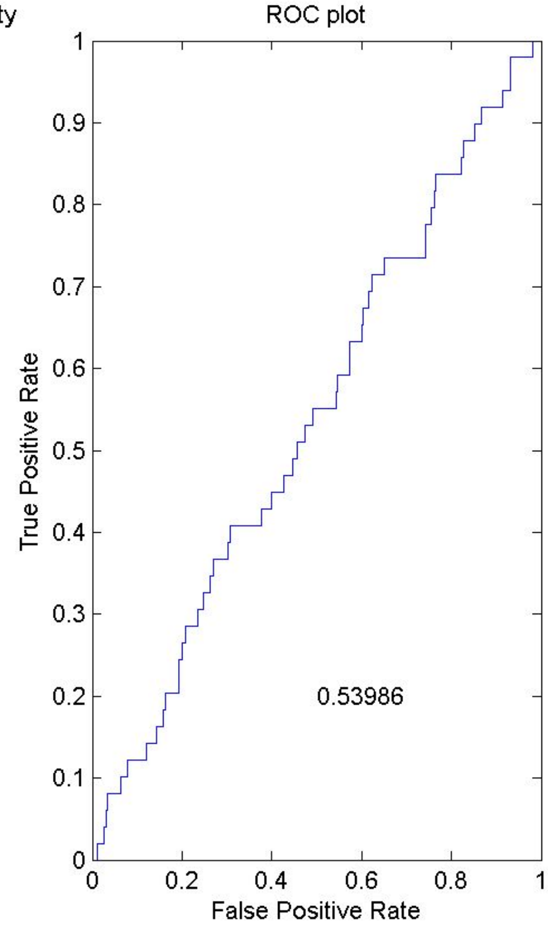
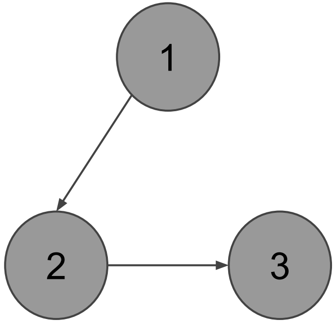
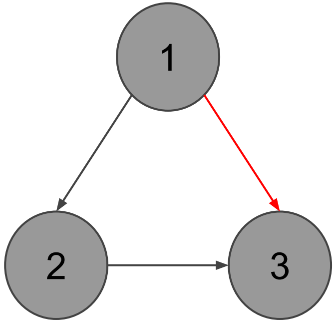


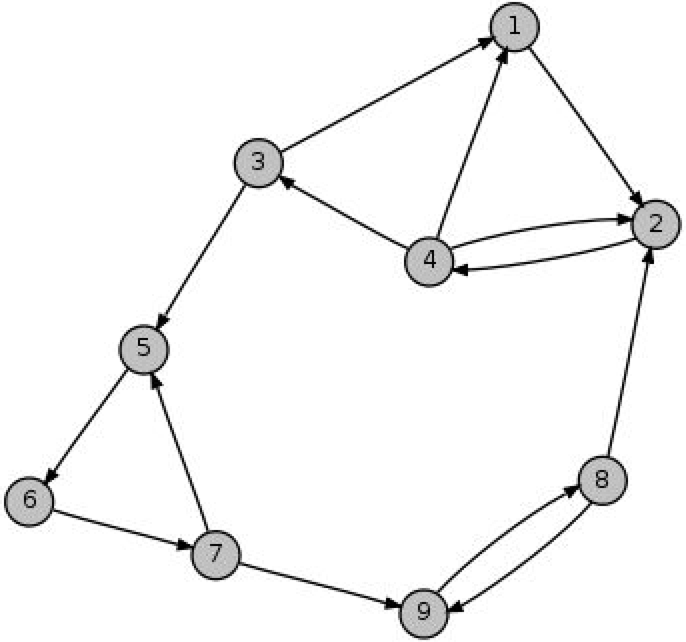


Explanation - Granger Causality (Pairwise)

- ➢ PGC cannot differentiate between direct and indirect causalities and thus, though recall is high, precision is low
- ➢ Non linear data







Results - Mutual Information

Size : 10

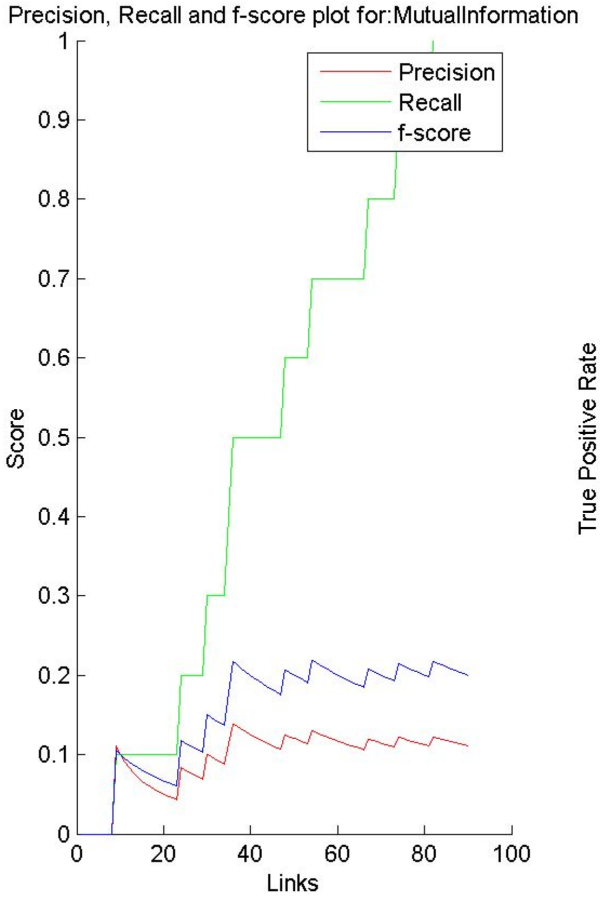
Type : Scale free

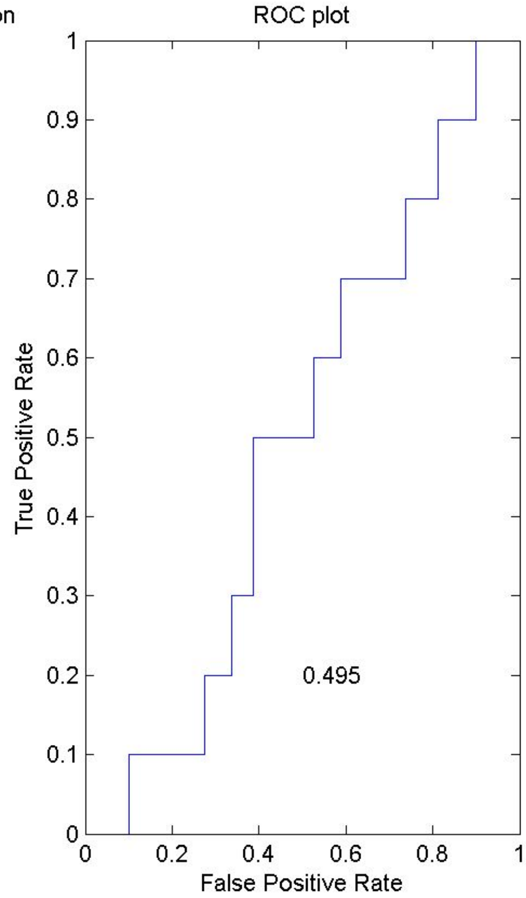
Average Degree : 3

Linearity : Non linear

Data points : 500

Bins : 2





Results - Mutual Information

Size : 10

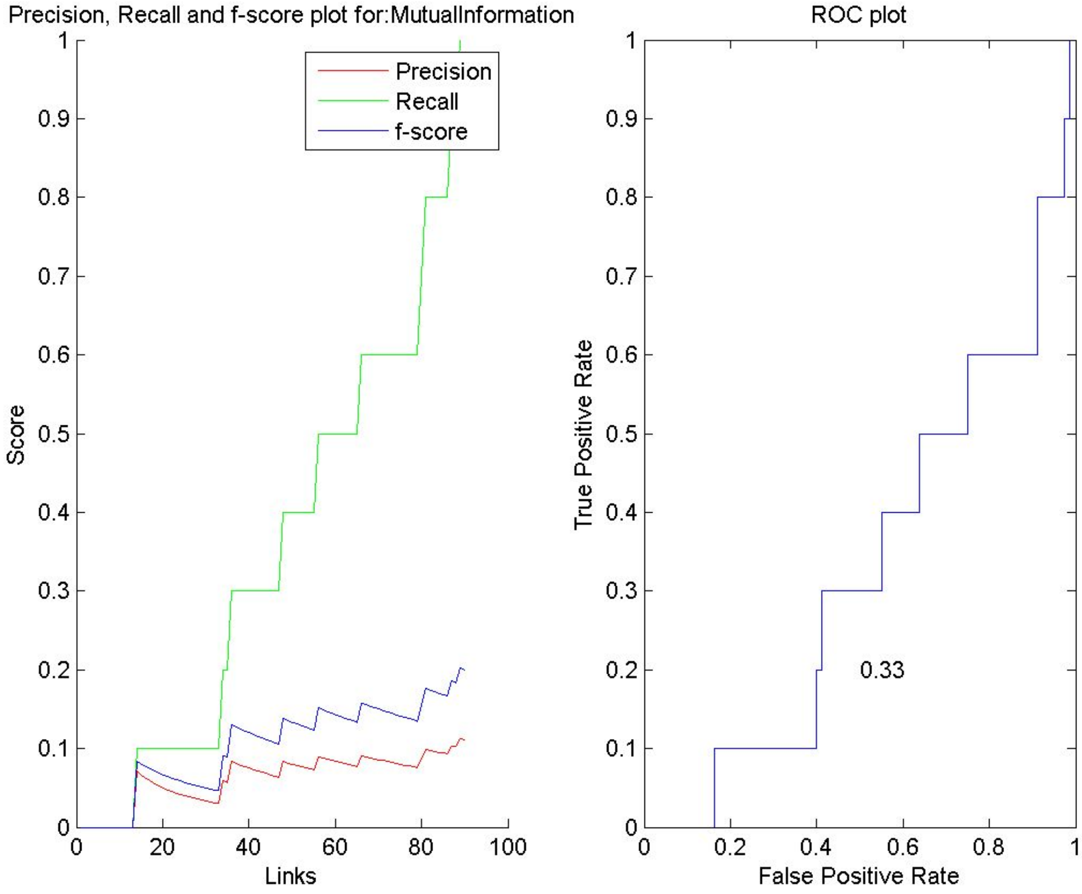
Type : Scale free

Average Degree : 3

Linearity : Non linear

Data points : 500

Bins : 5



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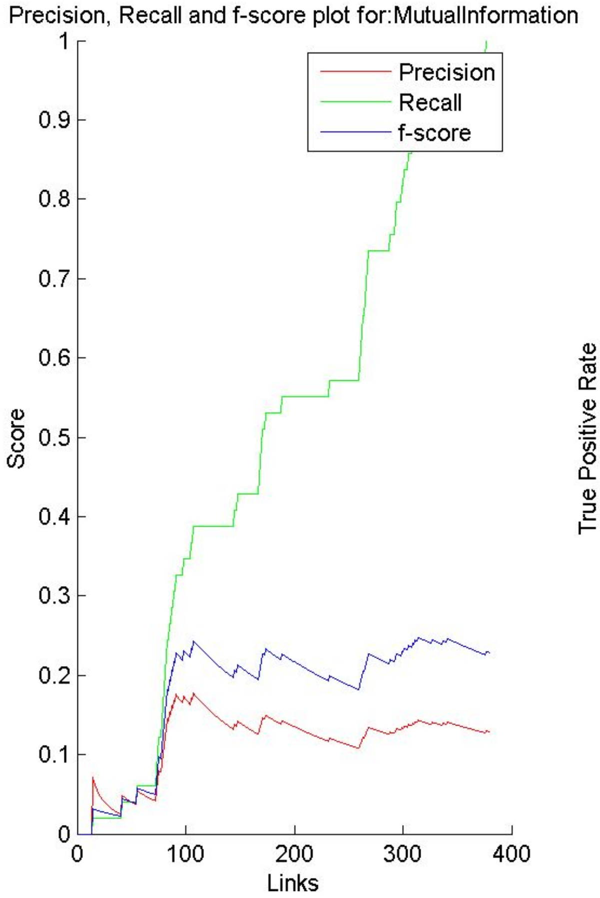

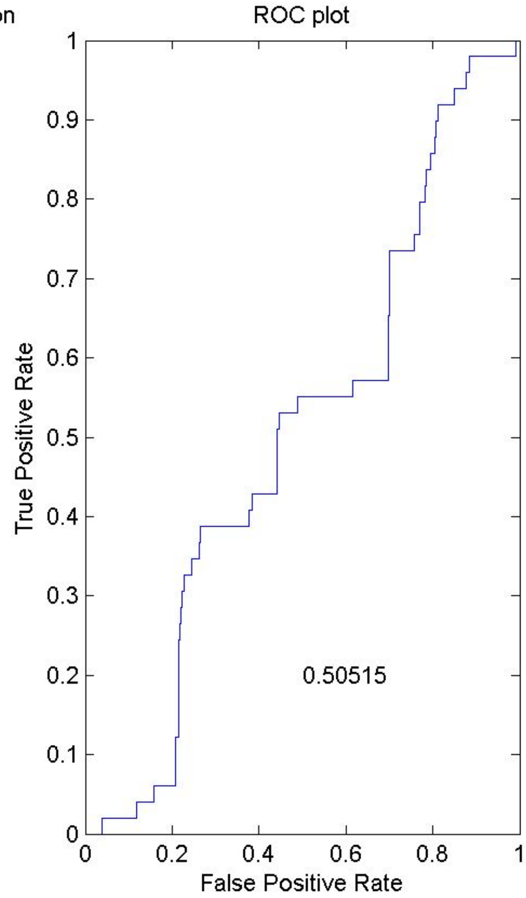

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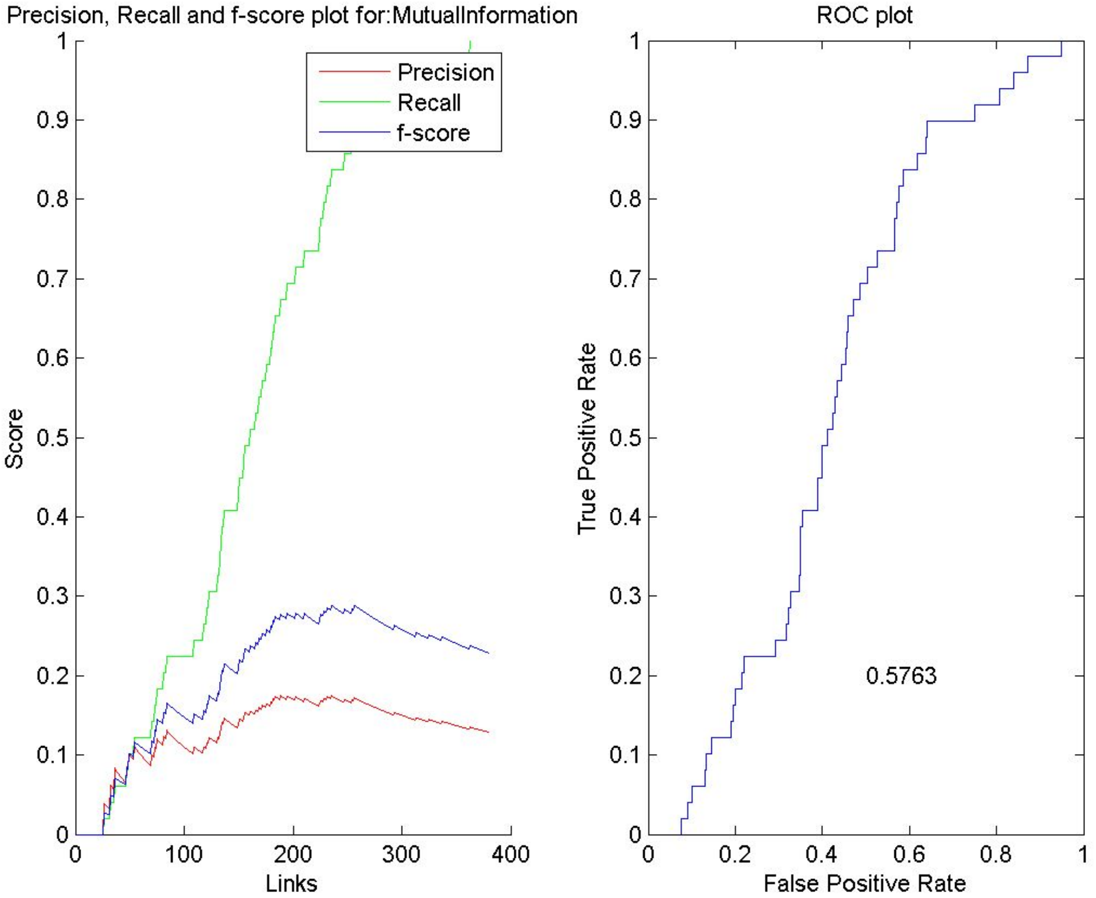


Explanation - Mutual Information

$$I(X, Y) = H(X) - H(X|Y) = H(Y) - H(Y|X)$$

- MI is not effective at predicting future events from current data. It is symmetric.
- It does not indicate the direction of the flow of information (unless we use the lag direction).

Results - Transfer Entropy

Size : 10

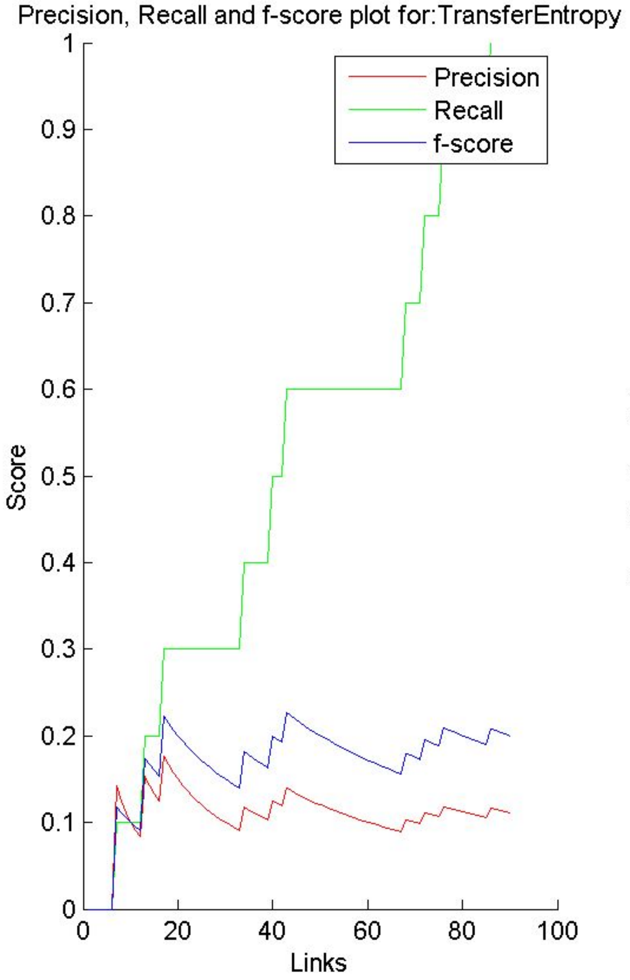
Type : Scale free

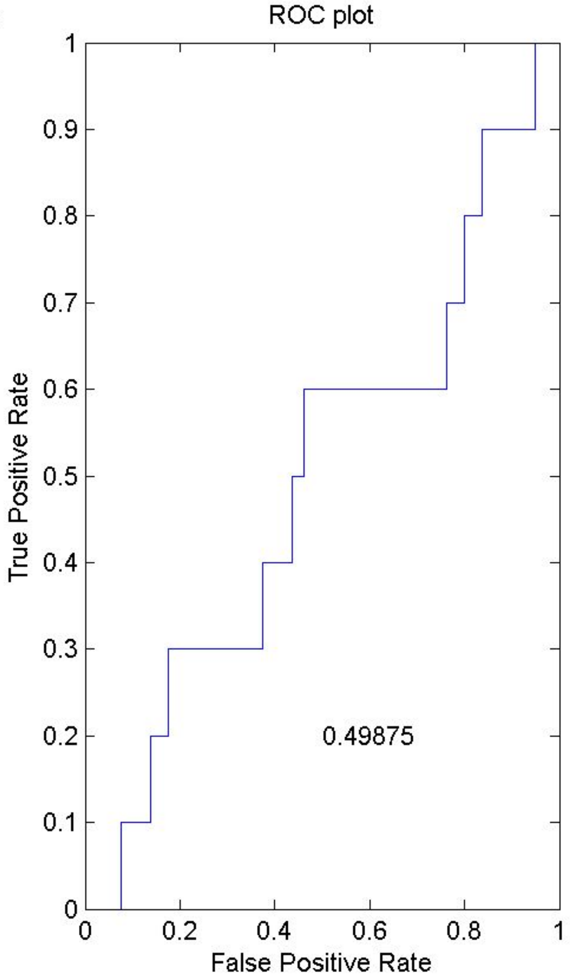
Average Degree : 3

Linearity : Non linear

Data points : 500

Bins : 2





Results - Transfer Entropy

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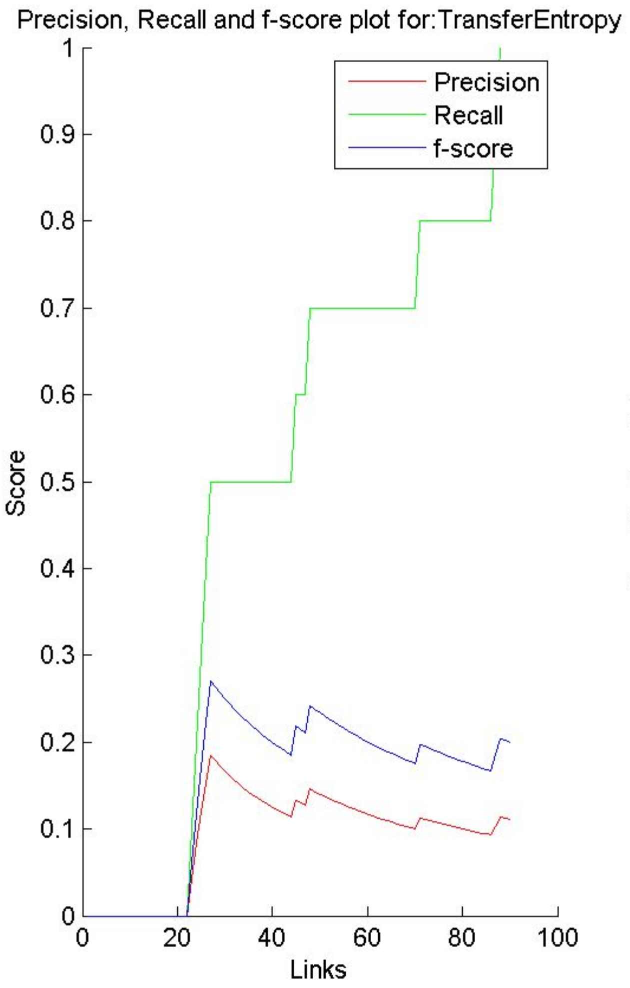

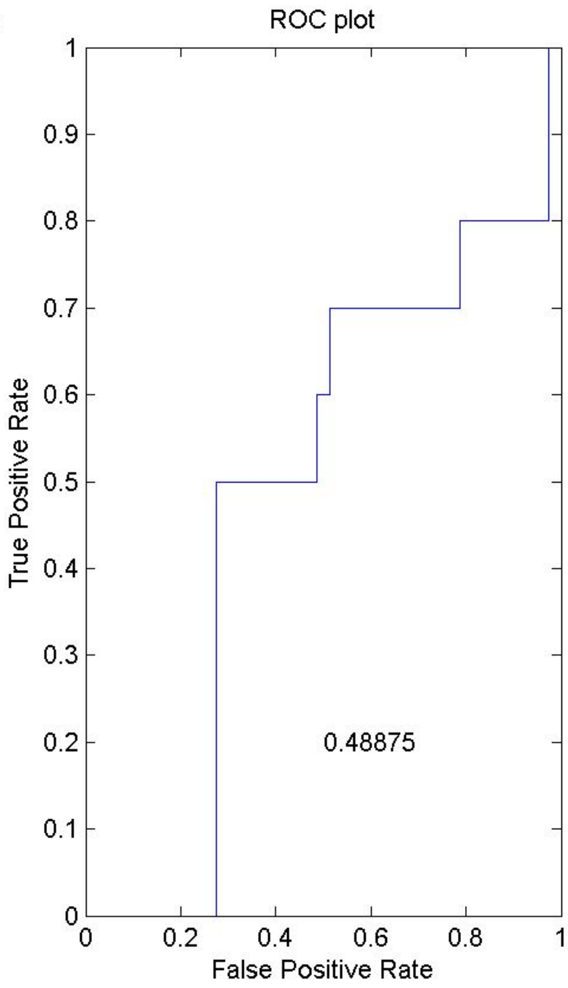

Results - Transfer Entropy

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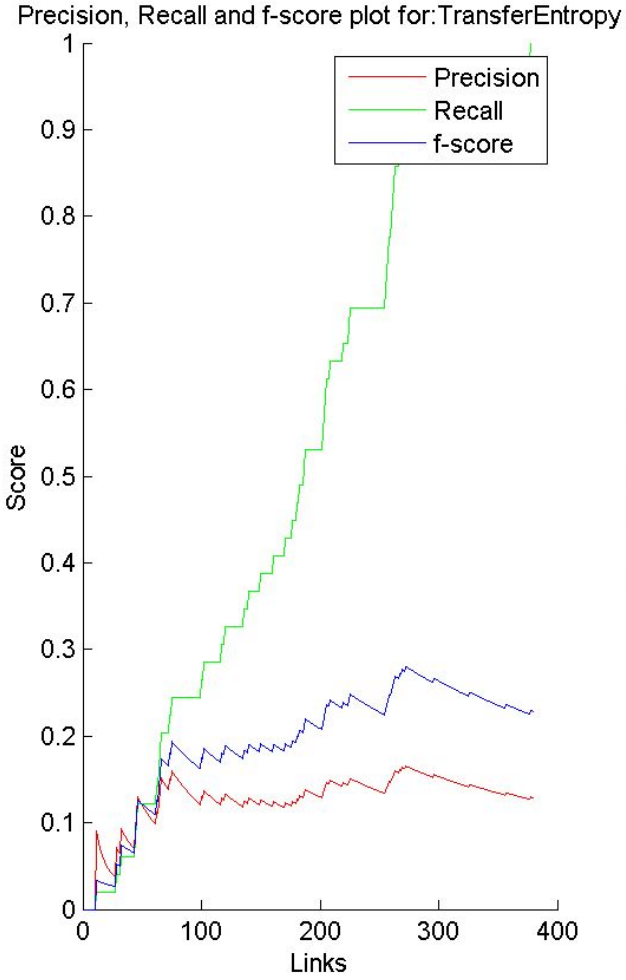

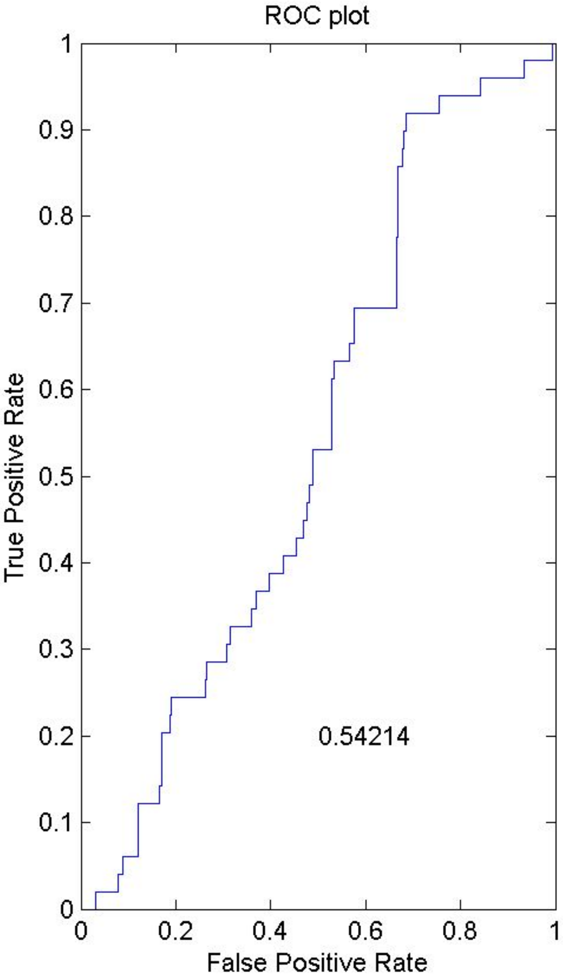

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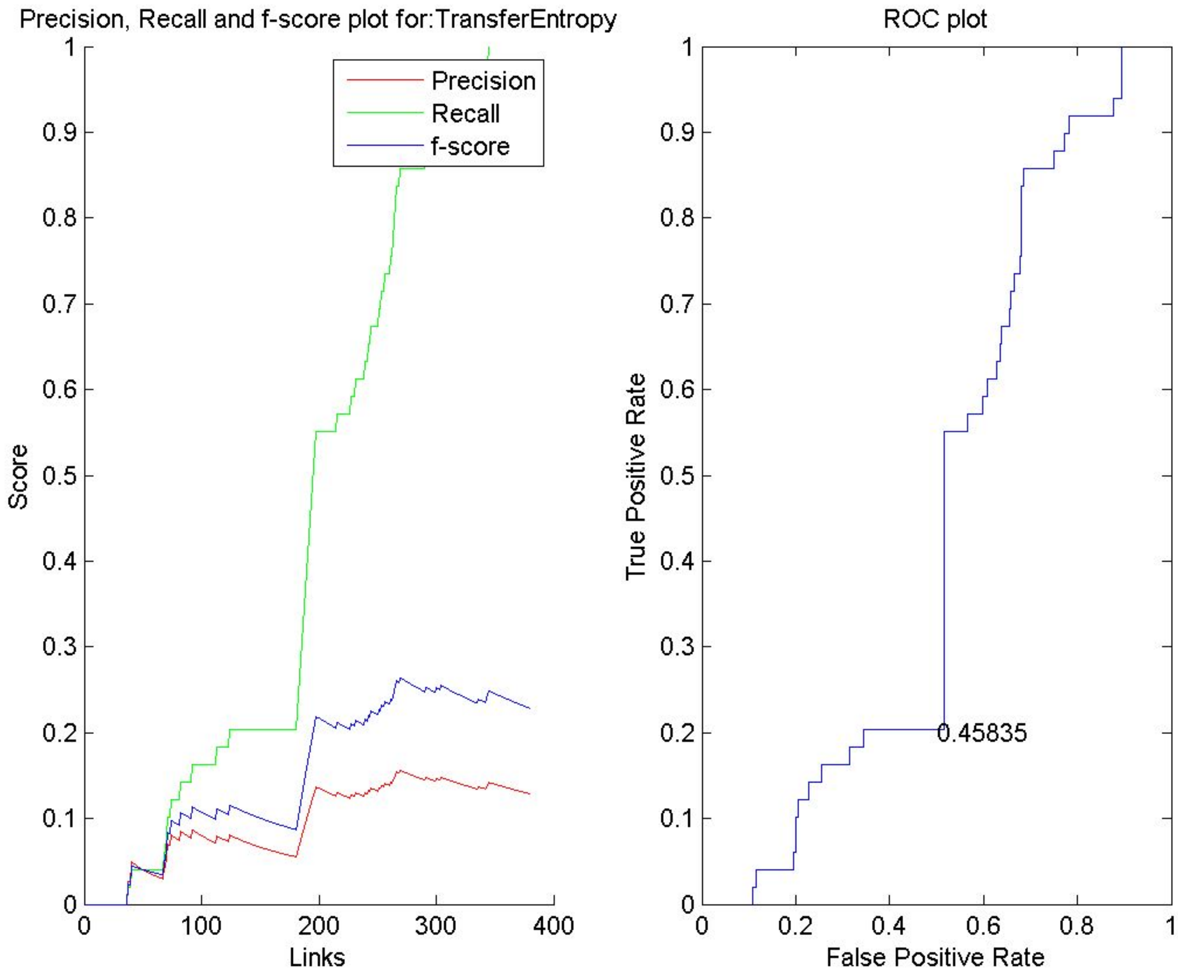


Parameters - Additive Smoothing

$$T_{J \to I} = \sum_{x_{n+1}, x_n, y_n} p(x_{n+1}, x_n, y_n) \log \left(\frac{p(x_{n+1}, x_n, y_n) \cdot p(x_n)}{p(x_n, y_n) \cdot p(x_{n+1}, x_n)} \right)$$

- Problem: signal is too short!

P(X=x) = (1+favourable(x))/(size(X)+total)

Results - Mutual Information

Size : 10

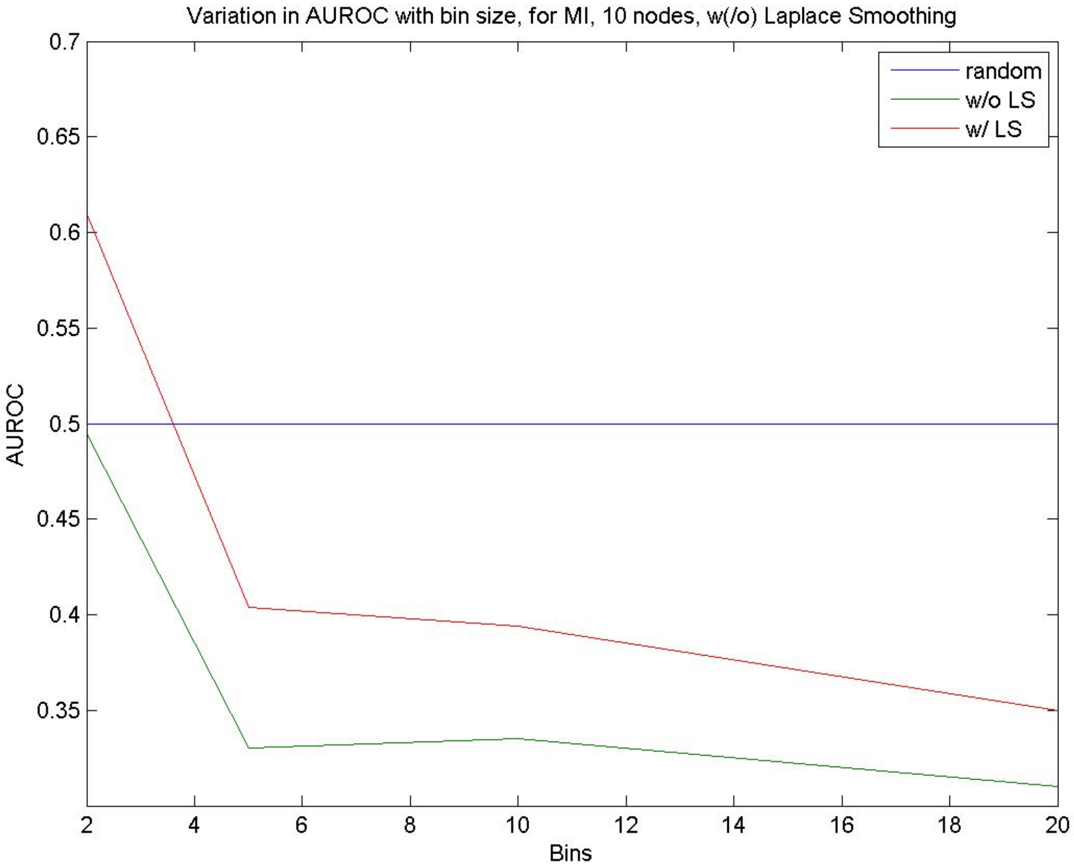
Type : Scale free

Average Degree : 3

Linearity : Non linear

Data points : 500

Smoothing : Additive



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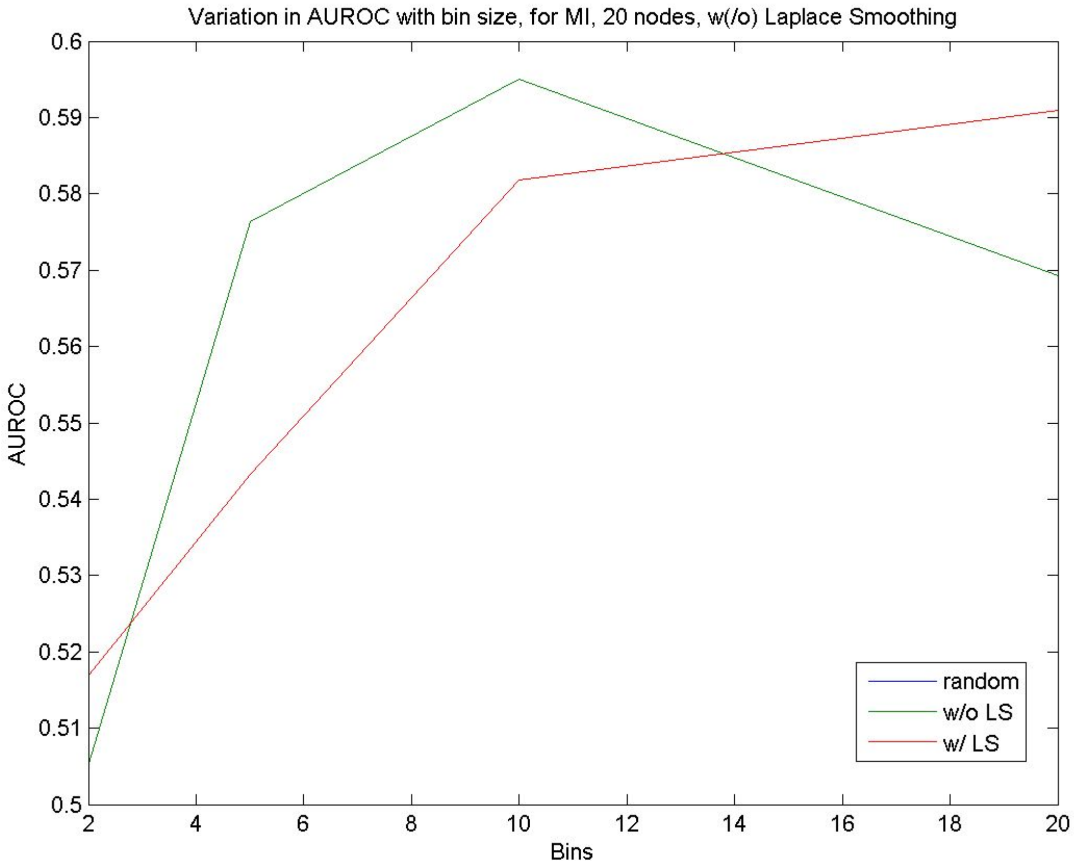

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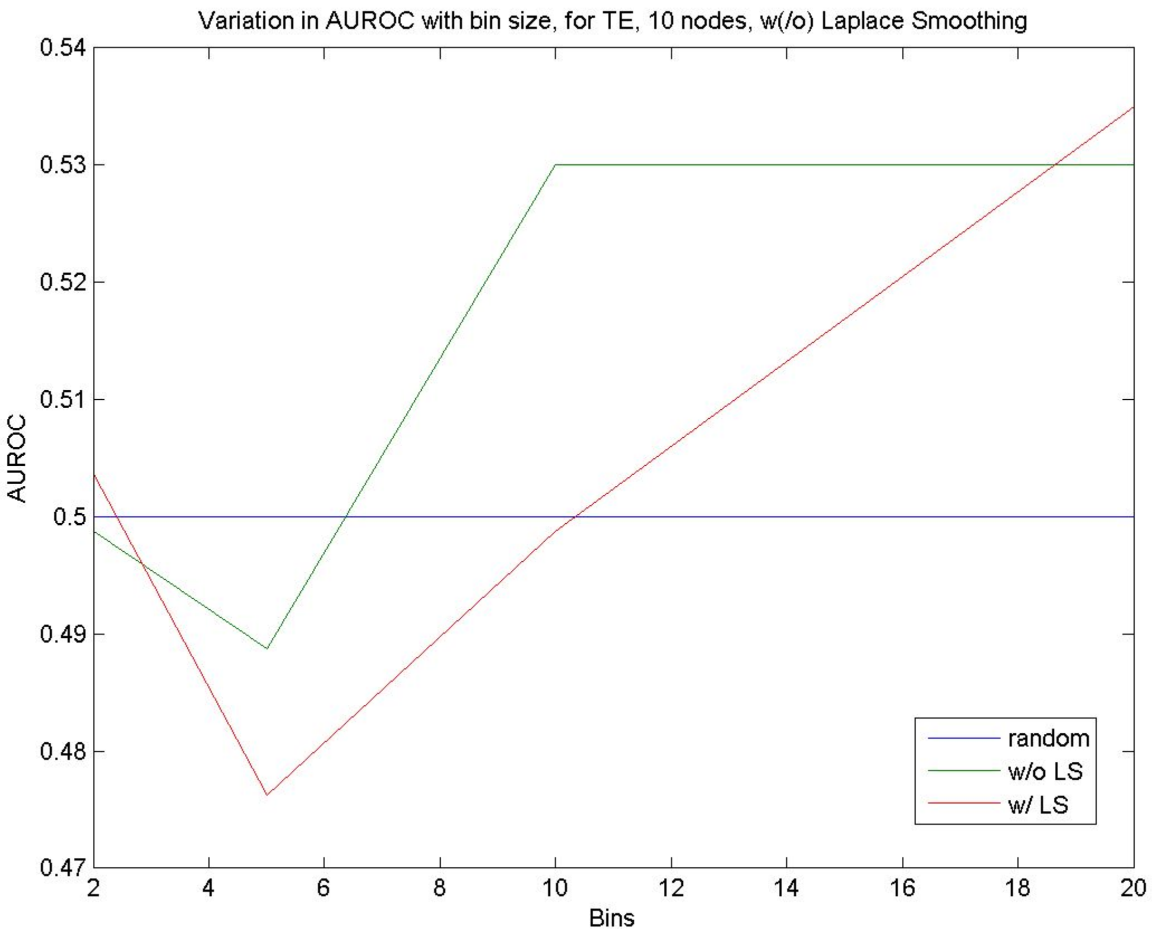

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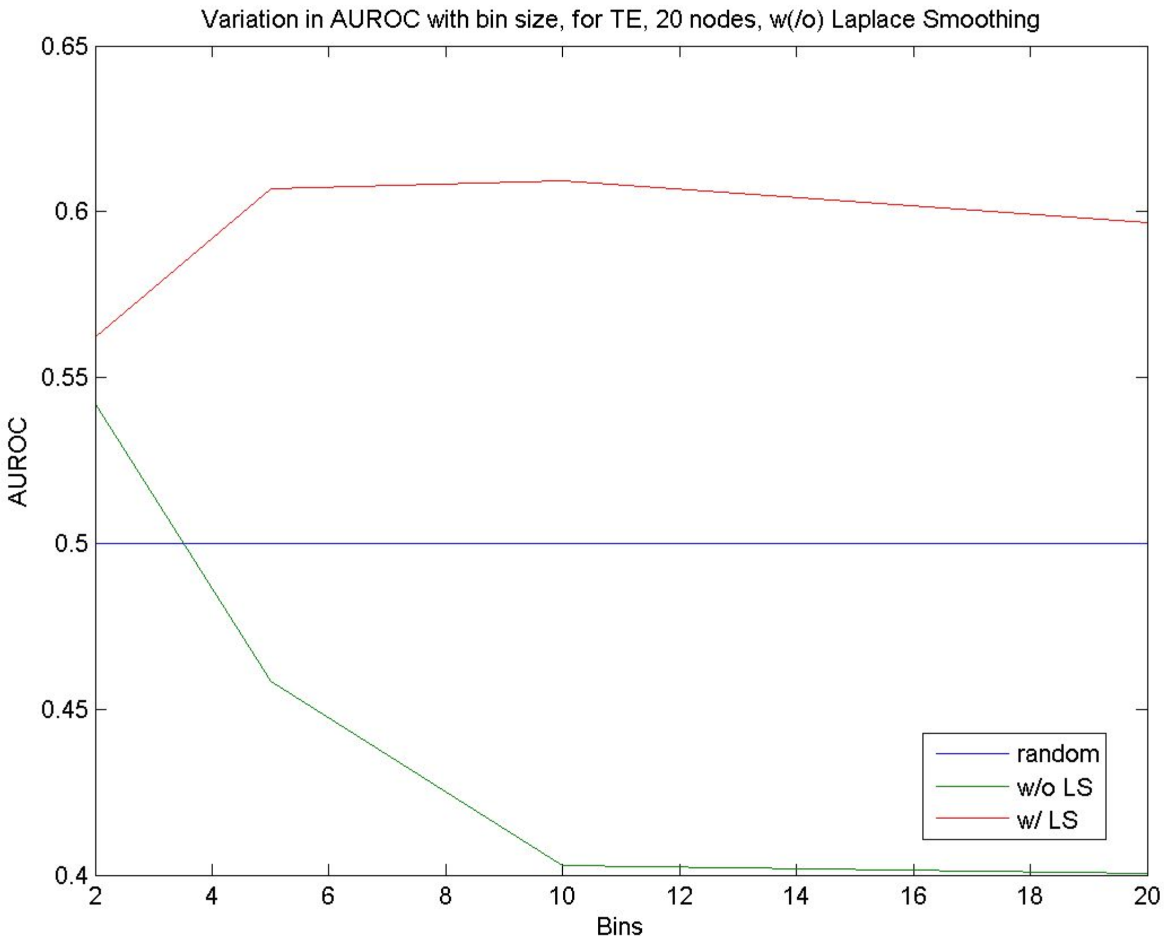
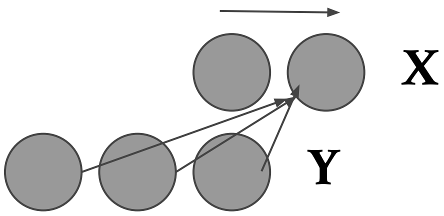


Explanations and Questions - Transfer Entropy

$$T_{X \rightarrow Y} = H(Y_t | Y_{t-1:t-L}) - H(Y_t | Y_{t-1:t-L}, X_{t-1:t-L})$$

- TE is the more generalised case for Granger Causality
- Does not assume linearity of the system being studied
- Additive Smoothing is a must, because of the large domain of the probability distributions involved
- Model Order can be increased?
- Optimal level of quantisation?



Summary of our Experience

- Poverty of data → Smoothing
- Abundance of parameters → Grid Search
- No strict trends in any direction, but largely:

$$\text{TE} \sim \text{MI} > \text{GC} > \text{Correlation}$$

- These methods, standalone, are not a good measure for the discovery of GRNs with high confidence
- Combination of multiple methods (akin to FP Correction, Structure Learning) can enhance the performance

Future Work

- Correction for False Positives: interplay of GC, MI, TE
  - Feature Weighting
- Treat signals being causally related if they belong to same dynamical system

As Random Variable

Correlation	Mutual Information
Granger Causality	Transfer Entropy

As Dynamical System

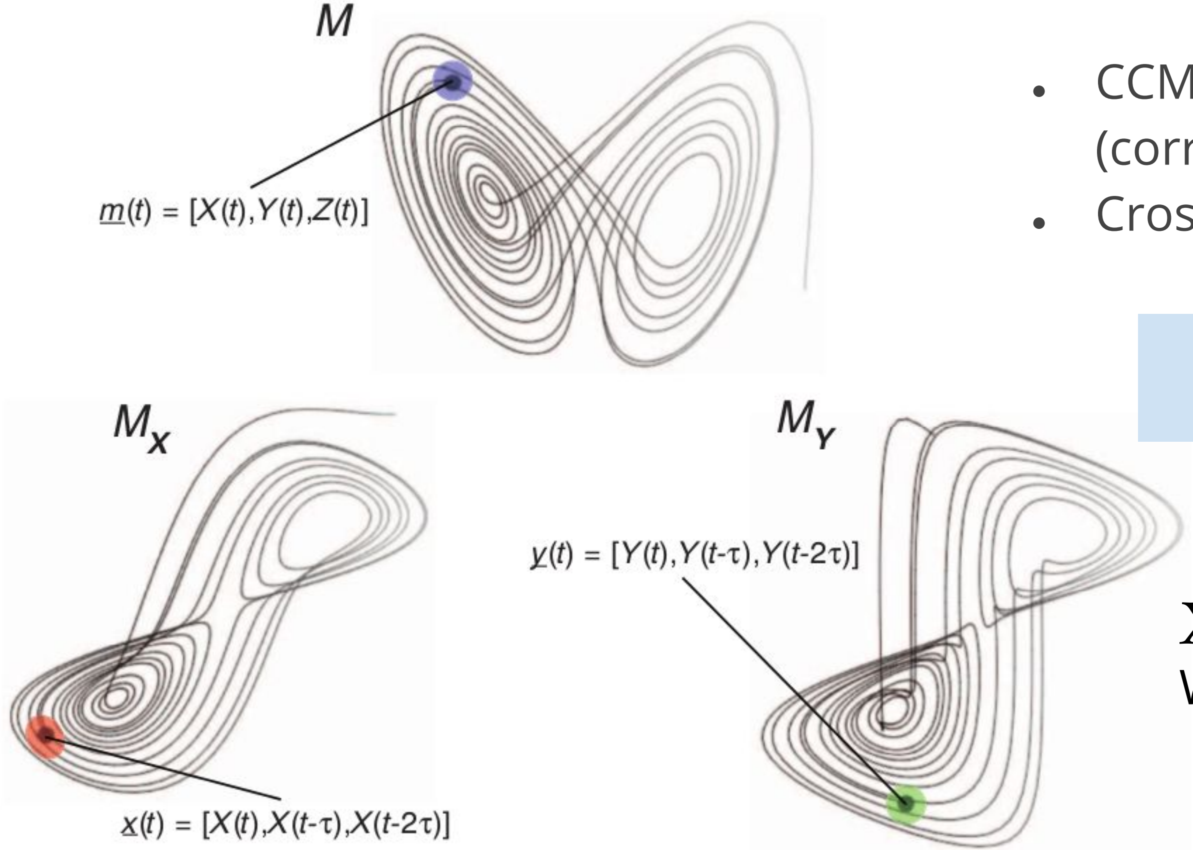
Convergent Cross Map

- Incorporate Network Substructures
- Use real Biological Datasets to validate so-formed technique

Thank You

Questions?

The Way Ahead - Convergent Cross Mapping



- CCM involves convergence (correlation =/= causation)
- Cross-map in:

One Direction

Both Directions

$X \rightarrow Y$

We can predict X from Y

The Hybrid Approach

Information Theory

- ✗ For stochastic, non-linear systems
- ✓ Can differentiate, through thresholding

Theory of Manifolds

- ✓ For possibly synergistic, deterministic systems
- ✗ No difference between first order and transitive causality

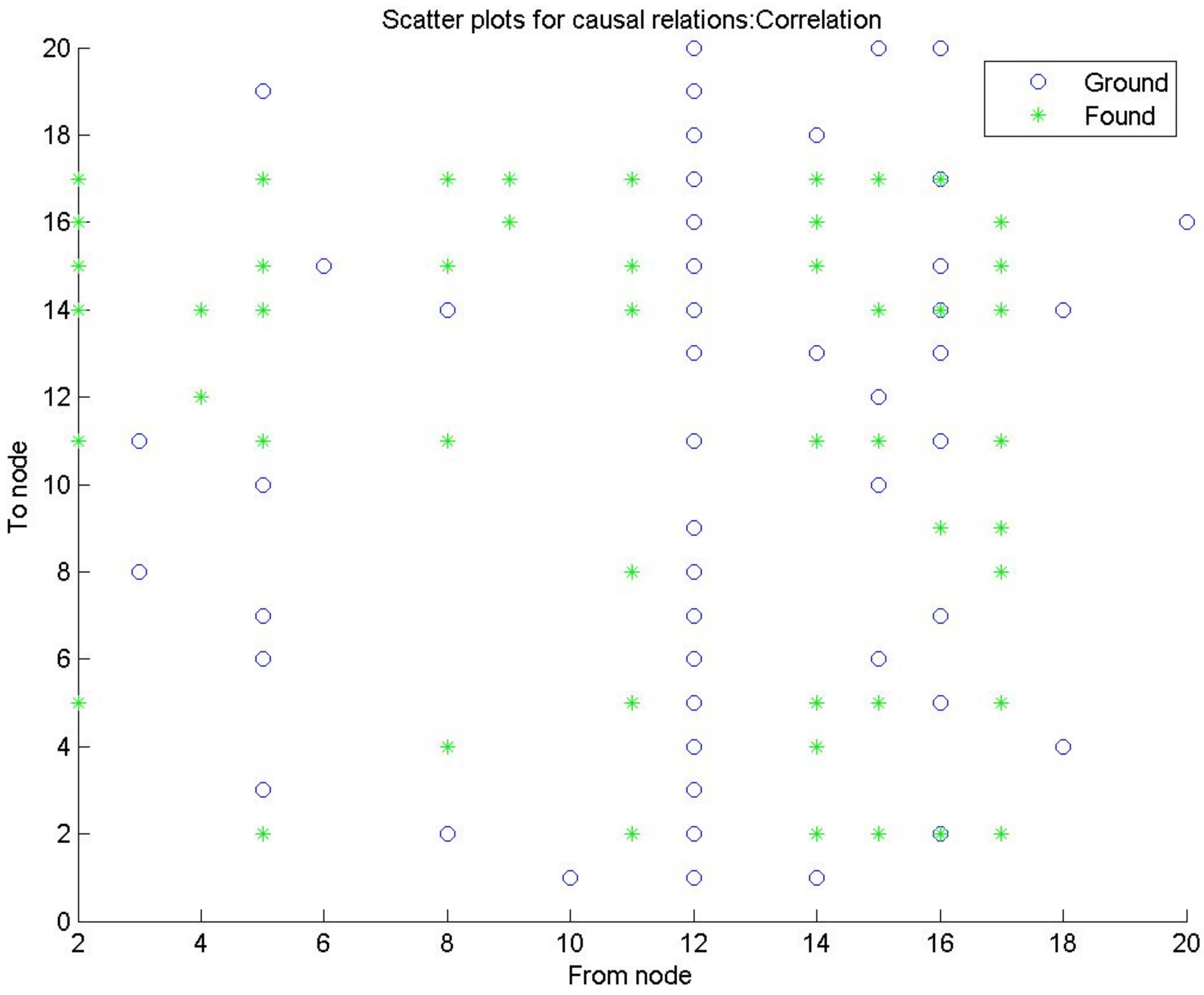
Scatter

Size : 20

Data Points : 500

Bins : 2

Method : Correlation



Scatter

Size : 20

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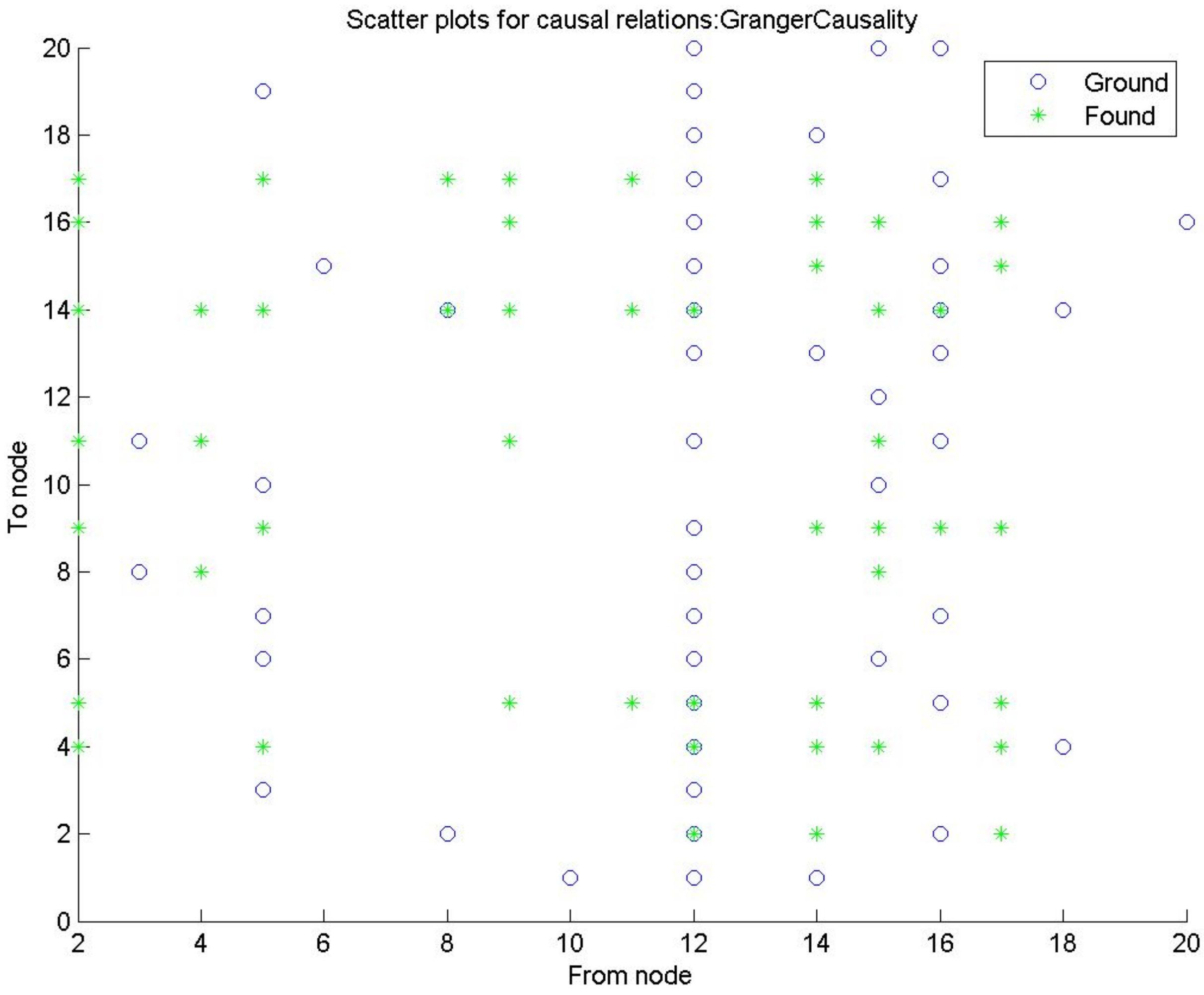
Bins : 2

Method :

Granger Causality



Scatter

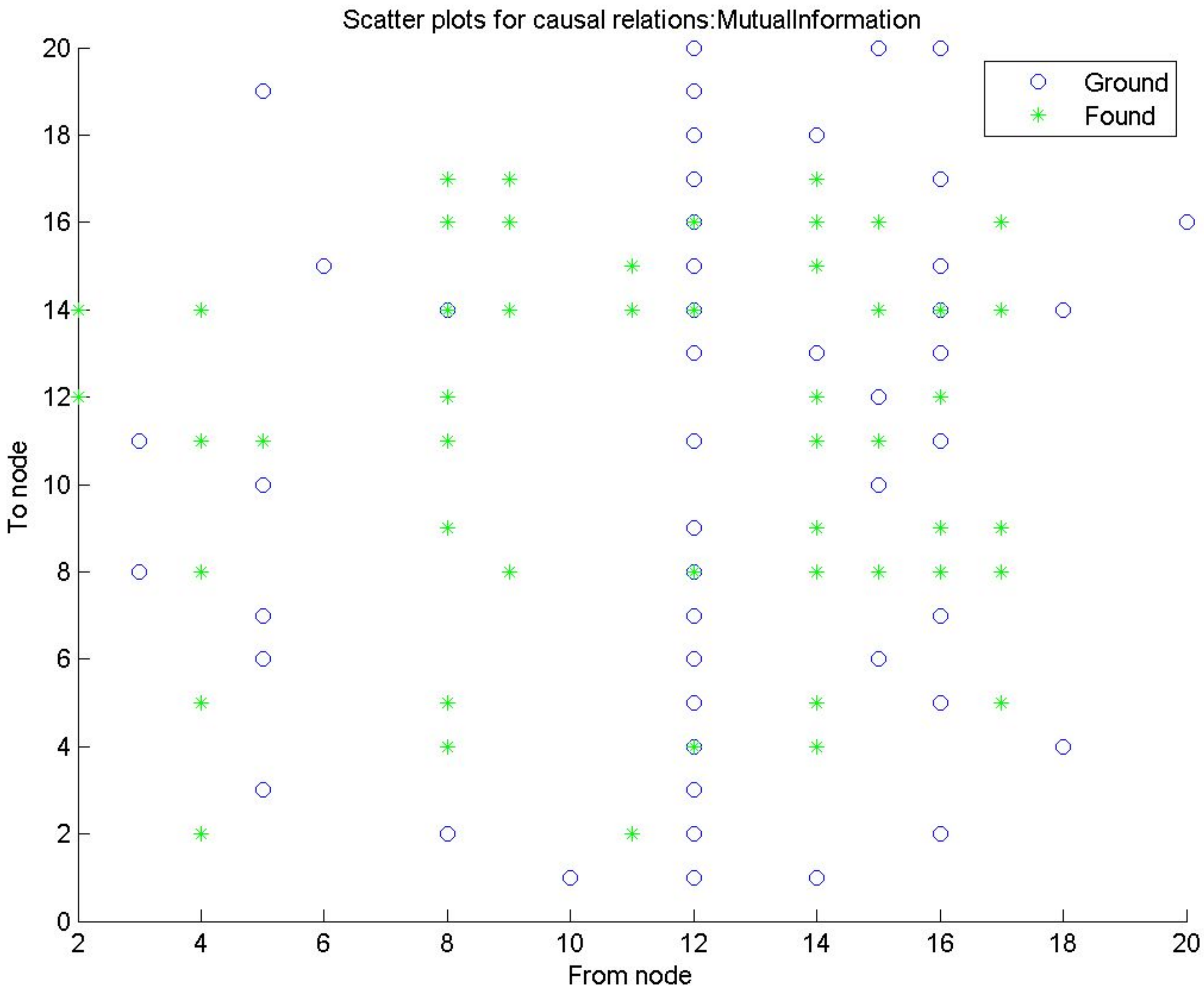
Size : 20

Data Points : 500

Bins : 2

Method :

Mutual Information



Scatter

Size : 20

Data Points : 500

Bins : 2

Method :

Transfer Entropy